Medicinrådet

Bilag til Medicinrådets anbefaling vedr. daratumumab i kombination med bortezomib, thalidomid og dexamethason til behandling af patienter med nydiagnosticeret knoglemarvs-kræft, som er kandidater til højdosis kemoterapi med stamcellestøtte

Vers. 1.0

Bilagsoversigt

1. Ansøgers endelige ansøgning
2. Forhandlingsnotat fra Amgros vedr. daratumumab (Darzalex)
3. Ansøgers notat til Rådet

Application for the assessment of Darzalex® in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant

[redacted]

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Darzalex®
Generic name	Daratumumab
Marketing authorization holder in Denmark	Janssen-Cilag A/S Bregnerødvej 133 3460 Birkerød
ATC code	L01XC24
Pharmacotherapeutic group	Antineoplastic agents, monoclonal antibodies
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 targeted immunotherapy; an IgG1κ-subtype, completely human monoclonal antibody which specifically targets tumor plasma cells expressing CD38, a transmembrane surface protein. CD38 is a distinct target from those of other approved agents for multiple myeloma. Daratumumab triggers direct immune effects against myeloma cells via complement-dependent cytotoxicity, antibody-dependent cell-mediated phagocytosis, and antibody-dependent cell-mediated cytotoxicity. Daratumumab additionally triggers apoptosis by cross-linking surface proteins on myeloma cells. Moreover, it also leads to the depletion of highly immunosuppressive CD38+ cells, which in turn leads to an increase in the numbers of helper T cells, cytotoxic T cells, and T-cell function.

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Overview of the pharmaceutical	
Dosage regimen	Dosing schedule of daratumumab in combination with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed multiple myeloma patients eligible for autologous stem cell transplant.(1) • The recommended dose is 1,800 mg of daratumumab solution for subcutaneous injection administered over approximately 3-5 minutes. • The recommended dose is 16 mg/kg of daratumumab administered as an intravenous infusion according to the following dosing schedule below. In part 1 of the CASSIOPEIA (MMY3006) daratumumab was administered by IV infusion (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. • Bortezomib was administered SC at a dose of 1.3 mg/m^2 twice a week (Days 1, 4, 8 and 11) for four 28-day induction cycles (Cycles 1 to 4), and two consolidation cycles (Cycles 5 and 6), with an option to change the schedule from twice weekly to once weekly, should toxicity be experienced. Cycles remained 28 days regardless of injection interval. On treatment days when both bortezomib and daratumumab were administered, bortezomib was administered after the end of the daratumumab infusion. • Thalidomide was administered orally at 100 mg daily for four 28-day induction cycles and two 28-day consolidation cycles. • Dexamethasone was administered at 40 mg on days 1, 2, 8, 9, 15, 16, 22, 23 of cycles 1 and 2. In cycles 3 and 4, dexamethasone was administered at 40 mg on days 1,2 and 20 mg on subsequent dosing days (8, 9, 15, 16). Dexamethasone 20 mg was administered on days 1, 2, 8, 9, 15, 16 of cycles 5 and 6.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Daratumumab in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
Other approved therapeutic indications	Daratumumab in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. Daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. Daratumumab as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.
Will dispensing be restricted to hospitals?	Yes

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Overview of the pharmaceutical

Combination therapy and/or co-medication

Daratumumab in combination with bortezomib, thalidomide and dexamethasone.

Recommended concomitant medications (SmPC).(1)

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.

Packaging – types, sizes/number of units, and concentrations

Marketed in Denmark:

Name	Strength	Pharmaceutical form	Route of administration	Immediate Packaging	Content (concentration)	Pack size
Darzalex	20 mg/ml	Concentrate for solution for infusion	Intravenous use	Vial (glass)	5 ml	1 vial
Darzalex					20 ml	
Darzalex	1800 mg	Solution of injection	Subcutaneous use		15 ml (120 mg/ml)	

Orphan drug designation

Yes

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2. Abbreviations

Abbreviations	Definition
ADR	Adverse drug reaction
AE	Adverse event
AHCT	Autologous hematopoietic cell transplantation
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
ASH	American Society of Hematology
BIC	Bayesian information criterion
BSA	Body surface area
CTCAE	Common Terminology Criteria for Adverse Events
CEAC	Cost-effectiveness acceptability curve
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CTd	Cyclophosphamide + thalidomide + dexamethasone
DMCG	Danske Multidisciplinære Cancer Grupper
DMSG	Dansk Myelomatose Studie Gruppe
DRd	Daratumumab + lenalidomide + dexamethasone
DSA	Deterministic sensitivity analyses
DSU	Decision Support Unit
DVd	Daratumumab + bortezomib + dexamethasone
DVMP	Daratumumab + bortezomib + melphalan + prednisone
DVTd	Daratumumab + bortezomib + thalidomide + dexamethasone
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EHA	European Hematology Association
EMA	European Medicines Agency
EMR	Electronic medical record
EORTC-CLQ-C30	European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30
EQ-5D-3L	EuroQoL Five-Dimension Three-Level questionnaire
EQ-5D-5L	EuroQoL Five-Dimension Five-Level questionnaire
ERd	Elotuzumab + lenalidomide + dexamethasone
ESMO	European Society of Medical Oncology
ESS	Effective sample size
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
FLC	Free light chains
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GHS	Global health status
HBV	Hepatitis B virus reactivation
HDM-ASCT	Autologous hematopoietic bone marrow transplantation
HDT	High-dose therapy
HDT/STS	High dose chemotherapy with stem cell support
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRQoL	Health-related quality of life

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HSUV	Health state utility values
HTA	Health technology assessment
ICd	Ixazomib + cyclophosphamide + dexamethasone
ICER	Incremental cost-effectiveness ratio
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent data monitoring committee
IFM	Intergroupe Francophone du Myelome
IMWG	International Myeloma Working Group
IMID	Immunomodulator
IPD	Individual patient-level data
IPW	Inverse probability weighting
IRd	Ixazomib + lenalidomide + dexamethasone
IRC	Independent review committee
IRR	Infusion-related reaction
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISS	International Staging System
ITT	Intention-to-treat
IV	Intravenous
IWRS	Interactive web response system
Kd	Carfilzomib + dexamethasone
KM	Kaplan-Meier
KRd	Carfilzomib + lenalidomide + dexamethasone
LCD	Light-chain disease
LDH	Lactic acid dehydrogenase
LEN	Lenalidomide
LEN-2Y	Lenalidomide maintenance for 2 years
LEN-CR	Lenalidomide until complete response
LS	Least-squares
LY	Life year
MAIC	Matching-adjusted indirect comparison
MGUS	Monoclonal gammopathy of undetermined significance
MM	Multiple myeloma
MP	Melphalan + prednisone
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
NA	Not available / not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDMM	Newly diagnosed multiple myeloma
NE	Not evaluable/estimable
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PAd	Bortezomib + doxorubicin + dexamethasone
PD	Progressive disease
Pd	Pomalidomide + dexamethasone
PET	Positron emission tomography
PFS	Progression-free survival
PFS2	Progression-free survival on subsequent line of therapy

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PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PVd	Pomalidomide + bortezomib + dexamethasone
QALY	Quality-adjusted life-years
QoL	Quality of life
RCT	Randomized control trial
Rd	Lenalidomide + dexamethasone
Rd18	Lenalidomide + dexamethasone, 18 cycles
R-ISS	Revised International Staging System
RKKP	Regionernes Kliniske Kvalitetsudviklingsprogram
SAE	Serious adverse event
SC	Subcutaneous
sCR	Stringent complete response
SCT	Stem cell transplant
SD	Standard deviation
SLR	Systematic literature review
SMM	Smoldering multiple myeloma
SmPC	Summary of Product Characteristics
SPEP	Serum protein electrophoresis
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
TTD	Time-to-treatment-discontinuation
TTP	Time to progression
UK	United Kingdom
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
US	United States
VAS	Visual analogue scale
VCd	Bortezomib + cyclophosphamide + dexamethasone
VCd-Len-2Y	Bortezomib + cyclophosphamide + dexamethasone (VCd) followed by lenalidomide consolidation and lenalidomide maintenance for 2 years
Vd	Bortezomib + dexamethasone
VGPR	Very good partial response
VMP	Bortezomib + melphalan + prednisone
VRd	Bortezomib + lenalidomide + dexamethasone
VTd	Bortezomib + thalidomide + dexamethasone
WHO	World Health Organization

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3. Tables and Figures

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4. Summary

This application is concerning daratumumab in combination with bortezomib, thalidomide and dexamethasone (DVTd) as standard treatment for patients with newly diagnosed multiple myeloma (NDMM) who are eligible for autologous stem cell transplant (ASCT). The relevant comparators for this application are the current standard of care in Denmark which are bortezomib in combination with lenalidomide and dexamethasone (VRd) and bortezomib in combination with cyclophosphamide and dexamethasone (VCd) according to the Medicines Council drug recommendation.(2) Bortezomib in combination with thalidomide and dexamethasone (VTd) is not a preferred regimen, but is an option in Denmark(3) and VTd is included as a relevant comparator as well. Furthermore, out of the three treatment options, VTd is the only treatment that is approved by the European Medicines Agency.(3)

In this application, the main efficacy outcomes presented are focusing on progression-free survival (PFS) and overall survival (OS) based on the high relevance of these endpoints, the comparative data available for comparators, and the inclusion in the cost-effectiveness model. The base case analysis is using data from the CASSIOPEIA (MMY3006) trial with a median follow-up of 29.2 months.(4, 5)

The CASSIOPEIA trial is a registrational phase III randomized controlled trial that directly compared DVTd against the comparator VTd. In the CASSIOPEIA trial, DVTd resulted in an unprecedented clinical benefit that was both statistically significant and clinically meaningful when compared with VTd alone.

CASSIOPEIA demonstrates a clear benefit for DVTd over VTd in terms of PFS with a ≈51% reduction in the risk of disease progression or death (PFS HR: 0.495; 95% CI: 0.378, 0.647; p<0.0001).(5) Although OS data from CASSIOPEIA is immature, the treatment benefit in favor of DVTd is clearly supporting the overall clinical benefit of DVTd regimen (OS HR: 0.52; 95% CI: 0.33, 0.85; nominal p=0.0070).(4, 5) In addition, prespecified subgroup analyses of PFS indicated similar PFS benefits with DVTd compared with VTd across patient subgroups.(6) Treatment with DVTd was associated with a statistically significant and clinically meaningful improvement in the rate of post-consolidation stringent complete response (primary endpoint) compared with VTd alone (28.9% vs 20.3%; OR: 1.60; 95% CI: 1.21, 2.12; p=0.0010. Minimal residual disease (MRD) was assessed in all patients in the ITT population, regardless of response. A statistically significant higher rate of post-consolidation MRD negativity, evaluated using multiparametric flow cytometry, was observed with DVTd compared with VTd alone at a threshold of 1 tumor cell per 10^{-5} white cells (63.7% vs 43.5%; OR: 2.27; 95% CI: 1.78, 2.90; p<0.0001).(6, 7)

In the absence of a viable network of studies with sufficient comparability to inform a network-meta analysis, an unanchored matching-adjusted indirect comparison (MAIC) was performed to compare PFS and OS for DVTd versus both VCd and VRd. MAIC analyses based on the CASSIOPEIA trial have been published by Moreau et al. 2020(8) in a full-text article, published in a scientific, peer-reviewed journal which is strengthening the basis for the evidence of the indirect comparison. Compared to Moreau et al. 2020(8) which is focusing on the 1st data-cut from CASSIOPEIA (median follow-up of 18.8 months), the analyses conducted in the application has incorporated a later data-cut with a median follow-up of 29.2 months for CASSIOPEIA. The MAIC analyses demonstrated a statistically significant benefit in terms of both PFS and OS for DVTd. For DVTd vs. VCd, there were a statistically significant benefit in favor of DVTd for PFS and OS before and after matching [after matching; PFS HR: 0.40 (95% CI: 0.26-0.61) and OS HR: 0.37 (95% CI: 0.18-0.76)]. Similarly for DVTd vs. VRd, a statistically significant benefit for DVTd before and after matching were observed [after matching; PFS HR: 0.50 (95% CI: 0.38-0.67) and OS HR: 0.40 (95% CI: 0.25-0.64)].

In the CASSIOPEIA trial, health-related quality of life (HRQoL) was generally maintained for patients treated with DVTd compared to VTd, with clinically and statistically significant improvement in pain, and statistically significant improvements in emotional functioning and cognitive decline.(9, 10) As noted in the application, improvements in pain and cognitive functioning are expected to be closely aligned to preferences for patients with multiple myeloma.

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Importantly, HRQoL assessment showed no negative HRQoL impact of the quadruplet DVTd therapy over the standard VTd triplet, suggesting that patients treated with DVTd will achieve improved clinical outcomes (i.e. PFS and OS) versus standard of care triplet therapy, without significant detriments in HRQoL as a result of the addition of daratumumab.

DVTd was well-tolerated with low rates of treatment discontinuations due to treatment-emergent adverse events (TEAEs), and a manageable safety profile consistent with the known safety profile of daratumumab and VTd, and no new safety signals were identified. Discontinuations due to TEAEs were numerically lower in the DVTd arm compared with the VTd group (7.5% vs 8.4%, respectively).(4, 6) Infusion-related reactions associated with the use of daratumumab were mild and manageable and are anticipated to reduce significantly with the use of daratumumab as subcutaneous injection (SC). Furthermore, SC daratumumab is expected to improve convenience for patients with administration time reduced from several hours to approximately 5 minutes.(11)

In addition to the significant clinical benefits of DVTd, the fixed treatment duration and a substantial increase in the treatment-free period post induction/consolidation therapy is expected to be highly valued by patients and caregivers.

A cost-effectiveness model was developed in Microsoft Excel® to assess the cost-effectiveness of DVTd versus VTd, VCd, and VRd for NDMM who are eligible for ASCT. A three-health state-transition cohort model structure was selected to follow patients from an initial line of treatment after diagnosis into later lines until death. The model was implemented through a partitioned survival approach, which was based on the use of independent PFS by treatment line and OS curves. 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, ASCT, AE management and terminal care, cost per LY gained and cost per QALY gained. Deterministic sensitivity analyses (DSAs), probabilistic sensitivity analyses (PSAs) and scenario analyses were used to test the influence of the uncertainty of the model parameters on the model's results.

The analysis takes a restricted societal perspective, using the best available clinical and economic evidence. Local Danish data inputs are used when available. The current model is based on results from the CASSIOPEIA trial with median follow-up of 29.2 months.(6, 12, 13)

At a median follow-up of 29.2 months, the CASSIOPEIA trial showed a clear increasing separation of OS and PFS curves between patients receiving DVTd vs. VTd. The MAIC showed that DVTd had significantly significant PFS and OS benefits compared with VCd and VRd. Consistent with the findings from the CASSIOPIEA trial and the MAIC analysis, the base case analysis showed that DVTd yielded better survival outcomes and was associated with longer LYs and QALYs vs. other comparators. The quality-of-life gains associated with DVTd came with a higher total cost compared with other treatments over a life-time horizon.

In the base case analysis, the incremental QALYs gained for DVTd vs. VTd was +2.75, DVTd vs. VCd (+3.74), and DVTd vs. VRd (+3.66). The incremental cost-effectiveness ratio for DVTd compared to VTd was (32,979DKK/QALY), DVTd vs. VCd (79,209 DKK/QALY), and DVTd vs. VRd (97,701 DKK/QALY). The results from the budget impact showed a budget impact of 5.04 million DKK in year 1; 7.04 million DKK in year 2; 8.79 million DKK in year 3; 7.47 million DKK in year 4; and -15.48 million DKK in year 5. The reduction of the cost in year 5 is primarily driven by patients starting subsequent treatments in the comparator arms at a faster rate than for DVTd where progression itself occurs later for patients on DVTd, given the better PFS.

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

5.1 The medical condition and patient population

Pathophysiology and clinical presentation/symptoms of the condition.

Multiple myeloma (MM) is a rare and incurable blood cancer with orphan disease designation in both the United States and Europe.(14-16) Globally, it is estimated to account for approximately 1% of all cancers and 15% to 20% of all hematologic malignancies.(17) MM is characterized by the clonal proliferation of malignant plasma cells in the bone marrow and in most cases associated with an elevated quantity of monoclonal immunoglobulin (types of monoclonal protein detected in serum include IgG, IgA, IgD and IgE and detected in urine includes light chains only) in the blood or urine (M-protein).

The proliferation of malignant plasma cells in the bone marrow and the accumulation of M-protein in the blood, lead to serious complications which require immediate medical treatment, including elevated calcium levels (hypercalcemia), renal impairment, anemia and bone disease.(18, 19) Additional presenting features include fatigue and bone pain, recurrent or persistent infection and hyperviscosity (i.e. increased blood viscosity).(18-20)

Aetiology and pathogenesis

MM is usually caused by a gradual accumulation of genetic errors in the plasma cell over time. Although the precise mechanism of the malignant transformation of these cells is not known, it is believed that the initial asymptomatic, premalignant proliferation of plasma cells, called monoclonal gammopathy of undetermined significance (MGUS), develops from either hyperdiploidy (presence of more than 46 chromosomes) or from a translocation of chromosomes (i.e. the switching of genetic material between two different chromosomes).(21, 22)

The development from this premalignant stage to smoldering multiple myeloma (SMM) and ultimately symptomatic MM is the result of another series of genetic changes and alterations between the plasma cell and its microenvironment (such as an altered expression pattern of adhesion molecules by the MM cells and a heightened response to growth stimuli coming from the microenvironment).(22)

In general, it can be assumed that, per year, 0.5% to 1% of patients with monoclonal gammopathy of undetermined significance (MGUS) will progress to MM, while 10% of SMM patients will progress to MM within the first five years after diagnosis.(21, 23) Patients with symptomatic MM may ultimately also develop plasma cell leukemia, a more dedifferentiated and aggressive subtype with malignant plasma cells now in the peripheral blood, causing rapid progression to death.(21)

Clinical presentation

The presence of tissue or organ damage constitutes the greatest difference between the symptomatic MM phase and the asymptomatic phase of MGUS and SMM. This damage is known as the so-called “SLiM CRAB criteria”: >60% (Sixty) plasma cells, Free light chain ratio >100 or focal lesion visible on MRI scan; or b) hypercalcemia, renal impairment, anemia and bone lesions.(24)

Hypercalcemia is an excessively high calcium level in the blood, predominantly caused by the tumor-induced bone disease. Approximately 30% of patients have this complication, which usually occurs in a later stage of MM disease. It can cause patients to be disoriented and confused, and experience muscle weakness, polyuria and abnormal heart rhythms.(25)

Renal impairment is found in 20% to 40% of newly diagnosed patients and can increase to 50% of the patients over the course of the disease.(26) The development of renal impairment is a negative prognostic factor for survival.(27) It is commonly the result of damage caused to the renal tubules by excessive amounts of M proteins.

Anemia and an increased bleeding tendency due to the myeloma cells in the bone marrow interfering with the normal cells from hematopoiesis, as well as due to the renal impairment. The increased bleeding tendency can be exacerbated by thrombocytopenia and the binding of M proteins to coagulation factors and/or blood platelets.

Bone lesions and the accompanying bone pain: this is the most common complication in MM, affecting approximately 80% to 90% of patients. Due to the invasion and spread of the plasma cells from the bone marrow, the bone will weaken and become damaged, leading to the formation of osteolytic bone destruction and the development of fractures, compression of the spinal cord, hypercalcemia and osteoporosis.(28)

In addition, other non-CRAB symptoms can occur:

- Immunoparesis: accumulation of myeloma cells in the bone marrow suppresses the normal production of immune cells and their immunoglobulins, making the patient more susceptible to infections. This is a very common phenomenon in MM patients and it is the most important cause of mortality in these patients.
- Peripheral neuropathy: on diagnosis, 20% of patients present with peripheral neuropathy. Possible causes include the direct antibody effects of the M protein and hyperviscosity on the nerves. The percentage of patients with neuropathy can continue to increase during disease progression, due to treatment with neurotoxic agents. This mainly involves sensory neuropathies, expressing as paraesthesias, a numb or burning sensation, and localized weakness.
- Hyperviscosity of the blood: this occurs in less than 10% of MM patients and is caused by high levels of M protein circulating in the blood. Hyperviscosity can cause problems such as bruises, nosebleeds, blurry vision, headache, gastrointestinal haemorrhages, insomnia and a series of ischaemic neurological symptoms caused by decreased blood and oxygen supply to the nerve tissue.

Diagnosis

The International Myeloma Working Group (IMWG) has defined diagnostic criteria (and subsequently further expanded those criteria) for determining MM. Due to the availability of new treatment options, new data showing that early treatment of high-risk asymptomatic patients may prolong survival, and advancements in laboratory techniques and imaging, the IMWG criteria have been amended accordingly(23, 29, 30), refer to Appendix O – The patient population, the intervention and choice of comparators(s), Table 163. In July 2019, the latest IMWG recommendations were published, covering the optimal use of current imaging modalities in the diagnosis and management of MM.(31)

Disease progression

The course of the disease is characterized by plateau periods of remissions, followed by relapse. Each subsequent remission is generally shorter and the response to therapy becomes less deep compared with the previous plateau phase, causing the disease to become ever more resistant to treatments. A diagram of the course is provided in Figure 1 below.

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Figure 1 Diagram of disease progression(32)

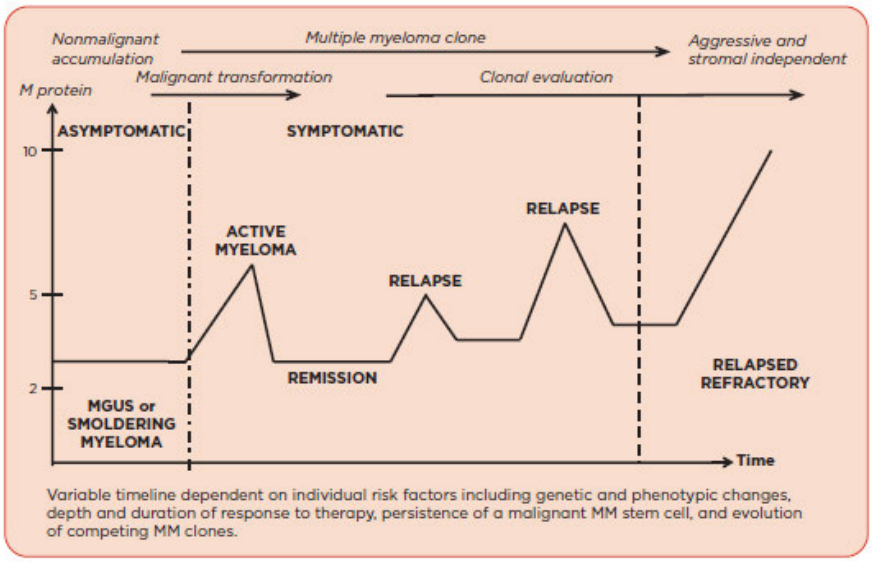

Figure reprinted from: Kurtin SE. Relapsed or relapsed/refractory multiple myeloma. Advanced Practioner. 2013;4(6 Suppl 1).(32)

MM is genetically complex and develops from the continued accumulation of genetic abnormalities over time.(33) The genetic heterogeneity of MM means it is a difficult disease to treat and that clinical outcomes varies.(34, 35) MM follows a relapsing-remitting course where all newly diagnosed patients eventually become refractory to therapy over time.(36-39) With each relapse, it becomes more difficult to induce deep and durable responses to treatment and attrition rates increase.(40, 41) Consequently, the prognosis of patients with relapsed/refractory disease is much poorer than those with newly diagnosed multiple myeloma (NDMM), with the prognosis worsening with each successive relapse (Figure 1). It is therefore important to use the most effective treatments in the first-line setting, as patients may not survive or be fit enough to receive treatment at later lines.(40, 42, 43)

Patients who reach active myeloma status will be offered first-line therapy. The objective of this first-line therapy is primarily to prevent or reverse organ damage by achieving a response that is as deep as possible in order to postpone progression of the disease and relapse, and extend survival while maintaining a quality of life. As indicated above, some patients will already have been treated at an earlier stage (SMM) within the context of a clinical study.

Due to the genetic heterogeneity of MM, there is a complex pattern of primary and secondary genetic abnormalities that precede diagnosis and therapy. MM patients show an average of five subclones, but sometimes ten. The relative frequency of these subclones vary over time and new subclones may manifest in the further disease progression.(44, 45)

Subsequently, when a patient relapses, the efficacy of treatments will reduce due to the increased genetic complexity of the surviving clones and subclones.(45) The accumulation of oncogenic mutations responsible for the tumor's development and maintenance has a negative impact on the survival of patients with MM, as shown in next-generation sequencing analysis (NGS) of the MM genomic landscape using bone marrow samples from MM patients.

Eligibility criteria based on age currently indicate that autologous stem cell transplantation (ASCT) is appropriate for patients aged younger than 65 years; however, these criteria have been reconsidered in recent years.(46-48) The European Medicines Agency (EMA) advises that in many countries within the European Union, ASCT eligibility may need to be determined based on the comorbidities and physiological age of an individual patient, rather than their chronological age.(48) 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.(48) Therefore, the EMA suggests that an age

threshold of ≥70 years may be more reflective of the ASCT eligibility criteria used in clinical practice than a 65-years threshold.(48)

Not all patients with MM are eligible for intensive treatment involving high dose therapy (HDT) and ASCT (HDT/ASCT referred to as ASCT). Patients are assessed for ASCT eligibility at diagnosis, based on a combination of different factors that vary between countries, including age (ASCT usually considered appropriate for patients aged younger than 65 years), performance status, comorbidities, frailty and disability.(49, 50)

Response criteria

The IMWG defined international criteria for response and disease progression in 2006 and those criteria are being applied in clinical practice and in studies. The overall response rate (or objective response rate; ORR) is defined as being the group of patients displaying at least a partial response. These response criteria were subsequently revised since depth of response has become an important parameter due to the introduction of new therapies.(51) Furthermore, new definitions for immunophenotypic complete response (CR) and molecular CR were included and free light chain (FLC) criteria were added to various response subcategories.

Staging, prognosis, and prognostic factors

Although the efficacy of a treatment reduces with each new relapse, various studies have shown that when patients receive new treatments and ASCT as first-line treatment, they achieve better outcomes and can also show better responses in subsequent lines of therapy. In recent decades, various new therapies for treating MM have been brought to the market, which has significantly improved the prognosis of MM patients, there is still a high degree of heterogeneity in the survival rate of MM patients.

Prognostic factors that define the survival rate of MM patients have not been clearly defined. Nonetheless, several groups of patients have been identified as having a poor prognosis, these include patients with(35, 49, 50, 52, 53):

- High-risk disease:
  - t(4;14) or t(14;16) translocations
  - deletion of 17p
- hypodiploidy
- high β2 microglobulin
- low serum albumin
- increased serum lactate dehydrogenase (LDH)
- being ineligible for stem cell transplantation (due to age, performance status, comorbidities or general weakness)

Various combinations of the above-mentioned factors have led to robust models to estimate the survival rate of MM patients (= risk stratification). This enables doctors to inform their patients better about their prognosis.

The most commonly used system for determining the stage of the disease is the International Staging System (ISS), developed by the IMWG. It is based on two biological parameters: serum β2-microglobulin (tumor parameter) and albumin (patient parameter). Albumin level provides the best indication regarding general performance status, while serum β2-microglobulin reflects the tumor burden and renal function. The choice of these two parameters ensued from a study into prognostic factors. This combination was found to provide the most robust prognostic value, in combination with the greatest applicability and reproducibility. Based on this categorization, patients are classified into one of three stages, each with a worse chance of survival.(54)

Since the ISS was developed, further research has been conducted into genetic abnormalities and it has been demonstrated that the prognostic impact of high-risk cytogenetic markers is independent of the ISS. Consequently, a combination of the ISS together with genetic markers would lead to a more robust model(55, 56), refer Appendix O –

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The patient population, the intervention and choice of comparators(s), Table 164. This staging was refined further and modified by the IMWG while taking into account chromosomal abnormalities (detected using the FISH method) and LDH levels (refer to Appendix O – The patient population, the intervention and choice of comparators(s), Table 165).

Epidemiological information

In the EU, there are an estimated 41,101 new cases and approximately 25,546 deaths per year due to MM (European Cancer Information System data, 2018 estimate).(57) According to the European Society of Medical Oncology (ESMO), within Europe, MM represents approximately 10% of all hematological malignancies, with a median age at diagnosis of between 65 and 70 years. The incidence rate amounts to 4.5-6/100,000/year.(58, 59) For Denmark, 318 incident patients were registered in 2016, with a somewhat stable trend/per year (2016-2019 reported).(60)

The Danish patient population

It is estimated that approximately 1.800 patients live with MM in Denmark. The MM Expert Committee within the Medicines Council has previously estimated that that approximately 450 new patients are diagnosed per year in Denmark at a median age of approximately 71 years at diagnosis. At diagnosis, 20% of the patients have SMM. Approximately 360 patients are diagnosed annually with a disease that requires treatment. It is estimated that the group that currently receives ASCT is approximately 120 patients annually. Patients that are not considered eligible for ASCT accounts for the remaining 240 patients per year.(3) The estimated number of patients reported previously by the MM Expert Committee are still in line with the most recent annual reports published by DMSG.(60, 61) Out of the 120 patients annually, it could be considered to exclude patients that are expected to be included in clinical protocols for first-line treatments.

The MM Expert Committee has stated that patients younger than 65-70 years and without significant comorbidity can be treated with ASCT if this is preferred.(3)

A Danish study was conducted based on the Danish Multiple Myeloma Registry in the period 2005 to 2014 focusing on early relapsed disease of MM following up-front autologous hematopoietic bone marrow transplantation. Selected relevant base-line characteristics of the patients included were provided and the median age was reported to be 60 (refer to Appendix O – The patient population, the intervention and choice of comparators(s), Table 166).(62) A recent real-world evidence study was conducted based on Swedish registry data (N=1479). The study focused on the NDMM patients who received frontline ASCT in Sweden.(63) The median age at ASCT was 60 years (IQR, 54.0-64.0) and a similar age distribution is expected in Denmark. The Swedish study also investigated the mean age which was 58.3 years where this is also expected to be similar in Denmark.

Dosing

The applicant expects that all patients will be offered the subcutaneous injection of daratumumab instead of intravenous infusion. Since the dose of the subcutaneous injection is not weight based, bodyweight is irrelevant for the daratumumab treatment dosing. Bortezomib is administered by subcutaneous injection or intravenous injection at a dose of 1.3 mg/m^2 body surface area (BSA).

The data for BSA is obtained from the evaluation of the therapeutic area of MM conducted by the Medicines Council. The data is stated to be unpublished data from Region Capital in Denmark.(3)

- BSA: 1.84 m^2

Prognosis

As stated above, prognosis in MM is dependent on different factors, including host factors (age, performance status, comorbidities, ASCT eligibility) and tumor characteristics (molecular cytogenetic markers, stage, disease aggressiveness, response to therapy).(50, 64) Patients have a considerably poorer prognosis once they have relapsed or become refractory to current treatments.(65) The choice of therapy for patients with NDMM depends on their eligibility for

ASCT. Typically, this includes younger (<65 years old) or fit patients (<70 years and in good clinical condition) who are eligible for ASCT.

Intensive therapy with ASCT provides better survival compared with conventional chemotherapy in patients with NDMM <65 years of age, and the use of novel agents such as thalidomide, bortezomib and lenalidomide has been linked to further improvements in survival outcomes over the last 15 years.(66-76) Patients with NDMM diagnosed after 2005 receiving stem cell transplant had a median survival of 71 months (approximately 6 years), with a 4-year survival rate of 80.6%, based on data from retrospective studies.(68, 77)

Data from Denmark is presented in Table 1 based on the annual reports from the Danish Multiple Myeloma database.(60, 61) As there is no specific subgroup data presented for patients that are eligible for ASCT / have received ASCT, data is presented for MM patients that are under or equal to 65 years. For the data available in the annual reports, this subgroup is expected to be the closest approximation for the patient group that are expected to receive the intervention in scope of this application. As indicated above, it should be noted that some patients older than 65 years will also receive ASCT, and some patients <=65 years may not receive ASCT. The 5-year overall survival rate is above 72%. In the most recent annual report published (annual report 2019, 01. January 2019 – 31. December 2019) (60), the following is stated[1]. Due to the highlighted issues with the data, even though this is unlikely to influence is survival rate results, data from the annual report from 2018 (61) is also reported in Table 1 below.

Table 1 Overall survival outcomes Denmark, <=65 years

Overall survival indicator	Annual report
1-year overall survival <=65 years (Denmark): 2017-2018: 93.0% (95% CI: 88.5 – 95.8)	2018 annual report (61)
1-year overall survival <=65 years (Denmark): 2018-2019: 93.3% (95% CI: 88.8 – 96.1)	2019 annual report (60)
3-year overall survival <=65 years (Denmark): 2015-2018: 84.5% (95% CI: 79.8 – 88.2)	2018 annual report (61)
3-year overall survival <=65 years (Denmark): 2016-2019: 84.7% (95% CI: 80.0 – 88.3)	2019 annual report (60)
5-year overall survival <=65 years (Denmark): 2013-2018: 72.1% (95% CI: 67.1 – 76.5)	2018 annual report (61)
5-year overall survival <=65 years (Denmark): 2014-2019: 73.4% (95% CI: 68.0 – 78.0)	2019 annual report (60)

While novel treatments have improved the outlook for patients with NDMM eligible for ASCT, patients eventually relapse, and with every subsequent line of therapy inducing durable responses becomes more difficult and attrition rates increase. Therefore, the most effective therapies for MM should be utilized in the first-line setting, as patients may not survive to receive these therapies in later lines of treatment.(40, 42, 43) Thus, there is a need for an effective, well-tolerated first line treatment that can induce a deep response in order to delay relapse and prolong survival, while maintaining patients' quality of life.

Table 2 Incidence and prevalence in transplant eligible and transplant ineligible NDMM the past 5 years

Year	2016	2017	2018	2019	2020
Incidence in Denmark*	318	328	317	327	NA
Prevalence in Denmark**	2407	NA	NA	NA	NA

*Annual report from the Danish Multiple Myeloma database; Newly diagnosed patients multiple myeloma patients where treatment is required(60)
**Based on NORCAN. Data available up to year 2016(78)

[1] *Under høringsperioden er der blevet gjort opmærksom på mangler i de rapporterede data. Det har vist sig, at der på landsplan mangler indrapportering af 45 patienter, som diagnosticeredes i 2019, men som ved en fejl var anført med dato i 2020 og ikke 2019 på de udsendte fejl- og mangellister*

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Table 3 Estimated number of patients eligible for treatment

Year	2021	2022	2023	2024	2025
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years*	120	120	120	120	120

*Numbers are based on the full ASCT population that is assumed to remain stable over the 5 years. 120 patients are based on the evaluation of the therapeutic area by the Medicines Council (3). It is expected that only certain parts of the full population will be receiving daratumumab in combination with bortezomib, thalidomide and dexamethasone which is justified further in the budget impact analysis.

Subgroups

In the CASSIOPEIA (MMY3006) trial, prespecified subgroup analyses of PFS indicated similar PFS benefits with daratumumab in combination with bortezomib, thalidomide and dexamethasone (DVTd) compared with bortezomib in combination with thalidomide and dexamethasone (VTd) across patient subgroups, including patients with a high-risk cytogenetic profile or ISS disease stage III. Prespecified subgroup analyses of minimal residual disease negativity also favored the DVTd group across all subgroups. The benefit of DVTd relative to VTd was consistent across prespecified subgroups in analyses of stringent complete response, with the exception of patients with poor prognosis (i.e., high-risk cytogenetic profile and International Staging System disease stage III), and CIs for these subgroups were wide. However, benefit was observed in terms of progression-free survival and proportions of patients who were minimal residual disease-negative as indicated above. These observations show that benefit from daratumumab is not limited to those who achieve stringent complete response.(6)

Effect on MM and relevance of endpoints

Effect on MM on patients and caregivers

There is evidence that patients with myeloma report worse symptoms and health-related quality of life (HRQoL) than those with other hematological cancers, including lymphoma or leukemia.(79) 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.(80)

Patients with MM live in fear of relapse.(81) Uncertainty about the future causes ongoing anxiety and often affects patients' relationships with family and friends who may act as informal caregivers.(81, 82) This leads to decreased independence and increased social isolation.(81) 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") 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.(83) 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.(84) This study also showed that a longer treatment-free interval was significantly associated with improved HRQoL.(84)

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.(85) 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(86)

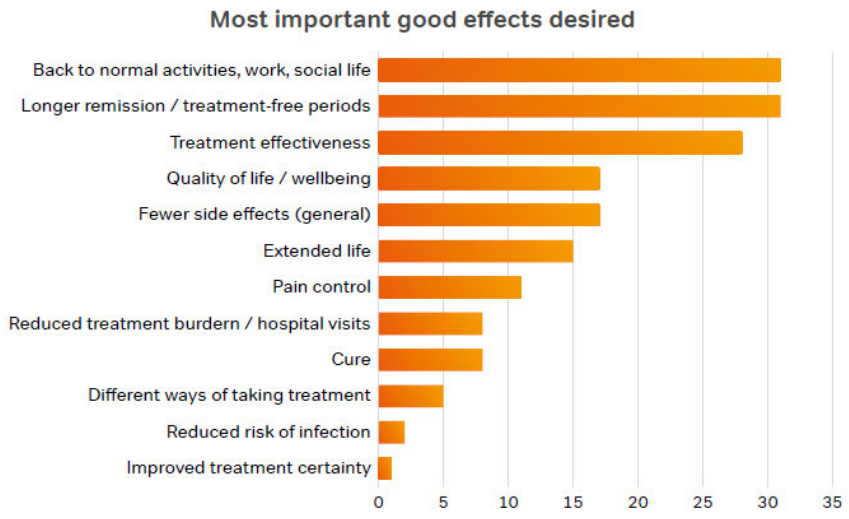

Figure reprinted from: MyelomaUK, Measuring Patient Preferences. 2019.(86)

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.(86) The negative effects of treatment that patients would most want to avoid were also assessed as part of the survey, thus 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.(87) 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.(87) Therefore, the detrimental effects of MM on working life are not only experienced by patients, but also their caregivers.(88) Almost half (49%) of the partners of patients with MM report symptoms of anxiety and 14% report symptoms of depression.(88) 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.(88)

Relevance of endpoints

Progression-free survival

Progression-free survival is used in clinical part of the application as well as the cost-effectiveness analysis. The relevance for patients for this outcome measure is therefore justified below.

Relevance for patients

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In addition to the extension of overall survival, another therapeutic goal is to prolong the progression free time and progression-free survival (PFS).(89) 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.(90, 91) EMA and FDA have approved drugs on the basis of PFS and currently accept it as a primary endpoint in clinical trials (92-94). In MM, the EMA has accepted PFS as a suitable primary endpoint for marketing authorization, (e.g., carfilzomib [Kyprolis] (95), elotuzumab [Empliciti] (96), ixazomib [Ninlaro] (97), panobinostat [Farydak](98), and pomalidomide [Imnovid] (99)). 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.(1)

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.(100)

In the published protocol for the MM evaluation conducted by the Medicines Council, PFS was stated to be a critical endpoint (3, 101) 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.(101) In addition, PFS reflects the duration of periods, where the patient achieve symptom-free periods thus presumed better quality of life.(102)

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.(103) 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.(104)

Response and MRD negativity rate

Minimal Residual Disease (MRD) negativity is reported in clinical part of the application (DVTd vs. VTd). The relevance for patients for this outcome measure is therefore justified below. MRD negativity is not used in the cost-effectiveness analysis.

Relevance for patients

Patients are increasingly demonstrating much better clinical response with new treatments, including increasing rates of complete remission.(105) However, complete response does not automatically translate to prolonged overall survival for all MM patients, since 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. 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.(106-108) The reduced mortality risk is a patient-relevant endpoint which is directly linked to the depth of response.(109, 110) In particular, evidence of early MRD negativity has developed into an independent and important predictor of prolonged PFS and overall survival.(111)

The EHA-ESMO guidelines from 2021 (112) 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

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NDMM and relapsed/refractory MM patients.(113, 114) In addition, the guidelines refer to a study where MRD has been found to be a surrogate endpoint for PFS in patients receiving first-line treatment.(115) Therefore, MRD may be used as an endpoint to accelerate drug development. The guidelines highlight 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.(112)

As a result of the correlation between MRD negativity and prolongation of PFS and OS (111) MRD negativity is considered to be a valid surrogate for the duration of survival of MM patients.

In particular, in studies of drugs that are intended to be approved in first line oncology or hematological indications, mature data for OS are difficult to realize, for example, for median OS. EMA has issued a guideline with the aim of the use of the endpoint MRD negativity to be addressed as an intermediate endpoint in multiple myeloma randomized clinical trials. The studies must be designed to demonstrate the efficacy as demonstrated by relevant hard endpoints at a later date.(116)

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

The current first-choice treatment options in Danish clinical practice for patients that are eligible for ASCT are bortezomib in combination with lenalidomide and dexamethasone (VRd) or bortezomib in combination with cyclophosphamide and dexamethasone (VCd) according current drug recommendation published by the Medicines Council. The current drug recommendation states bortezomib in combination with thalidomide and dexamethasone (VTd) should not be used routinely, but the regimen is an option.(2) Of the three treatment options, VTd is the only treatment option approved by EMA where VRd and VCd is used off-label in Danish clinical practice and recommended by the Medicines Council. In the treatment guidelines, it is stated that the MM Expert Committee assess that VCd, VRd, and VTd all can be used as induction therapy. VTd has shown to give a better response but will often not be the first choice due to side effects, which can be irreversible. The choice of induction therapy is based on knowledge on side effects and comorbidities.((3)(p. 26.))

Table 4 Treatment regimens for ASCT-eligible patients (Medicines Council)

1L - Transplant eligible patients (2)	
Prioritized use	**Treatment**
Use	Induction therapy (bortezomib + lenalidomide + dexamethasone or bortezomib + cyclophosphamide + dexamethasone)[1] + Stem cell mobilization chemotherapy (cyclophosphamide) and peripheral stem cell harvest + High-dose chemotherapy (melphalan) with stem cell support Maintenance treatment after HDT/STS (lenalidomide)
Consider	Consolidating therapy (repetition of HDT/STS, bortezomib + lenalidomide + dexamethasone or lenalidomide + dexamethasone)[1]
Do not use routinely	Induction therapy (bortezomib + thalidomide + dexamethasone) Consolidating therapy (bortezomib + thalidomide + dexamethasone, bortezomib + thalidomide, bortezomib)

1. Combinations are not approved by EMA for the transplant eligible indication.
Abbreviations: ASCT= Autologous stem cell transplant; HDT/STS: High dose chemotherapy with stem cell support
Approval date of guidelines: 22. January 2020

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Overall, the treatment guidelines are in line with the clinical guidelines published by Danske Multidisciplinære Cancer Grupper (DMCG) / Dansk Myelomatose Studie Gruppe (DMSG) / Regionernes Kliniske Kvalitetsudviklingsprogram (RKKP). The guidelines describe that the VRd regimen is preferred and alternatively, VCd can be used.(117)

5.2.2 Choice of comparator(s)

The three selected comparators for this application (VTd, VCd, and VRd) are included in the Medicines Council guidelines and have been used in clinical practice for an extended period and assessed to be established treatment options in Danish clinical practice. In addition, the three treatments are administered for a limited time period and includes drugs for which several are without patent protection (e.g. dexamethasone, bortezomib) and are therefore rather inexpensive. Bortezomib is part of all three combinations and the patent for bortezomib has expired. Hence, it is assessed that all three comparators can be used in the analysis without additional examination of its cost-effectiveness.

DVTd is expected to replace VTd from Danish clinical practice in addition to replacing some of the use of VCd and VRd.

5.2.3 Description of the comparator(s)

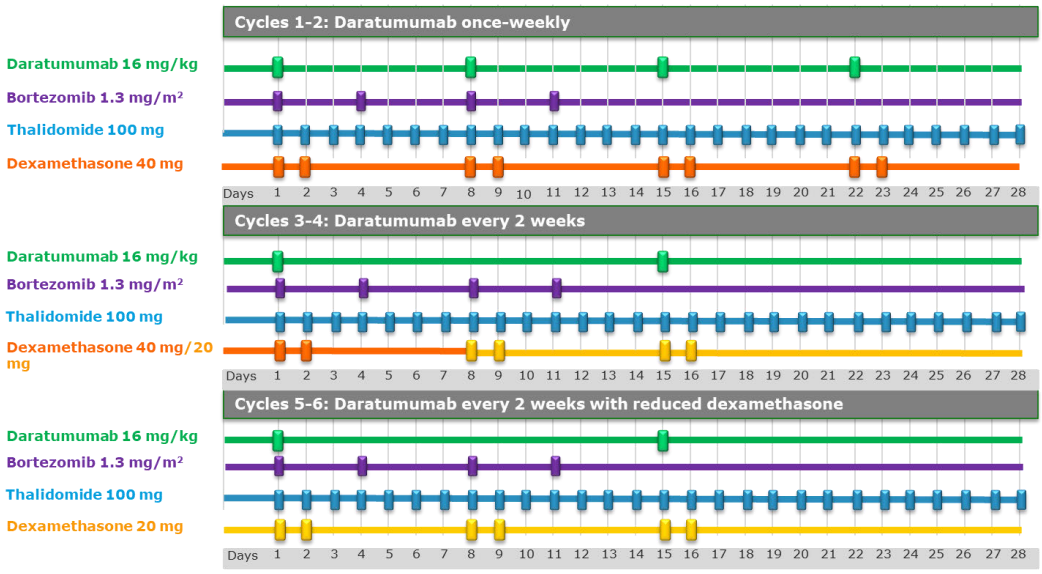
Refer to Appendix O – The patient population, the intervention and choice of comparators(s), Table 170 (VTd), Table 171 (VCd), Table 172 (VRd).

5.3 The intervention

Dosing, method of administration, treatment duration/criteria for treatment discontinuation

Daratumumab is administered in combination with bortezomib, thalidomide and dexamethasone. Daratumumab is either administered as intravenous formulation (refer to Figure 3) or by subcutaneous injection formulation.(1) Dosing of DVTd is described in the section, Basic information and Appendix O – The patient population, the intervention and choice of comparators(s), Table 168. Below, is a schematic representation with the intravenous formulation (in Figure 3) with further details described below for the CASSIOPEIA trial.

Figure 3: Overview of CASSIOPEIA dosing schedule:



Note: Cycle duration was 4 weeks (28 days). If daratumumab is administered by subcutaneous formulation, the recommended dose is 1,800 mg of daratumumab solution for subcutaneous injection administered.

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In Danish clinical practice administration of daratumumab is expected to be offered as the subcutaneous injection of daratumumab instead of intravenous infusion.

The treatment phase for Part 1 of the trial consisted of up to a maximum of six 28-day (4-week) cycles, split between four induction cycles and two consolidation cycles with or without daratumumab in Part 1 of the study (Induction/ASCT/Consolidation Phase).(118) For the study design and explanation of Part 1 and Part 2 of the CASSIOPEIA trial, refer to Appendix B Main characteristics of included studies, Table 72.

The screening phase was up to 28 days prior to randomization, with a treatment phase consisting of various cycles of therapy. Patients from the DVTd arm receive four 28-day cycles of DVTd as induction therapy followed by high-dose chemotherapy and autologous stem cell transplantation, followed by two 28-day cycles of DVTd as consolidation therapy. Patients from the VTd arm receive four 28-day cycles of VTd as induction therapy followed by high-dose chemotherapy and an autologous stem cell transplantation, followed by two 28-day cycles of VTd as consolidation therapy. With completion of consolidation therapy, Part 1 of the study is completed.(118)

The consolidation phase of treatment began a minimum of 30 days post-ASCT, when the patient had recovered sufficiently, and engraftment was complete. Response was evaluated at Day 100 post ASCT. Subjects with at least a PR at approximately Day 100 post-ASCT entered the Maintenance Phase upon completion of consolidation therapy. Patients who did not achieve a response entered the follow-up Phase and were followed until disease progression or death, even if they receive subsequent treatment.(118)

For the Primary Analysis for Part 1 (1st data cut, median follow-up of 18.8 months), the median treatment duration in the DVTd arm is 8.87 months and in the VTd arm 8.74 months.(4)

Criteria for treatment discontinuation in the CASSIOPEIA trial included treatment discontinuation due to progressive disease, unacceptable toxicity, ineligibility for second randomization or 2 years of maintenance therapy/observation. (118)

Administration with other medicines

Refer to section, Basic information.

Necessary monitoring, during administration, during the treatment period, and after the end of treatment

Safety evaluations include adverse event monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and ECOG performance status assessment.(118)

Need for diagnostics or other tests (i.e. companion diagnostics)

Patients should be typified and screened prior to starting daratumumab treatment due to possible blood typing interference with daratumumab.(118)

Due to cases reported with hepatitis B virus reactivation (HBV) during daratumumab treatment, screening should be considered before initiation of treatment with daratumumab, including monitoring for clinical and laboratory signs of HBV reactivation during, and for at least 6 months following the end of daratumumab treatment for patients with evidence of positive HBV serology.(118)

Introduction of DVTd in Danish clinical practice

Based on the treatment guidelines for MM, DVTd is expected to be included as a primary treatment for patients that are eligible for ASCT and considered superior to the current treatment options.

If DVTd is recommended as a standard treatment, it is assessed that only parts of the total patient population will receive the treatment in clinical practice. This is assessed to be the case due to preferences from the treating hematologist and

the patient. It is the applicants understanding that the VTd regimen is currently not that commonly used in Denmark. However, having the option to combine VTd with daratumumab (DVTd) is expected to increase the usage of the VTd regimen making it a relevant and efficacious treatment option in Denmark.

Other considerations

Influence on stem cell mobilization:
The addition of daratumumab to VTd during induction therapy did not impair the feasibility and safety of transplantation with successful engraftment, though stem cell yield was lower with DVTd versus VTd alone. Both stem cell mobilization and collection were feasible after DVTd induction, and the proportion of patients proceeding to transplantation as well as the rate and timing of engraftment did not differ between treatment groups.

Hulin et al. 2019 reported stem cell yield and transplantation results among patients receiving induction therapy with DVTd vs VTd in part 1 of the CASSIOPEIA study. The median number of CD34+ stem cells transplanted for DVTd vs VTd was 3.3 x 106/kg vs 4.3 x106/kg and hematopoietic reconstitution rates were similar for transplanted patients receiving DVTd vs VTd (99.8% vs 99.6%). In the DVTd arm 506 patients completed mobilization versus 492 patients in the VTd arm; more patients in the DVTd arm received plerixafor during mobilization (21.7% vs 7.9%). The median number of CD34+ cells collected was lower for DVTd vs VTd (6.3×106/kg vs 8.9×106/kg). However, similar percentage of intent-to-treat (ITT) patients received DVTd vs VTd underwent ACST (90.1% vs 89.3%).(119) Based on these results, Hulin et al. 2019, concluded that stem cell mobilization and collection was feasible with DVTd induction.

Laurent et al. 2020 reported stem cell collection in 325 NDMM who received VTd or VRd induction in a retrospective study, and reported increased plerixafor usage for VRd induction compared to VTd induction (19.3% versus 5.4%, p = 0.004). Although the majority of patients underwent ASCT (93% versus 98% in the VRd and VTd group respectively) there were more patients experiencing collection failure in the VRd group (6% versus 1.8%, p= 0.004). The median number of CD34-positive cells (×106/kg) was lower in the VRd group: 8.5 versus 9.3 (p = 0.05) in the VTd group.(120)

By comparing plerixafor usage in the DVTd arm in the CASSIOPEIA study (21.7%) versus plerixafor usage for the VRd group, reported by Laurent et al. 2020 (19.3%), the use of plerixafor is comparable.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

The systematic literature review (SLR) of the published literature reporting the clinical efficacy and safety data for daratumumab in combination with bortezomib, thalidomide, and dexamethasone as a treatment for patients with NDMM who are eligible for ASCT. An initial SLR was conducted in May 2018, followed by two updates that were conducted in May 2020 and November 2020 separately.

The search for clinical efficacy and safety evidence in patients with NDMM who are eligible for ASCT was conducted in the following indexed databases:

- MEDLINE and MEDLINE In-Process (via PubMed)
- Embase (via embase.com)
- The Cochrane Library:
  - Cochrane Database of Systematic Reviews (CDSR)
  - Cochrane Central Register of Controlled Trials (CENTRAL)

- Database of Abstracts of Reviews of Effects (DARE; archive database only).

The abstracts published since 2015 from the following conferences were also searched for relevant information:

- American Society of Clinical Oncology (ASCO) annual meetings
- American Society of Hematology (ASH) annual meetings
- European Hematology Association (EHA) annual meetings
- International Myeloma Working Group (IMWG) biannual international workshops
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR). Annual international meetings and European congresses.

Lastly, to help address gaps in the published efficacy and safety data, relevant literature was also identified from the clinical registries, EMA and FDA. Details of the searches can be found in Appendix A – Literature search for efficacy and safety of intervention and comparator(s).

The initial SLR and its subsequent updates resulted in 115 publications across 63 RCTs in total.

- In the initial SLR, 53 trials across 90 publications were deemed relevant for the SLR. The clinical study report for CASSIOPEIA was included (Figure 22).
- As in the first SLR update, a total number of 17 trials across 24 publications were captured, of which 7 of them were already included in the original SLR. The clinical study report included in the initial SLR was published in 2019 and captured by this update. Therefore, the actual number of new studies identified in this update is 23 publications, including 9 new clinical trials. Detailed results of the screening phase are presented in the PRISMA flow diagram in Appendix A – Literature search for efficacy and safety of intervention and comparator(s), Figure 23.
- Additionally, the second update of the SLR resulted in a total of 2 publications, capturing 2 RCTs (Figure 24).

6.2 List of relevant studies

Although the SLR and its updates captured a large number of studies for patients with NDMM who are eligible for ASCT, among those, 51 trials investigated the treatments which are not relevant for decision problem; seven trials do not have sufficient information for indirect comparison justification; three trials were considered not optimal for indirect comparison (refer to Table 69). Thus, three studies remained for the indirect comparison and economic model in this application: CASSIOPEIA, GMMG-MM5 and IFM/DFCI 2009 (Table 5). In Appendix A – Literature search for efficacy and safety of intervention and comparator(s), the full list of primary studies captured in the SLR and the following updates (Table 69) can be found as well as a list of completed and ongoing studies not included (Table 70). For detailed information about the three included studies, refer to Appendix B Main characteristics of included studies. A recently published manuscript on an indirect comparison between DVTd/VTd vs. VRd and VCd is included and HRQoL studies for DVTd vs. VTd (Table 6) as additional relevant studies for this application.

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Table 5 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Mai, E. K., et al. "Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (Pad) in newly diagnosed myeloma." *Leukemia* 29.8 (2015): 1721-1729.(121) Merz, Maximilian, et al. "Subcutaneous versus intravenous bortezomib in two different induction therapies for newly diagnosed multiple myeloma: an interim analysis from the prospective GMMG-MM5 trial." *Haematologica* 100.7 (2015): 964.(122)	GMMG-MM5	EudraCT No. 2010-019173-16	Jul 2010 to Oct 2012	VCd vs. Pad
Attal, Michel, et al. "Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma." *New England Journal of Medicine* 376.14 (2017): 1311-1320.(123) Attal, Michel, et al. "Autologous transplantation for multiple myeloma in the era of new drugs: a phase III study of the Intergroupe Francophone Du Myelome (IFM/DFCI 2009 Trial)." (2015): 391-391.(124)	IFM/DFCI 2009	NCT01191060	Aug 2010 to Apr 2019	VRd + ASCT vs VRd
Moreau, Philippe, et al. "Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomized, open-label, phase 3 study." The Lancet 394.10192 (2019): 29-38.(6) Hulin, Cyrille, et al. "Stem cell (SC) yield and transplantation results from transplant-eligible newly diagnosed multiple myeloma (TE NDMM) patients (pts) receiving daratumumab (DARA)+ bortezomib/thalidomide/dexamethasone (D-VTd) in the phase 3 CASSIOPEIA study." (2019): 8042-8042.(119)	CASSIOPEIA/MMY006	NCT02541383	Since September 2015 (study is ongoing)	DVTd vs. VTd

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Avet-Loiseau, Herve, et al. "Efficacy of daratumumab (DARA)+ bortezomib/thalidomide/dexamethasone (D-VTd) in transplant-eligible newly diagnosed multiple myeloma (TE NDMM) based on minimal residual disease (MRD) status: Analysis of the CASSIOPEIA trial." (2019): 8017-8017.(125)				
Moreau, Philippe, et al. "Phase 3 randomized study of daratumumab (DARA)+ bortezomib/thalidomide/dexamethasone (D-VTd) vs VTd in transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM): CASSIOPEIA Part 1 results." (2019): 8003-8003.(126)				
Moreau P., et al. "Evaluation of the prognostic value of positron emission tomography-computed tomography (PET-CT) at diagnosis and follow-up in transplant-eligible newly diagnosed multiple myeloma (TE NDMM) patients treated in the phase 3 cassiopeia study: Results of the cassiopet companion study." Blood (2019) 134 (Supplement_1): 692.(127)				
Study of Daratumumab (JNJ-54767414 [HuMax® CD38]) in Combination with Bortezomib (VELCADE), Thalidomide, and Dexamethasone (VTd) in the First Line Treatment of Transplant Eligible Subjects with Newly Diagnosed Multiple Myeloma: Clinical Study Report. 2019.(12)				
Sonneveld P., et al. "Daratumumab Plus Bortezomib, Thalidomide, and Dexamethasone (DVTd) in Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): Subgroup Analysis of High-risk Patients (Pts) in CASSIOPEIA." Clinical Lymphoma, Myeloma & Leukemia, 2019-10-01, Volume 19, Issue 10, Pages e2-e3.(128)				

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide, dexamethasone ; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, and dexamethasone; VRd = bortezomib, lenalidomide and dexamethasone; Pad = bortezomib, doxorubicin, and dexamethasone.

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Table 6 Additional relevant studies included via hand search

Study title	Notes
Moreau, Philippe, et al. "Front-line daratumumab-VTd versus standard-of-care in ASCT-eligible multiple myeloma: matching-adjusted indirect comparison." Immunotherapy 13.2 (2021): 143-154.(8)	MAIC results of DVTd/VTd vs. VRd/Vd/VCd (1st data-cut)
Roussel, Murielle, et al. "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 37andomized, open-label, phase 3 trial." The Lancet Haematology 7.12 (2020): e874-e883.(9)	Latest publication of HRQoL in CASSIOPEIA trial
Roussel M, Moreau P, Attal M, Eisenmann JC. Improvement in health-related quality of life (HRQoL) for newly diagnosed multiple myeloma (NDMM) transplant eligible patients treated with daratumumab, bortezomib, thalidomide, and dexamethasone (D-VTd) vs VTd alone: CASSIOPEIA. European Hematology Association (EHA, Poster) (2019).(129)	HRQoL in CASSIOPEIA trial

Abbreviations: MAIC = matching-adjusted indirect comparison; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = daratumumab, bortezomib, thalidomide, dexamethasone; Vd = bortezomib and dexamethasone; VCd = bortezomib, cyclophosphamide, and dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone

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7. Efficacy and safety

DVTd vs. VTd

There was one study (CASSIOPEIA, MMY3006) that investigated DVTd vs. VTd directly which was used for the comparison between DVTd and VTd.

DVTd/VTd vs. VCd and VRd

To date, there is no head-to-head comparison of the efficacy and safety of DVTd/VTd vs. VRd and VCd. While the SLR provides some preliminary evidence of the potential value of daratumumab combination therapy (specifically, DVTd) as a treatment option for patients with NDMM who are eligible for ASCT, it also highlights the wide range of longer established comparators that have been or are being used for this indication. As CASSIOPEIA assessed response using a strict computerized algorithm, while other trials used investigator-assessed response, comparison of response outcomes in a network meta-analysis (NMA) is challenging. As response rates would not be comparable in an NMA, the current focus is on comparability of OS and PFS. However, the networks of trials that report these long-term survival outcomes and that connect to CASSIOPEIA are small and, crucially, would not provide relative-effectiveness data for the comparators of interest.

In the absence of direct evidence, an indirect treatment comparison can be done to assess the relative effectiveness of both regimens. Indirectly comparing unadjusted, unweighted or ''naïve'' outcomes of different trials is prone to bias due to heterogeneity in the sample patient population.(130) Alternatively, multivariate regressions or propensity scoring approaches can be utilized for an adjusted indirect comparison of treatments tested in different study populations. However, this requires individual patient-level data (IPD) for both regimens, which is not always publicly available. An alternative method, requiring IPD from only one treatment, is a matching-adjusted indirect comparison (MAIC), with the potential of providing unbiased relative treatment effects after adjustment of the heterogeneity in the target study population. MAICs have increasingly and successfully been used in submissions to national reimbursement agencies such as the National Institute for Health Care and Excellence (NICE) in England.(130) As per the NICE guidelines, for an unanchored indirect comparison, population adjustment methods should adjust for all effect modifiers and prognostic variables.((130)p.6) Thus, a series of MAICs were performed to compare DVTd/VTd with comparators of interest, namely VCd and VRd.

As supporting evidence, the results from the MAIC analyses will also report the findings for VTd vs. VRd and VTd vs. VCd. These results are reported to examine any potential efficacy differences between the regimens, and the results may substantiate the expected findings if DVTd had been investigated directly versus VRd and VCd in a head-to-head trial. Hence, from a naïve perspective, if no differences are found between VTd vs. VRd and VTd vs. VCd, this may indicate that we can expect similar results for DVTd vs. VRd and DVTd vs. VCd as observed in the CASSIOPEIA trial examining DVTd vs. VTd directly. However, the MAICs for DVTd vs. VCd and DVTd vs. VRd will serve as the primary evidence.

The MAIC analyses descriptions are based on the Moreau et al. 2020(8), a full-text article published in a scientific, peer-reviewed journal focusing on the 1st data-cut (median follow-up of 18.8 months). The MAIC analyses have incorporated an updated analysis (2nd data-cut) with a median follow-up of 29.2 months for CASSIOPEIA.

Comparative results of DVTd/VTd vs. VCd, and VRd

Table 7 provides an overview of the comparative results of DVTd for the three relevant comparators. These results will be presented in the following sections for each comparator.

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Table 7 Comparative analysis results of DVTd vs VTd, VCd, and VRd

	Endpoints	DVTd vs. VCd[a]	DVTd vs. VRd[a]	VTd vs. VCd[a]	VTd vs. VRd[a]	DVTd vs. VTd[b]
OS HR	Base case analysis	0.37 (0.18 – 0.76) p=0.006	0.40 (0.25-0.64) p<.001	0.77 (0.40-1.47) p=0.43	0.78 (0.53-1.16) p=0.100	0.52 (0.33-0.85) p=0.0070
	Sensitivity analysis	0.35 (0.14–0.86) p=0.023	0.31 (0.16-0.57) p<.001	0.93 (0.41-2.10) p=0.869	0.82 (0.51-1.32) p=0.419	0.43 (0.23-0.80) p<0.0001
PFS HR	Base case analysis	0.40 (0.26 – 0.61) p<.001	0.50 (0.38-0.67) p<.001	0.93 (0.64-1.35) p=0.688	1.04 (0.82-1.32) p=0.755	0.50 (0.38-0.65) p<.0001
	Sensitivity analysis	0.35 (0.21–0.58) p<.001	0.47 (0.33-0.69) p<.001	1.00 (0.62-1.61) P=0.987	1.13 (0.84-1.53) p=0.419	0.47 (0.33-0-67) p<0.0001

Base case: median follow-up of 29.2 months; Sensitivity analysis: median follow-up of 18.8 months
a) Data sources: MAIC analyses. Base case – Janssen internal report from 2nd data-cut; Sensitivity analysis: Moreau et al. 2020(8)
b) Data sources: Base case - OS from first randomization regardless of second randomization: Darzalex EPAR DVTd (4); Sensitivity analysis – OS from first randomization regardless of second randomization: Moreau et al. 2019 (6); Base case – PFS from first randomization regardless of second randomization: Data-on-file; Sensitivity analysis – PFS from first randomization regardless of second randomization: Moreau et al. 2019 (6) & Darzalex EPAR DVTd (4)
Abbreviations: HR = Hazard ratio; MAIC = matching-adjusted indirect comparison; OS = Overall survival; PFS = Progression-free survival; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, and dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone
Note: Numbers are rounded.

Incorporation of MAIC Results into the cost-effectiveness model

Based on the results from the MAIC, OS and PFS for VCd and VRd are to be modelled by applying hazard ratios (HRs) estimated from the MAIC to a reference curve from CASSIOPEIA. VRd and VCd were modelled by using VTd from CASSIOPEIA as the reference curve, as this approach benefits from the greater number of events in the VTd arm compared with DVTd. Additionally, the base case for the MAIC was used in the base case analysis for the cost-effectiveness model (CASSIOPEIA 2nd data-cut, median follow-up of 29.2 months).

7.1 Efficacy and safety of DVTd compared to VTd for patients with NDMM patients who are eligible for ASCT

7.1.1 Relevant studies

CASSIOPEIA is a randomized, open-label, active control, parallel group, multicenter phase III study comparing the efficacy and safety of DVTd vs VTd in patients with NDMM who are eligible for ASCT.(6) Evidence from the CASSIOPEIA trial was used as the primary source of data to support the use of DVTd in this indication in the marketing authorization application to the EMA. Pre-specified analysis for Part 1 applied a clinical cut-off date of 19 June 2018, representing a median follow-up of 18.8 months (1st data-cut). During the regulatory process, Janssen received a Request for Supplementary Information from the EMA which resulted in an unplanned post-hoc interim analysis with a clinical cut-off of 01 May 2019, representing an additional 10.4 months of study follow-up (median follow-up of 29.2 months; 2nd data-cut).

A total of 1,085 patients were randomized between 22 September 2015 and 1 August 2017 at 111 European sites; 543 patients were assigned to the DVTd group and 542 to the VTd group. As of the clinical cut-off date for the primary analysis (19 June 2018), 536 patients in the DVTd group and 538 patients in VTd groups were treated (98.7% and 99.3% of the total number of patients randomized in each group, respectively).(6) Demographic and clinical characteristics were well balanced between the two treatment groups (Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety, Table 75).(6) The median age of patients in the study was 58 years, with 84.1% of patients being older than 50 years of age, with a median time since diagnosis of less than a month (0.92 months).(6) For main characteristics for the study refer to Appendix B Main characteristics of included studies.

7.1.2 Efficacy and safety – results per study

7.1.2.1 Efficacy

The primary endpoint in the CASSIOPEIA study was the proportion of patients who achieved a stringent complete response after consolidation. Key secondary efficacy endpoints included the proportion of patients who were minimal residual disease negative after consolidation, the proportion of patients who achieved a complete response or better after consolidation, and progression-free survival and overall survival from first randomization.

CASSIOPEIA demonstrated that the addition of daratumumab to VTd resulted in a statistically significant and clinically meaningful improvement in depth of response post consolidation (stringent complete response (sCR), CR or better, very good partial response (VGPR) or better and MRD-negative rate).(6) These responses translated into a statistically significant and clinically meaningful improvement in PFS (refer to section 5.1, Effect on MM and relevance of endpoints).(6) As a fixed treatment duration, DVTd offers a sustained treatment-free interval which, as reported in Section 5.1 (Effect on MM and relevance of endpoints), combined with a longer remission is an important positive effect of treatment and as such is highly valued by patients. Treatment with DVTd was associated with a statistically significant, and clinically meaningful improvement in the risk of disease progression or death compared with VTd. Whilst the OS data remains immature, there is already a clear statistically significant difference supporting the clinical benefit of DVTd compared with VTd. Furthermore, SC daratumumab is expected to improve convenience for patients with administration time reduced from several hours to approximately 5 minutes.(11)

Efficacy analysis, including the assessment of MRD negativity, were performed for the ITT population that included all patients that underwent the first randomization. A summary of the key clinical efficacy results from the primary analysis for part 1 (1st data-cut) and the Post-hoc Interim Analysis (2nd data-cut) is presented in Table 8, with a discussion of each endpoint provided in the remainder of this section. In addition, data with longer follow-up is provided in the following section to address a request from the MM Expert Committee concerning DVTd-observation vs. VTd-observation (i.e. the subgroup of patients randomized to observation in the maintenance phase following 1st randomization to either DVTd or VTd).

Table 8: Summary of key clinical efficacy results (5-7, 118)

	1st data-cut (median follow-up = 18.8 months)		2nd data-cut (median follow-up = 29.2 months)	
	VTd	DVTd	VTd	DVTd
Response				
Post-consolidation sCR rate	110 (20.3%)	157 (28.9%)	n/a	n/a
Post-consolidation sCR Odds ratio (95% CI)	n/a	1.60 (1.21, 2.12) p=0.0010	n/a	n/a
MRD-negative status (10^{-5})[a]				
Post-consolidation MRD-negative rate regardless of response	236 (43.5%)	346 (63.7%)	n/a	n/a

Post-consolidation MRD-negative rate Odds ratio (95% CI)	n/a	2.27 (1.78, 2.90) p<0.0001	n/a	n/a
Survival outcomes				
PFS HR (95% CI); P-value	n/a	0.47 (0.33-0.67); p<0.0001	n/a	0.495 (0.378-0.647); p<0.0001
OS HR (95% CI); P-value	n/a	0.43 (0.23-0.80); p=0.0065	n/a	0.52 (0.33-0.85); p=0.0070
Health-related quality of life				
EORTC-CLQ-C30 GHS subscale LS mean change from baseline to 100 days post-ASCT (95% CI)	8.7 (6.5-11)	9.7 (7.4-11.9)	n/a	n/a
P-value	p=0.4523		n/a	

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC-CLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; GHS = global health status; HR = hazard ratio; LS = least-squares; MRD = minimal residual disease; n/a = not applicable; OS = Overall survival; PFS = Progression-free survival; sCR = stringent complete response.
[a] Post-consolidation MRD-negative rate was measured by a standardized Euroflow based multiparametric assay.

7.1.2.1.1 Response results

Treatment with DVTd was associated with a statistically significant and clinically meaningful improvement in the rate of post-consolidation sCR (primary endpoint) compared with VTd alone (28.9% vs 20.3%; OR: 1.60; 95% CI: 1.21, 2.12; p=0.0010.(6)

MRD was assessed in all patients in the ITT population, regardless of response. This contrasts with previous MM trials where MRD was assessed in patients who achieved a pre-specified level of response (e.g. patients with CR).(6) A statistically significant higher rate of post-consolidation MRD negativity, evaluated using multiparametric flow cytometry, was observed with DVTd compared with VTd alone at a threshold of 1 tumor cell per 10^{-5} white cells (63.7% vs 43.5%; OR: 2.27; 95% CI: 1.78, 2.90; p<0.0001).(6, 7)

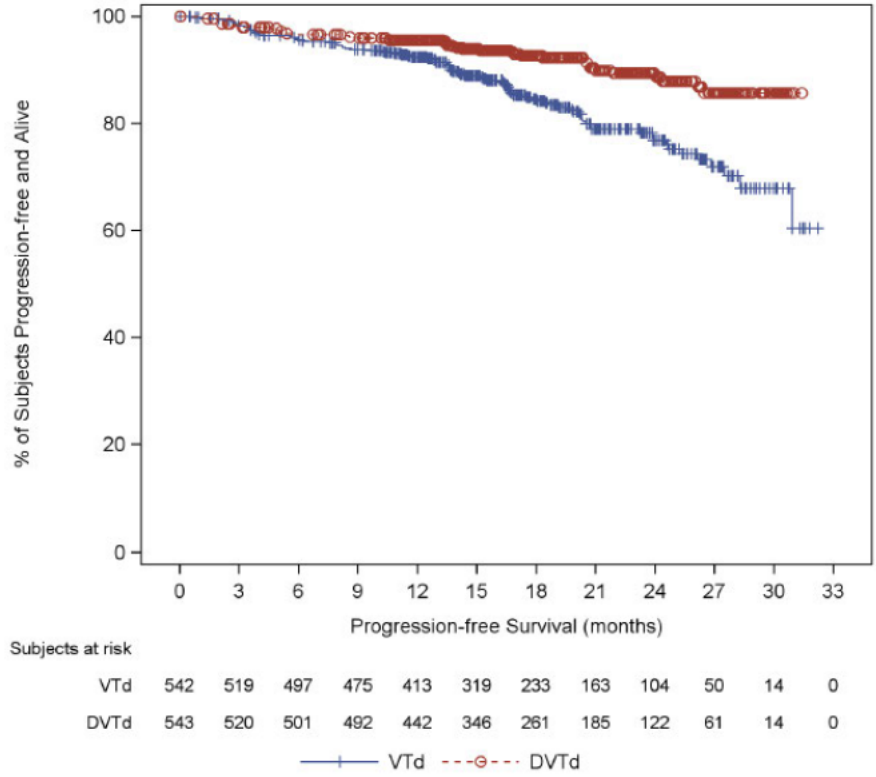
7.1.2.1.2 Survival results

7.1.2.1.2.1 Progression-free survival

Survival analysis: Progression-free survival (1st data-cut) (key secondary endpoint)

After a median follow-up of 18.8 months, a total of 45 (8.3%) PFS events had occurred in the DVTd arm compared to 91 (16.8%) events in the VTd arm.(6) Treatment with DVTd was associated with a statistically significant, and clinically meaningful improvement in the risk of disease progression or death compared with VTd (HR: 0.47; 95% CI: 0.33, 0.67; p<0.0001).(6) DVTd resulted in a 53% reduction in the risk of disease progression or death compared with VTd, with 2-year PFS rates of 89.4% and 76.9% respectively.(7) Figure 4 presents the Kaplan-Meier (KM) plot for PFS from the 1st data-cut of CASSIOPEIA.

Figure 4: Kaplan-Meier plot for PFS from 1st randomization for induction/ASCT/consolidation, regardless of 2nd randomization (ITT population, median follow-up = 18.8 months) (6, 7)



Abbreviations: ASCT = autologous stem cell transplant; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; ITT = intention-to-treat; PFS: progression-free survival; VTd = bortezomib, thalidomide and dexamethasone.

PFS adjusted for maintenance (6, 7)

To mitigate potential bias to the PFS outcomes for Part 1 caused by study maintenance, a per-protocol pre-specified statistical analysis was performed using the inverse probability weighting (IPW) method to adjust for the second randomization (Table 9). The IPW method provides an unbiased PFS estimate and maintains the Type 1 error rate by stratifying two groups based on their maintenance treatment (i.e. DVTd versus VTd for patients who received daratumumab maintenance, and DVTd versus VTd for patients who received observation maintenance).(7) All patients including those who were not re-randomized were included in this PFS analysis. This analysis was performed and reviewed by a sequestered group independent of the study team to protect the integrity of the Part 2 analysis.

Consistent results in favor of DVTd versus VTd were seen when PFS was analyzed after adjustment for the second randomization, demonstrating that the observed treatment effect is attributable to the 1st part of the study (HR: 0.47; 95% CI: 0.33, 0.67; p<0.0001).(7) The similarity of adjusted and unadjusted analyses results was expected given the high proportion of patients re-randomized in both treatment groups and the relatively short duration of maintenance therapy. Refer to Appendices N – IPW methodology for details regarding the IPW methodology.

Table 9: PFS results with and without IPW adjustments (ITT population, median follow-up = 18.8 months)(7)

IPW Analysis; DVTd versus VTd	
HR (95% CI)	0.47 (0.33, 0.67)
P-value	<0.0001

Analysis without adjustment for second randomisation; DVTd versus VTd	
HR (95% CI)	0.47 (0.33, 0.67)
P-value	<0.0001

Abbreviations: VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; HR = hazard ratio; IPW = inverse probability weighting; ITT = intention-to-treat; PFS = progression-free survival.

PFS updated results (2nd data-cut)

At the time of clinical cut-off for the 2nd data-cut, a total of 83 (15.3%) PFS events had occurred in the DVTd group, and 151 (27.9%) events in the VTd group.(5) A comparison of PFS results from the 1st data-cut and 2nd data-cut without adjustment for the second randomization is presented in Table 10 with the associated Kaplan-Meier plot shown in Figure 5. After a median follow-up of 29.2 months, median PFS was not reached in either treatment group.(5)

Table 10: Comparison of updated PFS (1st data-cut vs 2nd data-cut), regardless of 2nd randomization (ITT population)(5, 7)

	1st data-cut (median follow-up = 18.8 months) (4)		2nd data-cut (median follow-up = 29.2 months) (5)	
	VTd	DVTd	VTd	DVTd
n/N (%)	91/542 (16.8%)	45/543 (8.3%)	151/542 (27.9%)	83/543 (15.3%)
Median (95% CI)	NE (941.00, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
HR (95% CI)	0.47 (0.33, 0.67)		0.495 (0.378, 0.647)	
P-value	<0.0001		<0.0001	
6-month PFS rate % (95% CI)	95.8 (93.7, 97.2)	96.6 (94.6, 97.8)	95.8 (93.8, 97.2)	96.6 (94.7, 97.8)
12-month PFS rate % (95% CI)	92.4 (89.8, 94.4)	95.6 (93.5, 97.1)	92.9 (90.3, 94.8)	95.4 (93.3, 96.9)
18-month PFS rate % (95% CI)	84.6 (80.7, 87.7)	92.7 (89.8, 94.7)	85.3 (82.0, 88.1)	92.5 (89.9, 94.5)
24-month PFS rate % (95% CI)	76.9 (71.5, 81.3)	89.4 (85.6, 92.3)	77.4 (73.4, 80.8)	88.4 (85.3, 90.9)

Abbreviations: VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; HR = hazard ratio; ITT = intention-to-treat; NE = Not evaluable/estimable; PFS = progression-free survival.

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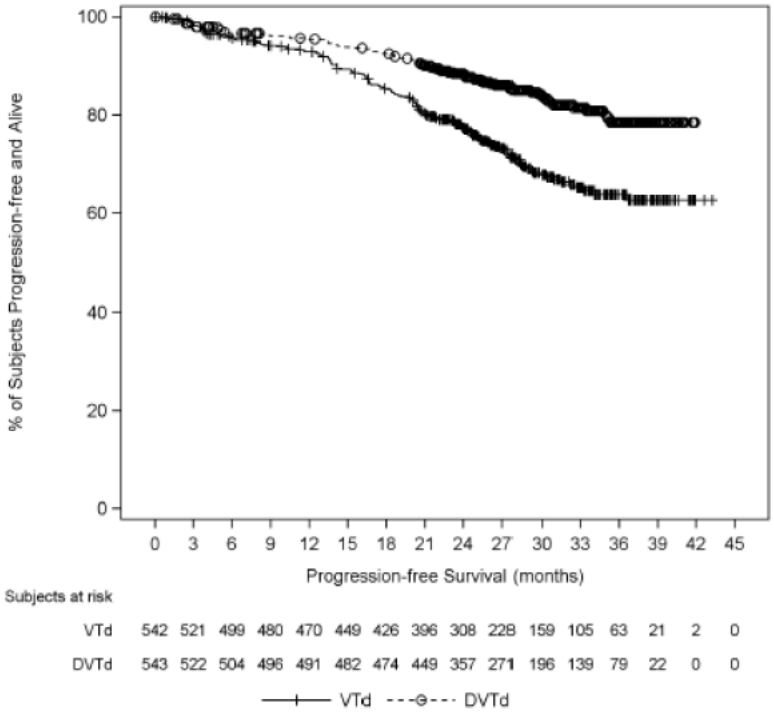
Figure 5: Kaplan-Meier plot for PFS from 1st randomization for induction/ASCT/consolidation, regardless of 2nd randomization (ITT population, median follow-up = 29.2 months)(4)



Abbreviations: ASCT = autologous stem cell transplant; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; ITT = intention-to-treat; PFS = progression-free survival; VTd = bortezomib, thalidomide and dexamethasone.

Results from the additional 10.4 months follow-up (2nd data-cut) demonstrates a consistent benefit for DVTd over VTd in terms of PFS with a ≈51% reduction in the risk of disease progression or death (HR: 0.495; 95% CI 0.378, 0.647; p<0.0001), while the 2-year PFS rates for DVTd and VTd remain stable at 88.4% and 77.4% respectively.(5) [redacted] (Table 12). At the request of the Committee for Medicinal Products for Human Use (CHMP), the updated PFS results were adjusted based on censoring of maintenance with consistent results indicating minimal impact of the second randomization on the PFS outcomes for Part 1 with longer study follow-up (HR: 0.50; 95% CI 0.50 (0.34, 0.75); p=0.0005) (Table 11).(4)

Table 11: PFS adjusted results for censoring of maintenance (ITT population, median follow-up = 29.2 months)(4)

	Induction/ASCT/Consolidation	
	HR (95% CI)[b]	P-value[c]
Analysis set: Intent-to treat [a]	0.50 (0.34, 0.75)	0.0005

Abbreviations: ASCT = autologous stem cell transplant; CI = confidence interval; HR = hazard ratio; IPW = inverse probability weighting; PFS = progression-free survival.
[a] Including all subjects randomized in Induction/ASCT/Consolidation
[b] Hazard ratio and 95% CI from a Cox regression analysis with treatment as the sole explanatory variable.
[c] The p-value is based on the log-rank test.
Patients randomized to daratumumab maintenance at the second randomization were censored at the date of the second randomization.

Table 12: PFS results with and without IPW adjustments (ITT population, median follow-up = 29.2 months)(5)

IPW Analysis; DVTd versus VTd	
HR (95% CI)[a]	[redacted]
P-value[a]	[redacted]
Analysis without adjustment for second randomization; DVTd versus VTd	
HR (95% CI)	0.495 (0.378, 0.647)
P-value	<0.0001

Abbreviations: VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; HR = hazard ratio; IPW = inverse probability weighting; ITT = intention-to-treat; PFS = progression-free survival.
[a]The overall comparison of induction treatments is made treating the 2 maintenance-specific comparisons as 2 strata with the variance estimated using the robust variance estimator (the sandwich estimate).

PFS updated results: DVTd-observation vs. VTd-observation

The MM Expert Committee has requested data for DVTd-observation vs. VTd-observation and this data is only available from an updated analysis. To address the request from the MM Expert Committee, data-on-file was used from an updated analysis (updated part 1 data from primary analysis of Part 2 (median follow-up of 44.5 months)). [redacted]

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Table 14: Summary of PFS results

	DVTd vs. VTd
PFS from 1st randomization, regardless of 2nd randomization (median follow-up = 18.8 months)[a]	HR (95% CI): 0.47 (0.33, 0.67)
PFS IPW analysis (median follow-up = 18.8 months)[b]	HR (95% CI): 0.47 (0.33, 0.67)
PFS from 1st randomization, regardless of 2nd randomization (median follow-up = 29.2 months)[a]	HR (95% CI): 0.495 (0.378, 0.647)
PFS adjusted results for censoring of maintenance (median follow-up = 29.2 months)[c]	HR (95% CI): 0.50 (0.34, 0.75)

Abbreviations: VTd = bortezomib + thalidomide + dexamethasone; CI = confidence interval; DVTd = daratumumab + bortezomib + thalidomide + dexamethasone; HR = Hazard ratio; IPW = inverse probability weighting; PFS = progression-free survival.
[a] Hazard ratio and 95% CI from a Cox regression analysis with treatment as the sole explanatory variable. Including all subjects randomized in Part I regardless of second randomization.
[b] The overall comparison of induction treatments is made treating the 2 maintenance-specific comparisons as 2 strata with the variance estimated using the robust variance estimator (the sandwich estimate).
[c] Hazard ratio and 95% CI from a Cox regression analysis with treatment as the sole explanatory variable. Including all subjects randomized in Induction/ASCT/Consolidation.
Patients 46 randomized to daratumumab maintenance at the second randomization were censored at the date of the second randomization.

[redacted]

Detailed summary of the results can be found in Appendix D Efficacy and safety results per study.

7.1.2.1.2.2 Overall survival

Survival analysis: Overall survival (1st data-cut) (key secondary endpoint)

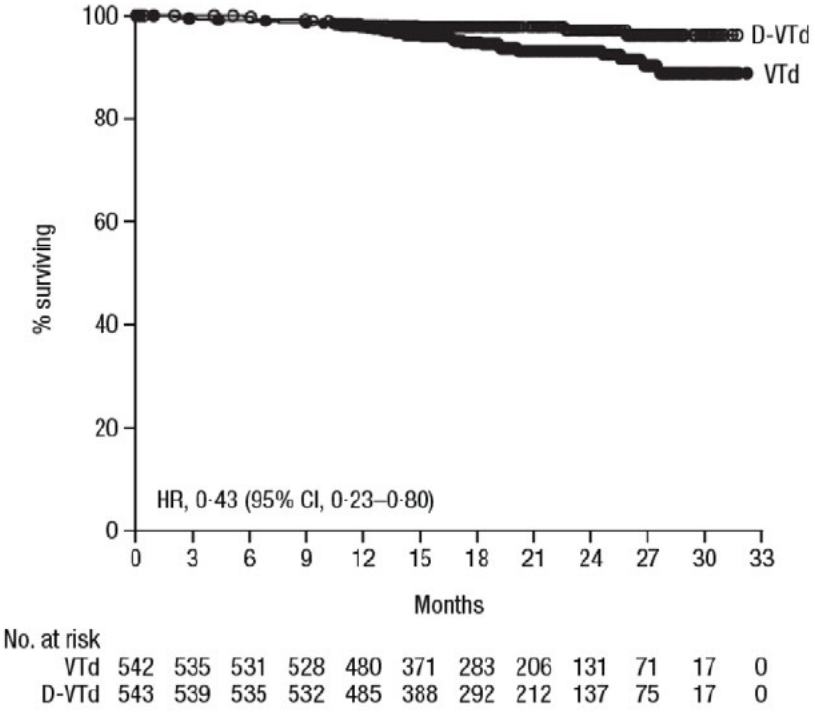
At the Primary Analysis for Part 1, a total of 46 death events had occurred, including 14 patients in the DVTd group and 32 patients in the VTd group (Table 15). Despite the immaturity of the survival data, a strong statistically significant trend for improved OS was observed for DVTd with a 57% reduction in the risk of death compared with VTd (HR: 0.43; 95% CI: 0.23, 0.80; nominal p=0.0065, not adjusted for second randomization).(6) Refer to Figure 6 for the KM plot from CASSIOPEIA after a median follow-up of 18.8 months.

Table 15: OS from 1st randomization, regardless of 2nd randomization (ITT population, median follow-up = 18.8 months)(7)

	VTd	DVTd
Analysis set: intention-to-treat	542	543
Overall survival (days)		
Number of events (%)[a]	32 (5.9%)	14 (2.6%)
Median (95% CI) [b]	NE (NE, NE)	NE (NE, NE)
P-value [c]	0.0065	
HR (95% CI) [d]	0.43 (0.23, 0.80)	
6-month Survival rate % (95% CI) [b]	98.9 (97.5, 99.5)	99.6 (98.5, 99.9)
12-month Survival rate % (95% CI) [b]	97.8 (96.1, 98.7)	98.1 (96.5, 99.0)
18-month Survival rate % (95% CI) [b]	94.7(92.2, 96.5)	97.6 (95.9, 98.7)
24-month Survival rate % (95% CI) [b]	93.2 (90.1, 95.3)	97.1 (94.7, 98.4)

Abbreviations: VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; HR = hazard ratio; NE = not estimable; ITT = intention-to-treat.
[a] Including all patients randomized in Part 1 regardless of second randomization.
[b] Based on Kaplan-Meier product limit estimates.
[c] P-value is based on the log-rank test.
[d] HR and 95% CI from a Cox regression analysis with treatment as the sole explanatory variable.

Figure 6: Kaplan-Meier plot for OS from 1st randomization, regardless of 2nd randomization (ITT population, median follow-up = 18.8 months)(6)



Abbreviations: D-VTd = daratumumab, bortezomib, thalidomide and dexamethasone; ITT = intention-to-treat; OS = overall survival; VTd = bortezomib, thalidomide and dexamethasone.

OS updated results (2nd data-cut)

An updated (post-hoc) analysis of OS was performed with a median follow-up of 29.2 months, representing an additional 10.4 months of follow-up (Table 16). At the time of clinical cut-off for the 2nd data-cut, there were an additional 28 reported deaths resulting in a total of 74 cumulative deaths in the overall study (26 in the DVTd group and 48 in the VTd group).(4) Although OS data from CASSIOPEIA remains immature with median OS not reached on either arm, the treatment benefit in favor of DVTd was maintained with longer study follow-up, further supporting the overall clinical benefit of the daratumumab combination (HR: 0.52; 95% CI: 0.33, 0.85; nominal p=0.0070, not adjusted for second randomization).(4) Refer to Figure 7 for the corresponding KM plot for OS.

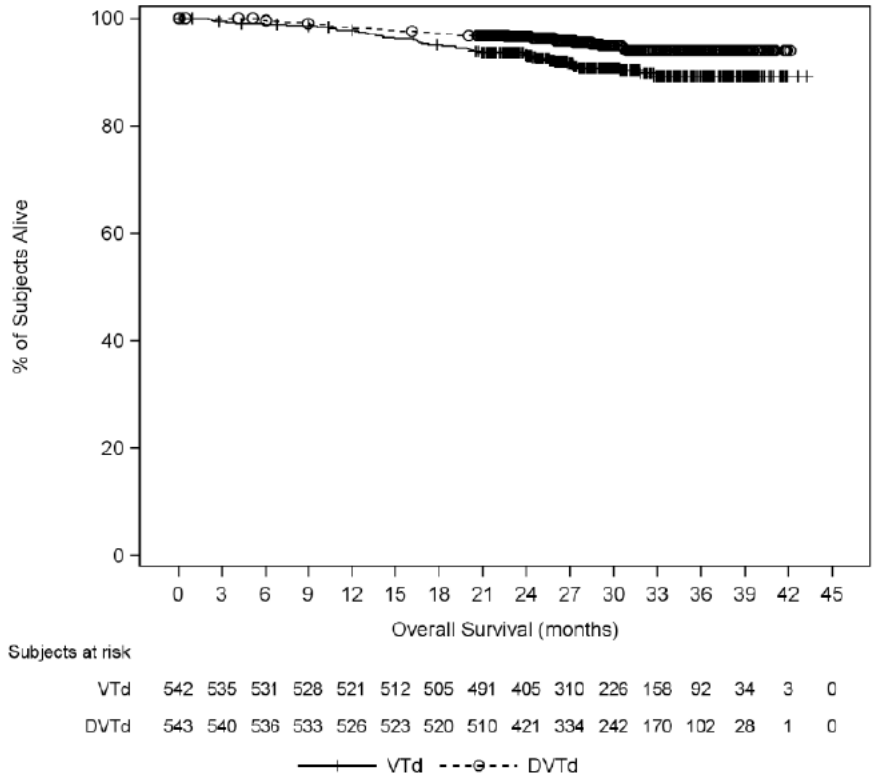
Table 16: OS from 1st randomization, regardless of 2nd randomization (ITT population, median follow-up = 29.2 months)(4)

	VTd	DVTd
Analysis set: intention-to-treat	542	543
Overall survival (days)		
Number of events (%) [a]	48 (8.9%)	26 (4.8%)
Median (95% CI) [b]	NE (NE, NE)	NE (NE, NE)
P-value [c]	0.0070	
HR (95% CI) [d]	0.52 (0.33, 0.85)	
6-month Survival rate % (95% CI) [b]	98.9 (97.5, 99.5)	99.6 (98.5, 99.9)

12-month Survival rate % (95% CI) [b]	97.8 (96.1, 98.7)	98.1 (96.6, 99.0)
18-month Survival rate % (95% CI) [b]	95.1 (92.9, 96.7)	97.2 (95.4, 98.3)
24-month Survival rate % (95% CI) [b]	93.2 (90.6, 95.0)	96.6 (94.7, 97.9)

Abbreviations: VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; HR = hazard ratio; NE = not estimable; ITT = intention-to-treat; OS = overall survival.
[a] Including all patients randomized in Part 1 regardless of second randomization.
[b] Based on Kaplan-Meier product limit estimates.
[c] P-value is based on the log-rank test.
[d] HR and 95% CI from a Cox regression analysis with treatment as the sole explanatory variable.

Figure 7: Kaplan-Meier plot for OS from 1st randomization, regardless of 2nd randomization (ITT population, median follow-up = 29.2 months)(4)



Abbreviations: DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; ITT = intention-to-treat; OS = overall survival; VTd = bortezomib, thalidomide and dexamethasone.

OS updated results: DVTd-observation vs. VTd-observation

The MM Expert Committee has requested data for DVTd-observation vs. VTd-observation and this data is only available from an updated analysis. To address the request from the Expert Committee, data-on-file was used from an updated analysis (updated part 1 data from primary analysis of Part 2 (median follow-up of 44.5 months)). [redacted]

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Table 18: Summary of OS results

	DVTd vs. VTd
OS from 1st randomization, regardless of 2nd randomization, median follow-up = 18.8 months)[a]	HR (95% CI): 0.43 (0.23, 0.80)
OS from 1st randomization, regardless of 2nd randomization (median follow-up = 29.2 months)[a]	HR (95% CI): 0.52 (0.33, 0.85)
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Abbreviations: VTd = bortezomib + thalidomide + dexamethasone; CI = confidence interval; DVTd = daratumumab + bortezomib + thalidomide + dexamethasone; HR = hazard ratio; IPW = inverse probability weighting; OS = overall survival.
[a] Hazard ratio and 95% CI from a Cox regression analysis with treatment as the sole explanatory variable. Including all subjects randomized in Part I regardless of second randomization.
[redacted]

A detailed summary of the results can be found in Appendix D Efficacy and safety results per study.

7.1.2.1.3 Health-related quality of life results

In Part 1 of CASSIOPEIA, pre-specified assessment of functional status and well-being were assessed using the European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30 (EORTC QLQ-C30) and the EuroQol-5D, 5 levels (EQ-5D-5L) tools at:(7, 9, 10)

- Screening (Baseline)
- Post-induction (Cycle 4 Day 28)
- Post-consolidation (Day 100 post ASCT)

Patients treated with both DVTd and VTd experienced meaningful and sustained improvements in HRQoL.(7, 9, 10) A statistically significant reduction in pain was seen with DVTd compared with VTd, while treatment with DVTd also resulted in significantly greater improvements in emotional functioning and a smaller decline in cognitive functioning on the EORTC QLQ-C30 subscales. As noted in Section 5.1, bone pain was one of the symptoms most frequently reported in a recent European study of MM patient perceptions whilst cognitive impairment was the most frequently reported side-effect for NDMM. Improvements in pain and cognitive functioning for patients treated with DVTd are therefore closely aligned to MM patient preferences. Similarly, improvements in emotional functioning on the EORTC QLQ-C30 subscale may be indicative of a psychological impact of achieving sustained remission and a prolonged treatment-free interval. This benefit, and the value of hope for the future associated with no detectable disease and long-term disease control, is not intrinsically captured in the quality-adjusted life-year (QALY) framework.

The overall health state of patients, as measured by EQ-5D-5L, was improved in both treatment groups over the course of treatment.(7, 9, 10) Importantly, quality of life (QoL) assessment showed no adverse QoL impact of a quadruplet therapy over the standard VTd triplet. This means that patients treated with the DVTd quadruplet therapy combination benefit from improved PFS and OS with no significant detriment to overall HRQoL versus the existing triplet therapy (VTd).

At the baseline and throughout the Part 1 of the study, both DVTd and VTd groups demonstrated high compliance rates for EORTC QLQ-C30 and EQ-5D-5L assessments (Table 19).

Table 19: EORTC QLQ C30 and EQ-5D-5L compliance rates at study time points (ITT population)(9)

	EORTC QLQ-C30		EQ-5D-5L	
	DVTd	VTd	DVTd	VTd
Baseline	94%	94%	93%	93%
Cycle 4 Day 28	84%	80%	82%	79%
Post-consolidation	90%	88%	89%	87%

Abbreviations: VTd = bortezomib, thalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; EQ-5D-5L = EuroQol-5D, 5 levels; ITT = intention-to-treat

EORTC QLQ-C30

The EORTC QLQ-C30 is a validated instrument that is widely used to measure QoL in patients with cancer.(132) This self-administered questionnaire captures symptoms that are relevant to MM patients and its results provide information about the possible side effects of treatment. It has five functional scales (physical, role, emotional, cognitive and social functioning), one Global Health Status (GHS) scale, three symptom scales (fatigue, nausea and vomiting, and pain) as well as single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea).

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Baseline values for all subscales of the EORTC QLQ-C30 were comparable for patients treated with DVTd and VTd (Table 20).

Table 20: Baseline values for the EORTC QLQ-C30 (CASSIOPEIA, ITT population) (9)

Subscale score, mean (SD)	DVTd	VTd
GHS	57.6 (24.2)	58.4 (24.5)
Symptom scales		
Fatigue	41.1 (28.4)	42.6 (29.6)
Nausea and vomiting	6.0 (15.2)	7.16 (17.0)
Pain score	47.4 (34.8)	46.4 (34.2)
Functional scales		
Cognitive functioning	84.8 (21.2)	85.6 (19.5)
Emotional functioning	67.9 (23.5)	65.7 (23.8)
Physical functioning	71.2 (27.5)	70.5 (28.4)
Role functioning	54.3 (37.8)	55.4 (36.9)
Social functioning	69.8 (34.4)	71.4 (32.7)

Abbreviations: VTd = bortezomib, thalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; GHS = global health status; ITT = intention-to-treat; SD = standard deviation.
Note: Higher scores indicate better GHS, better functioning and more symptoms. Lower scores indicate worsening symptoms. The highest possible score is 100 at baseline.

At post-consolidation, both DVTd and VTd treatment groups had demonstrated improvements in overall HRQoL with regards to GHS, symptom, and function EORTC QLQ-C30 subscales.(7, 9, 10) For GHS, there was an improvement in least-squares (LS) mean change from baseline for both DVTd and VTd through to Day 100 post ASCT, with change for both groups exceeding the minimally important difference of 8 points (LS mean change from baseline; DVTd = 9.7 [95% CI:7.4, 11.9], VTd = 8.7 [95% CI: 6.5,11]; p=0.4523).(133, 134) The difference between the DVTd and VTd groups was not statistically significant.(7, 9, 10)

Figure 8: EORTC QLQ-C30 GHS change from baseline among patients treated with either DVTd or VTd (mixed effects model for repeated measures)(129)

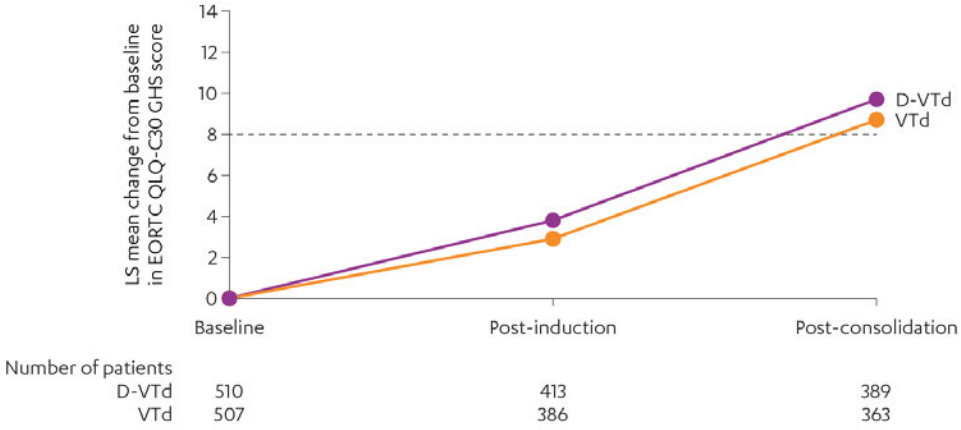
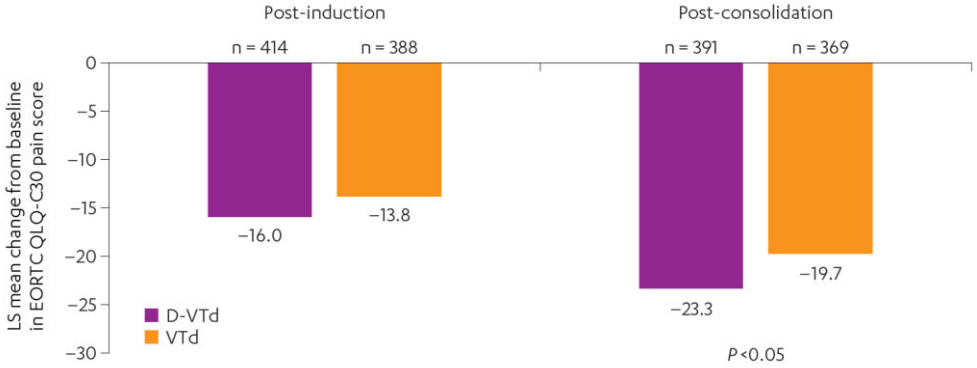


Figure reprinted from: Roussel R et al. Improvement in health-related quality of life for newly diagnosed multiple myeloma transplant-eligible patients treated with daratumumab, bortezomib, thalidomide, and dexamethasone: CASSIOPIA study. 2019. EHA Poster.(10)
Abbreviations: D-VTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire-C30; GHS = Global Health Status; LS = least-squares; VTd = bortezomib, thalidomide and dexamethasone.
Least square means are derived based on the mixed effects model with repeated measures, in which the dependent variable is change from baseline in score and independent variables are baseline, visit, treatment, visit by treatment interaction and randomization stratification factors – ISS staging (I, II, III), region (Europe vs Other) and age (<75 years vs ≥75 years) as fixed effects and individual subject as random effect.

For patients in the DVTd group, a statistically significant reduction in pain symptoms compared with the VTd group was reported post-consolidation (LS mean change from baseline -23.3 and -19.7, respectively; p=0.0416) (Figure 9).

Figure 9: EORTC QLQ-C30 change from baseline in pain subscale scores (mixed effects model for repeated measures)(129)



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Abbreviations: D-VTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire-C30; LS = least-squares; VTd = bortezomib, thalidomide and dexamethasone.

The reduction in pain symptoms score was clinically meaningful for both DVTd and VTd (exceeding a 15.7 point threshold for clinical significance),(135) with a particularly pronounced LS mean change from baseline over 20 points in the DVTd group, suggesting a large reduction in pain post-consolidation.(129) The proportion of patients using analgesics in the DVTd and VTd groups were similar (91.2% vs 92.1% respectively), indicating pain reduction was not confounded by use of concomitant pain management.(7)

For the EORTC QLQ-C30 functional scales, a statistically significant improvement in emotional functioning was reported in the DVTd group compared with that in the VTd group post-consolidation (LS mean change from baseline 13.0 vs 9.5 respectively; p=0.0131)(Figure 10).(7, 9, 10)

Figure 10: EORTC QLQ-C30 change from baseline in emotional function subscale scores (mixed effects model for repeated measures)(129)

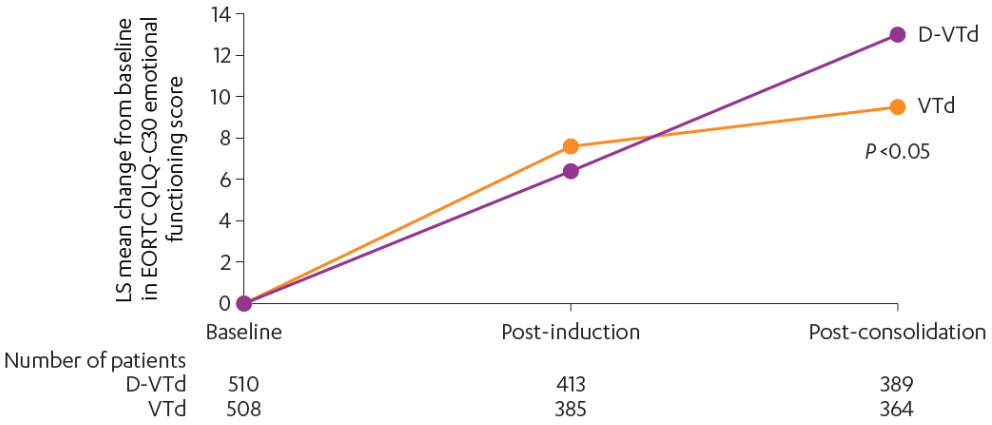
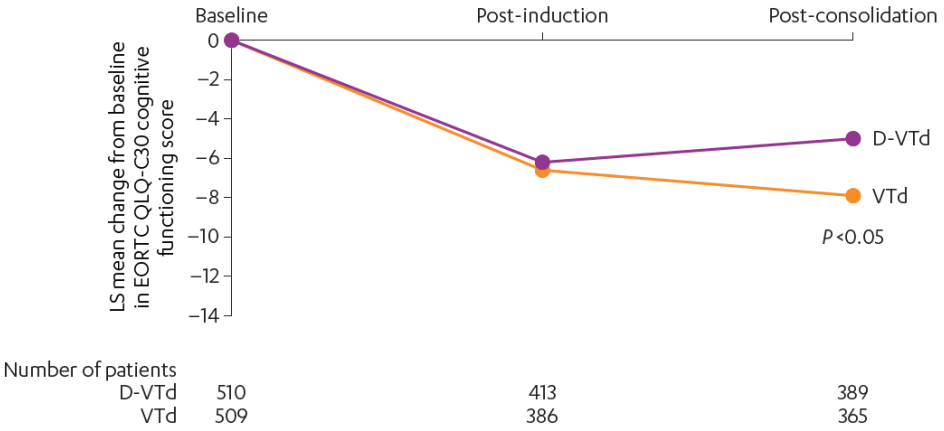


Figure reprinted from: Roussel R et al. Improvement in health-related quality of life for newly diagnosed multiple myeloma transplant-eligible patients treated with daratumumab, bortezomib, thalidomide, and dexamethasone: CASSIOPIA study. 2019. EHA Poster.(10)
Abbreviations: D-VTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire-C30; LS = least-squares; VTd = bortezomib, thalidomide and dexamethasone.

Use of DVTd was associated with significantly less decline in cognitive function compared with VTd at Day 100 post ASCT (LS mean change from baseline -5.0 vs -7.9, respectively; p=0.0358) (Figure 11).(7, 9, 10)

Figure 11: EORTC QLQ-C30 change from baseline in cognitive function subscale scores (mixed effects model for repeated measures)(129)



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Abbreviations: D-VTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Core Cancer Quality of Life Questionnaire-C30; LS = least-squares; VTd = bortezomib, thalidomide and dexamethasone.

While a decline in cognitive function was observed in both DVTd and VTd groups, the mean change from baseline was not clinically meaningful based on the pre-specified threshold of 10 points or the 0.5 standard deviation threshold calculated using distribution-based criteria in the clinical trial population.(129)

Least square mean changes from baseline were not statistically significantly different between treatment groups for the other function (physical, role and social) and symptom scales (fatigue and nausea and vomiting). For further details refer to Appendix D Efficacy and safety results per study.

EQ-5D-5L

Both EQ-5D-5L utility and visual analogue scale (VAS) scores(9) were comparable at baseline for patients treated with DVTd and VTd (refer to Appendix J Utility Data Analysis for EQ-5D-5L utility). Over the course of treatment there was an improvement in EQ-5D-5L utility and VAS, measured from baseline at Cycle 4 Day 28 and post-consolidation (Day 100 post-ASCT). Improvements were similar between the DVTd and VTd groups (Table 21).(129)

The EQ-5D provides a single measure across multiple domains of health and therefore does not highlight the benefits of treatment on specific aspects of health which may be most meaningful for patients. For example, although no statistically significant differences in EQ-5D-5L were observed between treatment arms, statistically significant and clinically meaningful reductions in pain and improvements in emotional functioning were observed for DVTd compared with VTd, as assessed by EORTC QLQ-C30.

The reported VAS score are not used in the health economic model and the data originates from the 1st data-cut. For the reporting of utility scores, the 2nd data-cut has been applied in the cost-effectiveness model allowing it to be aligned with the data-cut used for clinical efficacy. The utility scores presented for the 2nd data-cut are based on the Danish preference weights. The EQ-5D-5L utility results are used in the health economic analysis according to the Medicines Council method handbook and detailed results of the analysis can be found in Appendix J Utility Data Analysis.

Table 21: EQ-5D-5L VAS change from baseline (ITT population, 18.8 months follow-up)(129)

	DVTd LS Means of Change from Baseline (95% CI)	VTd LS Means of Change from Baseline (95% CI)	P-values
VAS			
Cycle 4 Day 28	2.7 (0.5, 4.8)	2.2 (0.1, 4.4)	0.7014
Post-consolidation	8.6 (6.5, 10.8)	7.7 (5.5, 9.9)	0.4408

Abbreviations: VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EQ-5D-5L = EuroQol-5D, 5 levels; ITT = intention-to-treat; LS = least-squares; VAS = visual analogue scale.

7.1.2.2 Safety

Safety was analyzed as a secondary outcome in CASSIOPEIA. No additional studies are available to provide evidence of safety and tolerability of DVTd. Results from CASSIOPEIA indicate that the safety profile of DVTd is consistent with the known safety profile of VTd and that of daratumumab as a monotherapy.(6)

Treatment exposure

The median treatment duration in CASSIOPEIA during Part 1 of the study was 8.9 months and 8.7 months for the DVTd and VTd groups, respectively (refer to Appendix E Safety data for intervention and comparator(s), Table 95).(4) For both the DVTd and the VTd groups, the median number of treatment cycles was six. Median dose intensities were similar for bortezomib, thalidomide and dexamethasone between treatment groups.(4)

Treatment emergent adverse events overall

At median follow-up of 18.8 months, almost all patients treated with DVTd or VTd had at least one treatment-emergent adverse event (TEAE) after the start of treatment (99.8% and 99.6%, respectively).(4, 6) Slightly higher rates of grade 3 and 4 TEAEs were observed in the DVTd group compared to the VTd group (80.6% vs. 75.8%), principally driven by hematological events including neutropenia and lymphopenia.(4) Serious TEAEs were comparable between groups (46.8% for DVTd and 47.4% for VTd).(4) The percentage of patients who discontinued treatment because of at least one TEAE was marginally lower for DVTd compared to VTd (7.5% and 8.4%, respectively), while TEAEs leading to death occurred in 1 patient (0.2%) in the DVTd group and 9 patients (1.7%) in the VTd group.(6) These results show that the addition of daratumumab to standard of care VTd is not linked to decreased tolerability or safety concerns. A summary of TEAEs at 18.8 months of follow-up is provided in Table 22.

Table 22: Summary of TEAEs[a] during the induction/ASCT/consolidation period (CASSIOPEIA, safety population) (4, 6)

	DVTd (n=536)	VTd (n=538)
Any TEAE, n (%)	535 (99.8%)	536 (99.6%)
Grade 3/4 TEAE, n (%)[a]	432 (80.6%)	408 (75.8%)
Serious TEAE, n (%)	251 (46.8%)	255 (47.4%)
TEAE leading to discontinuation, n (%)[b]	40 (7.5%)	45 (8.4%)
TEAEs leading to death, n (%)	1 (0.2%)	9 (1.7%)

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; TEAE = treatment-emergent adverse event.
[a] TEAEs during induction, ASCT, or consolidation Treatment Phase; incidence reflects the number of patients experiencing at least one TEAE associated with at least one of the study treatments.
[b] Include those subjects indicated as having discontinued all study treatments due to adverse events or treatment delay for toxicity for more than 7 weeks on the end of treatment CRF page.
Note: During transplant period, according to protocol, only limited AE were collected.

Treatment emergent adverse events by preferred term

Overall, the safety profile was similar between treatment groups, including the incidence of TEAEs occurring in ≥10% of patients in either treatment group. However, a higher frequency (≥5% difference) was reported in the DVTd group for nausea (DVTd: 30.2%; VTd 24.2%), neutropenia (DVTd: 29.3%; VTd 16.5%), thrombocytopenia (DVTd: 20.3%; VTd: 13.6%), lymphopenia (DVTd: 18.5%; VTd: 12.5%), and cough (DVTd: 17.2%; VTd: 10.4%). Other most common TEAEs (≥20% in either group) were balanced between the two treatment groups, including peripheral sensory neuropathy, paraesthesia, constipation, asthenia, peripheral oedema, and pyrexia.(4, 6)

Frequently reported Grade 3 or 4 TEAEs (occurring in ≥10% of patients in either treatment group) were neutropenia, lymphopenia, stomatitis and thrombocytopenia.(6, 133) The incidence of Grade 3 or Grade 4 TEAEs was increased for patients receiving daratumumab, driven by the hematological events of neutropenia and lymphopenia, which occurred more frequently in the DVTd group compared with the VTd group (neutropenia: 27.6% vs 14.7%; lymphopenia: 17.0% vs 9.7%). The increased rate of neutropenia in patients receiving daratumumab was not associated with any increased risk of neutropenic fever, as patients in the both treatment groups reported comparable levels of febrile neutropenia. (4)

Refer to Appendix E Safety data for intervention and comparator(s), Table 96.

Adverse Drug Reactions

All TEAEs reported in ≥10% subjects in the DVTd treatment group and occurred at a higher incidence (≥5% difference) in the DVTd treatment group compared with the VTd treatment group were considered adverse drug reactions (ADRs).

In the safety analysis, the DVTd arm reported with 35.5% infusion reactions. The incidence of Grade 3 ADRs in the daratumumab arm included; nausea 3.9%, vomiting 2.2%, pyrexia 2.2%, upper respiratory tract infection 0.6%, bronchitis 1.5%, hypertension 4.1%. Grade 3 ADRs in the VTd arm included; nausea 2.0%, vomiting 1.7%, pyrexia 2.2%, upper respiratory tract infection 0.6%, bronchitis 1.1%, hypertension 2.2%. For Grade 4 ADRs, 0.4% was reported in the DVTd arm for infusion reactions, 0% nausea (DVTd) versus 0.2% (VTd), pyrexia 0.4% (DVTd) versus 0% (VTd), 0% infections and infestations in both arms and 0% grade 4 vascular disorders for both arms.(4)

Refer to Appendix E Safety data for intervention and comparator(s), Table 97.

Serious treatment emergent adverse events

Serious TEAEs occurred at similar rates in the DVTd group and the VTd group with overall incidence of 46.8% and 47.4% respectively. The most commonly reported serious TEAEs (≥2%) in the CASSIOPEIA safety population included neutropenia (DVTd 3.9%, VTd 1.5%), pneumonia (DVTd 3.5%, VTd 1.7%), pyrexia (DVTd 2.8%, VTd 4.3%) and pulmonary embolism (DVTd 1.5%, VTd 3.7%).(4, 6)

Refer to Appendix E Safety data for intervention and comparator(s), Table 98.

Infusion-related reactions

At median follow-up of 18.8 months, infusion-related reactions (IRRs) of any grade associated with daratumumab were observed in 35.4% of the patients, with 26.9% experiencing IRR at first infusion, 1.9% with the second infusion, and 11.7% cumulative with subsequent infusions (the latter mainly occurring at the first infusion after ASCT (10.7%).(4, 6) The IRRs were mostly limited to Grade 1 or 2 events. The results for IRRs in CASSIOPEIA are in line with the previous studies as listed in the SmPC.(4) The most frequently reported TEAE term (reported in ≥5% of subjects) used to describe IRRs was chills (5.6%). Overall, IRRs were manageable with a low frequency of Grade 3 (3.2%) or 4 Grade events (0.4%) and no fatal events.

As referred to in the section, Basic information, a license extension for a subcutaneous formulation of daratumumab was received in June 2020. Results from the non-inferiority phase III study COLUMBA demonstrated that the rate of IRRs was significantly reduced with SC versus IV (12.7% vs 34.5%; odds ratio, 0.28; 95% CI, 0.18-0.44; P <0.0001).(136) It is therefore anticipated that IRRs associated with administering DVTd will be substantially reduced following the availability of daratumumab as a SC injection. Furthermore, SC daratumumab is expected to improve convenience for patients with administration time reduced from several hours to approximately 5 minutes.(136)

Discontinuation due to adverse events

Discontinuation of study treatment (i.e. all study drugs) due to TEAEs was similar between treatment groups; 7.5% of patients discontinued treatment due to TEAEs in the DVTd group, compared with 8.4% in the VTd group (Table 99).(6) The TEAE associated with the highest number of discontinuations was peripheral sensory neuropathy, reported in 10 patients (1.9%) in the DVTd group and 23 patients (4.3%) in the VTd group.(6)

Refer to Appendix E Safety data for intervention and comparator(s), Table 99.

Discontinuation of treatment irrespective of reason

The most common reasons for discontinuation were adverse events, progressive disease, and death. The primary and final analysis of part 1 evaluated efficacy after all patients either completed the day 100 response evaluation or discontinued from study treatment. A total of 24 (4%) patients in the DVTd group and 31 (6%) patients in the VTd group discontinued treatment during induction, and five (1%) and 11 (2%) patients during consolidation; 23 (4%) and 36 (7%) patients did not continue to consolidation therapy after transplantation.(6)

Refer to Appendix E Safety data for intervention and comparator(s), Table 100.

Overall

Overall, DVTd was well-tolerated in CASSIOPEIA, with clinically manageable side effects consistent with the known safety profiles of daratumumab monotherapy and the VTd regimen.(4, 6) No new safety signals were identified.(6) IRRs associated with the use of daratumumab were mild and manageable and are anticipated to reduce significantly with the use of SC daratumumab.(6)

7.1.3 Comparative analyses of efficacy and safety

Since a single head-to-head study comparing the intervention and comparator directly is included as evidence of efficacy and safety, the following section describing comparative analysis is omitted.

7.2 Efficacy of DVTd/VTd compared to VCd for patients with NDMM patients who are eligible for ASCT

The analysis aims to compare PFS and OS of patients receiving DVTd and VTd to those VCd induction therapy for the treatment of patients with NDMM patients who are eligible for ASCT. In the absence of RCTs comparing DVTd/VTd to VCd induction therapy, an unanchored MAIC(137, 138) can be used to compare PFS and OS. This type of comparison derives relative treatment effects by assigning weights to patients to balance differences in baseline characteristics between the arms being compared. As PFS and OS are influenced by differences in the maintenance therapies used, a comparison of the induction therapies alone is challenging. Instead, a comparison of the trials' treatment overall schemas, adjusted for population differences can be explored.

The aim of this analysis was to conduct an unanchored MAIC comparing PFS and OS among patients receiving DVTd/VTd followed by daratumumab / observation maintenance for 2 years to:

- VCd followed by ASCT and lenalidomide consolidation and lenalidomide maintenance for 2 years (VCd-Len-2Y)

The MAIC analyses descriptions are primarily based on the Moreau et al. 2020(8), a full-text article published in a scientific, peer-reviewed journal. Compared to Moreau et al. 2020(8) which was focusing on the 1st data-cut from CASSIOPEIA (median follow-up of 18.8 months), the below analysis has incorporated 2nd data-cut with a median follow-up of 29.2 months for CASSIOPEIA.

7.2.1 Relevant studies

This MAIC was conducted on basis of two trials: CASSIOPEIA(6, 12) and GMMG-MM5(121, 139):

- In Part 1 of the Phase 3 CASSIOPEIA study, patients with NDMM who were eligible for ASCT received DVTd or VTd as pre-ASCT induction (four 28-day cycles) and post-ASCT consolidation therapy (two 28-day cycles). In Part 2 (ongoing), patients with a partial response or better were re-randomized to daratumumab maintenance every 8 weeks or observation for a maximum of 2 years.(6, 12)
- GMMG-MM5 is a randomized, open-label phase III trial with newly diagnosed, transplant-eligible patients.(139, 140) Patients were equally randomized to receive induction therapy with PAd (bortezomib/ doxorubicin/dexamethasone) or VCd, followed by ASCT and then lenalidomide (LEN) consolidation, followed by either LEN maintenance therapy for a fixed duration of 2 years (LEN-2Y) or until achievement of complete response (CR) (LEN-CR, intention-to-treat population n = 502): arms A1:PAd + LEN-2Y (n = 125), B1:PAd + LEN-CR (n = 126), A2:VCd + LEN-2Y (n = 126), B2:VCd + LEN-CR (n = 125).(139)

The CASSIOPEIA(5, 10) and GMMG-MM5(121, 139) study designs are shown in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety, Figure 25. Efficacy outcomes assessed in each study are summarized in Table 76 in Appendix C Baseline characteristics of patients in studies used for the

comparative analysis of efficacy and safety. For main characteristics for the included studies refer to Appendix B Main characteristics of included studies.

Eligibility criteria were generally comparable across the studies. The CASSIOPEIA included patients up to 65 years of age, whereas the GMMG-MM5 study included patients up to 70 years of age. Various diagnostic criteria were used to diagnose MM in CASSIOPEIA (SliM-CRAB criteria, i.e., 60% plasmacytosis, light chains, MRI, hypercalcemia, renal insufficiency, anemia and lytic bone lesions(141)), GMMG-MM5 (CRAB criteria, i.e., hypercalcemia, renal insufficiency, anemia and lytic bone lesions(142)).((8)(p.2))

7.2.2 Efficacy and safety – results per study

For DVTd vs. VTd, refer to the previous section, 7.1.2.

In the GMMG-MM5 trial, the median follow-up for PFS was 59.4 months. In total, 321 PFS events had occurred. Median PFS was 43.2 vs. 40.9 vs. 35.9 vs. 35.7 months and PFS rates after 36 months were 58.5% vs. 53.8% vs. 49.4% vs. 49.4% in the arms A1 (PAd + LEN-2Y), A2 (VCd + LEN-2Y) , B1 (PAd + LEN-CR) and B2 (VCd + LEN-CR), respectively.(139)

The median follow-up for OS was 60.1 months. In total, 162 OS events had occurred. OS was not significantly different between the four study arms applying a stratified log-rank test (p = 0.15). On unstratified, single comparison of the four treatment arms, OS was significantly shorter in the PAd-LEN-CR (B1) vs. PAd-LEN-2Y (A1) arm (p = 0.047). The 36-month OS rates were 82.9% vs. 85.2% vs. 75.1% vs. 77.1% in the arms A1, A2, B1, and B2, respectively. Median OS was not reached in either arm.(139)

Adverse events were higher in the VCd arm 64% versus the PAd arm with 61.3% (included all AE Common Terminology Criteria for Adverse Events (CTCAE) Grade ⩾3 or ⩾2 for infections, cardiac disorders, neuropathy and thromboembolic events. Events with a lower CTCAE grade were not considered). Higher levels of leukocytopenia and/or neutropenia was reported in the VCd arm versus PAd arm (CTCAE ⩾3°, VCd 35.2% versus Pad 11.3%, P = 0.001). Neuropathy (CTCAE ⩾2°) was observed more frequently in the PAd arm than in the VCd arm (14.9 versus 7.6%, P = 0.03). Serious adverse events (SAEs) were reported significantly higher in PAd group (32.7 versus 24.0%, P = 0.04).(121)

7.2.3 Comparative analyses of efficacy and safety

7.2.3.1 Efficacy

Method of synthesis

Matching-adjusted indirect comparison

Two clinical data cuts were available for CASSIOPEIA for the MAIC analysis: 1st data-cut (median follow-up of 18.8 months) and the 2nd data-cut (median follow-up of 29.2 months). In the base case analysis, the 2nd data-cut was used. In the sensitivity analysis, DVTd data was used from the 1st data-cut, where the findings have been published by Moreau et al. 2020.(8)

A naïve comparison was conducted that directly compared the treatment groups without any adjustments for differences between trial populations. The MAIC analysis was performed, which weighted individual patients in the DVTd and VTd groups with regard to their characteristics to match those in the comparator trial regimens (Appendix F Comparative analysis of efficacy and safety, Table 103). An anchored indirect comparison was not feasible, since common comparators among the trials were not available; thus, an unanchored indirect comparison was conducted. All available effects modifiers and prognostic factors were included, and the analyses followed guidelines published by the UK National Institute for Health and Care Excellence (137).((8)(p.2))

Effect modifiers & prognostic factors

For the two comparisons described in this application (VCd & VRd), variables considered for adjustment differed due to data availability and different definitions among studies; however, there was sufficient overlap in most baseline characteristics to conduct an MAIC analysis.((8)(p.3))

Identified baseline characteristics

For the DVTd, VTd and VCd groups, the baseline characteristics for adjustment in the analysis included age, sex, ISS stage, Eastern CooperativeOncologyGroup performance status, cytogenetic risk (proportions of patients with t(4;14) translocation and/or del(17p) abnormality), creatinine, bone disease, calcium levels, hemoglobin, platelet count, serum lactic acid dehydrogenase (LDH) and myeloma type. Anemia was excluded from the analysis due to lack of overlap in reported values between studies (CASSIOPEIA: 41.1% with DVTd and 35.2% with VTd; GMMG-MM5: 55%), resulting in substantial reduction in the effective sample size (ESS) after matching (51% for DVTd and 50% for VTd); mean hemoglobin was adjusted for instead.((8)(p.3)) Based on clinical feedback, it was determined that anemia was not a critical aspect of prognosis compared to other factors and could be excluded from the analysis; mean hemoglobin concentration and platelet count were adjusted instead. Of note, as there was only 1 patient in each arm in CASSIOPEIA with renal insufficiency (defined as creatinine >177 µmol/l), this baseline characteristic could not be adjusted.

Lack of overlap between the CASSIOPEIA and GMMG-MM5 trials was observed in the reported proportion of patients with LDH above the upper limit of normal. In CASSIOPEIA, the assessment of LDH was based on local laboratory assays with upper limit of normal patient-dependent cutoffs of 213 U/l or 225 U/l, whereas for GMMG-MM5, the cutoffs were not reported and, therefore, it was not known if the LDH values were comparable between the two trials.((8)(p.3)) However, based on clinical feedback, it was determined that LDH was an important prognostic factor and should be included in the matching model.

Analysis variables & statistical methodology / DVTd/VTd vs. VCd

Outcome variables for this analysis were identified following comparison of the efficacy outcome definitions used in each trial (Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety, Table 76). As efficacy outcomes (PFS and OS) that are analyzed in this MAIC are influenced by differences among the trials in the maintenance therapies used, a comparison of the induction therapies alone is challenging. Instead, a comparison of the trials' overall treatment schemas, adjusted for population differences, was conducted. The MAIC adjusted for differences in study populations by taking individual patient data from CASSIOPEIA and weighting it to match the published aggregate data from VCd to adjust heterogeneity of baseline among different study comparisons (refer to Appendix F Comparative analysis of efficacy and safety, Table 103).((8)(p.3))

Aggregate baseline and outcome data for VCd were obtained from the GMMG-MM5 study publication (Goldschmidt H et al., 2020), with a median follow-up time of 60.1 months.(139)

Individual patient data (e.g., time and censoring status) were derived from digitized Kaplan–Meier curves from each comparator study using the method Guyot et al.(143) Median PFS and OS (when available) and numbers at risk over time were compared to ensure a reasonably close replication of the published results. Due to data availability, investigator-assessed PFS was used for matching adjustment of DVTd and VTd to VCd. The relative effect of DVTd and VTd versus each comparator for PFS and OS was derived as the hazard ratio (HR) obtained using a weighted Cox regression analysis with a robust sandwich estimator for calculation of standard errors. Noninferiority margins for PFS and OS were identified from a targeted literature review as HRs of 1.333 and 1.298, respectively.(144) Results that did not achieve superiority or inferiority and did not qualify per the noninferiority criteria were treated as inconclusive. .((8)(p.4))

Detailed descriptions of statistical methods can be found in Appendix F Comparative analysis of efficacy and safety.

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Results from the comparative analysis

Baseline characteristics before and after matching D-VTd and VTd to VCd are summarized in Appendix F Comparative analysis of efficacy and safety, Table 103. Before matching adjustment, there were imbalances in some baseline characteristics including myeloma type, calcium levels, renal insufficiency and anemia. After matching, all baseline characteristics were balanced among DVTd, VTd and VCd groups, except anemia and renal insufficiency. In the model, ESS was reduced from the original sample size by 62% for DVTd and 61% for VTd.((8)(p.7)) PFS and OS KM curves for DVTd/VTd before and after adjustment vs. VCd can be found in Appendix F Comparative analysis of efficacy and safety, Figure 27, Figure 28, Figure 29, Figure 30.

For DVTd vs. VCd, the results for the naïve (before matching, median follow-up of 29.2 months), base case (after matching, median follow-up of 29.2 months) and sensitivity analysis (after matching, median follow-up of 18.8 months) are presented in Appendix F Comparative analysis of efficacy and safety, Table 101. For DVTd vs. VCd with a median follow-up of 29.2 months for CASSIOPEIA, PFS and OS were statistically significantly different for DVTd before [PFS HR: 0.43 (95%CI: 0.30-0.60) and OS HR: 0.39 (95%CI: 0.21-0.71)] and after matching [PFS HR: 0.40 (95%CI: 0.26-0.61) and OS HR: 0.37 (95%CI: 0.18-0.76)] in the analysis. Adjustment in the analysis shifted the point estimates for PFS slightly in favor of DVTd but had little to no impact on OS. The results after matching are used in the base case for the cost-effectiveness model.

For VTd vs. VCd, the results are presented in Appendix F Comparative analysis of efficacy and safety, Table 102. For VTd vs. VCd with a median follow-up of 29.2 months for CASSIOPEIA, there was no statistically significant difference in PFS and OS before [PFS HR: 0.85 (95%CI: 0.62-1.17) and OS HR: 0.72 (95%CI: 0.42-1.24)] and after matching [PFS HR: 0.93 (95%CI: 0.64-1.35) and OS HR: 0.77 (95%CI: 0.40-1.47)] in the analysis. Adjustment shifted the PFS and OS point estimates slightly towards the null value and in favor of VCd.

Discussion and limitations

A MAIC analysis was used to compare outcomes from the CASSIOPEIA trial with VCd induction regimen from the GMMG-MM5 trial among transplant-eligible patients with NDMM. Data from the EMN02 study, in which patients with NDMM received VCd induction therapy, were recently published.(145) In EMN02, PFS and OS were reported starting from the time of randomization, which occurred after the VCd induction period (145); this difference in reporting of survival times precluded inclusion in this analysis.((8)(p.8))

MAIC methodology has been used within oncology and other therapeutic areas to compare treatment effects across trials, as it allows for adjustment of population differences among studies (130, 138, 146) and can aid clinical decision making for choosing the optimal treatment regimen. Using an unanchored MAIC, patient population differences were adjusted via weighting to compare PFS and OS across the studies. Although, after matching adjustment, there was a substantial reduction in ESS from the original sample size, all baseline characteristics were balanced between studies in analysis.((8)(p.8))

In this MAIC analysis, PFS and OS were significantly in favor of DVTd compared with VCd in transplant-eligible patients with NDMM. Conversely, comparisons of the VTd treatment arm in CASSIOPEIA with VCd did not show statistically significant differences in PFS or OS before or after matching.((8)(p.8))

The OS data should be interpreted with the caveat that CASSIOPEIA is ongoing, so the follow-up period (18.8 months for the 1st data-cut and 28.2 months for the 2nd data-cut) is limited versus the comparator trial (GMMG-MM5, 60.1 months), and median OS has not yet been reached in either treatment arm (DVTd and VTd) in CASSIOPEIA. The extent of bias caused by different median follow-up times is difficult to predict, given that OS data can be confounded by subsequent therapies and evolving therapeutic options in relapsed MM. ((8)(p.9))

There were several limitations to this MAIC analysis. Although MAIC effectively adjusts for baseline variables when individual patient data from only one study are available, it effectively assumes that absolute outcomes can be predicted from baseline variables.(130) Additionally, information bias does exist when individual patient data are recreated based on Kaplan–Meier curves, because the true censor is not known. The different lengths of follow-up among the studies may also contribute to information bias. There is the likely possibility for residual bias from unaccounted prognostic factors or effect modifiers, differences in study designs and inclusion criteria (and thus differences in patient, treatment and disease characteristics), and differences in postinduction therapy treatments and maintenance regimens (e.g., lenalidomide vs daratumumab, and limited, as well as differing, durations of maintenance therapies in the different trials). Different length and cycle number of induction therapies may add additional bias to the analyses. Comparing the effect of induction therapies alone using MAIC methodology is challenging, since PFS and OS are influenced by differences in consolidation and maintenance strategies, and it was not feasible to adjust for differences in treatment schema (e.g., receipt of a second ASCT in the GMMG-MM5 trial). Consequently, the analysis reflects a comparison of the overall treatment schema of the studies rather than a comparison of the induction therapies alone. It should also be noted that the CASSIOPEIA trial began in 2015, whereas the GMMG-MM5 trial were initiated in 2010. Changes in clinical practice and management of patients with NDMM over time may have influenced efficacy outcomes, and availability of newer options may have led to biased longevity. However, improved PFS and OS with DVTd, but not VTd, with VCd suggests that inclusion of daratumumab in the regimen, rather than advances in patient care, contributed to this effect.((8)(p.9))

7.2.3.2 Safety

Overall, no sufficiently comparable data has been published for VCd to conduct a fair naïve comparison between DVTd vs. VCd.

In the phase 2 study (EVOLUTION) (Kumar et al. 2012) bortezomib in combination with dexamethasone, cyclophosphamide, and lenalidomide (VDCR), bortezomib in combination with dexamethasone and lenalidomide (VDR), and VCd was investigated.(147) Treatment consisted of eight 3-week cycles of induction therapy followed by four 6-week cycles of bortezomib maintenance therapy and was therefore not seen as comparable to the VCd dosing expected in Danish clinical practice. The study reported the following for VCd: At least one Grade 3 or above AE: 26 (79%); At least one drug-related Grade 3 or above AE: 20 (61%); AE resulting in discontinuation: 4 (12%).

In the phase 3 randomized IFM2013-04 trial (Moreau et al. 2016), patients were centrally randomized to receive 4 cycles of VTd or VCd. VCd treatment consisted of four 3-week cycles of 1.3 mg/m^2 bortezomib administered subcutaneously (SC) on days 1, 4, 8, and 11; 40 mg dexamethasone on days 1–4 and 9–12; plus 500 mg/m^2 cyclophosphamide administered orally on days 1, 8, and 15. The safety population included all 338 patients (169 in each arm). For the induction therapy with VCd, any AEs (Grade 3-4) was 68.2%. 3 (1.8%) patients died during induction therapy for VCd – from progression to extramedullary myeloma (1) and infections (2).(148)

Safety data is reported based on the same study used to document the efficacy of both the intervention (CASSIOPEIA) and the comparator (GMMG-MM5) according with the method guidelines. Safety data from GMMG-MM5 has been included in a naïve comparison but differences exists in method and detail of reporting, and the comparison should be interpreted with caution. In terms of safety data from GMMG-MM5, the AEs published for VCd is only reported during induction (Mai et al. 2015)(121) or separately during maintenance (Goldschmidt et al. 2020)(139). In addition, the GMMG-MM5 trial did not report data for any Grade TEAE; the reported data for any AE (64.0%; induction only) included all AE CTCAE Grade⩾3or⩾2 for infections, cardiac disorders, neuropathy and thromboembolic events. Events with a lower CTCAE Grade were not considered.

Although differences exist in collection/definition of AEs between the two studies and it should be interpreted with caution, this data may serve as a proxy for Grade 3/4 TEAE for the comparison versus DVTd. DVTd reported 80.6% Grade 3/4 TEAE during induction/ASCT/consolidation. Based on maximum severity, DVTd reported 41.0% Grade 3 TEAE and

17.4% Grade 4 TEAE during induction.(4) VCd reported 64.0% Grade 3/4 TEAE during induction.(121) For any serious TEAEs in the induction phase, 33.6% was reported for DVTd, and serious TEAE reported for VCd was 24.0%.(121)

Table 23: Summary of naïve safety comparison between DVTd and VCd

	DVTd (n=536) (4) Induction/ASCT/consolidation	DVTd (536) (4) Induction	VCd (n= 250) (121) Induction only
Any TEAE, n (%)	535 (99.8%)	530 (98.9%)	NA
Grade 3/4 TEAE, n (%)	432 (80.6%)	NA	160 (64.0%)[a]
Grade 3 TEAE[b]	*287 (53.5%)*	220 (41.0%)	NA
Grade 4 TEAE[b]	*144 (26.9%)*	93 (17.4%)	NA
Serious TEAE, n (%)	251 (46.8%)	180 (33.6%)	60 (24.0%)
TEAE leading to discontinuation, n (%)	40 (7.5%)	28 (5.2%)	NA
TEAEs leading to death, n (%)	1 (0.2%)	NA	1 (0.4%)

Abbreviations: ASCT = autologous stem cell transplant; VCd = bortezomib, cyclophosphamide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; NA = Not available; TEAE = treatment-emergent adverse event.
[a] Reported in publication as "Any AE" defined as: 'Any AE' included all AE CTCAE grade ⩾ 3 or ⩾ 2 for infections, cardiac disorders, neuropathy and thromboembolic events. Events with a lower CTCAE grade were not considered.
[b] Maximum severity of any TEAE.
Note: During transplant period, according to protocol, only limited AE were collected in the CASSIOPEIA trial.

7.3 Efficacy of DVTd/VTd compared to VRd for patients with NDMM patients who are eligible for ASCT

Similarly as described for the comparison for DVTd/VTd vs. VCd (section 7.2), the aim of this analysis was to compare the efficacy (PFS & OS) of DVTd/VTd (CASSIOPEIA) vs. VRd (IFM 2009 study) using a MAIC in the absence of RCTs.

- VRd induction followed by HDT / ASCT and consolidation and lenalidomide maintenance treatment for 1 year (VRd + ASCT)

The MAIC analyses descriptions are primarily based on the Moreau et al. 2020(8), a full-text article published in a scientific, peer-reviewed journal. Compared to Moreau et al. 2020(8) which was focusing on the 1st data-cut from CASSIOPEIA (median follow-up of 18.8 months), the below analysis has incorporated 2nd data-cut with a median follow-up of 29.2 months for CASSIOPEIA.

7.3.1 Relevant studies

This MAIC was conducted on basis of two trials: CASSIOPEIA(6, 12) and IFM/DFC1 2009 (referred to at IFM 2009)(123):

- In Part 1 of the Phase 3 CASSIOPEIA study, patients with NDMM who are eligible for ASCT received DVTd or VTd as pre-ASCT induction (four 28-day cycles) and post-ASCT consolidation therapy (two 28-day cycles). In Part 2 (ongoing), patients with a partial response or better were re-randomized to daratumumab maintenance every 8 weeks or observation for a maximum of 2 years.(6, 12)
- The IFM 2009 is a randomized, open-label, phase III trial with 700 NDMM assigned to receive induction therapy with three cycles of VRd and then consolidation therapy with either five additional cycles of VRd (350 patients) or

HDT and ASCT followed by two additional cycles of VRd (350 patients). Patients in both groups received maintenance therapy with lenalidomide for 1 year.(123)

The CASSIOPEIA and IFM 2009 study designs are shown in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety , Figure 26. Efficacy outcomes assessed in each study are summarized in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety, Table 78. For main characteristics for the included studies refer to Appendix B Main characteristics of included studies. The MAIC analyses are using the VRd + ASCT (transplantation) group.

Eligibility criteria were generally comparable across the studies. The CASSIOPEIA and IFM 2009 studies included patients up to 65 years of age. Various diagnostic criteria were used to diagnose MM in CASSIOPEIA (SliM-CRAB criteria, i.e., 60% plasmacytosis, light chains, MRI, hypercalcemia, renal insufficiency, anemia and lytic bone lesions(141)), IFM 2009 (Myeloma Group Uniform Response Criteria(123), adapted from International Uniform Response Criteria for Multiple Myeloma(142)).((8)(p.2))

7.3.2 Efficacy and safety – results per study

For DVTd vs. VTd, refer to the previous section, 7.1.2.

With a median follow up of 43 months, the median PFS was significantly longer in the VRd transplantation group versus the group with VRd alone (50 months vs. 36 months; adjusted hazard ratio for disease progression or death, 0.65; P<0.001). Overall survival at 4 years did not differ significantly between the two groups; the rate was 82% in the VRd-alone group and 81% in the transplantation group (adjusted hazard ratio for death, 1.16; 95% CI, 0.80 to 1.68; P = 0.87). Median survival was not reached in either group.(123)

Discontinuation due to AEs were higher in the VRd transplant group 11% versus 9% in the VRd group. Grade 3/4 AEs were 97.1% in the VRd transplant group versus 84.3% in VRd group.(123)

7.3.3 Comparative analyses of efficacy and safety

7.3.3.1 Efficacy

Method of synthesis

Matching-adjusted indirect comparison

Two clinical data cuts were available for CASSIOPEIA for the MAIC analysis: 1st data-cut (median follow-up of 18.8 months) and the 2nd data-cut (median follow-up of 29.2 months). In the base case analysis, the 2nd data-cut was used. In the sensitivity analysis, DVTd data was used from the 1st data-cut, where the findings have been published by Moreau et al. 2020.(8) The MAIC analyses are using the VRd transplant group (VRd + ASCT) but referred to as VRd.

A naïve comparison was conducted that directly compared the treatment groups without any adjustments for differences between trial populations. The MAIC analysis was performed, which weighted individual patients in the DVTd and VTd groups with regard to their characteristics to match those in the comparator trial regimen (refer to Appendix F Comparative analysis of efficacy and safety, Table 108). An anchored indirect comparison was not feasible, since common comparators among the trials were not available; thus, an unanchored indirect comparison was conducted. All available effects modifiers and prognostic factors were included, and the analyses followed guidelines published by the UK National Institute for Health and Care Excellence(137).((8)(p.2))

Effect modifiers & prognostic factors

For the two comparisons described in this application (VCd & VRd), variables considered for adjustment differed due to data availability and different definitions among studies; however, there was sufficient overlap in most baseline characteristics to conduct an MAIC analysis.((8)(p.3))

Identified baseline characteristics

The following baseline characteristics were identified for the analysis of the DVTd, VTd and VRd treatment groups based on clinical opinion: age, sex, myeloma type and International Staging System (ISS) stage. The definition of cytogenetic risk differed between IFM 2009 (t(4;14) translocation, del(17p) abnormality and t(14;16) translocation evaluated) and CASSIOPEIA (only t(4;14) translocation and del(17p) abnormality evaluated). Additionally, a smaller proportion of patients in the IFM 2009 study were tested for cytogenetic abnormalities compared with those in the CASSIOPEIA study. In IFM 2009, 26.0% were not tested for t(4;14) translocation and 26.3% were not tested for del(17p) abnormality; in CASSIOPEIA, 7.7% of patients in the DVTd arm and 7.2% in the VTd arm were not tested for both t(4;14) translocation and del(17p) abnormality. Therefore, cytogenetic risk was excluded from the analysis.((8)(p.3))

Analysis variables & statistical methodology / DVTd/VTd vs VRd

Outcome variables for this analysis were identified following comparison of the efficacy outcome definitions used in each trial (Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety, Table 78). As efficacy outcomes (PFS and overall survival [OS]) that are analyzed in this MAIC are influenced by differences among the trials in the maintenance therapies used, a comparison of the induction therapies alone is challenging. Instead, a comparison of the trials' overall treatment schemas, adjusted for population differences, was conducted. The MAIC adjusted for differences in study populations by taking individual patient data from CASSIOPEIA and weighting it to match the published aggregate data from VRd to adjust heterogeneity of baseline among different study comparisons (refer to Appendix F Comparative analysis of efficacy and safety, Table 108).((8)(p.3))

Aggregate baseline and outcome data for VRd transplant group were obtained from the IFM 2009 study publication, with a median follow-up time of 43 months.(123)

Individual patient data (e.g., time and censoring status) were derived from digitized Kaplan–Meier curves from each comparator study using the method Guyot et al.(143) Median PFS and OS (when available) and numbers at risk over time were compared to ensure a reasonably close replication of the published results. The relative effect of DVTd and VTd versus VRd for PFS and OS was derived as the hazard ratio (HR) obtained using a weighted Cox regression analysis with a robust sandwich estimator for calculation of standard errors. Noninferiority margins for PFS and OS were identified from a targeted literature review as HRs of 1.333 and 1.298, respectively.(144) Results that did not achieve superiority or inferiority and did not qualify per the noninferiority criteria were treated as inconclusive.((8)(p.4))

Detailed descriptions of statistical methods can be found in Appendix F Comparative analysis of efficacy and safety.

Results from the comparative analysis

The baseline characteristics for efficacy analyses before and after matching DVTd and VTd to VRd are summarized in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety, Table 108. Before matching, the baseline characteristics of age, sex, myeloma subtype and ISS stage were similar for patients treated with DVTd, VTd and VRd. Consequently, there were no marked reductions in the ESS after matching. In the model, ESS was reduced from the original sample size by 2.5% for DVTd and 5.0% for VTd.((8)(p.4)) PFS & OS KM curves for DVTd/VTd before and after adjustment vs. VRd can be found in Appendix F Comparative analysis of efficacy and safety, Figure 33, Figure 34, Figure 35, and Figure 36.

For DVTd vs. VRd, the results for the naïve (before matching, median follow-up of 29.2 months), base case (after matching, median follow-up of 29.2 months) and sensitivity analysis (after matching, median follow-up of 18.8 months) are presented in Appendix F Comparative analysis of efficacy and safety, Table 106. For DVTd vs. VRd with a median follow-up of 29.2 months for CASSIOPEIA, PFS and OS were statistically significantly different for DVTd before [PFS HR: 0.50 (95%CI: 0.38-0.67) and OS HR: 0.39 (95%CI: 0.24-0.62)] and after matching [PFS HR: 0.50 (95%CI: 0.38-0.67) and OS HR: 0.40 (95%CI: 0.25-0.64)] in the analysis. Adjustment in the analysis had little to no impact on PFS and OS. The results after matching are used in the base case for the cost-effectiveness model.

For VTd vs. VRd, the results are presented in Appendix F Comparative analysis of efficacy and safety, Table 107. For VTd vs. VRd with a median follow-up of 29.2 months for CASSIOPEIA, there was no statistically significant difference in PFS and OS before [PFS HR: 0.99 (95%CI: 0.78-1.26) and OS HR: 0.72 (95%CI: 0.48-1.07)] and after matching [PFS HR: 1.04 (95%CI: 0.82-1.32) and OS HR: 0.78 (95%CI: 0.53-1.16)] in the analysis. Adjustment shifted the PFS and OS point estimates slightly towards the null value and in favor of VRd.

Discussion and limitations

A MAIC analysis was used to compare outcomes from the CASSIOPEIA trial with VRd induction regimen from the IFM 2009 trial among transplant-eligible patients with NDMM. The Phase III PETHEMA/GEM2012 study also evaluated VRd in this patient population [22] (149), but did not include detailed information on PFS and OS to enable a comparison here. The Phase II GRIFFIN trial evaluated daratumumab in combination with VRd (D-VRd) versus VRd induction as front-line therapy for MM(150), but was not powered for PFS for inclusion here.((8)(p.8))

MAIC methodology has been used within oncology and other therapeutic areas to compare treatment effects across trials, as it allows for adjustment of population differences among studies(130, 138, 146) and can aid clinical decision making for choosing the optimal treatment regimen. Using an unanchored MAIC, patient population differences were adjusted via weighting to compare PFS and OS across different studies. After matching adjustment, there were no marked reductions in the ESS after matching, in ESS from the original sample size, all baseline characteristics were balanced between studies in analysis.((8)(p.8))

In this MAIC analysis, PFS and OS were significantly in favor of DVTd compared with VRd in transplant-eligible patients with NDMM. Conversely, comparisons of the VTd treatment arm in CASSIOPEIA with VRd did not show statistically significant differences in PFS or OS before or after matching.((8)(p.8))

The OS data should be interpreted with the caveat that CASSIOPEIA is ongoing, so the follow-up period (18.8 months for the 1st data-cut and 28.2 months for the 2nd data-cut) is shorter versus the comparator trial (IFM 2009, 43 months), and median OS has not yet been reached in either treatment arm (DVTd and VTd) in CASSIOPEIA. The extent of bias caused by different median follow-up times is difficult to predict, given that OS data can be confounded by subsequent therapies and evolving therapeutic options in relapsed MM.((8)(p.9))

There were several limitations to this MAIC analysis. Although MAIC effectively adjusts for baseline variables when individual patient data from only one study are available, it effectively assumes that absolute outcomes can be predicted from baseline variables.(130) Additionally, information bias does exist when individual patient data are recreated based on Kaplan–Meier curves, because the true censor is not known. The different lengths of follow-up among the studies may also contribute to information bias. There is the likely possibility for residual bias from unaccounted prognostic factors or effect modifiers, differences in study designs and inclusion criteria (and thus differences in patient, treatment and disease characteristics), and differences in postinduction therapy treatments and maintenance regimens (e.g., lenalidomide vs daratumumab, and limited, as well as differing, durations of maintenance therapies in the different trials). Different length and cycle number of induction therapies may add additional bias to the analyses. Comparing the effect of induction therapies alone using MAIC methodology is challenging, since PFS and OS are influenced by differences in consolidation and maintenance strategies, and it was not feasible to adjust for differences in treatment schema (e.g., receipt of a second ASCT in the IFM 2009 trial). Consequently, the analysis reflects a comparison of the overall treatment schema of the studies rather than a comparison of the induction therapies alone. It should also be noted that the CASSIOPEIA trial began in 2015, whereas the IFM 2009 trial were initiated in 2010. Changes in clinical practice and management of patients with NDMM over time may have influenced efficacy outcomes, and availability of newer options may have led to biased longevity. However, improved PFS and OS with DVTd, but not VTd, with VRd suggests that inclusion of daratumumab in the regimen, rather than advances in patient care, contributed to this effect.((8)(p.9))

7.3.3.2 Safety

Safety data was examined based on the same study used to document the efficacy of both the intervention (CASSIOPEIA) and the comparator (IFM 2009) according with the method guidelines. Another study that is available is the PETHEMA GEM2012 trial, which was designed to compare two transplant conditioning regimens (IV busulfan + melphalan vs melphalan) in 458 patients in total who received six 28-day cycles of VRD induction (and 397 patients receiving additional two cycles of VRd consolidation).

TEAEs for DVTd is primarily reported during induction/ASCT/consolidation treatment phase in the CASSIOPEIA study. However, certain TEAE data during induction for DVTd is reported in the EPAR.(4) TEAEs published for VRd in the PHETEMA GEM2012 study is reported during induction and separately during consolidation treatment phase for most common TEAEs based on the publication from Rosiñol et. al 2019(149) reporting grouped response analysis of induction, transplant, and consolidation (referred to as GEM2012 publication in this section). In the EPAR for VRd (assessment of VRd in the transplant ineligible setting) safety data from both IFM 2009 and PETHEMA GEM2012 are reported.(151) AEs were collected during initial treatment (6 cycles; 24 weeks) and did not include ASCT or consolidation in the reporting of AEs. Furthermore, both arms were combined for safety reporting in the EPAR of VRd and the GEM2012 publication, in which, conditioning regimen with IV busulfan + melphalan is not considered comparable to Danish clinical practice, where conditioning regimen with only melphalan is used.

The Medicines Council guidelines states that in cases where there is data from a safety population that is significantly larger than the one included in the studies of clinical effect, then this data should be used instead((152)(p.17)). The safety population in PETHEMA GEM2012 is not assessed to be significantly larger than IFM 2009, and taking above factors into account, the results from PETHEMA GEM2012 study have not been used as it is not comparable with the CASSIOPEIA trial.

Safety data from IFM 2009 trial has been included in a naïve comparison but differences exists in method and detail of reporting. The IFM 2009 trial was designed to compare induction therapy with three cycles of VRd and then consolidation therapy with either five additional cycles of VRd (Arm A) or high-dose melphalan plus stem-cell transplantation followed by two additional cycles of VRd (Arm B) including a total of 700. Patients in both groups received maintenance therapy with lenalidomide for 1 year.

The IFM 2009 publication by Attal et al. 2017 (123), reported AEs most likely representing AEs collected throughout the whole study including the maintenance phase, which is not comparable to the DVTd-arm where TEAEs are reported after induction/ASCT/consolidation. Based on the EPAR of VRd, TEAEs are available for the nontransplant group (Arm A) only, and hence not directly comparable to the DVTd arm. Despite these limitations and the fact that the naïve comparison should be interpreted with caution, TEAEs/AEs from Attal et al. 2017 (IFM 2009 publication) and data from the EPAR of VRd are summarized below in Table 24 below.

TEAEs from the EPAR of VRd for the nontransplant group (Arm A) and AEs from IFM 2009 publication (Arm B) are reported in Table 24, including TEAEs for the DVTd arm from the CASSIOPEIA study. Based on the IFM 2009 publication, only Grade 3/4 AEs are available with 97.1% in the VRd ASCT arm (most likely including AEs collected during maintenance phase), with 86.0% Grade 3/4 AEs reported in EPAR of VRd for VRd nontransplant arm (Arm A), and 80.6% Grade 3/4 AEs events reported for the DVTd arm during induction/ASCT/consolidation. Based on maximum severity, DVTd reported 41.0% Grade 3 TEAE and 17.4% Grade 4 TEAE during induction.(4) For any Grade TEAE, 99.4% was reported for VRd nontransplant arm and 99.8% in the DVTd arm during induction/ASCT/consolidation, and 98.9% during induction. Serious TEAEs was lower in the VRd nontransplant arm, with 30.3% reported versus 46.8% in the DVTd arm for induction/ASCT/consolidation, and 33.6% during induction. However, importantly AEs were collected during induction phase in the VRd nontransplant arm based on EPAR of VRd and differences in the definition and reporting of serious TEAE may exist. TEAEs leading to discontinuation was lower in the DVTd arm with 7.5% during induction/ASCT/consolidation and 5.2% for induction versus 8.4% in the VRd nontransplant arm.

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Table 24: Summary of naïve safety comparison between DVTd and VRd

	DVTd (n=536) (4) Induction/ASCT/consolidation	DVTd (536) (4) Induction	VRd (n=356) (151) IFM 2009 EPAR Arm A[a]	VRd (n=350) (123) IFM 2009 publication Arm B
Any TEAE, n (%)	535 (99.8%)	530 (98.9%)	354 (99.4%)	NA
Grade 3/4 TEAE, n (%)	432 (80.6%)	NA	306 (86.0%)	340 (97.1%)[b]
Grade 3 TEAE[c]	*287 (53.5%)*	220 (41.0%)	NA	NA
Grade 4 TEAE[c]	*144 (26.9%)*	93 (17.4%)	NA	NA
Serious TEAE, n (%)	251 (46.8%)	180 (33.6%)	108 (30.3%)	NA
TEAE leading to discontinuation, n (%)	40 (7.5%)	28 (5.2%)	30 (8.4%)	NA
TEAEs leading to death, n (%)	1 (0.2%)	NA	1 (0.3%)	NA

Abbreviations: ASCT = autologous stem cell transplant; VRd= bortezomib, lenalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; TEAE = treatment-emergent adverse event.
[a] TEAEs in the 8 cycles (24 weeks) of initial VRd therapy for Arm A in the IFM 2009 study are referred to as "initial treatment" in EPAR of Revlimid.
[b]Grade 3 and 4 Adverse Events That Occurred in At Least 2% of Patients (IFM 2009 publication).
[c] Maximum severity of any TEAE.
Note: During transplant period, according to protocol, only limited AE were collected in the CASSIOPEIA trial.

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8. Health economic analysis

An economic model was developed in Microsoft Excel® to assess the cost-effectiveness of DVTd versus VTd, VCd, and VRd for the treatment of patients with NDMM who are eligible for ASCT. 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.

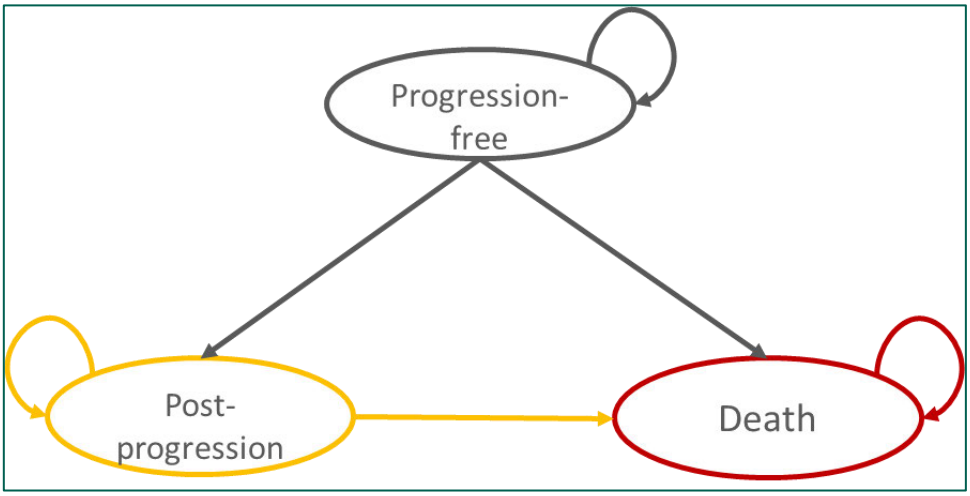
8.1 Model

A three-health state transition cohort model was chosen to follow patients from an initial line of treatment after diagnosis into later lines and until death. The three health states modelled were progression-free (induction, ASCT, consolidation and maintenance), post-progression (second line and beyond) and death.

The key efficacy inputs in the model are OS, PFS and treatment duration. The CASSIOPEIA trial was used to derive clinical data for DVTd and VTd,(6) as patient-level data were available.

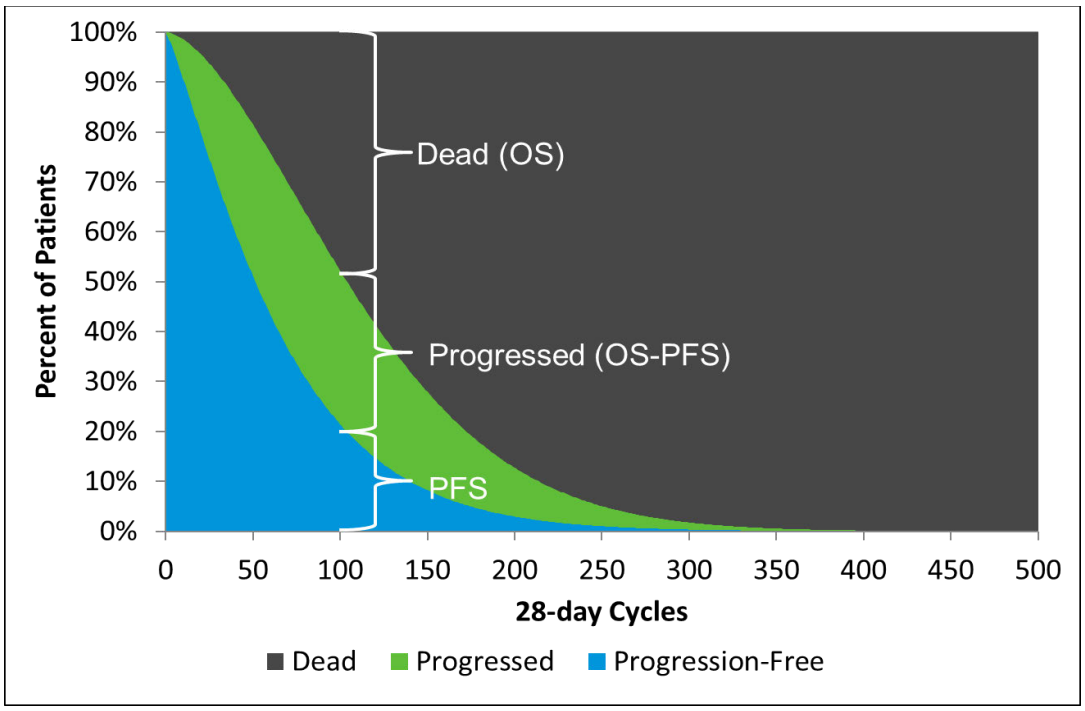
Figure 12 illustrates the three health states used to model patients' survival outcomes over the time horizon: progression-free, post-progression and death. This structure was implemented through a partitioned survival model (PSM) approach,(153) which was based on the use of independent PFS and OS curves.

Figure 12. Model Structure



The 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 13). In the PSM, the efficacy of treatment with respect to PFS does not directly impact OS (PFS and OS are independent).

Figure 13. Partitioned Survival Approach



Abbreviations: OS = overall survival; PFS = progression-free survival

For the adequate modelling of treatment-related costs, it was necessary to keep track of treatment status for different treatment phases in both the progression-free and post-progression health states.

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

Patients with NDMM who are eligible for ASCT enter the model and receive induction treatment. Following induction treatment, patients who are progression-free receive ASCT, consolidation and maintenance treatment; patients who experience non-fatal progression during the induction do not receive ASCT. Patients who experience non-fatal disease progression at any time (i.e., during induction, ASCT, consolidation or maintenance treatment) move to the post-progression health state in which they switch to a subsequent line of treatment. Patients may discontinue treatment or die at any time in the model.

Costs and utilities were assigned depending on the patient's health state (i.e., progression-free and post-progression); however, the utility values for patients who are in the progression-free health state also depend on the treatment phase (i.e., induction, ASCT, consolidation or maintenance). Costs and utilities are accrued and summarized for each cycle of

the model (four weeks) so that the difference in cumulative cost and utilities can be analyzed and compared between comparators.

8.1.1 Modelling Approach to Track Progression and Death

8.1.1.1 Progression-free

The PFS curve for each induction treatment is assumed to track the proportion of patients in the progression-free health state covering the induction, ASCT, consolidation and maintenance treatment phases. The impact of ASCT (or the lack of it) on progression was assumed to be implicit in the PFS curve. Similarly, the effect of consolidation and maintenance treatment administered in the clinical trials was assumed to be captured in the PFS curve associated with each induction regimen.

While progression-free, patients could stop receiving treatments based on the specified treatment duration and stop accruing treatment-related costs; patients will not switch to second-line treatment unless they progress.

8.1.1.2 Post-progression

Following a non-fatal progression event during any treatment phase (i.e., induction, ASCT, consolidation or maintenance), patients will switch to receive a second-line treatment. If a non-fatal progression event occurs while patients are on second-line treatment, then patients switch to receive a third-line treatment. PFS curves for second-line are not modelled by specific treatment; instead an aggregated PFS curve was used to derive the transitions from progression-free to post-progression health states during second-line. To derive the aggregated PFS curve for second-line treatment, first a weighted average of the median PFS of the second-line treatments was derived by weighting the individual median PFS of each second-line treatment option by its corresponding market share. Then, the weighted average of the median PFS was used to derive an exponential curve that was used in the model to drive the transitions to progression during second-line.

Once patients experience progression while receiving second-line treatment, they can receive a third-line treatment. However, unlike with second-line treatment, progression is not explicitly modelled for third-line treatment, since no additional lines of treatment are modelled (i.e., fourth and subsequent); therefore, only treatment costs are accrued while the patient is receiving third-line treatment based on the duration for this line of treatment.

8.1.1.3 Overall Survival

A single OS curve was used to model mortality for patients starting on each induction treatment, i.e. determining the proportion of patients dying over the time horizon. The impact of ASCT (or the lack of it) on survival was assumed to be implicit in the OS curve. The effect of consolidation, maintenance and subsequent lines of treatment (i.e., second- and third-line treatment) on survival was assumed to be captured by the same OS curve.

A background mortality curve was also included in the model to represent the mortality of the general Danish population.(154) This background mortality is used as a cap on the survival estimates coming from the trial data, to avoid patients with NDMM who are eligible for ASCT and are receiving treatment having lower rates of death than the general population.

8.1.1.4 Treatment Duration

For the induction and consolidation regimens, the treatment duration was captured explicitly according to each regimen's clinical protocol, and it was used to determine the timing of transitions between treatment phases. In addition to the treatment duration per clinical protocol, the model utilizes the median treatment duration reported in clinical trials to accrue the treatment-related costs during each treatment phase. The median treatment duration is used to derive an exponential curve that was used in the model to drive the treatment discontinuation.

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For maintenance and subsequent treatment after progression, the model offers two options to model treatment duration: a median treatment duration can be used, in which case the treatment costs are accrued based on a time-to-treatment-discontinuation (TTD) curve generated by the median duration of each treatment, assuming an exponential distribution; or the treatment duration can be set as treat-to-progression, in which case patients will remain on treatment until they progress and treatment costs are accrued as long as patients are progression-free.

8.1.1.5 Including the Impact of Maintenance for PFS and OS Projections

The use of the available data from CASSIOPEIA, including the data observed during the maintenance phase, is not expected to impact the difference in survival between the induction treatment arms (i.e., DVTd and VTd) given the similar treatment experience in maintenance for both induction arms. That is, the proportion of patients going on to maintenance and what patients receive in maintenance is similar, because of the second randomization that occurs before the start of maintenance: 84.3% in the DVTd arm and 79% in the VTd arm underwent second randomization. Patients who underwent second randomization were then exposed to the maintenance treatments in the same proportion (50% daratumumab monotherapy and 50% observation). This means that the OS and PFS results observed in CASSIOPEIA for both induction treatments are not biased by the treatments that patients received during the maintenance phase, and that the OS and PFS benefit/difference observed for DVTd vs. VTd may be attributed to the benefit from the induction and consolidation treatment.

Based on the MAICs comparing a treatment pathway or sequence of regimens during induction, consolidation and maintenance, there were no significant differences in OS and PFS between the treatment pathway in CASSIOPEIA that started with VTd as induction and consolidation treatment, and other treatment pathways that initiated with VCd (GMMG-MM5 trial) and VRd (IFM 2009 trial). In addition, there are no significant differences in OS and PFS between the different induction treatments, after which daratumumab monotherapy, lenalidomide or observation were administered during maintenance. This suggests that which maintenance is received does not impact OS and PFS estimates.

For OS, it is possible to compare outcomes from CASSIOPEIA with OS from trials with lenalidomide-only maintenance to assess the impact of differential maintenance on OS. In the VCd trial (GMMG-MM5), patients received up to two years of lenalidomide maintenance. Patients in this trial had very similar patient characteristics compared with CASSIOPEIA (with the exception of LDH).

In addition, there is good evidence to suggest the treatments received in maintenance have a limited impact on PFS. Assessment of the HRs for DVTd vs. VTd adjusting for maintenance results in very similar HRs, suggesting a limited impact of maintenance on PFS outcomes (Table 25).

Table 25. Results for PFS IPW Analysis Adjusting for Maintenance

IPW Analysis (1st data-cut)	
Hazard ratio (95% CI)	0.47 (0.33, 0.67)
Analysis Without Adjustment for Second Randomization (1st data-cut)	
Hazard ratio (95% CI)	0.47 (0.33, 0.67)
IPW Analysis (2nd data-cut)	
Hazard ratio (95% CI)	[redacted]
Analysis Without Adjustment for Second Randomization (2nd data-cut)	
Hazard ratio (95% CI)	0.495 (0.378, 0.647)

Abbreviations: CI = confidence interval; IPW = inverse probability weighting; PFS = Progression-free survival.

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8.1.2 Model Outcome Measures

The model aggregates the health outcomes and costs from each health state and reports the following outcomes:

- LYs, stratified by induction/ASCT/consolidation, maintenance and subsequent treatments (second- and third line)
- QALYs, stratified by induction/ASCT/consolidation, maintenance and subsequent treatments
- Disutility associated with AEs
- Induction and consolidation, second- and third-line drug acquisition, administration, ASCT costs, medical resource costs, AE management costs (for induction and consolidation treatment regimens only) and terminal care costs
- ICERs: cost per QALY 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.(155)

The base case analysis was conducted from a restricted societal perspective. A 40-year time horizon was used in the base case analysis, reflecting lifetime for patients in the target population. This time horizon was considered appropriate to capture the long-term clinical and economic consequences of MM for patients who are eligible for ASCT, an incurable disease requiring treatment until the end of life where multiple lines of treatment are administered in most cases.

All costs and health outcomes were discounted at a rate of 3.5% per year in the base case analysis for year 1-35. 2.5% were applied for year 36-40 based on the discount rates from the Danish Ministry of Finance.(152, 156).

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 26 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 26 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)	The results for the OS are presented in section 19.1.1. The OS from CASSIOPEIA shows a clear, increasing separation between patients receiving DVTd vs. VTd as induction and consolidation treatment.	For DVTd and VTd; Joint Weibull distribution with treatment as predictor (CASSIOPEIA) presented in section 19.1.1.1. For VCd and VRd; HR vs. VTd (CASSIOPEIA) from MAIC base case (Table 7).	Refer to section 19.1 and section 19.1.2 to see how the OS curve has been modeled.

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Progression-free survival (PFS)	The results for the PFS are presented in section 19.2.1. The PFS from CASSIOPEIA shows a clear increasing separation between patients receiving DVTd versus VTd as induction and consolidation treatment.	For DVTd and VTd; Joint Weibull distribution with treatment as predictor (CASSIOPEIA) presented in section 19.2.1.1. For VCd and VRd HR vs. VTd (CASSIOPEIA) from MAIC base case (Table 7) For second line and third line treatments the PFS are presented in Table 173 and Table 174	Refer to section 19.2 to see how the PFS curve has been modeled. Second and Third line PFS was collected from clinical trials.
Treatment duration	Results are presented in 19.3. Observed TTD from CASSIOPEIA. Median treatment duration for VCd and VRd. For second line and third line treatments the median treatment duration is presented in Table 173 and Table 174	For DVTd and VTd; Observed TTD (CASSIOPEIA) (Table 136 and Table 137). For VCd and VRd; Median treatment duration (Table 135) For second line and third line treatments the median treatment duration is presented in Table 173 and Table 174. Median treatment duration is used in the base case.	Refer to section 8.3.1.1 to see how treatment duration was modeled. Second and Third line PFS was collected from clinical trials.
Adverse Events	Refer to section 8.4.3 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 35 the disutilities.	Based on reported AEs from clinical trials and disutilities primarily based on previous NICE evaluations
Utilities			
Induction	0.752	0.752	The utility values were derived from an analysis of EuroQoL Five-Dimension Five-Level (EQ-5D-5L) data from the CASSIOPEIA trial. Danish population weights applied to estimate health-state utility values (refer to Appendix J Utility Data Analysis)
ASCT*	0.752	0.752	
Consolidation	0.810	0.810	
Maintenance	0.835	0.835	
Post-Progression	0.784	0.784	

Abbreviations: AE = adverse event; EQ-5D-5L = EuroQoL Five-Dimension Five-Level; TTD = time-to-treatment-discontinuation; ASCT = autologous stem cell transplant; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; MAIC = Matching-Adjusted Indirect Comparison; HR = Hazard ratio; OS = Overall survival; PFS = Progression-free survival.
*Assumed same as induction

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

8.2.2.1 Patient population

The Danish patient population:

The target population of DVTd are patients with documented NDMM who are eligible for ASCT. Refer to section 5 for a description of the Danish population. 120 Danish patients are estimated to be eligible for ASCT annually whereas only a certain proportion of the total population are expected to be treated with DVTd.

Patient population in the clinical documentation submitted:
The recruited patients were with newly diagnosed multiple myeloma at 111 European sites. The ITT population were patients with documented NDMM who were eligible for high-dose chemotherapy with ASCT. The mean age at baseline was 56.6 years.(6)

Patient population in the health economic analysis submitted:
The patient population characteristics are based of the CASSIOPEIA trial, described above. Relevant patient characteristics for the model are presented in Table 27.

Table 27 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	56.6 CASSIOPEIA Clinical Study Report(7)	56.6 CASSIOPEIA Clinical Study Report(7)	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	75.67 CASSIOPEIA Clinical Study Report(7)	75.67 CASSIOPEIA Clinical Study Report(7)	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	1.88 CASSIOPEIA Clinical Study Report(7)	1.88 CASSIOPEIA Clinical Study Report(7)	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

Intervention in the clinical documentation submitted:
One clinical trial for DVTd regarding the relevant indication are used as clinical documentation, CASSIOPEIA Clinical Study Report(7). Patients were randomly assigned (1:1) to receive four pre-transplant induction cycles and two post-transplant consolidation cycles of VTd alone (VTd group) or in combination with daratumumab (DVTd group). The submitted clinical documentation have previously been described in detail, refer to section 5.3.

Intervention as in the health economic analysis submitted:
Inputs regarding DVTd in the model are informed by the clinical trial CASSIOPEIA (Table 27). The intervention is described below in Table 28.

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Table 28 Intervention

Intervention: DVTd	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology	CASSIOPEIA Clinical Study Report(7), EMA SmPC Darzalex(1), refer to Appendix O – The patient population, the intervention and choice of comparators(s), Table 168.	Same as in clinical documentation	Expected to be similar in Danish clinical practice
Length of treatment		Same as in clinical documentation. Fixed treatment duration according to dosing schedule.	Expected to be similar in Danish clinical practice
Criteria for discontinuation	CASSIOPEIA Clinical Study Report(7), EMA SmPC Darzalex (1), Refer to section 5.3	Patients are assumed to discontinue treatment and switch to second-line treatment only when progression occurs	Expected to be similar in Danish clinical practice
Position in Danish clinical practice		First-line induction and consolidation	First-line induction and potentially consolidation

Abbreviations: EMA = European Medicines Agency; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; SmPC = Summary of Product Characteristics

8.2.2.3 Comparators

The current Danish clinical practice (as described in 5):

In current Danish clinical practice, VCd and VRd are recommended as first line treatments (refer to section 5.2.1 Table 4) and VTd is an option. The same patient population are relevant for treatment, and VTd, VCd and VRd are considered relevant treatment options.

Comparators in the clinical documentation submitted:

The comparators presented in the clinical documentation submitted are CASSIOPEIA (DVTd and VTd), GMMG-MM5 (VCd), and IFM 2009 (VRd) trials. Refer to section 7.2 and 7.3 where these clinical trials has been described as well as related appendences.

Comparators in the health economic analysis submitted:

The different comparators included in the model are VTd, VCd and VRd , which is in line with treatment options in Danish clinical practice. The clinical inputs are mainly collected from the clinical trials CASSIOPEIA (DVTd and VTd), GMMG-MM5 (VCd), and IFM 2009 (VRd).

Table 29 Comparators

Comparator		Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)
VTd	Posology			

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	Length of treatment	CASSIOPEIA Clinical Study Report(7), EMA SmPC Darzalex(1), refer to Appendix O – The patient population, the intervention and choice of comparators(s), Table 168.	Same as in clinical documentation	Expected to be similar in Danish clinical practice
	The comparator's position in the Danish clinical practice	First-line treatment	First-line treatment	Expected to be similar in Danish clinical practice
VCd	Posology	GMMG-MM5(139, 140), refer to Appendix O – The patient population, the intervention and choice of comparators(s), Table 168.	Same as in clinical documentation	Expected to be similar in Danish clinical practice
	Length of treatment			
	The comparator's position in the Danish clinical practice	First-line treatment	First-line treatment	First-line treatment as described by the Medicines Council.
VRd	Posology	IFM 2009(123), refer to Appendix O – The patient population, the intervention and choice of comparators(s), Table 168.	Same as in clinical documentation	Expected to be similar in Danish clinical practice
	Length of treatment			
	The comparator's position in the Danish clinical practice	First-line treatment	First-line treatment	First-line treatment as described by the Medicines Council.

Abbreviations: EMA = European Medicines Agency; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; SmPC = Summary of Product Characteristics

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes in the submitted clinical documentation:
The relative efficacy outcomes are summarized in section 7 (Table 7). A head to head trial is available for DVTd vs. VTd(12) and efficacy results for DVTd/VTd compared to VCd and VRd have been estimated via indirect comparisons. Efficacy results for the included trials were OS, PFS and TTD.

Relevance of the documentation for Danish clinical practice:
The clinical documentation are relevant to the Danish population as it presents efficacy results for the proposed treatment in Denmark using relevant efficacy measures (refer to section 5.1, Effect on MM and relevance of endpoints).

The relative efficacy outcomes in the submitted health economic analysis:

The key efficacy inputs in the model are OS, PFS and treatment duration. These are derived from a direct comparison (DVTd vs VCd) and via indirect comparison (VCd and VRd) (refer to section 7, Table 7 for a summary of the results). The economic analysis uses the modelled efficacy results presented in section 19.1, 19.2, 8.3.1.1.

Table 30 Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Overall survival (OS)	CASSIOPEIA Clinical Study Report(5)	Extrapolations of OS (2nd data-cut), refer to Section 19.1
Progression-free survival (PFS)	CASSIOPEIA Clinical Study Report(5)	Extrapolations of PFS (2nd data-cut), refer to Section 19.2
Time-to-treatment-discontinuation (TTD)	CASSIOPEIA Clinical Study Report(5)	For information of how TTD (2nd data-cut) has been modelled, refer to Section 8.3.1.1.

Table 31 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
Overall survival (OS)	Kaplan Meier curves	Very relevant	Very relevant
Progression-free survival (PFS)	Kaplan Meier curves	Very relevant, refer section 5.1, Effect on MM and relevance of endpoints	Very relevant
Time-to-treatment-discontinuation	Median duration per trial	Relevant	Relevant

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 CASSIOPEIA and GMMG-MM5. For more details of the adverse events refer to section 8.4.3 and 8.5.4.

Adverse reaction outcomes in the health economic analysis submitted:

Additional information on AEs can be found in section 7.1.2.2 (DVTd and VTd), 7.2.3.2 (VCd), 7.3.3.2 (VRd).

Table 32 presents the cumulative probabilities of grade 3-4 AEs occurrence during the treatment period which are used in the cost-effectiveness model. The AE probabilities used in the model are the same as reported in the clinical trials. For CASSIOPEIA (DVTd and VTd), Grade 3/4 AEs reported during induction/ASCT/Consolidation was used in the model. The GMMG-MM5 study (VCd) reported AEs only in the induction phase.(139, 140) Therefore, only AEs occurring in the induction phase were included for VCd, which is a conservative approach favoring the comparator. The IFM 2009 study did not report AE occurrence stratified by treatment phases.(123) Therefore, probabilities of AE occurrence for VRd

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were assumed to be 0%, also conservative. Additional information on AEs can be found in section 7.1.2.2 (DVTd and VTd), 7.2.3.2 (VCd), 7.3.3.2 (VRd).

Table 32. Cumulative Probability of AEs

AE	DVTd During Induction/ASCT/ Consolidation	VTd During Induction/ASCT/ Consolidation	VCd During induction
Neutropenia	27.60%	14.70%	35.20%*
Lymphopenia	17.00%	9.70%	0.00%
Thrombocytopenia	11.00%	7.40%	4.00%
Febrile neutropenia	6.70%	5.20%	0.00%
Stomatitis	12.70%	16.40%	0.00%
Peripheral sensory neuropathy	8.80%	8.60%	0.00%
Clinical documentation	CASSIOPEIA(6, 12)	CASSIOPEIA(6, 12)	GMMG-MM5(121)
Used in model	Yes	Yes	Yes

Abbreviations: AE = adverse event; ASCT = autologous stem cell transplant; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone
CASSIOPEIA: Most Common (at least 5%) Grade 3 or 4 Treatment-emergent Adverse Events During Induction/ASCT/Consolidation Phase
GMMG-MM5: AEs during VCd induction therapy. Reported in publication as "Any AE" defined as: 'Any AE' included all AE CTCAE grade ⩾ 3 or ⩾ 2 for infections, cardiac disorders, neuropathy and thromboembolic events. Events with a lower CTCAE grade were not considered. Grade ⩾3 gastrointestinal disorders was 6.4% in the study for VCd but was excluded in the above overview serving as a conservative approach as well as Anemia (6.8%).
*Leukocytopenia/neutropenia
IFM 2009 data available from VRd EPAR (EPAR for VRd transplant ineligible indication): Grade 3 or 4 TEAEs Reported in at Least 5% of Subjects in Any Treatment Arm – Initial Treatment. 8 cycles (24 weeks) of initial VRd therapy in the IFM 2009 study are referred to as "initial treatment.". Neutropenia: 44.7%; Thrombocytopenia: 18.5%; Febrile neutropenia: 3.4%; Peripheral sensory neuropathy: 5.1%; Anemia: 7.6%; Leukopenia: 35.7% (151)

8.3 Extrapolation of relative efficacy

The key efficacy inputs in the model are OS, PFS and treatment duration. The CASSIOPEIA trial was used to derive clinical data for DVTd and VTd, as patient-level data were available. 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.(157) These are the exponential distribution, the Weibull and Gompertz distributions, the log-logistic and log-normal distributions and the generalized gamma distribution. Following considerations based on e.g. observed data regarding goodness-of-fit and plausibility of results the "best-fitting" distribution was selected for the base case analysis (refer to Appendix G – Extrapolation, section 19.1 and 19.2).(157, 158)

8.3.1 Time to event data – summarized:

The full method used and results are provided in Appendix G – Extrapolation where OS (section 19.1) and PFS (section 19.2) are presented. Treatment duration is described in section 8.3.1.1 below.

For OS and PFS, joint parametric distributions with treatment as predictor are used in the base case analysis. The base case for modelling of OS and PFS for DVTd and VTd are using a joint Weibull distribution with treatment as predictor. To model OS and PFS for comparators other than DVTd and VTd, the HRs from the MAICs vs. VTd from CASSIOPEIA are applied (i.e., using VTd as the reference treatment as this approach benefits from the greater number of events in the VTd arm compared with DVTd).

8.3.1.1 Treatment Duration

Treatment duration is a key driver of costs, and thus cost-effectiveness. In the model, stopping treatment affects only cost-outcomes and not efficacy-outcomes, which are determined by PFS/OS.

8.3.1.1.1 Treatment Duration During Induction and Consolidation

Induction and consolidation treatment costs are accrued according to the predicted duration of induction and consolidation treatment based on TTD. For DVTd and VTd, it is possible to select whether to use the median treatment duration from CASSIOPEIA or the actual observed percentage of patients who continued receiving treatment over time from the trial (i.e., the observed TTD). When using the median treatment duration, the TTD curve is modelled based on the median treatment duration of the induction and consolidation treatments (refer to Appendix G – Extrapolation, section 19.3, Table 135). In this approach, the TTD curves are exponential (i.e., assuming a constant rate of treatment discontinuation) and match the median treatment duration reported in the corresponding trials (using the equation below).

$$Weekly\ treatment\ discontinuation\ rate = \frac{-\ln(0.5)}{median\ treatment\ duration\ (in\ weeks)}$$

The model calculations ensure that, irrespective of the approach selected to model TTD, the TTD curve is never above the PFS curve; patients are assumed to discontinue their current treatment when progression occurs and they switch to the next line of treatment. Discontinuing treatment does not mean that patients switch to second-line treatment. Patients switch from first- to second-line treatment only when disease progression occurs, based on PFS.

In addition, induction and consolidation treatments have a fixed duration per the clinical trial protocols (i.e., the duration of the induction and consolidation phases in the clinical trials), which also caps the TTD for each treatment, irrespective of the approach selected to model TTD.

8.3.1.1.2 Observed TTD – DVTd and VTd

Instead of using the median treatment duration, TTD for DVTd and VTd can be modelled based on the observed percentage of patients who continued receiving treatment over time during induction and consolidation in CASSIOPEIA (i.e., the observed TTD).(12) The observed TTD for DVTd and VTd are shown in Appendix G – Extrapolation, section 19.3, Table 136 and Table 137 for induction and consolidation treatment phases, respectively. When the observed TTD is used, the proportion of patients who remain on treatment is given directly by the observed data in (Table 136 and Table 137). In the base case analysis, observed TTD is used for DVTd and VTd since this is available, while the median treatment duration is used for the VCd and VRd as data on actual TTD in respective trial is not published. The impact of using the median treatment duration for DVTd and VTd instead of observed TTD are shown in scenario analysis. The advantage of using the median treatment duration for DVTd and VTd is the comparability with the other comparators, where the median treatment duration reported from their respective clinical trial is used (VCd and VRd).

8.3.1.1.3 Treatment Duration during Maintenance

Maintenance treatment costs are accrued according to the predicted duration of maintenance treatment based on one of two approaches.

- **Median treatment duration**: In this approach (used in the base case for lenalidomide maintenance treatment), the TTD curves are exponential (i.e., with a constant rate of treatment discontinuation). This approach is not available for observation in maintenance, as patients on observation are not receiving treatment.
- **Treat to Progression**: In this approach, treatment discontinuation is not modelled for maintenance treatment. The duration of treatment is determined by the PFS assigned from the beginning of the model according to the treatment that patients received at the start of the induction phase.

Irrespective of the approach selected to model TTD for maintenance treatment, the TTD curve is never above the PFS curve; patients are assumed to discontinue treatment and switch to second-line treatment only when progression occurs. The maintenance treatment accounted for in the economic model are presented in Table 33.

Table 33. Maintenance comparators

	Approach selection	Median duration (weeks)
Lenalidomide	Median duration	110.37(159)
Observation	Treat to progression	-

Note: NICE evaluation, p. 112 in PDF. 25.4 months stated and converted to 110.37 weeks.

8.3.1.1.4 Second-line TTD and PFS

Second-line treatment duration is required for costing purposes. For all second-line treatment comparators, a TTD curve is assigned to each comparator according to the following options.

- **Median duration per trial:** In this approach (used in the base case analysis), the TTD curves are exponential (i.e., with a constant rate of treatment discontinuation)
- **Treat to progression:** Using the median PFS for second-line treatments

The median treatment duration for each second-line treatment (refer to Appendix P Health economic analysis – model input, Table 173) is used to calculate the costs of second-line therapies for the duration the treatment is given. The median treatment duration of each second-line treatment is used to model a TTD curve assuming an exponential distribution, to calculate the proportion of patients who stop receiving treatment over time and stop accruing treatment-related costs. As with the induction, consolidation and maintenance treatments, being off second-line treatment does not mean that patients switch to third-line treatment. Patients switch from second-line to third-line only after disease progression occurs, based on the median PFS of the second-line treatment options (refer to Appendix P Health economic analysis – model input, Table 173).

Using the median duration reported in clinical trials may underestimate the true TTD due to censoring.(160) This is especially true for fixed-duration treatments, however, most second-line treatments in Danish clinical practice are not fixed-duration treatments. As an alternative option, it is possible to assume that second-line treatments are treat-to-progression, and the median treatment duration for each second-line treatment is assumed to be the same as its median PFS (Appendix P Health economic analysis – model input, Table 173) to model the TTD curve assuming an exponential distribution.

For second-line treatments, the incidence of progression in each model cycle is calculated to track patients switching to receive third-line treatment. PFS curves are not modelled for each second-line treatment. Instead, an aggregated PFS curve is derived to calculate the number of patients who remain progression-free over time and who would not switch to third-line treatment. To derive the aggregated PFS curve for second-line, the first step is to derive a weighted average of the median PFS of all second-line treatment options by weighting the individual PFS of each second-line treatment (Appendix P Health economic analysis – model input, Table 173) by their respective market share (Table 48). Then, the weighted average of the median PFS is used to derive an exponential curve to calculate the number of patients who remain progression-free over time and who would not switch to third-line treatment. Mortality is also captured during second-line by the Danish general population mortality and the modelled OS curves for DVTd and respective comparators.

8.3.1.1.5 Third-line TTD and PFS

As with the second-line treatment, for all third-line treatment comparators, a TTD curve is assigned to each comparator according to the following options:

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- **Median duration per trial**: In this approach **(used in the base case analysis)**, the TTD curves are exponential (i.e., with a constant rate of treatment discontinuation)
- **Treat to progression**: Using the median PFS for third-line treatments

Once patients start receiving third-line treatment, they stay on treatment based on the median treatment duration (Appendix P Health economic analysis – model input, Table 174). As with second-line treatments, the median treatment duration for each third-line treatment (Appendix P Health economic analysis – model input, Table 174) is used to calculate the costs of third-line therapies for the duration the treatment is given. The median treatment duration of each third-line treatment is used to model a TTD curve assuming an exponential distribution, to calculate the proportion of patients who stop receiving treatment over time and stop accruing treatment-related costs. As an alternative option, it is possible to assume that third-line treatments are treat-to-progression, and the median treatment duration for each third-line treatment is assumed to be the same as its median PFS (Appendix P Health economic analysis – model input, Table 174) to model the TTD curve assuming an exponential distribution.

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; a treatment switch happens only when progression occurs. However, the CEM does not model the treatment switch from third- to fourth-line treatment or beyond. After patients stop third-line treatment, they continue to accrue non-treatment-related costs (e.g., medical resource) until they die, or the end of the model time horizon is reached.

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

HRQoL was used based on the CASSIOPEIA trial. 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.

8.4.1 Overview of health state utility values (HSUV)

Refer to Appendix J Utility Data Analysis for the results of the utility data analysis and Table 35 to see a summary of the utilities applied during different treatment phases in the model.

Table 34 Overview of the HSUV measured during clinical trials forming the basis for the relative efficacy

	Results Mean [SE]	Instrument	Tariff (value set) used	Comments
Pre-progression	0.798 [0.006]	EQ-5D-5L	DK	Mean estimate is based on mean of both trial arms.
Induction	0.752 [0.008]	EQ-5D-5L	DK	Mean estimate is based on mean of both trial arms.
Consolidation	0.810 [0.007]	EQ-5D-5L	DK	Mean estimate is based on mean of both trial arms.
Maintenance	0.835 [0.004]	EQ-5D-5L	DK	Mean estimate is based on mean of both trial arms.
Post-progression	0.784 [0.020]	EQ-5D-5L	DK	Mean estimate is based on mean of both trial arms.

Abbreviations: EQ-5D-5L = EuroQoL Five-Dimension Five-Level; HSUV = health state utility values..

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8.4.2 Health state utility values used in the health economic model

Utility values were applied to each health state 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 CASSIOPEIA trial. Trial data were preferred as a source of utility inputs given that this allowed the use of utility and efficacy data from the exact population from which efficacy data had been derived.

The mean and standard error of the utility during induction, consolidation, maintenance and post-progression states are shown in Table 35.(6, 12)

Table 35. Utilities during Treatment Phases

Treatment Phases	Estimate	Mean SE	Source	Tariff
Induction	0.752	0.008	EQ-5D-5L, CASSIOPEIA	Danish weights
ASCT*	0.752	0.008		
Consolidation	0.810	0.007		
Maintenance	0.835	0.004		
Post-Progression	0.784	0.020		

*Assumed the same as Induction. Abbreviation: ASCT = autologous stem-cell transplant; EQ-5D-5L = EuroQoL Five-Dimension Five-Level.

8.4.3 AE Duration and Disutility

Table 36 shows the disutility and duration associated with each AE that has been included in the model.

Table 36. AE Duration and Disutility

AE	Disutility	Duration (Days)	Source
Neutropenia	-0.15	28	Based on TA573/TA510 (Brown 2013/Partial Review TA171) (161, 162)
Lymphopenia	-0.07	28	
Thrombocytopenia	-0.31	28	
Febrile neutropenia	-0.39	28	
Stomatitis	-0.15	28	Lloyd et al. 2006 (163)
Peripheral sensory neuropathy	-0.07	28	Based on TA573/TA510 (Brown 2013/Partial Review TA171) (161, 162)

Abbreviation: AE =adverse event; TA = technology appraisal
The utility decrements used in the model were primarily based on those used in previous UK (NICE) HTA of daratumumab: TA510 - Daratumumab monotherapy for treating relapsed and refractory multiple myeloma NICE TA510(161) ; TA573: Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma(162).
It was assumed that the loss of utility associated with adverse events would not last for the entire duration of induction, ASCT and consolidation therapy (~37 weeks in both treatment arms). The utility values applied were therefore adjusted such that the duration of disutility was assumed to be 28 days (equivalent to one cycle of induction therapy), as per the assumption used in NICE TA510(161)

8.5 Resource use and costs

Disease- and treatment-related costs are applied to each health state in the model. Categories include costs of drug acquisition and administration applied for the duration of active treatment (determined by dosing regimen and treatment duration), costs of medical resource, costs of AEs, patient costs, and terminal care costs.

8.5.1 Drug Acquisition Costs

Drug acquisition costs for the different treatment options included in the model, including induction and consolidation, second- and third-line treatments, are shown in Table 37. The model utilizes daratumumab subcutaneous formulation across the daratumumab indications.

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Table 37. Drug Acquisition Cost

Treatment	Pack #1			Pack #2			Pack #3			Pack #4		
	Strength per Unit	# Units per Pack	Cost of pack	Strength per Unit	# Units per Pack	Cost of pack	Strength per Unit	# Units per Pack	Cost of pack	Strength per Unit	# Units per Pack	Cost of pack
DaratumumabIV*	100	1	3,311.47	400	1	12,967.06						
Bortezomib	3.5	1	1,940.00									
Lenalidomide	10	21	34,498.46	15	21	36,314.54	20	21	38,069.63	25	21	39,824.68
Dexamethasone	1	20	133.00	1	100	523.00	4	20	155.85	4	100	553.29
Thalidomide	50	28	2,296.29									
Cyclophosphamide	200	1	61.50	500	1	153.75	1000	1	307.50			
Carfilzomib	10	1	1,406.74	30	1	4,220.23	60	1	8,440.47			
Ixazomib	2.3	3	49,231.23	3	3	49,231.23	4	3	49,231.23			
Elotuzumab	300	1	7,106.96	400	1	9,475.95						
Pomalidomide	1	21	54,440.88	2	21	55,296.51	3	21	56,151.29	4	21	57,006.06
DaratumumabSC	1800	1	38,901.18									

Source: Medicinpriser.dk(164), Accessed 19-04-2021, All prices DKK AIP (Pharmacy purchase price)
Abbreviations: IV = Intravenous; SC = Subcutaneous
*In the model, Daratumumab SC is used across daratumumab treatments.

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Dosing regimens for the induction treatment comparators included in the model are shown in Appendix O – The patient population, the intervention and choice of comparators(s), Table 168. Dose regimens are used in the model to inform the cost of treatment.

8.5.1.1 Maintenance dosing and market shares

After high-dose chemotherapy with ASCT, most patients are expected to receive maintenance therapy. There are multiple maintenance treatments available in Denmark, but currently, lenalidomide or observation are recommended. Observation means that the patients' health status is followed after induction/consolidation with no further treatment given during the maintenance period. The drug costs associated with maintenance therapy are provided in the table below.

Table 38: Maintenance Treatment Dosing Regimens

Treatment Regimens		Dose/Admin	Days of Admin/Cycle	Cycle Length (Days)	Assumed relative Dose Intensity	Source
Lenalidomide	Cycles 1-3	10 mg	1-28	28	100%	SmPC and meta-analysis(165, 166)
	Cycles 4-26	15 mg	1-28	28	100%	

Abbreviations: SmPC = Summary of Product Characteristics

The proportion of patients who received each maintenance treatment option is shown in Table 39 and was based on input from the MM Expert Committee. The market shares from induction treatment to maintenance treatment was assumed equal across the intervention and comparators serving as a conservative assumption. It is possible that a smaller proportion of patients will receive lenalidomide maintenance after DVTd in Danish clinical practice where the impact is shown in a scenario analysis.

Table 39. Treatment Market Shares from Induction Treatment to Maintenance Treatment

Maintenance Treatment	From Induction Treatment			
	DVTd	VTd	VCd	VRd
Lenalidomide	70%	70%	70%	70%
Observation	30%	30%	30%	30%

Abbreviations: DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone
Reference: Input from the MM Expert Committee

8.5.1.2 Drug Wastage and dose intensity

For treatments that are dependent on weight or body surface area (BSA), there is the potential that some 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 75.67 kg and mean BSA of 1.88 m^2 (obtained from the baseline characteristics of patients in CASSIOPEIA) were utilized for therapies that depend on a patient's weight and BSA.(7)

The model considers both dose intensity and treatment discontinuation in the drug cost calculation. 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 trials.

Dose intensity was considered separately for each of the components of each combination treatment (Appendix O – The patient population, the intervention and choice of comparators(s), Dosing and Posology

Table 168). For DVTd and VTd, the dose intensity was available from the CASSIOPEIA clinical study reports. For other induction treatment comparators for which dose intensity data were not available from trial publications, the same dose intensities were assumed as for the components of DVTd and VTd (Appendix O – The patient population, the intervention and choice of comparators(s), Table 168.

The model is flexible regarding whether to consider wastage and dose intensity. The base case analysis considers dose intensity and 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. The impact of allowing for vial sharing is shown in a scenario analysis.

8.5.2 Drug Administration Costs

Administration of intravenous (IV) and subcutaneous (SC) treatment regimens requires an outpatient visit that results in additional costs. Therefore, administration costs for IV and SC treatments were programmed explicitly in the model.

The cost by mode of administration is shown in Table 40.

Table 40. Drug Administration Costs

Mode of Administration	Unit Cost (DKK)	Reference*
Initial daratumumab SC	3,203	DRG Takster 2021, DRG group: 17MA98 MDC17, BWAA31 - Medicingivning ved subkutan injektion
Subsequent daratumumab SC	3,203	DRG Takster 2021, DRG group: 17MA98 MDC17, BWAA31 - Medicingivning ved subkutan injektion
IV*	3,203	DRG Takster 2021, DRG group: 17MA98 MDC17, BWAA62 - Medicingivning ved intravenøs infusion
SC*	3,203	DRG Takster 2021, DRG group: 17MA98 MDC17, BWAA31 - Medicingivning ved subkutan infusion

Source: Sundhedsdatastyrelsen 2021(167)
*Bortezomib can be administered via IV or SC injection. In the base case scenario, it is assumed that 100% of bortezomib's administrations were SC. Abbreviations: IV = intravenous; SC = subcutaneous.

8.5.3 Concomitant Medications

Costs of concomitant medications are accrued explicitly only during the induction and consolidation treatment phases. The drug costs of concomitant medications included in the model are shown in Table 41. The proportion of patients receiving each of the concomitant medications included in the model are shown in Table 42 and are based on the required comedications for the different individual components of the combination therapies.

Table 41. Concomitant Medication Drug Costs

	Units per Pack	Strength (mg)	Price per Pack (DKK)	Dosage per admin (mg)	Cost per admin	Medication
Analgesics	100	500	12.06	825	0.20	Medicinpriser.dk 19-04-2021 - Pinex
Antibiotics	48	500	20.61	800	0.69	Medicinpriser.dk 19-04-2021 - Sulfametizol "Alternova"
Antithrombotic	100	75	21.95	300	0.88	Medicinpriser.dk 19-04-2021 - Acetylsalicylsyre "Teva"
Antiviral prophylaxis	100	150	54.5	400	1.45	Medicinpriser.dk 19-04-2021 - Acetylsalicylsyre "Teva"

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	Units per Pack	Strength (mg)	Price per Pack (DKK)	Dosage per admin (mg)	Cost per admin	Medication
Bisphosphonate	1	4	70.06	4	70.06	Medicinpriser.dk 19-04-2021 - Zoledronsyre "Fresenius Kabi"
Antihistamine	100	25	29.75	20	0.24	Medicinpriser.dk 19-04-2021 - Phenergan

Source: Medicinpriser.dk (164), Accessed 19-04-2021, All prices DKK AIP, Abbreviation: mg = milligram

Table 42. Percentage of Patients Receiving Concomitant Medications

Treatment Regimens	Analgesics	Antibiotics	Anti-thrombotic	Antiviral prophylaxis	Bisphosph-onate	Anti-histamine	Source
DVTd	91%	95%	98%	97%	60%	100%	Assumed the same as in CASSIOPEIA Clinical Study Report(12)
VTd	92%	95%	98%	98%	57%	0%	
VCd	0%	100%	0%	100%	0%	0%	Assumption (121, 139)
VRd	0%	100%	100%	100%	0%	0%	Assumed the same as in IFM 2009(123)

Abbreviations: DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone
VCd consolidation: It was assumed that no patients received concomitant medications.

8.5.4 AE Management Cost

The costs of managing the AEs that were considered in the model are presented in Table 43. Based on feedback from a former clinician, the only adverse event that is usually considered to require hospitalization is febrile neutropenia (estimated to be 70% of patients). The costs per adverse events for febrile neutropenia are calculated as a weighted average of the "Not hospitalized" (30%) and "Hospitalized" (70%) costs. For the patients being hospitalized, a cost for hospitalization is added per event.

Table 43. Cost of AE Management

AE	Cost per Event (Not hospitalized)	Source (DRG Takster 2021)	Cost per Event (Hospitalized)	Source (DRG Takster 2021)
Neutropenia	3,203	DRG group: 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år.	Not relevant	
Lymphopenia	3,203		Not relevant	
Thrombocytopenia	3,203		Not relevant	
Febrile neutropenia	3,203		35,483	17MA01
Stomatitis	3,203		Not relevant	
Peripheral sensory neuropathy	3,203		Not relevant	

Source: Sundhedsdatastyrelsen 2021(167)
Abbreviations: AE = adverse event.

8.5.5 ASCT Cost

The percentage of patients undergoing ASCT for each induction treatment regimen are based on clinical trials and are shown in Table 44. Details of the ASCT costs are shown in Table 45; the total cost of ASCT is 826,681 DKK.

Table 44. Percent of Patients Undergoing ASCT

Induction Regimens	% of Patients undergoing ASCT	Source
DVTd	90.10%	CASSIOPEIA(6)
VTd	89.30%	CASSIOPEIA(6)
VCd	90.48%	GMMG-MM5(121, 139)
VRd	92.29%	IFM 2009(123)

Abbreviations: ASCT = autologous stem cell transplant; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone

Table 45. Details of ASCT Costs

Drug/Intervention	Unit Cost (DKK)	Source
Stem Cell Mobilization/Harvest	15,944	DRG Takster 2021 – 16PR03 (BOUW2) Stamcelleopsamling fra perifert blod + (BOUW7) Isolering og nedfrysning af stamceller (7972*2)
High-Dose Chemotherapy	-	Assumed to be included in DRG-code 26MP24 used below
Transplantation	166,707	DRG Takster 2021 – 26MP24 - Kemoterapi, højdosis, m. autolog stamcellestøtte

Source: Sundhedsdatastyrelsen 2021(167)

8.5.6 Medical Resource Costs

Medical resource costs were accrued in each health state (i.e., induction, consolidation and maintenance [progression-free] and post-progression) separately in the model. The medical resource frequency and use is assumed to be the same for all comparators and the values are based on the clinical trials and NICE guidance. The values are presented in Table 46.

Table 46. Frequency of Medical Resource Use (Every 4 Weeks)

Treatment Phase	Hematologist Initial Visit	Hematologist Follow-up Visit	Full Blood Count	Urine Disease Evaluations (UPEP)	Liver Function Tests	Calcium	Serum Free Light Chain	Serum Disease Evaluations (SPEP)
Progression-free: Induction & Consolidation	0*	0*	0.14	0.13	0.10	0.13	0.03	0.13
Progression-free: Maintenance	—	0.13*	0.14	0.13	0.10	0.13	0.03	0.13
Source		CASSIOPEIA protocol(118)	NICE TA311(168)	CASSIOPEIA protocol(118)	NICE TA311(168)	CASSIOPEIA protocol(118)	NICE TA311(168)	CASSIOPEIA protocol(118)
Post-progression	—	0.23*	0.39	0.10				0.19
Source	NICE TA 228, Picot et al. 2011(169)							

Abbreviations: NICE = National Institute for Health and Care Excellence; SPEP = serum protein electrophoresis; TA = technology appraisal; UPEP = urine protein electrophoresis

*Note: It is assumed that regular hospital visits are already reflected in the administration costs (IV & SC treatment administration). For treatments administered orally and not requiring hospital visits, additional medical resource use was assumed for the following to reflect regular follow-up visits: Maintenance treatment - lenalidomide maintenance, observation (0.13); Second-line treatment – Rd, Ixazomib+Rd (0.23); Third-line treatment – Pomalidomide (0.23).

Table 47 shows the unit costs for the medical resources and laboratory tests.

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Table 47. Unit Costs of Healthcare Resources and Tests

Item	Unit Cost (DKK)	Reference
Hematologist initial visit	417.05	Værdisætning af enhedsomkostninger, version 1.3(170); Sygehuslæge; Lønniveau Jan 2021 (based on full 2021 gross pay), 20 minutes consultation assumed
Hematologist follow-up visit	417.05	Værdisætning af enhedsomkostninger, version 1.3(170); Sygehuslæge; Lønniveau Jan 2021 (based on full 2021 gross pay), 20 minutes consultation assumed
Full blood count	290.00	"LMV 2021"- 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)
Urine disease evaluations (UPEP)	126.00	"LMV 2021"- Klorid;P, Kalium;P, Natrium;P, (NPU01536, NPU03230, NPU03429)
Liver function tests	102.00	"LMV 2021"- Albumin;Plv, Alanintransaminase [ALAT];P, Bilirubiner;P, Bilirubin konjugeret;P, Aspartattransaminase [ASAT];P, Protein;P. (NPU19674, NPU19651, NPU01370, NPU17194, NPU19654, NPU03278)
Calcium	15.00	"LMV 2021"- Calcium;P (NPU01443)
Serum free light chain (SFLC)	357.00	"LMV 2021"- Kappa-kæde(Ig) frit;P,Lambda-kæde(Ig) frit;P (NPU19606, NPU19607)
Serum disease evaluations (SPEP)	15.00	"LMV 2021"- Protein;P (NPU03278)
CRP (Infection marker)	15.00	"LMV 2021"- C-reaktivt protein [CRP];P (NPU19748)
Blood cultures	20.75	"Takstkort 29A, 01 April 2021"- Laboratorieundersøgelser – blod – (7110)

Abbreviations: SFLC = serum free light chain; CRP = infection marker; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; LMV = Laboratoriemedicinsk vejledning ((prices valid fra 01. January 2021, analysis prices pr. 09. March 2021) (http://lmv.regionsjaelland.dk/dokument.asp?DokID=548551) ; KRL = Kommunernes og regionernes løndatakontor (https://www.krl.dk/#/sirka); Takstkort, Generelle laboratorieundersøgelse – takstkort 1. april 2021 (https://www.laeger.dk/takstkort)

8.5.7 Subsequent Treatment Costs

Drug costs for second- and third-line treatment after progression are included in the model. These post-progression costs are a combination of drug costs (Table 37), administration costs (Table 40) and the medical resource costs (Table 46 and Table 47), which were assumed to be the same regardless of prior treatment. In the base case scenario, wastage (i.e., no vial sharing) was considered, while dose intensity was assumed to be 100% for all subsequent treatments, to avoid the possibility of penalizing comparators (thus favoring DVTd) by associating them with second- and third-line treatments that are more expensive (due to higher dose intensity) than the second- and third-line treatments associated with DVTd.

The dosing schedules for subsequent treatments are shown in Appendix O – The patient population, the intervention and choice of comparators(s), Table 169.

8.5.7.1 Subsequent treatment mix

The assumed proportion of patients who received each second-line treatment option is shown in Table 48 and was provided by Janssen in order to represent expected clinical practice in Denmark. The base case reflects considerations around the current treatment guidelines and the drug recommendation published by the Medicines Council as well as expected clinical practice.(2, 3) The treatment mix for the second-line treatment setting is primarily based on the evaluation by the MM Expert Committee for the evaluation of daratumumab in

combination with bortezomib, melphalan and prednisolone (DVMP).(171) Despite two different patient populations (transplant eligible (DVTd) and transplant ineligible (DVMP)), the subsequent treatment mix is likely to be transferable to the transplant eligible setting to inform the expected market shares. However, some key differences exists when evaluating the subsequent treatments. In the transplant ineligible setting, according to label, VRd is administered to progression which is not the case in the transplant eligible setting. In addition, the subsequent treatment mix is expected to be impacted by whether the patient will receive lenalidomide maintenance treatment or not. To inform the final treatment mix in the model, a weighted average approach is applied to account for the patients that are expected to receive observation (30%) and the patients that are expected to receive lenalidomide maintenance (70%) after being treated with either DVTd, VCd, VTd or VRd. This is done to account for the differences in the subsequent treatment mix depending on whether lenalidomide maintenance treatment have been administered or not.

Second-line treatment mix

Second-line subsequent treatment mix for VCd and VTd followed by observation

After being treated with bortezomib in combination with melphalan and prednisolone (VMP), the MM Expert Committee assessed that 80% of patients would receive daratumumab in combination with lenalidomide and dexamethasone (DRd), 10% carfilzomib in combination with lenalidomide and dexamethasone (KRd), 5% lenalidomide in combination with dexamethasone (Rd), and 5% elotuzumab in combination with lenalidomide and dexamethasone (ERd) in the assessment of DVMP.(171)

As VCd and VTd in the transplant eligible setting is administered for a fixed treatment duration and both regimens contain bortezomib, a similar treatment mix is expected for VCd and VTd as the MM Expert Committee assessed for VMP (VMP is a fixed treatment duration regimen and contains bortezomib). The subsequent treatment mix provided for DVMP is assessed to be relevant and transferable in a setting where lenalidomide maintenance is not used in Danish clinical practice. The above shares provided by the MM Expert Committee in the evaluation for DVMP are applied to the patients expected to receive observation (30% of the population). For VCd and VTd followed by observation in the transplant eligible setting, this results in the following second-line treatment mix: 24% DRd (80%*30%), 3% KRd (10%*30%), 1.5% Rd (5%*30%), and 1.5% ERd (5%*30%), totaling 30%.

Second-line subsequent treatment mix for VRd followed by observation

After being treated with lenalidomide in combination with dexamethasone for 18 cycles (Rd18), the MM Expert Committee assessed that 60% of patients would receive DRd, 30% daratumumab in combination with bortezomib and dexamethasone (DVd), and 10% would receive Rd in the assessment of DVMP.(171)

As VRd in the transplant eligible setting is administered for a fixed treatment duration, a similar treatment mix is expected as the MM Expert Committee identified for the fixed treatment duration regimen, Rd18 in the transplant ineligible setting. The subsequent treatment mix provided for the DVMP evaluation is relevant in a setting where lenalidomide maintenance is not used in Danish clinical practice. Hence, the above shares are applied to the patients expected to receive observation (30% of the population). For VRd followed by observation in the transplant eligible setting, this will result in the following second-line treatment mix: 18% DRd (60%*30%), 9% DVd (30%*30%), and 3% Rd (10%*30%), totaling 30%.

Second-line subsequent treatment mix for VCd, VTd, and VRd followed by lenalidomide maintenance

For VCd, VTd and VRd, the above assumptions are only applied for the patients that are expected to receive observation as maintenance treatment (estimated to be 30% of the patient population). For patients expected to receive lenalidomide maintenance (70% of the patient population), additional adjustments are needed.

After being treated with VRd in the transplant ineligible setting, the MM Expert Committee assessed that 65% of patients would receive DVd, 25% carfilzomib in combination with dexamethasone (Kd), and 10% pomalidomide in combination with bortezomib and dexamethasone (PVd) in the assessment of DVMP.(171)

To adjust for the patients that are expected to receive lenalidomide maintenance, the subsequent treatment mix that the MM Expert Committee applied for VRd in the DVMP evaluation for transplant ineligible patients were used as lenalidomide is administered to progression in the VRd regimen in the transplant ineligible setting, similarly to lenalidomide maintenance in the transplant eligible setting. For VCd, VTd, and VRd followed by lenalidomide maintenance, this will result in the following second-line treatment mix: 45.5% DVd (65%*70%), 17.5% Kd (25%*70%), and 7% PVd (10%*70%), totaling 70%.

Second-line subsequent treatment mix for DVTd followed by observation

After being treated with DVMP, the MM Expert Committee assessed that 40% of patients would receive KRd, 10% Rd, 40% ERd, and 10% ixazomib in combination with lenalidomide and dexamethasone (IRd).

The same subsequent treatment mix has been applied for DVTd in the case where lenalidomide maintenance is not considered (observation). A similar subsequent treatment mix is expected since lenalidomide is not administered in the DVMP and DVTd regimen and both regimens contain bortezomib. This will result in the following second-line treatment mix: 12.0% KRd (40%*30%), 3% Rd (10%*30%), 12% ERd (40%*30%), 3% IRd (10%*30%), totaling 30%.

Second-line subsequent treatment mix for DVTd followed by lenalidomide maintenance

There were no sufficiently comparable data to inform about the expected subsequent treatment mix for DVTd followed by lenalidomide maintenance. It is assumed that no lenalidomide regimens are used since it is administered during maintenance which is in line with the assumption for the other comparators. It is assumed that 40% of patients will receive Kd and 30% will receive PVd. Since PVd has been on the market for some time, it is assumed that the regimen is more commonly used than it was the case for the DVMP evaluation.

Final treatment subsequent treatment mix for VCd, VTd, VRd, and DVTd

To obtain the final market shares applied in the model (Table 48), the subsequent treatment mix for each comparator for observation and lenalidomide was added together.

Third Line treatment mix

Third-line treatments are also modelled, and the treatment mix is based on the second-line treatment regimen administered. There was limited comparative validated data from the MM Expert Committee from previous evaluations. The market shares were provided by Janssen to represent expected clinical practice in Denmark.

For DRd and ERd administered in the second-line setting, it is assumed that 40% will receive Kd, 50% PVd, and 10% pomalidomide in combination dexamethasone (Pd) subsequently. If ERd is administered in the second-line setting, it is unlikely that these patients were eligible for daratumumab. Based on data from the OPTIMISMM trial (172), the Medicines Council evaluation (133), as well as increased pomalidomide sales on the Danish market, PVd is expected to be strongly preferred over Pd. However, some patients are expected have developed peripheral neuropathy due to previous bortezomib treatment, which is the reason for the 10% assigned shares to Pd. The relative preference (60% vs. 40%) of pomalidomide vs carfilzomib based treatment is assumed due to the advantage of the oral route of administration of pomalidomide vs. the twice weekly intravenous administration in a partially frail relapsed/refractory MM population.

For DVd administered in the second-line setting, it is assumed that 10% will receive Kd, 30% KRd, 30% ERd, 20% PVd, and 10% Pd subsequently. Triple combinations have shown to be more efficacious and since these patients have not been administered an immunomodulator (IMID) in the second-line setting, triples combinations are

expected to be used in the third-line setting. ERd is still not widely used in Denmark which is the reason for the equal market shares compared to KRd even though ERd is the first choice in the Medicines Council drug recommendation if daratumumab is contraindicated.(2) It is assumed that the majority of patients will receive a lenalidomide containing regimen in the third-line setting after being administered DVd due to a prolonged period without administration of lenalidomide and a lenalidomide non-refractory status due to time-limited first-line treatments with lenalidomide. PVd use is expected for some patients due to bortezomib not being administered until progression in the DVd regimen. However, some patients may have developed peripheral neuropathy due to bortezomib treatment, which is the reason for the 10% assigned shares to Pd.

For patients administered PVd in second-line, it is assumed that 100% will receive Kd in the third-line setting. For these patients, there has been a clinical rationale for administering PVd instead of DVd in the second-line setting, and a rationale for administering a later generation IMID in the second-line setting. In addition, no studies have demonstrated a clinical rationale for administering lenalidomide after pomalidomide narrowing down the possible third-line treatment options for this patient group to Kd.

For Kd and KRd, it is assumed that 100% will received Pd subsequently. No use of bortezomib (in PVd) compared to the case of DRd is due to the use of a second-generation proteasome inhibitor (carfilzomib) in the previous line. Thus, all patients are expected to receive Pd.

For patients receiving Rd or IRd in second-line, it is assumed that 100% will received Pd in 3L due to a likely preference for an oral treatment regimen.

The final market shares applied in the model for third-line treatment is shown in Table 49 .

Table 48. Treatment Market Shares for second line Treatment

To Second-line Treatment	From Induction Treatment			
	DVTd	VTd	VCd	VRd
DRd	0.0%	24.0%	24.0%	18.0%
DVd	0.0%	45.5%	45.5%	54.5%
Kd	40.0%	17.5%	17.5%	17.5%
KRd	12.0%	3.0%	3.0%	0.0%
Rd	3.0%	1.5%	1.5%	3.0%
ERd	12.0%	1.5%	1.5%	0.0%
PVd	30.0%	7.0%	7.0%	7.0%
IRd	3.0%	0.0%	0.0%	0.0%

Abbreviations: DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; DRd = daratumumab, lenalidomide, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; Kd = Carfilzomib, dexamethasone; KRd = Carfilzomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone; ERd: Elotuzumab, lenalidomide, dexamethasone PVd=pomalidomide, bortezomib, dexamethason; IRd: Ixazomib, lenalidomide, dexamethasone

Table 49. Treatment Market Shares from Second-line Treatment to Third-line Treatment

To Third-Line Treatment	From Second-Line Treatment							
	DRd	DVd	Kd	KRd	Rd	ERd	PVd	IRd

Kd	40.0%	10.0%	0.0%	0.0%	0.0%	40.0%	100.0%	0.0%
KRd	0.0%	30.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
ERd	0.0%	30.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
PVd	50.0%	20.0%	0.0%	0.0%	0.0%	50.0%	0.0%	0.0%
Pd	10.0%	10.0%	100.0%	100.0%	100.0%	10.0%	0.0%	100.0%

Abbreviations: DRd = daratumumab, lenalidomide, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; Kd = Carfilzomib, dexamethasone; KRd = Carfilzomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone; ERd: Elotuzumab, lenalidomide, dexamethasone PVd=pomalidomide, bortezomib, dexamethason; IRd: Ixazomib, lenalidomide, dexamethasone; Pd = Pomalidomide, dexamethasone

8.5.8 Other Costs

8.5.8.1 Terminal Care

Terminal care costs are relevant since patients will require additional resources shortly before death (end-of-life costs). To reflect the resource use, terminal care costs were estimated based on a study from the UK which focused on advanced cancers.(173) This study has been used due to a lack of more accurate Danish specific tariffs or studies. A difference between resource use in the UK and Denmark are expected, but this study is evaluated to be the best estimate and similarities exists between the health care system in the UK and Denmark. In addition, this study has been referenced in other evaluations by the Medicines Council. Lastly, the terminal care costs are expected to have limited impact on the overall results which is shown in the scenario analyses. The mean costs used from the study consists of hospital care and social care (informal care costs and charity care have excluded).

The related UK cost (£ 6083) has been adjusted using relevant purchasing power parities (1.083) followed by use of the annual average exchange rate for 2014 (9.251). This cost was then projected using the consumer price index without energy (1.070; 2014 January to 2021 January) following the methodology put forward by the Medicines Council resulting in a cost of 65,273.71 DKK.

8.5.8.2 Time consumption

Time consumption has been calculated for induction-, consolidation-, and post-progression treatment. The patient cost for time consumption has been calculated according the Medicines Council guidelines and equals 179 DKK per hour.(170)

The number of visits for administration, and thereby the time spent, is related to the overall treatment regimen. Based on the drug dosing schedule (refer to Appendix O – The patient population, the intervention and choice of comparators(s), Table 168 and Table 169), the number of visits to the hospital for administration depends on which drugs are included in the treatment regimen and at what days these should be administered.

The time spent on drug administration is different depending on which combination of drugs the patient receive at each visit (refer to “days of administration” in the drug dosing schedule, refer to Appendix O – The patient population, the intervention and choice of comparators(s), Table 168 and Table 169). In the cost-effectiveness model patient cost for time consumption are only included when treatment are administered. Each treatment administration visit are assumed to include 30 minutes of waiting time at the hospital, independent on treatment regimen.

The number of times the patients’ needs to go to the hospital for treatment administration has been calculated per cycle. It is assumed that the time consumption for patients having regular hematologist visits are reflected in the administration visits. The cost of time consumption are only applied to SC or IV administration of drugs. It is assumed that the number of patients treated with ASCT is similar across treatments and therefore patients costs are excluded.

See Table 50 for the time consumption costs for patients included for each treatment regimen. This cost is included in the base case.

8.5.8.3 Transport

The direct non-medical costs of transportation is added to the model, to account for transportation costs for patients who require travel for treatment administration.

The transportation cost has been calculated for induction-, consolidation-, and post-progression treatment. The cost has been calculated according the Medicines Council guidelines and equals the 100 DKK per visit to the hospital.(170) Based on the drug dosing schedule, the number of times the patients' needs to go to the hospital for treatment administration has been calculated per cycle. The cost of transport is the same independent of how many drugs that are administered at the same visit.

This cost is included in the base case. See Table 50 for the transport cost included for each treatment regimen.

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Table 50 Patient costs

Phase	Treatment Regimen	Drug	Waiting time (min)	Waiting time cost	Transportation costs	Admin minutes	Admin costs	Total costs
Induction	DVTd	Dara	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
		V	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
		Dara+V	30.00	89.50 DKK	100.00 DKK	30	89.50 DKK	279.00 DKK
	VTd	V	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
	VCd	V	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
		C	30.00	89.50 DKK	100.00 DKK	30	89.50 DKK	279.00 DKK
		V+C	30.00	89.50 DKK	100.00 DKK	30	89.50 DKK	279.00 DKK
	VRd	V	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
Consolidation	DVTd	Dara	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
		V	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
		Dara+V	30.00	89.50 DKK	100.00 DKK	30	89.50 DKK	279.00 DKK
	VTd	V	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
	VCd*							
	VRd	V	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
Post-progression	DRd	Dara	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
	DVd	Dara	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
		V	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK
		Dara+V	30.00	89.50 DKK	100.00 DKK	30	89.50 DKK	279.00 DKK
	Kd	K	30.00	89.50 DKK	100.00 DKK	30	89.50 DKK	279.00 DKK
	KRd	K	30.00	89.50 DKK	100.00 DKK	30	89.50 DKK	279.00 DKK
	ERd	E	30.00	89.50 DKK	100.00 DKK	60	179.00 DKK	368.50 DKK
	PVd	V	30.00	89.50 DKK	100.00 DKK	15	44.75 DKK	234.25 DKK

Abbreviations: Dara= daratumumab; V= bortezomib; C= cyclophosphamide; K= carfilzomib; E= elotuzumab; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; DRd = daratumumab, lenalidomide, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; Kd = Carfilzomib, dexamethasone; KRd = Carfilzomib, lenalidomide, dexamethasone; ERd: Elotuzumab, lenalidomide, dexamethasone; PVd=pomalidomide, bortezomib, dexamethason.*Revlimid assumed to be administered as consolidation treatment after VCd induction based on the treatment guidelines from the Medicines Council. No patient costs applied as Revlimid is an oral drug.

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8.6 Results

This section present the base case results for DVTd compared to VTd, VCd and VRd in section 8.6.2. Below in Table 51 an overview of the base case is presented.

8.6.1 Base case overview

Table 51 Base case overview

Comparators		VTd VCd VRd
Perspective		Restricted Societal perspective
Type of model		The model is a partitioned survival model (PSM)
Time horizon		40 years (life time)
Discount rates		Cost and Health benefits: Year 1-35: 3.5%; Year 36-40: 2.5%
Mean age, mean BSA, mean weight		Mean age 56.6; mean BSA: 1.88; mean weight: 75.67kg
Induction treatment duration	DVTd	Observed TTD (CASSIOPEIA) see Table 136
	VTd	Observed TTD (CASSIOPEIA) see Table 136
	VCd, VRd	Median treatment duration (Table 135)
Parametric function for PFS	DVTd	Joint Weibull distribution with treatment as predictor (CASSIOPEIA), section 19.2.1.1
	VTd	Joint Weibull distribution with treatment as predictor (CASSIOPEIA) section 19.2.1.1
	VCd, VRd	HR vs. VTd (CASSIOPEIA) from MAIC base case Table 7
Parametric function for OS	DVTd	Joint Weibull distribution with treatment as predictor (CASSIOPEIA) section 19.1.1.1
	VTd	Joint Weibull distribution with treatment as predictor (CASSIOPEIA) section 19.1.1.1
	VCd, VRd	HR vs. VTd (CASSIOPEIA) from MAIC base case Table 7
Treatment line		Induction/consolidation treatment
Consolidation treatment		Included
Maintenance treatment		Included

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Second- and third-line treatment	Included, Median treatment duration Table 173 and Table 174,
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in CASSIOPEIA(6). Danish population weights were used to estimate health-state utility values
Included costs	Drug costs and ASCT costs Administration Costs Concomitant medications Routine monitoring Costs of adverse events Patient costs Terminal care costs
Dosage of pharmaceutical	See Drug dosing schedule in section 8.5
Market shares	Expected Danish market shares Table 48, Table 49 and Table 39
Drug wastage	Included
Relative dose intensity	Included

Abbreviations: DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; EQ-5D-5L = EuroQoL Five-Dimension Five-Level questionnaire; HR = hazard ratio; MAIC = matching-adjusted indirect comparison; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone

8.6.2 Base case results

Table 52 shows the results for the base case analysis. Patients on DVTd had improved survival compared with all the other treatments and spent more time progression-free. Consequently, DVTd was associated with the highest LYs and QALYs but also higher costs.

The primary cost driver for DVTd was costs acquired during the induction/consolidation phase and the costs were primarily related to drug acquisition costs of daratumumab. The cost component with the largest savings for DVTd vs. comparators were second-line treatment costs which is explained by the subsequent treatment mix expected in Danish clinical practice, and also because patients on DVTd induction treatment take longer to switch to subsequent treatment lines. Hence, patients on the comparator treatments are switched to other therapies following progression, which occurs sooner.

The base case analysis showed that DVTd yielded better survival outcomes and was associated with longer LYs and QALYs vs. other comparators (incremental QALYs for DVTd vs. VTd (+2.75), DVTd vs. VCd (+3.74), and DVTd vs. VRd (+3.66). The ICER for DVTd vs. VTd was 32,979 DKK/QALY, DVTd vs. VCd (79,209 DKK/QALY) and, DVTd vs. VRd (97,701 DKK/QALY).

Table 52 Base case results

Projected medians	DVTd	VTd	VCd	VRd
Median PFS (Years)	6.72	4.00	3.90	4.20
Median OS (Years)	17.34	10.86	8.92	9.12
Health Outcomes	**DVTd**	**VTd**	**VCd**	**VRd**
Quality Life Years (QALYs)				
Induction/ASCT/Consolidation	0.54	0.53	0.42	0.42
Maintenance	4.94	3.03	2.99	3.24
Post-progression	4.97	4.13	3.29	3.12
Disutilities	-0.01	-0.01	0.00	0.00
TOTAL	**10.43**	**7.69**	**6.70**	**6.78**
Life Years (LYs)				
Induction/ASCT/Consolidation	0.64	0.63	0.49	0.49
Maintenance	5.92	3.63	3.58	3.88
Post-progression	6.34	5.27	4.20	3.98
TOTAL	**12.89**	**9.54**	**8.27**	**8.35**
Costs	**DVTd**	**VTd**	**VCd**	**VRd**
Induction/Consolidation Treatment				
Drug acquisition	473,184	54,546	48,961	82,652
Drug administration	90,522	55,434	16,648	36,995
Concomitant medications	1,029	986	11	35
Routine monitoring	1,736	1,718	1,105	1,107
Patient Cost	6,666	4,613	3,077	3,479
Total	**573,137**	**117,299**	**69,803**	**124,268**
Maintenance Treatment				
Drug acquisition	633,221	590,153	601,181	608,243
Drug administration	0	0	0	0
Routine monitoring	40,981	25,157	24,803	26,864
Total	**674,202**	**615,309**	**625,984**	**635,107**
Post-Progression				
Second-line Treatment				
Drug acquisition	556,199	915,455	808,696	690,618
Drug administration	95,669	114,223	100,902	91,405
Routine monitoring	6,857	9,157	8,089	7,213
Patient Cost	8,029	6,000	5,300	4,252
Total	**666,753**	**1,044,834**	**922,988**	**793,488**
Third-line Treatment				
Drug acquisition	213,812	261,119	222,180	225,592
Drug administration	17,320	31,206	26,552	26,622
Routine monitoring	51,318	31,613	24,222	23,395
Patient Cost	1,475	2,608	2,219	2,242
Total	**283,925**	**326,545**	**275,172**	**277,852**

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Terminal Care	36,129	43,648	46,613	46,434
Adverse Event Management	4,198	3,161	1,256	0
ASCT	161,490	158,502	161,885	165,365
TOTAL	**2,399,836**	**2,309,298**	**2,103,701**	**2,042,513**
Incremental Results	**DVTd**	**VTd**	**VCd**	**VRd**
QALYs	Ref	2.75	3.74	3.66
LYs	Ref	3.36	4.62	4.55
Costs	Ref	90,537	296,134	357,322
Cost per QALY	**Ref**	**32,979**	**79,209**	**97,701**
Cost per LY	Ref	26,973	64,035	78,592

Abbreviations: ASCT = autologous stem cell transplant; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; LY = Life years; OS = Overall survival; PFS = Progression-free survival; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; QALY = quality-adjusted life-years

8.7 Sensitivity analyses

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

8.7.1 Deterministic sensitivity analyses

Major model variables were tested in a one-way DSA to identify model drivers and examine key areas of uncertainty. Where possible, CIs were used to define the upper and lower bounds tested for the parameters in the DSA. In the absence of CIs, upper and lower bounds tested in the one-way DSA were calculated as ±20% of the mean value apart from the annual discount rate and the time horizon. The annual discount rate was varied by 1.5% and 5% according to NICE guidance(174) where the base case discount rate was 3.5%. The adjusted discount rates were applied for year 1-35 and year 36-40 followed the base case of 2.5%. The model horizon was decreased by 5 and 10 years compared to the model horizon in the base case (40 years) to assess the impact of a short time-horizon. The parameters tested in the one-way DSA and how they were varied are shown in the model sheet DSA inputs and Appendix K Deterministic sensitivity analysis, Table 157. The top 15 parameters by order of the influence they have on the ICERs are illustrated in Figure 14, Figure 15 and Figure 16 for each comparator. In the DSA, the parameters of the survival fits (i.e., intercept and scale) were set to their lower or upper bounds at the same time. The impact of the HR for VCd and VRd was also tested based on their lower and upper CIs versus VTd. The associated ICERs of the lower and upper values of each variable for each comparator can be found in table format in Appendix K Deterministic sensitivity analysis (Table 158, Table 159, Table 160). In case the incremental costs and incremental QALYs were both negative (south west quadrant of the cost-effectiveness plane), the ICER was set to the base case as this produces none-interpretable ICERs. The ICER of VTd was most sensitive to changes in the PFS Weibull intercept on VTd, the OS Weibull scale on VTd, and the OS Weibull scale for VTd with treatment as predictor. The ICER of VCd and VRd was most sensitive to changes in the OS Weibull intercept on VTd, the OS Weibull intercept on DVTd, and OS HR for VCd and VRd.

In the template provided by the Medicines Council, it is requested to provide an ICER curve with different drug prices for the intervention which can be found in Figure 17. The shape of the curves are primarily due to the impact of subsequent treatment with daratumumab in the comparator arms where the price of daratumumab is also impacted in later lines of treatments.

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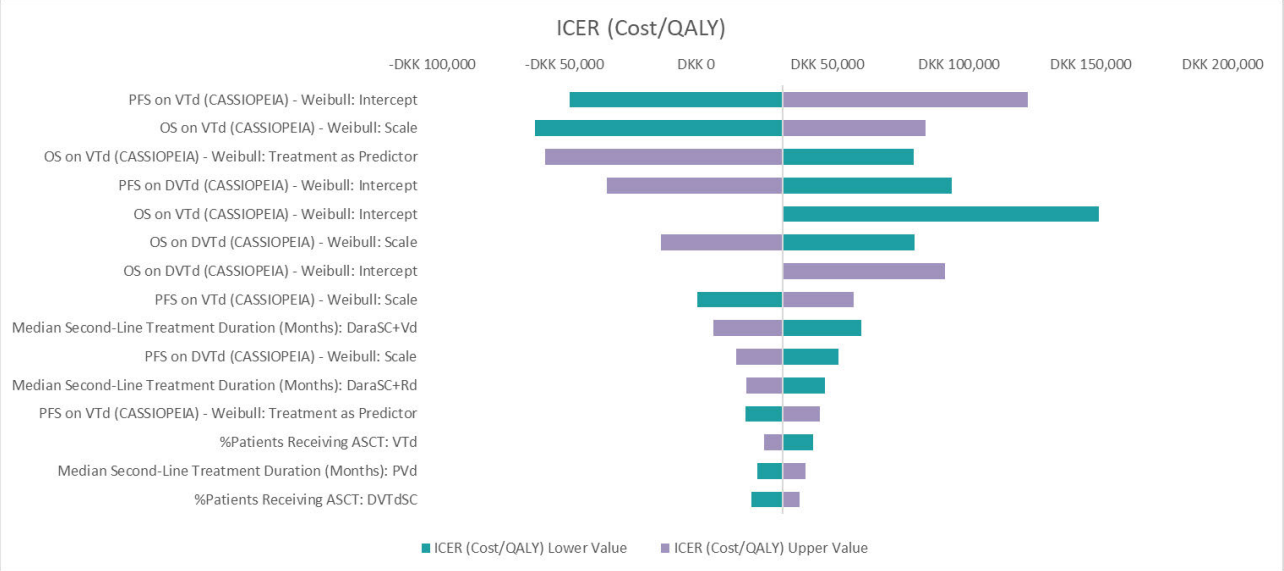
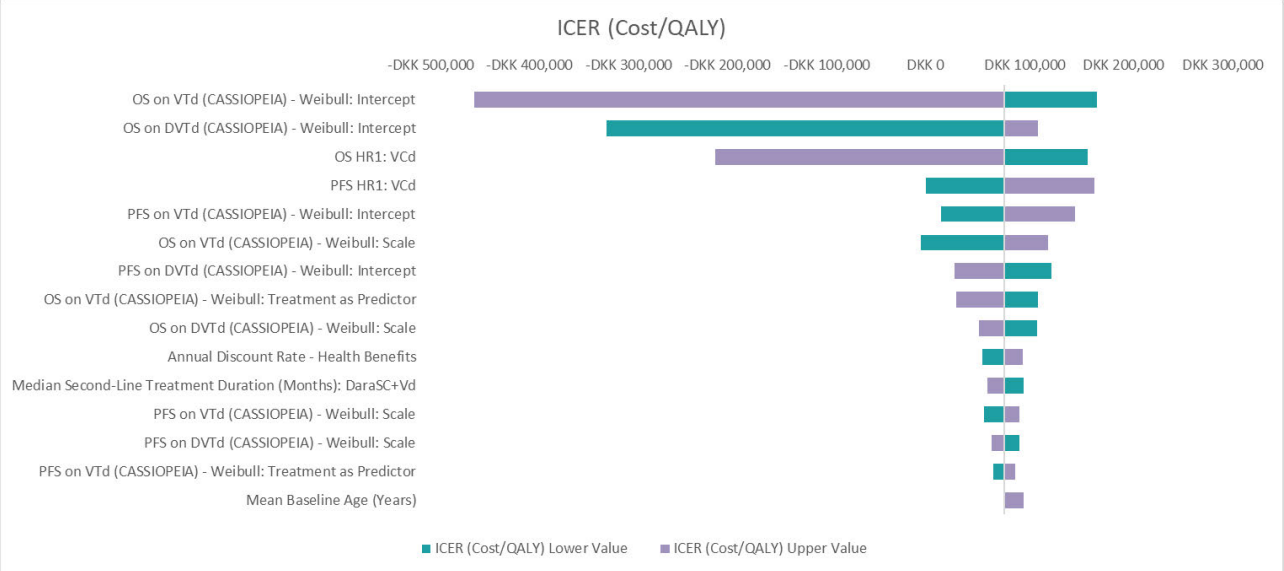
Figure 14. DSA Results (DVTd vs. VTd)



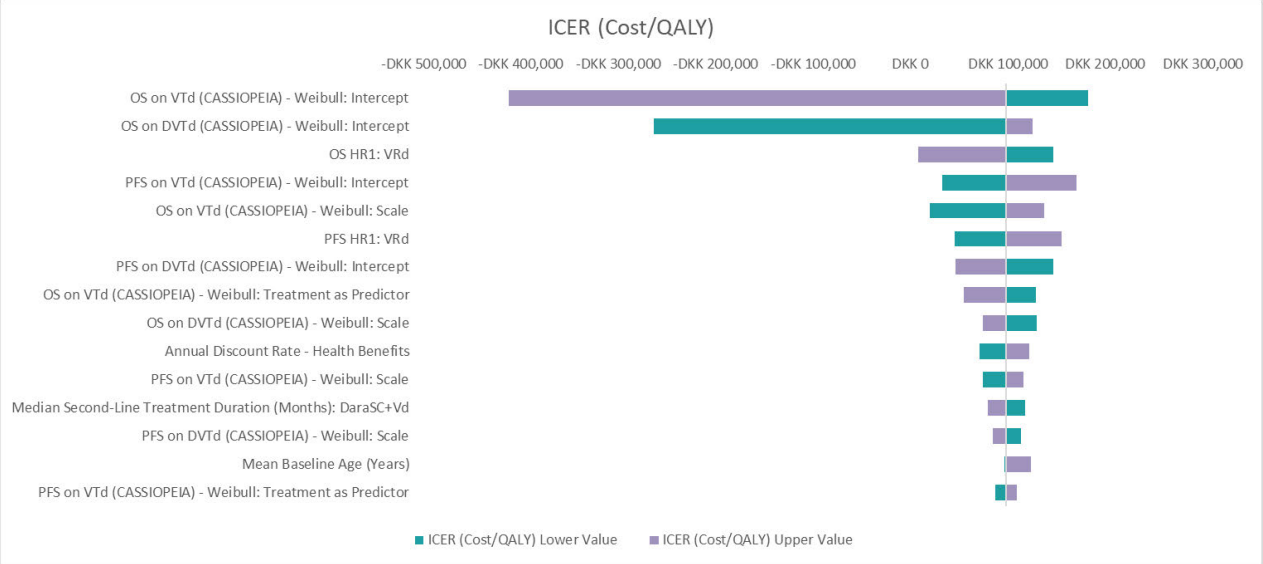
*Intercept, scale and treatment as predictor were set to lower or upper bound at the same time for Weibull distribution.
Abbreviations: DSA = deterministic sensitivity analysis; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-years; OS = overall survival; PFS = progression-free survival; ASCT = autologous stem cell transplant; DVTd/DVTdSC = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; DaraSC + Vd = daratumumab, bortezomib, dexamethasone; DaraSC + Rd = daratumumab, lenalidomide, dexamethasone; PVd = pomalidomide, bortezomib, dexamethason
Note: For the scenarios with negative ICER values, cost savings and higher QALYs were observed. In these cases, it should be interpreted as cost-effective irrespective of the ICER threshold and no numerical interpretation is needed. In case the incremental costs and incremental QALYs were both negative (south west quadrant on the cost-effectiveness plane), the ICER was set to the base case as this produces none-interpretable ICERs.

Figure 15. DSA Results (DVTd vs. VCd)



*Intercept, scale and treatment as predictor were set to lower or upper bound at the same time for Weibull distribution. HR for VCd was tested based on the lower and upper CI versus VTd.
Abbreviations: DSA = deterministic sensitivity analysis; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-years; OS = overall survival; PFS = progression-free survival; HR = hazard ratio; ; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; DaraSC + Vd = daratumumab, bortezomib, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone.
Note: For the scenarios with negative ICER values, cost savings and higher QALYs were observed. In these cases, it should be interpreted as cost-effective irrespective of the ICER threshold and no numerical interpretation is needed. In case the incremental costs and incremental QALYs were both negative (south west quadrant on the cost-effectiveness plane), the ICER was set to the base case as this produces none-interpretable ICERs.

Figure 16. DSA Results (DVTd vs. VRd)



*Intercept, scale and treatment as predictor were set to lower or upper bound at the same time for Weibull distribution. HR for VRd was tested based on the lower and upper CI versus VTd.

Abbreviations: DSA = deterministic sensitivity analysis; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-years; OS = overall survival; PFS = progression-free survival; HR = hazard ratio; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; DaraSC + Vd = daratumumab, bortezomib, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone.

Note: For the scenarios with negative ICER values, cost savings and higher QALYs were observed. In these cases, it should be interpreted as cost-effective irrespective of the ICER threshold and no numerical interpretation is needed. In case the incremental costs and incremental QALYs were both negative (south west quadrant on the cost-effectiveness plane), the ICER was set to the base case as this produces none-interpretable ICERs.

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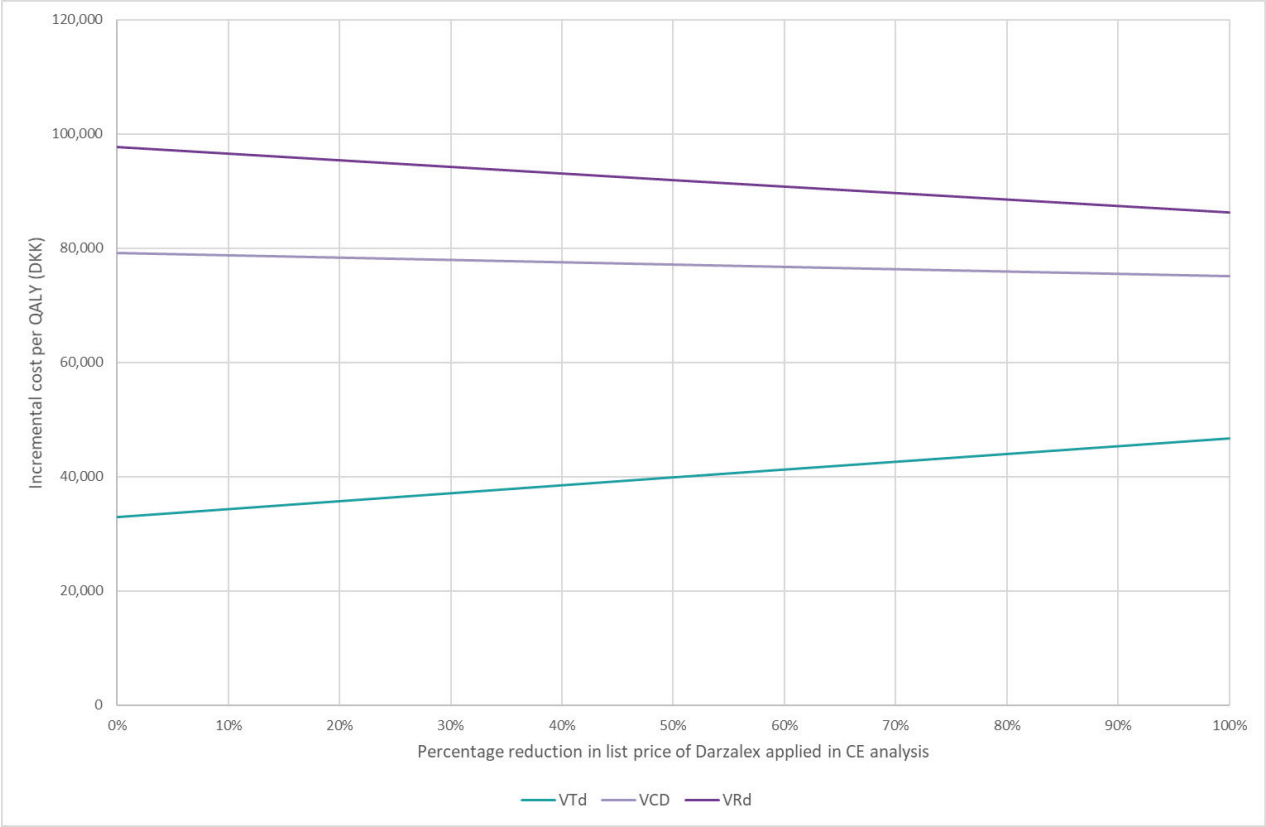
Figure 17. ICERs estimated with different values for the drug price of the intervention



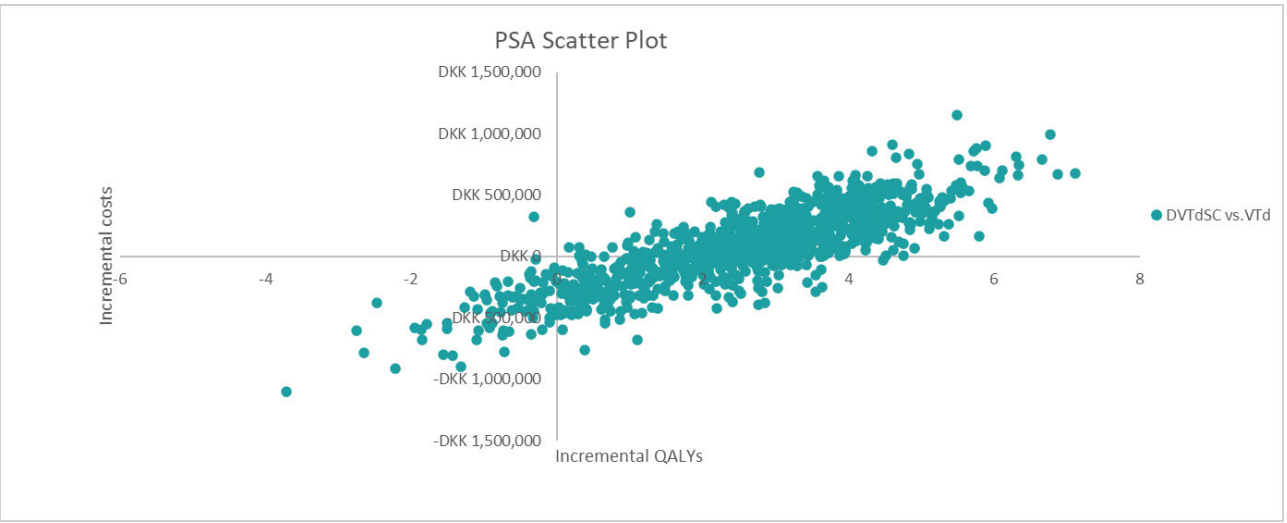
Abbreviations: CE = Cost-effectiveness; VTd = bortezomib, thalidomide, dexamethasone; ICER = incremental cost effectiveness ratio; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone

8.7.2 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 L Probabilistic sensitivity analyses, Table 161.

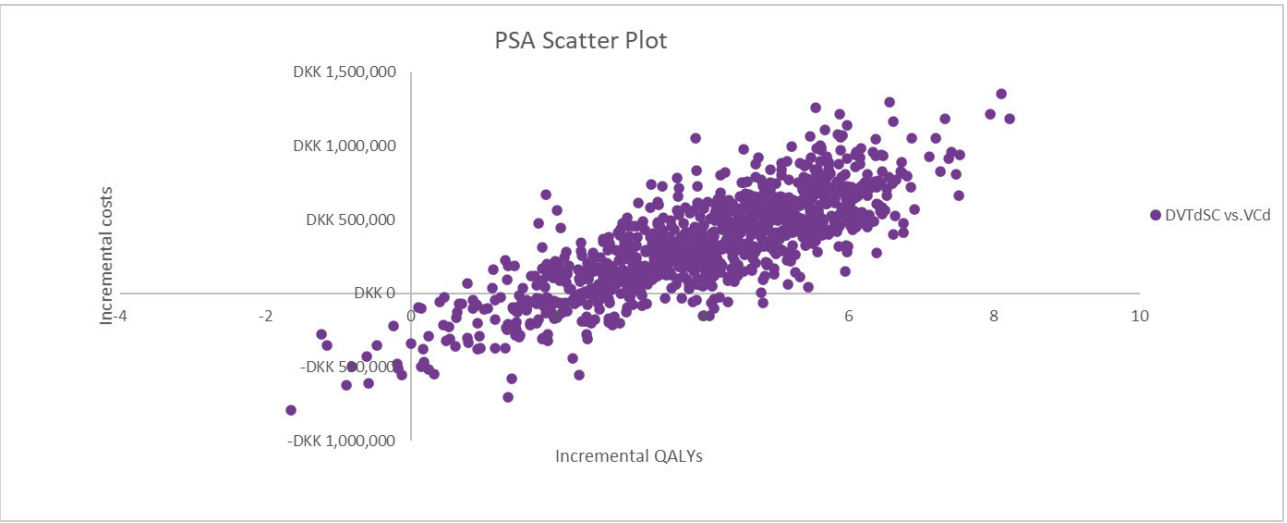
The PSA was performed using 1,000 iterations. As the PSA scatter plots demonstrated that a good distribution of the clouds were around the mean, 1,000 iterations was seen as the right amount of runs for the PSA. The incremental health outcomes in terms of QALYs gained were plotted against the incremental total cost of DVTd vs. VTd, VCd and VRd on the cost-effectiveness plane. The results of the PSA are presented in Figure 18 (DVTd vs. VTd), Figure 19 (DVTd vs. VCd), Figure 20 (DVTd vs. VRd). Based on the results of 1,000 iterations, DVTd compared with VTd resulted in a mean incremental total cost 80,589 DKK, mean incremental QALYs of 2.54 and ICER of 31,782 DKK/QALY. DVTd compared with VCd resulted in a mean incremental total cost of DKK 335,127, mean incremental QALYs of 4.00 and ICER of DKK 83,874 DKK/QALY. DVTd compared with VRd resulted in a mean incremental total cost of 365,611 DKK, mean incremental QALYs of 3.73 and ICER of 98,033 DKK/QALY. The average outcomes are displayed in Table 53. Summary statistics for each treatment regimen are presented in Appendix L Probabilistic sensitivity analyses, Table 162.

Figure 18. PSA Scatter Plot DVTd vs. VTd



Abbreviations: DVTdSC = daratumumab, bortezomib, thalidomide, dexamethasone; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-years; VTd = bortezomib, thalidomide, dexamethasone

Figure 19. PSA Scatter Plot DVTd vs. VCd



Abbreviations: DVTdSC = daratumumab, bortezomib, thalidomide, dexamethasone; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-years; VCd = bortezomib, cyclophosphamide, dexamethasone

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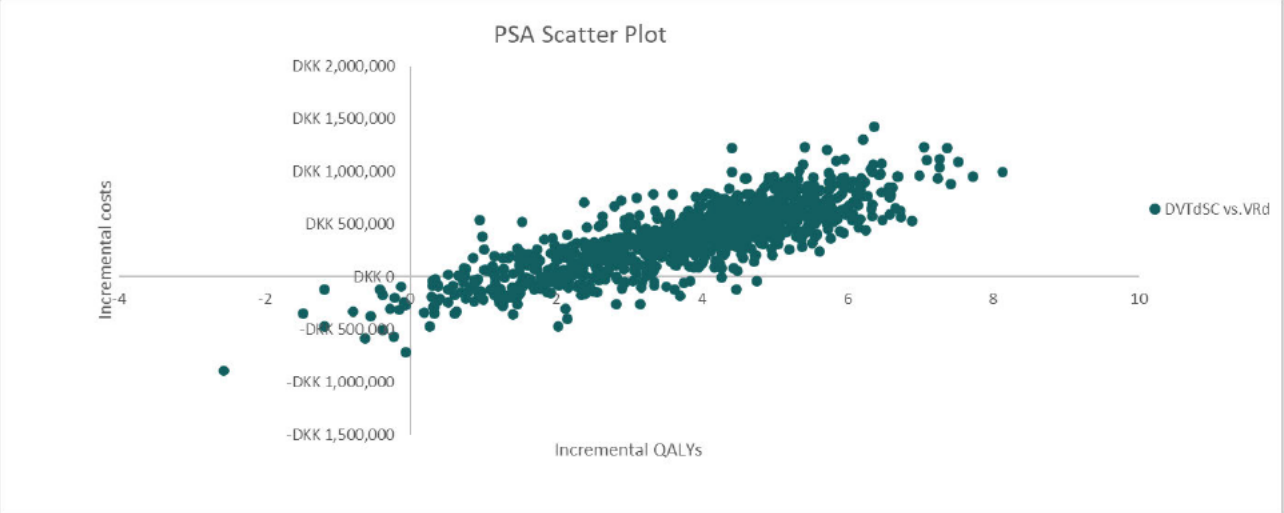
Figure 20. PSA Scatter Plot DVTd vs. VRd



Abbreviations: DVTdSC = daratumumab, bortezomib, thalidomide, dexamethasone; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-years; VRd = bortezomib, lenalidomide, dexamethasone

Table 53 Average Outcomes from PSA

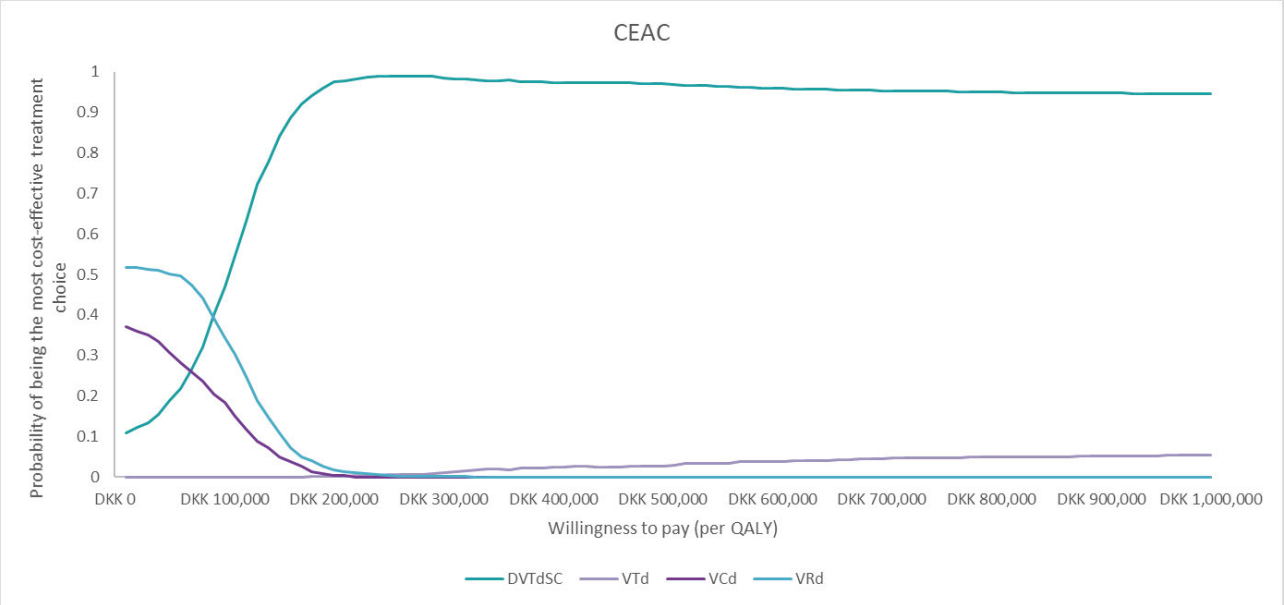
Outcomes	DVTd	VTd	VCd	VRd
Total cost (DKK)	2,386,904	2,306,315	DKK 2,051,777	2,021,293
LYs	12.70	9.61	7.76	8.07
QALYs	10.28	7.74	6.28	6.55
ICER (DVTd vs.) (DKK)	Ref	31,782	83,874	98,033

Abbreviations: DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; LY = life year; PSA = probabilistic sensitivity analyses; QALY = quality-adjusted life year; ICER = incremental cost effectiveness ratio

It should be noted that it is expected that there will be a difference between the DSA and PSA results. With the DSA, one parameter is varied at a time, keeping all other parameters constant. With the PSA, all parameters are varied at the same time based on probability distributions. Therefore, these results cannot be compared directly.

The results of the PSA when all treatment comparators are included are presented as multi-way cost-effectiveness acceptability curves (Figure 21), illustrating the probabilities (proportion of simulations) that an intervention was considered the most cost-effective alternative over a range of thresholds representing the maximum amount payers are willing to pay per QALY gained. The cost-effectiveness acceptability curves highlight that DVTd is the treatment choice most likely to be cost-effective, representing the maximum net benefit, over all other comparators at any willingness-to-pay threshold above 90,000 DKK/QALY.

Figure 21. Cost-effectiveness acceptability curve



Abbreviations: CEAC: Cost-effectiveness acceptability curve; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; QALY = quality-adjusted life-years;

8.7.3 Scenario Analyses

In the scenario analyses, specific parametric distributions and values and assumptions for one or more model parameters were varied, to further identify potential drivers of the ICER. Table 54 presents the scenarios, the justifications for running the scenario, and the corresponding ICER results.

Table 54 Scenario Analyses

Scenario #	Scenario	Justification	ICER vs. DVTd		
			VTd	VCd	VRd
	Base Case		32,979	79,209	97,701
	Different survival curve modelling: Treatment as a predictor and common VTd/DVTd curves				
1	**PFS**: Alternative fit for VTd and DVTd: **Gompertz for both arms** rather than Weibull (base case) **OS: Weibull** (base case)	Weibull for DVTd and VTd is best fit to trial data (base/reference case), but Gompertz is assessed in the scenario analysis as it has a reasonable fit to the trial data and is not crossed by OS curve; although it is pessimistic for both DVTd and VTd, it is explored as a conservative option.	63,686	106,016	117,561
2	**PFS: Weibull** (base case) **OS**: Alternative fit for VTd and DVTd: **Gompertz for both arms** rather than Weibull (base case)	Weibull for DVTd and VTd is best fit to trial data (base/reference case), but Gompertz is assessed in the scenario analysis; although it is pessimistic for both DVTd and VTd, it is explored as a conservative option.	4,125	91,947	134,137
3	**Both** OS and PFS distributions for DVTd and VTd changed at the same time **OS**: **Gompertz** (instead of Weibull) **PFS**: **Gompertz** (instead of Weibull)	Weibull for DVTd and VTd is best fit to trial data (base/reference case), but the joint impact of Gompertz is assessed in the scenario analysis; although it is pessimistic for both DVTd and VTd, it is explored as a conservative.	101,418	187,444	218,776
	Different survival curve modelling: Individual curves				
4	**PFS**: **Weibull** distribution for both arms using individual curves **OS: Weibull** (Treatment as a predictor & common VTd/DVTd curves, base case)	Based on borderline significant p-value for the Schoenfeld residual plot of PFS, proportionality might not hold to model OS and PFS and, therefore, this scenario is explored.	-39,260	25,841	42,316
5	**PFS**: Alternative fit for VTd and DVTd: **Gompertz** rather than Weibull using individual curves **OS: Weibull** (Treatment as a predictor & common VTd/DVTd curves, base case)	Weibull for DVTd and VTd is best fit to trial data, but Gompertz is assessed in the scenario analysis.	30,449	81,026	91,942
6	**PFS**: **Weibull** distribution (Treatment as a predictor & common VTd/DVTd curves, base case) **OS**: **Weibull** distribution for both arms using individual curves	Based on borderline significant p-value for the Schoenfeld residual plot of PFS, proportionality might not hold to model OS and PFS and, therefore, these are explored.	17,934	73,008	93,057
7	**PFS**: **Weibull** distribution (Treatment as a predictor & common VTd/DVTd curves, base case)	Investigation of alternative extrapolations, Weibull for DVTd and VTd is best fit to trial data but log-logistic is explored in the scenario analysis for VTd.	-90,391	64,651	93,487

Scenario #	Scenario	Justification	ICER vs. DVTd		
			VTd	VCd	VRd
	OS: Alternative distributions for OS for **VTd log-logistic** and **Weibull** for **DVTd** using individual curves				
Reference curves – VCd and VRd PFS and OS are extrapolated by applying HRs from MAIC to a reference curve					
8	All comparators use **DVTd** as reference curve for MAIC HRs	Using alternative reference curve, VTd from PETHEMA/GEM has longer term follow-up	33,062	62,367	95,848
9a	All comparators use **VTd** from **PETHEMA/GEM** as reference curve for MAIC HRs		121,729	143,307	158,581
9b	Extrapolate **DVTd via MAIC HR** to **VTd curves from PETHEMA/GEM**		68,087	104,528	118,733
Different TTD assumptions					
10	Duration of DVTd and VTd treatment for induction treatment assumed to be equal to the **Median TTD**	Using different assumption for TTD, DVTd and VTd same assumption as VRd and VCd applying the median TTD	7,713	55,729	73,699
11	Comparator treatment for second- and third-line treatment duration assumed to be **equal to PFS** (i.e., treat to progression)	Uncertainty in true TTD for comparators as only median treatment duration is available and therefore treat to progression is explored	53,349	103,292	132,856
Maintenance treatment					
12	**Maintenance treatment**	Alternative maintenance treatment distributions From Induction Treatment: DVTdSC / VTd / VCd / VRd Lenalidomide: 50% / 70% / 70% / 70% Observation: 50% / 30% / 30% / 30%	-32,207	31,178	47,223
Additional Scenarios					
13	**25-year time horizon**	Shorter time horizon explored compared to the base case and the DSA	37,137	94,450	117,950
14	**20-year time horizon**	Shorter time horizon explored compared to the base case and the DSA	42,889	111,541	140,286
15	**Discount rates** using Belgian discount rates of **3%** for **costs** and **1.5%** health **outcomes**	To demonstrate the impact of discounting used in another country	23,131	56,668	69,808
16	**Age at baseline** 58.3 (Real-world evidence)	Uncertainty in baseline age – impact of higher baseline starting age is explored	33,559	80,340	99,147
17	**Body weight** 73.4 kg (Region Hovedstaden)	Uncertainty in body weight – the impact of a lower body weight is explored	32,979	79,209	97,701
18	**Body surface area** 1.84 m^2 (Region Hovedstaden)	Uncertainty in body surface area– the impact of a lower body surface area is explored	32,974	79,058	97,356

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Scenario #	Scenario	Justification	ICER vs. DVTd		
			VTd	VCd	VRd
19	**Costs - Mode of administration (SC costs)** 1601.5 DKK (reduced by 50%)	Based on DRG, IV and SC administration have the same costs. However, SC administration is expected to have a lower cost.	35,222	74,491	95,381
20a	**One-Time off per death** 32636.8 DKK (cost reduced by 50%)	Due to uncertainty in the end-of-life costs, scenario analyses are conducted	34,348	80,611	99,110
20b	**One-Time off per death** Specialiseret Palliativ indsats, stor – DRG 2021 26MP25:DKK 88,471		32,005	78,212	96,700
21	**Hematologist initial visit and follow-up visit** 3,203 DKK (DRG 2021: 17MA98 MDC17)	Showing impact of using DRG even though this is likely overestimated and regular follow-up visits are already included for administration.	73,287	111,454	129,626
22	**Exclude wastage**	Vial sharing may be possible in Danish clinical practice	30,577	73,655	92,895
23	**No consolidation for DVTd, VTd, VCd, and VRd**	Show cost impact of no consolidation. Efficacy is assumed the same as the base case but costs for consolidation treatment not considered	-13,457	47,479	67,558

Abbreviations: DSA = Deterministic sensitivity analyses; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; HR = Hazard ratio; ICER = incremental cost effectiveness ratio; IV = Intravenous; MAIC = Matching-adjusted indirect comparison; OS = Overall survival; SC = Subcutaneous; PFS = Progression-free survival; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; TTD = time to treatment discontinuation.

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8.7.3.1 OS and PFS Curves

Scenarios 1–7 investigate the impact of changing different assumptions related to the OS and PFS curves. The base case assumes that PFS and OS are modelled using a common curve with treatment as a predictor with the Weibull distribution selected. Using a common curve assumes that there is evidence that the proportional hazard assumption holds. However, as the p-value for the Schoenfeld residual plot is only slightly statistically significant for both PFS and OS, proportionality may not hold (section 19.1.1). Therefore, different assumptions on the OS and PFS curves were tested, including using different parametric distributions, as well as looking at the impact of using individual curves. The importance of doing this is to test the impact of uncertainty in survival settings, as well as looking at any key drivers of results. As the OS and PFS data are immature, they are subject to uncertainty in long-term extrapolations.

In scenario 1, by using Gompertz, there was decreased separation in PFS curves for DVTd and VTd, and much lower PFS for both which resulted in an increased post-progression cost which increased the ICERs from the base case. In scenario 2, the change in OS distribution to Gompertz caused a decreased separation between DVTd and VTd. This resulted in lower incremental QALYs. The shorter OS for DVTd and comparators resulted in decreased post-progression costs, resulting in a lower ICER vs. VTd and increased ICERs from base case vs. VCd and VRd. Combining both the changes in the OS and PFS curves in scenario 3 resulted in decreased separation in both OS and PFS and therefore lower incremental QALYs and increased post-progression costs which shifted the ICERs upwards.

The results of scenarios 4-7 show that using individual PFS and OS parametric distributions for DVTd and VTd from CASSIOPEIA in general yielded lower and similar ICERs for most scenarios compared with using joint PFS and OS parametric distributions for DVTd and VTd from CASSIOPEIA. The results are primarily driven by the long-term extrapolations for OS and PFS (section 19.1.3 and section 19.2.3), as individual distributions result in better survival outcomes for DVTd, compared with joint parametric distributions with treatment as predictor. However, the immaturity of the data as well as potential violation of the proportional hazards assumption should be considered. For scenario 4, independently fitted PFS curves gave more separation between DVTd and VTd resulting in increased incremental progression-free QALYS and hence a reduction in ICERs. For scenario 5, using individual Gompertz curves results in lower PFS and hence lower progression-free QALYs, but also increased post-progression costs, and the ICERs are only changed minorly. For scenario 6, the independently fitted OS curves were similar to the joint Weibull distribution and the ICERs only changed minimally. In scenario 7, a different distribution was used for DVTd to VTd, with the resulting OS for VTd was much closer to the DVTd curve. This resulted in higher QALYs for comparators but also increased subsequent treatments costs for the comparators. The ICERs were decreased vs. VCd and VRd and in the comparison vs VTd a cost-saving result was obtained.

8.7.3.2 MAIC Reference Curves

Scenarios 8–9 assess the impact of using different reference curves for the indirect comparisons for OS and PFS. Reference curves are used to generate curves for the other comparators not investigated within the CASSIOPEIA trial. This is done by applying an HR obtained from the MAIC to either the VTd or DVTd curves from CASSIOPEIA, or the VTd curve from the PETHEMA trial, which is based on longer follow-up data than CASSIOPEIA. In the base case, the HRs used for VCd and VRd use the VTd curve from CASSIOPEIA as the reference. Using VTd as the reference benefits from the greater number of events in the VTd arm, compared with DVTd. However, there is uncertainty around which treatment curve should be used as the reference curve to apply the HRs for VCd and VRd, and therefore it is tested if there is any impact by using the DVTd arm, or VTd from PETHEMA/GEM as the reference curve.

Using DVTd as the reference curve for all comparators results in similar ICER vs VTd and slightly lower ICERs vs VCd and VRd, as using DVTd curve confers OS benefits to all comparators, however due to the subsequent treatments following comparators, the post-progression costs are also impacted. In scenario 9A, using the VTd curve from PETHEMA/GEM for comparators results in lower OS for comparators resulting in lower subsequent treatment costs, therefore higher

ICERs. Extrapolating all comparators including DVTd via HR to PETHEMA VTd curve (scenario 9b), resulted in lower PFS and lower costs and resulted in ICERs that were lower than scenario 9A, but higher than the base case. Scenarios 9A and 9B are associated with methodological limitations. There are fewer patients in the VTd curve from the PETHEMA/GEM trial, so this causes concern for using this as the reference curve. In addition, as PETHEMA/GEM is not the CASSIOPEIA trial, it may not be an appropriate reference curve to use. Using scenario 9B may be problematic as DVTd data is available from the trial.

8.7.3.3 TTD and maintenance distributions

Scenarios 10–12 assess the impact of different treatment duration assumptions, as well as different maintenance treatment distributions.

There is uncertainty in the true treatment duration for both induction treatment and subsequent lines of treatment in clinical practice, as the median duration is only reported in the trial publications for comparators. Scenarios 10–11 test the different assumptions related to treatment duration. For scenario 12, in the base case, the maintenance phase consists of lenalidomide (70%) and observation (30%) based on the expected DK clinical practice, meaning there are drug costs accumulated during this period for the patients receiving lenalidomide. However, since DVTd is a new regimen, there is uncertainty related to the proportion of patients that will received lenalidomide maintenance subsequently. Scenarios 12 were included to test the impact of an alternative maintenance treatment distribution for DVTd.

In scenario 10, using the median treatment duration for induction and consolidation (for DVTd and VTd) decreased costs for DVTd and thus ICERs were reduced. However, this approach may be inappropriate since TTD evidence is available from the trial, although this approach is in line with the method for other comparators. Using the median PFS for the estimation of the TTD of subsequent treatments resulted in higher ICERs compared with the base case (scenario 11). Using a differing maintenance distribution (scenario 12) assumes a less expensive maintenance treatment distribution for DVTd in comparison to its comparators, and therefore, this reduced the ICERs. Since daratumumab maintenance is not approved by EMA and not used in Danish clinical practice, 50% lenalidomide maintenance treatment was assumed. The base case maintenance distribution was kept for VTd, VCd and VRd to allow for following expected clinical practice. The subsequent treatment mix was assumed the same as the base case for scenario 12.

8.7.3.4 Additional Scenarios

Scenarios 13–23 assessed different time horizons, discounting rates, impact of age, body weight, body surface area, different cost input, excluding drug wastage, and the impact of not using consolidation to see the impact of changing these model settings on the ICERs.

When using a 20 and 25-year time horizon (scenario 13 and 14), the long-term QALY benefits are not captured to the same degree but drug acquisition costs are mainly captured, and therefore this drives the ICERs up. These scenarios were tested even though applying a 40-year time horizon is recommendation to reflect a life-time horizon. For the scenario for alternative discount rates from Belgium with different discount rates for costs and health outcomes (scenario 15), the ICERs decreased. Adjustments to age, body weight and body surface area had minimal impact on the ICERs (scenario 16, 17, and 18). The scenarios for cost input (19-21) had generally minimal impact the ICERs, except adjustments to the cost of hematologist visits which increased the ICERs. Excluding wastage (scenario 22) resulted in lower ICERs. Assuming no consolidation treatment across all treatments (scenario 23) resulted in decreased ICERs, but it should be noted that efficacy is assumed the same as the base case in this scenario and only consolidation costs are impacted.

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9. Budget impact analysis

The calculations of the budget impact analysis can be found in the cost-effectiveness Excel model. The number of transplant eligible patients per year are assumed to be 120 based on treatment guidelines from the Medicines Council (3). For the reference scenario (DVTd not recommended), it is assumed that 0% of patients will be administered DVTd, 5% are administered VTd, 47.5% are administered VCd, and 47.5% are administered VRd. In the budget impact analysis where DVTd is recommended, a gradual uptake for DVTd is assumed starting at 10% (12 patients) in year 1, 15% (18 patients) in year 2, and stable market share at 20% (24 patients) in year 3, year 4, and year 5 (see Table 55). The relatively low market shares are assumed due to thalidomide is not currently widely used in Denmark and thalidomide is part of the DVTd combination. It is assumed that DVTd will take all market shares from VTd and equally split market shares from VCd and VRd. The cost included in the analysis are the same as included in the base case analysis but excluding patient costs and undiscounted according to the Medicines Council guidelines. The budget impact results are presented in Table 59.

Table 55 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
DVTd	12 (10%)	18 (15%)	24 (20%)	24 (20%)	24 (20%)
VTd	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
VCd	54 (45%)	51 (42.5%)	48 (40%)	48 (40%)	48 (40%)
VRd	54 (45%)	51 (42.5%)	48 (40%)	48 (40%)	48 (40%)

Abbreviations: DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone

Table 56 Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
DVTd	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
VTd	6 (5%)	6 (5%)	6 (5%)	6 (5%)	6 (5%)
VCd	57 (47.5%)	57 (47.5%)	57 (47.5%)	57 (47.5%)	57 (47.5%)
VRd	57 (47.5%)	57 (47.5%)	57 (47.5%)	57 (47.5%)	57 (47.5%)

Abbreviations: DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone

Table 57 Costs per year - if the pharmaceutical is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Induction/Consolidation Treatment					
Drug acquisition	12,892,628	15,355,126	17,817,624	17,817,624	17,817,624
Drug administration	4,006,308	4,392,273	4,778,238	4,778,238	4,778,238
Concomitant medications	14,959	21,052	27,145	27,145	27,145
Routine monitoring	141,306	145,148	148,991	148,991	148,991
Total	***17,055,201***	***19,913,599***	***22,771,998***	***22,771,998***	***22,771,998***
Maintenance Treatment					
Drug acquisition	19,370,763	59,995,017	75,925,420	76,477,986	76,849,805
Drug administration	0	0	0	0	0
Routine monitoring	317,290	1,019,197	1,614,332	2,113,480	2,183,115
Total	***19,688,053***	***61,014,215***	***77,539,752***	***78,591,466***	***79,032,921***

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Post-Progression					
Second-line Treatment					
Drug acquisition	2,995,337	12,002,978	24,743,373	38,974,871	39,225,226
Drug administration	512,746	1,900,338	3,708,202	5,635,945	5,736,624
Routine monitoring	15,976	79,644	183,607	311,090	315,989
Total	***3,524,059***	***13,982,959***	***28,635,182***	***44,921,906***	***45,277,839***
Third-line Treatment					
Drug acquisition	140,079	1,285,381	3,889,427	7,711,109	7,867,177
Drug administration	18,771	164,631	482,830	935,662	933,898
Routine monitoring	1,328	15,538	58,569	142,079	152,780
Total	***160,179***	***1,465,550***	***4,430,827***	***8,788,850***	***8,953,855***
Terminal Care	212,369	573,692	980,742	1,408,571	1,405,905
Adverse Event Management	118,178	139,599	161,021	161,021	161,021
ASCT	19,744,256	19,733,939	19,723,622	19,723,622	19,723,622
TOTAL	**60,502,293**	**116,823,553**	**154,243,143**	**176,367,433**	**177,327,161**

Abbreviations: ASCT = autologous stem cell transplant

Table 58 Costs per year - if the pharmaceutical is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Induction/Consolidation Treatment					
Drug acquisition	7,899,402	7,899,402	7,899,402	7,899,402	7,899,402
Drug administration	3,408,204	3,408,204	3,408,204	3,408,204	3,408,204
Concomitant medications	8,606	8,606	8,606	8,606	8,606
Routine monitoring	137,354	137,354	137,354	137,354	137,354
Total	***11,453,566***	***11,453,566***	***11,453,566***	***11,453,566***	***11,453,566***
Maintenance Treatment					
Drug acquisition	19,698,904	60,355,272	75,968,971	75,968,971	75,968,971
Drug administration	0	0	0	0	0
Routine monitoring	322,586	1,024,079	1,610,678	2,085,714	2,460,699
Total	***20,021,490***	***61,379,351***	***77,579,649***	***78,054,685***	***78,429,670***
Post-Progression					
Second-line Treatment					
Drug acquisition	3,207,690	12,874,617	26,721,285	42,345,344	57,709,216
Drug administration	544,282	2,014,640	3,942,980	6,000,708	7,941,489
Routine monitoring	16,807	84,129	195,142	332,409	478,026
Total	***3,768,778***	***14,973,386***	***30,859,407***	***48,678,461***	***66,128,731***
Third-line Treatment					
Drug acquisition	145,893	1,345,261	4,098,553	8,182,879	13,068,933
Drug administration	20,055	176,672	522,806	1,023,374	1,611,855
Routine monitoring	1,360	15,916	60,047	145,730	278,912
Total	***167,309***	***1,537,849***	***4,681,407***	***9,351,983***	***14,959,700***
Terminal Care	223,168	609,577	1,055,413	1,528,793	2,010,904

Adverse Event Management	90,533	90,533	90,533	90,533	90,533
ASCT	19,736,477	19,736,477	19,736,477	19,736,477	19,736,477
TOTAL	**55,461,320**	**109,780,739**	**145,456,452**	**168,894,497**	**192,809,580**

Abbreviations: ASCT = autologous stem cell transplant

Budget impact

Table 59 presents the budget impact analysis for the possible introduction of DVTd. The analysis includes all treatment related costs relevant for the regions. The number of patients in the reference and alternative scenarios are based on Table 55 and Table 56. The budget impact of recommending DVTd ranges from an increase of costs of 5,068,402 DKK in year one to a reduction of cost of -15,527,747 DKK in year five, with the market share for DVTd increasing from 10% to 20%. The reduction of the cost in year 5 is primarily driven by patients starting subsequent treatments in the comparator arms at a faster rate than for DVTd where progression itself occurs later for patients on DVTd, given the better PFS.

Table 59 Expected incremental budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Induction/Consolidation Treatment					
Drug acquisition	4,993,225	7,455,724	9,918,222	9,918,222	9,918,222
Drug administration	598,104	984,069	1,370,034	1,370,034	1,370,034
Concomitant medications	6,353	12,446	18,539	18,539	18,539
Routine monitoring	3,952	7,795	11,637	11,637	11,637
Total	***5,601,635***	***8,460,033***	***11,318,432***	***11,318,432***	***11,318,432***
Maintenance Treatment					
Drug acquisition	-328,141	-360,255	-43,551	509,015	880,834
Drug administration	0	0	0	0	0
Routine monitoring	-5,296	-4,882	3,654	27,766	-277,584
Total	***-333,437***	***-365,137***	***-39,897***	***536,781***	***603,251***
Post-Progression					
Second-line Treatment					
Drug acquisition	-212,353	-871,639	-1,977,912	-3,370,473	-18,483,990
Drug administration	-31,535	-114,302	-234,778	-364,763	-2,204,865
Routine monitoring	-831	-4,485	-11,535	-21,319	-162,036
Total	***-244,719***	***-990,426***	***-2,224,225***	***-3,756,555***	***-20,850,892***
Third-line Treatment					
Drug acquisition	-5,814	-59,879	-209,126	-471,770	-5,201,756
Drug administration	-1,284	-12,041	-39,977	-87,712	-677,957
Routine monitoring	-32	-378	-1,478	-3,651	-126,131
Total	***-7,130***	***-72,299***	***-250,580***	***-563,133***	***-6,005,844***
Terminal Care	-10,799	-35,885	-74,671	-120,221	-604,999
Adverse Event Management	27,645	49,066	70,488	70,488	70,488
ASCT	7,779	-2,538	-12,855	-12,855	-12,855
TOTAL	**5,040,973**	**7,042,815**	**8,786,691**	**7,472,935**	**-15,482,420**

Abbreviations: ASCT = autologous stem cell transplant

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10. Discussion on the submitted documentation

CASSIOPEIA is a randomized, open-label, active control, parallel group, multicenter phase III study comparing the efficacy and safety of DVTd vs VTd in patients with NDMM who are eligible for ASCT. The study was conducted in line with The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements. Steps taken to ensure the accuracy and reliability of the data included the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by sponsor representatives, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. The study had an open label design because of the difference in mode of administration for the trial drugs (daratumumab infusions are administered over a longer duration than bortezomib injections). However, the risk for bias was minimized since patients were randomized using a central interactive web response system (IWRS). In addition, outcomes were reviewed by an Independent Data Monitoring Committee (IDMC) which considered efficacy and safety outcomes to be robust, leading to regulatory approval by EMA.

CASSIOPEIA enrolled participants generally expected to be representative of NDMM who are eligible for ASCT in Denmark. While all patients were recruited outside of the Denmark, all the sites were in countries expected to have similar demographics to Denmark (France, Belgium and the Netherlands). Limited real world evidence from Denmark exists around patient characteristics and prognostic factors for patients with NDMM who are eligible for ASCT. However, as described in section 15.1.2, based on the evidence available, prognostic factors in the CASSIOPEIA trial compared with the Danish patient population, such as age, gender, staging and high risk are evaluated to be comparable.

The clinical documentation from CASSIOPEIA clearly demonstrated statistically significant differences in favor of DVTd over VTd for both PFS and OS across all data-cuts as well as the different types of analyses. These analyses included assessing PFS and OS regardless of 2nd randomization and a per-protocol pre-specified statistical analysis performed using the inverse probability weighting (IPW) method to adjust for the second randomisation to mitigate for the potential bias caused by study maintenance treatment.

In the absence of a viable network of studies with sufficient comparability to inform a network-meta analysis, an unanchored matching-adjusted indirect comparison (MAIC) was performed to compare PFS and OS for DVTd versus both VCd and VRd. MAIC analyses based on the CASSIOPEIA have been published by Moreau et al. 2020(8) in a full-text article published in a scientific, peer-reviewed journal which is strengthening the basis for the evidence of the indirect comparison. Compared to Moreau et al. 2020(8) which was focusing on the 1st data-cut from CASSIOPEIA (median follow-up of 18.8 months), the analyses conducted in the application has incorporated 2nd data-cut with a median follow-up of 29.2 months for CASSIOPEIA. The original as well as the updated MAIC showed that DVTd had significantly significant benefits for PFS and OS compared with VCd and VRd.

The analyses from the MAIC was not without limitations as emphasized in the discussion and limitation section 7.2.3.1 and 7.3.3.1. A MAIC is the best method to adjust for baseline variables in cases where IPD is only available from one treatment arm. However, it effectively assumes that absolute outcomes can be predicted from the covariates (baseline variables).(130). The OS results should be interpreted with some caution due to the immaturity of OS data in CASSIOPEIA. A more stringent assessment method (strict computerized algorithm) was used in CASSIOPEIA for progressive disease assessment, which could potentially favor comparators by underestimating the treatment effect observed in CASSIOPEIA. It was not feasible to adjust for differences in the post-induction treatment schema, which involved receipt of a second ASCT and different maintenance therapies (daratumumab vs. lenalidomide) between the trials in the MAIC. Therefore, the results of the analysis reflect a comparison of the overall treatment schema of the trials rather than a comparison of the induction therapies alone. Finally, there is a possibility for residual bias due to

unaccounted prognostic factors or effect modifiers, differences in trial designs and inclusion criteria and differences in post-induction therapy treatment schema and maintenance regimens.

Nevertheless, in the absence of patient level data for both studies, MAIC is the best method to derive indirect evidence between regimens. In addition, it should be noted that MM Expert Committee did not conclude that there was an efficacy difference between VTd, VCd, and VRd (other than better response for VTd)(3) which means that we may expect similar findings if DVTd had been compared directly with VCd and VRd in a head-to-head trial. Therefore, from a naïve perspective, the results from the CASSIOPEIA trial are also indicative for the other comparators. Lastly, the results of MAIC conducted between VTd and VCd and VRd similarly did not show significant differences between the regimens.

A three-health state-transition cohort model structure, accepted by health technology assessment bodies and commonly used in peer-reviewed publications for the target indication of this analysis, was selected to follow patients from an initial line of treatment after diagnosis into later lines until death. The model was implemented through a partitioned survival approach, which was based on the use of independent progression-free survival (PFS) by treatment line and overall survival (OS) curves. The model was developed based on the clinical and treatment pathways for patients with NDMM who are eligible for ASCT; consideration of key clinical aspects (PFS, OS, treatment duration) that affect clinical outcomes, costs and treatment decisions. The cost-effectiveness of DVTd was evaluated compared with VTd, VCd and VRd using the best available clinical and economic evidence and local Danish data inputs were applied when available. The model incorporates utility values to each health state in the model to capture the quality of life associated with treatment and disease outcomes. The utility values were derived from an analysis of EQ-5D-5L which is the preferred instrument by the Medicines Council where data originated from the CASSIOPEIA trial. In addition, preference weights based on the general Danish population was applied.(175) There were uncertainty related to some of the input in the model. However, deterministic sensitivity analyses, probabilistic sensitivity analyses, and scenario analyses were used to test the influence of the uncertainty of the model parameters on the model's results.

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Not applicable

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13. Appendix A – Literature search for efficacy and safety of intervention and comparator(s)

13.1 Objective of the literature search

The literature search aimed to address the following research questions:

- According to the evidence from RCTs, what is the efficacy of DVTd and relevant comparators as induction and consolidation therapy in transplant-eligible patients with NDMM?
- According to the evidence from RCTs, what is the safety of DVTd and relevant comparators as induction and consolidation therapy in transplant-eligible patients with NDMM?

13.2 Databases:

Searches were performed in the following indexed databases on May 2018, May 2020, and November 2020 to identify studies published since 1995 (Table 60):

- MEDLINE and MEDLINE In-Process (via PubMed)
- Embase (via embase.com)
- Cochrane Database of Systematic Reviews (CDSR; via the Cochrane Library)
- Cochrane Central Register of Controlled Trials (CENTRAL; via the Cochrane Library)
- Database of Abstracts of Reviews of Effects (DARE; via the Cochrane Library, archive database only)

Key proceedings from 2015 were reviewed for relevant abstracts from the following conferences (Table 60):

- American Society of Clinical Oncology (ASCO) Annual Meetings
- American Society of Hematology (ASH) Annual Meetings
- European Hematology Association (EHA) Annual Meetings
- International Myeloma Working Group (IMWG) Biannual International Workshops
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Annual International Meetings and European Congresses.

Supplementary searches were also conducted on the websites of the European Medicines Agency (EMA) and the United States (US) Food and Drug Administration (FDA) to identify any missing or supplementary data on clinical efficacy and safety.

Table 60 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	1995-2018	31.05.2018 (Initial SLR)
		2018-04.29.2020	29.04.2020 (1st update)
		01.04.2020 – 02.11.2020	02.11.2020 (2nd update)
MEDLINE and MEDLINE In-Process	Pubmed.ncbi.nlm.nih.gov	1995-2018	31.05.2018 (Initial SLR)
		2018-04.29.2020	29.04.2020 (1st update)
		01.04.2020 – 02.11.2020	02.11.2020 (2nd update)

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Cochrane Central Register of Controlled Trials	cochranelibrary.com	1995-2018	31.05.2018 (Initial SLR)
		2018-04.30.2020	30.04.2020 (1st update)
		01.04.2020 – 02.11.2020	02.11.2020 (2nd update)
Cochrane Database of Systematic Reviews	cochranelibrary.com	1995-2018	31.05.2018 (Initial SLR)
		2018-04.30.2020	30.04.2020 (1st update)
		01.04.2020 – 02.11.2020	02.11.2020 (2nd update)
ASCO	Embase.com	2015-2018	31.05.2018 (Initial SLR)
		2018-2020	30.04.2020 (1st update)
		2020	02.11.2020 (2nd update)
ASH	Embase.com	2015-2018	31.05.2018 (Initial SLR)
		2018-2020	30.04.2020 (1st update)
		2020	02.11.2020 (2nd update)
EHA	Embase.com	2015-2018	31.05.2018 (Initial SLR)
		2018-2020	30.04.2020 (1st update)
		2020	02.11.2020 (2nd update)
IMWG	Embase.com	2015-2018	31.05.2018 (Initial SLR)
		2018-2020	30.04.2020 (1st update)
		2020	02.11.2020 (2nd update)
ISPOR	Embase.com	2015-2018	31.05.2018 (Initial SLR)
		2018-2020	30.04.2020 (1st update)
		2020	02.11.2020 (2nd update)

Abbreviations: SLR = systematic literature review; ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; EHA = European Hematology Association; ESMO = European Society for Medical Oncology; IMWG = International Myeloma Working Group; ISPOR = International Society for Pharmacoeconomics and Outcomes Research

Table 61 Supplementary manual searches

Database	Platform	Relevant period for the search	Date of search completion
EMA	https://www.ema.europa.eu/en	1995-2018	31.05.2018 (Initial SLR)
		2018-2021	11.03.2021 (Additional search)*
FDA	https://www.fda.gov	1995-2018	31.05.2018 (Initial SLR)

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	2018-2021	11.03.2021 (Additional search)*

Abbreviations: EMA = European Medicines Agency; FDA = Food and Drug Administration; SLR = systematic literature review
*No new study or data was identified in this update.

13.3 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 62.

Table 62 PICOS Selection Criteria for Efficacy and Safety

Category	Inclusion Criteria	Exclusion Criteria
Population	Transplant-eligible patients with previously untreated NDMM	Transplant-ineligible or previously treated patients with MM
Interventions/ Comparators	Licensed treatments, treatments used in routine care, or treatments under investigation provided as a single agent or a combination treatment. These included, but were not limited to, the following^: DVTd VTd PAD VRd VCd Vd VDd Rd IRd KTd KRd	Interferon alpha used as monotherapy or in combination Studies evaluating the preferred sequence of treatments Treatments aimed at managing complications of MM that are not provided as part of best supportive care or as a combination treatment with a drug of interest (i.e., calcium, zoledronic acid, antibiotics, or bisphosphonate) Studies analyzing the efficacy of maintenance therapy only
Outcomes	Clinical efficacy Response (including for example, ORR, sCR, CR, VGPR, PR, SD, and MRD)~ Survival (OS, PFS, TTP, PFS2) Clinical safety Discontinuations due to AEs Grade 3/4 AEs	Publications that do not report on clinical efficacy or safety outcomes (i.e., study protocols)

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Study design	RCTs (phase II and III)	Case reports, comments and editorials, animal/in-vitro studies, observational studies, single-arm trials, and SLRs
Date limit*	Abstracts and other material from conferences from 2015 through 2020	Conference abstracts or materials presented prior to 2015
	Publications indexed in electronic databases since 1995	Publications indexed in 1994 or earlier

^ Decisions on which treatments to focus on will occur during the feasibility assessment and will be based on comparators of relevance and will be informed by treatment guidelines (including ESMO, NCCN, etc.) to help inform decision-making. Comparators not directly relevant in the Danish setting was included to assess whether a network meta-analysis can be conducted for the indirect treatment comparison.
~ Response is a relevant outcome and has shown to correlate with PFS and OS. Response was included as a relevant outcome to assess whether it was feasible to conduct an indirect treatment comparison for this outcome measure.
* Date limit for initial SLR and the two updates
Abbreviations: AE = adverse event; CR = complete response; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; IRd = ixazomib, lenalidomide, and dexamethasone; KRd = carfilzomib, lenalidomide, and dexamethasone; KTd = carfilzomib, thalidomide, and dexamethasone; MM = multiple myeloma; MRD = minimal residual disease; NDMM = newly diagnosed multiple myeloma; ORR =overall response rate; OS = overall survival; PAD = bortezomib, doxorubicin, and dexamethasone; PFS = progression-free survival; PFS2 = time to second disease progression; PR = partial response; RCT = randomized controlled trial; Rd = lenalidomide and dexamethasone; sCR = stringent complete response; SD = stable disease; SLR = systematic literature review; TTP = time to progression; VCd = bortezomib, cyclophosphamide, and dexamethasone; Vd = bortezomib and dexamethasone; VDd = bortezomib, doxil, and dexamethasone; VGPR = very good partial response; VRd = bortezomib, lenalidomide, and dexamethasone; VTd = bortezomib, thalidomide, and dexamethasone

13.3.1 Search syntaxes:

13.3.1.1 MEDLINE AND MEDLINE® via PubMed)

Table 63 MEDLINE and MEDLINE® Search Strategy

Search Criteria	Search Algorithm	Search Yield (Apr 24, 2020) #	Search Yield (Apr 29, 2020)	Search Yield (Nov 02, 2020)
1	("Multiple Myeloma"[MeSH] OR ("multiple"[TIAB] AND myelom*[TIAB]) OR "plasma cell myeloma"[TIAB] OR "Kahler's disease"[TIAB] OR "Plasmacytoma"[MeSH] OR plasmacytom*[TIAB])	60,028	60,069	61,751
2	("naïve"[TIAB] OR (new*[TIAB] AND diagnos*[TIAB]) "untreated"[TIAB] OR (("primary"[TIAB] OR "initial"[TIAB] OR "induction"[TIAB] OR "naïve"[TIAB]) AND ("therapy"[TIAB] OR "treatment"[TIAB])) OR (("front"[TIAB] OR "first"[TIAB] OR "1st"[TIAB]) AND ("line"[TIAB])) OR consolidat*[TIAB])	1,4968,20	1,498,135	1,485,628^
3	("randomized"[TIAB] OR "randomised"[TIAB] OR "controlled trial"[TIAB] OR "clinical trial"[TIAB] OR "cross over"[tiab] OR "cross-over"[tiab] OR "crossover"[tiab] OR (doubl* AND blind*[TIAB]) OR (singl* AND blind*[TIAB]) OR ("open"[TIAB] AND label*[TIAB]) OR "placebo"[TIAB] OR "Clinical Trial" [Publication Type])	1,308,573	1,309,554	1,350,172
4	#1 AND #2 AND #3	1,708	1,708	1,547
5	"Animals"[MeSH] NOT "Humans"[MeSH]	4,693,580	4,694,863	4,752,218
6	"letter"[PT] OR "editorial"[PT] OR "congresses"[PT]	1,595,549	1,597,265	1,650,558
7	((review[PT]) NOT (systematic OR meta-analy* OR ((indirect OR mixed) AND "treatment comparison")))	2,360,604	2,362,310	2,419,291

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8	#4 NOT #5 NOT #6 NOT #7	1,497	1,497	1,356
9	#8 AND Filters on: Publication date from 1995/01/01 to 2018/05/31	**1,190**	-	-
10	#8 AND Filters on: Publication date from 2018/05/31 to 2020/05/01	-	196	-
11	#8 AND Filters on: Publication date from 01/04/2020 to 31/12/2020	-	-	71

The limits for this search included only items with abstracts. We have also limited the search to exclude animal-only studies (search row "5" above), letters and editorials (search row "6"), and non-systematic reviews (search row "7").
#The initial search was conducted in May 2018, with an amendment on April 24, 2020.
* In-process records are captured by searching in the title/abstract fields, identifying relevant papers that have not yet been indexed with MeSH headings.
^ Compared to the first update, the number of hits was lower in second update as the PubMed website was completed rebuilt last May, resulting a change in number of hits. See KA-05275 · NLM Customer Support Center (nih.gov) for more details

13.3.1.2 EMBASE

Table 64 EMBASE Search Strategy*

Search Criteria	Search Algorithm	Search Yield (May 31, 2018)	Search Yield (Apr 30, 2020)	Search Yield (Nov 02, 2020)
1	'multiple myeloma'/exp OR 'multiple myeloma' OR ('multiple':ab,ti AND myeloma*:ab,ti) OR 'plasma cell myeloma':ab,ti OR (kahler*:ab,ti AND 'disease':ab,ti) OR 'plasmacytoma'/exp OR 'plasmacytoma' OR plasmacytom*:ab,ti	85,626	97,662	100,720
2	'naïve':ab,ti OR (new*:ab,ti AND diagnos*:ab,ti) OR 'untreated':ab,ti OR (('primary':ab,ti OR 'initial':ab,ti OR 'induction':ab,ti OR 'naïve':ab,ti) AND ('therapy':ab,ti OR 'treatment':ab,ti)) OR (('front':ab,ti OR 'first':ab,ti OR '1st':ab,ti) AND ('line':ab,ti)) OR consolidat*:ab,ti	1,950,220	2,286,870	2,378,243
3	'randomized':ab,ti OR 'randomised':ab,ti OR 'controlled trial':ab,ti OR 'clinical trial':ab,ti OR 'cross over':ab,ti OR 'crossover':ab,ti OR 'cross-over':ab,ti OR (doubl* AND blind*:ab,ti) OR (singl* AND blind*:ab,ti) OR ('open':ab,ti AND label*:ab,ti) OR 'placebo':ab,ti	1,062,056	1,243,811	1,295,307
4	#1 AND #2 AND #3	2,749	3,464	3,611
5	[animals]/lim NOT [humans]/lim	5,369,071	5,779,705	5,868,170
6	letter:it OR editorial:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim	5,357,243	6,263,156	6,450,628
7	review:it NOT ((systematic OR meta) AND analy* OR ((indirect OR mixed) AND 'treatment comparison'))	2,251,368	2,456,494	2,521,807
8	#4 NOT #5 NOT #6 NOT #7	781	927	985
9	#8 AND ([article]/lim OR [article in press]/lim OR [in process]/lim) AND [1995-2018]/py	654	-	-
10	#8 AND ([article]/lim OR [article in press]/lim OR [in process]/lim) AND [2018-2020]/py	-	169	-

11	#8 AND ([article]/lim OR [article in press]/lim OR [in process]/lim) AND [1-4-2020/sd	-	-	79

The limits for this search included only items with abstracts. We have also limited the search to exclude animal-only studies (search row "5" above), letters and editorials (search row "6"), and non-systematic reviews (search row "7").
* In-process records are captured by searching in the title/abstract fields, identifying relevant papers that have not yet been indexed with Emtree terms.

13.3.1.3 The Cochrane Library

1. Cochrane Database of Systematic Reviews (CDSR)
2. Cochrane Central Register of Controlled Trials (CENTRAL)
3. Database of Abstracts of Reviews of Effects (DARE; archive database only)[2]

Table 65 Cochrane Library Search Strategy

Search Criteria	Search Algorithm	Search Yield (May 31, 2018)	Search Yield (April 29, 2020)	Search Yield (Nov 02, 2020)
1	MeSH descriptor: [Multiple Myeloma] OR MeSH descriptor: [Plasmacytoma] OR (("multiple" and myelom*) or "plasma cell myeloma" or "Kahler's disease" or plasmacytom*):ti,ab,kw	3,814	5,053	5,234
2	(naïve or "newly diagnosed" or "front*line" or untreated or "first*line" or "induction therapy" or "primary therapy" or "primary treatment" or untreated or "treatment naïve" or "treatment-naïve" or consolidat*):ti,ab,kw	38,129	67,184	70,409
3	#1 and #2	1,179	1,680	1,821
4	(randomized controlled trial or controlled clinical trial or clinical trial):pt	535,843	568,582	582,422
5	("random" or "trial").tw	8,234	9,432	9,714
6	#4 or #5	541,369	575,094	589,139
7	#3 and #6	342	389	425
8	Publication Year from 1995 to 2018, in Trials	275	-	
9	Publication Year from 1995 to 2018, in Cochrane Reviews (Reviews and Protocols) and Other Reviews	16	-	-
10	#8 and #9	291	-	-
11	Publication Year from 2018 to 2020, in Trials	-	93	-
12	Publication Year from 2018 to 2020, in Cochrane Reviews (Reviews and Protocols) and Other Reviews	-	119	-
13	#11 AND #12	-	88	-
14	#10 with Cochrane Library publication date from Apr 2020 to Dec 2020, in Cochrane Reviews and Trials	-	-	6

[2] Of note: funding for this database lapsed in 2015 and so it is now available only as non-updated archives.

Below is the search for abstracts on clinical data indexed in EMBASE for ASCO, ASH, EHA, IMWG, and ISPOR. This search will be validated and supplemented by searching the conferences websites directly.

13.3.1.4 ASCO, ASH, EHA, ISPOR and IMWG

Table 66 EMBASE Search Strategy (Conference Abstracts 2015–2020)

Search Criteria	Search Algorithm	Search Yield (May 31, 2018)	Search Yield (May 04, 2020)	Search Yield (Nov 02, 2020)
1	'multiple myeloma'/exp OR 'multiple myeloma' OR ('multiple':ab,ti AND myeloma*:ab,ti) OR 'plasma cell myeloma':ab,ti OR (kahler*:ab,ti AND 'disease':ab,ti) OR 'plasmacytoma'/exp OR 'plasmacytoma' OR plasmacytom*:ab,ti	85,626	97,662	100,720
2	'naïve':ab,ti OR (new*:ab,ti AND diagnos*:ab,ti) OR 'untreated':ab,ti OR (('primary':ab,ti OR 'initial':ab,ti OR 'induction':ab,ti OR 'naïve':ab,ti) AND ('therapy':ab,ti OR 'treatment':ab,ti)) OR (('front':ab,ti OR 'first':ab,ti OR '1st':ab,ti) AND ('line':ab,ti)) OR consolidat*:ab,ti	1,950,220	2,286,870	2,378,243
3	'randomized':ab,ti OR 'randomised':ab,ti OR 'controlled trial':ab,ti OR 'clinical trial':ab,ti OR 'cross over':ab,ti OR 'crossover':ab,ti OR 'cross-over':ab,ti OR (doubl* AND blind*:ab,ti) OR (singl* AND blind*:ab,ti) OR ('open':ab,ti AND label*:ab,ti) OR 'placebo':ab,ti	1,062,056	1,243,811	1,295,307
4	#1 AND #2 AND #3	2,749	3,464	3,611
5	#4 NOT ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim)	2,736	3,447	3,591
6	#5 NOT [animals]/lim	2,505	3,150	3,287
7	#6 NOT (review:it NOT (systematic OR meta AND analy* OR (indirect OR mixed AND 'treatment comparison')))	2,335	2,957	3,092
ASCO				
8	#7 AND ('journal of clinical oncology':jt NOT 'asia-pacific journal of clinical oncology':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2015-2018]/py)	61	-	-
9	#7 AND ('journal of clinical oncology':jt NOT 'asia-pacific journal of clinical oncology':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2018-2020]/py)	-	57	-
10	#7 AND ('journal of clinical oncology':jt NOT 'asia-pacific journal of clinical oncology':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [1-04-2020]/sd)	-	-	0
ASH				
11	#7 AND ('blood':jt NOT ('blood purification':jt OR 'blood coagulation and fibrinolysis':jt OR 'biology of blood and marrow transplantation':jt OR 'blood transfusion':jt OR 'blood pressure':jt) AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2015-2018]/py)	284	-	-

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12	#7 AND ('blood':jt NOT ('blood purification':jt OR 'blood coagulation and fibrinolysis':jt OR 'biology of blood and marrow transplantation':jt OR 'blood transfusion':jt OR 'blood pressure':jt) AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2018-2020]/py)	-	194	-
13	#7 AND ('blood':jt NOT ('blood purification':jt OR 'blood coagulation and fibrinolysis':jt OR 'biology of blood and marrow transplantation':jt OR 'blood transfusion':jt OR 'blood pressure':jt) AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [1-04-2020]/sd)	-	-	0
EHA				
14	#7 AND ('haematologica':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2015-2018]/py)	123	-	-
15	#7 AND ('haematologica':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2018-2020]/py)	-	19	-
16	#7 AND ('haematologica':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [1-04-2020]/sd)	-	-	0
ISPOR				
17	#7 AND ('value in health':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2015-2018]/py)	15	-	-
18	#7 AND ('value in health':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2018-2020]/py)	-	14	-
19	#7 AND ('value in health':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [1-04-2020]/sd)	-	-	0
IMWG				
20	#7 AND ('clinical lymphoma myeloma and leukemia':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2015-2018]/py)	51	-	-
21	#7 AND ('clinical lymphoma myeloma and leukemia':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2018-2020]/py)	-	85	-
22	#7 AND ('clinical lymphoma myeloma and leukemia':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [1-04-2020]/sd)	-	-	0

Abbreviations: ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; EHA = European Hematology Association; IMWG = International Myeloma Working; ISPOR = International Society for Pharmacoeconomics and Outcomes Research

A search in registries was carried out to give an update on current trials on newly diagnosed transplant-eligible multiple myeloma. No new study identified, and the result has been presented in Table 70.

Table 67 Registers included in the searches

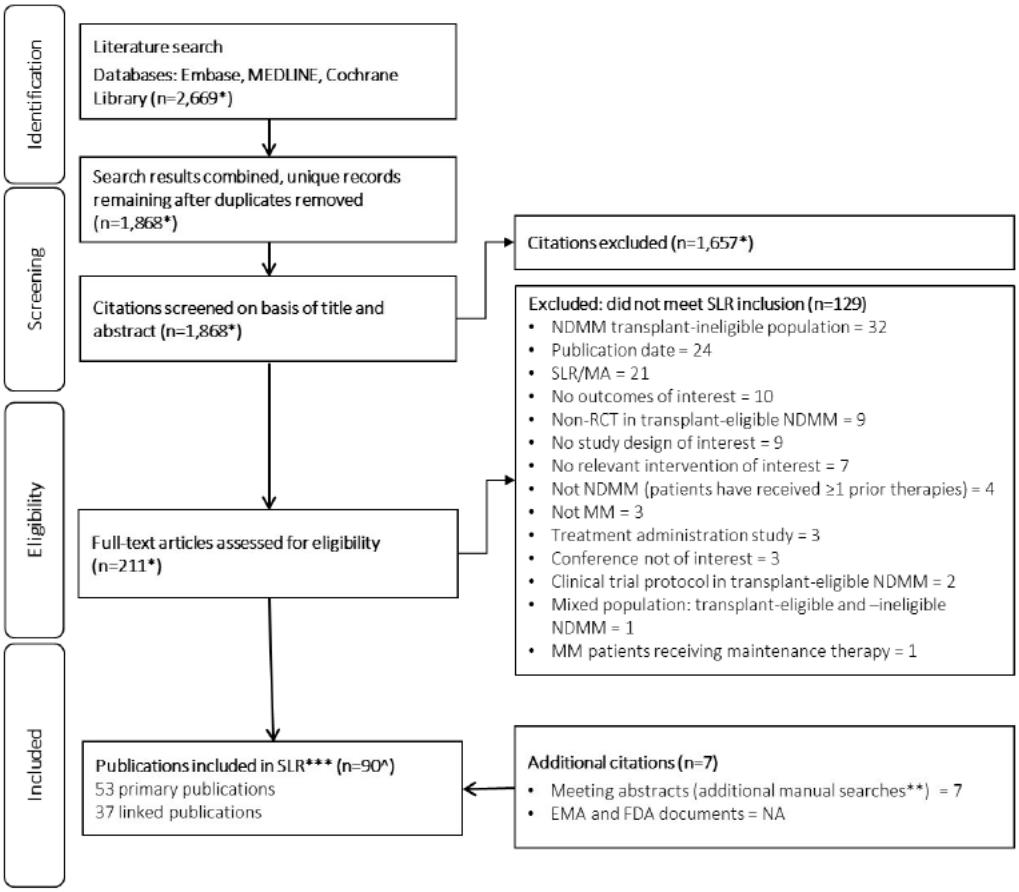
Database	Platform	Search strategy	Date of search
US NIH registry & results database	https://clinicaltrials.gov	Newly diagnosed multiple myeloma	24.02.2021
WHO ICTRP registry	https://apps.who.int/trialsearch/	Newly diagnosed multiple myeloma	24.02.2021
EU Clinical Trials Register	EU Clinical Trials Register	Newly diagnosed multiple myeloma	24.02.2021

Abbreviations: NIH = National Institutes of Health; ICTRP = International Clinical Trials Registry Platform

13.4 Systematic selection of studies

The PRISMA flows of literature reviews are presented below. Table 68 shows the studies that were included in the analysis. Full list of studies identified in the review is listed in Table 69. Table 70 shows the completed or ongoing studies that were not included in the literature review. Table 71 lists studies excluded during full text review.

Figure 22. PRISMA Flow Diagram (Initial SLR, May 2018)



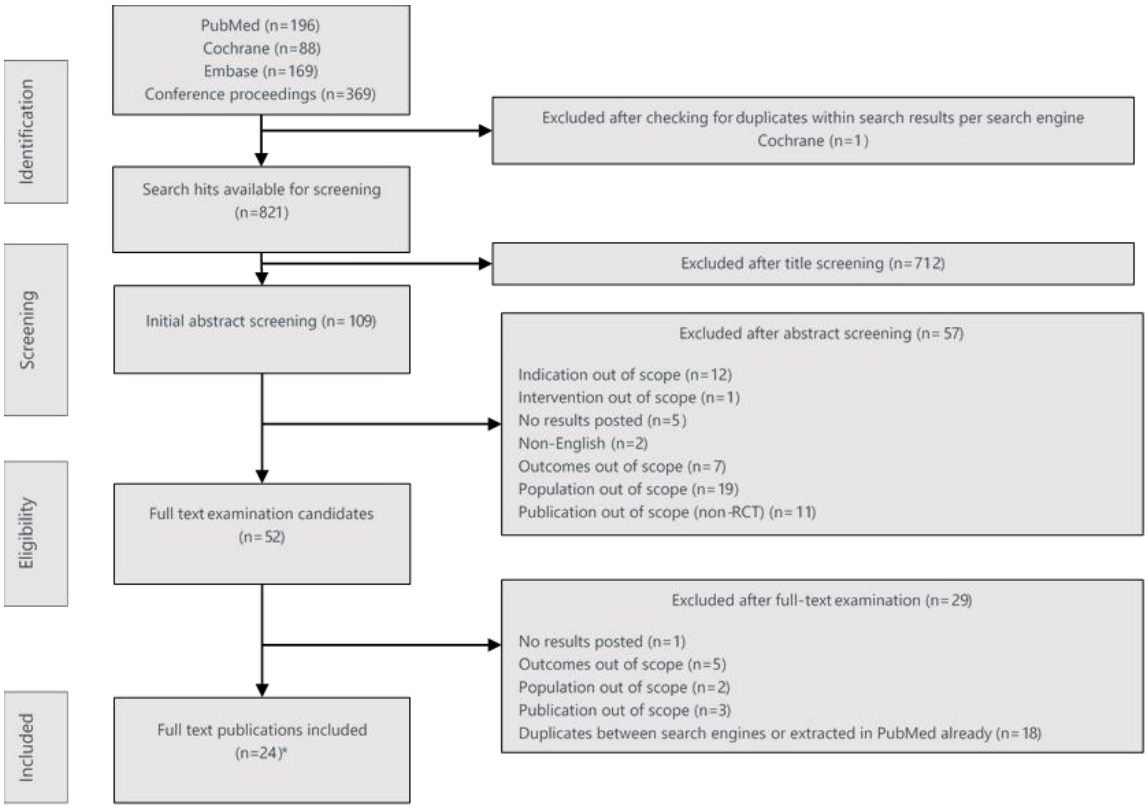
Abbreviations: EMA = European Medicines Agency; FDA = Food and Drug Administration; MA = meta-analysis; MM = multiple myeloma; NA = not applicable; NDMM = newly diagnosed multiple myeloma; NMA = network meta-analysis; RCT = randomized controlled trial; SLR = systematic literature review

* Includes meeting abstracts searched via Embase.com.

**Additional manual searches of meetings abstracts were also performed

^ The clinical study report for CASSIOPEIA was added as a primary publication to the final count of publications included in the SLR.

Figure 23 PRISMA Flow Diagram (1st update, 04 May 2020)



Abbreviations: RCT = Randomized controlled trial.
*The clinical study report included in the initial SLR was published in 2019 and captured by this update. Therefore, the actual number of new studies identified is 23.

Figure 24 PRISMA Flow Diagram (2nd update, 02 Nov 2020)

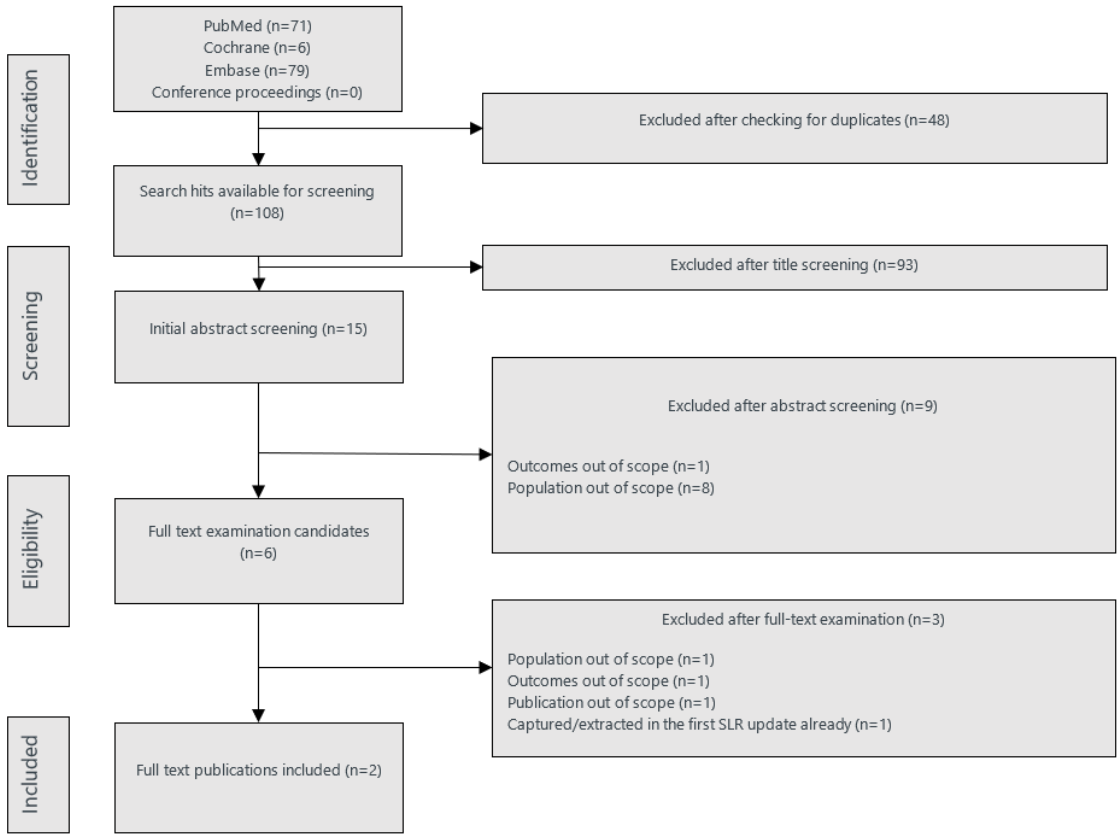


Table 68 lists the study design for the three studies included in this application, for detailed information, refer to Appendix B Main characteristics of included studies

Table 68 Overview of study design for studies included in the technology assessment/analysis:

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
CASSIOPEIA(5, 6) **(NCT02541383)**	To determine if the addition of daratumumab to VTd will increase the proportion of subjects achieving stringent complete response post completion of consolidation therapy compared with VTd alone.	An open label, multicenter, randomized phase 3 trial	Patients with NDMM eligible for high dose therapy and ASCT	DVTd (n=543) VTd (n=542)	sCR after consolidation therapy PFS after maintenance therapy Median follow-up: 29.2 months	PFS from first randomization Time to disease progression proportion of Post ASCT/consolidation CR rate; MRD rate proportion of post induction sCR PFS2 Overall survival Median follow-up: 29.2 months
GMMG-MM5(139, 140) **(EudraCT No. 2010-019173-16)**	To assess two independent primary end points: 1. Demonstration of non-inferiority of VCd compared to Pad induction therapy with respect to response rates (VGPR or better, ⩾ VGPR) 2. Determination of the best of four treatment strategies with respect to PFS. The treatment strategies are defined by PAd or VCD induction therapy followed by standard intensification therapy (HDM+ASCT), lenalidomide consolidation and maintenance treatment with either lenalidomide for 2 years or	A prospective, open-label, randomized, multicenter phase 3 trial	Newly diagnosed, transplant-eligible multiple myeloma patients	VCd-LEN-2Y (n=126) VCd-LEN-CR (n=125) PAd-LEN-2Y (n=125) PAd-LEN-CR (n=126)	VGPR or better rate PFS; median follow-up: 59.4 (95%CI 58.2–61.0) months	OS; median follow-up: 60.1 (95%CI 9.2–61.9) months response after lenalidomide consolidation treatment best response rates toxicity during induction treatment, lenalidomide consolidation and maintenance treatment with respect to adverse events CTC grade 3 or higher

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Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
	lenalidomide until complete response (CR) is achieved					
IFM 2009(123) (NCT01191060)	To determine if, in the era of novel drugs, high dose therapy (HDT) is still necessary in the initial management of multiple myeloma in younger patients. HDT as compared to conventional dose treatment would be considered superior if it significantly prolongs Progression-free survival	An open label, multicenter, randomized phase 3 trial	NDMM patients up to 65 years of age who are transplant-eligible	VRd (n=350) VRd + ASCT (n=350)	PFS Median follow-up: 43 months for VRd + ASCT; 44 months for VRd	Response rate Time to disease progression Overall survival Adverse event rates Median follow-up: 43 months for VRd + ASCT; 44 for VRd

Abbreviations: ASCT: Autologous Stem Cell Transplantation; HDT = high dose therapy; PFS: progression-free survival; PFS2 = Progression-free survival on subsequent line of therapy; VRd: bortezomib, lenalidomide, dexamethasone ; NDMM: newly diagnosed multiple myeloma; D: daratumumab; VTd: bortezomib, thalidomide, and dexamethasone; Pad: bortezomib, doxorubicin, and dexamethasone; VCd: bortezomib, cyclophosphamide, and dexamethasone; CR: complete response; sCR: stringent complete response; VGPR: very good partial response; MRD: minimal residual disease; LEN-2Y: lenalidomide maintenance for 2 years; LEN-CR: lenalidomide maintenance till complete response

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Table 69 Relevant studies included in SLR

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
Cavo, Michele, et al. "Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study." *The Lancet* 376.9758 (2010): 2075-2085.(176)	GIMEMA-MMY-3006	NCT01134484	May 2006 to Apr 2008	VTd vs. Td Treatment regimens irrelevant for decision problem
Cavo, Michele, et al. "Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma." *Blood* 120.1 (2012): 9-19.(177)				
Tacchetti, P., et al. "A triplet bortezomib-and immunomodulator-based therapy before and after double ASCT improves overall survival of newly diagnosed MM patients: Final analysis of phase 3 GIMEMA-MMY-3006 study." *EHA Learning Center* 214500 (2018).(178)				
Tacchetti, Paola, et al. "Bortezomib-thalidomide-dexamethasone versus thalidomide-dexamethasone before and after double autologous stem cell transplantation for newly diagnosed multiple myeloma: final analysis of phase 3 Gimema-MMY-3006 study and prognostic score for survival outcomes." *Blood* 132.Supplement 1 (2018): 125-125.(179)				
Mookerjee, Anjali, et al. "Bortezomib, Lenalidomide and Low-Dose Dexamethasone (VRD) Versus Lenalidomide and Low-Dose Dexamethasone (Ld) for Newly-Diagnosed Multiple Myeloma-a Randomized Phase III Study." *Blood* 130.Supplement 1 (2017): 906-906.(180)	NR	Ref IEC/NP-264/01-08-2014, RP-7/2014	Sep 2014 to Oct 2016	VRd vs. Rd Insufficient information for comparison justification
Mookerjee, Anjali, et al. "Bortezomib, Lenalidomide and Low-dose Dexamethasone (VRD) Versus Lenalidomide and Low-dose Dexamethasone (Ld) for Newly-diagnosed Multiple Myeloma-A Randomized Phase III Study-Interim Results." Clinical Lymphoma, Myeloma and Leukemia 17.1 (2017): e5-e6.(181)				
Jin, S., Xu, Y., Zhou, J., Shang, J., Yan, L., Fu, C., & Wu, D. (2017). Bortezomib, Liposome Doxorubicin and Dexamethasone (PDd) Is Superior in Safety and Not Inferior in Efficiency to Bortezomib, Doxorubicin and Dexamethasone (PAd) As Induction Therapy in New-Diagnosed Multiple Myeloma Patients: An Interim Report from China's Multicenter Study.(182)	NR	NCT02577783	up to 2018	PDd vs. Pad

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
Shuang, Yan, et al. "Bortezomib, Liposome Doxorubicin and Dexamethasone (PDd) is Superior in Safety and Not Inferior in Efficiency to Bortezomib, Doxorubicin and Dexamethasone (PAd) As Induction Therapy in New-Diagnosed Multiple Myeloma Patients." *Clinical Lymphoma, Myeloma and Leukemia* 19.10 (2019): e204-e205.(183)				Treatment regimens irrelevant for decision problem
Jackson, Graham H., et al. "Lenalidomide induction and maintenance therapy for transplant eligible myeloma patients: Results of the Myeloma XI study." *Journal of Clinical Oncology* (2017): 35(15).(184)	Myeloma XI Study	NCT01554852	2010 to 2016	CTd vs. CRd Treatment regimens irrelevant for decision problem
Jackson, Graham H., et al. "Lenalidomide induction and maintenance therapy for transplant eligible myeloma patients: Results of the Myeloma XI study." (2017): 8009-8009.(185)				
Jones, J. R., et al. "Second malignancies in the context of lenalidomide treatment: an analysis of 2732 myeloma patients enrolled to the Myeloma XI trial." *Blood cancer journal* 6.12 (2016): e506-e506.(186)				
Bradbury, Charlotte A., et al. "Thrombotic events in patients with myeloma treated with immunomodulatory drugs; results of the myeloma XI study." *Blood* 130.Supplement 1 (2017): 553-553.(187)				
Jackson G., Pawlyn C., Cairns D., Jones J.R., Kishore B., Garg M., Williams C., Karunanithi K., et al. (2019). Lenalidomide induction and maintenance maximizes outcome for newly diagnosed transplant eligible myeloma patients irrespective of risk status: Long-term follow-up of the myeloma Xi trial. *Blood* (2019) 134 (Supplement_1): 1910.(188)				
Jackson, Graham H., et al. "Lenalidomide before and after ASCT for transplant-eligible patients of all ages in the randomized, phase III, Myeloma XI trial." *Haematologica* (2020).(189)				
Knop, Stefan, et al. "Lenalidomide, doxorubicin hydrochloride and dexamethasone versus bortezomib, lenalidomide, and dexamethasone prior to scheduled stem cell transplant in newly diagnosed myeloma." (2017): 8001-8001.(190)	DSMM XIV study	NCT01685814	May 2012 to Jun 2016	RAd vs. VRd Insufficient information for comparison justification
Stuebig, Thomas, et al. "Lenalidomide, Adriamycin and Dexamethasone (RAD) Versus Bortezomib, Lenalidomide and Dexamethasone (VRD) in Newly Diagnosed Multiple Myeloma (MM)-Post-Induction				

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
Response and MRD Results By Flow Cytometry and NGS from a Phase 3 Randomized Controlled Clinical Trial (RCT)." *Blood* 132.Suppl1 (2018).(191)				
Kumar, L., et al. "Low dose dexamethasone plus lenalidomide (Len-dexa) versus thalidomide (Thal-dexa) as induction therapy for newly diagnosed multiple myeloma: a phase III, randomized study." *Clinical Lymphoma, Myeloma and Leukemia* 15 (2015): e146.(192)	NR	CTRI2010 001187	Apr 2009 to Sep 2014	Rd vs. Td Treatment regimens irrelevant for decision problem
Rajkumar, S. Vincent, et al. "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." *Journal of clinical oncology* 24.3 (2006): 431-436.(193)	NR	NR	Jun 2002-Apr 2003	Td vs. d Treatment regimens irrelevant for decision problem
Ludwig, Heinz, et al. "Randomized phase II study of bortezomib, thalidomide, and dexamethasone with or without cyclophosphamide as induction therapy in previously untreated multiple myeloma." *Journal of Clinical Oncology* 31.2 (2013): 247-255.(58) Ludwig, Heinz, et al. "Bortezomib, thalidomide and dexamethasone, with or without cyclophosphamide, for patients with previously untreated multiple myeloma: 5-year follow-up." *British journal of haematology* 171.3 (2015): 344-354.(194)	NR	NCT00531453	Oct 2007 to Sep 2008	VTd vs. CVTd Treatment regimens irrelevant for decision problem
Kumar, Shaji, et al. "Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma." *Blood* 119.19 (2012): 4375-4382.(147)	EVOLUTION	NCT00507442	Jun 2008 to Sep 2009 (patient enrollment)	VRd vs. VCd Insufficient information for comparison justification
Rosiñol, Laura, et al. "Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study." *Blood* 120.8 (2012): 1589-1596.(195)	PETHEMA	NCT00461747	Apr 2006 to Aug 2009	VTd vs. Td

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
Rosiñol, L., et al. "Pretransplant induction with VTD (Bortezomib/Thalidomide/Dexamethasone) significantly improves PFS: long-term results of the randomized phase 3 PETHEMA/GEM study." *Clinical Lymphoma, Myeloma and Leukemia* 15 (2015): e49-e50.(196)				Treatment regimens irrelevant for decision problem
Gay, F. M., Rota Scalabrini, D., Belotti, A., Offidani, M., Petrucci, M. T., Esma, F., ... & Gamberi, B. (2017). Carfilzomib-lenalidomide-dexamethasone (KRd) vs carfilzomib-cyclophosphamide-dexamethasone (KCd) induction: Planned interim analysis of the randomized FORTE trial in newly diagnosed multiple myeloma (NDMM). *Journal of Clinical Oncology,* 35(15).(197)	FORTE	NCT02203643	NR	KCd vs. KRd Treatment regimens irrelevant for decision problem
Gay, F., et al. "Updated efficacy and MRD data according to risk-status in newly diagnosed myeloma patients treated with carfilzomib plus lenalidomide or cyclosphosphamide: Results from the FORTE trial." *HemaSphere* 2.S1 (2018): 6.(198)				
Gay, Francesca Maria, et al. "A randomized study of carfilzomib-lenalidomide-dexamethasone vs carfilzomib-cyclophosphamide-dexamethasone induction in newly diagnosed myeloma patients eligible for transplant: high efficacy in high-and standard-risk patients." *Blood* 130.Supplement 1 (2017): 4541-4541.(199)				
Gay, F., et al. "carfilzomib-lenalidomide-dexamethasone vs carfilzomib-cyclophosphamide-dexamethasone induction: planned interim analysis of the randomized forte trial in newly diagnosed multiple myeloma." *haematologica*. vol. 102. via giuseppe belli 4, 27100 Pavia, Italy: ferrata storti foundation, 2017.(200)				
Gay, Francesca Maria, et al. "Updated efficacy data and MRD analysis according to risk status in newly diagnosed myeloma patients treated with carfilzomib+ lenalidomide or cyclophosphamide (FORTE trial)." (2018): 8009-8009.(201)				
Oliva, Stefania, et al. "Minimal residual disease evaluation by multiparameter flow cytometry and next generation sequencing in the Forte Trial for newly diagnosed multiple myeloma patients." (2019): 4322-4322.(202)				

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
Morgan, Gareth J., et al. "Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results." *Haematologica* 97.3 (2012): 442.(203) Morgan, Gareth J., et al. "Effects of induction and maintenance plus long-term bisphosphonates on bone disease in patients with multiple myeloma: the Medical Research Council Myeloma IX Trial." *Blood, The Journal of the American Society of Hematology* 119.23 (2012): 5374-5383.(204)	MRC Myeloma IX	ISRCTN: 68454111	2003 to 2007	CVAd vs. CTd Treatment regimens irrelevant for decision problem
Voorhees, Peter M., et al. "Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial." *Blood, The Journal of the American Society of Hematology* 136.8 (2020): 936-945.(150) Voorhees, Peter M., et al. "Depth of response to daratumumab (DARA), lenalidomide, bortezomib, and dexamethasone (RVd) improves over time in patients (pts) with transplant-eligible newly diagnosed multiple myeloma (NDMM): Griffin study update." (2019): 691-691.(205)	GRIFFIN	NCT02874742	2016 to 2018	D-RVd vs. VRd Insufficient information for comparison justification
Moreau, Philippe, et al. "Bortezomib plus dexamethasone versus reduced-dose bortezomib, thalidomide plus dexamethasone as induction treatment before autologous stem cell transplantation in newly diagnosed multiple myeloma." Blood, *The Journal of the American Society of Hematology* 118.22 (2011): 5752-5758.(206)	IFM 2007-02	NCT00910897	Mar 2008 to Jan 2009	VTd vs. Vd Treatment regimens irrelevant for decision problem
Moreau, Philippe, et al. "VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial." *Blood* 127.21 (2016): 2569-2574.(148) Moreau, Philippe, et al. "Bortezomib, thalidomide and dexamethasone (VTD) is superior to bortezomib, cyclophosphamide and dexamethasone (VCD) prior to autologous stem cell transplantation for patients with de novo multiple myeloma. Results of the prospective IFM 2013-04 trial." (2015): 393-393.(207)	IFM2013-04	NCT01971658	Nov 2013 to Mar 2015	VTd vs. VCd Treatment regimens irrelevant for decision problem
Luoma, Sini, et al. "RVD induction and autologous stem cell transplantation followed by lenalidomide maintenance in newly diagnosed multiple myeloma: a phase 2 study of the Finnish Myeloma Group." *Annals of hematology* 98.12 (2019): 2781-2792.(208)	FMG-MM02	NCT01790737	2013 to 2019	VRd Not optional for comparison: small patient population

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
Rosiñol, Laura, et al. "Bortezomib, lenalidomide, and dexamethasone as induction therapy prior to autologous transplant in multiple myeloma." *Blood* 134.16 (2019): 1337-1345.(149)	GEM2012 MENOS65	NCT01916252	2013 to 2016	VRd Insufficient information for comparison justification
Sunami, Kazutaka, et al. "Bortezomib-based strategy with autologous stem cell transplantation for newly diagnosed multiple myeloma: a phase II study by the Japan Study Group for Cell Therapy and Transplantation (JSCT-MM12)." *International journal of clinical oncology* 24.8 (2019): 966-975.(209)	JSCT-MM12	NR	2012 to 2013	VCd Not optional for comparison: Asian population
Tanaka, Keisuke, et al. "Efficacy and Safety of a Weekly Cyclophosphamide-Bortezomib-Dexamethasone Regimen as Induction Therapy Prior to Autologous Stem Cell Transplantation in Japanese Patients with Newly Diagnosed Multiple Myeloma: A Phase 2 Multicenter Trial." *Acta haematologica* 141.2 (2019): 111-118.(210)	NR	NR	2013 to 2015	VCd Not optional for comparison: Asian population
van de Donk, Niels WCJ, et al. "Thalidomide before and after autologous stem cell transplantation in recently diagnosed multiple myeloma (HOVON-50): long-term results from the phase 3, randomised controlled trial." *The Lancet Haematology* 5.10 (2018): e479-e492.(211)	HOVON-50	NTR238	2001 to 2005	VAd vs. TAd Treatment regimens irrelevant for decision problem
Breitkreutz, I., et al. "Thalidomide in newly diagnosed multiple myeloma: influence of thalidomide treatment on peripheral blood stem cell collection yield." *Leukemia* 21.6 (2007): 1294-1299.(212)				
Lokhorst, Henk M., et al. "A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma." *Blood, The Journal of the American Society of Hematology* 115.6 (2010): 1113-1120.(213)				
Lokhorst, Henk M., et al. "Thalidomide in induction treatment increases the very good partial response rate before and after high-dose therapy in previously untreated multiple myeloma." *Haematologica* 93.1 (2008): 124-127.(214)				

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
van de Donk, Niels, et al. "Improved Survival with Thalidomide Before and after Autologous Stem Cell Transplantation in Newly Diagnosed Multiple Myeloma: Long-Term Results from the HOVON-50 Study." (2018).(215)				
Gregersen, Henrik, et al. "A randomized placebo-controlled phase II study of clarithromycin or placebo combined with VCD induction therapy prior to high-dose melphalan with stem cell support in patients with newly diagnosed multiple myeloma." *Experimental hematology & oncology* 7.1 (2018): 1-8.(216)	CLAIM	NCT02573935	2015 to 2016	Clarithromycin + VCd vs. placebo + VCd Treatment regimens irrelevant for decision problem
Gregersen, Henrik, et al. "A Randomized Placebo-Controlled Phase II Study of Clarithromycin or Placebo Combined with VCD Induction Therapy Prior to High-Dose Melphalan with Stem Cell Support in Patients with Newly Diagnosed Multiple Myeloma." *Blood* 130.Supplement 1 (2017): 3129-3129. (217)				
Roussel, Murielle, et al. "Twice weekly induction with ixazomib-lenalidomide-dexamethasone (IRd) combination followed by extended IRD consolidation and lenalidomide maintenance in transplant eligible patients with newly diagnosed multiple myeloma (NDMM): a phase 2 study from the Intergroupe Francophone Du Myelome (IFM 2014-03)." (2019): 3159-3159.(218)	IFM 2014-03	NCT02897830	2016-2017	IRd Treatment regimens irrelevant for decision problem
Roussel, Murielle, et al. "Bortezomib and high-dose melphalan vs. high-dose melphalan as conditioning regimen before autologous stem cell transplantation in de novo multiple myeloma patients: a phase 3 study of the Intergroupe Francophone Du Myelome (IFM 2014-02)." *Blood* 130.Supplement 1 (2017): 398-398.(219)	IFM 2014-02	NCT02197221	Jan 2015 to Sep 2016	Bortezomib + melphalan vs melphalan Treatment regimens irrelevant for decision problem
Kumar, Lalit, et al. "VRd versus VCd as induction therapy for newly diagnosed multiple myeloma: A Phase III, randomized study." *Clinical Lymphoma, Myeloma and Leukemia* 19.10 (2019): e361.(220)	NR	REF/2016/08/01 2008	NR	VRd vs. VCd Insufficient information for comparison justification
Cavo, Michele, et al. "Autologous haematopoietic stem-cell transplantation versus bortezomib–melphalan–prednisone, with or without bortezomib–lenalidomide–dexamethasone consolidation therapy, and lenalidomide maintenance for newly diagnosed multiple myeloma (EMN02/HO95): A multicentre, randomised, open-label, phase 3 study." *The Lancet Haematology* 7.6 (2020): e456-e468.(145)	EMN02/HO95	NCT01208766	2011 to 2014	HSCT vs. VMP

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
Sonneveld, Pieter, et al. "Consolidation followed by maintenance therapy versus maintenance alone in newly diagnosed, transplant eligible patients with multiple myeloma (MM): a randomized phase 3 study of the European Myeloma Network (EMN02/HO95 MM trial)." (2016): 242-242.(221)				Treatment regimens irrelevant for decision problem
Cavo, Michele, et al. "Autologous stem cell transplantation versus bortezomib-melphalan-prednisone for newly diagnosed multiple myeloma: second interim analysis of the phase 3 EMN02/HO95 study." *Blood* 130.Suppl 1 (2017): 397-LP.(222)				
Cavo, Michele, et al. "Intensification therapy with bortezomib-melphalan-prednisone versus autologous stem cell transplantation for newly diagnosed multiple myeloma: an intergroup, multicenter, phase III study of the European Myeloma Network (EMN02/HO95 MM Trial)." (2016): 673-673.(223)				
Cavo, Michele, et al. "Upfront autologous stem cell transplantation (ASCT) versus novel agent-based therapy for multiple myeloma (MM): a randomized phase 3 study of the European Myeloma Network (EMN02/HO95 MM trial)." (2016): 8000-8000.(224)				
Cavo, Michele, et al. "Upfront single versus double autologous stem cell transplantation for newly diagnosed multiple myeloma: an intergroup, multicenter, phase III study of the European Myeloma Network (EMN02/HO95 MM Trial)." (2016): 991-991.(225)				
Pawlyn, Charlotte, et al. "Quadruplet KCRD (Carfilzomib, Cyclophosphamide, Lenalidomide and Dexamethasone) Induction for Newly Diagnosed Myeloma Patients." *Clinical Lymphoma, Myeloma and Leukemia* 19.10 (2019): e2.(226)	NR	NR	NR	KCRd vs. CTd/CRd Treatment regimens irrelevant for decision problem
Scheid, C., et al., Bortezomib-based induction and maintenance overcomes the negative prognostic impact of renal impairment and del17p in transplant-eligible myeloma patients: Long term results from the phase iii hovon-65/gmmg-HD4 study after median 137 months follow up. Blood, 2019. 134.(227)	HOVON-65/GMMG-HD4	ISRCTN64455289	May 2005 to Sep 2011 (patient enrollment)	VAd vs. TAd Treatment regimens irrelevant for decision problem
Sonneveld, Pieter, et al. "Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial." *Journal of clinical oncology* 30.24 (2012): 2946-2955.(228)				

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
Scheid, Christof, et al. "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." *haematologica* 99.1 (2014): 148.(229)				
Mai, Elias Karl, et al. "Impact of Severe Infections during Induction Therapy on Dosage, Response and Survival in Newly Diagnosed Multiple Myeloma-a Subgroup Analysis from the Randomized Phase III Trial GMMG-HD4." (2015): 3187-3187.(140)				
Goldschmidt, Hartmut, et al. "Bortezomib before and after high-dose therapy in myeloma: long-term results from the phase III HOVON-65/GMMG-HD4 trial." *Leukemia* 32.2 (2018): 383-390.(230)				
Broyl, Annemiek, et al. "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." *The lancet oncology* 11.11 (2010): 1057-1065.(231)				
Horvath, N., et al., Phase 3 study of subcutaneous bortezomib, thalidomide, and prednisolone consolidation after subcutaneous bortezomib-based induction and autologous stem cell transplantation in patients with previously untreated multiple myeloma: the VCAT study. *Leuk Lymphoma*, 2019. 60(9): p. 2122-2133.(232)	VCAT study	NR	2012 to 2016	PAd vs. VAd Treatment regimens irrelevant for decision problem
Yong, K., et al., Efficacy and safety of carfilzomib at 56mg/m with cyclophosphamide and dexamethasone (K56Cd) in newly diagnosed multiple myeloma patients followed by ASCT or K56Cd consolidation: Initial results of the phase 2 cardamon study. *Blood*, 2019. 134.(233)	Cardamon study	NR	2015 to 2019	K56Cd Treatment regimens irrelevant for decision problem
Straka, Christian, et al. "Autotransplant with and without induction chemotherapy in older multiple myeloma patients: long-term outcome of a randomized trial." *Haematologica* 101.11 (2016): 1398.(234)	DSMM-II	NCT02288741	Aug 2001 to Aug 2006 (patient enrollment)	Induction: VAd or ID or CAd vs No induction: dexamethasone Treatment regimens irrelevant for decision problem

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
Mellqvist, Ulf-Henrik, et al. "Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial." *Blood, The Journal of the American Society of Hematology* 121.23 (2013): 4647-4654.(235)	NMSG 15/05	NCT00417911	Oct 2005 to Apr 2009 (patient enrollment)	Bortezomib vs no treatment Treatment regimens irrelevant for decision problem
Mellqvist, Ulf-Henrik, et al. "Cyclophosphamide plus dexamethasone is an efficient initial treatment before high-dose melphalan and autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of a randomized comparison with vincristine, doxorubicin, and dexamethasone." *Cancer: Interdisciplinary International Journal of the American Cancer Society* 112.1 (2008): 129-135.(236)	NR	NR	Nov 2001 to Oct 2003 (patient enrollment)	Cd vs VAd Treatment regimens irrelevant for decision problem
Gay, Francesca, et al. "Chemotherapy plus lenalidomide versus autologous transplantation, followed by lenalidomide plus prednisone versus lenalidomide maintenance, in patients with multiple myeloma: a randomised, multicentre, phase 3 trial." *The lancet oncology* 16.16 (2015): 1617-1629.(237) Gay, Francesca, et al. "Autologous transplantation versus cyclophosphamide-lenalidomide-prednisone followed by lenalidomide-prednisone versus lenalidomide maintenance in multiple myeloma: long-term results of a phase III trial." *Blood* 126.23 (2015).(238) Gay, F., et al. "Improved overall survival with autologous transplantation vs cyclophosphamide-lenalidomide-dexamethasone in newly diagnosed myeloma: a phase 3 trial." *HAEMATOLOGICA*. Vol. 100. VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY: FERRATA STORTI FOUNDATION, 2015.(239)	NR	NCT01091831	Jul 2009 to May 2011 (patient enrollment)	Melphalan + ASCT vs CLd Treatment regimens irrelevant for decision problem
Porter, Christopher A., and Robert M. Rifkin. "Clinical benefits and economic analysis of pegylated liposomal doxorubicin/vincristine/dexamethasone versus doxorubicin/vincristine/dexamethasone in patients with newly diagnosed multiple myeloma." *Clinical Lymphoma and Myeloma* 7 (2007): S150-S155.(240)	NR	NR	NR	Modified VAd [with PLD] vs VAd Treatment regimens irrelevant for decision problem
Stadtmauer, Edward A., et al. "Comparison of autologous hematopoietic cell transplant (autoHCT), bortezomib, lenalidomide (Len) and dexamethasone (RVD) consolidation with Len maintenance (ACM), tandem autoHCT with Len maintenance (TAM) and autoHCT with Len maintenance (AM) for up-front	StaMINA	NCT01109004	Jun 2010 to Nov 2013 (patient enrollment)	Melphalan + single autoHCT + BLd vs

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
treatment of patients with multiple myeloma (MM): primary results from the randomized phase III trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702-StaMINA trial)." (2016): LBA-1.(241)				melphalan + tandem autoHCT Treatment regimens irrelevant for decision problem
Rajkumar, S. Vincent, et al. "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." *The lancet oncology* 11.1 (2010): 29-37.(242)	NR	NCT00098475	Nov 2004 to Apr 2006 (patient enrollment)	Ld (high dose) vs Ld (low dose) Treatment regimens irrelevant for decision problem
Björkstrand, Bo, et al. "Feasibility of fludarabine added to VAD during induction therapy in multiple myeloma: a randomised phase II-study." *European journal of haematology* 70.6 (2003): 379-383.(243)	NR	NR	NR	Fludarabine + VAd vs VAd Treatment regimens irrelevant for decision problem
Cavo, Michele, et al. "Melphalan-prednisone versus alternating combination VAD/MP or VND/MP as primary therapy for multiple myeloma: final analysis of a randomized clinical study." *haematologica* 87.9 (2002): 934-942.(244)	NR	NR	Nov 1990 to Apr 1994	VNd MP vs VAd + MP Treatment regimens irrelevant for decision problem
Segeren, Christine M., et al. "Overall and event-free survival are not improved by the use of myeloablative therapy following intensified chemotherapy in previously untreated patients with multiple myeloma: a prospective randomized phase 3 study." *Blood, The Journal of the American Society of Hematology* 101.6 (2003): 2144-2151.(245)	NR	NR	Nov 1995 to Apr 2000	Melphalan + ASCT vs melphalan Treatment regimens irrelevant for decision problem
Rifkin, Robert M., et al. "Pegylated liposomal doxorubicin, vincristine, and dexamethasone provide significant reduction in toxicity compared with doxorubicin, vincristine, and dexamethasone in patients	NR	NR	NR	PLD + vincristine + dexamethasone vs VAd

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
with newly diagnosed multiple myeloma: a Phase III multicenter randomized trial." *Cancer* 106.4 (2006): 848-858.(246)				Treatment regimens irrelevant for decision problem
Dimopoulos, M. A., et al. "Prospective randomized comparison of vincristine, doxorubicin and dexamethasone (VAD) administered as intravenous bolus injection and VAD with liposomal doxorubicin as first-line treatment in multiple myeloma." *Annals of oncology* 14.7 (2003): 1039-1044.(247)	NR	NR	Feb 1999 to Jun 2001 (patient enrollment)	VAd [with liposomal doxorubicin] vs VAd Treatment regimens irrelevant for decision problem
Qazilbash, M. H., et al. "A Randomized Phase III Trial Of Busulfan+ Melphalan (Bu-Mel) Vs Melphalan Alone For Multiple Myeloma: Longer PFS In The Bu-Mel Arm." *Clinical Lymphoma, Myeloma and Leukemia* 15 (2015): e72-e73.(248) Qazilbash, Muzaffar H., et al. "A randomized phase III trial of busulfan+ melphalan vs melphalan alone for multiple myeloma." *Blood* 130.Supplement 1 (2017): 399-399.(249)	NR	NR	Oct 2011 to Mar 2017	Busulfan + melphalan vs melphalan Treatment regimens irrelevant for decision problem
Cook, G., et al. "A randomized 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." *British journal of haematology* 126.6 (2004): 792-798.(250)	WOS MM1	NR	NR	Id vs VAd Treatment regimens irrelevant for decision problem
Bensinger, William I., et al. "A randomized study of melphalan 200 mg/m 2 vs 280 mg/m 2 as a preparative regimen for patients with multiple myeloma undergoing auto-SCT." *Bone marrow transplantation* 51.1 (2016): 67-71.(251)	NR	NR	NR	Melphalan (high dose) vs melphalan (low dose) Treatment regimens irrelevant for decision problem
Blade, Joan, et al. "Survival of multiple myeloma patients who are potential candidates for early high-dose therapy intensification/autotransplantation and who were conventionally treated." *Journal of clinical oncology* 14.7 (1996): 2167-2173.(252)	NR	NR	Jan 1985 to Dec 1989 (patient enrollment)	VCMP + BVAP vs MP Treatment regimens irrelevant for decision problem

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
Barlogie, Bart, et al. "Thalidomide and hematopoietic-cell transplantation for multiple myeloma." *New England Journal of Medicine* 354.10 (2006): 1021-1030.(253)	NR	NR	Oct 1998 to Feb 2004 (patient enrollment)	Thalidomide + melphalan vs melphalan Treatment regimens irrelevant for decision problem
Barlogie, Bart, et al. "Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities." *Blood, The Journal of the American Society of Hematology* 112.8 (2008): 3115-3121.(254)	TT2	NCT00573391	2007 to 2011	VMd vs VTd Treatment regimens irrelevant for decision problem
Zangari, M., et al. "Actiated protein C resistance in the absence of factor V Leiden mutation is a common finding in multiple myeloma and is associated with an increased risk of thrombotic complications." *Blood coagulation & fibrinolysis* 13.3 (2002): 187-192.(255)				
Zangari, Maurizio, et al. "Eight-year median survival in multiple myeloma after total therapy 2: roles of thalidomide and consolidation chemotherapy in the context of total therapy 1." *British journal of haematology* 141.4 (2008): 433-444.(256)				
Zangari, Maurizio, et al. "Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy." Blood, The Journal of the American Society of Hematology 98.5 (2001): 1614-1615.(257)				
Zervas, K., et al. "VAD-doxil versus VAD-doxil plus thalidomide as initial treatment for multiple myeloma: results of a multicenter randomized trial of the Greek Myeloma Study Group." *Annals of Oncology* 18.8 (2007): 1369-1375.(258)	NR	NR	Jun 2002 to Feb 2006 (patient enrollment)	VAd vs VTAd Treatment regimens irrelevant for decision problem
Lentzsch, Suzanne, et al. "Lenalidomide and low-dose dexamethasone (Ld) is equivalent to Ld plus autologous stem cell transplant (ASCT) in newly diagnosed multiple myeloma (NDMM): Results of a randomized, phase III trial." (2015): 8530-8530.(259)	NR	NCT01731886	Feb 2009 to Aug 2014	Rd vs Rd + melphalan + ASCT

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
				Treatment regimens irrelevant for decision problem
Kalff, Anna, et al. "Thalidomide and prednisolone versus prednisolone alone as consolidation therapy after autologous stem-cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the ALLG MM6 multicentre, open-label, randomised phase 3 study." *The Lancet Haematology* 1.3 (2014): e112-e119.(260)	ALLG MM6	ACTRN12607000382471	Jan 2002 to Mar 2005	Thalidomide + prednisolone vs prednisolone Treatment regimens irrelevant for decision problem
Child, J. Anthony, et al. "High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma." *New England Journal of Medicine* 348.19 (2003): 1875-1883.(261)	MRC Myeloma VII	ISRCTN66518389	1993 to 2000	Doxorubicin + carmustine + cyclophosphamide + melphalan + SCT vs doxorubicin + vincristine + methylprednisolone + cyclophosphamide and melphalan + methylprednisolone + SCT Treatment regimens irrelevant for decision problem
Fermand, J. P., et al. "High-dose therapy and autologous blood stem cell transplantation in multiple myeloma: Preliminary results of a randomized trial involving 167 patients." *Stem Cells* 13.S2 (1995): 156-159.(262)	NR	NR	1990 to Jun 1994 (patient enrollment)	Carmustine + etoposide + melphalan + cyclophosphamide and ASCT vs VCMP

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Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
				Treatment regimens irrelevant for decision problem
Fermand, Jean-Paul, et al. "High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe." *Journal of clinical oncology* 23.36 (2005): 9227-9233.(263)	NR	NR	NR	VCMP vs VCMP + VAMP + melphalan + ASC Treatment regimens irrelevant for decision problem
Fermand, Jean-Paul, et al. "High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial." *Blood, The Journal of the American Society of Hematology* 92.9 (1998): 3131-3136.(264)	NR	NR	NR	VAMP vs VCMP Treatment regimens irrelevant for decision problem
Sezer, O., et al. "Improved tumor response and survival outcomes with post-transplant bortezomib (Btz) consolidation versus observation (Obs) alone in patients with newly diagnosed multiple myeloma (MM): Results from a randomized, open-label, multicenter, parallel-group phase 2 study." Clinical Lymphoma Myeloma and Leukemia 15.S3 (2015): e129-e130.(265) Sezer, Orhan, et al. "Effects of single-agent bortezomib as post-transplant consolidation therapy on multiple myeloma-related bone disease: a randomized phase II study." British journal of haematology 178.1 (2017): 61-71.(266)	NR	NCT01286077	Jul 2009 to May 2012 (patient enrollment)	Bortezomib vs no treatment Treatment regimens irrelevant for decision problem
Harousseau, Jean-Luc, et al. "Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial." *J clin Oncol* 28.30 (2010): 4621-4629.(267) Moreau, Philippe, et al. "Achievement of VGPR to induction therapy is an important prognostic factor for longer PFS in the IFM 2005-01 trial." *Blood, The Journal of the American Society of Hematology* 117.11 (2011): 3041-3044.(268)	IFM 2005-01	NCT00200681	Aug 2005 to Jan 2008	Vd vs VAd Treatment regimens irrelevant for decision problem

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of* and reason not to include in indirect treatment comparison
El-Ghammaz, Amro MS, and Essam Abdelwahed. "Bortezomib-based induction improves progression-free survival of myeloma patients harboring 17p deletion and/or t (4; 14) and overcomes their adverse prognosis." *Annals of hematology* 95.8 (2016): 1315-1321.(269)	NR	NR	Jan 2011 to Aug 2015 (patient enrollment)	VAd vs Vd Treatment regimens irrelevant for decision problem
Oken, Martin M., et al. "Comparison of melphalan and prednisone with vincristine, carmustine, melphalan, cyclophosphamide, and prednisone in the treatment of multiple myeloma: results of Eastern Cooperative Oncology Group Study E2479." *Cancer* 79.8 (1997): 1561-1567.(270)	ECOG Study E2479	NR	Aug 1979 to Jul 1983 (patient enrollment)	MP vs carmustine + VCMP Treatment regimens irrelevant for decision problem
Spencer, Andrew, et al. "Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure." *Journal of Clinical Oncology* 27.11 (2009): 1788-1793.(271)	NR	NR	Jan 2002 to Mar 2005 (patient enrollment)	Thalidomide + prednisolone vs prednisolone Treatment regimens irrelevant for decision problem
Palumbo, Antonio, et al. "Melphalan 200 mg/m2 versus melphalan 100 mg/m2 in newly diagnosed myeloma patients: a prospective, multicenter phase 3 study." Blood, *The Journal of the American Society of Hematology* 115.10 (2010): 1873-1879.(272)	GISMM2001	NCT00950768	Oct 2001 to Jul 2006 (patient enrollment)	Melphalan (high dose) vs melphalan (low dose) Treatment regimens irrelevant for decision problem

Abbreviations: ASCT = autologous stem cell transplant; CSR = clinical study report; CRd = carfilzomib, lenalidomide, and dexamethasone; CTd = carfilzomib, thalidomide, and dexamethasone; CAd = cyclophosphamide, doxorubicin, and dexamethasone; CVAd = cyclophosphamide, vincristine, doxorubicin, and dexamethasone; CVTd = carfilzomib, bortezomib, thalidomide, dexamethasone; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; KCd = carfilzomib, cyclophosphamide, and dexamethasone; KRd = carfilzomib, lenalidomide, and dexamethasone; MC = multicenter; NR = not reported; PAd = bortezomib, doxorubicin, and dexamethasone; PDd = bortezomib, daratumumab, and dexamethasone; RAd = lenalidomide, adriamycin and dexamethasone; RCT = randomized controlled trial; Rd = lenalidomide and dexamethasone; TAd = thalidomide, adriamycin, dexamethasone; Td = thalidomide and dexamethasone; Vd = bortezomib and dexamethasone; VCd = bortezomib, cyclophosphamide, and dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; VTd = bortezomib, thalidomide, and dexamethasone; PLD = pegylated liposomal doxorubicin; VCMP = vincristine, cyclophosphamide, melphalan, prednisone; VAMP = vincristine, doxorubicin, methylprednisolone; VNd = vincristine, mitoxantrone, dexamethasone; Id = idarubicin, dexamethasone; BVAP = vincristine, carmustine, doxorubicin, prednisone; VMd = velcade, melphalan, and dexamethasone; VTAd = vincristine, thalidomide, doxorubicin, dexamethasone; VMP = vincristine, melphalan, prednisone

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Table 70 Completed and ongoing studies not included (Initial SLR and Feb 2021 update)

NCT#	Trial Name	Notes
NCT00205751	Thalidomide/Dexamethasone vs MP for Induction Therapy and Thalidomide/Intron A vs Intron A for Maintenance Therapy	No results available
NCT00382694	Fludarabine Added to Induction Treatment in Untreated Multiple Myeloma Patients	No results available
NCT00551928	Lenalidomide Melphalan and Prednisone Versus High Dose Melphalan in Newly Diagnosed Multiple Myeloma Patients	No results available
NCT01070862	Multiple Myeloma Treated With Thalidomide Before Autotransplant or With Conventional Chemotherapy and as Consolidation/Maintenance Treatment in Young and Elderly Patients : 3 Randomized Studies.	No results available
NCT01863550	Bortezomib or Carfilzomib With Lenalidomide and Dexamethasone in Treating Patients With Newly Diagnosed Multiple Myeloma	No results available
NCT02086942	Tolerability and Efficacy of Modified VCD Regimens in Previously Untreated Multiple Myeloma.	No results available
NCT02248428	Clarithromycin Plus CTd Regimen for Patients With Newly Diagnosed Multiple Myeloma	No results available
NCT02362165	CyBorD vs. PAD in the Treatment of Newly Diagnosed Multiple Myeloma	No results available
NCT02495922	A Phase III Trial on the Effect of Elotuzumab in VRD Induction /Consolidation and Lenalidomide Maintenance in Patients With Newly Diagnosed Myeloma	No results available
NCT02969837	Study of Initial Treatment With Elotuzumab, Carfilzomib, Lenalidomide and Dexamethasone in Multiple Myeloma	No results available
NCT03402295	Superiority of VCD Versus CTD in Patients With Newly Diagnose Multiple Myeloma Eligible for Transplantation	No results available
NCT02471820	Lenalidomide & Adriamycin & Dexamethasone (RAD) in Newly Diagnosed, Multiple Myeloma Patients	study design out of scope: single arm
NCT00287872	Bortezomib and Thalidomide in Treating Patients With Newly Diagnosed Stage II or Stage III Multiple Myeloma	study design out of scope: single arm
NCT01852799	A Study of PAD Followed by Autologous Stem Cell Transplantation (ASCT) to Treat Newly Diagnosed Multiple Myeloma	study design out of scope: single arm

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NCT#	Trial Name	Notes
NCT00097981	A Study of Thalidomide Plus Dexamethasone (Thal-Dex) Versus DOXIL plusThalidomide Plus Dexamethasone (DOXIL -Thal-Dex) in Patients With Newly Diagnosed Multiple Myeloma	Population out of scope
NCT02843074	Elotuzumab, Lenalidomide and Dexamethasone in Treatment of Transplant-Eligible Newly Diagnosed Multiple Myeloma Patients	study design out of scope: single arm
NCT01264315	Safety And Efficacy Of Lenalidomide As Maintenance Therapy In Patients With Newly Diagnosed Multiple Myeloma Following A Tandem Autologous-Allogeneic Transplant	study design out of scope: single arm
NCT02217163	Carfilzomib, Cyclophosphamide, Dexamethasone in Transplant Eligible Newly Diagnosed High-risk Multiple Myeloma	study design out of scope: single arm
NCT03617731	Trial on the Effect of Isatuximab to Lenaliodomide/Bortezomib/Dexamethasone (RVd) Induction and Lenalidomide Maintenance in Patients With Newly Diagnosed Myeloma (GMMG HD7)	No Results Available
NCT02375555	Study of Bortezomib,Lenalidomide,Dexamethasone & Elotuzumab in Newly Diagnosed MM	study design out of scope: single arm
NCT00609167	Cyclophosphamide, Bortezomib, and Dexamethasone in Treating Patients With Newly Diagnosed Multiple Myeloma	study design out of scope: single arm
NCT00925821	Lenalidomide-Adriamycin-Dexamethasone (RAD) Induction Followed by Stem Cell Transplant in Newly Diagnosed Multiple Myeloma	study design out of scope: single arm
NCT01255514	Sequential High-dose Dexamethasone and Response Adopted PAD or VAD Induction Chemotherapy Followed by High-dose Chemotherapy With Autologous Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma	study design out of scope: single arm
NCT02880228	Pembrolizumab, Lenalidomide, and Dexamethasone in Treating Patients With Newly Diagnosed Multiple Myeloma Eligible for Stem Cell Transplant	study design out of scope: single arm
NCT03376672	Ixazomib Plus Lenalidomide Plus Dexamethasone for Newly Diagnosed Myeloma Patients	No Results Available
NCT01702831	Busulfan & Melphalan Conditioning for Autologous Stem Cell Transplant (ASCT) and Lenalidomide Maintenance	study design out of scope: single arm

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NCT#	Trial Name	Notes
NCT01559935	Carfilzomib, Clarithromycin (Biaxin®), Lenalidomide (Revlimid®), and Dexamethasone (Decadron®) [Car-BiRD] Therapy for Subjects With Multiple Myeloma	study design out of scope: single arm
NCT01370434	Two Cycles of PAD Combination by AHCT in MM	study design out of scope: single arm
NCT02439112	Exercise in Patients With Multiple Myeloma	study design out of scope: supportive treatment
NCT02237261	Bendamustine, Prednisone and Velcade® for First-line Treatment of Patients With Symptomatic Multiple Myeloma	study design out of scope: single arm
NCT02406144	Trial Studying Maintenance Treatment With Lenalidomide and Dexamethasone Versus Lenalidomide, Dexamethasone and MLN9708 After Autologous Hematopoietic Stem Cell Transplantation in Patients With Newly-diagnosed Symptomatic Multiple Myeloma	No Results Available
NCT01341262	THAL-DEX Incorporated Into Double PBSC Autotransplantation for Untreated Multiple Myeloma (MM)	study design out of scope: single arm
NCT00054158	Combination Chemotherapy and Thalidomide in Treating Patients With Stage I, Stage II, or Stage III Multiple Myeloma	No Results Available
NCT01376401	Bendamustine, Bortezomib (Velcade) and Prednisone (BVP) in Patients Newly Diagnosed Multiple Myeloma	study design out of scope: single arm
NCT01706666	Bortezomib Based Consolidation in Multiple Myeloma Patients Completing Stem Cell Transplant	study design out of scope: consolidation treatment
NCT00205764	Tandem High Dose Melphalan Versus Triple Intermediate Dose Melphalan and Stem Cell Transplantation in Induction Phase and Prednisolone/IFN Versus IFN in Maintenance Therapy	study design out of scope: maintenance therapy
NCT02420860	Elotuzumab and Lenalidomide After Stem Cell Transplant in Treating Patients With Newly Diagnosed Multiple Myeloma	study design out of scope: single arm

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NCT#	Trial Name	Notes
NCT01718743	Ixazomib Citrate and Lenalidomide After Stem Cell Transplant in Treating Patients With Newly Diagnosed Multiple Myeloma	study design out of scope: single arm
NCT00702247	Tandem Autologous- Nonmyeloablative Allogeneic Transplant for Newly Diagnosed Multiple Myeloma (Trapianto Tandem Autologo-Allogenico Non Mieloablativo Nel Mieloma Alla Diagnosi)	study design out of scope: single arm
NCT01402284	Carfilzomib, Lenalidomide, and Dexamethasone in New Multiple Myeloma Patients	study design out of scope: single arm
NCT00083551	UARK 98-026 TT II: Multiple Myeloma Evaluating Anti-Angiogenesis With Thalidomide and Post-Transplant Consolidation Chemotherapy	study design out of scope: consolidation treatment
NCT02405364	Front-line Therapy With Carfilzomib, Lenalidomide, and Dexamethasone Induction	study design out of scope: single arm
NCT03004287	2015-12: A Study Exploring the Use of Early and Late Consolidation/Maintenance Therapy	study design out of scope: single arm
NCT00378222	Autologous Transplantation for Multiple Myeloma	No Results Available
NCT00040937	S0204 Thalidomide, Chemotherapy, and Peripheral Stem Cell Transplant in Treating Patients With Multiple Myeloma	study design out of scope: single arm
NCT02181413	A Study of Oral Ixazomib Citrate (MLN9708) Maintenance Therapy in Participants With Multiple Myeloma Following Autologous Stem Cell Transplant	study design out of scope: maintenance therapy
NCT03710603	Daratumumab, VELCADE (Bortezomib), Lenalidomide and Dexamethasone Compared to VELCADE, Lenalidomide and Dexamethasone in Subjects With Previously Untreated Multiple Myeloma	No Results Available
NCT00222105	A Study Evaluating Efficacy, Toxicity, Harvest Yield and Quality of Life	study design out of scope: single arm
NCT01208662	Randomized Trial of Lenalidomide, Bortezomib, Dexamethasone vs High-Dose Treatment With SCT in MM Patients up to Age 65	No Results Available

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NCT#	Trial Name	Notes
NCT00116961	Velcade, Doxil, and Dexamethasone (VDd) as First Line Therapy for Multiple Myeloma	study design out of scope: single arm
NCT00006184	Chemotherapy, Stem Cell Transplantation and Donor and Patient Vaccination for Treatment of Multiple Myeloma	study design: non-randomized trial
NCT01206205	Frontline Therapy in de Novo Multiple Myeloma Patients Under 65	study design out of scope: single arm
NCT00357084	Methotrexate and Glucocorticoids in Treating Patients With Newly Diagnosed Acute Graft-Versus-Host Disease After Donor Stem Cell Transplant	study design out of scope: supportive treatment
2016-002557-38	Cyclophosphamide as graft-versus-host prophylaxis after allogeneic stem cell transplantation for multiple myeloma. A phase II study.	No Results Available
2005-004714-32	A PHASE II, MULTI-CENTER STUDY OF BORTEZOMIB, ADRIAMYCIN, DEXAMETHASONE (PAD) as induction and MELPHALAN 100 mg/m2 (MEL 100) as transplant, IN ELDERLY NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS.	No Results Available
2005-004730-41	A PHASE II, MULTI-CENTER STUDY OF MELPHALAN 100 mg/m2 (MEL 100) as transplant, REVLIMID and PREDNISONE (RP) as consolidation and REVLIMID ALONE as maintenance IN ELDERLY NEWLY DIAGNOSED MULTIPLE M.	No Results Available
JPRN-UMIN000009700	CBD (cyclophohamide,bortezomib,dexamethasone) induction followed by autologous stem cell transplantation for patients with newly diagnosed multiple myeloma	study design out of scope: single arm
JPRN-UMIN000009765	Bortezomib, cyclophosphamide plus dexamethasone as induction treatment prior to autologous stem cell transplantation in newly diagnosed multiple myeloma	study design out of scope: single arm
ACTRN12612000419864	A randomized phase III study to compare Bortezomib, Melphalan, Prednisone (VMP) with High Dose Melphalan followed by Bortezomib, Lenalidomide, Dexamethasone (VRD) consolidation and Lenalidomide maintenance in patients with newly diagnosed multiple myeloma	No Results Available
JPRN-jRCTs071180034	Newly diagnosed multiple myeloma: a phase2 study -JSCT-MM14-	study design out of scope: single arm

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NCT#	Trial Name	Notes
ACTRN12618001490268	Daratumumab-lenalidomide-dexamethasone (DRd) salvage for newly diagnosed Multiple Myeloma patients who fail bortezomib induction therapy	study design out of scope: single arm

Abbreviations: MP = melphalan, prednisone; VCd = bortezomib, cyclophosphamide, dexamethasone; CTd = cyclophosphamide, thalidomide, dexamethasone; Pad = bortezomib, doxorubicin, dexamethasone; AHCT = autologous hematopoietic cell transplantation

Table 71 The list of excluded references/full text papers (Initial SLR, 1st update and 2nd update)

Full Citation	Reason of Exclusion
Sonneveld, Pieter, et al. "Bortezomib induction and maintenance in patients with newly diagnosed multiple myeloma: long-term follow-up of the HOVON-65/GMMG-HD4 trial." (2015): 27-27.	Clinical outcomes in patients receiving maintenance therapy after ASCT
Greipp, Philip R. "Eastern Cooperative Oncology Group E1A00: phase III randomized study of dexamethasone with or without thalidomide in patients with newly diagnosed multiple myeloma." *Clinical advances in hematology & oncology: H&O* 1.3 (2003): 188-189.	Clinical trial protocol
Goldschmidt, Hartmut, et al. "Joint HOVON-50/GMMG-HD3 randomized trial on the effect of thalidomide as part of a high-dose therapy regimen and as maintenance treatment for newly diagnosed myeloma patients." *Annals of hematology* 82.10 (2003): 654-659.	Clinical trial protocol
Durie, Brian, et al. "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): results of the randomized phase III trial SWOG S0777." (2015): 25-25.	Mixed populations: NDMM transplant-eligible and transplant-ineligible
Jethava, Yogesh S., et al. "Adverse metaphase cytogenetics can be overcome by adding bortezomib and thalidomide to fractionated melphalan transplants." *Clinical Cancer Research* 23.11 (2017): 2665-2672.	Treatment administration study
Rodriguez-Otero, Paula, et al. "Early myeloma-related death in elderly patients: development of a clinical prognostic score and evaluation of response sustainability role." *Leukemia* 32.11 (2018): 2427-2434.	Treatment administration study
Riccardi, A., et al. "Long-term survival of stage I multiple myeloma given chemotherapy just after diagnosis or at progression of the disease: a multicentre randomized study." *British Journal of Cancer* 82.7 (2000): 1254-1260.	Treatment administration study
Popat, Rakesh, et al. "Bortezomib, doxorubicin and dexamethasone (PAD) front-line treatment of multiple myeloma: updated results after long-term follow-up." *British journal of haematology* 141.4 (2008): 512-516.	Non-RCT in transplant-eligible NDMM

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Full Citation	Reason of Exclusion
Sonneveld, Pieter, et al. "Bortezomib induction and maintenance in patients with newly diagnosed multiple myeloma: long-term follow-up of the HOVON-65/GMMG-HD4 trial." (2015): 27-27.	Clinical outcomes in patients receiving maintenance therapy after ASCT
Greipp, Philip R. "Eastern Cooperative Oncology Group E1A00: phase III randomized study of dexamethasone with or without thalidomide in patients with newly diagnosed multiple myeloma." *Clinical advances in hematology & oncology: H&O* 1.3 (2003): 188-189.	Clinical trial protocol
Wester, Ruth, et al. "Carfilzomib combined with thalidomide and low-dose dexamethasone for remission induction and consolidation in newly diagnosed, transplant eligible patients with multiple myeloma: the Carthadex trial." *Blood* 130.Supplement 1 (2017): 3141-3141.	Non-RCT in transplant-eligible NDMM
Wester, Ruth, et al. "Phase 2 study of carfilzomib, thalidomide, and low-dose dexamethasone as induction/consolidation in newly diagnosed, transplant eligible patients with multiple myeloma, the carthadex trial." (2016): 1141-1141.	Non-RCT in transplant-eligible NDMM
Hussein, Mohamad A., et al. "Phase 2 study of pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide in newly diagnosed and relapsed-refractory multiple myeloma." *Mayo Clinic Proceedings*. Vol. 81. No. 7. Elsevier, 2006.	Non-RCT in transplant-eligible NDMM
Biran, Noa, et al. "A phase II trial of the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475)+ lenalidomide+ dexamethasone as post autologous stem cell transplant consolidation in patients with high-risk multiple myeloma." *Blood* 130.Supplement 1 (2017): 1831-1831.	Non-RCT in transplant-eligible NDMM
Gozzetti, Alessandro, et al. "Safety and efficacy of bortezomib, melphalan and low doses dexamethasone (VM-dex) in newly diagnosed patients with multiple myeloma." *Leukemia research* 34.11 (2010): e288-9.	Non-RCT in transplant-eligible NDMM
Barlogie, Bart, et al. "Superiority of tandem autologous transplantation over standard therapy for previously untreated multiple myeloma." *Blood, The Journal of the American Society of Hematology* 89.3 (1997): 789-793.	Non-RCT in transplant-eligible NDMM
Pineda-Roman, Mauricio, et al. "Sustained complete remissions in multiple myeloma linked to bortezomib in total therapy 3: comparison with total therapy 2." *British journal of haematology* 140.6 (2008): 625-634.	Non-RCT in transplant-eligible NDMM
Barlogie, Bart, et al. "Total therapy 2 without thalidomide in comparison with total therapy 1: role of intensified induction and posttransplantation consolidation therapies." *Blood* 107.7 (2006): 2633-2638.	Non-RCT in transplant-eligible NDMM
Mateos, Maria-Victoria, et al. "Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: updated follow-up and impact of subsequent therapy in the phase III VISTA trial." *Journal of Clinical Oncology* 28.13 (2010): 2259-2266.	Not transplant-eligible NDMM
Mateos, María Victoria, et al. "Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: updated time-to-events results and prognostic factors for time to progression." (2008).	Not transplant-eligible NDMM

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Full Citation	Reason of Exclusion
Durie, Brian GM, 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." *The Lancet* 389.10068 (2017): 519-527.	Not transplant-eligible NDMM
Mateos, María-Victoria, et al. "Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial." *The lancet oncology* 11.10 (2010): 934-941.	Not transplant-eligible NDMM
Chen, R. A., et al. "Bortezomib-dexamethasone or vincristine-doxorubicin-dexamethasone as induction therapy followed by thalidomide as maintenance therapy in untreated multiple myeloma patients." *Journal of International Medical Research* 39.5 (2011): 1975-1984.	Not transplant-eligible NDMM
Palumbo, Antonio, et al. "Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial." *Journal of Clinical Oncology* 28.34 (2010): 5101-5109.	Not transplant-eligible NDMM
Picot, J., et al. "The clinical effectiveness and cost-effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma: a systematic review and economic evaluation." *Health technology assessment (Winchester, England)* 15.41 (2011): 1.	Not transplant-eligible NDMM
Niesvizky, Ruben, et al. "Community-based phase IIIB trial of three UPFRONT bortezomib-based myeloma regimens." *J Clin Oncol* 33.33 (2015): 3921-3929.	Not transplant-eligible NDMM
Liu, Xiaoping, et al. "Comparing efficacy and survivals of initial treatments for elderly patients with newly diagnosed multiple myeloma: a network meta-analysis of randomized controlled trials." *OncoTargets and therapy* 10 (2017): 121.	Not transplant-eligible NDMM
Fonseca, Rafael, and S. Vincent Rajkumar. "Consolidation therapy with bortezomib/lenalidomide/dexamethasone versus bortezomib/dexamethasone after a dexamethasone-based induction regimen in patients with multiple myeloma: a randomized phase III trial." *Clinical Lymphoma and Myeloma* 8.5 (2008): 315-317.	Not transplant-eligible NDMM
Palumbo, Antonio, et al. "Continuous therapy versus fixed duration of therapy in patients with newly diagnosed multiple myeloma." (2015): 3459-3466.	Not transplant-eligible NDMM
Mateos, María-Victoria, et al. "Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma." *New England Journal of Medicine* 378.6 (2018): 518-528.	Not transplant-eligible NDMM

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Full Citation	Reason of Exclusion
Hulin, Cyrille, et al. "Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial." *Journal of Clinical Oncology* 27.22 (2009): 3664-3670.	Not transplant-eligible NDMM
Mateos, María-Victoria, et al. "GEM2005 trial update comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators?." *Blood* 124.12 (2014): 1887-1893.	Not transplant-eligible NDMM
Palumbo, Antonio, et al. "Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial." *Blood* 104.10 (2004): 3052-3057.	Not transplant-eligible NDMM
Zonder, Jeffrey A., et al. "Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: a randomized Southwest Oncology Group trial (S0232)." *Blood, The Journal of the American Society of Hematology* 116.26 (2010): 5838-5841.	Not transplant-eligible NDMM
Gentile, Massimo, et al. "Lenalidomide and low-dose dexamethasone (Rd) versus bortezomib, melphalan, prednisone (VMP) in elderly newly diagnosed multiple myeloma patients: a comparison of two prospective trials." *American journal of hematology* 92.3 (2017): 244-250.	Not transplant-eligible NDMM
Dimopoulos, Meletios A., et al. "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 randomized phase III trial." *haematologica* 98.5 (2013): 784.	Not transplant-eligible NDMM
Bringhen, Sara, et al. "Long term outcome of lenalidomide-dexamethasone (Rd) vs melphalan-lenalidomide-prednisone (MPR) vs cyclophosphamide-prednisone-lenalidomide (CPR) as induction followed by lenalidomide-prednisone (RP) vs lenalidomide (R) as maintenance in a community-based newly diagnosed myeloma population: updated analysis of EMN01 phase III study." Blood 130.Supplement 1 (2017): 901-901.	Not transplant-eligible NDMM
Waage, Anders, et al. "Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma." *Blood, The Journal of the American Society of Hematology* 116.9 (2010): 1405-1412.	Not transplant-eligible NDMM
Zweegman, S., et al. "Lenalidomide plus melphalan and prednisone, followed by lenalidomide maintenance versus thalidomide plus melphalan and prednisone, followed by thalidomide maintenance; results of the randomised phase 3 HOVON 87/NMSG18 trial." *Blood* 127.9 (2016): 1109-1116.	Not transplant-eligible NDMM
Stewart, A. Keith, et al. "Melphalan, prednisone, and thalidomide vs melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma." *Blood, The Journal of the American Society of Hematology* 126.11 (2015): 1294-1301.	Not transplant-eligible NDMM

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Full Citation	Reason of Exclusion
Rajkumar, S. Vincent, et al. "Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma." *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 26.13 (2008): 2171.	Not transplant-eligible NDMM
Palumbo, Antonio, et al. "Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial." *The Lancet* 367.9513 (2006): 825-831.	Not transplant-eligible NDMM
San-Miguel, Jesús, et al. "Phase 2 randomized study of bortezomib-melphalan-prednisone with or without siltuximab (anti–IL-6) in multiple myeloma." *Blood, The Journal of the American Society of Hematology* 123.26 (2014): 4136-4142.	Not transplant-eligible NDMM
Takenaka, Takeaki, et al. "Phase III study of ranimustine, cyclophosphamide, vincristine, melphalan, and prednisolone (MCNU-COP/MP) versus modified COP/MP in multiple myeloma: a Japan clinical oncology group study, JCOG 9301." *International journal of hematology* 79.2 (2004): 165-173.	Not transplant-eligible NDMM
Wijermans, Pierre, et al. "Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: the HOVON 49 Study." *Journal of Clinical Oncology* 28.19 (2010): 3160-3166.	Not transplant-eligible NDMM
Shustik, Chaim, et al. "A randomised comparison of melphalan with prednisone or dexamethasone as induction therapy and dexamethasone or observation as maintenance therapy in multiple myeloma: NCIC CTG MY. 7." *British journal of haematology* 136.2 (2007): 203-211.	Not transplant-eligible NDMM
Nagura, Eiichi, et al. "A randomized study comparing VMCP and MMPP in the treatment of multiple myeloma." *Cancer chemotherapy and pharmacology* 39.4 (1997): 279-285.	Not transplant-eligible NDMM
Riccardi, A., et al. "Response to first-line chemotherapy and long-term survival in patients with multiple myeloma: results of the MM87 prospective randomised protocol." *European Journal of Cancer* 39.1 (2003): 31-37.	Not transplant-eligible NDMM
Morabito, Fortunato, et al. "Safety and efficacy of bortezomib-melphalan-prednisone-thalidomide followed by bortezomib-thalidomide maintenance (VMPT-VT) versus bortezomib-melphalan-prednisone (VMP) in untreated multiple myeloma patients with renal impairment." *Blood, The Journal of the American Society of Hematology* 118.22 (2011): 5759-5766.	Not transplant-eligible NDMM
Mateos, María-Victoria, et al. "Sequential vs alternating administration of VMP and Rd in elderly patients with newly diagnosed MM." *Blood* 127.4 (2016): 420-425.	Not transplant-eligible NDMM
Moritz, Binder, et al. "Early Paraprotein Kinetics and Response to Treatment in Multiple Myeloma." *Blood* 130.Supplement 1 (2017): 4355-4355.	Not NDMM (patients have been treated with ≥1 prior therapy)

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Full Citation	Reason of Exclusion
Fenk, R., et al. "High-dose idarubicin, cyclophosphamide and melphalan as conditioning for autologous stem cell transplantation increases treatment-related mortality in patients with multiple myeloma: results of a randomised study." *British journal of haematology* 130.4 (2005): 588-594.	Not NDMM (patients have been treated with ≥1 prior therapy)
Sharma, Manish, et al. "A randomized phase 2 trial of a preparative regimen of bortezomib, high-dose melphalan, arsenic trioxide, and ascorbic acid." *Cancer* 118.9 (2012): 2507-2515.	Not NDMM (patients have been treated with ≥1 prior therapy)
Bashir, Qaiser, et al. "A randomized phase II trial of fludarabine/melphalan 100 versus fludarabine/melphalan 140 followed by allogeneic hematopoietic stem cell transplantation for patients with multiple myeloma." *Biology of Blood and Marrow Transplantation* 19.10 (2013): 1453-1458.	Not NDMM (patients have been treated with ≥1 prior therapy)
Rosinol, Laura, et al. "Bortezomib, lenalidomide and dexamethasone (VRD-GEM) as induction therapy prior autologous stem cell transplantation (ASCT) in multiple myeloma (MM): results of a prospective phase III pethema/GEM trial." *Blood* 130.Supplement 1 (2017).	No relevant intervention of interest
Lokhorst, Henk M., et al. "Donor versus no-donor comparison of newly diagnosed myeloma patients included in the HOVON-50 multiple myeloma study." *Blood* 119.26 (2012): 6219-6225.	No relevant intervention of interest
Cavo, Michele, et al. "Double autologous stem cell transplantation significantly prolongs progression-free survival and overall survival in comparison with single autotransplantation in newly diagnosed multiple myeloma: an analysis of phase 3 EMN02/HO95 study." *Blood* 130.Supplement 1 (2017): 401-401.	No relevant intervention of interest
Sonneveld, Pieter, et al. "Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON 24 trial." (2007).	No relevant intervention of interest
Biran, N., et al. "Outcome with lenalidomide plus dexamethasone followed by early autologous stem cell transplantation in patients with newly diagnosed multiple myeloma on the ECOG-ACRIN E4A03 randomized clinical trial: long-term follow-up." *Blood cancer journal* 6.9 (2016): e466-e466.	No relevant intervention of interest
Attal, Michel, et al. "A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma." *New England Journal of Medicine* 335.2 (1996): 91-97.	No relevant intervention of interest
Mai, Elias K., et al. "Single versus tandem high-dose melphalan followed by autologous blood stem cell transplantation in multiple myeloma: long-term results from the phase III GMMG-HD 2 trial." *British journal of haematology* 173.5 (2016): 731-741.	No relevant intervention of interest

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Full Citation	Reason of Exclusion
Kay, Neil E., et al. "Blood levels of immune cells predict survival in myeloma patients: results of an Eastern Cooperative Oncology Group phase 3 trial for newly diagnosed multiple myeloma patients." *Blood, The Journal of the American Society of Hematology* 98.1 (2001): 23-28.	No outcomes of interest
Merz, Maximilian, et al. "Clinical Risk Factors for Peripheral Neuropathy in Patients Treated with Subcutaneous or Intravenous Bortezomib for Newly Diagnosed Multiple Myeloma." (2015): 4233-4233.	No outcomes of interest
Scheid, Christof, et al. "Direct Assessment of IgA and IgG Paraprotein By Hevylite Assay and Correlation to IMWG Response and Progression-Free Survival in Newly Diagnosed, Transplant-Eligible Multiple Myeloma Patients in the Prospective Phase III GMMG-MM5 Trial." *Blood* 130.Supplement 1 (2017): 1784-1784.	No outcomes of interest
Zangari, Maurizio, et al. "Effect on survival of treatment-associated venous thromboembolism in newly diagnosed multiple myeloma patients." *Blood coagulation & fibrinolysis* 18.7 (2007): 595-598.	No outcomes of interest
Avet-Loiseau, Herve, et al. "Evaluation of minimal residual disease (MRD) by next generation sequencing (NGS) is highly predictive of progression free survival in the IFM/DFCI 2009 trial." (2015): 191-191.	No outcomes of interest
Facon, Thierry, et al. "Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial." *The Lancet* 370.9594 (2007): 1209-1218.	No outcomes of interest
Avet-Loiseau, Hervé, et al. "Minimal residual disease in multiple myeloma: final analysis of the IFM2009 trial." *Blood* 130.Supplement 1 (2017): 435-435.	No outcomes of interest
Jones, John R., et al. "Myeloma XI trial for newly diagnosed multiple myeloma (NDMM); A report of Second Primary Malignancy (SPM) rates and the importance of review of reported cases." (2015): 1847-1847.	No outcomes of interest
Riccardi, A., et al. "Relevance of age on survival of 341 patients with multiple myeloma treated with conventional chemotherapy: updated results of the MM87 prospective randomized protocol." *British journal of cancer* 77.3 (1998): 485-491.	No outcomes of interest
Ho, P. Joy, et al. "Thalidomide consolidation improves progression-free survival in myeloma with normal but not up-regulated expression of fibroblast growth factor receptor 3: analysis from the Australasian Leukaemia and Lymphoma Group MM6 clinical trial." *Leukemia & lymphoma* (2012).	No outcomes of interest
Mateos, María-Victoria, et al. "Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma." *New England Journal of Medicine* 369.5 (2013): 438-447.	Disease (not MM)

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Full Citation	Reason of Exclusion
Mateos, María-Victoria, et al. "Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial." *The Lancet Oncology* 17.8 (2016): 1127-1136.	Disease (not MM)
Brighton, Timothy, et al. "A phase 2, randomized, double-blind, placebo-controlled, multicenter study of siltuximab (anti IL-6 monoclonal antibody) in patients with high-risk smoldering multiple myeloma." *Blood* 130.Supplement 1 (2017): 3155-3155.	Disease (not MM)
Dhakal, Binod, et al. "Autologous stem cell transplant (ASCT) for newly diagnosed multiple myeloma (MM) in the era of novel agents: A meta-analysis of phase III randomized controlled trials." (2017): 8022-8022.	Study design (editorial, narrative, case study)
Scott, K., et al. "BORTEZOMIB FOR THE TREATMENT OF MULTIPLE MYELOMA: A SYSTEMATIC REVIEW AND META-ANALYSIS." *HAEMATOLOGICA*. Vol. 100. VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY: FERRATA STORTI FOUNDATION, 2015.	Study design (editorial, narrative, case study)
Ahuja, A., et al. "Hrqol And Health Utility Impact On Patients With Newly Diagnosed Multiple Myeloma In Us And Europe: A Systematic Literature Review." *Value in Health* 18.7 (2015): A468.	Study design (editorial, narrative, case study)
Offidani, Massimo, et al. "Infection complications in 476 patients with newly diagnosed multiple myeloma treated with lenalidomide or bortezomib combinations." (2015): 5365-5365.	Study design (editorial, narrative, case study)
Mezo, Melinda, et al. "Peripheral Neuropathy (PN) with Immunomodulatory Drugs in Patients with Multiple Myeloma (MM)." (2016): 5677-5677.	Study design (editorial, narrative, case study)
Jacobus, S. J., et al. "Randomized phase III trial of consolidation therapy with bortezomib–lenalidomide–Dexamethasone (VRd) vs bortezomib–dexamethasone (Vd) for patients with multiple myeloma who have completed a dexamethasone based induction regimen." *Blood cancer journal* 6.7 (2016): e448-e448.	Study design (editorial, narrative, case study)
Kim, J-C., et al. "SYSTEMATIC LITERATURE REVIEW AND NETWORK META-ANALYSIS OF INDUCTION TREATMENT FOR NEWLY DIAGNOSED TRANSPLANT-ELIGIBLE MULTIPLE MYELOMA PATIENTS." *HAEMATOLOGICA*. Vol. 102. VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY: FERRATA STORTI FOUNDATION, 2017.	Study design (editorial, narrative, case study)
Kharfan-Dabaja, Mohamed, et al. "Three-drug versus two-drug induction therapy regimens for patients with transplant-eligible multiple myeloma." *The Cochrane Database of Systematic Reviews* 2016.10 (2016).	Study design (editorial, narrative, case study)
Gay, F., et al. "Upfront or rescue transplant in young patients with newly diagnosed multiple myeloma: a pooled analysis of 529 patients." *Haematologica*. Vol. 101. VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY: FERRATA STORTI FOUNDATION, 2016.	Study design (editorial, narrative, case study)

Full Citation	Reason of Exclusion
Zou, Yandun, et al. "Bortezomib and lenalidomide as front-line therapy for multiple myeloma." *Leukemia & lymphoma* 55.9 (2014): 2024-2031.	Publication date (SLR prior to 2015)
Zeng, Zhiyong, Junfang Lin, and Junmin Chen. "Bortezomib for patients with previously untreated multiple myeloma: a systematic review and meta-analysis of randomized controlled trials." *Annals of hematology* 92.7 (2013): 935-943.	Publication date (SLR prior to 2015)
Wang, Long, Yan-Li Xu, and Xiu-Qun Zhang. "Bortezomib in combination with thalidomide or lenalidomide or doxorubicin regimens for the treatment of multiple myeloma: a meta-analysis of 14 randomized controlled trials." *Leukemia & lymphoma* 55.7 (2014): 1479-1488.	Publication date (SLR prior to 2015)
Kouroukis, T. C., et al. "Bortezomib in multiple myeloma: systematic review and clinical considerations." *Current oncology* 21.4 (2014): e573.	Publication date (SLR prior to 2015)
Wang, Anyou, et al. "(Bortezomib plus lenalidomide/thalidomide)-vs (bortezomib or lenalidomide/thalidomide)-containing regimens as induction therapy in newly diagnosed multiple myeloma: a meta-analysis of randomized controlled trials." *Annals of hematology* 91.11 (2012): 1779-1784.	Publication date (SLR prior to 2015)
Sonneveld, Pieter, et al. "Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials." *J Clin Oncol* 31.26 (2013): 3279-3287.	Publication date (SLR prior to 2015)
Nooka, Ajay K., et al. "Bortezomib-containing induction regimens in transplant-eligible myeloma patients: A meta-analysis of phase 3 randomized clinical trials." *Cancer* 119.23 (2013): 4119-4128.	Publication date (SLR prior to 2015)
Leiba, Merav, et al. "Bortezomib-Cyclophosphamide-Dexamethasone (VCD) versus Bortezomib-Thalidomide-Dexamethasone (VTD)-based regimens as induction therapies in newly diagnosed transplant eligible patients with multiple myeloma: a meta-analysis." *British journal of haematology* 166.5 (2014): 702-710.	Publication date (SLR prior to 2015)
Huang, Hejing, et al. "Bortezomib–thalidomide-based regimens improved clinical outcomes without increasing toxicity as induction treatment for untreated multiple myeloma: a meta-analysis of phase III randomized controlled trials." *Leukemia research* 38.9 (2014): 1048-1054.	Publication date (SLR prior to 2015)
Zou, Yandun, et al. "Continuous treatment with new agents for newly diagnosed multiple myeloma." *Anti-Cancer Drugs* 24.5 (2013): 527-533.	Publication date (SLR prior to 2015)
Gao, Minjie, et al. "Early versus deferred treatment for smoldering multiple myeloma: a meta-analysis of randomized, controlled trials." *PloS one* 9.10 (2014): e109758.	Publication date (SLR prior to 2015)

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Full Citation	Reason of Exclusion
Naumann-Winter, Frauke, et al. "First-line tandem high-dose chemotherapy and autologous stem cell transplantation versus single high-dose chemotherapy and autologous stem cell transplantation in multiple myeloma, a systematic review of controlled studies." *Cochrane database of systematic reviews* 10 (2012).	Publication date (SLR prior to 2015)
Koreth, John, et al. "High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: a systematic review and meta-analysis of randomized controlled trials." *Biology of Blood and Marrow Transplantation* 13.2 (2007): 183-196.	Publication date (SLR prior to 2015)
Yang, Bo, et al. "Lenalidomide treatment for multiple myeloma: systematic review and meta-analysis of randomized controlled trials." *PLoS One* 8.5 (2013): e64354.	Publication date (SLR prior to 2015)
Zou, Yandun, et al. "Lenalidomide versus thalidomide based regimens as first-line therapy for patients with multiple myeloma." *Leukemia & lymphoma* 54.10 (2013): 2219-2225.	Publication date (SLR prior to 2015)
Hicks, Lisa K., et al. "A meta-analysis and systematic review of thalidomide for patients with previously untreated multiple myeloma." *Cancer treatment reviews* 34.5 (2008): 442-452.	Publication date (SLR prior to 2015)
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Faussner, Florian, and Wolfram CM Dempke. "Multiple myeloma: myeloablative therapy with autologous stem cell support versus chemotherapy: a meta-analysis." *Anticancer research* 32.5 (2012): 2103-2109.	Publication date (SLR prior to 2015)
Wang, Lida, et al. "Novel agents-based regimens as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis of randomized controlled trials." *Hematological oncology* 30.2 (2012): 57-61.	Publication date (SLR prior to 2015)
Wang, Lida, et al. "Postrelapse survival rate correlates with first-line treatment strategy with thalidomide in patients with newly diagnosed multiple myeloma: a meta-analysis." *Hematological oncology* 30.4 (2012): 163-169.	Publication date (SLR prior to 2015)
Palumbo, Antonio, et al. "Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data." *The lancet oncology* 15.3 (2014): 333-342.	Publication date (SLR prior to 2015)
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Kumar, Ambuj, et al. "Thalidomide versus bortezomib based regimens as first-line therapy for patients with multiple myeloma: A systematic review." *American journal of hematology* 86.1 (2011): 18-24.	Publication date (SLR prior to 2015)
Mhaskar, A. R., et al. "Timing of first-line cancer treatments–Early versus late–A systematic review of phase III randomized trials." *Cancer treatment reviews* 36.8 (2010): 621-628.	Publication date (SLR prior to 2015)
Tacchetti, P., et al. "Intensification therapy with autologous stem cell transplantation versus bortezomib-melphalan-prednisone for newly diagnosed multiple myeloma patients: A multicenter, phase III study of the european myeloma network (EMN02/HO95 MM trial)." *Haematologica* 102.Supplement 3 (2017): 26.	Conference not of interest
Gay, F., et al. "INTERIM ANALYSIS OF CARFILZOMIB-LENALIDOMIDE-DEXAMETHASONE VS CARFILZOMIB-CYCLOPHOSPHAMIDE-DEXAMETHASONE IN THE FORTE TRIAL." *HAEMATOLOGICA*. Vol. 102. VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY: FERRATA STORTI FOUNDATION, 2017.	Conference not of interest
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Mainou, Maria, et al. "Association between response rates and survival outcomes in patients with newly diagnosed multiple myeloma. A systematic review and meta-regression analysis." *European journal of haematology* 98.6 (2017): 563-568.	SLR/MA of RCTs in NDMM (bibliography checked)
Gay, Francesca, et al. "Autologous transplant vs oral chemotherapy and lenalidomide in newly diagnosed young myeloma patients: a pooled analysis." *Leukemia* 31.8 (2017): 1727-1734.	SLR/MA of RCTs in NDMM (bibliography checked)
Dhakal, Binod, et al. "Autologous transplantation for newly diagnosed multiple myeloma in the era of novel agent induction: a systematic review and meta-analysis." *JAMA oncology* 4.3 (2018): 343-350.	SLR/MA of RCTs in NDMM (bibliography checked)
Straka, Christian, et al. "Bortezomib consolidation following autologous transplant equalizes the outcome for older patients with less intensive pretreatment compared to younger patients with newly diagnosed multiple myeloma." (2016): 516-516.	SLR/MA of RCTs in NDMM (bibliography checked)
Scott, Kathleen, et al. "Bortezomib for the treatment of multiple myeloma." *Cochrane Database of Systematic Reviews* 4 (2016).	SLR/MA of RCTs in NDMM (bibliography checked)
Lentzsch, Suzanne, et al. "Continuous Treatment with Lenalidomide Plus Low-Dose Dexamethasone (Ld) Versus Ld Induction Followed By Autologous Stem Cell Transplant (ASCT) in Patients with Newly Diagnosed Multiple Myeloma (NDMM): A Pooled Analysis of Two Randomized Clinical Trials." (2015): 1975-1975.	SLR/MA of RCTs in NDMM (bibliography checked)

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Full Citation	Reason of Exclusion
Lahuerta, Juan-Jose, et al. "Depth of response in multiple myeloma: a pooled analysis of three PETHEMA/GEM clinical trials." *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 35.25 (2017): 2900.	SLR/MA of RCTs in NDMM (bibliography checked)
Aguiar, Patricia Melo, et al. "Efficacy and safety of bortezomib, thalidomide, and lenalidomide in multiple myeloma: An overview of systematic reviews with meta-analyses." *Critical reviews in oncology/hematology* 113 (2017): 195-212.	SLR/MA of RCTs in NDMM (bibliography checked)
Qiao, Shu-Kai, et al. "Efficacy and safety of lenalidomide in the treatment of multiple myeloma: a systematic review and meta-analysis of randomized controlled trials." *Chinese medical journal* 128.9 (2015): 1215.	SLR/MA of RCTs in NDMM (bibliography checked)
Porcher, R., et al. "Evaluating high dose therapy in multiple myeloma: use of quality-adjusted survival analysis." *Quality of Life Research* 11.2 (2002): 91-99.	SLR/MA of RCTs in NDMM (bibliography checked)
Chen, Min, et al. "Immunomodulatory drugs and the risk of serious infection in multiple myeloma: systematic review and meta-analysis of randomized and observational studies." *Annals of hematology* 97.6 (2018): 925-944.	SLR/MA of RCTs in NDMM (bibliography checked)
Zeng, Zi-Hang, et al. "Induction regimens for transplant-eligible patients with newly diagnosed multiple myeloma: a network meta-analysis of randomized controlled trials." *Cancer management and research* 9 (2017): 287.	SLR/MA of RCTs in NDMM (bibliography checked)
Teh, Benjamin W., et al. "Infection risk with immunomodulatory and proteasome inhibitor–based therapies across treatment phases for multiple myeloma: A systematic review and meta-analysis." *European Journal of Cancer* 67 (2016): 21-37.	SLR/MA of RCTs in NDMM (bibliography checked)
Robinson Jr, Don, et al. "The influence of baseline characteristics and disease stage on health-related quality of life in multiple myeloma: findings from six randomized controlled trials." *British journal of haematology* 174.3 (2016): 368-381.	SLR/MA of RCTs in NDMM (bibliography checked)
Peng, Ling, et al. "Meta-analysis of incidence and risk of peripheral neuropathy associated with intravenous bortezomib." *Supportive Care in Cancer* 23.9 (2015): 2813-2824.	SLR/MA of RCTs in NDMM (bibliography checked)
Straka, Christian, et al. "Results from two phase III studies of bortezomib (BTZ) consolidation vs observation (OBS) post-transplant in patients (pts) with newly diagnosed multiple myeloma (NDMM)." (2015): 8511-8511.	SLR/MA of RCTs in NDMM (bibliography checked)
Gao, Minjie, et al. "Single-agent bortezomib or bortezomib-based regimens as consolidation therapy after autologous hematopoietic stem cell transplantation in multiple myeloma: a meta-analysis of randomized controlled trials." *International journal of clinical and experimental medicine* 8.8 (2015): 12202.	SLR/MA of RCTs in NDMM (bibliography checked)
Cavo, M., et al. "SUPERIOR EFFICACY OF VTD OVER VCD BEFORE AND AFTER AUTOLOGOUS STEM-CELL TRANSPLANTATION IN NEWLY DIAGNOSED MULTIPLE MYELOMA." *h aematologica h aemat* 100.s3 (2015): 30.	SLR/MA of RCTs in NDMM (bibliography checked)

Full Citation	Reason of Exclusion
Cavo, M., et al. "SUPERIOR EFFICACY OF VTD OVER VCD BEFORE AND AFTER AUTOLOGOUS STEM-CELL TRANSPLANTATION IN NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS." *HAEMATOLOGICA*. Vol. 100. VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY: FERRATA STORTI FOUNDATION, 2015.	SLR/MA of RCTs in NDMM (bibliography checked)
Gao, Minjie, et al. "Thalidomide treatment for patients with previously untreated multiple myeloma: a meta-analysis of randomized controlled trials." *Tumor Biology* 37.8 (2016): 11081-11098.	SLR/MA of RCTs in NDMM (bibliography checked)
Ying, L. I., et al. "Lenalidomide and the risk of serious infection in patients with multiple myeloma: a systematic review and meta-analysis." *Oncotarget* 8.28 (2017): 46593.	SLR/MA of RCTs in NDMM (bibliography checked)
Chen, Min, et al. "Immunomodulatory drugs and the risk of serious infection in multiple myeloma: systematic review and meta-analysis of randomized and observational studies." *Annals of hematology* 97.6 (2018): 925-944.	SLR/MA of RCTs in NDMM (bibliography checked)
Goldschmidt, Hartmut, et al. "Response-adapted lenalidomide maintenance in newly diagnosed myeloma: results from the phase III GMMG-MM5 trial." Leukemia 34.7 (2020): 1853-1865.	Outcome out of scope
Bashir, Qaiser, et al. "Conditioning with busulfan plus melphalan versus melphalan alone before autologous haemopoietic cell transplantation for multiple myeloma: an open-label, randomised, phase 3 trial." The Lancet Haematology 6.5 (2019): e266-e275.	Outcome out of scope
Nielsen, Lene Kongsgaard, et al. "Clarithromycin added to bortezomib-cyclophosphamide-dexamethasone impairs health-related quality of life in multiple myeloma patients." European journal of haematology 102.1 (2019): 70-78.	Publication out of scope
Paquin, Ashley R., et al. "Overall survival of transplant eligible patients with newly diagnosed multiple myeloma: comparative effectiveness analysis of modern induction regimens on outcome." Blood cancer journal 8.12 (2018): 1-7.	Publication out of scope
Moreau, Philippe, et al. "Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study." The Lancet 394.10192 (2019): 29-38.	Extracted in PubMed already
Bashir, Qaiser, et al. "Conditioning with busulfan plus melphalan versus melphalan alone before autologous haemopoietic cell transplantation for multiple myeloma: an open-label, randomised, phase 3 trial." The Lancet Haematology 6.5 (2019): e266-e275.	Extracted in PubMed already
van de Donk, Niels WCJ, et al. "Thalidomide before and after autologous stem cell transplantation in recently diagnosed multiple myeloma (HOVON-50): long-term results from the phase 3, randomised controlled trial." The Lancet Haematology 5.10 (2018): e479-e492.	Extracted in PubMed already

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Full Citation	Reason of Exclusion
Horvath, Noemi, et al. "Phase 3 study of subcutaneous bortezomib, thalidomide, and prednisolone consolidation after subcutaneous bortezomib-based induction and autologous stem cell transplantation in patients with previously untreated multiple myeloma: the VCAT study." Leukemia & lymphoma 60.9 (2019): 2122-2133.	Extracted in PubMed already
Nielsen, Lene Kongsgaard, et al. "Clarithromycin added to bortezomib-cyclophosphamide-dexamethasone impairs health-related quality of life in multiple myeloma patients." European journal of haematology 102.1 (2019): 70-78.	Duplicate
van de Donk, Niels WCJ, et al. "Thalidomide before and after autologous stem cell transplantation in recently diagnosed multiple myeloma (HOVON-50): long-term results from the phase 3, randomised controlled trial." The Lancet Haematology 5.10 (2018): e479-e492.	Extracted in PubMed already
F. Gay, A. Spadano, M. Cavo, T. Caravita, L. Canepa, N. Giuliani, S. Spada, F. Patriarca, F. Morabito, P. Tacchetti, F. Narni, G. De Sabbata, F. De Santis, A. Pascarella, S. Palmieri, A. M. Liberati, F. Pisani, M. Genuardi, P. Tosi, O. Annibali, M. Ruggeri, P. Curci, L. De Rosa, A. Palumbo, P. Musto, M. Boccadoro (2017). Interim analysis of carfilzomib-lenalidomide-dexamethasone vs carfilzomib-cyclophosphamide-dexamethasone in the FORTE trial Haematologica, 102(#issue#), 1	Outcome out of scope
Gregersen, Henrik, et al. "A randomized placebo-controlled phase II study of clarithromycin or placebo combined with VCD induction therapy prior to high-dose melphalan with stem cell support in patients with newly diagnosed multiple myeloma." Experimental hematology & oncology 7.1 (2018): 1-8.	Extracted in PubMed already
Jones, John R., et al. "Myeloma XI Trial for Newly Diagnosed Multiple Myeloma (NDMM); Long Term Second Primary Malignancy (SPM) Incidence in the Context of Lenalidomide Maintenance." (2019): 3132-3132.	Outcome out of scope
Zamagni, Elena, et al. "MRD evaluation by PET/CT according to Deauville criteria combined with multiparameter flow cytometry in newly diagnosed transplant eligible multiple myeloma (MM) patients enrolled in the phase II randomized Forte trial." (2019): 4321-4321.	Outcome out of scope
Voorhees, Peter, et al. "Daratumumab+ lenalidomide, bortezomib & dexamethasone improves depth of response in transplant-eligible newly diagnosed multiple myeloma: GRIFFIN." Clinical Lymphoma, Myeloma and Leukemia 19.10 (2019): e353-e354.	Extracted in PubMed already
Chari, Ajai, et al. "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 (2019): e16-e17.	Population out of scope
Avet-Loiseau, Herve, et al. "Concordance of post-consolidation minimal residual disease rates by multiparametric flow cytometry and next-generation sequencing in CASSIOPEIA." Clinical Lymphoma, Myeloma and Leukemia 19.10 (2019): e3-e4.	Outcome out of scope

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Full Citation	Reason of Exclusion
Larocca, A., et al. "TREATMENT WITH DOSE/SCHEDULE-ADJUSTED RD-R vs CONTINUOUS RD IN ELDERLY INTERMEDIATE-FIT NEWLY DIAGNOSED MULTIPLE MYELOMA PATIENTS: RESULTS OF RV-MM-PI-0752 PHASE III RANDOMIZED STUDY." HAEMATOLOGICA. Vol. 104. VIA GIUSEPPE BELLI 4, 27100 PAVIA, ITALY: FERRATA STORTI FOUNDATION, 2019.	Population out of scope
McEllistrim, Cian, et al. "Weekly CyborD-DARA Is a Safe and Effective Upfront Treatment for Newly Diagnosed Multiple Myeloma. Preliminary Results of the Early Phase 16-Bcni-001/Ctrial-IE (ICORG) 16-02 Study." Blood 130.Supplement 1 (2017): 3163-3163.	Publication out of scope
Bashir, Qaiser, et al. "Conditioning with busulfan plus melphalan versus melphalan alone before autologous haemopoietic cell transplantation for multiple myeloma: an open-label, randomised, phase 3 trial." The Lancet Haematology 6.5 (2019): e266-e275.	Extracted in PubMed already
Rosiñol, Laura, et al. "Bortezomib, lenalidomide, and dexamethasone as induction therapy prior to autologous transplant in multiple myeloma." Blood 134.16 (2019): 1337-1345.	Extracted in PubMed already
van de Donk, Niels WCJ, et al. "Thalidomide before and after autologous stem cell transplantation in recently diagnosed multiple myeloma (HOVON-50): long-term results from the phase 3, randomised controlled trial." The Lancet Haematology 5.10 (2018): e479-e492.	Extracted in PubMed already
Moreau, Philippe, et al. "Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study." The Lancet 394.10192 (2019): 29-38.	Extracted in PubMed already
Luoma, Sini, et al. "RVD induction and autologous stem cell transplantation followed by lenalidomide maintenance in newly diagnosed multiple myeloma: a phase 2 study of the Finnish Myeloma Group." *Annals of hematology* 98.12 (2019): 2781-2792.	Extracted in PubMed already
Nielsen, Lene Kongsgaard, et al. "Clarithromycin added to bortezomib-cyclophosphamide-dexamethasone impairs health-related quality of life in multiple myeloma patients." *European journal of haematology* 102.1 (2019): 70-78.	Duplicate
Jackson, Graham H., et al. "Response-adapted intensification with cyclophosphamide, bortezomib, and dexamethasone versus no intensification in patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial." *The Lancet Haematology* 6.12 (2019): e616-e629.	Duplicate
Nielsen, Lene Kongsgaard, et al. "Clarithromycin added to bortezomib-cyclophosphamide-dexamethasone impairs health-related quality of life in multiple myeloma patients." *European journal of haematology* 102.1 (2019): 70-78.	Duplicate
Nielsen, Lene Kongsgaard, et al. "Clarithromycin added to the VCD regimen causes reduced health-related quality of life in multiple myeloma patients." (2018).	Duplicate

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Full Citation	Reason of Exclusion
Gregersen, Henrik, et al. "A randomized placebo-controlled phase II study of clarithromycin or placebo combined with VCD induction therapy prior to high-dose melphalan with stem cell support in patients with newly diagnosed multiple myeloma." *Experimental hematology & oncology* 7.1 (2018): 1-8.	Extracted in PubMed already
Voorhees, Peter M., et al. "Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial." *Blood, The Journal of the American Society of Hematology* 136.8 (2020): 936-945.	CAPTURED IN FIRST SLR UPDATE ALREADY
Dimopoulos, Meletios A., et al. "Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial." *J Clin Oncol* (2020): 4030-4041.	Publication out of scope
Moreau, Philippe, et al. "Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study." *The Lancet* 394.10192 (2019): 29-38.	Publication out of scope
Kaiser, Martin, et al. "Adverse event management in the TOURMALINE-MM3 study of post-transplant ixazomib maintenance in multiple myeloma." *Annals of hematology* 99.8 (2020): 1793-1804.	Outcome out of scope

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13.5 Quality assessment

This SLR strictly followed NICE guidelines which is also in line with the guidelines from the Medicines Council. One of the strengths of this review was that a comprehensive list of treatment specific endpoints has been extracted from the available studies i.e. OS, PFS, response outcomes, discontinuation due to AEs and any reported adverse events. In addition, all available data sources were reviewed to obtain as much information as possible for the trials.

This review study has a few limitations. The lack of long-term follow-up, even though not the case for most trials, was prominent in some trials. Another limitation is that data from a number of conference abstracts were included in this review instead of respective full-text publications, even though every lead author of all relevant conference abstracts was contacted for availability of full-text publication. Finally, the diversity of analyzed treatments in the trials limits comparability of trial results.

13.6 Unpublished data

The majority of the documentation of clinical effect and safety are derived from full-text articles published in scientific-peer-reviewed journals and EPARs as preferred by the Medicines Council. Certain unpublished data has been included as it is assessed to be scientifically reasonable and supporting the evidence base. The unpublished data primarily consists of data with longer follow-up periods as well as supporting data that has been requested by the Expert Committee. The methods applied for the unpublished data follows published sources.

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14. Appendix B Main characteristics of included studies

Table 72, Table 73, and Table 74 present the main characteristics of CASSIOPEIA, GMMG-MM5, and IFM 2009 trial.

Table 72 Main characteristics of CASSIOPEIA

Trial name: Cassiopeia, MMY3006	NCT number: NCT02541383
Objective	The purpose of this study is to evaluate if the addition of daratumumab to bortezomib, thalidomide and dexamethasone will increase the stringent complete response rate after consolidation therapy and increase the progression free survival after daratumumab maintenance therapy in transplant eligible participants with previously untreated multiple myeloma.
Publications – title, author, journal, year	Main publications: • Philippe Moreau, Michel Attal, Cyrille Hulin, Bertrand Arnulf, Karim Belhadj, et al. (2019). Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet 2019; 394: 29–38.(6) • Roussel M, Moreau P, Hebraud B, Laribi K, Jaccard A, Dib M, Slama B, Dorvaux V, Royer B, Frenzel L, Zweegman S. 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. 2020 Dec 1;7(12):e874-83.(9) Other publications: • Roussel M, Moreau P, Attal M, Eisenmann JC. Improvement in health-related quality of life (HRQoL) for newly diagnosed multiple myeloma (NDMM) transplant eligible patients treated with daratumumab, bortezomib, thalidomide, and dexamethasone (D-VTd) vs VTd alone: CASSIOPEIA. European Hematology Association (EHA, Poster) (2019).(129) • Moreau P., Zweegman S., Perrot A., Hulin C., Caillot D., Facon T., et al. (2019). Evaluation of the prognostic value of positron emission tomography-computed tomography (PET-CT) at diagnosis and follow-up in transplant-eligible newly diagnosed multiple myeloma (TE NDMM) patients treated in the phase 3 cassiopeia study: Results of the cassiopet companion study. Blood (2019) 134 (Supplement_1): 692.(127) • Moreau P., Attal M., Hulin C., Béné M.-C., Broijl A., Caillot D., Delforge M., Dejoie T., Facon T., Lambert J., Leleu X., MacRo M., Perrot A., Zweegman S., Ahmadi T., Chiu C., Pei L., Vermeulen J., Avet-Loiseau H., Sonneveld P. (2019). Phase 3 randomized study of daratumumab (DARA) + bortezomib/thalidomide/dexamethasone (D-VTd) vs VTd in transplant-eligible (TE) newly diagnosed multiple myeloma (NDMM): CASSIOPEIA Part 1 results. Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 8003-8003.(126) • Hulin C., Moreau P., Attal M., Belhadj K., Benboubker L., Caillot D., Facon T., et al. (2019). Stem cell (SC) yield and transplantation results from transplant-eligible newly diagnosed multiple myeloma (TE NDMM) patients (pts) receiving daratumumab (DARA) + bortezomib/thalidomide/dexamethasone (D-VTd) in the phase 3 CASSIOPEIA study. Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 8042-8042.(119) • Avet-Loiseau H., Moreau P., Attal M., Hulin C., Arnulf B., Corre J., Garderet L., Karlin L., Lambert J., MacRo M., Perrot A., Sonneveld P., Levin M.-D., Klein S., Chiu C., Pei L., De Boer C., Kampfenkel T., Wuilleme S., Béné M.-C. (2019). Efficacy of daratumumab (DARA) + bortezomib/thalidomide/dexamethasone (D-VTd) in transplant-eligible newly diagnosed multiple myeloma (TE NDMM) based on minimal residual disease (MRD) status: Analysis of the CASSIOPEIA trial. Journal of Clinical Oncology 37, no. 15_suppl (May 20, 2019) 8017-8017.(125) • Sonneveld P., Attal M., Perrot A., Hulin C., Caillot D., Facon T., et al. (2019). Daratumumab Plus Bortezomib, Thalidomide, and Dexamethasone (D-VTd) in Transplant-eligible Newly Diagnosed Multiple Myeloma (NDMM): Subgroup Analysis of High-risk Patients (Pts) in CASSIOPEIA. Clinical Lymphoma, Myeloma & Leukemia, 2019-10-01, Volume 19, Issue 10, Pages e2-e3.(273)

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Trial name: Cassiopeia, MMY3006	NCT number: NCT02541383

Study type and design

Cassiopeia is randomized, open-label, active-controlled, parallel-group, multicenter, Phase III trial. Cassiopeia was designed as a 2-part clinical study comparing DVTd with VTd in NDMM patients who are eligible for ASCT. The 'Treatment Phase' was conducted in two parts with Part 1 covering the induction/ASCT/consolidation phase. The study consists of three phases as follows (274):

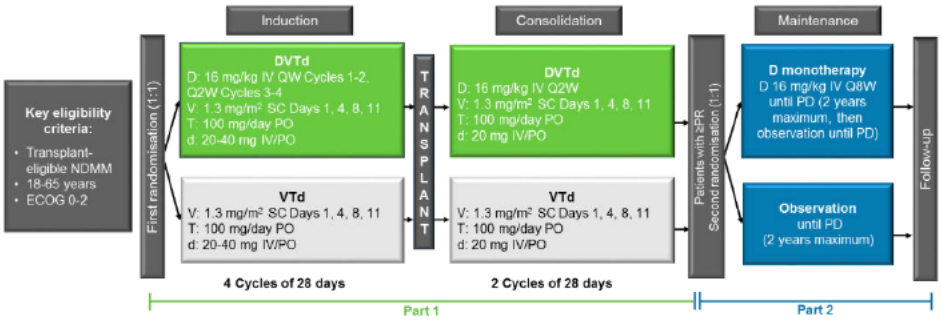
- Screening Phase: extends up to 28 days prior to Cycle 1, Day 1
- Treatment Phase: conducted in two parts:
    - Part 1: Induction/ASCT/Consolidation phase (1:1 Randomization). The consolidation phase of treatment began approximately 30 days after ASCT with response evaluated at Day 100 post ASCT.
    - Part 2: Maintenance phase (1:1 Re-randomization of patients achieving at least a partial response [PR] after consolidation). Patients who have not achieved a response enter the Follow-up Phase and are followed until disease progression or death, even if they receive subsequent treatment.
- Follow-up Phase: Extends from treatment discontinuation until death, loss to follow-up, withdrawal of consent, or study end, whichever occurs first

The license for this indication covers Part 1 only (induction and consolidation phase) upon which EMA granted marketing authorization for DVTd. The study is ongoing.

Patients in Cassiopeia were randomized 1:1 to receive either DVTd or VTd using a permuted block randomization. The stratification factors included were as follows (274):

- Site affiliation (Intergroupe Francophone du Myelome [IFM] or Dutch-Belgium Cooperative Trial Group for Hematology Oncology [HOVON])
- ISS staging (I, II, or III)
- Cytogenetic risks (standard risk or high risk as defined by presence of del17p or t(4;14), as centrally confirmed during screening)

An overview of the study design for CASSIOPEIA is shown below



Abbreviations: D = daratumumab; d = dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; ECOG = Eastern Cooperative Oncology Group; IV = intravenous; NDMM = newly diagnosed multiple myeloma; QW = weekly; Q2W = every 2 weeks; SC = subcutaneous; PO = per os (oral); Q8W = every 8 weeks; PD = progressive disease; T = thalidomide; V = bortezomib; VTd = bortezomib, thalidomide and dexamethasone

Sample size (n)	The planned sample size for Part 1 was 1080 subjects. 1085 Patients were enrolled.

Trial name: Cassiopeia, MMY3006	NCT number: NCT02541383

Main inclusion and exclusion criteria	Inclusion Criteria (clinicaltrials.gov): • Diagnosis of previously untreated multiple myeloma • Have a confirmed diagnosis and eligible for high dose chemotherapy and autologous stem cell transplantation, and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1 or 2 Exclusion Criteria (clinicaltrials.gov): • Previous treatment for Multiple Myeloma • Primary amyloidosis, Plasma Cell Leukemia or Smoldering Multiple Myeloma • Prior or concurrent exposure to systemic therapy or SCT (Stem Cell Transplantation) for any plasma cell dyscrasia, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment, or received an investigational drug or used an invasive investigational medical device within 4 weeks before Cycle 1, Day 1 • History of malignancy (other than Multiple Myeloma) within 10 years before the date of randomization, except for the following if treated and not active: basal cell or nonmetastatic squamous cell carcinoma of the skin, cervical carcinoma in situ, ductal carcinoma in situ of breast, or International Federation of Gynecology and Obstetrics (FIGO) Stage 1 carcinoma of the cervix • Known chronic obstructive pulmonary disease or moderate to severe asthma Any concurrent medical or psychiatric condition or disease (eg, autoimmune disease, active systemic disease, myelodysplasia) 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	Drug: Bortezomib, Thalidomide, Dexamethasone (VTD) + daratumumab 1085 patients were enrolled, of which 543 were randomly assigned to the DVTd group. 536 in the DVTd group received at least one dose of treatment. **Part 1: 4 Cycles of Bortezomib, Thalidomide and Dexamethasone plus daratumumab 16mg/kg induction therapy, followed by Autologous Stem Cell Transplantation, followed by 2 cycles of Bortezomib, Thalidomide and Dexamethasone plus daratumumab 16 mg/kg consolidation** All patients received up to four 28-day, pre-transplant induction cycles and two 28-day, post-transplant consolidation cycles of subcutaneous bortezomib (1·3 mg/m² twice per week in week 1 [days 1 and 4] and week 2 [days 8 and 11] of each cycle), oral thalidomide (100 mg daily in all cycles), and oral or intravenous dexamethasone (40 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 of induction cycles 1 and 2 and days 1 and 2 of induction cycles 3 and 4 and 20 mg on days 8, 9, 15, and 16 of induction cycles 3 and 4 and days 1, 2, 8, 9, 15, and 16 of both consolidation cycles). Daratumumab was administered intravenously at a dose of 16 mg/kg of bodyweight once weekly in induction cycles 1 and 2 and once every 2 weeks during induction cycles 3 and 4 and consolidation. After induction cycle 4, patients underwent stem-cell mobilisation with cyclophosphamide (3 g/m² [recommended dose]) and granulocyte colony-stimulating factor, and peripheral blood stem cells were harvested based on response to mobilisation. Plerixafor was permitted according to institutional practice. Patients underwent conditioning with intravenous melphalan 200 mg/m², followed by autologous stem-cell transplantation. Consolidation began after haematopoietic reconstitution but not earlier than 30 days after transplant. **Part 2: Drug: Observation or daratumumab** In part 2, patients achieving a partial response or better at day 100 post-transplant underwent a second randomisation to observation or maintenance therapy with daratumumab (16 mg/kg) every 8 weeks until disease progression or for a maximum of 2 years.

Trial name: Cassiopeia, MMY3006	NCT number: NCT02541383

Comparator(s)	Drug: Bortezomib (VELCADE), Thalidomide, and Dexamethasone (VTD) 1085 patients were enrolled, of which 542 were randomly assigned to the VTd group. A total of 538 in the VTd group received at least one dose of treatment. **Part 1: 4 Cycles of Bortezomib, Thalidomide and Dexamethasone induction therapy, followed by Autologous Stem Cell Transplantation, followed by 2 cycles of Bortezomib, Thalidomide and Dexamethasone consolidation.** All patients received up to four 28-day, pre-transplant induction cycles and two 28-day, post-transplant consolidation cycles of subcutaneous bortezomib (1·3 mg/m² twice per week in week 1 [days 1 and 4] and week 2 [days 8 and 11] of each cycle), oral thalidomide (100 mg daily in all cycles), and oral or intravenous dexamethasone (40 mg on days 1, 2, 8, 9, 15, 16, 22, and 23 of induction cycles 1 and 2 and days 1 and 2 of induction cycles 3 and 4 and 20 mg on days 8, 9, 15, and 16 of induction cycles 3 and 4 and days 1, 2, 8, 9, 15, and 16 of both consolidation cycles). After induction cycle 4, patients underwent stem-cell mobilisation with cyclophosphamide (3 g/m² [recommended dose]) and granulocyte colony-stimulating factor, and peripheral blood stem cells were harvested based on response to mobilisation. Plerixafor was permitted according to institutional practice. Patients underwent conditioning with intravenous melphalan 200 mg/m², followed by autologous stem-cell transplantation. Consolidation began after haematopoietic reconstitution but not earlier than 30 days after transplant. **Part 2: Observation or daratumumab** In part 2, patients achieving a partial response or better at day 100 post-transplant underwent a second randomisation to observation or maintenance therapy with daratumumab (16 mg/kg) every 8 weeks until disease progression or for a maximum of 2 years.
Follow-up time	Evidence from the CASSIOPEIA trial was used as the primary source of data to support the use of DVTd in this indication in the marketing authorization application to the EMA. Pre-specified analysis for Part 1 applied a clinical cut-off date of 19 June 2018, representing a median follow-up of 18.8 months. During the regulatory process, Janssen received a Request for Supplementary Information from the EMA which resulted in an unplanned post-hoc interim analysis with a clinical cut-off of 1 May 2019, representing an additional 10.4 months of study follow-up (total median follow-up of 29.2 months).(4) • 1st data-cut of CASSIOPEIA – Median duration of follow-up was 18.8 months • 2nd data-cut of CASSIOPEIA - Median duration of follow-up was 29.2 months • 3rd data-cut of CASSIOPEIA – Median duration of follow-up was 44.5 months
Is the study used in the health economic model?	Yes

Trial name: Cassiopeia, MMY3006	NCT number: NCT02541383

Primary, secondary and exploratory endpoints

Endpoints included/reported in this application:

Primary endpoint(s)

- Stringent complete response (sCR) after consolidation therapy

Secondary endpoint(s)

- Progression-free survival (PFS) from first randomization
- Overall survival (OS) from first randomization
- Minimal residual disease (MRD) negative rate 100 days post-ASCT (post-consolidation)

Other secondary objectives throughout the study

- Health-related quality of life (HRQoL) - EORTC-QLQ-C30 and EQ-5D-5L
- To assess the safety and tolerability of daratumumab in combination with VTd

Other endpoints not included in application

Primary endpoint(s)

- Progression free survival after maintenance therapy

Secondary endpoint(s)

- Time to progression (TTP) from first randomization
- Complete response (CR) rate or better at 100 days post-ASCT (post-consolidation)
- Post-induction stringent complete response (sCR) rate
- Progression-free survival after next line of therapy (PFS2) from first randomization
- Post-induction overall response rate (ORR) and rate of very good partial response (VGPR) or better
- Duration of CR and sCR
- Time to response, CR and sCR

Other secondary objectives throughout the study

- Health economic/resource utilization
- To assess the immunogenicity of daratumumab

Method of analysis

The primary analysis population was the intention-to-treat population of all patients who underwent the first randomization. The safety population included patients who underwent the first randomization and received at least one dose of trial treatment. A validated computer algorithm was used to determine response and disease progression. Response rates and other binary endpoints were assessed using the Cochran–Mantel–Haenszel chi square test, and odds ratios and two-sided 95% confidence intervals were calculated. If the between-group difference in the primary endpoint was statistically significant, the secondary efficacy endpoints of post-consolidation minimal residual disease–negative rate, post-consolidation rate of complete response or better, progression-free survival from first randomization, and overall survival from first randomization, as ordered here, were to be tested sequentially using a hierarchical testing approach, each with an overall two-sided alpha level of 0.05. At the primary analysis cutoff, an interim analysis of progression-free survival was performed (an alpha of 0.0001 was spent) and descriptive statistics of overall survival were available.

Trial name: Cassiopeia, MMY3006	NCT number: NCT02541383
Subgroup analyses	Pre-specified subgroups (275): • Sex (male, female) • Age (<50 years, ≥50 years) • Site (IFM, Hovon) • ISS staging (I, II, III) • Cytogenetic risk (high risk, standard risk) • Baseline renal function (CrCl) (>90 mL/min, ≤90 mL/min) • Baseline hepatic function (normal, impaired) • Type of MM (IgG, non-IgG) • ECOG performance score (0, ≥1) Subgroup Analysis of Efficacy Endpoints in Part 1: For assessment of internal consistency and investigation of homogeneity of the treatment effect across subgroups, a subgroup analysis of the primary and secondary endpoints of sCR, PFS, and MRD on pre-specified subgroups defined will be conducted. Subgroup analyses will be performed if data warrants such investigation. Forest plots of subgroup analysis on sCR, PFS, and MRD will be generated.
Other relevant information	

Table 73 Main characteristics of GMMG-MM5

Trial name: GMMG-MM5	EudraCT No. 2010-019173-16
Objective	**Primary objectives** The MM5 trial is designed to address two independent primary objectives. The primary objectives of the study are 1. Demonstration of non-inferiority of bortezomib/cyclophosphamide/ dexamethasone (VCd) induction therapy compared to bortezomib/ doxorubicin/dexamethasone (PAd) induction therapy with respect to response rates (very good partial response (VGPR) or better, ⩾ VGPR) 2. Determination of the best of four treatment strategies with respect to PFS. The treatment strategies are defined by PAd or VCd induction therapy followed by standard intensification therapy (HDM+ASCT), lenalidomide consolidation and maintenance treatment with either lenalidomide for 2 years or lenalidomide until complete response (CR) is achieved **Secondary objectives** The secondary objectives of this trial are to determine and compare treatment arms with respect to - overall survival rates (OS) - response rates after lenalidomide consolidation treatment - best response rates - toxicity during induction treatment, lenalidomide consolidation and maintenance treatment with respect to adverse events of CTCAE grade ≥ 3
Publications – title, author, journal, year	• Goldschmidt H, Mai EK, Dürig J, Scheid C, Weisel KC, Kunz C, Bertsch U, Hielscher T, Merz M, Munder M, Lindemann HW. Response-adapted lenalidomide maintenance in newly diagnosed myeloma: results from the phase III GMMG-MM5 trial. Leukemia. 2020 Jul;34(7):1853-65.

- Goldschmidt H, Mai EK, Dürig J, et al. Response-Adapted Lenalidomide Maintenance in Newly Diagnosed, Transplant-Eligible Multiple Myeloma: Results from the Multicenter Phase III GMMG-MM5 Trial. Blood. 2017;130(Suppl 1):400-400
- Mai, E. K., et al. "Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCd) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma." Leukemia 29.8 (2015): 1721-1729.
- Merz, Maximilian, et al. "Subcutaneous versus intravenous bortezomib in two different induction therapies for newly diagnosed multiple myeloma: an interim analysis from the prospective GMMG-MM5 trial." haematologica 100.7 (2015): 964.

Study type and design

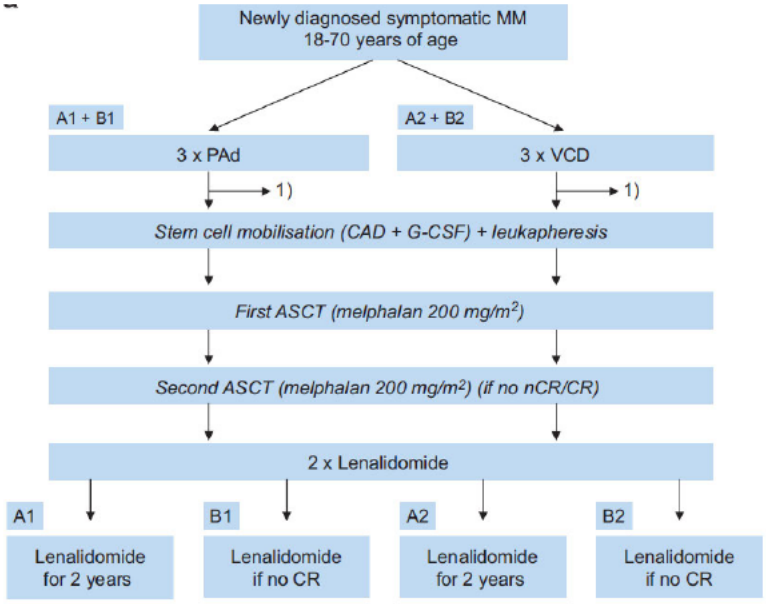
An open-label, randomized multicenter phase 3 clinical trial

Patients were equally randomized to each of the four treatment arms (A1, A2, B1, B2) using block randomization, stratified by the International Staging System (ISS) stage20 . Treatment consisted of either three 4-week cycles of PAd (A1+B1) or three 3-week cycles of VCd (A2+B2). Thereafter, standard intensification according to local protocols (GMMG standard) was performed, including stem cell mobilization and leukapheresis followed by single HDM+ASCT or, for patients not achieving near complete response (nCR) or better, Tandem-HDM+ASCT. Subsequently, consolidation therapy consisted of two cycles of lenalidomide (25mg, days 1-21) followed by lenalidomide maintenance (for the first three months 10mg/day continuously and thereafter 15mg/day continuously) for either two years (A1+A2) or until CR (B1+B2).

The study has been completed.

Unintended crossovers on study were as follows: one patient was randomized to arm A1 (PAd induction) but received VCd induction (A2). Two additional patients randomized to arm B1 (LEN-CR) were treated as arm A1 (LEN-2Y) during maintenance.

An overview of the study design for GMMG-MM5 is shown below



1) High Risk Patients, optional in Phase II trial for auto-allo SCT

Figure reprinted from: Mai EK, Bertsch U, Dürig J, Kunz C, Haenel M, Blau IW, Munder M, Jauch A, Schurich B, Hielscher T, Merz M. Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCd) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma. Leukemia. 2015 Aug;29(8):1721-9.(121)

Abbreviations: ASCT = autologous stem cell transplantation; CAD = cyclophosphamide/doxorubicin/dexamethasone; G-CSF = granulocyte-colony stimulating factor (lenograstim); ITT = intention-to-treat population; MM = multiple myeloma; nCR = near complete remission; PAd = bortezomib/doxorubicin/dexamethasone; PP = per-protocol population; safety = safety population; VCd = bortezomib/cyclophosphamide/dexamethasone.

Trial name: GMMG-MM5	EudraCT No. 2010-019173-16

Sample size (n)	ITT population: 504 pts
Main inclusion and exclusion criteria	Key inclusion criteria were patients 18-70 years of age with newly diagnosed MM who require systemic chemotherapy based on 'CRAB' criteria; World Health Organization (WHO) performance status 0-2 or 3, if MM related; and measurable MM disease. Key exclusion criteria included: systemic light chain amyloidosis; peripheral neuropathy/neuropathic pain ⩾ 2° (National Cancer Institute Common Terminology Criteria for Adverse Events, NCI CTCAE, version 4.0). Patients with renal impairment (RI) or renal failure were not excluded from the study.
Intervention	Treatment consisted of either three 4-week cycles of PAd (A1+B1) or three 3-week cycles of VCd (A2+B2). Thereafter, standard intensification according to local protocols (GMMG standard) was performed, including stem cell mobilization and leukapheresis followed by single HDM+ASCT or, for patients not achieving near CR (nCR) or better, tandem HDM+ASCT. Subsequently, consolidation therapy consisted of two cycles of lenalidomide (25 mg, days 1–21) followed by lenalidomide maintenance (for the first 3 months 10 mg/day continuously and thereafter 15 mg/day continuously) for either 2 years (A1+A2) or until CR (B1+B2). The PAd induction therapy consisted of bortezomib 1.3 mg/m2 on days 1, 4, 8 and 11; doxorubicin 9 mg/m2 intravenously (i.v.) on days 1–4; and oral (p.o.) dexamethasone 20 mg on days 1–4, 9–12 and 17–20 (240 mg/cycle, repeated every 28 days). VCd consisted of bortezomib 1.3 mg/m2 on days 1, 4, 8 and 11; cyclophosphamide 900 mg/m2 i.v. on day 1; and p.o. dexamethasone 40 mg on days 1–2, 4–5, 8–9 and 11–12 (320 mg/cycle, repeated every 21 days The number of ITT patients in the intervention arm was 251, and 249 patients received the intervention (VCd). The number of ITT patients in the comparator arm was 251, and 248 patients received the comparator (PAd).
Comparator(s)	See PAd above.
Follow-up time	median follow-up for PFS was 59.4 months (58.2-61.0) median follow-up for OS was 60.1 months (59.2-61.9)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** • Primary endpoint: Progression free survival (i.e., time from randomisation to progression or death from any cause whichever occurs first). • Secondary endpoint: Overall survival defined as time from randomisation to death from any cause. Patients still alive or lost to follow up are censored at the date they were last known to be alive. • Secondary objectives: Toxicity during induction treatment, lenalidomide consolidation and maintenance treatment with respect to adverse events of CTCAE grade >= 3 **Other endpoints:** <u>Primary endpoints</u> • Response to treatment (very good partial remission or better) after induction therapy <u>Secondary endpoints</u>

Trial name: GMMG-MM5	EudraCT No. 2010-019173-16
	• Response rates (response rates will be assessed using the following subcategories: SD, MR, PR, VGPR (with subgroup nCR), CR, sCR, mCR) • Toxicity ((serious) adverse events CTC grade 3 and grade 4, CTC-AE v4.0)
Method of analysis	To guarantee a family-wise error rate of 5.0%, each primary objective is tested with the two-sided alpha level of 2.5%. The first primary objective was tested in a group-sequential way with a significance level split into 0.1% for the interim and 2.4% for the final analysis. In the final analysis, the non-inferiority analysis was performed for the intention-to-treat (ITT) and the per-protocol (PP) population with a noninferiority margin of 10% for the difference in ⩾VGPR rates. Therefore two-sided confidence intervals were calculated by using the Newcombe's hybrid score interval. The test of Farrington and Manning was used to test the one-sided null hypothesis of the non-inferiority of VCd to PAd. The two-sided significance level for this final analysis was set to 2.4%, the onesided level accordingly to 1.2%. To demonstrate non-inferiority of VCd, non-inferiority for both ITT and PP populations needs to be confirmed. Adverse events (AEs) are summarized per patient and Fisher's exact test is used to compare AE frequencies and response rates.
Subgroup analyses	The subgroup analyses were not indicated as pre-specified or post-hoc.(121) The response rates for the PAd and VCd group based on ISS staging. The multivariate analyses were not indicated as pre-specified or post-hoc.(139) Multivariate analyses are carried out using a Cox regression model (n = 420). Adverse cytogenetics were defined as either deletion 17p13 and/or translocation t(4;14) and/or gain 1q21 (>3 copies). Bold p values are statistically significant. Factors analyzed in the multivariate model are: • Age • Maintenance strategy • Sex • ISS stage II • ISS stage III • LDH (>ULN) • Adverse cytogenetics • IgA subtype

Table 74 Main characteristics of IFM-2009

Trial name: IFM-2009	NCT number: NCT01191060
Objective	To determine if, in the era of novel drugs, high dose therapy (HDT) is still necessary in the initial management of multiple myeloma in younger patients. HDT as compared to conventional dose treatment would be considered superior if it significantly prolongs Progression-free survival (by at least 9 months). To address these issues, a phase 3 trial was conducted to compare the efficacy and safety of combination therapy with lenalidomide, bortezomib, and dexamethasone (VRd) alone with the efficacy and safety of VRD plus autologous stem-cell transplantation for the treatment of newly diagnosed multiple myeloma in adults up to 65 years of age.
Publications – title, author, journal, year	Attal, Michel, et al. "Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma." New England Journal of Medicine 376.14 (2017): 1311-1320.

Trial name: IFM-2009	NCT number: NCT01191060
	Attal, Michel, et al. "Autologous transplantation for multiple myeloma in the era of new drugs: a phase III study of the Intergroupe Francophone Du Myelome (IFM/DFCI 2009 Trial)." (2015): 391-391.
Study type and design	An open-label, randomized multicenter phase 3 clinical trial. 700 patients with multiple myeloma were assigned to receive induction therapy with three cycles of VRD and then consolidation therapy with either five additional cycles of VRD (350 patients) or high-dose melphalan plus stem-cell transplantation followed by two additional cycles of VRD (350 patients). Patients in both groups received maintenance therapy with lenalidomide for 1 year. The study has competed.
Sample size (n)	764 Patients were screened for eligibility, among which 700 underwent randomization.
Main inclusion and exclusion criteria	– Patients diagnosed with multiple myeloma based on International Myeloma Foundation 2003 Diagnostic Criteria. – Patients must have symptomatic myeloma with myeloma-related organ damage. – Patients must have myeloma that is measurable by either serum or urine evaluation of the monoclonal component or by assay of serum free light chains. – Age between 18 and 65 years at the time of signing the informed consent document. – ECOG performance status <2 (Karnofsky ≥ 60%) – Negative HIV blood test
Intervention	All the patients received induction therapy with three 21-day cycles of VRD, which consisted of lenalidomide (25 mg, administered orally on days 1 through 14), bortezomib (1.3 mg per square meter of body-surface area, administered intravenously on days 1, 4, 8, and 11), and dexamethasone (20 mg, administered orally on days 1, 2, 4, 5, 8, 9, 11, and 12). After the induction phase, all the patients underwent stem-cell mobilization with cyclophosphamide and granulocyte colony-stimulating factor. During the consolidation phase, the patients received five cycles of VRD with a reduced daily dose of dexamethasone of 10 mg. Maintenance therapy with lenalidomide (10 mg per day for the first 3 months, with a possible dose increase to 15 mg thereafter, depending on side effects) was initiated within the first 3 weeks after the completion of consolidation therapy and was continued for 1 year or until the occurrence of disease progression or unacceptable adverse events or the withdrawal of patient consent (whichever came first). The number of ITT patients in the intervention arm was 350, and 331 patients (95%) entered the consolidation phase and 321 (92%) entered the maintenance phase.
Comparator(s)	All the patients received induction therapy with three 21-day cycles of VRD, which consisted of lenalidomide (25 mg, administered orally on days 1 through 14), bortezomib (1.3 mg per square meter of body-surface area, administered intravenously on days 1, 4, 8, and 11), and dexamethasone (20 mg, administered orally on days 1, 2, 4, 5, 8, 9, 11, and 12). After the induction phase, all the patients underwent stem-cell mobilization with cyclophosphamide and granulocyte colony-stimulating factor. During the consolidation phase, the patients received melphalan at a dose of 200 mg per square meter plus autologous stem-cell transplantation followed by two cycles of VRD with a reduced daily dose of dexamethasone of 10 mg.

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Trial name: IFM-2009	NCT number: NCT01191060
	Maintenance therapy with lenalidomide (10 mg per day for the first 3 months, with a possible dose increase to 15 mg thereafter, depending on side effects) was initiated within the first 3 weeks after the completion of consolidation therapy and was continued for 1 year or until the occurrence of disease progression or unacceptable adverse events or the withdrawal of patient consent (whichever came first). The number of ITT patients in the intervention arm was 350, and 323 patients (92%) underwent transplantation, and 315 (90%) began to receive VRD therapy after transplantation, and 311 (89%) entered the maintenance phase.
Follow-up time	The median duration of follow-up after randomization was 44 months in the VRD-alone group and 43 months in the transplantation group.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** - Progression Free Survival [Time Frame: up to 4 years] Progression-free survival was defined as the time from randomization until either the first documentation of disease progression or death from any cause. Censoring rules for progression-free survival followed the Food and Drug Administration guidance on endpoints in cancer trials. - Overall survival Overall survival was defined as the time from randomization until death from any cause. - Toxicity comparison [Time Frame: up to 4 years] **Other endpoints:** – Response Rates [Time Frame: up to 4 years] – Time To Progression [Time Frame: up to 4 years] Time to progression was defined as the time from randomization until either the first documentation of disease progression or death owing to myeloma. – Genetic prognostic groups definition [Time Frame: up to 4 years] – Best treatment examination in each GEP-defined prognostic group. [Time Frame: up to 4 years]
Method of analysis	Time-to-event end points were analyzed by means of the Kaplan–Meier method, with the use of a two-sided stratified log-rank test to compare the treatment groups and a multivariate Cox proportional- hazards model adjusted for stratification factors to estimate adjusted hazard ratios and 95% confidence intervals. A competing-risk analysis was performed to assess the effect of censoring events on progression-free survival.
Subgroup analyses	Analyses of progression-free survival in specific subgroups were prespecified in the statistical analysis plan and were performed with the use of Cox proportional-hazards models with terms for treatment group, subgroup, and the interaction between subgroup and treatment group. The interaction terms were evaluated for statistical significance. Response rates were compared between groups with the use of a chi-square test or Fisher's exact test. P values for secondary efficacy end points and subgroup analyses were separately adjusted for multiplicity testing with the use of the Holm procedure to control the family-wise error rate at 0.05. Analyses were prespecified in the statistical analysis plan and were performed according to the intention-to-treat principle.

The primary efficacy endpoint will be further analyzed using selected covariates expected to have a strong or moderate association with the occurrence of progressive disease. Selected covariates will include the following:

- Randomization stratification factors: cytogenetic risk factors at screening (standard vs. high risk vs.FISH failures) and ISS stage at screening (stage I vs. stage II vs. stage III). Randomization stratification factors will be based on data reported on the "Cytogenetics" eCRF form and on the "DSS at Screening" eCRF form.
- Age at diagnosis (<60 years vs. ≥60 years).
- Gender (male vs. female).
- Type of myeloma - Monoclonal protein isotype at screening (IgA vs. IgG vs. Light chain vs. Other)
- Beta2 microglobulin (central data; in case of missing central data, use of local data) at screening (<3.5 mg/L vs. ≥3.5 - <5.5 mg/L vs. ≥5.5 mg/L).
- Cytogenetic abnormality - t(4;14) translocation (Presence of t(4;14) vs. Absence of t(4;14)).
- Cytogenetic abnormality - Deletion of the 17p chromosomal region (Presence of del(17p) vs. Absence of del(17p))

The primary efficacy endpoint will be analyzed for each covariate through the following survival analysis approach considering the same censoring rules as those used for the primary analysis:

- Kaplan –Meier survival curves for PFS in each subgroup will be displayed by arm. Median PFS and corresponding two-sided 95% CI in each covariate subgroup will also be computed and provided by arm.
- Treatment effect in each subgroup covariate will be estimated by means of HR of Arm B to Arm A using for each subgroup covariate an univariate Cox's proportional hazards model with arm as only covariate; point estimate and corresponding two-sided 95% CI will be provided. Arm by covariate interaction will be explored using a multivariate Cox's proportional hazards model with main effects for arm and covariate, plus arm by covariate interaction term; arm by covariate interaction will be tested at a significance level of 0.10.

The primary efficacy endpoint will be further analyzed through the following multivariate Cox's proportional hazard models considering the same censoring rules as those used for the primary analysis:

- Multivariate Cox's proportional hazards model with arm, gender, age at diagnosis, cytogenetic profile and ISS stage at screening, as baseline covariates, and with complete response as assessed by the investigator according to the IMWG criteria (No vs. Yes over time) as time-dependent covariate. For the time-dependent complete response covariate, patients will be accounted "No" from the day of the randomization to the day before the first documentation of complete response as assessed by the investigator according to the IMWG criteria, and accounted "Yes" from the day of the first documentation of complete response as assessed by the investigator according to the IMWG criteria. First order interaction between arm and covariates remaining in the final model will be tested.
- Multivariate Cox's proportional hazards model with arm, gender, age at diagnosis, cytogenetic profile and ISS stage at screening, as baseline covariates, and with MRD-negative (No vs. Yes over time) as time-dependent covariate. For the time-dependent MRD-negative covariate, patients will be accounted "No" from the day of the randomization to the

Trial name: IFM-2009	NCT number: NCT01191060
	day before the first assessment of MRD with a result of "Negative", and accounted "Yes" from the day of the first assessment of MRD with a result of "Negative". First order interaction between arm and covariates remaining in the final model will be tested.

Abbreviations: IFM = Intergroupe Francophone du Myelome; ISS = International Staging System; ITT = Intention-to-treat; MRD = Minimal residual disease; MM = multiple myeloma; PFS = Progression-free survival; VRD = bortezomib, lenalidomide, dexamethasone

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

15.1 DVTd vs. VTd

15.1.1 Comparability of patients across studies - DVTd vs. VTd

Table 75: Baseline patient demographics and disease characteristics in CASSIOPEIA (ITT population)(6, 7)

Characteristic	DVTd (N = 543)	VTd (N = 542)
Sex (F), n (%)	227 (41.8)	223 (41.1)
Age, years		
Median (range), years	59.0 (22, 65)	58.0 (26, 65)
<50, n (%)	83 (15.3)	90 (16.6)
≥50-65, n (%)	460 (84.7)	452 (83.4)
ECOG performance status, n (%)		
0	265 (48.8)	257 (47.4)
1	225 (41.4)	230 (42.4)
2	53 (9.8)	55 (10.1)
Type of measurable disease, n (%)		
IgG	331 (61.0)	314 (57.9)
IgA	80 (14.7)	99 (18.3)
Other*	13 (2.4)	22 (4.1)
Detected in urine only	70 (12.9)	67 (12.4)
Detected in serum free light chains only	48 (8.8)	40 (7.4)
Unknown	1 (0.2)§	0
ISS disease stage, n (%)		
I	204 (37.6)	228 (42.1)
II	255 (47.0)	233 (43.0)
III	84 (15.5)	81 (14.9)
Cytogenetic profile†, n/total (%)		
Standard risk	460/542 (84.9)	454/540 (84.1)
High risk**	82/542 (15.1)	86/540 (15.9)
Time since initial MM diagnosis to randomization, months		
Median (range)	0.92 (0.2, 66.6)	0.95 (0.2, 31.0)

Abbreviations: DVTd = daratumumab-bortezomib-thalidomide-dexamethasone; ECOG = Eastern Cooperative Oncology Group; Ig = immunoglobulin; ISS = International Staging System; ITT = intent-to-treat; MM = multiple myeloma; VTd = bortezomib-thalidomide-dexamethasone

* Includes IgD, IgM, IgE, and biclonal.

† Cytogenetic risk was assessed by fluorescence in situ hybridisation among patients with available cytogenetic risk data.

** High risk patients were defined as having ≥1 high-risk abnormality: del17p (≥50% abnormal cells) or t(4;14) (≥30% abnormal cells)

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

Due to limited real world evidence data available for patients with NDMM who are eligible for ASCT in Denmark, only selected prognostic factors are available from publications, specifically focusing on transplant eligible patients. Below are the reported prognostic factors, such as patients fitness (age) and disease biology (ISS stage and risk status) representing the Danish transplant eligible patient population described (refer to Table 166 and Table 167 in Appendix O – The patient population, the intervention and choice of comparators(s).(62)

Helm-Petersen et al. 2018, reported prognostic factors in 575 multiple myeloma patients treated with autologous hematopoietic bone marrow transplantation (HDM-ASCT) between 2005 and 2014 at one of the four participating Danish centers (Odense, Roskilde, Herlev and Rigshospitalet) and registered in the population-based Danish Multiple Myeloma Registry.(62) This study population has been used to compare to the DVTd arm in the CASSIOPEIA study.

Gender & Age

In the CASSIOPEIA study, median age in the DVTd arm was 59 years (22-65), where Helm-Petersen et al, reported a median age of 60 years for patients at diagnosis (30-72). The study population in the CASSIOPEIA study aligns well with patients treated in Danish clinical practice reported by Helm-Petersen et al. 2018.

In addition, comparing gender across the study and danish patient population, gender is comparable with 58.2% males and 41.8% females in the DVTd arm of the CASSIOPEIA study versus 57% males and 43% females reported in the Danish patient population.

Cytogenetic risk

The Danish patient population included 39% of patients with ISS stage I compared to 38% in the DVTd arm of the CASSIOPEIA study. Patients defined with ISS stage II accounted for 36% of patients and 47% of patients respectively, and for ISS stage III 26% of patients in the Danish patient population compared to 15% in the DVTd arm in the CASSIOPEIA study. The described ISS stage ranges across the two populations, shows comparable numbers for ISS stage I, however there are differences in stage II and stage III, with more patients defined as ISS stage II in the study population versus the Danish patient population and more patients in the Danish patient population with ISS stage III.

Although there are fewer patients included in stage III group in the CASSIOPEIA study compared to the Danish patient population, there are more patients included in ISS stage II in the study population and in addition taking into account high risk status between the two populations were similar, it makes the transferability of results between the two studies to Danish clinical practice possible.

In the Danish patient population, High risk myeloma (HR1) was defined as the presence of t(4;14), t(14;16) or loss of 17p (positive cut-off levels for a cytogenetic aberration was 10%). In addition, the same high risk markers and additional markers were used to define patients as High Risk 2 (HR2). In the CASSIOPEIA study, cytogenetic risk status was defined as the presence (or absence of standard risk) of del17p (≥50% abnormal cells) or t[4;14] (≥30% abnormal cells) cytogenetic abnormalities.

For this comparison, we have used HR1 from the Danish patient population to the CASSIOPEIA study high risk group as the two high risk markers t(4;14) and del17p are screened for in both populations. The inclusion of an additional marker such as t(14;16), and lower threshold of positive cut-off levels in the Danish patient population would allow for including additional patients which would be the main difference in high risk inclusion between the two populations.

In the DVTd arm in the CASSIOPEIA study 82 out of 542 patients (15%) were defined as high risk, according to above classification. In the Danish patient population, 142 patients of 575 ASCT treated patients with available cytogentic profile, reported 25 patients (17.6%) as HR1. The high risk groups in the study and Danish patient populations are therefore deemed comparable and transferable to Danish clinical practise.

In conclusion, prognostic factors in the CASSIOPEIA study compared with the Danish patient population, such as age, gender, staging and high risk are evaluated to be comparable.

15.2 DVTd vs. VCd

15.2.1 Comparability of patients across studies – DVTd/VTd vs. VCd

15.2.1.1 Definitions of efficacy outcomes

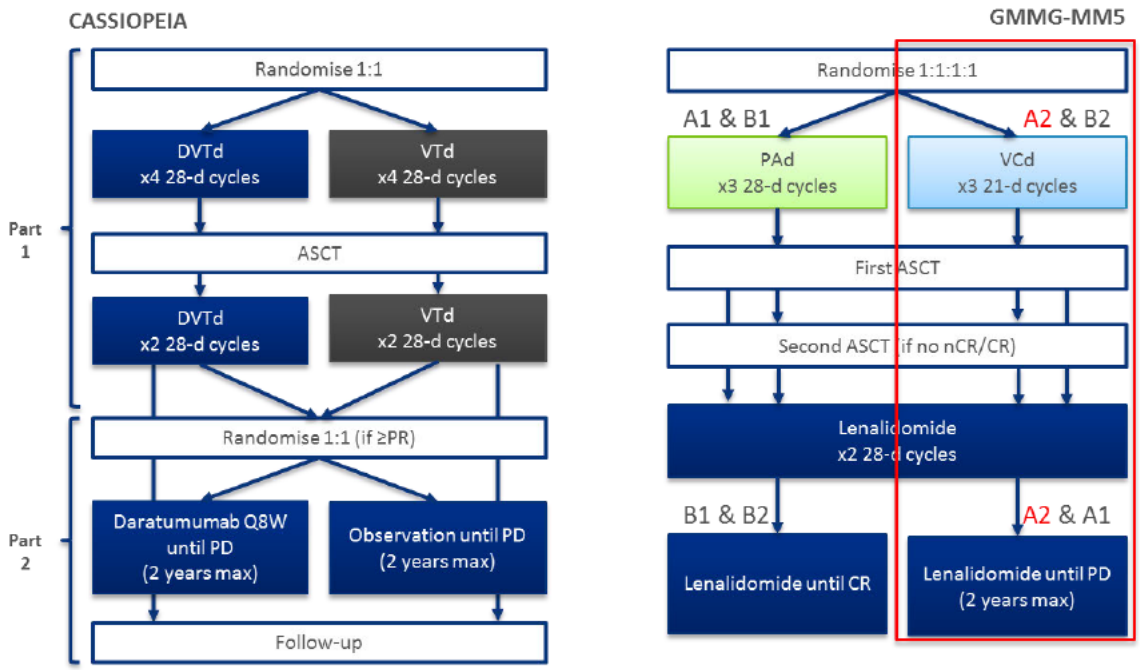
Table 76. Efficacy Outcomes Definitions

Treatment	DVTd vs. VTd	VCd-LEN-2Y
Trial	**CASSIOPEIA (6, 12)**	**GMMG-MM5(121, 139)**
PFS Definition	From first randomization to either progressive disease, according to the IMWG response criteria, or death, whichever occurred first	From randomization to progression or death from any cause, whichever occurs first
PD criteria	IMWG (Strict computer algorithm)	IMWG for response
Evaluation	Investigator and IRC	Investigator
Median follow-up	29.2 months	60.1 months
OS	Time from initial randomization to date of subject's death; If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.	Time from randomization to death from any cause; Patients still alive or lost to follow-up are censored at the date they were last known to be alive.

Abbreviations: DVTd = Daratumumab + bortezomib + thalidomide + dexamethasone; IMWG = International Myeloma Working Group; IRC = independent review committee; OS = Overall survival; PD = progressive disease; PFS = Progression-free survival; VCd-LEN-2Y = Bortezomib + cyclophosphamide + dexamethasone (VCd) followed by lenalidomide consolidation and lenalidomide maintenance for 2 years; VTd = Bortezomib + thalidomide + dexamethasone

15.2.1.2 Comparison of the overall study designs of CASSIOPEIA and GMMG-MM5

Figure 25. Comparison of the overall study designs of CASSIOPEIA and GMMG-MM5



Abbreviations: ASCT = autologous stem cell transplant; CR = complete response; DVTd = daratumumab-bortezomib-thalidomide-dexamethasone; MAIC = matching-adjusted indirect comparison; nCR = near complete response; PAd = bortezomib-Adriamycin-dexamethasone; PD = progressive disease; PR = partial response; Q8W = every 8 weeks; VCd = bortezomib-cyclophosphamide-dexamethasone; VTd = bortezomib-thalidomide-dexamethasone

15.2.1.3 Baseline Characteristics

Table 77 presents a comparison of the baseline characteristics of the patients assigned to CASSIOPEIA and GMMG-MM5.

Table 77. Baseline Characteristics of CASSIOPEIA(6, 12) and GMMG-MM5(139)

	VTd (CASSIOPEIA) (N=542)	DVTd (CASSIOPEIA) (N=543)	VCd* (GMMG-MM5) (N=251)
Age (years)			
≥65, n (%)	43 (7.9)	38 (7.0)	NR
<65, n (%)	499 (92.1)	505 (93.0)	NR
Mean (SD)	56.5 (7.0)	56.8 (6.93)	NR
Median (min - max)	58 (26–65)	59 (22–65)	58.7 (33–70)
Male, n (%)	319 (58.9)	316 (58.2)	153 (60.9)
ISS stage, n (%)			
I	228 (42.1)	204 (37.6)	94 (37.5)
II	233 (43.0)	255 (47.0)	82 (32.7)
III	81 (14.9)	84 (15.5)	75 (29.9)
Not determined/missing	0	0	NR
ECOG, n (%)			
0	257 (47.4)	265 (48.8)	114 (45.4)
1	230 (42.4)	225 (41.4)	116 (46.2)
2	55 (10.1)	53 (9.8)	17 (6.8)
3	0	0	4 (1.6)
B2-microglobulin (mg/L)			
Missing, n	0	0	NR
Median (min - max)	3.25 (1.2–21.2)	3.2 (1.2–18.4)	NR
>3 mg/L, n (%)	300 (55.4)	296 (54.5)	NR
Cytogenetics, n (%)			
del(13) by FISH	NR	NR	NR
t(4;14) and/or del(17p)	86 (17.1)	82 (16.4)	NR
Adverse cytogenetics del17p, n (%)			
Performed	503 (100)	501 (100)	222 (100)
Positive (% performed)	39 (7.8)	42 (8.4)	23 (10.4)
Missing	39 (7.2)	42 (7.7)	29 (11.6)
t(4;14), n (%)			
Performed	503 (100)	501 (100)	219 (100)
Positive (% performed)	53 (10.5)	51 (10.2)	22 (10.1)
Missing	39 (7.2)	42 (7.7)	32 (12.8)
Hemoglobin (g/dL)			
Mean	11.5	11.2	NR
Median (min - max)	11.5 (5.9–17)	11.1 (7.0–16.1)	10.7 (6.0–16.3)
Anemia (Hb <10 g/dL or 2 g/dL <normal, n (%)	191 (35.2)	223 (41.1)	138 (55)
Creatinine			
Mean (µmol/L)	78.9	76.2	NR
Median (µmol/L)	75	73	88
Median (Min - Max) (mg/dL)	0.8 (0.1–2.7)	0.8 (0.1–2.4)	1 (0.4–11.3)
Renal insufficiency (creatinine >177 µmol/L)[a], n (%)	2 (0.4)	1 (0.2)	39 (15.5)
Calcium (mmol/L)			
Mean	2.4	2.4	NR
Median (min-max)	2.4 (1.8–3.7)	2.4 (0.2–3.6)	2.4 (1.7–5.4)
Missing, n (%)	22 (4.1)	9 (1.7)	0
Calcium elevation (calcium >2.65 mmol/L) [a], n (%)	38 (7.0)	55 (10.1)	31 (12.3)
Missing	22 (4.1)	9 (1.7)	0
LDH (serum) , n (%)			
≤ULN	344 (63.5)[b]	302 (55.6) [c]	207 (82.5)
>ULN	189 (34.9) [c]	226 (41.6)[c]	44 (17.5)
Unknown	9 (1.7) [c]	15 (2.8) [c]	0 (0)
Platelets (per nL)			
Median (min–max)	250 (22–584)	241 (49–999)	240 (22–533)

Bone disease (lytic lesions or myeloma-related osteopenia / osteoporosis) [c], n (%)	462 (85.2) [d]	465 (85.6) [d]	223 (88.8)
Missing	2 (0.4)	3 (0.6)	NR
Heavy-chain isotype /Type of myeloma by Immunofixation, n (%)			
IgG	333 (61.4)	351 (64.6)	148 (59.0)
IgA	104 (19.2)	87 (16.0)	51 (20.3)
LCD	66 (12.2) [e]	83 (15.3) [e]	47 (18.7)
Other	39 (7.2) [f]	22 (4.1) [f]	5 (2.0)
Light-chain isotype, n (%)			
Kappa	NR	NR	160 (63.8)
Lambda	NR	NR	91 (36.2)
Gain 1q21 (>2 copies), n (%)			
Performed	NR	NR	213 (100)
Positive (% performed)	NR	NR	79 (37.1)
Missing	NR	NR	38 (15.1)

Abbreviations: VTd=Daratumumab + Bortezomib, Thalidomide, and Dexamethasone. ASCT=autologous stem cell transplantation. ISS=International Staging System. FISH=fluorescence in situ hybridization. ECOG=Eastern Cooperative Oncology Group. LCD = Light-chain disease. NR=not reported. ULN = Upper limit of normal.

a Calcium elevation, renal impairment, anemia and bone disease are defined according to CRAB criteria for symptomatic MM.

b ULN for LDH was not reported for GMMG-MM5 trial; CASSIOPEIA was defined using patient-dependent cut-offs of 213 U/L or 225 U/L.

c Derived from CASSIOPEIA IPD assuming that bone disease is defined as presence of lytic bone lesions.

d Derived from CASSIOPEIA trial data as "Baseline Presence of Diffuse Myeloma-related Osteopenia" or "Baseline Number of Lytic Bone Lesions >1".

e Light Chain disease (LCD) includes Kappa and Lambda.

f Derived from CASSIOPEIA trial data by combining IgD, IgM, Biclonal and Negative Immunofixation.

*Please note, the baseline characteristics of VCd include both VCd-LEN-2Y and VCd-LEN-CR

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

The DVTd study population is assessed to be comparable with the Danish patients eligible for treatment as described in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety (DVTd vs. VTd), Comparability of the study populations with Danish patients eligible for treatment. The study population in GMMG-MM5 (VCd-arm) appear similar in most baseline characteristics compared to the DVTd study population and is therefore also considered comparable to the Danish patients eligible for treatment before and after the MAIC adjustments. Subjects in both studies had previously untreated, documented, and measurable multiple myeloma. Baseline disease characteristics (i.e., age, sex, myeloma subtype, International Staging System [ISS], and cytogenetic abnormalities) were also comparable between studies (Table 77).

15.3 DVTd vs. VRd

15.3.1 Comparability of patients across studies – DVTd/VTd vs. VRd

15.3.1.1 Definitions of efficacy outcomes

Table 78. Efficacy Outcomes Definitions

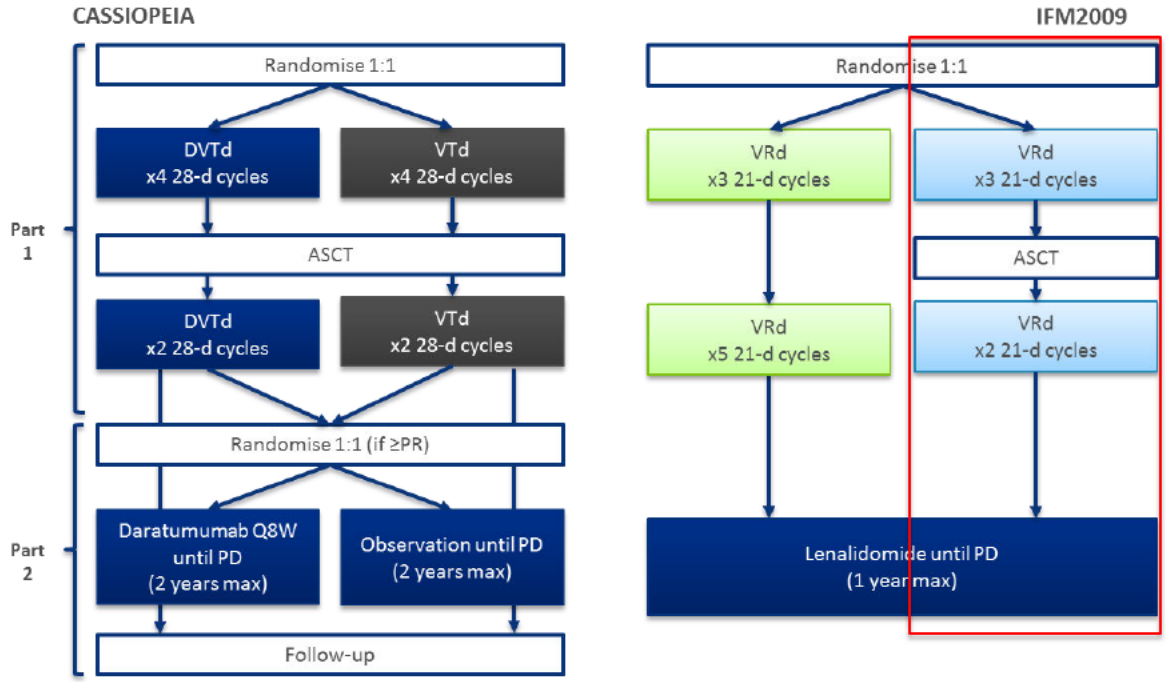
Treatment	DVTd vs. VTd	VRd + ASCT
Trial	CASSIOPEIA (6, 12)	IFM 2009 (123)
PFS Definition	From first randomization to either progressive disease, according to the IMWG response criteria, or death, whichever occurred first	From randomization until either the first documentation of disease progression or death from any cause
PD criteria	IMWG (Strict computer algorithm)	Investigator assessment in accordance with the IMWG criteria
Evaluation	Investigator and IRC	Investigator
Median follow-up	29.2 months	43.0 months
OS	Time from initial randomization to date of subject's death; If the subject is alive or the vital status is unknown, then the subject's	From randomization until death from any cause

data will be censored at the date the subject was last known to be alive.

Abbreviations: ASCT = Autologous stem cell transplant; DVTd = Daratumumab + bortezomib + thalidomide + dexamethasone; IMWG = International Myeloma Working Group; IRC = independent review committee; PD = progressive disease; PFS = Progression-free survival; VRd = Bortezomib + lenalidomide + dexamethasone; VTd = Bortezomib + thalidomide + dexamethasone

15.3.1.2 Comparison of the overall study designs of CASSIOPEIA and IFM 2009

Figure 26. Comparison of the overall study designs of CASSIOPEIA and IFM 2009



Abbreviations: ASCT = autologous stem cell transplant; DVTd = daratumumab-bortezomib-thalidomide-dexamethasone; MAIC = matching-adjusted indirect comparison; PD = progressive disease; PR = partial response; Q8W = every 8 weeks; VRd = bortezomib-lenalidomide-dexamethasone; VTd = bortezomib-thalidomide-dexamethasone

15.3.1.3 Baseline characteristics

Table 79 presents a comparison of the baseline characteristics of the patients assigned to CASSIOPEIA and IFM 2009.

Table 79 Comparison of Baseline Characteristics in CASSIOPEIA(6, 12) for both treatment arms and VRd arm (IFM 2009) (123)

	DVTd (CASSIOPEIA)	VTd (CASSIOPEIA)	VRd + ASCT (IFM 2009)
Number of subjects	543	542	350
Median age (years)	59	58	60
Male (%)	58	59	61
Myeloma type (%)			
IgG	65	61	64
Others	35	39	36
ISS staging (%)			
ISS I	38	42	34
ISS II	47	43	49
ISS III	15	15	17
Cytogenetic abnormalities, n (%)			

t(4;14) translocation			
Normal	450 (82.9)	450 (83.0)	231 (66)
Abnormal	51 (9.4)	53 (9.8)	28 (8)
Testing not done	42 (7.7)	39 (7.2)	91 (26)
17p deletion			
Normal	459 (84.5)	464 (85.6)	242 (69.1)
Abnormal	42 (7.7)	39 (7.2)	16 (4.6)
Testing not done	42 (7.7)	39 (7.2)	92 (26.3)
t(14;16) translocation			
Normal	NA	NA	252 (72)
Abnormal	NA	NA	6 (1.7)
Testing not done	NA	NA	92 (26.3)

Abbreviations: ASCT = autologous stem cell transplant; DVTd= daratumumab plus bortezomib, thalidomide, and dexamethasone; IgG = Immunoglobulin G; NA = Not available; ISS = International Staging System; NR = not reported; VTd = bortezomib, thalidomide, and dexamethasone; VRd = bortezomib, lenalidomide, and dexamethasone

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

The DVTd study population is assessed to be comparable with the Danish patients eligible for treatment as described in Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety (DVTd vs. VTd), Comparability of the study populations with Danish patients eligible for treatment. The study population in IFM 2009 (VRd + ASCT arm) appear similar in most baseline characteristics compared to the DVTd study population and is therefore also considered comparable to the Danish patients eligible for treatment before and after the MAIC adjustments. Subjects in both studies had previously untreated, documented, and measurable multiple myeloma. Baseline disease characteristics (i.e., age, sex, myeloma subtype, International Staging System [ISS], and cytogenetic abnormalities) were also comparable between studies (Table 79).

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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. OS, PFS and the safety endpoints listed below are the most commonly used, reliable and interpretable ones in multiple myeloma trials. Validity and clinical relevance of progression-free survival, refer to section 5.1 – Effect on MM and relevance of endpoints.

Table 80 Efficacy and Safety outcomes in CASSIOPEIA, GMMG-MM5, IFM 2009

Outcome measure	Definition	Evaluation
Efficacy endpoint		
Overall survival	CASSIOPEIA: Time from initial randomization to date of subject's death; If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.	CASSIOPEIA: Investigator and IRC
	GMMG-MM5: Time from randomization to death from any cause; Patients still alive or lost to follow-up are censored at the date they were last known to be alive.	GMMG-MM5: Investigator
	IFM 2009: From randomization until death from any cause	IFM 2009: Investigator
Progression-free survival	CASSIOPEIA: From first randomization to either progressive disease, according to the IMWG response criteria, or death, whichever occurred first	CASSIOPEIA trial: IMWG (Strict computer algorithm). Investigator and IRC
	GMMG-MM5: From randomization to progression or death from any cause, whichever occurs first	GMMG-MM5: Investigator assessment in accordance with the IMWG criteria.
	IFM 2009: From randomization until either the first documentation of disease progression or death from any cause	IFM 2009: Investigator assessment in accordance with the IMWG criteria.
Safety endpoint		
Any AE	Number/proportion of patients with at least one adverse event for any reason	CASSIOPEIA trial: National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4

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Outcome measure	Definition	Evaluation
Discontinuation due to AE	TEAE leading to discontinuation of study treatment	GMMG-MM5: Adverse events (AEs) were recorded applying the NCI CTCAE criteria (only if ≥ 3°, and ≥ 2° for infections, cardiac disorders, neuropathy, or thromboembolic events). Serious AEs (SAEs) were recorded independent from the CTCAE grade. AEs and SAEs were systematically analyzed using the MedDRA terminology. IFM 2009: Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria of Adverse Events (version 4.0 reported in publication and v3.0 reported in protocol). Serious adverse events and interim efficacy analyses were reviewed by an independent data and safety monitoring committee.
Discontinuation due to any reason	The proportion of patients who discontinue treatment for any reason	
Adverse reaction	The proportion of patients with at least one adverse reaction	
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	

Abbreviations: AE = Adverse event; IFM = Intergroupe Francophone du Myelome; **NCI CTCAE** = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = Serious adverse event; TEAE = Treatment-emergent adverse event

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16.2 Results per study

16.2.1 DVTd vs. VTd (CASSIOPEIA)

Table 81 Results of [CASSIOPEIA], median follow-up time: 18.8 months

Efficacy results in CASSIOPEIA (1st data-cut, median follow-up 18.8 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% CI	*P* value		
OS^	DVTd	543	NA	NA	NA	NA	0.43	0.23-0.80	0.0065	Progression-free survival and overall survival from first randomization were to be tested sequentially using a hierarchical testing approach, each with an overall two-sided alpha level of 0.05.	Moreau et al. 2019(6)
	VTd	542	NA								
PFS^	DVTd	543	NA	NA	NA	NA	0.47	0.33-0.67	<0.0001		
	VTd	542	NA								
PFS*	DVTd	543	NA	NA	NA	NA	0.47	0.33-0.67	<0.0001	IPW adjustment	
	VTd	542	NA								

Abbreviations: CI = Confidence interval; DVTd = Daratumumab + bortezomib + thalidomide + dexamethasone; NA = Not applicable; OS = Overall survival; PFS = Progression-free survival; IPW = Inverse probability weighting; VTd = Bortezomib + thalidomide + dexamethasone

^OS, PFS HR regardless of second randomization. OS & PFS by Induction/ASCT/Consolidation Treatment Group from First Randomization for Overall Comparison Regardless of Second Randomization Based on Computerized Algorithm; ITT Analysis Set. Including all subjects randomized in Part I regardless of second randomization. Hazard ratio and 95% CI from a Cox regression analysis with treatment as the sole explanatory variable. p-value is based on the log-rank test

*PFS with inverse probability weighting (IPW). PFS by Induction/ASCT/Consolidation Treatment Group from First Randomization for Overall Comparison Based on Computerized Algorithm; ITT Analysis Set. The overall comparison of induction treatments is made treating the 2 maintenance-specific comparisons as 2 strata with the variance estimated using the robust variance estimator (the sandwich estimate).

Note: Numbers are rounded. Safety data for DVTd vs. VTd is presented in Appendix E Safety data for intervention and comparator(s) and results from EORTC QLQ-C30 is presented below.

Table 82: Change from baseline in EORTC QLQ-C30 Global Health Status Score during induction/ASCT/consolidation: mixed model for repeated measures (ITT population)(7, 9)

	Induction/ASCT/Consolidation				
	VTd		DVTd		Difference (DVTd-VTd)
	n	LSMEANS of change from baseline (95% CI)	n	LSMEANS of change from baseline (95% CI)	P-value[a]
Analysis set: ITT	542		543		
Physical functioning score					
Baseline	507		510		
Cycle 4 Day 28	386	2.9 (0.7, 5.1)	413	3.8 (1.6, 6)	0.4319
Day 100 post ASCT	363	8.7 (6.5, 11)	389	9.7 (7.4, 11.9)	0.4523

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30.
[a] p value was calculated using a mixed-effects model with repeated measures.

Table 83: Change from baseline in EORTC QLQ-C30 physical functioning score during induction/ASCT/consolidation: mixed model for repeated measures (ITT population)(7, 9)

	Induction/ASCT/Consolidation				
	VTd		DVTd		Difference (DVTd-VTd)
	n	LSMEANS of change from baseline (95% CI)	n	LSMEANS of change from baseline (95% CI)	P-value[a]
Analysis set: ITT	542		543		
Physical functioning score					
Baseline	510		511		
Cycle 4 Day 28	388	0.6 (-1.7, 2.8)	415	2.2 (0, 4.4)	0.1578
Day 100 post ASCT	369	6.5 (4.2, 8.8)	391	6.9 (4.7, 9.2)	0.7371

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; ITT = Intention-to-treat.
[a] p value was calculated using a mixed-effects model with repeated measures.

Table 84: Change from baseline in EORTC QLQ-C30 role functioning score during induction/ASCT/consolidation: mixed model for repeated measures (ITT population)(7, 9)

	Induction/ASCT/Consolidation		
	VTd	DVTd	Difference (DVTd-VTd)

	n	LSMEANS of change from baseline (95% CI)	n	LSMEANS of change from baseline (95% CI)	P-value[a]
Analysis set: ITT	542		543		
Role functioning score					
Baseline	510		511		
Cycle 4 Day 28	388	1.9 (-1.6, 5.4)	413	5.6 (2.1, 9.1)	0.0513
Day 100 post ASCT	369	11 (7.4, 14.6)	391	13.1 (9,5, 16.7)	0.2743

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; ITT = Intention-to-treat.
[a] p value was calculated using a mixed-effects model with repeated measures.

Table 85: Change from baseline in EORTC QLQ-C30 emotional functioning score during induction/ASCT/consolidation: mixed model for repeated measures (ITT population)(7, 9)

	Induction/ASCT/Consolidation				
	VTd		DVTd		Difference (DVTd-VTd)
	n	LSMEANS of change from baseline (95% CI)	n	LSMEANS of change from baseline (95% CI)	P-value[a]
Analysis set: ITT	542		543		
Emotional functioning score					
Baseline	508		510		
Cycle 4 Day 28	385	7.6 (5, 10.1)	413	6.4 (3.9, 8.9)	0.4004
Day 100 post ASCT	364	9.5 (6.9, 12.1)	389	13 (10.4, 15.5)	0.0131

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; ITT = Intention-to-treat.
[a] p value was calculated using a mixed-effects model with repeated measures.

Table 86: Change from baseline in EORTC QLQ-C30 cognitive functioning score during induction/ASCT/consolidation: mixed model for repeated measures (ITT population)(7, 9)

	Induction/ASCT/Consolidation				
	VTd		DVTd		Difference (DVTd-VTd)
	n	LSMEANS of change from baseline (95% CI)	n	LSMEANS of change from baseline (95% CI)	P-value[a]
Analysis set: ITT	542		543		
Cognitive functioning score					
Baseline	509		510		

Cycle 4 Day 28	386	-6.6 (-9.2, -4)	413	-6.2 (-8.8, -3.7)	0.8024
Day 100 post ASCT	365	-7.9 (-10.6, -5.3)	389	-5 (-7.6, -2.4)	0.0358

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; ITT = Intention-to-treat.
[a] p value was calculated using a mixed-effects model with repeated measures.

Table 87: Change from baseline in EORTC QLQ-C30 social functioning score during induction/ASCT/consolidation: mixed model for repeated measures (ITT population)(7, 9)

	Induction/ASCT/Consolidation				
	VTd		DVTd		Difference (DVTd-VTd)
	n	LSMEANS of change from baseline (95% CI)	n	LSMEANS of change from baseline (95% CI)	P-value[a]
Analysis set: ITT	542		543		
Social functioning score					
Baseline	507		508		
Cycle 4 Day 28	385	-3 (-6.1, 0.2)	412	-1.7 (-4.9, 1.4)	0.4667
Day 100 post ASCT	364	3.5 (0.2, 6.7)	387	5.6 (2.4, 8.8)	0.2196

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; ITT = Intention-to-treat.
[a] p value was calculated using a mixed-effects model with repeated measures.

Table 88: Change from baseline in EORTC QLQ-C30 fatigue symptom score during induction/ASCT/consolidation: mixed model for repeated measures (ITT population)(7, 9)

	Induction/ASCT/Consolidation				
	VTd		DVTd		Difference (DVTd-VTd)
	n	LSMEANS of change from baseline (95% CI)	n	LSMEANS of change from baseline (95% CI)	P-value[a]
Analysis set: ITT	542		543		
Fatigue symptom score					
Baseline	510		511		
Cycle 4 Day 28	388	3.6 (0.6, 6.5)	415	0.8 (-2.1, 3.7)	0.0785
Day 100 post ASCT	369	-4.3 (-7.4, -1.3)	391	-5.2 (-8.1, -2.2)	0.5957

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; ITT = Intention-to-treat.
[a] p value was calculated using a mixed-effects model with repeated measures.

Table 89: Change from baseline in EORTC QLQ-C30 pain symptom score during induction/ASCT/consolidation: mixed model for repeated measures (ITT population)(7, 9)

	Induction/ASCT/Consolidation				
	VTd		DVTd		Difference (DVTd-VTd)
	n	LSMEANS of change from baseline (95% CI)	n	LSMEANS of change from baseline (95% CI)	P-value[a]
Analysis set: ITT	542		543		
Pain symptom score					
Baseline	510		510		
Cycle 4 Day 28	388	-13.8 (-17.1, -10.5)	414	-16 (-19.2, -12.7)	0.2150
Day 100 post ASCT	369	-19.7 (-23, -16.3)	391	-23.3 (-26.6, -20)	0.0416

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; ITT = Intention-to-treat.
[a] p value was calculated using a mixed-effects model with repeated measures.

Table 90: Change from baseline in EORTC QLQ-C30 nausea and vomiting symptom score during induction/ASCT/consolidation: mixed model for repeated measures (ITT population)(7, 9)

	Induction/ASCT/Consolidation				
	VTd		DVTd		Difference (DVTd-VTd)
	n	LSMEANS of change from baseline (95% CI)	n	LSMEANS of change from baseline (95% CI)	P-value[a]
Analysis set: intention-to-treat	542		543		
Nausea and vomiting symptom score					
Baseline	510		511		
Cycle 4 Day 28	388	0.3 (-1.4, 1.9)	415	-0.5 (-2.2, 1.2)	0.4067
Day 100 post ASCT	369	-0.9 (-2.7, 0.8)	391	-1.9 (-3.5, -0.2)	0.3282

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; CI = confidence interval; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire-C30; ITT = Intention-to-treat.
[a] p value was calculated using a mixed-effects model with repeated measures.

Table 91 Results of [CASSIOPEIA], median follow-up time: 29.2 months

Efficacy results in CASSIOPEIA (2nd data-cut, median follow-up of 29.2 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% CI	*P* value		
OS^	DVTd	543	NA	NA	NA	NA	0.52	0.33-0.85	0.007	Progression-free survival and overall survival from first randomisation were to be tested sequentially using a hierarchical testing approach, each with an overall two-sided alpha level of 0.05.	DVTd EPAR(4)
	VTd	542	NA								
PFS^	DVTd	543	NA	NA	NA	NA	0.50	0.38-0.65	<0.0001		Data-on-file (5)
	VTd	542	NA								
PFS*	DVTd	543	NA	NA	NA	NA	[redacted]	[redacted]	[redacted]	IPW adjustment	Data-on-file (5)
	VTd	542	NA								
PFS~	DVTd	543	NA	NA	NA	NA	0.50	0.34-0.75	0.0005	PFS adjusted results for censoring of maintenance	DVTd EPAR(4)
	VTd	542	NA								

Abbreviations: CI = Confidence interval; DVTd = Daratumumab + bortezomib + thalidomide + dexamethasone; NA = Not applicable; OS = Overall survival; PFS = Progression-free survival; VTd = Bortezomib + thalidomide + dexamethasone

^OS, PFS HR regardless of second randomization. OS & PFS by Induction/ASCT/Consolidation Treatment Group from First Randomization for Overall Comparison Regardless of Second Randomization Based on Computerized Algorithm; ITT Analysis Set. Including all subjects randomized in Part I regardless of second randomization. Hazard ratio and 95% CI from a Cox regression analysis with treatment as the sole explanatory variable. p-value is based on the log-rank test.

* PFS with inverse probability weighting (IPW). PFS by Induction/ASCT/Consolidation Treatment Group from First Randomization for Overall Comparison Based on Computerized Algorithm; ITT Analysis Set. The overall comparison of induction treatments is made treating the 2 maintenance-specific comparisons as 2 strata with the variance estimated using the robust variance estimator (the sandwich estimate).

~ PFS by Induction/ASCT/Consolidation Treatment Group from First Randomization for Overall Comparison by censoring subjects randomized to Daratumumab Maintenance at Second randomization based on computerized algorithm. Including all subjects randomized in Induction/ASCT/Consolidation. Hazard ratio and 95% CI from a Cox regression analysis with treatment as the sole explanatory variable. Subjects randomized to daratumumab maintenance at the second randomization were censored at the date of the second randomization. P-value is based on the log-rank test.

Note: Numbers are rounded.

[redacted]

Efficacy results in CASSIOPEIA (3rd data-cut, median follow-up of 44.5 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% CI	*P* value		
[redacted]											

Abbreviations: CI = Confidence interval; DVTd = Daratumumab + bortezomib + thalidomide + dexamethasone; IPW = Inverse probability weighting; NA = Not applicable; OS = Overall survival; PFS = Progression-free survival; VTd = Bortezomib + thalidomide + dexamethasone

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[redacted]

16.2.2 VCd vs. PAd (GMMG-MM5)

Table 93 Results of [GMMG-MM5(EudraCT No. 2010-019173-16)]

Efficacy and safety results in GMMG-MM5											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
OS	VCd	251	NA	NA	NA	NA	NA	NA	NA	HR of PFS and OS were not reported in publications.	Mai et al. 2015 (121) and Goldschmidt et al. 2020 (139)
	PAd	251	NA								
	A1:PAd + LEN-2Y	125	NA	NA	NA	NA	NA	NA	0.15		
	B1:PAd + LEN-CR	126	NA								
	A2:VCd + LEN-2Y	126	NA								
	B2:VCd + LEN-CR	125	NA								
PFS	VCd	251	NA	NA	NA	NA	NA	NA	NA		
	PAd	251	NA								
	A1:PAd + LEN-2Y	125	43.2 months	NA	NA	NA	NA	NA	0.60		
	B1:PAd + LEN-CR	126	35.9 months								

	A2:VCd + LEN-2Y	126	40.9 months								
	B2:VCd + LEN-CR	125	35.7 months								
Any AE*	VCd	250	64.0%	NA	NA	NA	NA	NA	0.58	Common Terminology Criteria for Adverse Events;	Mai et al. 2015 (121)
	PAd	248	61.3%								
Serious AEs*	VCd	250	24.0%	NA	NA	NA	NA	NA	0.04		
	PAd	248	32.7%								

Abbreviations: AE = Adverse event; CI = Confidence interval; HR = Hazard ratio; LEN-CR = Lenalidomide until complete response; LEN-2Y Lenalidomide maintenance for 2 years; NA = Not applicable; OS = Overall survival; PAd = Bortezomib + doxorubicin + dexamethasone; PFS = Progression-free survival; VCd = Bortezomib + cyclophosphamide + dexamethasone

*AEs During induction. Reported in publication as "Any AE" defined as: 'Any AE' included all AE CTCAE grade ⩾ 3 or ⩾ 2 for infections, cardiac disorders, neuropathy and thromboembolic events. Events with a lower CTCAE grade were not considered.

Note: The median follow-up for PFS was 59.4 months and 60.1 months for OS.(139)

16.2.3 VRd vs. VRd ASCT (IFM 2009)

Table 94 Results of [IFM 2009]

Efficacy and safety results in IFM 2009											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (median/%)	Difference	95% CI	P value	Difference	95% CI	P value		
PFS	VRd + ASCT	350	50 months	NA	NA	NA	0.65	0.53-0.80	<0.001	Using Cox models with terms for treatment arm, subgroup, and the interaction between subgroup and treatment. The interaction terms were evaluated for statistical significance. Adjusted hazard ratio for disease progression or death & adjusted hazard ratio for death	Attal, M., 2017(123)
	VRd	350	36 months								
OS	VRd + ASCT	350	NR	NA	NA	NA	1.16	0.80- 1.68	0.87		
	VRd	350	NR								
	VRd + ASCT	350	11%	NA	NA	NA	NA	NA	NA		

Discontinuation due to AEs	VRd	350	9%								Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria of Adverse Events (version 4.0).
Grade 3/4 AEs	VRd + ASCT	350	97.1%	NA	NA	NA	NA	NA	NA		
	VRd	350	83.4%								

Abbreviations: AE = Adverse event; ASCT = Autologous stem cell transplant; CI = Confidence interval; IFM = Intergroupe Francophone du Myelome; NA = Not applicable; NR = Not reported; OS = Overall survival; PFS = Progression-free survival; VRd = Bortezomib + lenalidomide + dexamethasone

Note: AEs collected most likely throughout induction, ASCT, consolidation and maintenance Treatment Phase.

The median duration of follow-up after randomization was 44 months in the VRd-alone group and 43 months in the VRd + ASCT group

17. Appendix E Safety data for intervention and comparator(s)

17.1 Safety data – DVTd vs. VTd

Table 95: Treatment exposure (CASSIOPEIA, safety analysis set) (4)

	DVTd (n=536)	VTd (n=538)
Median duration of treatment (months)	8.9	8.7
Number of treatment cycles, total, median (range)	6 (1; 6)	6 (1; 6)
Treatment cycles at induction stage, median (range)	4 (1; 4)	4 (1; 4)
Treatment cycles at consolidation stage, median (range)	2 (1; 2)	2 (1; 2)
Daratumumab relative dose intensity, induction/consolidation (%)		
Mean (SD)	98.38 (6.306)	-
Median	99.72	-
Q1, Q3	(97.76; 100.78)	-
Range	(7.3; 113.1)	-
Bortezomib relative dose intensity, induction/consolidation (%)		
Mean (SD)	91.5 (12.057)	91.31 (11.211)
Median	96.77	96.30
Q1, Q3	(87.02; 99.45)	(84.73; 99.17)
Range	(24.5; 105.7)	(49.2; 106.7)
Thalidomide relative dose intensity, induction/consolidation (%)		
Mean (SD)	86.6 (19.30)	86.1 (18.36)
Median	96.4	95.4
Q1, Q3	(79.2; 100.0)	(78.0; 100.0)
Range	(2; 150)	(0; 104)
Dexamethasone relative dose intensity, induction/consolidation (%)		
Mean (SD)	96.8 (10.14)	96.2 (11.84)
Median	100.0	100.0
Q1, Q3	(96.7; 100.0)	(96.7; 100.0)
Range	(13; 120)	(0; 125)

Abbreviations: VTd = bortezomib, thalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; SD = standard deviation.

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Table 96: TEAEs[a] by MedDRA system organ class and preferred term during the induction/ASCT/consolidation period (CASSIOPEIA, safety population)(4)

	DVTd (n=536)		VTd (n=538)	
	All grades (≥10%)	Grade3/4 (≥5%)	All grades (≥10%)	Grade3/4 (≥5%)
Blood and lymphatic system disorders	**303 (56.5%)**	**249 (46.5%)**	**253 (47.0%)**	**196 (36.4%)**
Neutropenia	157 (29.3%)	148 (27.6%)	89 (16.5%)	79 (14.7%)
Thrombocytopenia	109 (20.3%)	59 (11.0%)	73 (13.6%)	40 (7.4%)
Lymphopenia	99 (18.5%)	91 (17.0%)	67 (12.5%)	52 (9.7%)
Anaemia	73 (13.6%)	n/a	81 (15.1%)	n/a
Febrile neutropenia	n/a	36 (6.7%)	n/a	28 (5.2%)
Infections and infestations	**351 (65.5%)**	**n/a**	**306 (56.9%)**	**n/a**
Bronchitis	102 (19.0%)	n/a	66 (12.3%)	n/a
General disorders and administration site conditions	**414 (77.2%)**	**n/a**	**398 (74.0%)**	**n/a**
Asthenia	171 (31.9%)	n/a	155 (28.8%)	n/a
Oedema peripheral	162 (30.2%)	n/a	148 (27.5%)	n/a
Pyrexia	140 (26.1%)	n/a	114 (21.2%)	n/a
Fatigue	70 (13.1%)	n/a	86 (16.0%)	n/a
Gastrointestinal disorders	**431 (80.4%)**	**124 (23.1%)**	**416 (77.3%)**	**131 (24.3%)**
Constipation	272 (50.7%)	n/a	262 (48.7%)	n/a
Nausea	162 (30.2%)	n/a	130 (24.2%)	n/a
Diarrhoea	103 (19.2%)	n/a	89 (16.5%)	n/a
Vomiting	87 (16.2%)	n/a	52 (9.7%)	n/a
Stomatitis	86 (16.0%)	68 (12.7%)	104 (19.3%)	88 (16.4%)
Musculoskeletal and connective tissue disorders	**245 (45.7%)**	**n/a**	**252 (46.8%)**	**n/a**
Bone pain	70 (13.1%)	n/a	82 (15.2%)	n/a
Back pain	59 (11.0%)	n/a	55 (10.2%)	n/a
Nervous system disorders	**437 (81.5%)**	**73 (13.6%)**	**456 (84.8%)**	**73 (13.6%)**
Peripheral sensory neuropathy	314 (58.6%)	47 (8.8%)	340 (63.2%)	46 (8.6%)
Paraesthesia	118 (22.0%)	n/a	108 (20.1%)	n/a
Tremor	71 (13.2%)	n/a	58 (10.8%)	n/a

Psychiatric disorders	**141 (26.3%)**	**n/a**	**153 (28.4%)**	**n/a**
Insomnia	61 (11.4%)	n/a	78 (14.5%)	n/a
Anxiety	58 (10.8%)	n/a	46 (8.6%)	n/a
Respiratory, thoracic and mediastinal disorders	**259 (48.3%)**	**n/a**	**185 (34.4%)**	**n/a**
Cough	90 (16.8%)	n/a	49 (9.1%)	n/a
Dyspnoea	77 (14.4%)	n/a	66 (12.3%)	n/a
Skin and subcutaneous tissue disorders	**255 (47.6%)**	**n/a**	**222 (41.3%)**	**n/a**
Rash	86 (16.0%)	n/a	67 (12.5%)	n/a
Erythema	61 (11.4%)	n/a	47 (8.7%)	n/a

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; n/a = not applicable; TEAE = treatment-emergent adverse event.
Note: During the transplant period, according to protocol, only limited AE were collected
[a] TEAEs during induction, ASCT, or consolidation Treatment Phase; incidence reflects the number of patients experiencing at least one TEAE associated with at least one of the study treatments.

Table 97: Adverse Drug reactions(4)

	DVTd (n=536)			VTd (n=538)		
	All grades (≥10%)	Grade 3 (≥5%)	Grade 4 (≥5%)	All grades (≥10%)	Grade 3 (≥5%)	Grade 4 (≥5%)
Infusion reactions[a]	190 (35.4%)	17 (3.2%)	2 (0.4%)	0	0	0
Gastrointestinal disorders						
Nausea	162 (30.2%)	21 (3.9%)	0	130 (24.2%)	11 (2.0%)	1 (0.2%)
Vomiting	87 (16.2%)	12 (2.2%)	0	52 (9.7%)	9 (1.7%)	0
General disorders and administration site conditions						
Pyrexia	140 (26.1%)	12 (2.2%)	2 (0.4%)	114 (21.2%)	12 (2.2%)	0
Infections and infestations						
Upper respiratory tract infection[b]	147 (27.4%)	3 (0.6%)	0	91 (16.9%)	3 (0.6%)	0
Bronchitis[c]	105 (19.6%)	8 (1.5%)	0	68 (12.6%)	6 (1.1%)	0
Respiratory, thoracic and mediastinal disorders						
Cough[d]	91 (17.0%)	0	0	49 (9.1%)	0	0
Vascular disorders						
Hypertension	51 (9.5%)	22 (4.1%)	0	29 (5.4%)	12 (2.2%)	0

Abbreviations: VTd = bortezomib, thalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone.
a Include terms determined by investigators to be related to infusions
b Laryngitis, Laryngitis viral, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsilitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection
c Bronchiolitis, Bronchitis, Bronchitis chronic, Respiratory syncytial virus bronchitis, Tracheobronchitis
d Cough, Productive cough
Note: Based on Part 1 of the MMY3006 study.
Adverse events are reported using MedDRA version 20.0
Percentages are calculated N as the denominator, the number of safety subjects in each treatment arm.

Table 98: Most common (≥2%) serious TEAEs by MedDRA system organ class and preferred term during the induction/ASCT/consolidation period (CASSIOPEIA, safety population)(4)

	Proportion of patients, n (%)	
	DVTd (n=536)	VTd (n=538)
Total number of patients with serious TEAEs	251 (46.8%)	255 (47.4%)
Infections and infestations	80 (14.9%)	67 (12.5%)
Pneumonia	19 (3.5%)	9 (1.7%)
Sepsis	7 (1.3%)	11 (2.0%)
Blood and lymphatic system disorders	57 (10.6%)	44 (8.2%)
Neutropenia	21 (3.9%)	8 (1.5%)
Febrile neutropenia	12 (2.2%)	15 (2.8%)
Thrombocytopenia	12 (2.2%)	4 (0.7%)
Febrile bone marrow aplasia	7 (1.3%)	11 (2.0%)
Respiratory, thoracic and mediastinal disorders	38 (7.1%)	38 (7.1%)
Lung disorder	11 (2.1%)	6 (1.1%)
Pulmonary embolism	8 (1.5%)	20 (3.7%)
General disorders and administration site conditions	33 (6.2%)	37 (6.9%)
Pyrexia	15 (2.8%)	23 (4.3%)
Nervous system disorders	33 (6.2%)	44 (8.2%)
Peripheral sensory neuropathy	11 (2.1%)	15 (2.8%)

Abbreviations: ASCT = autologous stem cell transplant; VTd = bortezomib, thalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; TEAE = treatment-emergent adverse event.
Notes: Period (induction, ASCT, consolidation) of serious TEAE are assigned by the start date of linked serious TEAE; Adverse events are reported using MedDRA version 20.0; During transplant period, according to protocol, only limited AE were collected; Percentages are calculated with the number of subjects in each phase/group as denominator.

Table 99: Most Common (at least 1%) Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment During Induction/ASCT/Consolidation Phase by MedDRA System Organ Class (CASSIOPEIA, safety population)(4)

	DVTd (n=536)			VTd (n=538)		
	All grades (≥1%)	Grade 3 or 4 (≥1%)	Grade 5 (≥1%)	All grades (≥1%)	Grade 3 or 4 (≥1%)	Grade 5 (≥1%)
Total number of subjects with TEAE leading to discontinuation of study treatment[a]	40 (7.5%)	30 (5.6%)	1 (0.2%)	45 (8.4%)	34 (6.3%)	0
Nervous system disorders	15 (2.8%)	11 (2.1%)	0	33 (6.1%)	25 (4.6%)	0
Peripheral sensory neuropathy	10 (1.9%)	7 (1.3%)	0	23 (4.3%)	18 (3.3%)	0

Abbreviations: ASCT = autologous stem cell transplant; VTd = VTd = bortezomib, thalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone; TEAE = treatment-emergent adverse event.
[a] Includes those subjects indicated as having discontinued treatment due to an adverse event or treatment delay for toxicity for more than 6 weeks on the end of treatment CRF page.
Note: Adverse events are reported using MedDRA version 20.0; During the transplant period, according to protocol, only limited AE were collected; Percentages are calculated with the number of subjects in each group as denominator.

Table 100: Treatment discontinuation for any reason(6)

	DVTd (n=536)	VTd (n=538)
Treatment discontinuation during Induction	24	31
	512 completed induction	507 completed induction
Treatment discontinuation after completing Induction	6	15
	506 completed mobilisation	492 completed mobilisation
Treatment discontinuation after completing mobilisation	17	9
	489 completed transplant	484 completed transplant*
Treatment discontinuation after transplant	23	36
	466 received consolidation	448 received consolidation
Treatment discontinuation during consolidation	5	11
	461 completed consolidation	437 completed consolidation
Treatment discontinuation after completing consolidation	2	1
	459 evaluated 100 days post transplant	436 evaluated 100 days post transplant

Abbreviations: VTd = bortezomib, thalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone.
* One patient had successful CD34+ stem cell collection without any previous mobilisation treatment

18. Appendix F Comparative analysis of efficacy and safety

18.1 DVTd compared to VRd for NDMM patients who are transplant-eligible

Refer to Appendix D Efficacy and safety results per study, DVTd vs. VTd (CASSIOPEIA).

18.2 DVTd/VTd compared to VCd for NDMM patients who are transplant-eligible

Table 101 MAIC of studies comparing DVTd to VCd for NDMM patients who are transplant eligible

Analysis		DVTd vs. VCd-LEN-2Y			Method used for quantitative synthesis	Result used in the health economic analysis?
		HR	95% CI	P-value		
Progression-free survival	Naïve comparison	0.43	0.30 – 0.60	<.001	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The naive HR was obtained using a Cox regression analysis without any weights for all patients in the index and comparator treatment arms	No
	Base case analysis	0.40	0.26 - 0.61	<.001	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The adjusted HR was obtained using a weighted Cox regression analysis with a robust sandwich estimator for calculation of the standard errors.	Yes
	Sensitivity analysis	0.35	0.21–0.58	<.001		No
Overall survival	Naïve comparison	0.39	0.21 - 0.71	0.002	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The naive HR was obtained using a Cox regression analysis without any weights for all patients in the index and comparator treatment arms	No
	Base case analysis	0.37	0.18–0.76	0.006	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The adjusted HR was obtained using a weighted Cox regression analysis with a robust sandwich estimator for calculation of the standard errors.	Yes
	Sensitivity analysis	0.35	0.14–0.86	0.023		No

Abbreviations: CI = Confidence interval; HR = Hazard ratio; VCd = Bortezomib + cyclophosphamide + dexamethasone; VCd-LEN-2Y = Bortezomib + cyclophosphamide + dexamethasone (VCd) followed by lenalidomide consolidation and lenalidomide maintenance for 2 years; VTd = bortezomib, thalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone.
Note: median follow-up time for CASSIOPEIA is 29.2 months in base case analysis, and 18.8 months in the sensitivity analysis

Table 102 MAIC of studies comparing VTd to VCd for NDMM patients who are transplant eligible

Analysis		VTd vs. VCd-LEN-2Y			Method used for quantitative synthesis	Result used in the health economic analysis?
		HR	95% CI	P-value		
Progression-free survival	Naïve comparison	0.85	0.62 - 1.17	0.3191	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The naive HR was obtained using a Cox regression analysis without any weights for all patients in the index and comparator treatment arms	No
	Base case analysis	0.93	0.64-1.35	0.688	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The adjusted HR was obtained using a weighted Cox regression analysis with a robust sandwich estimator for calculation of the standard errors.	Yes
	Sensitivity analysis	1.00	0.62-1.61	0.987‡		No
Overall survival	Naïve comparison	0.72	0.42 - 1.24	0.2338	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The naive HR was obtained using a Cox regression analysis without any weights for all patients in the index and comparator treatment arms	No

Base case analysis	0.77	0.40-1.47	0.43	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The adjusted HR was obtained using a weighted Cox regression analysis with a robust sandwich estimator for calculation of the standard errors.	Yes
Sensitivity analysis	0.93	0.41-2.10	0.869‡		No

Abbreviations: CI = Confidence interval; HR = Hazard ratio; VCd = Bortezomib + cyclophosphamide + dexamethasone; VCd-LEN-2Y = Bortezomib + cyclophosphamide + dexamethasone (VCd) followed by lenalidomide consolidation and lenalidomide maintenance for 2 years; VTd = bortezomib, thalidomide and dexamethasone; DVTd = daratumumab, bortezomib, thalidomide and dexamethasone.
Note: median follow-up time for CASSIOPEIA is 29.2 months in base case analysis, and 18.8 months in the sensitivity analysis
‡Noninferior: identified as HR of 1.333 for PFS and 1.298 for OS.(8)

18.2.1 Statistical methods

The MAIC analysis followed the method described by Signorovitch et al. 2012(138) and guidelines from NICE.(276) This process involved the following three key steps:

- Deriving balancing weights and applying them to estimate the average baseline characteristics that match the published aggregate characteristics of the comparator populations
- Comparing adjusted outcomes for CASSIOPEIA vs. GMMG-MM5(121, 139)
- Quantifying the relative treatment effect of CASSIOPEIA vs. GMMG-MM5(121, 139) across balanced study populations

Details of these steps are described below.

Deriving Balancing Weights

A propensity score-type logistic regression equation was used to estimate weights; this equation predicts whether a given type of patient originates from the index trial or the comparator trial as a function of baseline characteristics. More specifically, weights were given by the odds calculated as $w_i = exp(\alpha + x_i'\beta)$, where x_i' is the vector of baseline variables included for matching. The β coefficients were determined by the method of moments rather than the maximum likelihood (as is usually the case) because only aggregate data for the x's are available for the competitor populations.(138, 146)

Once the coefficients were estimated, the equation was applied to the patients from the CASSIOPEIA trial to calculate the individual patient weights. The weights were then used to calculate the effective sample size (ESS) achieved after weighting patients. The ESS was calculated by $(\sum w_i)^2/(\sum w_i^2)$. If the populations were perfectly balanced before adjustment, all patients would have $w_i = 1$ and the ESS would equal the original size of the index population. Adjustment for population differences assigns patients uneven weights, leading to the inevitable loss of ESS. A low ESS indicates an irregular distribution of weights across patients, meaning that only a small fraction of patients drives the treatment effect. To account for an increased uncertainty caused by the reduction in ESS in the analyses, the weights were normalized by dividing each w_i by their sum $(\sum w_i)$ and then multiplying by the ESS. The sum of the normalized weights for all patients in CASSIOPEIA equals 1.

Table 111 presents a summary of the ESS, an average of individual weights, and the distribution of individual (rescaled) weights for all MAIC analyses. The ESS is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. Weighting always reduces the effective sample size. When the ESS is markedly reduced, or the weights are highly variable, estimates become unstable and inferences depend heavily on just a small number of individuals. ESS was reduced from the original sample size by 62% for DVTd and 61% for VTd. The rescaled weights were mostly small with some skewness to the right (median of 0.58) without presence of very large outliers (range 0.00-9.92) for DVTd (Figure 31) and mostly small with some skewness to the right (median of 0.64) without presence of very large outliers (range 0.00-10.01) for VTd (Figure 32)

Comparing Adjusted Outcomes for CASSIOPEIA vs. VCd

After the weights were obtained, a pooled dataset was prepared from the CASSIOPEIA data and IPD from the comparator treatments. The re-constructed IPD for the comparator treatments were assigned weights of 1, while patients from CASSIOPEIA were assigned the normalized weights derived from the MAIC. The adjusted KM CASSIOPEIA curves were estimated by a weighted KM analysis and plotted alongside the unadjusted CASSIOPEIA and comparator

curves to illustrate the direction of shift due to the adjustment. The adjusted median time to event was also estimated when feasible.

Quantifying the Relative Treatment Effect of CASSIOPEIA vs. VCd

The relative effect of CASSIOPEIA vs. GMMG-MM5(139) for OS and PFS was quantified as a hazard ratio (HR) with a 95% CI. The adjusted HR was obtained using a weighted Cox regression analysis with a robust sandwich estimator for calculation of the standard errors. The naive HR was obtained using a Cox regression analysis without any weights for all patients in the index and comparator treatment arms.

18.2.2 MAIC analysis results

Table 103 presents the baseline characteristics before and after matching DVTd/VTd (CASSIOPEIA) to VCd-LEN-2Y (GMMG-MM5).(8) After weighting, all commonly reported baseline characteristics between CASSIOPEIA and the GMMG-MM5 study except anemia and renal insufficiency were balanced for DVTd vs. VCd-LEN-2Y. ESS was reduced from the original sample size by 62% for DVTd and 61% for VTd. The rescaled weights were mostly small with some skewness to the right (median of 0.58) without presence of very large outliers (range 0.00-9.92) for DVTd (refer to section 18.2.3, Figure 31) and mostly small with some skewness to the right (median of 0.64) without presence of very large outliers (range 0.00-10.01) for VTd (refer to section 18.2.3, Figure 32).

Table 103 Baseline Characteristics before and after Matching DVTd/VTd to VCd-LEN-2Y

Characteristic	Before Matching		After Matching		Target
	DVTd (N=543)	VTd (N=542)	DVTd (ESS=206)	VTd (ESS=211)	VCd (N=251) ǂ
Age (years)					
Median (Min–Max)	59.0 (22.0-65.0)	58.0 (26-65)	58.0 (35.0-65.0)	58.0 (34-65)	58.7 (33-70)
% above 58.7	51	48.2	50	50	50
Gender, %					
Male	58.2	58.9	61	61	61
ECOG/WHO Performance Status, %					
0	48.8	47.4	45.4	45.4	45.4 (114/251)
1	41.4	42.4	46.2	46.2	46.2 (116/251)
2-3	9.8	10.1	8.4	8.4	8.4 (21/251)
Heavy-chain isotype /Type of myeloma by Immunofixation, %					
IgG	64.6	61.4	59	59	59
IgA	16	19.2	20.3	20.3	20.3
LCD	15.3	12.2	18.7	18.7	18.7
Other	4.1	7.2	2	2	2
Calcium elevation (calcium >2.65 mmol/L), %					
Yes	10.1	7	12.3	12.3	12.3
Missing	1.7	4.1	0	0	0
Renal insufficiency (creatinine >177 µmol/L), %*					
Yes	0.2	0.4	0.8	0.4	15.5
Anemia (Hb <10 g/dL or 2 g/dL <normal), %*					
Yes	41.1	35.2	46.9	50.5	55
Bone disease (lytic lesionsǂ), %					
Yes	85.6	85.2	88.8	88.8	88.8
Missing	0.6	0.4	0	0	0

ǂ Or myeloma-related osteopenia/osteoporosis (Mai et a. 2015). Derived from CASSIOPEIA trial data as 'Baseline Presence of Diffuse Myeloma-related Osteopenia' or 'Baseline Number of Lytic Bone Lesions >1'.

ISS Stage, %					
I	37.6	42.1	37.4	37.4	37.4
II	47	43	32.7	32.7	32.7
III	15.5	14.9	29.9	29.9	29.9
LDH (serum), %					
>ULN	41.6	34.9	17.5	17.5	17.5
Unknown	2.8	1.7	0	0	0
Adverse cytogenetics - del17p, %					
Performed	92.3	92.8	100	100	100 (222/251)
Positive (% performed)	8.4	7.8	10.4	10.4	10.4 (23/222)
Missing	7.7	7.2	0	0	11.6 (29/251)
Adverse cytogenetics – t (4;14), %					
Performed	92.3	92.8	100	100	100 (219/251)
Positive (% performed)	10.2	10.5	10	10	10.0 (22/219)
Missing	7.7	7.2	0	0	12.7 (32/251)
Calcium (serum, mmol/L)					
Median (Min–Max)	2.4 (0.2-3.6)	2.4 (1.8-3.7)	2.4 (1.8-3.4)	2.4 (1.8-3.7)	2.4 (1.7-5.4)
% above 2.4	42.5	39.7	50	50	50
Missing	1.7	4.1	0	0	0
Creatinine (serum, mg/dL)					
Median (Min–Max)	0.8 (0.1-2.4)	0.8 (0.1-2.7)	1.0 (0.4-2.4)	1.0 (0.4-2.7)	1.0 (0.4-11.3)
% above 1.0	23	27.5	50	50	50
Hemoglobin (g/dL)					
Median (Min–Max)	11.1 (7.0-16.1)	11.5 (5.9-17.0)	10.6 (7.1-16.1)	10.7 (7.9-16.0)	10.7 (6.0-16.3)
% above 10.7	58.9	65.7	50	50	50
Platelets (per nL)					
Median (Min–Max)	241.0 (49.0-999.0)	250 (22-584)	238.0 (49.0-525.0)	239 (70-519)	240 (22-533)
% above 240	50.6	55.9	50	50	50

Abbreviations: DVTd = Daratumumab + Bortezomib + Thalidomide + Dexamethasone; ISS = International Staging System; VTd = Bortezomib + Thalidomide + Dexamethasone; VCd-LEN-2Y = bortezomib, cyclophosphamide and dexamethasone + lenalidomide maintenance for 2 years; ECOG = Eastern Cooperative Oncology Group; WHO = World Health Organization; LDH = Lactic acid dehydrogenase; LCD = light-chain disease

‡ Source: Baseline characteristics for the VCd arm were extracted from Mai et al. 2015.

*There is a small discrepancy between the 1st and the 2nd data-cut for VTd. The discrepancy is due to the fact that one patient had different baseline creatine value in for the 2nd data-cut in the VTd arm. This affected the derivation of renal insufficiency, the final ESS and the proportions before and after of other unmatched characteristics such as anemia. For the variable renal insufficiency (creatinine >177 µmol/L): 1st data-cut 0.2% before matching and 0.2% after matching vs. 0.4% before matching and 0.4% after matching for the 2nd data-cut. For the variable anemia (Hb <10 g/dL or 2 g/dL <normal): 1st data-cut 50.6% after matching and 50.5% after matching for the 2nd data-cut. However, this is only related to VTd.

Excluded from MAIC analysis: Anemia was excluded from the base case MAIC due to lack of overlap (or similarity) in the reported values between GMMG-MM5 and CASSIOPEIA, resulting in substantial effective sample size (ESS) reduction (51% for DVTd and 50% for VTd) after matching. Based on clinical feedback, it was determined that anemia was not a critical aspect of prognosis compared to other factors and could be excluded from the base case analysis; mean hemoglobin concentration and platelet count were adjusted instead. Beta-2 macroglobulin was not reported in primary publication, so not matched in MAIC analysis

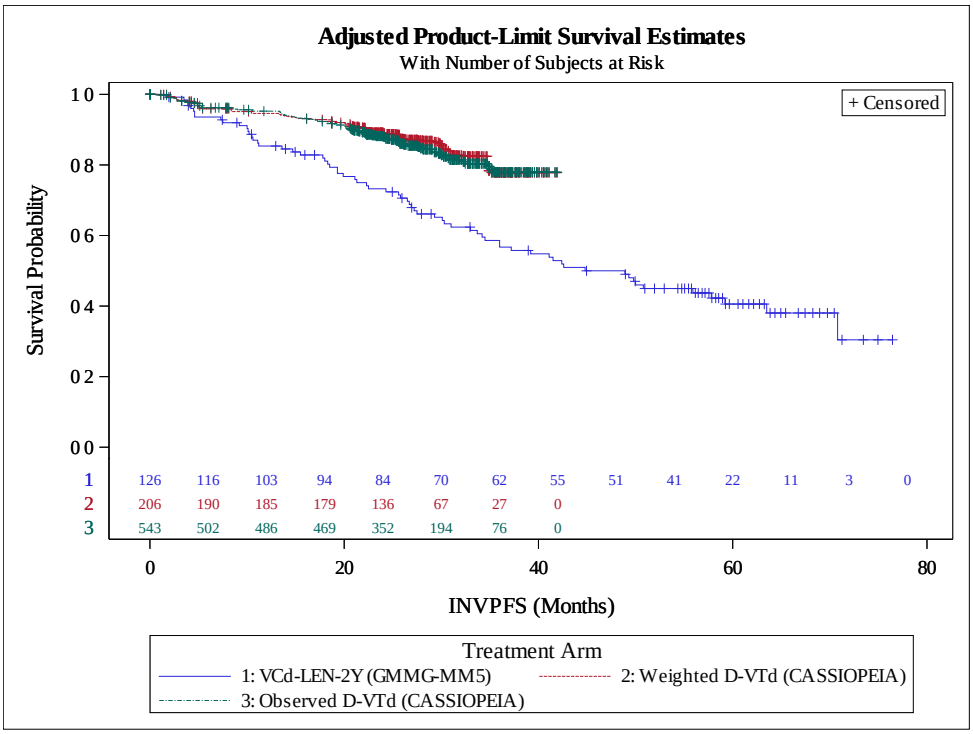
Of note, as there was only 1 patient in each arm in CASSIOPEIA with renal insufficiency, this baseline characteristic could not be adjusted for. Differences in LDH between the two studies also posed a concern about potential substantial ESS reductions. LDH was based on local lab in CASSIOPEIA, whereas in GMMG-MM5(121, 139), it was not reported. There is no uniform upper limit of normal (ULN) for LDH. However, based on clinical feedback, it was determined that LDH was an important prognostic factor and should be included in the matching model.

18.2.2.1 PFS for DVTd/VTd Before and After Adjustment vs. VCd

For DVTd vs. VCd-LEN-2Y, there was a statistically significant difference in PFS before and after matching in the analysis (Figure 27). For VTd vs. VCd-LEN-2Y, there was no statistically significant difference in PFS before and after matching in the analysis (Figure 28).

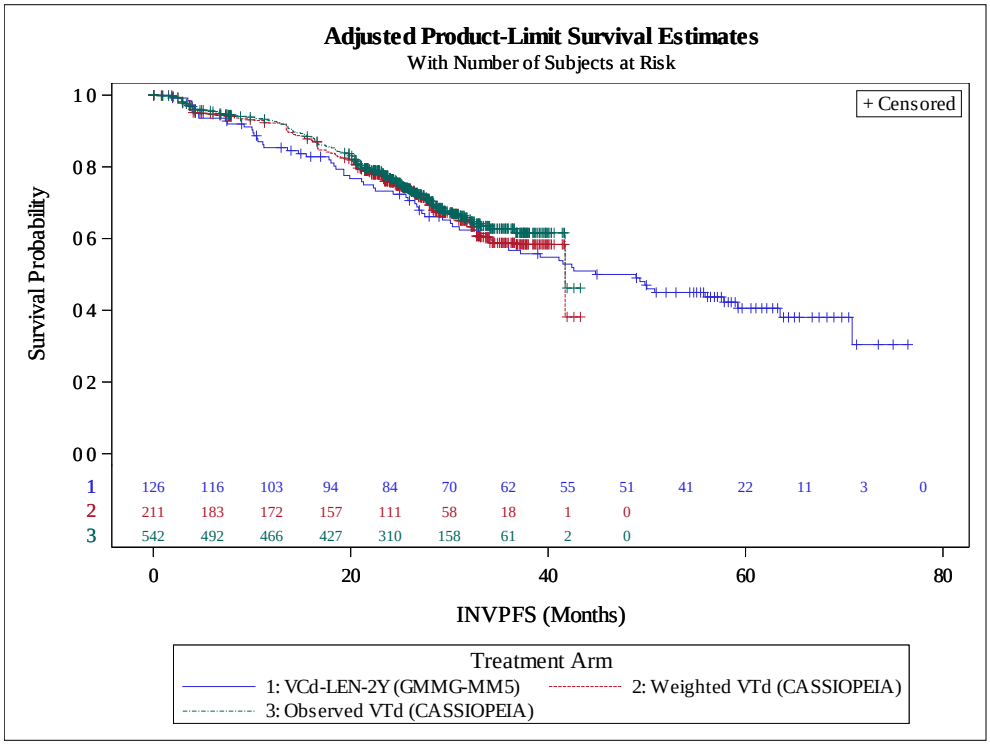
Table 104 presents a summary of the PFS HR point estimates before and after adjustment for DVTd/VTd vs VCd-LEN-2Y.

Figure 27. PFS for DVTd before and after Adjustment vs. VCd-LEN-2Y



Abbreviations: DVTd = Daratumumab + bortezomib + thalidomide + dexamethasone; INV PFS =Investigator Progression Free Survival; VCd-LEN-2Y = Bortezomib + cyclophosphamide + dexamethasone (VCd) followed by lenalidomide consolidation and lenalidomide maintenance for 2 years

Figure 28. PFS for VTd before and after Adjustment vs. VCd-LEN-2Y



Abbreviations: INV PFS =Investigator Progression Free Survival; VCd-LEN-2Y = Bortezomib + cyclophosphamide + dexamethasone (VCd) followed by lenalidomide consolidation and lenalidomide maintenance for 2 years; VTd = Bortezomib + thalidomide + dexamethasone

Table 104 PFS for DVTd/VTd before and after Adjustment vs. VCd

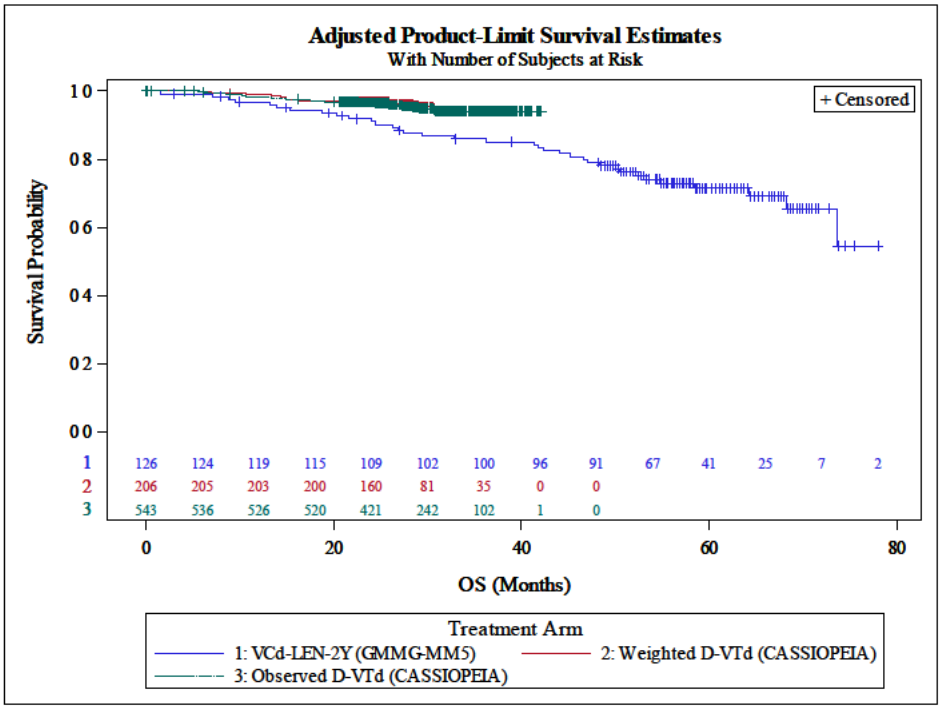
Analysis	VCd-LEN-2Y		DVTd vs. VCd-LEN-2Y				VTd vs. VCd-LEN-2Y			
	N	Median for VCd (months)	N/ESS	Median for DVTd (Months)	HR (95% CI)	p-value	N/ESS	Median for VTd (Months)	HR (95% CL)	p-value
Naïve comparison	126	44.8	543	NE	0.43 (0.30 – 0.60)	**<.0001**	542	41.7	0.85 (0.62 - 1.17)	0.3191
MAIC (Base Case)			206	NE	0.40 (0.26 - 0.61)	**<.0001**	211	41.7	0.93 (0.64 – 1.35)	0.6881

Abbreviations: DVTd = Daratumumab + Bortezomib + Thalidomide + Dexamethasone; ESS = Effective sample size; CI = Confidence interval; VTd = Bortezomib + Thalidomide + Dexamethasone; HR = Hazard ratio; VCd = Bortezomib + cyclophosphamide + dexamethasone; VCd-LEN-2Y = bortezomib, cyclophosphamide and dexamethasone + lenalidomide maintenance for 2 years; ESS = Effective sample size

18.2.2.2 OS for DVTd/VTd Before and After Adjustment vs VCd

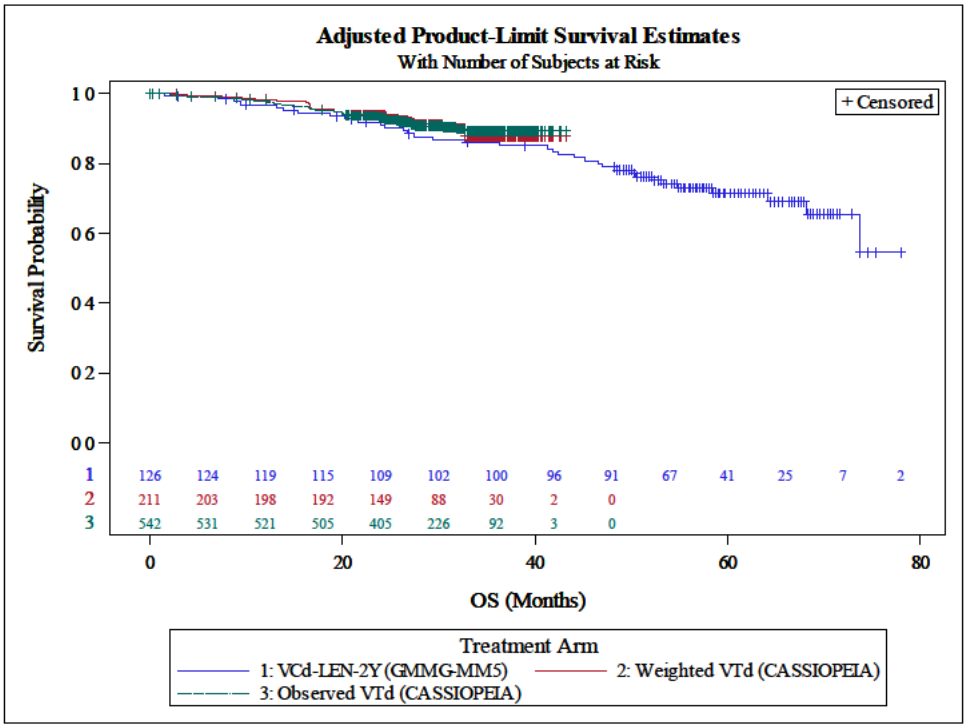
For DVTd vs. VCd-LEN-2Y, there was a statistically significant difference in OS before and after matching in the analysis (Figure 29). For VTd vs. VCd-LEN-2Y, there was no statistically significant difference in OS before and after matching in the base case (Figure 30). Table 105 presents a summary of the OS HR point estimates before and after adjustment for DVTd/VTd vs VCd-LEN-2Y.

Figure 29. OS for DVTd before and after Adjustment vs. VCd-LEN-2Y



Abbreviations: DVTd = Daratumumab + Bortezomib + Thalidomide + Dexamethasone; VCd-LEN-2Y = bortezomib, cyclophosphamide and dexamethasone + lenalidomide maintenance for 2 years

Figure 30. OS for VTd before and after Adjustment vs. VCd-LEN-2Y



Abbreviations: OS = Overall survival; VTd = Bortezomib + Thalidomide + Dexamethasone; VCd-LEN-2Y = bortezomib, cyclophosphamide and dexamethasone + lenalidomide maintenance for 2 years

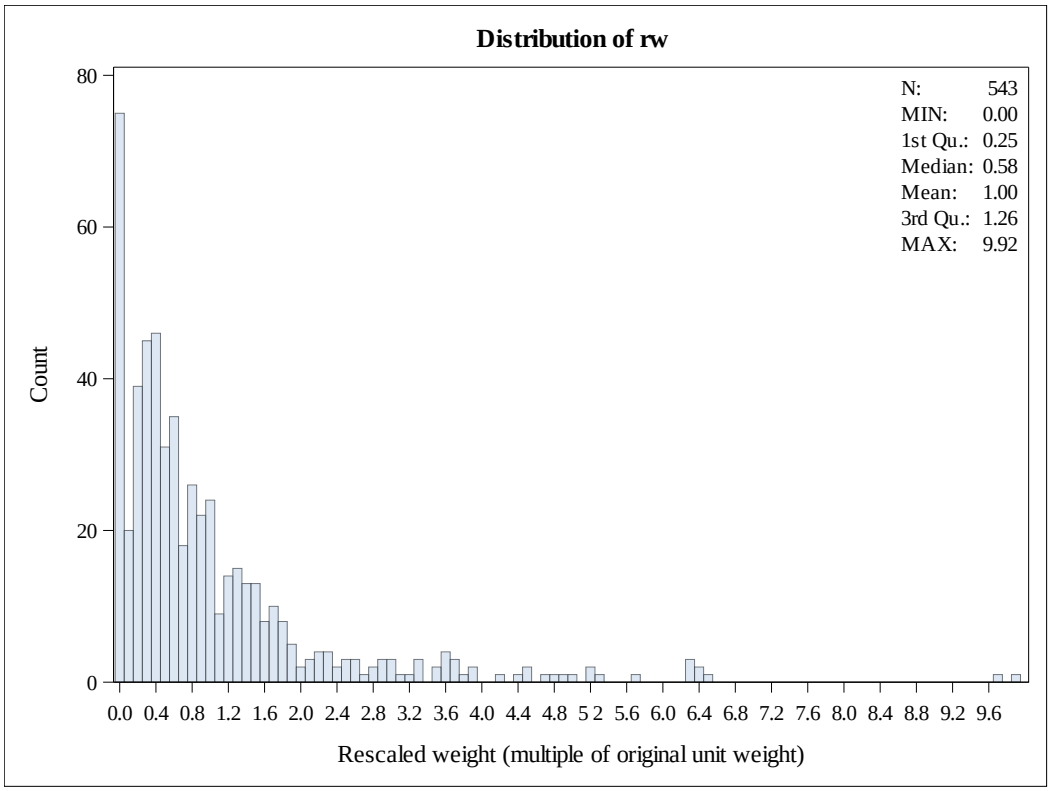
Table 105 OS for DVTd/VTd before and after Adjustment vs. VCd

Analysis	VCd-LEN-2Y		DVTd vs. VCd-LEN-2Y				VTd vs. VCd-LEN-2Y			
	N	Median for VCd (months)	N/ESS	Median for DVTd (Months)	HR (95% CI)	p-value	N/ESS	Median for VTd (Months)	HR (95% CL)	p-value
Naïve comparison	126	NR	543	NE	0.39 (0.21 - 0.71)	**0.0023**	542	NE	0.72 (0.42 - 1.24)	0.2338
MAIC (Base Case)			206	NE	0.37 (0.18 – 0.76)	**0.0064**	211	NE	0.77 (0.40 – 1.47)	0.4295

Abbreviations: CI = Confidence interval; DVTd = Daratumumab + Bortezomib + Thalidomide + Dexamethasone; VTd = Bortezomib + Thalidomide + Dexamethasone; MAIC = Matching-adjusted indirect comparison; HR = Hazard ratio; VCd = Bortezomib + cyclophosphamide + dexamethasone; VCd-LEN-2Y = bortezomib, cyclophosphamide and dexamethasone + lenalidomide maintenance for 2 years; ESS = Effective sample size

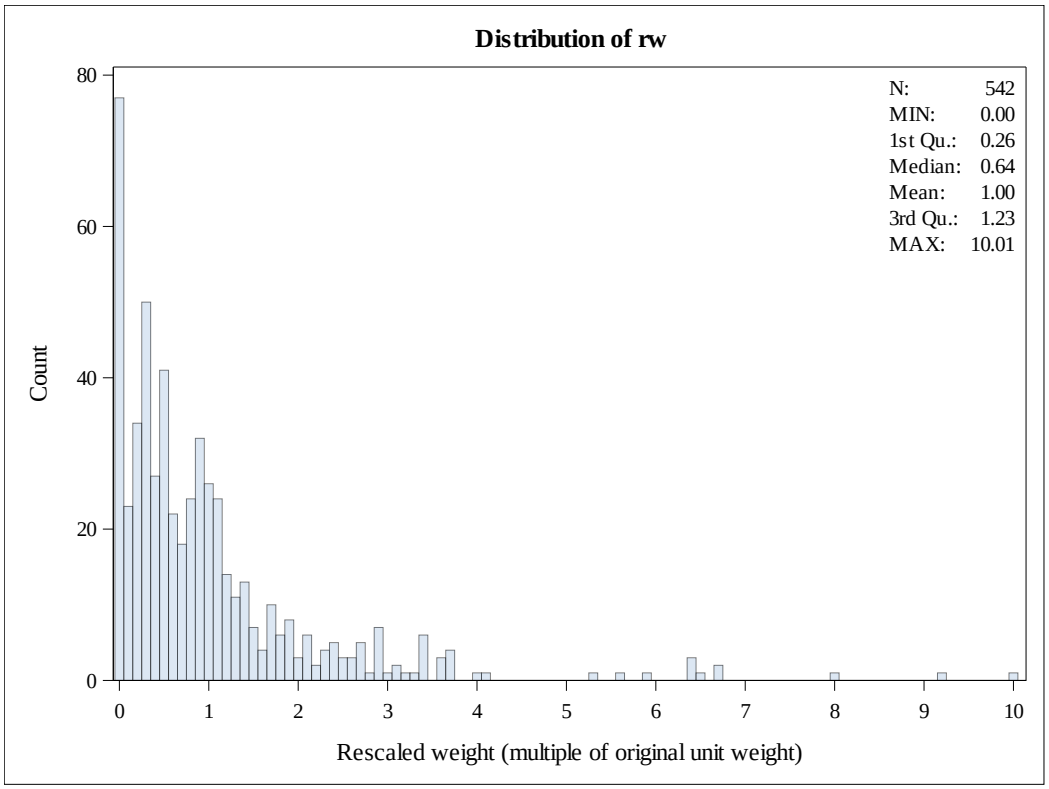
18.2.3 Supplementary MAIC information (DVTd/VTd vs. VCd)

Figure 31. DVTd vs VCd-LEN-2Y Effective Sample Size and Rescaled Weight (RW) Distribution



Abbreviations: DVTd = Daratumumab + Bortezomib + Thalidomide + Dexamethasone; VCd-LEN-2Y = bortezomib, cyclophosphamide and dexamethasone + lenalidomide maintenance for 2 years;

Figure 32. VTd vs VCd-LEN-2Y Effective Sample Size and Rescaled Weight (RW) Distribution



Abbreviations: VTd = Bortezomib + Thalidomide + Dexamethasone; VCd-LEN-2Y = bortezomib, cyclophosphamide and dexamethasone + lenalidomide maintenance for 2 years;

18.3 DVTd compared to VRd for NDMM patients who are transplant-eligible

Table 106 MAIC results of studies comparing DVTd to VRd for NDMM patients who are transplant eligible

Analysis		DVTd vs VRd + ASCT			Method used for quantitative synthesis	Result used in the health economic analysis?
		HR	95% CI	P-value		
*Overall survival**	Naïve	0.39	0.24-0.62	<.001	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The regression coefficients derived from the Cox model provide estimates of the hazard ratios (HR) with two sides 95% confidence intervals (CI)	No
	Base case analysis	0.40	0.25-0.64	<.001	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The adjusted HR was obtained using a weighted Cox regression analysis with a robust sandwich estimator for calculation of the standard errors.	Yes
	Sensitivity analysis	0.31	0.16-0.57	<.001		No
*Progression-free survival**	Naïve	0.50	0.38-0.67	<.001	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The regression coefficients derived from the Cox model provide estimates of the hazard ratios (HR) with two sides 95% confidence intervals (CI)	No
	Base case analysis	0.50	0.38-0.67	<.001	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The adjusted HR was obtained using a weighted Cox regression analysis with a robust sandwich estimator for calculation of the standard errors.	Yes
	Sensitivity analysis	0.47	0.33-0.69	<.001		No

Abbreviations: ASCT = Autologous stem cell transplant; CI = Confidence interval; DVTd = Daratumumab + Bortezomib + Thalidomide + Dexamethasone; HR = Hazard ratio; NDMM = Newly diagnosed multiple myeloma; VRd = Bortezomib + lenalidomide + dexamethasone
Note: median follow-up time for CASSIOPEIA is 29.2 months in base case analysis, and 18.8 months in the sensitivity analysis
* In the MAIC for efficacy outcomes, the intention to treat (ITT) population was used (n= 543).

Table 107 MAIC results of studies comparing VTd to VRd for NDMM patients who are transplant eligible

Analysis		VTd vs VRd + ASCT			Method used for quantitative synthesis	Result used in the health economic analysis?
		HR	95% CI	P-value		
*Overall survival**	Naïve	0.72	0.48-1.07	0.100	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The regression coefficients derived from the Cox model provide estimates of the hazard ratios (HR) with two sides 95% confidence intervals (CI)	No
	Base case analysis	0.78	0.53-1.16	0.100	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The adjusted HR was obtained using a weighted Cox regression analysis with a robust sandwich estimator for calculation of the standard errors.	Yes
	Sensitivity analysis	0.82	0.51-1.32	0.419‡		No
*Progression-free survival**	Naïve	0.99	0.78-1.26	0.963	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The regression coefficients derived from the Cox model provide estimates of the hazard ratios (HR) with two sides 95% confidence intervals (CI)	No
	Base case analysis	1.04	0.82-1.32	0.755	The relative effect was quantified as a hazard ratio (HR) with a 95% CI. The adjusted HR was obtained using a weighted Cox regression analysis with a robust sandwich estimator for calculation of the standard errors.	Yes
	Sensitivity analysis	1.13	0.84-1.53	0.419‡		No

Abbreviations: ASCT = Autologous stem cell transplant; CI = Confidence interval; HR = Hazard ratio; MAIC = Matching-adjusted indirect comparison; NDMM = Newly diagnosed multiple myeloma; VRd = Bortezomib + lenalidomide + dexamethasone; VTd = Bortezomib + thalidomide + dexamethasone
* In the MAIC for efficacy outcomes, the intention to treat (ITT) population was used (n= 543).

‡Noninferior: identified as HR of 1.333 for PFS and 1.298 for OS.(8)
Note: median follow-up time for CASSIOPEIA is 29.2 months in base case analysis, and 18.8 months in the sensitivity analysis

18.3.1 Statistical methods

A MAIC analysis was performed, which aims to weight individual patients in CASSIOPEIA's treatment arms (each arm compared separately) with regards to their characteristics to match those in the VRd + ASCT arm (referred to as VRd in this section). This is an unanchored indirect comparison since no pairwise comparison was published in the literature, and data availability didn't allow to conduct one. All available effects modifiers and prognostic factors were included, and the R code published by the NICE was used to conduct the analysis(276). A weight was attached to every patient in CASSIOPEIA's treatment arms based on observed characteristics. These weights were then used to calculate weighted outcomes.

The variables used in the MAICs are:

- Median age (year)
- Male (%)
- Patients with IgG Myeloma (%)
- ISS staging (%)

With regards to the comparison of DVTd + ASCT/VTd + ASCT vs VRd + ASCT, the MAIC analyses were run separately for efficacy and safety outcomes. In the MAIC for efficacy outcomes, the intention to treat (ITT) population was used (n= 543). For safety endpoint, the safety population was used (n= 538).

There were differences between the CASSIOPEIA and IFM 2009 studies that were not possible to adjust for. This includes differences in treatment cycles, length of follow-up, and maintenance therapy, detailed information has been presented in the limitation section.

Each patient in the IPD dataset is assigned a weight. The minimum weight is always above zero and the mean weight in the data sets equals to one. These weights are used to estimate the MAIC. For the IPD, the observed endpoint results per patient are evaluated using the assigned weight. As for the comparator, all patients receive a weight of one.

Table 111 presents a summary of the effective sample size (ESS), an average of individual weights, and the distribution of individual (rescaled) weights for all MAIC analyses. The effective sample size (ESS) is the number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample estimate. Weighting always reduces the effective sample size. When the ESS is markedly reduced, or the weights are highly variable, estimates become unstable and inferences depend heavily on just a small number of individuals. In all analyses, no marked reduction in the ESS nor any extreme weights were seen. This is most likely because the observed baseline characteristics are similar between treatment arms.

18.3.2 MAIC analysis results

Table 108 presents the baseline characteristics before and after matching DVTd/VTd (CASSIOPEIA) to VRd (IFM2009).(8)

After matching, no marked reduction in the ESS nor any extreme weights were seen. This is most likely because the observed baseline characteristics are similar between treatment arms. A summary of the effective sample size (ESS), an average of individual weights, and the distribution of individual (rescaled) weights for MAIC analyses can be found in section 18.3.3, Table 111.

Table 108 Baseline characteristics before and after matching adjustment of DVTd and VTd to VRd(6, 8)

Characteristics	Before matching adjustment		After matching adjustment		VRd + ASCT (N=350)
	DVTd (N=543)	VTd (N=542)	DVTd (ESS = 529)	VTd (ESS = 515)	
Age (years), median	59	58	60	60	60
Male, %	58.2	58.9	61.1	61.1	61.1

ISS stage, n (%)					
I	37.6	42.1	33.7	33.7	33.7
II	47.0	43.0	48.9	48.9	48.9
III	15.4	14.9	17.4	17.4	17.4
Myeloma type, %					
IgG	64.6	61.4	63.7	63.7	63.7
Others	35.4	38.6	36.3	36.3	36.3

DVTd: Daratumumab + Bortezomib + Thalidomide + Dexamethasone; ESS: effective sample size; IFM: Intergroupe Francophone du Myélome; IgG: immunoglobulin G; ISS: International Staging System; MAIC = Matching-adjusted indirect comparison; VRd: bortezomib, lenalidomide and dexamethasone; VTd: bortezomib + thalidomide + dexamethasone

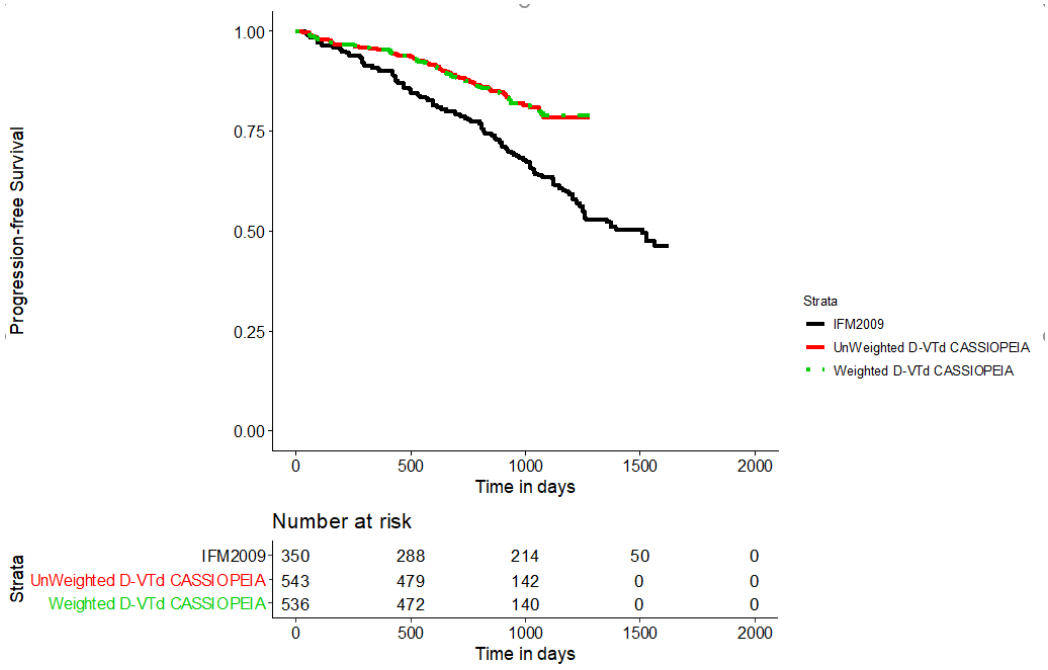
Not reported in primary publication, so not matched in MAIC analysis: ECOG/WHO performance status, Hemoglobin level, Platelets level, Calcium level, Calcium elevation (> 2.65 mmol/L), Bone disease (lytic lesions), Creatinine level, Renal insufficiency (creatinine > 177 µmol/L), Anemia, LDH level, Beta-2 macroglobulin

Excluded from MAIC analysis: cytogenetic abnormalities. Cytogenetic abnormalities were excluded from the primary analysis for two reasons: 1. t(14;16) translocation was not tested for in CASSIOPEIA but tested for in IFM 2009; 2: Relatively more patients in the IFM 2009 were not tested for cytogenetic abnormalities compared to CASSIOPEIA. In the IFM 2009 study, 26.0% of patients were not tested for t(4;14) translocation and 26.3% were not tested for 17p deletion. In CASSIOPEIA, 7.7% and 7.2% of patients were not tested for both t(4;14) translocation and 17p deletion in the DVTd + ASCT and VTd + ASCT arms, respectively.

18.3.2.1 PFS for DVTd/VTd Before and After Adjustment vs VRd

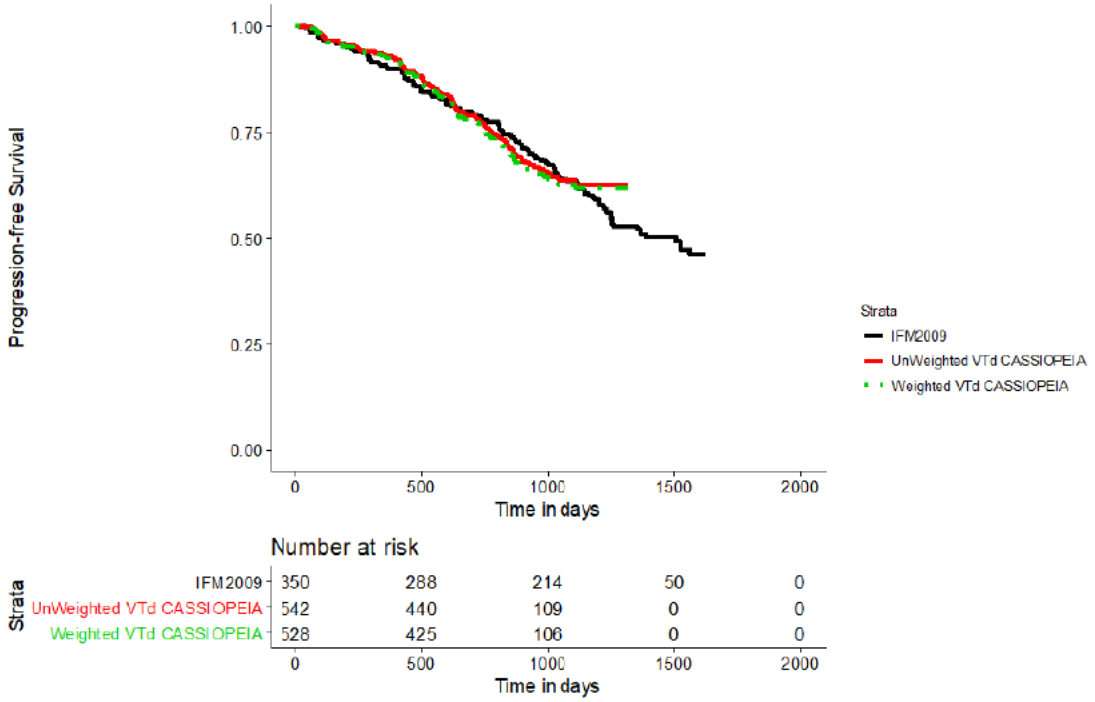
For DVTd vs. VRd + ASCT, there was a statistically significant difference in PFS before and after matching in the analysis (Figure 33). For VTd vs. VRd + ASCT, there was no statistically significant difference in PFS before and after matching in the analysis (Figure 34). Table 109 presents a summary of the PFS HR point estimates before and after adjustment for DVTd/VTd vs. VRd + ASCT.

Figure 33 PFS for DVTd before and after Adjustment vs. VRd



Abbreviations: DVTd = daratumumab + bortezomib + thalidomide + dexamethasone; PFS = Progression-free survival; VRd = Bortezomib + lenalidomide + dexamethasone; IFM2009: Reflecting VRd + ASCT arm

Figure 34 PFS for VTd before and after Adjustment vs. VRd



Abbreviations: PFS = Progression-free survival; VRd = Bortezomib + lenalidomide + dexamethasone; VTd = Bortezomib + thalidomide + dexamethasone; IFM2009: Reflecting VRd + ASCT arm

Table 109 PFS for DVTd/VTd before and after Adjustment vs VRd

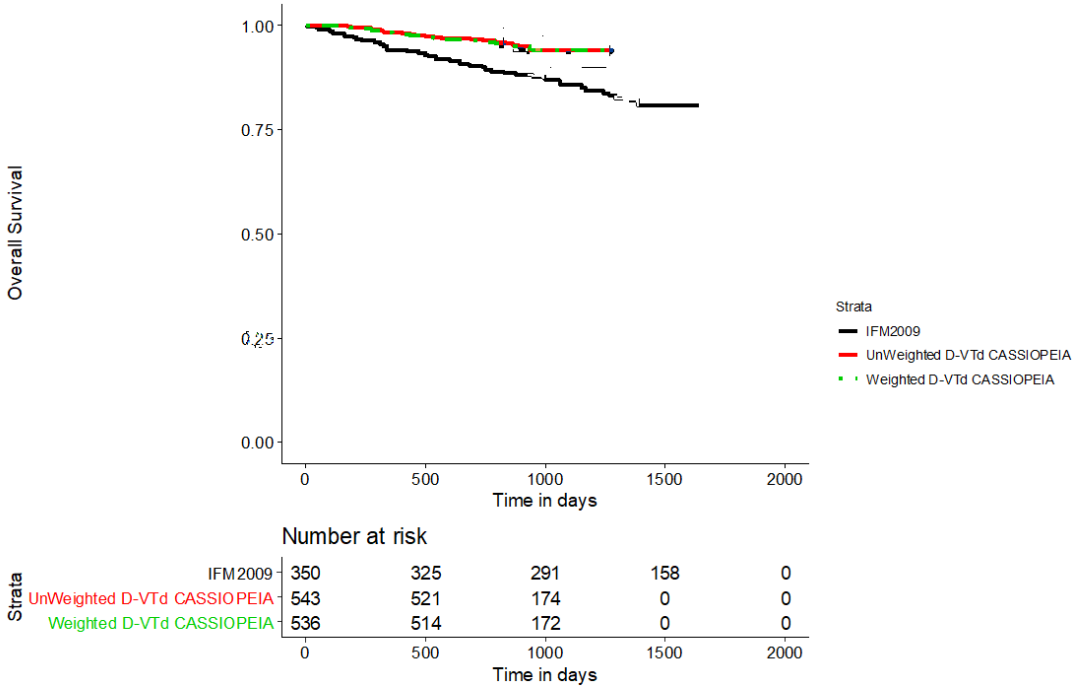
Analysis	VRd + ASCT	DVTd vs. VRd + ASCT			VTd vs. VRd + ASCT		
	N	N/ESS	HR (95% CI)	Score (log-rank) test, p-value	N/ESS	HR (95% CL)	Score (log-rank) test, p-value
Naïve comparison	350	543	0.504 (0.381-0.665)	**< 0.001**	542	0.994 (0.784-1.261)	0.963
MAIC (Base Case)		529	0.504 (0.381-0.666)	**< 0.001**	515	1.038 (0.820-1.315)	0.755

Abbreviations: ASCT = Autologous stem cell transplant; DVTd = Daratumumab + Bortezomib + Thalidomide + Dexamethasone; CI: Confidence interval; HR = Hazard ratio; VTd = bortezomib + thalidomide + dexamethasone; MAIC = Matching-adjusted indirect comparison; VRd = bortezomib + lenalidomide + dexamethasone ESS = Effective sample size

18.3.2.2 OS for DVTd/VTd Before and After Adjustment vs VRd

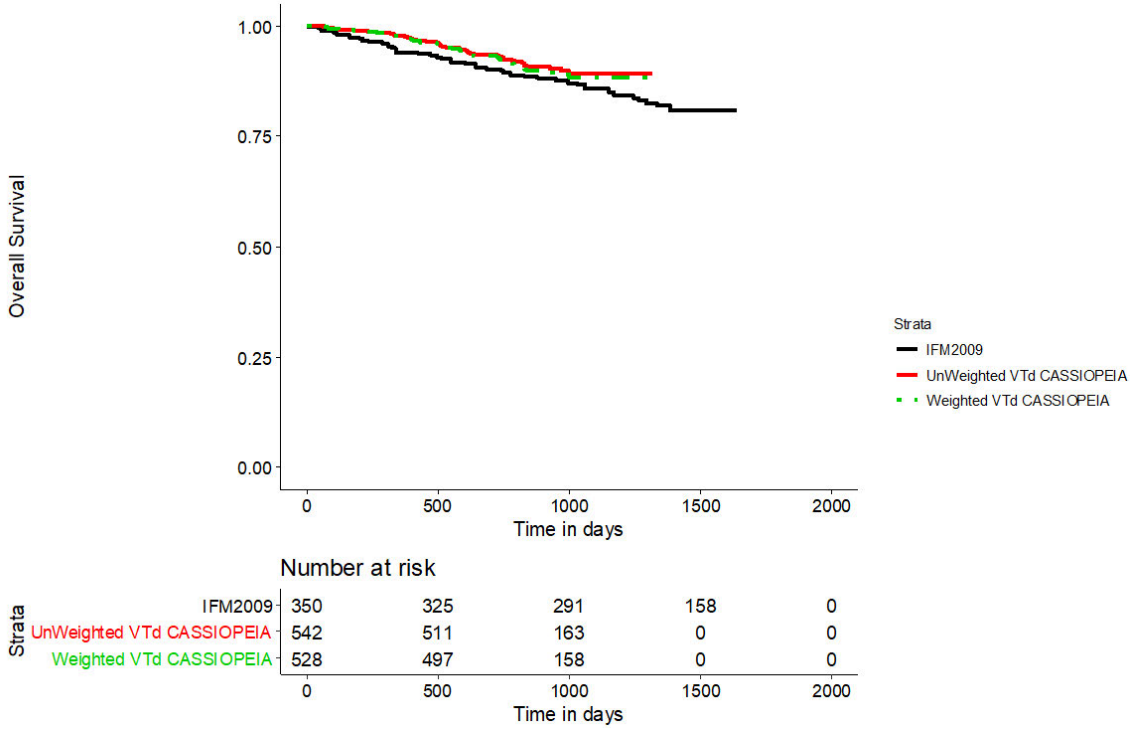
For DVTd vs. VRd + ASCT, there was a statistically significant difference in OS before and after matching in the analysis (Figure 35). For VTd vs. VRd + ASCT, there was no statistically significant difference in OS before and after matching in the base case (Figure 36). Table 105 presents a summary of the OS HR point estimates before and after adjustment for DVTd/VTd vs VRd + ASCT.

Figure 35 OS for DVTd before and after Adjustment vs. VRd



Abbreviations: DVTd = daratumumab + bortezomib + thalidomide + dexamethasone; OS = Overall survival; VRd = Bortezomib + lenalidomide + dexamethasone; IFM2009: Reflecting VRd + ASCT arm

Figure 36 OS for VTd before and after Adjustment vs. VRd



Abbreviations: VTd = bortezomib + thalidomide + dexamethasone; OS = Overall survival; VRd = Bortezomib + lenalidomide + dexamethasone; IFM2009: Reflecting VRd + ASCT arm

Table 110 OS for DVTd/VTd before and after Adjustment vs VRd

Analysis	VRd + ASCT	DVTd vs. VRd + ASCT			VTd vs. VRd + ASCT		
	N	N/ESS	HR (95% CI)	Score (log-rank) test, p-value	N/ESS	HR (95% CL)	Score (log-rank) test, p-value
Naïve comparison	350	543	0.386 (0.239-0.622)	**< 0.001**	542	0.721 (0.484-1.074)	0.100
MAIC (Base Case)		529	0.399 (0.249-0.641)	**< 0.001**	515	0.783 (0.529-1.159)	0.100

Abbreviations: DVTd = Daratumumab + Bortezomib + Thalidomide + Dexamethasone; VTd = bortezomib + thalidomide + dexamethasone; VRd = bortezomib + lenalidomide + dexamethasone ESS = Effective sample size; OS = Overall survival; HR = Hazard ratio; CI: Confidence interval

18.3.3 Supplementary MAIC information (DVTd/VTd vs. VRd)

Table 111 Overview of ESS and weights distribution after the MAIC (DVTd/VTd vs. VRd)

Comparison	DVTd vs VRd + ASCT	VTd vs VRd + ASCT
Sample size	543	542
Effective sample size	529.3	514.9
Average of individual weights	0.987	0.974
Sum of weights	536.1	528
Distribution of individual (rescaled) weights		
Min.	0.7437	0.6371
1st Qu.	0.8765	0.8608
Median	0.9589	0.9951
Mean	1	1
3rd Qu.	1.1302	1.1859
Max.	1.3602	1.4303

Abbreviations: ASCT = autologous stem cell transplant; DVTd= daratumumab plus bortezomib, thalidomide, and dexamethasone; ESS = Effective sample size; MAIC = Matching-adjusted indirect comparison; VTd = bortezomib, thalidomide, and dexamethasone; VRd = bortezomib, lenalidomide, and dexamethasone

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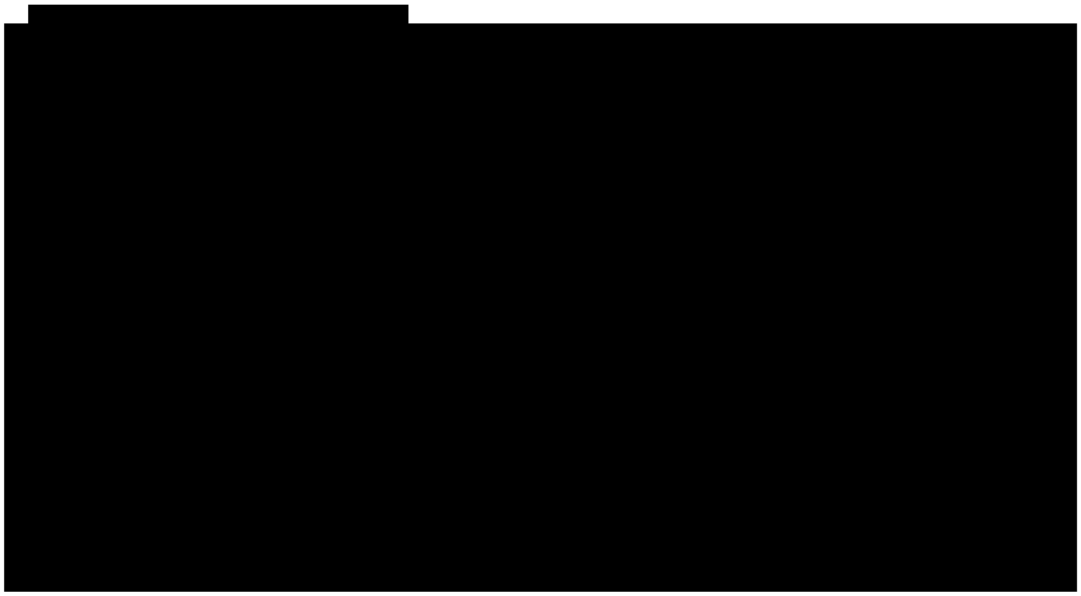

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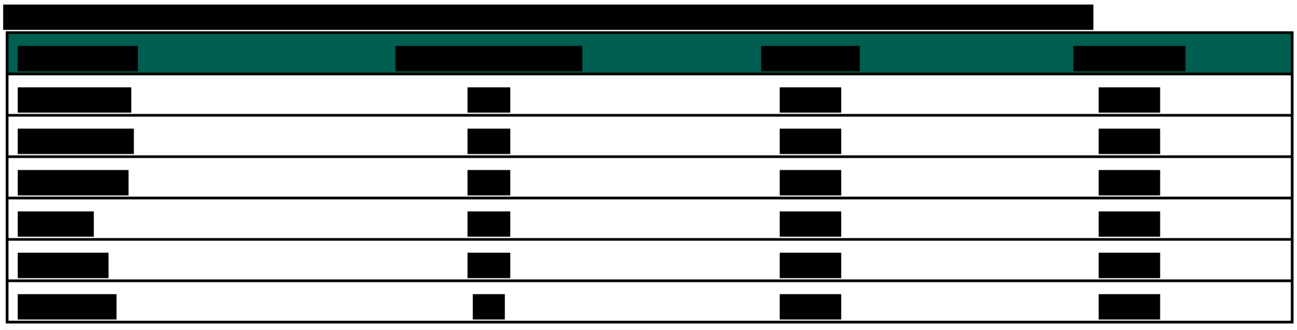

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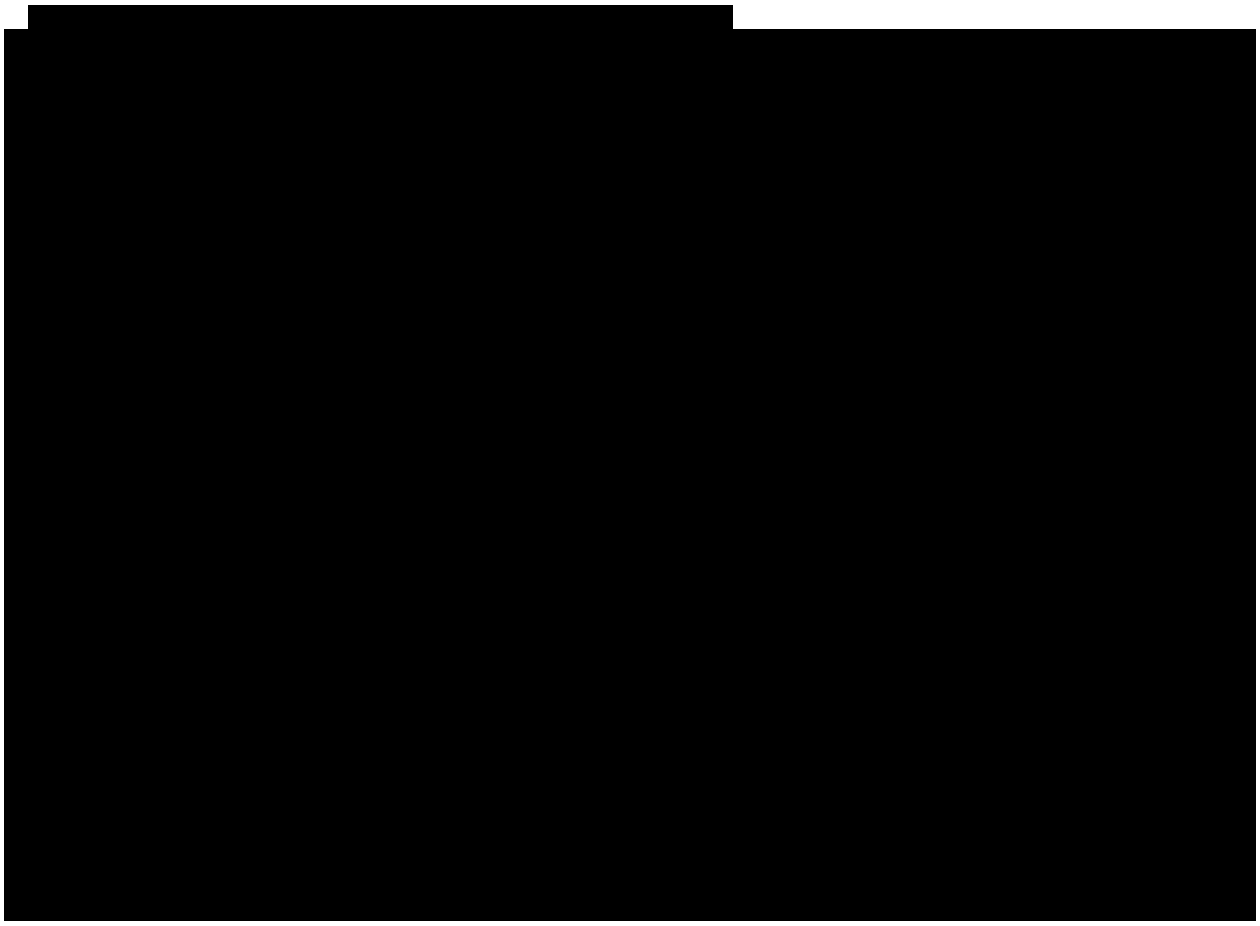

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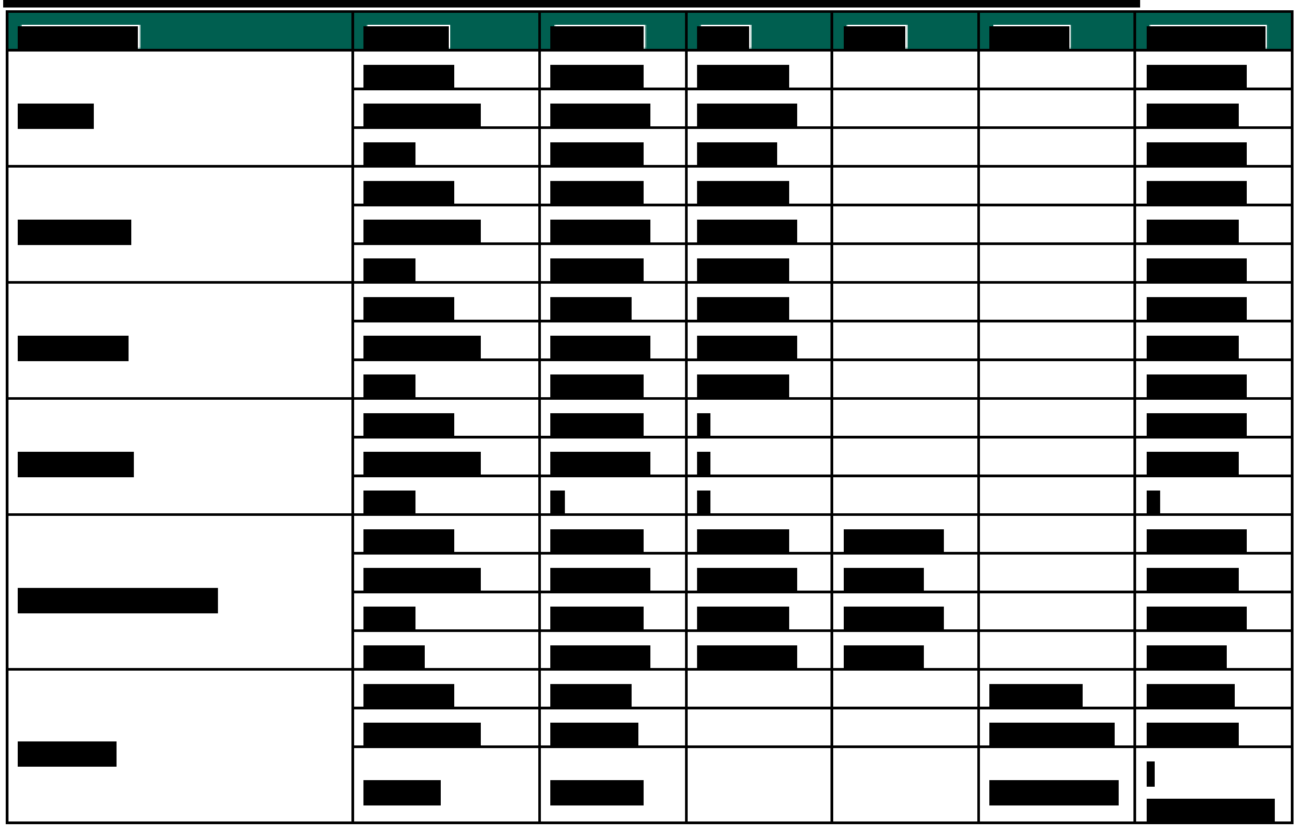

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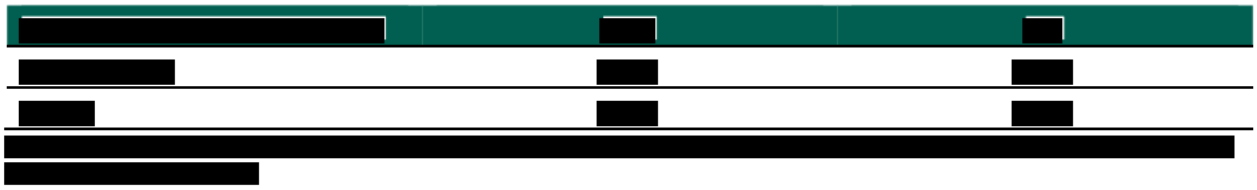

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20. Appendix H – Literature search for HRQoL data

20.1 Objective of the literature search:

The SLR aimed to address the following research question:

- What is the humanistic burden (e.g., HRQoL, utility, caregiver burden) associated with NDMM, particularly in transplant-eligible patients?

20.2 Databases:

Searches were performed in the following indexed databases on May 2018, May 2020, and November 2020 to identify studies published since 1995, as required by most health technology assessment (HTA) bodies (Table 138).

- MEDLINE and MEDLINE In-Process (via PubMed)
- Embase (via embase.com)
- DARE; archive database only (via the Cochrane Library)
- NHS-EED; archive database only (via the Cochrane Library)
- EconLit.

Key proceedings from 2015 were reviewed for relevant abstracts from the following conferences (Table 138).

- American Society of Clinical Oncology (ASCO) Annual Meetings
- American Society of Hematology (ASH) Annual Meetings
- European Hematology Association (EHA) Annual Meetings
- International Myeloma Working Group (IMWG) Biannual International Workshops
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR), Annual International Meetings and European Congresses.

Search of the following HTA bodies to identify relevant humanistic data from technology appraisals (TA) published in English were also conducted. Data from HTA documents were used to supplement the findings from the peer-reviewed publications and fill any evidence gaps where possible.

- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Institute of Health Carlos III (ISCIII)
- Institute for Quality and Efficiency in Health Care (IQWiG)
- Italian Medicines Agency (AIFA)
- Haute Autorité de Santé (HAS)
- National Institute for Health and Care Excellence (NICE)
- Pharmaceutical Benefits Advisory Committee (PBAC)
- Scottish Medicines Consortium (SMC)

Table 138 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	1995-2018	24.04.2018 (Initial SLR)
		2018-04.29.2020	07.05.2020 (1st update)
		01.04.2020 – 02.11.2020	12.11.2020 (2nd update)
MEDLINE and MEDLINE In-Process	Pubmed.ncbi.nlm.nih.gov	1995-2018	24.04.2018 (Initial SLR)
		2018-04.29.2020	07.05.2020 (1st update)
		01.04.2020 – 02.11.2020	12.11.2020 (2nd update)
Cochrane Central Register of Controlled Trials	cochranelibrary.com	1995-2018	13.03.2018 (Initial SLR)
Cochrane Database of Systematic Reviews	cochranelibrary.com	1995-2018	13.03.2018 (Initial SLR)
EconLit	Ovid	1995-2018	24.04.2018 (Initial SLR)
		2018-04.30.2020	30.04.2020 (1st update)
		01.04.2020 – 02.11.2020	02.11.2020 (2nd update)
ASCO	Embase.com	2015-2017	31.05.2018 (Initial SLR)
		2018-2020	07.05.2020 (1st update)
		2020	12.11.2020 (2nd update)
ASH	Embase.com	2015-2017	31.05.2018 (Initial SLR)
		2018-2020	07.05.2020 (1st update)
		2020	12.11.2020 (2nd update)
EHA	Embase.com	2015-2017	31.05.2018 (Initial SLR)
		2018-2020	07.05.2020 (1st update)
		2020	12.11.2020 (2nd update)
IMWG	Embase.com	2015-2017	31.05.2018 (Initial SLR)
		2018-2020	07.05.2020 (1st update)
		2020	12.11.2020 (2nd update)
ISPOR	Embase.com	2015-2017	31.05.2018 (Initial SLR)
		2018-2020	07.05.2020 (1st update)
		2020	12.11.2020 (2nd update)

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Abbreviations: SLR, systematic literature review; ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; EHA, European Hematology Association; ESMO, European Society for Medical Oncology; IMWG, International Myeloma Working Group; ispor, International Society for Pharmacoeconomics and Outcomes Research

20.3 Search strategy

20.3.1 PICOS

Studies were initially screened and selected for inclusion based on the Population, Intervention, Comparison, Outcome, Study Design (PICOS) criteria outlined in Table 139.

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 were 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 were resolved by a third investigator.

Table 139 PICOS-T Selection Criteria for HRQoL

Category	Inclusion Criteria	Exclusion Criteria
Population	Patients with NDMM, particularly the transplant-eligible population	Patients without a primary diagnosis of MM or previously treated MM patients
Interventions/ Comparators	Not restricted by intervention or comparator Where applicable, licensed pharmacological treatment, standard of care/best supportive care, or pharmacological treatment under investigation will be included. Humanistic burden related to NDMM in general, not specific to any intervention	Studies that report on HRQoL for non-pharmacological treatment or treatments not considered standard of care/best supportive care
Outcomes	HRQoL Utilities/disutilities Caregiver burden	Publications that do not report on humanistic outcomes
Study design	Observational/real-world studies[a]	Case reports, comments and editorials, animal/in-vitro studies, RCTs that do not report humanistic outcomes, and SLRs published prior to 2015
Date limit*	Abstracts and other material from conferences from the last three years/meetings (from 2015 onwards) Publications indexed in the databases from 2008 onwards	Conference abstracts or materials presented prior to 2015 Publications indexed in 2007 or earlier

* Date limit for initial SLR and the two updates

a Please note, RCTs were not specifically searched as part of this SLR; however, RCTs reporting HRQoL identified by the searches were included in this application.

Abbreviations: HCRU = healthcare resource use; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; MM = multiple myeloma; NDMM = newly diagnosed multiple myeloma; PICOS-T = Population, Intervention, Comparison, Outcome, Study Design, and Time; QALY = quality-adjusted life-year; RCT = randomized controlled trial; SLR = systematic literature review

20.3.2 Search syntaxes:

MEDLINE AND MEDLINE® via PubMed)

Table 140. MEDLINE and MEDLINE® Search Strategy

Search Criteria	Search Algorithm	Search Yield (Apr 24, 2018)	Search Yield (May 7, 2020)	Search Yield (Nov 02, 2020)
1	("Multiple Myeloma"[MeSH] OR ("multiple"[TIAB] AND myelom*[TIAB]) OR "plasma cell myeloma"[TIAB] OR "Kahler's disease"[TIAB] OR "Plasmacytoma"[MeSH] OR plasmacytom*[TIAB])	60,028	60,143	61,863
2	("naïve"[TIAB] OR (new*[TIAB] AND diagnos*[TIAB]) OR "untreated"[TIAB] OR (("primary"[TIAB] OR "initial"[TIAB] OR "induction"[TIAB] OR "naïve"[TIAB]) AND ("therapy"[TIAB] OR "treatment"[TIAB])) OR ("front"[TIAB] OR "first"[TIAB] OR "1st"[TIAB] AND "line"[TIAB]) OR consolidat*[TIAB])	1,496,820	1,500,416	1,490,155^
3	("Quality of Life"[MeSH] OR "QALY"[TIAB] OR "QALYs"[TIAB] OR "Quality-Adjusted Life Years"[MeSH] OR "quality adjusted life year"[TIAB] OR "quality adjusted life years"[TIAB] OR "daly"[TIAB] OR "dalys"[TIAB] OR "disability adjusted life year"[TIAB] OR "disability adjusted life years"[TIAB] OR "Quality of Life"[TIAB] OR "patient reported outcome"[TIAB] OR "patient reported outcomes"[TIAB] OR "satisfaction"[TIAB] OR "utility"[TIAB] OR "utilities"[TIAB] OR "disutility"[TIAB] OR "disutilities"[TIAB] OR disab*[TIAB] OR "functional status"[TIAB] OR "physical function"[TIAB] OR "sf 36"[TIAB] OR "short form 36"[TIAB] OR "sf 12"[TIAB] OR "short form 12"[TIAB] OR "EQ 5D"[TIAB] OR "EuroQOL 5D"[TIAB] OR "EORTC"[TIAB] OR "QLQ"[TIAB] OR ("caregiver"[TIAB] AND "burden"[TIAB]))	872,153	874,657	918,842
4	#1 AND #2 AND #3	521	521	467
5	"Animals"[MeSH] NOT "Humans"[MeSH]	4,693,580	4,697,119	4,756,281
6	"letter"[PT] OR "editorial"[PT]	1,595,549	1,600,146	1,653,290
7	((review[pt]) NOT (systematic OR meta-analy* OR ((indirect OR mixed) AND "treatment comparison")))	2,360,604	2,364,884	2,423,326
8	#4 NOT #5 NOT #6 NOT #7	393	393	393
9	#8 AND Publication date from 2008/01/01 to 2018/03/13	202	-	-
10	#8 AND Publication date from 2018/03/13 to 2020/05/01	-	93	-
11	#4 NOT #5 NOT #6 NOT #7 AND Publication date from 2020/4/1 - 2020/12/31	-	-	26

The limits for this search included only items with abstracts. The search was also limited to exclude animal-only studies (search row "5" above), letters and editorials (search row "6"), and non-systematic reviews (search row "7").
* In-process records are captured by searching in the title/abstract fields, identifying relevant papers that have not yet been indexed with MeSH headings.
^ Compared to the first update, the number of hits was lower in second update as the PubMed website was completed rebuilt last May, resulting a change in number of hits. See KA-05275 · NLM Customer Support Center (nih.gov) for more details

EMBASE

Table 141. EMBASE Search Strategy*

Search Criteria	Search Algorithm	Search Yield (May 31, 2018)	Search Yield (May 7, 2020)	Search Yield (Nov 02, 2020)
1	'multiple myeloma'/exp OR 'multiple myeloma' OR ('multiple':ab,ti AND myeloma*:ab,ti) OR 'plasma cell myeloma':ab,ti OR (kahler*:ab,ti AND 'disease':ab,ti) OR 'plasmacytoma'/exp OR 'plasmacytoma' OR plasmacytom*:ab,ti	97,585	97,794	97,794
2	'naïve':ab,ti OR (new*:ab,ti AND diagnos*:ab,ti) OR 'untreated':ab,ti OR (('primary':ab,ti OR 'initial':ab,ti OR 'induction':ab,ti OR 'naïve':ab,ti) AND ('therapy':ab,ti OR 'treatment':ab,ti)) OR ('front':ab,ti OR 'first':ab,ti OR '1st':ab,ti AND 'line':ab,ti) OR consolidat*:ab,ti	2,284,487	2,289,863	2,289,863
3	'quality of life'/exp OR 'qaly':ab,ti OR 'qalys':ab,ti OR 'quality adjusted life year'/exp OR 'quality adjusted life year':ab,ti OR 'quality adjusted life years':ab,ti OR 'daly':ab,ti OR 'dalys':ab,ti OR 'disability adjusted life year':ab,ti OR 'disability adjusted life years':ab,ti OR 'quality of life':ab,ti OR 'patient reported outcome':ab,ti OR 'patient reported outcomes':ab,ti OR 'satisfaction':ab,ti OR 'utility':ab,ti OR 'utilities':ab,ti OR 'disutility':ab,ti OR 'disutilities':ab,ti OR disab*:ab,ti OR 'functional status':ab,ti OR 'physical function':ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'sf 12':ab,ti OR 'short form 12':ab,ti OR 'eq 5d':ab,ti OR 'euroqol 5d':ab,ti OR 'eortc':ab,ti OR 'qlq':ab,ti OR (('caregiver'/exp OR caregiver) AND ('burden'/exp OR burden)) OR ('caregiver':ab,ti AND 'burden':ab,ti)	1,325,217	1,325,510	1,325,510
4	#1 AND #2 AND #3	1,806	1,811	1,811
5	[animals]/lim NOT [humans]/lim	5,776,562	5,782,593	5,782,593
6	letter:it OR editorial:it OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim	6,253,631	6,270,599	6,270,599
7	review:it NOT ((systematic OR meta) AND analy* OR ((indirect OR mixed) AND 'treatment comparison'))	2,455,149	2,458,746	2,458,746
8	#4 NOT #5 NOT #6 NOT #7	542	545	545
9	([article]/lim OR [article in press]/lim OR [in process]/lim)	25,530,957	25,562,824	25,562,824
10	#8 AND #9	480	482	482
11	#10 AND [1-1-2008]/sd NOT [14-3-2018]/sd	255	-	-
12	#10 AND [14-3-2018]/sd NOT [1-5-2020]/sd	-	131	
13	#10 AND [1-4-2020]/sd	-	-	46

The limits for this search included only items with abstracts. The search was also limited to exclude animal-only studies (search row "5" above), letters and editorials (search row "6"), and non-systematic reviews (search row "7").
* In-process records are captured by searching in the title/abstract fields, identifying relevant papers that have not yet been indexed with Emtree terms.

The Cochrane Library

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Table 142. Cochrane Library Search Strategy

Search Criteria	Search Algorithm	Search Yield (March 13, 2018)
1	MeSH descriptor: [Multiple Myeloma] OR MeSH descriptor: [Plasmacytoma] OR (("multiple" and myelom*) or "plasma cell myeloma" or "Kahler's disease" or plasmacytom*):ti,ab,kw	3,384
2	(naïve or "newly diagnosed" or "front*line" or untreated or "first*line" or "induction therapy" or "primary therapy" or "primary treatment" or untreated or "treatment naïve" or "treatment-naïve" or consolidat*):ti,ab,kw	35,100
3	#1 AND #2	1,006
4	Publication Year from 2008 to 2018, in Other Reviews, Technology Assessments and Economic Evaluations	16

The EconLit

Table 143. EconLit Search Strategy

Search Criteria	Search Algorithm	Search Yield (May 31, 2018)	Search Yield (May 7, 2020)	Search Yield (Nov 12, 2020)
1	AB (multiple and myelom*) OR TI (multiple and myelom*)	8	12	13
2	AB Plasma cell myeloma OR TI Plasma cell myeloma	1	0	0
3	AB Kahler's disease OR TI Kahler's disease	0	0	0
4	AB Plasmacytom* OR TI Plasmacytom*	0	0	0
5	S1 OR S2 OR S3 OR S4	9	12	13
6	Published Date: 20080101-20181231	6	-	-
7	Published Date: 20180101-20201231	-	4	-
8	Published Date: 20200401-20201231	-	-	1

ASCO, ASH, EHA, ISPOR and IMWG

Below is the search for abstracts on clinical data indexed in EMBASE for ASCO, ASH, EHA, IMWG, and ISPOR. This search will be validated and supplemented by searching the conferences websites directly.

Table 144. EMBASE Search Strategy (Conference Abstracts 2015–2020)

Search Criteria	Search Algorithm	Search Yield (May 31, 2018)	Search Yield (May 07, 2020)	Search Yield (Nov 02, 2020)
1	'multiple myeloma'/exp OR 'multiple myeloma' OR ('multiple':ab,ti AND myeloma*:ab,ti) OR 'plasma cell myeloma':ab,ti OR (kahler*:ab,ti AND 'disease':ab,ti) OR 'plasmacytoma'/exp OR 'plasmacytoma' OR plasmacytom*:ab,ti	97,585	97,794	97,794
2	'naïve':ab,ti OR (new*:ab,ti AND diagnos*:ab,ti) OR 'untreated':ab,ti OR (('primary':ab,ti OR 'initial':ab,ti OR	2,284,487	2,289,863	2,289,863

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	'induction':ab,ti OR 'naïve':ab,ti) AND ('therapy':ab,ti OR 'treatment':ab,ti)) OR ('front':ab,ti OR 'first':ab,ti OR '1st':ab,ti AND 'line':ab,ti) OR consolidat*:ab,ti			
3	'quality of life'/exp OR 'qaly':ab,ti OR 'qalys':ab,ti OR 'quality adjusted life year'/exp OR 'quality adjusted life year':ab,ti OR 'quality adjusted life years':ab,ti OR 'daly':ab,ti OR 'dalys':ab,ti OR 'disability adjusted life year':ab,ti OR 'disability adjusted life years':ab,ti OR 'quality of life':ab,ti OR 'patient reported outcome':ab,ti OR 'patient reported outcomes':ab,ti OR 'satisfaction':ab,ti OR 'utility':ab,ti OR 'utilities':ab,ti OR 'disutility':ab,ti OR 'disutilities':ab,ti OR disab*:ab,ti OR 'functional status':ab,ti OR 'physical function':ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'sf 12':ab,ti OR 'short form 12':ab,ti OR 'eq 5d':ab,ti OR 'euroqol 5d':ab,ti OR 'eortc':ab,ti OR 'qlq':ab,ti OR (('caregiver'/exp OR caregiver) AND ('burden'/exp OR burden)) OR ('caregiver':ab,ti AND 'burden':ab,ti)	1,325,217	1,328,510	1,328,510
4	#1 AND #2 AND #3	1,806	1,811	1,811
5	#4 NOT ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim)	1,787	1,791	1,791
6	#5 NOT [animals]/lim	1,658	1,662	1,662
7	#6 NOT (review:it NOT (systematic OR meta AND analy* OR (indirect OR mixed AND 'treatment comparison')))	1,460	1,463	1,463
ASCO				
8	#7 AND ('journal of clinical oncology':jt NOT 'asia-pacific journal of clinical oncology':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2015-2017]/py)	14	-	-
9	#7 AND 'clinical lymphoma myeloma and leukemia'.jt AND ([conference abstract]/lim OR [conference paper]/lam OR [conference review]/lim) AND [2017-2020]/py	-	37	-
10	#7 AND 'journal of clinical oncology':jt NOT 'asia-pacific journal of clinical oncology':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [1-4-2020]/sd	-	-	0
ASH				
11	#7 AND ('blood':jt NOT ('blood purification':jt OR 'blood coagulation and fibrinolysis':jt OR 'biology of blood and marrow transplantation':jt OR 'blood transfusion':jt OR 'blood pressure':jt) AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2015-2017]/py)	111	-	-
12	#7 AND 'blood'.jt NOT ('blood purification.jt OR 'blood coagulation and fibrinolysis'.jt OT 'biology of blood and marrow transplantation'.jt OR 'bloodtransfusion'.jt OT 'blood pressure'.jt) AND ([conference abstract]/lim OR [conference paper]/lam OR [conference review]/lim) AND [2017-2020]/py	-	127	-

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13	#7 AND 'blood':jt NOT ('blood purification':jt OR 'blood coagulation and fibrinolysis':jt OR 'biology of blood and marrow transplantation':jt OR 'blood transfusion':jt OR 'blood pressure':jt) AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [1-4-2020]/sd	-	-	0
EHA				
14	#7 AND ('haematologica':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2015-2017]/py)	41	-	-
15	#7 AND 'haematologica'.jt AND ([conference abstract]/lim OR [conference paper]/lam OR [conference review]/lim) AND [2017-2020]/py	-	20	-
16	#7 AND 'haematologica':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [1-4-2020]/sd	-	-	0
ISPOR				
17	#7 AND ('value in health':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2015-2017]/py)	18	-	-
18	#7 AND 'value in health'.jt AND ([conference abstract]/lim OR [conference paper]/lam OR [conference review]/lim) AND [2017-2020]/py	-	24	-
19	#7 AND 'value in health':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [1-4-2020]/sd	-	-	3
IMWG				
20	#7 AND ('clinical lymphoma myeloma and leukemia':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2015-2017]/py)	16	-	-
21	#7 AND ('journal of clinical oncology':jt NOT 'asia-pacific journal of clinical oncology':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2015-2017]/py)	-	21	-
22	#7 AND 'clinical lymphoma myeloma and leukemia':jt AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [1-4-2020]/sd	-	-	1

20.4 Systematic selection of studies

Figure 60 to Figure 62 present the PRISMA diagram for study selection.

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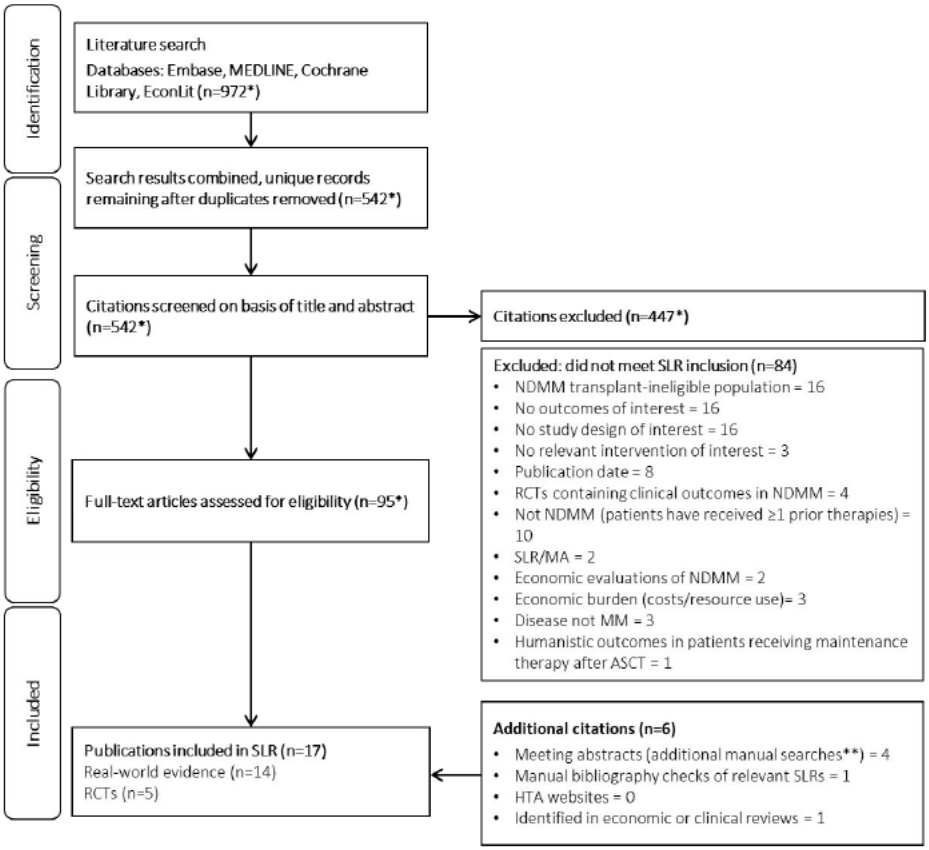
Figure 60. PRISMA Humanistic Burden initial SLR



* Includes meeting abstracts searched via Embase.com
**Additional manual searches of meetings abstracts were also performed

Figure 61 PRISMA humanistic burden SLR update 1.0

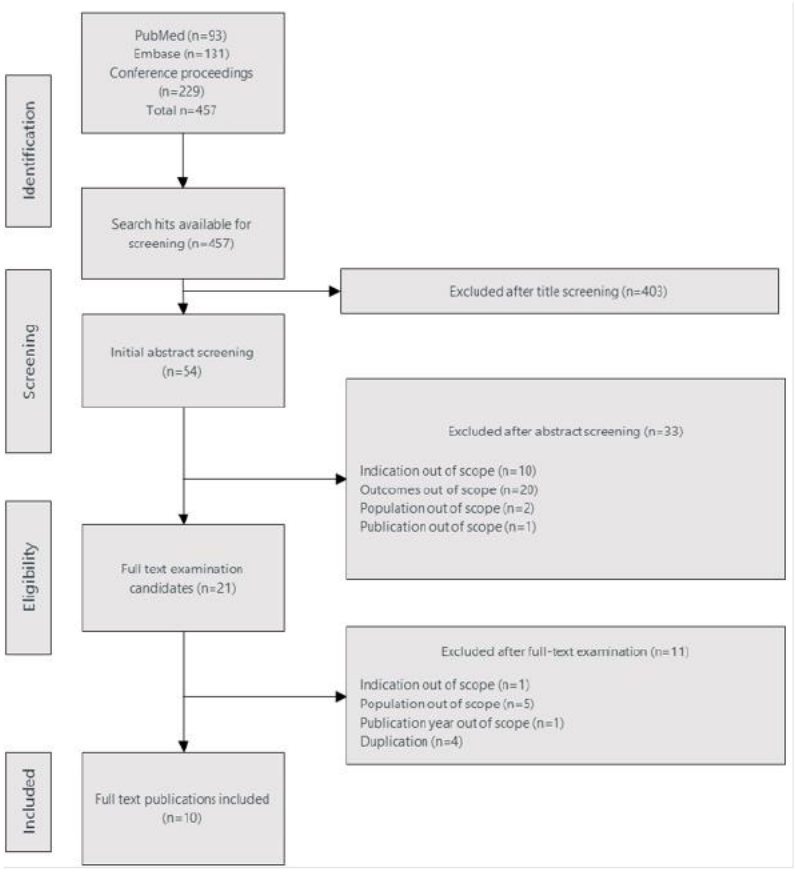
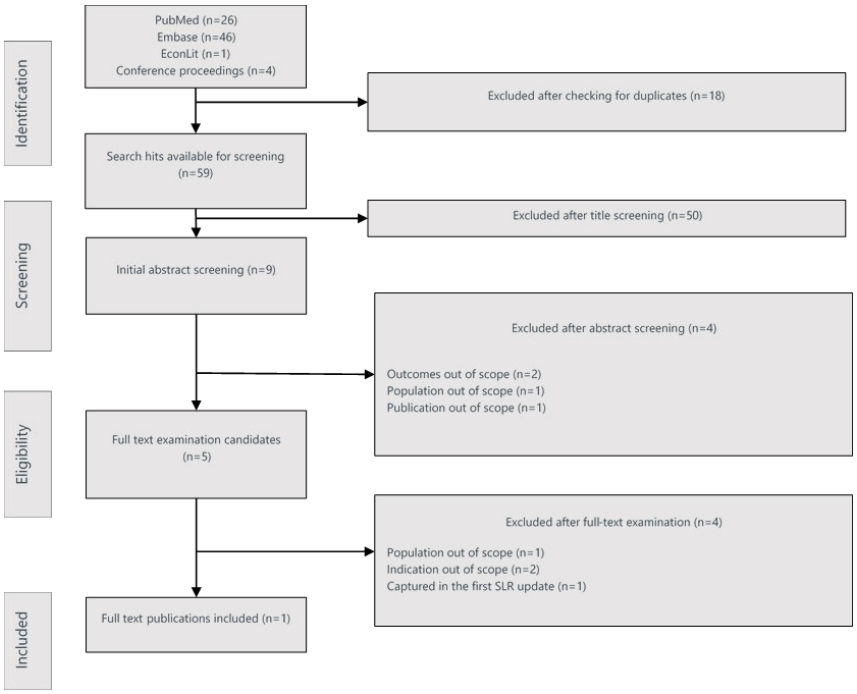


Figure 62 PRISMA humanistic burden SLR update 2.0



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20.5 Summary of studies included in health-related quality of life SLR

Table 145 lists all studies captured in literature search of health-related quality of life. An additional study of CASSIOPEIA is included in Table 146.

Table 145 Study characteristics of included publications in HRQoL SLR

Publication	Population Sample Size	Study Design	Country	Setting	Treatments Received	Method of Elicitation and Assessment Timepoint*
Tuchman (2015)(285)	Patients who received induction treatment and ASCT and were in remission n=22	Cross-sectional	US	Hospital/clinic	Induction chemotherapy BOR-containing: 22/22 (100%) LEN-containing: 14/22 (64%) Anthracycline-containing: 1/22 (5%) LEN- and BOR-containing: 14/22 (64%)	Method of elicitation: FACT-G BMT FACT-BMT CES-D Brief Pain Inventory Pittsburgh Sleep Inventory Assessment timepoint: Post-ASCT
Jones (2013)(286)	Patients recruited pre-autologous HSCT n=53	Prospective cohort	US	Hospital/clinic	All patients received prior induction chemotherapy	Method of elicitation: Cognitive Function Index based on RCI-PE including following domains: WAIS HVLT-R Trail Making Test MAE Controlled Oral Word Association Assessment timepoints: Post-induction 1-month post- autologous HSCT
Kroemeke (2018)(287)	Patients who underwent HSCT n=58	Retrospective cohort study	Poland	Hospital/clinic	All patients had an HSCT	Method of elicitation: Daily physical symptoms Assessment timepoint: Baseline and over time
Khalafallah (2011)(288)	Patients who underwent tandem ASCT n=18	Prospective cohort study	Australia	Hospital/clinic	Pre-transplant chemotherapy: VAD: 17% Td: 50% V: 22% R: 11%	Method of elicitation: EORTC QLQ-C30 v.3 EORTC QLQ-MY24 v.3 Assessment timepoints: Pre-transplant (baseline) First follow-up (three months) Second and subsequent follow-ups (six months and every three months thereafter)

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						After first and second transplant
Jones (2013)(286)	Patients who had received ≤2 cycles of chemotherapy (induction sample) n=64 Patients undergoing autologous HSCT (transplant sample) n=68	Psychometric validation	US	Hospital	Induction sample: ≤2 cycles of chemotherapy Transplant sample: High-dose melphalan and autologous HSCT	Method of elicitation: MDASI-MM Assessment timepoint Induction sample: Upon enrollment End of induction Transplant sample: Pre- autologous HSCT 7 days post-HSCT
Etto (2011)(289)	Three groups of patients with transplant-eligible MM (total n=70): 1. Upon diagnosis group: n=29 2. Post-treatment/pre-ASCT group: n=27 (including 9 from upon diagnosis group) 3. D+100 ASCT group: n=14 (including 12 from upon diagnosis group)	Cross-sectional	Brazil	Hospital/clinic	Groups 2 and 3 received ASCT	Method of elicitation: SF-36 EORTC QLQ-C30 Assessment timepoint: Three groups assessed at different timepoints: Upon diagnosis Post-treatment/pre-ASCT Day+100 ASCT
Roussel (2020)(290)	NDMM TE population in IFM 2009 trial; 604	RCT	France, Belgium, and Switzerland	NA; details follow IFM 2009 trial	RVd-ASCT	EORTC QLQ-C30; EORTC QLQ-MY20 administered at baseline, during induction, consolidation, and maintenance, at the end of treatment, and during follow-up visits
Schjesvold (2019)(291)	NDMM TE population in TOURMALINE-MM3 trial; 637	RCT	NA	NA	Ixazomib	EORTC QLQ-C30; EORTC QLQ-MY20 The EORTC QLQ-C30 was administered at screening (study days –15 to –1 prior to initiation of protocol therapy), the start of every cycle, end of treatment, every 4 weeks until start of next line of therapy after progression and twice thereafter. The EORTC QLQ-MY20 was administered at screening, the start of every 3 cycles between cycles 1 and 25, end of treatment, every 4 weeks until start of next line of therapy after progression and twice thereafter.
Nielsen (2019)(292)	NDMM TE patients with treatment-demanding disease according to the	RCT	NA (author affiliation and	NA	Clarithromycin + VCD induction therapy	EORTC QLQ-C30, EORTC QLQ-MY20, and FACT/GOG- ntx Administered at inclusion, before cyclophosphamide priming, and two months after high-dose therapy

	International Myeloma Working Group (IMWG) criteria; 55 (Clarithromycin group: 25; placebo group: 30)		EC approval in Denmark)			
Abonour (2018)(293)	NDMM patients enrolled in CONNECT MM registry design in the USA; 548 received ASCT (any maintenance: 244, LEN-only maintenance therapy: 169; no maintenance: 167)	Real world, observational, prospective cohort, data registry	USA	Clinic	ASCT + Maintenance therapy	FACT-G, FACT-MM, BPI, EQ-5D Administered at study entry and quarterly thereafter until death or study discontinuation
Royle (2018)(294)	NDMM TE and TIE patients ≥18 years from 120 centres in the United Kingdom between 2003 and 2007 who were among the ITT population recruited in Myeloma IX trial; 1822 (intensive pathway: 1061; non-intensive pathway: 758) and for the 751 patients at maintenance randomisation.	RCT	UK	Medical center	Intensive pathway: sodium clodronate or zoledronic acid and induction treatment: cyclophosphamide, vincristine, doxorubicin and dexamethasone (CVAD) or cyclophosphamide, thalidomide and dexamethasone (CTD) followed by autologous stem cell transplant (ASCT); Non-intenstive pathway: attenuated CTD or melphalan and prednisolone (MP)	EORTC QLQ-C30, EORTC QLQ-MY24. The protocol specified four subscales of interest: Pain, Fatigue, Global Health Status/Quality of Life and Physical Functioning Administered at 3, 6 and 12 months and annually thereafter
Gregersen (2018)(216)	NDMM TE patients from six Danish sites with treatment demanding disease according to the IMWG criteria;	RCT	Denmark	NA	Oral clarithromycin 500 mg	EORTC QLQ-C30, EORTC QLQ-MY20 Administered at inclusion and after 2 and 6 months

	58 (36% of the planned study population); clarithromycin: 27; placebo: 31					
Biran (2018)(295)	NDMM TE patients receiving ASCT; 28 enrolled in which 22 (79%) included in assessment	Observational, longitudinal study to compare before-after transplantation	NA (author affilication USA)	Medical center	ASCT	PROMIS, COST Administered prior to transplant and 6-months later
Gupta S (2018)(296)	NDMM patients vs. second or later regimen (LR) MM patients (transplant eligibility not defined) 162 (ND: 83; 51.2%; LR: 79; 48.8%)	Observational, cross-sectional study	NA (author affiliation in USA)	NA	NR	WPAI, FACT-MM, and MM-specific questions Not mentioned (one time off completion)
Wagner I (2018)(297)	NDMM patients in the connect® mm registry; 3011 Transplant eligibility not defined	Real world, observational, prospective cohort, data registry	NA (author affiliation in USA)	NA	NR	FACT-MM TOI, FACT-MM subscale, EQ-5D and a fatigue item Assessed at baseline and quarterly until progressive disease, discontinuation or death at baseline and quarterly until progressive disease, discontinuation or death
Mian (2019)(298)	Consecutive NDMM patients aged 65 and older 40; 19 patients as SCT eligible and 21 patients as ineligible for SCT	Real world, observational, prospective cohort	NA (author affiliation in USA)	Medical institution	High dose therapy with SCT	FACT-G, FACTt/GOG-Ntx Administered at baseline and 6-month follow up
Rifkin (2020)(299)	NDMM patients; 188	Cross-sectional study	USA	NR	NR	Treatment Satisfaction Questionnaire for Medication (TSQM-9), an adapted patient-reported version of the Eastern Cooperative Oncology Group performance status (ECOG PS), and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP)

Abbreviations: LEN= lenalidomide; RVD=lenalidomide/bortezomib/dexamethasone induction therapy; ASCT=autologous stem cell transplant; EORTC QLQ-C30/MY20= European Organization for Research and Treatment for Cancer Quality of Life Questionnaire; ITT=intent to treat; NDMM=newly diagnosed Multiple Myeloma; RCT=randomized controlled trial; SCT = stem cell transplant; USA= United States of America; MID=minimally important differences.

Table 146 Additional relevant studies included via hand search

Study title	Notes
Roussel, Murielle, et al. "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 (2020): e874-e883.(9)	Latest publication of HRQoL in CASSIOPEIA trial
Roussel M, Moreau P, Attal M, Eisenmann JC. Improvement in health-related quality of life (HRQoL) for newly diagnosed multiple myeloma (NDMM) transplant eligible patients treated with daratumumab, bortezomib, thalidomide, and dexamethasone (D-VTd) vs VTd alone: CASSIOPEIA. European Hematology Association (EHA, Poster) (2019).(129)	HRQoL in CASSIOPEIA trial

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The primary objective of this SLR was to identify the available evidence for health state utility values in previously untreated MM patients who are transplant eligible to inform the economic model.

However, the review found inconsistent results regarding the impact of transplant on HRQoL in patients with NDMM who are transplant eligible. In general, studies from the US showed that HRQoL declines from pre-transplant to post-transplant.(285, 286) Conversely, studies conducted in Brazil, Australia, and Poland showed an improvement in HRQoL and other PROs from induction to pre-transplant and/or from pre-transplant to post-transplant, often significantly.(287-289) These inconsistent findings bring into question the variability in practices between the countries and show potential areas for improvement for enhancing these patients' QoL.

In addition, due to the limited available evidence on HRQoL from interventional RCTs, no judgements can be made as to how the different treatment options compare in patients with NDMM who are eligible for transplant. This indicates a considerable unmet need among patients receiving such interventions. The studies providing evidence for this research question compared HRQoL after regimens for induction and consolidation, respectively, so trends across the studies were difficult to identify. (235, 300)

Therefore, the utility value from unpublished data of CASSIOPEIA trial and previous NICE submissions for disutilities were used in the economic model. Refer to section 8.4.2 (Table 35) and 8.4.3 (Table 36)

20.5.1 Quality assessment and generalizability of estimates

Since CASSIOPEIA is a multi-country phase III trial conducted in France, Belgium, and the Netherlands, the patient population is slightly different, but assessed to be comparable to the Danish population (refer to Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety, Comparability of the study populations with Danish patients eligible for treatment). Danish preference weights were used in the economic model to adjust the preferences for a Danish context.

20.5.2 Unpublished data

The data reported for DVTd vs. VTd in section 7.1.2.1.3 mainly follows published sources.(9, 10). Utility data for CASSIOPEIA (2nd data-cut) is not published. The analysis used the direct EQ-5D-5L value set for Denmark based on a hybrid model published by Jensen et al. 2021.(175) The value set published by Jensen et al. 2021 was based on a hybrid model composing of composite time trade-off (cTTO) and seven health states using discrete-choice experiment (DCE). This direct EQ-5D-5L value set was used to derive EQ-5D-5L utility values using the EQ-5D-5L survey responses in the CASSIOPEIA trial (2nd data-cut). The resulting utility values was used to estimate pre-progression and post-progression utilities for the CASSIOPEIA trial and results are to be used as inputs in the economic model.

21. Appendix I Mapping of HRQoL data

Section not applicable.

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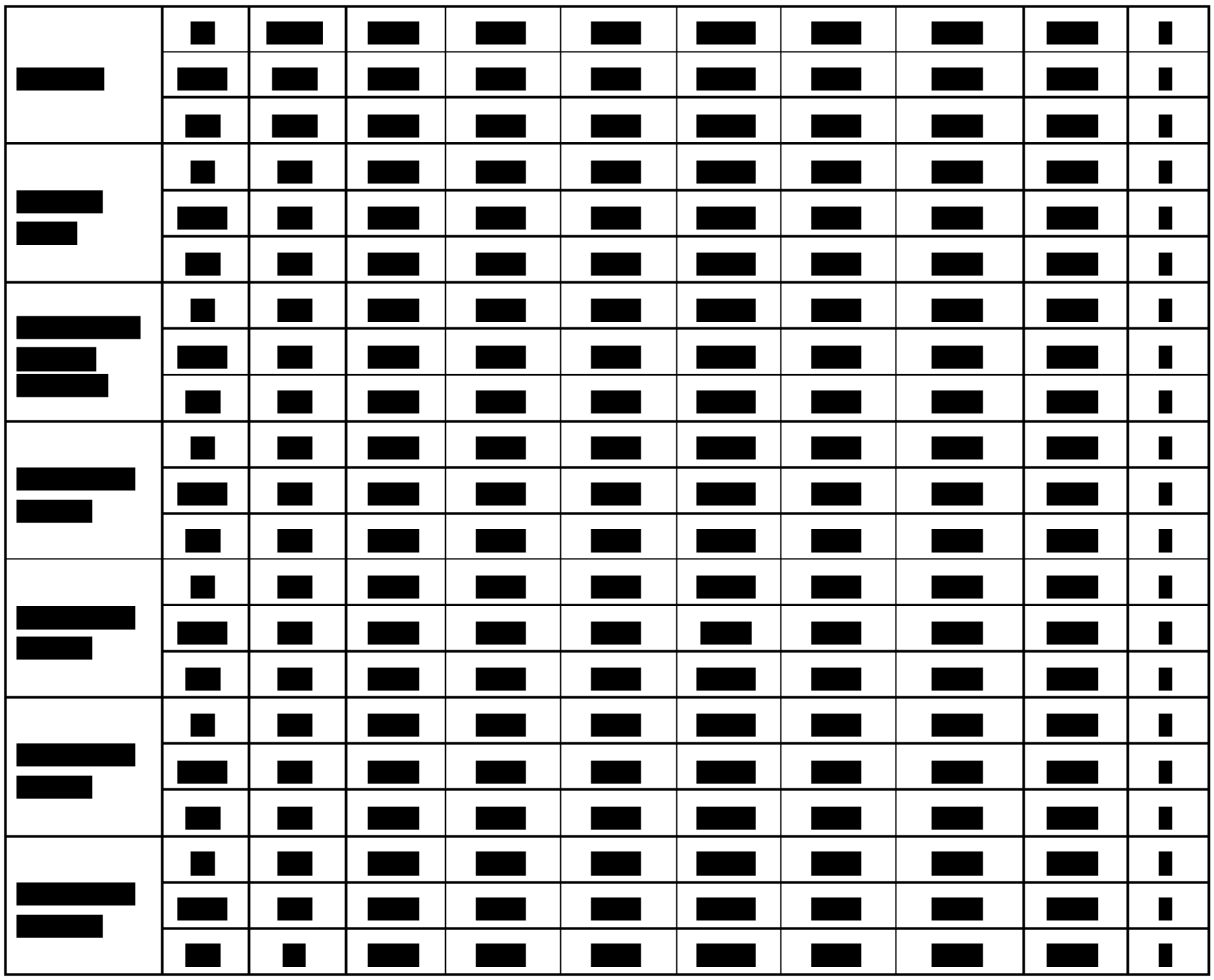

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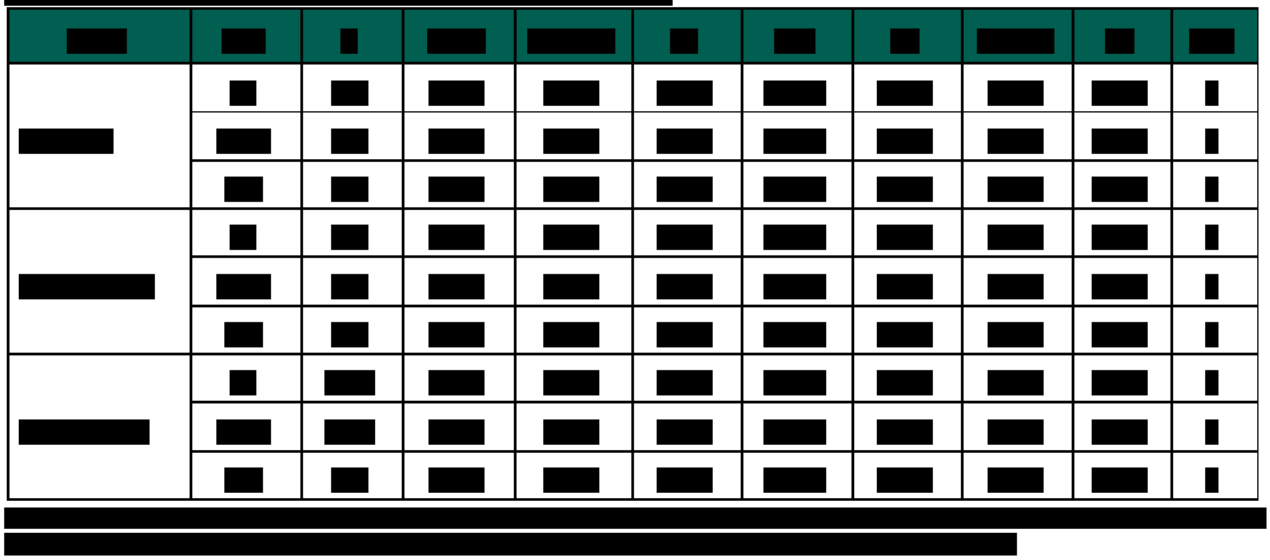

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23. Appendix K Deterministic sensitivity analysis

Table 157 Parameters varied in DSA

Parameter	Mean	Lower Value	Upper Value	Source of Variation
Settings				
Mean Baseline Age (Years)	56.60	45.28	67.92	Assumed ±20% of the mean value
Time Horizon (Years)	40	30	35	-5 and -10 years shorter
Annual Discount Rate - Costs	3.5%	1.5%	5.0%	Guide to the methods of technology appraisal 2013. Discount rates for year 36-40 was set to the base case.
Annual Discount Rate - Health Benefits	3.5%	1.5%	5.0%	
Percent of Patients Undergoing ASCT				
DVTd	90.10%	72.08%	100.00%	Assumed ±20% of the mean value
VTd	89.30%	71.44%	100.00%	
VCd	90.48%	72.38%	100.00%	
VRd	92.29%	73.83%	100.00%	
PFS Parametric Distribution Parameters – PFS on DVTd and DVT				
Weibull Distribution - Intercept	6.12	5.90	6.34	Parametric survival analysis. Lower and upper value calculated based on estimated SE for each parameter*
Weibull Distribution - Scale	0.72	0.60	0.84	
Weibull Distribution - Treatment as Predictor: VTd	-0.50	-0.54	-0.47	
HR vs. VTd in PFS				
VCd	0.93	0.64	1.35	Confidence interval from MAIC (Table 7)
VRd	1.04	0.82	1.32	
OS Parametric Distribution Parameters – OS on DVTd and VTd				
Weibull Distribution - Intercept	7.08	6.52	7.63	Parametric survival analysis. Lower and upper value calculated based on estimated SE for each parameter*
Weibull Distribution - Scale	0.73	0.51	0.95	
Weibull Distribution - Treatment as Predictor: VTd	-0.47	-0.64	-0.30	
HR vs. VTd in OS				
VCd	0.77	0.40	1.47	Confidence interval from MAIC (Table 7)
VRd	0.78	0.53	1.16	
Maintenance Treatment Median Treatment Duration (Weeks)				
Lenalidomide	110.37	88.30	132.44	Assumed ±20% of the mean value
Second-Line Median Treatment Duration (Months)				
DRd	45.70	36.56	54.84	Assumed ±20% of the mean value
DVd	24.00	19.20	28.80	
Kd	9.60	7.68	11.52	
KRd	19.09	15.27	22.91	
Rd	14.70	11.76	17.64	
ERd	17.00	13.60	20.40	
PVd	15.10	12.08	18.12	
IRd	15.70	12.56	18.84	
Third-Line Median Treatment Duration (Months)				
Kd	8.75	7.00	10.49	

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Parameter	Mean	Lower Value	Upper Value	Source of Variation
KRd	20.84	16.67	25.00	Assumed ±20% of the mean value
ERd	13.89	11.11	16.67	
PVd	4.40	3.52	5.28	
Pd	3.40	2.72	4.08	
Utility				
Induction Treatment	0.75	0.74	0.77	Confidence interval from utility analysis
Transplantation	0.75	0.74	0.77	
Consolidation Treatment	0.81	0.80	0.82	
Progression-Free on Maintenance Treatment	0.84	0.83	0.84	
Second-Line Treatment	0.78	0.74	0.82	
Third-Line Treatment	0.78	0.74	0.82	
AEs - Percent of Patients Experiencing Adverse Events During Induction/ASCT/Consolidation				
DVTd				
Neutropenia	0.28	0.22	0.33	Assumed ±20% of the mean value
Lymphopenia	0.17	0.14	0.20	
Thrombocytopenia	0.11	0.09	0.13	
Febrile neutropenia	0.07	0.05	0.08	
Stomatitis	0.13	0.10	0.15	
Peripheral sensory neuropathy	0.09	0.07	0.11	
VTd				
Neutropenia	0.15	0.12	0.18	Assumed ±20% of the mean value
Lymphopenia	0.10	0.08	0.12	
Thrombocytopenia	0.07	0.06	0.09	
Febrile neutropenia	0.05	0.04	0.06	
Stomatitis	0.16	0.13	0.20	
Peripheral sensory neuropathy	0.09	0.07	0.10	
VCd				
Neutropenia	0.35	0.28	0.42	Assumed ±20% of the mean value
Thrombocytopenia	0.04	0.03	0.05	
AE Disutility (Varied at the Same Time for All AEs in the DSA)				
Neutropenia	-0.15	-0.12	-0.18	Assumed ±20% of the mean value
Lymphopenia	-0.07	-0.06	-0.08	
Thrombocytopenia	-0.31	-0.25	-0.37	
Febrile neutropenia	-0.39	-0.31	-0.47	
Stomatitis	-0.15	-0.12	-0.18	
Peripheral sensory neuropathy	-0.07	-0.06	-0.08	
AE Duration (Weeks) (Varied at the Same Time for All AEs in the DSA)				
Neutropenia	4.0	3.2	4.8	Assumed ±20% of the mean value
Lymphopenia	4.0	3.2	4.8	
Thrombocytopenia	4.0	3.2	4.8	
Febrile neutropenia	4.0	3.2	4.8	
Stomatitis	4.0	3.2	4.8	
Peripheral sensory neuropathy	4.0	3.2	4.8	
AE Costs (Varied at the Same Time for All AEs in the DSA) - DKK				

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Parameter	Mean	Lower Value	Upper Value	Source of Variation
Neutropenia	3203	2562.4	3843.6	Assumed ±20% of the mean value
Lymphopenia	3203	2562.4	3843.6	
Thrombocytopenia	3203	2562.4	3843.6	
Febrile neutropenia	25799	20639.2	30958.8	
Stomatitis	3203	2562.4	3843.6	
Peripheral sensory neuropathy	3203	2562.4	3843.6	
Drug Acquisition Costs - DKK				
DaratumumabSC 1800 mg	38,901.18	31,120.9	46,681.42	Assumed ±20% of the mean value
Bortezomib 3.5 mg	1940	1552.00	2328.00	
Lenalidomide	Multiple	Multiple	Multiple	
Dexamethasone	Multiple	Multiple	Multiple	
Thalidomide 50 mg	2296.29	1837.03	2755.548	
Cyclophosphamide	Multiple	Multiple	Multiple	
Carfilzomib	Multiple	Multiple	Multiple	
Ixazomib	Multiple	Multiple	Multiple	
Elotuzumab	Multiple	Multiple	Multiple	
Pomalidomide	Multiple	Multiple	Multiple	
Drug Administration Cost - DKK				
Initial Daratumumab SC	3,203	2,562	3,844	Assumed ±20% of the mean value
Subsequent Daratumumab SC	3,203	2,562	3,844	
Administration Cost per IV Infusion	3,203	2,562	3,844	
Administration Cost per SC Administration	3,203	2,562	3,844	
ASCT Costs – DKK				
Stem Cell Mobilisation/Harvest	166,707	133,366	200,048	Assumed ±20% of the mean value
Transplantation Cost	659,974	527,979	791,969	
Medical Resource Costs				
Haematologist initial visit	417	334	500	Assumed ±20% of the mean value
Haematologist follow-up visit	417	334	500	
Other Costs – DKK				
One-time off per patient (end-of-life)	65,274	52,219	78,328	Assumed ±20% of the mean value

*Lower value = mean - 1.96xSE; Upper value = mean + 1.96xSE

Abbreviations: AE = adverse event; ASCT = autologous stem cell transplant; HR = hazard ratio; DSA = deterministic sensitivity analysis; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; DRd = daratumumab, lenalidomide, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; IV = Intravenous; Kd = Carfilzomib, dexamethasone; KRd = Carfilzomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone; ERd: Elotuzumab, lenalidomide, dexamethasone PVd=pomalidomide, bortezomib, dexamethason; IRd: Ixazomib, lenalidomide, dexamethasone; PVd= pomalidomide, dexamethasone; SC = Subcutaneous.

Note: Cost of concomitant medications and MRU (Full blood count, urine disease evaluations, liver function tests, calcium, serum free light chain, serum disease evaluations, CRP, blood cultures) were not included due the very limited impact on the results as well as the actual impact (see base case results table). However, this can be included in the DSA if preferred. Adjustment to Kg and BSA was not included in the DSA due to substantial increase in processing time for the model. The impact of Kg and BSA is low and are shown in scenario analyses.

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Table 158 DSA Results, ICER (Cost/QALY) for DVTd versus VTd

Rank	Parameter name	Lower value	Upper value
1	PFS on VTd (CASSIOPEIA) - Weibull: Intercept	-DKK 47,769	DKK 126,246
2	OS on VTd (CASSIOPEIA) - Weibull: Scale	-DKK 60,954	DKK 87,379
3	OS on VTd (CASSIOPEIA) - Weibull: Treatment as Predictor	DKK 82,680	-DKK 57,261
4	PFS on DVTd (CASSIOPEIA) - Weibull: Intercept	DKK 97,191	-DKK 33,712
5	OS on VTd (CASSIOPEIA) - Weibull: Intercept	DKK 152,912	DKK 32,979
6	OS on DVTd (CASSIOPEIA) - Weibull: Scale	DKK 83,135	-DKK 13,077
7	OS on DVTd (CASSIOPEIA) - Weibull: Intercept	DKK 32,979	DKK 94,764
8	PFS on VTd (CASSIOPEIA) - Weibull: Scale	DKK 522	DKK 60,077
9	Median Second-Line Treatment Duration (Months): DaraSC+Vd	DKK 62,873	DKK 6,670
10	PFS on DVTd (CASSIOPEIA) - Weibull: Scale	DKK 54,277	DKK 15,400
11	Median Second-Line Treatment Duration (Months): DaraSC+Rd	DKK 49,054	DKK 19,319
12	PFS on VTd (CASSIOPEIA) - Weibull: Treatment as Predictor	DKK 19,041	DKK 47,246
13	%Patients Receiving ASCT: VTd	DKK 44,526	DKK 26,061
14	Median Second-Line Treatment Duration (Months): PVd	DKK 23,226	DKK 41,542
15	%Patients Receiving ASCT: DVTdSC	DKK 21,214	DKK 39,442

*Intercept, scale and treatment as predictor were set to lower or upper bound at the same time for Weibull distribution.
Abbreviations: DSA = deterministic sensitivity analysis; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-years; OS = overall survival; PFS = progression-free survival; ASCT = autologous stem cell transplant; DVTd/DVTdSC = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; DaraSC + Vd = daratumumab, bortezomib, dexamethasone; DaraSC + Rd = daratumumab, lenalidomide, dexamethasone; PVd=pomalidomide, bortezomib, dexamethason
Note: For the scenarios with negative ICER values, cost savings and higher QALYs were observed. In these cases, it should be interpreted as cost-effective irrespective of the ICER threshold and no numerical interpretation is needed. In case the incremental costs and incremental QALYs were both negative (south west quadrant on the cost-effectiveness plane), the ICER was set to the base case as this produces none-interpretable ICERs.

Table 159 DSA Results, ICER (Cost/QALY) for DVTd versus VCd

Rank	Parameter name	Lower value	Upper value
1	OS on VTd (CASSIOPEIA) - Weibull: Intercept	DKK 173,357	-DKK 455,451
2	OS on DVTd (CASSIOPEIA) - Weibull: Intercept	-DKK 321,981	DKK 113,327
3	OS HR1: VCd	DKK 163,242	-DKK 212,854
4	PFS HR1: VCd	DKK 427	DKK 170,567
5	PFS on VTd (CASSIOPEIA) - Weibull: Intercept	DKK 15,439	DKK 151,258
6	OS on VTd (CASSIOPEIA) - Weibull: Scale	-DKK 5,089	DKK 123,675
7	PFS on DVTd (CASSIOPEIA) - Weibull: Intercept	DKK 126,797	DKK 29,174
8	OS on VTd (CASSIOPEIA) - Weibull: Treatment as Predictor	DKK 113,830	DKK 30,863
9	OS on DVTd (CASSIOPEIA) - Weibull: Scale	DKK 112,222	DKK 53,985
10	Annual Discount Rate - Health Benefits	DKK 57,507	DKK 98,477
11	Median Second-Line Treatment Duration (Months): DaraSC+Vd	DKK 98,600	DKK 62,143
12	PFS on VTd (CASSIOPEIA) - Weibull: Scale	DKK 59,060	DKK 94,822
13	PFS on DVTd (CASSIOPEIA) - Weibull: Scale	DKK 94,855	DKK 66,263
14	PFS on VTd (CASSIOPEIA) - Weibull: Treatment as Predictor	DKK 68,301	DKK 90,335
15	Mean Baseline Age (Years)	DKK 78,262	DKK 98,783

*Intercept, scale and treatment as predictor were set to lower or upper bound at the same time for Weibull distribution. HR for VCd was tested based on the lower and upper CI versus VTd.
Abbreviations: DSA = deterministic sensitivity analysis; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-years; OS = overall survival; PFS = progression-free survival; HR = hazard ratio; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; DaraSC + Vd = daratumumab, bortezomib, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone.
Note: For the scenarios with negative ICER values, cost savings and higher QALYs were observed. In these cases, it should be interpreted as cost-effective irrespective of the ICER threshold and no numerical interpretation is needed. In case the incremental costs and incremental QALYs were both negative (south west quadrant on the cost-effectiveness plane), the ICER was set to the base case as this produces none-interpretable ICERs.

Table 160 DSA Results, ICER (Cost/QALY) for DVTd versus VRd

Rank	Parameter name	Lower value	Upper value
1	OS on VTd (CASSIOPEIA) - Weibull: Intercept	DKK 182,555	-DKK 412,364
2	OS on DVTd (CASSIOPEIA) - Weibull: Intercept	-DKK 263,210	DKK 125,213
3	OS HR1: VRd	DKK 146,912	DKK 7,978
4	PFS on VTd (CASSIOPEIA) - Weibull: Intercept	DKK 32,814	DKK 170,576
5	OS on VTd (CASSIOPEIA) - Weibull: Scale	DKK 19,736	DKK 137,331
6	PFS HR1: VRd	DKK 45,531	DKK 155,015
7	PFS on DVTd (CASSIOPEIA) - Weibull: Intercept	DKK 146,648	DKK 46,258
8	OS on VTd (CASSIOPEIA) - Weibull: Treatment as Predictor	DKK 128,626	DKK 54,835
9	OS on DVTd (CASSIOPEIA) - Weibull: Scale	DKK 129,175	DKK 74,620
10	Annual Discount Rate - Health Benefits	DKK 70,803	DKK 121,634
11	PFS on VTd (CASSIOPEIA) - Weibull: Scale	DKK 74,336	DKK 115,849
12	Median Second-Line Treatment Duration (Months): DaraSC+Vd	DKK 117,842	DKK 79,701
13	PFS on DVTd (CASSIOPEIA) - Weibull: Scale	DKK 113,698	DKK 84,454
14	Mean Baseline Age (Years)	DKK 96,573	DKK 123,323
15	PFS on VTd (CASSIOPEIA) - Weibull: Treatment as Predictor	DKK 86,632	DKK 108,981

*Intercept, scale and treatment as predictor were set to lower or upper bound at the same time for Weibull distribution. HR for VRd was tested based on the lower and upper CI versus VTd.
Abbreviations: DSA = deterministic sensitivity analysis; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life-years; OS = overall survival; PFS = progression-free survival; HR = hazard ratio; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; DaraSC + Vd = daratumumab, bortezomib, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone.
Note: For the scenarios with negative ICER values, cost savings and higher QALYs were observed. In these cases, it should be interpreted as cost-effective irrespective of the ICER threshold and no numerical interpretation is needed. In case the incremental costs and incremental QALYs were both negative (south west quadrant on the cost-effectiveness plane), the ICER was set to the base case as this produces none-interpretable ICERs.

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24. Appendix L Probabilistic sensitivity analyses

Table 161 Parameters varied in PSA

Parameter	Mean	SE	Distribution	Source of Variation
Percent of Patients Undergoing ASCT				
DVTd	90.10%	0.09	Beta	Assumed 10% of the mean value
VTd	89.30%	0.09		
VCd	90.48%	0.09		
VRd	92.29%	0.09		
Parametric Distribution Parameters – PFS on DVTd and DVT				
Weibull Distribution - Intercept	6.12	0.11	Normal	Parametric survival analysis
Weibull Distribution - Scale	0.72	0.04		
Weibull Distribution - Treatment as Predictor: VTd	-0.50	0.10		
HR vs. VTd in PFS				
VCd	0.93	0.18	Log-normal	Confidence interval from MAIC* (Table 7)
VRd	1.04	0.13		
OS Parametric Distribution Parameters - OS on DVTd and DVT				
Weibull Distribution - Intercept	7.08	0.28	Normal	Parametric survival analysis
Weibull Distribution - Scale	0.73	0.08		
Weibull Distribution - Treatment as Predictor: VTd	-0.47	0.19		
HR vs. VTd in OS				
VCd	0.77	0.27	Log-normal	Confidence interval from MAIC* (Table 7)
VRd	0.78	0.16		
Maintenance Treatment Median Treatment Duration (Weeks)				
Lenalidomide	110.37	11.04	Normal	Assumed 10% of the mean value
Second-Line Median Treatment Duration (Months)				
DRd	45.70	4.57	Normal	Assumed 10% of the mean value
DVd	24.00	2.40		
Kd	9.60	0.96		
KRd	19.09	1.91		
Rd	14.70	1.47		
ERd	17.00	1.70		
PVd	15.10	1.51		
IRd	15.70	1.57		
Third-Line Median Treatment Duration (Months)				
Kd	8.75	0.87	Normal	Assumed 10% of the mean value
KRd	20.84	2.08		
ERd	13.89	1.39		
PVd	4.40	0.44		
Pd	3.40	0.34		
AEs - Percent of Patients Experiencing Adverse Events During Induction/ASCT/Consolidation				
DVTd				
Neutropenia	0.28	0.028		

Parameter	Mean	SE	Distribution	Source of Variation
Lymphopenia	0.17	0.017	Beta	Assumed 10% of the mean value
Thrombocytopenia	0.11	0.011		
Febrile neutropenia	0.07	0.007		
Stomatitis	0.13	0.013		
Peripheral sensory neuropathy	0.09	0.009		
VTd				
Neutropenia	0.15	0.015	Beta	Assumed 10% of the mean value
Lymphopenia	0.10	0.010		
Thrombocytopenia	0.07	0.007		
Febrile neutropenia	0.05	0.005		
Stomatitis	0.16	0.016		
Peripheral sensory neuropathy	0.09	0.009		
VCd				
Neutropenia	0.35	0.035	Beta	Assumed 10% of the mean value
Thrombocytopenia	0.04	0.004		
Utility				
Induction Treatment	0.75	0.008	Beta	Utility analysis(Table 35)
Transplantation	0.75	0.007		
Consolidation Treatment	0.81	0.008		
Progression-Free on Maintenance Treatment	0.84	0.004		
Second-Line Treatment	0.78	0.020		
Third-Line Treatment	0.78	0.020		
AE Disutility (Varied at the Same Time for All AEs in the PSA)				
Neutropenia	-0.15	-0.015	Log-normal	Assumed 10% of the mean value
Lymphopenia	-0.07	-0.007		
Thrombocytopenia	-0.31	-0.031		
Febrile neutropenia	-0.39	-0.039		
Stomatitis	-0.15	-0.015		
Peripheral sensory neuropathy	-0.07	-0.007		
AE Duration (Weeks) (Varied at the Same Time for All AEs in the PSA)				
Neutropenia	4.0	0.4	Normal	Assumed 10% of the mean value
Lymphopenia	4.0	0.4		
Thrombocytopenia	4.0	0.4		
Febrile neutropenia	4.0	0.4		
Stomatitis	4.0	0.4		
Peripheral sensory neuropathy	4.0	0.4		
AE Costs (Varied at the Same Time for All AEs in the PSA) - DKK				
Neutropenia	3203	320.30	Gamma	Assumed 10% of the mean value
Lymphopenia	3203	320.30		
Thrombocytopenia	3203	320.30		
Febrile neutropenia	25799	2579.90		
Stomatitis	3203	320.30		
Peripheral sensory neuropathy	3203	320.30		
Drug Acquisition Costs - DKK				
DaratumumabSC 1800 mg	38,901.18	3890.12	Gamma	

Parameter	Mean	SE	Distribution	Source of Variation
Bortezomib 3.5 mg	1940	194.00		
Lenalidomide	Multiple	Multiple		
Dexamethasone	Multiple	Multiple		
Thalidomide 50 mg	2296.29	229.63		
Cyclophosphamide	Multiple	Multiple		Assumed 10% of the mean value
Carfilzomib	Multiple	Multiple		
Ixazomib	Multiple	Multiple		
Elotuzumab	Multiple	Multiple		
Pomalidomide	Multiple	Multiple		
Drug Administration Cost - DKK				
Initial Daratumumab SC	3,203	320.30		
Subsequent Daratumumab SC	3,203	320.30		
Administration Cost per IV Infusion	3,203	320.30	Gamma	Assumed 10% of the mean value
Administration Cost per SC Administration	3,203	320.30		
ASCT Costs – DKK				
Stem Cell Mobilisation/Harvest	166,707	16670.70	Gamma	Assumed 10% of the mean value
Transplantation Cost	659,974	65997.40		
Medical Resource Costs				
Haematologist initial visit	417	41.71	Gamma	Assumed 10% of the mean value
Haematologist follow-up visit	417	41.71		
Other Costs – DKK				
One-time off per patient (end-of-life)	65,274	6527.37	Gamma	Assumed 10% of the mean value

*SE = (Upper value – lower value)/(2x1.96)

Abbreviations: AE = adverse event; ASCT = autologous stem cell transplant; HR = hazard ratio; IV = Intravenous; SC = Subcutaneous; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; DRd = daratumumab, lenalidomide, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; Kd = Carfilzomib, dexamethasone; KRd = Carfilzomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone; ERd: Elotuzumab, lenalidomide, dexamethasone PVd=pomalidomide, bortezomib, dexamethason; IRd: Ixazomib, lenalidomide, dexamethasone; Pd= pomalidomide, dexamethasone.

Summary statistics of the PSA iterations for each treatment regimen are presented in Table 162.

Table 162 PSA Summary statistics

	VTd	VCd	VRd
Incremental Costs (DKK)			
Mean	DKK 80,589	DKK 335,127	DKK 365,611
SD	DKK 309,033	DKK 329,837	DKK 321,163
Min	-DKK 1,098,576	-DKK 795,053	-DKK 892,520
Max	DKK 1,147,955	DKK 1,356,039	DKK 1,429,998
95% CI lower	-DKK 544,671	-DKK 333,038	-DKK 257,875
95% CI upper	DKK 651,965	DKK 968,364	DKK 963,103

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	VTd	VCd	VRd
Incremental QALYs			
Mean	2.54	4.00	3.73
SD	1.67	1.61	1.61
Min	-3.71	-1.65	-2.57
Max	7.11	8.21	8.13
95% CI lower	-0.91	0.51	0.33
95% CI upper	5.48	6.60	6.46
Incremental LYs			
Mean	3.09	4.94	4.63
SD	2.13	2.05	2.05
Min	-4.92	-2.30	-3.45
Max	8.91	10.37	10.24
95% CI lower	-1.31	0.46	0.26
95% CI upper	6.85	8.21	8.15

Abbreviations: CI = Confidence interval; DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; VCd = bortezomib, cyclophosphamide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; SD = Standard deviation; QALYs: quality-adjusted life-years; LYs = Life-years.

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25. Appendices N – IPW methodology

Since the PFS from 1st randomization was impacted by the 2nd randomization for maintenance, the IPW method was used to compare the two arms unbiasedly. Analysis of PFS from 1st randomization is based on the ITT analysis set. Two 'ITT'-type of induction comparisons, one specific to each maintenance treatment, were conducted:

- DVTd-daratumumab versus VTd-daratumumab
- DVTd-observation versus VTd-observation

The weighted Kaplan-Meier method was used to estimate the distribution of PFS for each of the four treatment sequences in the two 'ITT'-type of induction comparisons.(303) A weight of 2 was assigned to patients randomized to the specific maintenance treatment and a weight of 1 was assigned to those patients who did not respond after the induction/ASCT/consolidation stage or did not consent to participate in the maintenance stage. The median PFS with 95% CI was also calculated. The PFS rates were summarized at landmarks (e.g. 6 months, 12 months, 18 months, 24 months etc.). The weighted Kaplan-Meier PFS curve was plotted by each induction treatment group for specific maintenance treatment in the 'ITT'-type of induction comparisons.

For each of the two comparisons, the p-value from the log-rank test with risk factor adjusted by the IPW method was reported for the two 'ITT'-type of induction comparisons. HRs and 95% CIs were estimated based on a Cox regression analysis with IPW, in which the weights used were the same as the above weighted Kaplan-Meier method.(304) Due to the expected small number of PFS events at the end of the Part 1 analyses, PFS from 1st randomization analyses was not stratified by the three randomization stratification factors in Part 1 (i.e. site affiliation, ISS and cytogenetics) in each of the two comparisons.

The overall comparison of induction treatments was made treating these two comparisons as two strata with the variance estimated using the robust variance estimated (the sandwich estimate). These three comparisons were tested with the significance level of 0.05 (2-sided) following the closed testing procedure. Essentially, the statistical significance was established for each of the two maintenance-specific comparisons if both itself and the overall induction comparison were significant at the 2-sided level of 0.05.

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26. Appendix O – The patient population, the intervention and choice of comparators(s)

26.1 Diagnostic criteria

Table 163 Diagnostic criteria for MGUS, SMM and MM according to IMWG(29)

Disorder	Disease definition
Non-IgM MGUS	All criteria must be met: • Serum M-protein <30 g/L • Clonal bone marrow plasma cells <10% • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, or bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder
IgM MGUS	• Serum IgM monoclonal protein <30g/L • No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to the plasma cell proliferative disorder
Light chain MGUS	• Abnormal free light chain (FLC) ratio (<0.26 or >1.65) • Increased level of the appropriate free light chain (increased kappa FLC in patients with ratio >1.65 and increased lambda FLC in patients with ratio <0.26) • No immunoglobulin heavy chain expression on immunofixation • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder • Clonal bone marrow plasma cells < 10% • Urinary monoclonal protein <500mg/24h
SMM	Both criteria must be met: • Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 hr and/or clonal bone marrow plasma cells 10%–60% • Absence of myeloma-defining events or amyloidosis

Symptomatic MM	Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma[a] and any one of more of the following CRAB features and myeloma-defining events:
	• Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
	  ○ Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
	  ○ Renal insufficiency: creatinine clearance <40 mL per min[b] or serum creatinine >177 µmol/L (>2 mg/dL)
	  ○ Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L
	  ○ Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET-CT). If bone marrow has <10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement
	• Any one or more of the following biomarkers of malignancy (MDEs):
	  ○ 60% or greater clonal plasma cells on bone marrow examination
	  ○ Serum involved / uninvolved free light chain (FLC) ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100mg/L (a patient's involved FLC either kappa or lambda is the one that is above the normal reference range; the uninvolved FLC is the one that is typically in, or below, the normal range)
	  ○ More than one focal lesion on magnetic resonance imaging (MRI) that is at least 5 mm or greater in size.

Abbreviations: IMWG = International Myeloma Working Group; MGUS = Monoclonal gammopathy of undetermined significance; MM = Multiple myeloma; SMM= Smoldering multiple myeloma;
[a]Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. [b]Measured or estimated by validated equations.

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26.2 ISS staging

Table 164 Combined ISS-genetic prognostic system (56)

	High Risk	Standard Risk	Low Risk
Parameters	ISS II/III and t(4;14)[a] or 17p13 deletion	Others	ISS I/II and absence of t(4;14), 17p13 deletion and +1q21 and age <55 years
Median OS	2 years	7 years	>10 years

Abbreviations: ISS = International Staging System; OS = Overall survival
[a]Survival of t(4;14) patients is improved with the use of bortezomib-based therapy.

Table 165 Revised ISS staging (R-ISS) according to IMWG(53)

	High Risk	Standard Risk	R-ISS i
Parameters	ISS III and high-risk CA (Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16) or high LDH level (larger than the upper limit of normal range)	Others	ISS I and no high-risk CA and normal LDH level (less than the upper limit of normal range)
OS (5-year survival)	40%	62%	82%

Abbreviations: IMWG = International Myeloma Working Group; ISS = International Staging System; LDH = Lactic acid dehydrogenase; OS = Overall survival

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Table 166 Characteristics for patients in Danish study(62)

	All
N with TX	575
Diagnosis	
2005-2008	229 (40%)
2009-2014	346 (60%)
Age (median and range)	60 (30-72)
Gender	
F	246 (43%)
M	329 (57%)
ISS	
I	189 (39%)
II	173 (36%)
III	124 (26%)
Missing	89
Creatinine	
(>177) (%)	81 (14.6)
Missing	19
Elevated LDH	141 (25.3%)
High LDH x 2	10 (1.8%)
EMD	59 (10.3%)

Abbreviations: EMD = Extramedullary disease; ISS = International Staging System; LDH = Lactic acid dehydrogenase; TX = Treatment; F = Female; M = Male

Table 167 Characteristics for patients with cytogenetic abnormalities in Danish study(62)

	Planned for ASCT	Treated with ASCT
High-risk markers		
t(4;14)	7/108 (6.5%)	11/128 (8.5%)
t(14;16)	6/81 (7.4%)	4/95 (4.2%)
del(17p)	13/113 (11.5%)	15/135 (11.1%)
Gain 1q	18/55 (32.7%)	24/75 (32.0%)
del(13)	50/104 (43.5%)	59/136 (43.4%)
High LDH x 2	5/117 (4.3%)	2/139 (1.4%)
Elevated LDH	36 /117 (30.8%)	45/139 (32.4%)
High risk: HR1	25/119 (21.0%)	25/142 (17.6%)
High risk: HR2	59/119 (49.6%)	76/142 (53.5%)

Abbreviations: ASCT = Autologous stem cell transplant; LDH = Lactic acid dehydrogenase

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26.3 Dosing and Posology

Table 168 Summary of treatment dosing

Treatment Regimens		Dose/Admin	Days of Admin/Cycle	Cycle Length (Days)	Relative dose intensity	Source
DVTd – Induction						
Daratumumab	Cycle 1–2	1800 mg	1, 8, 15, 22	28	98.3%	EMA SmPC Darzalex(1), DVTd EPAR(4)
	Cycle 3–4	1800 mg	1, 15	28	98.4%	
Bortezomib	Cycle 1–4	1.3 mg/m^2	1, 4, 8, 11	28	91.5%	
Thalidomide	Cycle 1–4	100.0 mg	1–28	28	86.6%	
Dexamethasone	Cycle 1–2	40.0 mg	1, 2, 8, 9, 15, 16, 22, 23	28	96.8%	
	Cycle 3–4	40.0 mg	1, 2	28	96.8%	
	Cycle 3–4	20.0 mg	8, 9, 15, 16	28	96.8%	
DVTd – Consolidation						
Daratumumab	Cycle 1–2	1800 mg	1, 15	28	99.9%	EMA SmPC Darzalex(1), DVTd EPAR(4)
Bortezomib	Cycle 1–2	1.3 mg/m^2	1, 4, 8, 11	28	91.5%	
Thalidomide	Cycle 1–2	100.0 mg	1-28	28	86.6%	
Dexamethasone	Cycle 1–2	20.0 mg	1, 2, 8, 9, 15, 16	28	96.8%	
VTd – Induction						
Bortezomib	Cycle 1–4	1.3 mg/m^2	1, 4, 8, 11	28	91.3%	EMA SmPC Darzalex(1), DVTd EPAR(4)
Thalidomide	Cycle 1–4	100.0 mg	1–28	28	86.1%	
Dexamethasone	Cycle 1–2	40.0 mg	1, 2, 8, 9, 15, 16, 22, 23	28	96.2%	
	Cycle 3–4	40.0 mg	1, 2	28	96.2%	
	Cycle 3–4	20.0 mg	8, 9, 15, 16	28	96.2%	
VTd – Consolidation						
Bortezomib	Cycle 1–2	1.3 mg/m^2	1, 4, 8, 11	28	91.3%	EMA SmPC Darzalex(1), DVTd EPAR(4)
Thalidomide	Cycle 1–2	100.0 mg	1-28	28	86.1%	
Dexamethasone	Cycle 1–2	20.0 mg	1, 2, 8, 9, 15, 16	28	96.2%	
VCd – Induction						
Bortezomib	Cycle 1–3	1.3 mg/m^2	1, 4, 8, 11	21	91.3%*	GMMG–MM5 (121, 139)
Cyclophosphamide	Cycle 1–3	900 mg/m^2	1[b]	21	86.1%†	
Dexamethasone	Cycle 1–3	40 mg	1, 2, 4, 5, 8, 9, 11, 12	21	96.2%‡	
VCd – Consolidation						
Lenalidomide	Cycle 1-2	25.0 mg	1-21	21	99.9%¨¨	GMMG–MM5 (121, 139)
VRd – Induction						
Lenalidomide	Cycle 1–3	25.0 mg	1-14	21	98.3%¨	IFM 2009(123)
Bortezomib	Cycle 1–3	1.3 mg/m^2	1, 4, 8, 11	21	91.3%*	
Dexamethasone	Cycle 1–3	20.0 mg	1, 2, 4, 5, 8, 9, 11, 12	21	96.8%‡	
VRd – Consolidation						
Lenalidomide	Cycle 1-2	25.0 mg	1-14	21	99.9%¨¨	IFM 2009(123)
Bortezomib	Cycle 1-2	1.3 mg/m^2	1, 4, 8, 11	21	91.3%**	
Dexamethasone	Cycle 1-2	10.0 mg	1, 2, 4, 5, 8, 9, 11, 12	21	96.2%‡‡	

* Assumed the same as bortezomib in VTd induction; ** Assumed the same as bortezomib in VTd induction;
† Assumed the same as thalidomide in VTd induction
‡Assumed the same as dexamethasone in VTd induction; ‡‡Assumed the same as dexamethasone in VTd consolidation
¨ Assumed the same as daratumumab in DVTd induction; ¨¨ Assumed the same as daratumumab in DVTd consolidation
Abbreviations: DVTd = daratumumab, bortezomib, thalidomide, dexamethasone; EMA = European Medicines Agency; IFM = Intergroupe Francophone du Myelome; VCd = bortezomib, cyclophosphamide, dexamethasone; VTd = bortezomib, thalidomide, dexamethasone; VRd = bortezomib, lenalidomide, dexamethasone; SmPC = Summary of Product Characteristics

Table 169. Summary of Subsequent Treatment Regimen Dosing

Comparator	Cycle(s)	Cycle Length (Days)	Dose (mg)	Days of Administration per Cycle	Source
DRd					
DaratumumabSC	1-2	28	1800	1, 8, 15, 22	SmPC – Darzalex(1)
	1-3	28	1800	1, 15	
	7+	28	1800	1	
Lenalidomide	1+	28	25	1-21	
Dexamethasone	1+	28	40	1, 8, 15, 22	
DVd					
DaratumumabSC	1-3	21	1800	1, 8, 15	SmPC – Darzalex(1)
	4-8	21	1800	1	
	9+	28	1800	1	
Bortezomib	1-8	21	1.3	1, 4, 8, 11	
Dexamethasone	1-8	21	20	1, 2, 4, 5, 8, 9, 11, 12	
Kd					
Carfilzomib	1	28	20	1, 2	SmPC - Kyprolis(95); ENDEAVOR trial Dimopoulos 2016(305)
	1	28	56	8, 9, 15, 16	
	2+	28	56	1, 2, 8, 9, 15, 16	
Dexamethasone	1+	28	20	1, 2, 8, 9, 15, 16, 22, 23	
KRd					
Carfilzomib	1	28	20	1, 2	SmPC - Kyprolis(95)
	1	28	27	8, 9, 15, 16	
	2-12	28	27	1, 2, 8, 9, 15, 16	
	13-18	28	27	1, 2, 15, 16	
Lenalidomide	1+	28	25	1-21	
Dexamethasone	1+	28	40	1, 8, 15, 22	
ERd					
Elotuzumab	1-2	28	10	1, 8, 15, 22	SmPC - Empliciti(96)
	3+	28	10	1, 15	
Lenalidomide	1+	28	25	1-21	
Dexamethasone	1-2	28	8	1, 8, 15, 22	
	1-2	28	28	1, 8, 15, 22	
	3+	28	8	1, 15	
	3+	28	28	1, 15	
	3+	28	40	8, 22	
IRd					
Ixazomib	1+	28	4	1, 8, 15	SmPC – Ninlaro (97); TOURMALINE study; Moreau, et al. 2016(306)
Lenalidomide	1+	28	25	1-21	
Dexamethasone	1+	28	40	1, 8, 15, 22	
Pd					
Pomalidomide	1+	28	4	1-21	SmPC – Imnovid(99)
Dexamethasone	1+	28	40	1, 8, 15, 22	
Rd					
Lenalidomide	1+	28	25	1-21	SmPC – Darzalex(1)
Dexamethasone	1+	28	40	1, 8, 15, 22	
PVd					
Pomalidomide	1-8	21	4	1-14	SmPC – Imnovid(99)
	9+	21	4	1-14	
Bortezomib	1-8	21	1.3	1, 4, 8, 11	
	9+	21	1.3	1, 8	
Dexamethasone	1-8	21	20	1, 2, 4, 5, 8, 9, 11, 12	
	9+	21	20	1, 2, 8, 9	

Abbreviations: DRd = daratumumab, lenalidomide, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; Kd = Carfilzomib, dexamethasone; KRd = Carfilzomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone; ERd: Elotuzumab, lenalidomide,

dexamethasone; Pd = Pomalidomide + dexamethasone; PVd=pomalidomide, bortezomib, dexamethason; IRd: Ixazomib, lenalidomide, dexamethasone; PVd= pomalidomide, dexamethasone; SmPC = Summary of Product Characteristics.

26.4 Description of comparators

Table 170 Description of comparator: Bortezomib, thalidomide, dexamethasone (VTd)

Bortezomib, thalidomide, dexamethasone (VTd)	
Generic name(s) (ATC-code)	Bortezomib (L01XG01), Thalidomide (L04AX02), dexamethasone (H02AB02)
Mode of action	Bortezomib: Bortezomib is a proteasome inhibitor, 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.(307) Thalidomide: Thalidomide shows immunomodulatory, anti-inflammatory and potential anti-neoplastic activities. Data from in vitro studies and clinical trials suggest that the immunomodulatory, anti-inflammatory and anti-neoplastic effects of thalidomide may be related to suppression of excessive tumour necrosis factor-alpha (TNF-α) production, down-modulation of selected cell surface adhesion molecules involved in leukocyte migration and anti-angiogenic activity. Thalidomide is also a non-barbiturate centrally active hypnotic sedative. It has no antibacterial effects.(308) Dexamethasone: Dexamethasone is a synthetic glucocorticoid; it combines high anti-inflammatory effects with low mineralocorticoid activity.(309)
Pharmaceutical form	Bortezomib: Powder for solution for injection Thalidomide: Hard capsule Dexamethasone: Tablet
Posology	See Dosing and Posology Table 168, Appendix O – The patient population, the intervention and choice of comparators(s)
Method of administration	Bortezomib: intravenous or subcutaneous administration Thalidomide: Oral Dexamethasone: Oral
Dosing	See Dosing and Posology Table 168, Appendix O – The patient population, the intervention and choice of comparators(s)
Should the pharmaceutical be administered with other medicines?	Bortezomib: Antiviral prophylaxis is recommended for herpes zoster reactivation(307) Thalidomide: Thromboprophylaxis should be administered for at least the first 5 months of treatment especially in patients with additional thrombotic risk factors. Prophylactic antithrombotic medicinal products, such as low molecular weight heparins or warfarin, should be recommended.(308)

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Bortezomib, thalidomide, dexamethasone (VTd)	
Treatment duration/criteria for end of treatment	See Dosing and Posology Table 168, Appendix O – The patient population, the intervention and choice of comparators(s) Criteria for end of treatment: The Treatment Phase begins on Cycle 1 Day 1 and continues until disease progression, completion of the planned maintenance treatment duration for a maximum of 2 years. If disease progression is diagnosed, the subject discontinues the study drugs, completes the End-of-Treatment Visit, and enters the Follow-up Phase.(118) Subjects will be treated for the maximal allowed treatment duration. Unless a subject withdraws consent for study participation, or is lost to follow-up, an End-of-Treatment Visit is to be scheduled 30 days after the last dose of all components of the treatment regimen have been discontinued, or as soon as possible before the start of subsequent therapy.(118)
Necessary monitoring, both during administration and during the treatment period	Bortezomib: Complete blood counts (CBC) with differential and including platelet counts should be frequently monitored throughout treatment with bortezomib. It is recommended that patients be carefully monitored for symptoms of neuropathy.(307) Thalidomide: Patients should be monitored for CBC including platelet counts, thromboembolic events, peripheral neuropathy, severe skin reactions, bradycardia, syncope, somnolence, neutropenia and thrombocytopenia.(308)
Need for diagnostics or other tests (i.e. companion diagnostics)	Thalidomide: Hepatitis B virus status should be established before initiating treatment with thalidomide(308)
Packaging	Marketed in Denmark

Generic name	Strength	Pharmaceutical form	Route of administration	Immediate Packaging	Content (concentration	Pack size
Bortezomib	3.5 mg	Powder for solution for injection	Intravenous & Subcutaneous use	vial (glass)	NA	1 vial
Thalidomide	50 mg	Capsule, hard	Oral use	Blister	N/A	28 capsules
Dexamethasone	Multiple	Multiple	Multiple	Multiple	N/A	Multiple

Table 171 Description of comparator: Bortezomib, cyclophosphamide, dexamethasone (VCd)

Bortezomib, cyclophosphamide, dexamethasone (VCd)	
Generic name(s) (ATC-code)	Bortezomib (L01XG01), cyclophosphamide (L01AA01), dexamethasone (H02AB02)
Mode of action	Bortezomib: See Table 170 Cyclophosphamide: Cyclophosphamide is an alkylating agent of the nitrogen mustard type. An activated form of cyclophosphamide, phosphoramide mustard, alkylates, or binds, to DNA. Its cytotoxic effect is mainly due to cross-linking of strands of DNA and RNA, and to inhibition of protein synthesis. These actions do not appear to be cell-cycle specific.(310) Dexamethasone: See Table 170

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Bortezomib, cyclophosphamide, dexamethasone (VCd)	
Pharmaceutical form	Bortezomib: Powder for solution for injection Cyclophosphamide: Hard capsule Dexamethasone: Tablet
Posology	See Dosing and Posology Table 168, Appendix O – The patient population, the intervention and choice of comparators(s)
Method of administration	Bortezomib: intravenous or subcutaneous administration Cyclophosphamide: Oral or intravenous or subcutaneous administration Dexamethasone: Oral
Dosing	See Dosing and Posology Table 168, Appendix O – The patient population, the intervention and choice of comparators(s)
Should the pharmaceutical be administered with other medicines?	Bortezomib: See Table 170 Cyclophosphamide: Antimicrobial prophylaxis may be indicated in certain cases of neutropenia. In case of neutropenic fever, antibiotic therapy is indicated. Antimycotics and/or antivirals may also be indicated.(311)
Treatment duration/criteria for end of treatment	See Dosing and Posology Table 168, Appendix O – The patient population, the intervention and choice of comparators(s) Criteria for end of treatment: NA
Necessary monitoring, both during administration and during the treatment period	Bortezomib: See Table 170 Cyclophosphamide: Monitoring of complete blood counts is recommended during cyclophosphamide treatment. Monitor patients with risk factors for cardiotoxicity and with pre-existing cardiac disease. In addition, monitor patients for signs and symptoms of pulmonary toxicity.(311)
Need for diagnostics or other tests (i.e. companion diagnostics)	Bortezomib: See Table 170 Cyclophosphamide: No
Packaging	Marketed in Denmark

Generic name	Strength	Pharmaceutical form	Route of administration	Immediate Packaging	Content (concentration	Pack size
Bortezomib	3.5 mg	Powder for solution for injection	Intravenous & Subcutaneous use	vial (glass)	NA	1 vial
Cyclophosphamide	Multiple	Multiple	Multiple	Multiple	N/A	Multiple
Dexamethasone	Multiple	Multiple	Multiple	Multiple	N/A	Multiple

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Table 172 Description of comparator: Bortezomib, lenalidomide, dexamethasone (VRd)

Bortezomib, lenalidomide, dexamethasone (VRd)	
Generic name(s) (ATC-code)	Bortezomib (L01XG01), lenalidomide (L04AX04), dexamethasone (H02AB02)
Mode of action	Bortezomib: See Table 170 Lenalidomide: 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.(165)Dexamethasone: See Table 170
Pharmaceutical form	Bortezomib: Powder for solution for injection Lenalidomide: Capsule, hard Dexamethasone: Tablet
Posology	See Dosing and Posology Table 168, Appendix O – The patient population, the intervention and choice of comparators(s)
Method of administration	Bortezomib: intravenous or subcutaneous administration Lenalidomide: Oral Dexamethasone: Oral
Dosing	See Dosing and Posology Table 168, Appendix O – The patient population, the intervention and choice of comparators(s)
Should the pharmaceutical be administered with other medicines?	Bortezomib: See Table 170 Lenalidomide: Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors.(165)
Treatment duration/criteria for end of treatment	See Dosing and Posology Table 168, Appendix O – The patient population, the intervention and choice of comparators(s) Duration of therapy (VRd cycles, stem cells collection and transplant, maintenance) will depend on individual response, evidence of disease progression and tolerance.(123) Treatment discontinuation if following occur: disease progression, treatment delay for toxicity for more than 6 weeks, pregnancy or suspected pregnancy, unacceptable adverse event(s)/serious adverse event(s).(123)
Necessary monitoring, both during administration and during the treatment period	Bortezomib: See Table 170 Lenalidomide: A complete blood cell count, including white blood cell count with differential count, platelet count and haemoglobin should be performed at baseline, every week for the first 8 weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias. Previously Hepatitit B virus infected patients should be closely monitored for signs and symptoms of viral reactivation, including active HBV infection, throughout therapy. Patients with known risk factors should be closely monitored.(165)

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Bortezomib, lenalidomide, dexamethasone (VRd)

Need for diagnostics or other tests (i.e. companion diagnostics)

Bortezomib: See Table 170

Lenalidomide: Hepatitis B virus status should be established before initiating treatment with lenalidomide(165)

Packaging

Currently marketed in Denmark

Generic name	Strength	Pharmaceutical form	Route of administration	Immediate Packaging	Content (concentration	Pack size
Bortezomib	3.5 mg	Powder for solution for injection	Intravenous & Subcutaneou use	vial (glass)	N/A	1 vial
Lenalidomide	Mg: 2.5; 5; 7.5; 10; 15; 20; 25	Capsule, hard	Oral use	Blister	N/A	21 capsules
Dexamethasone	Multiple	Multiple	Multiple	Multiple	N/A	Multiple

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27. Appendix P Health economic analysis – model input

Table 173. Second-line TTD and PFS

Second-line Treatment	Median Treatment Duration (Months)	Median Treatment Duration Source	Median PFS (Months)	Median PFS Source
DRd	[redacted]	[redacted]	53.3	MMY3003, 1 prior line,, ASH2019(312)
DVd	[redacted]	[redacted]	27.0	MMY3004, 1 prior line, NR, ASH 2019 data cut(313)
Kd	9.6	ENDEAVOR study, 1 prior line (estimate based on mean duration)(314)	22.2	ENDEAVOR study, 1 prior line(314)
KRd	19.1	ASPIRE study, 1 prior line(305)	29.6	ASPIRE study, 1 prior line(305)
Rd	14.7	ASPIRE study, 1 prior line(305)	17.6	ASPIRE study, 1 prior line(305)
ERd	17.0	ELOQUENT-2, ITT, Dimopoulos et al. Blood Cancer Journal 2020(315)	30.6	ELOQUENT-2, 1 prior line, Dimopoulos et al. Blood Cancer Journal 2018(316)
PVd	15.1	OPTIMISMM, 1 prior line estimate, calculated based on table 2 in manuscript(317)	20.7	OPTIMISMM, 1 prior line (172)
IRd	15.7	TOURMALINE study, ITT Moreau, et al. 2016(318)	20.6	TOURMALINE study, ITT, Moreau, et al. 2016(318)

Abbreviations: DRd = daratumumab, lenalidomide, dexamethasone; DVd = daratumumab, bortezomib, dexamethasone; ITT = Intention-to-treat; Kd = Carfilzomib, dexamethasone; KRd = Carfilzomib, lenalidomide, dexamethasone; Rd = lenalidomide, dexamethasone; ERd: Elotuzumab, lenalidomide, dexamethasone PVd=pomalidomide, bortezomib, dexamethason; IRd: Ixazomib, lenalidomide, dexamethasone; TTD = Time-to-treatment-discontinuation; PFS = Progression-free survival

Table 174. Third-line TTD and PFS

Third-line Treatment	Median Treatment Duration (Months)	Median Treatment Duration Source	Median PFS (Months)	Median PFS Source
Kd	8.7	ENDEAVOR study, ≥2 prior lines, estimate based on mean duration(314)	14.9	ENDEAVOR study, ≥2 prior lines (314)
KRd	20.8	ASPIRE study, ≥2 prior lines(305)	25.8	ASPIRE study, ≥2 prior lines (305)
ERd	13.9	Assumption proportional to PFS based on Dimopoulos 2020(315)	25.0	ELOQUENT-2, 1 prior line, Dimopoulos et al. Blood Cancer Journal 2018(316)

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Third-line Treatment	Median Treatment Duration (Months)	Median Treatment Duration Source	Median PFS (Months)	Median PFS Source
PVd	4.4	OPTIMISMM, assumption based on IQR3 in Suppl Table 3(172)	9.5	OPTIMISMM, assumption
Pd	3.4	Assumed same as daratumumab, SIRIUS (MMY2002) NICE TA510(319)	4	NIMBUS 2013(320)

Abbreviations: Kd = Carfilzomib, dexamethasone; KRd = Carfilzomib, lenalidomide, dexamethasone; ERd: Elotuzumab, lenalidomide, dexamethasone PVd=pomalidomide, bortezomib, dexamethason; Pd=pomalidomide, bortezomib, dexamethason; TTD = Time-to-treatment-discontinuation; PFS = Progression-free survival

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Forhandlingsnotat

Dato for behandling i Medicinrådet	26.01.2022
Leverandør	Janssen-Cilag
Lægemiddel	Daratumumab (Darzalex)
Ansøgt indikation	Daratumumab i kombination med bortezomib, thalidomid og dexamethason til behandling af patienter med nydiagnosticeret knoglemarvskræft, som er kandidater til højdosis kemoterapi med stamcellestøtte.

Forhandlingsresultat

[redacted]

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

[redacted]

[redacted]

Konkurrencesituationen:

Den årlige behandlingspris i lægemiddelomkostninger for daratumumab, lenalidomid, carfilzomib, ixazomib og pomalidomid vises i tabellen herunder (priser pr 1.1.2022).

Lægemiddel	Dosering	1 års behandling (DKK)
Daratumumab	1800 mg s.c. ugentligt i fra uge 1-6 (6 doser) og hver tredje uge fra uge 7-52(16 doser)	[redacted]
Lenalidomid	25 mg dag 1-14 af 21 dage i 8 serier Dernæst serier af 28 dage Lenalidomid 25 mg p.o. på dag 1-21	[redacted]
Carfilzomib	Serie 1: 20 mg/m2 dag 1 og 2-56 mg/m2 dag 8, 9, 15 og 16 Serie 2 og over: 56 mg/m2 dag 1, 2, 8, 9, 15 og 16	[redacted]
Ixazomib	4 mg Dag 1, 8 og 15 ud af 28, hver 4 uge	[redacted]
Pomalidomid	4 mg. Dag 1-21 hver 4 uge	[redacted]

Konklusion

Amgros forventer ikke at kunne få en bedre pris før der kommer større konkurrence på området.

[redacted]

Note from Janssen-Cilag on the evaluation of Darzalex® in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant

Assessment of relative effect

Janssen strongly disagrees with the conclusion that it is not possible to determine an effect difference in favor of DaraBorThalDex (DVTd) compared to the BorLenDex (VRd) regimen. Firstly, Janssen disagrees with not using the results from the matching adjusted indirect comparison (MAIC) and solely relying on a naïve cross-trial comparison. Secondly, the naïve comparison presented in the evaluation report by the Danish Medicines Council (DMC) is biased in favor of VRd.

In the MAIC, both progression-free survival (PFS) and overall survival (OS) were included to estimate the difference in efficacy of DVTd vs VRd. The possibility to adjust for effect modifiers in a MAIC is dependent on the availability of baseline characteristics in publications, in this case the IFM-2009 study. We agree with the DMC that the patient populations in CASSIOPEIA and IFM-2009 are broadly similar and that an indirect comparison therefore is possible to perform. One main critique leading to the assessment of high degree of uncertainty in the results from the MAIC seems to stem from the difference in time periods when patients were recruited in the CASSIOPEIA and IFM-2009 studies. While it is correct that there was a 5-year difference in the recruitment period, we believe that this time gap does not impact the degree of uncertainty related to the estimated PFS and OS differences in the analysis. We agree with the DMC that the introduction of new effective therapies in the recent years has improved the survival prognosis for myeloma patients in both first- and later treatment lines. However, for the assessment of PFS, the difference in availability of more effective later line therapies during the period the CASSIOPIEA study was performed has no impact on the assessment of relative efficacy vs VRd.

The use of maintenance treatment was not explicitly adjusted for in the MAIC, but we believe that the results are biased in favor of VRd in this respect. In CASSIOPEIA, patients underwent a second randomization after consolidation at which only half of patients in the DVTd group received daratumumab maintenance for a maximum of two years. In IFM-2009 on the other hand, all patients were planned to receive lenalidomide maintenance. Assuming both maintenance regimens have a positive impact on survival, the impact on PFS is biased in favor of VRd as maintenance was intended for all patients in IMF-2009, while only approximately 50% received maintenance in CASSIOPEIA. Lenalidomide maintenance has proven to be effective in prolonging both PFS and OS [1] and is also approved by EMA. In contrast, the results from CASSIOPEIA part 2 show that daratumumab maintenance every 8 weeks had no significant impact on the PFS of patients receiving DVTd as induction and consolidation [2]. Overall, the impact of maintenance is therefore biasing the results in favor of VRd rather than in favor of DVTd.

Regarding OS, it is possible that use of different second- or later line therapies can impact the results. As relapse is inevitable for almost all patients, the majority of patients in a study setting or in real life would receive subsequent therapy. However, the impact of subsequent therapies in the MAIC is likely limited in this case since a minority of patients in the study had received a second or later line therapy. In the data cut used from the IFM-2009 study, only 35% of the patients (123 of 350) had received a second line treatment after progression [3]. While newer therapies such as daratumumab or carfilzomib were not available at the timepoint patients were recruited to IFM-2009, the use of different subsequent treatments would only have had a potential impact on approximately one third of the patient group in the study. Similarly, in CASSIOPEIA the share of patients that received subsequent therapy is limited (approx. 20% in the most recent data-cut [2]). Hence, even though patients could be treated with more effective subsequent therapies in CASSIOPEIA compared to in the IFM-2009 study, it only applies to a subset of the patients in the indirect comparison and therefore has a limited impact on the MAIC results. As for PFS, the impact of differences in maintenance in IFM-2009 and CASSIOPEIA is biasing results in favor for VRd since lenalidomide is proven to have a positive impact on OS – an advantage which has not been adjusted for in the MAIC.

On a separate note, in the evaluation of the therapeutic area of multiple myeloma by the DMC, it is stated that both BorCyDex (VCd), VRd, and VTd can be used for induction treatment [4]. Overall, the Medicines Council did not conclude that there was an efficacy difference between VTd, VCd, and VRd. However, it is stated by the Medicines Council that *VTd has shown to give a better response* [4, p. 26], which may indicate this is the most efficacious regimen of the three from a response perspective. In addition to these points in the evaluation of the therapeutic area of multiple myeloma conducted by the DMC, Janssen has provided supporting MAIC analyses showing that no statistically significant differences in OS and PFS were observed between VRd and VTd. In turn, from a naïve perspective, one would expect similar findings to what has been observed in CASSIOPEIA if DVTd had been compared directly with VRd in a head-to-head trial and hence, show superiority vs. VRd.

Regarding the naïve comparison of DVTd vs. VRd from the GRIFFIN study conducted by the DMC, we believe the analysis is insufficient to conclude equal effect of these regimens. The GRIFFIN trial is a phase II study designed to evaluate response with stringent complete response as primary endpoint. Hence, it is not powered to evaluate PFS or OS. GRIFFIN has a much smaller patient population size compared to both CASSIOPEIA and IFM-2009 which are both phase III RCTs. Hence, using PFS and OS rates from GRIFFIN is associated with uncertainty in an indirect comparison. Even if a comparison is made, it should be noticed that once

again, the difference in maintenance is also here biased in favor of VRd as all patients in GRIFFIN received an approved regimen that has a proven PFS and OS benefit, while the PFS and OS rates from CASSIOPEIA used in the comparison reflect patients not receiving maintenance (DVTd-OBS).

With the uncertainties in mind for the GRIFFIN study, the OS rates that the DMC reports in table 8 of the evaluation report shows survival differences already at month 24 and 36. For DVTd-OBS, an OS rate of [redacted] was observed and 93.3% for VRd (GRIFFIN) at month 24. At month 36, the OS-rate was [redacted] for DVTd-OBS vs. 87% for VRd (FMG-MM02). Furthermore, in terms of the change in OS-rate over time with reference to table 8 of the evaluation report, there is a clear trend that DVTd is outperforming VRd with lower drops in OS-rate over time.

- From month 12 to 24, we observe a drop of [redacted] percentage points for DVTd (CASSIOPEIA), 4.6 percentage points drop for VRd (GRIFFIN) and 4 percent points for VRd (FMG-MM02).
- From month 24 to 36, we observe a drop of [redacted] percentage points for DVTd (CASSIOPEIA) and 9 percentage points for VRd (FMG-MM02).

Depth of response after consolidation is another important endpoint. Rates of stringent complete response (sCR) were similar between GRIFFIN and CASSIOPEIA, despite the fact that it was "easier" to achieve sCR in the GRIFFIN study as clonality in the bone marrow evaluation was done locally, while CASSOIPEIA required a central lab flow cytometry. Even more importantly, response based on the most modern methods is doubled after DVTd vs. VRd (GRIFFIN) with a MRD negativity (for patients in CR or better, same sensitivity 10^{-5}) of 34% vs. 16.5%.

We believe that a correct interpretation of the stated studies provides evidence for a response and survival advantage of DVTd as compared to VRd.

Survival extrapolation in MC model adaptation

Regarding the predicted PFS and OS in DMC's base case, we find them extremely conservative towards DVTd. There is no clear rationale for why [redacted] is being applied for both PFS and OS. We acknowledge that there is uncertainty regarding long term predictions given that the CASSIOPEIA survival data is not yet mature. However, for both PFS and OS the modeled survival for DVTd is significantly shorter than what has been observed in CASSIOPEIA. For example, median PFS for DVTd is estimated at 48 months in DMC's base case, while in CASSIOPEIA the Kaplan-Meier estimated PFS rate at 48 months is [redacted] and hence at 44.5 months follow-up of CASSIOPEIA, the median PFS for DVTd has not yet been reached. Similarly for OS, the modeled survival predictions significantly underestimate the observed survival rates in CASSIOPEIA. For example, at 36 months and 48 months the modeled OS rates are approximately [redacted] lower in the DMC base case compared to the observed rates in CASSIOPEIA.

Conclusion

In conclusion, we advocate for more emphasis on studies with high level of evidence (IFM-2009 superior to GRIFFIN) and a more balanced interpretation of the results as exemplified in the above argumentation. In our opinion, this demonstrates that DVTd is superior for induction/consolidation with respect to depth of response and survival when compared to VRd and with similar toxicity to the current standard of care in Denmark. We hope this note will result in a reassessment of the naïve cross-trial comparisons approach applied by the DMC to determine whether efficacy differences exist by the DMC, and this will result in an actual assessment of the submitted cost-utility analysis as we believe efficacy differences exists.

Best regards,
Janssen-Cilag A/S

References

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