Medicinrådet

Bilag til direkte indplacering af daratumumab i kombination med bortezomib, lenalidomid og dexamethason (D-VRd) i Medicinrådets evidensgennemgang vedr. lægemidler til nydiagnosticerede patienter med knoglemarvskræft, der ikke er kandidater til HDT

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. daratumumab i kombination med bortezomib, lenalidomid og dexamethason (D-VRd)
2. Ansøgers endelige ansøgning vedr. daratumumab i kombination med bortezomib, lenalidomid og dexamethason (D-VRd)

Johnson&Johnson

20-04-2026

Til Medicinrådet

Vedr. den direkte indplacering af DaraBorLenDex (DVRd) i behandlingsvejledningen for patienter med nydiagnosticeret knoglemarvskræft, som ikke er HDT-egnede.

Tak for muligheden for at gennemgå dele af det materiale, der ligger til grund for den direkte indplacering af DaraBorLenDex i behandlingsvejledningen.

Det er vanskeligt at forholde sig fuldt ud meningsfuldt til vurderingen, når væsentlige dele af vurderingsgrundlaget er udeladt fra det fremsendte materiale. Dette begrænser vores mulighed for at vurdere sammenhængen mellem data, fortolkning og konklusioner samt at identificere eventuelle faktuelle fejl og bidrage til en tilstrækkeligt oplyst sagsbehandling, som ellers er forudsat ved vurdering og indplacering af nye lægemidler.

Med dette forbehold har vi gennemgået materialet. Overordnet vurderer vi, at data stemmer overens med det indsendte grundlag i forbindelse med ansøgningen om direkte indplacering. Vi har dog identificeret en nogle konkrete afvigelser, herunder i beregninger til omkostningsanalysen, som er fremsendt særskilt til sekretariatet.

Proces, metodik og effektmål

Vi vil understrege, at dialogen med sekretariatet har været god og konstruktiv. Set i et samlet perspektiv har processen dog været præget af uklarhed, idet sagsbehandlingen har haft karakter af både en direkte indplacering og en opdatering af behandlingsvejledningen, uden at dette har været klart afgrænset. At der midt i en allerede igangsat sagsbehandling er fremkommet en protokol for behandsvejledningen den 18. februar 2026, hvori metoderne for evidensgennemgangen beskrives, har yderligere bidraget til uklarhed om det proces- og metodegrundlag, vurderingen hviler på.

I den sammenhæng giver valg og vægtning af effektmål anledning til bemærkninger, idet de indebærer en risiko for at favorisere mere intensive og toksiske regimer. I førstelinjebehandling af nydiagnosticeret knoglemarvskræft, hvor den samlede overlevelse ofte er lang, og hvor efterfølgende behandlingslinjer og crossover har væsentlig betydning, er samlet overlevelse ikke altid et modent eller metodisk velegnet primært beslutningsgrundlag. En valgt tærskel (MKRF) på seks måneders forbedring i median OS vurderes derfor som høj i denne kontekst. Sikkerhed, tolerabilitet og livskvalitet tillægges ikke proportionel vægt, hvilket ellers er relevant i en ældre og mere skrøbelig patientpopulation.

Mere overordnet giver det anledning til refleksion over, hvordan der i behandlingsvejledningen defineres, hvad der anses for *tilstrækkelig* behandling. I sygdomsområder som knoglemarvskræft sker behandlingsudviklingen i høj grad gennem inkrementelle forbedringer, hvor gradvise gevinster i effekt, tolerabilitet, administrationsform og livskvalitet samlet bidraget væsentligt til patienternes prognose og behandlingsforløb. En vurdering, der lægger overvejende vægt på snævre effektmål eller høje tærskler for klinisk relevans, kan indebære en risiko for at undervurdere sådanne fremskridt.

Johnson&Johnson

Hjemmebehandling med daratumumab

Afslutningsvis bemærkes, at **daratumumab som det eneste CD38-antistof og eneste subkutane onkologiske lægemiddel nu er EMA-godkendt til selvadministration i hjemmet**. Dette er en væsentlig milepæl for patienter og for udviklingen af hjemmebehandling og understøtter både ambitionerne i Medicinrådets strategi for 2025-2027 om øget behandling uden for sygehusene, samt målsætninger i sundhedsreformen.

Vi håber, at ovenstående bemærkninger kan indgå i den videre behandling, hvor vi ønsker at bidrage konstruktivt til et fagligt robust beslutningsgrundlag, og står naturligvis til rådighed for eventuel yderligere dialog.

Application for the assessment of daratumumab (Darzalex) in combination with bortezomib, lenalidomide, and dexamethasone (D-VRd) by updating the treatment guideline for multiple myeloma

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Tables and Figures

Abbreviations

Abbreviation	
ASCT	Autologous stem cell transplant
ATT	Average treatment effect on the treated population
CR	Complete response
DMC	Danish Medicines Council
DoR	Duration of response
DRd	Daratumumab in combination with lenalidomide and dexamethasone
DVRd	Daratumumab in combination with bortezomib, lenalidomide, and dexamethasone
EGOC PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire 30-item core module
EQ-5D-5L	EuroQol 5 Dimension 5-Level
HRQoL	Health-related quality of life
IPD	Individual patient data
IPTW	Inverse probability of treatment weighting
ITC	Indirect treatment comparison
IV	Intravenous infusion
KME	Kaplan-Meier estimates
MM	Multiple myeloma
MRD	Minimal Residual Disease
NDMM	Newly diagnosed multiple myeloma
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival

PFS2	Progression-free survival until patients' second progression
PO	Oral administration
PRO	Patient-reported outcome
Rd	Lenalidomide and dexamethasone
SC	Subcutaneous
sCR	Stringent complete response
TIE	Transplant ineligible
VGPR	Very good partial response
VRd	Bortezomib, lenalidomide and dexamethasone
ASCT	Autologous stem cell transplant

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Darzalex
Generic name	Daratumumab
Therapeutic indication as defined by EMA	Darzalex is indicated in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma
Marketing authorization holder in Denmark	Janssen-Cilag A/S, a Johnson & Johnson Company
ATC code	L01FC01
Combination therapy and/or co-medication	Yes. Bortezomib, lenalidomide and dexamethasone
(Expected) Date of EC approval	07-04-2025
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	Yes

Overview of the pharmaceutical	
Orphan drug designation (include date)	Yes. 17th July 2013
Other therapeutic indications approved by EMA	• Daratumumab in combination with bortezomib, melphalan, and prednisone (DaraBorMelPred) for adult patients with newly diagnosed • Daratumumab in combination with lenalidomide and dexamethasone (DaraLenDex) for patients who have not received daratumumab in the first line • Daratumumab in combination with lenalidomide and dexamethasone (DaraLenDex) for adult patients with newly diagnosed myeloma who are not candidates for autologous stem cell transplantation • Daratumumab in combination with cyclophosphamide, bortezomib, and dexamethasone (Dara-CyBorD) for adult patients with newly diagnosed systemic AL amyloidosis • Daratumumab in combination with bortezomib, thalidomide, and dexamethasone (DaraBorThalDex) for adult patients with newly diagnosed myeloma who are candidates for autologous stem cell transplantation • Daratumumab in combination with bortezomib, lenalidomide and dexamethasone (DaraBorLenDex) for adult patients with newly diagnosed myeloma who are candidates for autologous stem cell transplantation
Other indications that have been evaluated by the DMC (yes/no)	Yes, see indications listed above
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	**Injection solution.** One vial (15 ml) contains 1,800 mg daratumumab

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Daratumumab in combination with bortezomib, lenalidomide, and dexamethasone for patients with newly diagnosed myeloma who are not eligible for autologous stem cell transplantation.
Dosage regiment and administration:	Cycle 1-8 (21-day cycles) • Daratumumab: 1,800 mg SC QW, cycle 1-2, thereafter Q3W cycle 3-8

Summary	
	• Bortezomib: 1.3 mg/m^2 SC days 1, 4, 8, 11 • Lenalidomide: 25 mg PO days 1-14 • Dexamethasone: 20 mg PO days 1, 2, 4, 5, 8, 9, 11, 12 Cycle 9+ (28-day cycles) • Daratumumab: 1,800 mg SC Q4W • Lenalidomide: 25 mg PO days 1-21 Dexamethasone: 40 mg PO Days 1, 8, 15, 22
Choice of comparator [if any]	Daratumumab in combination with lenalidomide and dexamethasone (DRd – DaraLenDex)
Most important efficacy endpoints (Difference/gain compared to comparator)	IPTW MRD negativity – base case: OR 2.97 (1.96,4.51), p-value: 0.000 PFS – base case: OR 0.68 (0.48, 0.95), p-value: 0.030 OS COVID-19 censored – base case: OR 0.66 (0.43, 1.03), p-value: 0.067 ORR – base case: OR 4.01 (0.90,17.81), p-value: 0.068
Most important serious adverse events for the intervention and comparator	Peripheral sensory neuropathy: DVRd (9.7%), DRd (<5%)

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

The current Danish Medicines Council (DMC) treatment guideline for multiple myeloma (version 1.15) was approved on 20 January 2025. DVRd is expected to be included in the guideline for newly diagnosed multiple myeloma (NDMM) patients who are not eligible for stem cell transplantation (TIE). An upcoming update will also include daratumumab combined with lenalidomide and dexamethasone (DRd, DaraLenDex), which the DMC recommended as a standard treatment on 21 May 2025. DVRd provides a statistically significant improvement in progression-free survival (PFS) compared with DRd; however, the latest DVRd data cut does not demonstrate a statistically significant overall survival (OS) benefit versus DRd. Therefore, DVRd is considered at least as effective as DRd.

3.2 The intervention

Overview of intervention	
Therapeutic indication relevant for the assessment	Daratumumab in combination with bortezomib, lenalidomide, and dexamethasone for patients with newly diagnosed myeloma who are not eligible for autologous stem cell transplantation.
Method of administration	Daratumumab: subcutaneous (SC) Bortezomib: SC Lenalidomide: oral Dexamethasone: oral
Dosing	Cycle 1-8 (21-day cycles) • Daratumumab: 1,800 mg SC QW, cycle 1-2, thereafter Q3W cycle 3-8 • Bortezomib: 1.3 mg/m^2 SC days 1, 4, 8, 11 • Lenalidomide: 25 mg PO days 1-14 • Dexamethasone: 20 mg PO days 1, 2, 4, 5, 8, 9, 11, 12 Cycle 9+ (28-day cycles) • Daratumumab: 1,800 mg SC Q4W • Lenalidomide: 25 mg PO days 1-21 Dexamethasone: 40 mg PO Days 1, 8, 15, 22
Should the pharmaceutical be administered with other medicines?	Yes. Bortezomib, lenalidomide and dexamethasone.
Treatment duration / criteria for end of treatment	Until progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	All patients should be monitored throughout the infusion for IRRs. Complete blood cell counts should be monitored periodically during treatment.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	N/A
Package size(s)	Injectable solution: 1 vial (15 ml) contains 1,800 mg daratumumab. Concentrate for infusion solution: 1 ml contains 20 mg daratumumab. Available in two packaging sizes: 5 ml and 20 ml.

3.2.1 The intervention in relation to Danish clinical practice

DVRd is approved as frontline treatment of patients with NDMM who are TIE. No additional tests or procedures are required to implement DVRd beyond the current standard of care.

4. Overview of literature

There is no Phase III clinical trial that directly compares the treatment regimens comprising daratumumab, bortezomib, lenalidomide, and dexamethasone (DVRd) and daratumumab, lenalidomide and dexamethasone (DRd). As a result, an indirect treatment comparison (ITC) was conducted to assess the efficacy and safety outcomes of DVRd versus DRd. The clinical efficacy and safety of DVRd and DRd were informed by the May 2024 clinical cut-off from the CEPHEUS trial and the February 2021, October 2021, and November 2023 clinical cut-offs from the MAIA trial.

The CEPHEUS trial is an ongoing Phase III randomized, controlled, open-label, multicenter study that evaluates the efficacy, safety, and patient-reported outcomes (PROs) of DVRd compared to the regimen comprising bortezomib, lenalidomide, and dexamethasone (VRd). This trial served as the pivotal study for the regulatory approval granted by the EMA for DVRd treatment in NDMM patients who are ineligible for transplantation (TIE)—the population relevant to this assessment. It is noteworthy that the CEPHEUS trial includes both NDMM patients who are TIE and those who are transplant deferred. However, the transplant deferred population is not relevant in the Danish context, and therefore, only the TIE cohort from CEPHEUS was considered for this assessment. All endpoints from the CEPHEUS trial included in this evaluation were informed by the May 2024 clinical cut-off, which had a median follow-up of 58.71 months.

The MAIA trial is a completed Phase III randomized, controlled, open-label, multicenter study that examines the efficacy, safety, and PROs of DRd compared to the regimen comprising lenalidomide and dexamethasone (Rd). This trial was pivotal for the EMA's regulatory approval of DRd treatment in newly diagnosed TIE MM patients. Unlike the CEPHEUS trial, the MAIA trial exclusively includes newly diagnosed TIE MM patients, with no transplant deferred patients. All endpoints from the MAIA trial, except for EQ-5D-5L and overall survival (OS), were informed by the October 2021 clinical cut-off (median follow-up of 64.5 months), while EQ-5D-5L and OS were informed by the February 2021 and November 2023 clinical cut-offs (median follow-up of 89.3 months), respectively. Notably, at the November 2023 clinical cut-off, only OS was assessed.

Neither the CEPHEUS nor the MAIA trial was selected based on a systematic literature review for the following reasons: The CEPHEUS trial is the pivotal study for DVRd in the population relevant to this assessment and is the only clinical trial evaluating the efficacy and safety of DVRd in this population. While the efficacy and safety of DVRd have also been assessed in the PERSEUS trial, this study includes newly diagnosed MM patients

who are eligible for transplantation, making the PERSEUS population irrelevant for evaluating outcomes among patients ineligible for transplantation.

Johnson & Johnson (J&J), the market authorization holder of daratumumab, is responsible for the market authorization of both the DVRd and DRd combinations. To date, no other clinical trial (apart from MAIA) has been conducted with DRd as the interventional regimen in the relevant population of newly diagnosed TIE MM patients. DRd was not identified as a comparator to an interventional regimen in any Phase III clinical trial based on a targeted literature review.

The use of J&J-sponsored trials ensures the availability of individual-level patient data (IPD). This availability enables more robust ITCs compared to those relying solely on aggregate-level data. Specifically, having IPD from all trials included in an ITC facilitates a more rigorous matching process of populations across different trials. Both CEPHEUS and MAIA were sponsored by J&J, ensuring IPD availability from both trials. Table 1 provides an overview of the relevant literature used for the clinical assessment of efficacy and safety, with further details outlined in Appendix A.

Table 1. Relevant literature included in the assessment of efficacy and safety

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
CEPHEUS, NCT03652064, (Usmani, S.Z., Facon, T., Hungria, V. et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. Nat Med 31, 1195–1202	Randomized phase III / open-label / DVRd versus VRd	The end of study was defined as the later of the primary PFS analysis (162 events) or 5 years after the last subject was randomized.	Start: 06/11/2018 Completion: Ongoing Data cut-off: 07/05/2024 Future data cut-offs: 08/10/2025*	Newly diagnosed TIE MM patients. The study also includes transplant deferred patients but these are not part of this assessment. The included patient population is therefore a (protocol-defined) subgroup in the CEPHEUS trial.	DVRd, type of administration and dosage are outlined in Table 2.	VRd, type of administration and dosage are outlined in Table 2.	1	• Overall Minimal Residual Disease (MRD) negativity rate (10^{-5} sensitivity threshold) • Overall Survival (OS) • Progression-Free Survival (PFS) • Overall Response Rate (ORR) • EORTC QLQ-C30 • EQ-5D-5L

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
(2025). https://doi.org/10.1038/s41591-024-03485-7 [1])								
MAIA, NCT02252172, (Facon, T., Moreau, P., Weisel, K. et al. Daratumumab/lenalidomide/dexamethasone in transplant-ineligible newly diagnosed myeloma: MAIA long-term outcomes. Leukemia. 2025 Apr;39(4):942-950. doi: 10.1038/s41375-024-02505-2 [2].	Randomized phase III / open-label / DRd versus Rd	The first of 330 deaths or 7 years after last patient randomized.	Start: 16/02/2015 Completion: 02/10/2024 Data cut-off: 19/02/2021 Future data cut-offs: 21/11/2021	Newly diagnosed TIE MM patients.	DRd, type of administration and dosage are outlined in Table 3.	Rd, type of administration and dosage are outlined in Table 3.	1	• EQ-5D-5L

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
MAIA, NCT02252172, (Facon, T., Moreau, P., Weisel, K. et al. Daratumumab/lenalidomide/dexamethasone in transplant-ineligible newly diagnosed myeloma: MAIA long-term outcomes. Leukemia. 2025 Apr;39(4):942-950. doi: 10.1038/s41375-024-02505-2 [2].	Randomized phase III / open-label / DRd versus Rd	The first of 330 deaths or 7 years after last patient randomized.	Start: 16/02/2015 Completion: 02/10/2024 Data cut-off: 21/10/2021 Future data cut-offs: 08/10/2023	Newly diagnosed TIE MM patients.	DRd, type of administration and dosage are outlined in Table 3.	Rd, type of administration and dosage are outlined in Table 3.	1	• Overall Minimal Residual Disease (MRD) negativity rate (10^{-5} sensitivity threshold) • PFS • ORR • EORTC QLQ-C30
MAIA, NCT02252172, (Facon, T.,	Randomized phase III /	The first of 330 deaths or 7 years after last	Start: 16/02/2015	Newly diagnosed TIE MM patients.	DRd, type of administration and dosage are	Rd, type of administration and dosage are	1	• OS

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
Moreau, P., Weisel, K. et al.	open-label / DRd versus Rd	patient randomized.	Completion: 02/10/2024 Data cut-off: 30/11/2023 Future data cut-offs: N/A		outlined in Table 3.	outlined in Table 3.		

* While the clinical cut-off have been conducted there is to date no data available.

Table 2. CEPHEUS, Dosage and Type of Administration

Treatment Regimen	Cycle	Dose per administration	Number of administrations per cycle	Cycle length (days)	Type of Administration	Source
DVRd						
Daratumumab	1-2	1800 mg	3	21	Subcutaneous injection (SC)	ClinicalTrials.gov [3]
	3-8	1800 mg	1	21	SC	
	9+	1800 mg	1	28	SC	
Bortezomib	1-8	1.3 mg per m^2	4	21	SC	ClinicalTrials.gov [3]
Lenalidomide	1-8	25 mg	14	21	Oral	ClinicalTrials.gov [3]
	9+	25 mg	21	28	Oral	
Dexamethasone	1-8	40 mg	8	21	Oral	ClinicalTrials.gov [3]

	9+	40 mg	4	28	Oral	
VRd						
Bortezomib	1-8	1.3 mg per m^2	4	21	SC	ClinicalTrials.gov [3]
Lenalidomide	1-8	25 mg	14	21	Oral	ClinicalTrials.gov [3]
	9+	25 mg	21	28	Oral	
Dexamethasone	1-8	40 mg	8	21	Oral	ClinicalTrials.gov [3]
	9+	40 mg	4	28	Oral	

Table 3. MAIA, Dosage and Type of Administration

Treatment Regimen	Cycle	Dose per administration	Number of administrations per cycle	Cycle length (days)	Type of Administration	Source
DRd						
Daratumumab	1-2	16 mg per m^2	4	28	Intravenous infusion (IV)*	ClinicalTrials.gov [4]
	3-4	16 mg per m^2	2	28	IV*	
	5+	16 mg per m^2	1	28	IV *	
Lenalidomide	1+	25 mg	21	28	Oral	ClinicalTrials.gov [4]
Dexamethasone	1+	40 mg	4	28	Oral	ClinicalTrials.gov [4]
Rd						
Lenalidomide	1+	25 mg	21	28	Oral	ClinicalTrials.gov [4]
Dexamethasone	1+	40 mg	4	28	Oral	ClinicalTrials.gov [4]

* SC administration of daratumumab (with a fixed dose of 1800 mg) was not yet introduced when the MAIA trial was initiated. However, since the introduction of this type of administration (SC), this type of administration with a fixed dose of 1800 mg is allowed for daratumumab as part of DRd.

5. Clinical question 1

5.1 Efficacy of DVRd compared to DRd for patients with newly diagnosed Multiple Myeloma who are ineligible for transplantation

5.1.1 Relevant studies

As noted in Section 4, there is no Phase III head-to-head clinical trial comparing the efficacy and safety outcomes of DVRd to DRd. Therefore, these outcomes were established through an ITC, utilizing data from the CEPHEUS trial and the MAIA trial to inform the efficacy and safety of DVRd and DRd, respectively. The rationale for selecting these two trials (CEPHEUS and MAIA) to inform the efficacy and safety of DVRd and DRd is outlined in the previous section (Section 4).

5.1.1.1 CEPHEUS

The CEPHEUS trial was a randomized, open-label, active-controlled, parallel-group, multicenter Phase III study designed to compare the efficacy of DVRd with VRd in patients with NDMM who were not planning to undergo ASCT as initial therapy. The primary endpoint of the study was the overall minimal residual disease (MRD) negativity rate. Important secondary endpoints included progression-free survival (PFS), complete response or better rate (≥CR), sustained MRD, and other secondary endpoints such as overall survival (OS), progression-free survival on the next line of therapy (PFS2), overall response rate (ORR), very good partial response (VGPR) or better, time to response, duration of response, time to next treatment, and patient-reported outcomes (PROs; e.g., EQ-5D-5L). [5]

Patients were considered transplant ineligible if they were ≥70 years of age or if they were <70 years of age with comorbid conditions that would have a negative impact on tolerability to high-dose chemotherapy used in ASCT. Patients <70 years of age who were eligible for ASCT but who refused or chose to defer high-dose chemotherapy with SCT as initial treatment were also considered eligible for inclusion in the CEPHEUS trial [6]. The eligibility criteria are further outlined in the section named Patient Eligibility, CEPHEUS.

Patients enrolled in the trial were stratified by International Staging System (ISS) category at screening (I, II or III based on β-2 microglobulin and albumin by central laboratory) and by age/ transplant eligibility (<70 years ineligible, or age <70 years and refusal to transplant, or age ≥70 years). Patients were randomized in a 1:1 ratio to treatment Arm A (VRd) or treatment Arm B (DVRd)[6]. An overview of the CEPHEUS study design is presented in Figure 1.

Bortezomib, lenalidomide and dexamethasone, administrated to both arms, were administrated and dosed as follows [7]:

- Bortezomib 1.3 mg/m^2 as a subcutaneous (SC) injection twice weekly on days 1, 4, 8, and 11 of each 21-day cycle for cycles 1-8 only
- Lenalidomide 25mg orally on days 1-14 of each 21-day cycle for cycles 1-8 (for patients with a creatinine clearance of ≥60 mL/min)
    - For cycles 9 and beyond, lenalidomide 25mg was administered daily on days 1-21 of each 28-day cycle (for patients with a creatinine clearance of ≥60 mL/min).
    - Patients with a creatinine clearance of 30 to 59mL/min received 10mg every 24 hours for days 1-14 for cycles 1-8 and days 1-21 for cycle 9 and beyond
- Dexamethasone 20mg once a day on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for cycles 1-8 (patients >75 years of age or with body mass index <18.5kg/m^2 received 20mg once a day on days 1, 4, 8, and 11)
    - For cycles 9 and beyond, dexamethasone 40mg was administered daily on days 1, 8, 15, 22 of each 28-day cycle (patients >75 years of age or with body mass index <18.5kg/m^2 received 20mg once a week)

Patients randomized to treatment with DVRd also received daratumumab 1,800 mg via SC injection weekly for 8 weeks (Cycles 1–2), every 3 weeks during Cycles 3–8, and every 4 weeks from Cycle 9 onward.[7]

Patients in both treatment arms continued treatment until disease progression or unacceptable toxicity. After documented disease progression, follow-up assessments were conducted at least every 16 weeks until the final PFS analysis. The end of the study was defined as the later of the primary PFS analysis (162 events) or 5 years after the last subject was randomized.[7]

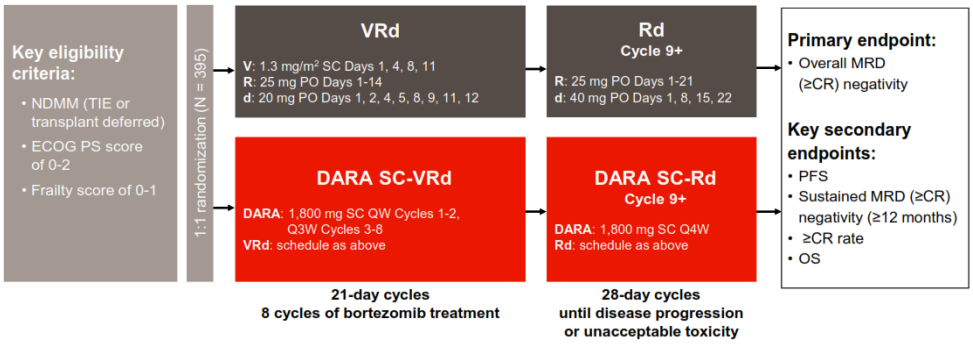


Figure 1. Overview of CEPHEUS study design [5]

DARA = daratumumab; CR = complete response; MRD = Minimal residual disease; NDMM = newly diagnosed multiple myeloma; OS = overall survival; PFS = progression-free survival; PO = orally; QW = every week; SC = subcutaneous; TIE = transplant ineligible; VRd = bortezomib, lenalidomide and dexamethasone
Source: Usmani et al. 2024 [8]

Patient Eligibility, CEPHEUS

The inclusion and criteria for CEPHEUS are summarized in Table 4 and Table 5, respectively.[6]

Table 4. CEPHEUS study inclusion criteria[6]

Inclusion criteria
▪ Newly diagnosed with multiple myeloma and not considered candidate for high-dose chemotherapy with SCT due to: ○ Being ≥65 years of age OR ○ age 18-65 years with presence of comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with SCT or who refuse high-dose chemotherapy with SCT as initial treatment
▪ Diagnosis of multiple myeloma as documented per IMWG criteria: Monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma and documented multiple myeloma satisfying at least one of the CRAB criteria or biomarkers of malignancy criteria: CRAB criteria: 1. Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL) 2. Renal insufficiency: creatinine clearance <40mL/min or serum creatinine >177 µmol/L (>2 mg/dL) 3. Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL 4. Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)-CT Biomarkers of Malignancy: a. Clonal bone marrow plasma cell percentage ≥60% b. Involved: uninvolved serum free light chain (FLC) ratio ≥100 c. >1 focal lesion on magnetic resonance imaging (MRI) studies
▪ Measurable disease at screening as defined by any of the following: ○ IgG, IgA, IgM, IgD, or IgE MM: serum monoclonal paraprotein (M-protein) level ≥1.0g/dL or urine M-protein level ≥200mg/24 hours OR ○ Light chain MM without measurable disease in the serum or the urine: serum Ig FLC ≥ 10mg/dL and abnormal serum Ig kappa lambda FLC ratio
▪ ECOG performance status score of 0, 1 or 2
▪ Pre-treatment clinical laboratory values meeting the following criteria: ○ Hemoglobin ≥7.5g/dL ○ Absolute neutrophil count ≥1.0x10^9/L ○ Platelet count ≥70x10^9/L (where <50% of bone marrow nucleated cells are plasma cells) or >50×10^9/L (otherwise) ○ AST and ALT ≤2.5x ULN ○ Total bilirubin ≤1.5x ULN (direct bilirubin ≤2.0x ULN for subjects with congenital bilirubinemia) ○ Creatinine clearance ≥30 mL/min ○ Corrected serum calcium ≤13.5mg/dL or free ionized calcium ≤6.5mg/dL

Table 5. CEPHEUS study exclusion criteria[6]

Exclusion criteria
Patient had:
▪ Frailty index of ≥2 according to Myeloma Geriatric Assessment score
▪ Prior therapy for multiple myeloma other than a short course of corticosteroids (equivalent of dexamethasone 40mg/day or equivalent per day, total of 160 mg dexamethasone or equivalent)

- A history of invasive malignancy (other than MM) within 5 years of randomization (excepting SCC, BCC, carcinoma *in situ* of the cervix or breast, or malignancy that is considered cured with minimal risk of recurrence within 3 years)
- Peripheral neuropathy or neuropathic pain Grade 2 or higher (as per NCI-CTCAE)
- Radiation therapy within 14 days or plasmapheresis within 28 days of randomization
- Clinical signs of meningeal involvement of MM
- COPD with FEV_1 <50% of predicted
- Moderate or severe persistent asthma within the last 2 years or uncontrolled asthma of any classification
- HIV, hepatitis B or hepatitis C seropositivity
- Concurrent medical or psychiatric condition or disease likely to interfere with the study procedures or results, or would constitute a hazard for participating in the study
    - Medical conditions such as, but not limited to; systemic amyloidosis, POEMS, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease
- Clinically significant cardiac disease, including:
    - Myocardial infarction within 6 months before randomization
    - Unstable or uncontrolled disease/condition related to or affecting cardiac function
    - Uncontrolled cardiac arrhythmia
    - Clinically significant ECG abnormalities
    - Screening ECG showing baseline QT interval as >470msec
- Prior therapy with a strong CYP3A4 inducer within 5 half-lives of randomization
- Allery/hypersensitivity/intolerance to boron, mannitol, corticosteroids, monoclonal antibodies, human proteins, mammalian derived products or lenalidomide

Baseline Characteristics, CEPHEUS

The baseline characteristics of the TIE population in CEPHEUS are outlined in Table 6.

Table 6. Baseline characteristics; TIE population; CEPHEUS

Characteristic	Measure	D-VRd (n=144)	VRd (n=145),	Total
Age (years)	**Mean (SD)**	72.02 (4.022)	71.97 (4.216)	72 (4.113)
	Median	72.0	72.0	72.0
	(Q1; Q3)	(70; 75)	(70; 75)	(70; 75)
	(Min; Max)	(58; 79)	(51; 80)	(51; 80)
	<70	35 (24.3%)	35 (24.1%)	70 (24.2%)
	≥70	109 (75.7%)	110 (75.9%)	219 (75.8%)
	<65	2 (1.4%)	2 (1.4%)	4 (1.4%)
	65<70	33 (22.9%)	33 (22.8%)	66 (22.8%)
Sex	**Female**	79 (54.9%)	63 (43.4%)	142 (49.1%)
	Male	65 (45.1%)	82 (56.6%)	147 (50.9%)
Region	**Europe**	96 (66.7%)	90 (62.1%)	186 (64.4%)
	North America	31 (21.5%)	28 (19.3%)	59 (20.4%)
	Other	17 (11.8%)	27 (18.6%)	44 (15.2%)
Weight (kg)	**Mean (SD)**	74.19 (16.45)	74.18 (15.09)	74.18 (15.755)

	Median	74.5	72.4	73.0
	(Q1; Q3)	(63.2; 83)	(63.6; 84)	(63.2; 83.6)
	(Min; Max)	(40.4; 122.9)	(44.5; 118)	(40.4; 122.9)
	≤65kg	46 (31.9%)	47 (32.4%)	93 (32.2%)
	>65≤85	69 (47.9%)	64 (44.1%)	133 (46%)
	>85	29 (20.1%)	34 (23.4%)	63 (21.8%)
ECOG PS (baseline)	**0**	52 (36.1%)	57 (39.3%)	109 (37.7%)
	1	75 (52.1%)	78 (53.8%)	153 (52.9%)
	2	17 (11.8%)	10 (6.9%)	27 (9.3%)
Race	**White**	122 (84.7%)	112 (77.2%)	234 (81%)
	Other	12 (8.3%)	22 (15.2%)	34 (11.8%)
	Missing	10 (6.9%)	11 (7.6%)	21 (7.3%)
Cytogenetic risk profile	**Standard**	105 (72.9%)	111 (76.6%)	216 (74.7%)
	High	20 (13.9%)	18 (12.4%)	38 (13.1%)
	Not evaluable	19 (13.2%)	16 (11%)	35 (12.1%)
Renal function	**<30**	2 (1.4%)	2 (1.4%)	4 (1.4%)
	30 -< 60	45 (31.3%)	43 (29.7%)	88 (30.4%)
	60 -< 90	63 (43.8%)	71 (49%)	134 (46.4%)
	>=90	34 (23.6%)	29 (20%)	63 (21.8%)
Hepatic function	**Normal**	131 (91%)	127 (87.6%)	258 (89.3%)
	Impaired	13 (9%)	18 (12.4%)	31 (10.7%)
Frailty score	**Fit (score 0)**	82 (56.9%)	88 (60.7%)	170 (58.8%)
	Intermediate (score 1)	62 (43.1%)	57 (39.3%)	119 (41.2%)
IMWG ISS disease stage	**Stage I**	50 (34.7%)	49 (33.8%)	99 (34.3%)
	Stage II	55 (38.2%)	56 (38.6%)	111 (38.4%)
	Stage III	39 (27.1%)	40 (27.6%)	79 (27.3%)
MM type	**IgG**	92 (63.9%)	78 (53.8%)	170 (58.8%)
	IgA	26 (18.1%)	42 (29%)	68 (23.5%)
	IgD	2 (1.4%)	2 (1.4%)	4 (1.4%)
	Kappa	10 (6.9%)	12 (8.3%)	22 (7.6%)
	Lambda	10 (6.9%)	6 (4.1%)	16 (5.5%)

Assessment of Clinical Endpoints, CEPHEUS

During the first 8 cycles (each lasting 21 days), clinical endpoints such as PFS and ORR were assessed every three weeks. Subsequently, these endpoints were evaluated every four weeks for the next 30 months, and then every 8 weeks until disease progression. PROs were assessed every three weeks during the first 8 cycles and then once every third cycle (28 days each), equivalent to once every 84 days, until disease progression. 13]

5.1.1.2 MAIA

The MAIA study was a randomized, open-label, active-controlled, parallel-group, multicenter, phase III trial designed to evaluate the efficacy of DRd compared to Rd in terms of PFS, which was the primary endpoint, in patients with NDMM who were ineligible for transplant. Patients were considered ineligible for transplant if they were aged ≥65 years or if they were <65 years with comorbid conditions that could negatively impact their ability to tolerate high-dose chemotherapy used in ASCT. A graphical overview of the study design is provided in . [9, 10]

In addition to the primary endpoint (PFS), several key secondary endpoints were assessed in the trial, including [9, 10]:

- OS
- sCR rate
- CR or better rate
- VGPR or better rate
- Minimal residual disease (MRD) negativity rate
- ORR
- PFS2 (time from randomization to progression on the next line of therapy or death, whichever occurred first)
- DoR
- PROs, such as EQ-5D-5L

Eligible patients were stratified based on the International Staging System (ISS; I, II, or III), region (North America versus Other), and age (<75 years versus ≥75 years). Patients were randomized in a 1:1 ratio to either treatment Arm A (Rd) or treatment Arm B (DRd). [9, 10]

Lenalidomide and dexamethasone, administered in both arms, were dosed as follows [9, 10]:

- Lenalidomide 25mg orally on Days 1 through 21 of each 28-day cycle (10mg every 24 hours for patients with creatinine clearance 30 to 50mL/min),
- Dexamethasone 40mg once weekly (patients >75 years of age or with body mass index <18.5kg/m^2 could receive 20mg weekly).

In addition, patients randomized to treatment with DRd received daratumumab 16mg/kg weekly for 8 weeks (cycles 1 to 2), then every other week for 16 weeks (cycles 3 to 6), then every 4 weeks (cycle 7 and beyond)[9, 10]. From April 3, 2020, patients receiving daratumumab were allowed to switch from the IV (16/mg/kg) to SC (1,800mg) formulation to provide flexibility during the COVID-19 global pandemic[11].

Patients in both treatment arms continued treatment until either disease progression or the occurrence of unacceptable toxicity [15]. The study is planned to conclude when 330 patients have died or 7 years have passed since the randomization of the last patient, whichever occurs first.

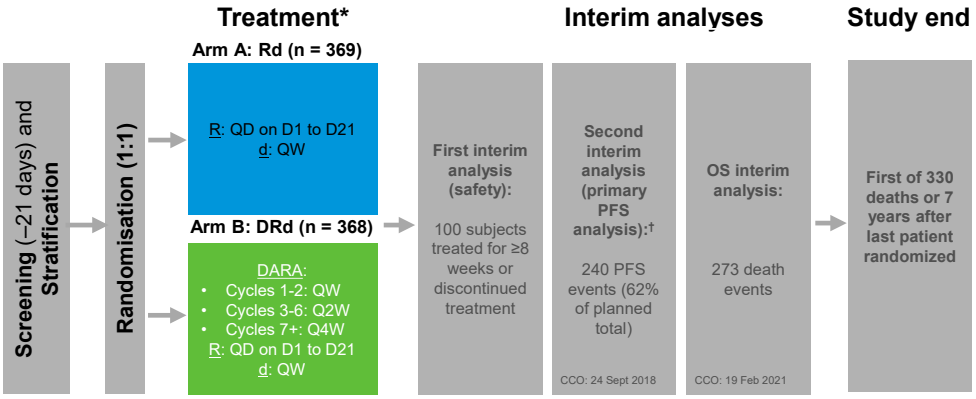


Figure 2. Overview of the MAIA study design [14,16]

DARA: 16mg/kg IV weekly for 8 weeks (cycles 1 to 2), then every other week for 16 weeks (cycles 3 to 6), then every 4 weeks (cycle 7 and beyond). Lenalidomide: 25mg PO on Days 1 through 21 of each 28-day cycle (10mg every 24 hours for patients with creatinine clearance 30 to 50 mL/min). Dexamethasone: 40mg weekly (20mg weekly for patients >75 years of age or with BMI <18.5 kg/m2).

† As treatment with DRd resulted in a statistically significant and clinically meaningful improvement in PFS compared with Rd alone, the second interim analysis served as the primary PFS analysis

BMI = body mass index; D = day; DARA = daratumumab; DRd = daratumumab, lenalidomide and dexamethasone; IV = intravenous; PD = disease progression; PO = oral; QD = daily; QW = weekly; Q2W = every 2 weeks; Q4W = every 4 weeks; PFS = progression-free survival; Rd = lenalidomide and dexamethasone.

Source: Janssen MMY3008 CSR, February 2019

Patient Eligibility, MAIA

The inclusion and exclusion criteria for the MAIA study are outlined in Table 7 and Table 8, respectively. [9, 12]

Table 7. MAIA study inclusion criteria [14, 17]

Inclusion criteria
▪ Patients ≥18 years of age
▪ Patients with documented MM as defined by the criteria below: ○ Diagnostic criteria of CRAB ○ Monoclonal plasma cells in the bone marrow ≥10% at some point in their disease history or presence of a biopsy-proven plasmacytoma
▪ Measurable disease at screening as defined by any of the following: ○ IgG MM: serum monoclonal paraprotein (M-protein) level ≥1.0g/dL or urine M-protein level ≥200mg/24 hours OR ○ IgA, IgD, IgE, IgM MM: serum M-protein level ≥0.5g/dL or urine M-protein level ≥200mg/24 hours OR ○ Light chain MM without measurable disease in the serum or the urine: serum Ig FLC ≥10mg/dL and abnormal serum Ig kappa lambda FLC ratio
▪ Newly diagnosed and not considered candidate for high-dose chemotherapy with SCT due to: ○ Being ≥65 years of age OR ○ In patients <65 years of age: presence of important comorbid condition(s) likely to have a negative impact on tolerability of high-dose chemotherapy with SCT. Sponsor review of these comorbid conditions and approval is required before randomisation
▪ Patients must have had an ECOG PS score of 0, 1 or 2

- Pre-treatment clinical laboratory values meeting the following criteria:
  - Haemoglobin ≥7.5g/dL
  - Absolute neutrophil count ≥1.0x10^9/L
  - Platelet count ≥70x10^9/L (where <50% of bone marrow nucleated cells are plasma cells) or >50×10^9/L (otherwise)
  - AST and ALT ≤2.5x ULN
  - Total bilirubin ≤2.0x ULN (direct bilirubin ≤2.0x ULN for subjects with congenital bilirubinaemia)
  - Creatinine clearance ≥30 mL/min
  - Corrected serum calcium ≤14mg/dL or free ionised calcium ≤6.5mg/dL

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRAB = calcium elevation, renal insufficiency, anaemia and bone abnormalities; ECOG = Eastern Cooperative Oncology Group; FLC = free light chain; Ig = immunoglobulin; MM = multiple myeloma; PS = performance status; SCT = stem cell transplant; ULN = upper limit of normal

Sources: Janssen MMY3008 CSR, February 2019; Janssen MMY3008 Study Protocol, November 2016

Table 8. MAIA study exclusion criteria[17]

Exclusion criteria
Patient had:
▪ A diagnosis of primary amyloidosis, MGUS or SMM
▪ A diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions
▪ Prior or current systemic therapy or ASCT for MM, with the exception of an emergency use of a short course (equivalent of dexamethasone 40mg/day for ≤4 days) of corticosteroids before treatment
▪ Plasma cell leukaemia (according to WHO criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of ≥2×10^9/L) or POEMS syndrome
▪ A history of malignancy (other than MM) within 5 years of randomisation (excepting SCC, BCC, carcinoma *in situ* of the cervix or malignancy that is considered cured with minimal risk of recurrence within 5 years)
▪ Radiation therapy within 14 days or plasmapheresis within 28 days of randomisation
▪ Clinical signs of meningeal involvement of MM
▪ HIV, hepatitis B or hepatitis C seropositivity
▪ Concurrent medical or psychiatric condition or disease likely to interfere with the study procedures or results, or would constitute a hazard for participating in the study
▪ COPD with FEV_1 <50% of predicted normal, moderate or severe persistent asthma within the last 2 years or uncontrolled asthma of any classification
▪ Clinically significant cardiac disease, including:
○ Myocardial infarction within 1 year before randomisation
○ Unstable or uncontrolled disease/condition related to or affecting cardiac function
○ Uncontrolled cardiac arrhythmia
○ Clinically significant ECG abnormalities

ASCT = autologous stem cell transplant; BCC = basal cell carcinoma; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; FEV_1 = forced expiratory volume in 1 second; HIV = human immunodeficiency virus; Ig = immunoglobulin; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; POEMS = polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes; SCC = squamous cell carcinoma; SMM = smoldering multiple myeloma; WHO = World Health Organization

Sources: Janssen MMY3008 CSR, February 2019; Janssen MMY3008 Study Protocol, November 201

Baseline Characteristics, MAIA

The baseline characteristics of the population enrolled in the MAIA trial (ITT [TIE] population) are summarized in Table 9.

Table 9. Baseline characteristics; Full (TIE) Population; MAIA

	Rd (n=369)	DRd (n=368)	Total (n=737)
Age, years			
Median	74.0	73.0	73.0
Range	(45; 89)	(50; 90)	(45; 90)
Sex, n (%)			
Male	195 (52.8)	189 (51.4)	384 (52.1)
Ethnicity, n (%)			
Hispanic or Latino	12 (3.3)	11 (3.0)	23 (3.1)
Not Hispanic or Latino	352 (95.4)	347 (94.3)	699 (94.8)
Unknown	3 (0.8)	6 (1.6)	9 (1.2)
Not Reported	2 (0.5)	4 (1.1)	6 (0.8)
Race, n (%)			
White	339 (91.9)	336 (91.3)	675 (91.6)
Black or African American	16 (4.3)	12 (3.3)	28 (3.8)
Asian	2 (0.5)	3 (0.8)	5 (0.7)
Native Hawaiian or other Pacific Islander	1 (0.3)	0	1 (0.1)
Other (includes multiple race)	6 (1.6)	6 (1.6)	12 (1.6)
Unknown	1 (0.3)	2 (0.5)	3 (0.4)
Not Reported	4 (1.1)	9 (2.4)	13 (1.8)
Baseline ECOG PS score, n (%)			
0	123 (33.3)	127 (34.5)	250 (33.9)
1	187 (50.7)	178 (48.4)	365 (49.5)
≥2	59 (16.0)	63 (17.1)	122 (16.6)
Time from MM diagnosis to randomization, months			
Mean (SD)	1.29 (1.404)	1.38 (1.503)	1.33 (1.454)
Median	0.89	0.95	0.92
Range	(0.0; 14.5)	(0.1; 13.3)	(0.0; 14.5)

Type of myeloma, n (%)			
IgG	246 (66.7)	241 (65.5)	487 (66.1)
IgA	71 (19.2)	70 (19.0)	141 (19.1)
IgM	1 (0.3)	1 (0.3)	2 (0.3)
IgD	4 (1.1)	2 (0.5)	6 (0.8)
IgE	1 (0.3)	0 1 (0.1)	
Light chain	38 (10.3)	46 (12.5)	84 (11.4)
Kappa	21 (5.7)	19 (5.2)	40 (5.4)
Lambda	13 (3.5)	21 (5.7)	34 (4.6)
FLC-Kappa	4 (1.1)	6 (1.6)	10 (1.4)
FLC-Lambda	0	0	0
Biclonal	8 (2.2)	8 (2.2)	16 (2.2)
Type of measurable disease, n (%)			
Serum IgG[a]	231 (62.6)	225 (61.1)	456 (61.9)
Serum IgA[a]	66 (17.9)	65 (17.7)	131 (17.8)
Other[a,b]	10 (2.7)	9 (2.4)	19 (2.6)
Urine only	34 (9.2)	40 (10.9)	74 (10.0)
Serum FLC	28 (7.6)	29 (7.9)	57 (7.7)
ISS staging[c], n (%)			
I	103 (27.9)	98 (26.6)	201 (27.3)
II	156 (42.3)	163 (44.3)	319 (43.3)
III	110 (29.8)	107 (29.1)	217 (29.4)
Cytogenetic risk, n (%)			
Standard risk	279 (86.4)	271 (85.0)	550 (85.7)
High risk[f]	44 (13.6)	48 (15.0)	92 (14.3)
del17p	29 (9.0)	25 (7.8)	54 (8.4)
t(4;14)	12 (3.7)	21 (6.6)	33 (5.1)
t(14;16)	5 (1.5)	4 (1.3)	9 (1.4)

Assessment of Clinical Endpoints, MAIA

Clinical endpoints, such as PFS and ORR, were assessed every cycle (28 days) during the first two years, and subsequently every 8 weeks until disease progression. Patient-reported outcomes (PROs) were collected during the first year on Day 1 of cycles 3, 6, 9, and 12. Following the first year, PRO data were collected every 6 months (±14 days) until disease progression. After disease progression, PROs were further collected at weeks 8 and 16. [13]

5.1.2 Comparability of studies

Naively, ahead of any matching/adjustment, the patients included in the two trials (CEPHEUS and MAIA) are generally similar, but not entirely without exceptions, the most

important being that in the CEPHEUS trial—as previously mentioned—both TIE and transplant-deferred patients were included, while the MAIA trial only included TIE patients. Only accounting for the TIE cohort from each study—which is a subgroup in the CEPHEUS trial but the full population in the MAIA trial—the similarities and differences between the two populations can be observed by comparing Table 6 (the baseline characteristics table for CEPHEUS, but limited to the TIE cohort) and Table 9 (the baseline characteristics table for MAIA).

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

The patient populations in CEPHEUS (TIE subgroup) and MAIA are generally comparable, however, to account for differences in populations the main comparative analysis—ITC—is an IPTW analysis using ATT weights, which is described in 5.2.3.

The target patient population for this assessment consist of adult Danish patients with NDMM who are TIE. The patient populations in CEPHEUS (subgroup TIE) and MAIA are assessed to reflect Danish patients eligible for treatment with DVRd and DRd.

Table 10. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	CEPHEUS vs MAIA	
	DVRd (n=144)	**DRd (n=368)**
Age, years		
Median	72.0	73.0
Range	(58;79)	(50;90)
Sex, n (%)		
Male	65 (45.1)	189 (51.4)
Baseline ECPG PS score, n (%)		
0	52 (36.1)	127 (34.5)
1	75 (52.1)	178 (48.4)
≥2	17 (11.8)	63 (17.1)
Cytogenetic risk profile, n(%)		
Standard	105 (72.9)	271 (73.6)

	CEPHEUS vs MAIA	
	DVRd (n=144)	DRd (n=368)
High	20 (13.9)	48 (13.0)
Unknown	19 (13.2)	49 (13.3)
Type of myeloma, n (%)		
IgG	92 (63.9%)	241 (65.5)
IgA	26 (18.1%)	70 (19.0)
IgM	N/A	1 (0.3)
IgD	2 (1.4%)	2 (0.5)
IgE	N/A	0 1 (0.1)
Light chain	N/A	46 (12.5)
Kappa	10 (6.9%)	19 (5.2)
Lambda	10 (6.9%)	21 (5.7)
FLC-Kappa	N/A	6 (1.6)
FLC-Lambda	N/A	0
Biclonal	N/A	8 (2.2)
ISS staging, n (%)		
I	50 (34.7%)	98 (26.6)
II	55 (38.2%)	163 (44.3)
III	39 (27.1%)	107 (29.1)

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

Efficacy and safety, CEPHEUS

As previously mentioned, the CEPHEUS trial evaluated the efficacy and safety of DVRd compared to VRd in patients with NDMM for whom autologous stem cell transplantation (ASCT) is not planned as initial therapy. However, the outcomes detailed below are specific to patients with NDMM who are TIE.

Overall MRD negativity rate (10^{-5} sensitivity threshold)
At the May 2024 clinical cut-off, DVRd demonstrated a statistically significant improvement in MRD negativity compared to VRd, with a higher proportion of patients achieving overall MRD negativity (10^-5 sensitivity threshold). The overall MRD negativity rate was approximately 21% higher with DVRd compared to VRd (60.4% vs. 39.3%, respectively; OR 2.37; 95% CI: 1.47, 3.82; nominal p=0.0004). All the results presented refer to the TIE population in CEPHEUS. [5, 14]

Overall Survival
The overall survival (OS) data, informed by the May 2024 clinical cut-off, remains immature, with a total of 80 deaths reported (33/144 [22.9%] in the DVRd arm and 47/145 [30.3%] in the VRd group). While DVRd showed a 34% reduction in the risk of death compared to VRd, the difference was not statistically significant (HR: 0.66; 95% CI: 0.42, 1.03). This lack of statistical significance is believed to be due to the short follow-up period and the impact of Covid-19. Although it is not possible for Johnson & Johnson Innovative Medicine to determine what might have occurred with longer follow-up, the impact of Covid-19 was explored through an additional analysis.

In this analysis, Covid-19-related deaths were censored rather than counted as events. The adjusted analysis revealed a 44% reduction in the risk of death, which was statistically significant (HR: 0.55; 95% CI: 0.34, 0.90; p-value = 0.0159). Johnson & Johnson Innovative Medicine therefore concludes that DVRd can be considered to prolong survival compared to VRd, particularly since other relevant endpoints (Overall MRD negativity rate [10^-5 sensitivity threshold], PFS, and ORR) also demonstrate the superiority of DVRd, with statistical significance.

Kaplan-Meier estimates (KMEs) for the non-Covid-19 adjusted analysis are presented in Figure 3, while the corresponding estimates for the Covid-19 adjusted analysis are found in Figure 4.

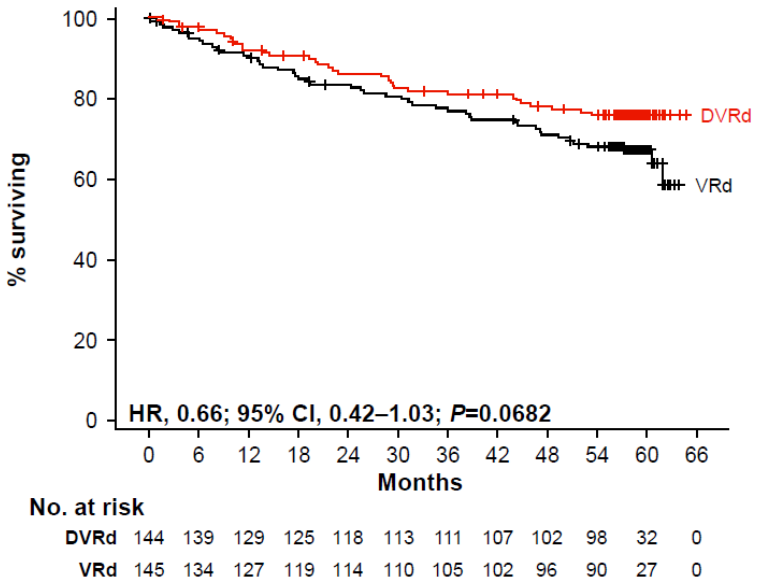


Figure 3. Kaplan-Meier plot for OS (CEPHEUS trial; ITT for TIE analysis set, median follow-up 58.7 months)

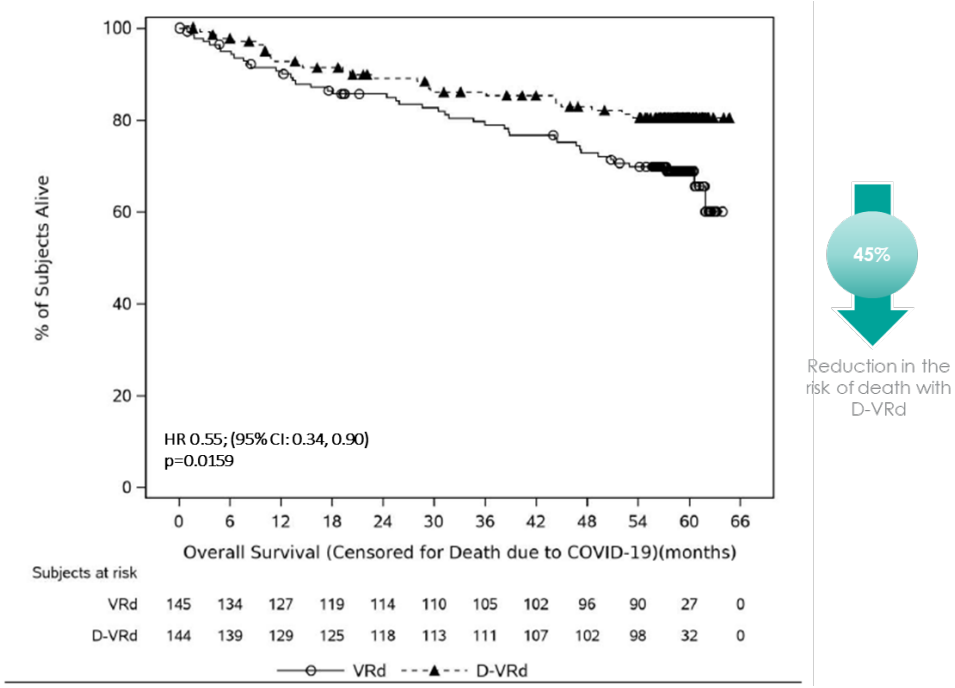


Figure 4. Kaplan-Meier plot for OS, censored for COVID-19-related deaths (CEPHEUS trial; ITT for TIE analysis set, median follow-up 58.7 months)

Progression-free Survival

The PFS data, informed by the May 2024 clinical cut-off, remains immature. A total of 113 PFS events were observed in the TIE population: 44 events in the DVRd arm (30.6% of patients in this treatment group) and 69 events in the VRd arm (47.6% of patients in this group). A statistically significant 49% reduction in the risk of progression or death was observed in favor of DVRd compared to VRd (HR: 0.51; 95% CI: 0.35, 0.74). It is

important to note that the PFS analysis was conducted using a computerized algorithm. The KMEs for PFS are presented in Figure 5.

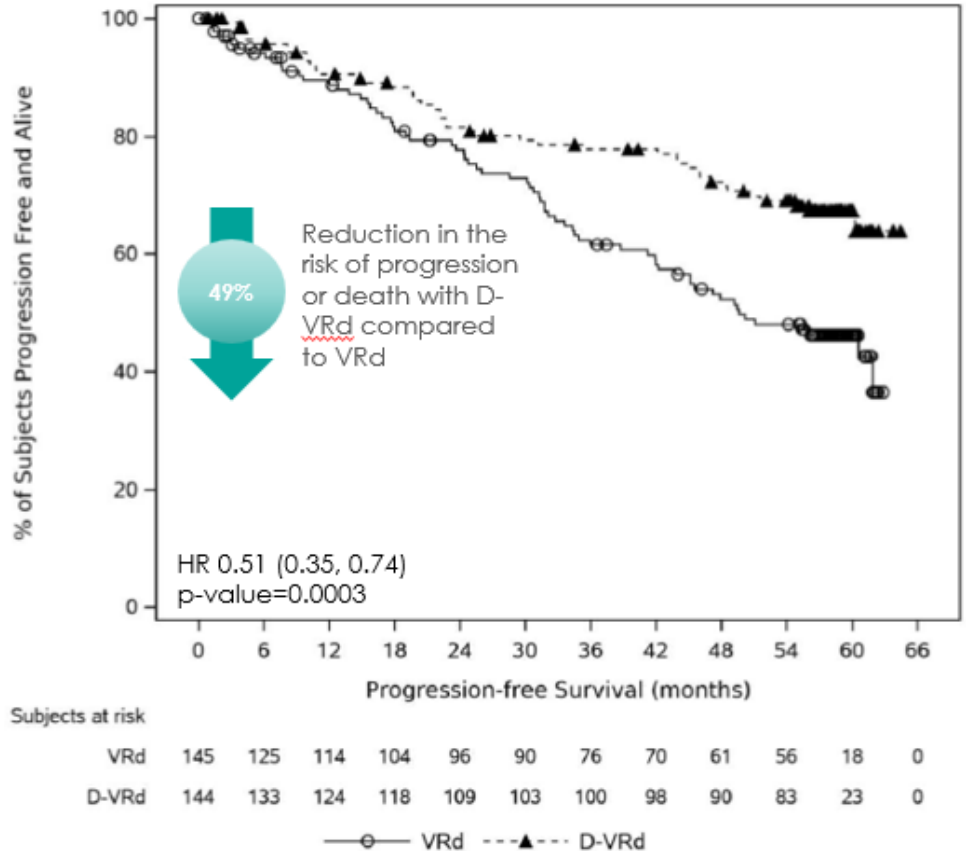


Figure 5. Kaplan-Meier plot for PFS based on computerized algorithm; ITT for TIE analysis set.

Overall Response Rate

Treatment with DVRd was associated with a statistically significant higher proportion of patients achieving an overall response compared to VRd. The ORR was 98.6% for DVRd and 91.0% for VRd (OR: 7.17; 95% CI: 1.60, 32.11; p=0.0033). A visual representation of the results is provided in Figure 6. The ORR data was obtained from the May 2024 clinical cut-off.

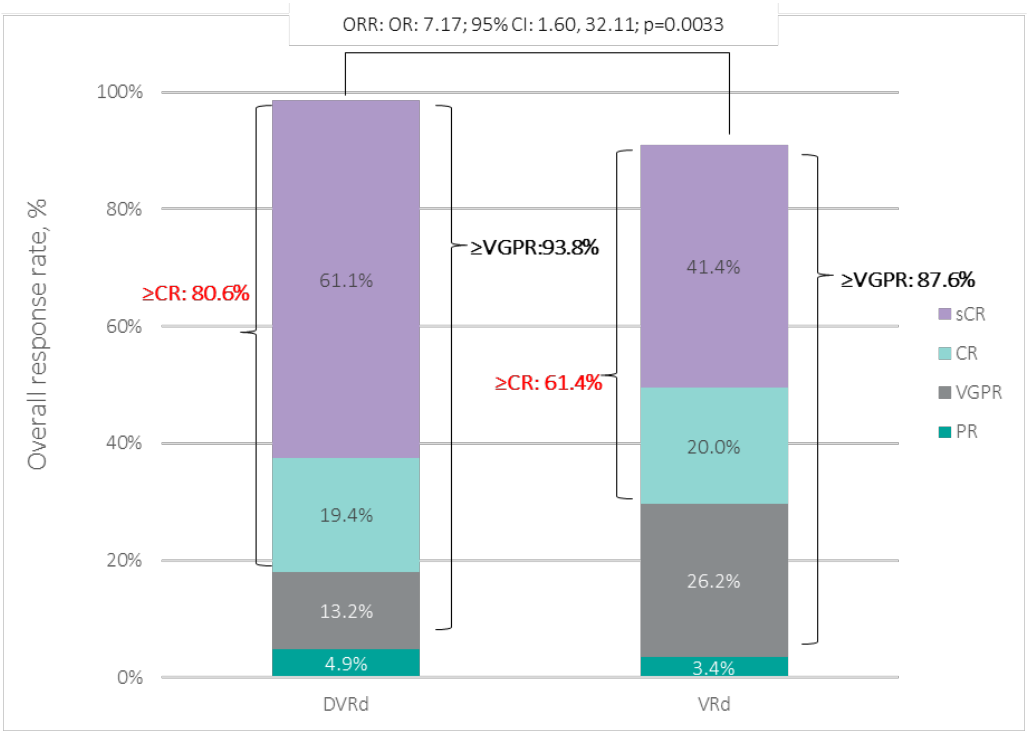


Figure 6. ORR (CEPHEUS; ITT for TIE analysis set)

EORTC QLQ-C30

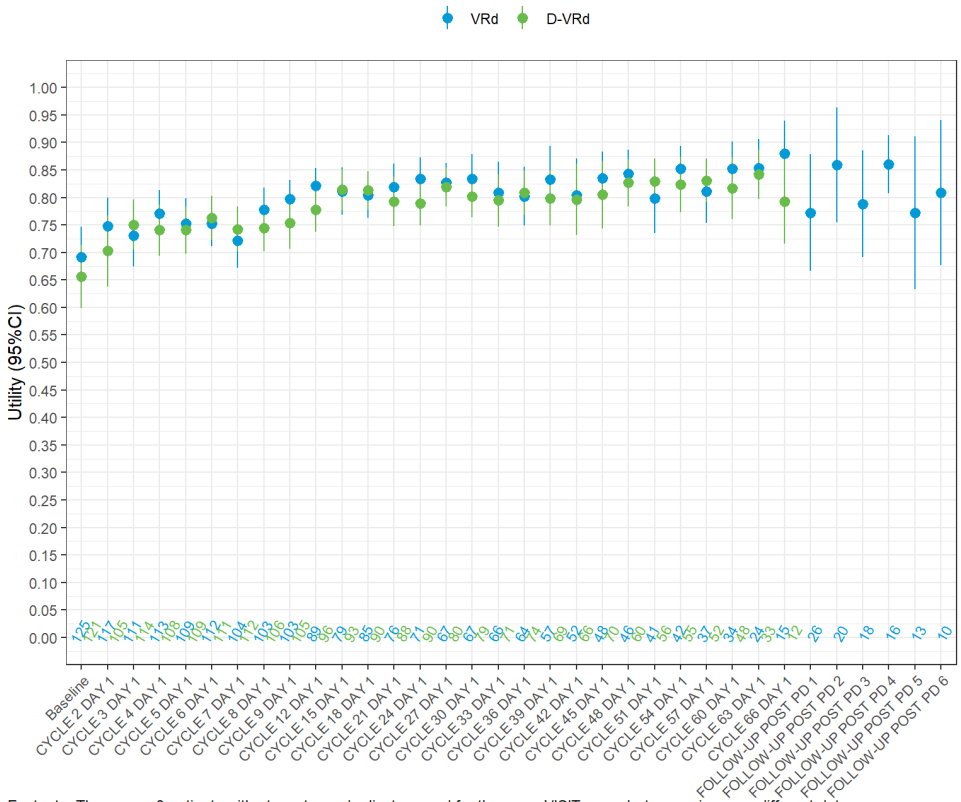
According to the EORTC QLQ-C30 Global Health Status (GHS) score, no significant differences were observed between DVRd and DRd patients in terms of changes from baseline, as detailed in Table 11.

Table 11. Change from Baseline in EORTC QLQ-C30 Global Health Status Score in TIE Patients: Mixed Model for Repeated Measures (Missing at Random); ITT Analysis Set (Study 54767414MMY3019)[10]

	VRd		D-VRd		Difference	p-value
	n	**LS Means of Change from Baseline (95% CI)**	**N**	**LS Means of Change from Baseline (95% CI)**	LS Mean[a] of Change from Baseline (95% CI)	
Analysis set: ITT, Transplant-ineligible	145		144			
Cycle 3	116	-0.9 (-4.1, 2.3)	120	-4.9 (-8, -1.7)	-3.9 (-8.5, 0.6)	0.0885
Cycle 6	114	-3.0 (-6.3, 0.2)	114	-0.7 (-4, 2.5)	2.3 (-2.3, 6.9)	0.3224
Cycle 9	104	2.1 (-1.3, 5.5)	108	1.5 (-1.8, 4.8)	-0.6 (-5.3, 4.1)	0.8014
Cycle 12	91	5.5 (2, 9)	97	2.7 (-0.8, 6.1)	-2.8 (-7.8, 2.1)	0.2575
Cycle 18	78	6.8 (3, 10.5)	88	6.8 (3.2, 10.3)	0.0 (-5.2, 5.1)	0.9975
Cycle 24	68	4.6 (0.7, 8.5)	88	6.0 (2.4, 9.5)	1.4 (-3.9, 6.7)	0.6109
Cycle 30	65	7.9 (3.9, 11.9)	79	7.5 (3.8, 11.2)	-0.4 (-5.9, 5)	0.8839
Cycle 36	63	6.7 (2.7, 10.8)	75	5.2 (1.4, 9)	-1.5 (-7, 4)	0.5944

EQ-5D-5L

The mean utility scores from the CEPHEUS trial (May 2024 clinical cut-off), based on EQ-5D-5L and the Danish tariff, are presented in Figure 7. Notably, the mean scores for the two treatment arms are generally comparable. However, during most cycles, the mean utility scores for the VRd arm are numerically higher than those of the DVRd arm.



Footnote: There were 3 patients with at most one duplicate record for the same VISIT name but ooccuring on a different date.
A total of 3 records bv VISIT were not excluded.

Figure 7. Mean (EQ-5D-5L, Danish tariff) utility scores in CEPHEUS (Median follow-up 58.71 months)

Safety

All TIE patients in both the DVRd and VRd groups who received study treatment experienced at least one treatment-emergent adverse event (TEAE) during the trial. Notably, three patients in the VRd group did not receive the study treatment, resulting in a sample size of 142 instead of 145 [15]. The most common TEAEs (≥20%) observed during the trial are detailed in Table 12[15]. Deaths due to TEAEs were infrequent in both groups, with two patients (1.4%) in the DVRd group and three patients (2.1%) in the VRd group succumbing to TEAEs [16].

The incidence of grade 3 and 4 TEAEs was slightly higher in the DVRd group compared to the VRd group (DVRd: 93.1%; VRd: 88.7%) [17]. Hematologic events (blood and lymphatic system disorders) of grade 3 or 4 were the most common system-type TEAEs in both groups (DVRd: 64.6%; VRd: 53.5%), with neutropenia being the most frequently reported event (DVRd: 43.8%; VRd: 31.7%) [17]. Other grade 3 and 4 TEAEs occurred at similar rates between the two groups, except for COVID-19 infections, which were more prevalent in the DVRd group compared to the VRd group (DVRd: 9.7%; VRd: 3.5) [17].

Table 12. Overview of TEAEs and most commonly (≥20%) reported treatment-emergent adverse events by system organ class and preferred term (safety, transplant ineligibility set)[11, 12]

	Proportion of patients, n (%)	
	D-VRd (n=144)	VRd (n=142)
Any TEAE	**144 (100)**	142 (100)
TEAEs leading to death	**19 (13.2)**	13 (9.2)
HEMATOLOGIC		
Blood and lymphatic system disorders	**123 (85.4)**	95 (66.9)
Neutropenia	81 (56.3)	57 (40.1)
Thrombocytopenia	70 (48.6)	51 (35.9)
Anemia	52 (36.1)	46 (32.4)
Lymphopenia	25 (17.4)	19 (13.4)
NON-HEMATOLOGIC		
Gastrointestinal disorder	**120 (83.3)**	115 (81.0)
Diarrhea	87 (60.4)	87 (61.3)
Constipation	57 (39.6)	65 (45.8)
Nausea	37 (25.7)	35 (24.6)
General disorders and administration-site conditions	**121 (84.0)**	109 (76.8)
Peripheral edema	63 (43.8)	59 (41.5)
Fatigue	48 (33.3)	54 (38.0)
Hypokalemia	49 (34.0)	22 (15.5)
Asthenia	43 (29.9)	34 (23.9)
Back pain	42 (29.2)	31 (21.8)
Rash	40 (27.8)	35 (24.6)
Cataract	38 (26.4)	31 (21.8)
Cough	37 (25.7)	32 (22.5)
Pyrexia	36 (25.0)	25 (17.6)
Arthralgia	37 (25.7)	29 (20.4)
Dizziness	34 (23.6)	36 (25.4)
Psychiatric disorders	72 (50.0)	71 (50.0)
Insomnia	51 (35.4)	47 (33.1)
Infections	134 (93.1)	120 (84.5)
COVID-19	52 (36.1)	26 (18.3)

Upper respiratory tract infection	49 (34.0)	38 (26.8)
Pneumonia	35 (24.3)	28 (19.7)
Urinary tract infections	35 (24.3)	25 (17.6)
Peripheral sensory neuropathy	86 (59.7)	90 (63.4)

Table 13. Incidence rate of TEAEs Grade 3 or 4 (safety, transplant ineligibility analysis set)[13]

	Proportion of patients, n (%)	
	D-VRd (n=144)	VRd (n=142)
	Grade 3 or 4	Grade 3 or 4
Any grade 3 or 4 TEAE	**134 (93.1)**	126 (88.7)
HEMATOLOGIC		
Blood and lymphatic system disorders	93 (64.6)	76 (53.5)
Neutropenia	63 (43.8)	45 (31.7)
Thrombocytopenia	44 (30.6)	33 (23.2)
Anemia	18 (12.5)	18 (12.7)
Lymphopenia	16 (11.1)	14 (9.9)
NON-HEMATOLOGIC		
Vascular disorders	21 (14.6)	16 (11.3)
Gastrointestinal disorders	27 (18.8)	29 (20.4)
Diarrhea	17 (11.8)	14 (9.9)
General disorders and administration-site conditions	33 (22.9)	25 (17.6)
Fatigue	13 (9.0)	15 (10.6)
Metabolism and nutrition disorders	35 (24.3)	30 (21.1)
Hypokalemia	21 (14.6)	12 (8.5)
Eye disorders	17 (11.8)	12 (8.5)
Cataract	14 (9.7)	9 (6.3)
Psychiatric disorders	8 (5.6)	7 (4.9)
Infections and infestations	57 (39.6)	45 (31.7)
COVID-19	14 (9.7)	5 (3.5)
Pneumonia	20 (13.9)	17 (12.0)
Renal and urinary disorders	13 (9.0)	9 (6.3)
Nervous system disorders	36 (25.0)	32 (22.5)
Peripheral sensory neuropathy	14 (9.7)	12 (8.5)
Neoplasms benign, malignant and unspecified	11 (7.6)	10 (7.0)

Efficacy and safety, MAIA

Overall Survival

As of the November 2023 clinical cut-off, the overall survival (OS) data was sufficiently mature to determine the median OS for both treatment arms. A total of 175 events (47.6%) were reported in the DRd arm and 218 events (59.1%) in the Rd arm. Median progression-free survival (PFS) was achieved at 90.25 months (95% CI: 80.75, NE) in the DRd arm and at 64 months (95% CI: 55.98, 70.80) in the Rd arm.

Reflecting the observed OS differences, treatment with DRd demonstrated a statistically significant 33% reduction in the risk of death compared to Rd (HR: 0.67; 95% CI: 0.55, 0.82). The KMEs for OS are presented in Figure .

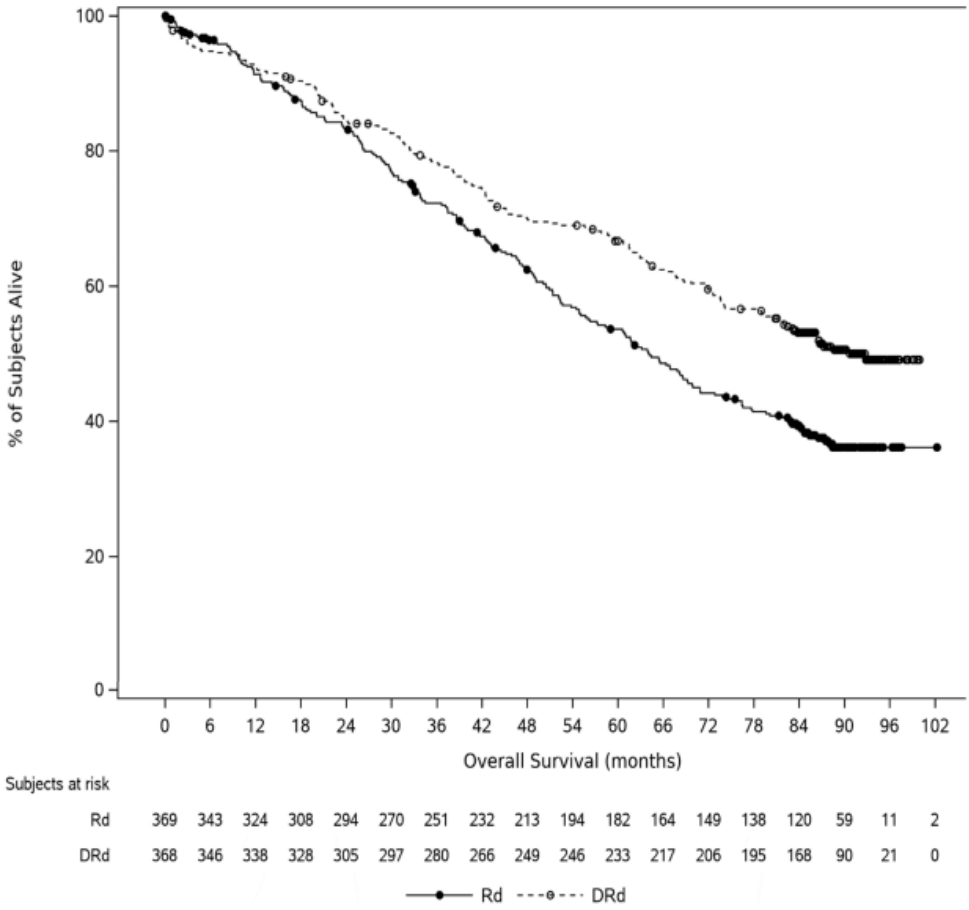


Figure 8. Kaplan-Meier plot for OS (MAIA; ITT, median follow-up 89.3 months)

Progression-free Survival

As of the October 2021 clinical cut-off, median PFS was observed in both treatment arms, with 176 events (47.8%) in the DRd arm and 228 events (61.8%) in the Rd arm. The median PFS was 61.86 months (95% CI: 54.80, NE) for the DRd arm and 34.43 months (95% CI: 29.57, 39.16) for the Rd arm.

Treatment with DRd demonstrated a statistically significant 45% reduction in the risk of progression and/or death compared to Rd (HR: 0.55; 95% CI: 0.45, 0.67). The Kaplan-Meier estimates (KMEs) for PFS are presented in Figure 9.

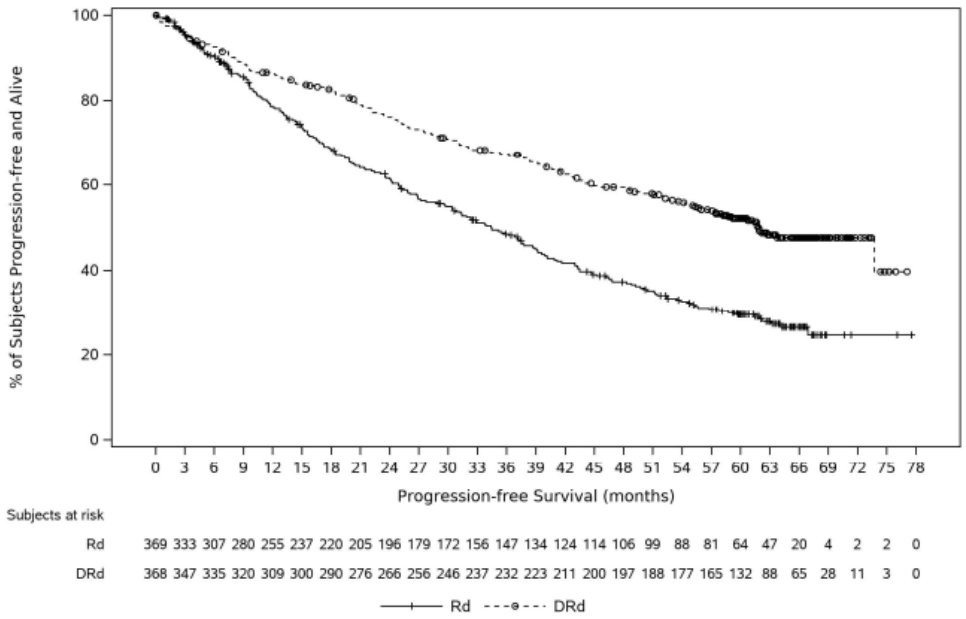


Figure 9. Kaplan-Meier plot for PFS (MAIA; ITT, median follow-up 64.5 months)

Overall Response Rate

As of the October 2021 clinical cut-off, treatment with DRd was associated with a statistically significant improvement in ORR, with an odds ratio (OR) of 3.00 (95% CI: 1.85, 4.86; p-value <0.0001). In absolute terms, this represents an 11.3 percentage point difference, with the ORR in the DRd arm being 92.9% compared to 81.6% in the Rd arm.

EORTC QLQ-C30

Baseline scores on all functional and symptom subscales were comparable between the treatment arms.

Improvement in the EORTC QLQ-C30 GHS was observed in both treatment groups and was maintained with treatment. A numerical benefit for the DRd group compared with the Rd group was observed beginning at Cycle 3 (LS mean change; DRd: 3.8 [95% CI: 1.7, 5.8], Rd: 1.4 [95% CI: -0.7, 3.5]) through Cycle 48 (LS mean change; DRd: 4.2 [95% CI: 1.6, 6.7], Rd: 3.4 [95% CI: -0.1, 6.9]). The median time to improvement in GHS was shorter for the DRd group compared with the Rd group (DRd: 2.3 [range: 1.8, 55.8], Rd: 4.6 [range: 1.7, 55.9] and the median time to worsening of GHS was longer for DRd compared with the Rd group (DRd: 26.8 [range: 17.5, 39.8], Rd: 21.3 [range: 11.4, 28.7].

EQ-5D-5L

The mean change from baseline in utility scores, derived from EQ-5D-5L and the Danish tariff, in the MAIA trial (February 2021 clinical cut-off) over time is presented in Figure 10. Notably, the mean change from baseline is consistently higher in the DRd arm compared to the Rd arm.

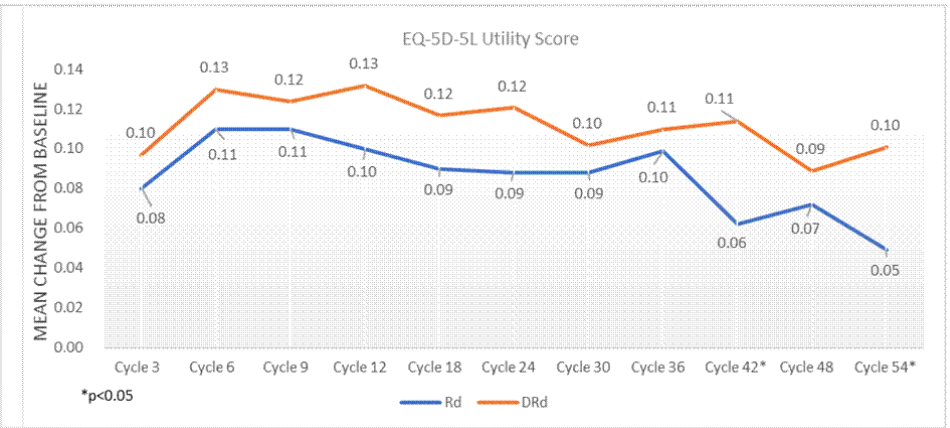


Figure 10. Mean change from baseline in EQ-5D-5L utility scores (Danish tariff) in MAIA (median follow-up 56.2 months)

Safety

The most common TEAEs with an incidence or frequency of at least 5% in the MAIA trial are summarized in Table 14. This data is based on the October 2021 clinical cut-off.

Table 14. Most Common (at Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set (Study 54767414MMY3008)

	Rd			DRd		
	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
Analysis set: safety	365			364		
Total number of subjects with toxicity grade 3 or 4 TEAE	324 (88.8%)	211 (57.8%)	133 (31.0%)	349 (95.9%)	202 (55.5%)	147 (40.4%)
Blood and lymphatic system disorders	199 (54.5%)	147 (40.3%)	52 (14.2%)	246 (44.8%)	163 (44.8%)	83 (22.8%)
Neutropenia	135 (37.0%)	97 (26.6%)	38 (10.4%)	197 (54.1%)	136 (37.4%)	61 (16.8%)
Anemia	79 (21.6%)	79 (21.6%)	0	62 (17.0%)	61 (16.8%)	1 (0.3%)
Lymphopenia	41 (11.2%)	35 (9.6%)	6 (1.6%)	60 (16.5%)	41 (11.3%)	19 (5.2%)
Leukopenia	23 (6.3%)	20 (5.5%)	3 (0.8%)	42 (11.5%)	37 (10.2%)	5 (1.4%)

	Rd			DRd		
	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
Thrombocytopenia	34 (9.3%)	23 (6.3%)	11 (3.0%)	33 (9.1%)	23 (6.3%)	10 (2.7%)
Infections and infestations	108 (29.6%)	81 (22.2%)	27 (7.4%)	155 (42.6%)	118 (32.4%)	37 (10.2%)
Pneumonia	39 (10.7%)	32 (8.8%)	7 (1.9%)	71 (19.5%)	63 (17.3%)	8 (2.2%)
Metabolism and nutrition disorders	84 (23.0%)	62 (17.0%)	22 (6.0%)	95 (26.1%)	77 (21.2%)	18 (4.9%)
Hypokalemia	38 (10.4%)	29 (7.9%)	9 (2.5%)	49 (13.5%)	44 (12.1%)	5 (1.4%)
Hyperglycemia	14 (3.8%)	12 (3.3%)	2 (0.5%)	28 (7.7%)	24 (6.6%)	4 (1.1%)
Gastrointestinal disorders	60 (16.4%)	53 (14.5%)	7 (1.9%)	85 (23.4%)	76 (20.9%)	9 (2.5%)
Diarrhea	22 (6.0%)	22 (6.0%)	0	33 (9.1%)	33 (9.1%)	0
General disorders and administration site conditions	66 (18.1%)	59 (16.2%)	7 (1.9%)	73 (20.1%)	69 (19.0%)	4 (1.1%)
Fatigue	17 (4.7%)	17 (4.7%)	0	33 (9.1%)	33 (9.1%)	0
Asthenia	18 (4.9%)	17 (4.7%)	1 (0.3%)	19 (5.2%)	18 (4.9%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	37 (10.1%)	30 (8.2%)	7 (1.9%)	59 (16.2%)	52 (14.3%)	7 (1.9%)
Pulmonary embolism	19 (5.2%)	16 (4.4%)	3 (0.8%)	26 (7.1%)	23 (6.3%)	3 (0.8%)
Vascular disorders	36 (9.9%)	33 (9.0%)	3 (0.8%)	57 (15.7%)	52 (14.3%)	5 (1.4%)
Hypertension	16 (4.4%)	16 (4.4%)	0	32 (8.8%)	30 (8.2%)	2 (0.5%)

	Rd			DRd		
	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
Eye disorders	44 (12.1%)	44 (12.1%)	0	47 (12.9%)	47 (12.9%)	0
Cataract	39 (10.7%)	39 (10.7%)	0	40 (11.0%)	40 (11.0%)	0
Renal and urinary disorders	43 (11.8%)	33 (9.0%)	10 (2.7%)	47 (12.9%)	338 (10.4%)	9 (2.5%)
Acute kidney injury	13 (3.6%)	9 (2.5%)	4 (1.1%)	19 (5.2%)	16 (4.4%)	3 (0.8%)
Chronic kidney disease	11 (3.0%)	8 (2.2%)	3 (0.8%)	19 (5.2%)	17 (4.7%)	2 (0.5%)

5.2.2 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

DVRd and DRd have similar safety profiles, although the addition of bortezomib in the DVRd regimen is associated with a higher toxicity burden. Notably, peripheral neuropathy is a recognized adverse effect of bortezomib, which can make DRd a choice for frailer patients. In analyses of grade 3–4 treatment-related adverse events occurring in ≥5% of patients, peripheral neuropathy was reported in 9.7% of patients in the DVRd arm (compared to 8.5% in the VRd arm in the CEPHEUS study). In the MAIA study, which compared DRd with Rd, bortezomib was not included in the treatment arms, and grade 3–4 neuropathy was not observed in ≥5% of cases.

5.2.3 Method of synthesis

To obtain reliable and valid estimates of the relative efficacy of DVRd compared to DRd, an ITC was performed using the method of inverse probability of treatment weighting (IPTW), rather than relying on a simple comparison of outcomes from the two trials. Specifically, for the base case analysis, IPTW with average treatment effect on the treated population (ATT) weights was applied. The application of ATT weights ensures that the comparator population (DRd [MAIA]) is adjusted and matched to align with the intervention population (DVRd [CEPHEUS]), while the intervention population remains unchanged. Alternative weighting methods were utilized for sensitivity analyses. Notably, IPTW is widely recognized for its robustness in comparative efficacy research, particularly in situations where direct clinical trials are unavailable [18].

In the CEPHEUS trial, 144 patients were included in the DVRd arm before the application of IPTW with ATT weights. Since ATT weights were applied in the base case analysis, the

same number of patients were included after matching and adjustment. It is important to note that all of these patients belonged to the TIE cohort (subgroup) in CEPHEUS.

The initial step in aligning the populations from CEPHEUS and MAIA involved excluding specific groups to achieve a basic population alignment. Patients under 70 years old who had refused transplantation (26.8% of the CEPHEUS trial population) were excluded, as this group was not represented in the MAIA trial population. This exclusion resulted in the sample size being reduced to the aforementioned 144 patients, indicating that the excluded patients were those who had deferred transplantation. Similarly, patients over 80 years old were excluded from the MAIA trial, as this group was not represented in the CEPHEUS trial population.

Following these exclusions, the two populations were matched using IPTW with ATT weights. The matching process in the base case analysis accounted for the following covariates: MM stage per International Staging System (ISS), cytogenetic risk, age, ECOG performance status, type of MM (IgG vs other), extramedullary disease (EMD), frailty (based on the simplified International Myeloma Working Group [IMWG] frailty score), sex, estimated glomerular filtration rate (eGFR; ≥ vs < 60mL/min/1.73 m^2), anemia (< vs ≥ 10 g/dL), and lactate dehydrogenase (LDH; > vs ≤ 280 U/L). For sensitivity analyses, additional variables were included, such as hypercalcemia (> vs ≤ 2.75 mmol/L), race (white vs other), and time since initial MM diagnosis.
The key outcomes from the ITC, relevant for this health technology assessment (HTA), include:

- Overall Minimal Residual Disease (MRD) negativity rate (10^{-5} sensitivity threshold)
- Overall Survival (OS)
- Progression-Free Survival (PFS)
- Overall Response Rate (ORR)

The results for overall MRD negativity rate (10^{-5} sensitivity threshold), PFS, and ORR are derived from the CEPHEUS clinical cut-off in May 2024 and the MAIA clinical cut-off in October 2021. The OS results are based on the CEPHEUS clinical cut-off in May 2024 and the MAIA clinical cut-off in November 2023.

In the MAIA trial, 321 patients were included in the DRd arm before the application of IPTW with ATT weights. After applying IPTW with ATT weights, the effective sample size (ESS) was reduced to 285. The balance of baseline characteristics before and after weighting for the base case covariates is presented in Table 15, while the kernel density plot of weights for the base case is outlined in Figure (found in Appendix D). The populations (CEPHEUS and adjusted MAIA) were generally well-balanced. The balance of baseline characteristics before and after weighting for all covariates, as part of the sensitivity analysis, is presented in Table (also found in Appendix D). Finally, to confirm the robustness of the results, sensitivity analyses incorporating multivariate regression and doubly robust methods were also conducted.

Table 15. Overview of Group Demographic Balance Before and After Weighting (CEPHEUS and MAIA), base case covariates

Variables	Unweighted			Weighted		
	DRd	DVRd	SMD	DRd	DVRd	SMD
N/ESS	321	144		284.58	144	
ISS (%)						
I	87.0 (27.1)	50.0 (34.7)	0.17	49.4 (34.2)	50.0 (34.7)	0.01
II	146.0 (45.5)	54.0 (37.5)	-0.16	54.2 (37.6)	54.0 (37.5)	0
III	88.0 (27.4)	40.0 (27.8)	0.01	40.7 (28.2)	40.0 (27.8)	-0.01
Baseline Cytogenetic profile (%)						
High-risk	41.0 (12.8)	20.0 (13.9)	0.03	20.3 (14.0)	20.0 (13.9)	0
Not Done	42.0 (13.1)	19.0 (13.2)	0	18.7 (13.0)	19.0 (13.2)	0.01
Standard-risk	238.0 (74.1)	105.0 (72.9)	-0.03	105.3 (73.0)	105.0 (72.9)	0
Age (%)						
<=69	78.0 (24.3)	35.0 (24.3)	0	35.6 (24.7)	35.0 (24.3)	-0.01
70-74	130.0 (40.5)	68.0 (47.2)	0.14	68.9 (47.7)	68.0 (47.2)	-0.01
75+	113.0 (35.2)	41.0 (28.5)	-0.14	39.8 (27.6)	41.0 (28.5)	0.02
ECOG performance status (%)						
0	114.0 (35.5)	52.0 (36.1)	0.01	52.4 (36.3)	52.0 (36.1)	0

1	155.0 (48.3)	75.0 (52.1)	0.08	75.3 (52.1)	75.0 (52.1)	0
2 and above	52.0 (16.2)	17.0 (11.8)	-0.13	16.6 (11.5)	17.0 (11.8)	0.01
Type of MM at diagnosis = IGG (%)	210.0 (65.4)	92.0 (63.9)	-0.03	90.1 (62.4)	92.0 (63.9)	0.03
EMD = 1 (%)	12.0 (3.7)	9.0 (6.2)	0.12	8.8 (6.1)	9.0 (6.2)	0.01
frailty based on Simplified frail score = 1 (%)	125.0 (38.9)	48.0 (33.3)	-0.12	46.8 (32.4)	48.0 (33.3)	0.02
MALE = MALE (%)	162.0 (50.5)	65.0 (45.1)	-0.11	65.6 (45.5)	65.0 (45.1)	-0.01
estimated GFR = >=60mL/min/1.73 m2 (%)	125.0 (38.9)	47.0 (32.6)	-0.13	47.0 (32.6)	47.0 (32.6)	0
Anemia, hemoglobin<100 mg/L = 1 (%)	119.0 (37.1)	45.0 (31.2)	-0.12	44.3 (30.7)	45.0 (31.2)	0.01
LDH>280 U/L = 1 (%)	64.0 (19.9)	29.0 (20.1)	0.01	27.9 (19.4)	29.0 (20.1)	0.02

Abbreviations: DRd, daratumumab, lenalidomide and dexamethasone; DVRd, daratumumab, bortezomib, lenalidomide and dexamethasone; ECOG, Eastern Cooperative Oncology Group; EMD, extramedullary disease; GFR, glomerular filtration rate; IGG, immunoglobulin G; ISS, International Staging System; LDH, lactate dehydrogenase; mL, milliliter; min, minute; m^2, square meters; MM, multiple myeloma; mg/L, milligrams per liter; nISS, number of patients with ISS staging data; SMD, standardized mean difference; U/L, units per liter.

5.2.4 Results from the comparative analysis

5.2.4.1 Overall MRD negativity rate (10^{-5} sensitivity threshold)

DVRd demonstrated statistically significant superiority over DRd in achieving MRD negativity at the 10^{-5} sensitivity threshold. Across all analyses, DVRd consistently outperformed DRd. For example, in the IPTW base case analysis, the odds ratio (OR) was 2.97 (95% CI: 1.96, 4.51; p-value = 0.000). Sensitivity analyses further supported this finding, with ORs reaching as high as 3.49 (95% CI: 2.20, 5.56; p-value = 0.000). These results provide robust evidence of DVRd's enhanced efficacy in achieving MRD negativity. Detailed MRD negativity results are presented in Table 16.

Importantly, the MRD negativity rate was defined as the proportion of patients who achieved both MRD negativity at the 10^{-5} sensitivity threshold and a treatment response of complete response (CR) or better (≥CR)."

Table 16. Overall MRD-negativity rate (10-5), DVRd (CEPHEUS) versus DRd (MAIA)

Model	OR (95% CI)					
	IPTW		Doubly robust		Multivariate regression	
Variables	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Unadjusted	2.93 (1.95, 4.39)	0.000	2.93 (1.95, 4.39)	0.000	2.93 (1.95, 4.39)	0.000
base case	2.97 (1.96, 4.51)	0.000	3.13 (2.01, 4.87)	0.000	3.11 (2.04, 4.74)	0.000
Sensitivity	3.21 (2.10, 4.90)	0.000	3.49 (2.20, 5.56)	0.000	3.27 (2.13, 5.03)	0.000

Note: MRD negativity rate was defined as proportion of patients achieving both MRD negative status (at 10^{-5} sensitivity threshold) and ≥CR

5.2.4.2 Overall Survival

The OS data for DVRd and DRd were immature, with 22.9% and 49.46% of patients experiencing events in the DVRd and DRd arms, respectively, in the base case analysis. Although DVRd demonstrated a numerical benefit (HR: 0.83 [95% CI: 0.55, 1.24]; p-value = 0.35) in the IPTW base case analysis, the results did not achieve statistical significance.

Detailed outcomes from the base case and other analyses are provided in Table 17. Adjusting for COVID-19-related deaths further improved the numerical advantage of DVRd (HR: 0.66 [95% CI: 0.43, 1.03]; p-value = 0.067 in the IPTW base case), but statistical significance remained unattained. All analyses adjusted for COVID-19-related deaths are outlined in Table 18. Johnson & Johnson attributes the lack of statistical significance to the limited follow-up period and the delayed nature of OS as an endpoint.

It is important to note that the adjustment for COVID-19-related deaths was performed by censoring these deaths rather than counting them as events.

KMEs for the non-COVID-19-adjusted analysis are presented in Figure 11, while the corresponding estimates for the COVID-19-adjusted analysis are shown in Figure 12.

Table 17. OS outcomes, DVRd (CEPHEUS) versus DRd (MAIA)

Model	HR (95% CI)					
	IPTW		Doubly robust		Multivariate regression	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Unadjusted	0.78 (0.52, 1.16)	0.216	0.78 (0.52, 1.16)	0.216	0.78 (0.52, 1.16)	0.216

base case	0.83 (0.55, 1.24)	0.351	0.84 (0.56, 1.27)	0.414	0.82 (0.55, 1.22)	0.326
Sensitivity	0.80 (0.53, 1.21)	0.286	0.81 (0.53, 1.23)	0.322	0.80 (0.53, 1.21)	0.292

Table 18. OS outcomes censored for COVID-19-related deaths, DVRd (CEPHEUS) versus DRd (MAIA)

Model	HR (95% CI)					
	IPTW		Doubly robust		Multivariate regression	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Unadjusted	0.63 (0.41, 0.97)	0.036	0.63 (0.41, 0.97)	0.036	0.63 (0.41, 0.97)	0.036
base case	0.66 (0.43, 1.03)	0.067	0.67 (0.43, 1.05)	0.08	0.66 (0.42, 1.02)	0.061
Sensitivity	0.65 (0.41, 1.01)	0.056	0.65 (0.41, 1.02)	0.062	0.65 (0.41, 1.02)	0.061

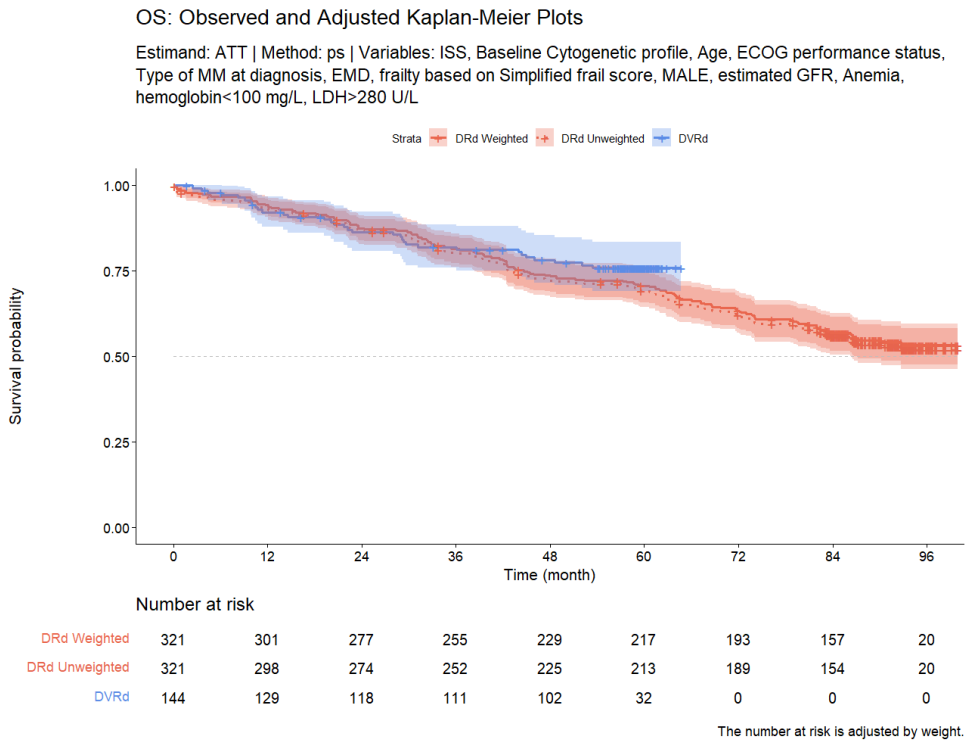


Figure 11. Kaplan-Meier plot for OS (DVRd [CEPHEUS] versus DRd [MAIA]), unadjusted and ATT adjusted analyses

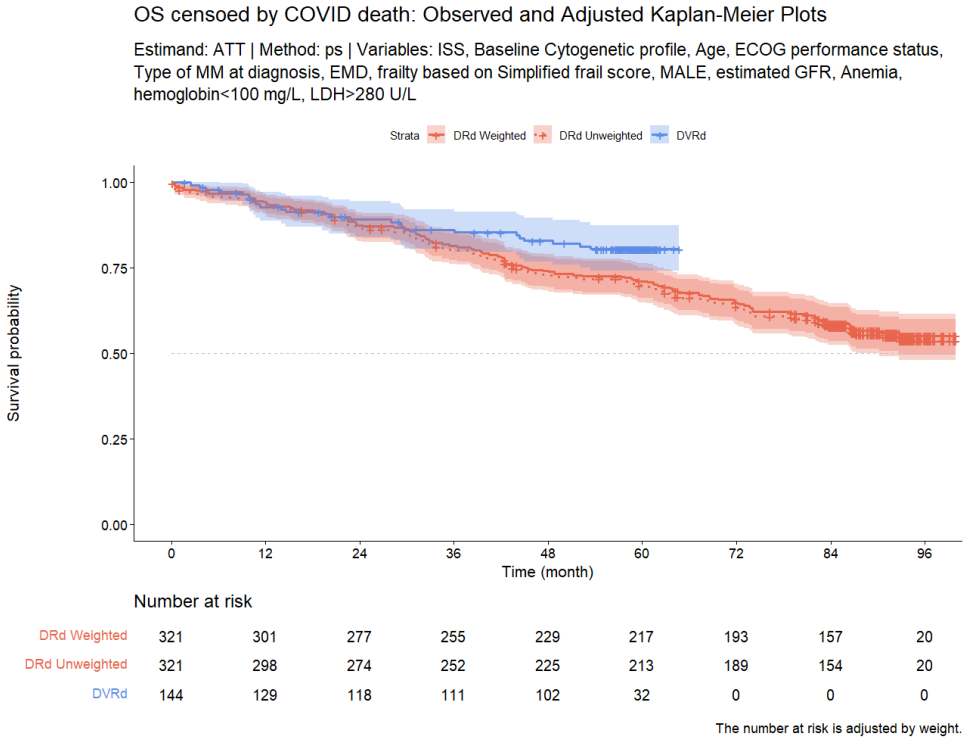


Figure 12. Kaplan-Meier plot for OS, censored for COVID-19-related deaths (DVRd [CEPHEUS] versus DRd [MAIA]), unadjusted and ATT adjusted analyses

5.2.4.3 Progression-free survival

DVRd demonstrated a significant improvement in PFS compared to DRd across all analyses. In the IPTW base case analysis, DVRd reduced the risk of disease progression or death by 32% (HR: 0.68 [95% CI: 0.48, 0.95]; p-value = 0.03). Sensitivity analyses further supported this benefit, with HRs as low as 0.63 (95% CI: 0.44, 0.90; p-value = 0.01). Detailed results from the base case and other analyses are provided in Table 19. These findings highlight the significant efficacy of DVRd in delaying disease progression and/or reducing the risk of death.

The Kaplan-Meier estimates (KMEs) for PFS are illustrated in Figure 13.

Table 19. PFS outcomes, DVRd (CEPHEUS) versus DRd (MAIA)

Model	HR (95% CI)					
	IPTW		Doubly robust		Multivariate regression	
Variables	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Unadjusted	0.66 (0.47, 0.93)	0.02	0.66 (0.47, 0.93)	0.02	0.66 (0.47, 0.93)	0.02
base case	0.68 (0.48, 0.95)	0.03	0.69 (0.49, 0.98)	0.04	0.67 (0.47, 0.94)	0.02
Sensitivity	0.64 (0.45, 0.90)	0.01	0.63 (0.44, 0.91)	0.01	0.63 (0.44, 0.90)	0.01

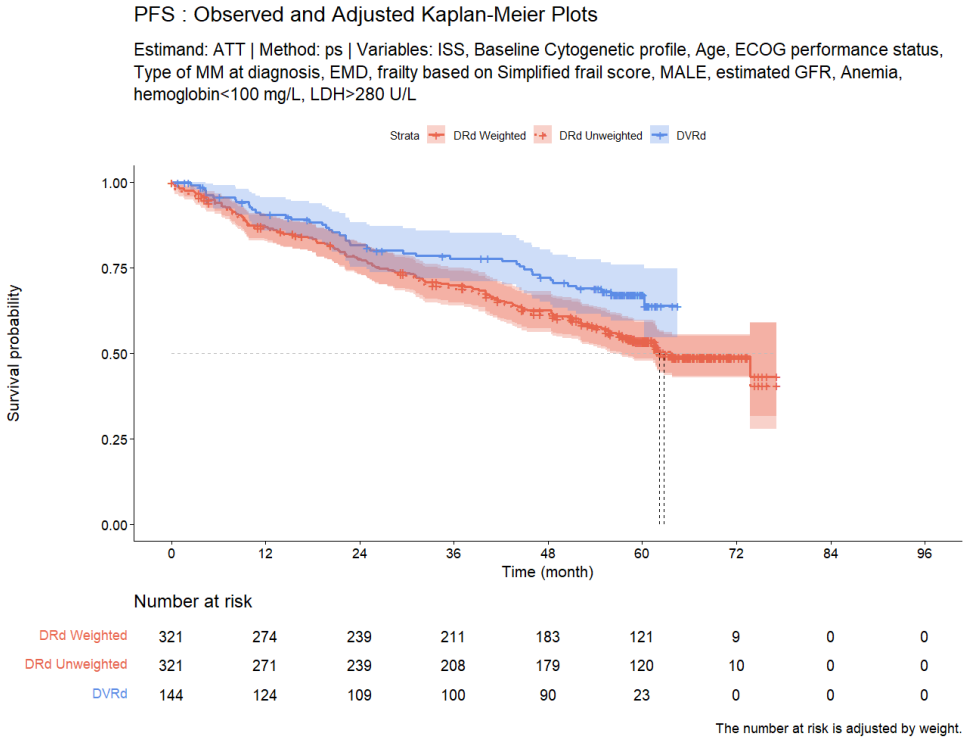


Figure 13. Kaplan-Meier plot for PFS (DVRd [CEPHEUS] versus DRd [MAIA]), unadjusted and ATT adjusted analyses

5.2.4.4 Overall Response Rate

DVRd demonstrated a numerically higher ORR compared to DRd; however, statistical significance was not consistently observed across all analyses. In the IPTW base case analysis, the OR was 4.01 (95% CI: 0.90, 17.81; p-value = 0.068). Notably, multivariate regression analyses yielded statistically significant results favoring DVRd, with ORs reaching as high as 6.27 (95% CI: 1.24, 31.68; p-value = 0.026) in sensitivity analyses. Detailed outcomes from these analyses, including unadjusted, base case, and sensitivity analyses, are provided in Table 20.

Table 20. ORR, DVRd (CEPHEUS) versus DRd (MAIA)

Model	OR (95% CI)					
	IPTW		Doubly robust		Multivariate regression	
Variables	OR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Unadjusted	4.72 (1.09, 20.46)	0.04	4.72 (1.09, 20.46)	0.038	4.72 (1.09, 20.46)	0.038
base case	4.01 (0.90, 17.81)	0.068	6.69 (0.86, 52.24)	0.070	5.75 (1.17, 28.39)	0.032

Sensitivity	4.72 (1.05, 21.11)	0.042	6.26 (0.86, 45.39)	0.070	6.27 (1.24, 31.68)	0.026

Table 21. Results from the comparative analysis of DVRd vs. DRd for patients with NDMM who are TIE

Outcome measure	DVRd (N=	DRd (N=)	IPTW results OR (95% CI), p-value
Overall MRD negativity rate (10^{-5} sensitivity threshold)	N/A	N/A	Unadjusted: 2.93 (1.95, 4.39), p-value: 0.000 Base case: 2.97 (1.96, 4.51), p-value: 0.000 Sensitivity: 3.21 (2.10, 4.90), p-value: 0.000
OS	N/A	N/A	Unadjusted: 0.78 (0.52,1.16), p-value: 0.216 Base case: 0.83 (0.55, 1.24), p-value: 0.351 Sensitivity: 0.80 (0.53, 1.21), p-value: 0.286
OS (censored for COVID-19-related deaths)	N/A	N/A	Unadjusted: 0.63 (0.41, 0.97), p-value: 0.036 Base case: 0.66 (0.43, 1.03), p-value: 0.067 Sensitivity: 0.65 (0.41, 1.01), p-value: 0.056
PFS	N/A	N/A	Unadjusted: 0.66 (0.47, 0.93), p-value: 0.02 Base case: 0.68 (0.48, 0.95), p-value: 0.03 Sensitivity: 0.64 (0.45, 0.90), p-value: 0.01
ORR	N/A	N/A	Unadjusted: 4.72 (1.09, 20.46), p-value: 0.040 Base case: 4.01 (0.90, 17.81), p-value: 0.068 Sensitivity: 4.72 (1.05, 21.11), p-value: 0.042

6. References

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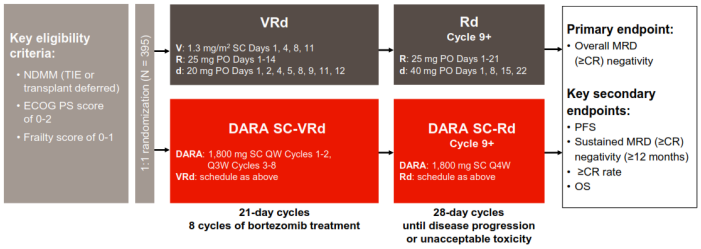
Appendix A. Main characteristics of studies included

Table 22. Main characteristic of CEPHEUS

Trial name: CEPHEUS	NCT number: 03652064
Objective	The purpose of this study to determine if the addition of daratumumab to bortezomib + lenalidomide + dexamethasone (VRd) will improve overall minimal residual disease (MRD) negativity rate compared with VRd alone. 
Publications – title, author, journal, year	*Title:* Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant-deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial; *Authors:* Usmani, S.Z., Facon, T., Hungria, V. et al. *Journal:* Nature Medicine *Year:* 2025 [1]
Study type and design	Phase III randomized, controlled, open-label multicenter study, comparing the efficacy, safety and patient reported outcomes. Enrolled patients randomly assigned 1:1. No crossover was allowed.
Sample size (n)	N=395 (TIE and transplant deferred); N=289 (TIE)
Main inclusion criteria	Diagnosis of multiple myeloma as documented per International Myeloma Working Group (IMWG) criteria Monoclonal plasma cells in the bone marrow greater than or equal to (>=)10 percentage (%) or presence of a biopsy proven plasmacytoma and documented multiple myeloma satisfying at least one of the calcium, renal, anemia, bone (CRAB) criteria or biomarkers of malignancy criteria. CRAB criteria: Hypercalcemia: serum calcium greater than (>) 0.25 millimoles per liter (mmol/L) (>1 milligram per deciliter [mg/dL]) higher than upper limit of normal (ULN) or >2.75 mmol/L (>11 mg/dL); Renal insufficiency: creatinine clearance less than (<) 40 milliliter per minute (mL/min) or serum creatinine >177 micro millimoles per liter (umol/L) (>2 mg/dL); Anemia: hemoglobin >2 g/dL below the lower limit of normal or hemoglobin <10 g/dL; Bone lesions: one or more osteolytic lesions on skeletal radiography, computed tomography (CT), or positron emission tomography (PET)-CT. [3]

Trial name: CEPHEUS	NCT number: 03652064
	Biomarkers of Malignancy: Clonal bone marrow plasma cell percentage >=60%; Involved: uninvolved serum free light chain (FLC) ratio >=100; >1 focal lesion on magnetic resonance imaging (MRI) studies. [3] • Must have measurable disease, as assessed by central laboratory, • Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2, • A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing, • A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 3 months after receiving the last dose of any component of the treatment regimen. [3]
Main exclusion criteria	• Frailty index of >=2 according to Myeloma Geriatric Assessment score, • Prior therapy for multiple myeloma other than a short course of corticosteroids (not to exceed 40 mg of dexamethasone, or equivalent per day, total of 160 mg dexamethasone or equivalent), • Prior or concurrent invasive malignancy (other than multiple myeloma) within 5 years of date of randomization (exceptions are adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years), • Peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5, • Focal radiation therapy within 14 days of randomization with the exception of palliative radiotherapy for symptomatic pain management. Radiotherapy within 14 days prior to randomization on measurable extramedullary plasmacytoma is not permitted even in the setting of palliation for symptomatic management. [3]
Intervention	DVRd (Daratumumab in combination with bortezomib, lenalidomide and dexamethasone). n = 197 (TIE and transplant deferred); n = 144 (TIE)

Trial name: CEPHEUS	NCT number: 03652064
	Daratumumab, Bortezomib, lenalidomide and dexamethasone, administrated and dosed as follows [7]: • Bortezomib 1.3 mg/m2 as a subcutaneous (SC) injection twice weekly on days 1, 4, 8, and 11 of each 21-day cycle for cycles 1-8 only • Lenalidomide 25mg orally on days 1-14 of each 21-day cycle for cycles 1-8 (for patients with a creatinine clearance of ≥60 mL/min) o For cycles 9 and beyond, lenalidomide 25mg was administered daily on days 1-21 of each 28-day cycle (for patients with a creatinine clearance of ≥60 mL/min). o Patients with a creatinine clearance of 30 to 59mL/min received 10mg every 24 hours for days 1-14 for cycles 1-8 and days 1-21 for cycle 9 and beyond • Dexamethasone 20mg once a day on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for cycles 1-8 (patients >75 years of age or with body mass index <18.5kg/m2 received 20mg once a day on days 1, 4, 8, and 11) o For cycles 9 and beyond, dexamethasone 40mg was administered daily on days 1, 8, 15, 22 of each 28-day cycle (patients >75 years of age or with body mass index <18.5kg/m2 received 20mg once a week) • Daratumumab 1,800mg by SC injection weekly for 8 weeks (cycles 1 to 2), every 3 weeks in Cycles 3-8, and every 4 weeks in Cycle 9 and beyond.[7]
Comparator(s)	VRd (Bortezomib in combination with lenalidomide and dexamethasone). n = 198 (TIE and transplant deferred); n = 145 (TIE) Bortezomib, lenalidomide and dexamethasone, administrated and dosed as follows [7]: • Bortezomib 1.3 mg/m2 as a subcutaneous (SC) injection twice weekly on days 1, 4, 8, and 11 of each 21-day cycle for cycles 1-8 only • Lenalidomide 25mg orally on days 1-14 of each 21-day cycle for cycles 1-8 (for patients with a creatinine clearance of ≥60 mL/min) o For cycles 9 and beyond, lenalidomide 25mg was administered daily on days 1-21 of each 28-day cycle (for patients with a creatinine clearance of ≥60 mL/min). o Patients with a creatinine clearance of 30 to 59mL/min received 10mg every 24 hours for days 1-14 for cycles 1-8 and days 1-21 for cycle 9 and beyond • Dexamethasone 20mg once a day on days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for cycles 1-8 (patients >75 years of age or with body mass index <18.5kg/m2 received 20mg once a day on days 1, 4, 8, and 11)

Trial name: CEPHEUS		NCT number: 03652064
	o For cycles 9 and beyond, dexamethasone 40mg was administered daily on days 1, 8, 15, 22 of each 28-day cycle (patients >75 years of age or with body mass index <18.5kg/m2 received 20mg once a week)	
Follow-up time	Median follow-up 58.7 months (May 2024 clinical cut-off)	
Primary, secondary and exploratory endpoints	**Primary endpoint** *Outcome Measure* Percentage of Participants with Negative Minimal Residual Disease (MRD) Status *Measure Description* Percentage of participants who achieve MRD negative status by evaluation of bone marrow aspirates using next generation sequencing (NGS) at 10^{-5} threshold will be assessed. **Secondary endpoint 1** *Outcome Measure* Progression-Free Survival *Measure Description* PFS is defined as the duration from date of randomization to either PD or death, whichever comes first. International Myeloma Working Group (IMWG) criteria for PD: Increase of 25 percentage (%) from lowest response value in any one of following: Serum M-component (absolute increase must be >= 0.5 gram per deciliter [g/dL],) Urine M-component (absolute increase must be >=200 mg/24 hours), participants without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 milligrams per deciliter [mg/dL]), participants without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC% (absolute percentage must be >=10%), definite development of new bone lesions or soft tissue plasmacytomas or increase in size of bone lesions or tissue plasmacytomas and development of hypercalcemia (serum calcium >11.5 mg/dL) that can be attributed solely to PC proliferative disorder. **Secondary endpoint 2** *Outcome Measure* MRD Negative Rate	

Measure Description

Percentage of participants who have achieved MRD negative status will be assessed and landmark timepoints (12, 18 and 24 months). MRD negativity will be evaluated as a potential surrogate for PFS and OS in multiple myeloma treatment.

Secondary endpoint 3

Outcome Measure

Durable MRD Negative Rate

Measure Description

Durable MRD negativity rate is defined as the number of participants who have achieved MRD negative status (at 10^-5) at 2 bone marrow aspirates examinations that are a minimum of 1 year apart, without any examination showing MRD positive status in between.

Secondary endpoint 4

Outcome Measure

Overall Response Rate

Measure Description

ORR is defined as the percentage of participants who achieve partial response (PR) or better responses prior to subsequent anti-myeloma therapy in accordance with IMWG criteria, during or after the study treatment. IMWG criteria for PR: greater than or equal to (>=) 50 reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90 % or to less than (<) 200 mg/24 hours, If the serum and urine M-protein are not measurable, a decrease of >=50% in the difference between involved and uninvolved free light chain (FLC) levels is required in place of the M-protein criteria, If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, >=50% reduction in bone marrow plasma cells (PCs) is required in place of M-protein, provided baseline bone marrow plasma cell percentage was >=30%. In addition to the above criteria, if present at baseline, a >=50% reduction in the size of soft tissue plasmacytomas is also required.

Secondary endpoint 5

Outcome Measure

Very Good Partial Response or Better Rate

Measure Description

VGPR or better rate is defined as the percentage of participants achieving VGPR and CR (including sCR) prior to subsequent anti-myeloma therapy in accordance with the IMWG criteria during or after the study treatment. IMWG criteria for VGPR: Serum and urine M-component detectable by immunofixation but not on electrophoresis, or greater than or equal to (>=) 90 % reduction in serum M-protein plus urine M-protein <100 milligram per 24 hours (mg/24 hours); CR: Negative immunofixation on the serum and urine, disappearance of any soft tissue plasmacytomas and <5% PCs in bone marrow. sCR: CR plus normal FLC ratio, and absence of clonal PCs by immunohistochemistry (IHC), immunofluorescence or 2- to 4 color flow cytometry.

Secondary endpoint 6

Outcome Measure

Complete Response or Better Rate

Measure Description

CR or better rate is defined as the percentage of participants achieving CR or sCR prior to subsequent anti-myeloma therapy in accordance with the IMWG criteria during or after the study treatment.

Secondary endpoint 7

Outcome Measure

PFS on the Next Line of Therapy

Measure Description

The PFS on the next line of therapy is defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment.

Secondary endpoint 8

Outcome Measure

Overall Survival

Measure Description

OS is defined as the time from the date of randomization to the date of the participant's death due to any cause.

Secondary endpoint 9

Outcome Measure

Time to Response

Measure Description

Time to response is defined as the time between the randomization and the first efficacy evaluation at which the participant meets all criteria for PR or better.

Secondary endpoint 10

Outcome Measure

Duration of Response

Measure Description

DOR is calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of PD, as defined in the IMWG evaluation before the start of any subsequent anti-myeloma therapy.

Secondary endpoint 11

Outcome Measure

Maximum Observed Serum Concentration of Daratumumab

Measure Description

The Cmax is the maximum observed serum concentration of daratumumab.

Secondary endpoint 12

Outcome Measure

Minimum Observed Serum Concentration of Daratumumab

Measure Description

The Cmin is the minimum observed serum concentration of daratumumab.

Secondary endpoint 13

Outcome Measure

Number of Participants with Anit-daratumumab Antibodies

Measure Description

Number of participants with anti-daratumumab antibodies will be assessed.

Secondary endpoint 14

Outcome Measure

Number of Participants with Anit-rHuPH20 Antibodies

Measure Description

Number of participants rHuPH20 antibodies will be assessed.

Secondary endpoint 15

Outcome Measure

Change from Baseline in Health-Related Quality of Life as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 item.

Measure Description

The EORTC- QLQ-Core-30 includes 30 items that make up 5 functional scales (physical, role, emotional, cognitive, and social), 1 global health status scale, 3 symptom scales (pain, fatigue, and nausea/vomiting), and 6 single symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The recall period is 1 week ("past week") and responses are reported using a verbal and numeric rating scales. The item and scale scores are transformed to a 0 to 100 scale. A higher score represents greater HRQoL, better functioning, and more (worse) symptoms.

Trial name: CEPHEUS	NCT number: 03652064

Secondary endpoint 16

Outcome Measure

Change from Baseline in HRQoL as Assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Multiple Myeloma 20-item.

Measure Description

The EORTC QLQ-MY20 is a validated, self -administered instrument to assess QoL in persons with MM. This 20-item questionnaire measures the following domains: symptom scales, including disease symptoms (6 items) and symptoms related to side effects of treatment (10 items); function scale and future perspective (3 items); and body image (1 item).

Secondary endpoint 17

Outcome Measure

Change from Baseline in HRQoL as Assessed by EuroQol Five Dimension Five Level Questionnaire

Measure Description

The EQ-5D-5L is a generic measure of health status. The EQ-5D-5L is a 5-item questionnaire that assesses 5 domains including mobility, self-care, usual activities, pain/discomfort and anxiety/depression plus a visual analog scale rating "health today" with anchors ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 separate questions are categorical and cannot be analyzed as cardinal numbers.

Method of analysis	All efficacy analyses were based on ITT subgroup for patients that were transplant ineligible. PFS: The treatment comparison of the distribution of overall PFS was based on a stratified log-rank test. The p-value from a stratified log-rank test was reported. Hazard ratio and its 95% confidence interval was estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable. The proportional hazard (PH) assumption of the PFS analysis was examined graphically (loglog plot of S(t)) and/or numerically (e.g., good of fitness test by Schoenfeld residual). MRD negativity rate: The stratified Cochran Mantel Haenszel (CMH) estimate of odds ratio and its 95% confidence interval and p-value from

Trial name: CEPHEUS	NCT number: 03652064
	Fisher's exact test was used to test if the MRD negativity rate is the same between the two treatment groups. CR or better rate: The CR or better rate was calculated for each treatment group based on the ITT subgroup analysis set. The corresponding 95% exact CI was provided. The stratified CMH estimate of odds ratio and its 95% confidence interval and p-value for testing treatment difference was reported.
Subgroup analyses	N/A – stratification based on transplant eligibility presented and used as base case.
Other relevant information	N/A

Table 23. Main characteristic of MAIA

Trial name: MAIA	NCT number: 02252172
Objective	The purpose of this study is to compare the efficacy of daratumumab in combination with lenalidomide and dexamethasone to that of lenalidomide and dexamethasone in terms of progression-free survival in participants with newly diagnosed multiple myeloma (a blood cancer of plasma cells) who are not candidates for high dose chemotherapy (treatment of disease, usually cancer, by chemical agents) and autologous stem cell transplant.
Publications – title, author, journal, year	**Publication 2** *Title:* Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma *Authors:* Facon, T., Kumar, S., Plesner, T. et al. *Journal:* The New England Journal of Medicine *Year:* 2019 [19] **Publication 1** *Title:* Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial *Authors:* Facon, T., Kumar, S., Plesner, T. et al. *Journal:* The Lancet *Year:* 2021 [20]

Trial name: MAIA		NCT number: 02252172
	Publication 3 *Title:* Daratumumab/lenalidomide/dexamethasone in transplant-ineligible newly diagnosed myeloma: MAIA long-term outcomes *Authors:* Facon, T., Moreau, P., Weisel, K. et al. *Journal:* Leukemia *Year:* 2025 [2]	
Study type and design	Phase III randomized, controlled, open-label multicenter study, comparing the efficacy, safety and patient reported outcomes. Enrolled patients randomly assigned 1:1. No crossover was allowed.	
Sample size (n)	N=737	
Main inclusion criteria	• Participant must have documented multiple myeloma satisfying the CRAB (calcium elevation, renal insufficiency, anemia and bone abnormalities) criteria, monoclonal plasma cells in the bone marrow greater than or equal to (>=) 10 percent (%) or presence of a biopsy proven plasmacytoma and measurable disease as defined by any of the following: (a) immunoglobulin (Ig) G myeloma (serum monoclonal paraprotein [M-protein] level >=1.0 gram/deciliter [g/dL] or urine M-protein level >=200 milligram[mg]/24 hours[hrs]; or (b) IgA, IgM, IgD, or IgE multiple myeloma (serum M-protein level >=0.5 g/dL or urine M-protein level >=200 mg/24 hrs); or (c) light chain multiple myeloma without measurable disease in serum or urine (serum immunoglobulin free light chain >=10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio) • Participant must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2 • Participants who are newly diagnosed and not considered for high-dose chemotherapy due to: being age >=65 years; or participants less than (<) 65 years with presence of important comorbid condition(s) likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation. Sponsor review and approval of participants below 65 years of age is required before randomization • Women of childbearing potential must commit to either abstain continuously from sexual intercourse or to use 2 methods of reliable birth control simultaneously as deemed appropriate by the Investigator. Contraception must begin 4 weeks prior to dosing and must continue for 3 months after the last dose of daratumumab • Man, who is sexually active with a woman of child-bearing potential must agree to use a latex or synthetic condom, even if he had a successful vasectomy, must agree to use an	

Trial name: MAIA		NCT number: 02252172
	adequate contraception method as deemed appropriate by the Investigator, and must also agree to not donate sperm during the study and for 4 weeks after last dose of lenalidomide and 4 months after last dose of daratumumab	
Main exclusion criteria	• Participant has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance (presence of serum M-protein <3 g/dL; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M-protein), or smoldering multiple myeloma (asymptomatic multiple myeloma with absence of related organ or tissue impairment end organ damage) • Participant has a diagnosis of Waldenström's disease, or other conditions in which IgM M protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions • Participant has a history of malignancy (other than multiple myeloma) within 5 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the Investigator, with concurrence with the Sponsor's medical monitor, is considered cured with minimal risk of recurrence within 5 years) • Participant has prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids before treatment • Participant has had radiation therapy within 14 days of randomization • Participant has known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume in 1 second [FEV1] <50% of predicted normal), persistent asthma, or a history of asthma within the last 2 years (controlled intermittent asthma or controlled mild persistent asthma is allowed) • Participants with known or suspected COPD must have a FEV1 test during Screening • Participant is known to be seropositive for human immunodeficiency virus (HIV) or hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg] or antibodies to hepatitis B surface and core antigens [anti-HBs and anti-HBc, respectively]) or hepatitis C (anti-HCV antibody positive or HCV-ribonucleic acid [RNA] quantitation positive)	
Intervention	DRd (daratumumab in combination with lenalidomide and dexamethasone). n = 368	

Trial name: MAIA	NCT number: 02252172
	Lenalidomide and dexamethasone, were administrated and dosed as follows [9, 10]: • Lenalidomide 25mg orally on Days 1 through 21 of each 28-day cycle (10mg every 24 hours for patients with creatinine clearance 30 to 50mL/min), • Dexamethasone 40mg once weekly (patients >75 years of age or with body mass index <18.5kg/m^2 could receive 20mg weekly). In addition, patients randomized to treatment with DRd received daratumumab 16mg/kg weekly for 8 weeks (cycles 1 to 2), then every other week for 16 weeks (cycles 3 to 6), then every 4 weeks (cycle 7 and beyond).[9, 10] From April 3, 2020, patients receiving daratumumab were allowed to switch from the IV (16/mg/kg) to SC (1,800mg) formulation to provide flexibility during the COVID-19 global pandemic[11].
Comparator(s)	DRd (daratumumab in combination with lenalidomide and dexamethasone). n = 368 Lenalidomide and dexamethasone, were administrated and dosed as follows [9, 10]: • Lenalidomide 25mg orally on Days 1 through 21 of each 28-day cycle (10mg every 24 hours for patients with creatinine clearance 30 to 50mL/min), • Dexamethasone 40mg once weekly (patients >75 years of age or with body mass index <18.5kg/m^2 could receive 20mg weekly).
Follow-up time	• Median follow-up 64.5 months (October 2021 clinical cut-off, informed all endpoints but OS), • Median follow-up 89.3 months (November 2023 clinical cut-off, only informed the OS endpoint).
Primary, secondary and exploratory endpoints	**Primary endpoint** *Outcome Measure* *Progression-free Survival* *Measure Description* *PFS was defined as time from date of randomization to either PD or death, whichever occurred first based on computerized algorithm as per IMWG criteria. PD was defined as an increase of 25 percent (%) from the lowest response value in one of the following: serum and urine M-component (absolute increase must be greater than or equal to [>=] 0.5 gram per deciliter [g/dL] and >=200 milligram [mg]/24 hours respectively); Only in participants without measurable serum and urine M-protein levels the difference between involved and uninvolved free*

light chain (FLC) levels (absolute increase must be greater than [>]10 mg/dL); Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas; Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that could be attributed solely to Plasma cell (PC) proliferative disorder.

Secondary endpoint 1

Outcome Measure

Percentage of Participants With Complete Response or Better

Measure Description

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

Secondary endpoint 2

Outcome Measure

Percentage of Participants With Very Good Partial Response or Better

Measure Description

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

Secondary endpoint 3

Outcome Measure

Percentage of Participants With Negative Minimal Residual Disease.

Measure Description

MRD negativity rate is defined as the percentage of participants who had negative MRD at any time point after the date of randomization and prior to subsequent antimyeloma therapy. MRD was assessed in participants who achieved CR or better.

Secondary endpoint 4

Outcome Measure

Percentage of Participants With Stringent Complete Response

Measure Description

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

Secondary endpoint 5

Outcome Measure

Overall Response Rate

Measure Description

ORR was the percentage of participants who achieved PR or better (PR, VGPR, CR or sCR) based on computerized algorithm as per IMWG criteria. PR: >=50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg/24 hours. If serum and urine M-protein were not measurable, a decrease of >=50% in the difference between involved and uninvolved FLC levels was required in place of the M-protein criteria. If present at baseline, a >=50% reduction in the size of soft tissue plasmacytomas was also required. VGPR: serum and urine M-component detectable by immunofixation but not on electrophoresis or >=90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours. CR: negative immunofixation on the serum and urine, Disappearance of any soft tissue plasmacytomas and < 5% PCs in bone marrow; sCR: CR in addition to having a normal FLC ratio and an absence of clonal cells in bone marrow by IHC, immunofluorescence, 2-4 color FC.

Secondary endpoint 6

Outcome Measure

Overall Survival

Measure Description

OS was measured from the date of randomization to the date of the death. Median OS was estimated by using the Kaplan-Meier method.

Secondary endpoint 7

Outcome Measure

Time to Disease Progression

Measure Description

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

Secondary endpoint 8

Outcome Measure

Time to Response

Measure Description

Time to first response, time to VGPR or better, time to CR or better and time to best response was reported for this endpoint. Time to response: time from date of randomization to first efficacy evaluation that met criteria for PR/better as their best response (PR, CR, or better) based on IMWG criteria. PR: >=50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by >=90% or to <200 mg/24 hours. If serum and urine M-protein were not measurable, a decrease of >=50% in difference between involved and uninvolved FLC levels was required in place of M-protein criteria. Based on computerized algorithm, according to IMWG response criteria, VGPR or better: proportion of participants with a response of VGPR or better (i.e.,

VGPR, CR or sCR), CR or better: proportion of participants with a response of CR or better (i.e., CR or sCR).

Secondary endpoint 9

Outcome Measure

Duration of Response

Measure Description

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

Secondary endpoint 10

Outcome Measure

Time to Subsequent Anti-myeloma Treatment

Measure Description

Time to subsequent anti-myeloma treatment was defined as the time from randomization to the start of subsequent anti-myeloma treatment. Kaplan-Meier method was used for the analysis.

Secondary endpoint 11

Outcome Measure

Progression-free Survival on Next Line of Therapy

Measure Description

PFS2 was defined as the time from randomization to progression on next line of therapy or death, whichever comes first. Disease

progression on next line of treatment was based on investigator judgment.

Secondary endpoint 12

Outcome Measure

Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 Global Health Status Score

Measure Description

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

Secondary endpoint 13

Outcome Measure

Change From Baseline in EuroQol-5 Dimensions-5 Levels Visual Analogue Scale

Measure Description

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

Secondary endpoint 14

Outcome Measure

Change From Baseline in EuroQol-5 Dimensions-5 Levels Utility Score

Measure Description

EQ-5D-5L was standardized, participant-reported questionnaire to assess health-related quality of life. EQ-5D-5L included 2 components: EQ-5D-5L health state profile (descriptive system) and EQ-5D-5L VAS. EQ-5D-5L descriptive system provided a profile of participant's health state 5 dimensions (5D): mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension had 5 response options (no problems, slight problems, moderate problems, severe problems and extreme problems) that reflected increasing levels of difficulty. Participants indicated their health state by selecting the most appropriate level in each of the 5D. Responses to the 5D scores were combined and converted into single preference-weighted health utility index score 0 (0.0- worst health state) to 1 (1.0- better health state) representing the general health status of individual (but allows for values less than 0 by United kingdom scoring algorithm). Higher score indicated better health state.

Secondary endpoint 15

Outcome Measure
Sub-group Analysis: Progression-free Survival

Measure Description

PFS for participants with cytogenic high risk was reported. PFS was time from date of randomization to either PD or death, whichever occurred first based on computerized algorithm as per IMWG criteria. PD: an increase of 25% from lowest response value in one of following: serum and urine M-component (absolute increase must be >=0.5 g/dL and >=200 mg/24h respectively); Only in participants without measurable serum and urine M-protein levels, difference between involved and uninvolved FLC levels (absolute >10 mg/dL); Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in size of existing bone lesions or soft tissue plasmacytomas; Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that could be attributed solely to PC proliferative disorder. High risk was defined as positive for any of del17p, t(14;16) or t(4;14) by (corrected serum calcium >11.5 mg/dL) Fluorescence In Situ Hybridization (FISH)/Karyotype.

Secondary endpoint 16

Outcome Measure

Trial name: MAIA	NCT number: 02252172

Sub-group Analysis: Overall Response Rate

Measure Description

ORR for participants with cytogenic high risk was reported. ORR: percentage of participants who achieved PR/better per IMWG criteria. PR: >=50% reduction of serum M-protein, reduction in 24h urinary M-protein by >=90% or <200mg/24h. If serum/urine M-protein were not measurable, decrease of >=50% in difference between involved and uninvolved FLC levels was required in place of M-protein criteria. If present at baseline, >=50% reduction in size of soft tissue plasmacytomas was required. VGPR: serum/urine M-component detectable by immunofixation but not on electrophoresis or >=90% reduction in serum and urine M-protein <100mg/24h. CR: negative immunofixation on serum/urine, disappearance of soft tissue plasmacytomas, <5% PCs in bone marrow; sCR: CR in addition to normal FLC ratio, absence of clonal cells in bone marrow by IHC, immunofluorescence, 2-4 color FC. High risk: positive for any of del17p, t(14;16) or t(4;14) by FISH/Karyotype.

Method of analysis	All efficacy analyses were ITT analyses. Continuous variables was summarized using descriptive statistics such as mean, standard deviation (SD), median and range. Categorical variables was summarized using frequency and percentage. For time-to-event variables, which is defined as from randomization to the date of the event, the Kaplan-Meier method was used for descriptive summaries. For the calculation of time-to-event and duration-of-event variables, the difference between the start date and the end date plus 1 day was used. Stratification factors used include ISS staging (I, II, III), region (North America vs other), and age (<75 years vs ≥75 years). PFS: The primary treatment comparison of the distribution of overall PFS was based on a stratified log-rank test. The p-value from a stratified log-rank test was reported. Hazard ratio and its 95% confidence interval was estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable. ORR: Stratified CMH test was used to test treatment difference in ORR, VGPR or better rate, CR or better rate and sCR rate. The CMH estimate of odds ratio and its 95% confidence interval and p-value for testing treatment difference was reported. OS: The Kaplan-Meier method was used to estimate the distribution of OS for each treatment group. Median OS with 95% CI was provided. In addition, the number and percentage of subjects who had died or were censored was reported.
Subgroup analyses	N/A

Trial name: MAIA		NCT number: 02252172
Other relevant information	N/A	

Appendix B. Efficacy results per study

Results per study

CEPHEUS

Table 24. Results, CEPHEUS (TIE population) per study

Results of CEPHEUS (NCT03652064)											
				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**		
Overall MRD Negativity (10^{-5} sensitivity threshold)	DVRd	144	60.4%	21.1%	-	-	OR: 2.37	1.47–3.82	0.0004	The stratified Cochran Mantel Haenszel (CMH) estimate of odds ratio and its 95% confidence interval and p-value from Fisher's exact test was used to test if the MRD negativity rate is the same between the two treatment groups. Stratification factors used in the analysis include ISS staging (I, II, III) and age/transplant eligibility (<70 years ineligible, <70 years and refusal to transplant, ≥70 years)	
	VRd	145	39.3%								

Results of CEPHEUS (NCT03652064)											
				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		
1-year OS	DVRd	144 (129)	92.2% (86.4–95.6)	1.4	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	VRd	145 (127)	90.8% (84.7–94.6)								
2-year OS	DVRd	144 (118)	86.4% (79.5–91.1)							The survival rates are based on the Kaplan–Meier estimator.	
	VRd	145 (114)	83.6% (76.3–88.8)								
3-year OS	DVRd	144 (111)	82.0% (74.5–87.4)	5	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	VRd	145 (105)	77.0% (69.1–83.1)								
4-year OS	DVRd	144 (102)	78.2% (70.3–84.2)	7.1	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	VRd	145 (96)	71.1% (62.7–77.9)								

Results of CEPHEUS (NCT03652064)											
				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		
HR OS	DVRd	144	NA	NA	NA	NA	HR: 0.66	0.42–1.03	0.0682	Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III) as randomized. P-value is based on the log-rank test stratified with ISS staging (I, II, III), as randomized.	
	VRd	145	NA								
1-year OS (COVID19-adjusted)	DVRd	144 (129)	92.9% (87.2–96.1)	2.1	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	VRd	145 (127)	90.8% (84.7–94.6)								
2-year OS (COVID19-adjusted)	DVRd	144 (118)	89.2% (82.7–93.3)	3.4	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	VRd	145 (114)	85.8% (78.8–90.6)								
	DVRd	144 (111)	86.2 (79.1–90.9)	7.2	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	

Results of CEPHEUS (NCT03652064)											
				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**		
3-year OS (COVID19-adjusted)	VRd	145 (105)	79.0 (71.2–84.9)								
4-year OS (COVID19-adjusted)	DVRd	144 (102)	83.0 (75.5–88.4)	10.1	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	VRd	145 (96)	72.9 (64.6–79.6)								
HR OS (COVID19-adjusted)	DVRd	144	NA	NA	NA	NA	HR: 0.55	0.34–0.90	0.0159	Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III) as randomized. P-value is based on the log-rank test stratified with ISS staging (I, II, III), as randomized.	
	VRd	145	NA								
1-year PFS	DVRd	144 (124)	90.6% (84.4–94.4)	1.8	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	

Results of CEPHEUS (NCT03652064)											
				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		
	VRd	145 (114)	88.8% (82.1–93.1)								
2-year PFS	DVRd	144 (109)	81.6% (74.0–87.2)	3.9	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	VRd	145 (96)	77.7% (69.5–84.0)								
3-year PFS	DVRd	144 (100)	77.8% (69.8–83.9)	16.3	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	VRd	145 (76)	61.5% (52.5–69.4)								
4-year PFS	DVRd	144 (61)	72.3% (63.8–79.1)	20.0	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	VRd	145 (90)	52.3 (43.2–60.6)								
HR PFS	DVRd	144	NA	NA	NA	NA	HR: 0.51	0.35–0.74	0.0003	Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the	
	VRd	145	NA								

Results of CEPHEUS (NCT03652064)											
				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		
										sole explanatory variable and stratified with ISS staging (I, II, III) as randomized. P-value is based on the log-rank test stratified with ISS staging (I, II, III), as randomized.	
ORR	DVRd	144	98.6%	7.6	NA	NA	OR: 7.17	1.60–32.11	0.0033	The stratified Cochran Mantel Haenszel (CMH) estimate of odds ratio and its 95% confidence interval and p-value from Fisher's exact test was used to test if the MRD negativity rate is the same between the two treatment groups. Stratification factors used in the analysis include ISS staging (I, II, III) and age/transplant eligibility (<70 years ineligible, <70 years and refusal to transplant, ≥70 years)	
	VRd	145	91.0								

MAIA

Table 25. Results, MAIA per study

Results of MAIA (NCT02252172)											
				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**		
1-year OS	DRd	368 (338)	92.6% (89.4–94.9)	1.3	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	Rd	369 (324)	91.3% (87.9–93.8)								
2-year OS	DRd	368 (305)	84.3% (80.2–87.7)	0.9	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	Rd	369 (294)	83.4% (79.1–86.9)								
3-year OS	DRd	368 (280)	78.2% (73.6–82.1)	5.9	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	Rd	369 (251)	72.3% (67.3–76.6)								
4-year OS	DRd	368 (249)	69.8% (64.8–74.3)	7.4	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	

Results of MAIA (NCT02252172)											
				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		
	Rd	369 (213)	62.4% (57.1–67.3)								
5-year OS	DRd	368 (233)	66.7% (61.6–71.3)	13.1	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	Rd	369 (182)	53.6% (48.2–58.7)								
6-year OS	DRd	368 (206)	59.5% (54.3–64.4)	15.3	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	Rd	369 (149)	44.2% (38.9–49.3)								
7-year OS	DRd	368 (168)	53.1% (47.8–58.2)	13.8	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	Rd	369 (120)	39.3% (34.1–44.5)								
HR OS	DRd	368	NA	NA	NA	NA	0.67	0.55–0.82	<0.0001	Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the	
	Rd	369	NA								

Results of MAIA (NCT02252172)											
				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		
										sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized	
1-year PFS	DRd	368 (309)	86.2% (82.2–89.4)	7.8	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	Rd	369 (255)	78.4% (73.6–82.4)								
2-year PFS	DRd	368 (266)	76.0% (71.2–80.1)	14.4	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	Rd	369 (196)	61.6% (56.1–66.6)								
3-year PFS	DRd	368 (232)	67.4% (62.3–72.0)	18.9	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	Rd	369 (147)	48.5% (42.9–53.8)								

Results of MAIA (NCT02252172)											
				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		
4-year PFS	DRd	368 (197)	59.4% (54.1–64.4)	22.1	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	Rd	369 (106)	37.3% (32.0–42.7)								
5-year PFS	DRd	368 (132)	52.1% (46.6–57.3)	22.5	NA	NA	NA	NA	NA	The survival rates are based on the Kaplan–Meier estimator.	
	Rd	369 (64)	29.6% (24.5–34.8)								
HR PFS	DRd	368	NA	NA	NA	NA	0.55	0.45–0.67	<0.0001	Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized.	
	Rd	369	NA								
ORR	DRd	368 (342)	92.9% (89.8–95.3)	11.3	NA	NA	OR: 3.00	1.85–4.86	<0.0001	Mantel-Haenszel estimate of the common odds ratio for	

Results of MAIA (NCT02252172)											
				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		
	Rd	369 (301)	81.6% (77.2–85.4)							stratified tables is used. The stratification factors are: ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized. P-value from the Cochran Mantel-Haenszel Chi-Squared test.	

Appendix C. Comparative analysis of efficacy

Table 26. Comparative analysis of studies comparing DVRd to DRd for patients with NDMM who are TIE

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
Overall MRD Negativity (10^{-5} sensitivity threshold), IPTW ATT	CEPHEUS; MAIA	NA	NA	NA	OR: 2.97	1.96–4.51	0.000	Binary outcomes were quantified as ORs on the log-scale through weighted logistic regression, with the treatment included as a covariate. The regression coefficient for treatment derived from this model provided estimates of the study-specific log-OR and its corresponding SE.	NA
Overall MRD Negativity (10^{-5} sensitivity threshold), Doubly robust	CEPHEUS; MAIA	NA	NA	NA	OR: 3.13	2.01–4.87	0.000		NA
Overall MRD Negativity (10^{-5} sensitivity threshold), Multivariate regression	CEPHEUS; MAIA	NA	NA	NA	OR: 3.11	2.04–4.74	0.000		NA
OS, IPTW ATT	CEPHEUS; MAIA	NA	NA	NA	HR: 0.83	0.55–1.24	0.351	Weighted Cox survival model were separately fitted to the CEPHEUS and MAIA IPD (using IPTW weights), with the treatment included as a	NA

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
								covariate. The regression coefficients derived from these models provided estimates of the study-specific log-HRs and their corresponding SE. The indirect comparisons of DVRd vs. DRd were then calculated on the log-scale. Where the SE of the weighted log-HR in CEPHEUS is computed using a robust sandwich estimator.	
OS, Doubly robust	CEPHEUS; MAIA	NA	NA	NA	HR: 0.84	0.56–1.27	0.414		NA
OS, Multivariate regression	CEPHEUS; MAIA	NA	NA	NA	HR: 0.82	0.55–1.22	0.326		NA
OS, COVID19-adjusted, IPTW ATT	CEPHEUS; MAIA	NA	NA	NA	HR: 0.66	0.43–1.03	0.067	Weighted Cox survival model were separately fitted to the CEPHEUS and MAIA IPD (using IPTW weights), with the treatment included as a covariate. The regression coefficients derived from these models provided estimates of the study-specific log-HRs and their corresponding SE. The	

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
								indirect comparisons of DVRd vs. DRd were then calculated on the log-scale. Where the SE of the weighted log-HR in CEPHEUS is computed using a robust sandwich estimator.	
OS, COVID19-adjusted, Doubly robust	CEPHEUS; MAIA	NA	NA	NA	HR: 0.67	0.43–1.05	0.08		
OS, COVID19-adjusted, Multivariate regression	CEPHEUS; MAIA	NA	NA	NA	HR: 0.66	0.42–1.02	0.061		
PFS, IPTW ATT	CEPHEUS; MAIA	NA	NA	NA	HR: 0.68	0.48–0.95	0.03	Weighted Cox survival model were separately fitted to the CEPHEUS and MAIA IPD (using IPTW weights), with the treatment included as a covariate. The regression coefficients derived from these models provided estimates of the study-specific log-HRs and their corresponding SE. The indirect comparisons of DVRd vs. DRd were then calculated on the log-scale. Where the SE of the weighted log-HR in	NA

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
								CEPHEUS is computed using a robust sandwich estimator.	
PFS, Doubly robust	CEPHEUS; MAIA	NA	NA	NA	HR: 0.69	0.49–0.98	0.04		NA
PFS, Multivariate regression	CEPHEUS; MAIA	NA	NA	NA	HR: 0.67	0.47–0.94	0.02		NA
ORR, IPTW ATT	CEPHEUS; MAIA	NA	NA	NA	OR: 4.01	0.90–17.81	0.068	Binary outcomes were quantified as ORs on the log-scale through weighted logistic regression, with the treatment included as a covariate. The regression coefficient for treatment derived from this model provided estimates of the study-specific log-OR and its corresponding SE.	NA
ORR, Doubly robust	CEPHEUS; MAIA	NA	NA	NA	OR: 6.69	0.86–52.24	0.07		NA
ORR, Multivariate regression	CEPHEUS; MAIA	NA	NA	NA	OR: 5.75	1.17–28.39	0.032		

Appendix D. Balance of Populations (CEPHEUS and MAIA)

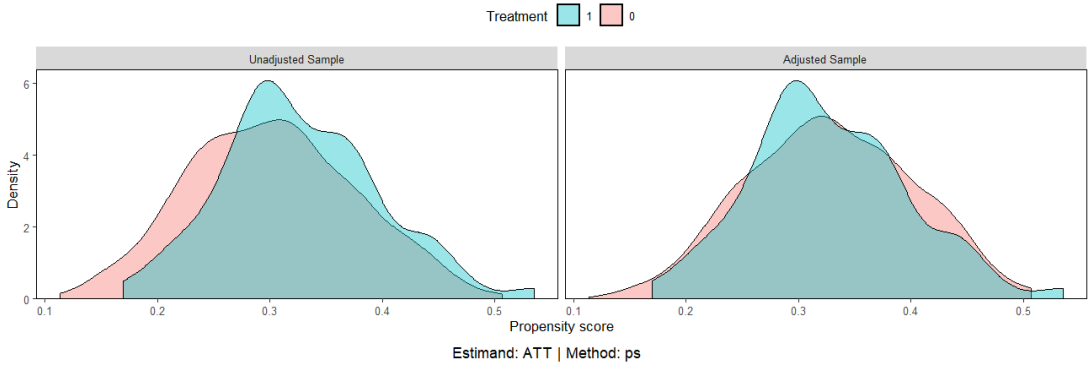


Figure 14. Kernel density of weights in the base-case model for DVRd versus DRd

Table 27. Overview of Group Demographic Balance Before and After Weighting (CEPHEUS and MAIA), all covariates (sensitivity analysis)

Variables	Unweighted			Weighted		
	DRd	DVRd	SMD	DRd	DVRd	SMD
n/ESS	321	144		256.51	144	
ISS (%)						
I	87.0 (27.1)	50.0 (34.7)	0.17	47.4 (33.0)	50.0 (34.7)	0.04
II	146.0 (45.5)	54.0 (37.5)	-0.16	54.3 (37.8)	54.0 (37.5)	-0.01
III	88.0 (27.4)	40.0 (27.8)	0.01	42.1 (29.3)	40.0 (27.8)	-0.03
Baseline Cytogenetic profile (%)						
High-risk	41.0 (12.8)	20.0 (13.9)	0.03	19.5 (13.5)	20.0 (13.9)	0.01
Not Done	42.0 (13.1)	19.0 (13.2)	0.00	18.6 (13.0)	19.0 (13.2)	0.01

Standard-risk	238.0 (74.1)	105.0 (72.9)	-0.03	105.6 (73.5)	105.0 (72.9)	-0.01
Age (%)						
<=69	78.0 (24.3)	35.0 (24.3)	0.00	34.6 (24.1)	35.0 (24.3)	0.01
70-74	130.0 (40.5)	68.0 (47.2)	0.14	69.2 (48.1)	68.0 (47.2)	-0.02
75+	113.0 (35.2)	41.0 (28.5)	-0.14	39.9 (27.8)	41.0 (28.5)	0.01
ECOG performance status (%)						
0	114.0 (35.5)	52.0 (36.1)	0.01	51.4 (35.8)	52.0 (36.1)	0.01
1	155.0 (48.3)	75.0 (52.1)	0.08	76.3 (53.1)	75.0 (52.1)	-0.02
2 and above	52.0 (16.2)	17.0 (11.8)	-0.13	16.0 (11.2)	17.0 (11.8)	0.02
Type of MM at diagnosis = IGG (%)	210.0 (65.4)	92.0 (63.9)	-0.03	90.6 (63.0)	92.0 (63.9)	0.02
EMD = 1 (%)	12.0 (3.7)	9.0 (6.2)	0.12	8.0 (5.6)	9.0 (6.2)	0.03
frailty based on Simplified frail score = 1 (%)	125.0 (38.9)	48.0 (33.3)	-0.12	46.9 (32.6)	48.0 (33.3)	0.01
MALE = MALE (%)	162.0 (50.5)	65.0 (45.1)	-0.11	66.3 (46.1)	65.0 (45.1)	-0.02
estimated GFR = >=60mL/min/1.73 m2 (%)	125.0 (38.9)	47.0 (32.6)	-0.13	48.3 (33.6)	47.0 (32.6)	-0.02
Anemia, hemoglobin<100 mg/L = 1 (%)	119.0 (37.1)	45.0 (31.2)	-0.12	44.5 (30.9)	45.0 (31.2)	0.01
LDH>280 U/L = 1 (%)	64.0 (19.9)	29.0 (20.1)	0.01	27.3 (19.0)	29.0 (20.1)	0.03
Calcium>2.75 mmol/L = 1 (%)	10.0 (3.1)	8.0 (5.6)	0.12	7.1 (4.9)	8.0 (5.6)	0.03
WHITE = 1 (%)	295.0 (91.9)	122.0 (84.7)	-0.22	122.3 (85.1)	122.0 (84.7)	-0.01
diagnosed>=1 month = 1 (%)	153.0 (47.7)	85.0 (59.0)	0.23	84.4 (58.7)	85.0 (59.0)	0.01

Appendix E. Literature searches for the clinical assessment

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

N/A

Table 28. Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion

Abbreviations:

Table 29. Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search

Abbreviations:

Table 30. Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search

Abbreviations:

D.1.2 Search strategies

N/A

Table 31. of search strategy table for [name of database]

No.	Query	Results

D.1.3 Systematic selection of studies

N/A

Table 32. Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria

Table 33. Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Interven-tion and compara-tor (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period

D.1.4 Quality assessment

N/A

D.1.5 Unpublished data

N/A

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