27 February 2025
EMA/CHMP/96363/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Darzalex

International non-proprietary name: Daratumumab

Procedure No. EMEA/H/C/004077/II/0076

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADAs	anti-daratumumab antibodies
ADR	adverse drug reaction
AE	adverse event
ALCYONE	Study 54767414MMY3007
AL	amyloidosis light chain amyloidosis
ASCT	autologous stem cell transplant
ATC	Anatomical Therapeutic Chemical
CCDS	Company Core Data Sheet
CCO	clinical cutoff
CD38	cluster of differentiation 38
CEPHEUS	Study 54767414MMY3019
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
COVID-19	Coronavirus disease 2019
CR	complete response
CSR	clinical study report
Cmax	maximum concentration
Cpeak,first	predicted peak concentration after the first dose
Cpeak,max	predicted maximum peak concentration
Cpeak,q4w	predicted peak concentration over the period of Cycle 9
Ctrough	trough concentration
Ctrough,C3D1	predicted trough concentration on Cycle 3 of Day 1
Ctrough,max	predicted maximum trough concentration
Ctrough,q4w	predicted trough concentration in Cycle 9
DRd	daratumumab- lenalidomide-dexamethasone
D-VMP	daratumumab-bortezomib-melphalan-prednisone
D-VRd	daratumumab SC, bortezomib, lenalidomide, and dexamethasone
ECOG	Eastern Cooperative Oncology Group
EHA-ESMO	European Hematology Association - European Society for Medical Oncology
E-R	exposure-response
FLC	free light chain

FOIA	Freedom of Information Act
GOF	goodness-of-fit
HBV	hepatitis B virus
HDT	high-dose chemotherapy
HRQoL	health-related quality of life
IDMC	Independent Data Monitoring Committee
ICH GCP	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice
IgG	immunoglobulin G
IMWG	International Myeloma Working Group
IRR	injection-related reaction
ISR	injection site reaction
ISS	International Staging System
MAIA	Study 54767414MMY3008
MAP	maximum a posteriori
MedDRA	Medical Dictional for Regulatory Activities
MM	multiple myeloma
MPT	melphalan, prednisone, and thalidomide
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NDMM	newly diagnosed multiple myeloma
NGS	next generation sequencing
OR	odds ratio
ORR	overall response rate
OS	overall survival
pcVPC	prediction-corrected visual predictive check
PD	pharmacodynamics
PERSEUS	Study 54767414MMY3014
PFS	progression-free survival
PFS2	progression-free survival on the next line of therapy
PK	pharmacokinetic
PPK	population pharmacokinetics
Rd	lenalidomide-dexamethasone

rHuPH20	recombinant human hyaluronidase
RRMM	relapsed/refractory multiple myeloma
SAE	serious adverse event
sARR	systemic administration-related reaction
SC	subcutaneous
sCR	stringent complete response
SOC	system organ class
SMQ	Standardized MedDRA Query
TEAE	treatment-emergent adverse event
TD	transplant deferred
TIE	transplant-ineligible
VGPR	very good partial response
VMP	bortezomib, melphalan, and prednisone
VRd	bortezomib, lenalidomide, and dexamethasone

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 10 October 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for Darzalex in combination with bortezomib, lenalidomide and dexamethasone for the treatment of newly diagnosed multiple myeloma, to include also adult patients who are not eligible for stem cell transplant (SCT), based on the results of the final PFS analysis from Study CEPHEUS (54767414MMY3019), a randomised, open-label, active-controlled, multicenter phase 3 study in adult participants, comparing the clinical outcome of D-VRd with VRd in participants with untreated multiple myeloma for whom stem cell transplant is not planned as initial therapy, in terms of the primary endpoint of MRD negativity rate in participants with CR or better rate and major secondary endpoints of CR or better rate, PFS and sustained MRD negativity.
As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 are updated and the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in the Package Leaflet.
An updated RMP version 11.1 has also been submitted.

Information relating to orphan designation

Darzalex, was designated as an orphan medicinal EU/3/13/1153 on 17 July 2013. Darzalex was designated as an orphan medicinal product in the following indication:

- Treatment of plasma cell myeloma

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0264/2017 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The MAH did not seek Protocol Assistance from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Boje Kvorning Pires Ehmsen Co-Rapporteur: <N/A>

Timetable	Actual dates
Submission date	10 October 2024
Start of procedure:	2 November 2024
CHMP Rapporteur Assessment Report	2 January 2025
PRAC Rapporteur Assessment Report	6 January 2025
PRAC members comments	8 January 2025
PRAC Outcome	16 January 2025
CHMP members comments	20 January 2025
Updated CHMP Rapporteur(s) (Joint) Assessment Report	22 January 2025
Request for supplementary information (RSI)	30 January 2025
CHMP Rapporteur Assessment Report	12 February 2025
CHMP members comments	17 February 2025
Updated CHMP Rapporteur Assessment Report	20 February 2025
Opinion	27 February 2025

2. Scientific discussion

2.1. Introduction

The MAH submitted an application to modify the approved indication of DARZALEX 1800 mg solution for injection in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) in adult patients who are eligible for autologous stem cell transplant (ASCT) by removing the transplant eligibility requirement.

This application is based upon the results of the final PFS analysis from the pivotal phase 3 study CEPHEUS (54767414MMY3019).

2.1.1. Problem statement

Claimed therapeutic indication

The newly proposed indication is: "DARZALEX is indicated in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma".

Epidemiology

Multiple myeloma (MM), a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone, is estimated to represent 1.0% to 1.8% of all new cancer cases worldwide and approximately 10% of hematological malignancies (Sung 2021; SEER 2022). In 2020, an estimated 176,404 patients were diagnosed with multiple myeloma globally, with a crude incidence rate of 2.3 cases per 100,000 persons and a world population age-standardized incidence rate of 1.8 cases per 100,000 persons (Ferlay 2020). In the EU-27 countries, the 2022 crude incidence rate was 7.9 cases per 100,000 persons, and the European population age-standardized incidence rate was 7.3 cases per 100,000 persons. The estimated number of new cases for the EU overall was 35,333 cases in 2022. In general, Western Europe had the highest incidence rates of multiple myeloma. Crude incidence rates ranged from 3.0 per 100,000 persons in Bulgaria to 11.3 per 100,000 persons in Denmark (European Cancer Information System 2023).

Despite the significant improvement in patients' survival in the recent decades, only 10%-15% of patients achieve expected survival compared with the matched general population (Usmani, Blood Cancer J. 2018).

The median age at diagnosis of MM is approximately 70 years (Palumbo 2011).

Biologic features

The proliferation of the malignant clonal plasma cells leads to subsequent replacement of normal bone marrow hematopoietic precursors and overproduction of monoclonal proteins. Multiple myeloma is characterized by osteolytic lesions, usually in the pelvis, spine, ribs, and skull. Lesions are caused by expanding plasmacytomas or by cytokines secreted by myeloma cells that activate osteoclasts and suppress osteoblasts. Increased bone loss may also lead to hypercalcemia. Solitary extraosseous plasmacytomas are unusual but may occur in any tissue. In many patients, renal failure is present at diagnosis or develops during the course of the disorder and is caused by the deposition of light chains in the distal tubules or by hypercalcemia. Patients also often develop anaemia due to kidney disease or suppression of erythropoiesis by cancer cells. These signs and symptoms are commonly denoted by the mnemonic acronym CRAB: Calcemia, Renal damage, Anaemia, and Bone lesions (Palumbo 2011).

Management

Different classes of drugs are approved for multiple myeloma (alkylators, steroids, proteasome inhibitors [PIs], immunomodulatory agents [IMiDs], histone deacetylase inhibitors [HDACIs] and monoclonal antibodies). Among these treatment options, lenalidomide (an IMiD) and bortezomib (a PI) have a prominent role. Both are approved and used as frontline treatment of multiple myeloma and used in combination with other drugs at relapse. Lenalidomide is also approved as maintenance therapy after ASCT in patients with NDMM.

Treatment choices for multiple myeloma vary with age, performance status, comorbidity, aggressiveness of the disease, and related prognostic factors (Palumbo 2011). Patients with NDMM are typically categorized into 2 subpopulations: Eligible for ASCT or transplant ineligible. Eligibility is usually defined by age and suitability for intensive treatment. Patients will typically receive an induction regimen followed by treatment with ASCT, followed by consolidation therapy and maintenance treatment. For those not considered eligible for ASCT, longer-term treatment with multiagent combinations, including alkylators, steroids, and agents such as PIs (e.g., bortezomib) and IMiDs (e.g., lenalidomide) are currently considered standards of care.

Over the past two decades, the introduction of new classes of drugs, such as PIs and IMiDs, have changed the management of frontline treatment in both transplant and nontransplant candidates (Kumar 2023 [NCCN Guidelines]; Durie 2017; Dimopoulos 2021 [ESMO Guidelines]; Cavo 2011; Palumbo 2014). Studies have indicated that multidrug combinations are superior to single- or double-agent combinations in treating multiple myeloma (Cavo 2012; van der Veer 2011).

The addition of new drugs to available regimens, or combinations of new drugs, improves depth of response, which in turn has been correlated with increased PFS and OS (Lahuerta 2008; Harousseau 2010; Chanan-Khan 2010; Dingli 2007). Contingent on the premise that the combined agents have nonoverlapping and synergistic mechanisms of actions, the immediate and effective targeting of the tumours with multiple agents appears to be a successful strategy in improving the clinical outcome of multiple myeloma therapy.

The availability of different efficacious multiagent regimens has provided clinicians with the opportunity of tailoring treatment for each patient. Selection is based on patients' comorbidities and biologic age, as well as the expected toxicity profiles of each treatment regimen (Gay 2011). However, despite the significant progress that has been made in the management of multiple myeloma, the disease relapses and it remains an incurable malignancy. Therefore, new treatment options and combinations directed at alternative mechanisms of action remain needed for these patients.

Patients with NDMM ineligible for ASCT

Patients with NDMM are typically categorized as 'transplant-eligible' or 'transplant-ineligible' (TIE). For patients not considered eligible for high-dose chemotherapy and ASCT (TIE) or for whom transplant was not planned as initial therapy, the current standard of care is longer-term treatment with triplet or quadruplet combinations. Current frontline standards of care recommended for these patients in the EHA-ESMO Guideline include daratumumab plus Lenalidomide and dexamethasone D-Rd), bortezomib plus lenalidomide and dexamethasone (VRd), daratumumab plus bortezomib plus melphalan plus prednisone (D-VMP), bortezomib plus melphalan and prednisone, (VMP), and lenalidomide plus dexamethasone (Rd), commonly on a treat-to-progression or unacceptable toxicity basis (Dimopoulos 2021).

Daratumumab in NDMM

Daratumumab has demonstrated efficacy when added to multiple combination regimens in the frontline setting, including in TIE patients in combination with Rd (Study 54767414MMY3008, hereafter referred to as MAIA) and VMP (Study 54767414MMY3007, hereafter referred to as ALCYONE). Data from MAIA and ALCYONE demonstrated a statistically significant improvement in PFS and OS with D-Rd (compared with Rd alone ([MAIA]) and D-VMP (compared with VMP alone [ALCYONE]).

Treatment with D-VRd in Study 54767414MMY3014 (hereafter referred to as PERSEUS) resulted in statistically significant improvements in PFS, overall CR or better rate, and overall MRD negativity rate compared with VRd alone in the NDMM-TE setting.

2.1.2. About the product

Daratumumab is a human mAb that binds with high affinity to CD38, a transmembrane glycoprotein expressed on tumour cells, and induces tumour-cell death through multiple mechanisms of action. These mechanisms of action include several immune-mediated activities, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, antibody dependent cellular phagocytosis, and direct cytotoxicity by induction of apoptosis by Fc γ receptor-mediated crosslinking of tumour-bound mAbs (Overdijk 2016).

Daratumumab is approved as monotherapy in subjects with relapsed and refractory multiple myeloma and in combination with standard of care regimens for transplant-ineligible and transplant-eligible newly diagnosed multiple myeloma and relapsed/refractory multiple myeloma.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The sponsor sought Scientific Advice from CHMP on the design of the pivotal study of this application.

Key points regarding study MMY3016 are summarized here:

1. The MAH was asked about plans to stratify the study population. The MAH confirmed that patients would be stratified for age and ISS and an additional stratification factor would also be considered.

2. The SAWP expressed concerns about patients that are anticipated to refuse transplant in the proposed study. The MAH estimated that approximately 20% of patients, primarily from the US, would fall under this category but the percentage of European patients would be lower (although would vary between countries). To address this concern, the MAH considered stratifying patients and conducting subgroups analyses.

3. The primary endpoint for study MMY3019 (previously referred to as study MMY3016) was PFS at the time of SA. However, before enrolment of the first patient the protocol had been changed resulting in overall MRD negativity rate becoming the primary endpoint and PFS becoming a key secondary endpoint along with overall CR or better rate and sustained MRD negativity rate. The MAH did not seek new scientific advice regarding this change in trial design.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Daratumumab is a monoclonal antibody and is consequently classified as a naturally occurring substance . In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 Revision 1), the MAH submitted a justification for not submitting ERA studies and it was agreed that daratumumab is unlikely to pose a risk to the environment. Consequently, no Environmental Risk Assessment studies for daratumumab were required for this application.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID EudraCT Number First Patient First Visit / Completion date (day Month year) Study Status	Countries/ Territories: Number of Centers	Phase Study Description/Design, Study Population, Primary Objective(s)	Total Number of Participants	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Participants Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
54767414MMY3019 (CEPHEUS) Synopsis 2018-001545-13 15 November 2018 NA Ongoing	Brazil, Canada, Czechia, France, Germany, Israel, Japan, Netherlands, Poland, Spain, Turkey, UK, and US 98	Phase 3 Randomized, open label, multicenter study Participants with NDMM for whom ASCT is not planned as initial therapy To determine if the addition of daratumumab to VRd improves overall MRD negativity compared with VRd alone	Randomized: 395 Treated: 392	Treatment Arm A (VRd): • Bortezomib SC 1.3 mg/m² twice weekly on Days 1, 4, 8, and 11 of each 21-day cycle for Cycles 1-8 • Lenalidomide PO at 25 mg daily on Days 1 through 14 of each 21-day cycle for Cycles 1-8. During Cycles 9 and beyond, lenalidomide PO at 25 mg daily on Days 1 through 21 of each 28-day cycle • Dexamethasone PO at 20 mg Days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for Cycles 1-8 In Cycle 9 and beyond, dexamethasone PO at 40 mg on Days 1, 8, 15, 22 of each 28-day cycle Treatment continues until disease progression or unacceptable toxicity Treatment Arm B (D-VRd): • VRd, as described above • Daratumumab SC 1800 mg weekly in Cycles 1-2, every 3 weeks in Cycles 3-8, and every 4 weeks in Cycle 9 and beyond Treatment continues until disease progression or unacceptable toxicity	VRd: 195 D-VRd: 197	Full Report (combined results of the primary MRD analysis, interim PFS analysis, and final PFS Analysis) 12 August 2024 EDMS-RIM-387751 Module 5.3.5.1

KEY: ASCT=autologous stem cell transplant; CTD=common technical document; D-VRd=daratumumab, bortezomib, lenalidomide, dexamethasone; MRD=minimal residual disease; NDMM= newly diagnosed multiple myeloma; PFS=progression-free survival; PO=per oral; SC=subcutaneous; VRd=bortezomib, lenalidomide, dexamethasone.

2.3.2. Pharmacokinetics

The clinical pharmacology of daratumumab SC has been well characterized as monotherapy and in combination with a variety of background therapies for participants with MM, with the PK and pharmacodynamics of daratumumab summarized in previous submissions. Clinical pharmacology information provided in the current submission focuses on evaluable data from participants treated with D-VRd in CEPHEUS in addition to PERSEUS data, to support a new indication of daratumumab SC in combination with VRd (D-VRd) for the treatment of patients with NDMM.

Population PK

The final Population PK (PopPK) dataset contained a total of 851 from a total of 197 PK-evaluable participants from CEPHEUS.

A sensitivity analysis was performed to verify that PK values obtained after final DBL (05 June 2024) were consistent with PK values obtained from the DBL on 19 December 2022. The sensitivity analysis was based on 858 daratumumab serum PK samples from the 197 participants. 7 PK samples from later cycles were added in the dataset after final DBL (05 June 2024).

A previously developed IV/SC PopPK model for daratumumab using data from participants with NDMM is used in the current PopPK analysis to conduct the external evaluation to verify the predictive performance of the previously developed PPK model with the current clinical SC PK data.

In the previously developed PPK model for NDMM, daratumumab was described by a 2-compartment PPK model with first-order absorption and parallel linear and nonlinear elimination pathways. Daratumumab absorption was parameterized in terms of Ka and F1 for SC administration relative to IV administration. The PK parameters describing the daratumumab disposition were nonspecific linear CL, V1, Q, V2, Vmax, KDES, and Km. The interindividual variability in structural parameters was modelled with an exponential error model. The residual variability of daratumumab serum concentrations was modelled on the log scale using an additive residual error model. The corresponding PK parameter estimates of the final model are reported in **Table 1**.

Table 1. Parameter estimates of the PopPK model of daratumumab in participants with NDMM

Parameter (Unit)	Description	Estimate	95% CI	%RSE	IIV (%CV)	%RSE IIV
CL (L/d)	Linear clearance	0.103	(0.0990; 0.107)	1.97	22.2	17.2
ALB on CL[a]	Effect of serum albumin concentration on linear clearance	-0.232	(-0.369; -0.0948)	30.2	-	-
WT on CL[a]	Effect of body weight on linear clearance	1.04	(0.888; 1.20)	7.59	-	-
TPMC on CL[a]	Effect of type of myeloma (IgG versus non-IgG) on linear clearance	0.175	(0.104; 0.245)	20.5	-	-
V_1 (L)	Volume of distribution in the central compartment	6.71	(6.44; 6.99)	2.12	19.1	18.4
WT on V_1[b]	Effect of body weight on volume of distribution in the central compartment	0.480	(0.364; 0.596)	12.3	-	-
SEX on V_1[b]	Effect of sex (female versus male) on volume of distribution in the central compartment	-0.0980	(-0.152; -0.0438)	28.3	-	-
V_2 (L)	Volume of distribution in the peripheral compartment	3.84	(3.62; 4.06)	2.89	-	-
Q (L/d)	Intercompartmental clearance	0.0384	(0.0360; 0.0409)	3.25	-	-
V_{max} (mg/h)	Maximum velocity of the saturable clearance process	0.741	(0.701; 0.782)	2.78	27.8	18.9
K_{DES} (L/h)	First-order rate for decrease of maximum velocity of the saturable clearance process over time	0.0000888	(0.0000820; 0.0000957)	3.93	129	15.1
K_m (µg/mL)	Michaelis-Menten constant	1.84	(1.73; 1.96)	3.24		-
K_a (L/h)	First-order absorption rate	0.0176	(0.0165; 0.0186)	3.11	54.2	13.0
F1	Bioavailability for SC dose	0.591	(0.572; 0.611)	1.71	44.0	16.9
ADD ERR (%CV)	Additive error term on the log-scale	68.3	(68.0 68.6)	0.412	-	-

ADD ERR=additive error term on the log-scale; ALB=albumin; CI=confidence interval; CV=coefficient of variation; IgG=immunoglobulin G; IIV=interindividual variance; NDMM=newly diagnosed multiple myeloma; PK=pharmacokinetic(s); PPK=population pharmacokinetic(s); RSE=residual standard error; $TPMC_{CL}$=effect of type of myeloma (IgG versus non-IgG) on linear clearance; TVCL=typical value of clearance; TVV=typical value of volume of distribution; V_1=central volume of distribution; WT=weight.

[a] $TVCL = 0.103 \cdot \left(\frac{WT}{77}\right)^{1.04} \cdot \left(\frac{ALB}{38}\right)^{-0.232} \cdot TPMC_{CL}$ where $TPMC_{CL}$ is a shift factor of 1 for participants with non-IgG multiple myeloma and 1 + 0.175 for participants with IgG multiple myeloma.

[b] $TVV1 = 6.71 \cdot \left(\frac{WT}{77}\right)^{0.480} \cdot SEX_{V1}$, where SEX_{V1} is a shift factor of 1 for male and 1-0.0980 for female.

Note: Objective function value=-164.913. Condition number=18.7.

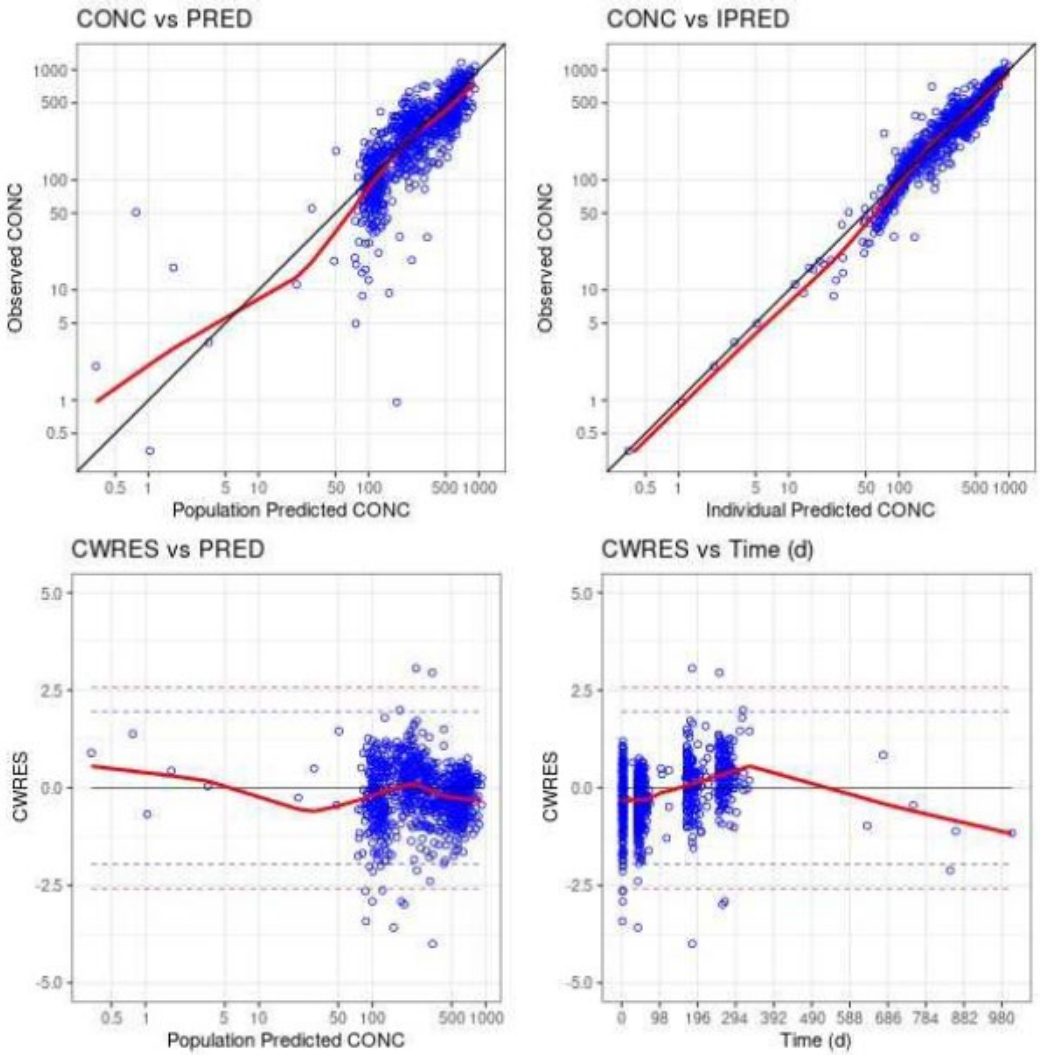
%RSE for IIV and ADD ERR are reported on the approximate standard deviation scale (standard error/variance estimate)/2.

%CV for IIV and ADD ERR are computed as sqrt(ω^2) and sqrt (σ^2), respectively.

95% CIs are calculated based on standard error from covariance matrix assuming PK parameters are normally distributed.

An external model evaluation was conducted to verify the predictive performance of the previous PopPK model in CEPHEUS participants with NDMM. The Goodness of Fit (GOF) plots and Prediction-Corrected Visual Predictive Checks (pcVPC) were used as external evaluation methods. GOF plots were generated by performing a maximum a posteriori (MAP) approach using current data with the previously estimated PPK model parameters as prior information (**Figure 1**).

Figure 1. GOF plots of the external validation model

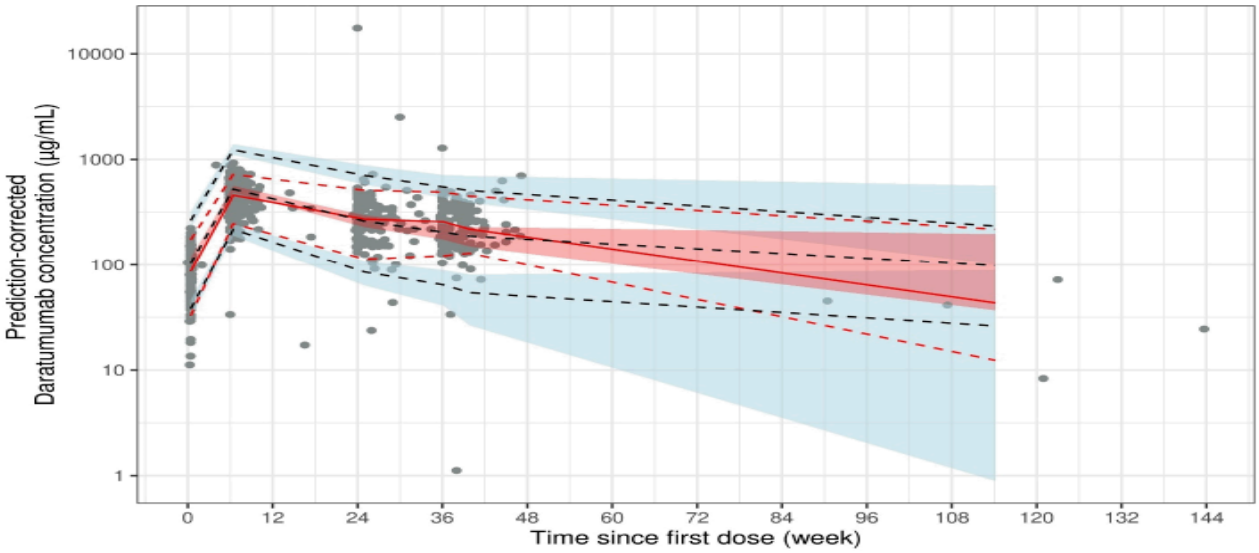


Key: CONC=daratumumab serum concentration; CWRES=conditional weighted residuals; d=day; GOF=goodness-of-fit; IPRED=individual prediction of concentration; PRED=population model prediction.

Notes: Red solid line represents the data smoother. The blue and red dash line represent the probability of 95% and 99% cutoff, respectively. Black line represents the line of identity for observed concentrations versus population prediction and individual prediction plots. For residual plots, black line represents horizontal line crossing the y-axis at value of zero.

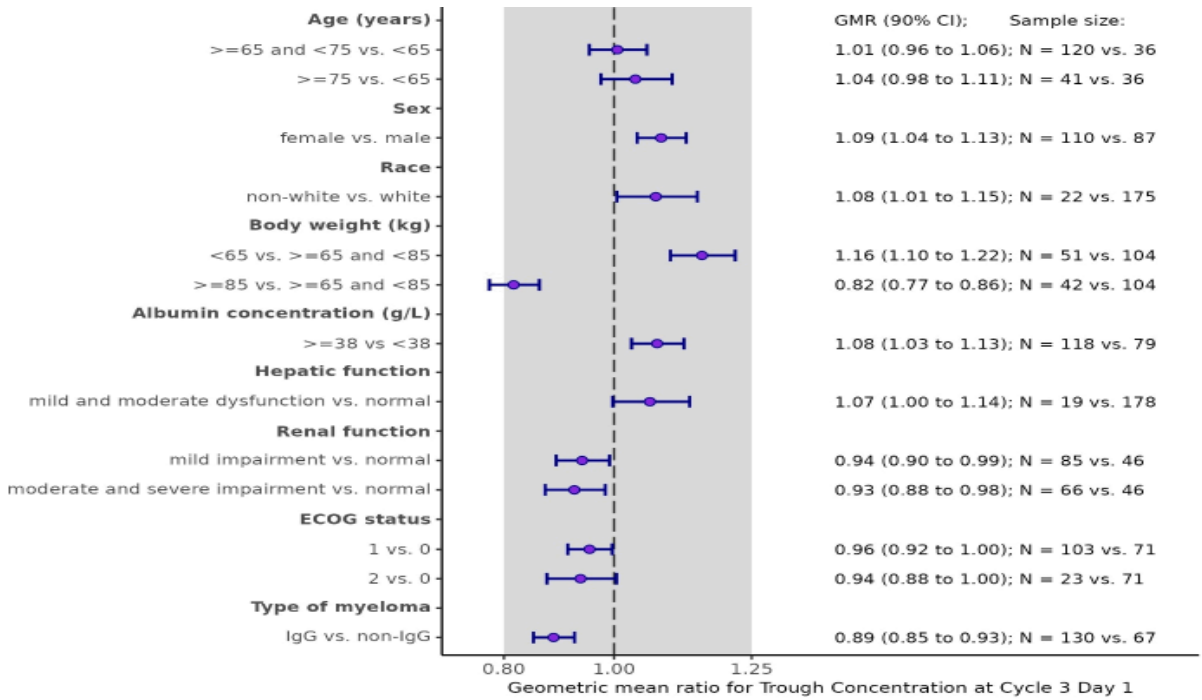
The evaluation with pcVPC was performed from 1,000 simulated replicates by using the previous PPK model parameters. Uncertainty in parameter estimates was excluded in these simulations (**Figure 2**). The pcVPC stratified by body weight was reported to assess the adequacy of the model across this covariate (data not shown). **Figure 3** displays a forest plot of subgroup analysis of daratumumab Ctrough, C3D1 derived using MAP.

Figure 2. pcVPC of the external validation model



Key: pcVPC=prediction-corrected visual predictive check.
Notes: Gray solid dots represent observations. The red solid and dashed lines represent the median and 5th and 95th percentiles of the observations; the black dashed lines represent the median and 5th and 95th percentiles of the predictions; the shaded red and blue areas represent the 95% confidence interval of the median, 5th, and 95th percentiles predicted by the model, respectively.

Figure 3. Forest plot of subgroup analyses for daratumumab $C_{ttough,\ C3D1}$ per the recommended dose schedule for D-VRd combination therapy



Key: CI=confidence interval; $C_{trough,C3D1}$=predicted trough concentration on Cycle 3 of Day 1; D-VRd=daratumumab in combination with VELCADE® (bortezomib), Revlimid® (lenalidomide), and dexamethasone; ECOG=Eastern Cooperative Oncology Group; GMR=geometric mean ratio; IgG=immunoglobulin G; N=comparator number of participants versus the reference number of participants.
Notes: Solid blue points represent GMR and short horizontal bars represent 90% CI. Dashed line represents reference value of 1. Shaded area spans represent the 80% to 125% range relative to the reference value. Values represent GMR and associated CI, adjusted for each covariate included in the analysis.

Serum Daratumumab Concentrations Over Time

The PK results from the D-VRd combination in CEPHEUS are summarised in **Table 2**.

Table 2. Summary of Serum Daratumumab Concentration (µg/mL); PK-evaluable Analysis Set (MMY3019, CEPHEUS)

	D-VRd
Analysis set: PK-evaluable	197
Cycle 1 Day 1 (predose)	
N	195
Mean (SD)	BQL (-)
Median	BQL
Range	(BQL; BQL)
CV (%)	-
Geometric mean	BQL
Cycle 1 Day 4	
N	180
Mean (SD)	**93.8 (46.6)**
Median	87.7
Range	(BQL; 265)
CV (%)	49.6
Geometric mean	79.6
Cycle 3 Day 1 (predose)	
N	178
Mean (SD)	407 (183)
Median	391
Range	(9.39; 970)
CV (%)	45.0%
Geometric mean	356
Cycle 3 Day 4	
N	169
Mean (SD)	**524 (216)**
Median	507
Range	(BQL; 1163)
CV (%)	41.3%
Geometric mean	438
Cycle 9 Day 1 (predose)	
N	141
Mean (SD)	289 (139)
Median	271
Range	(BQL; 760)
CV (%)	48.0%
Geometric mean	244
Cycle 12 Day 1 (predose)	
N	139
Mean (SD)	260 (121)
Median	239
Range	(0.959; 708)
CV (%)	46.4%
Geometric mean	225
Post-treatment Week 8	
N	8
Mean (SD)	132 (231)
Median	18.8
Range	(11.2; 682)
CV (%)	175.1%
Geometric mean	42.3

Key: BQL=below quantification limit (0.2 µg/mL); CV=coefficient of variation; D-VRd=daratumumab in combination with bortezomib (VELCADE), lenalidomide, and dexamethasone; N=number of participants; PK=pharmacokinetic(s); QW=once every week; QxW=once per x weeks; SC=subcutaneous; SD=standard deviation.

Notes: Cycles 1 to 8 were 21 days in length while Cycle 9 and beyond are 28 days in length. Daratumumab 1800 mg SC was administered QW in Cycles 1 to 2, Q3W in Cycles 3 to 8, and Q4W thereafter. Geometric mean was calculated by using half of lowest quantifiable concentration in a sample (0.5*0.2 µg/mL) in place of BQL values (ie, 0.2 µg/mL).

Immunogenicity and PK

A low incidence (<1%) of antibodies to daratumumab was reported in monotherapy and combination clinical studies of daratumumab SC and IV in participants with MM to date. Consistent with other populations, in CEPHEUS, 1 (0.6%) of 170 participants in the daratumumab SC immunogenicity-evaluable analysis set had treatment-emergent anti-daratumumab antibodies.

A relatively low incidence of antibodies to rHuPH20 (<10%) was reported in monotherapy and combination clinical studies of daratumumab SC in participants with MM to date. In CEPHEUS, 12 (7.1%) of the 169 participants in the rHuPH20 immunogenicity-evaluable analysis set had treatment-emergent anti-rHuPH20 antibodies after the first administration of daratumumab SC. This is similar to previously reported incidence of anti-rHuPH20 antibodies for other therapeutic proteins administered with rHuPH20.

No clinically meaningful differences in the PK profiles of daratumumab SC were observed in participants who tested positive for anti-daratumumab and/or anti-rHuPH20 antibodies.

Dose proportionality and time dependencies

Dose proportionality and time dependencies were evaluated in previous submissions. In this procedure, daratumumab is administered as a flat dose of 1800 mg in combination with rHuPH20 (2000 U/mL) and daratumumab drug substance (120 mg/mL) in a single vial.

Special populations

Serum Daratumumab Concentrations by Baseline Body Weight

The observed serum daratumumab concentrations were summarised by baseline body weight cutoffs (≤65 kg, >65 to ≤85 kg, >85 kg and ≤50 kg, >50 to ≤85 kg, and >85 kg) based on baseline body weight distribution in CEPHEUS and other daratumumab SC studies. In the PK evaluable population of CEPHEUS, the baseline body weight range was 40.4 to 125.0 kg, which was similar to that in other daratumumab SC studies. Descriptive statistics for serum daratumumab concentrations at various sampling timepoints for PK-evaluable participants in the D-VRd treatment arm are summarized by baseline body weight in

Table 3.

Table 3. Summary of serum daratumumab concentration (µg/mL) following SC administration of daratumumab in combination with VRd by body weight subgroups-CEPEUS; pK evaluable analysis set

	D-VRd 1800 mg Daratumumab SC			
	Total	≤50 kg	>50 to ≤85 kg	>85 kg
Analysis set: PK	197	14	145	38
Cycle 1, Day 1 (Predose)				
N	195	14	143	38
Mean (SD)	BQL (-)	BQL (-)	BQL (-)	BQL (-)
Coefficient of variation				
Geometric mean	BQL	BQL	BQL	BQL
Median	BQL	BQL	BQL	BQL
Range	(BQL; BQL)	(BQL; BQL)	(BQL; BQL)	(BQL; BQL)
Cycle 1, Day 4				
N	180	13	132	35
Mean (SD)	93.8 (46.6)	101 (58.8)	98.2 (46.5)	74.5 (37.3)
Coefficient of variation	49.6%	58.0%	47.3%	50.1%
Geometric mean	79.6	87.1	83.2	65.1
Median	87.7	77.4	91.1	65.5
Range	(BQL; 265)	(42.0; 199)	(BQL; 265)	(14.4; 162)
Cycle 3, Day 1 (Predose)				
N	178	13	130	35
Mean (SD)	407 (183)	523 (200)	425 (176)	293 (152)
Coefficient of variation	45.0%	38.2%	41.3%	51.9%
Geometric mean	356	491	383	240
Median	391	464	404	270
Range	(9.39; 970)	(262; 914)	(41.0; 970)	(9.39; 643)
Cycle 3, Day 4				
N	169	13	124	32
Mean (SD)	524 (216)	682 (237)	543 (207)	385 (175)
Coefficient of variation	41.3%	34.8%	38.1%	45.4%
Geometric mean	438	643	447	347
Median	507	672	521	358
Range	(BQL; 1163)	(332; 1083)	(BQL; 1163)	(83.9; 819)
Cycle 9, Day 1 (Predose)				
N	141	10	102	29
Mean (SD)	289 (139)	395 (138)	301 (138)	211 (104)
Coefficient of variation	48.0%	35.0%	45.8%	49.3%
Geometric mean	244	374	267	152
Median	271	392	285	200
Range	(BQL; 760)	(230; 641)	(30.2; 760)	(BQL; 433)
Cycle 12, Day 1 (Predose)				
N	139	10	103	26
Mean (SD)	260 (121)	399 (163)	264 (110)	190 (94.4)
Coefficient of variation	46.4%	40.7%	41.5%	49.7%
Geometric mean	225	364	232	167
Median	239	398	258	180
Range	(0.959; 708)	(125; 708)	(0.959; 559)	(39.2; 415)
Post-treatment Week 8				
N	8	2	4	2
Mean (SD)	132 (231)	15.0 (5.35)	206 (321)	101 (116)
Coefficient of variation	175.1%	35.7%	155.8%	115.1%
Geometric mean	42.3	14.5	61.3	58.6
Median	18.8	15.0	65.1	101
Range	(11.2; 682)	(11.2; 18.8)	(11.7; 682)	(18.8; 183)

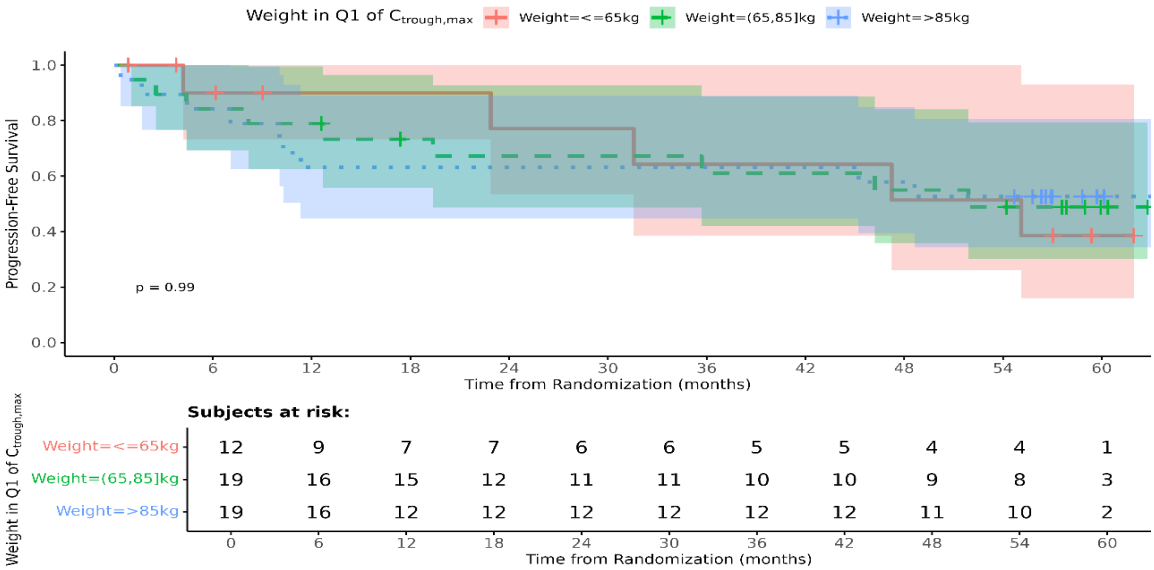
Key: BQL=below quantification limit (0.2 µg/mL); D-VRd=daratumumab in combination with bortezomib (VELCADE), lenalidomide, and dexamethasone; N number of participants; PK=pharmacokinetic(s); QW=once every week; Q4W=once every 4 weeks; SC=subcutaneous; SD=standard deviation; VRd=VELCADE® (bortezomib), Revlimid® (lenalidomide), and dexamethasone.

Notes: Daratumumab 1800 mg SC QW for Cycles 1 to 2, then Q3W for Cycles 3 to 8. For Cycle 9 and beyond, Q4W.

Table includes participants who received at least 1 administration of daratumumab and had at least 1 PK sample concentration value after the first administration.

A KM analysis was stratified by body weight in the daratumumab exposure Q1 subgroup, and shown in **Figure 4.**

Figure 4. Kaplan-Meier Curves of PFS by Body Weight in Daratumumab Exposure Q1 Subgroup Population



Key: $C_{trough,max}$=predicted maximum trough concentration over the entire treatment period; PFS=progression-free survival; Q1=lowest exposure quartile (51.2-379 µg/mL).

Race

Descriptive statistics for serum daratumumab concentrations at specified sampling timepoints for PK-evaluable participants in the D-VRd treatment arm were calculated. The observed mean [SD] Ctrough, max of daratumumab at Cycle 3 Day 1 predose in black/African American participants (n=10) was 350 [154] µg/mL, 12.5% lower compared with white participants (400 [184] µg/mL, n=145). The observed mean [SD] Ctrough,max at Cycle 3 Day 1 predose in Asian participants (488 [178] µg/mL, n=10) was 22% higher compared to that of white participants. Given the small number of participants in the black or African American and Asian groups in this study and considerable overlap in daratumumab exposure across race, only limited conclusions regarding the effect of race/ethnicity on daratumumab SC PK can be made from the observed data for these subgroups. In the PPK analysis, race did not have a clinically meaningful effect on daratumumab PK (See **Figure 3** in the popPK section).

Pharmacokinetic interaction studies

No dedicated drug-drug interaction studies were performed for daratumumab SC.

As an IgG1κ mAb, the biotransformation of daratumumab is expected to be similar to endogenous IgG (i.e., degraded into small peptides and amino acids via catabolic pathways) and subject to similar elimination pathways (Mascelli 2007; Tabrizi 2006). Renal excretion and hepatic enzyme mediated metabolism of intact daratumumab are therefore unlikely to represent major elimination routes. Due to the high affinity to a unique epitope on CD38, daratumumab is also not anticipated to alter the activity of drug-metabolizing enzymes.

Because there is no overlapping pathway of elimination, no interactions are expected between daratumumab and small-molecule drugs including VRd.

2.3.3. Pharmacodynamics

Mechanism of action

Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed on the surface of cells in a variety of haematological malignancies, including clonal plasma cells in multiple myeloma and AL amyloidosis, as well as other cell types and tissues. CD38 protein has multiple functions such as receptor mediated adhesion, signalling, and enzymatic activity.

Daratumumab has been shown to potently inhibit the *in vivo* growth of CD38-expressing tumour cells. Based on *in vitro* studies, daratumumab may utilise multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38. A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+Tregs) and B cells (CD38+Bregs) are decreased by daratumumab mediated cell lysis. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immune modulatory effects that may contribute to clinical response.

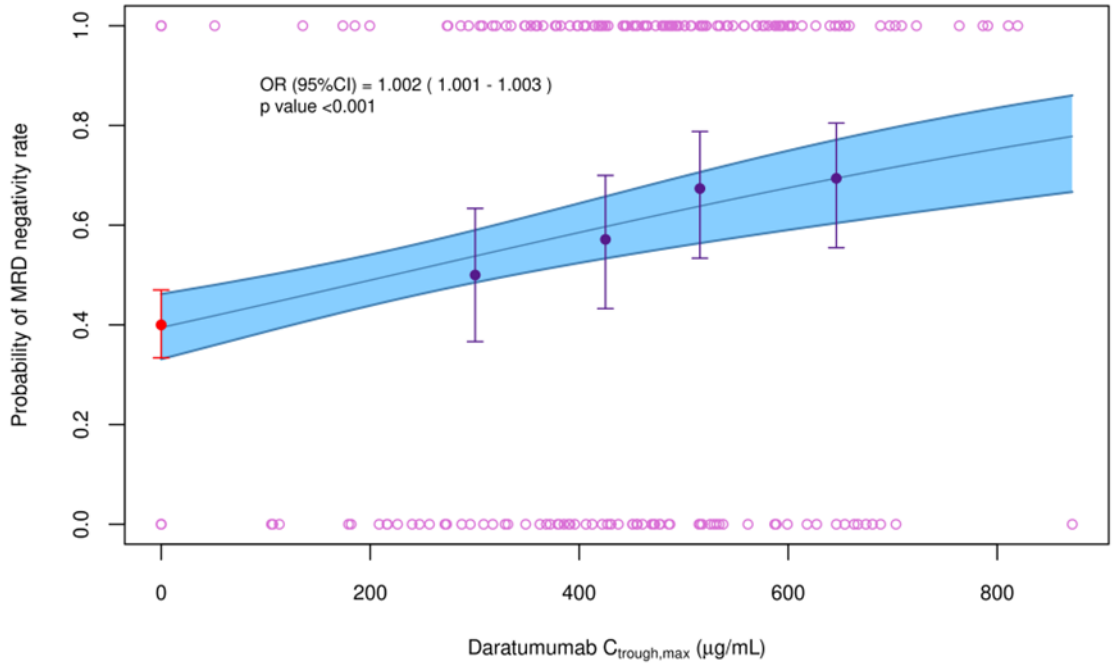
Daratumumab induced apoptosis *in vitro* after Fc mediated cross-linking. In addition, daratumumab modulated CD38 enzymatic activity, inhibiting the cyclase enzyme activity and stimulating the hydrolase activity. The significance of these *in vitro* effects in a clinical setting, and the implications on tumour growth, are not well-understood.

Efficacy exposure-response analysis

A total of 392 participants (197 from the D-VRd arm and 195 from the VRd arm) from the intent-to-treat population were included in the dataset. All participants assigned to the D-VRd arm had received at least 1 dose of daratumumab with at least 1 evaluable PK sample post-dose and had PK exposure metrics (ie, $C_{trough,max}$) for the exposure-efficacy analysis. The participants in the VRd arm were assigned a daratumumab PK exposure of zero.

The MRD negativity rate in the E-R analysis set was 60.9% (n=120/197) in participants randomly assigned to D-VRd and 40.0% (n=78/195) in participants randomly assigned to VRd treatment. MRD negativity rate showed a numerical increase as daratumumab $C_{trough,max}$ increased (**Figure 5**).

Figure 5. MRD negativity rate as function of Daratumumab $C_{trough,max}$ (µg/mL)



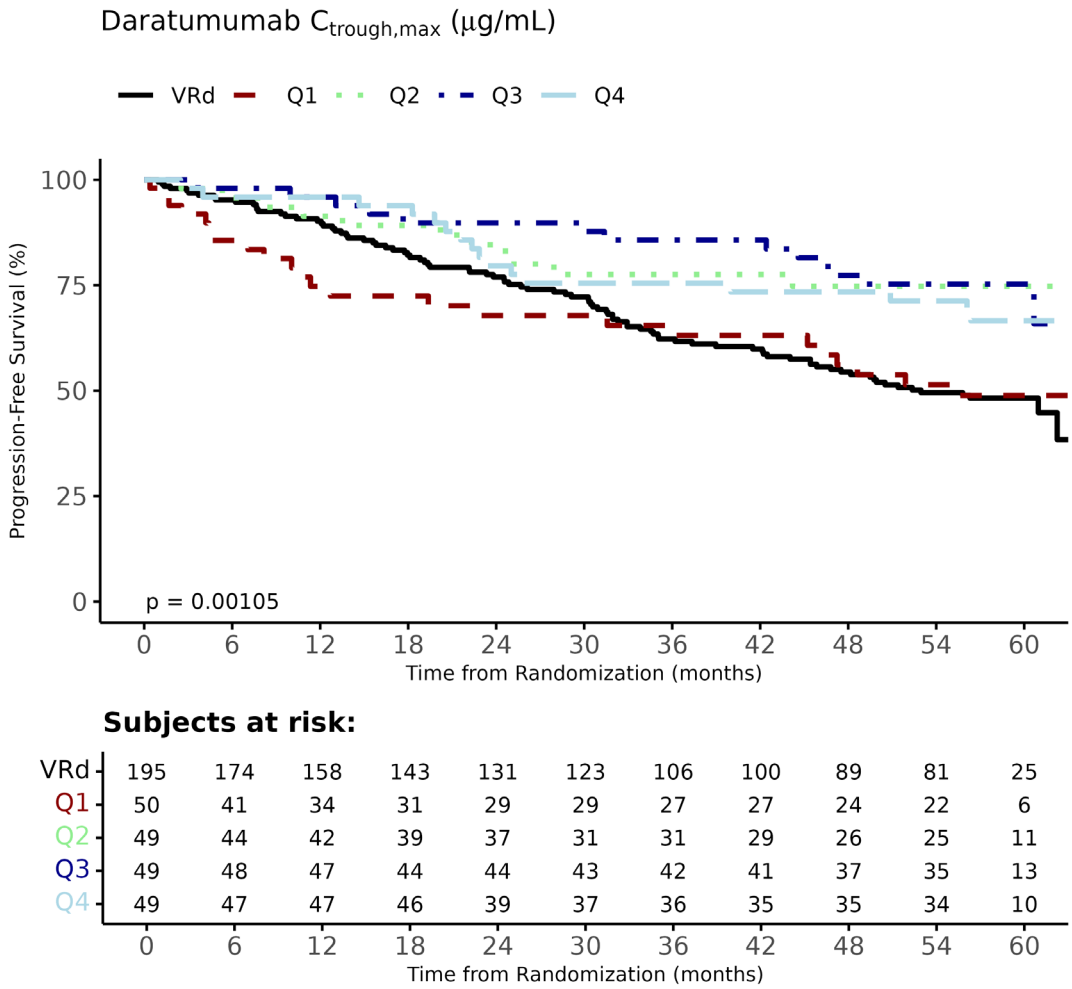
Key: CI=confidence interval; $C_{trough,max}$=predicted maximum trough concentration over the entire treatment period; D-VRd=daratumumab in combination with VELCADE® (bortezomib), Revlimid® (lenalidomide), and dexamethasone; MRD=minimum residual disease; OR=odds ratio; VRd=VELCADE® (bortezomib), Revlimid® (lenalidomide), and dexamethasone.

Notes: The upper and lower open circles represent the presence or absence of response across the range of daratumumab $C_{trough,max}$. The purple dots depict the observed incidence for the exposure quartile of participants receiving D-VRd and the corresponding vertical bars represent the 95% CI. The red dot depicts the observed incidence of participants receiving VRd and the corresponding vertical bars represent the 95% CI. The full blue line and the associated shaded area represents the model-based exposure-efficacy relationship and its 95% CI.

The relationship between MRD negativity rate and daratumumab $C_{trough,max}$ is shown in **Figure 5** and was relatively shallow. The MRD negativity rate increased with higher daratumumab $C_{trough,max}$ as shown by an OR of 1.002 (95% CI: 1.001-1.003) for a 1 µg/mL change in daratumumab $C_{trough,max}$ (p-value <0.001).

A statistically significant exposure-PFS relationship was found for daratumumab when categorized by quartiles of exposure (**Figure 6**) or when used as a continuous variable in the univariate Cox regression model (p<0.001) (**Table 4**).

Figure 6. Kaplan-Meier curves of PFS by daratumumab exposure subgroups in combination with VRd in CEPHEUS



Key: $C_{trough,max}$=predicted maximum trough concentration over the entire treatment period; PFS=progression-free survival; Q1=lowest exposure quartile; Q2=second exposure quartile; Q3=third exposure quartile; Q4=highest exposure quartile; VRd=VELCADE® (bortezomib), Revlimid® (lenalidomide), and dexamethasone.

Note: The quartiles for $C_{trough,max}$ were Q1 (51.2-379 µg/mL), Q2 (381-469 µg/mL), Q3 (471-570 µg/mL), and Q4 (570-872 µg/mL).

Table 4. Cox Proportional Hazard E-R Models for PFS

Model	Treatment or PK Metrics	N	Number of Events (%)	HR	95% CI	p-Value
Model A	VRd	195	91 (46.7)	-	-	-
	D-VRd	197	63 (32.0)	0.592	0.429,0.817	0.00126
Model B	$C_{trough,max}$ (per 1 µg/mL increase)	392	154 (39.3)	0.999	0.998,0.999	0.000107
Model C	VRd	195	91 (46.7)	-	-	-
	Q1 $C_{trough,max}$ 300 [51.2,379]	50	23 (46.0)	1.06	0.669,1.67	0.814
	Q2 $C_{trough,max}$ 425 [381,469]	49	11 (22.4)	0.438	0.234,0.820	0.00981
	Q3 $C_{trough,max}$ 515 [471,570]	49	13 (26.5)	0.423	0.236,0.756	0.00371
	Q4 $C_{trough,max}$ 646 [570,872]	49	16 (32.7)	0.556	0.327,0.947	0.0307

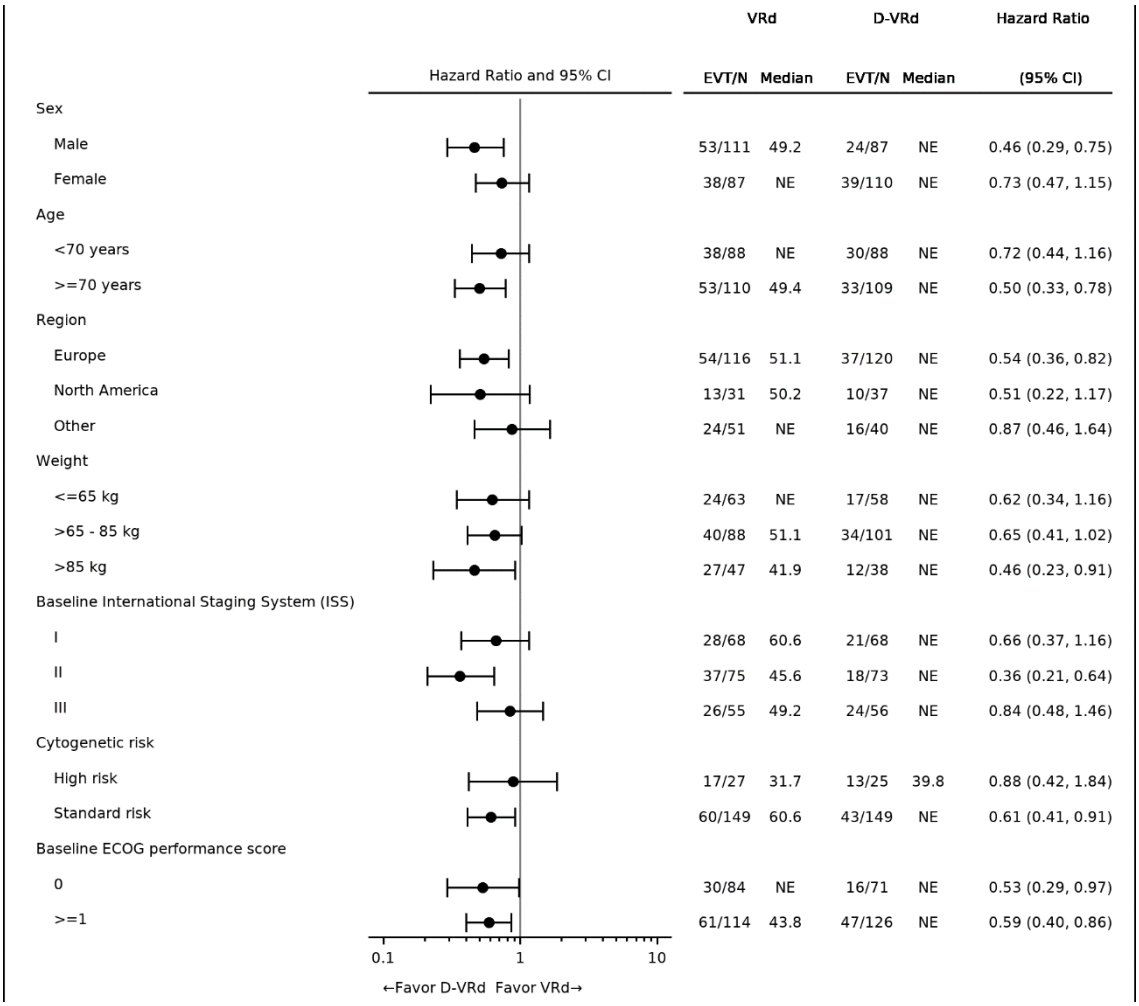
Key: CI=confidence interval; $C_{trough,max}$=predicted maximum trough concentration over the entire treatment period; D-VRd=daratumumab in combination with VELCADE® (bortezomib), Revlimid® (lenalidomide), and dexamethasone; E-R=exposure-response; HR=hazard ratio; max=maximum; min=minimum; N=number of participants; PFS=progression-free survival; PK=pharmacokinetic(s); Q1=lowest exposure quartile; Q2=second

exposure quartile; Q3=third exposure quartile; Q4=highest exposure quartile; VRd=VELCADE® (bortezomib), Revlimid® (lenalidomide), and dexamethasone.

Note: The quartiles for $C_{trough,max}$ were Q1 (51.2-379 µg/mL), Q2 (381-469 µg/mL), Q3 (471-570 µg/mL), and Q4 (570-872 µg/mL). The median and range [min, max] of $C_{trough,max}$ for Model C are shown in the table.

A subgroup analysis for PFS, based on various baseline characteristic is shown in **Figure 7.**

Figure 7. Forest Plot of Subgroup Analyses on Progression-free Survival Based on Computerized Algorithm; Intent-to-treat Analysis Set; Final PFS Analysis (Study 54767414MMY3019)



Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; CI = confidence interval.
Note: Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. A hazard ratio <1 indicates an advantage for D-VRd.
Note: High risk is defined by FISH testing: t (4; 14), t (14; 16), and 17p deletion.

Exposure safety analysis

The exposure-safety analysis for all selected TEAEs included 392 participants (D-VRd: 197, VRd: 195) who had evaluable daratumumab PK (ie, $C_{peak,first}$ for sARRs and $C_{peak,max}$ for other endpoints).

There was no apparent increase in TEAE rates with increasing exposure ($C_{peak,first}$ or $C_{peak,max}$) for sARRs, thrombocytopenia, anemia, neutropenia, lymphopenia, or infections and infestations (all grades and Grades ≥3) within the studied drug concentration range in CEPHEUS (**Table 5**). A decreasing trend in

the event rate of thrombocytopenia (all grades and Grades ≥3) was observed based on $C_{peak,max}$ (ie, a higher rate of TEAEs was observed with the lower $C_{peak,max}$). This could partially be due to the reason that participants with TEAEs may have dose interruption or delays, which led to lower concentrations in these participants.

Table 5. Comparison of TEAE rates across predicted daratumumab exposure subgroups in CEPHEUS

	VRd	D-VRd			
	% (95% CI)	Exposure Quartiles, % (95% CI)			
		Q1	Q2	Q3	Q4
TEAE	N=195	N=50	N=49	N=49	N=49
Neutropenia	39.0 (32.4, 46.0)	60.0 (46.2, 72.4)	59.2 (45.2, 71.8)	63.3 (49.3, 75.3)	40.8 (28.2, 54.8)
Grade ≥3	29.7 (23.8, 36.5)	50.0 (36.6, 63.4)	51.0 (37.5, 64.4)	55.1 (41.3, 68.1)	20.4 (11.5, 33.6)
Infections	85.6 (80.0, 89.9)	90.0 (78.6, 95.7)	85.7 (73.3, 92.9)	98.0 (89.3, 99.6)	93.9 (83.5, 97.9)
Grade ≥3	33.3 (27.1, 40.2)	48.0 (34.8, 61.5)	36.7 (24.7, 50.7)	40.8 (28.2, 54.8)	36.7 (24.7, 50.7)
Lymphopenia	17.4 (12.8, 23.4)	18.0 (9.8, 30.8)	22.4 (13.0, 35.9)	12.2 (5.7, 24.2)	20.4 (11.5, 33.6)
Grade ≥3	10.3 (6.7, 15.3)	14.0 (7.0, 26.2)	12.2 (5.7, 24.2)	8.2 (3.2, 19.2)	14.3 (7.1, 26.7)
Anemia	31.8 (25.7, 38.6)	38.0 (25.9, 51.8)	42.9 (30.0, 56.7)	38.8 (26.4, 52.8)	28.6 (17.8, 42.4)
Grade ≥3	11.8 (8.0, 17.1)	18.0 (9.8, 30.8)	12.2 (5.7, 24.2)	12.2 (5.7, 24.2)	10.2 (4.4, 21.8)
Thrombo-cytopenia	33.8 (27.6, 40.7)	66.0 (52.2, 77.6)	49.0 (35.6, 62.5)	36.7 (24.7, 50.7)	34.7 (22.9, 48.7)
Grade ≥3	20.0 (15.0, 26.2)	44.0 (31.2, 57.7)	26.5 (16.2, 40.3)	24.5 (14.6, 38.1)	18.4 (10.0, 31.4)
sARRs	0	0	4.1 (1.1, 13.7)	4.1 (1.1, 13.7)	6.1 (2.1, 16.5)
Grade ≥3	0	0	0	0	2.0 (0.4, 10.7)

Key: CI=confidence interval; $C_{peak,first}$=predicted peak concentration after the first dose; $C_{peak,max}$=predicted maximum peak concentration; D-VRd=daratumumab in combination with VELCADE® (bortezomib), Revlimid® (lenalidomide), and dexamethasone; N=number of participants; Q1=lowest exposure quartile; Q2=second exposure quartile; Q3=third exposure quartile; Q4=highest exposure quartile; sARR=systemic administration-related reaction; TEAE=treatment-emergent adverse event; VRd=VELCADE® (bortezomib), Revlimid® (lenalidomide), and dexamethasone.

Notes: The relationship of sARRs was evaluated with $C_{peak,first}$ because this TEAE mainly occurs during the first dose, whereas the relationship with other safety endpoints was investigated using $C_{peak,max}$. The quartiles for $C_{peak,max}$ were Q1 (106-446 µg/mL), Q2 (448-547 µg/mL), Q3 (548-650 µg/mL), and Q4 (650-997 µg/mL). The quartiles for $C_{peak,first}$ were Q1 (42.6-99.5 µg/mL), Q2 (99.6-114 µg/mL), Q3 (114-135 µg/mL), and Q4 (136-185 µg/mL).

2.3.4. Discussion on clinical pharmacology

Pharmacokinetics

A previously developed 2-compartment IV/SC PPK model was used to fit CEPHEUS data by external validation. Based on pcPVC and GOF plots the fit was considered reasonable, with no needs for re-estimation.

Mean [SD] maximum Cmax at Cycle 3 Day 4 (524 [216] µg/mL) was 5.59-fold that of the Cmax at Cycle 1 Day 4 (93.8 [46.6] µg/mL), indicating systemic accumulation of serum daratumumab concentration following weekly daratumumab SC administrations during induction treatment. Mean [SD] Ctrough,max of daratumumab of 407 [183] µg/mL was observed immediately prior to dose administration at Cycle 3 Day 1 predose.

The pharmacokinetics of daratumumab as observed from the sampling schedule in the CEPHEUS MMY3019 study is consistent with the pharmacokinetics in previous studies. This was confirmed by external model validation using a PPK model build on data from the PERSEUS study. Direct tabular

comparison of Cmax, Ctrough etc. for each cycle with other studies was not provided as the dosing schedule for the indication in scope of this application is new.

Mean maximum C_{trough} is stated in SmPC section 5.2 for each individual indication. Mean maximum C_{trough} is slightly lower for the indication in scope of this application as the dosing schedule is slightly less frequent in the beginning as compared to the two other dosing schedules (6 weeks of weekly dosing as opposed to 8 weeks of weekly dosing). However, it is agreed that mean maximum C_{trough} is similar to the other dosing schedule (407 vs 526or 537 µg/mL). The amendment to section 5.2 of the SmPC is accepted.

The incidence of immunogenicity towards daratumumab was very low as only 1 patient out of 170 was positive for treatment emergent neutralising anti-daratumumab antibodies. However, this patient had similar levels of exposure to daratumumab as patients negative for ADA. This is consistent with previous clinical studies with daratumumab, where Nabs have not been found to interfere with exposure. The incidence of immunogenicity towards rHuPH20 was higher, but still consistent with previous submissions for this excipient. Immunogenicity towards rHuPH20 is not expected to impact exposure to daratumumab or rHuPH20 due to its already very short half-life (6 minutes). The wording on immunogenicity in section 5.1 of the SmPC is still valid.

Dose proportionality and time dependencies were evaluated in previous submissions. The dosing schedule is slightly different for the indication in the scope of this application (6 weeks of weekly dosing vs 8 weeks of weekly dosing). Therefore, the accumulation is expected to be slightly lower.

There was considerable overlap in serum daratumumab concentrations at PK sampling timepoints across body weight subgroups. However, consistent with a mAb administered SC by flat dose, higher serum daratumumab concentrations were observed in participants with lowest body weight (≤65 and ≤50 kg) and lower serum daratumumab concentrations were observed in participants with highest body weight (>85 kg) at all PK sampling timepoints. For the lowest body weight subgroups (≤65 and ≤50 kg), mean Ctrough,max of daratumumab at Cycle 3 Day 1 predose was 9.8% and 23.1% higher, respectively, compared with that of the middle body weight subgroups (>65 to ≤85 kg and >50 to ≤85 kg). For the highest body weight subgroup (>85 kg), mean Ctrough,max of daratumumab at Cycle 3 Day 1 predose was 43.0% and 45.1% lower, respectively, compared with that of the middle body weight subgroups (>65 to ≤85 kg and >50 to ≤85 kg). For the middle body weight subgroups (>65 to ≤85 kg and >50 to ≤85 kg), the mean concentration of daratumumab at Cycle 3 Day 1 predose was comparable to that of the total PK-evaluable analysis set.

Fourteen participants in the PK-evaluable analysis set had a body weight ≤50 kg and had mean (SD) maximum daratumumab Cmax at Cycle 3 Day 4 of 682 (237) µg/mL, which was within the range of maximum Cmax (Cycle 3 Day 4) for participants in the total PK-evaluable analysis set (below the quantification limit to 1,163 µg/mL).

The flat-dose administration of daratumumab SC 1800 mg achieved adequate systemic exposure for all body weight subgroups in the D-VRd treatment arm, i.e., the systemic exposure in the majority of participants exceeded the 236 µg/mL threshold previously established to be necessary for 99% model-predicted target saturation.

Direct comparison of mean PK data from the CEPHEUS study and a POPPK model evaluation showed that race had no clinical meaningful effect on exposure.

Pharmacokinetic drug-drug interactions were not submitted as these are not expected when daratumumab is co-administered with small molecule drugs.

Pharmacodynamics

The MRD negativity rate increased with higher daratumumab $C_{trough,max}$, but the relationship between between $C_{trough,max}$ and MRD negativity was not strong and the confidence intervals between all quartiles were overlapping.

Kaplan-Meier stratified by body weight show slightly lower PFS in patients >85 kg vs <65 to 85 kg although differences were not statistically significant. This could be explained by the lower exposure observed and predicted in patients with body weight >85 kg. To separate the body weight effect and the exposure effect on progression-free survival, Kaplan-Meier plot of PFS of the different weight groups with exposure in the lower quartile, showed that PFS was more or less comparable in patients of similar "low" exposure and that the mean of the low and the high body weight group lies within the confidence interval of the middle weight group. Therefore, body weight in itself does not impact the survival, in patients within the lower exposure quartile.

The E-R analysis on efficacy data suggests that the daratumumab effect on PFS has been attained for the majority of the participants (>75%, ie, participants with exposures greater than or equal to the first exposure quartile [Q1]) at the studied 1800 mg SC dose). This finding is consistent with observations in other studies (MMY3003, MMY3004, MMY3007, MMY3008, CANDOR, and APOLLO). The seemingly similar PFS between participants in daratumumab exposure Q1 and the VRd arm needs to be interpreted with caution, likely due to the imbalance of unknown confounders given the small sample size. A difference in PFS is observed when Q1 and Q4 are compared (2.15-fold increase in median $C_{trough,max}$); however, no difference in PFS is seen when Q2 and Q4 are compared (1.52-fold increase in median $C_{trough,max}$), suggesting that individual variation in daratumumab exposure at 1800 mg SC is not expected to introduce clinically meaningful differences in PFS in participants with NDMM for whom ASCT is not planned as initial therapy. In addition, the relatively narrow exposure range (1.42-, 1.72-, and 2.15-fold increase in median $C_{trough,max}$ when Q2, Q3, and Q4, respectively, are compared with Q1), due to the single dose level in CEPHEUS, limits the interpretation of the E-R relationship. Overall, these results support that the dose regimen provides efficacious exposure in the majority of participants with NDMM for whom ASCT is not planned as initial therapy.

The exposure-safety relationship showed no apparent increase in TEAE rates with increasing daratumumab exposure for sARRs, anaemia, neutropenia, lymphopenia, or infections.

2.3.5. Conclusions on clinical pharmacology

The provided pharmacokinetics data, exposure-efficacy results and exposure-safety results support the approval of daratumumab SC at the recommended dose in combination with VRd in patients with NDMM who are ineligible for ASCT.

2.4. Clinical efficacy

2.4.1. Dose response study

Not applicable. The present application concerns a fixed dose of daratumumab SC which has previously been established.

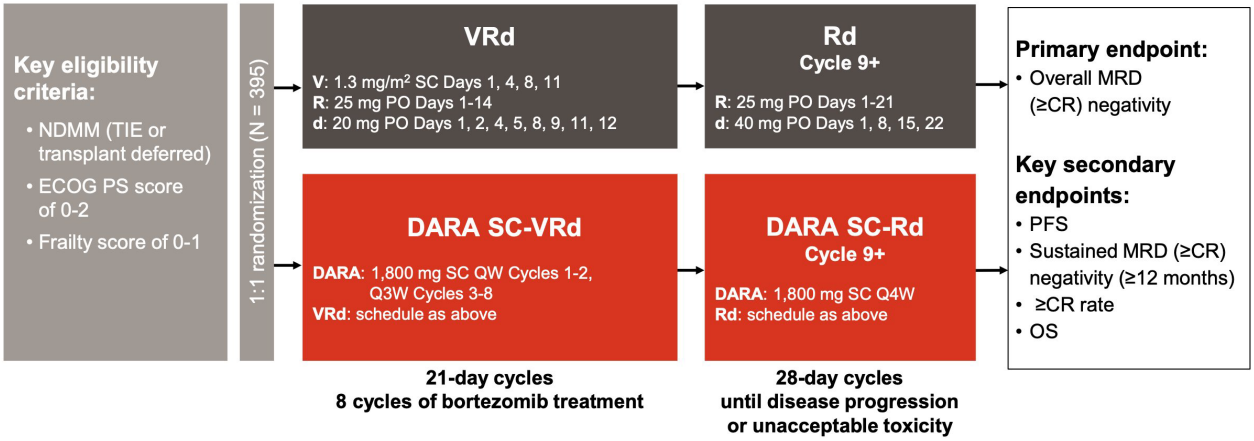
2.4.2. Main study

CEPHEUS (54767414MMY3019): A Phase 3 Study comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) with VELCADE, Lenalidomide, and Dexamethasone (VRd) in subjects with untreated Multiple Myeloma and for whom Hematopoietic Stem Cell Transplant is not planned as initial therapy

Methods

A diagrammatic representation of the study design is presented in **Figure 8**.

Figure 8. Schematic Overview of CEPHEUS



NDDM=newly diagnosed multiple myeloma; TIE=Transplant ineligible; D-VRd=daratumumab, bortezomib, lenalidomide, and dexamethasone; MRD=minimal residual disease; OS=overall survival; PFS=progression-free survival; VRd=bortezomib, lenalidomide, and dexamethasone

Study participants

Main inclusion criteria

1. Newly diagnosed and not considered candidate for high-dose chemotherapy with stem cell transplantation (SCT) due to:
    - Being age ≥65 years

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.

2. 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 (calcium, renal, anaemia, bone) 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. Anaemia: haemoglobin >2 g/dL below the lower limit of normal or haemoglobin <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

3. Must have measurable disease, as assessed by central laboratory, defined by any of the following:
- IgG, IgA, IgM, IgD, or IgE multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
- Light chain multiple myeloma without measurable disease in serum or urine: Serum Ig FLC ≥10 mg/dL and abnormal serum Ig kappa lambda FLC ratio.

4. ECOG performance status score of 0, 1, or 2.

5. Adequate Clinical laboratory values and organ function during the Screening Phase.

6. Female subjects must not be pregnant and avoid pregnancy through adequate means.

Main exclusion criteria

1. Frailty index of ≥2 according to Myeloma Geriatric Assessment score.

2. 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).

3. 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 sponsors medical monitor, is considered cured with minimal risk of recurrence within 3 years).

4. 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.

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.

6. Plasmapheresis within 28 days of randomization.

7. Clinical signs of meningeal involvement of multiple myeloma.

8. Chronic obstructive pulmonary disease (COPD) with a FEV1 <50% of predicted. (FEV1 testing is required for subjects suspected of having COPD).

9. Moderate or severe persistent asthma within the past 2 years, uncontrolled asthma of any classification. (Subjects who have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

10. Known to be seropositive for human immunodeficiency virus (HIV) or active HBV or HCV infection.

11. Concurrent medical or psychiatric condition or disease (such as but not limited to, systemic amyloidosis, POEMS, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with study procedures or results, or that in the opinion of the investigator would constitute a hazard if enrolled in the study.

12. Has clinically significant cardiac disease, including: Myocardial infarction within 6 months before signing the ICF, or unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV; Uncontrolled cardiac arrhythmia or clinically significant ECG abnormalities Screening 12-lead ECG showing a baseline QT interval as corrected by Frederica' s formula (QTcF) >470 msec.

13. Received a strong CYP3A4 inducer within 5 half-lives prior to randomization.

14. Allergy, hypersensitivity, or intolerance to boron or mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients, or sensitivity to mammalian-derived products or lenalidomide.

Treatments

The study consisted of 3 phases: A Screening Phase, a Treatment Phase (Intervention Phase), and a Follow-up Phase (Postintervention Phase). The Screening Phase was up to 28 days before randomization. Subjects received either D-VRd or VRd for 8 cycles. No subject received bortezomib after completion of the first 8 cycles of VRd. After completing 8 cycles of therapy, subjects continued with DRd or Rd until disease progression or unacceptable toxicity.

Participants assigned to the D-VRd treatment arm were to receive **daratumumab** SC administered at 1800 mg weekly in Cycles 1 and 2, every 3 weeks in Cycles 3 through 8, and every 4 weeks in Cycle 9 and beyond until the participant had disease progression or experienced an unacceptable toxicity. Cycles 1-8 were 21 days in length, and Cycles 9 and beyond were 28 days in length.

Participants in both treatment arms were to receive bortezomib, lenalidomide, and dexamethasone as stated below:

Bortezomib: 1.3 mg/m2 administered as an SC injection twice a week (Days 1, 4, 8, and 11) for Cycles 1-8. For participants who experienced injection-site reactions, bortezomib could have been administered by IV injection (per local prescribing information). Per protocol, bortezomib was a fixed dose for the first 8 cycles of treatment only.

Lenalidomide: administered PO at 25 mg on Days 1 to 14 in Cycles 1-8 for participants with CrCl $\geqslant$60 mL/min. During Cycles 9 and beyond, lenalidomide 25 mg was administered daily on Days 1 through 21 of each 28-day cycle. Lenalidomide was taken (with or without food) as a single dose at the same time daily. Lenalidomide dosing continued until disease progression or unacceptable toxicity.

Dexamethasone (or an equivalent corticosteroid): administered PO at 20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12 of each 21-day cycle for Cycles 1-8. For participants who were older than 75 years of age or participants who were underweight (BMI <18.5), dexamethasone could have been administered at a dose of 20 mg on Days 1, 4, 8, and 11. In Cycles 9 and beyond, dexamethasone 40 mg PO was administered on Days 1, 8, 15, 22 of each 28-day cycle. For participants older than 75 years or underweight (BMI <18.5), the dexamethasone dose could have been administered at a dose of 20 mg weekly.

For participants in the D-VRd arm, the dexamethasone PO or IV dose administered as a pre-injection medication on daratumumab injection days replaced the PO/IV dexamethasone dose for that day. Dexamethasone was administered until the participant experienced disease progression or unacceptable toxicity during the treatment phase.

For participants potentially planning an SCT at a later time, stem cell harvest following mobilization with G-CSF, plerixafor, or cyclophosphamide (or any combination of the 3) was permitted after Cycle 4 while on study treatment.

Pre-administration Medication
To decrease the risk of IRRs, all subjects received the following medications 1 to 3 hours prior to each study drug administration:

- Paracetamol (acetaminophen) 650-1000 mg IV or orally (PO).
- An antihistamine: diphenhydramine 25-50 mg IV or PO, or equivalent.
- Dexamethasone 20 mg Cycles 1-8 and 40 mg for Cycle 9 and beyond IV or PO on injection days. For subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone 20 mg may be administered as appropriate. An equivalent intermediate-acting or long-acting corticosteroid may substitute.
- Montelukast 10 mg (or equivalent) is recommended on Cycle 1 Day 1 only up to 24 hours prior to daratumumab injection.

Objectives

Primary objective
The primary objective is to determine if the addition of daratumumab to VRd will improve overall MRD negativity rate compared with VRd alone.

Secondary Objectives (selection)
The secondary objectives are:

To determine if the addition of daratumumab to VRd will improve clinical outcome as measured by:
- PFS
- MRD negativity rate at 1 year
- Durability of MRD negativity
- ORR, rate of very good partial response (VGPR) or better, and rate of CR or better
- Time to response
- Duration of response
- Time to next treatment
- Progression-free survival on the next line of therapy (PFS2; defined as time from randomization to progression on the next line of therapy or death, whichever comes first)
- OS

Outcomes/endpoints

Primary Endpoint

Overall MRD negativity rate, which is defined as the proportion of subjects who have achieved MRD negative status (at 10^{-5}) by bone marrow aspirate after randomization and prior to progressive disease (PD) or subsequent anti-myeloma therapy.

Subjects who have achieved MRD negative status on or after PD or after the switch to subsequent anti-myeloma therapy before PD, were not considered MRD negative in the primary endpoint analysis. MRD positive subjects included subjects of which all tested samples were found to be MRD positive or indeterminate. For subjects with missing MRD samples, failure to calibrate baseline MRD, or otherwise unevaluable samples, MRD status were considered as MRD positive.

The primary estimand, the main clinical quantity of interest to be estimated in the study, was defined by the following 5 components:

• Treatments:
- Daratumumab, bortezomib, lenalidomide and dexamethasone (D-VRd, investigational treatment) for eight 21-day cycles followed by daratumumab, lenalidomide, and dexamethasone (VRd) therapy until disease progression or unacceptable toxicity
- Bortezomib, lenalidomide and dexamethasone (VRd) for eight 21-day cycles followed by lenalidomide and dexamethasone (Rd, control treatment) until disease progression or unacceptable toxicity

• Population: subjects with untreated multiple myeloma and for whom hematopoietic stem cell transplant was not planned as initial therapy

• Variable: MRD negativity status (yes or no, yes defined as achieving CR or better response and MRD negative status (at 10-5) by bone marrow biopsy/aspirate any time after treatment assignment but prior to either of the intercurrent events: subsequent antimyeloma therapy or progressive disease)

• Population-level summary: odds ratio (OR) of D-VRd vs. VRd

• Intercurrent events:
- Subsequent antimyeloma therapy
- Progressive disease

Composite strategy was used to count for the intercurrent events as reflected in the variable definition.

Major Secondary Endpoints

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

The estimand corresponding to the major secondary endpoint, CR or better rate, in the study, was defined as:
• Variable: CR or better response (yes or no, yes defined as achieving CR or better response any time after treatment assignment but prior to subsequent antimyeloma therapy)
• Intercurrent events: - Subsequent antimyeloma therapy

Composite strategy was used to count for the intercurrent events as reflected in the variable definition.

PFS
PFS is defined as the duration from the date of randomization to either progressive disease (PD) or death due to any cause, whichever comes first. Disease progression was determined according to the International Myeloma Working Group (IMWG) criteria. Subjects who started subsequent anti-myeloma therapies for multiple myeloma without disease progression were censored at the last disease assessment before the start of subsequent therapies. Subjects who withdrew consent from the study before disease progression were censored at the last disease assessment. Subjects who were lost to follow-up were censored at the last disease assessment before subjects were lost to follow-up. Subjects who had not progressed and were still alive at the cutoff date for analysis were censored at the last disease assessment. Subjects without any post-baseline disease assessment were censored at the date of randomization.

Determination of dates of PFS event and dates for censoring is summarized in **Table 6** as follows.

Table 6. PFS event and censoring method

Situation	Outcome	Date of Event or Censoring
Disease progression prior to start of subsequent antimyeloma therapy	PFS event	Earliest date that indicates disease progression
Death (due to any cause) *	PFS event	Date of death
Disease progression or death immediately preceded by 2 or more consecutive missed disease assessments	Censored	At the last adequate disease assessment before the consecutive missed disease assessments
No postbaseline disease assessment	Censored	Date of randomization
Other, such as: • Withdrawal of consent to study participation • Lost to follow-up • Start of subsequent antimyeloma therapy prior to disease progression or death	Censored	Date of last disease assessment prior to withdrawal of consent to study participation, lost to follow-up, start of subsequent antimyeloma therapy

*Subjects who died after consent withdrawal will be censored at the date of consent withdrawal for PFS analysis

The estimand corresponding to the major secondary endpoint PFS for this study was defined by the following 5 components:

• Treatments:
- Daratumumab, bortezomib, lenalidomide and dexamethasone (D-VRd, investigational treatment) for eight 21-day cycles followed by daratumumab, lenalidomide, and dexamethasone (VRd) therapy until disease progression or unacceptable toxicity
- Bortezomib, lenalidomide and dexamethasone (VRd, control treatment) for eight 21-day cycles followed by lenalidomide and dexamethasone (Rd) until disease progression or unacceptable toxicity

• Population: subjects with untreated multiple myeloma and for whom hematopoietic stem cell transplant was not planned as initial therapy

• Variable: progression-free survival

• Population-level summary: hazard ratio (HR) of D-VRd vs. VRd

• Intercurrent events:
- Start of subsequent antimyeloma therapy prior to disease progression or death
- COVID-19 infection with the outcome of death prior to disease progression.

Hypothetical strategy was applied to the intercurrent events of subsequent antimyeloma therapy prior to disease progression or death, as if the subjects would not had experienced such an intercurrent event. Treatment policy was used for COVID-19 infection with the outcome of death prior to disease progression, whether such an intercurrent event occurred or not was irrelevant.

<u>Sustained MRD negativity rate</u>
Sustained MRD negativity rate is defined as the proportion of subjects who achieve CR or better response and have achieved MRD negative status (at 10-5) at two bone marrow biopsy/aspirate examinations that are a minimum of one year apart (and the two examinations should be prior to progressive disease (PD), subsequent anti-myeloma therapy, or both), without any examination showing MRD positive status in between.

The estimand corresponding to the major secondary endpoint, durable MRD negativity rate, in the study, was defined as:
• Variable: durable MRD negativity status (yes or no, yes defined as achieving CR or better response and MRD negative status (at 10-5) at two bone marrow biopsy/aspirate examinations that are a minimum of

one year apart without any examination showing MRD positive status in between, and prior to either of the intercurrent events: subsequent antimyeloma therapy or progressive disease).

Other secondary endpoints

MRD negativity rate at one year is defined as the proportion of subject who achieved CR or better response and MRD negative status (at 10-5) by bone marrow biopsy/aspirate at 12 months after the first dose of study treatment and prior to progressive disease (PD), subsequent anti-myeloma therapy, or both. But the subjects who had achieved MRD negative status on or after PD or the start of subsequent anti-myeloma therapy, were not considered as MRD negative. Similar definitions apply to the MRD negativity rates at other scheduled time points, which were 18, 24, 30, or 36 months after the first dose of study treatment.

Overall response rate (ORR) is defined as the proportion of subjects who achieve PR or better responses (i.e., PR, VGPR, CR, or sCR) based on the computerized algorithm, in accordance with the IMWG criteria, during or after the study treatment but before the start of subsequent anti-myeloma therapy.

VGPR or better rate is defined as the proportion of subjects achieving VGPR, CR, and sCR based on the computerized algorithm, in accordance with the IMWG criteria, during or after the study treatment but before the start of subsequent anti-myeloma therapy.

Progression-free survival on the next line of therapy (PFS2) is defined as the time from randomization to progression on the next line of treatment or death (due to any cause), whichever comes first. Disease progression was based on investigator judgment. Subjects who were still alive and not yet progressed on the next line of treatment were censored on the last date of follow-up. Subjects who withdraw consent or lost to follow-up prior to any subsequent antimyeloma therapy were censored at the date of last disease assessment during the course of study. Subjects without any post-baseline follow-up were censored at the randomization.

Overall survival (OS) is defined as the time from the date of randomization to the date of the subject's death due to any cause. Subjects who were lost to follow-up were censored at the time of lost to follow-up. Subjects who died after consent withdrawal were considered as having an OS event. If the subject was alive at the cutoff date for the analysis or the survival status was unknown, then the subject's data was censored at the date the subject was last known to be alive. The date of last known alive was determined by the maximum collection/assessment date from among selected data domains within the clinical database.

Time to response (TTR, i.e., time to the first response) is defined as the time between the randomization and the first efficacy evaluation at which the subject meets all criteria for PR or better based on the computerized algorithm, according to IMWG response criteria.

Sample size

Based on the available data from studies CASTOR, POLLUX, and ALCYONE, approximately 64% of MRD negative subjects at a threshold of 10^{-4} were also MRD negative at a threshold of 10^{-5}. The IFM2009-TE NDMM study showed a 49% overall MRD negativity rate at 10^{-4} for all the VRd subjects without transplant. Thus, the anticipated overall MRD negativity rate (10^{-5}) for the control arm in this study is estimated to be at most 35%. This study assumes that the addition of daratumumab to VRd would lead to a 15% absolute increase in overall MRD negativity rate (50% D-VRd vs. 35% VRd alone). A sample size of 360 subjects (180 each arm) is needed to achieve a power of 80% to detect such a treatment difference at a 2-sided alpha of 0.05.

This sample size was to provide approximately 80% power to detect a 37% reduction in the risk of progression or death (HR=0.63, translating to an improvement in median PFS from 43 months to 68 months) with a log-rank test at a 2-sided alpha of 0.05. To ensure adequate power for PFS, an adaptive approach may be used to determine the timing of the final PFS analysis (162 events). If the observed HR for PFS at the interim analysis (i.e., 60% of events) was higher than expected, the final analysis of PFS may be delayed until approximately 205 events have been observed (roughly 3 years later). If the HR of 0.7 was observed for PFS at the interim, 205 events were to provide approximately 80% conditional power (CP) for the final analysis of PFS. The event size for the final analysis of PFS was not to be decreased from 162. The ADDPLAN®2 targeting the CP=80% subject to the maximum number of events 205 has been used to plan the adaptive design. To maintain a strong control of the type I error rate for the PFS analysis, an inverse normal p-value combination method was used if the number of events for the final analysis increased to approximately 205. The method allows flexible adaptations at an IA and creates a valid test that controls the type I error rate in a strong sense analytically. In this proposed design, the adaptation is the potential adjustment of the required number of events for the final analysis.

Randomisation

Central randomization was implemented in this study. Eligible subjects were stratified by ISS (Stage I, II, or III, based on β-2 microglobulin and albumin by central laboratory), and age/transplant eligibility (<70 years ineligible, or age <70 years and refusal to transplant, or age ≥70 years), and then assigned randomly to 1 of 2 treatment groups in a 1:1 ratio based on an algorithm implemented in the interactive web response system (IWRS) before the study. The randomization was balanced by using randomly permuted blocks. Based on the randomization code, the IWRS assigned a unique intervention code, which dictated the intervention assignment and matching study drug kit for the subject.

Blinding (masking)

This was an open label study.

Statistical methods

Primary endpoint

For this study, threshold value of 10^{-5} was used for the primary MRD negativity analysis. Other threshold values (10^{-4} and 10^{-6}) could also be explored.

MRD negativity on or after disease progression or switch to subsequent anti-myeloma therapy without confirmed progression on study treatment, were not considered as MRD negative in the analysis.

The overall MRD negativity rate was calculated for each treatment group based on the ITT analysis set. The corresponding 95% exact CI was provided. Reasons for missing or unevaluable MRD status were tabulated by treatment group.

The stratified Cochran Mantel Haenszel (CMH) estimate of odds ratio and its 95% confidence interval and p-value from Fisher's exact test were 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).

Following supplementary analyses may be performed in a similar manner as described above:
- Overall MRD negativity rate based on the "modified ITT" analysis set (if ≥10% subjects who have discontinued study treatment/ study or died due to COVID-19)
- Overall MRD negativity rate based on the CR or better subjects only.

Secondary endpoints

CR or better responses after switch to subsequent anti-myeloma therapy were not counted as CRs in the analysis. The CR or better rate were calculated for each treatment group based on the ITT 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. Stratification factors used in the analysis was the same as for the primary endpoint.

Analysis of PFS were based on the ITT analysis set. The Kaplan-Meier method was used to estimate the distribution of overall PFS for each treatment group. The median PFS with 95% CI was provided. In addition, the number and percentage of subjects who had a PFS event or were censored was reported. The reasons for PFS censoring were summarized accordingly. The Kaplan-Meier PFS curve was plotted by treatment group. 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. Stratification factors used in the analyses aligned with those for the primary endpoint. In addition, landmark PFS rate with 95% CI was estimated by Kaplan-Meier method and reported for each treatment group. The proportional hazard (PH) assumption of the PFS analysis was examined graphically (log-log plot of S(t)) and/or numerically (e.g., good of fitness test by Schoenfeld residual). If the PH assumption was not met, additional analyses may be performed to address the issue, such as the Inverse probability of censoring weighting (IPCW) analysis to take the confounding factors (e.g., daratumumab-containing subsequent therapy) into account because non-PH may be caused by potential treatment change (or crossover). Additionally, following sensitivity or supplementary analyses may be performed in a similar manner as described above: Sensitivity • Unstratified analysis of PFS • Progressive disease is based on investigator assessment according to the IMWG response criteria Supplementary • Not censor the events after the start of subsequent antimyeloma therapies • Censor the death due to COVID-19 • Censor the subjects who permanently discontinue treatment/study due to COVID-19 (censor at last disease evaluation before treatment/study discontinuation).

The durable MRD negativity rate was calculated for each treatment group based on the ITT analysis set. The corresponding 95% exact CI was also provided. Chi-square estimate of the common odds ratio with 95% confidence interval and p-value from Fisher's exact test for treatment difference was reported.

The analysis of MRD negativity rate at 1 year and other timepoints (i.e., 18, 24, 30, or 36 months), ORR and VGPR or better rate was performed in a similar manner as for CR or better response. The analysis of OS, PFS2, time to subsequent antimyeloma therapy, and DOR was performed in a similar manner as for PFS. At the primary MRD analysis, OS analysis was exploratory and descriptive. The Kaplan-Meier curves of OS were also provided by treatment group. Time to first response was analyzed for subjects who achieved a response (PR or better) and descriptive statistics (N, mean, SD, median, and range) was provided.

Interim analysis and Multiplicity

There was no interim analysis planned for the overall MRD negativity rate. After the primary analysis of MRD negativity rate, disease assessment continued for the secondary endpoint PFS, for which one interim analysis was planned after approximately 98 events (i.e., 60% of the total 162 events) have been accumulated. The significance levels at this interim analysis of PFS to establish the superiority (or declare the futility) of daratumumab plus VRd over VRd alone were determined based on the observed number of PFS events at this analysis using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha- and beta-spending method.

If the primary endpoint of overall MRD negativity rate was statistically significant, the key secondary endpoints (i.e., CR or better rate, PFS, and durable MRD negativity rate) were sequentially tested, each with an overall two-sided alpha of 0.05, by utilizing a hierarchical testing approach as proposed by Tang and Geller (1999) that strongly controls family wise Type I error rate.

Due to the short follow-up time at the primary MRD data cut, PFS and durable MRD negativity data were premature, hence hierarchical test starting at the interim PFS data cut (98 events occurred) could be performed. The final PFS analysis (162 events occurred) was skipped if the PFS interim result crosses the pre-specified stopping boundary. The significance level at each data cut was determined by the alpha-spending function specific to endpoints:

- For CR or better rate, the information fraction is expected to be 80% at the primary MRD cut. The O'Brien-Fleming alpha-spending function as implemented by the Lan-DeMets method was used for alpha spending: 0.0244 (two-sided) at the primary MRD cut and 0.0428 (two-sided) at the interim PFS cut.

- For PFS, the exact significance level at the interim analysis and final PFS analysis was determined by the observed number of events per the O'Brien-Fleming alpha spending function. Assuming 98 PFS events are observed at the interim analysis, the alpha to be spent was 0.0076 (2-sided) for the interim analysis and 0.0476 (2-sided) for the final PFS analysis (162 PFS events occur).

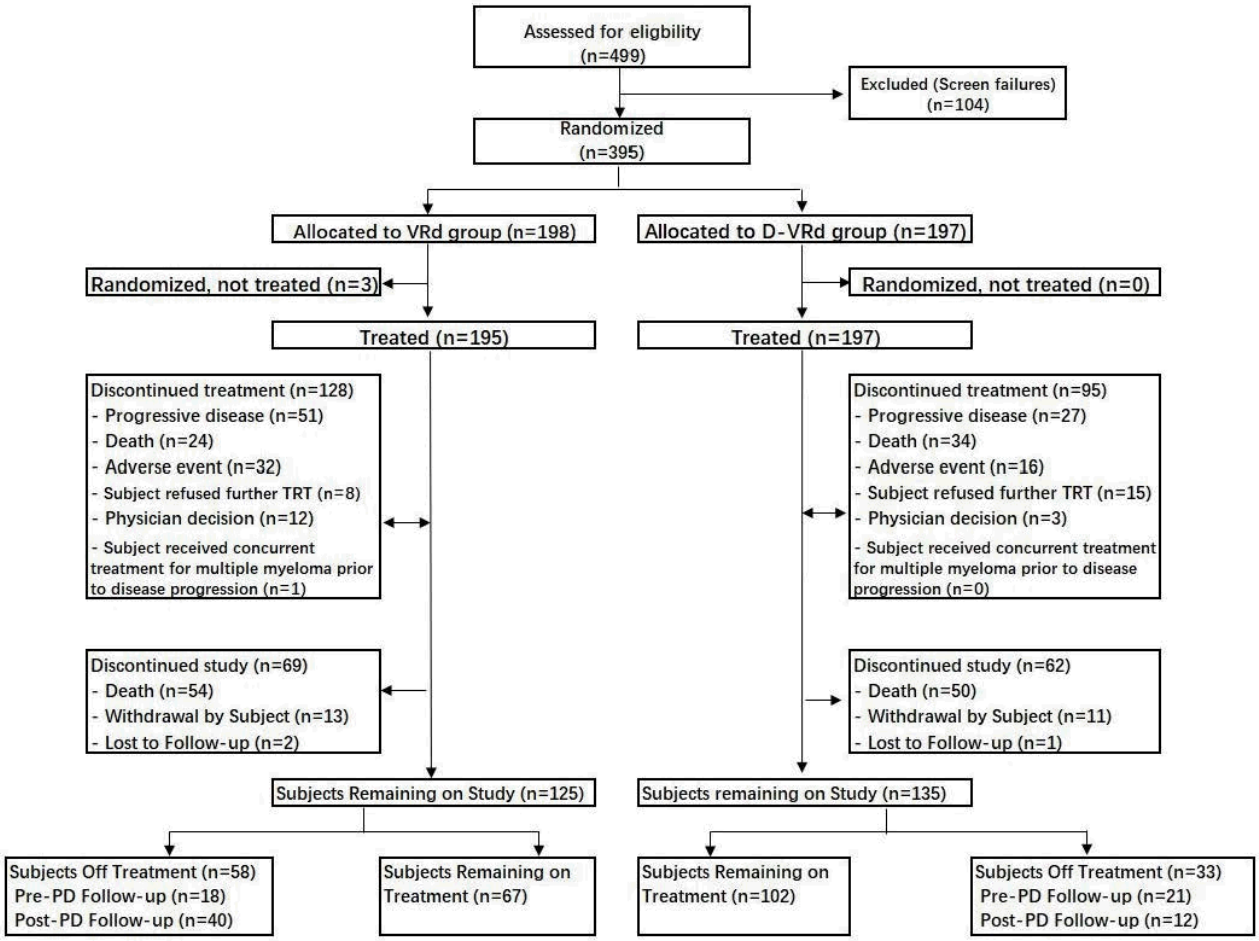
  To ensure adequate power for PFS, an adaptive approach may be used to determine the timing of the final PFS analysis. If the observed HR for PFS at the interim analysis (i.e., 60% of events) is higher than expected (e.g., 0.7 or higher), the final analysis of PFS may be delayed until approximately 205 events have been observed. To control the overall type I error rate, the inverse normal test with the same fixed weights (i.e., information fractions of interim and final analyses) as originally planned was used to combine the log-rank statistics before and after the interim analysis.

- For durable MRD negativity rate, the information fraction is expected to be 80% at the interim PFS cut. The O'Brien-Fleming alpha-spending function as implemented by the Lan-DeMets method was used for alpha spending: 0.0244 (two-sided) at the interim PFS cut and 0.0428 (two-sided) at the final PFS cut.

If the null hypothesis for any of these endpoints failed to be rejected at the interim analysis, then any subsequent endpoint(s) listed above were not tested until the next analysis time point (e.g., final PFS analysis), if applicable. If the null hypothesis for an endpoint was rejected at any interim analysis, it remained being rejected and would not be re-tested at any subsequent time points, if any.

Results

Participant flow



Recruitment

Study Initiation Date: 15 November 2018 (Date first participant was screened)

Primary MRD Analysis Clinical Cutoff: 08 April 2021 (Date of the last observation recorded as part of the database for the primary analysis)

Final PFS Analysis Clinical Cutoff: 07 May 2024 (Date of last observation recorded as part of the database for final PFS analysis)

Conduct of the study

The protocol was amended 6 times as summarised below.

Amendment 1 (10 September 2018)
To add language describing hepatitis testing, which is now required across daratumumab studies for subjects who are positive for anti-HBc and/or anti-HBs.

Amendment 2 (18 January 2019)
The overall reason for the amendment was in response to identification of a new important risk (hepatitis B virus [HBV] reactivation). Additionally, revisions and clarifications were made to considerations for

lenalidomide use, sequence of secondary endpoints, as well as other measurement parameters throughout the Protocol.

Amendment 3 (19 November 2019)
The overall reason for the amendment was to expand the scope of efficacy review by Independent Data Monitoring Committee (IDMC) at different stages in the study. Additionally, to ensure that the subjects continue to receive treatment with other components of study treatment even if any one component is held, discontinued or reduced, to clarify that subsequent anti-myeloma therapies should not be administered until disease progression and in subjects who discontinue study treatment for reasons other than disease progression, should be monitored and subsequent treatment should not be started until documented disease progression.

Amendment 4 (1 October 2020)
To update the timeframes and landmark analyses for primary analysis of minimal residual disease (MRD) negativity rate. Primary endpoint of MRD negativity remains unchanged, but primary analysis will now occur at approximately 18 months in order to maximize MRD samples available for primary analysis, to ensure the maturity of MRD negativity at the primary analysis, and to mitigate the impact of Coronavirus Disease 2019 (COVID-19) pandemic on MRD sample collection.

Amendment 5 (24 March 2022)
To mitigate the impact of Coronavirus Disease 2019 (COVID-19) pandemic.

Amendment 6 - 14 March 2024
The overall rationale for the amendment was to continue the study with limited data collection after the planned final PFS analysis. Subjects benefitting from treatment with daratumumab could have continued access to study treatment after the end of data collection.

Protocol deviations

Major protocol deviations are summarised in **Table 7**.

Table 7. Summary of Major Protocol Deviations; Intent-to-treat Analysis Set; Final PFS Analysis (Study 54767414MMY3019)

	VRd n (%)	D-VRd n (%)	Total n (%)
Analysis set: intent-to-treat	198	197	395
Total number of subjects with major protocol deviation	13 (6.6%)	8 (4.1%)	21 (5.3%)
Type of major protocol deviation			
Entered but did not satisfy criteria	2 (1.0%)	3 (1.5%)	5 (1.3%)
Received a disallowed concomitant treatment	8 (4.0%)	3 (1.5%)	11 (2.8%)
Other	3 (1.5%)	3 (1.5%)	6 (1.5%)
Other - COVID-19 related	1 (0.5%)	0	1 (0.3%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; COVID-19 = Coronavirus Disease 2019.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.

Baseline data

Table 8. Summary of demographics and baseline characteristics; Intent-to-treat Analysis Set; Final PFS analysis (Study 54767414MMY3019)

	VRd	D-VRd	Total
Analysis set: intent-to-treat	198	197	395
Age, years			
N	198	197	395
Category, n (%)			
<65	35 (17.7%)	36 (18.3%)	71 (18.0%)
65 - <70	53 (26.8%)	52 (26.4%)	105 (26.6%)
≥70	110 (55.6%)	109 (55.3%)	219 (55.4%)
Mean (SD)	68.9 (7.31)	69.0 (7.01)	69.0 (7.15)
Median	70.0	70.0	70.0
Range	(31; 80)	(42; 79)	(31; 80)
Sex			
N	198	197	395
Female	87 (43.9%)	110 (55.8%)	197 (49.9%)
Male	111 (56.1%)	87 (44.2%)	198 (50.1%)
Race			
N	198	197	395
White	156 (78.8%)	162 (82.2%)	318 (80.5%)
Black or African American	9 (4.5%)	10 (5.1%)	19 (4.8%)
Asian	14 (7.1%)	11 (5.6%)	25 (6.3%)
Native Hawaiian or other Pacific Islander	1 (0.5%)	0	1 (0.3%)
Other	2 (1.0%)	1 (0.5%)	3 (0.8%)
Not reported	16 (8.1%)	13 (6.6%)	29 (7.3%)
Ethnicity			
N	198	197	395
Hispanic or Latino	35 (17.7%)	31 (15.7%)	66 (16.7%)
Not Hispanic or Latino	147 (74.2%)	154 (78.2%)	301 (76.2%)
Not reported	16 (8.1%)	12 (6.1%)	28 (7.1%)
Weight, kg			
N	198	197	395
Category, n (%)			
≤65	63 (31.8%)	58 (29.4%)	121 (30.6%)
>65 and ≤ 85	88 (44.4%)	101 (51.3%)	189 (47.8%)
>85	47 (23.7%)	38 (19.3%)	85 (21.5%)
Mean (SD)	74.35 (15.770)	73.92 (16.342)	74.14 (16.039)
Median	72.55	73.60	73.00
Range	(38.0; 125.0)	(40.4; 125.0)	(38.0; 125.0)
Baseline ECOG score			
N	198	197	395
0	84 (42.4%)	71 (36.0%)	155 (39.2%)
1	100 (50.5%)	103 (52.3%)	203 (51.4%)
2	14 (7.1%)	23 (11.7%)	37 (9.4%)
Total Additive (Frailty) Score			
N	198	197	395
Fit (score=0)	132 (66.7%)	124 (62.9%)	256 (64.8%)
Intermediate-fitness (score=1)	66 (33.3%)	73 (37.1%)	139 (35.2%)
Frail (score>=2)	0	0	0

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; BSA = Body Surface Area; ECOG = Eastern Cooperative Oncology Group.
Note: Subjects reporting multiple races are included under other.
Note: Percentages calculated with the number of subjects in each treatment group with available data as denominator.

Table 9. Summary of baseline disease characteristics; Intent-to-treat Analysis Set; Final PFS analysis (Study 54767414MMY3019)

	VRd	D-VRd	Total
Analysis set: intent-to-treat	198	197	395
Type of myeloma by immunofixation or serum FLC assay			
N	198	197	395
IgG	114 (57.6%)	130 (66.0%)	244 (61.8%)
IgA	52 (26.3%)	38 (19.3%)	90 (22.8%)
IgM	0	0	0
IgD	3 (1.5%)	2 (1.0%)	5 (1.3%)
IgE	0	0	0
Light chain	25 (12.6%)	22 (11.2%)	47 (11.9%)
Kappa	15 (7.6%)	10 (5.1%)	25 (6.3%)
Lambda	9 (4.5%)	11 (5.6%)	20 (5.1%)
FLC-Kappa [e]	0	1 (0.5%)	1 (0.3%)
FLC-Lambda [f]	1 (0.5%)	0	1 (0.3%)
Biclonal	3 (1.5%)	5 (2.5%)	8 (2.0%)
Negative Immunofixation	0	0	0
Unknown	1 (0.5%)	0	1 (0.3%)
Type of measurable disease [a]			
N	198	197	395
Serum only	108 (54.5%)	120 (60.9%)	228 (57.7%)
IgG	76 (38.4%)	89 (45.2%)	165 (41.8%)
IgA	31 (15.7%)	27 (13.7%)	58 (14.7%)
Other [b]	1 (0.5%)	4 (2.0%)	5 (1.3%)
Serum and urine	45 (22.7%)	41 (20.8%)	86 (21.8%)
Urine only	24 (12.1%)	20 (10.2%)	44 (11.1%)
Serum FLC	21 (10.6%)	16 (8.1%)	37 (9.4%)
ISS Staging [c]			
N	198	197	395
I	68 (34.3%)	68 (34.5%)	136 (34.4%)
II	75 (37.9%)	73 (37.1%)	148 (37.5%)
III	55 (27.8%)	56 (28.4%)	111 (28.1%)
Time since initial MM diagnosis, months			
N	198	197	395
Mean (SD)	1.60 (1.100)	1.49 (1.028)	1.54 (1.065)
Median	1.26	1.15	1.18
Range	(0.3; 8.0)	(0.4; 5.8)	(0.3; 8.0)
Number of lytic bone lesions			
N	198	197	395
None	49 (24.7%)	34 (17.3%)	83 (21.0%)
1-3	51 (25.8%)	43 (21.8%)	94 (23.8%)
4-10	34 (17.2%)	44 (22.3%)	78 (19.7%)
More than 10	64 (32.3%)	76 (38.6%)	140 (35.4%)
Presence of extramedullary plasmacytomas			
N	198	197	395
Yes	13 (6.6%)	11 (5.6%)	24 (6.1%)
No	185 (93.4%)	186 (94.4%)	371 (93.9%)
Presence of evaluable bone marrow assessment			
N	198	197	395
Yes	198 (100.0%)	196 (99.5%)	394 (99.7%)
No	0	1 (0.5%)	1 (0.3%)

% Plasma cells, bone marrow biopsy/aspirate			
N	198	196	394
<10	7 (3.5%)	6 (3.1%)	13 (3.3%)
10-30	102 (51.5%)	82 (41.8%)	184 (46.7%)
>30-60	48 (24.2%)	60 (30.6%)	108 (27.4%)
>60	41 (20.7%)	48 (24.5%)	89 (22.6%)
% Plasma cells, bone marrow biopsy			
N	86	89	175
<10	3 (3.5%)	4 (4.5%)	7 (4.0%)
10-30	27 (31.4%)	26 (29.2%)	53 (30.3%)
>30-60	31 (36.0%)	25 (28.1%)	56 (32.0%)
>60	25 (29.1%)	34 (38.2%)	59 (33.7%)
% Plasma cells, bone marrow aspirate			
N	187	183	370
<10	15 (8.0%)	21 (11.5%)	36 (9.7%)
10-30	107 (57.2%)	86 (47.0%)	193 (52.2%)
>30-60	40 (21.4%)	52 (28.4%)	92 (24.9%)
>60	25 (13.4%)	24 (13.1%)	49 (13.2%)
Bone marrow cellularity by biopsy			
N	70	73	143
Hypercellular	30 (42.9%)	32 (43.8%)	62 (43.4%)
Normocellular	29 (41.4%)	24 (32.9%)	53 (37.1%)
Hypocellular	5 (7.1%)	6 (8.2%)	11 (7.7%)
Indeterminate	6 (8.6%)	11 (15.1%)	17 (11.9%)
Bone marrow cellularity by aspirate			
N	27	39	66
Hypercellular	10 (37.0%)	8 (20.5%)	18 (27.3%)
Normocellular	16 (59.3%)	18 (46.2%)	34 (51.5%)
Hypocellular	1 (3.7%)	8 (20.5%)	9 (13.6%)
Indeterminate	0	5 (12.8%)	5 (7.6%)
Cytogenetic risk			
N	198	197	395
Standard risk [d]	149 (75.3%)	149 (75.6%)	298 (75.4%)
High risk [d]	27 (13.6%)	25 (12.7%)	52 (13.2%)
del(17p)	14 (7.1%)	12 (6.1%)	26 (6.6%)
t(4; 14)	13 (6.6%)	12 (6.1%)	25 (6.3%)
t(14; 16)	2 (1.0%)	4 (2.0%)	6 (1.5%)
Un-evaluable or missing	22 (11.1%)	23 (11.7%)	45 (11.4%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; FLC = free light chain; ISS = International Staging System; MM = multiple myeloma; NE = not evaluable.

[a] Includes subjects without measurable disease in serum and urine.

[b] Includes IgD, IgM, IgE and biclonal.

[c] ISS staging is derived based on the combination of serum β2-microglobulin and albumin.

[d] Standard risk includes subjects who are negative for del17p, t(14;16), or t(4;14) by FISH. High risk includes the subjects who are positive for any of del17p, t(14;16), or t(4;14) by FISH.

[e] Includes subjects without a positive immunofixation but with evidence of free light chain kappa by FLC testing.

[f] Includes subjects without a positive immunofixation but with evidence of free light chain lambda by FLC testing.

Note: Percentages calculated with the number of subjects in each dose level with available data as denominator.

Table 10. Summary of subsequent antimyeloma therapy by therapeutic class, pharmacologic class, and drug; Safety Analysis Set; Final PFS Analysis (Study 54767414MMY3019)

	VRd n (%)	D-VRd n (%)	Total n (%)
Analysis set: safety	195	197	392
Total number of subjects with 1 or more subsequent antimyeloma therapies [a]	65 (33.3%)	22 (11.2%)	87 (22.2%)
Total number of subjects with 1 or more subsequent autologous stem cell transplants [a]	4 (2.1%)	0	4 (1.0%)
Therapeutic class/pharmacologic class/drug [b]			
Antineoplastic agents	54 (83.1%)	21 (95.5%)	75 (86.2%)
Other antineoplastic agents	52 (80.0%)	20 (90.9%)	72 (82.8%)
Daratumumab	34 (52.3%)	1 (4.5%)	35 (40.2%)
Bortezomib	19 (29.2%)	9 (40.9%)	28 (32.2%)
Carfilzomib	13 (20.0%)	9 (40.9%)	22 (25.3%)
Monoclonal antibodies	5 (7.7%)	2 (9.1%)	7 (8.0%)
Isatuximab	5 (7.7%)	1 (4.5%)	6 (6.9%)
Ixazomib	2 (3.1%)	2 (9.1%)	4 (4.6%)
Cisplatin	2 (3.1%)	1 (4.5%)	3 (3.4%)
Other antineoplastic agents	1 (1.5%)	1 (4.5%)	2 (2.3%)
Belantamab mafodotin	0	1 (4.5%)	1 (1.1%)
Car t-cells nos	1 (1.5%)	0	1 (1.1%)
Cc 92480	1 (1.5%)	0	1 (1.1%)
Elotuzumab	1 (1.5%)	0	1 (1.1%)
Isatuximab irfc	0	1 (4.5%)	1 (1.1%)
Ixazomib citrate	1 (1.5%)	0	1 (1.1%)
Panobinostat	1 (1.5%)	0	1 (1.1%)
Venetoclax	1 (1.5%)	0	1 (1.1%)
Alkylating agents	16 (24.6%)	5 (22.7%)	21 (24.1%)
Cyclophosphamide	14 (21.5%)	3 (13.6%)	17 (19.5%)
Melphalan	5 (7.7%)	1 (4.5%)	6 (6.9%)
Bendamustine	0	1 (4.5%)	1 (1.1%)
Cyclophosphamide monohydrate	0	1 (4.5%)	1 (1.1%)
Lomustine	1 (1.5%)	0	1 (1.1%)
Plant alkaloids and other natural products	3 (4.6%)	2 (9.1%)	5 (5.7%)
Etoposide	2 (3.1%)	1 (4.5%)	3 (3.4%)
Vincristine	1 (1.5%)	1 (4.5%)	2 (2.3%)
Cytotoxic antibiotics and related substances	2 (3.1%)	2 (9.1%)	4 (4.6%)
Doxorubicin	2 (3.1%)	1 (4.5%)	3 (3.4%)
Doxorubicin hydrochloride	0	1 (4.5%)	1 (1.1%)
Antimetabolites	1 (1.5%)	0	1 (1.1%)
Fludarabine	1 (1.5%)	0	1 (1.1%)
Corticosteroids for systemic use	54 (83.1%)	17 (77.3%)	71 (81.6%)
Corticosteroids for systemic use, plain	54 (83.1%)	17 (77.3%)	71 (81.6%)
Dexamethasone	51 (78.5%)	17 (77.3%)	68 (78.2%)
Prednisone	6 (9.2%)	1 (4.5%)	7 (8.0%)
Methylprednisolone sodium succinate	1 (1.5%)	0	1 (1.1%)

Immunosuppressants	38 (58.5%)	11 (50.0%)	49 (56.3%)
Immunosuppressants	38 (58.5%)	11 (50.0%)	49 (56.3%)
Pomalidomide	21 (32.3%)	7 (31.8%)	28 (32.2%)
Lenalidomide	17 (26.2%)	4 (18.2%)	21 (24.1%)
Thalidomide	3 (4.6%)	1 (4.5%)	4 (4.6%)
Iberdomide	1 (1.5%)	0	1 (1.1%)
Investigational drug	4 (6.2%)	0	4 (4.6%)
Uncoded	4 (6.2%)	0	4 (4.6%)
Investigational drug	4 (6.2%)	0	4 (4.6%)
All other therapeutic products	1 (1.5%)	0	1 (1.1%)
All other therapeutic products	1 (1.5%)	0	1 (1.1%)
All other therapeutic products	1 (1.5%)	0	1 (1.1%)
Blood substitutes and perfusion solutions	1 (1.5%)	0	1 (1.1%)
Blood and related products	1 (1.5%)	0	1 (1.1%)
Other blood products	1 (1.5%)	0	1 (1.1%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone.
[a] - Percentages calculated with the number of subjects in each treatment group as denominator.
[b] - Percentages are calculated with the number of subjects who received subsequent antimyeloma therapies in each group as denominators.

Numbers analysed

Table 11. Summary of subjects per analysis aet; (Study 54767414MMY3019)

	VRd	D-VRd	Total
Study population			
Subjects screened			499
Intent-to-treat (ITT)	198	197	395
Safety	195	197	392
Pharmacokinetic evaluable [a]		197	197
Daratumumab immunogenicity [b]		170	170
rHuPH20 immunogenicity [c]		169	169

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone.
a Includes subjects assigned to D-VRd group who received at least 1 administration of daratumumab and have at least 1 pharmacokinetic sample concentration value after the first injection.
b Includes subjects assigned to D-VRd group who received at least 1 dose of daratumumab and have appropriate serum samples for detection of antibodies to daratumumab (i.e., subjects with at least 1 sample obtained after their first dose daratumumab).
c Includes subjects assigned to D-VRd group who received at least 1 dose of daratumumab and have at least 1 serum sample for detection of antibodies to anti-rHuPH20 either pre- or post- treatment.

Outcomes and estimation

Primary efficacy endpoint: Overall MRD negativity rate

Table 12. Summary of MRD negativity Rate at 10^{-5} in Bone Marrow; Intent-to-treat Analysis Set; Primary MRD Analysis-data cut off: 08 April 2021 (Study 54767414MMY3019)

	VRd	D-VRd
Analysis set: intent-to-treat	198	197
MRD negativity rate (10^{-5})	70 (35.4%)	105 (53.3%)
95% CI[a] of MRD negativity rate	(28.7%, 42.4%)	(46.1%, 60.4%)
Odds ratio with 95% CI[b]		2.07 (1.38, 3.10)
P-value[c]		0.0004

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; CI = confidence interval; CR = complete response.
a Exact 95% confidence interval.
b Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: ISS staging (I,
II, III), age/transplant eligibility (<70 years ineligible, or age<70 years and refusal to transplant, or age ≥70 years) as
randomized. An odds ratio > 1 indicates an advantage for D-VRd.
c P-value from Fisher's exact test.

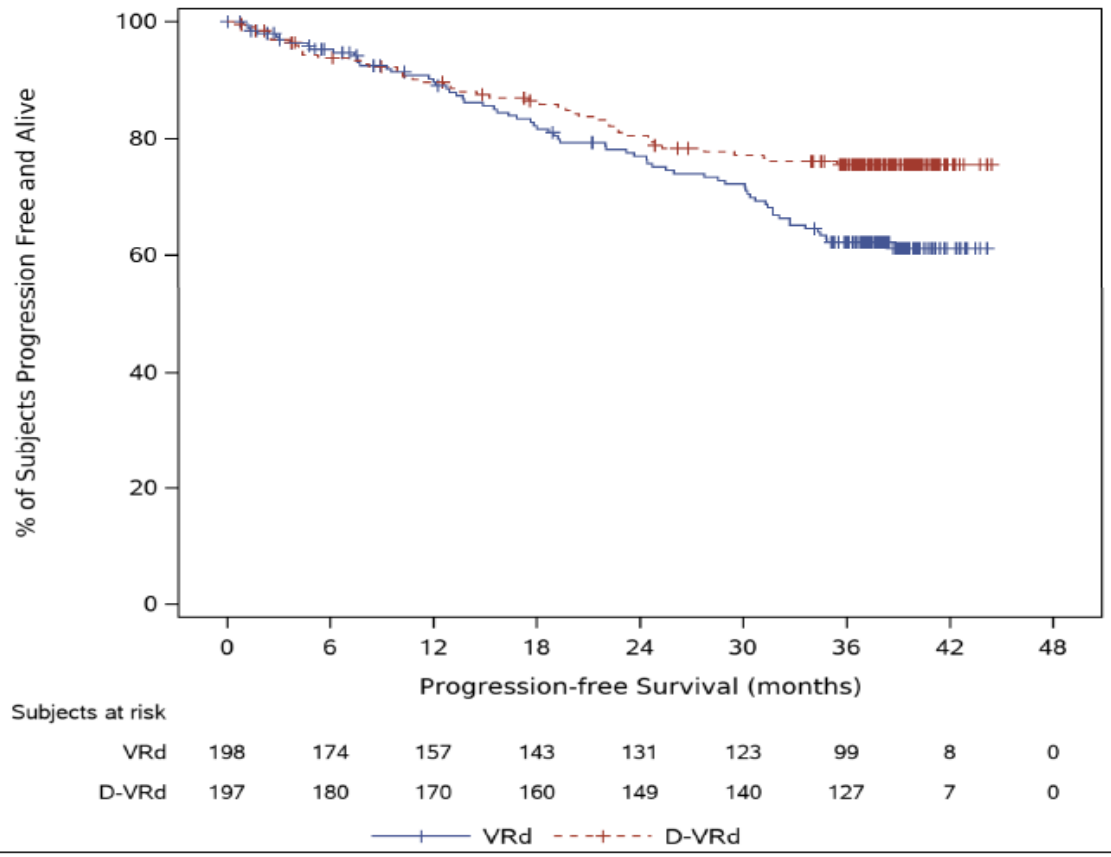
Key secondary endpoint: PFS

Table 13. Summary of progression-free survival based on computerised algorithm; Intent-to treat Analysis Set; Interim PFS Analysis-data cut off: 08 September 2022 (Study 54767414MMY3019)

	VRd	D-VRd
Analysis set: intent-to-treat	198	197
Progression-free survival (PFS)		
Number of events (%)	67 (33.8%)	46 (23.4%)
Number of censored (%)	131 (66.2%)	151 (76.6%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	25.53 (18.69, 31.41)	NE (22.74, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		0.0104
Hazard ratio (95% CI)[b]		0.61 (0.42, 0.90)
12-month PFS rate % (95% CI)	89.6 (84.2, 93.3)	89.6 (84.3, 93.2)
18-month PFS rate % (95% CI)	82.2 (75.7, 87.0)	86.4 (80.7, 90.5)
24-month PFS rate % (95% CI)	76.9 (70.0, 82.5)	80.5 (74.1, 85.4)
30-month PFS rate % (95% CI)	72.2 (65.0, 78.2)	77.2 (70.5, 82.6)
36-month PFS rate % (95% CI)	62.2 (54.6, 69.0)	75.5 (68.7, 81.1)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; CI = confidence interval; COVID-19 = Coronavirus Disease 2019.
a p-value is based on the log-rank test stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible,
or age<70 years and refusal to transplant, or age ≥70 years) as randomized.
b 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), and age/transplant eligibility (<70 years ineligible, or age<70 years and refusal to transplant, or age ≥70 years) as randomized. A hazard ratio <1 indicates an advantage for D-VRd.
Note: Subjects who had disease progression or death immediately preceded by 2 or more consecutive missed disease
assessments would be censored at the last adequate disease assessment before the consecutive missed disease assessments.
Note: Subjects who died due to COVID-19 without progression are considered as having PFS events.

Figure 9. Kaplan-Meir plot for progression-free survival based on computerised algorithm; Intent-to treat Analysis Set; Interim PFS Analysis-data cut off: 08 September 2022 (Study 54767414MMY3019)



Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone.

Key secondary endpoint: Overall CR or better rate

Table 14. Summary of overall best confirmed response based on computerised algorithm; Intent-to-treat Analysis Set- data cut off: 08 April 2021 (Study 54767414MMY3019)

TEFRESP01_PA: Summary of Overall Best Confirmed Response Based on Computerized Algorithm; Intent-to-treat Analysis Set (Study 54767414MMY3019)

	VRd		D-VRd			
	n (%)	95% CI for %	n (%)	95% CI for %	Odds Ratio (95% CI)[a]	P-value[b]
Analysis set: intent-to-treat	198		197			
Response category						
Stringent complete response (sCR)	71 (35.9%)	(29.2%, 43.0%)	102 (51.8%)	(44.6%, 58.9%)	1.94 (1.29, 2.92)	0.0015
Complete response (CR)	46 (23.2%)	(17.5%, 29.7%)	49 (24.9%)	(19.0%, 31.5%)		
Very good partial response (VGPR)	52 (26.3%)	(20.3%, 33.0%)	30 (15.2%)	(10.5%, 21.0%)		
Partial response (PR)	12 (6.1%)	(3.2%, 10.3%)	11 (5.6%)	(2.8%, 9.8%)		
Stable disease (SD)	10 (5.1%)	(2.4%, 9.1%)	4 (2.0%)	(0.6%, 5.1%)		
Progressive disease (PD)	0	(NE, NE)	0	(NE, NE)		
Not evaluable (NE)	7 (3.5%)	(1.4%, 7.1%)	1 (0.5%)	(0.0%, 2.8%)		
Overall response (sCR+CR+VGPR+PR)	181 (91.4%)	(86.6%, 94.9%)	192 (97.5%)	(94.2%, 99.2%)	3.52 (1.28, 9.67)	0.0090
VGPR or better (sCR + CR + VGPR)	169 (85.4%)	(79.6%, 90.0%)	181 (91.9%)	(87.1%, 95.3%)	1.92 (1.01, 3.66)	0.0430
CR or better (sCR + CR)	117 (59.1%)	(51.9%, 66.0%)	151 (76.6%)	(70.1%, 82.4%)	2.31 (1.48, 3.60)	0.0002

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-*dexamethasone; CI = confidence interval.*

a Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: ISS staging (I, II, III), age/transplant eligibility (<70 years ineligible, or age<70 years and refusal to transplant, or age ≥70 years) as randomized. An odds ratio > 1 indicates an advantage for D-VRd.
b P-value from the Cochran Mantel-Haenszel Chi-Squared test.
Note: Response was assessed by computerized algorithm, based on International Uniform Response Criteria Consensus Recommendations.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Key secondary endpoint: Sustained MRD negativity

Table 15. Summary of Durable MRD-negative Rate at 10^{-5} in Bone Marrow; Intent-to-treat Analysis Set- data cut off: 08 September 2022 (Study 54767414MMY3019)

	VRd	D-VRd
Analysis set: intent-to-treat	198	197
Durable MRD-negativity rate (10^{-5}) [a]	50 (25.3%)	84 (42.6%)
Exact 95% CI[b] of MRD negativity rate	(19.4%, 31.9%)	(35.6%, 49.9%)
Odds ratio with 95% CI[c]		2.18 (1.42, 3.34)
P-value[d]		0.0003

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; CI = confidence interval.
a Durable MRD-negative is defined as MRD negative and confirmed by at least 1 year apart without MRD positive in between.
b Exact 95% confidence interval.
c Chi-square estimate of the common odds ratio is used. An odds ratio > 1 indicates an advantage for D-VRd.
d P-value from Fisher's exact test.
Note: Subjects who had negative or positive MRD assessment are considered as having MRD assessment.
Note: Durable MRD negativity rate is defined as the proportion of subjects who achieve CR or better response and have achieved MRD negative status (at 10 -5) at 2 bone marrow aspirate examinations that are a minimum of 1 year apart (and the 2 examinations should be prior to progressive disease (PD), subsequent anti-myeloma therapy, or both), without any examination showing MRD positive status in between.

Secondary endpoint: Overall survival

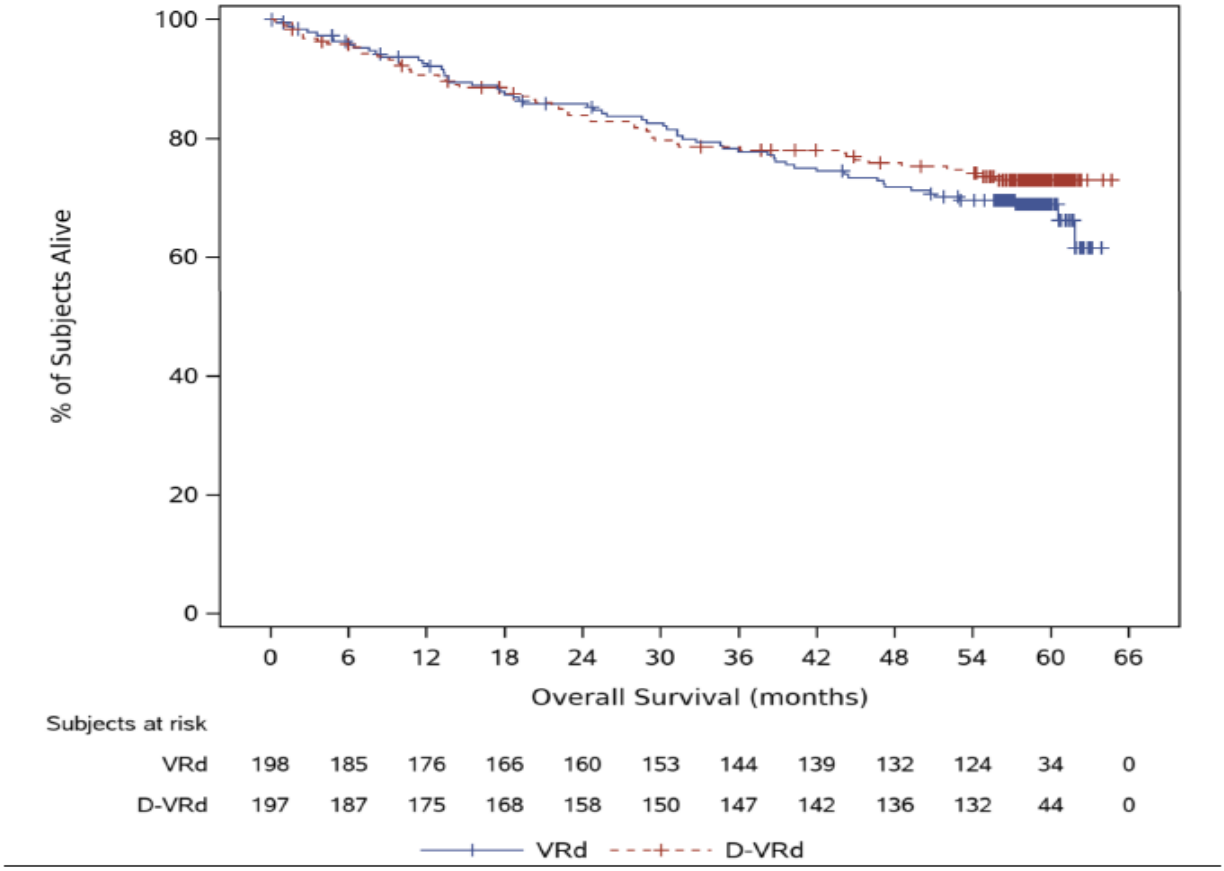
Table 16. Summary of Overall Survival; Intent-to-treat Analysis Set- data cut-off: 07 May 2024 (Study 54767414MMY3019)

	VRd	D-VRd
Analysis set: intent-to-treat	198	197
Overall survival (OS)		
Number of events (%)	60 (30.3%)	51 (25.9%)
Number of censored (%)	138 (69.7%)	146 (74.1%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	42.02 (31.31, 60.58)	52.04 (28.94, NE)
Median (95% CI)	NE (61.86, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		0.3950
Hazard ratio (95% CI)[b]		0.85 (0.58, 1.24)
12-month survival rate % (95% CI)	92.7 (88.0, 95.6)	90.8 (85.7, 94.1)
18-month survival rate % (95% CI)	88.0 (82.4, 91.8)	88.7 (83.3, 92.4)
24-month survival rate % (95% CI)	85.8 (80.0, 90.1)	83.9 (77.9, 88.4)
30-month survival rate % (95% CI)	82.6 (76.4, 87.3)	79.7 (73.2, 84.7)
36-month survival rate % (95% CI)	77.7 (71.1, 83.0)	78.6 (72.1, 83.8)
48-month survival rate % (95% CI)	71.8 (64.8, 77.7)	75.9 (69.1, 81.3)
54-month survival rate % (95% CI)	69.6 (62.5, 75.7)	74.2 (67.3, 79.8)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; CI = confidence interval.
a - p-value is based on the log-rank test stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years

ineligible, or age<70 years and refusal to transplant, or age ≥70 years) as randomized.
b - 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), and age/transplant eligibility (<70 years ineligible, or age<70 years and refusal to transplant, or age ≥70 years) as randomized. A hazard ratio <1 indicates an advantage for D-VRd.

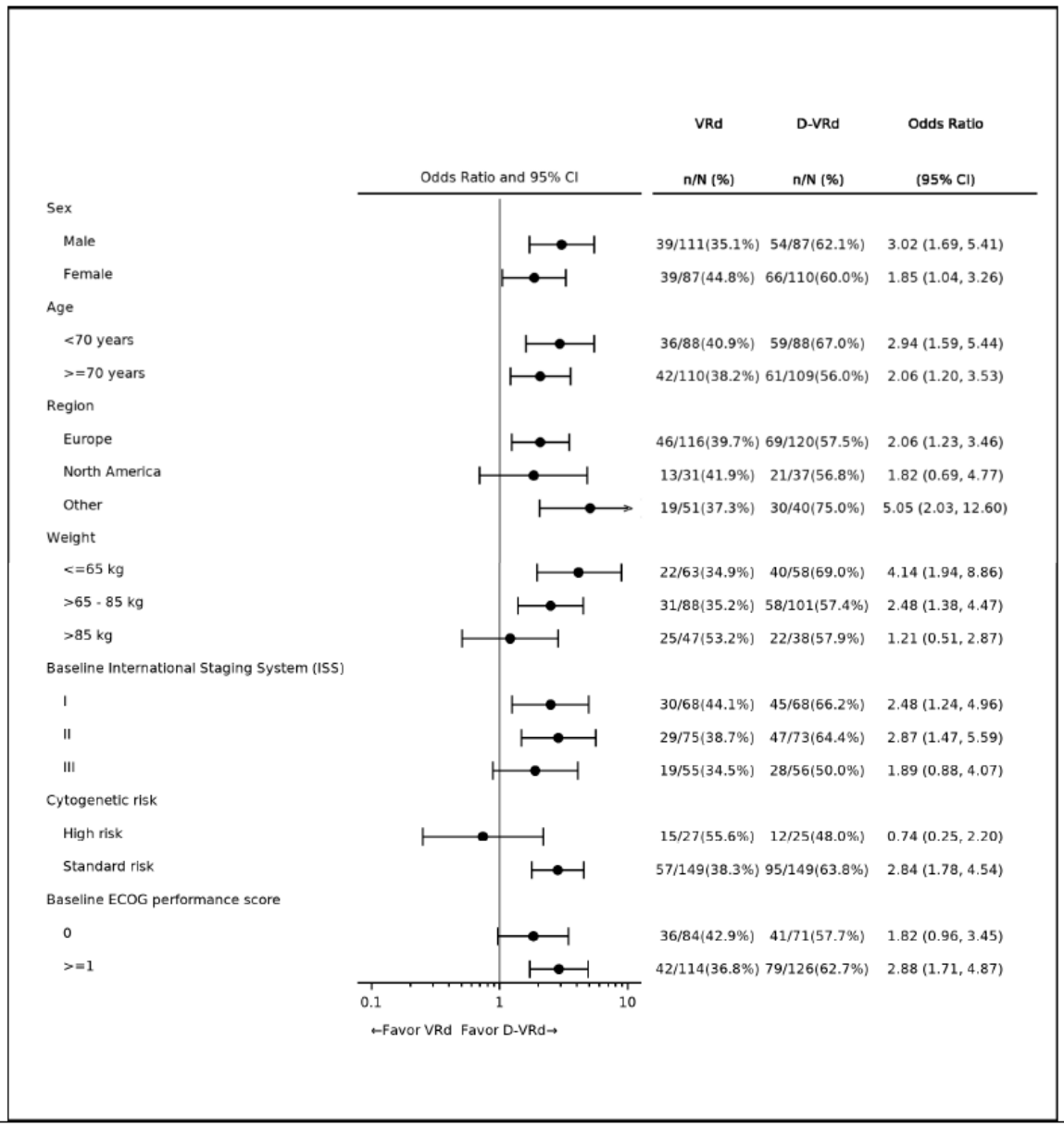
Figure 10. Kaplan-Meier Plot for Overall Survival; Intent-to-treat Analysis Set; Final PFS Analysis-data cut-off: 07 May 2024 (Study 54767414MMY3019)



Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone.

Ancillary analyses

Figure 11. Forest Plot of subgroup analyses on MRD Negativity Rate at 10-5 in Bone Marrow; Intent-to-treat Analysis Set; Final PFS Analysis- data cut-off: 07 May 2024 (Study 54767414MMY3019)



Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomidedexamethasone;
CI = confidence interval; N = number of subjects; n = number of subjects with negative MRD at 10 -5 ; CR = complete response; sCR = stringent complete response; ECOG = Eastern Cooperative Oncology Group; FISH = fluorescence in situ hybridization.
Note: High risk is defined by FISH testing: t (4; 14), t (14; 16), and 17p deletion.
Note: Mantel-Haenszel estimate of the common odds ratio for un-stratified tables is used. An odds ratio > 1 indicates an advantage for D-VRd.

Figure 12. Forest plot of sensitivity and supplementary analyses for Progression-free Survival based on computerised algorithm; Final PFS Analysis- data cut-off: 07 May 2024 (Study 54767414MMY3019)

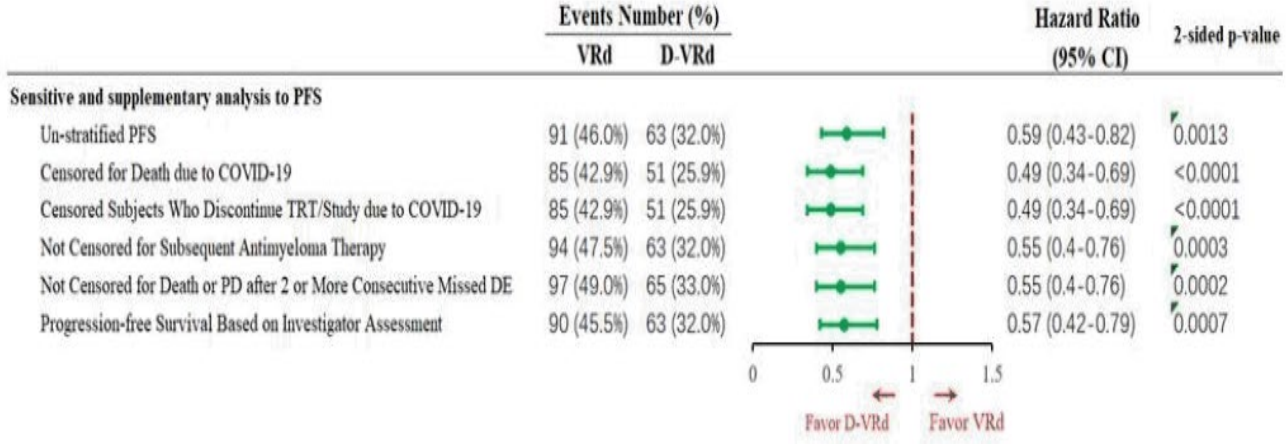
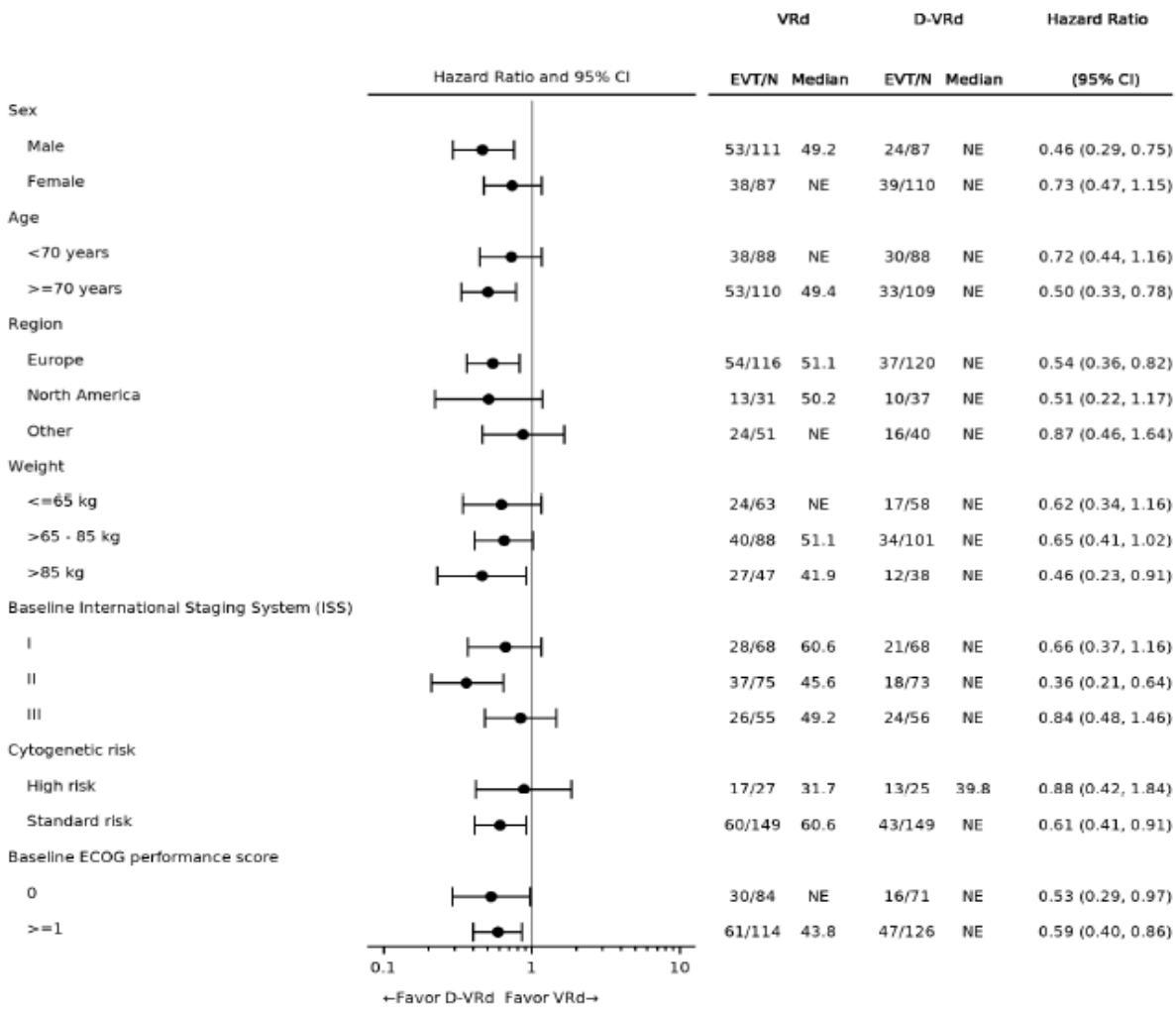


Figure 13. Forest Plot of subgroup analyses on progression-free survival based on computerised algorithm; Intent-to-treat Analysis Set; Final PFS Analysis data cut-off: 07 May 2024 (Study 54767414MMY3019)



Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; CI = confidence interval.
Note: Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. A hazard ratio <1 indicates an advantage for D-VRd.
Note: High risk is defined by FISH testing: t (4; 14), t (14; 16), and 17p deletion.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 17. Summary of Efficacy for trial MMY3019 (Cepheus)

Title: A Phase 3 Study Comparing Daratumumab, VELCADE (bortezomib), Lenalidomide, and Dexamethasone (D-VRd) with VELCADE, Lenalidomide, and Dexamethasone (VRd) in Subjects with Untreated Multiple Myeloma and for Whom Hematopoietic Stem Cell Transplant is Not Planned as Initial Therapy			
Study identifier	Study Number: 54767414MMY3019 (Cepheus) EudraCT Number: 2018-001545-13 EU TRIAL NUMBER: 2023-507312-13 NCT Number: NCT03652064		
Design	A randomized (1:1), open-label, multicenter, Phase 3 study comparing D-VRd vs. VRd in patients with NDMM who are ineligible for treatment with ASCT		
	Study initiation Screening phase Treatment phase		15 November 2018 (first participant screened) Starts up to 28 days before randomization Extends from C1D1 to discontinuation of all study treatment
	Follow-up Phase		Starts when a participant experiences documented disease progression or unacceptable toxicity leading to all study treatment discontinuation
Hypothesis	Superiority of D-VRd over VRd		
Treatments groups	VRd		**Bortezomib** s.c. 1.3 mg/m2 (Days 1, 4, 8, and 11) for Cycles 1-8. Fixed duration of 8 cycles. **Lenalidomide** 25 mg PO - D1 to D14 in cycles 1-8. Cycle 9 and beyond 25mg PO D1-D21 until PD or unacceptable toxicity. **Dexamethasone** 20mg PO Days 1, 2, 4, 5, 8, 9, 11, 12 in Cycles 1-8. In Cycles 9 and beyond, 40 mg PO on Days 1, 8, 15, 22, until PD or unacceptable toxicity Cycles 1-8: 21D in length Cycles 9 and beyond: 28D in length
	D-VRd		**VRd** as above **Daratumumab** SC 1800 mg weekly in Cycles 1-2, every 3 weeks in Cycles 3-8, and every 4 weeks in Cycle 9 and beyond until PD or unacceptable toxicity
Endpoints and definitions	Primary endpoint	Overall MRD negativity rate	The proportion of ITT subjects who have achieved MRD negative status (at 10^{-5}) by bone marrow aspirate after randomization and prior to progressive disease (PD) or subsequent anti-myeloma therapy.
	Key Secondary endpoint	PFS by computerised algorithm	Time from the date of randomization to the date of PD (assessed by 2011 IMWG criteria) or death

	Key Secondary endpoint	Overall CR or better rate	The percentage of ITT participants who achieved CR or sCR status anytime during the study per the 2011 IMWG criteria
	Key Secondary endpoint	Sustained MRD negativity rate	The proportion of ITT participants who achieved CR or better response and maintained MRD-negative status for at least 12 months, without any MRD-positive results in between.
	Secondary endpoint	Overall survival	Measured from the date of randomization to the date of the participant's death
Database lock	05 June 2024		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, n = 395 Median follow-up of 22.3 months at primary MRD analysis (08 APR 2021) Median follow-up of 39.9 months at interim PFS analysis (08 SEP 2022) Median follow-up of 58.7 months at final PFS analysis (07 MAY 2024)		
Descriptive statistics and estimate variability	Treatment group	D-VRd	VRd
	Number of subjects	N = 197	N = 197
	Overall MRD negativity rate, n (%)	**105** (53.3%)	**70** (35.4%)
	% (95% CI)	(46.1%, 60.4%)	(28.7%, 42.4%)
	PFS event by computerised algorithm, n	**46**	**67**
	%	23.4%	33.8%
	Overall CR or better rate, n (%) % (95% CI)	**151** (76.6%) (70.1%, 82.4%)	**117** (59.1%) (51.9%, 66.0%)
	Sustained MRD negativity rate, n (%)	**84** (42.6%)	**50** (25.3%)
	% (95% CI)	(35.6%, 49.9%)	(19.4%, 31.9%)
	Overall survival events, n	51	60
	%	(25.9%)	(30.3)

Effect estimate per comparison	Primary endpoint - Overall MRD negativity rate	Comparison groups	D-VRd vs VRd
		Odds ratio[a]	**2.07**
		95% CI	(1.38, 3.10)
		P-value[b]	0.0004
	Secondary endpoint - PFS by computerised algorithm	Comparison groups	D-VRd vs VRd
		HR[c]	**0.61**
		95% CI	(0.42, 0.90)
		P-value[d]	0.0104
	Secondary endpoint – Overall CR or better	Comparison groups	D-VRd vs VRd
		Odds ratio[a]	**2.31**
		95% CI	(1.48, 3.60)
		P-value[e]	0.0002
	Secondary endpoint – Sustained MRD negativity rate	Comparison groups	D-VRd vs VRd
		Odds ratio[f]	**2.18**
		95% CI	(1.42, 3.34)
		P-value[b]	0.0003
	Secondary endpoint – Overall survival[g]	Comparison groups	D-VRd vs VRd
		HR[c]	0.85
		95% CI	(0.58, 1.24)
		P-value[d] (nominal)	0.395

Notes	All results mentioned are from CCO at primary MRD analysis (08 APR 2021) except PFS results and sustained MRD rate results which are from CCO at interim PFS analysis (08 SEP 2022), and OS results which are from CCO at final PFS analysis (07 MAY 2024). a - Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: ISS staging (I, II, III), age/transplant eligibility (<70 years ineligible, or age<70 years and refusal to transplant, or age ≥70 years) as randomized. b - P-value from Fisher's exact test. c - 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), and age/transplant eligibility (<70 years ineligible, or age<70 years and refusal to transplant, or age ≥70 years) as randomized. d - p-value is based on the log-rank test stratified with ISS staging (I, II, III), and age/transplant eligibility (<70 years ineligible, or age<70 years and refusal to transplant, or age ≥70 years) as randomized. e - P-value from the Cochran Mantel-Haenszel Chi-Squared test. f - Chi-square estimate of the common odds ratio is used. g – All OS analyses are descriptive

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

CEPHEUS is a randomised (1:1), open-label, multicentre, Phase 3 study that evaluated the efficacy and safety of daratumumab SC in combination with D-VRd vs VRd in participants with NDMM for whom ASCT was not planned as initial therapy. At randomization, participants were stratified by ISS stage (I, II, or III) and age/transplant eligibility (<70 years ineligible, or <70 years and refusal to transplant [meaning transplant was not planned as initial therapy], or ≥70 years).

The stratification factors have prognostic implications in this setting and are deemed appropriate.

Study participants

Inclusion and exclusion criteria are overall acceptable. The trial allowed for inclusion of patients who refused ASCT as initial therapy but in fact were eligible for such treatment. It can be assumed that patients who are eligible for treatment with ASCT but refuse that treatment option are more fit and less comorbid than patients who are "truly" ineligible and this could potentially affect efficacy and safety outcomes of the trial. This potentially hampers the generalisability of study results to a truly ineligible population.

The diagnostic criteria for multiple myeloma are acceptable and widely recognized (Monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma and presence of at least one CRAB or SLiM CRAB criteria). However, it should be noted that a screening period of 28 days before randomisation to treatment excluded patients with NDMM who needed acute or sub-acute anti-myeloma treatment with more than just 40mg x 4 of dexamethasone to alleviate severe kidney disease, severe hypercalcemia or significant bone disease. Early death in multiple myeloma is, among other factors, correlated with hypercalcemia, fractures and impaired renal function (Augustson, JCO, 2005). The exclusion of NDMM patients with an acute or sub-acute presentation at diagnosis can be considered justifiable as management of acutely ill NDMM patients in the strict framework of a clinical trial can be complicated. However, the exclusion of NDMM patients with a more acute presentation should be kept in mind when extrapolating trial results to non-trial settings. Patients with active systemic infection were also excluded from the trial. Infection is common in NDMM patients and is one of the leading causes of early death in NDMM. It is acceptable to exclude such patients in a trial where the main goal is to

investigate long-term efficacy of an anti-myeloma agent. Importantly, the included patients were randomised and patients with bad prognostic markers such as ISS stage III and high-risk cytogenetics were also included.

Treatments

Treatment regimens were standard and acceptable.

Objectives/endpoints

The primary endpoint was overall MRD negativity rate defined as the proportion of ITT subjects who have achieved MRD negative status (at 10^{-5}) by bone marrow aspirate after randomization and prior to progressive disease (PD) or subsequent anti-myeloma therapy. The key secondary endpoints were PFS by computerised algorithm (assessed by 2011 IMWG criteria), overall CR or better rate and sustained MRD negativity rate. Overall survival analyses were not type 1 error controlled.

The Scientific Advice given in November 2017 recommended that PFS was a preferable endpoint to MRD negativity rate. Despite the SA, the primary endpoint for study MMY3019 was changed from PFS to overall MRD negativity rate and PFS was downgraded to a key secondary endpoint before enrolment began.

Statistical methods

This was an open-label trial in which the endpoints, including PFS, were assessed by investigators rather than through an IBCR. EMA guidelines recommend the use of IBCR in open-label trials to ensure objective and consistent evaluation of endpoints like PFS. The absence of IBCR in this study represents a potential limitation, as investigator-based assessments are inherently prone to bias due to knowledge of treatment assignments. While an IDMC was established to review safety and efficacy during the trial, its role does not include assessing individual endpoints such as PFS.

The primary endpoint of MRD negativity was analysed using a 10^{-5} threshold on the ITT analysis set, with 95% CI calculated. MRD negativity after progression or subsequent therapy was excluded. Odds ratios and p-values were estimated using the stratified Cochran Mantel Haenszel method, stratified by ISS stage and age/transplant eligibility.

Censoring rules for PFS primarily involved administrative censoring at the study cut-off, which accounted for the majority of censored cases in both arms (73.8% in VRd vs. 89.6% in D-VRd). Non-administrative censoring, such as withdrawal of consent, initiation of subsequent anti-myeloma therapy, or missed assessments, occurred less frequently in the D-VRd arm (8 participants withdrew, 3 missed two assessments or experienced death, and 1 was lost to follow-up in the D-VRd arm compared to 9, 11, 6, and 1, respectively, in the VRd arm), indicating a lower likelihood of bias arising from these factors in the treatment group. Given the minimal impact of non-administrative censoring in the D-VRd arm and the lower frequency of such cases compared to the VRd arm, conducting additional sensitivity analyses may not be necessary to confirm the robustness of the PFS results. PFS was analysed using the ITT analysis set. Kaplan-Meier curves were plotted, and hazard ratios with 95% CIs were estimated using a stratified Cox proportional hazards model, with treatment as the sole explanatory variable. Treatment differences were tested using a stratified log-rank test, and landmark PFS rates with 95% CIs were estimated by the Kaplan-Meier method.

No interim analysis was conducted for the primary endpoint (MRD negativity), so no alpha adjustment was required. For PFS, a single interim analysis was planned after 60% of events, using O'Brien-Fleming boundaries with the Lan-DeMets alpha-spending method to control type I error. The amendment in Protocol 2 clarified the hierarchical testing approach for key secondary endpoints to ensure control of the family-wise Type I error rate. This update was made well before the primary MRD analysis and interim PFS analysis. While the timing of these amendments raises theoretical concerns about procedural bias, this is mitigated by the fact that the primary endpoint and all key secondary endpoints were statistically significant, indicating robust results.

Study conduct

Protocol amendments have been appropriately justified and are not believed to have affected trial integrity. Enrolment began before the COVID-19 pandemic, but much of the study was conducted through the main waves of the COVID-19 pandemic and this is likely to have affected trial conduct but it is not believed to invalidate trial results. In particular, many deaths due to COVID-19 in Brazil was observed.

Major protocol deviations were few and mostly balanced between study arms. Receiving a disallowed concomitant treatment happened more frequently in the VRd arm than the D-VRd arm (8 vs 3, respectively). The majority of these events in both arms were due to administration of subsequent anticancer treatment before progressive disease being confirmed.

Protocol deviations are believed not to have had major impact on trial conduct or study results.

Baseline characteristics

The demographic and clinical characteristics of the patients at baseline were generally balanced in the two groups and reflect a rather fit patient population with NDMM that could go up to 28 days without initiation of anti-myeloma treatment other than 4 x 40mg of dexamethasone and thus selecting a population with less aggressive debut of multiple myeloma without immediate need of treatment.

The median age was 70.0 (range: 31 to 80) years. Half of the participants were female (49.9%). The proportion of participants with an ECOG performance score of 0, 1 and 2 was 39.2%, 51.4%, and 9.4%, respectively. More participants in the VRd arm had an ECOG performance score of 0 (D-VRd: 36.0%; VRd: 42.4%), while more participants in the D-VRd arm had an ECOG performance score of 2 (D-VRd: 11.7%; VRd: 7.1%). Based on total frailty scores at baseline, 64.8% of participants were fit (score of 0), 35.2% had intermediate fitness (score of 1), and per protocol no participant was frail (score of 2).

Of the 350 participants who had evaluable baseline cytogenetic data reported, 52 (14.9%) participants had a high-risk cytogenetic abnormality (presence of del[17p] [7.4%], t[4;14] [7.1%] or t[4;16] [1.7%]). Cytogenetic risk factors were overall balanced between study arms.

The median time from initial diagnosis of MM to randomization was 1.18 months across both arms.

Stratification factors of ISS stage and age or transplant eligibility were balanced between study arms. A total of 106 (26.8%) patients were considered eligible for ASCT but refused this treatment option. The remaining 289 (73.2%) patients were in fact ineligible for ASCT due to age or comorbidities. They reflect the target population that is the basis for this application for extension of indication. The efficacy and safety of daratumumab in combination with VRd has already been assessed and is considered established in the transplant eligible population on basis of study MMY3014 (PERSEUS); EMEA/H/C/004077/II/0072.

Efficacy data and additional analyses

At the primary MRD analysis (08 April 2021), with a median follow-up of 22.3 months, the addition of daratumumab SC to VRd resulted in a statistically significant improvement in the primary endpoint overall MRD negativity rate as measured by NGS for participants achieving CR or better compared with VRd alone, with an absolute increase of 17.9% favoring D-VRd (D-VRd: 105 (53.3%); VRd: 70 (35.4%); OR=2.07 with 95% CI: 1.38, 3.10; 2-sided p=0.0004). Treatment effect on overall MRD negativity rate (D-VRd over VRd) was generally consistent across the pre-specified subgroups with the exception of high risk cytogenetics.

As of the interim PFS analysis cutoff date (08 SEP 2022), with a median follow-up of 39.0 months, a total of 113 PFS events were observed (D-VRd: 46 [23.4%]; VRd: 67 [33.8%]) corresponding to a maturity of 28.6% PFS events (113/395). The addition of daratumumab to VRd resulted in a statistically significant improvement in the key secondary endpoint of PFS with a HR of 0.61 (95% CI: 0.42, 0.90; 2-sided p=0.0104) crossing the prespecified 2-sided stopping boundary of 0.0145 in favor of the D-VRd arm). The median PFS was not reached in either treatment arm. Prespecified sensitivity and

supplementary analyses were consistent with the final PFS result per the computerized algorithm supporting results of the interim PFS analysis.

This improvement in a time-to-event endpoint is an important finding that supports the primary response-based endpoint (overall MRD negativity rate) and reinforces efficacy claims of adding daratumumab to VRd in NDMM patients who are ineligible for treatment with ASCT. Whether MRD negativity can be considered a validated trial level surrogate marker for PFS in NDMM is yet to be robustly confirmed (Landgren, Blood, 2024; Paiva, Blood Adv, 2023; Ficek, Clin lymp myel leuk, 2023). However, in study MMY3019 the positive results from the primary endpoint of MRD negativity rate are supported by PFS results.

At the primary MRD analysis cutoff (08 April 2021), the addition of daratumumab to VRd resulted in a statistically significant improvement in the key secondary endpoint of overall CR or better rate compared with VRd alone, with an absolute increase of 17.5% favoring D-VRd (D-VRd: 76.6%; VRd: 59.1%; OR=2.31 with 95% CI: 1.48, 3.60, 2-sided p=0.0002), crossing the prespecified stopping boundary of p=0.0244 in favor of the D-VRd arm.

As of the interim PFS analysis cutoff (08 SEP 2022), the key secondary endpoint of sustained MRD negativity rate was 42.6% (n=84) in the D-VRd arm vs 25.3% (n=50) in the VRd arm. The common odds ratio from Chi-square estimate was 2.18 (95% CI: 1.42, 3.34) and the 2-sided p-value was 0.0003, crossing the prespecified boundary of 2-sided p=0.0244 in favor of the D-VRd arm.

At the final PFS analysis CCO (07 MAY 2024) with a median follow-up of 58.7 months, OS data were still not mature, with a total of 111 deaths [D-VRd: 51/197 (25.9%); VRd: 60/198 (30.3%)]. The median OS was not reached for either treatment arm. The hazard ratio for death (D-VRd vs. VRd) was 0.85 (95% CI: 0.58, 1.24). All OS analyses in study MMY3019 are descriptive. There seems to be no obvious OS detriment by adding daratumumab to VRd in NDMM patients who are ineligible for treatment with ASCT.

2.4.4. Conclusions on the clinical efficacy

Results from the study MMY3019 showed a statistically significant improvement in the event-based endpoint PFS from the addition of daratumumab to VRd in patients with NDMM who are ineligible for treatment with ASCT. This improvement is considered clinically significant and is consistent with the effect seen on the primary endpoint of the trial, overall MRD negativity rate, and the improvements in overall CR or better rate and sustained MRD negativity rate.

OS data are immature but do not show any sign of detriment in the experimental arm.

2.5. Clinical safety

Patient exposure

The Safety Analysis Set includes all patients that received at least one dose of any study treatment in study 54767414MMY3019 corresponding to a total of 392 participants (D-VRd: 197; VRd: 195). It also includes patients that were eligible for ASCT but opted out (n=53 in each arm corresponding to 27%). A summary of the duration of treatment in that trial is presented in **Table 18**.

Table 18. Summary of Duration of Treatment, by Treatment Phase; Safety Analysis Set (Study 54767414MMY3019)

	VRd	D-VRd
Analysis set: safety	195	197
Duration of study treatment (months)		
N	195	197
Mean (SD)	35.11 (22.063)	42.83 (21.341)
Median	34.33	56.28
Range	(0.5; 63.8)	(0.1; 64.6)
Bortezomib dose intensity (mg/m^2/cycle) [a]		
N	195	197
Mean (SD)	4.22 (0.863)	4.28 (0.864)
Median	4.41	4.51
Range	(1.7; 5.3)	(1.3; 5.4)
Lenalidomide dose intensity (mg/cycle) [b]		
N	195	197
Mean (SD)	291.27 (117.375)	291.68 (124.463)
Median	291.50	270.00
Range	(60.0; 504.1)	(45.0; 504.7)
Lenalidomide dose intensity (Cycle 1-8, mg/cycle) [b]		
N	195	197
Mean (SD)	258.53 (90.879)	259.41 (91.097)
Median	291.25	297.50
Range	(60.0; 350.0)	(45.0; 371.9)
Lenalidomide dose intensity (Cycle 9+, mg/cycle) [b]		
N	167	169
Mean (SD)	319.86 (130.271)	319.77 (139.006)
Median	305.38	289.47
Range	(70.0; 525.0)	(30.0; 525.0)
Dexamethasone dose intensity (mg/cycle) [b]		
N	195	197
Mean (SD)	106.86 (38.549)	95.02 (44.841)
Median	101.59	87.62
Range	(17.5; 160.0)	(11.4; 160.0)
Dexamethasone dose intensity (Cycle 1-8, mg /cycle) [b]		
N	195	197
Mean (SD)	129.91 (36.514)	128.11 (39.017)
Median	150.00	150.00
Range	(40.0; 160.0)	(18.8; 177.5)
Dexamethasone dose intensity (Cycle 9+, mg /cycle) [b]		
N	158	173
Mean (SD)	88.62 (41.356)	82.95 (48.329)
Median	80.00	77.50
Range	(10.0; 160.0)	(10.0; 160.0)
Daratumumab dose intensity (mg/cycle) [c]		
N		197
Mean (SD)		2106.08 (532.170)
Median		1918.03
Range		(1800.0; 5400.0)

	VRd	D-VRd
Daratumumab dose intensity (Cycle 1-2, mg/cycle)		
N		197
Mean (SD)		4981.52 (780.805)
Median		5400.00
Range		(1800.0; 5700.0)
Daratumumab dose intensity (Cycle 3-8, mg/cycle)		
N		191
Mean (SD)		1803.40 (43.449)
Median		1800.00
Range		(1800.0; 2400.0)
Daratumumab dose intensity (Cycles 9+, mg/cycle)		
N		175
Mean (SD)		1800.13 (0.835)
Median		1800.00
Range		(1800.0; 1806.3)
Number of daratumumab injections		
N		197
Mean (SD)		49.1 (22.85)
Median		61.0
Range		(1; 75)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone.
[a] Dose intensity (mg/m^2/cycle) is calculated as the sum of total doses (mg/m^2) received in all cycles divided by the number of treatment cycles on bortezomib.
[b] Dose intensity (mg/cycle) is calculated as the sum of total doses (mg) received in all cycles divided by the number of treatment cycles on lenalidomide and dexamethasone, respectively.
[c] Dose intensity (mg /cycle) is calculated as the sum of total doses (mg) received in all cycles divided by the number of treatment cycles on daratumumab.

Adverse events

An overview of the treatment emergent adverse events (TEAEs) reported Study 54767414MMY3019 is summarised in **Table 19.**

Table 19. Overview of Treatment-emergent Adverse Events; Safety Analysis Set (Study 54767414MMY3019)

	VRd n (%)	D-VRd n (%)
Analysis set: safety	195	197
Any TEAE	195 (100.0%)	197 (100.0%)
At least one related[a]	190 (97.4%)	195 (99.0%)
Maximum toxicity grade		
Grade 1	1 (0.5%)	0
Grade 2	26 (13.3%)	15 (7.6%)
Grade 3	113 (57.9%)	88 (44.7%)
Grade 4	34 (17.4%)	61 (31.0%)
Grade 5	21 (10.8%)	33 (16.8%)
Any serious TEAE	131 (67.2%)	142 (72.1%)
At least one related[a]	82 (42.1%)	74 (37.6%)
TEAE leading to discontinuation of bortezomib	32 (16.4%)	25 (12.7%)
At least one related to bortezomib	24 (12.3%)	18 (9.1%)
TEAE leading to discontinuation of lenalidomide	48 (24.6%)	63 (32.0%)
At least one related to lenalidomide	24 (12.3%)	30 (15.2%)
TEAE leading to discontinuation of dexamethasone	69 (35.4%)	47 (23.9%)
At least one related to dexamethasone	32 (16.4%)	14 (7.1%)
TEAE leading to discontinuation of daratumumab		34 (17.3%)
At least one related to daratumumab		7 (3.6%)
TEAE leading to discontinuation of study treatment[b]	31 (15.9%)	15 (7.6%)
Adverse event (COVID-19)	51 (26.2%)	81 (41.1%)
Serious adverse event (COVID-19)	20 (10.3%)	30 (15.2%)
AE leading to death (COVID-19)	6 (3.1%)	12 (6.1%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event; COVID-19 = Coronavirus Disease 2019.
[a] TEAEs related to at least 1 of the 4 components of study treatment: bortezomib, lenalidomide, dexamethasone, daratumumab.
[b] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
Note: Adverse events are reported using MedDRA version 23.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

The most commonly reported TEAEs (≥10% in either treatment arm) and Grade 3 or 4 TEAEs ((≥5% in either treatment arm are presented in **Table 20** and **Table 21**, respectively.

Table 20. Most common (at Least 10% in Either VRd or D-VRd) Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414MMY3019)

	VRd n (%)	D-VRd n (%)
Analysis set: safety	195	197
Total number of subjects with TEAE	195 (100.0%)	197 (100.0%)
MedDRA system organ class / Preferred term		
Infections and infestations	167 (85.6%)	181 (91.9%)
Upper respiratory tract infection	64 (32.8%)	78 (39.6%)
COVID-19	48 (24.6%)	75 (38.1%)
Pneumonia	39 (20.0%)	48 (24.4%)
Urinary tract infection	29 (14.9%)	41 (20.8%)
Nasopharyngitis	22 (11.3%)	35 (17.8%)
Bronchitis	19 (9.7%)	29 (14.7%)
Influenza	15 (7.7%)	27 (13.7%)
Blood and lymphatic system disorders	126 (64.6%)	163 (82.7%)
Neutropenia	76 (39.0%)	110 (55.8%)
Thrombocytopenia	66 (33.8%)	92 (46.7%)
Anaemia	62 (31.8%)	73 (37.1%)
Lymphopenia	34 (17.4%)	36 (18.3%)
Leukopenia	19 (9.7%)	28 (14.2%)
Nervous system disorders	155 (79.5%)	161 (81.7%)
Peripheral sensory neuropathy	119 (61.0%)	110 (55.8%)
Dizziness	41 (21.0%)	41 (20.8%)
Headache	16 (8.2%)	30 (15.2%)
Neuralgia	30 (15.4%)	28 (14.2%)
Paraesthesia	18 (9.2%)	25 (12.7%)
Dysgeusia	22 (11.3%)	19 (9.6%)
General disorders and administration site conditions	147 (75.4%)	159 (80.7%)
Oedema peripheral	76 (39.0%)	83 (42.1%)
Fatigue	60 (30.8%)	63 (32.0%)
Asthenia	40 (20.5%)	51 (25.9%)
Pyrexia	30 (15.4%)	46 (23.4%)
Injection site erythema	10 (5.1%)	25 (12.7%)
Influenza like illness	21 (10.8%)	24 (12.2%)
Malaise	20 (10.3%)	10 (5.1%)
Gastrointestinal disorders	159 (81.5%)	157 (79.7%)
Diarrhoea	115 (59.0%)	112 (56.9%)
Constipation	82 (42.1%)	75 (38.1%)
Nausea	48 (24.6%)	49 (24.9%)
Abdominal pain	20 (10.3%)	31 (15.7%)
Dyspepsia	17 (8.7%)	26 (13.2%)
Vomiting	23 (11.8%)	23 (11.7%)
Musculoskeletal and connective tissue disorders	142 (72.8%)	146 (74.1%)
Back pain	43 (22.1%)	55 (27.9%)
Arthralgia	39 (20.0%)	45 (22.8%)
Muscular weakness	29 (14.9%)	38 (19.3%)
Muscle spasms	31 (15.9%)	36 (18.3%)
Pain in extremity	30 (15.4%)	35 (17.8%)
Musculoskeletal pain	21 (10.8%)	24 (12.2%)
Metabolism and nutrition disorders	105 (53.8%)	120 (60.9%)
Hypokalaemia	25 (12.8%)	58 (29.4%)
Decreased appetite	39 (20.0%)	42 (21.3%)
Hypocalcaemia	18 (9.2%)	28 (14.2%)
Hyperglycaemia	19 (9.7%)	24 (12.2%)
Hyponatraemia	20 (10.3%)	15 (7.6%)
Skin and subcutaneous tissue disorders	110 (56.4%)	118 (59.9%)
Rash	48 (24.6%)	50 (25.4%)
Pruritus	22 (11.3%)	21 (10.7%)
Respiratory, thoracic and mediastinal disorders	86 (44.1%)	112 (56.9%)
Cough	38 (19.5%)	53 (26.9%)
Dyspnoea	29 (14.9%)	35 (17.8%)
Eye disorders	88 (45.1%)	92 (46.7%)
Cataract	51 (26.2%)	55 (27.9%)
Vision blurred	19 (9.7%)	24 (12.2%)
Psychiatric disorders	96 (49.2%)	91 (46.2%)
Insomnia	63 (32.3%)	63 (32.0%)
Vascular disorders	73 (37.4%)	90 (45.7%)
Hypertension	14 (7.2%)	35 (17.8%)
Hypotension	23 (11.8%)	31 (15.7%)
Investigations	80 (41.0%)	79 (40.1%)
Alanine aminotransferase increased	27 (13.8%)	26 (13.2%)
Weight decreased	22 (11.3%)	15 (7.6%)
Renal and urinary disorders	60 (30.8%)	74 (37.6%)
Renal impairment	20 (10.3%)	14 (7.1%)
Injury, poisoning and procedural complications	58 (29.7%)	72 (36.5%)
Contusion	20 (10.3%)	24 (12.2%)
Cardiac disorders	49 (25.1%)	56 (28.4%)
Atrial fibrillation	20 (10.3%)	17 (8.6%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 23.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Table 21. Most common (at Least 5% in Either VRd or D-VRd) Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414MMY3019)

	VRd n (%)	D-VRd n (%)
Analysis set: safety	195	197
Total number of subjects with toxicity grade 3 or 4 TEAE	167 (85.6%)	182 (92.4%)
MedDRA system organ class / Preferred term		
Blood and lymphatic system disorders	98 (50.3%)	126 (64.0%)
Neutropenia	58 (29.7%)	87 (44.2%)
Thrombocytopenia	39 (20.0%)	56 (28.4%)
Anaemia	23 (11.8%)	26 (13.2%)
Lymphopenia	20 (10.3%)	24 (12.2%)
Leukopenia	7 (3.6%)	15 (7.6%)
Infections and infestations	62 (31.8%)	79 (40.1%)
Pneumonia	25 (12.8%)	28 (14.2%)
COVID-19	9 (4.6%)	22 (11.2%)
Nervous system disorders	38 (19.5%)	45 (22.8%)
Peripheral sensory neuropathy	16 (8.2%)	16 (8.1%)
Syncope	10 (5.1%)	8 (4.1%)
Metabolism and nutrition disorders	36 (18.5%)	44 (22.3%)
Hypokalaemia	12 (6.2%)	24 (12.2%)
Musculoskeletal and connective tissue disorders	30 (15.4%)	43 (21.8%)
Muscular weakness	9 (4.6%)	17 (8.6%)
Gastrointestinal disorders	40 (20.5%)	41 (20.8%)
Diarrhoea	18 (9.2%)	24 (12.2%)
General disorders and administration site conditions	28 (14.4%)	40 (20.3%)
Fatigue	16 (8.2%)	18 (9.1%)
Vascular disorders	22 (11.3%)	31 (15.7%)
Hypertension	4 (2.1%)	15 (7.6%)
Respiratory, thoracic and mediastinal disorders	14 (7.2%)	23 (11.7%)
Pulmonary embolism	5 (2.6%)	10 (5.1%)
Eye disorders	20 (10.3%)	21 (10.7%)
Cataract	17 (8.7%)	17 (8.6%)
Investigations	15 (7.7%)	19 (9.6%)
Alanine aminotransferase increased	4 (2.1%)	10 (5.1%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 23.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

A review of safety data in the CEPHEUS study identified new ADR terms of abdominal pain and hypokalaemia.

The frequency of the known ADRs associated with daratumumab use were updated with data from Study 54767414MMY3019 study which were combined with other daratumumab monotherapy and combination studies to obtain ADR frequencies from a pooled safety data (**Table 22**).

Table 22. Adverse Reactions in Multiple Myeloma and AL Amyloidosis participants treated with daratumumab IV or daratumumab SC (pooled data including data from study 54767414MMY3019)

	Any Grades	Any Grades	Grade 3-4
Infections and infestations			
Upper respiratory tract infection[a]	Very Common	45%	3%
COVID-19[a,g]	Very Common	39%	10%
Pneumonia[a]	Very Common	19%	11%
Bronchitis[a]	Very Common	14%	1%
Urinary tract infection	Common	8%	1%
Sepsis[a]	Common	4%	4%
Cytomegalovirus infection[a]	Uncommon	<1%	<1%#
Hepatitis B reactivation[a]	Uncommon	<1%	<1%
Blood and lymphatic system disorders			
Neutropenia[a]	Very Common	43%	37%
Thrombocytopenia[a]	Very Common	32%	19%
Anaemia[a]	Very Common	27%	11%
Lymphopenia[a]	Very Common	13%	10%
Leukopenia[a]	Very Common	11%	6%
Immune system disorders			
Hypogammaglobulinaemia[a]	Common	3%	<1%#
Anaphylactic reaction[b]	Rare		
Metabolism and nutrition disorders			
Hypokalaemia[a]	Very Common	11%	3%
Decreased appetite	Very Common	10%	1%
Hyperglycaemia	Common	7%	3%
Hypocalcaemia	Common	6%	1%
Dehydration	Common	2%	1%#
Psychiatric disorders			
Insomnia	Very Common	17%	1%#
Nervous system disorders			
Peripheral neuropathy[a]	Very Common	33%	4%
Headache	Very Common	10%	<1%#
Dizziness	Common	9%	<1%#
Paraesthesia	Common	9%	<1%
Syncope	Common	3%	2%#
Cardiac disorders			
Atrial fibrillation	Common	4%	1%
Vascular disorders			
Hypertension[a]	Common	9%	4%
Respiratory, thoracic and mediastinal disorders			
Cough[a]	Very Common	22%	<1%#
Dyspnoea[a]	Very Common	18%	2%
Pulmonary oedema[a]	Common	1%	<1%
Gastrointestinal disorders			
Diarrhoea	Very Common	33%	5%
Constipation	Very Common	29%	1%
Nausea	Very Common	22%	1%#
Abdominal pain[a]	Very Common	13%	1%
Vomiting	Very Common	13%	1%#
Pancreatitis[a]	Common	1%	1%
Skin and subcutaneous tissue disorders			
Rash	Very Common	12%	1%#
Pruritus	Common	6%	<1%#

	Any Grades	Any Grades	Grade 3-4
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain[a]	Very Common	35%	3%
Arthralgia	Very Common	14%	1%
Muscle spasms	Very Common	12%	<1%[#]
General disorders and administration site conditions			
Fatigue	Very Common	24%	4%
Oedema peripheral[a]	Very Common	24%	1%
Pyrexia	Very Common	22%	1%
Asthenia	Very Common	19%	2%
Chills	Common	8%	<1%[#]
Injection site reactions[d,f]	Common	8%	0
Injury, poisoning and procedural complications			
Infusion related reactions[c]			
Daratumumab IV[e]	Very Common	39%	5%
Daratumumab SC[f]	Common	7%	1%

[#] No grade 4.
[a] Indicates a grouping of terms.
[b] Based on post-marketing adverse reactions.
[c] Infusion-related reactions includes terms determined by investigators as related to infusion/injection of daratumumab.
[d] Injection site reactions includes terms determined by investigators as related to injection of daratumumab.
[e] Frequency based on daratumumab IV studies only (N=2324).
[f] Frequency based on daratumumab SC studies only (N=1380).
[g] Frequency based on MMY3014 and MMY3019 studies only (N=548) due to the onset of the pandemic during the studies.
Note: Based on 3704 multiple myeloma and AL amyloidosis patients treated with daratumumab IV or daratumumab SC (daratumumab + rHuPH20).
Note: Studies included are AMY3001, MMY1001, MMY1002, MMY1004, MMY1008, MMY2002, MMY2040, MMY3003, MMY3004, MMY3006, MMY3007, MMY3008, MMY3012, MMY3013, MMY3014, MMY3019, GEN501, GEN503

Serious adverse event/deaths/other significant events

Serious Adverse Events

The treatment-emergent SAEs with a frequency ≥2% in either treatment arm are presented in **Table 23**.

Table 23. Most common (at Least 2% in Either VRd or D-VRd treatment-emergent serious adverse events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414MMY3019)

	VRd n (%)	D-VRd n (%)
Analysis set: safety	195	197
Total number of subjects with serious TEAE	131 (67.2%)	142 (72.1%)
MedDRA system organ class / Preferred term		
Infections and infestations	69 (35.4%)	78 (39.6%)
Pneumonia	25 (12.8%)	27 (13.7%)
COVID-19	16 (8.2%)	22 (11.2%)
COVID-19 pneumonia	4 (2.1%)	8 (4.1%)
Sepsis	4 (2.1%)	7 (3.6%)
Urinary tract infection	4 (2.1%)	7 (3.6%)
Septic shock	1 (0.5%)	6 (3.0%)
Gastroenteritis	4 (2.1%)	4 (2.0%)
Influenza	1 (0.5%)	4 (2.0%)
Gastrointestinal disorders	24 (12.3%)	24 (12.2%)
Diarrhoea	6 (3.1%)	10 (5.1%)
Cardiac disorders	17 (8.7%)	22 (11.2%)
Atrial fibrillation	7 (3.6%)	7 (3.6%)
General disorders and administration site conditions	13 (6.7%)	21 (10.7%)
Asthenia	2 (1.0%)	6 (3.0%)
Pyrexia	3 (1.5%)	5 (2.5%)
Metabolism and nutrition disorders	17 (8.7%)	19 (9.6%)
Hypokalaemia	3 (1.5%)	5 (2.5%)
Hyponatraemia	1 (0.5%)	5 (2.5%)
Dehydration	5 (2.6%)	0
Nervous system disorders	16 (8.2%)	18 (9.1%)
Syncope	6 (3.1%)	3 (1.5%)
Respiratory, thoracic and mediastinal disorders	12 (6.2%)	16 (8.1%)
Pulmonary embolism	5 (2.6%)	11 (5.6%)
Blood and lymphatic system disorders	7 (3.6%)	15 (7.6%)
Anaemia	2 (1.0%)	6 (3.0%)
Febrile neutropenia	4 (2.1%)	4 (2.0%)
Thrombocytopenia	2 (1.0%)	4 (2.0%)
Vascular disorders	17 (8.7%)	15 (7.6%)
Deep vein thrombosis	2 (1.0%)	4 (2.0%)
Hypotension	4 (2.1%)	3 (1.5%)
Orthostatic hypotension	5 (2.6%)	2 (1.0%)
Renal and urinary disorders	6 (3.1%)	8 (4.1%)
Acute kidney injury	3 (1.5%)	6 (3.0%)
Eye disorders	4 (2.1%)	6 (3.0%)
Cataract	4 (2.1%)	5 (2.5%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 23.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Deaths

Participants in the D-VRd arm and in the VRd arm of the safety analysis set in Study 4767414MMY3019 that had died and cause of death at the time of the clinical cut-off date (07 May 2024) is summarised in **Table 24**.

Table 24. Summary of death and cause of death; Safety Analysis Set (Study 54767414MMY3019)

	n (%)	n (%)	n (%)
Analysis set: safety	195	197	392
Total number of subjects who died during study	59 (30.3%)	51 (25.9%)	110 (28.1%)
Primary cause of death			
Adverse event	25 (12.8%)	37 (18.8%)	62 (15.8%)
At least one related [a]	6 (3.1%)	5 (2.5%)	11 (2.8%)
AE(s) unrelated	19 (9.7%)	32 (16.2%)	51 (13.0%)
Adverse event (COVID-19)	6 (3.1%)	13 (6.6%)	19 (4.8%)
Progressive disease	16 (8.2%)	8 (4.1%)	24 (6.1%)
Other	18 (9.2%)	6 (3.0%)	24 (6.1%)
COVID-19	3 (1.5%)	2 (1.0%)	5 (1.3%)
Total number of subjects who died within 30 days of last study treatment dose	16 (8.2%)	28 (14.2%)	44 (11.2%)
Primary cause of death			
Adverse event	16 (8.2%)	28 (14.2%)	44 (11.2%)
At least one related [a]	3 (1.5%)	5 (2.5%)	8 (2.0%)
AE(s) unrelated	13 (6.7%)	23 (11.7%)	36 (9.2%)
Adverse event (COVID-19)	5 (2.6%)	9 (4.6%)	14 (3.6%)
Total number of subjects who died within 60 days of first study treatment dose	3 (1.5%)	3 (1.5%)	6 (1.5%)
Primary cause of death			
Adverse event	3 (1.5%)	3 (1.5%)	6 (1.5%)
At least one related [a]	0	1 (0.5%)	1 (0.3%)
AE(s) unrelated	3 (1.5%)	2 (1.0%)	5 (1.3%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; COVID-19 = Coronavirus Disease 2019.
[a] Includes adverse events that were related to at least 1 of the 4 components of study treatment: bortezomib, lenalidomide, dexamethasone or daratumumab.

The majority of Grade 5 TEAEs occurred during Cycle 9 and onward, after the participants in both arms had completed the 8 cycles of bortezomib per study protocol. Of the 33 participants who experienced Grade 5 TEAEs in the D-VRd arm, 9 died during the first 8 cycles and 24 during Cycle 9 and onward; of the 21 participants who experienced Grade 5 TEAEs in the VRd arm, 6 died during the first 8 cycles and 15 during Cycle 9 and onward. The post Cycle 8 (ie, after bortezomib was completed) incidence of Grade 5 TEAEs was 13.7% and 9% in the D-VRd and VRd arms, respectively.

TEAEs with an outcome of death reported for >2 participants in either treatment arm were:

- COVID-19 (D-VRd: 3.6%; VRd: 2.6%)
- COVID-19 pneumonia (D-VRd: 2.5%; VRd: 0.5%)
- Pneumonia (D-VRd: 1.5%; VRd: 2.1%)

There was also substantial regional variation in the incidences of COVID-19 deaths and SAEs, with 54.2% of the total COVID-19 deaths and 44.0% of the COVID-19 SAEs reported in Brazil. Eleven of the 15 (73.3%) COVID-19 deaths in the D-VRd arm and 2 of the 9 (22.2%) COVID 19 deaths in the VRd arm occurred in Brazil. The country with the next highest COVID 19 incidence was Poland, with 16.7% of the total COVID-19 deaths and 14% of the total COVID 19 SAEs.

Adverse Events of Special Interest

Infusion-related reactions (IRRs=Systemic Administration-related Reactions)

There was a low proportion of participants with sARRs reported in the D-VRd arm (7 [3.6%] participants), and the majority were Grade 1 or 2 events. The most frequently reported (≥1%) sARRs were Chills and Pyrexia in 2 (1.0%) participants each. A Grade 3 sARR of Hypertension was reported in 1 participant. Daratumumab was not discontinued in any participant due to sARRs.

sARRs were reported with the first administration of daratumumab in 5 of the 7 participants, with the second administration in 1 participant, and with subsequent administrations in 2 participants. Recurrent low grade sARRs were reported in 1 participant.

Local Injection-site Reactions

Local ISRs were reported in 24 (12.2%) participants in the D-VRd arm. All ISRs were Grade 1 or 2. ISRs led to interruption of study treatment in 2 participants. The most frequently reported (≥2 participants) ISRs were Injection site erythema in 10 (5.1%) participants, Rash in 5 (2.5%) participants, and Injection site bruising and Injection site reaction in 2 (1.0%) participants each.

Cytopenia

The incidence of treatment-emergent cytopenia is provided in **Table 25** and a summary of growth factor use in

Table 26.

Table 25. Treatment-emergent Cytopenia by MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414MMY3019)

	VRd		D-VRd	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Analysis set: safety	195		197	
Total number of subjects with treatment-emergent Cytopenia	124 (63.6%)	98 (50.3%)	156 (79.2%)	126 (64.0%)
Neutropenia [a]	76 (39.0%)	58 (29.7%)	112 (56.9%)	89 (45.2%)
Neutropenia	76 (39.0%)	58 (29.7%)	110 (55.8%)	87 (44.2%)
Febrile neutropenia	4 (2.1%)	4 (2.1%)	7 (3.6%)	7 (3.6%)
Granulocytopenia	1 (0.5%)	1 (0.5%)	0	0
Neutrophil count decreased	1 (0.5%)	0	0	0
Anaemia [a]	64 (32.8%)	23 (11.8%)	73 (37.1%)	26 (13.2%)
Anaemia	62 (31.8%)	23 (11.8%)	73 (37.1%)	26 (13.2%)
Anaemia macrocytic	2 (1.0%)	0	0	0
Thrombocytopenia [a]	66 (33.8%)	39 (20.0%)	92 (46.7%)	56 (28.4%)
Thrombocytopenia	66 (33.8%)	39 (20.0%)	92 (46.7%)	56 (28.4%)
Lymphopenia [a]	34 (17.4%)	20 (10.3%)	36 (18.3%)	24 (12.2%)
Lymphopenia	34 (17.4%)	20 (10.3%)	36 (18.3%)	24 (12.2%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
[a] Preferred term grouping.
Note: Adverse events are reported using MedDRA version 23.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Table 26. Summary of Growth Factor Use by Therapeutic Class, Pharmacologic Class and Drug; Intent-to-treat Analysis Set (Study 54767414MMY3019)

	VRd n (%)	D-VRd n (%)	Total n (%)
Analysis set: intent-to-treat	198	197	395
Total number of subjects with 1 or more growth factor use	49 (24.7%)	86 (43.7%)	135 (34.2%)
Therapeutic class/pharmacologic class/drug			
Immunostimulants	49 (24.7%)	86 (43.7%)	135 (34.2%)
Immunostimulants	49 (24.7%)	86 (43.7%)	135 (34.2%)
Filgrastim	38 (19.2%)	71 (36.0%)	109 (27.6%)
Granulocyte colony stimulating factor	14 (7.1%)	15 (7.6%)	29 (7.3%)
Lenograstim	1 (0.5%)	7 (3.6%)	8 (2.0%)
Pegfilgrastim	3 (1.5%)	3 (1.5%)	6 (1.5%)
Lipegfilgrastim	3 (1.5%)	1 (0.5%)	4 (1.0%)
Filgrastim sndz	1 (0.5%)	1 (0.5%)	2 (0.5%)
Filgrastim aafi	0	1 (0.5%)	1 (0.3%)
Filgrastim biosimilar 1	0	1 (0.5%)	1 (0.3%)
Pegfilgrastim cbqv	1 (0.5%)	0	1 (0.3%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.
Note: WHO drug dictionary, September 2020 version.

Haemorrhage

The overall incidence of haemorrhagic events (SMQ, excluding injection site reactions) was 31.0% in the D-VRd arm and 26.2% in the VRd arm. The incidence of Grade 3 or 4 hemorrhagic events was low and similar in both treatment arms (D-VRd: 3.0%; VRd: 1.5%). The treatment-emergent hemorrhagic events at a ≥5% frequency in either treatment arm were:

- Contusion (D-VRd: 12.2%; VRd: 10.3%)
- Hematoma (D-VRd: 6.1%; VRd: 0.5%)

Infections and Infestations

The incidences of Infections and Infestations (SOC), including overall (D-VRd: 91.9%; VRd: 85.6%), Grade 3 or 4 (D-VRd: 40.1%; VRd: 31.8%), and SAEs (D-VRd: 39.6%; VRd: 35.4%), were all higher in the D-VRd arm compared with the VRd arm.

The most common TEAEs of Infections and Infestations (frequency ≥10% in either treatment arm) were:

- Upper respiratory tract infection (D-VRd: 39.6%; VRd: 32.8%)
- COVID-19 (D-VRd: 38.1%; VRd: 24.6%)
- Pneumonia (D-VRd: 24.4%; VRd: 20.0%)
- Urinary tract infection (D-VRd: 20.8%; VRd: 14.9%)
- Nasopharyngitis (D-VRd: 17.8%; VRd: 11.3%)
- Bronchitis (D-VRd: 14.7%; VRd: 9.7%)
- Influenza (D-VRd: 13.7%; VRd: 7.7%)

The most common Grade 3 or 4 Infections and Infestations (frequency ≥5% in either treatment arm) were Pneumonia (D-VRd: 14.2%; VRd: 12.8%) and COVID-19 (D-VRd: 11.2%; VRd: 4.6%).

Hepatitis B Reactivation

Four (2%) participants in the D-VRd arm and 7 (3.5%) participants in the VRd arm had a medical history of Hepatitis B. Two (1.0%) participants in the D-VRd arm and none of the participants in the VRd arm had events of Hepatitis B virus reactivation. Neither participant discontinued study treatment due to Hepatitis B virus reactivation.

Opportunistic Infections

The incidences of treatment-emergent opportunistic infections (SMQ), both overall (D VRd: 2.5%; VRd: 3.1%) and Grade 3 or 4 (D-VRd: 2.0%; VRd: 1.0%), were low and similar in both treatment arms. There were no opportunistic infections by PT reported in ≥2% of participants in either treatment arm. No fatal treatment emergent opportunistic infections were reported in either treatment arm.

New Malignancies

The overall incidence of new malignancies, previously known as second primary malignancies, was numerically lower in the D-VRd arm compared with the VRd arm, despite much longer treatment exposure in the D-VRd arm (D VRd: 7.6%; VRd: 9.2%).

Treatment-emergent Interferences for Blood Typing

No treatment-emergent events related to interference with blood typing were reported.

Peripheral Neuropathy

The overall incidence of treatment-emergent peripheral neuropathies (High Level Term) was similar in both treatment arms (D-VRd: 61.9%; VRd: 66.2%). The incidence of Grade 2 peripheral neuropathies was lower in the D-VRd arm compared with the VRd arm (D-VRd: 31.5%; VRd: 36.9%) and the incidence of Grade 3 or 4 peripheral neuropathies was similar in both treatment arms (D VRd: 11.2%; VRd: 10.8%).

In addition, the overall incidences of treatment discontinuation (all study treatment and bortezomib alone) and dose modification (any study treatment and bortezomib alone) due to treatment emergent peripheral neuropathies were similar in both treatment arms.

Laboratory findings

Overall, the data showed no clinically meaningful changes for any **chemistry parameter** and the results were consistent between treatment arms (data not shown).

The only Grade 3 or 4 chemistry laboratory abnormalities reported at a frequency ≥10% in either treatment arm were hyponatremia (D-VRd 18.0% and VRd 12.9%) and hypokalaemia (D-VRd 19.1% and VRd 12.4%).

Safety in special populations

Age

The distribution of participants in the <65 years, 65 to <70 years and ≥70 years subgroups was as follows:

- <65 years: D-VRd: 18.3%; VRd: 17.7%
- 65 years to <70 years: D-VRd: 26.4%; VRd: 26.8%
- ≥70 years: D-VRd: 55.3%; VRd: 55.6%

No increased safety concerns were observed in the 65 to <70 years and ≥70 years subgroups.

The incidence of Grade 3 or 4 TEAEs was not increased in the 2 older subgroups (65 to <70 years and ≥ 70 years) compared with the <65 years age subgroup in the D-VRd arm and was similar in the 2 older subgroups and higher than the <65 years age subgroup in the VRd arm:

The most frequently reported TEAE Grade 3 or 4 (at least 10% in one subgroup) by Age group is summarised in **Table 27.**

Table 27. Number of subjects with 1 or more Grade 3 or 4 (at least 10%) Treatment-emergent Adverse Events by Age MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414MMY3019)

	VRd n (%)				D-VRd n (%)			
	Total	<65 years	65 -< 70 years	≥ 70 years	Total	<65 years	65 -< 70 years	≥ 70 years
Analysis set: safety	195	35	53	107	197	36	52	109
Total number of subjects with toxicity grade 3 or 4 TEAE	167 (85.6%)	25 (71.4%)	46 (86.8%)	96 (89.7%)	182 (92.4%)	33 (91.7%)	46 (88.5%)	103 (94.5%)
MedDRA system organ class / Preferred term								
Blood and lymphatic system disorders	98 (50.3%)	16 (45.7%)	23 (43.4%)	59 (55.1%)	126 (64.0%)	21 (58.3%)	32 (61.5%)	73 (67.0%)
Neutropenia	58 (29.7%)	10 (28.6%)	14 (26.4%)	34 (31.8%)	87 (44.2%)	14 (38.9%)	25 (48.1%)	48 (44.0%)
Thrombocytopenia	39 (20.0%)	5 (14.3%)	6 (11.3%)	28 (26.2%)	56 (28.4%)	8 (22.2%)	10 (19.2%)	38 (34.9%)
Anaemia	23 (11.8%)	5 (14.3%)	6 (11.3%)	12 (11.2%)	26 (13.2%)	7 (19.4%)	4 (7.7%)	15 (13.8%)
Lymphopenia	20 (10.3%)	4 (11.4%)	6 (11.3%)	10 (9.3%)	24 (12.2%)	6 (16.7%)	7 (13.5%)	11 (10.1%)
Infections and infestations	62 (31.8%)	10 (28.6%)	22 (41.5%)	30 (28.0%)	79 (40.1%)	16 (44.4%)	16 (30.8%)	47 (43.1%)
Pneumonia	25 (12.8%)	4 (11.4%)	8 (15.1%)	13 (12.1%)	28 (14.2%)	5 (13.9%)	6 (11.5%)	17 (15.6%)
COVID-19	9 (4.6%)	3 (8.6%)	3 (5.7%)	3 (2.8%)	22 (11.2%)	7 (19.4%)	4 (7.7%)	11 (10.1%)
Nervous system disorders	38 (19.5%)	5 (14.3%)	8 (15.1%)	25 (23.4%)	45 (22.8%)	2 (5.6%)	15 (28.8%)	28 (25.7%)
Metabolism and nutrition disorders	36 (18.5%)	7 (20.0%)	5 (9.4%)	24 (22.4%)	44 (22.3%)	6 (16.7%)	11 (21.2%)	27 (24.8%)
Hypokalaemia	12 (6.2%)	0	2 (3.8%)	10 (9.3%)	24 (12.2%)	2 (5.6%)	5 (9.6%)	17 (15.6%)
Musculoskeletal and connective tissue disorders	30 (15.4%)	6 (17.1%)	7 (13.2%)	17 (15.9%)	43 (21.8%)	9 (25.0%)	10 (19.2%)	24 (22.0%)
Gastrointestinal disorders	40 (20.5%)	8 (22.9%)	13 (24.5%)	19 (17.8%)	41 (20.8%)	9 (25.0%)	11 (21.2%)	21 (19.3%)
Diarrhoea	18 (9.2%)	3 (8.6%)	5 (9.4%)	10 (9.3%)	24 (12.2%)	5 (13.9%)	6 (11.5%)	13 (11.9%)
General disorders and administration site conditions	28 (14.4%)	2 (5.7%)	7 (13.2%)	19 (17.8%)	40 (20.3%)	3 (8.3%)	9 (17.3%)	28 (25.7%)
Vascular disorders	22 (11.3%)	3 (8.6%)	8 (15.1%)	11 (10.3%)	31 (15.7%)	3 (8.3%)	9 (17.3%)	19 (17.4%)
Respiratory, thoracic and mediastinal disorders	14 (7.2%)	1 (2.9%)	5 (9.4%)	8 (7.5%)	23 (11.7%)	1 (2.8%)	8 (15.4%)	14 (12.8%)
Eye disorders	20 (10.3%)	5 (14.3%)	6 (11.3%)	9 (8.4%)	21 (10.7%)	4 (11.1%)	8 (15.4%)	9 (8.3%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA 23.0.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator. Percentages of subgroups were calculated with the number of subjects in each subgroup as denominator.

The incidence of SAEs was higher in the ≥70 years age subgroup compared with the other subgroups in the D-VRd arm and was higher in the 2 older subgroups compared with the youngest subgroup in the VRd arm (**Table 28**).

Table 28. Number of subjects Treatment-emergent Serious Adverse Events (at least 5%) by Age MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414MMY3019)

	VRd n (%)				D-VRd n (%)			
	Total	<65 years	65 -< 70 years	≥ 70 years	Total	<65 years	65 -< 70 years	≥ 70 years
Analysis set: safety	195	35	53	107	197	36	52	109
Total number of subjects with serious TEAE	131 (67.2%)	20 (57.1%)	37 (69.8%)	74 (69.2%)	142 (72.1%)	24 (66.7%)	35 (67.3%)	83 (76.1%)
MedDRA system organ class / Preferred term								
Infections and infestations	69 (35.4%)	17 (48.6%)	23 (43.4%)	29 (27.1%)	78 (39.6%)	17 (47.2%)	14 (26.9%)	47 (43.1%)
Pneumonia	25 (12.8%)	4 (11.4%)	8 (15.1%)	13 (12.1%)	27 (13.7%)	5 (13.9%)	7 (13.5%)	15 (13.8%)
COVID-19	16 (8.2%)	9 (25.7%)	4 (7.5%)	3 (2.8%)	22 (11.2%)	7 (19.4%)	3 (5.8%)	12 (11.0%)
Gastrointestinal disorders	24 (12.3%)	2 (5.7%)	11 (20.8%)	11 (10.3%)	24 (12.2%)	6 (16.7%)	2 (3.8%)	16 (14.7%)
Diarrhoea	6 (3.1%)	0	2 (3.8%)	4 (3.7%)	10 (5.1%)	2 (5.6%)	0	8 (7.3%)
Cardiac disorders	17 (8.7%)	0	7 (13.2%)	10 (9.3%)	22 (11.2%)	3 (8.3%)	5 (9.6%)	14 (12.8%)
General disorders and administration site conditions	13 (6.7%)	1 (2.9%)	3 (5.7%)	9 (8.4%)	21 (10.7%)	3 (8.3%)	4 (7.7%)	14 (12.8%)
Metabolism and nutrition disorders	17 (8.7%)	3 (8.6%)	4 (7.5%)	10 (9.3%)	19 (9.6%)	4 (11.1%)	6 (11.5%)	9 (8.3%)
Nervous system disorders	16 (8.2%)	1 (2.9%)	3 (5.7%)	12 (11.2%)	18 (9.1%)	1 (2.8%)	9 (17.3%)	8 (7.3%)
Musculoskeletal and connective tissue disorders	16 (8.2%)	4 (11.4%)	5 (9.4%)	7 (6.5%)	17 (8.6%)	1 (2.8%)	1 (1.9%)	15 (13.8%)
Respiratory, thoracic and mediastinal disorders	12 (6.2%)	0	5 (9.4%)	7 (6.5%)	16 (8.1%)	0	6 (11.5%)	10 (9.2%)
Pulmonary embolism	5 (2.6%)	0	3 (5.7%)	2 (1.9%)	11 (5.6%)	0	4 (7.7%)	7 (6.4%)
Blood and lymphatic system disorders	7 (3.6%)	1 (2.9%)	4 (7.5%)	2 (1.9%)	15 (7.6%)	4 (11.1%)	1 (1.9%)	10 (9.2%)
Vascular disorders	17 (8.7%)	0	7 (13.2%)	10 (9.3%)	15 (7.6%)	3 (8.3%)	1 (1.9%)	11 (10.1%)
Injury, poisoning and procedural complications	12 (6.2%)	2 (5.7%)	2 (3.8%)	8 (7.5%)	10 (5.1%)	0	3 (5.8%)	7 (6.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (5.1%)	1 (2.9%)	0	9 (8.4%)	10 (5.1%)	1 (2.8%)	1 (1.9%)	8 (7.3%)

Key: VRd = bortezomib-lenalidomide-dexamethasone; D-VRd = daratumumab-bortezomib-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA 23.0.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator. Percentages of subgroups were calculated with the number of subjects in each subgroup as denominator.

The incidence of COVID-19 (PT) SAEs was higher in the youngest subgroup (<65 years age) compared with the older subgroups (65 to <70 years and ≥70 years) in both treatment arms.

The proportion of participants with TEAEs leading to discontinuation of all study treatment was higher in the 2 older subgroups (65 to <70 years and ≥70 years) compared with the <65 years subgroup in both treatment arms:

- D-VRd: <65 years, 2.8%; 65 to <70 years, 7.7%; ≥70 years, 9.2%
- VRd: <65 years, 2.9%; 65 to <70 years, 17.0%; ≥70 years, 19.6%

The proportion of participants with TEAEs leading to discontinuation of lenalidomide in the <65 years subgroup was higher in the D-VRd arm compared with the VRd arm (D VRd: 33.3%; VRd: 14.3%).

The incidence of Grade 5 TEAEs was higher in the youngest subgroup compared with the 2 older subgroups in both treatment arms.

- D-VRd: <65 years, 30.6%; 65 to <70 years, 13.5%; ≥70 years, 13.8%
- VRd: <65 years, 17.1%; 65 to <70 years, 11.3%; ≥70 years, 8.4%

The incidence of Grade 5 TEAEs in the <65 years age group was higher in the D-VRd arm than in the VRd arm. This is likely due to the higher number of COVID 19 deaths in the D VRd arm in the <65 years age group compared with the VRd arm. The incidence of Grade 5 COVID-19 TEAEs was higher in the youngest subgroup compared with the 2 older subgroups in both treatment arms.

- D-VRd: <65 years, 11.1%; 65 to <70 years, 3.8%; ≥70 years, 5.5%
- VRd: <65 years, 8.6%; 65 to <70 years, 3.8%; ≥70 years, 0.9%

Baseline Renal Function

The distribution of participants by baseline renal function (creatinine clearance of <30, 30 to <60, 60 to <90, or ≥90 mL/min/1.73 m^2) was as follows:

- <30 mL/min/1.73 m^2: D-VRd: 3/197 (1.5%) participants; VRd: 3/195 (1.5%) participants
- 30 to <60 mL/min/1.73 m^2: D-VRd: 56/197 (28.4%) participants; VRd: 56/195 (28.7%) participants
- 60 to <90 mL/min/1.73 m^2: D-VRd: 91/197 (46.2%) participants; VRd: 97/195 (49.7%) participants
- ≥90 mL/min/1.73 m^2: D-VRd: 47/197 (23.9%) participants; VRd: 39/195 (20.0%) participants

Interpretation of the subgroup analysis by baseline renal function is limited due to the small number of participants enrolled in the <30 mL/min/1.73 m^2 subgroup compared with the other subgroups in both treatment arms. There was a higher incidence of Grade 3 or 4 TEAEs and SAEs in the 60 to <90 mL/min and ≥90 mL/min subgroups in the D-VRd arm compared with the VRd arm.

Baseline Hepatic Function

Interpretation of the subgroup analysis by baseline hepatic function is limited due to the small number of participants with impaired hepatic function enrolled in the study.

Transplant eligibility

Eligibility for transplant in NDMM is based on age, fitness, and co-morbidities. However, in clinical practice, many patients who are transplant-eligible choose to defer/delay transplant to the first salvage therapy after relapse from frontline therapy. The CEPHEUS study was designed and powered based on the ITT study population that included participants who were either TIE (transplant ineligible) or TD (transplant deferred).

The main difference between the TIE and the TD subgroups is seen in the countries of enrollment. Brazil (38.7%) and Poland (32.1%) recruited 70.8% of the TD participants.

Safety results and most commonly reported TEAEs in these two subgroups are summarised in **Table 29** and **Table 30** respectively.

Table 29. Key safety results by transplant eligibility status, Safety Analysis Set (Study 54767414MMY3019)

	TIE Subgroup		TD Subgroup	
Event, n (%)	**VRd (n=142)**	**D-VRd (n=144)**	**VRd (n = 53)**	**D-VRd (n = 53)**
Any TEAE	142 (100)	144 (100)	53 (100)	53 (100)
Maximum Toxicity Grade				
Grade 1-2 TEAE	16 (11.3)	10 (6.9)	11 (20.8)	5 (9.4)
Grade 3 TEAE	81 (57.0)	68 (47.2)	32 (60.4)	20 (37.7)
Grade 4 TEAE	32 (22.5)	47 (32.6)	2 (3.8)	14 (26.4)
Grade 5 TEAE	13 (9.2)	19 (13.2)	8 (15.1)	14 (26.4)
COVID-19 Related	1 (0.7)	6 (4.2)	5 (9.4)	6 (11.3)
Non COVID-19 Related	12 (8.5)	13 (9.0)	3 (5.7)	8 (15.1)
Cycles 1 – 8	6 (4.2)	3 (2.1)	0 (0.0)	6 (11.3)
Cycles 9+	7 (4.9)	16 (11.1)	8 (15.1)	8 (15.1)
Exposure-Adjusted	0.27/100 pt months	0.31/100 pt months	0.40/100 pt months	0.62/100 pt months
Grade 5 TEAEs > 2 subjects in either arm				
COVID-19	1 (0.7)	3 (2.1)	4 (7.5)	4 (7.5)
COVID-19 Pneumonia	0 (0.0)	3 (2.1)	1 (1.9)	2 (3.8)
Pneumonia	3 (2.1)	1 (0.7)	1 (1.9)	2 (3.8)
Any Serious TEAE	99 (69.7)	104 (72.2)	32 (60.4)	38 (71.1)
TEAE leading to discontinuation of all study treatment	27 (19.0)	11 (7.6)	4 (7.5)	4 (7.5)

Table 30. Most commonly reported TEAEs by transplant eligibility status, Safety Analysis Set (Study 54767414MMY3019)

	TIE Subgroup				TD Subgroup			
	VRd (n = 142)		D-VRd (n = 144)		VRd (n = 53)		D-VRd (n = 53)	
Event, n (%)	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
HEMATOLOGIC								
Neutropenia	57 (40.1)	45 (31.7)	81 (56.3)	63 (43.8)	19 (35.8)	13 (24.5)	29 (54.7)	24 (45.3)
Thrombocytopenia	51 (35.9)	33 (23.2)	70 (48.6)	44 (30.6)	15 (28.3)	6 (11.3)	22 (41.5)	12 (22.6)
Anemia	46 (32.4)	18 (12.7)	52 (36.1)	18 (12.5)	16 (30.2)	5 (9.4)	21 (39.6)	8 (15.1)
NON-HEMATOLOGIC								
Diarrhea	87 (61.3)	14 (9.9)	87 (60.4)	17 (11.8)	28 (52.8)	4 (7.5)	25 (47.2)	7 (13.2)
Constipation	65 (45.8)	2 (1.4)	57 (39.6)	3 (2.1)	17 (32.1)	3 (5.7)	18 (34.0)	1 (1.9)
Fatigue	54 (38.0)	15 (10.6)	48 (33.3)	13 (9.0)	6 (11.3)	1 (1.9)	15 (28.3)	5 (9.4)
Peripheral edema	59 (41.5)	0	63 (43.8)	4 (2.8)	17 (32.1)	1 (1.9)	20 (37.7)	0
Insomnia	47 (33.1)	2 (1.4)	51 (35.4)	3 (2.1)	16 (30.2)	0	12 (22.6)	1 (1.9)
Hypokalemia	22 (15.5)	12 (8.5)	49 (34.0)	21 (14.6)	3 (5.7)	0	9 (17.0)	3 (5.7)
Cataract	31 (21.8)	9 (6.3)	38 (26.4)	14 (9.7)	20 (37.7)	8 (15.1)	17 (32.1)	3 (5.7)
Cough	32 (22.5)	2 (1.4)	37 (25.7)	0	6 (11.3)	0	16 (30.2)	1 (1.9)
INFECTION								
COVID-19 (Group term)	26 (18.3)	5 (3.5)	52 (36.1)	14 (9.7)	22 (41.5)	4 (7.5)	23 (43.4)	8 (15.1)
Upper respiratory tract infection	38 (26.8)	1 (0.7)	49 (34.0)	1 (0.7)	26 (49.1)	1 (1.9)	29 (54.7)	0
PERIPHERAL NEUROPATHY (Group term)	96 (67.6)	16 (11.3)	95 (66.0)	18 (12.5)	33 (62.3)	5 (9.4)	27 (50.9)	4 (7.5)

Safety related to drug-drug interactions and other interactions

No dedicated drug-drug interaction studies were performed for daratumumab SC.

Discontinuation due to adverse events

Adverse Events Leading to Daratumumab Discontinuation

The proportion of participants with TEAEs leading to discontinuation of daratumumab was 17.3%. This included 5.1% of participants with Grade 3 or 4 TEAEs. TEAEs resulting in discontinuation of daratumumab which occurred in >2 participants were:

- Pneumonia (2.0%)
- COVID-19 (1.5%)
- General physical health deterioration (1.5%)

Adverse Events Leading to Bortezomib Discontinuation

The proportion of participants with TEAEs leading to discontinuation of bortezomib was similar in both treatment arms (D-VRd: 12.7%; VRd: 16.4%). TEAEs resulting in discontinuation of bortezomib which occurred in >2 participants in either treatment arm were:

- Peripheral sensory neuropathy (D-VRd: 5.1%; VRd: 7.2%)
- Peripheral sensorimotor neuropathy (D-VRd: 1.5%; VRd: 1.0%)
- Pneumonia (D-VRd: 1.5%; VRd: 0%)
- Neuralgia (D-VRd: 1.0%; VRd: 1.5%)

Adverse Events Leading to Lenalidomide Discontinuation

The proportion of participants with TEAEs leading to discontinuation of lenalidomide was higher in the D-VRd arm compared with the VRd arm (D-VRd: 32.0%; VRd: 24.6%). TEAEs leading to discontinuation of lenalidomide which occurred in >2 participants in either treatment arm were:

- Peripheral sensory neuropathy (D-VRd: 3.0%; VRd: 2.6%)
- Diarrhoea (D-VRd: 3.0%; VRd: 2.1%)
- Pneumonia (D-VRd: 2.5%; VRd: 1.5%)
- COVID-19 (D-VRd: 2.0%; VRd: 1.5%)
- COVID-19 pneumonia (D-VRd: 1.5%; VRd: 1.0%)
- Rash (D-VRd: 1.5%; VRd: 1.0%)
- General physical health deterioration (D-VRd: 1.5%; VRd: 0%)
- Pulmonary embolism (D-VRd: 1.5%; VRd: 0%)
- Peripheral sensorimotor neuropathy (D-VRd: 0%; VRd: 1.5%)

Adverse Events Leading to Dexamethasone Discontinuation

The proportion of participants with TEAEs leading to discontinuation of dexamethasone was lower in the D-VRd arm compared with the VRd arm (D-VRd: 23.9%; VRd: 35.4%). TEAEs leading to discontinuation of dexamethasone which occurred in >2 participants in either treatment arm were:

- Insomnia (D-VRd: 2.0%; VRd: 2.1%)
- COVID-19 (D-VRd: 2.0%; VRd: 1.0%)
- Pneumonia (D-VRd: 2.0%; VRd: 0.5%)
- General physical health deterioration (D-VRd: 1.5%; VRd: 0.5%)
- Cataract (D-VRd: 1.0%; VRd: 2.6%)
- Muscular weakness (D-VRd: 0.5%; VRd: 2.6%)

- Fatigue (D-VRd: 0%; VRd: 2.1%)
- Oedema peripheral (D-VRd: 0%; VRd: 2.1%)

Adverse Events Leading to Cycle Delays or Dose Modification

TEAEs leading to treatment cycle delays or dose modifications that occurred at a frequency ≥20% in either treatment arm were:

- Neutropenia (D-VRd: 39.6%; VRd: 28.7%)
- Peripheral sensory neuropathy (D-VRd: 36.5%; VRd: 43.6%)
- Diarrhea (D-VRd: 31.0%; VRd: 20.5%)
- COVID-19 (D-VRd: 30.5%; VRd: 20.5%)
- Upper respiratory tract infection (D-VRd: 24.9%; VRd: 17.4%)
- Thrombocytopenia (D-VRd: 21.3%; VRd: 10.3%)

The Grade 3 or 4 TEAEs leading to treatment cycle delays or dose modifications that occurred at a frequency ≥5% in either treatment arm were:

- Neutropenia (D-VRd: 37.6%; VRd: 28.2%)
- Thrombocytopenia (D-VRd: 15.7%; VRd: 8.7%)
- Pneumonia (D-VRd: 10.7%; VRd: 8.2%)
- Diarrhea (D-VRd: 8.6%; VRd: 5.6%)
- Peripheral sensory neuropathy (D-VRd: 8.1%; VRd: 6.7%)
- COVID-19 (D-VRd: 7.6%; VRd: 3.1%)
- Fatigue (D-VRd: 7.6%; VRd: 7.7%)
- Muscular weakness (D-VRd: 7.1%; VRd: 4.6%)

Post marketing experience

Post-marketing safety information is available for both daratumumab SC and daratumumab IV.

A cumulative review was performed for all medically confirmed spontaneous cases (serious and nonserious) of daratumumab received in the global safety database through 01 February 2024. A separate cumulative review of cases reporting SC administration was also performed.

Of the 7,838 serious cases, 960 (12.2%) reported 1,445 serious events with SC administration of daratumumab. The most frequently reported serious PTs (≥2% of the reported serious events) involving the SC administration of daratumumab were Neutropenia (5.0%; 72/1,445), Plasma cell myeloma (4.7%; 68/1,445), Pneumonia (3.0%; 43/1,445), Thrombocytopenia (2.8%; 41/1,445), Infusion related reaction (2.5%; 36/1,445), and Neuropathy peripheral (2.4%; 34/1,445).

The cumulative review of the post-marketing spontaneous cases through 01 February 2024 revealed that based on the most commonly reported events, serious events, and fatal events, the post-marketing experience of daratumumab SC remained generally consistent with the overall post-marketing experience.

No new safety signals were identified from the cumulative review of post-marketing spontaneous cases, both overall and separately for SC daratumumab. The post-marketing experience was consistent with the known safety profile of daratumumab or clinical experience of the population under treatment.

2.5.1. Discussion on clinical safety

The Safety Analysis Set includes all patients that received at least one dose of any study treatment in study MMY3019 (Cepheus) corresponding to a total of 392 participants (D-VRd: 197; VRd: 195). It also includes patients that were eligible for ASCT but opted out (n=53 in each arm corresponding to 27%).

Generally, demographic and baseline characteristics were balanced between the two treatment arms and did not favour the D-VRD arm. In the D-VRd the median number of treatment cycles was 59 (1-71) and the median duration of treatment was 56 months, whereas in the VRd arm the median number of treatment cycles was 37 (1-70) and the median duration of treatment was 34 months corresponding to a difference of 22 months for the median duration of treatment. Bortezomib was given for 8 3-week cycles and daratumumab (in the D-VRd arm), lenalidomide and dexamethasone continued until disease progression or unacceptable toxicity.

Adverse events

Several of the most frequent TEAEs are considered related to one of the VRd components (diarrhoea, sensory neuropathy, oedema peripheral, constipation, insomnia, fatigue) and also the disease itself (infections), whereas cytopenias are considered related both to VRd and to daratumumab as there is a higher frequency in the D-VRD arm compared to the VRd arm [(neutropenia 55.8% and 39.0%, respectively and for thrombocytopenia (46.7% and 33.8%, respectively)].

The most pronounced differences between the two arms in relation to Grade 3-4 TEAEs were for Neutropenia (D-VRd: 44.2%; VRd: 29.7%), Thrombocytopenia (D-VRd: 28.4%; VRd: 20.0%), Hypokalaemia (D-VRd: 12.2%; VRd: 6.2%), and COVID-19 (D-VRd: 11.2%; VRd: 4.6%).

The incidence of Grade 5 AEs was higher in the D-VRd arm compared with the VRd arm (D-VRd: 16.8%; VRd: 10.8%). Longer exposure in D-VRd arm compared to the VRd arm (+22 months) as well as longer time during the COVID-19 epidemic for the D-VRd arm due to this longer exposure, is considered to account for a major part of this difference.

The main differences in the frequency of SAEs by SOC were seen in the SOCs Infections and infestations (D-VRd; 39.6% vs VRd; 35.4%) with COVID-19 (including COVID-19 pneumonia) being more frequent in the D-VRd arm; 15.3% vs 10.3%.

A review of safety data in the CEPHEUS study identified new ADR terms of abdominal pain and hypokalaemia which are now included in Section 4.8 of the SmPC.

Abdominal pain was higher in the D-VRD arm compared to the VRD arm (15.7% and 10.3%, respectively). The corresponding frequencies of Grade 3-4 AE (1.0% and 1.5%, respectively) and SAE (0.5% and 1.5%, respectively) were low and comparable between the two arms. No patients in either arm discontinued due to abdominal pain.

Hypokalaemia was higher in the D-VRD arm compared to the VRD arm (29.4% and 12.8%, respectively). These events could be secondary to gastrointestinal ADRs of daratumumab (e.g., vomiting, diarrhoea). The corresponding Grade 3-4 AE frequencies were 12.2% and 6.2%. Serious hypokalaemia was comparable between the two arms; D-VRD 2.5% and VRd: 1.5%.

Adverse Events of Special Interest

Systemic Administration-related Reactions (sARR=IRR) occurred with a relatively low frequency of 3.6% with the highest grade being grade 3 occurring in one patient.

Local injection site reactions were reported in 12.2% of patients in the D-VRd arm and were grade ≤2.

Cytopenia were seen more frequently in the D-VRd arm. The use of G-CSF was almost twice as high in the D-VRd arm compared to the VRd arm (43.7 vs 24.7%, respectively). Despite a frequency of 28.4%

of thrombocytopenia in the D-VRd arm (20.0% in the VRd arm) grade 3-4 haemorraghe was low: 3.0% vs 1.5%.

Infections and Infestations by SOC were observed with a higher frequency in the D-VRd arm compared to the VRd arm (Grade 3-4; 40.1% and 31.8%, respectively). Particularly COVID-19 was more frequent in the D-VRd arm. Longer exposure in D-VRd arm compared to the VRd arm (+22 months) as well as longer time during the COVID-19 epidemic for the D-VRd arm due to this longer exposure, is expected to account for a major part of this difference. The frequencies of opportunistic infections were low and comparable.

Peripheral sensory neuropathy was comparable between the arms and is considered due to bortezomib.

The only Grade 3 or 4 chemistry laboratory abnormalities reported at a frequency ≥10% in either treatment arm were hyponatremia (D-VRd 18.0% and VRd 12.9%) and hypokalaemia (D-VRd 19.1% and VRd 12.4%). Hypokalaemia (in the SOC Metabolism and nutrition disorders) has been added as a new ADR.

Safety in special populations

The incidence of Grade 3 or 4 TEAEs was not increased in the 2 older subgroups (65 to <70 years and ≥ 70 years) compared with the <65 years age subgroup in the D-VRd arm and was similar in the 2 older subgroups and higher than the <65 years age subgroup in the VRd arm.

The incidence of SAEs was higher in the ≥70 years age subgroup compared with the other subgroups in the D-VRd arm and was higher in the 2 older subgroups compared with the youngest subgroup in the VRd arm.

In the context of the current indication (ASCT ineligible) it is important to be able to evaluate adverse events in the various age groups given that 27% of the patients (in each arm) were eligible for transplant, and age is one of the main modifiers of eligibility for ASCT. A post-hoc analysis of safety in the two treatment arms in true ASCT-ineligible patients revealed no new concerns compared to the overall safety population.

AEs leading to discontinuation of all study treatment were higher in the VRd arm compared to the D-VRd arm (all grades 15.9% and 7.6%, and grade 3-4 9.7% and 4.6%, respectively). The difference was especially pronounced with regards to peripheral neuropathy (sensory and sensorimotor) with 4.1% of events in the VRd arm and 0.5% in the D-VRd arm regards to peripheral neuropathy are based on small numbers and are not considered clinically meaningful.

2.5.2. Conclusions on clinical safety

The safety profile of daratumumab in study MMY3019 is considered to be consistent with the known safety profile for SC daratumumab in combination with VRd and manageable also in patients with NDMM ineligible for treatment with ASCT. Review of the safety data from this study identified new ADR terms of abdominal pain and hypokalaemia, which are now included in the product information.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted to submit an updated RMP version 11.1 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 11.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 11.1 with the following content:

Safety concerns

Summary of Safety Concerns	
Important identified risks	Interference for blood typing (minor antigen) (positive indirect Coombs' test)
	Hepatitis B virus reactivation
Important potential risks	None
Missing information	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement

Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 - Required additional pharmacovigilance activities				
A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis. Ongoing	Primary objective is to further characterize cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome.	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	Draft Protocol: Interim report: Final report:	Aug 2021 2nd Quarter 2024 1st Quarter 2026

Risk minimisation measures

Summary Table of Risk Minimisation Activities

Safety Concern	Risk Minimization Measures
Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Routine risk minimization measures: • SmPC Section 4.4, which advises that patients should be typed and screened, and phenotyping or genotyping be considered prior to starting daratumumab treatment; • SmPC Sections 4.4, which advises HCPs to notify blood transfusion centers of this interference with indirect antiglobulin tests in the event of a planned transfusion; • SmPC Section 4.4, which recommend that if an emergency transfusion is required, non-cross-matched ABO/RhD compatible RBCs can be given per local blood bank practices; • SmPC Section 4.5, which recommend mitigating daratumumab interference by treating reagent RBCs with DTT to disrupt daratumumab binding or other locally validated methods, and that Kell negative units should be supplied after ruling out or identifying alloantibodies using DTT treated RBCs; • PL Section 2, which instructs patients to inform the person doing the blood test to match blood type that they are receiving treatment with daratumumab. Additional risk minimization measures: • Distribution of educational materials and Patient Alert Cards to HCPs and blood banks as described in the PL, in Annex II, D.
Hepatitis B virus reactivation	Routine risk minimization measures: • SmPC Section 4.8 and PL Section 4; • SmPC Section 4.4 and PL Section 2, which advise HBV screening before initiation of treatment with daratumumab and to monitor for clinical and laboratory signs of HBV reactivation during and for at least 6 months following the end of daratumumab treatment for patients with evidence of positive HBV serology; • SmPC Section 4.4, which advises to manage patients according to current clinical guidelines, and to consider consulting a hepatitis disease expert as clinically indicated; • SmPC Section 4.4, which advises to suspend treatment with daratumumab and to institute appropriate treatment in patients who develop reactivation of HBV while on daratumumab. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV; • PL Section 2, which includes a warning to patients with history or current HBV infection; Additional risk minimization measures: • Distribution of a DHPC to HCPs who prescribe daratumumab was issued in the EU member states in June 2019.
Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	Routine risk minimization measures: • SmPC Section 5.1. Additional risk minimization measures: • None.

Key: AL amyloidosis = light chain amyloidosis; DHPC = Direct Healthcare Professional Communication; DTT = dithiothreitol; HBC = hepatitis B virus; HCP = healthcare professional; PL = package leaflet; RBC = red blood cell; SmPC = Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Germany and Slovenia.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and was found acceptable for the following reasons:

With the currently proposed indication extension, minimal changes have been introduced to the package leaflet and the proposed changes reflect language and a format that is consistent with that in the currently approved leaflet. The use of lay language for additional symptoms and side effects is consistent with the current approved leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Multiple myeloma is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone. The clinical presentation is characterized by osteolytic lesions, usually in the pelvis, spine, ribs, and skull. Lesions are caused by expanding plasmacytomas or by cytokines secreted by myeloma cells that activate osteoclasts and suppress osteoblasts. Increased bone loss may also lead to hypercalcemia. Solitary extraosseous plasmacytomas are unusual but may occur in any tissue. In many patients, renal failure is present at diagnosis or develops during the course of the disorder and is caused by the deposition of light chains in the distal tubules or by hypercalcemia. Patients also often develop anaemia due to kidney disease or suppression of erythropoiesis by cancer cells. These signs and symptoms are commonly denoted by the mnemonic acronym CRAB (Calcemia, Renal damage, Anaemia, Bone lesions).

The MAH submitted an application to remove the transplant eligibility requirement in the approved indication of DARZALEX 1800 mg solution for injection in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant (SCT).

The proposed modified indication for multiple myeloma is:

DARZALEX is indicated in combination with bortezomib, lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma.

3.1.2. Available therapies and unmet medical need

Patients with NDMM are typically categorized as 'transplant-eligible' or 'transplant-ineligible' (TIE). For patients not considered eligible for high-dose chemotherapy and ASCT (TIE) or for whom transplant was not planned as initial therapy, the current standard of care is longer-term treatment with triplet or quadruplet combinations. Current frontline standards of care recommended for these patients in the EHA-ESMO Guideline include D-Rd, VRd, D-VMP, VMP, and Rd, commonly on a treat-to-progression or unacceptable toxicity basis (Dimopoulos 2021).

Over the past two decades, the introduction of new classes of drugs, such as PIs, IMiDs and anti-CD38 antibodies, have changed the management of frontline treatment in both transplant eligible and ineligible candidates. Despite the significant progress that has been made in the management of multiple myeloma, the disease relapses and it remains an incurable malignancy. Therefore, new treatment options and combinations directed at alternative mechanisms of action are needed for these patients.

3.1.3. Main clinical studies

Study MMY3019 (CEPHEUS) is a randomised (1:1), open-label, multicentre, Phase 3 study that evaluated the efficacy and safety of daratumumab SC in combination with D-VRd vs VRd in participants with NDMM for whom ASCT was not planned as initial therapy.

The primary endpoint was overall MRD negativity rate defined as the proportion of ITT subjects who have achieved MRD negative status (at 10-5) by bone marrow aspirate after randomization and prior to progressive disease (PD) or subsequent anti-myeloma therapy. The key secondary endpoints were PFS by computerised algorithm (assessed by 2011 IMWG criteria), overall CR or better rate and sustained MRD negativity rate.

At randomization, participants were stratified by ISS stage (I, II, or III) and age/transplant eligibility (<70 years ineligible, or <70 years and refusal to transplant [meaning transplant was not planned as initial therapy], or ≥70 years).

3.2. Favourable effects

At the primary MRD analysis (08 April 2021), with a median follow-up of 22.3 months, the addition of daratumumab SC to VRd resulted in a statistically significant improvement in the primary endpoint overall MRD negativity rate as measured by NGS for participants achieving CR or better compared with VRd alone, with an absolute increase of 17.9% favouring D-VRd (D-VRd: 105 (53.3%); VRd: 70 (35.4%); OR=2.07 with 95% CI: 1.38, 3.10; 2-sided p=0.0004).

The primary endpoint was supported by key secondary endpoint PFS. As of the interim PFS analysis cutoff date (08 SEP 2022), with a median follow-up of 39.0 months, a total of 113 PFS events were observed (D-VRd: 46 [23.4%]; VRd: 67 [33.8%]) corresponding to a maturity of 28.6% PFS events (113/395). The addition of daratumumab to VRd resulted in a statistically significant improvement in the key secondary endpoint of PFS with a HR of 0.61 (95% CI: 0.42, 0.90; 2-sided p=0.0104) crossing the prespecified 2-sided stopping boundary of 0.0145 in favor of the D-VRd arm). Efficacy in the claimed indication was further supported by two other key secondary endpoints: Overall CR rate or better and sustained MRD negativity rate. Both endpoints favoured D-VRd treatment over VRd treatment. With a total of 111 deaths (D-VRd: 51; VRd: 60), the median OS was not reached for either treatment arm.

3.3. Uncertainties and limitations about favourable effects

Whether MRD negativity can be considered a validated trial level surrogate marker for PFS in NDMM is yet to be robustly confirmed (Landgren, Blood, 2024; Paiva, Blood Adv, 2023; Ficek, Clin lymp myel leuk, 2023). Currently, MRD negative CR is not considered a clinical benefit per se but a mechanistic endpoint which has individual prognostic value based on different meta-analyses. This uncertainty however is negated by the improvement in PFS, a time-to-event endpoint.

OS data are immature. Furthermore, whether the PFS benefit will translate into OS superiority from D-VRd vs VRd is also doubtful, since it is likely that many patients randomised to the VRd arm will receive daratumumab in subsequent treatment lines, confounding OS analysis. The CHMP nevertheless recommended that the MAH submits the final OS analysis when available.

3.4. Unfavourable effects

The main safety concerns associated with daratumumab use are cytopenias and infections.

The most pronounced differences between the two arms in relation to Grade 3-4 TEAEs were for Neutropenia (D-VRd: 44.2%; VRd: 29.7%), Thrombocytopenia (D-VRd: 28.4%; VRd: 20.0%), Hypokalemia (D-VRd: 12.2%; VRd: 6.2%), and COVID-19 (D-VRd: 11.2%; VRd: 4.6%).

The incidence of Grade 5 AEs was higher in the D-VRd arm compared with the VRd arm (D-VRd: 16.8%; VRd: 10.8%). Longer exposure in D-VRd arm compared to the VRd arm (+22 months) as well as longer time during the COVID-19 epidemic for the D-VRd arm due to this longer exposure, is considered to account for a major part of this difference.

The main differences in the frequency of SAEs by SOC were seen in the SOCs Infections and infestations (D-VRd; 39.6% vs VRd; 35.4%) with COVID-19 (including COVID-19 pneumonia) being more frequent in the D-VRd arm; 15.3% vs 10.3%.

3.5. Uncertainties and limitations about unfavourable effects

The AEs related to non-ASCT eligibility are diluted by the fact that 27% of patients in each arm were considered eligible for ASCT, for which the D-VRd regimen already is approved. However, a post-hoc analysis of safety in the two treatment arms in true ASCT-ineligible patients revealed no new concerns compared to the overall safety population.

The COVID-19 epidemic had a negative impact on safety, which possibly impacted more the D-VRd arm due to the longer exposure of treatment compared to the control arm.

3.6. Effects Table

Table 1. Effects Table for Darzalex in combination with bortezomib, lenalidomide and dexamethasone for the treatment of NDMM (data cut-off: 07 May 2024).

Effect	Short description	Unit	D-VRd n=197	VRd n=198	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Time from randomisation to first disease progression (according to the	N %	46 23.4%	67 33.8%	SoE: HR 0.61 95% CI: 0.42, 0.90 MRD negativity 10^{-5}: OR: 2.07%; 95% CI: 1.38, 3.10.	CEPHEUS

Effect	Short description	Unit	D-VRd n=197	VRd n=198	Uncertainties / Strength of evidence	References
	IMWG response criteria) or death					
Unfavourable Effects			**D-VRd n=197**	**VRd n=195**		
Death	Due to AE	%	18.8	12.8		CEPHEUS
Neutropenia	Any AE Grade 3-4	% %	56.9 45.2	39.0 29.7	Growth factor use: 43.7% (D-VRd) 24.7% (VRd)	
Thrombo-cytopenia	Any AE Grade 3-4	% %	46.7 28.4	33.8 20.0	Grade haemorrhage: 3.0% (D-VRd) and 1.5% (VRd)	
SOC Infections	Grade 3-4	%	40.1	31.8	+22 months exposure in the D-VRd arm.	

Abbreviations: D= daratumumab; VRd= bortezomib, lenalidomide and dexamethasone; PFS = Progression free survival; IMWG= International Myeloma Working Group; HR = Hazard ratio; OR = Odds ratio; CI = Confidence Interval, CR: Complete response; MRD: Minimal residual disease

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Results showed that the addition of daratumumab to VRd treatment in patients with newly diagnosed multiple myeloma who are not eligible for treatment with ASCT resulted in a statistically significant improvement in PFS. This is further supported by the primary endpoint of the study which also showed a statistically significant improvement in overall MRD negativity as well as in overall CR or better rate and sustained MRD negativity rate. These improvements are considered clinically meaningful. OS data are immature but do not show any sign of detriment in the experimental arm.

The safety profile is in general as expected in the context of the patient population, the backbone therapy and the known safety profile of daratumumab SC. New ADRs which were identified in patients with NDMM ineligible for treatment with ASCT have been added to the product information. Existing warnings in the product information and additional risk minimisation measures are considered adequate to manage the knowns risks associated with daratumumab use in the new target population.

3.7.2. Balance of benefits and risks

The benefit-risk balance of D-VRd in the proposed patient population is positive, since the demonstrated clinically relevant benefits of D-VRd for the treatment of adult patients with newly diagnosed multiple myeloma that are not eligible for autologous stem cell transplant are considered to outweigh the toxicity of the combination, which is considered generally acceptable and manageable in the current clinical setting.

3.8. Conclusions

The overall B/R of Darzalex in combination with bortezomib, lenalidomide and dexamethasone for the

treatment of adult patients with newly diagnosed multiple myeloma is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for Darzalex in combination with bortezomib, lenalidomide and dexamethasone (D-VRd) for the treatment of adult patients with newly diagnosed multiple myeloma and who are ineligible for stem cell transplant (SCT), based on the results from Study CEPHEUS (54767414MMY3019), a randomised, open-label, active-controlled, multi-centre phase 3 study.

As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Darzalex is not similar to Talvey, Carvykti, Abecma, Farydak, Ninlaro and Kyprolis within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Darzalex-EMEA/H/C/004077/II/76’.