20 May 2021
EMA/CHMP/266131/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Darzalex

International non-proprietary name: daratumumab

Procedure No. EMEA/H/C/004077/II/0044

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

ADA	anti-daratumumab antibodies
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
BLQ	below limit of quantitation
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CR	complete response
CRO	clinical research organization
CSR	clinical study report
DoR	duration of response
DPd	daratumumab, pomalidomide, dexamethasone
DT	drug tolerant
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EMN	European Myeloma Network
EU	European Union
FISH	fluorescence in situ hybridization
HBV	hepatitis B virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality-of-life
IDMC	Independent Data Monitoring Committee
IEC	Institutional Ethics Committee
IMiD	immunomodulatory agents
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IRR	infusion-related reactions
ISS	International Staging System
ITT	intent-to-treat

IV	intravenous
IWRS	interactive web response system
MRD	minimal residual disease
Nabs	neutralizing antibodies
NGS	next-generation sequencing
ORR	overall response rate
OS	overall survival
Pd	pomalidomide, dexamethasone
PI	proteasome inhibitor
PFS	progression-free survival
PFS2	progression-free survival after the next line of therapy
PK	pharmacokinetic
PO	orally
PR	partial response
PRO	patient-reported outcome
rHuPH20	Recombinant Human Hyaluronidase PH20
R-ISS	revised International Staging System
SAP	statistical analysis plan
SC	subcutaneous
sCR	stringent complete response
SD	standard deviation
SOC	standard of care
SOP	Standard Operating Procedure
SDR	source data review
SDV	source data verification
SPM	secondary primary malignancy
TEAE	treatment-emergent adverse event
TMF	trial master file
US	United States
VGPR	very good partial response

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 NV submitted to the European Medicines Agency on 11 November 2020 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 subcutaneous formulation to include combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition section 4.8 of the SmPC for the intravenous formulation is also updated based on the pooled safety analysis. The Package Leaflet is updated in accordance. Version 8.2 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Darzalex, was designated as an orphan medicinal product EU/3/13/1153 on 17/07/2013. Darzalex was designated as an orphan medicinal product in the following indication: Treatment of plasma cell myeloma.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) 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 at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Blanca Garcia-Ochoa

Timetable	Actual dates
Submission date	11 November 2020
Start of procedure:	28 November 2020
CHMP Co-Rapporteur Assessment Report	4 February 2021
CHMP Rapporteur Assessment Report	22 January 2021
PRAC Rapporteur Assessment Report	29 January 2021
PRAC members comments	3 February 2021
Updated PRAC Rapporteur Assessment Report	4 February 2021
PRAC Outcome	11 February 2021
CHMP members comments	15 February 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 February 2021
Request for supplementary information (RSI)	25 February 2021
CHMP Rapporteur Assessment Report	28 April 2021
CHMP members comments	10 May 2021
Updated CHMP Rapporteur Assessment Report	12 May 2021
Opinion	20 May 2021
The CHMP adopted a report on similarity of Darzalex with Imnovid, Farydak, Kyprolis, Ninlaro and Blenrep on 20 May 2021 (Appendix 1)	20 May 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The proposed addition to the existing indication is only for the subcutaneous use of daratumumab.

The initial proposed addition to the existing indication statement in section 4.1 of the Summary of Product Characteristics (SmPC) was as follows (proposed text in **bold)**:

*"DARZALEX is indicated **in combination with pomalidomide and dexamethasone, or** as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy."*

The indication was entered as a separate one from monotherapy and updated during the procedure to better reflect the population included in study MMY3013. The following wording is agreed:

"DARZALEX is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy (see section 5.1)."

2.1.2. Epidemiology

Multiple myeloma is an incurable malignant plasma cell disorder diagnosed annually in approximately 160,000 patients worldwide (Bray 2018). The median age at diagnosis is 72 years.

2.1.3. Biologic features, aetiology and pathogenesis

The proliferation of the malignant clonal plasma cells leads to subsequent replacement of normal bone marrow hematopoietic precursors and overproduction of M-proteins. Characteristic hallmarks of multiple myeloma include osteolytic lesions, anemia, increased susceptibility to infections, hypercalcemia, renal insufficiency or failure, and neurological complications (Palumbo 2011).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

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, especially in the upper respiratory tract. 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 anemia due to kidney disease or suppression of erythropoiesis by cancer cells, but sometimes also due to iron deficiency. These signs and symptoms are commonly denoted as CRAB.

The prognosis of patients with multiple myeloma who become refractory to lenalidomide and a PI is poor, indicating the need for new, convenient therapeutic strategies for these patients.

2.1.5. 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. Patients who have been treated with lenalidomide and a PI are a challenge to treat as they have already been exposed to 2 major drug classes. Patients who relapse during ongoing treatment or within 60 days of last dose of lenalidomide are per IMWG definition "lenalidomide refractory" and represent an additional challenge for choosing an effective subsequent treatment choice.

Patients with exposure to lenalidomide and a PI as well as patients refractory to lenalidomide have a high unmet medical need, and new effective and convenient treatment options are needed (Moreau 2019).

2.1.6. About the product

Daratumumab is a human, CD38-targeted, IgG1κ monoclonal antibody 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. The addition of daratumumab to standard of care regimens in Phase 3 studies has consistently improved PFS, resulting in a benefit that is both significant and clinically meaningful. The addition of daratumumab also induced higher rates of deep responses, including increases in MRD-negativity rates compared with standard of care alone. Daratumumab in combination with the IMiD lenalidomide and dexamethasone (D-Rd) resulted in a significant PFS benefit versus Rd alone in patients with relapsed/refractory multiple myeloma with at least 1 prior line of therapy (Dimopoulos 2016).

Recently, the daratumumab SC formulation has been approved in the European Union and United States. The SC administration of daratumumab provides a convenient treatment option for patients with a reduced incidence of IRRs, decreased administration burden to both patients and healthcare professionals, and reduced in-hospital time.

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

No CHMP advice was sought for study MMY3013.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.2.1. Ecotoxicity/environmental risk assessment

Daratumumab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no Environmental Risk Assessment for daratumumab is required.

2.3. Clinical aspects

2.3.1. Introduction

The pharmacology package contains data from two combination studies (a Phase 3 Study 54767414MMY3013 and a Phase 1b Study 54767414MMY1001) that evaluated the use of DPd in subjects with relapsed or refractory MM (RRMM) (see Table 1).

In addition, PK data from a phase 1b study (study MMY1001) is used as supporting data. MMY1001 is a multicohort study and the PK data come from the cohort of subjects who received daratumumab IV in combination with Pd (n=103).

In addition to these two studies, PK data are derived from a popPK analysis (described below).

The current work focuses on the characterization of the pharmacokinetics (PK) and exposure-response (E-R) relationships of daratumumab SC or intravenous (IV) in subjects with relapsed or refractory multiple myeloma (RRMM) in combination with pomalidomide and dexamethasone (DPd), a new combination therapy being developed for daratumumab SC.

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

Table 1 Overview of studies and data included in the PPK and E-R analysis

Study No.	Study Title and Design	Brief Description of PK and Efficacy/Safety Data
MMY3013 ongoing PK cut-off date: 06 April 2020 Clinical cut-off date: 21 July 2020	A randomized, open-label, Phase 3 study comparing pomalidomide and dexamethasone (Pd) with or without daratumumab in subjects with relapsed or refractory MM who have received at least 1 prior line of therapy with both lenalidomide and a PI **Daratumumab (DPd subjects):** Doses: daratumumab SC 1800 mg or 16 mg/kg IV. Dose schedule: QW for 8 weeks (Cycles 1 and 2), then Q2W for an additional 16 weeks (Cycles 3 to 6), and then Q4W thereafter (Cycle 7 and beyond). A cycle is 4 weeks **Pomalidomide (all subjects):** Doses and Dose schedule: 4 mg PO on Days 1-21 of each 28-day cycle **Dexamethasone (all subjects):** Doses: 40 mg (20 mg for subjects ≥75 years of age) PO Dose schedule: Once daily on Days 1, 8, 15, and 22 of each 28-day cycle. Split IV/PO when together with daratumumab	304 randomized subjects; DPd: 151, Pd: 153 **PK:** Subjects on daratumumab SC only C1D1+4, C3D1+4, C5-7-12D1 Subjects switched from daratumumab IV to daratumumab SC SC predose first 3 cycles (starting with Cycle 3 or later)+2 FU (possible each cycle D1 after C3) Subjects on daratumumab IV only C1D1 predose, C1D1 EOI, C3D1, C7D1, 4 and 8 weeks after last dose **Efficacy:** Primary endpoint: Progression free survival Secondary endpoints include overall response rate Response or disease progression are derived based on a validated computer algorithm at Day 1 of each cycle **Safety:** Safety is a secondary endpoint. Monitoring for TEAEs takes place continuously throughout the study
MMY1001 (DPd cohort) completed	An open-label, multicenter, Phase 1b study of daratumumab in combination with backbone regimens for the treatment of subjects with MM in either newly diagnosed subjects or those who had received prior therapies, depending in the background treatment regimen **Daratumumab:** Doses: 16 mg/kg. Dose schedule: 16 mg/kg IV QW for 8 weeks (Cycles 1 and 2), then Q2W for an additional 16 weeks (Cycles 3 to 6), and then Q4W thereafter (Cycle 7 and beyond). A cycle is 4 weeks **Pomalidomide:** Doses and Dose schedule: 4 mg PO once daily on Days 1-21 of each 28-day cycle **Dexamethasone:** Doses: 40 mg (20 mg for subjects ≥75 years of age) PO Dose schedule:	103 subjects receiving DPd **PK:** C1-4D1, C1D22 predose+EOI+2 FU (week 3+9) **Efficacy:** Secondary endpoints include overall response rate **Safety:** Safety is a primary endpoint. Monitoring for TEAEs takes place continuously throughout the study Note that this study was pooled with MMY3013 for the PPK analysis, but was only used for side-by-side comparison of safety in the E-R analysis

Study No.	Study Title and Design	Brief Description of PK and Efficacy/Safety Data
	Once daily on Days 1, 8, 15, and 22 of each 28-day cycle. Split IV/PO when together with daratumumab	

Abbreviations: C=cycle; D=day; DPd=daratumumab SC or IV in combination with pomalidomide and dexamethasone; ECOG=Eastern Cooperative Oncology Group; EOI=end-of-infusion; E-R=exposure-response; FU=follow up; IV=intravenous; MM=multiple myeloma; Pd=pomalidomide-dexamethasone; PI=proteasome inhibitor; PK=pharmacokinetic(s); PO=per oral; PPK=population pharmacokinetic; QW=once weekly; Q2W=every 2 weeks; Q4W=every 4 weeks; SC=subcutaneous; TEAE=treatment-emergent adverse event.

[a] PK-evaluable population defined as subjects who received at least 1 dose of daratumumab and had at least 1 serum daratumumab concentration value after the first dosing.

[b] Subjects who started treatment with daratumumab IV and switched to daratumumab SC on Day 1 of any cycle starting with Cycle 3 or later.

Source: IV MM Mod5.3.5.4/MMY1001rrmm; Mod5.3.5.1/MMY3013

2.3.2. Pharmacokinetics

Bioanalysis

Validated electro-chemiluminescent immunoassay (ECLIA)-based methods were used to determine daratumumab concentrations and anti-daratumumab antibodies in human serum samples. A new enhanced drug tolerant PandA ECLIA method was used for the detection of anti-daratumumab antibodies in human serum in Study MMY3013. Daratumumab SC is a co-formulation of daratumumab and rHuPH20. A validated ECLIA method was used for assessment of anti-rHuPH20 antibodies in human plasma after SC administration. A validated in vitro hyaluronidase activity assay with a chromogenic readout was used to test for neutralising capacity.

The cut-off date for pharmacokinetic and immunogenicity data was 06. Apr 2020 (MMY3013).

Population PK analyses

A previously developed (Xu, X et al, 2017 assessed in variations II/29, II/30) population pharmacokinetic (PPK) model was used to characterize the PK of daratumumab following SC or IV administration in combination with dexamethasone and pomalidomide in subjects with RRMM. The PPK analysis was based on 1,146 daratumumab PK samples (473 SC samples and 673 IV samples) from 239 PK-evaluable subjects of Phase 3 Study MMY3013 (N=140) and the DPd cohort of Phase 1b Study MMY1001 (N=99). All subjects from Study MMY1001 received daratumumab IV 16 mg/kg. In Study MMY3013, 95% of PK-evaluable subjects (133/140) received daratumumab SC 1800 mg Seven PK-evaluable subjects received daratumumab IV 16 mg/kg (4 subjects started daratumumab IV 16 mg/kg and switched to SC 1800 mg; 3 subjects received IV 16 mg/kg only). The proportion of PK data below the limit of quantification of 0.2 µg/mL was 1.5% (27/1743) and excluded from the PPK analysis. Two serum daratumumab concentrations were regarded as data outliers and excluded.

The average baseline characteristics of subjects included in the PPK analysis were high age (median 66 years), normal body weight (median 76 kg), White race (84.1%), normal renal function or mild renal impairment (73.6%) and normal hepatic function (84.9%). Note that 4 subjects had body weights <50 kg and 3 subjects had body weights ≥120 kg. Disease characteristics included low Eastern Cooperative Oncology Group (ECOG) status (0 and 1: 92.9%), high number of prior therapies (2 and 3: 62.3%), IgG myeloma (55.2%), refractory to both immunomodulatory imide drug (IMiD) and PI (64.9%) and low International Staging System (ISS) (1: 27.6%). Covariate distributions were in general similar between the 2 studies. Some differences between studies were apparent for ECOG status (lower in MMY3013), and number of prior therapies (higher in MMY1001).

The previous IV/SC 2-compartment PPK model with parallel linear and Michaelis-Menten nonlinear elimination pathways was used to fit the serum concentration-time data of daratumumab using the first-order conditional estimation with the interaction method in NONMEM. PsN Version 3.4.2 or higher was used to execute NONMEM (Nonlinear Mixed Effects Modelling) analyses. Absorption was parameterised in terms

of bioavailability and first-order absorption rate for SC administration. The linear CL represents the nonspecific CL for IgG and the Michaelis-Menten elimination represents the saturable target-mediated CL. Because of the treatment effect of daratumumab, the total target (CD38) number may decrease over time. This was investigated using the empirical function: $TDVM = V_{MAX} \cdot \exp(-K_{DES} \cdot t)$

TDVM represents the time-dependent maximum capacity of the saturable CL and KDES represents first-order rate constant, describing the decrease of the maximum velocity of the saturable CL process over time (t). An additive model was used to model residual variability.

The covariates (body weight, albumin concentration, type of myeloma [IgG versus non-IgG], and sex) that were previously identified were also found to be statistically significant in the PPK model (ie, the 95% CI of the estimated covariate effect did not include the value corresponding to no effect).

The final model was evaluated by means of parameter estimates (Table 5), goodness-of-fit diagnostic plots and visual predictive checks (data not shown).

Table 2 **Parameter Estimates of the PPK Model of Daratumumab Based on Combined Daratumumab SC and Daratumumab IV Data Following DPd Combination Therapy**

Parameter, unit	Description	Estimate	95% CI	RSE on Estimate (%)	IIV (%CV)	RSE on IIV (%)
CL (L/h)	Linear clearance	0.00432	(0.00351;0.00513)	9.51	43.5	8.65
ALB on CL[a]	Effect of serum albumin concentration on linear clearance	-0.665	(-1.13;-0.199)	35.8	-	-
WT on CL[a]	Effect of body weight on linear clearance	0.832	(0.483;1.18)	21.4	-	-
TPMC on CL[a]	Effect of type of myeloma (IgG versus non-IgG) on linear clearance	0.833	(0.517;1.15)	19.3	-	-
V_1 (L)	Volume of distribution in the central compartment	4.36	(3.86;4.86)	5.87	28.0	10.8
WT on V_1[b]	Effect of body weight on volume of distribution in the central compartment	0.562	(0.25;0.874)	28.3	-	-
SEX on V_1[b]	Effect of sex (female versus male) on volume of distribution in the central compartment	-0.168	(-0.28;-0.0563)	33.9	-	-
V_2 (L)	Volume of distribution in the peripheral compartment	2.80	(2.00;3.60)	14.6	-	-
Q (L/h)	Intercompartmental clearance	0.00814	(0.00483;0.0115)	20.8	-	-
V_{max} (mg/h)	Maximum velocity of the saturable clearance process	1.47	(1.09;1.85)	13.1	59.6	13.4
K_{DES} (1/h)	First-order rate for decrease of maximum velocity of the saturable clearance process over time	0.000282	(0.000154;0.000410)	23.2	75.3	20.2
K_m (µg/mL)	Michaelis-Menten constant	3.81	(1.20;6.42)	34.9		-
Ka (1/h)	First-order absorption rate	0.0120	(0.00967;0.0143)	9.9	55.4	12.2
F1	Bioavailability	0.689 (FIX)	-	-	-	-
ADD ERR (%CV)	Additive error term on the log-scale	27.7	(26.7;28.7)	1.8	-	-

Abbreviations: CI=confidence interval; CV=coefficient of variation; DPd=daratumumab SC or IV in combination with pomalidomide and dexamethasone; FIX=not estimated; IgG=immunoglobulin G; IIV=interindividual variability; IV=intravenous; PK=pharmacokinetic(s); PPK=population pharmacokinetic; RSE=relative standard error; SC=subcutaneous; TV=typical values; TVCL=typical value of clearance; TVV=typical value of volume of distribution.

[a] $TVCL = 0.00432 \cdot \left(\frac{WT}{76}\right)^{0.832} \cdot \left(\frac{ALB}{38}\right)^{-0.665} \cdot TPMC_{CL}$ where $TPMC_{CL}$ is a shift factor of 1 for non-IgG multiple myeloma subjects and 1+ 0.833 for IgG multiple myeloma subjects.

[b] $TVV1 = 4.36 \cdot \left(\frac{WT}{76}\right)^{0.562} \cdot SEX_{V1}$, where SEX_{V1} is a shift factor of 1 for male and 1-0.168 for female.

Note: Objective function value=-780.8. Condition number=41.7. 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(ω2) and sqrt (σ2), respectively.

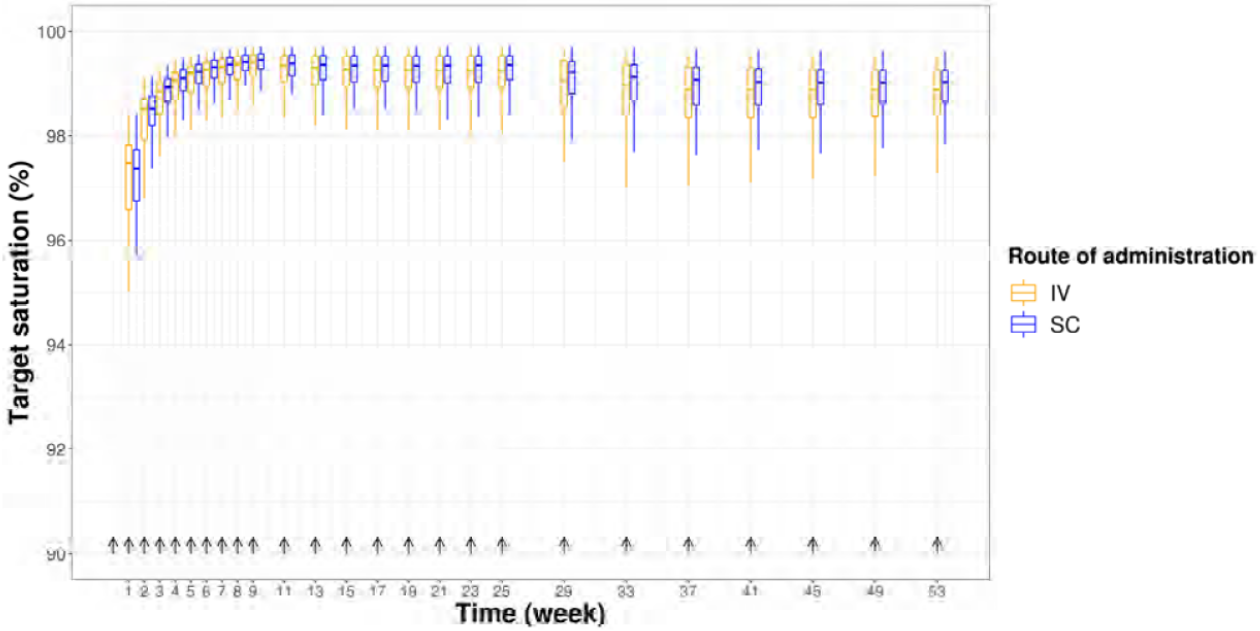
95% CIs are calculated based on standard error from covariance matrix assuming PK parameters are normally distributed.

PK simulations and subgroup analyses

Simulations were performed to graphically show the simulated daratumumab serum concentrations versus time and their 90% variability after SC 1800 mg and IV dosing 16 mg/kg and for sub-group analysis. Subgroup analysis of Ctrough,C3D1 showed that body weight, albumin concentration, and type of myeloma (IgG versus non-IgG) had an impact of <20% on Ctrough,C3D1.(data not shown).

In addition, target saturation versus time and its variability was simulated and plotted according to: TSAT = 100×(Conc×(Km+Conc)), where TSAT is the saturation ratio, Conc is the simulated daratumumab serum concentration and Km is the estimated Michaelis-Menten constant in the final PK model. Target saturation versus time was simulated based on the estimated Km of 3.81 µg/mL (95% CI 1.2-6.42) in the final Pop PK model.

Figure 1 **Simulated Target Saturation Over Time After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Administration per the Recommended Dose Schedule for DPd Combination Therapy**



Abbreviations: DPd=daratumumab SC or IV in combination with pomalidomide and dexamethasone; IV=intravenous; SC=subcutaneous.

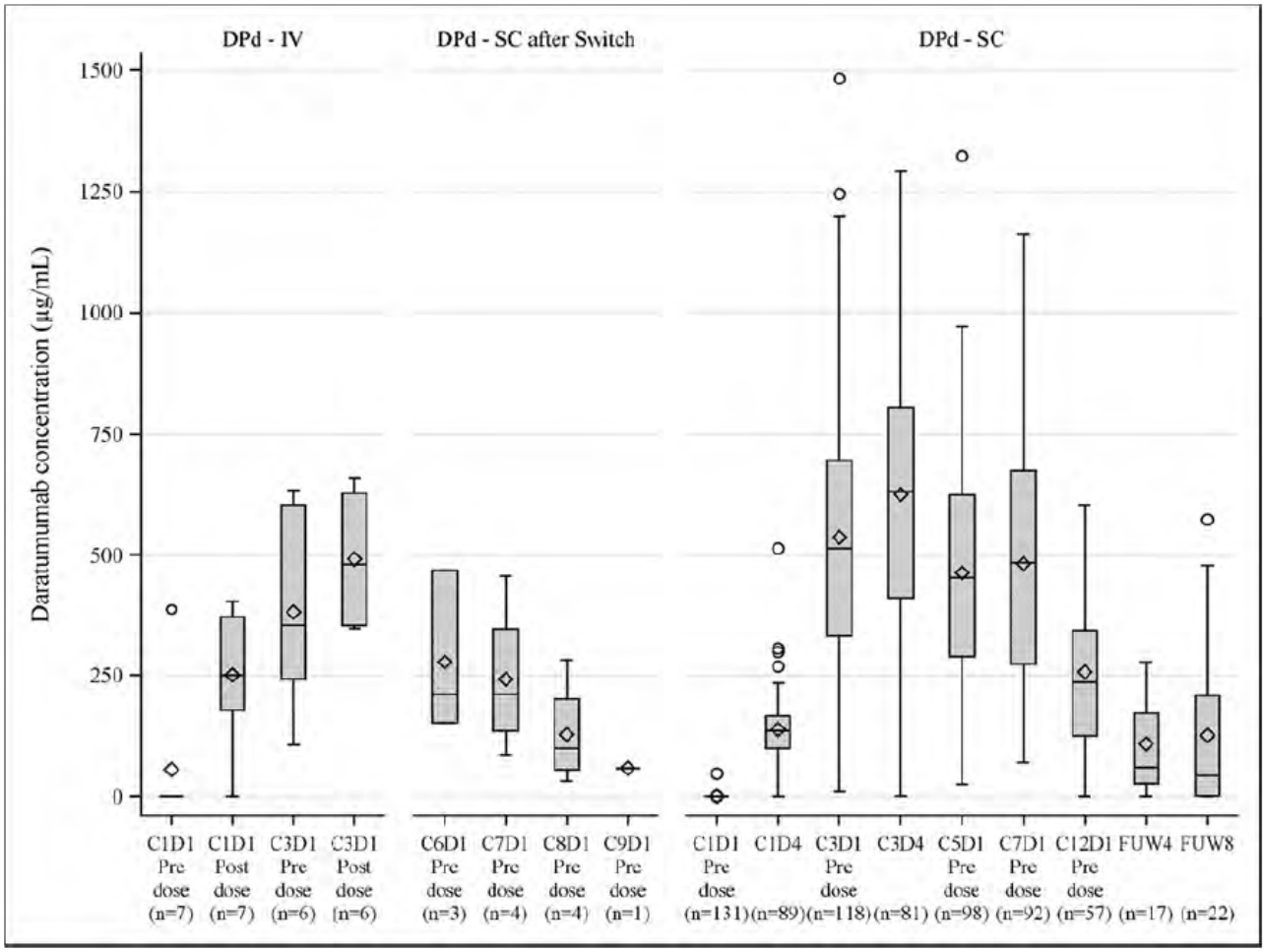
Note: The pharmacokinetics simulation was performed with N=133 subjects for SC from MMY3013 and N=106 subjects for IV (99 from MMY1001 and 7 from MMY3013).

Absorption and bioavailability

In the phase 3 study MMY3013, a total of 140 subjects were included for the assessment of Cmax and Ctrough of daratumumab as the PK-evaluable population, ie, subjects who received at least 1 dose of daratumumab and had at least 1 serum daratumumab concentration value after the first dose (SC or IV). Most subjects (133/140, 95%) received daratumumab SC starting from the first dose; 3 subjects received daratumumab IV only and 4 subjects received daratumumab IV initially and then switched to daratumumab SC.

Cmax of daratumumab SC 1800 mg dosed in combination with Pd was consistent with historical data following daratumumab SC 1800 mg monotherapy or in other combinations at the same dose schedule. Following the first SC dose of 1800 mg daratumumab, the mean±standard deviation (SD) maximum concentration (Cycle 1 Day 4) was 138±71.2 µg/mL (**Figure** 2). The accumulation ratio in mean peak Cmax from the first dose (Cycle 1 Day 4; 138±71.2 µg/mL) to the ninth dose (Cycle 3 Day 4; 625±286 µg/mL) was approximately 4.5-fold.

Figure 2: Box Plot of serum daratumumab C_{trough} and C_{max} concentrations (µg/mL) over time; PK Analysis Set (54767414MMY3013)



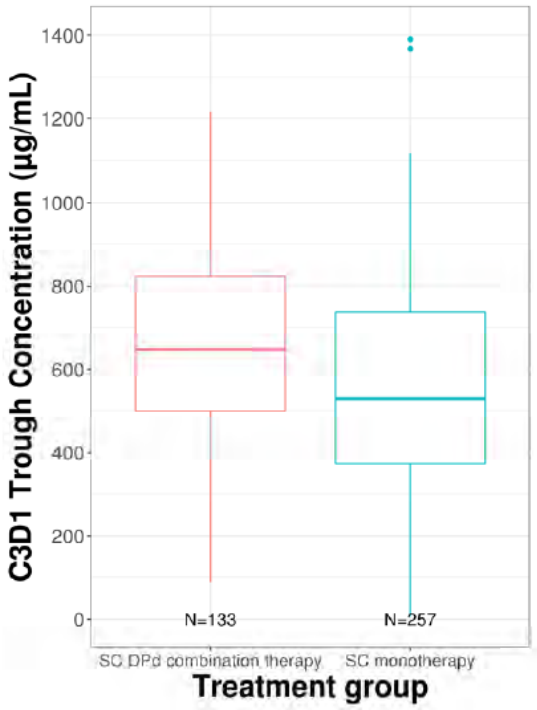
C=Cycle; Cmax=peak serum concentration; Ctrough=trough concentration; D=Day; DPd=daratumumab SC or IV in combination with pomalidomide and dexamethasone; FU=follow-up; IQR=interquartile range; IV=intravenous; PK=pharmacokinetic(s); Q=quartile; SC=subcutaneous.
Note: Ctrough was defined as the observed pre-dose concentration immediately before daratumumab administration; Cmax was defined as concentrations observed at the end-of-infusion for IV treatment or on Day 4 for SC administration.
The boxplot displays a box with the 3 lines representing Q1, median (Q2), and Q3, respectively, upper whisker of Q3+1.5*IQR, and lower whisker of Q1-1.5*IQR. Outlier values beyond the whiskers are displayed as circles. The diamond inside the box represents the arithmetic mean.
DPd-IV includes subjects with daratumumab IV only and also the IV administrations of subjects who were randomized to DPd group and administrated with daratumumab IV (prior to Amendment 1) and then switched to daratumumab SC during the study.
DPd-SC after switch includes only the SC administrations of subjects who switched to daratumumab SC during the study (after Amendment 1).

The absorption of the SC formulation was modeled as a first-order absorption process. In the popPK analysis, Cmax following the recommended dose schedule for DPd combination therapy was determined to be 697 µg/mL.

In study MMY3013, trough serum concentrations increased to the maximum Ctrough on Cycle 3 Day 1 pre-dose (537±277 µg/mL [mean±SD]).

Based on the same dosing regimen of daratumumab SC, the simulated cycle 3 predose C_{trough} of daratumumab SC as monotherapy or part of Dpd combination therapy is shown in **Figure 3** below.

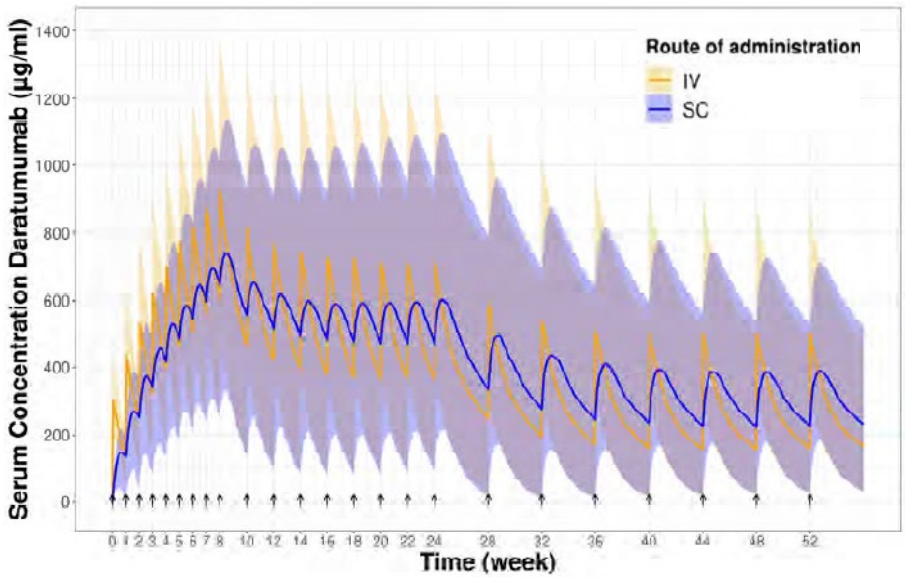
Figure 3. Simulated Daratumumab trough concentrations at cycle 3 day 1 after daratumumab SC 1800 mg administration for DPd combination therapy (MMY3013) and monotherapy (MMY3012) per the recommended dose schedule



Abbreviations: C3D1=Cycle 3 Day 1; DPd=daratumumab SC or IV in combination with pomalidomide and dexamethasone; SC=subcutaneous.

A comparison of daratumumab exposure between SC DPd regimen and IV DPd regimen (most subjects from MMY1001) was made in the popPK analysis (*Figure 4*). As shown, the SC exposure lies within the fluctuations of the IV exposure curve.

Figure 4. Simulated Median PK Profile and 90% Prediction Interval of Daratumumab After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Administration per the Recommended Dose Schedule for DPd Combination Therapy



Abbreviations: DPd=daratumumab SC or IV in combination with pomalidomide and dexamethasone; IV=intravenous; PK=pharmacokinetic(s); QW=once weekly; Q2W=every 2 weeks; Q4W=every 4 weeks; SC=subcutaneous.

Key: Black arrows represent dose events. The shaded orange and blue areas represent the 90% prediction interval of daratumumab PK (N=133 subjects for SC from MMY3013, N=106 subjects for IV [99 from MMY1001 and 7 from MMY3013],). Note: Recommended dose schedule consisted of QW for 8 weeks (8 doses), Q2W for 16 weeks (8 doses), and Q4W thereafter (eg, 8 doses).

The estimated **bioavailability** for the SC formulation is approximately 0.69, which is consistent with other mAbs subcutaneously co-administered with rHuPH20.

Peak concentrations after administration of the first SC dose (Cycle 1 Day 4) were in general comparable across monotherapy and combination therapies (ie, DPd and other combinations).

In study MMY3013, peak Cmax was reached on cycle 3 day 4 and averaged 625±286 µg/mL. The accumulation ratio from the first dose was approximately 4.5-fold. The estimated bioavailability for the SC formulation is approximately 69%. Peak concentration after the first dose is in average reached on C1D4.

Median cycle 3 Ctrough (predose level) of the SC 1800 mg cohort was found to be a bit higher than in the IV 16 mg/kg cohort, although the information from the IV data is limited by the very small sample size.

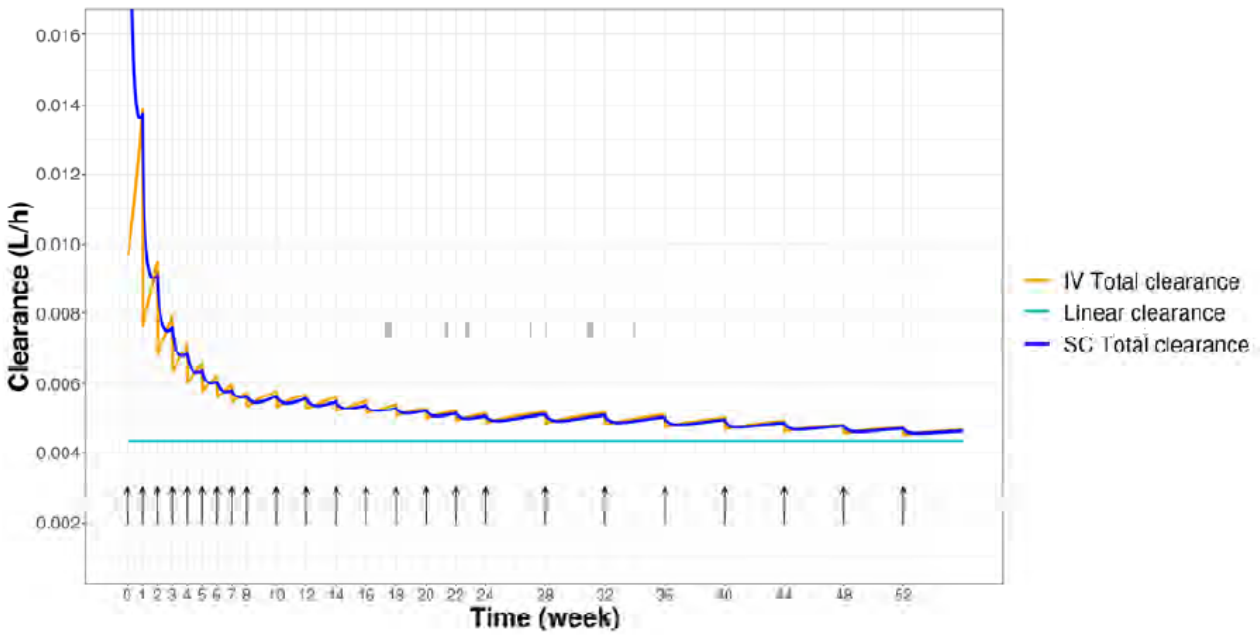
Distribution

From the popPK analysis, the volume of distribution of the central compartment was estimated to 4.36 L which is close to plasma volume.

Elimination

Typical clearance profiles of daratumumab SC and IV in combination with Pd is shown in **Figure 5**.

Figure 5: Simulated Typical Total and Linear Clearance Versus Time Profiles After Daratumumab SC 1800 mg or Daratumumab IV 16 mg/kg Administration per the Recommended Dose Schedule for DPd Combination Therapy



Abbreviations: DPd=daratumumab SC or IV in combination with pomalidomide and dexamethasone; IV=intravenous; SC=subcutaneous.
Key: Black arrows represent dose events.

The estimated linear CL of 0.00432 L/h [0.104 L/day] is close to the reported CL of nonspecific endogenous IgG.

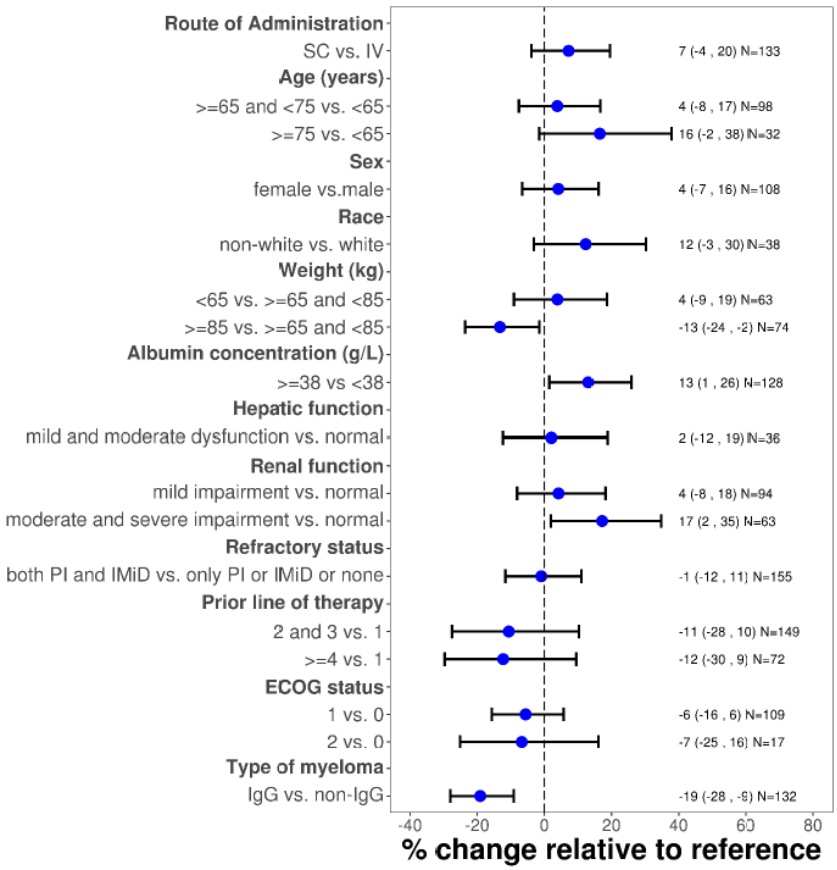
The model-derived geometric mean (CV%) half-life associated with linear elimination was 19.7 days (15.3%), comparable to the estimated half-life derived from the previous monotherapy of 20.4 days (22.4%).

Special populations

Renal and hepatic impairment

No formal studies of daratumumab in subjects with renal or hepatic function have been conducted. The effect of renal or hepatic function on daratumumab PK for DPd has been evaluated by a popPK approach (pooled data from Studies MMY3013 and MMY1001, Figure 6), and no clinically relevant impact has been identified for subjects with mild and moderate renal or hepatic impairment. As regards the latter, 34 subjects had mild and only 2 subjects had moderate hepatic impairment. There were only N=3 subjects with severe renal impairment and N=0 with severe hepatic impairment so it was not possible to make any or meaningful conclusions for these subgroups. The results are consistent with the previous results from daratumumab SC monotherapy.

Figure 6. Forest Plot of Subgroup Analyses on Percent Change and 95% CI Relative to Reference Value for Simulated Trough Concentration at Cycle 3 Day 1 per the Recommended Dose Schedule for DPd Combination Therapy



CI=confidence interval; DPd=daratumumab SC or IV in combination with pomalidomide and dexamethasone; ECOG=Eastern Cooperative Oncology Group; IgG=immunoglobulin G; IMiD=immunomodulatory imide drug; IV=intravenous; PI=proteasome inhibitor; PK=pharmacokinetics; Q2W=every 2 weeks; Q4W=every 4 weeks; SC=subcutaneous.

Key: Solid blue point represents percentage change of geometric mean and short horizontal bar represents 95% CI. Dashed line represents reference value of 0. Numbers represent percentage of change and the associated CI. Note: Analyses assumed that all PK-evaluable subjects in DPd groups of Studies MMY3013 and MMY1001 received 16 mg/kg weekly for 8 weeks (8 doses), Q2W for 16 weeks (8 doses), and then Q4W thereafter. The 4 subjects first administered daratumumab IV 16 mg/kg and then switched to SC 1800 mg were assumed to have received IV administration throughout. The number of subjects in the reference group for each covariate: route of administration IV (N=106 [99 from MMY1001 and 7 from MMY3013]), age <65 years (N=109); male (N=131); White (N=201); body weight 65 to 85 kg (N=102); albumin concentration ≥38 g/L (N=111); normal hepatic function (N=203); normal renal function (N=82); PI/IMiD refractory status only PI or IMiD or none (N=84), number of prior lines of therapy 1 (N=18), ECOG=0 (N=113); non-IgG myeloma (N=71). IgG myeloma status of 36 subjects were missing and not present in the plot. Two subject had moderate hepatic impairment and were combined with subjects with mild hepatic impairment. Three subjects had severe renal impairment and were combined with subjects with moderate renal impairment. Subjects refractory to a certain regimen are considered refractory to all drugs in such regimen. Source: Mod5.3.3.5/PPK Report/Fig9

Gender

PopPK simulations (Figure 6), based on post hoc PK parameters, demonstrated that the simulated daratumumab $C_{trough, C3D1}$ was 4% higher (95% CI: -7% to +16%) in females versus males.

Weight

Body weight was a statistically significant covariate identified for CL and volume of distribution in the central compartment of daratumumab.

PopPK simulations (Figure 6), based on post hoc PK parameters, demonstrated that simulated daratumumab $C_{trough, C3D1}$ was similar in subjects with body weight <65 kg versus subjects with body weight ≥65 kg to <85 kg, while subjects with body weight ≥85 kg had 13% (95% CI: -24% to -2%) lower $C_{trough, C3D1}$ exposure when compared with those with body weight ≥65 kg to <85 kg. There was no notable impact of body weight on efficacy or safety during the E-R analyses.

Age

Approximately 45.6% of the subjects in the PK analysis dataset were <65 years (N=109/239), 41.0% between ≥65 and <75 years (N=98/239), and 13.4% of subjects ≥75 years (N=32/239).

PopPK simulations (Figure 6), based on post hoc PK parameters, demonstrated that simulated daratumumab $C_{trough, C3D1}$ was approximately 4% higher (95% CI:-8% to +17%) in subjects ≥65 and <75 years and 16% higher (95% CI: -2% to +38%) in subjects ≥75 years, respectively, compared with subjects <65 years.

Drug-drug interaction studies

No dedicated drug-drug interaction studies were performed for daratumumab SC. Since there is no overlapping pathway of elimination, no interactions are expected between daratumumab and small-molecule drugs including Pd.

Daratumumab SC PK data in DPd combination from study MMY3013 was assessed relative to daratumumab SC monotherapy (study MMY3012) and the exposures were comparable. The PK profiles of small-molecule combination agents including pomalidomide when dosed in combination with daratumumab IV (study MMY1001) or without daratumumab (literature value) were found to be comparable. In addition, the PK of daratumumab dosed SC or IV in multiple combination therapy studies were similar to SC or IV monotherapy. These data indicate a lack of PK interaction between daratumumab and the small-molecule medicinal products tested, including the DPd combination agents of pomalidomide and dexamethasone.

Immunogenicity

Anti-daratumumab Antibodies

In the anti-daratumumab immunogenicity-evaluable analysis set, the cumulative incidence of anti-daratumumab antibodies was low in subjects who received daratumumab treatment in combination with Pd (**Table below**):

Table 3 : Anti-daratumumab Antibody Status; Daratumumab Immunogenicity-evaluable Analysis Set in Subjects Revived DPd Treatment (MMY3013, MMY1001)

	DPd-SC (MMY3013)	DPd-IV then SC (MMY3013)	DPd-IV		
			MMY3013	MMY1001	Total IV
Analysis set: daratumumab immunogenicity-evaluable for subjects with appropriate samples[a]	119	4	0	45	45
Subjects positive for anti-daratumumab antibodies[b,c]	2 (1.7%)	0	0	0	0
Subjects positive for neutralizing antibodies[d]	2 (1.7%)	0	0	0	0
Subjects negative for anti-daratumumab antibodies[b]	117 (98.3%)	4 (100%)	0	45 (100%)	45 (100%)

DPd=daratumumab in combination with pomalidomide and dexamethasone; IV=intravenous; SC=subcutaneous.
[a] Subjects who received at least 1 dose of daratumumab SC or daratumumab IV and had appropriate serum samples for detection of antibodies to daratumumab (at least 1 sample after the start of the first dose of daratumumab).
[b] Percentages are calculated with the number of subjects with appropriate sample as the denominators.
[c] Includes all subjects who had at least 1 positive sample at any time after start of treatment, including those who did not have a baseline sample. Baseline positive subjects were included only if post-treatment sample titers increased by at least 2-fold compared with baseline.
[d] Only samples positive for anti-daratumumab antibodies from anti-daratumumab positive subjects were assayed for neutralizing antibodies.
Source: IV MM Study MMY1001 CSR; Mod5.3.5.1/MMY3013/Tab12

Anti-rHuPH20 Antibodies

In study MMY3013, six (6/122, 4.9%) subjects had baseline positive anti-rHuPH20 samples, and the incidence of treatment-emergent anti-rHuPH20 antibodies was 7.4% (9/122) after the first daratumumab SC administration, all non-neutralizing. Daratumumab exposure was comparable between subjects with treatment emergent anti-rHuPH20 antibodies and those who were negative for anti-rHuPH20 antibodies.

These data were consistent with the historical daratumumab SC findings in subjects with MM.

2.3.3. Pharmacodynamics

Mechanism of action

Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumour cells, as well as other cell types and tissues at various levels. Daratumumab has been shown to potently inhibit the in vivo growth of CD38-expressing tumour cells. 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.

Translational biomarker studies of samples from subjects treated with daratumumab in Phase 1 and Phase 2 studies have revealed previously unknown immunomodulatory effects of daratumumab (Krejcik 2016). Daratumumab leads to the rapid and sustained elimination of highly immunosuppressive subsets of CD38+ regulatory T cells, CD38+ myeloid-derived suppressor cells, and CD38+ regulatory B cells (Krejcik 2016). The elimination of these immunosuppressive cells, modulation of CD38 enzymatic activity, and destruction of the malignant myeloma cells are followed by the increase in T cell clonality (Chiu 2016) and subsequent expansion of CD8+ and CD4+ subsets (Krejcik 2016). In particular, patients responding to daratumumab

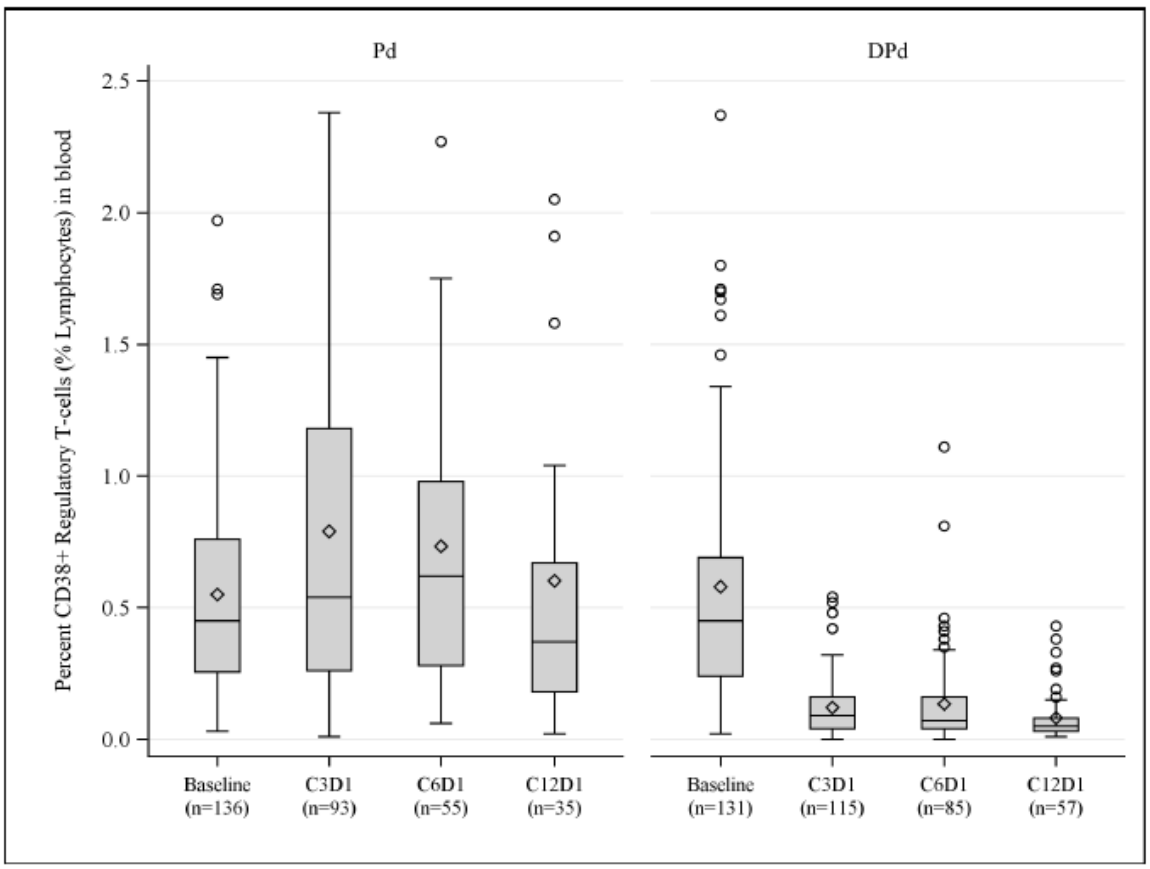
treatment showed an increase in the activated CD8+ T cells expressing high levels of granzyme B (Adams 2019). Together, daratumumab's cytotoxic and immunomodulatory mechanisms of action are hypothesized to synergistically result in deep anti-myeloma responses.

Primary pharmacology

As described in the MMY3013 CSR, addition of daratumumab SC to the treatment regimen resulted in a decrease in the NK cell and CD38+ regulatory T cell populations in the blood (**Figure 8** below).

Figure 7

T14.02-11.16F: Plot of Percent CD38+ Regulatory T-cells (% Lymphocytes) in Blood over Time; Biomarker Analysis Set (Study 54767414MMY3013)

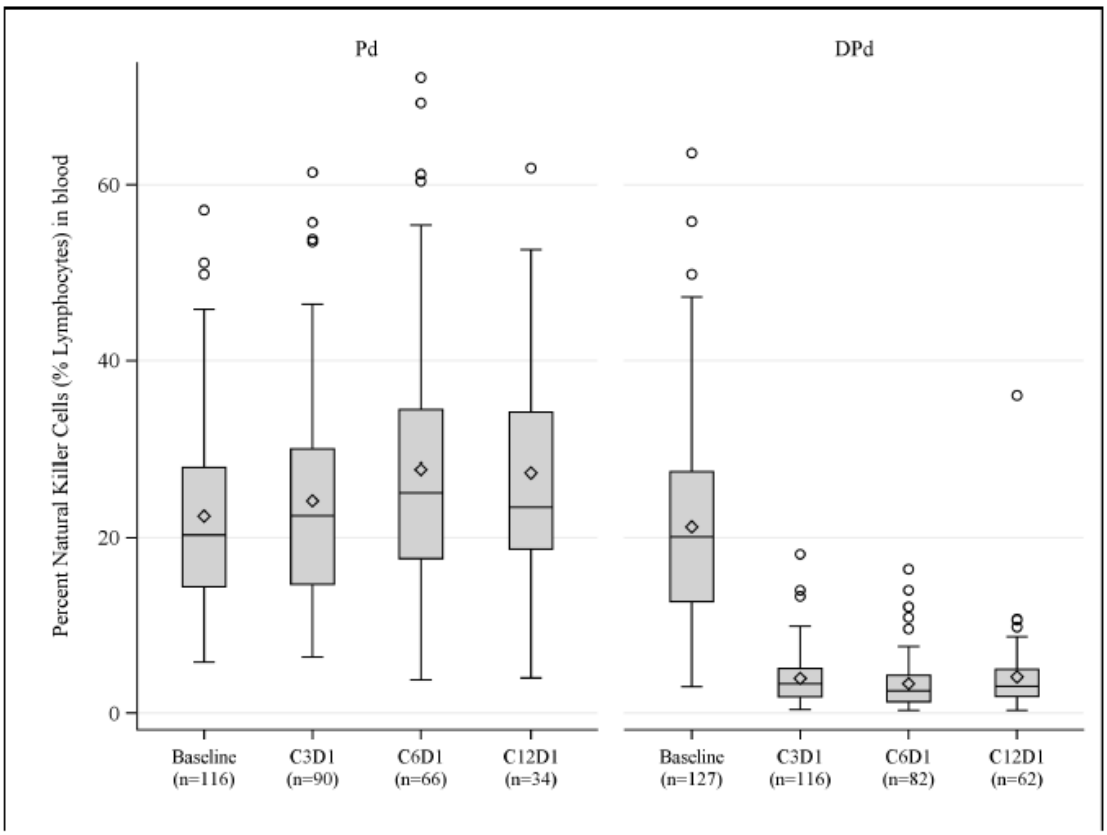


Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
The boxplot displays a box with the 3 lines representing Q1, Median (Q2) and Q3 respectively, upper whisker of Q3 + 1.5*IQR (interquartile range) and lower whisker of Q1 - 1.5*IQR.
Outlier values beyond the whiskers are displayed as circles. The diamond inside the box represents the arithmetic mean.
Note: The outlier values above 2.5% were not included in this graph.

Filename: T14.02-11.16F.RTF / Program: T14.02-11.Plot.sas (05OCT2020 20:58)

Figure 8

T14.02-11.06F: Plot of Percent Natural Killer Cells (% Lymphocytes) in Blood over Time; Biomarker Analysis Set (Study 54767414MMY3013)



Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
The boxplot displays a box with the 3 lines representing Q1, Median (Q2) and Q3 respectively, upper whisker of Q3 + 1.5*IQR (interquartile range) and lower whisker of Q1 - 1.5*IQR.
Outlier values beyond the whiskers are displayed as circles. The diamond inside the box represents the arithmetic mean.
Filename: T14.02-11.06F.RTF / Program: T14.02-11.Plot.sas (05OCT2020 20:58)

Exploratory exposure-response analyses

The purpose of the Exposure response (E-R) analysis was to supplement the evidence of efficacy and safety of daratumumab in combination with Pd in subjects with RRMM and to confirm the selected dosing regimen.

The final E-R dataset, used for both efficacy and safety E-R analyses, contained data from 290 subjects in Study MMY3013 who had received at least 1 dose of Pd (N=150) or DPd (N=140). For the DPd group, only subjects with at least 1 evaluable PK concentration were included in the final E-R dataset to be able to derive individual exposure. Subjects randomized but not receiving a dose (N=3 for Pd group, N=2 for DPd group) were not included. All other subjects were pooled in the E-R analysis.

Table 4 **Quantiles of the PK Exposure Metrics Used in the E-R Analysis**

Quantile	$C_{peak,first}$ (µg/mL)	$C_{trough,first}$ (µg/mL)	$C_{peak,max}$ (µg/mL)	$C_{trough,max}$ (µg/mL)
0%	6.50	0.400	125	14.8
25%	121	109	491	398
50%	151	135	651	544
75%	185	161	839	722
100%	374	238	1440	1261

Abbreviations: $C_{peak,first}$=predicted peak concentration after first dose; $C_{trough,first}$=predicted trough concentration after first dose; $C_{peak,max}$=predicted maximum peak concentration; $C_{trough,max}$=predicted overall maximum trough concentration; E-R=exposure-response; PK=pharmacokinetic(s).

Efficacy exposure-response analysis

Three PK exposure metrics derived by Pop PK were used for the efficacy E-R analysis: Cpeak,first, Ctrough,first, and Ctrough,max. Covariates used in the case matching analysis were selected from a set of predefined covariates based on a Cox proportional hazard model.

Table 5

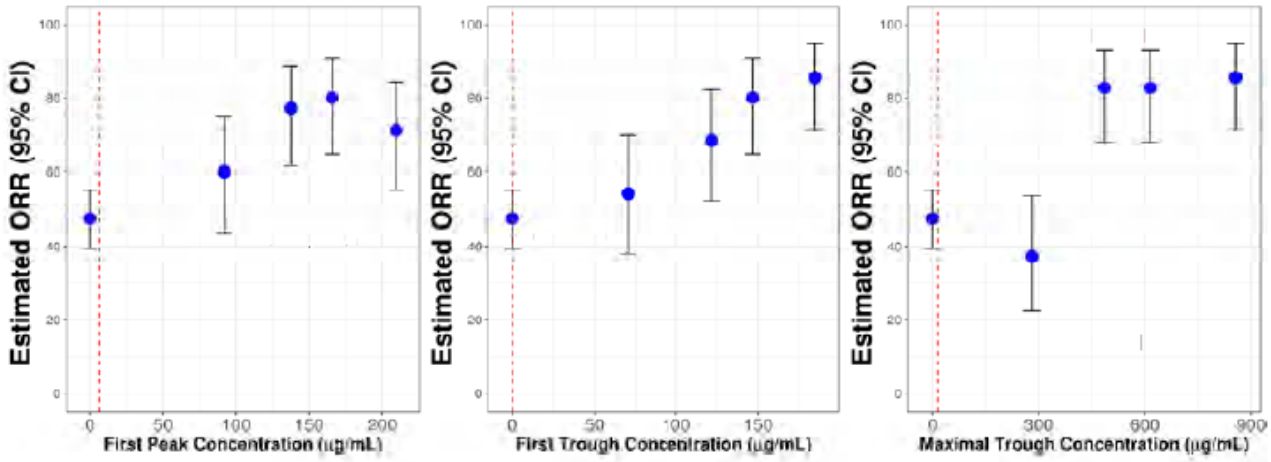
Final Covariate Model for PFS (MMY3013 Pd Subjects)

Covariate	Hazard Ratio Estimate	Lower Limit of 95%CI	Upper Limit of 95%CI	p-value
ISS (≥2 vs 1)	1.73	1.16	2.58	0.007
High cytogenetic risk (no vs yes)	0.61	0.39	0.96	0.031
Refractory to Lenalidomide (yes vs no)	1.75	1	3.05	0.049
Race (Non-White vs White)	2.13	1.17	3.87	0.013

Abbreviations: CI=confidence interval; ISS=International Staging System; Pd=pomalidomide-dexamethasone; PFS=progression-free survival; vs=versus.

The relationship between exposure and the primary efficacy endpoint PFS was investigated (Figure 9). The ORR by exposure was also compared (Figure 8). The relationship between drug exposure and PFS was analysed graphically using Kaplan-Meier plots.

Figure 9: Overall Responder Rate by Daratumumab Exposure Subgroups for DPd Combination Therapy



Abbreviations: CI=confidence interval; $C_{peak,first}$=predicted peak concentration after first dose; $C_{trough,first}$=predicted trough concentration after first dose; $C_{trough,max}$=predicted overall maximum trough concentration; DPd=daratumumab SC or IV in combination with pomalidomide and dexamethasone; ORR=overall response rate; Pd=pomalidomide-dexamethasone; Q1=first quartile, Q2=second quartile, Q3=third quartile, Q4=fourth quartile of daratumumab exposure.

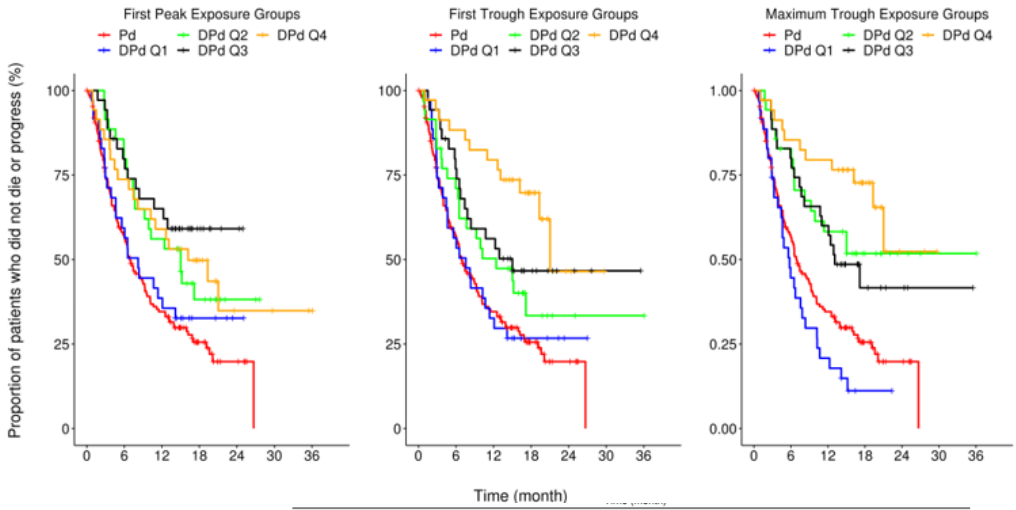
Key: The dashed red line represents the lowest exposure in the DPd group.

Estimated responder rates and 95% CIs are reported for the Pd group at concentration=0 ug/mL, and for each of the daratumumab DPd exposure quartiles at the median exposure of the quartile.

The quartiles for $C_{peak,first}$ were: first quartile (≤121 µg/mL), Q2 (>121 to ≤151 µg/mL), Q3 (>151 to ≤185 µg/mL), and Q4 (>185 to ≤374 µg/mL). The quartiles for $C_{trough,first}$ were: first quartile (≤109 µg/mL), Q2 (>109 to ≤135 µg/mL), Q3 (>135 to ≤161 µg/mL), and Q4 (>161 to ≤239 µg/mL). The quartiles for $C_{trough,max}$ were: first quartile (≤398 µg/mL), Q2 (>398 to ≤544 µg/mL), Q3 (>544 to ≤722 µg/mL), and Q4 (>722 to ≤1,261 µg/mL).

The same trend of lower efficacy in the lowest exposure quartile is seen for PFS (Figure below):

Figure 10 *Kaplan-Meier Curves of Progression-free Survival by Daratumumab Exposure Subgroups in Combination With Pd in Study MMY3013*



Abbreviations: DPd=daratumumab SC or IV in combination with pomalidomide and dexamethasone; Pd=pomalidomide-dexamethasone; Q1=first quartile, Q2=second quartile, Q3=third quartile, Q4=fourth quartile of daratumumab exposure.

Note: First trough is trough concentration after the first administration; first peak is peak concentration after the first administration; maximum trough is the overall maximum trough concentration.

The quartiles for $C_{peak,first}$ were: Q1 (≤121 µg/mL), Q2 (>121 to ≤151 µg/mL), Q3 (>151 to ≤185 µg/mL), and Q4 (>185 to ≤374 µg/mL). The quartiles for $C_{trough,first}$ were: Q1 (≤109 µg/mL), Q2 (>109 to ≤135 µg/mL), Q3 (>135 to ≤161 µg/mL), and Q4 (>161 to ≤239 µg/mL). The quartiles for $C_{trough,max}$ were: Q1 (≤398 µg/mL), Q2 (>398 to ≤544 µg/mL), Q3 (>544 to ≤722 µg/mL), and Q4 (>722 to ≤1,261 µg/mL).

Safety exposure-response analysis

Two PK exposure metrics were used for the safety E-R analysis: Cpeak,first for IRRs and Cpeak,max for all other TEAEs. The E-R relationship for selected TEAEs of clinical interest considered the safety endpoints: IRRs, neutropenia, anemia, thrombocytopenia, and infections. The TEAEs were stratified by the appropriate exposure metrics to evaluate whether there was a relationship between the TEAEs and exposure to daratumumab. The results were compared with those obtained from the DPd cohort of Study MMY1001.

There was no apparent increase in TEAEs rates with increasing exposure (Cpeak,first or Cpeak,max) for IRRs, thrombocytopenia, anemia, neutropenia, and infections (all Grades and Grades ≥3) within the studied drug concentration range in Study MMY3013 (Table 6). A decreasing trend in the event rate of neutropenia, anemia, and trombocytopenia was observed based on Cpeak,max (ie, a higher rate of TEAEs was observed in the lowest Cpeak,max at Q1). This is likely because subjects with TEAEs tended to have dose interruption or delays, which led to lower concentrations in these subjects. No increase in the rates of the TEAEs investigated in this E-R analysis had been observed in the clinical statistical analysis with decreasing body weights subgroup, except for anemia. The increased anemia rate with low body weight was not related to an increase in exposure, as in the E-R analysis increased exposure led to lower anemia rates.

Table 6: Comparison of Treatment-emergent Adverse Event Rates Across Predicted Daratumumab Exposure Subgroups for DPd Combination Therapy in Study MMY3013

TEAE	Pd % (95% CI) N=150	DPd Exposure Quartiles, % (95% CI) Q1 N=35	Q2 N=35	Q3 N=35	Q4 N=35
Neutropenia	53.3 (45.3;61.2)	82.9 (68.3;92.8)	77.1 (61.6;88.8)	71.4 (55.3;84.5)	71.4 (55.3;84.5)
Grade ≥3	50.7 (42.7;58.6)	74.3 (58.4;86.7)	74.3 (58.4;86.7)	71.4 (55.3;84.5)	71.4 (55.3;84.5)
Infections	55.3 (47.3;63.1)	74.3 (58.4;86.7)	74.3 (58.4;86.7)	71.4 (55.3;84.5)	71.4 (55.3;84.5)
Grade ≥3	23.3 (17.1;30.5)	42.9 (27.4;59.3)	31.4 (17.7;47.7)	25.7 (13.3;41.6)	20.0 (9.1;35.1)
Anemia	44.7 (36.9;52.7)	48.6 (32.6;64.8)	42.9 (27.4;59.3)	28.6 (15.5;44.7)	25.7 (13.3;41.6)
Grade ≥3	21.3 (15.3;28.3)	34.3 (20.1;50.7)	17.1 (7.2;31.7)	5.7 (1.0;16.6)	8.6 (2.2;20.7)
Thrombocytopenia	33.3 (26.1;41.1)	42.9 (27.4;59.3)	37.1 (22.5;53.6)	22.9 (11.2;38.4)	20.0 (9.1;35.1)
Grade ≥3	18.0 (12.4;24.7)	31.4 (17.7;47.7)	25.7 (13.3;41.6)	5.7 (1.0;16.6)	8.6 (2.2;20.7)
IRRs	0 (0;0)	8.6 (2.2;20.7)	5.7 (1.0;16.6)	2.9 (0.2;12.0)	5.7 (1.0;16.6)
Grade ≥3	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)	0 (0;0)

Abbreviations: CI=confidence interval; $C_{peak,first}$=predicted peak concentration after first dose; $C_{peak,max}$=predicted maximum peak concentration; DPd=daratumumab SC or IV in combination with pomalidomide and dexamethasone; IRRs=infusion-related reactions; N=maximum number of subjects with data; Pd=pomalidomide-dexamethasone; Q1=first quartile, Q2=second quartile, Q3=third quartile, Q4=fourth quartile of daratumumab exposure;; TEAE=treatment-emergent adverse event.

Key: $C_{peak,max}$ was used as the exposure measure for analyses on all adverse events except IRRs, where $C_{peak,first}$ was used.

The quartiles for $C_{peak,max}$ were: Q1 (≤491 µg/mL), Q2 (>491 to ≤651 µg/mL), Q3 (>651 to ≤839 µg/mL), and Q4 (>839 to ≤1,440 µg/mL). The quartiles for $C_{peak,first}$ were: Q1 (≤121 µg/mL), Q2 (>121 to ≤151 µg/mL), Q3 (>151 to ≤185 µg/mL), and Q4 (>185 to ≤374 µg/mL).

The absence of apparent increase in selected TEAEs rates and increasing daratumumab exposure was in line with results from the DPd cohort of Study MMY1001.

2.3.4. PK/PD modelling

See above.

2.3.5. Discussion on clinical pharmacology

The purpose of the presented PK package is to support a new indication for SC daratumumab: combination treatment with daratumumab SC, pomalidomide, and dexamethasone (DPd) for the treatment of patients with multiple myeloma (MM) who have received at least 1 prior line of therapy. The pharmacology package contains data from two combination studies; a phase 3 Study 54767414MMY3013 and a phase 1b Study 54767414MMY1001) that evaluated the use of DPd in subjects with relapsed or refractory MM (RRMM). In addition, popPK analyses have been performed. The analytical methods were assessed in previous procedures. The combination with small molecules pomalidomide and dexamethasone is not thought to interfere with assay performance or target. Interim reports for sample analysis conducted in study MMY1001 and MMY3013 were provided

The effect of daratumumab is known from both an IV formulation and an SC formulation used as monotherapy or in combination with other anticancer medicines.

Since an identical daratumumab SC product is already marketed and in clinical use, the primary purpose of the presented PK package is to a) evaluate the exposure of daratumumab SC in combination with Pd compared to daratumumab SC monotherapy, b) evaluate efficacy and safety exposure-response relationships of the SC DPd regimen, and c) assess the applicability of a fixed dose of daratumumab in combination with Pd for the treatment of patients with MM.

In the popPK analysis, the final parameters were estimated with reasonable precision. The variability was large on the parameters describing the non-linear elimination and Ka. Effects of weight on clearance and volume in central compartment were estimated to 0.832 and 0.562 respectively. Subgroup analysis of $C_{trough,C3D1}$ showed that body weight, albumin concentration, and type of myeloma (IgG versus non-IgG) had an impact of <20% on $C_{trough,C3D1}$.

The subcutaneous DPd regimen resulted in similar plasma concentrations as observed with subcutaneous daratumumab monotherapy, indicating a lack of interactions between daratumumab and pomalidomide or dexamethasone. No dedicated drug-drug interaction studies were performed, this is acceptable.

From the popPK analysis, the volume of distribution of the central compartment was estimated to 4.36 L which is close to plasma volume and similar to other mAbs. No study on protein binding has been conducted which is acceptable.

The primary elimination pathways for daratumumab are clearance by the reticulo-endothelial system (in the same way as that for an endogenous IgG) and target-mediated elimination. Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in the clearance. Therefore, the potential risk of PK interactions between daratumumab and other drugs is low.

As regards special populations, no clinically relevant impact of sex, age, or weight on the PK of daratumumab has been reported. Mild to moderate renal and hepatic impairment do not seem to affect the PK of SC daratumumab.

The incidence of treatment emergent anti-daratumumab antibodies (1.6%) and anti-rHuPH20 antibodies (approximately 8%) is similar to previous reports, indicating a low risk of immunogenicity of daratumumab when combined with pomalidomide and dexamethasone in subjects with MM.

Evaluation of efficacy exposure-response relationship indicated a similar effect in the three upper (Q2-Q4) exposure quartiles and a lower effect for the Q1 subgroup on both PFS and ORR. The safety exposure-response relationship showed no apparent increase in TEAEs rate with increasing daratumumab SC exposure, indicating that the obtained exposure levels overall do not exceed the tolerability threshold. These exposure-response results, together with the daratumumab plasma concentration obtained, similar to daratumumab SC monotherapy, indicate that the fixed 1800 mg dose in combination with pomalidomide and dexamethasone is applicable and reasonable.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology program consists of one pivotal and one supportive study as well as pop PK analyses. Based on the comprehensive existing knowledge of daratumumab, the pharmacology package is considered adequate to support the application of an extension of indication and the proposed dosing regimen of subcutaneous daratumumab in combination with pomalidomide and dexamethasone for the treatment of MM.

2.4. Clinical efficacy

2.4.1. Dose response study

The present application concerns a fixed dose of daratumumab SC, which has previously been established: The effect of daratumumab is known from both an IV formulation and an SC formulation used as monotherapy or in combination with other anticancer medicines. See also section 2.1.1. regarding the approved indications and section 2.3.1.

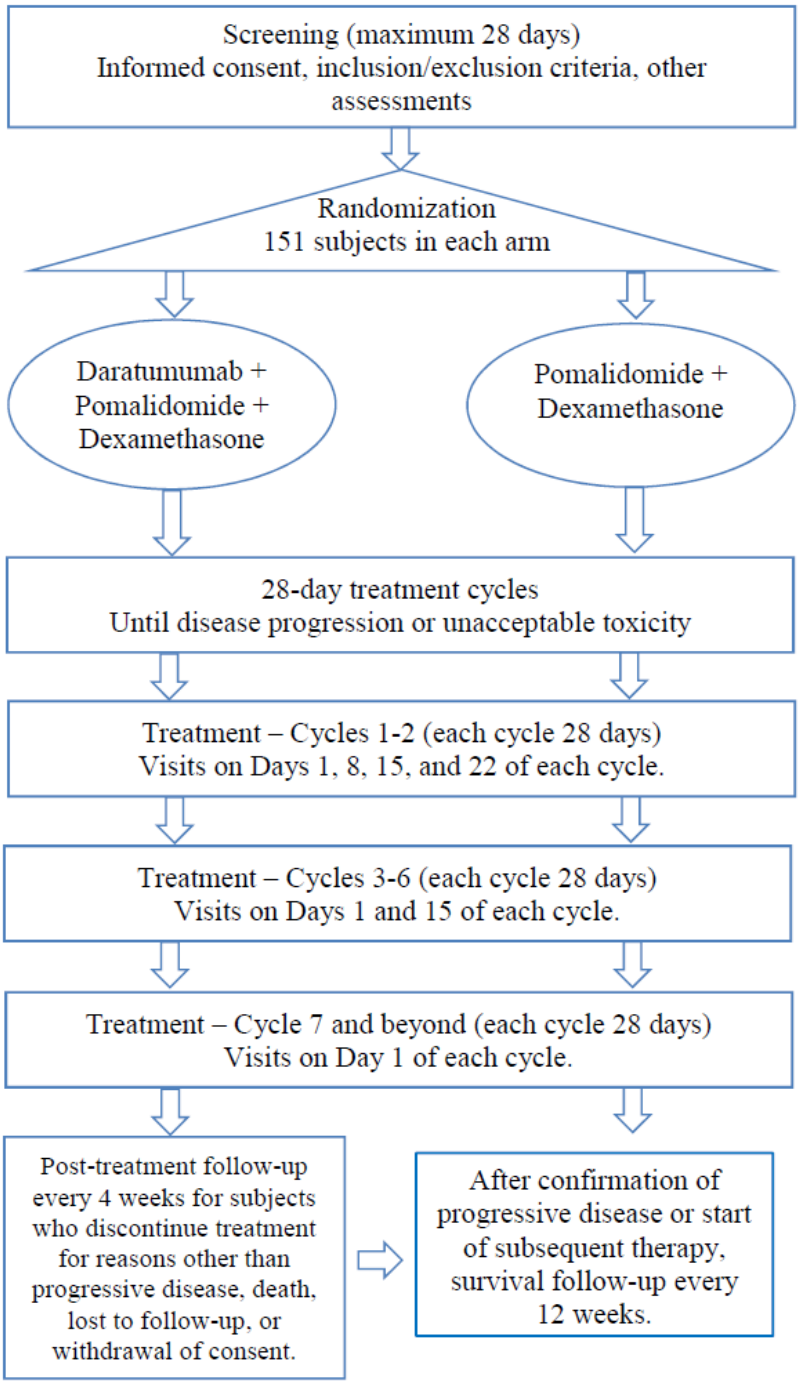
2.4.2. Main study

Title of Study

A Phase 3 Study Comparing Pomalidomide and Dexamethasone with or without Daratumumab in Subjects with Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor: The APOLLO Study

See Figure 11 for an overview of the study.

Figure 11: Schematic Overview of Study MMY3013



Methods

Study participants

Main Inclusion criteria:

1. Males and females at least 18 years of age.
2. Voluntary written informed consent before performance of any study-related procedure.
3. Subject must have measurable disease of MM as defined by the criteria below:
    - IgG multiple myeloma: Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours, or
    - IgA, IgD, IgE, IgM multiple myeloma: Serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
    - Light chain multiple myeloma, for subjects without measurable disease in the serum or urine: Serum immunoglobulin FLC ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.
4. Subjects must have received prior anti-myeloma treatment. The prior treatment must have included both a PI- and lenalidomide-containing regimens. The subject must have had a response (ie, PR or better based on the investigator's determination of response as defined by the modified IMWG criteria) to prior therapy.
5. Subjects must have documented evidence of PD based on the investigator's determination of response as defined by the modified IMWG criteria on or after the last regimen.
6. Subjects who received only 1 line of prior treatment must have demonstrated PD on or within 60 days of completion of the lenalidomide-containing regimen (ie, lenalidomide refractory).
7. Eastern Cooperative Oncology Group (ECOG) performance status score of ≤2.
8. For subjects experiencing toxicities resulting from previous therapy, the toxicities must be resolved or stabilized to ≤Grade 1.
9. All of the following laboratory test results during Screening:
    a) Absolute neutrophil count ≥1.0 × 10^9/L;
    b) Hemoglobin level ≥7.5 g/dL (≥4.65 mmol/L) (transfusions are not permitted to reach this level);
    c) Platelet count ≥75 × 10^9/L in subjects in whom <50% of bone marrow nucleated cells are plasma cells and platelet count ≥50 x 10^9/L in subjects in whom ≥50% of bone marrow nucleated cells are plasma cells (transfusions are not permitted to reach this level);
    d) Alanine aminotransferase (ALT) level ≤2.5 times the upper limit of normal (ULN);
    e) Aspartate aminotransferase (AST) level ≤2.5 x ULN;
    f) Total bilirubin level ≤1.5 x ULN, (except for Gilbert Syndrome: direct bilirubin ≤1.5 × ULN);
    g) Creatinine clearance ≥30 mL/min (Appendix 6);
    h) Serum calcium corrected for albumin ≤14.0 mg/dL (≤3.5 mmol/L), or free ionized calcium ≤6.5 mg/dL (≤1.6 mmol/L).

Main Exclusion criteria:

1. Previous therapy with any anti-CD38 monoclonal antibody.
2. Previous exposure to pomalidomide.
3. Subject has received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever is longer, before the date of randomization. The only exception is emergency use of a short course of corticosteroids (equivalent of dexamethasone 40 mg/day for a maximum of 4 days) for palliative treatment before Cycle 1, Day 1 (C1D1).
4. Previous allogenic stem cell transplant; or autologous stem cell transplantation (ASCT) within 12 weeks before C1D1.

5. History of malignancy (other than MM) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast, or other non-invasive lesion that in the opinion of the investigator, with concurrence with the Sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).

6. Clinical signs of meningeal involvement of MM.

7. Chronic obstructive pulmonary disease (COPD) with a Forced Expiratory Volume in 1 second (FEV1) <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal. (Appendix 4).

8. Clinically significant cardiac disease, including:

   a) Myocardial infarction within 6 months before C1D1, or unstable or uncontrolled condition (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV).

   b) Cardiac arrhythmia (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or higher) or clinically significant electrocardiogram (ECG) abnormalities.

   c) Electrocardiogram showing a baseline QT interval as corrected QTc >470 msec.

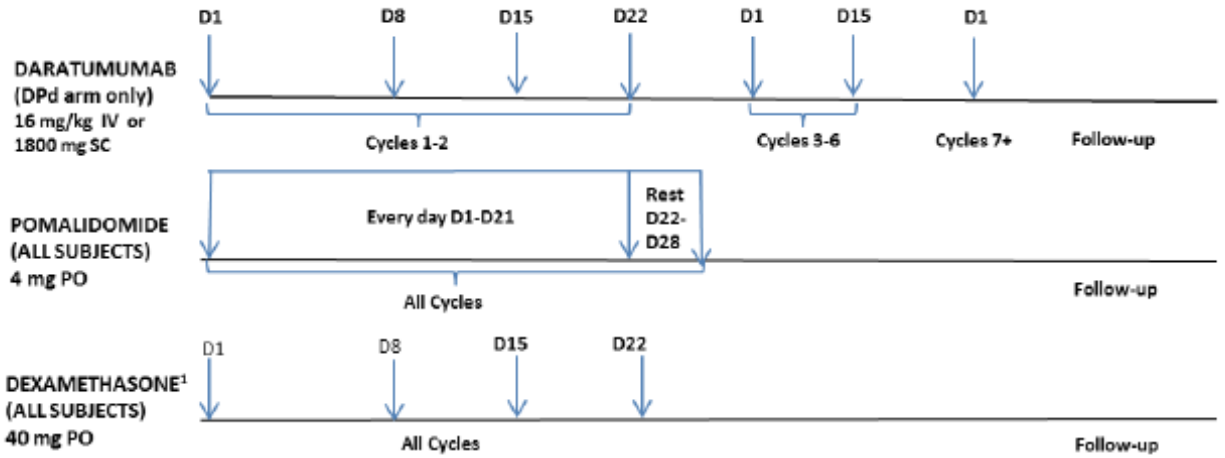
9. Ongoing ≥Grade 2 peripheral neuropathy.

10. Subject had ≥Grade 3 rash during prior therapy.

Treatments

Subjects randomized to the DPd group received daratumumab (1800 mg Dara SC or 16 mg/kg Dara IV [prior to Amendment 1]) at weekly intervals for 8 weeks, then every 2 weeks for 16 weeks (Cycles 3-6), then every 4 weeks (from Cycle 7 and beyond). Subjects in both treatment arms received pomalidomide at a dose of 4 mg PO on Days 1 through 21 of each 28-day cycle, and dexamethasone at a total dose of 40 mg PO once a week (20 mg for subjects ≥75 years).

Figure 12: Dosing and Administration in Study MMY3013



1. On days when daratumumab is administered, dexamethasone will be administered to subjects in DPd arm in the clinic and will serve as the treatment dose of steroid as well as the required pre-medication prior to daratumumab infusion. Note 20 mg PO weekly for subjects ≥75 years of age.

Subjects were to continue to receive study treatment until disease progression or unacceptable toxicity.

Dose delay was permitted and was the primary method for managing daratumumab-related toxicities as described in detail in the protocol . Subjects received pre- and post-dose medications to prevent IRRs and, if applicable, respiratory complications.

According to the study protocol treatment would have been withhold if any of the following criteria were met, to allow for recovery from toxicity, regardless of relationship to study drug:

- Grade 4 haematologic toxicity, except for Grade 4 lymphopenia

- Grade 3 or higher thrombocytopenia
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher non-haematologic toxicities with the following exceptions:
  - Grade 3 nausea that responds to antiemetic treatment within 7 days
  - Grade 3 vomiting that responds to antiemetic treatment within 7 days
  - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
  - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Study treatment would be resumed when the toxicity had resolved to ≤Grade 2. If study drug administration did not commence within the prespecified window of the scheduled administration date, then the dose would be considered a missed dose. Administration could be resumed at the next planned dosing date. A missed dose would not be made up.

Objectives

The purpose of this study was to evaluate the effects of the addition of daratumumab to pomalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma.

Outcomes/endpoints

The primary objective of this study was to compare **PFS** between treatment arms:

> The time, in months, from the date of randomization to the date of the first documented disease progression (based on a validated computer algorithm using modified IMWG criteria [Durie 2006, Rajkumar 2011]) or death due to any cause, whichever comes first

Key secondary efficacy objectives were:

- To compare ORR between treatment arms: The proportion of randomized subjects who achieve a best response of PR or better (ie, sCR, CR, VGPR, or PR) based on a validated computer algorithm using the modified IMWG criteria
- To compare OS between treatment arms: The time, in months, from the date of randomization to the date of death from any cause
- To assess the depth of response by analyzing MRD negativity rate for confirmed or suspected CR or better: The proportion of subjects who have negative MRD at any timepoint after the date of randomization (threshold value of 10^{-5})

The primary analysis of efficacy variables associated with response/progression will be performed using response or disease progression as derived from a validated computer algorithm according to the modified IMWG criteria.

Sample size

Approximately 302 subjects (151 per arm) were planned to be randomized in this study. The sample size calculation was based on the primary endpoint PFS, at a one-sided significance level of 0.025, assuming exponential survival distribution with a HR of 0.621 (DPd versus Pd). A total of 280 evaluable subjects (140 per arm) was required to observe 188 events to test the hypothesis with 90% power. The sample size calculation has taken into consideration 7% rate for permanent early censoring before the study cut-off,

and 1 interim analysis to assess superiority potentially at an early timepoint (ie, approximately 113 [60% of total planned events] PFS events observed).

Long-term survival follow-up is to continue until 166 deaths have been observed or 5 years after the last subject was randomized, whichever comes first. The study was planned to achieve approximately 70% power to detect a 34% reduction in the risk of death (HR=0.66; DPd versus Pd) with a log-rank test (one-sided alpha=0.025).

The sample size has taken into consideration one interim analysis to assess superiority potentially at an early timepoint (i.e. approximately 113 (60% of total planned events) PFS events observed).

Randomisation

Subjects were assigned randomly in a 1:1 ratio to receive either DPd or Pd via the IWRS provider using a validated system. Randomization was stratified by the number of lines of prior therapy (1, 2-3, ≥4) and ISS stage (1, 2, 3).

Blinding (masking)

Study MMY3013 was an open-label study.

Statistical methods

Primary endpoint PFS

The primary analysis was based on a stratified log-rank test for the comparison of the PFS distribution between the 2 treatment arms. The Kaplan-Meier method was used to estimate the distribution of overall PFS for each treatment. The treatment effect (hazard ratio) and its two-sided 95% CIs were estimated using a stratified Cox regression model with treatment as an explanatory variable, stratified by ISS staging (1, 2, 3), and number of lines of prior therapy (1, 2-3, ≥4).

Table 7: PFS Event and Censoring Method

Situation	Date of Progression or Censoring	Outcome
Disease progression	Earliest date that indicates disease progression	PFS event
Death	Date of death	PFS event
No post-baseline disease assessment	Randomization	Censored
Other (e.g., withdrawal of consent to study participation, lost to follow-up, start of subsequent antimyeloma therapy, etc.)	Date of last disease assessment prior to Other	Censored

Sensitivity analyses for PFS

- PFS based on investigator assessment of disease progression.
- Censored for death/PD after missing more than one disease evaluations.
- Censored for death due to COVID-19 without PD

Secondary endpoints: Response rate (ORR, VGPR or better, CR or better)

The overall response rate, along with its exact two-sided 95% CI (obtained from the Clopper-Pearson method), would be computed within each treatment group. Overall response rate would be compared between treatment groups using a stratified Cochran-Mantel-Haenszel (CMH) chi-squared test. The

stratification factor is that used in the randomization, i.e., number of lines of prior therapy (1, 2-3, ≥4) and ISS stage (1, 2, 3). The CMH estimate of odds ratio and its two-sided 95% CI for the difference in overall response rates between treatment groups will be reported.

For the response rates, subjects discontinuing before reaching a response would be considered as non-responders.

A sensitivity analysis of ORR would be performed based on the investigator assessment of response.

A supplementary analysis of ORR would be conducted by excluding those subjects who already began treatment with Dara IV prior to Amendment 1 on the ITT Set.

Secondary endpoint: Minimal Residual Disease Negativity Rate

The MRD negativity rate would be calculated for each treatment group based. The corresponding 95% exact CI would be provided. For each threshold value, Fisher's exact test would be used to test if the MRD negativity rate is the same between the two treatment groups. For the purpose of hierarchical testing, the threshold value of 10^{-5} will be employed.

MRD positive subjects include subjects of which all tested samples were found to be MRD positive, or ambiguous, or subjects who were not tested.

As sensitive analyses, the MRD negativity and CR or better rate based on ITT population would be calculated.

Secondary endpoint: OS

OS in months will be analyzed similarly to PFS.

For subject who withdraw consent from study, if death information is recorded in the clinical database, the death reported after withdrawal will be considered as OS event. Subjects who have not died at the cut-off date for the final analysis will be censored at the last known alive date. The date of last known alive will be determined by the maximum collection/assessment date within the clinical database.

A sensitivity analysis of OS will be conducted using an unstratified Cox proportional hazard model with treatment arm as single factor. OS will be compared between treatment groups using the log rank test (unstratified).

Interim analyses and multiplicity issues

An interim analysis was planned when approximately 113 PFS events occurred (60% of the total planned events). Efficacy testing boundaries of PFS at interim analysis and primary analysis were determined using the pre-specified alpha-spending function described by Lan and DeMets which approximated the boundaries of O'Brien and Fleming. For OS, a modified linear alpha spending function will be used, i.e., the alpha to be spent on the interim efficacy analysis (113 PFS event, which is 60% of the total planned PFS events) is 0.0001 (1-sided), a total alpha of 0.0001 (1-sided) will be spent. The major secondary hypotheses are to be tested at the nominal 0.025 (1-sided) significance level by utilizing a sequential, hierarchical testing approach as proposed by Tang and Geller (1999) that strongly controls Type I error rate. The major secondary endpoints are ordered as follows:

1) ORR
2) Rate of VGPR or better
3) Rate of CR or better
4) MRD negativity rate
5) Overall survival

If the testing of the primary endpoint of PFS is statistically significant, these major secondary endpoints ordered above will be sequentially tested, each with an overall one-sided alpha of 0.025. The significance level at the interim analysis will be determined by the alpha-spending function specific to that endpoint.

Results

Participant flow

Table 8: Subject Disposition by Study Phase; Intent-To-Treat Analysis Set (Study 54767414MMY3013)

	Pd n (%)	DPd n (%)	Total n (%)
Analysis set: intent-to-treat	153	151	304
Subjects randomized but not treated	3 (1.96)	2 (1.32)	5 (1.64)
Subjects treated	150 (98.04)	149 (98.68)	299 (98.36)
Treatment disposition[a]			
Subject status			
Ongoing	33 (22.00)	60 (40.27)	93 (31.10)
Discontinued	117 (78.00)	89 (59.73)	206 (68.90)
Reason for discontinuation			
Adverse Event	4 (2.67)	3 (2.01)	7 (2.34)
Death	7 (4.67)	10 (6.71)	17 (5.69)
Lost to Follow-Up	0	1 (0.67)	1 (0.33)
Physician Decision	7 (4.67)	4 (2.68)	11 (3.68)
Progressive Disease	87 (58.00)	66 (44.30)	153 (51.17)
Non-compliance with study drug[b]	12 (8.00)	5 (3.36)	17 (5.69)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
Percentages are computed on subjects in the intent-to-treat analysis set.
a. Numbers and percentages are based on the subjects treated.
b. Based on the reason 'Subject refused further study treatment' recorded on the End of Treatment case report form.

Source: Modified from Attachment T14.01-01.03.
Analysis Dataset Variables included ADSL: ITTFL, SAFFL, TRT01PN; ADDS: AVALC, PARAMCD

Recruitment

Study Initiation Date: 14 June 2017

Data cut off: 21 July 2020. The study is ongoing.

Study Centers: Greece (5), Turkey (7), Italy (6), Spain (7), France (6), Belgium (4), Germany (5), Netherlands (3), Czech Republic (2), Serbia (1), Denmark (1), Poland (1)

Conduct of the study

Amendments:

There were 2 global amendments to the protocol. Details of each amendment are included in the summary of changes (Appendix 1). The rationale for each amendment is summarized below:

Table 9: Summary of Protocol Amendments for 54767414MMY3013

Amendment 1 (13 Oct 2017)	• To expand the study design to include the SC administration of daratumumab • Other changes including update to IMWG criteria definition of progressive disease
Amendment 2 (03 Apr 2018)	• To update the Pomalidomide Risk Evaluation Mitigation Strategy or Global Pregnancy Prevention Plan based on recommendations from a health authority • To update exclusion criteria with regards to hepatitis and HIV testing, hypersensitivity, and prior vaccinations based on recommendations from a health authority • Other changes to provide clarification through the protocol

In addition, 2 country-specific protocol amendments were adopted:

- Germany: amended to include baseline hepatitis C and HIV testing
- France: amended to include HBV testing at 6 months after the last dose of daratumumab for subjects who are being monitored for HBV reactivation, and serology hepatitis B testing for subjects with unknown HBV status receiving daratumumab on the study (DPd arm) or within 6 months after the last dose of daratumumab.

Protocol deviations:

Table 10: Summary of Subjects with Major Protocol Deviations; Intent-To-Treat Analysis Set (Study 54767414MMY3013)

	Pd n (%)	DPd n (%)	Total n (%)
Analysis set: intent-to-treat	153	151	304
Total number of subjects with major protocol deviations	2 (1.31)	7 (4.64)	9 (2.96)
Type of major protocol deviations			
Entered but did not satisfy criteria	2 (1.31)	2 (1.32)	4 (1.32)
Received wrong treatment or incorrect dose	0	5 (3.31)	5 (1.64)
COVID-19 related	0	0	0
Developed withdrawal criteria but not withdrawn	0	0	0
Received a disallowed concomitant treatment	0	0	0
Other	0	0	0

Keys: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
Percentages are computed on subjects in the intent-to-treat analysis set.
Each subject could have more than one protocol deviation; subjects are counted only once in each row.

Filename: T14.01-01.05.RTF / Program: T14.01-01.05.sas (05OCT2020 20:41)
Analysis Dataset Variables included ADSL: ITTFL, TRT01PN; DV: DVDECOD

Baseline data

Table 11: Demography and Baseline Characteristics; Intent-To-Treat Analysis Set (Study 54767414MMY3013)

	Pd	DPd	Total
Analysis set: intent-to-treat	153	151	304
Age (years)			
n	153	151	304
Mean (SD)	66.5 (9.70)	65.4 (9.57)	66.0 (9.63)
Median	68.0	67.0	67.0
Range	35; 90	42; 86	35; 90
Age class, n (%)			
n	153	151	304
<65 years	60 (39.22)	63 (41.72)	123 (40.46)
65 - <75 years	62 (40.52)	63 (41.72)	125 (41.12)
≥75 years	31 (20.26)	25 (16.56)	56 (18.42)
Gender, n (%)			
n	153	151	304
Male	82 (53.59)	79 (52.32)	161 (52.96)
Female	71 (46.41)	72 (47.68)	143 (47.04)
Race, n (%)			
n	153	151	304
White	137 (89.54)	135 (89.40)	272 (89.47)
Black or African American	0	1 (0.66)	1 (0.33)
Asian	1 (0.65)	1 (0.66)	2 (0.66)
Other	1 (0.65)	0	1 (0.33)
Unknown	14 (9.15)	14 (9.27)	28 (9.21)
Ethnicity, n (%)			
n	153	151	304
Hispanic or Latino	4 (2.61)	4 (2.65)	8 (2.63)
Not Hispanic or Latino	138 (90.20)	134 (88.74)	272 (89.47)
Unknown	2 (1.31)	4 (2.65)	6 (1.97)
Not Reported	9 (5.88)	9 (5.96)	18 (5.92)
Baseline ECOG performance status, n (%)			
n	153	151	304
0	77 (50.33)	91 (60.26)	168 (55.26)
1	57 (37.25)	54 (35.76)	111 (36.51)
2	19 (12.42)	6 (3.97)	25 (8.22)
Height (cm)			
n	153	151	304
Mean (SD)	166.4 (9.49)	166.8 (9.93)	166.6 (9.70)
Median	168.0	165.5	167.0
Range	142; 189	144; 192	142; 192
Weight (kg)			
n	153	151	304
Mean (SD)	75.5 (15.06)	75.1 (14.62)	75.3 (14.82)
Median	74.2	74.0	74.1
Range	44; 142	49; 111	44; 142
Weight class, n (%)			
n	153	151	304
<65 kg	30 (19.61)	45 (29.80)	75 (24.67)
65 - <85 kg	89 (58.17)	69 (45.70)	158 (51.97)

	Pd	DPd	Total
≥85 kg	34 (22.22)	37 (24.50)	71 (23.36)
BMI (kg/m^2)			
n	153	151	304
Mean (SD)	27.22 (4.589)	26.90 (4.139)	27.06 (4.367)
Median	26.45	26.06	26.20
Range	18.1; 44.8	19.9; 37.1	18.1; 44.8

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
SD = Standard deviation.
Percentages are computed on subjects in the intent-to-treat analysis set with available data.
Subject's age is computed in years elapsed from the date of birth to the date of the informed consent signature.
For subjects whose ages were entered by the investigator, their ages are used without any computation.

Filename: T14.01-03.01.RTF / Program: T14.01-03.01.sas (05OCT2020 20:41)
Analysis Dataset Variables included ADSL: ITTFL, TRT01PN, AGE, AGEGR2, SEX, RACE, ETHNIC ECOGBL; ADVS: ABLFL, AVAL, PARAMCD in (HEIGHT WEIGHT BMI)

Table 12: Baseline Disease and Other Baseline Characteristics; Intent-To-Treat Analysis Set (Study 54767414MMY3013)

	Pd	DPd	Total
Analysis set: intent-to-treat	153	151	304
Type of myeloma by immunofixation, n (%)			
n	153	151	304
IgG	87 (56.86)	83 (54.97)	170 (55.92)
IgA	30 (19.61)	34 (22.52)	64 (21.05)
IgM	1 (0.65)	0	1 (0.33)
IgD	2 (1.31)	2 (1.32)	4 (1.32)
Light chain	30 (19.61)	26 (17.22)	56 (18.42)
Light chain - Kappa	20 (13.07)	14 (9.27)	34 (11.18)
Light chain - Lambda	10 (6.54)	12 (7.95)	22 (7.24)
Biclonal	0	2 (1.32)	2 (0.66)
Negative immunofixation	3 (1.96)	4 (2.65)	7 (2.30)
Type of measurable disease[a], n (%)			
n	153	151	304
Serum only	83 (54.25)	87 (57.62)	170 (55.92)
IgG	63 (41.18)	62 (41.06)	125 (41.12)
IgA	20 (13.07)	24 (15.89)	44 (14.47)
Other[b]	0	1 (0.66)	1 (0.33)
Urine only	17 (11.11)	17 (11.26)	34 (11.18)
Serum and Urine	28 (18.30)	23 (15.23)	51 (16.78)
Serum FLC only	25 (16.34)	24 (15.89)	49 (16.12)
ISS staging at study entry, n (%)			
n	153	151	304
1	69 (45.10)	68 (45.03)	137 (45.07)
2	51 (33.33)	50 (33.11)	101 (33.22)
3	33 (21.57)	33 (21.85)	66 (21.71)
Revised ISS staging, n (%)			
n	127	119	246
1	25 (19.69)	26 (21.85)	51 (20.73)
2	88 (69.29)	74 (62.18)	162 (65.85)
3	14 (11.02)	19 (15.97)	33 (13.41)
Time from MM diagnosis to randomization (years)			
n	153	151	304
Mean (SD)	5.20 (3.546)	5.19 (3.633)	5.20 (3.584)
Median	4.48	4.39	4.41
Range	0.6; 19.0	0.5; 20.0	0.5; 20.0
Number of lytic bone lesions, n (%)			
n	153	151	304
None	38 (24.84)	33 (21.85)	71 (23.36)
1-3	25 (16.34)	24 (15.89)	49 (16.12)
4-10	28 (18.30)	44 (29.14)	72 (23.68)
More than 10	62 (40.52)	50 (33.11)	112 (36.84)
Presence of extramedullary (soft tissue) plasmacytomas at baseline, n (%)			
n	153	151	304
No	145 (94.77)	136 (90.07)	281 (92.43)

	Pd	DPd	Total
Yes	8 (5.23)	15 (9.93)	23 (7.57)
Plasma cells, bone marrow biopsy, n (%)			
n	11	17	28
<10%	4 (36.36)	2 (11.76)	6 (21.43)
10% - 30%	3 (27.27)	6 (35.29)	9 (32.14)
>30%	4 (36.36)	9 (52.94)	13 (46.43)
Plasma cells, bone marrow aspirate, n (%)			
n	149	147	296
<10%	33 (22.15)	35 (23.81)	68 (22.97)
10% - 30%	59 (39.60)	54 (36.73)	113 (38.18)
>30%	57 (38.26)	58 (39.46)	115 (38.85)
Plasma cells, bone marrow biopsy/aspirate, n (%)			
n	152	151	303
<10%	34 (22.37)	35 (23.18)	69 (22.77)
10% - 30%	59 (38.82)	52 (34.44)	111 (36.63)
>30%	59 (38.82)	64 (42.38)	123 (40.59)
Any cytogenetic abnormalities, n (%)			
n	108	103	211
Standard risk	73 (67.59)	64 (62.14)	137 (64.93)
High risk	35 (32.41)	39 (37.86)	74 (35.07)
del17p	18 (16.67)	16 (15.53)	34 (16.11)
t(4;14)	16 (14.81)	19 (18.45)	35 (16.59)
t(14;16)	6 (5.56)	7 (6.80)	13 (6.16)
Baseline renal function (Creatinine Clearance), n (%)			
n	153	151	304
≤60 mL/min	47 (30.72)	40 (26.49)	87 (28.62)
>60 mL/min	106 (69.28)	111 (73.51)	217 (71.38)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
Ig = Immunoglobulin; FLC = Free light chain; ISS = International staging system; NE = Not evaluable; MM = Multiple Myeloma; SD = Standard deviation.
ISS staging at study entry is as recorded on the MM medical diagnosis/history case report form.
Percentages are computed on subjects in the intent-to-treat analysis set with available data.
a. Includes subjects without measurable disease in serum and urine.
b. Includes IgD, IgM, IgE and biclonal.
Each subject could have more than one cytogenetic abnormality but is only counted once for each abnormality.
Cytogenetic abnormalities are based on the FISH testing with a 50% cut-off for del17p and 30% for t(4;14) and t(14;16).

Filename: T14.01-03.03.RTF / Program: T14.01-03.03.sas (05OCT2020 20:41)
Analysis Dataset Variables included ADSL: ITTFL, TRT01PN; ADBL: AVALC, AVALCAT1, PARAMCD in (IMMFIX MEAS CANSTG RISS DIARND LESNUM EXPLCYT PLCEBMB PLCEBMA PLCEBMBA CYTABN DEL17P13 T4_14 T14_16 CRCLBL)

Subjects received a median of 2 prior lines of therapy, with approximately 11% of subjects receiving 1 prior line of therapy (Table 13).

Table 13: Prior Therapies for Multiple Myeloma; Intent-To-Treat Analysis Set (Study 54767414MMY3013)

	Pd	DPd	Total
Analysis set: intent-to-treat	153	151	304
Number of subjects with any prior therapy for multiple myeloma, n (%)	153 (100.00)	151 (100.00)	304 (100.00)
Prior systemic therapy	153 (100.00)	151 (100.00)	304 (100.00)
Prior autologous stem cell transplant (ASCT)	81 (52.94)	90 (59.60)	171 (56.25)
Prior radiotherapy	35 (22.88)	36 (23.84)	71 (23.36)
Prior cancer-related surgery	29 (18.95)	21 (13.91)	50 (16.45)
Number of prior lines of therapy, n (%)			
1	18 (11.76)	16 (10.60)	34 (11.18)
2-3	113 (73.86)	114 (75.50)	227 (74.67)
≥4	22 (14.38)	21 (13.91)	43 (14.14)
Number of prior lines of therapy			
n	153	151	304
Mean (SD)	2.4 (0.91)	2.4 (0.94)	2.4 (0.92)
Median	2.0	2.0	2.0
Range	1; 5	1; 5	1; 5
Number of subjects with any prior PI, n (%)	153 (100.00)	151 (100.00)	304 (100.00)
Bortezomib	146 (95.42)	145 (96.03)	291 (95.72)
Carfilzomib	47 (30.72)	36 (23.84)	83 (27.30)
Ixazomib	16 (10.46)	18 (11.92)	34 (11.18)
Number of subjects with any prior IMiD, n (%)	153 (100.00)	151 (100.00)	304 (100.00)
Lenalidomide	153 (100.00)	151 (100.00)	304 (100.00)
Thalidomide	46 (30.07)	43 (28.48)	89 (29.28)
Number of subjects with any prior corticosteroids, n (%)	153 (100.00)	151 (100.00)	304 (100.00)
Dexamethasone	152 (99.35)	150 (99.34)	302 (99.34)
Prednisone	45 (29.41)	26 (17.22)	71 (23.36)
Prior alkylating agents, n (%)	139 (90.85)	135 (89.40)	274 (90.13)
Prior anthracyclines, n (%)	38 (24.84)	40 (26.49)	78 (25.66)
Prior PI+IMiD, n (%)	153 (100.00)	151 (100.00)	304 (100.00)
Prior PI+IMiD+ALKY, n (%)	139 (90.85)	135 (89.40)	274 (90.13)
Prior BORT+LEN, n (%)	146 (95.42)	145 (96.03)	291 (95.72)
Prior ELOT, n (%)	6 (3.92)	8 (5.30)	14 (4.61)
Prior PANO, n (%)	5 (3.27)	4 (2.65)	9 (2.96)
Prior BORT+LEN+CARF, n (%)	41 (26.80)	31 (20.53)	72 (23.68)
Prior BORT+LEN+CARF+THAL, n (%)	17 (11.11)	15 (9.93)	32 (10.53)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
ALKY = Alkylating agents; BORT = Bortezomib; CARF = Carfilzomib; ELOT=Elotuzumab; IMiD = Immunomodulatory agent; LEN = Lenalidomide; PANO = Panobinostat; PI = Proteasome inhibitor; SD = Standard deviation; THAL = Thalidomide.
Percentages are computed on subjects in the intent-to-treat analysis set.
Number of lines of prior therapy are recorded on the Prior systemic therapy case report form.
Terms are coded using WHO dictionary, version Q1 2020.

Filename: T14.01-03.04.RTF / Program: T14.01-03.04.sas (23OCT2020 9:38)
Analysis Dataset Variables included ADSL: ITTFL, TRT01PN; ADCM: CMCAT, CMDECOD; ADPR: PRCAT, PRDECOD; ADBL: AVAL, PARAMCD=PNLINE; ADCMD: AVALC, PARAMCD in (ALKY ANTH PIIMID PIIMIDAL BORTLEN ELOT PANO BORTLENC BOLECATH)

Numbers analysed

The primary analysis population was the ITT population, which included all randomized subjects.

Table 14: Analysis Sets; Intent-To-Treat Analysis Set (Study 54767414MMY3013)

	Pd n (%)	DPd n (%)	Total n (%)
Analysis set: intent-to-treat	153	151	304
Intent-to-treat analysis set	153 (100.00)	151 (100.00)	304 (100.00)
Response-evaluable analysis set	142 (92.81)	145 (96.03)	287 (94.41)
Safety analysis set	150 (98.04)	149 (98.68)	299 (98.36)
Pharmacokinetic analysis set		140 (92.72)	140 (46.05)
Daratumumab immunogenicity analysis set		123 (81.46)	123 (40.46)
rHuPH20 immunogenicity analysis set		122 (80.79)	122 (40.13)
Biomarker analysis set	150 (98.04)	147 (97.35)	297 (97.70)

Keys: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
Percentages are computed on subjects in the intent-to-treat analysis set.
The intent-to-treat analysis set comprises all subjects to whom study treatment has been assigned by randomization in the interactive web response system (IWRS).
The response-evaluable analysis set includes subjects who had a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening. In addition, subjects must have received at least one component of study treatment and have adequate post-baseline disease assessment prior to the start of subsequent therapy.
The safety analysis set consists of all subjects who received at least one administration of any study treatment (partial or complete).
The pharmacokinetic analysis set consists of subjects who received at least one administration of daratumumab and had at least one pharmacokinetic sample concentration value after their first daratumumab administration.
The daratumumab immunogenicity analysis set consists of all subjects who received at least one dose of daratumumab IV (intravenous) or SC (subcutaneous)
and had at least one immunogenicity sample after the first dose of daratumumab for detection of anti-daratumumab antibodies.
The rHuPH20 immunogenicity analysis set consists of all subjects who received at least one dose of daratumumab SC and had at least one immunogenicity sample after the first dose of daratumumab SC for detection of anti-rHuPH20 antibodies.
The biomarker analysis set consists of all subjects from the intent-to-treat analysis set who had appropriate samples for biomarker evaluations.
The intent-to-treat analysis set, response-evaluable analysis set and biomarker analysis set are presented according to the randomized treatment groups.
The safety analysis set, pharmacokinetic analysis set, daratumumab immunogenicity analysis set and rHuPH20 immunogenicity analysis set are presented according to the actual treatment received.

Filename: T14.01-02.01.RTF / Program: T14.01-02.01.sas (05OCT2020 20:41
Analysis Dataset Variables included ADSL: ITTFL, RESEVFL, SAFFL, PKFL, IMDARAFL, IMRHUPFL, BMFL, TRT01PN

Outcomes and estimation

Primary endpoint: PFS

At a **median overall follow-up of 16.9 months** (DPd: 17.5 months; Pd: 16.4 months), the addition of daratumumab SC to Pd resulted in a statistically significant and clinically meaningful improvement in PFS, with a **37% reduction in the risk of disease progression** or death compared with Pd alone (HR=0.63; 95% CI: 0.47, 0.85; 2-sided p=0.0018; Table 15 and Figure 13).

The **median PFS** and 95% CI was **12.4 months** (8.3, 19.3) for the DPd treatment group and 6.9 months (5.5, 9.3) for the Pd treatment group.

Most PFS events were attributed to disease progression (46.4% in the DPd group and 61.4% in the Pd group). Data from 44.4% of subjects in the DPd group and 30.7% of subjects in the Pd group were censored for the primary endpoint analysis. The majority of these subjects were censored due to clinical cut-off. No subjects were censored for death due to COVID-19 without disease progression.

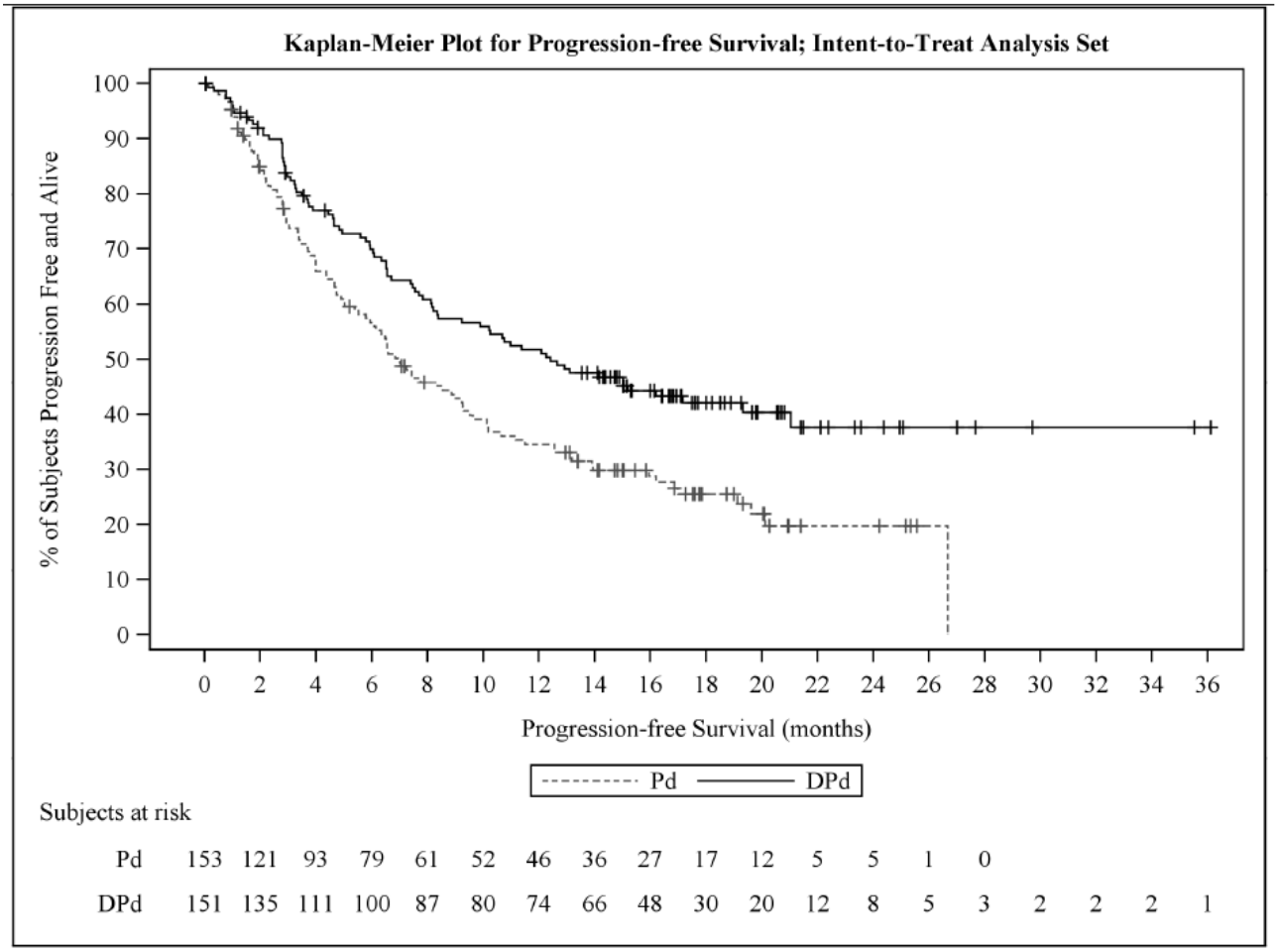
Table 15: Summary of Progression-free Survival based on Computerized Algorithm; Intent-to-Treat Analysis Set (Study 54767414MMY3013)

	Pd	DPd
Analysis set: intent-to-treat	153	151
Progression-free survival (PFS)		
Number of events, n (%)	106 (69.28)	84 (55.63)
Disease progression	94 (61.44)	70 (46.36)
Death	12 (7.84)	14 (9.27)
Number of censored, n (%)	47 (30.72)	67 (44.37)
Kaplan-Meier estimates (months)		
25% quantile (95% CI)	2.92 (2.20, 3.98)	4.63 (3.22, 6.34)
Median (95% CI)	6.93 (5.52, 9.26)	12.42 (8.34, 19.32)
75% quantile (95% CI)	19.12 (13.14, 26.68)	NE (NE, NE)
p-value (two-sided)		0.0018
Hazard ratio (DPd vs. Pd) (95% CI)		0.63 (0.47, 0.85)
6-month PFS rate (%) (95% CI)	56.7 (48.1, 64.3)	69.9 (61.8, 76.7)
12-month PFS rate (%) (95% CI)	34.6 (26.7, 42.5)	51.7 (43.3, 59.5)
18-month PFS rate (%) (95% CI)	25.5 (18.2, 33.4)	42.1 (33.6, 50.2)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
CI = Confidence Interval; PFS = Progression-free survival.
Percentages are computed on subjects in the intent-to-treat analysis set.
P-value is obtained from the two-sided log-rank test stratified with ISS (1, 2, 3), and number of lines of prior therapy (1, 2-3, ≥ 4).
Hazard ratio and 95% CI are obtained from a Cox proportional hazards model with treatment as an explanatory variable in the model, stratified with ISS (1, 2, 3), and number of lines of prior therapy (1, 2-3, ≥ 4). A hazard ratio < 1 favors DPd.

Filename: T14.02-01.01.01.RTF / Program: T14.02-PFS.sas (05OCT2020 20:43)
Analysis Dataset Variables included ADTTE: ITTFL TRT01PN, STRAT1N, STRAT2N, AVAL, CNSR, PARAMCD=PFS

Figure 13: Kaplan-Meier Plot of Progression-free Survival based on Computerized Algorithm; Intent-to-Treat Analysis Set (Study 54767414MMY3013)



Filename: T14.02-01.01.01F.RTF / Program: T14.02-KMFig.sas (05OCT2020 20:44)
Analysis Dataset Variables included ADTTE: ITTFL TRT01PN, AVAL, CNSR, PARAMCD=PFS

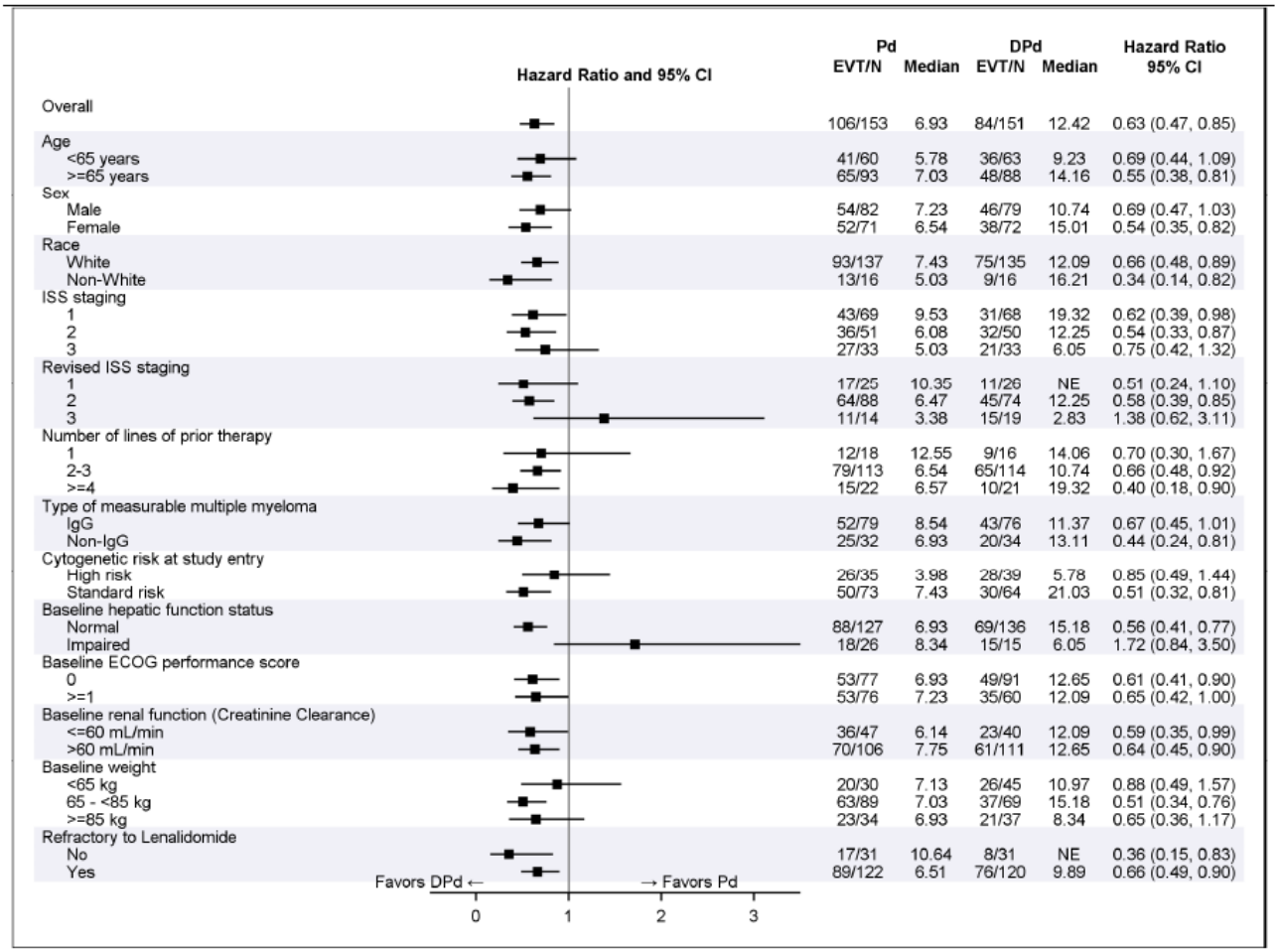
Subgroup Analyses of Progression-free Survival

The **PFS results were generally consistent across subgroups** demonstrating improvement for subjects in the DPd group compared with subjects in the Pd group, including subgroups for subjects refractory to lenalidomide, high-risk cytogenetics, ISS staging, number of lines of prior therapy, and baseline ECOG performance score (Figure 4).

No analyses were performed for extreme high body weight as too few subjects were available (no subjects in the DPd group and 1 subject in Pd group weighed >120 kg at baseline).

All "number of prior therapies" subgroups consistently favoured DPd, including subjects with only 1 prior line of therapy.

Figure 14: Forest Plot of Subgroup Analysis of Progression-free Survival based on Computerized Algorithm; Intent-to-Treat Analysis Set (Study 54767414MMY3013)



	Pd EVT/N	Pd Median	DPd EVT/N	DPd Median	Hazard Ratio 95% CI
Overall	106/153	6.93	84/151	12.42	0.63 (0.47, 0.85)
Age					
<65 years	41/60	5.78	36/63	9.23	0.69 (0.44, 1.09)
>=65 years	65/93	7.03	48/88	14.16	0.55 (0.38, 0.81)
Sex					
Male	54/82	7.23	46/79	10.74	0.69 (0.47, 1.03)
Female	52/71	6.54	38/72	15.01	0.54 (0.35, 0.82)
Race					
White	93/137	7.43	75/135	12.09	0.66 (0.48, 0.89)
Non-White	13/16	5.03	9/16	16.21	0.34 (0.14, 0.82)
ISS staging					
1	43/69	9.53	31/68	19.32	0.62 (0.39, 0.98)
2	36/51	6.08	32/50	12.25	0.54 (0.33, 0.87)
3	27/33	5.03	21/33	6.05	0.75 (0.42, 1.32)
Revised ISS staging					
1	17/25	10.35	11/26	NE	0.51 (0.24, 1.10)
2	64/88	6.47	45/74	12.25	0.58 (0.39, 0.85)
3	11/14	3.38	15/19	2.83	1.38 (0.62, 3.11)
Number of lines of prior therapy					
1	12/18	12.55	9/16	14.06	0.70 (0.30, 1.67)
2-3	79/113	6.54	65/114	10.74	0.66 (0.48, 0.92)
>=4	15/22	6.57	10/21	19.32	0.40 (0.18, 0.90)
Type of measurable multiple myeloma					
IgG	52/79	8.54	43/76	11.37	0.67 (0.45, 1.01)
Non-IgG	25/32	6.93	20/34	13.11	0.44 (0.24, 0.81)
Cytogenetic risk at study entry					
High risk	26/35	3.98	28/39	5.78	0.85 (0.49, 1.44)
Standard risk	50/73	7.43	30/64	21.03	0.51 (0.32, 0.81)
Baseline hepatic function status					
Normal	88/127	6.93	69/136	15.18	0.56 (0.41, 0.77)
Impaired	18/26	8.34	15/15	6.05	1.72 (0.84, 3.50)
Baseline ECOG performance score					
0	53/77	6.93	49/91	12.65	0.61 (0.41, 0.90)
>=1	53/76	7.23	35/60	12.09	0.65 (0.42, 1.00)
Baseline renal function (Creatinine Clearance)					
<=60 mL/min	36/47	6.14	23/40	12.09	0.59 (0.35, 0.99)
>60 mL/min	70/106	7.75	61/111	12.65	0.64 (0.45, 0.90)
Baseline weight					
<65 kg	20/30	7.13	26/45	10.97	0.88 (0.49, 1.57)
65 - <85 kg	63/89	7.03	37/69	15.18	0.51 (0.34, 0.76)
>=85 kg	23/34	6.93	21/37	8.34	0.65 (0.36, 1.17)
Refractory to Lenalidomide					
No	17/31	10.64	8/31	NE	0.36 (0.15, 0.83)
Yes	89/122	6.51	76/120	9.89	0.66 (0.49, 0.90)

Filename: T14.02-01.10F.RTF / Program: T14.02-PFS FPlot.sas (23OCT2020 9:40)
Analysis Dataset Variables included ADTTE: AVAL, CNSR, PARAMCD=PFS; ADSL: ITTFL TRT01PN, AGEGR1N, SEXN, RACEGR1N, CANSTGN, RISSN, PTLINEN, MEASMMN, CYTRISKN, HEPFSBLN, ECOGBLN, CRCLBLN, WTBLN, LENREFN

Key Secondary Analyses

Overall Response Rate

Table 16: Summary of Overall Best Confirmed Response based on Computerized Algorithm; Intent-to-Treat Analysis Set (Study 54767414MMY3013)

	Pd		DPd			
	n (%)	Exact 95% CI for %	n (%)	Exact 95% CI for %	Odds ratio (95% CI)	p-value (two-sided)
Analysis set: intent-to-treat	153		151			
Response categories						
Stringent Complete Response (sCR)	2 (1.31)	0.16, 4.64	14 (9.27)	5.16, 15.07		
Complete Response (CR)	4 (2.61)	0.72, 6.56	23 (15.23)	9.91, 21.97		
Very Good Partial Response (VGPR)	24 (15.69)	10.32, 22.43	40 (26.49)	19.65, 34.28		
Partial Response (PR)	41 (26.80)	19.97, 34.55	27 (17.88)	12.13, 24.94		
Minimal Response (MR)	15 (9.80)	5.59, 15.65	11 (7.28)	3.69, 12.66		
Stable Disease (SD)	49 (32.03)	24.72, 40.04	26 (17.22)	11.57, 24.20		
Progressive Disease (PD)	7 (4.58)	1.86, 9.20	4 (2.65)	0.73, 6.64		
Not Evaluable (NE)	11 (7.19)	3.64, 12.50	6 (3.97)	1.47, 8.45		
Overall response (sCR + CR + VGPR + PR)	71 (46.41)	38.32, 54.64	104 (68.87)	60.84, 76.15	2.68 (1.65, 4.35)	<.0001
Clinical benefit (Overall response + MR)	86 (56.21)	47.97, 64.21	115 (76.16)	68.55, 82.71	2.57 (1.55, 4.25)	0.0002
Very good partial response or better (sCR + CR + VGPR)	30 (19.61)	13.64, 26.79	77 (50.99)	42.74, 59.21	4.32 (2.57, 7.26)	<.0001
Complete response or better (sCR + CR)	6 (3.92)	1.45, 8.34	37 (24.50)	17.88, 32.16	8.24 (3.35, 20.26)	<.0001

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
CI = Confidence Interval.
Percentages are computed on subjects in the intent-to-treat analysis set.
The exact two-sided 95% CI for a percentage is obtained from the Clopper-Pearson method.
Odds ratio and its two-sided 95% CI are obtained from the Mantel-Haenszel estimate of the common odds ratio, stratified with ISS (1, 2, 3), and number of lines of prior therapy (1, 2-3, ≥ 4). An odds ratio > 1 favors DPd.
P-value is obtained from the two-sided Cochran-Mantel-Haenszel chi-squared test, stratified for ISS (1, 2, 3), and number of lines of prior therapy (1, 2-3, ≥ 4).

Filename: T14.02-02.01.01.RTF / Program: T14.02-Resp.sas (05OCT2020 20:43)
Analysis Dataset Variables include ADSL: ITTFL TRT01PN; ADEFF1: AVALC PARAMCD=BRESP

Minimal Residual Disease

Table 17: Summary of MRD Negative Rate at 10-5 in Bone Marrow; Intent-to-Treat Analysis Set (Study 54767414MMY3013)

	Pd	DPd
Analysis set: intent-to-treat	153	151
MRD negativity rate (10^{-5})	3 (1.96%)	13 (8.61%)
95% CI[a] MRD negativity rate	0.41, 5.62	4.66, 14.27
Odds ratio with 95% CI[b]		4.71 (1.31, 16.88)
p-value (two-sided)[c]		0.0102

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
CI = Confidence Interval; MRD = Minimal Residual Disease.
Percentages are computed on subjects in the intent-to-treat analysis set.
a. Exact 95% confidence interval.
b. Mantel-Haenszel estimate of the odds ratio for unstratified tables is used. An odds ratio > 1 indicates an advantage for DPd.
c. p-value from Fisher's exact test.
MRD negativity status is based on post-randomization assessments prior to progressive disease or subsequent antimyeloma therapy.

Filename: T14.02-07.01.RTF / Program: T14.02-07.01to03.sas (05OCT2020 20:45)
Analysis Dataset Variables included ADSL: ITTFL TRT01PN; ADMARD: AVALC PARAMCD=MRD5

Overall Survival

With a median overall follow-up of 16.9 months (DPd: 17.5 months; Pd: 16.4 months; Attachment T14.02-08.01), median OS was not reached in either treatment group (see Table and Figure below). Similar numbers of deaths were observed for DPd and Pd treatment groups (DPd: 48 [31.8%]; Pd: 51 [33.3%]), with an HR=0.91 (95% CI: 0.61, 1.35; 2-sided p=0.6359). The participants will continue to be followed up for the OS data until 166 deaths have been observed or 5 years after the last subject was randomized.

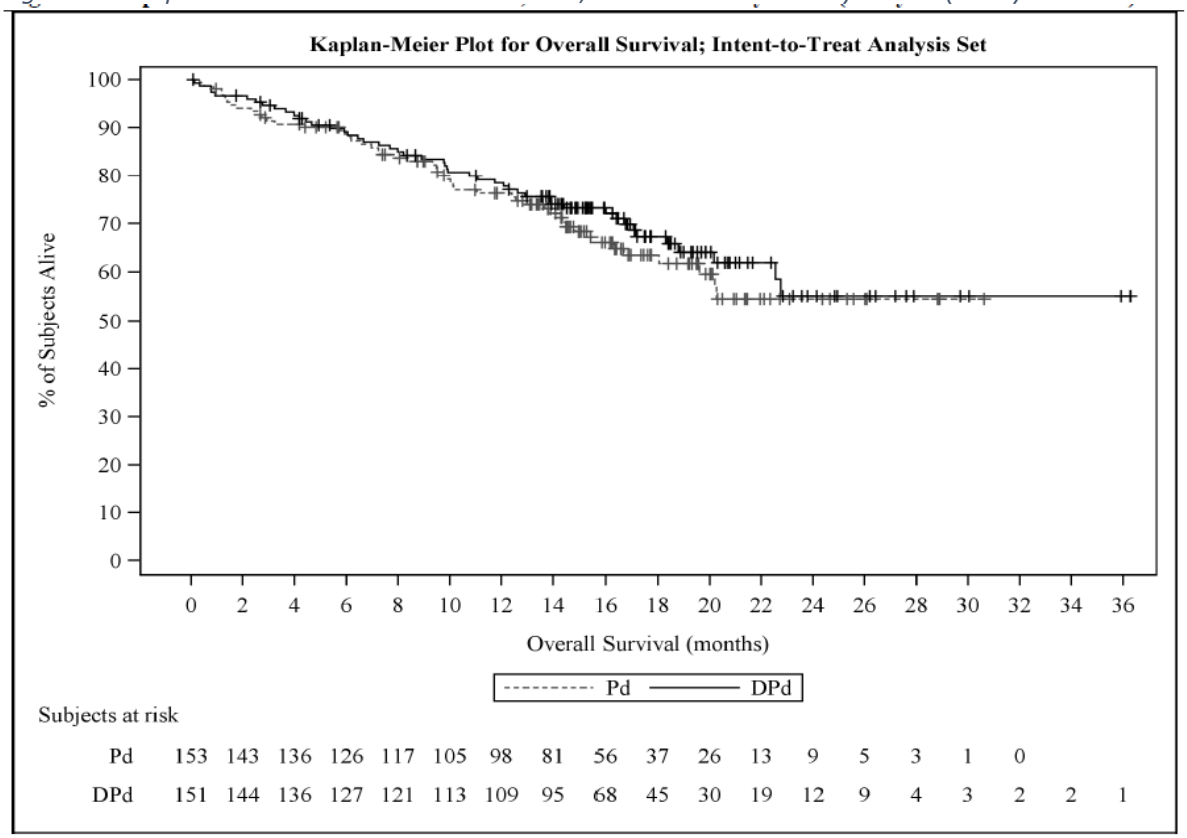
Table 18: Summary of Overall Survival; Intent-to-Treat Analysis Set (Study 54767414MMY3013)

	Pd	DPd
Analysis set: intent-to-treat	153	151
Overall survival (OS)		
Number of deaths, n (%)	51 (33.33)	48 (31.79)
Number of censored, n (%)	102 (66.67)	103 (68.21)
Kaplan-Meier estimates (months)		
25% quantile (95% CI)	12.55 (9.49, 15.44)	13.90 (9.79, 17.18)
Median (95% CI)	NE (19.61, NE)	NE (22.54, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value (two-sided)		0.6359
Hazard ratio (DPd vs. Pd) (95% CI)		0.91 (0.61, 1.35)
6-month survival rate (%) (95% CI)	88.7 (82.4, 92.8)	89.1 (82.9, 93.2)
12-month survival rate (%) (95% CI)	76.3 (68.4, 82.5)	78.5 (70.8, 84.4)
18-month survival rate (%) (95% CI)	63.4 (54.0, 71.5)	67.3 (58.2, 74.9)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
CI = Confidence Interval; OS = Overall survival.
Percentages are computed on subjects in the intent-to-treat analysis set.
P-value is obtained from the two-sided log-rank test stratified with ISS (1, 2, 3), and number of lines of prior therapy (1, 2-3, ≥ 4).
Hazard ratio and 95% CI are obtained from a Cox proportional hazards model with treatment as an explanatory variable in the model, stratified with ISS (1, 2, 3), and number of lines of prior therapy (1, 2-3, ≥ 4). A hazard ratio < 1 favors DPd.

Filename: T14.02-03.01.RTF / Program: T14.02-OS.sas (05OCT2020 20:43)
Analysis Dataset Variables included ADTTE: ITTFL TRT01PN, STRAT1N, STRAT2N, AVAL, CNSR, PARAMCD=OS

Figure 15: Kaplan-Meier Plot of Overall Survival; Intent-to-Treat Analysis Set (Study 54767414MMY3013)



Filename: T14.02-03.01F.RTF / Program: T14.02-KMFig.sas (05OCT2020 20:44)
Analysis Dataset Variables included ADTTE: ITTFL TRT01PN, AVAL, CNSR, PARAMCD=OS

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 19: Summary of Efficacy for trial MMY3013

Title: A Phase 3 Study Comparing Pomalidomide and Dexamethasone With or Without Daratumumab in Subjects With Relapsed or Refractory Multiple Myeloma Who Have Received at Least One Prior Line of Therapy With Both Lenalidomide and a Proteasome Inhibitor			
Study identifier	54767414MMY3013 / 2017-001618-27		
Design	Multicentre, Phase 3, randomized, open-label, active-controlled study		
	Duration of main phase:		Study initiation date: 14-June-2017, data cut-off 21 July 2020, ongoing
Hypothesis	Superiority		
Treatments groups	D-Pd		• Daratumumab: 1800 mg SC, QW Cycles 1-2, Q2W: Cycles 3-6, Q4W Cycles 7 + until PD • Pomalidomide: 4mg PO on days 1-21 of every cycle until PD • Dexamethasone: 40 mg (or 20 mg) PO or IV QW until PD
	Pd		• Pomalidomide: 4mg PO on days 1-21 of every cycle until PD • Dexamethasone: 40 mg (or 20 mg) PO or IV QW until PD
Endpoints and definitions	Primary endpoint	PFS	Progression Free Survival, defined as the time, in months, from the date of randomization to the date of the first documented disease progression (based on a validated computer algorithm using modified IMWG criteria) or death due to any cause, whichever comes first.
	Secondary endpoint	ORR	Response Rate, defined as the proportion of randomized subjects who achieve a best response of PR or better (ie, sCR, CR, VGPR, or PR) based on a validated computer algorithm using the modified IMWG criteria.
	Secondary endpoint	VGPR or better	Rate of Very Good Partial Response or better, defined as the proportion of randomized subjects who achieve a best response of VGPR or better (ie, VGPR, or PR) based on a validated computer algorithm using the modified IMWG criteria.
	Secondary endpoint	CR or better	Rate of Complete Response or better, defined as the proportion of randomized subjects who achieve a best response of CR or better (ie, CR, VGPR, or PR) based on a validated computer algorithm using the modified IMWG criteria.

	Secondary endpoint	MRD negativity rate	MRD negativity rate, defined as the proportion of subjects who have negative MRD at any timepoint after the date of randomization (threshold value of 10-5).
	Secondary endpoint	OS	Overall Survival, defined as the time, in months, from the date of randomization to the date of death from any cause.
Database lock	Database lock: 28 July 2020 Clinical cut-off date: 21 July 2020		

Results and Analysis

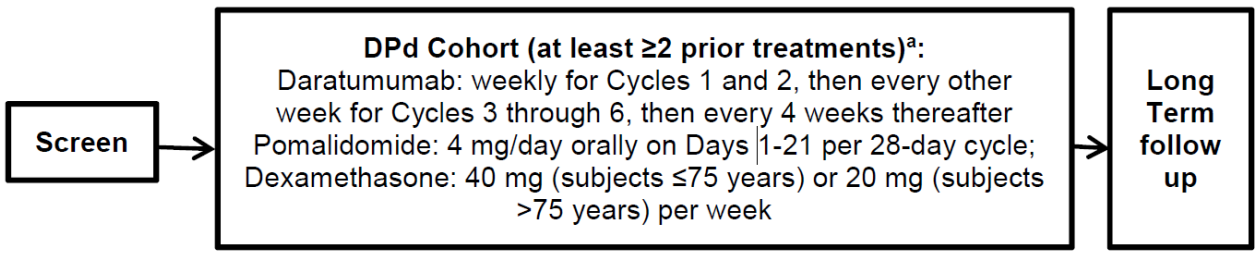
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat / clinical cut-off date (21 July 2020)		
Descriptive statistics and estimate variability	Treatment group	Pd	D-Pd
	Number of subjects	153	151
	PFS	6.9 months	12.4 months
	95% CI	(5.5 – 9.3) months	(8.3 – 19.3) months
	ORR	46.4 %	68.9 %
	95% CI	38.3 % - 54.6 %	60.8 % - 76.2 %
	VGPR or better	19.6 %	51.0 %
	95% CI	13.6 % - 26.8 %	42.7 % - 59.2 %
	CR or better	3.9 %	24.5 %
	95% CI	1.5 % - 8.3 %	17.9 % - 32.2 %
	MRD negativity rate	2.0 %	8.6 %
	95% CI	0.4 % - 5.6 %	4.7 % - 14.3 %
	OS	Median not reached, deaths observed: 51 (33.3%)	Median not reached, deaths observed: 48 (31,8%)
	95% CI	n/a	n/a
Effect estimates per comparison	Primary endpoint PFS		D-Pd
		Hazard ratio (D-Pd vs Pd)	0.63
		95% CI	0.47 – 0.85
		P-value (2-sided)	0.0018
	Secondary endpoint ORR	Odds ratio	2.68
		95% CI	1.65 – 4.35
		P-value (2-sided)	<0.0001
	Secondary endpoint VGPR or better	Odds ratio	4.32
		95% CI	2.57 – 7.26
		P-value (2-sided)	<0.0001
	Secondary endpoint CR or better	Odds ratio	8.24
		95% CI	3.35 – 20.26
		P-value (2-sided)	<0.0001

	Secondary endpoint MRD negativity rate	Odds ratio 95% CI P-value (2-sided)	4.71 1.31 – 16.88 0.0102
	Secondary endpoint OS (median OS not reached in either group)	Hazard ratio (D-Pd vs Pd) 95% CI P-value (2-sided)	0.91 0.61 – 1.35 0.6359
Notes	The participants will continue to be followed up for the OS data until 166 deaths have been observed or 5 years after the last subject was randomized. Deaths for subjects with COVID-19 were limited (1 DPd subject) and did not impact interpretation of data.		

Supportive study

Study MMY1001 was a Phase 1b open-label, non-randomized, multicenter study to evaluate the safety, tolerability, and dose regimen of daratumumab IV when administered in combination with various background treatment regimens for multiple myeloma in either newly diagnosed patients or those who had received prior therapies, depending on the background treatment regimen. The treatment regimens combined with daratumumab IV in this study included regimens used for newly diagnosed patients (ie, VELCADE-dexamethasone [Vd], VELCADE-melphalan-prednisone [VMP], VELCADE-thalidomide-dexamethasone [VTd], carfilzomib + lenalidomide + dexamethasone [KRd] and regimens used for previously treated patients (ie, Pd, and carfilzomib-dexamethasone [Kd]. Among relapsed and refractory subjects, 1 cohort, daratumumab IV in combination with Pom-dex (DPd), was expanded to 103 subjects to evaluate the safety and efficacy of DPd. Efficacy data from this DPd cohort is summarized below.

Figure 16: Schematic Overview of Study MMY1001



a:DPd cohort provides data for this SCE.
Note: Other treatment cohorts in Study MMY1001 are not represented in the figure above.

The primary objective for the DPd cohort was to evaluate the safety, tolerability, and dosing of daratumumab IV in combination with Pd when administered to subjects with multiple myeloma who had received ≥2 prior lines of therapy. The primary efficacy endpoint was ORR, defined as the proportion of subjects with PR or better. Secondary efficacy endpoints included DOR, TTR, TTP, PFS, and OS. Efficacy assessment was performed in accordance with IMWG guidelines (Durie 2006; Rajkumar 2011). The primary analysis was based on response assessed by an IDSMB; investigator assessment and algorithm assessment were performed as sensitivity analyses.

One hundred three (103) subjects were enrolled in the DPd cohort with median age of 64 years (range: 35-86 years), with 50% of subjects ≥65 years of age and 55% of subjects were male. A majority of subjects had an ECOG status score of 0-1 (88%). All subjects in the DPd cohort received prior therapy for multiple myeloma. The majority of subjects (51%) received >3 lines of prior multiple myeloma therapy; median number of prior therapies was 4. Ninety-eight percent of subjects had previous exposure to both bortezomib and lenalidomide.

As of the clinical cut-off, median duration of study treatment for the 103 subjects in the DPd cohort was 6.0 months (range: 0-17 months). Median relative dose intensity was 97% for daratumumab, 78% for pomalidomide and 90% for dexamethasone.

Primary Efficacy Endpoint – Overall Response Rate

The ORR (PR or better) based on IDSMB assessment was 59.2%, with 42% of subjects having a rate of VGPR or better and 14% of subjects having a rate of CR or better.

Table 20: Overall Best Response based on IDSMB Assessment; Dara + Pom/Dex Treated (Study 54767414MMY1001)

	D-Pom-dex	
	n (%)	95% CI for %
Analysis set: : Dara + Pom/Dex treated	103	
Best response		
Stringent complete response (sCR)	8 (7.8%)	(3.4%, 14.7%)
Complete response (CR)	6 (5.8%)	(2.2%, 12.2%)
Very good partial response (VGPR)	29 (28.2%)	(19.7%, 37.9%)
Partial response (PR)	18 (17.5%)	(10.7%, 26.2%)
Minimal response (MR)	3 (2.9%)	(0.6%, 8.3%)
Stable disease (SD)	26 (25.2%)	(17.2%, 34.8%)
Progressive disease (PD)	3 (2.9%)	(0.6%, 8.3%)
Not evaluable (NE)	10 (9.7%)	(4.8%, 17.1%)
Overall response (sCR+CR+VGPR+PR)	61 (59.2%)	(49.1%, 68.8%)
Clinical benefit (Overall response + MR)	64 (62.1%)	(52.0%, 71.5%)
VGPR or better (sCR + CR + VGPR)	43 (41.7%)	(32.1%, 51.9%)
CR or better (sCR + CR)	14 (13.6%)	(7.6%, 21.8%)

Keys: CI = exact confidence interval; D-Pom-dex = daratumumab-pomalidomide-dexamethasone.
Note: Response was assessed by IDSMB, based on international Uniform Response Criteria Consensus Recommendations.
Note: Percentages are calculated with the number of subjects in each group as denominator.

[TEFRSP01.RTF] [JNJ-54767414\MMY1001\DBR_SBLA_2016\RE_SBLA_2016\PROD\TEFRSP01.SAS] 05MAY2016, 09:26

Key Secondary Efficacy Endpoints

Based on IDSMB assessment of response, median **DOR** was 13.6 months for responders (61 subjects) in the response-evaluable cohort. Estimated DOR was 84% at 6 months, and 67% at 12 months.

Based on IDSMB assessment, **time to response** (61 subjects) in the response-evaluable cohort was as follows. Median time to first response (PR or better) was 0.99 months; median time to best response (PR or better) was 2.1 months; median time to VGPR or better response (43 subjects) was 1.9 months; and median time to CR or better response (14 subjects) was 5.4 months.

Based on IDSMB assessment, 49 (48%) PFS events were observed; median **PFS** was 10.4 months (CI: 4.63, NE). Three-month disease progression-free rate was 74%; 6-month disease progression-free rate was 57%; and 12-month disease progression-free rate was 45%.

Based on IDSMB assessment, 42 (41%) TTP events were observed; median **TTP** was 10.9 months (CI: 6.70, NE). Three-month disease progression-free rate was 78%; 6-month disease progression-free rate was 62%; and 12-month disease progression-free rate was 48%.

At the clinical data cut-off, with a median follow-up of 9.8 months, 28 deaths (27%) were observed and 75 subjects (73%) were censored. Median **survival** was not estimable. Estimated survival rates were 89% at 3 months; 79% at 6 months; and 72% at 12 months.

2.4.3. Discussion on clinical efficacy

The current submission is supported by study MMY3013, which is a Phase 3 study comparing pomalidomide and dexamethasone with or without daratumumab in subjects with relapsed or refractory multiple myeloma who have received at least one prior line of therapy with both lenalidomide and a proteasome inhibitor.

The proposed daratumumab SC dose is the same proposed as part of other drug-combinations. Safety and tolerability data have been generated with IV daratumumab in combination with Pd in the DPd cohort of study MMY1001 and confirmed in the phase 3 randomized clinical study MMY3013 (where daratumumab was given subcutaneously). The view of the Applicant that no additional dose studies need to be conducted is supported.

Design and conduct of clinical studies

The purpose of the pivotal phase 3 study MMY3013 was to evaluate the efficacy and safety of DPd to Pd in subjects with relapsed or refractory multiple myeloma having received prior lenalidomide and an IMiD (96% had received bortezomib) using the primary endpoint of PFS based on IMWG criteria.

Daratumumab was given SC (7 patients received IV before amendment 2). Pd dose was given according to Imnovid SmPC. Treatment continued until PD or unacceptable toxicity.

Subjects were randomized 1:1 to DPd or Pd. Randomization was stratified by number of lines of prior therapy and ISS stage. The study was open-label. An IDMC conducted the interim analysis.

The primary population for the efficacy analysis is the ITT, which includes all randomized subjects. This is endorsed. PFS was analysed using a stratified log-rank test and the hazard ratio was estimated using a stratified Cox model. In both cases, the stratification factors were those used at randomisation. The implementation of a stratified log-rank test and a stratified Cox model is endorsed. The censoring rules are not fully agreed, since censoring due to start of a subsequent therapy before PD or withdrawal of consent could bias the results. However, the MAH presented sensitivity analyses, which yielded similar results as those corresponding to the primary analysis.

An interim analysis for PFS with the possibility of stopping for superiority was planned. To control the type I error due to multiple looks, alpha spending functions were used. There are several key secondary endpoints, which were to be tested using a pre-define hierarchical approach. The implemented strategy to control for multiplicity issues is agreed.

The baseline characteristics including disease characteristics and prior treatment were generally comparable between the two arms in study 3013.

Subjects received a median of 2 prior lines of therapy, with approximately 11% of subjects receiving 1 prior line of therapy. The MAH is applying for DPd after at least one prior therapy as long as the "prior therapy included a proteasome inhibitor and an immunomodulatory agent".

The indication sought is for patients having received a prior PI and IMiD. All patients had received lenalidomide (this was an inclusion criterion) and 96% of patients had received prior bortezomib treatment. The fact that all patients received lenalidomide has now been reflected in the indication (instead of IMiD), also in line with other approved products. Thirty percent of patients had also received thalidomide, and for the PI category approximately 25% had received carfilzomib and 11% ixazomib (in the DPd arm). Based

on that and to better reflect the study population the CHMP considered that the most appropriate indication would be

"DARZALEX is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received ***one prior therapy containing a proteasome inhibitor and lenalidomide*** *and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy (see section 5.1).*

Supportive data where derived from 103 DPd-treated patients in the phase 1b study MMY1001, which was an open-label, non-randomized, multicenter study to evaluate the safety, tolerability, and dose regimen of daratumumab IV when administered in combination with various background treatment regimens for multiple myeloma in either newly diagnosed patients or those who had received prior therapies, depending on the background treatment regimen.

Efficacy data and additional analyses

A total of 304 subjects (DPd: 151, Pd: 153) were randomized in a 1:1 ratio according to planned stratification factors (number of lines of prior therapy and ISS staging), and 299 subjects (DPd: 149, Pd: 150) received study treatment. At the time of the clinical cut-off date of 21 July 2020, 40.3% DPd subjects and 22% of Pd subjects were still on study treatment.

Treatment discontinuations were higher in the Pd group compared with the experimental arm, (78% in Pd arm vs. 59.73% in the DPd arm). Differences appear mainly driven by the higher rate of treatment discontinuation in the Pd arm due to progressive disease (Pd: 58%; DPd: 44.3%), which is not unexpected considering the reported efficacy data of the study. A low proportion of subjects discontinued study treatment due to death (DPd: 6.7%; Pd: 4.7%; including 1 death due to COVID-19 in the DPd group), non-compliance with study drug (DPd: 3.4%; Pd: 8%), and AE (DPd: 2%; Pd: 2.7%).

Demographic characteristics were well balanced between the 2 treatment groups. The median age was 67 years (range: 35 to 90 years), with 18.4% of the subjects ≥75 years of age. The majority of the subjects were white (89.5%) and had an ECOG performance score of 0 or 1 (91.8%).

Of note, an imbalance between treatment arms is noted for patients with worse general condition (i.e. 6 vs. 19 patients with ECOG PS2 in the DPd and Pd arms, respectively) and in patients over 75 years of age (i.e. 25 vs. 31 patients in the DPd and Pd arms, respectively). Both are small subgroups.

Baseline disease characteristics. The majority of subjects had measurable disease in serum only (55.9%) with IgG (41.1%) and IgA (14.5%). Approximately 25% of ITT subjects (35% of those with available information [DPd: 37.9%; Pd: 32.4%]) had a high-risk cytogenetic abnormality (presence of del17p, t[14;16] or t[4;14]). The distribution of ISS stages (a stratification factor at randomization) was balanced between treatment groups, with 45.1% of subjects overall reported as Stage 1, 33.2% as Stage 2, and 21.7% as Stage 3. When subjects were additionally assessed according to revised ISS (R-ISS) criteria (i.e. those with available information; n=246), a higher proportion of R-ISS Stage 3 was reported in the DPd group (16%) compared with the Pd group (11%).

The types of prior therapies for MM were consistent with standard of care for the population enrolled in the study and similar between treatment groups. All subjects were previously treated with both lenalidomide and a PI, and >95% of subjects were previously treated with bortezomib therapy.

Subjects received a median of 2 prior lines of therapy, with approximately 11% of subjects receiving 1 prior line of therapy. Eighty percent of subjects were refractory to lenalidomide, 48% subjects were refractory to a PI, and 42.4% subjects were refractory to both PI and IMiD. For subjects who received only 1 prior line of therapy, all were refractory to lenalidomide and 32.4% were double refractory to both a PI and an IMiD.

Primary endpoint

At a median overall follow-up of 16.9 months (DPd: 17.5 months; Pd: 16.4 months) the addition of daratumumab SC to Pd resulted in a statistically significant improvement in PFS with a 37% reduction in the risk of disease progression or death compared with Pd alone (HR=0.63; 95% CI: 0.47, 0.85; 2-sided p=0.0018,). The median PFS was 12.4 months for the DPd treatment group (95% CI; 8.3, 19.3) and 6.9 months for the Pd treatment group (95% CI; 5.5, 9.3), which is considered clinically relevant particularly in a population that had received a median of 2 prior treatments that included lenalidomide and a PI. Most PFS events were attributed to disease progression (46.4% in the DPd group and 61.4% in the Pd group). Data from 44.4% of subjects in the DPd group and 30.7% of subjects in the Pd group were censored for the primary endpoint analysis. The majority of these subjects were censored due to clinical cut-off. No subjects were censored for death due to COVID-19 without disease progression. No patients had received prior anti-CD38-containing therapy. The MAH has agreed with the recommendation to provide the final study report for Study MMY3013, estimated to be available by approximately Q4 2022.

Sensitivity analyses supported the findings of the primary analysis. PFS results were also generally consistent across subgroups though interpretation of the results in some of them is limited by the small sample size, e.g. 'non-white' race, ≥4 and 1 prior lines of therapy, R-ISS Stage 3, and baseline impaired hepatic function. Of note, according to the HRs reported, there is some uncertainty that patients pertaining to the R-ISS Stage 3 group and those with impaired hepatic function would derive benefit from the addition of daratumumab to Pd. It is acknowledged that the confidence intervals are wide and the number of patients low.

Key secondary endpoints

DPd showed a statistically significant higher **ORR** compared with the Pd group (DPd: 68.9%; Pd: 46.4%); the stratified CMH estimate of odds ratio was 2.68 with 95% CI (1.65, 4.35) and 2-sided p<0.0001. The median duration of response had not been reached in the D-Pd group (range: 1 to 34.9+ months) and was 15.9 months (range: 1+ to 24.8 months) in the Pd group.

DPd also showed a statistically significant higher **rate of CR** (sCR and CR) or better compared with the Pd group (DPd: 24.5%; Pd: 3.9%; stratified CMH odds ratio=8.24 with 95% CI: [3.35, 20.26]; p<0.0001.

The **MRD negativity rate** at the sensitivity threshold of 105 was 8.6% for DPd and 2.0% for Pd (odds ratio=4.71; 95% CI: 1.31, 16.88; 2-sided p=0.0102).

There is a statistical relationship between the achievement of complete response (CR), MRD negativity and PFS or OS (ESMO guidelines; Moreau et al., 2017), and thus the higher CR and MRD-negativity rates in the DPd arm are considered clinically important responses.

OS data are still immature. The MAH has agreed to provide updated survival data in the final study report for Study MMY3013, estimated to be available by approximately Q4 2022.

Supportive study MMY1001

Comparing studies 3013 and 1001 is difficult due to different patient populations, objectives, primary endpoints, daratumumab treatment durations, formulation (IV vs SC), and follow-up times. Generally, the results support study MMY3013.

2.4.4. Conclusions on the clinical efficacy

The addition of daratumumab to the combination of pomalidomide and dexamethasone translates into a significant delay in the progression of the disease in the targeted patient population, i.e. patients with multiple myeloma who have received at least one prior line of therapy with both lenalidomide, to which 80% were refractory, and a proteasome inhibitor (PI) and had demonstrated disease progression.

This benefit in terms of PFS is supported by several secondary endpoints. Importantly, despite the immaturity of the OS data, no evidence of detrimental effects on survival has so far been observed.

To better reflect the study population the CHMP considered that the most appropriate indication would be:

"DARZALEX is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy (see section 5.1)."

The MAH has agreed to provide the final study report for Study MMY3013 and updated survival data, estimated to be available by approximately Q4 2022.

2.5. Clinical safety

Introduction

The safety population consists of data from 299 treated subjects from the Phase 3 Study MMY3013 (DPd: 149; Pd: 150). In addition, supportive safety data from Study MMY1001, a Phase 1b evaluation of daratumumab administered in combination with Pd (N=103), are summarized in the Efficacy section.

As of the clinical cut-off date of 21 July 2020, 304 subjects were randomized into Study MMY3013. Of these, 299 subjects were treated (DPd: 149 subjects; Pd: 150 subjects) and represents the Safety Analysis Set. At the time of the clinical cut-off date, 60 subjects (40.3%) in the DPd group and 33 subjects (22.0%) in the Pd group were still receiving study treatment.

In Study MMY1001, 57.3% of subjects discontinued treatment [PD (33.0%), AEs (13.6%), physician decision (3.9%), death (1.9%), and other (1%)].

Patient exposure

In study 3013 the median duration of treatment for subjects in the DPd group (11.5 months) was 1.7 times that of the Pd group (6.6 months). The median number of treatment cycles received was 12 in the DPd group and 7 in the Pd group (Table 21).

The median daratumumab relative dose intensity in Study MMY3013 was 93.6%. The median relative dose intensity was lower in the DPd group for pomalidomide (74.3%) and dexamethasone (83.3%) compared with the Pd group (91.1% and 87.5%, respectively).

Table 21: Treatment Duration and Number of Treatment Cycles; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort)

	APOLLO (Study MMY3013)		EQUULEUS (Study MMY1001)
	Pd	DPd	DPd
Analysis set: safety	150	149	103
Duration of study treatment (months)			
N	150	149	103
Mean (SD)	8.9 (6.84)	11.7 (7.70)	6.3 (4.51)
Median	6.6	11.5	6.0
Range	(0; 27)	(0; 36)	(0; 17)
Distribution of subjects treated in and beyond each cycle			
≥ 1 cycle	150 (100.0%)	149 (100.0%)	103 (100.0%)
≥ 2 cycles	137 (91.3%)	143 (96.0%)	89 (86.4%)
≥ 3 cycles	129 (86.0%)	139 (93.3%)	80 (77.7%)
≥ 4 cycles	114 (76.0%)	131 (87.9%)	72 (69.9%)
≥ 5 cycles	102 (68.0%)	119 (79.9%)	64 (62.1%)
≥ 6 cycles	92 (61.3%)	109 (73.2%)	54 (52.4%)
≥ 7 cycles	86 (57.3%)	105 (70.5%)	51 (49.5%)
Total number of treatment cycles received			
1	13 (8.7%)	6 (4.0%)	14 (13.6%)
2	8 (5.3%)	4 (2.7%)	9 (8.7%)
3	15 (10.0%)	8 (5.4%)	8 (7.8%)
4	12 (8.0%)	12 (8.1%)	8 (7.8%)
5	10 (6.7%)	10 (6.7%)	10 (9.7%)
6	6 (4.0%)	4 (2.7%)	3 (2.9%)
7	12 (8.0%)	4 (2.7%)	6 (5.8%)
8	4 (2.7%)	5 (3.4%)	3 (2.9%)
9	5 (3.3%)	11 (7.4%)	6 (5.8%)
10	6 (4.0%)	4 (2.7%)	10 (9.7%)
11	4 (2.7%)	3 (2.0%)	2 (1.9%)
12	9 (6.0%)	4 (2.7%)	9 (8.7%)
13	2 (1.3%)	4 (2.7%)	3 (2.9%)
14	2 (1.3%)	5 (3.4%)	5 (4.9%)
15	3 (2.0%)	5 (3.4%)	3 (2.9%)
16	9 (6.0%)	7 (4.7%)	3 (2.9%)
17	3 (2.0%)	9 (6.0%)	0
18	5 (3.3%)	6 (4.0%)	1 (1.0%)
19	3 (2.0%)	8 (5.4%)	0
20	4 (2.7%)	6 (4.0%)	0
21	4 (2.7%)	5 (3.4%)	0
22	2 (1.3%)	3 (2.0%)	0
23	4 (2.7%)	6 (4.0%)	0
25	1 (0.7%)	2 (1.3%)	0
26	1 (0.7%)	2 (1.3%)	0
28	2 (1.3%)	0	0
29	0	2 (1.3%)	0
30	1 (0.7%)	0	0
31	0	1 (0.7%)	0
32	0	1 (0.7%)	0
36	0	1 (0.7%)	0
39	0	1 (0.7%)	0
Mean (SD)	9.7 (7.22)	12.7 (8.05)	7.0 (4.70)
Median	7.0	12.0	6.0
Range	(1; 30)	(1; 39)	(1; 18)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
Note: Percentages are calculated with the number of subjects in each group as denominators.
[TSIEXP01.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_DPD_2020\RE_MMY_RR_DPD_2020\PROD\TSIEXP01.SAS] 17SEP2020, 15:50

Table 22 Total Dose and Relative Dose Intensity; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort)

	APOLLO		EQUULEUS
	Pd	DPd	DPd
Analysis set: safety	150	149	103
Total daratumumab dose received (mg)			
N	-	149	103
Mean (SD)	-	36520.40 (17133.624)	17928.84 (11475.380)
Median	-	36000.00	17280.00
Range	-	(1800.0; 82936.0)	(20.3; 63840.0)
Total daratumumab dose received (mg/kg)			
N	-	149	103
Mean (SD)	-	474.52 (239.038)	223.90 (120.704)
Median	-	469.40	223.11
Range	-	(24.7; 1267.4)	(0.2; 448.0)
Daratumumab relative dose intensity (%)			
N	-	149	103
Mean (SD)	-	88.89 (15.120)	90.12 (17.474)
Median	-	93.55	96.82
Range	-	(25.0; 100.0)	(1.3; 104.8)
Total pomalidomide dose received (mg)			
N	150	149	97
Mean (SD)	722.92 (570.712)	773.62 (529.099)	451.53 (328.791)
Median	553.00	702.00	389.00
Range	(0.0; 2520.0)	(16.0; 2532.0)	(4.0; 1264.0)
Pomalidomide relative dose intensity (%)			
N	149	149	97
Mean (SD)	83.71 (19.001)	73.73 (21.250)	74.69 (21.614)
Median	91.07	74.34	77.50
Range	(4.8; 100.0)	(19.1; 100.0)	(5.7; 100.0)
Total dexamethasone equivalents dose received (mg)			
N	149	149	103
Mean (SD)	1142.89 (984.968)	1335.42 (1002.023)	752.50 (579.147)
Median	840.00	1160.00	680.00
Range	(40.0; 4800.0)	(20.0; 6120.0)	(20.0; 2800.0)
Dexamethasone equivalents relative dose intensity (%)			
N	149	149	103
Mean (SD)	79.03 (24.935)	75.17 (25.331)	84.60 (17.891)
Median	87.50	83.33	90.00
Range	(25.0; 200.0)	(12.5; 187.5)	(14.3; 106.3)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
Note: Dexamethasone equivalents include prednisolone and methylprednisolone.
[TSIEXP02.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_DPD_2020\RE_MMY_RR_DPD_2020\PROD\TSIEXP02.SAS] 17SEP2020, 15:50

Adverse events

Treatment-emergent Adverse Events are summarised in Table below.

Table 23: Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort)

	APOLLO (Study MMY3013)		EQUULEUS (Study MMY1001)
	Pd	DPd	DPd
Analysis set: safety	150	149	103
Any TEAE	146 (97.3%)	145 (97.3%)	103 (100.0%)
At least one related[a]	116 (77.3%)	135 (90.6%)	100 (97.1%)
At least one related to pomalidomide	108 (72.0%)	131 (87.9%)	95 (92.2%)
At least one related to dexamethasone	76 (50.7%)	93 (62.4%)	81 (78.6%)
At least one related to daratumumab	-	87 (58.4%)	95 (92.2%)
Maximum toxicity grade[b]			
Grade 1	4 (2.7%)	0	0
Grade 2	19 (12.7%)	14 (9.4%)	1 (1.0%)
Grade 3	82 (54.7%)	47 (31.5%)	40 (38.8%)
Grade 4	30 (20.0%)	73 (49.0%)	55 (53.4%)
Grade 5	11 (7.3%)	11 (7.4%)	7 (6.8%)
Any serious TEAE	59 (39.3%)	75 (50.3%)	50 (48.5%)
At least one related[a]	15 (10.0%)	40 (26.8%)	23 (22.3%)
At least one related to pomalidomide	12 (8.0%)	37 (24.8%)	18 (17.5%)
At least one related to dexamethasone	9 (6.0%)	22 (14.8%)	16 (15.5%)
At least one related to daratumumab	-	26 (17.4%)	17 (16.5%)
TEAE leading to discontinuation of pomalidomide	4 (2.7%)	8 (5.4%)	15 (14.6%)
At least one related to pomalidomide	0	6 (4.0%)	4 (3.9%)
TEAE leading to discontinuation of dexamethasone	5 (3.3%)	6 (4.0%)	17 (16.5%)
At least one related to dexamethasone	1 (0.7%)	3 (2.0%)	6 (5.8%)
TEAE leading to discontinuation of daratumumab	-	4 (2.7%)	16 (15.5%)
At least one related to daratumumab	-	2 (1.3%)	3 (2.9%)
TEAE leading to discontinuation of study treatment[c]	4 (2.7%)	3 (2.0%)	13 (12.6%)
Grade ≥3 TEAE	123 (82.0%)	131 (87.9%)	102 (99.0%)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
TEAE = treatment-emergent adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Each subject could have more than one event, and multiple occurrences of each event, but is only counted once for each row.
[a] TEAEs related to at least 1 of the 3 study treatments: pomalidomide, dexamethasone or daratumumab. Study drug-related TEAEs are the TEAEs with relationship recorded on the case report form as 'definitely related', 'probably related', and 'possibly related'. If the relationship to a study drug is missing, the TEAE is considered drug-related as well.
[b] For each subject and each adverse event, the maximum toxicity grade is selected. Adverse events were graded according to NCI CTCAE version 4.03.
[c] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
Adverse events are reported using MedDRA version 23.0.
Percentages are calculated with the number of subjects in each group as denominator.
[TSFAE01.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_DPD_2020\RE_MMY_RR_DPD_2020\PROD\TSFAE01.SAS] 17SEP2020, 15:35

Common Adverse Events

The most commonly reported TEAEs (≥10% in either treatment group) are presented in Table 21. TEAEs with a frequency ≥10% in either treatment group and that occurred at a ≥5% higher frequency in the DPd group compared with the Pd group included:

- Neutropenia (DPd: 70.5%; Pd: 53.3%),
- Leukopenia (DPd: 26.2%; Pd: 12.0%),
- Upper respiratory tract infection (DPd: 22.8%; Pd: 16.0%),
- Asthenia (DPd: 22.2%; Pd: 16.0%),
- Diarrhea (DPd: 22.2%; Pd: 14.0%),
- Pneumonia (DPd: 20.1%; Pd: 12.7%),
- Pyrexia (DPd: 19.5%; Pd: 14.0%),
- Lymphopenia (DPd: 14.8%; Pd: 8.0%),
- Peripheral edema (DPd: 14.8%; Pd: 7.3%).

TEAEs with a frequency ≥10% and that occurred at a ≥5% higher frequency in the Pd group compared with the DPd group included anemia (DPd: 36.9%; Pd: 44.0%).

Table 24: Most Common (At Least 10%) Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort)

	APOLLO (Study MMY3013)		EQUULEUS (Study MMY1001)
	Pd	DPd	DPd
Analysis set: safety	150	149	103
Number of subjects with any treatment-emergent adverse events	146 (97.3%)	145 (97.3%)	103 (100.0%)
MedDRA system organ class/preferred term			
Blood and lymphatic system disorders	118 (78.7%)	131 (87.9%)	91 (88.3%)
Neutropenia	80 (53.3%)	105 (70.5%)	81 (78.6%)
Anaemia	66 (44.0%)	55 (36.9%)	54 (52.4%)
Thrombocytopenia	50 (33.3%)	48 (32.2%)	42 (40.8%)
Leukopenia	18 (12.0%)	39 (26.2%)	38 (36.9%)
Lymphopenia	12 (8.0%)	22 (14.8%)	22 (21.4%)
Infections and infestations	83 (55.3%)	105 (70.5%)	72 (69.9%)
Upper respiratory tract infection	24 (16.0%)	34 (22.8%)	26 (25.2%)
Pneumonia	19 (12.7%)	30 (20.1%)	13 (12.6%)
Lower respiratory tract infection	24 (16.0%)	29 (19.5%)	0
Bronchitis	18 (12.0%)	20 (13.4%)	10 (9.7%)
Sinusitis	0	1 (0.7%)	13 (12.6%)
General disorders and administration site conditions	79 (52.7%)	98 (65.8%)	82 (79.6%)
Fatigue	38 (25.3%)	38 (25.5%)	51 (49.5%)
Asthenia	24 (16.0%)	33 (22.1%)	15 (14.6%)
Pyrexia	21 (14.0%)	29 (19.5%)	26 (25.2%)
Oedema peripheral	11 (7.3%)	22 (14.8%)	16 (15.5%)
Non-cardiac chest pain	5 (3.3%)	4 (2.7%)	15 (14.6%)
Chills	0	3 (2.0%)	21 (20.4%)
Pain	3 (2.0%)	2 (1.3%)	11 (10.7%)
Gastrointestinal disorders	52 (34.7%)	67 (45.0%)	81 (78.6%)
Diarrhoea	21 (14.0%)	33 (22.1%)	39 (37.9%)
Constipation	22 (14.7%)	21 (14.1%)	34 (33.0%)
Nausea	10 (6.7%)	11 (7.4%)	31 (30.1%)
Vomiting	3 (2.0%)	8 (5.4%)	22 (21.4%)
Musculoskeletal and connective tissue disorders	62 (41.3%)	65 (43.6%)	74 (71.8%)
Back pain	14 (9.3%)	15 (10.1%)	26 (25.2%)
Bone pain	19 (12.7%)	14 (9.4%)	13 (12.6%)
Muscle spasms	7 (4.7%)	12 (8.1%)	27 (26.2%)
Pain in extremity	10 (6.7%)	9 (6.0%)	15 (14.6%)
Musculoskeletal chest pain	4 (2.7%)	8 (5.4%)	13 (12.6%)
Arthralgia	4 (2.7%)	6 (4.0%)	23 (22.3%)
Nervous system disorders	36 (24.0%)	47 (31.5%)	61 (59.2%)
Tremor	13 (8.7%)	15 (10.1%)	20 (19.4%)
Headache	6 (4.0%)	5 (3.4%)	17 (16.5%)
Dizziness	6 (4.0%)	3 (2.0%)	22 (21.4%)
Metabolism and nutrition disorders	42 (28.0%)	45 (30.2%)	49 (47.6%)
Hyperglycaemia	19 (12.7%)	15 (10.1%)	13 (12.6%)
Hypokalaemia	7 (4.7%)	12 (8.1%)	16 (15.5%)
Decreased appetite	3 (2.0%)	5 (3.4%)	11 (10.7%)
Respiratory, thoracic and mediastinal disorders	36 (24.0%)	45 (30.2%)	80 (77.7%)
Cough	10 (6.7%)	17 (11.4%)	37 (35.9%)
Dyspnoea	11 (7.3%)	16 (10.7%)	31 (30.1%)
Productive cough	2 (1.3%)	3 (2.0%)	12 (11.7%)
Nasal congestion	1 (0.7%)	1 (0.7%)	16 (15.5%)
Psychiatric disorders	29 (19.3%)	29 (19.5%)	47 (45.6%)
Insomnia	18 (12.0%)	12 (8.1%)	24 (23.3%)
Anxiety	8 (5.3%)	4 (2.7%)	13 (12.6%)
Skin and subcutaneous tissue disorders	27 (18.0%)	29 (19.5%)	39 (37.9%)
Pruritus	6 (4.0%)	4 (2.7%)	12 (11.7%)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
Each subject could have more than one event, and multiple occurrences of each event, but is only counted once for each row.
Terms are coded using MedDRA dictionary, version 23.0.
Percentages are calculated with the number of subjects in each group as denominator.
[TSFAE02A.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_DPD_2020\RE_MMY_RR_DPD_2020\PROD\TSFAE02A.SAS] 17SEP2020, 15:39

Grade 3 or 4 Treatment-emergent Adverse Events

Grade 3 or 4 Treatment-emergent Adverse Events are summarised in Table below.

No Grade 3 or 4 TEAEs occurred at a ≥5% higher frequency in the Pd group compared with the DPd group.

Table 25: Most Common (At Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort)

	APOLLO (Study MMY3013)		EQUULEUS (Study MMY1001)
	Pd	DPd	DPd
Analysis set: safety	150	149	103
Number of subjects with any grade 3 or 4 treatment-emergent adverse events	123 (82.0%)	130 (87.2%)	102 (99.0%)
MedDRA system organ class/preferred term			
Blood and lymphatic system disorders	97 (64.7%)	112 (75.2%)	87 (84.5%)
Neutropenia	76 (50.7%)	101 (67.8%)	79 (76.7%)
Thrombocytopenia	27 (18.0%)	26 (17.4%)	18 (17.5%)
Anaemia	32 (21.3%)	25 (16.8%)	28 (27.2%)
Leukopenia	7 (4.7%)	25 (16.8%)	25 (24.3%)
Lymphopenia	5 (3.3%)	18 (12.1%)	14 (13.6%)
Febrile neutropenia	4 (2.7%)	13 (8.7%)	7 (6.8%)
Infections and infestations	34 (22.7%)	42 (28.2%)	29 (28.2%)
Pneumonia	10 (6.7%)	20 (13.4%)	9 (8.7%)
Lower respiratory tract infection	14 (9.3%)	17 (11.4%)	0
General disorders and administration site conditions	10 (6.7%)	20 (13.4%)	15 (14.6%)
Fatigue	7 (4.7%)	12 (8.1%)	10 (9.7%)
Asthenia	1 (0.7%)	8 (5.4%)	0
Metabolism and nutrition disorders	13 (8.7%)	20 (13.4%)	16 (15.5%)
Hyperglycaemia	7 (4.7%)	8 (5.4%)	6 (5.8%)
Gastrointestinal disorders	6 (4.0%)	10 (6.7%)	8 (7.8%)
Diarrhoea	1 (0.7%)	8 (5.4%)	3 (2.9%)
Respiratory, thoracic and mediastinal disorders	5 (3.3%)	9 (6.0%)	19 (18.4%)
Dyspnoea	1 (0.7%)	4 (2.7%)	7 (6.8%)
Musculoskeletal and connective tissue disorders	6 (4.0%)	2 (1.3%)	18 (17.5%)
Back pain	1 (0.7%)	0	6 (5.8%)
Injury, poisoning and procedural complications	5 (3.3%)	1 (0.7%)	10 (9.7%)
Fall	0	0	6 (5.8%)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
Each subject could have more than one event, and multiple occurrences of each event, but is only counted once for each row.
Terms are coded using MedDRA dictionary, version 23.0.
Percentages are calculated with the number of subjects in each group as denominator.
[TSFAE04A.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_DPD_2020\RE_MMY_RR_DPD_2020\PROD\TSFAE04A.SAS] 17SEP2020,

Treatment-emergent Adverse Events by Baseline ECOG Performance Status are presented in Table below

Table 26: Overview of Treatment-emergent Adverse Events by Baseline ECOG Performance Status; Safety Analysis Set (Study 54767414MMY3013)

	Pd				DPd			
	0 n (%)	1 n (%)	2 n (%)	Total n (%)	0 n (%)	1 n (%)	2 n (%)	Total n (%)
Analysis set: safety	75	56	19	150	91	52	6	149
Any TEAE	74 (98.7%)	54 (96.4%)	18 (94.7%)	146 (97.3%)	88 (96.7%)	51 (98.1%)	6 (100.0%)	145 (97.3%)
At least one related[a]	63 (84.0%)	40 (71.4%)	13 (68.4%)	116 (77.3%)	85 (93.4%)	45 (86.5%)	5 (83.3%)	135 (90.6%)

Table 26: Overview of Treatment-emergent Adverse Events by Baseline ECOG Performance Status; Safety Analysis Set (Study 54767414MMY3013)

	Pd				DPd			
	0 n (%)	1 n (%)	2 n (%)	Total n (%)	0 n (%)	1 n (%)	2 n (%)	Total n (%)
At least one related to pomalidomide	59 (78.7%)	37 (66.1%)	12 (63.2%)	108 (72.0%)	81 (89.0%)	45 (86.5%)	5 (83.3%)	131 (87.9%)
At least one related to dexamethasone	46 (61.3%)	24 (42.9%)	6 (31.6%)	76 (50.7%)	56 (61.5%)	35 (67.3%)	2 (33.3%)	93 (62.4%)
At least one related to daratumumab					60 (65.9%)	24 (46.2%)	3 (50.0%)	87 (58.4%)
Maximum toxicity grade[b]								
Grade 1	2 (2.7%)	1 (1.8%)	1 (5.3%)	4 (2.7%)	0	0	0	0
Grade 2	11 (14.7%)	6 (10.7%)	2 (10.5%)	19 (12.7%)	9 (9.9%)	5 (9.6%)	0	14 (9.4%)
Grade 3	45 (60.0%)	33 (58.9%)	4 (21.1%)	82 (54.7%)	30 (33.0%)	16 (30.8%)	1 (16.7%)	47 (31.5%)
Grade 4	13 (17.3%)	10 (17.9%)	7 (36.8%)	30 (20.0%)	43 (47.3%)	26 (50.0%)	4 (66.7%)	73 (49.0%)
Grade 5	3 (4.0%)	4 (7.1%)	4 (21.1%)	11 (7.3%)	6 (6.6%)	4 (7.7%)	1 (16.7%)	11 (7.4%)
Any serious TEAE	19 (25.3%)	29 (51.8%)	11 (57.9%)	59 (39.3%)	38 (41.8%)	33 (63.5%)	4 (66.7%)	75 (50.3%)
At least one related[a]	6 (8.0%)	5 (8.9%)	4 (21.1%)	15 (10.0%)	23 (25.3%)	15 (28.8%)	2 (33.3%)	40 (26.8%)
At least one related to pomalidomide	5 (6.7%)	4 (7.1%)	3 (15.8%)	12 (8.0%)	21 (23.1%)	14 (26.9%)	2 (33.3%)	37 (24.8%)
At least one related to dexamethasone	4 (5.3%)	3 (5.4%)	2 (10.5%)	9 (6.0%)	13 (14.3%)	8 (15.4%)	1 (16.7%)	22 (14.8%)
At least one related to daratumumab					17 (18.7%)	8 (15.4%)	1 (16.7%)	26 (17.4%)
TEAE leading to discontinuation of pomalidomide	0	1 (1.8%)	3 (15.8%)	4 (2.7%)	3 (3.3%)	4 (7.7%)	1 (16.7%)	8 (5.4%)
At least one related to pomalidomide	0	0	0	0	1 (1.1%)	4 (7.7%)	1 (16.7%)	6 (4.0%)
TEAE leading to discontinuation of dexamethasone	1 (1.3%)	1 (1.8%)	3 (15.8%)	5 (3.3%)	4 (4.4%)	1 (1.9%)	1 (16.7%)	6 (4.0%)
At least one related to dexamethasone	1 (1.3%)	0	0	1 (0.7%)	1 (1.1%)	1 (1.9%)	1 (16.7%)	3 (2.0%)
TEAE leading to discontinuation of daratumumab					2 (2.2%)	2 (3.8%)	0	4 (2.7%)
At least one related to daratumumab					0	2 (3.8%)	0	2 (1.3%)
TEAE leading to discontinuation of study treatment[c]	0	1 (1.8%)	3 (15.8%)	4 (2.7%)	2 (2.2%)	1 (1.9%)	0	3 (2.0%)
Grade ≥3 TEAE	61 (81.3%)	47 (83.9%)	15 (78.9%)	123 (82.0%)	79 (86.8%)	46 (88.5%)	6 (100.0%)	131 (87.9%)
COVID-19 related TEAE	0	0	0	0	1 (1.1%)	1 (1.9%)	0	2 (1.3%)
COVID-19 related serious TEAE	0	0	0	0	1 (1.1%)	1 (1.9%)	0	2 (1.3%)
COVID-19 related non-serious TEAE	0	0	0	0	0	0	0	0
COVID-19 related Grade ≥ 3 TEAE	0	0	0	0	1 (1.1%)	1 (1.9%)	0	2 (1.3%)

Table 26: Overview of Treatment-emergent Adverse Events by Baseline ECOG Performance Status; Safety Analysis Set (Study 54767414MMY3013)

	Pd				DPd			
	0 n (%)	1 n (%)	2 n (%)	Total n (%)	0 n (%)	1 n (%)	2 n (%)	Total n (%)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone; SC = subcutaneous.
TEAE = treatment-emergent adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
"DPd" includes all subjects who received daratumumab, regardless of the route of administration, with pomalidomide and dexamethasone.
Each subject could have more than one event, and multiple occurrences of each event, but is only counted once for each row
a. TEAEs related to at least 1 of the 3 study treatments: pomalidomide, dexamethasone or daratumumab. Study treatment-related TEAEs are the TEAEs with relationship recorded on the case report form as "definitely related", "probably related", and "possibly related". If the relationship to a study treatment is missing, the TEAE is considered treatment-related as well
b. For each subject and each adverse event, the maximum toxicity grade is selected. Adverse events were graded according to NCI CTCAE version 4.03.
c. Includes those subjects indicated as having discontinued treatment due to an adverse event on the End of Treatment case report form.
Adverse events are reported using MedDRA version 23.0.
Percentages are calculated with the number of subjects in each group as denominator

Adverse drug reactions (ADRs)

In Study MMY3013, the most frequently reported (≥20%) daratumumab-related TEAE as assessed by the investigator was neutropenia (28.9%). The most frequently reported pomalidomide-related TEAEs were neutropenia (DPd: 65.1%; Pd: 48.7%), thrombocytopenia (DPd: 22.8%; Pd: 22.0%), and leukopenia (DPd: 22.2%; Pd: 9.3%).

Most common ADRs with at least 5% greater incidence in the DPd Arm are summarised in Table 23.

Table 27: Adverse Reactions Reported in at Least 10% of Subjects in the DPd Arm With at Least 5% Greater Incidence in the DPd Arm; Safety Analysis Set (Study 54767414MMY3013)

	Pd				DPd			
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
Analysis set: safety	150				149			
General disorders and administration site conditions								
Fatigue[a]	58 (38.7%)	8 (5.3%)	0	0	68 (45.6%)	19 (12.8%)	1 (0.7%)	0
Pyrexia	21 (14.0%)	0	0	0	29 (19.5%)	0	0	0
Oedema peripheral[b]	14 (9.3%)	0	0	0	22 (14.8%)	0	0	0
Infections and infestations								
Pneumonia[c]	41 (27.3%)	18 (12.0%)	3 (2.0%)	4 (2.7%)	56 (37.6%)	25 (16.8%)	5 (3.4%)	4 (2.7%)
Upper respiratory tract infection[d]	33 (22.0%)	3 (2.0%)	0	0	54 (36.2%)	1 (0.7%)	0	0
Gastrointestinal disorders								
Diarrhoea	21 (14.0%)	1 (0.7%)	0	0	33 (22.1%)	8 (5.4%)	0	0
Respiratory, thoracic and mediastinal disorders								
Cough[e]	12 (8.0%)	0	0	0	19 (12.8%)	0	0	0

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
[a]Fatigue includes asthenia, and fatigue.
[b]Oedema peripheral includes oedema, oedema peripheral, and peripheral swelling.
[c]Pneumonia includes atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, pneumonia bacterial, and pneumonia respiratory syncytial viral.
[d]Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, sinusitis, tonsillitis, upper respiratory tract infection, and viral upper respiratory tract infection.
[e]Cough includes cough, and productive cough.
Note: Denominator is based on the number of subjects in the safety analysis set. As ADR determination has been based on rounding to the nearest whole number, some preferred terms may appear between 9.5% - <10% in this table where rounding is based on one decimal place.
Adverse events are reported using MedDRA Version 23.0.
[TSFAE40_SCS.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_DPD_2020\RE_MMY_RR_DPD_2020\PROD\TSFAE40_SCS.SAS] 17SEP2020, 15:44

A review of Study MMY3013 identified the new ADR term of syncope which now meets the pre-defined ADR threshold (reported in ≥10% of subjects and occurred at a higher incidence (≥5% difference) in the DPd treatment group as compared with the Pd).

The incidence of syncope was higher in the DPd group compared to the Pd group (DPd: 6.7%; Pd: 0.7%) . All cases were Grade 2 or Grade 3, and all recovered. Syncope was reported as a serious TEAE in only the DPd group (2.0%) (Table 27). These cases were confounded by medical history, including cardiac disorders and/or dehydration/procedures contributing to the events of syncope. However, daratumumab contribution to these events could not be excluded.

Table 28: Treatment-emergent Serious Adverse Events That Have ⩾ 2% Higher Incidence in DPd Than Pd; Safety Analysis Set (Study MMY3013)

	APOLLO	
	Pd	DPd
Analysis set: safety	150	149
MedDRA system organ class/preferred term		
Infections and infestations		
Pneumonia[a]	26 (17%)	39 (26%)
Blood and lymphatic system disorders		
Neutropenia[b]	4 (3%)	7 (5%)
Thrombocytopenia[c]	1 (1%)	4 (3%)
Gastrointestinal disorders		
Syncope	0	3 (2%)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone
[a]Includes Atypical pneumonia, Lower respiratory tract infection, Pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia respiratory syncytial viral
[b]Includes Febrile neutropenia, Neutropenia
[c]Includes Thrombocytopenia
Adverse events are reported using MedDRA version 23.0.
Percentages are calculated with N as the denominator, the number of safety subjects in each treatment arm.
[TSFAE40A.RTF] [JNJ-54767414\Z SCS\DBR MMY RR DPD 2020\RE MMY RR DPD 2020\PROD\TSFAE40A.SAS] 14OCT2020, 12:49

Serious adverse event/deaths/other significant events

The incidence of **serious TEAEs** was higher for subjects in the DPd group compared to the Pd group in Study MMY3013 (DPd: 50.3%, Pd: 39.3%; Table 28).

*Table 29: Most Common (At Least 2%) Treatment-emergent **Serious Adverse Events** by System Organ Class and Preferred Term; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort)*

	APOLLO (Study MMY3013)		EQUULEUS (Study MMY1001)
	Pd	DPd	DPd
Analysis set: safety	150	149	103
Number of subjects with any treatment-emergent serious adverse events	59 (39.3%)	75 (50.3%)	50 (48.5%)
MedDRA system organ class/preferred term			
Infections and infestations	37 (24.7%)	49 (32.9%)	21 (20.4%)
Pneumonia	12 (8.0%)	23 (15.4%)	8 (7.8%)
Lower respiratory tract infection	14 (9.3%)	18 (12.1%)	0
Upper respiratory tract infection	3 (2.0%)	3 (2.0%)	1 (1.0%)
Bronchitis	5 (3.3%)	1 (0.7%)	0
Sepsis	0	1 (0.7%)	4 (3.9%)
Blood and lymphatic system disorders	4 (2.7%)	9 (6.0%)	8 (7.8%)
Febrile neutropenia	3 (2.0%)	5 (3.4%)	4 (3.9%)
Thrombocytopenia	1 (0.7%)	4 (2.7%)	2 (1.9%)
Anaemia	1 (0.7%)	1 (0.7%)	3 (2.9%)
Respiratory, thoracic and mediastinal disorders	4 (2.7%)	8 (5.4%)	11 (10.7%)
Dyspnoea	1 (0.7%)	3 (2.0%)	3 (2.9%)
Gastrointestinal disorders	5 (3.3%)	7 (4.7%)	5 (4.9%)
Diarrhoea	1 (0.7%)	3 (2.0%)	1 (1.0%)
General disorders and administration site conditions	4 (2.7%)	5 (3.4%)	4 (3.9%)
Pyrexia	1 (0.7%)	3 (2.0%)	0
General physical health deterioration	3 (2.0%)	1 (0.7%)	2 (1.9%)
Nervous system disorders	3 (2.0%)	5 (3.4%)	5 (4.9%)
Syncope	0	3 (2.0%)	1 (1.0%)
Injury, poisoning and procedural complications	3 (2.0%)	1 (0.7%)	7 (6.8%)
Fall	1 (0.7%)	0	4 (3.9%)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
Each subject could have more than one event, and multiple occurrences of each event, but is only counted once for each row.
Terms are coded using MedDRA dictionary, version 23.0.
Percentages are calculated with the number of subjects in each group as denominator.
[TSFAE05A.RTF] [JNJ-54767414\Z SCS\DBR MMY RR DPD 2020\RE MMY RR DPD 2020\PROD\TSFAE05A.SAS] 17SEP2020, 15:42

Deaths and Cause of Death and Treatment-emergent Adverse Events with Outcome **Death** by Preferred Term and Relationship are summarised in Tables 27 and 28 respectively.

Table 30: Deaths and Cause of Death; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort)

	APOLLO (Study MMY3013)		EQUULEUS (Study MMY1001)
	Pd	DPd	DPd
Analysis set: safety	150	149	103
Total number of subjects who died during the study	51 (34.0%)	47 (31.5%)	28 (27.2%)
Primary cause of death			
Adverse event	12 (8.0%)	14 (9.4%)	8 (7.8%)
At least one related[a]	0	4 (2.7%)	1 (1.0%)
Unrelated	12 (8.0%)	10 (6.7%)	7 (6.8%)
Disease progression	30 (20.0%)	26 (17.4%)	19 (18.4%)
Other	9 (6.0%)	7 (4.7%)	1 (1.0%)
Total number of subjects who died within 30 days of last study treatment	15 (10.0%)	16 (10.7%)	7 (6.8%)
Primary cause of death			
Adverse event	12 (8.0%)	11 (7.4%)	5 (4.9%)
At least one related[a]	0	4 (2.7%)	1 (1.0%)
Unrelated	12 (8.0%)	7 (4.7%)	4 (3.9%)
Disease progression	3 (2.0%)	5 (3.4%)	2 (1.9%)
Total number of subjects who died within 60 days of first study treatment	9 (6.0%)	4 (2.7%)	7 (6.8%)
Primary cause of death			
Adverse event	6 (4.0%)	3 (2.0%)	5 (4.9%)
At least one related[a]	0	2 (1.3%)	1 (1.0%)
Unrelated	6 (4.0%)	1 (0.7%)	4 (3.9%)
Disease progression	3 (2.0%)	1 (0.7%)	2 (1.9%)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
Study drug-related adverse events are the adverse events with relationship recorded on the case report form as "definitely related", "probably related", and "possibly related". If the relationship to a study drug is missing, the adverse event is considered drug-related as well.
Percentages are calculated with the number of subjects in each group as denominator.
[a] Includes adverse events that were related to at least 1 of the 3 study treatments: pomalidomide, dexamethasone, or daratumumab.

[TSFDTH01.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_DPD_2020\RE_MMY_RR_DPD_2020\PROD\TSFDTH01.SAS] 17SEP2020, 15:46

*Table 31: Treatment-emergent Adverse Events with Outcome **Death** by Preferred Term and Relationship; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort)*

	APOLLO (Study MMY3013)							EQUULEUS (Study MMY1001)			
		Pd			DPd				DPd		
	Total	Related to Pomalidomide	Related to Dexamethasone	Total	Related to Daratumumab	Related to Pomalidomide	Related to Dexamethasone	Total	Related to Daratumumab	Related to Pomalidomide	Related to Dexamethasone
Analysis set: safety	150			149				103			
Number of subjects with any treatment-emergent adverse events with outcome death	11 (7.3%)	0	0	11 (7.4%)	3 (2.0%)	4 (2.7%)	3 (2.0%)	7 (6.8%)	0	0	1 (1.0%)
MedDRA preferred term											
Pneumonia	2 (1.3%)	0	0	3 (2.0%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0	0	0
Bone marrow failure	0	0	0	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0	0	0	0
COVID-19	0	0	0	1 (0.7%)	0	0	0	0	0	0	0
Campylobacter infection	0	0	0	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0	0	0	0
Dyspnoea	0	0	0	1 (0.7%)	0	0	0	0	0	0	0
Liver disorder	0	0	0	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0	0	0	0
Lower respiratory tract infection	1 (0.7%)	0	0	1 (0.7%)	0	0	0	0	0	0	0
Respiratory failure	0	0	0	1 (0.7%)	0	0	0	1 (1.0%)	0	0	0
Sepsis	0	0	0	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (1.0%)	0	0	0
Septic shock	2 (1.3%)	0	0	1 (0.7%)	0	1 (0.7%)	1 (0.7%)	0	0	0	0
Sudden death	0	0	0	1 (0.7%)	0	0	0	0	0	0	0
Systemic candida	0	0	0	1 (0.7%)	0	0	0	0	0	0	0
Acute myocardial infarction	1 (0.7%)	0	0	0	0	0	0	0	0	0	0
Cerebral haemorrhage	1 (0.7%)	0	0	0	0	0	0	0	0	0	0
Cerebrovascular accident	0	0	0	0	0	0	0	1 (1.0%)	0	0	0
General physical health deterioration	2 (1.3%)	0	0	0	0	0	0	1 (1.0%)	0	0	0
Hypertensive hydrocephalus	1 (0.7%)	0	0	0	0	0	0	0	0	0	0
Interstitial lung disease	0	0	0	0	0	0	0	1 (1.0%)	0	0	0
Pleural effusion	0	0	0	0	0	0	0	1 (1.0%)	0	0	0
Pneumonia aspiration	1 (0.7%)	0	0	0	0	0	0	0	0	0	0
Progressive multifocal leukoencephalopathy	0	0	0	0	0	0	0	1 (1.0%)	0	0	1 (1.0%)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
Each subject could have more than one event, and multiple occurrences of each event, but is only counted once for each row.
TEAEs with outcome death are TEAEs with 'fatal' recorded as outcome on the Adverse Event case report form.
Terms are coded using MedDRA dictionary, version 23.0.
Percentages are calculated with the number of subjects in each group as denominator.
[TSFAE13A.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_DPD_2020\RE_MMY_RR_DPD_2020\PROD\TSFAE13A.SAS] 17SEP2020, 15:44

Other significant adverse events

Infusion-related Reactions (IRR)

IRRs were defined as systemic reactions related to daratumumab administration, regardless of the route of administration. IRRs were recorded by the investigator in the eCRF.

In Study MMY3013, 7 of 149 subjects received daratumumab IV administration prior to Protocol Amendment 1. IRRs were reported for 5.4% of subjects in the DPd group, with pyrexia as the most common preferred term reported by subjects (2.0%). None of the 7 subjects starting treatment with daratumumab IV experienced IRRs. All IRRs reported occurred in subjects treated with daratumumab SC only. All IRRs reported were Grade 1 or 2, and none resulted in discontinuation or interruption of treatment.

Injection-site reactions (ISR)

Localized reactions at the site of administration of daratumumab SC were referred to as injection-site reactions.

Injection-site reactions were reported for 3 subjects (2.0%) in the DPd group. The following preferred terms were experienced as Grade 1 for 1 subject each: erythema, rash, and contusion. None of these resulted in discontinuation or interruption of treatment.

Cytopenia AEs

The addition of daratumumab to Pd in Study MMY3013 resulted in higher incidences of neutropenia, lymphopenia, and febrile neutropenia compared to subjects receiving Pd alone. Overall, the incidence of cytopenia-related events was higher in the DPd group (84.6%) compared to the Pd group (78.0%).

Table 32: Summary of Treatment-emergent Cytopenia Events by Preferred Term; Safety Analysis Set (Study 54767414MMY3013)

	Pd n (%)	DPd n (%)	DPd - SC n (%)
Analysis set: safety	150	149	142
Number of subjects with any treatment-emergent cytopenia events	117 (78.00)	126 (84.56)	119 (83.80)
MedDRA Preferred term			
Neutropenia[a]	80 (53.33)	109 (73.15)	104 (73.24)
Neutropenia	80 (53.33)	105 (70.47)	101 (71.13)
Febrile neutropenia	4 (2.67)	13 (8.72)	12 (8.45)
Anaemia[a]	67 (44.67)	55 (36.91)	53 (37.32)
Anaemia	66 (44.00)	55 (36.91)	53 (37.32)
Anaemia macrocytic	1 (0.67)	0	0
Iron deficiency anaemia	1 (0.67)	0	0
Thrombocytopenia[a]	50 (33.33)	48 (32.21)	47 (33.10)
Thrombocytopenia	50 (33.33)	48 (32.21)	47 (33.10)
Lymphopenia[a]	12 (8.00)	22 (14.77)	19 (13.38)
Lymphopenia	12 (8.00)	22 (14.77)	19 (13.38)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone; SC = subcutaneous.
TEAE = Treatment-emergent adverse event.
'DPd' includes all subjects who received daratumumab, regardless of the route of administration, with pomalidomide and dexamethasone.
a. Preferred term grouping.
Each subject could have more than one event, and multiple occurrences of each event, but is only counted once for each row.
Terms are coded using MedDRA dictionary, version 23.0.
Percentages are calculated with the number of subjects in each group as denominator.
Filename: T14.03.01-06.26.RTF / Program: T14.03.01-ByCatPt.sas (05OCT2020 21:13)

Haemorrhagic Events

The incidence of haemorrhagic events was balanced between the treatment groups in Study MMY3013 (DPd: 4.0%; Pd: 6.0%), and the majority of events were Grade 1 or 2. One subject in the DPd group (anal haemorrhage) and 2 subjects in the Pd group (gastrointestinal haemorrhage and epistaxis) experienced Grade 3 events and one subject in the Pd group experienced a Grade 5 event (cerebral haemorrhage) resulting in death.

Two subjects (1.3%) in the DPd group and 2 subjects in the Pd group (1.3%) in Study MMY3013 received fresh frozen plasma transfusions.

The incidence of haemorrhagic events was higher (25.2%) in Study MMY1001 compared to Study MMY3013.

Infections and infestations

Subjects in the DPd group had a higher incidence of any grade TEAE of infection (DPd: 70.5%; Pd: 55.3%; Table 24). Grade 3 or 4 TEAEs of infections were reported in 28.2% of subjects in the DPd group and 22.7% of subjects in the Pd group (Table 25). The most common (≥5%) Grade 3 or 4 infections included pneumonia (DPd: 13.4%; Pd: 6.7%) and lower respiratory tract infection (DPd: 11.4%; Pd: 9.3%).

Second primary malignancies (SPM)

The rate of SPMs was balanced in both treatment groups in Study MMY3013 (DPd: 2.0%; Pd: 2.0%). A haematologic SPM was reported for 1 subject in the Pd group (acute myeloid leukemia). No single malignancy predominated.

No SPMs were reported in Study MMY1001.

Laboratory findings

Haematology

Consistent with the incidence of treatment-emergent cytopenia events in Study MMY3013, Grade 4 haematology values of low WBC (DPd: 21.6%; Pd: 4.0%), low platelets (DPd: 10.1%; Pd: 6.7%), low neutrophils (DPd: 48.0%; Pd: 20.1%), and low lymphocytes (DPd: 15.5%; Pd: 3.4%) were reported at higher incidences in subjects from the DPd group compared with the Pd group. Grade 3 haematology values of low haemoglobin were reported for 16.2% of subjects in the DPd group and 20.1% of subjects in the Pd group. There were no Grade 4 haematology values of low hemoglobin in either treatment group.

All laboratory parameters in Study MMY3013 were reviewed. No laboratory parameters had an incidence of Grade 3 or 4 values ≥10% except for haematology parameters. Thrombocytopenia, neutropenia, lymphopenia, leukopenia, and anemia were listed in a separate haematology laboratory table based on haematology laboratory parameters regardless of the incidence and difference between groups (Table 32).

In Study MMY1001, the most common Grade 3 or 4 haematology laboratory abnormalities were neutrophils low (82.4%) and lymphocytes low (72.5%). Grade 3 or 4 platelets low was reported by 19.6% of subjects. Grade 3 hemoglobin low was reported for 32.4% of subjects. No Grade 4 hemoglobin low was reported.

Clinical chemistry

The incidence of treatment-emergent Grade 3 or 4 chemistry laboratory abnormalities in Study MMY3013 was low (<5%) in both treatment groups with the exception of Grade 3 low potassium (DPd: 5.4%; Pd: 3.4%).

Table 33: Treatment-emergent Haematology Lab Abnormalities; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort)

	APOLLO (Study MMY3013)						EQUULEUS (Study MMY1001)		
	Pd			DPd			DPd		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Analysis set: safety	150			149			103		
Anemia	85 (56.7%)	22 (14.7%)	0	76 (51.0%)	23 (15.4%)	0	59 (57.3%)	31 (30.1%)	0
Thrombocytopenia	89 (59.3%)	21 (14.0%)	8 (5.3%)	111 (74.5%)	13 (8.7%)	15 (10.1%)	77 (74.8%)	10 (9.7%)	10 (9.7%)
Leukopenia	122 (81.3%)	53 (35.3%)	6 (4.0%)	141 (94.6%)	63 (42.3%)	32 (21.5%)	99 (96.1%)	47 (45.6%)	20 (19.4%)
Neutropenia	125 (83.3%)	64 (42.7%)	30 (20.0%)	143 (96.0%)	54 (36.2%)	71 (47.7%)	98 (95.1%)	37 (35.9%)	47 (45.6%)
Lymphopenia	117 (78.0%)	44 (29.3%)	5 (3.3%)	137 (91.9%)	66 (44.3%)	22 (14.8%)	97 (94.2%)	46 (44.7%)	27 (26.2%)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: The laboratory toxicity grades are derived based on NCI CTCAE version 4.03.
For each parameter, the percentage of subjects represents those subjects for whom the toxicity grade worsened during treatment compared to baseline; percentages are calculated with the number of safety subjects in each treatment arm.
For each subject and each parameter, the worst toxicity grade is selected.
[TSFLAB04.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_DPD_2020\RE_MMY_RR_DPD_2020\PROD\TSFLAB04.SAS] 17SEP2020, 15:47

Safety in special populations

Age

Table 34: Overview of Treatment-emergent Adverse Events by Age; Safety Analysis Set (Study 54767414MMY3013)

T14.03.01-06.02: Overview of Treatment-emergent Adverse Events by Age; Safety Analysis Set (Study 54767414MMY3013)

	Pd			DPd			DPd - SC		
	<65 years n (%)	≥65 years n (%)	Total n (%)	<65 years n (%)	≥65 years n (%)	Total n (%)	<65 years n (%)	≥65 years n (%)	Total n (%)
Analysis set: safety	58	92	150	61	88	149	56	86	142
Any TEAE	57 (98.28)	89 (96.74)	146 (97.33)	57 (93.44)	88 (100.00)	145 (97.32)	52 (92.86)	86 (100.00)	138 (97.18)
At least one related[a]	41 (70.69)	75 (81.52)	116 (77.33)	50 (81.97)	85 (96.59)	135 (90.60)	47 (83.93)	83 (96.51)	130 (91.55)
At least one related to pomalidomide	36 (62.07)	72 (78.26)	108 (72.00)	47 (77.05)	84 (95.45)	131 (87.92)	45 (80.36)	82 (95.35)	127 (89.44)
At least one related to dexamethasone	28 (48.28)	48 (52.17)	76 (50.67)	32 (52.46)	61 (69.32)	93 (62.42)	29 (51.79)	59 (68.60)	88 (61.97)
At least one related to daratumumab				37 (60.66)	50 (56.82)	87 (58.39)	37 (66.07)	49 (56.98)	86 (60.56)
Maximum toxicity grade[b]									
Grade 1	3 (5.17)	1 (1.09)	4 (2.67)	0	0	0	0	0	0
Grade 2	8 (13.79)	11 (11.96)	19 (12.67)	5 (8.20)	9 (10.23)	14 (9.40)	5 (8.93)	9 (10.47)	14 (9.86)
Grade 3	32 (55.17)	50 (54.35)	82 (54.67)	19 (31.15)	28 (31.82)	47 (31.54)	16 (28.57)	27 (31.40)	43 (30.28)
Grade 4	11 (18.97)	19 (20.65)	30 (20.00)	28 (45.90)	45 (51.14)	73 (48.99)	28 (50.00)	44 (51.16)	72 (50.70)
Grade 5	3 (5.17)	8 (8.70)	11 (7.33)	5 (8.20)	6 (6.82)	11 (7.38)	3 (5.36)	6 (6.98)	9 (6.34)
Any serious TEAE	19 (32.76)	40 (43.48)	59 (39.33)	25 (40.98)	50 (56.82)	75 (50.34)	23 (41.07)	49 (56.98)	72 (50.70)
At least one related[a]	2 (3.45)	13 (14.13)	15 (10.00)	14 (22.95)	26 (29.55)	40 (26.85)	13 (23.21)	26 (30.23)	39 (27.46)
At least one related to pomalidomide	2 (3.45)	10 (10.87)	12 (8.00)	12 (19.67)	25 (28.41)	37 (24.83)	11 (19.64)	25 (29.07)	36 (25.35)
At least one related to dexamethasone	1 (1.72)	8 (8.70)	9 (6.00)	6 (9.84)	16 (18.18)	22 (14.77)	5 (8.93)	16 (18.60)	21 (14.79)
At least one related to daratumumab				9 (14.75)	17 (19.32)	26 (17.45)	9 (16.07)	17 (19.77)	26 (18.31)
TEAE leading to discontinuation of pomalidomide	1 (1.72)	3 (3.26)	4 (2.67)	1 (1.64)	7 (7.95)	8 (5.37)	1 (1.79)	7 (8.14)	8 (5.63)
At least one related to pomalidomide	0	0	0	1 (1.64)	5 (5.68)	6 (4.03)	1 (1.79)	5 (5.81)	6 (4.23)
TEAE leading to discontinuation of dexamethasone	1 (1.72)	4 (4.35)	5 (3.33)	1 (1.64)	5 (5.68)	6 (4.03)	1 (1.79)	5 (5.81)	6 (4.23)
At least one related to dexamethasone	0	1 (1.09)	1 (0.67)	1 (1.64)	2 (2.27)	3 (2.01)	1 (1.79)	2 (2.33)	3 (2.11)
TEAE leading to discontinuation of daratumumab				1 (1.64)	3 (3.41)	4 (2.68)	1 (1.79)	3 (3.49)	4 (2.82)
At least one related to daratumumab				1 (1.64)	1 (1.14)	2 (1.34)	1 (1.79)	1 (1.16)	2 (1.41)
TEAE leading to discontinuation of study treatment[c]	1 (1.72)	3 (3.26)	4 (2.67)	0	3 (3.41)	3 (2.01)	0	3 (3.49)	3 (2.11)
Grade ≥3 TEAE	46 (79.31)	77 (83.70)	123 (82.00)	52 (85.25)	79 (89.77)	131 (87.92)	47 (83.93)	77 (89.53)	124 (87.32)
COVID-19 related TEAE	0	0	0	0	2 (2.27)	2 (1.34)	0	2 (2.33)	2 (1.41)
COVID-19 related serious TEAE	0	0	0	0	2 (2.27)	2 (1.34)	0	2 (2.33)	2 (1.41)
COVID-19 related non-serious TEAE	0	0	0	0	0	0	0	0	0
COVID-19 related Grade ≥3 TEAE	0	0	0	0	2 (2.27)	2 (1.34)	0	2 (2.33)	2 (1.41)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone; SC = subcutaneous.
TEAE = treatment-emergent adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
'DPd' includes all subjects who received daratumumab, regardless of the route of administration, with pomalidomide and dexamethasone.
Each subject could have more than one event, and multiple occurrences of each event, but is only counted once for each row
a. TEAEs related to at least 1 of the 3 study treatments: pomalidomide, dexamethasone or daratumumab. Study treatment-related TEAEs are the TEAEs with relationship recorded on the case report form as 'definitely related', 'probably related', and 'possibly related'. If the relationship to a study treatment is missing, the TEAE is considered treatment-related as well.
b. For each subject and each adverse event, the maximum toxicity grade is selected. Adverse events were graded according to NCI CTCAE version 4.03.
c. Includes those subjects indicated as having discontinued treatment due to an adverse event on the End of Treatment case report form.
Adverse events are reported using MedDRA version 23.0.
Percentages are calculated with the number of subjects in each group as denominator.
Filename: T14.03.01-06.02.RTF / Program: T14.03.01-SumAE_subgr.sas (05OCT2020 21:20)

Table 35: Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Age; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort – 1st part of table)

TSFAE05C: Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Age; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort)

	APOLLO						EQUULEUS		
	Pd			DPd			DPd		
	<65 years	≥65 years	Total	<65 years	≥65 years	Total	<65 years	≥65 years	Total
Analysis set: safety	58	92	150	61	88	149	52	51	103
Number of subjects with any treatment-emergent serious adverse events	19 (32.8%)	40 (43.5%)	59 (39.3%)	25 (41.0%)	50 (56.8%)	75 (50.3%)	25 (48.1%)	25 (49.0%)	50 (48.5%)
MedDRA system organ class/preferred term									
Infections and infestations	15 (25.9%)	22 (23.9%)	37 (24.7%)	16 (26.2%)	33 (37.5%)	49 (32.9%)	9 (17.3%)	12 (23.5%)	21 (20.4%)
Pneumonia	7 (12.1%)	5 (5.4%)	12 (8.0%)	9 (14.8%)	14 (15.9%)	23 (15.4%)	3 (5.8%)	5 (9.8%)	8 (7.8%)
Lower respiratory tract infection	7 (12.1%)	7 (7.6%)	14 (9.3%)	5 (8.2%)	13 (14.8%)	18 (12.1%)	0	0	0
Upper respiratory tract infection	0	3 (3.3%)	3 (2.0%)	0	3 (3.4%)	3 (2.0%)	0	1 (2.0%)	1 (1.0%)
COVID-19	0	0	0	0	2 (2.3%)	2 (1.3%)	0	0	0
Influenza	0	0	0	1 (1.6%)	1 (1.1%)	2 (1.3%)	0	1 (2.0%)	1 (1.0%)
Urinary tract infection	0	0	0	0	2 (2.3%)	2 (1.3%)	0	1 (2.0%)	1 (1.0%)
Atypical pneumonia	0	1 (1.1%)	1 (0.7%)	0	1 (1.1%)	1 (0.7%)	0	0	0
Bronchitis	1 (1.7%)	4 (4.3%)	5 (3.3%)	0	1 (1.1%)	1 (0.7%)	0	0	0
Campylobacter infection	0	0	0	0	1 (1.1%)	1 (0.7%)	0	0	0

Safety related to drug-drug interactions and other interactions

See the Pharmacokinetics section (4.3.2).

Discontinuation and dose modifications due to adverse events

Adverse Events leading to dose modifications of Daratumumab

TEAEs leading to daratumumab cycle delays or dose skipping were reported in 57.1% of subjects in the DPd group. The most commonly reported (≥5%) TEAEs leading to daratumumab cycle delays or dose skipping included:

- Neutropenia (32.2%),
- Thrombocytopenia (10.7%),
- Lower respiratory tract infection (10.7%),
- Pneumonia (8.7%),
- Upper respiratory tract infection (8.1%).

Adverse Events leading to dose modifications of Pomalidomide

TEAEs leading to pomalidomide cycle delays or dose modifications occurred more frequently in the DPd group (76.5%) compared with the Pd group (56.7%). The most commonly reported (≥5% in either treatment group) TEAEs leading to pomalidomide cycle delays or dose modifications included:

- Neutropenia (DPd: 46.3%; Pd: 23.3%),
- Thrombocytopenia (DPd: 12.1%; Pd: 6.7%),
- Pneumonia (DPd: 12.8%; Pd: 5.3%),
- Lower respiratory tract infection (DPd: 10.1%; Pd: 10.0%),
- Fatigue (DPd: 8.7%; Pd: 5.3%),
- Upper respiratory tract infection (DPd: 7.4%; Pd: 6.0%),
- Febrile neutropenia (DPd: 7.4%; Pd: 1.3%),
- Pyrexia (DPd: 6.7%; Pd: 4.7%;),
- Leukopenia (DPd: 6.0%; Pd: 0%),

- Diarrhoea (DPd: 5.4%; Pd: 0.7%)

Adverse Events leading to dose modifications of Dexamethasone

TEAEs leading to dexamethasone cycle delays or dose modifications were reported for 69.8% in the DPd group and 57.3% of subjects in the Pd group. The most commonly reported (≥5% in either treatment group) TEAEs leading to dexamethasone cycle delays or dose modifications included:

- Neutropenia (DPd: 26.9%; Pd: 6.0%),
- Pneumonia (DPd: 12.1%; Pd: 7.3%),
- Lower respiratory tract infection (DPd: 10.1%; Pd: 11.3%),
- Upper respiratory tract infection (DPd: 9.4%; Pd: 6.0%),
- Thrombocytopenia (DPd: 7.4%; Pd: 4.0%),
- Bronchitis (DPd: 7.4%; Pd: 4.0%),
- Insomnia (DPd: 5.4%; Pd: 7.3%),
- Hyperglycaemia (DPd: 4.7%; Pd: 5.3%).
- Febrile neutropenia (DPd: 4.7%; Pd: 2.0%)

Adverse Events leading to discontinuation

Table 36: Treatment-emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class, Preferred Term and Grade 3 or 4; Safety Analysis Set (Studies: MMY3013 and MMY1001 DPd Cohort)

	APOLLO (Study MMY3013)				EQUULEUS (Study MMY1001)	
	Pd		DPd		DPd	
Analysis set: safety	Grade 3 or 4	All Grades 150	Grade 3 or 4	All Grades 149	Grade 3 or 4	All Grades 103
Number of subjects with any treatment-emergent adverse events leading to treatment discontinuation	4 (2.7%)	5 (3.3%)	8 (5.4%)	11 (7.4%)	12 (11.7%)	18 (17.5%)
MedDRA system organ class/preferred term						
Blood and lymphatic system disorders	1 (0.7%)	1 (0.7%)	3 (2.0%)	3 (2.0%)	1 (1.0%)	1 (1.0%)
Neutropenia	1 (0.7%)	1 (0.7%)	2 (1.3%)	2 (1.3%)	0	0
Thrombocytopenia	0	0	1 (0.7%)	1 (0.7%)	1 (1.0%)	1 (1.0%)
Infections and infestations	0	0	2 (1.3%)	3 (2.0%)	4 (3.9%)	5 (4.9%)
COVID-19	0	0	1 (0.7%)	1 (0.7%)	0	0
Lower respiratory tract infection	0	0	0	1 (0.7%)	0	0
Meningoencephalitis bacterial	0	0	1 (0.7%)	1 (0.7%)	0	0
Mastitis	0	0	0	0	1 (1.0%)	1 (1.0%)
Pneumonia	0	0	0	0	1 (1.0%)	1 (1.0%)
Progressive multifocal leukoencephalopathy	0	0	0	0	1 (1.0%)	1 (1.0%)
Sepsis	0	0	0	0	0	1 (1.0%)
Urinary tract infection	0	0	0	0	1 (1.0%)	1 (1.0%)
Gastrointestinal disorders	0	0	0	1 (0.7%)	0	0
Diarrhoea	0	0	0	1 (0.7%)	0	0
Musculoskeletal and connective tissue disorders	0	0	0	1 (0.7%)	1 (1.0%)	1 (1.0%)
Muscle atrophy	0	0	0	1 (0.7%)	0	0
Muscular weakness	0	0	0	0	1 (1.0%)	1 (1.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.7%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0
Cholangiocarcinoma	0	0	1 (0.7%)	1 (0.7%)	0	0
Adenocarcinoma of colon	1 (0.7%)	1 (0.7%)	0	0	0	0
Nervous system disorders	0	0	1 (0.7%)	1 (0.7%)	0	2 (1.9%)
Peripheral sensory neuropathy	0	0	1 (0.7%)	1 (0.7%)	0	0
Cerebrovascular accident	0	0	0	0	0	1 (1.0%)
Tremor	0	0	0	0	0	1 (1.0%)
Psychiatric disorders	0	0	0	1 (0.7%)	0	1 (1.0%)
Mood altered	0	0	0	1 (0.7%)	0	0
Depression	0	0	0	0	0	1 (1.0%)
Renal and urinary disorders	0	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0
Acute kidney injury	0	1 (0.7%)	1 (0.7%)	1 (0.7%)	0	0
Cardiac disorders	2 (1.3%)	2 (1.3%)	0	0	1 (1.0%)	2 (1.9%)
Angina pectoris	0	0	0	0	0	1 (1.0%)
Atrial fibrillation	0	0	0	0	1 (1.0%)	1 (1.0%)
Cardiac failure	1 (0.7%)	1 (0.7%)	0	0	0	0
Cardiac failure congestive	0	0	0	0	1 (1.0%)	1 (1.0%)
Palpitations	1 (0.7%)	1 (0.7%)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	4 (3.9%)	5 (4.9%)
Dyspnoea	0	0	0	0	1 (1.0%)	1 (1.0%)
Hypoxia	0	0	0	0	1 (1.0%)	1 (1.0%)
Interstitial lung disease	0	0	0	0	1 (1.0%)	1 (1.0%)
Pleural effusion	0	0	0	0	1 (1.0%)	1 (1.0%)
Respiratory failure	0	0	0	0	0	1 (1.0%)
Vascular disorders	0	0	0	0	1 (1.0%)	1 (1.0%)
Aortic dissection	0	0	0	0	1 (1.0%)	1 (1.0%)

Key: Pd = pomalidomide - dexamethasone; DPd = daratumumab - pomalidomide - dexamethasone.
NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Each subject could have more than one event, and multiple occurrences of each event, but is only counted once for each row.
TEAEs leading to discontinuation of at least one of the study treatment components are the TEAEs with 'drug withdrawn' recorded as action taken on the Adverse Event case report form.
Adverse events were graded according to NCI CTCAE version 4.03.
Terms are coded using MedDRA dictionary, version 23.0.
Percentages are calculated with the number of subjects in each group as denominator.
[TSFAE11A.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_DPD_2020\RE_MMY_RR_DPD_2020\PROD\TSFAE11A.SAS] 17SEP2020, 15:43

Post marketing experience

Daratumumab SC has only recently been authorized for use in the US, EU and other countries worldwide.

Postmarketing safety information is available for daratumumab IV and from a commercially available rHuPH20 formulation, Hylenex.

A cumulative review was performed on all post-marketing spontaneous cases of **daratumumab IV** and all events received by the Global Medical Safety (GMS) global safety database cumulatively through 31 March 2020. The results suggest that the drug's post-marketing safety profile is consistent with the known safety profile of daratumumab as a single agent or in combination therapy.

Overall, review of post-marketing spontaneous reports did not identify any new safety signal.

rHuPH20 is the active ingredient of Halozyme's commercial product Hylenex recombinant (hyaluronidase human injection), hereafter referred to as HYLENEX, which was approved in December 2005 by FDA for marketing in the U.S. HYLENEX is a tissue permeability modifier indicated as an adjuvant in SC fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs, and in SC urography, for improving resorption of radiopaque agents (HYLENEX PI 2016).

The MAH has provided information about post-marketing experience for SC daratumumab up to 31 January 2021. There is limited information since SC formulation was approved in the US and EU in May and June 2020, respectively. The estimated exposure to SC daratumumab is 7,413 person-years and to IV daratumumab is 112,010 person-years. From the global safety database, 7,257 events have been further analysed but including both IV and SC formulations. The most commonly reported PTs for overall AEs and AEs with a fatal outcome were generally in line with the widely reported in all daratumumab studies. Frome these 7,257 events, 160 reported SC administration of daratumumab but no relevant differences have been observed in reported PTs for them and the overall safety population. No new safety signals have been identified from this updated safety data which seems to confirm the similar safety profile of the SC formulation, with the exception of those related to the administration route

2.5.1. Discussion on clinical safety

The safety profile of daratumumab, in combination with pomalidomide and dexamethasone, for patients with relapsed or refractory multiple myeloma who have received, at least, one prior line of therapy with both lenalidomide and a proteasome inhibitor (PI), is based on the results from the open-label Phase 3 Study MMY3013, APOLLO study. Supportive data from the cohort of subjects who received the same treatment combination in the Phase 1b Study MMY1001 have been provided. In this previous study, patients had received at least 2 prior lines of therapy.

The adverse event profile of daratumumab with Pd was consistent with the known safety profiles of daratumumab and Pd regimens alone. Syncope was added as a new ADR: As an SAE this occurred in 2% in the DPd arm and 0 in the Pd arm and overall 6.7% and 0.7%, respectively. Syncope Grade 3 occurred in 4% (there were no grade 4).

The most clinically important adverse events (all grades, preferred terms) more frequently reported in the DPd arm compared to the Pd arm in study 3013 were neutropenia (70.5% vs 53.3%), diarrhoea (22.1% vs 14.0%), and pneumonia (20.1% vs 12.7%), see Table 24.

Focusing on maximum toxicity grade, 87.9% of subjects in the DPd group reported any Grade ≥3 TEAE while this figure was 82% in the Pd treatment group. Higher differences between both groups were found in neutropenia (67.8% DPd vs 50.7% Pd), leukopenia (16.8% vs 4.7%), pneumonia (13.4% vs 6.7%), lymphopenia (12.1% vs 3.3%) and febrile neutropenia (8.7% vs 2.7%). As previously observed with other daratumumab combinations, differences were mostly driven by haematological AEs.

The incidence of SAEs was higher in the DPd group (50.3%) compared to the Pd group (39.3%). The most common preferred terms were: Pneumonia (DPd: 15.4%, Pd: 8.0%) and Lower respiratory tract infection (DPd: 12.1%, Pd: 9.3%).

Cytopenias and infections are well-known AEs for both daratumumab and pomalidomide and thus, not unexpectedly, occurring more frequently in the DPd arm.

The number of subjects with any Grade TEAEs leading to treatment discontinuation was 11 (7.4%) in the DPd arm and 5 (3.3%) in the Pd treatment arm. For Grade 3 or 4, this proportion was similar (5.4% DPd vs 2.7% Pd) and also higher for the experimental treatment.

TEAEs with an outcome of death were similar between treatment groups (DPd: 7.4%; Pd: 7.3%).

The incidence of haemorrhagic events in study 1001 was six times higher than in study 3013. There were no fatal haemorrhagic events and no cerebral haemorrhagic events in the DPd arm in any of these studies. The patients in study 1001 had a median of 4 prior treatments compared to 2 prior treatments in study

3013. The median age was 64 and 67, respectively. Differences in baseline and disease characteristics likely contributed to the difference in haemorrhagic events between study MMY3013 and MMY1001. The MAH showed that difference in haemorrhagic events observed between studies was primarily driven by Grade 1 events, which are of low clinical significance. In general, the incidence of TEAEs was lower or consistent in Study MMY3013 compared to Study MMY1001. Study MMY1001 represented a more heavily pre-treated study population with a median of 4 prior lines of treatment (compared to a median of 2 prior lines for Study MMY3013). This could in part explain the higher rates of TEAEs observed in Study MMY1001 despite a shorter treatment duration than Study MMY3013.

Infections are known ADRs for daratumumab, which in study 3013 in combination with Pd clearly increases with age as opposed to what is seen in the Pd arm (Table 34). The SmPC includes a warning to alert physicians to the higher incidence of serious adverse reactions in elderly patients. Among patients with relapsed and refractory multiple myeloma, the most common serious adverse reactions that occurred more frequently in elderly were pneumonia and sepsis." This is considered sufficient information to minimise the risk in this age group.

2.5.2. Conclusions on clinical safety

Safety is generally unchanged from previous studies. Deaths due to TEAEs were comparable between the two arms, but the median age of the study population was 67 years (and a median of 4.4 years after diagnosis), so outside clinical trials SAEs and deaths due to infections would be expected to be higher. Overall, the safety profile of daratumumab in this new combination can be considered in line with the already known safety profile.

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 CHMP endorsed the Risk Management Plan version 8.2 with the following content:

Summary of the safety concerns

Table 37 . Summary of the 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	None

Pharmacovigilance plan

No additional pharmacovigilance activities apply. No updates to this section were introduced by the MAH. The targeted follow-up questionnaire to collect additional information concerning AE associated with interference and transfusion reactions is maintained.

Risk minimisation measures

Table 38. Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern:

Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Routine risk minimization measures: • SmPC Section 4.4 and 4.5 • PL Section 2 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.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • A guided targeted follow-up questionnaire to collect additional information concerning adverse events associated with interference and transfusion reactions. Additional pharmacovigilance activities: • None.
Hepatitis B virus reactivation	Routine risk minimization measures: • SmPC Sections 4.4 and 4.8; • PL Sections 2 and 4; Additional risk minimization measures: • Distribution of a DHPC to HCPs who prescribe daratumumab was issued in the EU member states in June 2019.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.

DHPC = Direct Healthcare Professional Communication; HBC = hepatitis B virus; HCP = healthcare professional; PL = package leaflet; 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, 4.5, 4.8, 5.1 and 5.2 of the SmPC of the subcutaneous formulation are updated. In addition section 4.8 of the SmPC for the intravenous formulation is also updated based on the pooled safety analysis. The Package Leaflet is updated in accordance. Version 8.5 of the RMP has also been submitted.

2.7.1. User consultation

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

- Full user testing in compliance with the above-mentioned legislative requirements was performed (n=20 participants) on the package leaflet developed for DARZALEX for the initial Marketing Authorisation Application.
- An additional user testing (n= 10 participants) was conducted for a bridging report on the package leaflet developed for the Line extension Application of the DARZALEX subcutaneous formulation.
- The package leaflet included in this current application has the same format as the one previously approved.

- 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 for the subcutaneous formulation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The proposed addition to the existing indication statement in section 4.1 of the Summary of Product Characteristics (SmPC) is as follows (proposed text in **bold)**:

*"DARZALEX is indicated **in combination with pomalidomide and dexamethasone, or** as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy."*

The Applicant has, upon request, separated the indication for the current application from the previous indication regarding Darzalex monotherapy, replaced "IMID" with "lenalidomide", removed '*relapsed or refractory' and clarified the indication after one and two prior therapies*.

*"DARZALEX is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received **one prior therapy containing a proteasome inhibitor and lenalidomide** and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy (see section 5.1)"*

3.1.1. Disease or condition

Multiple myeloma is an incurable malignant plasma cell disorder diagnosed annually in approximately 160,000 patients worldwide (Bray 2018). The median age at diagnosis is 72 years.

Multiple myeloma is characterised 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, especially in the upper respiratory tract. 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 anemia due to kidney disease or suppression of erythropoiesis by cancer cells, but sometimes also due to iron deficiency.

3.1.2. Available therapies and unmet medical need

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 newly diagnosed multiple myeloma. Patients who have been treated with lenalidomide and a PI are a challenge to treat as they have already been exposed to 2 major drug classes. Patients who relapse during ongoing treatment or within 60 days of last dose of lenalidomide are per IMWG definition "lenalidomide refractory" and represent an additional challenge for choosing an effective subsequent treatment choice.

Patients with exposure to lenalidomide and a PI as well as patients refractory to lenalidomide have a high unmet medical need, and new effective and convenient treatment options are needed (Moreau 2019).

3.1.3. Main clinical studies

The purpose of the pivotal phase 3 study MMY3013 was to evaluate the efficacy and safety of DPd to Pd in subjects with relapsed or refractory multiple myeloma having received prior lenalidomide and an IMiD (96% had received bortezomib) using the primary endpoint of PFS based on IMWG criteria.

Daratumumab was given SC (7 patients received IV before amendment 2). Pd dose was given according to Imnovid SmPC. Treatment continued until PD or unacceptable toxicity.

Subjects were randomized 1:1 to DPd or Pd. Randomization was stratified by number of lines of prior therapy and ISS stage. The study was open-label. An IDMC conducted the interim analysis. The study was initiated in June 2017 in centres in 12 European countries. Data cut-off July 2020. In the DPd arm and the Pd arm 151 and 153 patients, respectively, made up the ITT population.

Supportive data where derived from 103 DPd-treated patients in the phase 1b study MMY1001, which was an open-label, non-randomized, multicenter study to evaluate the safety, tolerability, and dose regimen of daratumumab IV when administered in combination with various background treatment regimens for multiple myeloma in either newly diagnosed patients or those who had received prior therapies, depending on the background treatment regimen.

3.2. Favourable effects

At a median overall follow-up of 16.9 months (DPd: 17.5 months; Pd: 16.4 months) the addition of daratumumab SC to Pd resulted in a statistically significant improvement in PFS (HR=0.63; 95% CI: 0.47, 0.85; 2-sided p=0.0018,). The median PFS was 12.4 months for the DPd treatment group (95% CI; 8.3, 19.3) and 6.9 months for the Pd treatment group (95% CI; 5.5, 9.3), which is considered clinically relevant particularly in a population that had received a median of 2 prior treatments that included lenalidomide and a PI. The results were generally consistent across multiple sensitivity analyses, and across pre-specified subgroups.

The result for the primary endpoint is supported by the key secondary endpoint ORR (including sCR and CR rates) and rate of MRD negativity, that were significantly better in the DPd arm compared to the Pd arm.

3.3. Uncertainties and limitations about favourable effects

The response rate is better in the DPd arm, with a higher rate of CR and also with a greater depth of response (MRD negativity). With this in mind continuing with a long-term maintenance treatment with daratumumab can be questioned in this RRMM population, as prolonged exposure to anti-CD38 could result in the emergence of long-term resistance or relapses that could potentially not respond to further treatment with anti-CD38 targeted therapy. It is acknowledged that even if these are relevant questions they cannot be addressed at this stage considering the design of the MMY3013 study. Results from the LYNX study (MMY2065), an ongoing, randomized, open-label, 2-arm, multicenter, phase 2 study evaluating the efficacy and safety of treatment with D-Kd versus carfilzomib and dexamethasone (Kd) alone in patients with relapsed or refractory multiple myeloma (RRMM) who have received 1-2 prior lines of therapy (at least one of which included daratumumab intravenous [IV] therapy) to evaluate daratumumab retreatment, are awaited, which will give further data of a potential benefit of retreatment with daratumumab after prior daratumumab use.

3.4. Unfavourable effects

The adverse event profile of daratumumab with Pd was consistent with the known safety profiles of daratumumab and Pd regimens alone.

The most clinically important adverse events (all grades, preferred terms) more frequently reported in the DPd arm compared to the Pd arm in study 3013 were neutropenia (70.5% vs 53.3%), diarrhoea (22.1% vs 14.0%), and pneumonia (20.1% vs 12.7%).

The frequency of Grade 3 or 4 TEAEs was higher in the DPd group compared with the Pd group (DPd: 80.5%; Pd: 74.7.0%). The incidence of serious TEAEs was higher in the DPd group (50.3%) compared to the Pd group (39.3%). The most common (≥5%) serious TEAEs reported were pneumonia (15.4% vs 8.0%) and lower respiratory tract infection (12.1% vs 9.3%).

The incidence of SAEs was higher in the DPd group (50.3%) compared to the Pd group (39.3%). The most common preferred terms were: Pneumonia (DPd: 15.4%, Pd: 8.0%) and Lower respiratory tract infection (DPd: 12.1%, Pd: 9.3%).

The number of subjects with any Grade TEAEs leading to treatment discontinuation was 11 (7.4%) in the DPd arm and 5 (3.3%) in the Pd treatment arm. For Grade 3 or 4, this proportion was similar (5.4% DPd vs 2.7% Pd) and also higher for the experimental treatment.

Syncope was added as a new ADR: As an SAE this occurred in 2% in the DPd arm and 0 in the Pd arm and overall 6.7% and 0.7%, respectively. Syncope Grade 3 occurred in 4% (there were no grade 4).

3.5. Uncertainties and limitations about unfavourable effects

Median duration of treatment was longer in DPd arm, 11.5 vs 6.6 months for patients treated with Pd. The MAH has provided exposure-adjusted incidence (EAIR) rates for both MMY3013 and DPd cohort in study MMY1001. As expected, incidences for TEAEs remain higher for the DPd arm but, when analysing the respective EAIRs, the imbalances seem less prominent suggesting that longer exposure plays a key role in the high AEs rates observed. Still, DPd combination shows higher incidences for some important TEAEs like infections and neutropenia.

Some imbalances were observed regarding baseline ECOG performance status. The MAH has submitted upon request a table including TEAEs incidences by baseline ECOG values to rule out any particular trend among subjects included (Table 26). The detailed results do not match the hypothesis that higher ECOG would lead to higher AEs incidence rates. Not in all cases subjects with ECOG 1 reported higher AEs incidences than subjects with ECOG 0. Although most of PTs were more commonly reported in subjects with ECOG 2, the small sample size of this subgroup (DPd: 6 subjects; Pd: 19 subjects) does not allow any definitive conclusion to be drawn. Overall, safety profile of this new combination does not seem to be affected by patients' ECOG PS.

There is limited information since SC formulation was approved in the US and EU in May and June 2020, respectively. The MAH has provided information about post-marketing experience for SC daratumumab up to 31 January 2021. From the global safety database, 7,257 events have been further analysed but include both IV and SC formulations. The most commonly reported PTs for overall AEs and AEs with a fatal outcome were generally in line with the widely reported in all daratumumab studies. From these 7,257 events, 160 reported SC administration of daratumumab but no relevant differences have been observed in reported PTs for them and the overall safety population.

3.6. Effects Table

Table 39: Effects Table for DPd vs PD; study MMY3013 (data cut-off: 21 July 2020)

Effect	Short description	Unit	Treatment: DPd	Control: Pd	Uncertainties/ Strength of evidence	Referen-ces
Favourable Effects[1]						
PFS	Median PFS	Mo.	12.42 *(8.34, 19.32)	6.93 *(5.52, 9.26)	HR; 0.36 *(0.47, 0.85)	**Table 15**
ORR	sCR+CR+VGPR +PR	%	68.87 *(60.64, 76.15)	46.41 *(38.32, 54.64)	OR: 2.68 4.35) Median duration of response not yet reached for the DPd arm (range: 1 to 34.9+ months) and was 15.9 months (range: 1+ to 24.8 months) in the Pd group	Table 16
MRD	MRD negativity	%	8.61 *(4.66, 14.27)	1.96 *(0.41, 5.62)	OR: 4.71 *(1.31, 16.88)	Table 17
Unfavourable Effects[1]						
Infecti ons (SOC)	All grades	%	70.5	55.3		Table 24
Neutro penia	All grades AE SAE Laboratory, Gr4	% % %	70.5 32.9 48.0	53.3 24.7 20.1		Table 24 Table 28

Abbreviations: *; 95% CI, CI; confidence intervals, CR; complete response, HR; hazard ratio, Mo.; months, OR; odds ratio, PFS; progression-free survival. [1]ITT: N=151 and 153 and for safety N=149 and 150 (DPd and Pd, respectively).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The median PFS was 12.4 months for the DPd treatment group (95% CI; 8.3, 19.3) and 6.9 months for the Pd treatment group (95% CI; 5.5, 9.3), which is considered clinically relevant particularly in a population that had received a median of 2 prior treatments that included lenalidomide and a PI. Although the number of patients with only 1 prior line was limited, the PFS point estimate was comparable to the overall group. Furthermore, there is a need for a line of therapy with another MoA in clinical practice for patients that are refractory to lenalidomide and have received a PI in first line.

There is a statistical relationship between the achievement of complete response (CR), MRD negativity and PFS or OS (ESMO guidelines; Moreau et al., 2017), and thus the higher CR and MRD-negativity rates in the DPd arm are considered clinically important responses.

Safety is generally unchanged from previous studies. Cytopenias and infections are well-known AEs for both daratumumab and pomalidomide and thus, not unexpectedly, occurring more frequently in the DPd arm. Infections are known ADRs for daratumumab. The rate of infections in study 3013 in the DPd arm clearly increases with age as opposed to what is seen in the Pd arm Increasing rate of adverse events with age is noted in the SmPC.

It is of concern, that infections are common and higher with age. Deaths due to TEAEs were comparable between the two arms, but the median age of the study population was 67 years (and a median of 4.4 years after diagnosis), so outside clinical trials SAEs and deaths due to infections could be expected to be higher considering that the median age at diagnosis for multiple myeloma patients is 72 years in Europe. However, these risks to a large extent can be managed with the warnings included in the product information.

3.7.2. Balance of benefits and risks

The improvement in PFS is considered clinically relevant. Well-known adverse events such as infection and neutropenia are frequent as well as a higher incidence of these AEs with increasing age. The benefits to patients from the prolongation of PFS by DPd treatment therefore outweighs the risks associated with its use.

The MAH has revised the wording of the indication to better reflect the target population and has also accepted to include it separately from the one covering the use of daratumumab in monotherapy. Furthermore, "IMID" has been replaced with "lenalidomide" and '*relapsed or refractory'* has been removed.

The following wording has been agreed:

"DARZALEX is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy (see section 5.1)."

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The overall B/R of Darzalex 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 subcutaneous formulation to include *combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy*; as a consequence, sections 4.1, 4.2,

4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. In addition, section 4.8 of the SmPC for the intravenous formulation is also updated based on the pooled safety analysis. The Package Leaflet is updated in accordance. Version 8.2 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) 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 Imnovid, Farydak, Kyprolis, Ninlaro and Blenrep 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-H-C-004077-II-0044

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted) as adopted by the CHMP on 20.05.2021.

Appendix

1. CHMP AR on similarity dated 20/5/2021

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by <No date in SIAMED>. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by <No date in SIAMED>. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.