EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 February 2017
EMA/193295/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Darzalex

International non-proprietary name: daratumumab

Procedure No. EMEA/H/C/004077/II/0002

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

ADCC	antibody dependent cell-mediated cytotoxicity
ADCP	antibody dependent cell phagocytosis
ADME	absorption, distribution, metabolism and excretion
ADR	adverse drug reaction
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
CDC	complement-dependent toxicity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	non-specific linear clearance
Cmax	end of infusion concentration
CR	complete response
DOR	duration of response
DPd	daratumumab + pomalidomide + dexamethasone
DRd	daratumumab + lenalidomide + dexamethasone
DVd	daratumumab + VELCADE + dexamethasone
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ERd	elotuzumab+lenalidomide+dexamethasone
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	hazard ratio
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IRD	ixazomib+lenalidomide+dexamethasone
IRR	infusion related reaction
ISS	International Staging System
IV	intravenous
Kd	carfilzomib+dexamethasone
kg	kilogram
KRd	carfilzomib+lenalidomide+dexamethasone
LEN	lenalidomide
mAb	monoclonal antibody
MDSCs	myeloid-derived suppressor cells
mg	milligram
min	minute
mL	milliliter
MoA	mechanism of action
MRD	minimal residual disease
NGS	next-generation sequencing
NK	natural killer
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PI	proteasome inhibitor
Pd	pomalidomide + dexamethasone
Rd	Lenalidomide + dexamethasone
RD	Lenalidomide + high dose dexamethasone
sCR	stringent complete response
SD	standard deviation
SOC	System Organ Class
SPM	secondary primary malignancy
TB	total bilirubin
TEAE	treatment emergent adverse event
TTP	time-to-progression
US	United States
V1	volume of distribution in the central compartment

V2	volume of distribution in the peripheral compartment
Vd	VELCADE-dexamethasone
VGPR	very good partial response
Vmax	saturable target-mediated drug disposition elimination process
VMP	bortezomib-melphalan-prednisone
VTD	bortezomib-thalidomide-dexamethasone
w	weeks

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 23 August 2016 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, II and IIIB

Extension of Indication for Darzalex in the treatment of adult patients with multiple myeloma who have received at least 1 prior therapy.
As a consequence, sections 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC are updated in order to update the information on posology, warnings, interactions, efficacy and pharmacokinetics. A new warning is introduced in section 4.4 regarding neutropenia/thrombocytopenia induced by background therapy.
Annex II is updated to remove all the specific obligations following submissions of the final results of studies MMY3003 and MMY3004.
The Package Leaflet and Risk Management Plan (RMP version 2) are updated in accordance.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

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

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

- treatment of plasma cell myeloma.

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 CW/1/2011 on the granting of a class 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Protocol assistance

The MAH received Protocol Assistance from the CHMP on 20 February 2014 (EMEA/H/SA/2456/1/FU/1/2014/PA/II). The Protocol Assistance pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	23 August 2016
Start of procedure:	17 September 2016
CHMP Rapporteur Assessment Report	14 November 2016
PRAC Rapporteur Assessment Report	18 November 2016
PRAC members comments	23 November 2016
PRAC Outcome	1 December 2016
CHMP members comments	5 December 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	9 December 2016
Request for supplementary information (RSI)	15 December 2016
CHMP Rapporteur Assessment Report	24 January 2017
PRAC Rapporteur Assessment Report	27 January 2017
PRAC members comments	1 February 2017
Updated PRAC Rapporteur Assessment Report	2 February 2017
PRAC Outcome	9 February 2017
CHMP members comments	13 February 2017
Updated CHMP Rapporteur Assessment Report	n.a.
Opinion	23 February 2017
The CHMP adopted a report on similarity of Dazalex with Thalidomide Celgene, Revlimid, Imnovid, Farydak, Kyprolis and Ninlaro	23 February 2017
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Darzalex in comparison with existing therapies (Appendix)	23 February 2017

2. Scientific discussion

2.1. Introduction

Multiple myeloma is an incurable malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone. The median age of patients at diagnosis is 65 years. The abnormal plasma cell proliferation accumulate in the bone marrow, displacing the normal hematopoietic tissue. The plasma cells produce a monoclonal antibody, paraprotein (M-protein and free-light chain), which is an immunoglobulin (Ig) or a fragment of one that has lost its function (Kyle 2009, Palumbo 2011). The normal immunoglobulins (Ig) are compromised leading to increased susceptibility to infections. Other important characteristics include dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture due to proliferation of multiple myeloma cells. This is reflected by clinical findings such as anemia, thrombocytopenia, myelosuppression, paraprotein in serum or urine, and bone resorption seen as diffuse osteoporosis or lytic lesions shown in radiographs (Kyle 2003). Furthermore, hypercalcemia, renal insufficiency or failure, and neurological complications are frequently seen (Palumbo 2011). At diagnosis, frequent and pronounced symptoms impacting health-related quality of life typically include anemia (approximately 73%), renal insufficiency (approximately 30%) and skeletal destruction (approximately 80%) (Sonneveld 2013).

For relapsed or refractory multiple myeloma, the treatment is determined on an individual basis where the patient's age, prior therapy, bone marrow function, co-morbidities, patient preference and time to relapse are taken into account. Current treatment options for patients with relapsed or refractory multiple myeloma include combination chemotherapy, proteasome inhibitors (PIs; eg, bortezomib, carfilzomib, ixazomib), immunomodulatory agents (IMiDs; eg, thalidomide, lenalidomide, and pomalidomide), histone deacetylase inhibitors (eg, panobinostat); monoclonal antibodies (mAb) (eg, daratumumab and elotuzumab), high-dose chemotherapy, and autologous stem cell transplantation (ASCT).

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. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity (SmPC, section 5.1).

The initial marketing authorisation application for Darzalex was based on data from 2 single agent studies (MMY2002 and GEN501) and the European Commission issued a conditional marketing for Darzalex on 20 May 2016 for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a Proteasome Inhibitor (PI) and an immunomodulatory agent (IMiD) and who demonstrated disease progression on the last therapy with the following conditions:

- In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3003, a phase III randomised study investigating lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.

- In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3004, a phase III randomised study investigating bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.

The MAH submitted the clinical study reports for MMY3003 and MMY3004 as part of this application.

The current indication for Darzalex is as follows:

Darzalex as monotherapy is indicated 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 (SmPC, section 4.1).

The MAH applied for the following extension of indication: Darzalex is indicated for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

The recommended indication for approval by CHMP after considering all data submitted is: Darzalex is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy (SmPC, section 4.1).

The recommended dose is Darzalex 16 mg/kg body weight administered as an intravenous infusion (SmPC, section 4.2).

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity/environmental risk assessment

No ERA studies were submitted (see discussion on non-clinical aspects).

2.2.2. Discussion and Conclusion on non-clinical aspects

The justification provided by the MAH for not performing environmental risk assessment studies was considered acceptable since daratumumab is a protein therefore, unlikely to result in significant risk to the environment. This is in accordance with the "Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 21*).

2.3. Clinical aspects

2.3.1. Introduction

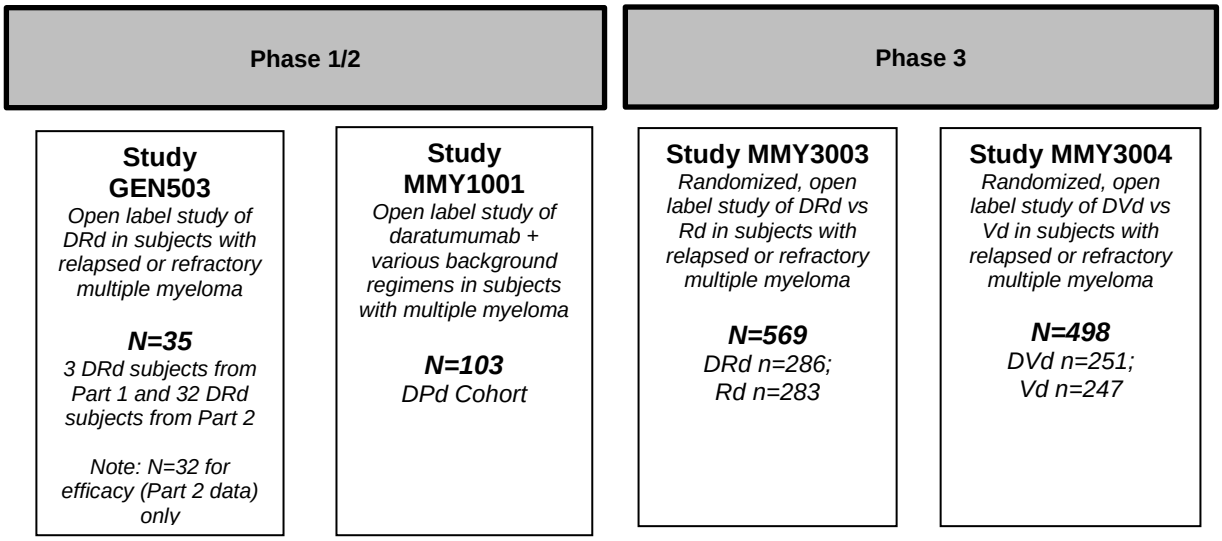
GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant 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.

A Tabular overview of Daratumumab Clinical Studies Included in the Safety and Efficacy Analyses is provided in Figure 1.

Figure 1. Daratumumab Clinical Studies Included in the Safety and Efficacy Analyses (N=Number of Subjects Enrolled or Randomized)



DPd=daratumumab, pomalidomide and dexamethasone; DRd=daratumumab, lenalidomide and dexamethasone; DVd=daratumumab, bortezomib and dexamethasone; Rd=lenalidomide and dexamethasone; Vd=bortezomib and dexamethasone

2.3.2. Pharmacokinetics

The clinical pharmacology properties of daratumumab in combination treatment were studied in 680 subjects in two Phase 1/2 and two Phase 3 combination studies (Table 1). These four studies as well as a population PK (Pop-PK) analysis support the PK data of the present application.

Table 1. Combination Studies Used to Support Pharmacokinetic Results

Study Number	Phase	Subject Population	Doses (Number of Subjects Dosed)	Number of Subjects Evaluable for Pharmacokinetic Analysis/Number of Subjects Treated
GEN503	1/2	relapsed or relapsed and refractory multiple myeloma	Phase 1: 2 mg/kg (3 subjects) 4 mg/kg (3 subjects) 8 mg/kg (4 subjects) 16 mg/kg (3 subjects)	45/45 Phase 1=13;
			Phase 2: 16 mg/kg (32 subjects)	Phase 2=32
MMY1001	1/2	multiple myeloma	16 mg/kg (133 subjects)	128/133
MMY3003	3	relapsed or refractory multiple myeloma	16 mg/kg (283 subjects)	282/283

MMY3004	3	relapsed or refractory multiple myeloma	16 mg/kg (243 subjects)	225/243

Total Subjects Evaluable for Pharmacokinetic Analysis/Total Subjects Treated: 680/704.

All daratumumab PK parameters were calculated using conventional non-compartmental methods using actual times of blood sampling. Background therapy PK parameters, including bortezomib, thalidomide, and pomalidomide were calculated using conventional non-compartmental methods using nominal times of blood sampling.

Values presented in the tables represent arithmetic mean, standard deviation (SD) and coefficient of variation (%CV); tmax values are presented as median (range).

Absorption

Absorption data are not required since all studies administered daratumumab as an IV infusion.

Distribution

In Study GEN503 (combination therapy), mean volume of distribution (Vd) for the 2 mg/kg and 4 mg/kg cohorts was estimated as 100.83 mL/kg and 88.35 mL/kg, respectively compared to 90.19±43.40 mL/kg after the first dose and 59.51±54.68 mL/kg following repeat dosing of 16 mg/kg in Study GEN501 (monotherapy). There was no data for the 16 mg/kg dose group. Overall, results showed that daratumumab is primarily localised to the vascular system with limited extravascular tissue distribution.

Elimination

By the initial assessment for the monotherapy indication, the elimination halftime (T½) increased with multiple doses: from 25.62±5.61 hours for 2 mg/kg to 154.65±36.48 hours for 24 mg/kg. In the 16 mg/kg group, mean T½ increased from 109.9±42.05 hours after the first full infusion to 586.56±486.89 hours after the seventh (last) full infusion (Study GEN501, Part 1).

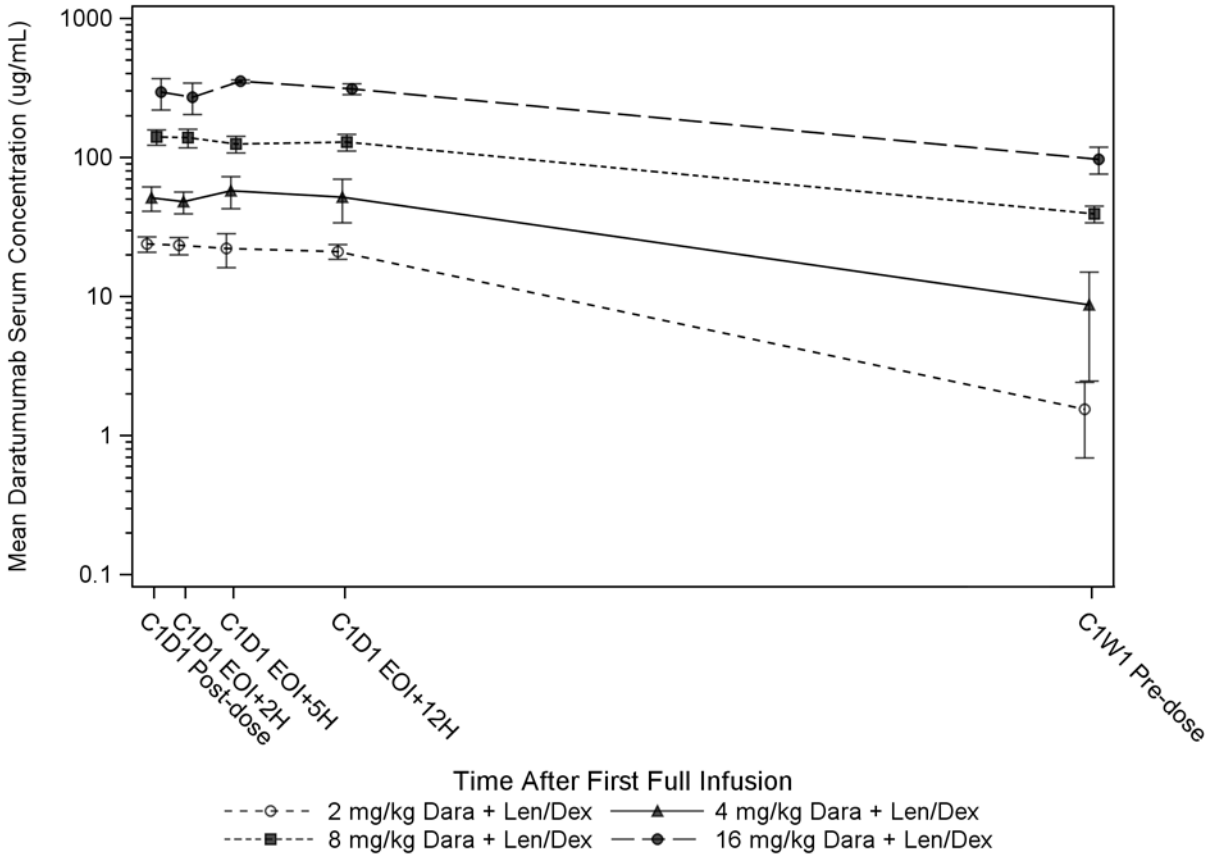
Regarding the elimination in the combination treatment, PK data from Study GEN503 showed that after the first full infusion mean T½ was estimated to be 37.92 hours for the 2 mg/kg cohort and 46.80 hours for the 4 mg/kg group. Daratumumab elimination showed nonlinear characteristics; Cmax after the first full infusion increased with dose while AUC_{last} increased in a greater than dose-proportional manner.

Dose proportionality and time dependencies

Dose proportionality

Only in Study GEN503, other doses than the recommended 16 mg/kg dosing regimen was used. Data for doses 2 mg/kg – 8 mg/kg is available for a total of 10 patients. In Phase 1 of Study GEN503, Cmax increased in approximate proportion to the daratumumab dose in the range of 2-16 mg/kg after the first full infusion. The observed mean Cmax after the first full dose rose in a ratio of 1: 2: 6: 11 as the dose increased in a ratio of 1: 2: 4: 8. Mean daratumumab serum concentrations (µg/mL) for the first full infusion for the different doses are presented in Figure 2.

Figure 2. Mean Daratumumab Serum Concentration (µg/mL) for the First Full Infusion; Subjects Evaluable for Daratumumab PK (Study GEN503 Phase 1)



Keys: C=cycle; D=day; H=hour; W=week; EOI=end ofinfusion; PK=pharmacokinetics.
The error bars are mean +/- standard error.

Time dependencies

Data is available from Study GEN503 (combination therapy). Accumulation appeared to continue throughout the first 2 cycles of weekly dosing in both Phase 1 and 2, after which concentrations began to decrease slightly with the less frequent daratumumab administration (Table 3). In the 16 mg/kg cohort (Phase 2), the mean±SD trough concentration at the end of weekly dosing (Cycle 3 Day 1 pre-dose) was 546.65±226.34 µg/mL. The mean±SD concentration at the end of the ninth planned full infusion (Cycle 3 Day 1 pre-dose; 898.53±242.27 µg/mL) was approximately 3-fold higher than the mean concentration following the first full infusion (Cycle 1 Day 1 post-dose; 289.11±90.39 µg/mL).

Table 2: Summary of daratumumab select serum predose and end of infusion concentrations; evaluable for daratumumab PK (Study GEN503 Phase 2)

	16 mg/kg Dara + Len/Dex
Analysis set: Subjects evaluable for daratumumab PK[a]	32
Cycle 1 day 1 pre-dose	
N	31
Mean (SD)	0.06 (0.238)
Cycle 1 day 1 post-dose	
N	24
Mean (SD)	289.11 (90.386)
Cycle 2 day 1 pre-dose	
N	14
Mean (SD)	343.05 (111.492)
Cycle 2 day 1 post-dose	
N	16
Mean (SD)	689.12 (207.219)
Cycle 3 day 1 pre-dose	
N	24
Mean (SD)	545.65 (226.336)
Cycle 3 day 1 post-dose	
N	25
Mean (SD)	898.53 (242.271)
Cycle 6 day 1 pre-dose	
N	20
Mean (SD)	432.20 (218.918)
Cycle 6 day 1 post-dose	
N	19
Mean (SD)	799.33 (246.240)
Cycle 12 day 1 pre-dose	
N	12
Mean (SD)	224.44 (168.530)
Cycle 12 day 1 post-dose	
N	12
Mean (SD)	616.68 (181.298)

[a] Subjects who treated with daratumumab and had at least one post-treatment PK assessment. Only 19 of these subjects are evaluable for PK parameter estimates.
Note: Samples outside of allowed sampling windows are not included. In addition, samples collected after an incomplete dose
(less than 80% intended dose was administered) and prior to the next complete dose are not included. Keys: Dara=daratumumab, Len/Dex=lenalidomide/dexamethasone.

In general, the area under the curve to the last quantifiable time point (AUC_{last}) increased in a greater than dose-proportional manner after the first doses. Observed mean AUC_{last} after the first full dose rose in a ratio of 1 : 3 : 7 : 43 as the dose increased in a ratio of 1 : 2 : 4 : 8. The results obtained in Study GEN503 were supported by the results obtained in Study MMY1001.

Similar results were observed in the two Phase 3 studies MMY3003 and MMY3004. In Study MMY3003, the mean±SD Cmax concentration after the 1st dose (Cycle 1 Day 1 post-infusion) was 329.07±95.89 µg/mL. Accumulation of daratumumab through the first 9 doses resulted in a 2.9-fold increase in Cmax to 972.12±272.35 µg/mL at Cycle 3 Day 1 post-dose. The mean±SD Cycle 3 Day 1 pre-dose trough concentration after 8 weekly doses was 607.73±231.98 µg/mL. In Study MMY3004, the mean±SD Cmax concentration after the 1st dose (Cycle 1 Day 1 post-infusion) was 317.68±98.87 µg/mL. Accumulation of daratumumab continued through at least the first 7 weekly doses (the last PK sampling time point in weekly dosing), resulting in a 2.7-fold increase in daratumumab Cmax concentration to 860.19±262.60 µg/mL at Cycle 3 Day 1 post-dose. The mean±SD Cycle 3 Day 1 pre-dose trough concentration after 6 weekly doses was 502.43±196.46µg/mL.

Special populations

See 2.3.4 PK/PD modelling section.

Pharmacokinetic interaction studies

No drug-drug interaction studies have been performed.

2.3.3. Pharmacodynamics

Mechanism of action

Primary and secondary pharmacology

In subjects treated with combination therapy, 2 (0.7%) of the 298 evaluable subjects were positive for anti-daratumumab antibodies (ADAs) (1 subject each in Studies MMY1001 and MMY3003). Both positive subjects demonstrated low titer (1:20) responses which were near the lower limit of the assay method sensitivity.

In Study MMY3003, the positive status was assigned to 1 subject due to the detection of ADAs following an IRR at Cycle 1 Day 1. The ADA positive sample inhibited daratumumab binding in the validated neutralising antibody assay; thus, the response was classified as neutralising. The pre-dose Cycle 1 Day 1 and the end of treatment (follow up Week 4) samples were both negative for ADAs, demonstrating that the immune response was transient. Despite the single positive ADA response, this subject demonstrated a stringent complete response (sCR) on Day 139, suggesting no impact of observed ADAs on efficacy, but the patient discontinued treatment on Day 302 due to disease progression.

In Study MMY1001, 1 subject in the DVTd cohort was positive for ADAs at the Week 9 Follow-Up visit; the antibodies were non-neutralising. This subject was negative for ADAs on 2 other visits (pre-dose on Cycle 1 Day 1 and Week 3 Follow-up) and was on treatment for 4 cycles. This subject was not evaluable for drug response per protocol and discontinued due to autologous stem cell transplantation. There was no notable safety signals observed in this subject.

The evaluation of QTc intervals versus serum concentration of daratumumab has been provided in the monotherapy submission. There are no new data to be summarised.

2.3.4. PK/PD modelling

Population Pharmacokinetic Analysis

The population pharmacokinetic (pop-PK) analysis was based on 4,426 PK samples from 694 subjects (684 subjects received daratumumab at 16 mg/kg). Nine subjects were excluded because they had no measurable post-dose concentrations of daratumumab. One subject was excluded because the actual dosing time of the first dose was missing.

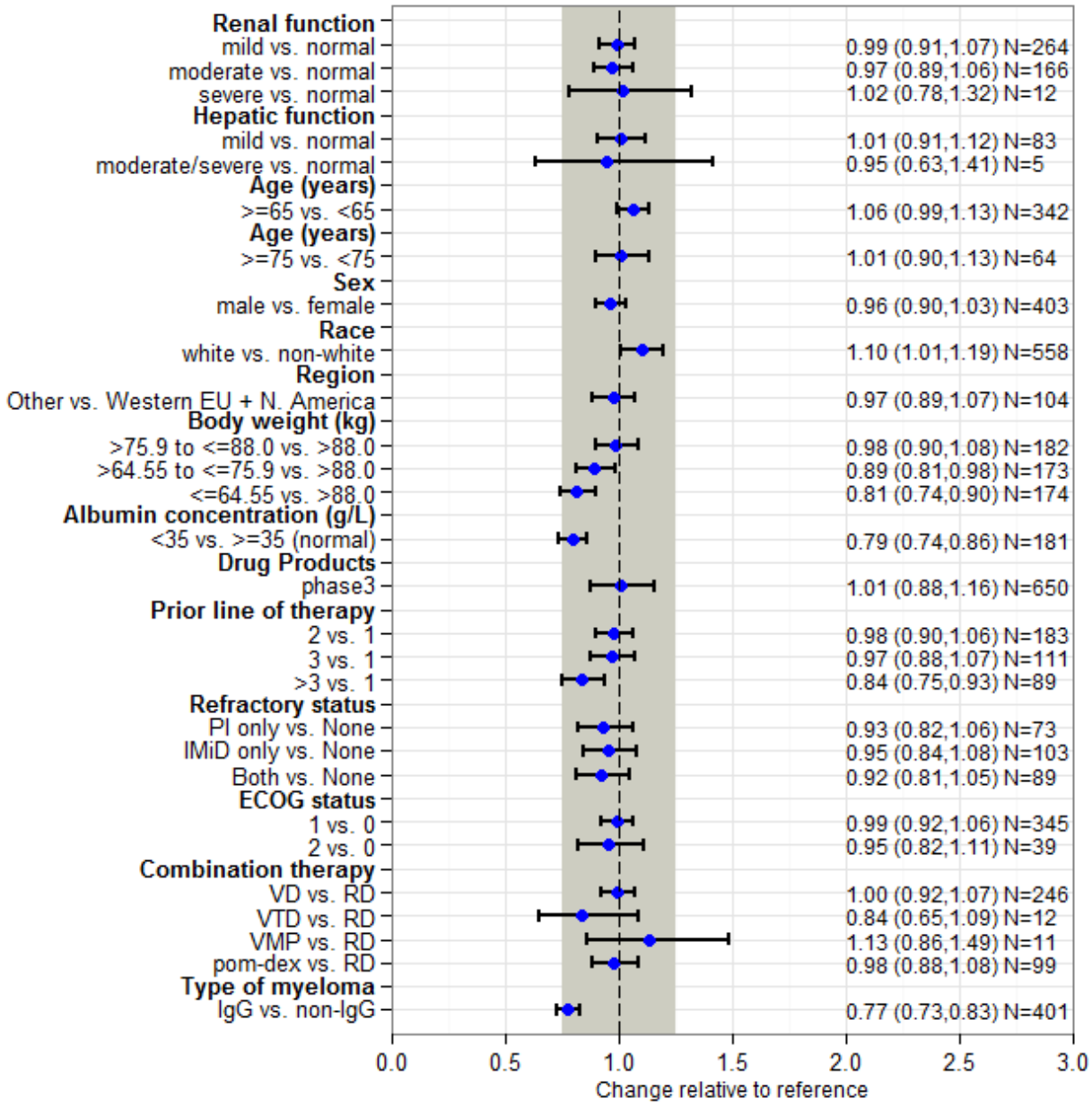
As expected, the PK of daratumumab was similar following the monotherapy and combination therapies. The observed concentration-time data of daratumumab were adequately described by a 2-compartment Pop-PK model with parallel linear and nonlinear Michaelis-Menten eliminations. The model was parameterised in terms of total systemic clearance (CL), volume of distribution in the central compartment (V1), inter-compartmental clearance (Q), volume of distribution in the peripheral compartment (V2), maximum rate of the saturable target-mediated drug disposition (TMDD) elimination process (Vmax), and daratumumab concentration (Km) associated with half of Vmax.

The estimated CL value was similar to the clearance of non-specific endogenous IgG reported in the literature and the estimated V1 value approached plasma volume. The model-derived half-life associated with linear elimination was approximately 23.3±11.8 days (mean±standard deviation), comparable to the half-life (18±9 days) derived from the monotherapy data. Similar to what was observed in monotherapy studies, apparent steady state seems to be reached approximately 5 months into the Q4W dosing period. The ratio of the steady-state peak concentration after Q4W dosing and the peak concentration after the first dose was 1.85±0.67 (mean±standard deviation).

Effects of Covariates

A forest plot was constructed to compare the exposure (maximal pre-infusion concentration) of daratumumab in subgroups defined by specific covariates (Figure 3).

Figure 3: Forest Plot of Subgroup Analyses on Change Relative to Reference Value of Predicted Maximal Pre-infusion (Trough) Concentration for MMY3003 Dosing Schedule



Key: Solid blue circle represents mean and error bar represents 95% confidence interval. Dashed line represents reference value of 1. Numbers represent ratio, confidence interval, and number of subjects in the comparison groups. Gray shaded region represents ±25% from reference value.

Note: Analyses assumed that all subjects in Studies GEN503, MMY1001, MMY3003 andMMY3004 received 16 mg/kg QW for 8 weeks (8 doses), Q2W for 16 weeks (8 doses), and then Q4W thereafter. Maximal pre-infusion (trough) concentration was derived as the pre-infusion concentration of the 1st dose of the every 2 week dosing period.

The number of subjects in the reference group for each covariate: normal renal function (N=251); normal hepatic function (N=598); age <65 yr (N=352); age <75 yr (N=630); female (N=291); non-white (N=136); western European N. America (N=590); body weight >88 kg (N=164); normal albumin concentration (N=513); Phase 2 product (N=44); 1 prior line of therapy (N=282); not refractory (N=42); ECOG = 0 (N=309); RD (N=326); non-IgG myeloma (N=293).Body Weight: When daratumumab was administered on a mg/kg basis, no clinically important differences (ie, <20%) in the exposure to daratumumab were observed in subjects with different weight despite a numeric trend. The CL and V1 of daratumumab significantly increased with increasing body weight. The difference in exposure had minimum impact on target saturation.

Age: Similar to monotherapy, no clinically important influence of age on the exposure to daratumumab was observed in the population PK analyses in patients receiving combination therapies. The difference in exposure was within 6% between younger (age < 65 years, n = 352; or age < 75 years, n = 630) and older subjects (age ≥ 65 years, n = 342; or age ≥ 75 years, n = 64) (SmPC, section 5.2).

Sex: No clinically important influence of sex on the exposure to daratumumab was observed. The difference in exposure was approximately 4% between males (n=403) and females (n=291) although V1 of daratumumab in female subjects was 15% lower than that of male subjects.

Race: In the population PK analysis in multiple myeloma patients that received daratumumab with various combination therapies, the exposure to daratumumab was also similar between white (n = 558) and non white (n = 136) subjects (SmPC, section 5.2).

Region: The majority (85%) of subjects were Western European (EU), United States (US), or Canadian (CA) subjects (EU+US+CA). The effect of region was evaluated in western EU+US+CA (n=590) and Other (n=104). The exposures were virtually identical in western EU+US+CA subjects and subjects from other regions as the difference was approximately 3%.

Renal Impairment: Additional population PK analyses in patients receiving combination treatments also showed no clinically important differences in exposure to daratumumab between patients with renal impairment (mild, n = 264; moderate, n = 166; severe, n = 12) and those with normal renal function (n = 251) (SmPC, section 5.2).

Hepatic Impairment: The PK analysis of patients with multiple myeloma that received daratumumab in various combination therapies included 598 patients with normal hepatic function, 83 patients with mild hepatic impairment and 5 patients with moderate (TB > 1.5 x to 3.0 x ULN), or severe (TB > 3.0 x ULN) hepatic impairment. No clinically important differences in the exposure to daratumumab were observed between patients with hepatic impairment and those with normal hepatic function (SmPC, section 5.2).

Baseline Albumin: No clinically important differences in the exposure to daratumumab were observed between subjects with abnormal albumin and those with normal albumin level. The exposure to daratumumab was 21% lower in subjects with abnormal albumin level (<35 g/L; n=181) compared with subjects who had normal albumin level (≥35 g/L; n=513). The difference in exposure had minimum impact on target saturation

Type of Myeloma: No clinically important differences in the exposure to daratumumab were observed between subjects with baseline IgG myeloma and non-IgG myeloma. The exposure to daratumumab was

approximately 23% lower in the IgG multiple myeloma subjects (n=401) compared to the non-IgG subjects (n=293). The difference in exposure had minimum impact on target saturation and the treatment effect on efficacy endpoints was similar for subjects with IgG and non-IgG myeloma.

Immunogenicity: Across all included studies, 2 out of 298 immunogenicity evaluable subjects (1 each in Study MMY1001 and Study MMY3003) in the pop-PK analysis were positive for ADA to daratumumab. No discernible differences in the PK between subjects with and without ADAs could be identified.

ECOG Score: No clinically important differences in the exposure to daratumumab (≤5%) were observed between subjects with ECOG scores of 1 (N=345) or 2 (N=39) and those with ECOG scores of 0 (N=309).

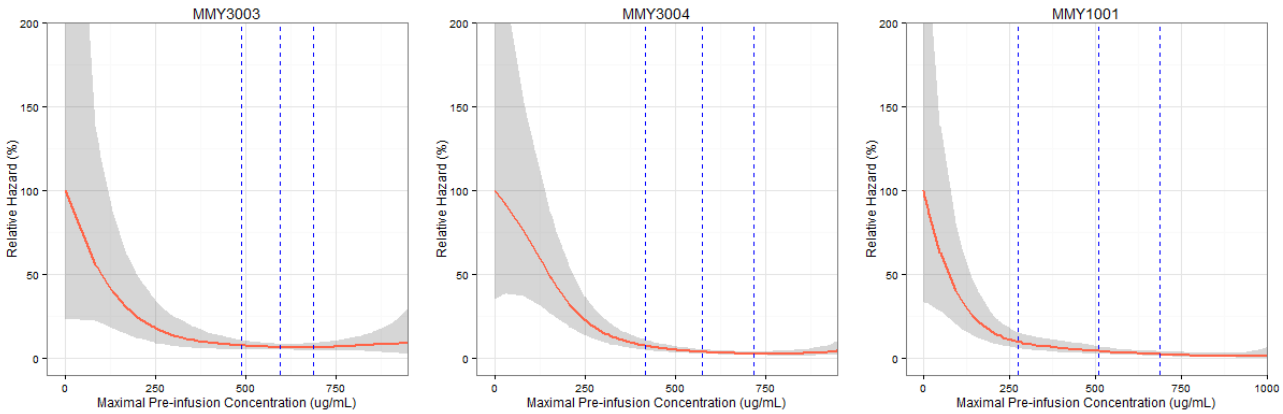
Refractory Status**:** No clinically important differences in the exposure to daratumumab (<10%) were observed between subjects refractory to IMiD only (N=103), PI only (N=73), or both (N=89) and those who were not refractory (N=42).

Other Baseline Variables: The effects of baseline disease status such as number of prior lines of therapy and various therapies in combination with daratumumab treatment were evaluated on the exposures to daratumumab. The daratumumab exposures were similar across the subgroups of these variables.

Exploratory Exposure-Response Relationships

The relative hazard for disease progression and death decreased rapidly with increasing daratumumab exposure based on the data from Studies MMY3003, MMY3004, and MMY1001 (DPd patients) (**Figure 4**).

Figure 4: Relative Hazard of Progression-free Survival at Different Predicted Maximal Trough Concentration

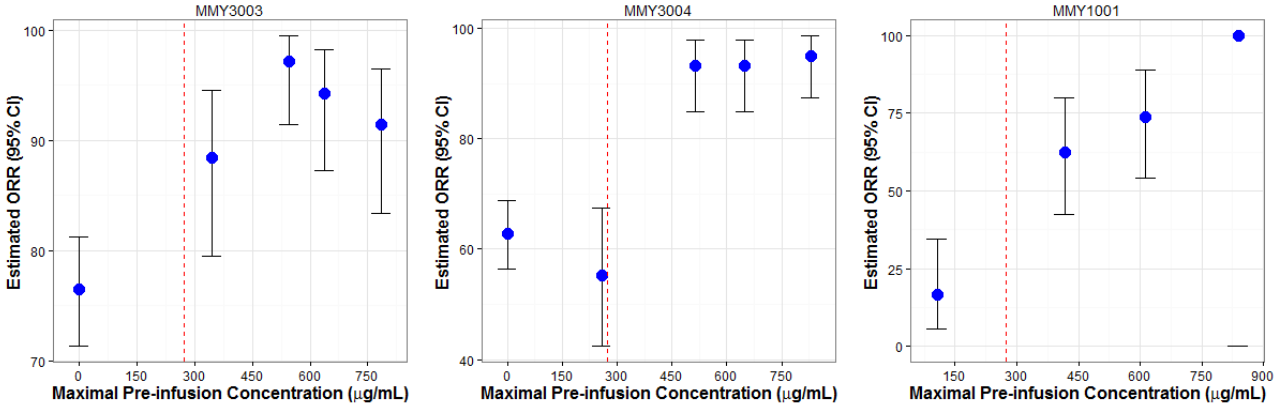


Key: the solid red line is the point estimate; the grey shaded areas represent the 95% confidence interval. The blue vertical dotted lines separate the quartiles of maximal pre-infusion concentration. Minimum Cpre-infusion,max for each study was used as the reference level. Cpre-infusion,max up to the 8th weekly dose for Studies MMY1001 (DPd), MMY3003, and MMY3004.

When maximal trough concentration was greater than ~250 µg/mL, the decreasing trend of relative hazards appears to slow down, suggesting limited additional benefit at higher concentrations. As the majority of the patients (>90% in Studies MMY3003 and MMY3004, and >80% in Study MMY1001) had maximal trough concentration greater than 250 µg/mL, it indicated that maximum clinical benefit on PFS has been attained for most subjects treated with 16 mg/kg. This observation was consistent with the EC_{90}^{ORR} (274 µg/mL) that was identified from the analyses based on the monotherapy studies.

The concentration-Duration of Response (DOR) relationship was similar to the observed concentration-PFS relationship. Furthermore, in all 3 studies (MMY3003, MMY3004, and MMY1001), when the maximal trough concentration was above the EC_{90}^{ORR} (274 µg/mL) identified from the monotherapy studies, the Overall Response Rate (ORR) was markedly higher compared to the those with maximal trough concentrations below 274 µg/mL (Figure 5).

Figure 5 Relative Hazard based on Duration of Response at Different Predicted Maximal Trough Concentration



Key: The solid blue dots at concentration 0 µg/mL represent the proportion of responders in control groups (ie, Rd in MMY3003 and Vd in MMY3004). The solid blue dots at concentrations greater than 0 represent the proportion of responders grouped by quantiles of maximal pre-infusion concentration and plotted at the geometric mean for each group. The bar represents the 95% confidence interval for the proportion in each group. The red vertical dotted lines represent the EC_{90}^{ORR} (274 µg/mL) that was identified from the analyses based on the monotherapy studies. Cpre-infusion,max up to the 8th weekly dose for Studies MMY1001 (DPd), MMY3003, and MMY3004.

There was no apparent exposure-response relationship within the studied concentration range between Cmax,1st and IRR, and Cpost-infusion,max and thrombocytopenia, anaemia, neutropenia, and lymphopenia based on the data from different combination therapies, ie, DRd subjects (Studies GEN503 and MMY3003), DVd subjects (Study MMY3004), and DPd (Study MMY1001). Although the event rate of infections (any grade) appeared to increase with drug exposure, this trend was not observed for Grade 3 or higher infections.

2.3.5. Discussion on clinical pharmacology

The clinical pharmacology of daratumumab used as monotherapy is well established. Clinical pharmacology data for the combination treatment derive from four clinical studies with a total of 680 patients evaluable for PK analyses. Additional, a pop-PK analysis contributed with data. The applied analytical methods for both the PK data analysis and the statistical analysis are appropriate.

The PK findings (bioavailability, volume of distribution and T½) from Study GEN503 are in line with the findings from the PK results from the mono-therapy studies (Study GEN501). The results support the expectations that as a mAb, the distribution of daratumumab is primarily localised to the vascular system, and the elimination is expected to occur via degradation of the daratumumab molecule into small peptides and amino acids. Overall, there were no unexpected findings with regards to absorption, distribution or elimination. The dose-dependent elimination (nonlinear characteristics) is consistent with target-mediated elimination (where clearance decreases as a function of dose).

No pharmacokinetic interactions are expected and it is acceptable that no formal drug-drug interaction studies have been performed. Serum concentrations of daratumumab as well as bortezomib, pomalidomide and thalidomide in various combination therapies show that there are no PK interactions for any of the products.

There is only very sparse PK data (from 10 patients) with regards to other doses than the 16 mg/kg daratumumab used in combination therapy. As treatment with 16 mg/kg is the recommended dose for monotherapy and is also proposed to be used in the combination treatment, more data with lower (or higher) dosing regimen is not considered necessary and thus, it is acceptable that there is only very limited experience with other doses and limited data regarding dose proportionality. Dose proportionality as observed in monotherapy is also expected to apply for combination therapy.

Results over time showed consistent results across the four studies and furthermore, in study MMY1001 where different combination treatments were used, consistent results were observed across the different combination therapies. As expected, the AUC last increased in a greater than dose-proportional manner after the first doses. Accumulation continued throughout the first 2 cycles due to the frequent dosing, thereafter concentrations began to decrease slightly with the less frequent daratumumab administration.

An additional population PK analysis was conducted in patients with multiple myeloma that received daratumumab in various combination therapies from four clinical trials (694 patients of which 684 received daratumumab at 16 mg/kg). Daratumumab concentration-time profiles were similar following the monotherapy and combination therapies. The mean (SD) estimated terminal half-life associated with linear clearance in combination therapy was approximately 23 (12) days (SmPC, section 5.2).

Several covariates were investigated in the pop-PK analysis. Consistent with the results from the initial (monotherapy) pop-PK analysis, results from the present pop-PK analysis showed that albumin level, type of myeloma and body weight were the covariates with the highest impact on the PK values. However, when further evaluated, it is concluded that though a few numeric and statistically significant differences were observed for a few covariates, these observation were in line with the observations from the monotherapy pop-PK analysis and more importantly, the differences are not expected to be of clinical relevance. No dose-adjustments are necessary.

A logistic regression analysis of overall response rate and predicted maximal pre-infusion (trough) daratumumab concentration showed that a lower dose than 16 mg/kg is not expected to be able to obtain a sufficient response in the majority of patients even when daratumumab is given as combination-therapy. From a clinical pharmacological point of view, it is acknowledged that the proposed dose of 16 mg/kg is a suitable daratumumab dose also when used in combination-therapy.

With regards to the pharmacodynamics, no new data related to mechanism of action or QTc evaluation is presented. This is overall acceptable. There is no formal experience regarding potential worsening of cardiac adverse when daratumumab is given in combination treatment (PD interaction), but as described in the clinical safety part of the assessment report, no increase in cardiac adverse events were observed, and the issue will not be pursued from a clinical pharmacological point of view.

Across the studies, two patients developed anti-daratumumab antibodies; in one of the patients, the antibodies were neutralising but transient. The MAH has provided sufficient information regarding the two patients. It is agreed that the immunogenicity profile of daratumumab still appears to be low. Immunogenicity is already included as an important potential risk in the RMP.

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology is sufficiently covered with PK data from four clinical studies and a pop-PK analysis. All results from the combination therapy are in line with the results obtained by the initial application for daratumumab used as monotherapy. From a clinical pharmacology point of view, no unexpected findings have been revealed and no concerns were identified.

2.4. Clinical efficacy

2.4.1. Dose response study

No dose-response studies were submitted. In the study GEN503, 16 mg/kg daratumumab was established as the optimal dose for administration of daratumumab as monotherapy (see 2.3.5 section discussion on clinical pharmacology).

2.4.2. Main studies

- **Study MMY3003** was a phase 3 open-label, multicentre study comparing the efficacy of daratumumab when combined with lenalidomide and low-dose dexamethasone (DRd) with lenalidomide and low-dose dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma.

- **Study MMY3004** was a phase 3, open-label, multicentre study comparing the efficacy of daratumumab when combined with bortezomib and low-dose dexamethasone (DVd) with bortezomib and low-dose dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma.

The MMY3003 and the MMY3004 studies are very similar in the study design. The methods part as well as the design is applied for both studies, unless otherwise specified.

Study MMY3003 and Study MMY3004

Methods

Study participants

The study population consisted of subjects with documented relapsed or refractory multiple myeloma (e.g., have documented multiple myeloma; have received at least 1 prior line of therapy for multiple myeloma; have achieved a response (partial response [PR] or better) to at least one prior regimen; have documented evidence of progressive disease as defined by the International Myeloma Working Group (IMWG) criteria on or after their last regimen) and an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1 or 2.

Refractory status is defined according to IMWG consensus criteria and documented by the treating physician. Refractory is defined as being nonresponsive while on therapy or progressed within 60 days of stopping therapy in subjects who have achieved minimal response (MR) or better.

The key inclusion criteria were the following:

- The patient's age had to be at least 18 years.
- Documented multiple myeloma as defined by the criteria below:

- Monoclonal plasma cells in the bone marrow ⩾ 10% or presence of a biopsy-proven plasmacytoma.

- Measurable disease at screening as defined by any of the following:

    - IgG multiple myeloma: Serum M-protein level ⩾1.0 g/dL or urine M-protein level ⩾200 mg/24h; or
    - IgA, IgD, IgR, IgM multiple myeloma: serum M-protein level ⩾1.0 g/dL (in the MMY3004 study it is ⩾ 0.5 g/dL) or urine M-protein level M-protein level ⩾200 mg/24h; or
    - Light chain multiple myeloma without measurable disease in the serum or the urine: serum immunoglobulin free light chain ⩾ 10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

- Evidence of a response (PR or better based on the investigator's determination of response by the IMWG criteria) to at least 1 prior regimen.
- ECOG performance status score of 0, 1, or 2.

The key exclusion criteria were the following:

- Previously received daratumumab or other anti-CD38 therapies.
- Received anti-myeloma treatment within 2 weeks or 5 pharmacokinetic half-lives of the treatment, whichever was longer, before the date of randomization or had received ASCT within 12 weeks before the randomization.
- Previously received an allogeneic stem cell transplant or ASCT.
- Subject had a history of malignancy (other than multiple myeloma) within 5 years before the date of randomization (exceptions were 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, was considered cured with minimal risk of recurrence within 5 years).
- Subject had known meningeal involvement of multiple myeloma.
- Subject had known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal.
- Subject had known moderate or severe persistent asthma within the past 2 years, or uncontrolled asthma of any classification.
- Subject was seropositive for human immunodeficiency virus, had hepatitis B surface antigen positivity, or had a history of hepatitis C.
- Subject had any concurrent medical condition or disease (eg, active systemic infection) that was likely to interfere with study procedures or results, or that in the opinion of the investigator could constitute a hazard for participating in this study.
- Subject had clinically significant cardiac disease.

MMY3003 only: Refractoriness or intolerance to lenalidomide.

MMY3004 only: Refractoriness to bortezomib, or another PI, like ixazomib and carfilzomib, i.e.subject had progression of disease while receiving bortezomib therapy or within 60 days of ending bortezomib therapy, or another PI therapy, like ixazomib and carfilzomib. This was added in Amendment 1 when 40 subjects were randomized. Intolerance to bortezomib.

Treatments

In both studies, daratumumab was administered as an IV infusion at a dose of 16 mg/kg until disease progression, unacceptable toxicity, or other reasons.

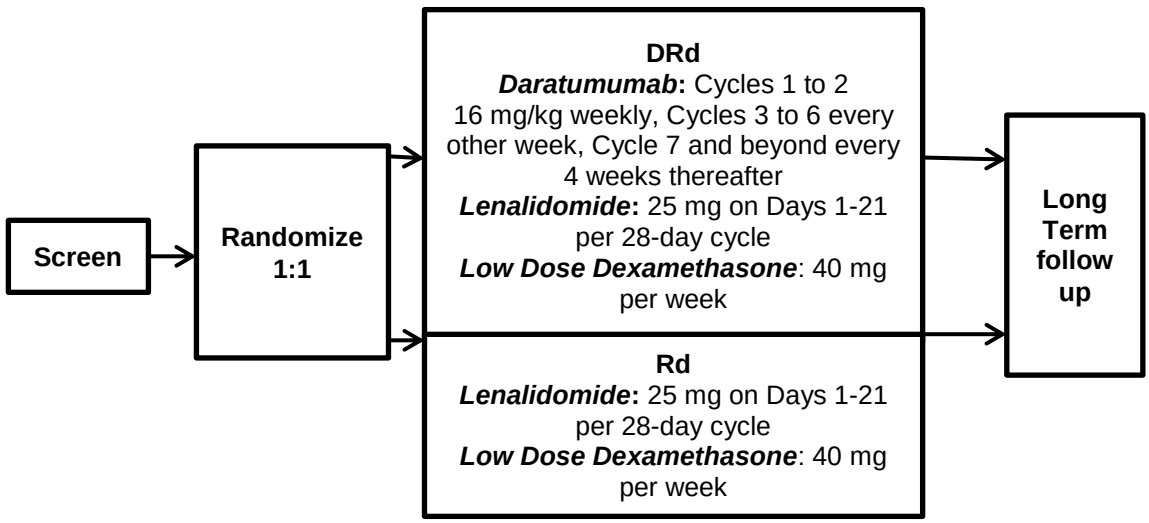
MMY3003

Daratumumab was administered weekly for 8 weeks, then every 2 weeks for 16 weeks, and then every 4 weeks thereafter.

Oral lenalidomide was administered as shown in figure 3 for patients with creatinine clearance > 60 mL/min. Patients with creatinine clearance between 30 and 60 mL/min received 10 mg every 24 h.

Oral dexamethasone was administered at a total dose of 40 mg weekly. Patients older than 75 years or underweight (body mass (BMI) <18.5) received a dose of 20 mg weekly. An overview of the MMY3003 is showed in Figure 6.

Figure 6: Schematic Overview Study MMY3003

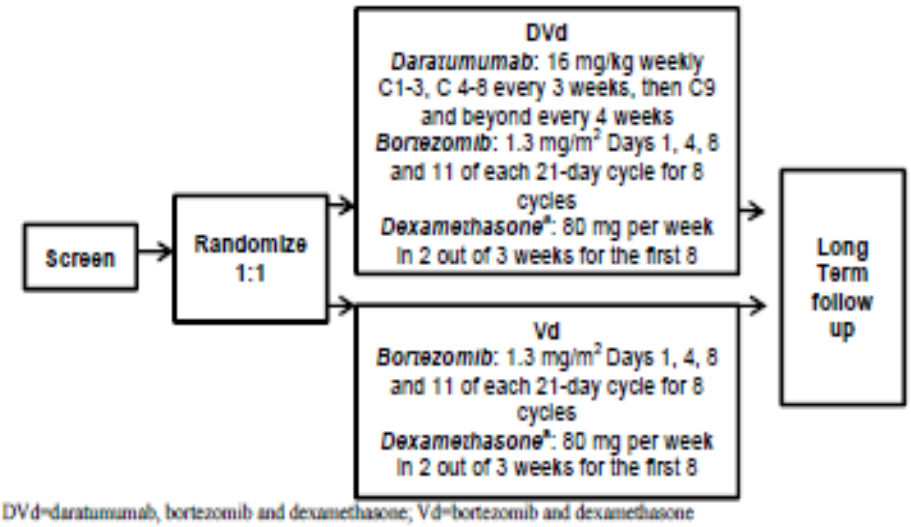


DRd=daratumumab, lenalidomide and dexamethasone; Rd=lenalidomide and dexamethasone
Note: Long-term follow up includes a visit 8 weeks after the end of treatment

MMY3004

Daratumumab was to be administered weekly for the first 3 cycles, on Day 1 of Cycles 4-8, and then every 4 weeks thereafter. Bortezomib was to be administered subcutaneously (SC) on Days 1, 4, 8, and 11 of each 21-day cycle. Eight bortezomib treatment cycles were to be administered. Oral dexamethasone was administered orally at a dose of 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12 of the first 8 bortezomib treatment cycles. For subjects who were older than 75 years, underweight (body mass index (BMI) <18.5), had poorly controlled diabetes mellitus or prior intolerance/ adverse event (AE) to steroid therapy, the dexamethasone dose could be administered at a dose of 20 mg weekly. An overview of the MMY3004 is showed in Figure 6.

Figure 7: Schematic Overview Study MMY3004



DVd=daratumumab, bortezomib and dexamethasone; Vd=bortezomib and dexamethasone

a. During weeks when the subject received an infusion of daratumumab, dexamethasone was administered on infusion days at a dose of 20 mg IV or PO before the infusion. The subject then continued to take dexamethasone 20 mg PO on Days 2, 4 and 5 of the first week, followed by Days 8, 9, 11, and 12 of the following week. During weeks when no daratumumab infusion was administered, dexamethasone was administered at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, 12 of the first 8 cycles (80 mg per week) (or 20 mg/week PO for subjects >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance/Adverse Event to steroid therapy)

Note: Cycles 1 through 8 were 21-day cycles, Cycle 9 and onward were 28-day cycles.

The median number of treatment cycles, the duration of study treatment and the median relative dose intensity are showed in

Table 34.

Objectives (MMY3003/MMY3004)

The primary objective of the **MMY3003** study was to compare the efficacy of daratumumab when combined with lenalidomide and dexamethasone (DRd) to that of lenalidomide and dexamethasone (Rd), in terms of progression-free survival (PFS) in patients with relapsed or refractory multiple myeloma.

The primary objective of the **MMY3004** study was to compare the efficacy of daratumumab when combined with bortezomib (velcade) and dexamethasone (DVd) to that of bortezomib and dexamethasone (Vd), in terms of PFS in patients with relapsed or refractory multiple myeloma.

The major secondary objectives were to compare the 2 treatment groups with respect to:

- Time to progression (TTP), overall ORR, and OS.
- Proportion of patients with a response of very good partial response (VGPR) or better.
- Duration of and time to response (DOR and TTR).
- Time to subsequent antimyeloma treatment **(MMY3003 only).**
- Minimal residual disease (MRD) negativity rate.
- Safety and tolerability of daratumumab when administered in combination with Rd/Vd respectively.

Other secondary endpoints were as follows:

- To assess the pharmacokinetics of daratumumab in combination with Rd/Vd respectively
- To assess the immunogenicity of daratumumab
- To determine ORR **(MMY3003)** and to evaluate clinical efficacy **(MMY3004)** in high risk molecular subgroups.
- To evaluate treatment effects on patient-reported outcome (PROs) including the EuroQol-2 Dimensrions (EQ-5D-5L) and European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.

The exploratory objective of both trials was to explore biomarkers predictive of response to daratumumab and potential mechanisms of treatment resistance.

Outcomes/endpoints (MMY3003/MMY3004)

The primary efficacy endpoint, PFS, was defined as the duration from the date of randomization to either progressive disease, according to the International Myeloma Working Group (IMWG) criteria, or death, whichever occurred first.

The secondary efficacy endpoints included:

- Time to disease progression (TTP), defined as the time between the date of randomization and the date of first documented evidence of confirmed progressive disease (PD), as defined in the IMWG criteria, or death due to PD, whichever occurred first.
- Response rate of VGPR or better, defined as the proportion of subjects with a response of VGPR or better (ie, VGPR, CR, or sCR) according to the IMWG criteria during or after the study treatment.
- Minimal residual disease (MRD) negative rate, defined as the proportion of subjects with negative MRD at any timepoint after the first dose by bone marrow aspirate or whole blood.
- Overall response rate (ORR), defined as the proportion of subjects who achieved a partial response (PR) or better (ie, PR, very good partial response (VGPR), complete response (CR), or stringent complete response (sCR)), according to the IMWG criteria, during or after the study treatment.
- Overall survival (OS), measured from the date of randomization to the date of death due to any cause.
- Time to response (TTR), defined as the time between the date of randomization and the first efficacy evaluation that the subject met all criteria for PR or better.
- Duration of response (DOR), defined for subjects with a confirmed response (PR or better) as the time between first documentation of response and disease progression, according to IMWG response criteria, or death due to PD, whichever occurs first.

Table 3 Comparison of Key Elements of Study MMY3003 and Study MMY3004

	Study MMY3003	Study MMY3004
Patient population	Subjects with relapsed or refractory multiple myeloma who received at least 1 prior therapy for multiple myeloma and had PD based on investigator's determination of response by the IMWG criteria on or after their last regimen were included	
	• Subjects excluded for refractoriness or intolerance to lenalidomide	• Subjects excluded for refractoriness to bortezomib or another PI
Primary efficacy endpoint	PFS	
Key Secondary efficacy endpoints	TTP, ORR, VGPR or better rate, TTR, DOR, MRD negativity, OS, time to subsequent antimyeloma therapy, PFS2	
Stratification	ISS (I, II, or III) at screening No. of prior lines (1 vs. 2 or 3 vs. >3)	
	Prior lenalidomide (no vs. yes)	Prior bortezomib (no vs. yes)
Duration of treatment	Rd: Until disease progression or unacceptable toxicity Daratumumab: Until disease progression or unacceptable toxicity	Vd 8 cycles in both treatment groups Daratumumab: Until disease progression or unacceptable toxicity

DOR=duration of response: ISS=International Staging System; MRD=minimum residual disease; ORR=overall response rate; OS=overall survival; PFS2=progression-free survival on next line of therapy; TTP=time to progression; TTR=time to response; VGPR=very good partial response

Sample size

Study MMY3003

The total sample size needed for the study was approximately 560 subjects (280 per treatment group). It was assumed, that DRd could reduce the risk of disease progression or death by 30%, ie, assuming the HR (DRd vs. Rd) of 0.70. Analysis of the primary endpoint PFS was planned to be performed when approximately 295 PFS events had occurred to achieve a power of 85% to detect a HR of 0.70 with a log-rank test (two-sided alpha being 0.05). Long-term survival follow-up was to continue until 330 deaths had been observed.

Study MMY3004

Approximately 480 subjects (240 per group) were to be randomized in the study. The sample size was based on the hypothesis of a 30% reduction in the risk of either progression or death. A total of 295 PFS events would provide a power of 85% to detect a reduction of 30% in the risk of either progression or death (HR [DVd vs Vd] of 0.70) with a log-rank test, assuming a two-sided significance level of 5%. A 16-month accrual period and an additional 10-month follow-up were assumed. Long-term survival follow-up was to continue until 320 deaths (ie. 2/3 of the randomized subjects) had been observed.

For **both the MMY3003 and the MMY3004** studies, the sample size calculation took into consideration an annual dropout rate of 5%.

Randomisation

In both studies, subjects were randomly assigned by an interactive web response system (IWRS) to 1 of 2 treatment groups based on a computer-generated randomization schedule. The randomization was stratified by ISS at screening (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3) and prior lenalidomide/bortezomib treatment (no vs. yes).

Blinding (masking)

Both studies were open-label.

Statistical methods

The statistical methods for key efficacy endpoints is provided in below Table:

Table 4 Statistical method for key efficacy endpoints (study MMY3003)

Endpoint	Statistical Methods
Primary Endpoint	
PFS	Kaplan-Meier method, stratified log-rank test, stratified Cox's regression model
Stratification for primary analysis	ISS staging (I, II, III), number of prior lines therapy (1 vs. 2 or 3 vs. >3), and prior lenalidomide treatment (no vs. yes)
Secondary Endpoints	
TTP	Kaplan-Meier method, stratified log-rank test, stratified Cox regression model
ORR	CMH $\chi 2$ test controlled for 3 stratification factors
Response rate of VGPR or better	CMH $\chi 2$ test controlled for 3 stratification factors
TTR	Kaplan-Meier method, stratified log-rank test
DOR	Kaplan-Meier method
MRD negativity rate	Fisher's exact test (Mantel-Haenszel odds ratio) and Likelihood-ratio (Chi-squared odds ratio)
OS	Kaplan-Meier method, unstratified Cox's regression model
Time to subsequent antimyeloma therapy	Kaplan-Meier method, stratified Cox's regression model
PFS2	Kaplan-Meier method

$\chi 2$=chi-square; CMH=Cochran-Mantel-Haenszel; DOR=duration of response; ISS=International Staging System; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; TTP=time-to-progression; TTR=time to response.

For both the MMY3003 and the MMY3004 studies, the analyses of efficacy endpoints were conducted on the ITT population, defined as subjects who have been randomised: PFS, TTP, MRD, OS, time to subsequent therapy, demographics and baseline characteristic.

Response-evaluable patients were defined as subjects who had a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening visit. In addition, subjects must have received at least 1 administration of study treatment and have at least 1 post baseline disease assessment. Analyses of major secondary endpoints of ORR, rate of VGPR or better, and duration of and time to response are based on this population.

The per-protocol population was defined as subjects who are randomized and have no major protocol deviations due to not meeting all inclusion/exclusion criteria.

The safety population was defined as subjects who have received at least 1 administration of any study treatment (partial or complete). This population is used for all safety analyses. The safety analysis grouping is according to the treatment actually received.

The immune response-evaluable population was defined as subjects assigned to the DRd group who have at least 1 immunogenicity sample obtained after their first daratumumab administration.

Two interim analyses were planned for the MMY3003 and the MMY3004 studies by an Independent Data Monitoring Committee (IDMC). The first interim analysis was to provide a comprehensive evaluation of safety after 80 subjects had been treated for at least 8 weeks or discontinued the study treatment.

The second interim analysis was to evaluate cumulative interim safety and efficacy data, and was to be performed when approximately 60% of the total planned events had been accumulated. The significance level at this interim analysis to establish the superiority of DRd over Rd and DVd over Vd respectively, with regard to PFS was determined based on the observed number of PFS events at the interim analysis, using

the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. IDMC continues to review safety data at regular intervals during the study.

Response to study treatment and progressive disease was based on IMWG response criteria (by a validated computer algorithm) with minimal response (MR) defined according to European Society for Blood and Marrow Transplantation criteria.

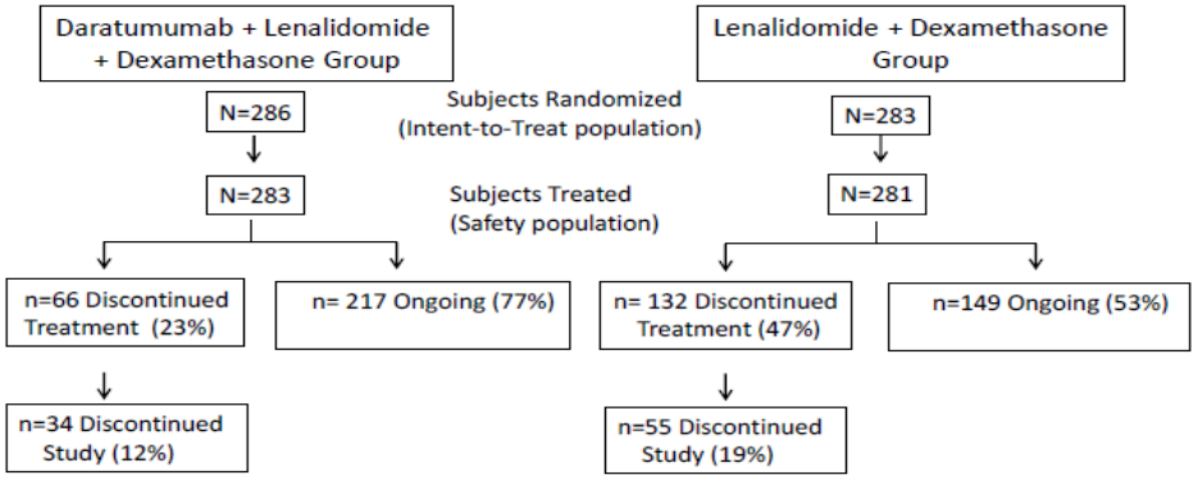
Results

MMY3003

Participant flow

The disposition of Subjects randomized into Study MMY3003 is shown in Figure 8.

Figure 8 Disposition of Subjects randomized into Study MMY3003



Recruitment

The study was conducted in 18 countries, 12 of the countries were in the EU region (68% of subjects), 4 in the Asia-Pacific region (20%) and 12% of subjects were from Canada and the United States.

The first subject was randomized on 16 June 2014 and the last subject started treatment on 15 July 2015. The clinical cut-off was 7 March 2016.

Conduct of the study

The original protocol was dated 10 February 2014. There were 2 global amendments and 4 country-specific amendments.

Amendment FRA-1 (8 May 2014): Exclusion Criteria #6 was modified to exclude subjects with a history of malignancy within 5 years, instead of 3 years.

Amendment INT-1 (16 June 2014): The sample size was changed to reflect the median PFS assumption for the comparator arm. Lenalidomide Global Pregnancy Prevention Plan was added. Feedback from investigators and Health Authorities was incorporated.

Amendment JPN-1 (26 August 2014): In response to PMDA comments, a section and attachment were added to describe the enhanced reporting, monitoring, and review of pre-specified safety events for Japanese subjects in the DRd group (minimum of 3 subjects).

Amendment INT-2 (20 November 2014): The requirements for bone marrow sample collection were modified to allow for differences across countries in local clinical practice. Other protocol procedures were clarified based on feedback from investigative sites. Changes from FRA-1 and JPN-1 amendments were rolled into the global INT-2 amendment.

Amendment DEU-1 (15 December 2014), INT-2/DEU-1 (7 April 2015): The exclusion criterion #9 text that was incorporated into Protocol Amendment INT-1 and INT-2 was replaced with the original protocol text.

A summary of protocol deviations occurred is shown in Table 5.

Table 5 Major protocol deviations, Intention-to-Treat Analysis Set (Study MMY3004)

	Rd n (%)	DRd n (%)	Total n (%)
Analysis set: intent-to-treat	283	286	569
Total number of subjects with major protocol deviation	16 (5.7%)	26 (9.1%)	42 (7.4%)
Type of major protocol deviation			
Entered but did not satisfy criteria	9 (3.2%)	9 (3.1%)	18 (3.2%)
Received wrong treatment or incorrect dose	2 (0.7%)	12 (4.2%)	14 (2.5%)
Efficacy assessment deviation	2 (0.7%)	5 (1.7%)	7 (1.2%)
Other	2 (0.7%)	0	2 (0.4%)
Developed withdrawal criteria but not withdrawn	0	1 (0.3%)	1 (0.2%)
Received a disallowed concomitant treatment	1 (0.4%)	0	1 (0.2%)

Keys: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.

[TSIDEM07.RTF] [JNJ-54767414\MMY3003\DBR_CSR\RE_CSR\PROD\TSIDEM07.SAS] 13MAY2016, 14:59

Baseline data

The demographic and baseline disease characteristics are presented in the following tables:

Table 6 Demographic and Baseline characteristics, ITT Analysis set (Study MMY3003)

	Rd	DRd	Total
Analysis set: intent-to-treat	283	286	569
Age, years			
N	283	286	569
Category, n (%)			
< 65	140 (49.5%)	133 (46.5%)	273 (48.0%)
65 - 74	108 (38.2%)	124 (43.4%)	232 (40.8%)
≥75	35 (12.4%)	29 (10.1%)	64 (11.2%)
Mean (SD)	64.3 (8.84)	64.4 (9.03)	64.4 (8.93)
Median	65.0	65.0	65.0
Range	(42; 87)	(34; 89)	(34; 89)
Sex, n (%)			
N	283	286	569
Male	164 (58.0%)	173 (60.5%)	337 (59.2%)
Female	119 (42.0%)	113 (39.5%)	232 (40.8%)
Ethnicity, n (%)			
N	283	286	569
Hispanic or Latino	3 (1.1%)	1 (0.3%)	4 (0.7%)
Not Hispanic or Latino	238 (84.1%)	258 (90.2%)	496 (87.2%)
Unknown	1 (0.4%)	2 (0.7%)	3 (0.5%)
Not Reported	41 (14.5%)	25 (8.7%)	66 (11.6%)
Race, n (%)			
N	283	286	569
White	186 (65.7%)	207 (72.4%)	393 (69.1%)
Black or African American	11 (3.9%)	5 (1.7%)	16 (2.8%)
Asian	46 (16.3%)	54 (18.9%)	100 (17.6%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	2 (0.7%)	1 (0.3%)	3 (0.5%)
Unknown	2 (0.7%)	1 (0.3%)	3 (0.5%)
Not Reported	36 (12.7%)	18 (6.3%)	54 (9.5%)
Weight (kg)			
N	2	280	282
Mean (SD)	64.00 (5.657)	73.69 (16.268)	73.62 (16.234)
Median	64.00	73.00	73.00
Range	(60.0; 68.0)	(37.0; 132.0)	(37.0; 132.0)
Height (cm)			
N	279	282	561
Mean (SD)	166.0 (10.59)	165.8 (10.54)	165.9 (10.56)
Median	166.0	165.8	166.0
Range	(137; 201)	(132; 195)	(132; 201)
Baseline ECOG score, n (%)			
N	283	286	569
0	150 (53.0%)	139 (48.6%)	289 (50.8%)
1	118 (41.7%)	136 (47.6%)	254 (44.6%)
2	15 (5.3%)	11 (3.8%)	26 (4.6%)
>2	0	0	0

Keys: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone.

[TSIDEM02.RTF] [JNJ-54767414\MMY3003\DBR_CSR\RE_CSR\PROD\TSIDEM02.SAS] 13MAY2016, 14:58

Table 7 Baseline disease characteristics, ITT Analysis set (Study MMY3003)

	Rd	DRd	Total
Analysis set: intent-to-treat	283	286	569
Type of myeloma by immunofixation, n (%)			
N	283	286	569
IgG	167 (59.0%)	164 (57.3%)	331 (58.2%
IgA	56 (19.8%)	55 (19.2%)	111 (19.5%
IgM	0	2 (0.7%)	2 (0.4%
IgD	6 (2.1%)	5 (1.7%)	11 (1.9%
IgE	0	0	0
Light chain	46 (16.3%)	55 (19.2%)	101 (17.8%
Kappa	32 (11.3%)	34 (11.9%)	66 (11.6%
Lambda	14 (4.9%)	21 (7.3%)	35 (6.2%
Biclonal	0	1 (0.3%)	1 (0.2%
Negative immunofixation	8 (2.8%)	4 (1.4%)	12 (2.1%
Type of measurable disease[a], n (%)			
N	283	286	569
IgG	158 (55.8%)	151 (52.8%)	309 (54.3%
IgA	51 (18.0%)	49 (17.1%)	100 (17.6%
Other[b]	2 (0.7%)	5 (1.7%)	7 (1.2%
Urine only	37 (13.1%)	41 (14.3%)	78 (13.7%
Serum FLC only	33 (11.7%)	39 (13.6%)	72 (12.7%
NE	0	1 (0.3%)	1 (0.2%
ISS staging[c], n (%)			
N	283	286	569
I	140 (49.5%)	137 (47.9%)	277 (48.7%
II	86 (30.4%)	93 (32.5%)	179 (31.5%
III	57 (20.1%)	56 (19.6%)	113 (19.9%
Time from MM diagnosis to randomization(years)			
N	283	286	569
Mean (SD)	4.82 (3.607)	4.56 (3.607)	4.69 (3.60
Median	3.95	3.48	3.64
Range	(0.4; 21.7)	(0.4; 27.0)	(0.4; 27.0

Table 8 Risk stratification in Multiple Myeloma, ITT analysis set (Study MMY3003)

	Rd	DRd	Total
	n (%)	n (%)	n (%)
Analysis set: intent-to-treat	283	286	569
Risk stratification[a]			
N	283	286	569
High-risk	18 (6.4%)	21 (7.3%)	39 (6.9%)
Standard-risk	167 (59.0%)	182 (63.6%)	349 (61.3%)
Low-risk	26 (9.2%)	25 (8.7%)	51 (9.0%)
Not done	72 (25.4%)	58 (20.3%)	130 (22.8%)

Keys: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone.
[a] Determination of a subjects risk stratification is based on three factors: International Staging System (ISS); presence of chromosomal abnormalities of t(4; 14), del17 or del17p by FISH or Karyotype testing and age.
Note: Percentages are calculated with the number of subjects in each group with available data as denominator.

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Table 9 Prior Therapies for Multiple Myeloma, ITT analysis set (Study MMY3003)

	Rd n (%)	DRd n (%)	Total n (%)
Analysis set: intent-to-treat	283	286	569
Total number of subjects with any prior therapies for multiple myeloma	283 (100.0%)	286 (100.0%)	569 (100.0%)
Prior systemic therapy	283 (100.0%)	286 (100.0%)	569 (100.0%)
Prior autologous stem cell transplant(ASCT)	180 (63.6%)	180 (62.9%)	360 (63.3%)
Prior radiotherapy	57 (20.1%)	65 (22.7%)	122 (21.4%)
Prior cancer-related surgery	42 (14.8%)	43 (15.0%)	85 (14.9%)
Number of prior lines of therapy[a]			
N	283	286	569
Category, n (%)			
1	146 (51.6%)	149 (52.1%)	295 (51.8%)
2	80 (28.3%)	85 (29.7%)	165 (29.0%)
3	38 (13.4%)	38 (13.3%)	76 (13.4%)
>3	19 (6.7%)	14 (4.9%)	33 (5.8%)
Mean (SD)	1.8 (1.14)	1.8 (1.17)	1.8 (1.15)
Median	1.0	1.0	1.0
Range	(1; 8)	(1; 11)	(1; 11)
Prior PI	242 (85.5%)	245 (85.7%)	487 (85.6%)
Bortezomib	238 (84.1%)	241 (84.3%)	479 (84.2%)
Carfilzomib	6 (2.1%)	6 (2.1%)	12 (2.1%)
Ixazomib	2 (0.7%)	2 (0.7%)	4 (0.7%)
Prior IMiD	156 (55.1%)	158 (55.2%)	314 (55.2%)
Lenalidomide	50 (17.7%)	50 (17.5%)	100 (17.6%)
Pomalidomide	0	2 (0.7%)	2 (0.4%)
Thalidomide	125 (44.2%)	122 (42.7%)	247 (43.4%)
Prior corticosteroids	281 (99.3%)	280 (97.9%)	561 (98.6%)
Dexamethasone	240 (84.8%)	249 (87.1%)	489 (85.9%)
Prednisone	83 (29.3%)	81 (28.3%)	164 (28.8%)
Prior alkylating agents	270 (95.4%)	268 (93.7%)	538 (94.6%)
Prior anthracyclines	79 (27.9%)	77 (26.9%)	156 (27.4%)
Prior PI+IMiD	125 (44.2%)	125 (43.7%)	250 (43.9%)
Prior PI+IMiD+ALKY	121 (42.8%)	118 (41.3%)	239 (42.0%)
Prior BORT+LEN	43 (15.2%)	44 (15.4%)	87 (15.3%)
Prior CARF+POM	0	2 (0.7%)	2 (0.4%)

Keys: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide -dexamethasone.
Keys: PI = proteasome inhibitor; IMiD = Immunomodulatory agent. ALKY=alkylating agents; BORT= bortezomib; LEN=lenalidomide; CARF=carfilzomib; POM=pomalidomide .
[a]Based on data recorded on prior systemic therapy eCRF page.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.

[TSIPM01.RTF] [JNJ-54767414\MMY3003\DBR_CSR\RE_CSR\PROD\TSIPM01.SAS] 13MAY2016, 15:04

Table 10: Refractory status to prior Multiple Myeloma Therapy ,ITT analysis set (MMY3003 and MMY3004 Study)

	MMY3003		MMY3004	
	Rd	DRd	Vd	DVd
Analysis set: intent-to-treat	283	286	247	251
Refractory at any point to prior therapy	96 (33.9%)	97 (33.9%)	113 (45.7%)	104 (41.4%)
Refractory Status				
PI only	46 (16.3%)	57 (19.9%)	4 (1.6%)	3 (1.2%)
IMiD only	11 (3.9%)	10 (3.5%)	90 (36.4%)	74 (29.5%)
Both PI and IMiD	14 (4.9%)	7 (2.4%)	7 (2.8%)	9 (3.6%)
Refractory to last line of prior therapy	76 (26.9%)	80 (28.0%)	85 (34.4%)	76 (30.3%)
Refractory to				
Bortezomib	58 (20.5%)	59 (20.6%)	2 (0.8%)	1 (0.4%)
Carfilzomib	3 (1.1%)	3 (1.0%)	4 (1.6%)	5 (2.0%)
Ixazomib	0	2 (0.7%)	5 (2.0%)	6 (2.4%)
Lenalidomide	0	0	81 (32.8%)	60 (23.9%)
Pomalidomide	0	2 (0.7%)	6 (2.4%)	7 (2.8%)
Thalidomide	26 (9.2%)	17 (5.9%)	27 (10.9%)	29 (11.6%)

Key: D=Daratumumab, Vd=bortezomib-dexamethasone, Rd=lenalidomide-dexamethasone
Keys: PI = proteasome inhibitor; IMiD = Immunomodulatory agent.
Note: Refractory to each medication refers to refractory to their most recent medication-containing line.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.
[TSIPM02.RTF] [JNJ-54767414\Z_SCE\DBR_MMY_RR_2016\RE_MMY_RR_2016\PROD\TSIPM02.SAS] 14JUL2016, 17:20

Numbers analysed

Five hundred sixty-nine (569) subjects were randomized in the MMY3003 study, 286 received the study drug arm DRd and 283 received Rd (ITT population). Numbers treated were 564 patients, 283 in the DRd arm and 281 in the Rd arm (safety population).

Outcomes and estimation

Primary endpoint – PFS

As of 7 March 2016 clinical cut-off, the median duration of follow-up, based on Kaplan-Meier estimate was 13.54 months (range:0.0;20.7) for the ITT population. In the DRd arm 13.60 months (range: 0.0; 20.7) and 13.54 months (range: 0.1;20.3) in the Rd arm.

Results in terms of Progressive-Free Survival are reported in Table 11 and Figure 9.

Table 11 Progression Free survival, ITT analysis set (study MMY03003)

	Rd	DRd
Analysis set: intent-to-treat	283	286
Progression-free survival (PFS)		
Number of events (%)	116 (41.0%)	53 (18.5%)
Number of censored (%)	167 (59.0%)	233 (81.5%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	6.70 (5.55, 8.34)	NE (13.17, NE)
Median (95% CI)	18.43 (13.86, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (18.43, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.37 (0.27, 0.52)
6-month PFS rate % (95% CI)	77.1 (71.6, 81.6)	89.6 (85.4, 92.7)
12-month PFS rate % (95% CI)	60.1 (54.0, 65.7)	83.2 (78.3, 87.2)
18-month PFS rate % (95% CI)	52.2 (44.3, 59.5)	77.9 (71.3, 83.2)

Keys: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test stratified with ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior lenalidomide treatment (no vs. yes).
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior lenalidomide treatment (no vs. yes). A hazard ratio < 1 indicates an advantage for DRd.

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Figure 9 Kaplan-Meier Plot for PFS, ITT population (Study MMY3003)

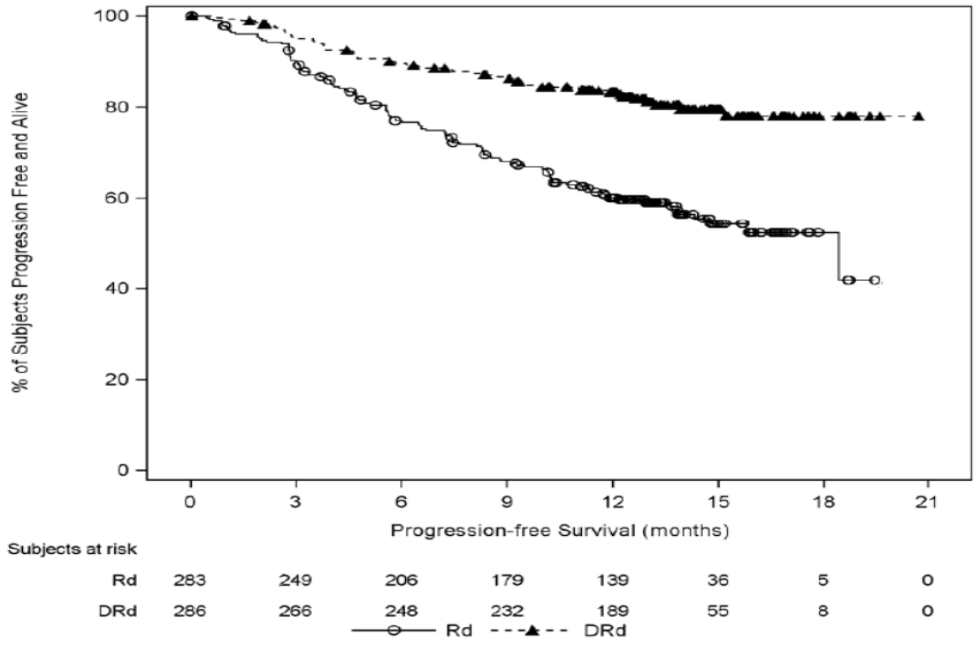

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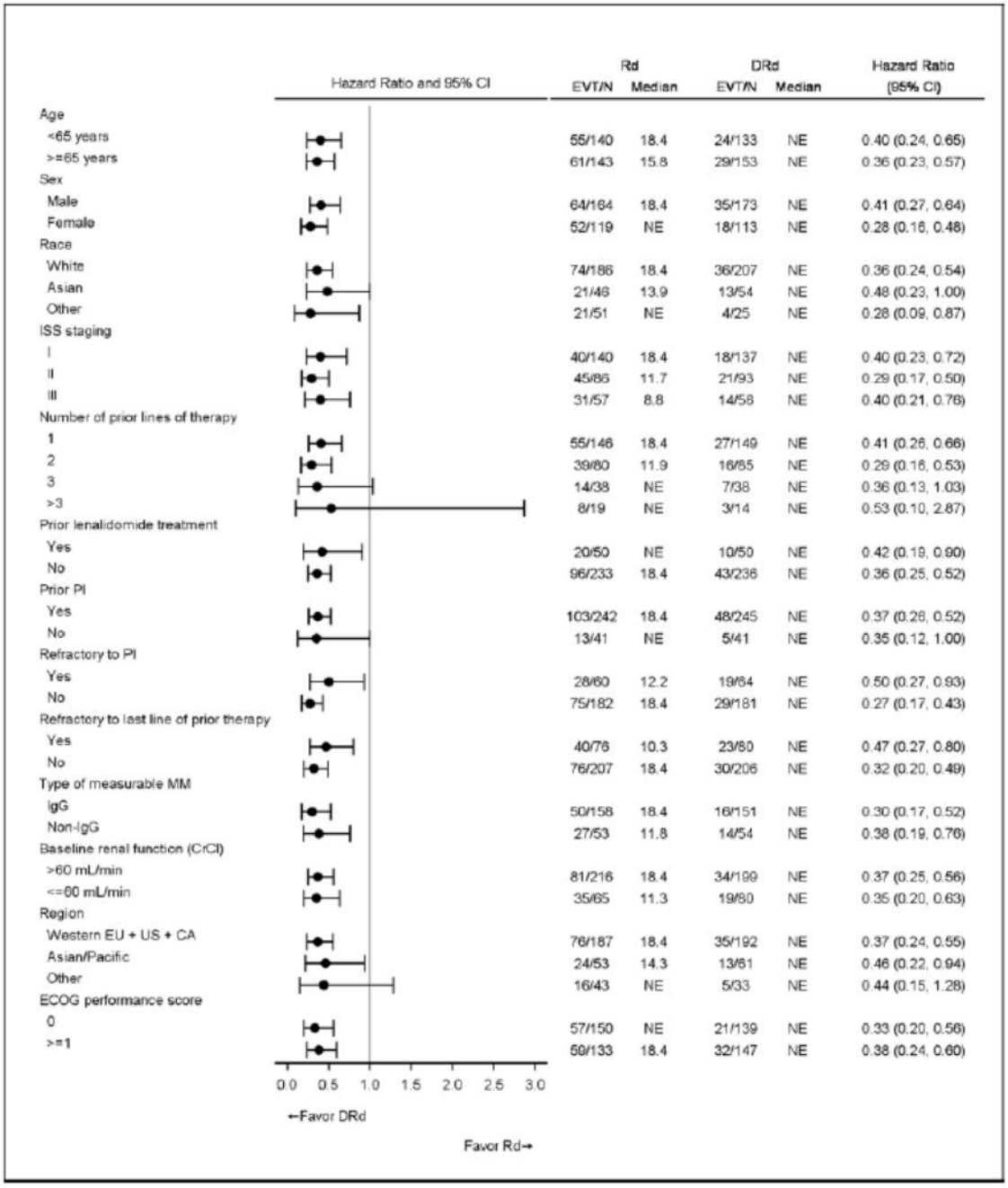
Figure 10 Subgroup Analyses of PFS, ITT population (Study MMY3003)



Note: Type of MM subgroup analysis is based on subjects with measurable disease in serum.
Note: Refractory to PI subgroup analysis is based on subjects who received prior PI therapy.

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Secondary endpoint: Time to disease progression

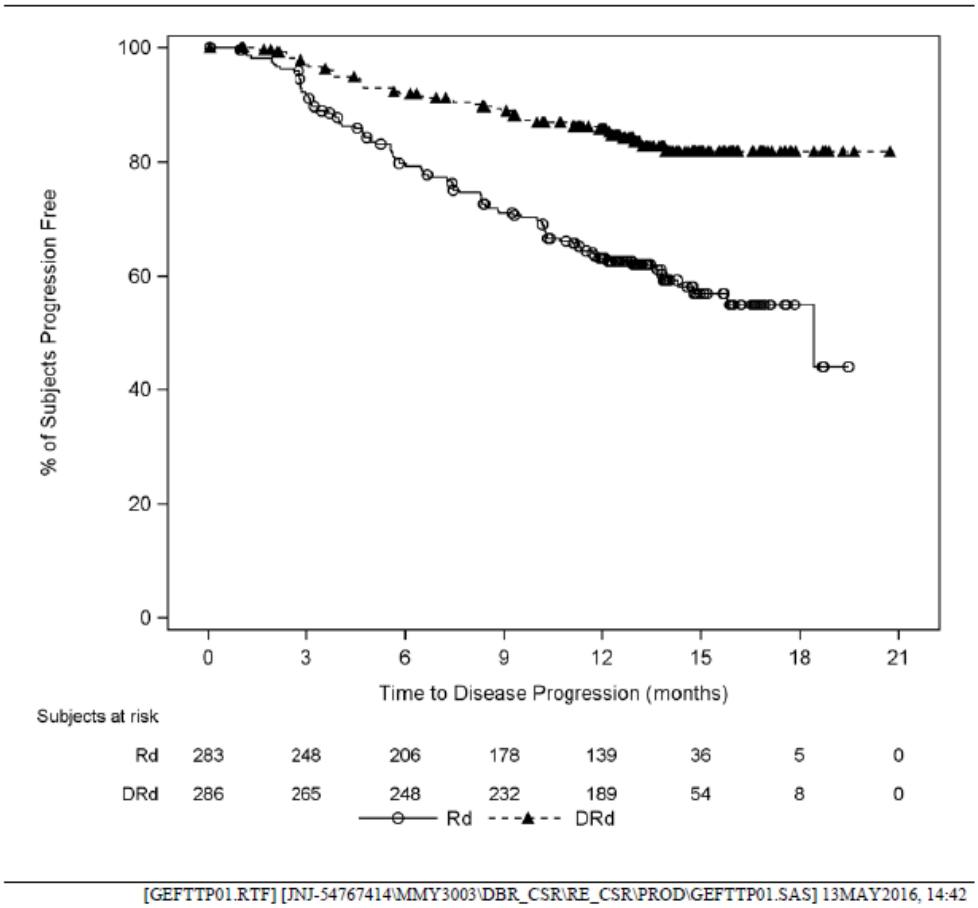
Table 12 Time to disease progression , ITT population (study MMY3003)

	Rd	DRd
Analysis set: intent-to-treat	283	286
Time to disease progression		
Number of events (%)	104 (36.7%)	44 (15.4%)
Number of censored (%)	179 (63.3%)	242 (84.6%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	7.66 (5.82, 10.12)	NE (NE, NE)
Median (95% CI)	18.43 (14.78, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (18.43, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.34 (0.23, 0.48)

Keys: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test stratified with ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior lenalidomide treatment (no vs. yes).
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior lenalidomide treatment (no vs. yes). A hazard ratio < 1 indicates an advantage for DRd.

[TEFTTP01.RTF] [JNJ-54767414\MMY3003\DBR_CSR\RE_CSR\PROD\TEFTTP01.SAS] 13MAY2016, 14:39

Figure 11 Kaplan-Meier plot for Time to Disease Progression, ITT population (study MMY3003)



[GEFTTP01.RTF] [JNJ-54767414\MMY3003\DBR_CSR\RE_CSR\PROD\GEFTTP01.SAS] 13MAY2016, 14:42

Secondary endpoint: Overall response rate

Table 13 Overall best confirmed response, Response-evaluable set (study MMY3003)

	Rd		DRd		Odds Ratio (95% CI)[a]	P-value[b]
	n (%)	95% CI for %	n (%)	95% CI for %		
Analysis set: response-evaluable	276		281			
Response category						
Stringent complete response (sCR)	20 (7.2%)	(4.5%, 11.0%)	51 (18.1%)	(13.8%, 23.2%)		
Complete response (CR)	33 (12.0%)	(8.4%, 16.4%)	70 (24.9%)	(20.0%, 30.4%)		
Very good partial response (VGPR)	69 (25.0%)	(20.0%, 30.5%)	92 (32.7%)	(27.3%, 38.6%)		
Partial response (PR)	89 (32.2%)	(26.8%, 38.1%)	48 (17.1%)	(12.9%, 22.0%)		
Minimal response (MR)	26 (9.4%)	(6.2%, 13.5%)	5 (1.8%)	(0.6%, 4.1%)		
Stable disease (SD)	33 (12.0%)	(8.4%, 16.4%)	13 (4.6%)	(2.5%, 7.8%)		
Progressive disease (PD)	4 (1.4%)	(0.4%, 3.7%)	0	(NE, NE)		
Not evaluable (NE)	2 (0.7%)	(0.1%, 2.6%)	2 (0.7%)	(0.1%, 2.5%)		
Overall response (sCR+CR+VGPR+PR)	211 (76.4%)	(71.0%, 81.3%)	261 (92.9%)	(89.2%, 95.6%)	4.62 (2.62, 8.15)	<0.0001
Clinical benefit (Overall response + MR)	237 (85.9%)	(81.2%, 89.8%)	266 (94.7%)	(91.3%, 97.0%)		
VGPR or better (sCR + CR + VGPR)	122 (44.2%)	(38.3%, 50.3%)	213 (75.8%)	(70.4%, 80.7%)	3.90 (2.72, 5.59)	<0.0001
CR or better (sCR + CR)	53 (19.2%)	(14.7%, 24.4%)	121 (43.1%)	(37.2%, 49.1%)	3.17 (2.16, 4.66)	<0.0001

Keys: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone.
Key: CI = exact confidence interval.
[a] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior lenalidomide treatment (no vs. yes). An odds ratio > 1 indicates an advantage for DRd.
[b] P-value from the Cochran Mantel-Haenszel Chi-Squared test.
Note: Response-evaluable is defined as subjects who have a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening visit. In addition, subjects must have received at least 1 administration of study treatment and have at least 1 post baseline disease assessment.
Note: Response was assessed by computerized algorithm, based on International Uniform Response Criteria Consensus Recommendations.
Note: Percentages are calculated with the number of subjects in each group as denominator.

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Secondary endpoint: Time to response/duration of response

The median time to response was 1.0 months (95% CI: 1.0, 1.1) in the DRd group compared with 1.3 months (95% CI: 1.1, 1.9) for the Rd group (p<0.0001). The duration of response (DOR) was not reached in the DRd group, and was 17.4 months (95% CI: 17.4, NE) in the RD group.

Table 14 Duration of Response, responders in the Response evaluable set (study MMY3003)

	Rd	DRd
Analysis set: responders (PR or better) in the response-evaluable set	211	261
Duration of response[a]		
Number of events (%)	58 (27.5%)	34 (13.0%)
Number of censored (%)	153 (72.5%)	227 (87.0%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	10.8 (9.0, 12.9)	NE (NE, NE)
Median (95% CI)	17.4 (17.4, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (17.4, NE)	NE (NE, NE)

Keys: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone.
Key: CI = confidence interval; PR = Partial response; NE = Not estimable.
[a] First response PR or better.
Note: Number of events refers to number of responders (PR or better) who developed disease progression or died due to disease progression.

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Secondary endpoint: Minimal residual disease (MRD)

Table 15 MRD Negative Rate at 10^{-4} in Bone Marrow, ITT analysis set (study MMY3003)

TBMKMRD02D: Summary of MRD Negative Rate at 10^{-4} in Bone Marrow; Intent-to-Treat Analysis Set (Study 54767414MMY3003)		
	Rd	DRd
Analysis set: intent-to-treat	283	286
MRD negative rate (10^{-4})	22 (7.8%)	83 (29.0%)
95% CI[a] of MRD negative rate	(4.9%, 11.5%)	(23.8%, 34.7%)
Odds ratio with 95% CI[b]		4.851 (2.929, 8.034)
P-value[c]		<0.000001

Keys: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; CI = exact confidence interval.
[a] Exact 95% confidence interval.
[b] Chi-squared estimate of the common odds ratio is used. An odds ratio > 1 indicates an advantage for DRd.
[c] P-value from likelihood-ratio chi-squared test.

[TBMKMRD02D.RTF] [JNJ-54767414\MMY3003\DBR_CSR\RE_CSR\PROD\TBMKMRD02D.SAS] 09JUN2016, 13:07

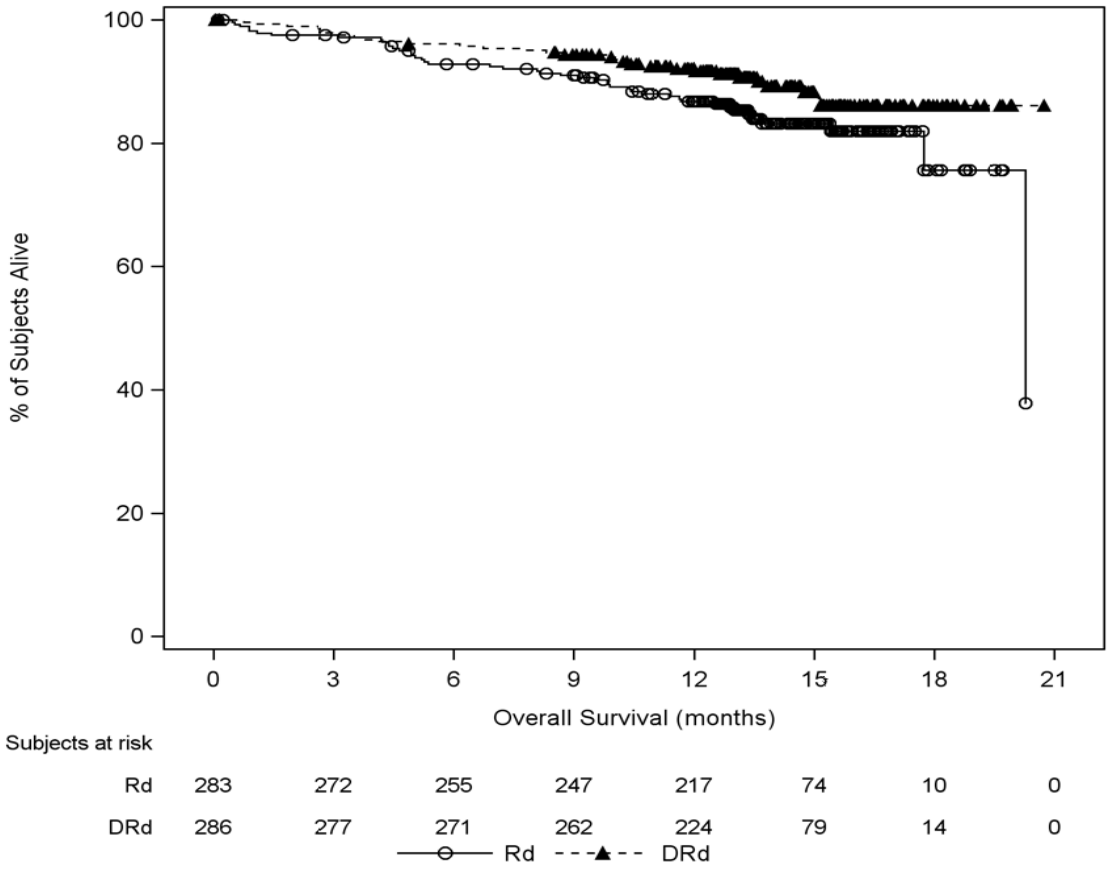
Secondary endpoint: Overall survival

Table 16 Overall survival , unstratified analysis, ITT population (study MMY3003)

	Rd	DRd
Analysis set: intent-to-treat	283	286
Overall survival		
Number of events (%)	45 (15.9%)	30 (10.5%)
Number of censored (%)	238 (84.1%)	256 (89.5%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	20.27 (17.74, NE)	NE (NE, NE)
Median (95% CI)	20.27 (20.27, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (20.27, NE)	NE (NE, NE)
P-value[a]		0.0534
Hazard ratio (95% CI)[b]		0.64 (0.40, 1.01)
12-month survival rate % (95% CI)	86.8 (82.2, 90.3)	92.1 (88.2, 94.7)
18-month survival rate % (95% CI)	75.6 (59.8, 85.9)	86.1 (79.9, 90.5)

Keys: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test.
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable.

Figure 12. Kaplan-Meier Plot for Overall Survival; Intent-to-Treat Population (Study MMY3003)



Ancillary analyses

The time to subsequent antimyeloma treatment was significantly delayed for patients in the DRd group compared with patients in the Rd group (HR=0.38, 95% CI: 0.26, 0.55; p< 0.0001). Forty (14%) and 89 (31%) of the patients in the DRd and Rd group, respectively, started subsequent anti-myeloma therapy. The median time to subsequent therapy or death due to progressive disease was not reached for either group (data not shown).

Patient-reported outcome were assessed using 2 PRO measures, the EORTC-QLQ-C30 and the EQ-5D-5L. No statistically significant difference was observed between DRd and Rd in change from baseline or median time to improvement or worsening in the Global Healts Status/QOL subscale of the EORTC-QLQ-C30 or the EQ-5D-5L Utility score or EQ-5D-5L Visual Analog Scale (VAS) (data not shown).

Study MMY3004

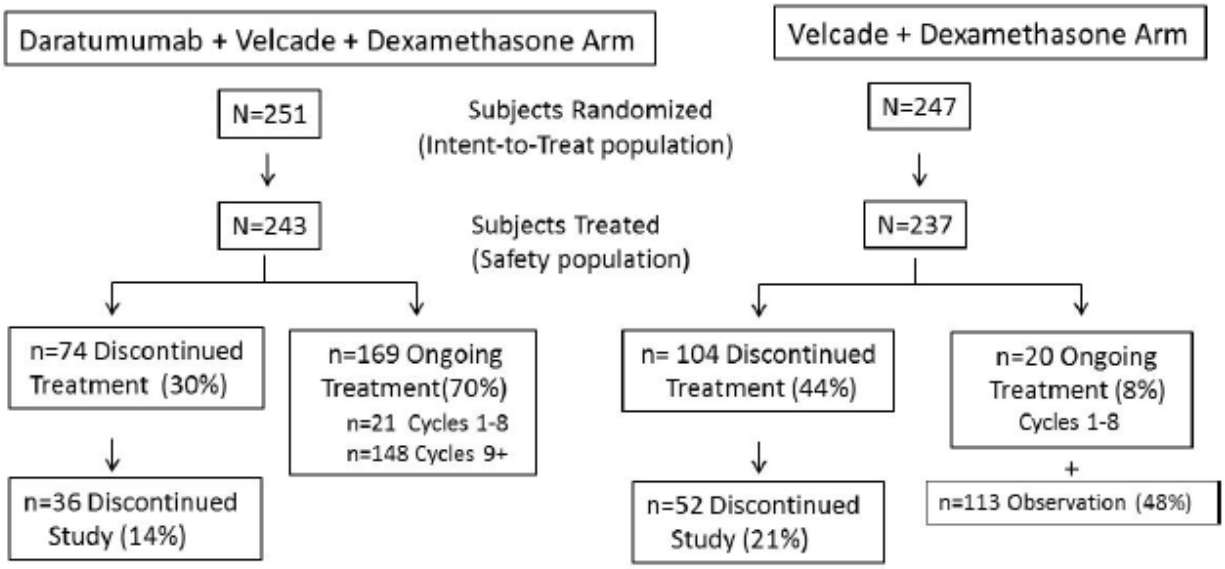
Results

Participant flow

The disposition of Subjects randomized into Study MMY3003 is shown in

Figure 13.

Figure 13 Disposition of Subjects randomized into Study 5476741MMY3004



Recruitment

The study was conducted in 16 countries, most of the subjects (75%) were enrolled in countries in the European Region (11 countries), 12% of the subjects were from the Asia-Pacific region (Australia and Korea), 7% of the subjects were from the United States, and 5% from Brazil and Mexico.

The first subject was randomized on 24 September 2014, and the last subject started treatment on 5 October 2015. The clinical cutoff was 11 January 2016.

Conduct of the study

The original protocol was dated 2 April 2014; there was 1 global and 1 country-specific amendment to the protocol.

Amendment INT-1 (23 December 2014): Clarification was made to the inclusion/exclusion criteria to align with other daratumumab protocols, and investigator feedback was incorporated into the protocol.

Amendment SWE-1 (10 July 2014): Specific concerns from the Health Authority in Sweden were addressed. Text was revised to indicate that study status updates were to be submitted to the Independent Ethics Committee/Institutional Review Board annually, or more frequently, if requested.

Protocol deviations

Major protocol deviations were reported for 49 subjects (19%) across both treatment groups, as listed in Table 17.

Table 17 Major Protocol Deviations, Intent-to-Treat analysis set (study MMY3004)

	Vd n (%)	DVd n (%)	Total n (%)
Analysis set: intent-to-treat	247	251	498
Total number of subjects with major protocol deviation	21 (8.5%)	28 (11.2%)	49 (9.8%)
Type of major protocol deviation			
Entered but did not satisfy criteria	15 (6.1%)	14 (5.6%)	29 (5.8%)
Received wrong treatment or incorrect dose	1 (0.4%)	10 (4.0%)	11 (2.2%)
Received a disallowed concomitant treatment	2 (0.8%)	2 (0.8%)	4 (0.8%)
Developed withdrawal criteria but not withdrawn	1 (0.4%)	1 (0.4%)	2 (0.4%)
Other	1 (0.4%)	1 (0.4%)	2 (0.4%)
Safety assessment deviation	1 (0.4%)	1 (0.4%)	2 (0.4%)

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.

[TSIDEM07.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\TSIDEM07.SAS] 05APR2016, 15:51

Baseline data

The demographic and baseline disease characteristics are presented in the following tables:

Table 18 Demographic and Baseline characteristics, Intent-to-Treat analysis set (study MMY3004)

	Vd	DVd	Total
Analysis set: intent-to-treat	247	251	498
Age, years			
N	247	251	498
Category, n (%)			
< 65	125 (50.6%)	132 (52.6%)	257 (51.6%)
65 - 74	87 (35.2%)	96 (38.2%)	183 (36.7%)
≥75	35 (14.2%)	23 (9.2%)	58 (11.6%)
Mean (SD)	63.9 (9.81)	62.8 (9.66)	63.3 (9.74)
Median	64.0	64.0	64.0
Range	(33; 85)	(30; 88)	(30; 88)
Sex, n (%)			
N	247	251	498
Male	147 (59.5%)	137 (54.6%)	284 (57.0%)
Female	100 (40.5%)	114 (45.4%)	214 (43.0%)
Ethnicity, n (%)			
N	247	251	498
Hispanic or Latino	24 (9.7%)	17 (6.8%)	41 (8.2%)
Not Hispanic or Latino	212 (85.8%)	227 (90.4%)	439 (88.2%)
Unknown	3 (1.2%)	1 (0.4%)	4 (0.8%)
Not Reported	8 (3.2%)	6 (2.4%)	14 (2.8%)
Race, n (%)			
N	247	251	498
White	219 (88.7%)	216 (86.1%)	435 (87.3%)
Black or African American	6 (2.4%)	14 (5.6%)	20 (4.0%)
Asian	11 (4.5%)	12 (4.8%)	23 (4.6%)
American Indian or Alaska Native	1 (0.4%)	1 (0.4%)	2 (0.4%)
Native Hawaiian or other Pacific Islander	0	1 (0.4%)	1 (0.2%)
Other	1 (0.4%)	5 (2.0%)	6 (1.2%)
Unknown	2 (0.8%)	0	2 (0.4%)
Not Reported	7 (2.8%)	2 (0.8%)	9 (1.8%)
Weight (kg)			
N	235	243	478
Mean (SD)	77.17 (16.256)	78.19 (17.010)	77.69 (16.634)
Median	76.00	77.00	76.00
Range	(37.5; 131.6)	(45.0; 134.8)	(37.5; 134.8)
Height (cm)			
N	247	251	498
Mean (SD)	166.8 (9.95)	166.8 (9.95)	166.8 (9.94)
Median	167.0	167.0	167.0
Range	(139; 192)	(141; 194)	(139; 194)
Baseline ECOG score, n (%)			
N	247	250	497
0	116 (47.0%)	106 (42.4%)	222 (44.7%)
1	112 (45.3%)	131 (52.4%)	243 (48.9%)
2	19 (7.7%)	13 (5.2%)	32 (6.4%)
>2	0	0	0

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone.
Note: Percentages calculated with the number of subjects in each treatment group with available data as denominator.

[TSIDEM02.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\TSIDEM02.SAS] 05APR2016, 15:50

Table 19 Baseline disease characteristics, Intent-to-Treat analysis set (study MMY3004)

	Vd	DVd	Total
Analysis set: intent-to-treat	247	251	498
Type of myeloma by immunofixation, n (%)			
N	247	251	498
IgG	148 (59.9%)	136 (54.2%)	284 (57.0%)
IgA	54 (21.9%)	59 (23.5%)	113 (22.7%)
IgM	1 (0.4%)	1 (0.4%)	2 (0.4%)
IgD	3 (1.2%)	6 (2.4%)	9 (1.8%)
IgE	0	0	0
Light chain	36 (14.6%)	43 (17.1%)	79 (15.9%)
Kappa	17 (6.9%)	30 (12.0%)	47 (9.4%)
Lambda	19 (7.7%)	13 (5.2%)	32 (6.4%)
Biclonal	3 (1.2%)	2 (0.8%)	5 (1.0%)
Negative immunofixation	2 (0.8%)	4 (1.6%)	6 (1.2%)
Type of measurable disease[a], n (%)			
N	247	251	498
IgG	138 (55.9%)	125 (49.8%)	263 (52.8%)
IgA	54 (21.9%)	56 (22.3%)	110 (22.1%)
Other[b]	4 (1.6%)	5 (2.0%)	9 (1.8%)
Urine only	36 (14.6%)	40 (15.9%)	76 (15.3%)
Serum FLC only	14 (5.7%)	25 (10.0%)	39 (7.8%)
NE	1 (0.4%)	0	1 (0.2%)
ISS staging[c], n (%)			
N	247	251	498
I	96 (38.9%)	98 (39.0%)	194 (39.0%)
II	100 (40.5%)	94 (37.5%)	194 (39.0%)
III	51 (20.6%)	59 (23.5%)	110 (22.1%)
Time from MM diagnosis to randomization(years)			
N	247	251	498
Mean (SD)	4.77 (3.284)	4.71 (3.228)	4.74 (3.253)
Median	3.72	3.87	3.77

	Vd	DVd	Total
Range	(0.6; 18.6)	(0.7; 20.7)	(0.6; 20.7)
Number of lytic bone lesions, n (%)			
N	246	249	495
None	50 (20.3%)	56 (22.5%)	106 (21.4%)
1-3	43 (17.5%)	50 (20.1%)	93 (18.8%)
4-10	55 (22.4%)	53 (21.3%)	108 (21.8%)
More than 10	98 (39.8%)	90 (36.1%)	188 (38.0%)
Presence of diffuse myeloma-related osteopenia, n (%)			
N	247	249	496
Yes	111 (44.9%)	88 (35.3%)	199 (40.1%)
No	136 (55.1%)	161 (64.7%)	297 (59.9%)
Number of extramedullary plasmacytomas, n (%)			
N	247	251	498
0	233 (94.3%)	242 (96.4%)	475 (95.4%)
≥ 1	14 (5.7%)	9 (3.6%)	23 (4.6%)
Presence of evaluable bone marrow assessment			
N	247	251	498
Yes	245 (99.2%)	249 (99.2%)	494 (99.2%)
No	2 (0.8%)	2 (0.8%)	4 (0.8%)
% Plasma cells, bone marrow biopsy			
N	96	102	198
<10	14 (14.6%)	12 (11.8%)	26 (13.1%)
10-30	37 (38.5%)	40 (39.2%)	77 (38.9%)
>30	45 (46.9%)	50 (49.0%)	95 (48.0%)
% Plasma cells, bone marrow aspirate			
N	232	240	472
<10	44 (19.0%)	65 (27.1%)	109 (23.1%)
10-30	111 (47.8%)	97 (40.4%)	208 (44.1%)
>30	77 (33.2%)	78 (32.5%)	155 (32.8%)
% Plasma cells, bone marrow biopsy/aspirate			
N	245	249	494
<10	42 (17.1%)	42 (16.9%)	84 (17.0%)
10-30	108 (44.1%)	106 (42.6%)	214 (43.3%)
>30	95 (38.8%)	101 (40.6%)	196 (39.7%)
Any cytogenetic abnormality[d]			
N	174	181	355
Standard risk	137 (78.7%)	140 (77.3%)	277 (78.0%)
High risk	37 (21.3%)	41 (22.7%)	78 (22.0%)
Del17p	21 (12.1%)	28 (15.5%)	49 (13.8%)
T(4;14)	15 (8.6%)	14 (7.7%)	29 (8.2%)
T(14;16)	5 (2.9%)	4 (2.2%)	9 (2.5%)

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone.
Key: FLC = serum free light chain; ISS = International staging system.
[a] Includes subjects without measurable disease in serum and urine.
[b] Includes IgD, IgM, IgE and biclonal.
[c] ISS staging is derived based on the combination of serum β2-microglobulin and albumin.
[d] Cytogenetic abnormalities are based on FISH or karyotype testing.

[TSIDEM03.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\TSIDEM03.SAS] 05APR2016, 15:50

Table 20 Risk stratification in Intent-to-Treat analysis set (study MMY3004)

	Vd n (%)	DVd n (%)	Total n (%)
Analysis set: intent-to-treat	247	251	498
Risk Stratification[a]			
N	247	251	498
High-risk	22 (8.9%)	19 (7.6%)	41 (8.2%)
Standard-risk	134 (54.3%)	137 (54.6%)	271 (54.4%)
Low-risk	18 (7.3%)	25 (10.0%)	43 (8.6%)
Not done	73 (29.6%)	70 (27.9%)	143 (28.7%)

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone.
[a] Determination of a subjects risk stratification is based on three factors: International Staging System (ISS); presence of chromosomal abnormalities of t(4; 14), del17 or del17p by FISH or Karyotype testing and age.
Note: Percentages are calculated with the number of subjects in each group with available data as denominator.

[TSICVTO02.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\TSICVTO02.SAS] 05APR2016, 15:

Table 21 Prior therapies for Multiple Myeloma, Intent-to-Treat analysis set (study MMY3004)

	Vd n (%)	DVd n (%)	Total n (%)
Analysis set: intent-to-treat	247	251	498
Total number of subjects with any prior therapies for multiple myeloma	247 (100.0%)	251 (100.0%)	498 (100.0%)
Prior systemic therapy	247 (100.0%)	251 (100.0%)	498 (100.0%)
Prior autologous stem cell transplant(ASCT)	149 (60.3%)	156 (62.2%)	305 (61.2%)
Prior radiotherapy	59 (23.9%)	63 (25.1%)	122 (24.5%)
Prior cancer-related surgery	35 (14.2%)	33 (13.1%)	68 (13.7%)
Number of prior lines of therapy[a]			
N	247	251	498
Category, n (%)			
1	113 (45.7%)	122 (48.6%)	235 (47.2%)
2	74 (30.0%)	70 (27.9%)	144 (28.9%)
3	32 (13.0%)	37 (14.7%)	69 (13.9%)
>3	28 (11.3%)	22 (8.8%)	50 (10.0%)
Mean (SD)	2.0 (1.38)	1.9 (1.21)	2.0 (1.29)
Median	2.0	2.0	2.0
Range	(1; 10)	(1; 9)	(1; 10)
Prior PI	172 (69.6%)	169 (67.3%)	341 (68.5%)
Bortezomib	164 (66.4%)	162 (64.5%)	326 (65.5%)
Carfilzomib	10 (4.0%)	12 (4.8%)	22 (4.4%)
Ixazomib	7 (2.8%)	12 (4.8%)	19 (3.8%)
Prior IMiD	198 (80.2%)	179 (71.3%)	377 (75.7%)
Lenalidomide	120 (48.6%)	89 (35.5%)	209 (42.0%)
Pomalidomide	7 (2.8%)	7 (2.8%)	14 (2.8%)
Thalidomide	121 (49.0%)	125 (49.8%)	246 (49.4%)
Prior corticosteroids	245 (99.2%)	244 (97.2%)	489 (98.2%)
Dexamethasone	233 (94.3%)	218 (86.9%)	451 (90.6%)
Prednisone	77 (31.2%)	83 (33.1%)	160 (32.1%)
Prior alkylating agents	224 (90.7%)	240 (95.6%)	464 (93.2%)
Prior anthracyclines	80 (32.4%)	72 (28.7%)	152 (30.5%)
Prior PI+IMiD	129 (52.2%)	112 (44.6%)	241 (48.4%)
Prior PI+IMiD+ALKY	121 (49.0%)	112 (44.6%)	233 (46.8%)
Prior BORT+LEN	89 (36.0%)	75 (29.9%)	164 (32.9%)
Prior CARF+POM	0	4 (1.6%)	4 (0.8%)

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone.
Keys: PI = proteasome inhibitor; IMiD = Immunomodulatory agent; ALKY=alkylating agents; BORT= bortezomib; LEN=lenalidomide; CARF=carfilzomib; POM=pomalidomide.
[a] Based on data recorded on prior systemic therapy eCRF page.
Note: Percentages calculated with the number of subjects in each treatment group as denominator.

[TSIPM01.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\TSIPM01.SAS] 05APR2016, 15:55

Numbers analysed

Four hundred ninety-eight (498) subjects were randomized in the MMY3004 study, 251 in the study drug arm DVd and 247 In the Vd arm (ITT population). Numbers treated were 480 patients, 243 received DVd and 237 received the Vd arm (safety population).

Outcomes and estimation

As of the data cutoff, the median duration of follow-up was 7.5 months (range: 0.1;14.9) for the DVd group and 7.4 months (0.0;14.5) for the Vd group, 67 subjects (27%) in the DVd group and 122 subjects (49%) in the Vd group had progressive disease or died.

Primary endpoint – PFS

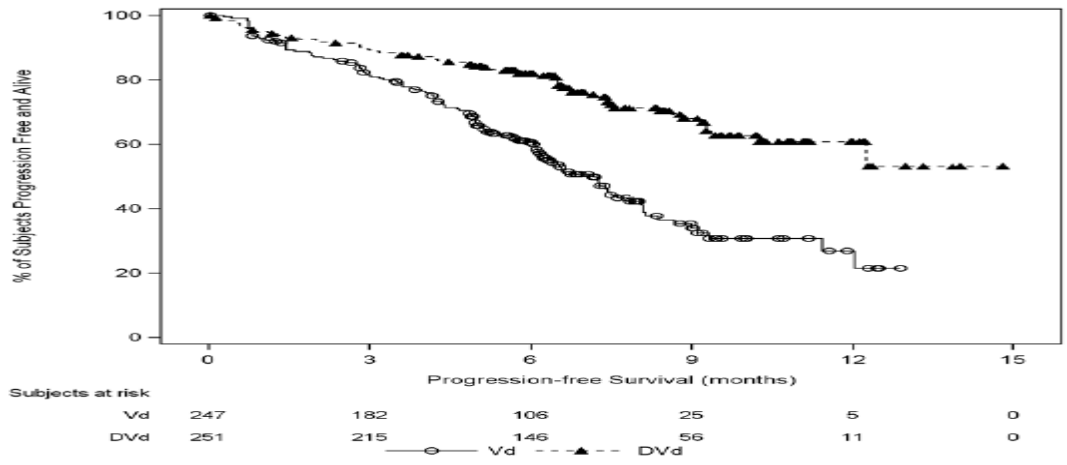
Table 22 Progression-free survival based on Computerized Algorithm; Intent-to-Treat analysis set (study MMY3004)

	Vd	DVd
Analysis set: intent-to-treat	247	251
Progression-free survival (PFS)		
Number of events (%)	122 (49.4%)	67 (26.7%)
Number of censored (%)	125 (50.6%)	184 (73.3%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	4.21 (3.19, 4.90)	7.20 (6.47, 8.84)
Median (95% CI)	7.16 (6.21, 7.85)	NE (12.25, NE)
75% quantile (95% CI)	12.02 (9.10, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.39 (0.28, 0.53)
6-month PFS rate % (95% CI)	60.6 (53.8, 66.8)	81.9 (76.3, 86.2)
12-month PFS rate % (95% CI)	26.9 (17.1, 37.5)	60.7 (51.2, 69.0)
18-month PFS rate % (95% CI)	NE (NE, NE)	NE (NE, NE)

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test stratified with ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior bortezomib treatment (no vs. yes).
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior bortezomib treatment (no vs. yes). A hazard ratio < 1 indicates an advantage for DVd.

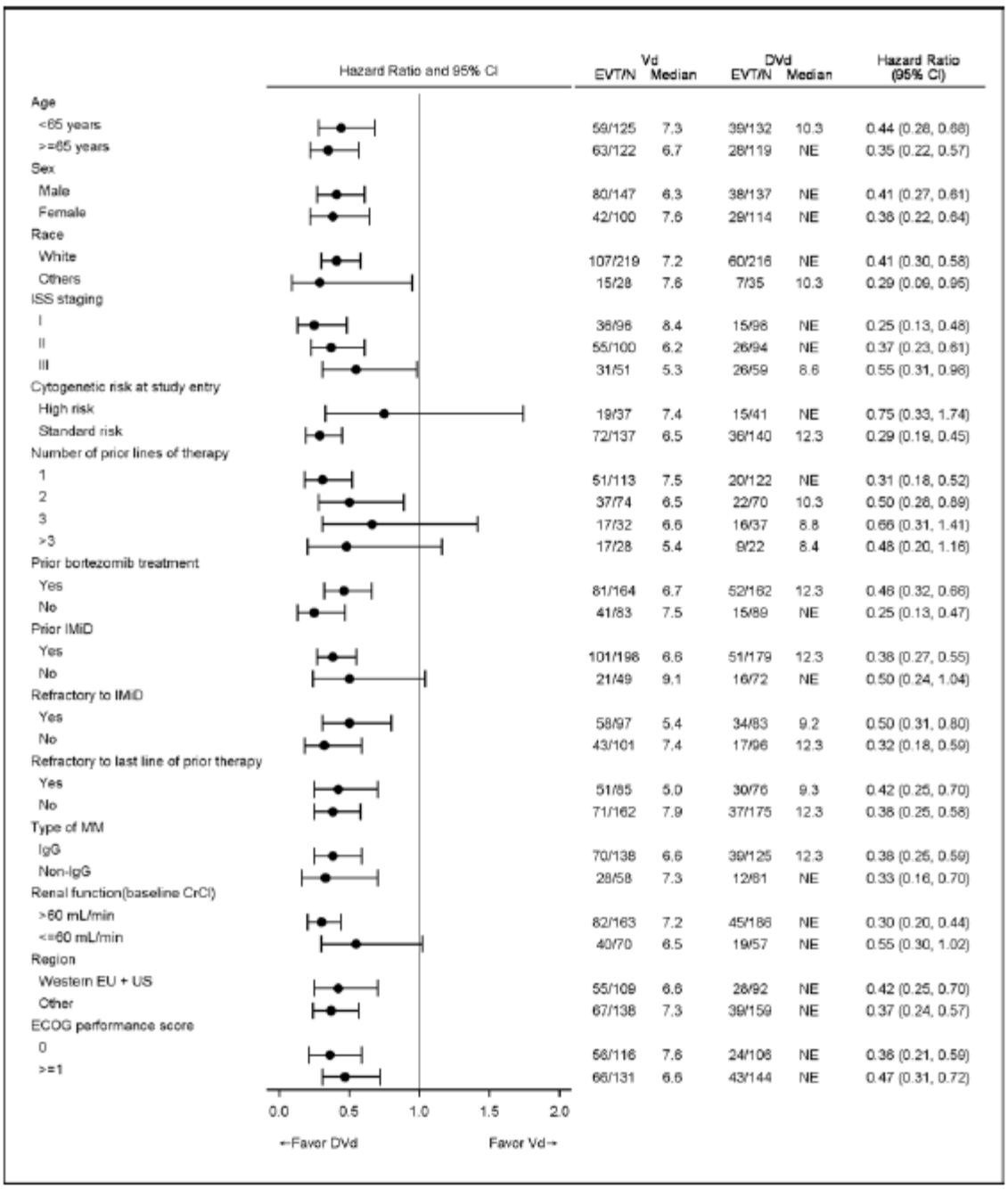
[TEFPFS01.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\TEFPFS01.SAS] 05APR2016, 14:55

Figure 14 Kaplan-Meier Plot for Progression-free Survival based on Computerized Algorithm; Intent-to-Treat analysis set (study MMY3004)



[GEFPFS01.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\GEFPFS01.SAS] 05APR2016, 14:55

Figure 15 Forest Plot of Subgroup Analyses of PFS based on Computerized Algorithm; Intent-to-Treat analysis set (study MMY3004)



Note: Type of MM subgroup analysis is based on subjects with measurable disease in serum.
Note: Refractory to IMiD subgroup analysis is based on subjects who received prior IMiD therapy.

[GEFPFSFP01.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\GEFPFSFP01.SAS] 20MAY2016, 08:50

Secondary endpoints: Time to disease progression

The TTP results and Kaplan-Meier curves for the ITT population are provided in Table 23 and Figure 16

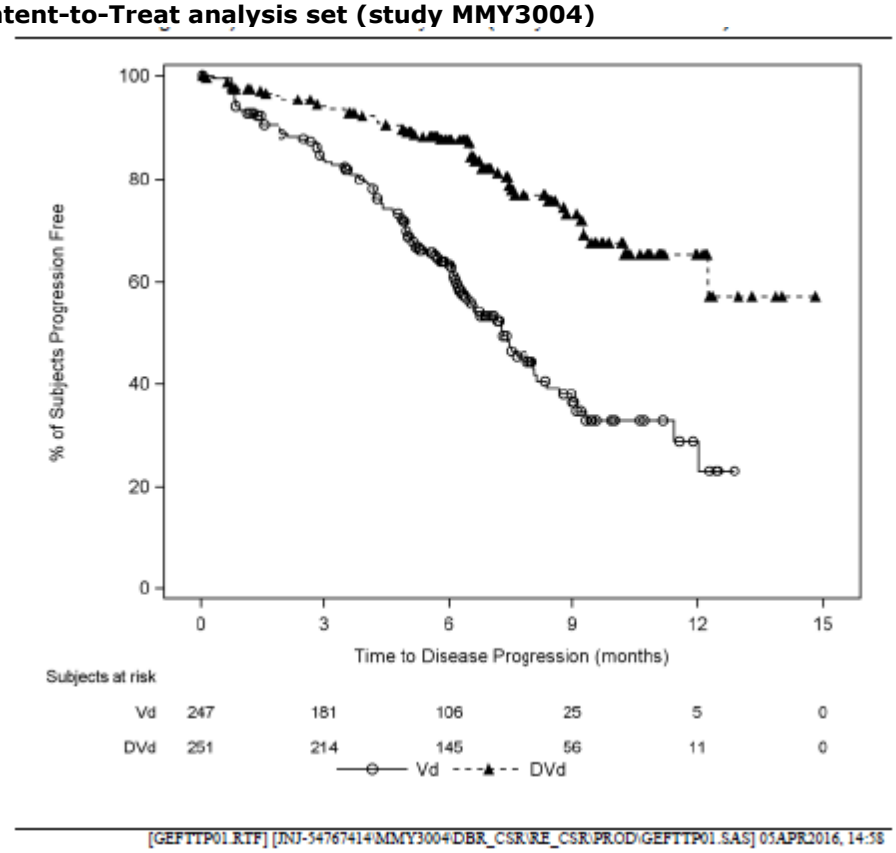
Table 23 Time to Disease Progression, Intent-to-Treat analysis set (study MMY3004)

	Vd	DVd
Analysis set: intent-to-treat	247	251
Time to disease progression		
Number of events (%)	112 (45.3%)	51 (20.3%)
Number of censored (%)	135 (54.7%)	200 (79.7%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	4.40 (3.78, 4.99)	8.64 (7.03, 10.25)
Median (95% CI)	7.29 (6.41, 8.08)	NE (12.25, NE)
75% quantile (95% CI)	12.02 (9.33, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.30 (0.21, 0.43)

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test stratified with ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior bortezomib treatment (no vs. yes).
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior bortezomib treatment (no vs. yes). A hazard ratio < 1 indicates an advantage for DVd.

[TEFTTP01.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\TEFTTP01.SAS] 05APR2016, 14:58

Figure 16 Kaplan-Meier plot for Time to Disease Progression, based on Computerized Algorithm; Intent-to-Treat analysis set (study MMY3004)



[GEFTTP01.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\GEFTTP01.SAS] 05APR2016, 14:58

Secondary endpoint: Overall response rate

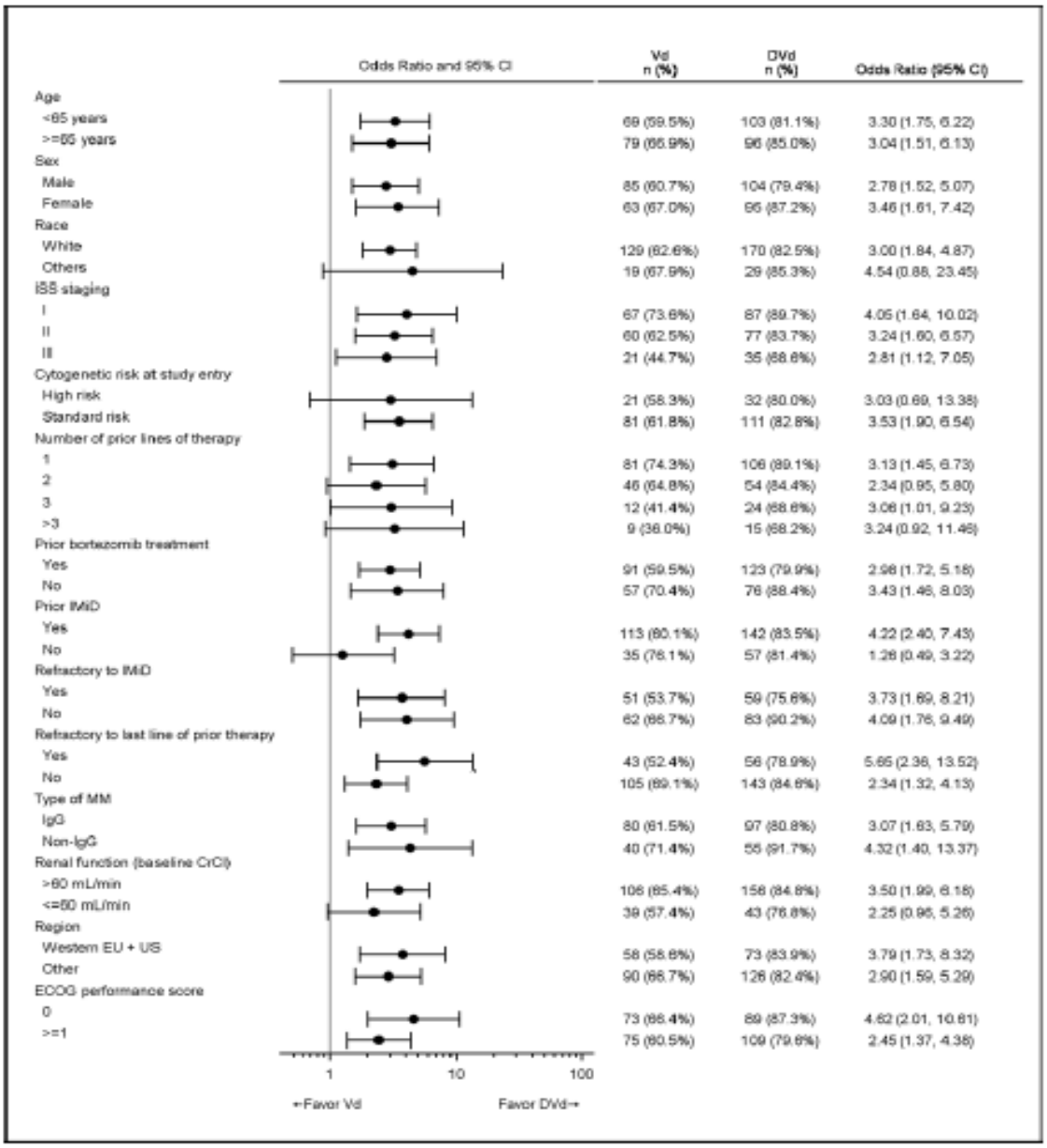
Table 24 Overall best confirmed response based on Computerized Algorithm; Response-evaluable analysis set (Study MMY3004)

	Vd		DVd		Odds Ratio (95% CI)[a]	P-value[b]
	n (%)	95% CI for %	n (%)	95% CI for %		
Analysis set: response-evaluable	234		240			
Response category						
Stringent complete response (sCR)	5 (2.1%)	(0.7%, 4.9%)	11 (4.6%)	(2.3%, 8.1%)		
Complete response (CR)	16 (6.8%)	(4.0%, 10.9%)	35 (14.6%)	(10.4%, 19.7%)		
Very good partial response (VGPR)	47 (20.1%)	(15.1%, 25.8%)	96 (40.0%)	(33.8%, 46.5%)		
Partial response (PR)	80 (34.2%)	(28.1%, 40.7%)	57 (23.8%)	(18.5%, 29.6%)		
Minimal response (MR)	20 (8.5%)	(5.3%, 12.9%)	10 (4.2%)	(2.0%, 7.5%)		
Stable disease	47 (20.1%)	(15.1%, 25.8%)	24 (10.0%)	(6.5%, 14.5%)		
Progressive disease (PD)	16 (6.8%)	(4.0%, 10.9%)	5 (2.1%)	(0.7%, 4.8%)		
Not evaluable (NE)	3 (1.3%)	(0.3%, 3.7%)	2 (0.8%)	(0.1%, 3.0%)		
Overall response (sCR+CR+VGPR+PR)	148 (63.2%)	(56.7%, 69.4%)	199 (82.9%)	(77.5%, 87.5%)	3.13 (1.97, 4.97)	<0.0001
Clinical benefit (Overall response + MR)	168 (71.8%)	(65.6%, 77.5%)	209 (87.1%)	(82.2%, 91.1%)		
VGPR or better (sCR + CR + VGPR)	68 (29.1%)	(23.3%, 35.3%)	142 (59.2%)	(52.7%, 65.4%)	3.99 (2.64, 6.02)	<0.0001
CR or better (sCR + CR)	21 (9.0%)	(5.6%, 13.4%)	46 (19.2%)	(14.4%, 24.7%)	2.53 (1.42, 4.51)	0.0012

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone.
Key: CI = exact confidence interval.
[a] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: ISS (I, II, or III), number of prior lines of therapy (1 vs. 2 or 3 vs. >3), and prior bortezomib treatment (no vs. yes). An odds ratio > 1 indicates an advantage for DVd.
[b] P-value from the Cochran Mantel-Haenszel Chi-Squared test.
Note: Response was assessed by computerized algorithm, based on International Uniform Response Criteria Consensus Recommendations.
Note: Percentages are calculated with the number of subjects in each group as denominator.
Note: Response-evaluable set includes subjects who have a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening. In addition, subjects must have received at least 1 administration of study treatment and have at least 1 post baseline disease assessment.

[TEFRESP01.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\TEFRESP01.SAS] 06APR2016, 10:28

Figure 17 Subgroup analysis on Overall Response rate based on Computerized Algorithm; Response-evaluable analysis set (Study MMY3004)

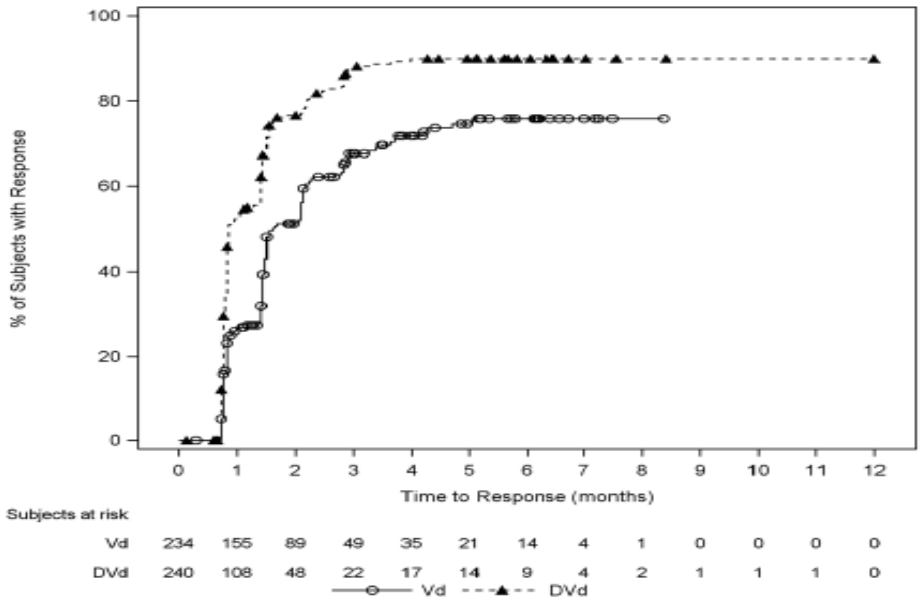


Note: Type of MM subgroup analysis is based on subjects with measurable disease in serum.
Note: Refractory to IMiD subgroup analysis is based on subjects who received prior IMiD therapy.
[GEFRESPFP01.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\GEFRESPFP01.SAS] 20MAY2016, 08:48

Secondary endpoint: Time to response/duration of response

The median time to response was 0.9 months (95% CI: 0.8, 1.4) in the DVd group compared with 1.6 months (95% CI: 1.5, 2.1) for the Vd group (p<0.0001).

Table 25 Kaplan-Meier Plot for Time to response based on Computerized Algorithm; Response evaluable analysis set (Study MMY3004)



[GEFTTR01.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\GEFTTR01.SAS] 05APR2016, 15:00

Table 26 Summary of Duration of Response based on computerized Algorithm, Response-evaluable analysis set (Study MMY3004)

	Vd	DVd
Analysis set: responders (PR or better) in the response-evaluable set	148	199
Duration of response[a]		
Number of events (%)	52 (35.1%)	30 (15.1%)
Number of censored (%)	96 (64.9%)	169 (84.9%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	4.9 (4.3, 5.7)	9.5 (7.9, NE)
Median (95% CI)	7.9 (6.7, 11.3)	NE (11.5, NE)
75% quantile (95% CI)	NE (10.7, NE)	NE (NE, NE)

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone.
Key: CI = confidence interval; PR = partial response; NE = not evaluable.
[a] First response PR or better.
Note: Number of events refers to number of responders (PR or better) who developed disease progression or died due to disease progression.

[TEFDOR01.RTF] [JNJ-54767414\MMY3004\DBR_CSR\RE_CSR\PROD\TEFDOR01.SAS] 05APR2016, 15:01

Seconday endpoint: Minimal residual disease (MRD)

Table 27 MRD Negative rate at 10^{-4} in Bone marrow, Intent-to-Treat analysis set (study MMY3004)

TBMKMRD02D: Summary of MRD Negative Rate at 10^{-4} in Bone Marrow; Intent-to-Treat Analysis Set (Study 54767414MMY3004)		
	Vd	DVd
Analysis set: intent-to-treat	247	251
MRD negative rate (10^{-4})	7 (2.8%)	34 (13.5%)
95% CI[a] of MRD negative rate	(1.1%, 5.8%)	(9.6%, 18.4%)
Odds ratio with 95% CI[b]		5.372 (2.333, 12.368)
P-value[c]		0.000006

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone; CI = exact confidence interval.
[a] Exact 95% confidence interval.
[b] Chi-squared estimate of the common odds ratio is used. An odds ratio > 1 indicates an advantage for DVd.
[c] P-value from likelihood-ratio chi-squared test.

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Secondary endpoint: Overall survival

Table 28 Overall Survival (unstratified analysis), Intent-to-Treat analysis set (study MMY3004)

	Vd	DVd
Analysis set: intent-to-treat	247	251
Overall survival		
Number of events (%)	36 (14.6%)	29 (11.6%)
Number of censored (%)	211 (85.4%)	222 (88.4%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	12.19 (9.69, NE)	NE (11.60, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		0.2975
Hazard ratio (95% CI)[b]		0.77 (0.47, 1.26)
12-month survival rate % (95% CI)	81.9 (74.7, 87.3)	82.2 (71.8, 89.1)
18-month survival rate % (95% CI)	NE (NE, NE)	NE (NE, NE)

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test.
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable. A hazard ratio < 1 indicates an advantage for DVd.

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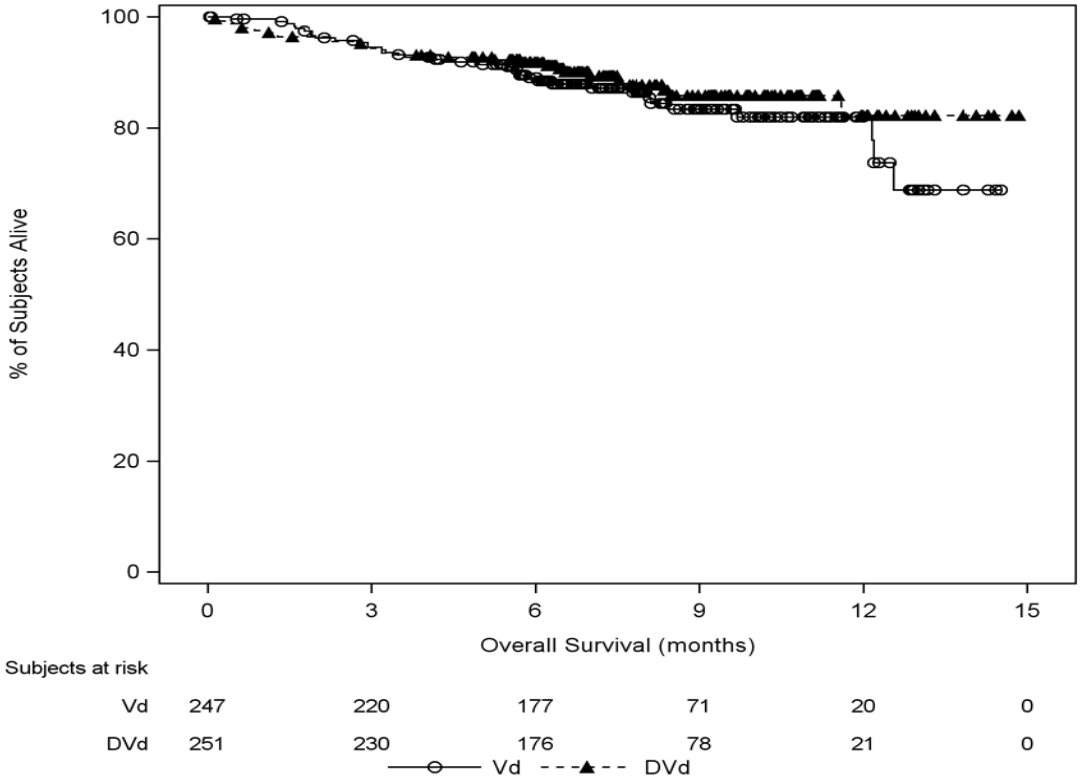
Figure 18. Kaplan-Meier Plot for Overall Survival; Intent-to-Treat Analysis Set (Study MMY3004)



Other efficacy analyses

The time to subsequent antimyeloma therapy was longer for patients in the DVd group compared with patients in the Vd group (HR=0.30, 95% CI: 0.20, 0.45; p<0.0001). The median time to subsequent therapy or death due to progressive disease was not estimable for the DVd group and 9.8 months for the Vd group (data not shown).

Best M-protein Response

The best M-protein response for the response-evaluable population is presented in Table 29.

Table 29 M protein Response, Response-evaluable Analysis Set (study MMY3004)

	Vd n (%)	DVd n (%)
Analysis set: response-evaluable	234	240
Best M-protein response in serum[a,b]		
N	184	178
100% reduction	49 (26.6%)	89 (50.0%)
≥ 90% to < 100% reduction	9 (4.9%)	16 (9.0%)
≥ 50% to < 90% reduction	78 (42.4%)	57 (32.0%)
≥ 25% to < 50% reduction	20 (10.9%)	6 (3.4%)
≥ 90% reduction	58 (31.5%)	105 (59.0%)
≥ 50% reduction	136 (73.9%)	162 (91.0%)
Best M-protein response in urine[a,c]		
N	33	36
100% reduction	12 (36.4%)	21 (58.3%)
≥ 90% to < 100% reduction	4 (12.1%)	3 (8.3%)
≥ 50% to < 90% reduction	8 (24.2%)	8 (22.2%)
≥ 90% reduction	16 (48.5%)	24 (66.7%)
≥ 50% reduction	24 (72.7%)	32 (88.9%)
Best response in serum dFLC[a,d]		
N	14	24
100% reduction	0	0
≥ 90% to < 100% reduction	8 (57.1%)	24 (100.0%)
≥ 50% to < 90% reduction	4 (28.6%)	0
≥ 90% reduction	8 (57.1%)	24 (100.0%)
≥ 50% reduction	12 (85.7%)	24 (100.0%)

Keys: Vd = bortezomib-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone.
Key: dFLC = difference between involved and uninvolved serum free light chain.
[a] The reference point is baseline.
[b] Measured as percent change from baseline in serum M-protein for subjects with measurable heavy chain disease at baseline.
[c] Measures as percent change from baseline in urine M-protein for subjects without measurable heavy chains, but with measurable light chain disease at baseline.
[d] Measures as percent change from baseline in the difference between involved and uninvolved serum FLC for subjects without measurable heavy chains and light chain disease at baseline.
Note: Response-evaluable set includes subjects who have a confirmed diagnosis of multiple myeloma and measurable disease at baseline or screening. In addition, subjects must have received at least 1 administration of study treatment and have at least 1 post baseline disease assessment.

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Patient-reported Outcomes

Functional status and well-being were assessed using PRO measures, the EORTC-QLQ-C30 and the EQ-5D-5L. Compliance was comparable between treatment groups and baseline scores on all subscales were comparable between treatment Groups. The PRO results indicated no statistically significant difference between DVd and Vd in change from baseline or median time to improvement or worsening in the Global Health Status/QOL subscale of the EORTC-QLQ-C30. For nearly all timepoints, no statistically significant differences between DVd and Vd were observed in change from baseline in the EQ-5D-5L Utility Score or EQ-5D-5L VAS and no statistically significant differences were observed between DVd and Vd in median time to worsening or improvement in the Utility Score or VAS (data not shown).

Summary of main studies

The following table 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 30 Summary of Efficacy for study MMY3003

Title: Daratumumab in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy.				
Study identifier	MMY3003			
Design	Open-label, randomised (1:1) multicentre, phase 3			
	Initiation of study Last subject started	16-June-2014 15-July-2015		
Hypothesis	Superiority			
Treatments groups	DRd	*Daratumumab*: C1 to C2 16 mg/kg weekly, C3 to C6 every other week, C7 and beyond every 4 weeks thereafter *Lenalidomide*: 25 mg on Days 1-21 per 28-day cycle *Low Dose Dexamethasone*: 40 mg per week		
	Rd	*Lenalidomide*: 25 mg on Days 1-21 per 28-day cycle *Low Dose Dexamethasone*: 40 mg per week		
Endpoints and definitions	Primary endpoint	PFS	The time from the date of randomization to either progressive disease, according to the IMWG response criteria, or death, whichever occurs first	
	Secondary endpoint	TTP	The time between the date of randomization and the date of first documented evidence of confirmed progressive disease, as defined in the IMWG response criteria, or death due to progressive disease, whichever occurs first	
	Secondary endpoint	ORR	The proportion of subjects who achieve a partial response or better (i.e, PR, VGPR, CR or sCR), according to IMWG response criteria, during or after the study treatment	
	Secondary endpoint	MRD negativity	The proportion of subjects who had negative MRD assessment at any time point after the first dose of study drugs	
Data cut-off	7 March 2016			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (N=569)			
Descriptive statistics and estimate variability/ Effect estimate per comparison	Treatment group		DRd (daratumumab, lenalidomide and dexamethasone)	Rd (lenalidomide and dexamethasone)
	Number of subject		286	283
	PFS, median (months)		NE	18,4 (13.9,NE)
	HR (95%CI) p-value		0.37(0.27, 0.52) p<0.0001	
	TTP, median (months)		NE	18.4 (14.8, NE)
	HR (95%CI) p-value		0.34 (0.23, 0.48) p<0.0001	
	ORR (95% CI) (sCR+CR+VGPR+PR)		89,2%;95.6%	71.0%;81.3%

	Odds ratio	4.6 (2.6;8.2) p<0.0001	
	MRD negative rate (95% CI) (10^{-4})	29.0 (23.8, 34.7)	7.8 (4.9, 11.5)
	Odds ratio with 95% CI	4.85 (2.93, 8.03)	
	p-value	p<0.0001	

Table 31 Summary of Efficacy for study MMY3004

Title: Daratumumab in combination with bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy.			
Study identifier	MMY3004		
Design	Open-label, randomised (1:1), multicentre, phase 3 study		
	Initiation of study Last subject started		24-Sept-2014 5-Oct-2015
Hypothesis	Superiority		
Treatments groups	DVd		***Daratumumab*****:** 16 mg/kg weekly C1-3, C 4-8 every 3 weeks, then C9 and beyond every 4 weeks ***Bortezomib*****:** 1.3 mg/m2 Days 1, 4, 8 and 11 of each 21-day cycle for 8 cycles ***Dexamethasone***: 80 mg per week in 2 out of 3 weeks for the first 8 cycles
	Vd		*Bortezomib*: 1.3 mg/m2 Days 1, 4, 8 and 11 of each 21-day cycle for 8 cycles *Dexamethasone*a: 80 mg per week in 2 out of 3 weeks for the first 8 cycles
Endpoints and definitions	Primary endpoint	PFS	The time from the date of randomization to either progressive disease, according to the IMWG response criteria, or death, whichever occurs first
	Secondary endpoint	TTP	The time between the date of randomization and the date of first documented evidence of confirmed progressive disease, as defined in the IMWG response criteria, or death due to progressive disease, whichever occurs first
	Secondary endpoint	ORR	The proportion of subjects who achieve a partial response or better (ie, PR, VGPR, CR or sCR), according to IMWG response criteria, during or after the study treatment
	Secondary endpoint	MRD negativity	The proportion of subjects who had negative MRD assessment at any time point after the first dose of study drugs
Database cut-off	11-Jan-2016		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat Intent to treat (N=498)		
Descriptive statistics and estimate variability/ Effect estimate per comparison	Treatment group	DVd (daratumumab, bortezomib and dexamethasone)	Vd (bortezomib and dexamethasone)
	Number of subject	251	247
	PFS, median (months)	NE	7.2 (6.2;7.9)

	HR (95%CI) p-value	0.39 (0.28;0.53) p<0.0001	
	TTP, median (months)	NE	7.3(6.4;8.1)
	HR (95%CI) p-value	0.30(0.21;0.43) p<0.0001	
	ORR (95% CI) (sCR+CR+VGPR+PR)	77.5%;87.5%	56.7%;69.4%
	Odds ratio p-value	3.13(1.97;4.97) p<0.0001	
	MRD negative rate (95%CI) (10^{-4})	13.5%	2.8%
	p-value	p<0.0001	

Analysis performed across trials (pooled analyses and meta-analysis)

N/A.

Clinical studies in special populations

N/A.

Supportive studies

Study MMY1001

The study MMY1001 was designed to evaluate daratumumab in combination with various background therapies, in this application the combination of daratumumab with pomalidomide and dexamethasone (DPd) was investigated. Additional data from bortezomib-containing cohorts are included in the pharmacokinetic and immunogenicity analyses. After a median duration of follow-up of 9.8 months, the median DOR was 13.6 months. At the time of the clinical cut-off, 48% of subjects had experienced PFS events; median PFS was 10.4 months. The median OS was not reached, but based on the Kaplan-Meier estimate, the 12-month OS rate was 72%.

Table 32 Overall Best Response based on IDSMB Assessment: Daratumumab+ Pomalidomide and Dexamethasone treated (study MMY1001)

	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.
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Study GEN503

The study GEN503 had 2 phases, phase 1 was a dose escalation study evaluating 4 doses of daratumumab (2-16 mg/kg), data are included in the pharmacokinetic and immunogenicity analyses. Patients in phase 2 received daratumumab with lenalidomide and dexamethasone (DRd). The ORR in the DRd group was 81%, consistent with the DRd group in Study MMY3003. Sixty-three percent of subjects had a response of VGPR

or better. After a median duration of follow-up of 23.0 months, the median DOR was not reached. The median TTP was not reached, but 72% of the patients remained progression-free after 18 months. The median OS was not reached and the 18-month OS rate based on Kaplan-Meier estimate was 90%.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Both the MMY3003 and the MMY3004 studies were large randomized, controlled open-label Phase 3 study where daratumumab was added to 2 different current standard of care regimens in multiple myeloma. For the MMY3003, daratumumab was added to lenalidomide + dexamethasone and compared with lenalidomide + dexamethasone alone and in the MMY3004 study, daratumumab was added to bortezomib + dexamethasone and compared with bortezomib + dexamethasone. Both studies included patients with relapsed or refractory multiple myeloma who have received at least 1 prior therapy. The study design was appropriate, as were the primary endpoint (PFS) and the secondary clinical endpoints. The clinical response was assessed based on IMWG criteria validated by computerized algorithm with 3 stratification factors: number of prior lines of therapy (1 vs. 2 and 2 vs. >3), ISS score at screening and whether subjects had received prior lenalidomide/bortezomib treatment (no vs. yes) which is endorsed.

The study population with its baseline characteristics reflected the target population as well as all patients had received at least one, and up to 10-11 prior therapies generally accepted in this population and clinical setting. The inclusion and exclusion criteria adequately defined the population covered by the proposed indication. The final inclusion criteria for IgG Multiple Myeloma is a serum M-protein of ≥1 g/dL, for other types of Multiple Myeloma, IgA, IgD, IgE and IgM, the serum M-protein is ≥0.5 g/dL.

Selection of the dose regimens for daratumumab was based on previous monotherapy data and available preliminary data from Study GEN503, where the dose of daratumumab monotherapy, 16 mg/kg in relapsed/refractory multiple myeloma, was approved weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter, administered intravenously until disease progression or unacceptable toxicity. The dosing schedule of daratumumab in the two combinations was adapted to align with the schedule of background therapies, this is considered acceptable.

Efficacy data and additional analyses

Study MMY3003

The primary efficacy analysis of PFS showed a statistically significant 63% reduction in the risk of disease progression or death for subjects, when daratumumab was added to the lenalidomide + dexamethasone regimen in subjects with relapsed or refractory multiple myeloma and compared with lenalidomide + dexamethasone alone (MMY3003) (HR=0.37; 95% CI: 0.27 to 0.52; p<0.0001). The median PFS was 18.4 months for the Rd group and was not reached for the DRd group. Sensitivity analyses of PFS were consistent across all prespecified subgroups of subjects tested.

The secondary efficacy analyses of TTP showed a statistically significant improvement for the DRd group (HR=0.34; 95% CI: 0.23 to 0.48) (p<0.0001). The ORR was also significantly improved in the DRd group, 93% versus 76%; p<0.0001. The rate of VGPR or better was 76% vs. 44%; p<0.0001, and rate of CR or better also showed significant improvements for subjects treated with DRd, 43% versus 19%; p<0.0001. The MRD negativity rate at 10^{-4} was significantly higher in subjects treated with DRd compared with those who received Rd, 29% versus 8%, p<0.0001. This data indicates a robust response. The ORRs and rates of VGPR or better for subgroups of subjects were consistent across the subgroups tested and showed an improvement for all subgroups for subjects in the DRd group. Daratumumab also induced more durable responses with the median duration of response not estimable (lower limit of the 95% CI was not estimable) for the DRd group versus 17.4 months for the Rd group. As of the clinical cutoff date of 7 March 2016,

median OS was not reached for either treatment group. The 18-month overall survival rate was 86.1% (95% CI: 79.9, 90.5) in the DRd group and 75.6% (95% CI: 59.8, 85.9) in the Rd group.

No statistically significant difference was observed between DRd and Rd in change from baseline or median time to improvement or worsening in the Global Healts Status/QOL subscale of the EORTC-QLQ-C30 or the EQ-5D-5L Utility score or EQ-5D-5L Visual Analog Scale (VAS) data.

Study MMY3004

When daratumumab was added to the bortezomib + dexamethasone regimen improved and compared to bortezomib + dexamethasone alone, the primary objective was met, PFS showed a 61% reduction in the risk of disease progression or death for subjects treated with DVd versus Vd (HR=0.39; 95% CI: 0.28, 0.53; p<0.0001). The median PFS was not reached for the DVd group and was 7.2 months for the Vd group. As in the MMY3003 study, the PFS results were consistent for all sensitivity analyses and across all subgroups of subjects tested.

Results of secondary efficacy analyses were supportive in improving TTP for the DVd group (HR=0.30; 95% CI: 0.21, 0.43) (p<0.0001). The effect on ORR was higher in the DVd group (83% versus 63%; p<0.0001). The rate of VGPR or better (59% versus 29%; p<0.0001), and rate of CR or better (19% versus 9.0%; p=0.0012) showed significant improvements for patients who received treatment with DVd. The ORRs and rates of VGPR or better for subgroups of subjects were consistent across the subgroups tested. Additionally, the MRD negativity rate at the 10-4 threshold was significantly higher in subjects treated with DVd compared with subjects treated with Vd (14% versus 3%, p<0.0001).

The effect of adding daratumumab seemed robust and deep, with the median duration of response of 7.9 months for the Vd group compared to not estimable (lower limit of the 95% CI was 11.5 months) for the DVd group. The time to subsequent therapy for multiple myeloma was 9.8 months in the Rd group compared with not estimable for the DRd group (HR= 0.30; p<0.0001). As of the clinical cutoff date of 11 January 2016, median OS was not reached for either treatment group.

Regarding the patient-reported outcomes for nearly all time points, no statistically significant differences between DVd and Vd were observed in change from baseline in the EQ-5D-5L Utility Score or EQ-5D-5L VAS and no statistically significant differences were observed between DVd and Vd in median time to worsening or improvement in the Utility Score or VAS.

During the assessment, the CHMP raised a major objection about the indication ''Daratumumab in the treatment of adult patients with multiple myeloma, who have received at least 1 prior therapy'' requesting for its restriction to include the combination treatments.

2.4.4. Conclusions on the clinical efficacy

Based on the results of studies MMY3003 and MMY3004 a PFS HR of 0.37 and 0.39 indicate a clinical benefit of adding daratumumab to standard of care regimens lenaliomide+dexamethasone and bortezomib+dexamethasone in relapsed and refractory multiple myeloma patients who have received at least one prior therapy.

2.5. Clinical safety

Introduction

The assessment of safety was based on safety data from 4 studies (two Phase 3 studies and two Phase 1/2 studies). Safety data from a total of 1182 subjects are summarized; 664 subjects received daratumumab in combination with standard background therapies and 518 subjects received background therapies alone.

- Phase 3 Study MMY3003 (n=564), where daratumumab (D) was administered in combination with lenalidomide and low-dose dexamethasone (Rd) (DRd=283 versus Rd=281)
- Phase 3 Study MMY3004 (n=480), where daratumumab was administered in combination with bortezomib and dexamethasone (Vd) (DVd=243 versus Vd=237)
- Phase 1b Study MMY1001 (n=103), cohort of daratumumab in combination with pomalidomide and dexamethasone (DPd)
- Phase 1/2 Study GEN503 (n=35), treatment group of daratumumab 16 mg/kg in combination with Rd; data from these subjects were pooled with the subjects receiving DRd in Study MMY3003.

From these 4 studies, 664 subjects were treated with daratumumab in combination with background therapy and 518 were treated with background therapy alone. Data from all subjects in the Phase 3 Studies MMY3003 and MMY3004 are presented in Table 33. In the Phase 1/2 studies, only data from subjects who received 16 mg/kg daratumumab in Study GEN503 or who received daratumumab in combination with pomalidomide-dexamethasone in Study MMY1001 are included in the safety analysis.

Table 33 Data included in the Summary of Clinical Safety

Study	Subject Data Included in SCS	
	Background Therapy	Daratumumab + Background Therapy
Phase 3 Studies		
MMY3004	237 (Vd)	243 (DVd)
MMY3003	281 (Rd)	283 (DRd)
Phase 1/2 Studies		
MMY1001		103 (DPd)
GEN503		35 (DRd)
TOTAL N	**518**	**664**

Due to similarities in subject population (relapsed/refractory multiple myeloma with at least 1 prior therapy) and study drugs administered (16 mg/kg daratumumab in combination with Rd), data from the DRd groups in Study MMY3003 and Study GEN503 were pooled. For subgroup analyses and AEs of interest, subjects receiving daratumumab in all 4 studies (n=664) were pooled for the all-daratumumab population.

Patient exposure

Results on treatment duration and exposure for patients included in the safety analysis set are summarized in

Table 34.

Table 34 Summary of treatment duration and exposure; Safety analysis Set (studies: MMY3003, MMY3004, MMY1001 and GEN503)

	MMY3004		MMY3003+GEN503		MMY1001
	Vd	DVd	Rd	DRd	DPd
Analysis set: safety	237	243	281	318	103
Duration of treatment (month)					
N	237	243	281	318	103
Mean (SD)	4.192 (1.6909)	6.711 (3.0154)	10.591 (4.9213)	12.505 (4.4630)	6.324 (4.5097)
Median	5.224	6.472	12.287	13.306	6.012
Range	(0.16; 8.02)	(0.03; 14.78)	(0.23; 20.14)	(0.03; 24.54)	(0.03; 16.89)
< 1 month	15 (6.3%)	16 (6.6%)	13 (4.6%)	8 (2.5%)	15 (14.6%)
>=1 - < 3 months	42 (17.7%)	14 (5.8%)	13 (4.6%)	12 (3.8%)	16 (15.5%)
>=3 - < 6 months	171 (72.2%)	72 (29.6%)	39 (13.9%)	16 (5.0%)	20 (19.4%)
>=6 - < 9 months	9 (3.8%)	82 (33.7%)	29 (10.3%)	20 (6.3%)	17 (16.5%)
>=9 - < 12 months	0	49 (20.2%)	39 (13.9%)	42 (13.2%)	21 (20.4%)
>=12 months	0	10 (4.1%)	148 (52.7%)	220 (69.2%)	14 (13.6%)
Total daratumumab dose received (mg/kg)					
N	0	243	0	318	103
Mean (SD)	-	235.82 (78.613)	-	358.70 (98.326)	223.90 (120.704)
Median	-	249.09	-	384.00	223.11
Range	-	(0.4; 386.5)	-	(0.8; 554.6)	(0.2; 448.0)
Total number of daratumumab infusions					
N	0	243	0	318	103
Mean (SD)	-	14.8 (4.88)	-	22.6 (6.20)	14.0 (7.56)
Median	-	16.0	-	24.0	14.0
Range	-	(1; 24)	-	(1; 36)	(1; 28)
Daratumumab relative dose intensity (%)					
N	0	243	0	318	103
Mean (SD)	-	93.36 (14.340)	-	95.66 (11.681)	90.12 (17.474)
Median	-	99.16	-	99.42	96.82
Range	-	(0.8; 105.3)	-	(1.2; 104.9)	(1.3; 104.8)
Bortezomib/Lenalidomide/Pomalidomide relative dose intensity (%)					
N	237	242	280	317	97
Mean (SD)	87.11 (15.237)	81.75 (19.128)	85.90 (18.417)	79.25 (22.483)	74.69 (21.614)
Median	93.48	86.54	95.77	90.87	77.50
Range	(32.7; 112.2)	(25.2; 103.6)	(16.8; 100.0)	(13.2; 100.0)	(5.7; 100.0)
Dexamethasone relative dose intensity (%)[a]					
N	237	243	281	283	103
Mean (SD)	91.00 (15.833)	87.35 (18.848)	99.38 (4.253)	99.00 (4.290)	84.60 (17.891)
Median	100.00	98.18	100.00	100.00	90.00
Range	(20.6; 104.7)	(20.3; 103.1)	(50.0; 104.2)	(63.9; 111.3)	(14.3; 106.3)

Key: D=Daratumumab, Vd=bortezomib-dexamethasone, Rd=lenalidomide-dexamethasone, Pd=pomalidomide-dexamethasone.
Rd is only from MMY3003.
Note: Percentages are calculated with the number of subjects in each group as denominator.
Note: MMY3004: Vd arm treated for 8 cycles and DVd arm treated until PD per protocol.
[a]GEN503 was excluded as relative dose intensity is hard to calculate due to the complexity on the planned dexamethasone dose.

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Adverse events

Common AEs

Only the TEAEs defined as: any AE with an onset date and time on or after that of the first dose of study drug through 30 days after the last study drug administration or any AE that was considered related to study drug regardless of the start date of the event were summarized. The severity of TEAEs was assessed using National Cancer Institute Common Terminology Criteria (NCI-CTC). Adverse event terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0 and were summarized by system organ class (SOC) and preferred term (PT) in table presentations.

Adverse events were summarized by frequency counts and percentages of subjects with a particular event. An exposure-adjusted analysis was performed for adverse events in the System Organ Class (SOC) of Infections and Infestations.

The adverse event profile for daratumumab in combination with background therapies demonstrates a manageable side effect profile as summarized below:

- Discontinuations and deaths due to TEAEs were low and balanced in the randomized studies.

- The most frequently reported TEAEs across treatment groups were cytopenias. Daratumumab may increase cytopenias associated with background therapies, with thrombocytopenia the most common preferred term reported for subjects receiving bortezomib-based regimens and neutropenia the most common preferred term reported for subjects receiving lenalidomide- or pomalidomide-based regimens.

- IRRs were reported in approximately half of subjects; mainly Grade 1 or 2. Most IRRs occurred during the first infusion only, and rarely led to treatment discontinuation.

- Although the overall incidence of infections were reported by a higher percentage of subjects in the daratumumab containing groups compared to the respective background therapy, the majority of all infections were mild (Grade 1 or 2) and did not require hospitalization.

    - The incidence of Grade 3 or 4 infection was similar between the daratumumab combinations and the background therapies, with the most common being pneumonia.
    - Discontinuations from treatment and deaths due to infection were low and balanced between groups.

- Second primary malignancies (SPM) were reported at a low frequency in the daratumumab combination groups (<4%).

Frequently reported TEAEs (by at least 10% of subjects in any treatment group) are summarized in Table 356 below.

Table 35 Number of Subjects with 1 or More TEAE with frequency of at least 10% in either treatment group by MedDRA System-Organ Class and Preferred Term: Safety Analysis Set (studies MMY3003, MMY3004, MMY1001 and GEN503)

Table 7: Number of Subjects With 1 or More Treatment-emergent Adverse Events With Frequency of at Least 10% in Either Treatment Group by MedDRA System-Organ Class and Preferred Term; Safety Analysis Set (Studies: MMY3003, MMY3004, MMY1001 and GEN503)

	MMY3004		MMY3003+GEN503		MMY1001
	Vd	DVd	Rd	DRd	DPd
Analysis set: safety	237	243	281	318	103
Total number of subjects with TEAE	226 (95.4%)	240 (98.8%)	274 (97.5%)	313 (98.4%)	103 (100.0%)
MedDRA system organ class / Preferred term					
Infections and infestations	126 (53.2%)	164 (67.5%)	204 (72.6%)	265 (83.3%)	72 (69.9%)
Upper respiratory tract infection	43 (18.1%)	60 (24.7%)	58 (20.6%)	98 (30.8%)	26 (25.2%)
Nasopharyngitis	9 (3.8%)	17 (7.0%)	43 (15.3%)	76 (23.9%)	8 (7.8%)
Bronchitis	13 (5.5%)	28 (11.5%)	34 (12.1%)	46 (14.5%)	10 (9.7%)
Pneumonia	28 (11.8%)	29 (11.9%)	37 (13.2%)	41 (12.9%)	11 (10.7%)
Respiratory tract infection	3 (1.3%)	0	22 (7.8%)	33 (10.4%)	0
Sinusitis	3 (1.3%)	10 (4.1%)	10 (3.6%)	19 (6.0%)	13 (12.6%)
Gastrointestinal disorders	110 (46.4%)	143 (58.8%)	164 (58.4%)	242 (76.1%)	81 (78.6%)
Diarrhoea	53 (22.4%)	77 (31.7%)	69 (24.6%)	136 (42.8%)	39 (37.9%)
Constipation	37 (15.6%)	48 (19.8%)	71 (25.3%)	90 (28.3%)	34 (33.0%)
Nausea	26 (11.0%)	34 (14.0%)	40 (14.2%)	77 (24.2%)	31 (30.1%)
Vomiting	9 (3.8%)	26 (10.7%)	15 (5.3%)	51 (16.0%)	22 (21.4%)
Blood and lymphatic system disorders	135 (57.0%)	163 (67.1%)	184 (65.5%)	231 (72.6%)	91 (88.3%)
Neutropenia	22 (9.3%)	43 (17.7%)	121 (43.1%)	197 (61.9%)	81 (78.6%)
Anaemia	74 (31.2%)	64 (26.3%)	98 (34.9%)	97 (30.5%)	54 (52.4%)
Thrombocytopenia	104 (43.9%)	143 (58.8%)	77 (27.4%)	86 (27.0%)	42 (40.8%)
Leukopenia	11 (4.6%)	19 (7.8%)	17 (6.0%)	28 (8.8%)	38 (36.9%)
Lymphopenia	9 (3.8%)	32 (13.2%)	15 (5.3%)	21 (6.6%)	22 (21.4%)
General disorders and administration site conditions	123 (51.9%)	131 (53.9%)	156 (55.5%)	226 (71.1%)	82 (79.6%)
Fatigue	58 (24.5%)	52 (21.4%)	78 (27.8%)	112 (35.2%)	51 (49.5%)
Pyrexia	27 (11.4%)	38 (15.6%)	31 (11.0%)	67 (21.1%)	26 (25.2%)
Oedema peripheral	19 (8.0%)	40 (16.5%)	37 (13.2%)	54 (17.0%)	16 (15.5%)
Asthenia	37 (15.6%)	21 (8.6%)	36 (12.8%)	50 (15.7%)	15 (14.6%)
Chills	3 (1.3%)	11 (4.5%)	9 (3.2%)	18 (5.7%)	21 (20.4%)
Non-cardiac chest pain	1 (0.4%)	1 (0.4%)	5 (1.8%)	11 (3.5%)	15 (14.6%)
Pain	5 (2.1%)	9 (3.7%)	4 (1.4%)	4 (1.3%)	11 (10.7%)
Respiratory, thoracic and mediastinal disorders	77 (32.5%)	130 (53.5%)	114 (40.6%)	196 (61.6%)	80 (77.7%)
Cough	30 (12.7%)	58 (23.9%)	35 (12.5%)	99 (31.1%)	37 (35.9%)
Dyspnoea	21 (8.9%)	45 (18.5%)	32 (11.4%)	56 (17.6%)	31 (30.1%)
Nasal congestion	3 (1.3%)	12 (4.9%)	4 (1.4%)	16 (5.0%)	16 (15.5%)
Productive cough	3 (1.3%)	9 (3.7%)	8 (2.8%)	16 (5.0%)	12 (11.7%)
Musculoskeletal and connective tissue disorders	87 (36.7%)	111 (45.7%)	154 (54.8%)	187 (58.8%)	74 (71.8%)
Muscle spasms	5 (2.1%)	19 (7.8%)	52 (18.5%)	90 (28.3%)	27 (26.2%)
Back pain	24 (10.1%)	33 (13.6%)	48 (17.1%)	57 (17.9%)	26 (25.2%)
Arthralgia	11 (4.6%)	23 (9.5%)	21 (7.5%)	26 (8.2%)	23 (22.3%)
Pain in extremity	16 (6.8%)	22 (9.1%)	30 (10.7%)	26 (8.2%)	15 (14.6%)
Bone pain	14 (5.9%)	14 (5.8%)	12 (4.3%)	24 (7.5%)	13 (12.6%)
Musculoskeletal chest pain	5 (2.1%)	16 (6.6%)	17 (6.0%)	16 (5.0%)	13 (12.6%)
Nervous system disorders	131 (55.3%)	153 (63.0%)	124 (44.1%)	160 (50.3%)	62 (60.2%)
Headache	14 (5.9%)	25 (10.3%)	19 (6.8%)	43 (13.5%)	17 (16.5%)
Peripheral sensory neuropathy	89 (37.6%)	115 (47.3%)	19 (6.8%)	31 (9.7%)	8 (7.8%)
Tremor	8 (3.4%)	3 (1.2%)	24 (8.5%)	28 (8.8%)	20 (19.4%)
Dizziness	24 (10.1%)	24 (9.9%)	24 (8.5%)	24 (7.5%)	22 (21.4%)
Neuralgia	26 (11.0%)	33 (13.6%)	3 (1.1%)	4 (1.3%)	1 (1.0%)
Metabolism and nutrition disorders	66 (27.8%)	93 (38.3%)	95 (33.8%)	127 (39.9%)	49 (47.6%)
Decreased appetite	12 (5.1%)	22 (9.1%)	29 (10.3%)	34 (10.7%)	11 (10.7%)
Hypokalaemia	11 (4.6%)	22 (9.1%)	22 (7.8%)	33 (10.4%)	16 (15.5%)
Hyperglycaemia	18 (7.6%)	21 (8.6%)	19 (6.8%)	27 (8.5%)	13 (12.6%)
Skin and subcutaneous tissue disorders	32 (13.5%)	49 (20.2%)	83 (29.5%)	125 (39.3%)	39 (37.9%)
Rash	7 (3.0%)	13 (5.3%)	29 (10.3%)	38 (11.9%)	3 (2.9%)
Pruritus	3 (1.3%)	5 (2.1%)	29 (10.3%)	29 (9.1%)	10 (9.7%)
Psychiatric disorders	53 (22.4%)	67 (27.6%)	93 (33.1%)	106 (33.3%)	47 (45.6%)
Insomnia	35 (14.8%)	41 (16.9%)	55 (19.6%)	60 (18.9%)	24 (23.3%)
Anxiety	6 (2.5%)	3 (1.2%)	12 (4.3%)	18 (5.7%)	13 (12.6%)

Key: D=Daratumumab, Vd=bortezomib-dexamethasone, Rd=lenalidomide-dexamethasone, Pd=pomalidomide-dexamethasone.
Keys: TEAE = treatment-emergent adverse event.
Rd is only from MMY3003.
Note: Percentages are calculated with the number of subjects in each group as denominator.

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Grade 3 or 4 TEAEs that occurred in at least 5% of subjects in any treatment group are summarized in Table 36 below.

Table 36 Number of subjects with 1 or more Toxicity Grade 3 or 4 TEAE with frequency of at least 5% in either treatment group by MedDRA System- Organ Class and Preferred Term, Safety Analysis Set (studies: MMY3003, MMY3004, MMY1001 and GEN503)

	MMY3004		MMY3003+GEN503		MMY1001
	Vd	DVd	Rd	DRd	DPd
Analysis set: safety	237	243	281	318	103
Total number of subjects with toxicity grade 3 or 4 TEAE	148 (62.4%)	185 (76.1%)	206 (73.3%)	260 (81.8%)	102 (99.0%)
MedDRA system organ class/Preferred term					
Blood and lymphatic system disorders	94 (39.7%)	131 (53.9%)	145 (51.6%)	191 (60.1%)	87 (84.5%)
Neutropenia	10 (4.2%)	31 (12.8%)	104 (37.0%)	174 (54.7%)	79 (76.7%)
Thrombocytopenia	78 (32.9%)	110 (45.3%)	38 (13.5%)	40 (12.6%)	18 (17.5%)
Anaemia	38 (16.0%)	35 (14.4%)	55 (19.6%)	39 (12.3%)	28 (27.2%)
Lymphopenia	6 (2.5%)	23 (9.5%)	10 (3.6%)	19 (6.0%)	14 (13.6%)
Febrile neutropenia	1 (0.4%)	4 (1.6%)	7 (2.5%)	17 (5.3%)	7 (6.8%)
Leukopenia	4 (1.7%)	5 (2.1%)	7 (2.5%)	11 (3.5%)	25 (24.3%)
Infections and infestations	45 (19.0%)	52 (21.4%)	64 (22.8%)	86 (27.0%)	29 (28.2%)
Pneumonia	23 (9.7%)	20 (8.2%)	23 (8.2%)	23 (7.2%)	8 (7.8%)
Metabolism and nutrition disorders	24 (10.1%)	33 (13.6%)	27 (9.6%)	43 (13.5%)	16 (15.5%)
Hyperglycaemia	6 (2.5%)	8 (3.3%)	9 (3.2%)	10 (3.1%)	6 (5.8%)
General disorders and administration site conditions	22 (9.3%)	19 (7.8%)	21 (7.5%)	36 (11.3%)	15 (14.6%)
Fatigue	8 (3.4%)	11 (4.5%)	7 (2.5%)	18 (5.7%)	10 (9.7%)
Respiratory, thoracic and mediastinal disorders	11 (4.6%)	27 (11.1%)	18 (6.4%)	27 (8.5%)	19 (18.4%)
Dyspnoea	2 (0.8%)	9 (3.7%)	2 (0.7%)	9 (2.8%)	7 (6.8%)
Gastrointestinal disorders	9 (3.8%)	18 (7.4%)	16 (5.7%)	26 (8.2%)	8 (7.8%)
Diarrhoea	3 (1.3%)	9 (3.7%)	9 (3.2%)	16 (5.0%)	3 (2.9%)
Nervous system disorders	25 (10.5%)	23 (9.5%)	15 (5.3%)	21 (6.6%)	13 (12.6%)
Peripheral sensory neuropathy	16 (6.8%)	11 (4.5%)	1 (0.4%)	2 (0.6%)	2 (1.9%)
Vascular disorders	11 (4.6%)	21 (8.6%)	8 (2.8%)	19 (6.0%)	6 (5.8%)
Hypertension	2 (0.8%)	16 (6.6%)	1 (0.4%)	12 (3.8%)	3 (2.9%)
Musculoskeletal and connective tissue disorders	12 (5.1%)	18 (7.4%)	18 (6.4%)	18 (5.7%)	18 (17.5%)
Back pain	3 (1.3%)	3 (1.2%)	4 (1.4%)	4 (1.3%)	6 (5.8%)
Injury, poisoning and procedural complications	5 (2.1%)	7 (2.9%)	9 (3.2%)	5 (1.6%)	10 (9.7%)
Fall	0	0	1 (0.4%)	0	6 (5.8%)

Key: D=Daratumumab, Vd=bortezomib-dexamethasone, Rd=lenalidomide-dexamethasone, Pd=pomalidomide-dexamethasone.
Keys: TEAE = treatment-emergent adverse event.
Rd is only from MMY3003.
Note: Adverse events are reported using MedDRA version 18.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.
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Drug-related Adverse Events

For adverse drug reactions summarized across daratumumab monotherapy studies (16 mg/kg daratumumab, n=156) and combination studies (all-daratumumab population, n=664), assessment of ADR terms was based on the terms identified in the randomized controlled studies. The occurrence of ADRs summarized across daratumumab monotherapy and combination studies (n=820) is provided in Table 37 (see also section 4.8 of the SmPC).

Table 37 Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg

	All Grades	All Grades	Grade 3-4
Infections and infestations			
Upper respiratory tract infection*	Very Common	52%	5%
Pneumonia*	Very Common	16%	10%
Influenza	Common	5%	1%**
Blood and lymphatic system disorders			
Neutropenia	Very Common	44%	37%
Thrombocytopenia	Very Common	37%	23%
Anaemia	Very Common	31%	16%
Lymphopenia	Very Common	10%	8%
Nervous system disorders			
Peripheral sensory neuropathy	Very Common	20%	2%**
Headache	Very Common	13%	< 1%**
Cardiac disorders			
Atrial fibrillation	Common	3%	1%
Respiratory, thoracic and mediastinal disorders			
Cough*	Very Common	31%	< 1%**
Dyspnoea*	Very Common	22%	3%
Gastrointestinal disorders			
Diarrhoea	Very Common	34%	4%
Nausea	Very Common	22%	1%**
Vomiting	Very Common	15%	1%**
Musculoskeletal and connective tissue disorders			
Muscle spasms	Very Common	18%	< 1%**
General disorders and administration site conditions			
Fatigue	Very Common	34%	5%
Pyrexia	Very Common	20%	1%**
Oedema peripheral*	Very Common	19%	1%**

**No grade 4
*Indicates a grouping of preferred terms.
Note: Based on 820 multiple myeloma patients treated with DARZALEX 16 mg/kg.

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In the DVd group, the most frequently reported TEAEs that the investigator considered related to daratumumab were thrombocytopenia (30%), dyspnea (13%), and cough, lymphopenia, and fatigue (11% each). The most frequently reported TEAEs that the investigator considered related to other study drugs were thrombocytopenia (DVd: 51%, Vd: 34%) and peripheral sensory neuropathy (DVd: 47%, Vd: 35%).

In the DRd group, the most frequently reported TEAEs that the investigator considered related todaratumumab were neutropenia (19%), cough (14%), fatigue (12%), and dyspnea and diarrhea (11% each). The most frequently reported TEAEs that the investigator considered related to other study drugs were neutropenia (DRd: 58%, Rd: 38%), fatigue (DRd: 29%, Rd: 20%) and diarrhea (DRd: 29%, Rd: 11%).

In the DPd cohort, the most frequently reported TEAEs that the investigator considered related to daratumumab were neutropenia (44%), anemia (31%), thrombocytopenia (26%), leukopenia (25%), lymphopenia (16%), cough (14%), fatigue (12%), and dyspnea and diarrhea (11% each).

Adverse Events of Special Interest (AESI)

Infusions related reactions

As was observed with daratumumab monotherapy, infusion related reactions (IRR) were frequently observed among the daratumumab-treated subjects in the combination studies. In all 4 studies, 47% of the 664 subjects who received daratumumab experienced an IRR. The vast majority of IRRs occurred during the first infusion and most subjects had IRRs only once at the first infusion and did not continue to experience IRRs with subsequent infusions. Only 3% of subjects had an IRR in more than 1 infusion. The majority of IRRs were mild (Grade 1 or 2). Grade 3 IRRs were reported by 6% of subjects. No Grade 4 or 5 IRRs

occurred. Infusion–related reactions were managed with supportive medications, a pause in infusion or a decrease in infusion rate, and did not usually result in treatment discontinuation.

The most frequently reported AE terms used to describe IRRs were respiratory disorders: dyspnea (10%), cough (9%), and bronchospasm (5%). Other common IRRs were chills (6%), nausea (5%), and vomiting (5%). The most frequently reported Grade 3 IRRs were hypertension (2%), dyspnea (1%), and bronchospasm (1%).

Of the 315 subjects who experienced IRRs, 307 subjects (97%) had the reaction during their first infusion. Nine subjects (1%) had an IRR in their second infusion and 21 subjects (3%) in subsequent infusions. The range of AE terms used to describe IRRs was similar between those that occurred in the first, second, and subsequent infusions. The median time to onset of an IRR was 85 minutes while delayed IRRs (onset more than 24 hours after start of infusion) were rare and only reported in two subjects. One subject with Grade 2 pyrexia after about 1 day and one subject with Grade 1 pruritus after about 3 days.

Pre-infusion medications required to manage infusion reactions included antihistamines, analgesics, and corticosteroids before each daratumumab infusion. In all 3 daratumumab containing treatment groups, 100% of subjects received an antihistamine, usually diphenhydramine, chlorpheniramine, dexchlorpheniramine, or clemastine. All but 1 subject in the DRd group and 2 subjects in the DVd group received paracetamol. The cortisteroids were administered per protocol as part of the background therapy.

In addition to regular administration of background corticosteroids as part of post-infusion medications, subjects at higher risk for respiratory complications were also recommended to use additional post-infusion medication. Only a small percentage of subjects were treated with such post-infusion medications. In the DRd and DVd groups, 6% to 7% of subjects received an antihistamine and 2% of subjects received salbumatol. Such post-infusion medications were not used by any subjects in the DPd cohort.

Treatment modifications in response to IRR included infusion interruption, infusion aborted/drug withdrawn, or infusion rate decrease. Nearly all subjects who experienced IRRs (280/315) had their infusion interrupted, aborted (or drug withdrawn in GEN503), or the infusion rate decreased. The TEAEs that led to infusion modifications, are nearly the same as the ones already identified as IRRs.

Neutropenia

More subjects receiving daratumumab combination therapy reported neutropenia compared to background therapy alone (DVd: 18%, Vd: 9%, DRd: 62%, Rd: 43%). Neutropenia was reported for 79% of subjects in the DPd cohort. Most frequently, neutropenia occurred in the first 2 or 3 cycles. Incidence of febrile neutropenia was low, 2% for the DVd group and 0.4% for the Vd group, 5% for the DRd group and 3% for the Rd group and 7% for DPd group, all were rade 3 or 4. Neutropenia was managed by dose modifications and growth factor use and rarely led to treatment discontinuation.

Infections and infestations

In the 4 daratumumab studies, adverse events in the Infections and Infestations SOC were overall among the most frequently reported TEAEs. Infections were reported by a higher percentage of subjects in the daratumumab containing groups (DVd: 68%, DRd: 83%) compared to the respective background therapy (Vd: 53%, Rd: 73%). However, Grade 3 or 4 infections were similar (DVd: 21%, Vd: 19%, DRd: 27%, Rd: 23%). In the DPd cohort, 70% of subjects had infections (28% Grade 3 or 4). The majority of infections were mild (Grade 1 or 2) and did not require hospitalization. The most common infections were respiratory disorders such as upper respiratory tract infection, bronchitis, sinusitis, or nasopharyngitis, which were common across all regimens.

Discontinuations from treatment (2% to 5%) and deaths (0.8% to 2%) due to infection were rare and balanced between groups. Pneumonia occurred in 11% to 13% of the study population and was the most

commonly reported severe (Grade 3 or 4) infection (7% to 10%) and also the most commonly reported serious infection (7% to 9%). The occurrence of pneumonia was balanced between treatment groups, and seldom resulted in treatment discontinuations or deaths (0.4% to 2%).

Herpes zoster

Bortezomib and lenalidomide exposure poses a known risk of herpes zoster reactivation and antiviral prophylaxis is recommended. The protocols recommended, but did not require, anti-viral prophylaxis for all study subjects.

Daratumumab with Bortezomib-Dexamethasone (DVd)

Herpes zoster as an adverse event was reported for 13 subjects (5%) in the DVd group (8 of these subjects received prophylactic anti-viral therapy) and 7 subjects (3%) in the Vd group (1 subject received prophylactic antiviral therapy). Grade 3 or 4 TEAEs of herpes zoster was reported for 4 subjects (1.6%) in the DVd group and 1 subject (0.4%) in the Vd group.

Daratumumab with Lenalidomide-Dexamethasone (DRd)

In Study 3003, Herpes zoster as an adverse event was reported for 6 subjects (2%) in the DRd group and 5 subjects (2%) in the Rd group. Two subjects in each group received prophylactic antiviral therapy. Grade 3 or 4 TEAEs of herpes zoster was reported for no subjects in the DRd group and 1 subject (0.4%) in the Rd group.

Daratumumab with Pomalidomide-Dexamethasone (DPd)

Two subjects (2%) had TEAEs of herpes zoster. Both events were Grade 3, neither was serious and neither led to treatment discontinuation. One of these 2 subjects was taking antiviral prophylaxis medication.

Thrombocypenia and bleeding

Thrombocytopenia was similar between the DRd group and Rd group (27% in each group). Thrombocytopenia was reported by more subjects in the DVd group (59%) compared to the Vd group (44%), but bleeding events were low and the majority were Grade 1 or 2 events. In the DPd cohort, thrombocytopenia was reported by 41% of subjects. Grade 3 or 4 bleeding events were experienced by 1% or less of subjects in all treatment groups.

Hemolysis and interference with blood typing

Daratumumab binds to CD38 found at low levels on red blood cells and could theoretically result in hemolysis. One subject (in the DPd cohort, Study MMY1001) experienced a Grade 1 TEAE of hemolysis on Study Day 70 which was diagnosed based on the presence of schistocytes on peripheral blood smear. The TEAE occurred 13 days after the last blood transfusion and 12 days after the last daratumumab infusion. There was no immediate exacerbation of anemia. No new cases of daratumumab interference with blood typing have been reported.

Cardiac events – atrial fibrillation

Atrial fibrillation was observed in 2% to 7% of subjects across all studies. Atrial fibrillation was balanced between the DRd and Rd groups but was slightly higher in the DVd group compared to the Vd group. The majority of subjects with atrial fibrillation had a prior history of atrial fibrillation or cardiac risk factors.

Cardiac events – QT prolongation

No subjects in DVd, Vd, or DPd groups had an AE of QT prolongation. QT prolongation was reported as an AE for 6 subjects (2%) in the DRd group and 1 subject (0.4%) in the Rd group. All were Grade 1 or 2. Only 1

subject, in the DRd group, had a corrected QT interval greater than 500 msec. This subject had an ongoing history of heart failure, and a one-time QTcF reading of 532 msec was reported on Study Day 50 as an AE of electrocardiogram QT prolonged. Baseline electrocardiogram findings were normal. The investigator considered this event as very likely related to lenalidomide and not related to daratumumab or dexamethasone. The event was considered resolved 7 days later and the subject continues to receive study treatment. No further QT prolongation has been reported.

Hepatobiliary disorders

A review of all AEs from hepatobiliary disorders showed the incidence of AEs to be very low and balanced between daratumumab combination therapy and background therapy alone. There is no specific AE event associated with hepatobiliary disorders identified. Liver enzymes were within the normal range for over 95% of subjects across all studies.

Second primary malignancies

Second primary malignancies (SPMs) were collected using a separate eCRF page in the Phase 3 studies throughout the study including long term follow-up. SPMs have been identified as a rare but important consideration in the treatment of multiple myeloma. A recent review evaluated the reports of SPM from several retrospective and prospective studies identified lenalidomide and alkylating agent exposure as potential (but not exclusive) risk factors. The incidence of SPMs is likely between 0.5% and 4.5% with a latency period of >12 months. Hematologic SPMs were more common than nonhematologic SPMs with a higher prevalence of myelodysplastic syndrome and acute myeloid leukemia. Based on data from all 4 studies, no increased risk of SPM due to daratumumab treatment has been observed.

Serious adverse event/deaths/other significant events

Serious adverse event

An overview of the SAEs occurred with frequency of at least 3% in MMY3003, MMY3004, MMY1001 and GEN503 studies is reported in Table 38 below:

Table 38 Number of Subjects with 1 or More Treatment-emergent SAE with frequency of at least 3% in either treatment group by MedDRA System Organ Class and Preferred Term: Safety Analysis Set (Studies: MMY3003, MMY3004, MMY1001 and GEN503)

	MMY3004		MMY3003+GEN503		MMY1001
	Vd	DVd	Rd	DRd	DPd
Analysis set: safety	237	243	281	318	103
Total number of subjects with serious TEAE	80 (33.8%)	102 (42.0%)	118 (42.0%)	156 (49.1%)	50 (48.5%)
MedDRA system organ class/Preferred term					
Infections and infestations	43 (18.1%)	48 (19.8%)	64 (22.8%)	94 (29.6%)	21 (20.4%)
Pneumonia	22 (9.3%)	19 (7.8%)	24 (8.5%)	24 (7.5%)	7 (6.8%)
Sepsis	2 (0.8%)	2 (0.8%)	5 (1.8%)	2 (0.6%)	4 (3.9%)
Blood and lymphatic system disorders	2 (0.8%)	15 (6.2%)	11 (3.9%)	21 (6.6%)	8 (7.8%)
Febrile neutropenia	0	2 (0.8%)	4 (1.4%)	12 (3.8%)	4 (3.9%)
Anaemia	1 (0.4%)	8 (3.3%)	2 (0.7%)	3 (0.9%)	3 (2.9%)
General disorders and administration site conditions	12 (5.1%)	9 (3.7%)	8 (2.8%)	16 (5.0%)	4 (3.9%)
Pyrexia	4 (1.7%)	4 (1.6%)	4 (1.4%)	10 (3.1%)	0
Injury, poisoning and procedural complications	5 (2.1%)	7 (2.9%)	8 (2.8%)	8 (2.5%)	7 (6.8%)
Fall	0	0	1 (0.4%)	0	4 (3.9%)

Key: D=Daratumumab, Vd=bortezomib-dexamethasone, Rd=lenalidomide-dexamethasone, Pd=pomalidomide-dexamethasone.
Keys: TEAE = treatment-emergent adverse event.
Rd is only from MMY3003.
Note: Adverse events are reported using MedDRA version 18.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

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Deaths

Table 39 Summary of Death and Cause of death: Safety Analysis Set(studies MMY3003, MMY3004, MMY1001 and GEN503)

	MMY3004		MMY3003+GEN503		MMY1001
	Vd	DVd	Rd	DRd	DPd
Analysis set: safety	237	243	281	318	103
Total number of subjects who died within 30 days of last study treatment dose	13 (5.5%)	13 (5.3%)	16 (5.7%)	13 (4.1%)	7 (6.8%)
Adverse events	10 (4.2%)	11 (4.5%)	12 (4.3%)	12 (3.8%)	5 (4.9%)
Disease progression	3 (1.3%)	2 (0.8%)	4 (1.4%)	1 (0.3%)	2 (1.9%)
Other	0	0	0	0	0
Total number of subjects who died within 60 days of first study treatment dose	9 (3.8%)	7 (2.9%)	7 (2.5%)	3 (0.9%)	7 (6.8%)
Adverse events	5 (2.1%)	7 (2.9%)	6 (2.1%)	3 (0.9%)	5 (4.9%)
Disease progression	4 (1.7%)	0	1 (0.4%)	0	2 (1.9%)
Other	0	0	0	0	0

Key: D=Daratumumab, Vd=bortezomib-dexamethasone, Rd=lenalidomide-dexamethasone, Pd=pomalidomide-dexamethasone.
Rd is only from MMY3003.
Note: Percentages are calculated with the number of subjects in each group as denominator.

[TSFDTH01.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_2016\RE_MMY_RR_2016\PROD\TSFDTH01.SAS] 21JUL2016, 12:14

Table 40 Number of Subjects with 1 or More TEAEs with outcome death by Preferred Term and Relationship; Safety Analysis Set (Studies : MMY3003, MMY3004, MMY1001 and GEN503)

	MMY3004					MMY3003+GEN503					MMY1001		
	Vd		DVd			Rd		DRd			DPd		
Analysis set: safety	Total n(%) 237	Related to Other	Total n(%) 243	Related to DARA	Related to Other	Total n(%) 281	Related to Other	Total n(%) 318	Related to DARA	Related to Other	Total n(%) 103	Related to DARA	Related to Other
Total number of subjects with TEAE with outcome death	14 (5.9%)	2 (0.8%)	13 (5.3%)	3 (1.2%)	5 (2.1%)	15 (5.3%)	1 (0.4%)	12 (3.8%)	3 (0.9%)	7 (2.2%)	7 (6.8%)	0	1 (1.0%)
MedDRA system organ class/Preferred term													
Infections and infestations	4 (1.7%)	2 (0.8%)	2 (0.8%)	1 (0.4%)	1 (0.4%)	4 (1.4%)	0	7 (2.2%)	2 (0.6%)	5 (1.6%)	2 (1.9%)	0	1 (1.0%)
Septic shock	1 (0.4%)	0	0	0	0	1 (0.4%)	0	3 (0.9%)	1 (0.3%)	1 (0.3%)	0	0	0
Pneumonia	2 (0.8%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	2 (0.7%)	0	2 (0.6%)	0	2 (0.6%)	0	0	0
Pneumonia bacterial	0	0	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	0	0
Pneumonia viral	0	0	0	0	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	0	0
Progressive multifocal leukoencephalopathy	0	0	0	0	0	0	0	0	0	0	1 (1.0%)	0	1 (1.0%)
Pulmonary sepsis	0	0	1 (0.4%)	0	0	0	0	0	0	0	0	0	0
Sepsis	0	0	0	0	0	1 (0.4%)	0	0	0	0	1 (1.0%)	0	0
Tracheobronchitis	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0	0	0	0	0
Cardiac disorders	1 (0.4%)	0	3 (1.2%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	1 (0.3%)	0	0	0	0	0
Cardiopulmonary failure	0	0	0	0	0	0	0	1 (0.3%)	0	0	0	0	0
Acute coronary syndrome	0	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0	0
Cardiac arrest	1 (0.4%)	0	1 (0.4%)	0	0	1 (0.4%)	0	0	0	0	0	0	0
Cardiogenic shock	0	0	1 (0.4%)	0	0	0	0	0	0	0	0	0	0
General disorders and administration site conditions	4 (1.7%)	0	1 (0.4%)	0	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (1.0%)	0	0
Multi-organ failure	0	0	0	0	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	0	0
Condition aggravated	1 (0.4%)	0	0	0	0	0	0	0	0	0	0	0	0
General physical health deterioration	3 (1.3%)	0	1 (0.4%)	0	0	0	0	0	0	0	1 (1.0%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	2 (0.7%)	0	1 (0.3%)	0	1 (0.3%)	0	0	0
Acute monocytic leukaemia	0	0	0	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	0	0
Lung adenocarcinoma	0	0	0	0	0	1 (0.4%)	0	0	0	0	0	0	0
Plasma cell leukaemia	0	0	0	0	0	1 (0.4%)	0	0	0	0	0	0	0
Renal and urinary disorders	1 (0.4%)	0	0	0	0	4 (1.4%)	1 (0.4%)	1 (0.3%)	0	0	0	0	0
Acute kidney injury	0	0	0	0	0	3 (1.1%)	1 (0.4%)	1 (0.3%)	0	0	0	0	0
Myeloma cast nephropathy	1 (0.4%)	0	0	0	0	0	0	0	0	0	0	0	0
Renal failure	0	0	0	0	0	1 (0.4%)	0	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.8%)	0	3 (1.2%)	1 (0.4%)	1 (0.4%)	2 (0.7%)	0	1 (0.3%)	0	0	3 (2.9%)	0	0
Pulmonary oedema	1 (0.4%)	0	0	0	0	1 (0.4%)	0	1 (0.3%)	0	0	0	0	0
Acute respiratory failure	0	0	0	0	0	1 (0.4%)	0	0	0	0	0	0	0
Interstitial lung disease	0	0	0	0	0	0	0	0	0	0	1 (1.0%)	0	0
Organising pneumonia	0	0	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	0	0	0	0	0	0	0
Pleural effusion	0	0	0	0	0	0	0	0	0	0	1 (1.0%)	0	0
Pulmonary embolism	1 (0.4%)	0	0	0	0	0	0	0	0	0	0	0	0
Respiratory failure	0	0	2 (0.8%)	0	0	0	0	0	0	0	1 (1.0%)	0	0
Gastrointestinal disorders	0	0	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0	0	0	0
Duodenal ulcer	0	0	1 (0.4%)	0	1 (0.4%)	0	0	0	0	0	0	0	0
Metabolism and nutrition disorders	1 (0.4%)	0	0	0	0	0	0	0	0	0	0	0	0
Hyponatraemia	1 (0.4%)	0	0	0	0	0	0	0	0	0	0	0	0
Nervous system disorders	1 (0.4%)	0	3 (1.2%)	0	1 (0.4%)	2 (0.7%)	0	0	0	0	1 (1.0%)	0	0
Cerebral haemorrhage	0	0	0	0	0	1 (0.4%)	0	0	0	0	0	0	0
Cerebral infarction	0	0	1 (0.4%)	0	0	0	0	0	0	0	0	0	0
Cerebrovascular accident	1 (0.4%)	0	0	0	0	0	0	0	0	0	1 (1.0%)	0	0
Ischaemic stroke	0	0	2 (0.8%)	0	1 (0.4%)	0	0	0	0	0	0	0	0
Nervous system disorder	0	0	0	0	0	1 (0.4%)	0	0	0	0	0	0	0

Key: D=Daratumumab, Vd=bortezomib-dexamethasone, Rd=lenalidomide-dexamethasone, Pd=pomalidomide-dexamethasone.
Keys: TEAE = treatment-emergent adverse event.
Rd is only from MMY3003.
Note: Adverse events are reported using MedDRA version 18.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

[TSFAE16.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_2016\RE_MMY_RR_2016\PROD\TSFAE16.SAS] 01JUN2016, 10:41

Laboratory findings

Hematology values

Daratumumab with Bortezomib-Dexamethasone

Low platelets are a common laboratory abnormality in subjects treated with bortezomib. The most common Grade 3 or 4 hematology abnormalities for both treatment groups were low platelets (DVd: 48%; Vd: 36%) and low lymphocytes (DVd: 51%; Vd: 30%). Grade 3 or 4 low neutrophils were 16% in the DVd group and 6% in the Vd group. Similar proportion of subjects in both treatment groups had Grade 3 low hemoglobin (DVd: 17%; Vd: 16%). No Grade 4 hemoglobin was reported in any of the treatment groups.

Daratumumab with Lenalidomide-Dexamethasone

The most common Grade 3 or 4 hematology laboratory abnormalities were low neutrophils (DRd group: 54%; Rd group: 41%) and low lymphocytes (DRd group: 54%; Rd group: 40%), with higher proportions reported in the DRd group compared with the Rd group. The percentage of subjects with Grade 3 or 4 low platelets was similar between the 2 treatment groups (DRd group: 14%; Rd group: 16%). Grade 3 hemoglobin low was reported for 14% of subjects in the DRd group and 21% of subjects in the Rd group. No Grade 4 low hemoglobin was reported in either treatment group.

Daratumumab with Pomalidomide-Dexamethasone

The most common Grade 3 or 4 hematology laboratory abnormalities were low neutrophils (82%) and lymphocytes (73%). Grade 3 or 4 low platelets was reported by 20% of subjects. Grade 3 low hemoglobin was reported for 32% of subjects, no Grade 4 low hemoglobin was reported.

Clinical Chemistry

The incidence of chemistry laboratory abnormalities was low, and the majority was Grade 0 or 1.

Daratumumab with Bortezomib-Dexamethasone

Changes in chemistry values to Grade 4 were uncommon, and did not exceed 5% of the population. Changes to Grade 3 values were also uncommon, and rarely exceeded 5% of the population except for Grade 3 low sodium levels (DVd: 5%, Vd: 6%) and Grade 3 low phosphate levels (DVd: 9%, Vd: 5%). The majority of Grade 3 and Grade 4 values represented shifts from Grade 0 or Grade 1 at baseline. Mean creatinine levels were generally lower for the DVd group compared with the Vd group over time during the study and reciprocally, creatinine clearance values were higher for the DVd group compared with the Vd group and increased over time for both treatment groups. This observation of improving creatinine clearance over time supports a beneficial impact of treatment since renal failure is a notable complication of untreated or poorly controlled multiple myeloma.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels were normal throughout the study for over 98% of subjects. Grade 4 AST high and ALT high were recorded for 1 subject (0.4%) each in the DVd and Vd groups, no subjects had Grade 4 bilirubin high. Grade 3 ALT high was reported for 5 subjects (2%) in the DVd group and 1 subject (0.4%) in the Vd group. Grade 3 AST high was reported for 2 subjects (0.8%) in the DVd group and no subjects in the Vd group. Grade 3 bilirubin high was reported for no subjects in the DVd group and 1 subject (0.4%) in the Vd group.

Daratumumab with Lenalidomide-Dexamethasone

Changes in chemistry values to Grade 4 were uncommon, and did not exceed 5% of the population. Changes to Grade 3 values were also rare, and rarely exceeded 5% of the population except for Grade 3 low

potassium levels (DRd: 5%, Rd: 3%) [and] Grade 3 low phosphate levels (DRd: 12%, Rd: 11%). The majority of Grade 3 and Grade 4 values represented shifts from Grade 0 or Grade 1 at baseline.

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin levels were normal throughout the study for over 95% of subjects. No Grade 4 values for these laboratory parameters were reported. Grade 3 ALT high was reported for 8 subjects (3%) in the DRd group and 5 subjects (2%) in the Rd group. Grade 3 AST high was reported for 3 subjects (1%) in the DVd group and no subjects in the Rd group. Grade 3 bilirubin high was reported for 2 subjects (0.6%) in the DRd group and 1 subject (0.4%) in the Rd group.

Daratumumab with Pomalidomide-Dexamethasone

Hypercalcemia (9%) was the only Grade 4 biochemistry value that was reported by more than 5% of subjects. Other frequently reported Grade 3 biochemistry parameters were low sodium (11%) and low phosphate levels (10%).

Alanine aminotransferase (ALT), AST, and bilirubin levels were normal throughout the study for over 95% of subjects. No Grade 4 values for these laboratory parameters were reported. Grade 3 AST high and ALT high were recorded for 3 subject (3%) each. Grade 3 bilirubin high was reported for 2 subjects (2%).

Immunogenicity Assessments

Evaluation of anti-daratumumab antibodies was conducted for all subjects participating in the 4 studies included in this submission. Evaluable blood samples were obtained after the first dose of daratumumab from 298 subjects. Results are summarized in the Table 41.

Table 41 Summary and Anti- Daratumumab Antibodies: Immune Response-evaluable Analysis Set (Studies: MMY3003, MMY3004, MMY1001 and GEN503)

	MMY3004	MMY3003	GEN503	MMY1001	Total
Analysis set: immune response-evaluable	102	96	37	64	299
Subjects with appropriate samples[a]	102	95	37	64	298
Subjects positive for anti-daratumumab antibodies[b,c]	0	1 (1.1%)	0	1 (1.6%)	2 (0.7%)
Titers 1:20	-	1	-	1	2
Subjects positive for neutralizing antibodies[d]	-	1	-	0	1
Subjects negative for anti-daratumumab antibodies[b]	102 (100.0%)	94 (98.9%)	37 (100.0%)	63 (98.4%)	296 (99.3%)

[a] Subjects with appropriate samples had 1 or more samples obtained after their first daratumumab administration.
[b] Denominator is subjects with appropriate samples.
[c] Includes all subjects who had at least 1 positive sample at any time after start of treatment and baseline positive subjects who had post-treatment sample titers increase at least 2-fold compared to baseline.
[d] Only samples positive for antibodies to daratumumab were assayed for neutralizing antibodies.
MMY3004 includes patients in the DVd arm, MMY3003 includes patients in the DRd arm, GEN503 includes patients treated with DRd 2 mg/kg to 16 mg/kg, MMY1001 includes patients treated with DVd, DVTd, DVMP, or DPd.
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As shown in the table above, one subject in Study MMY1001, in the DVTd cohort, was positive for ADA at the Week 9 Follow-Up visit; the antibodies were non-neutralizing. This subject was negative for ADA on 2 other

visits (predose on Cycle 1 Day 1 and Week 3 Follow-up) and was on treatment for 4 cycles. This subject was not evaluable for response per protocol and discontinued due to autologous stem cell transplantation. There were no notable safety signals observed in this subject.

Daratumumab binds to CD38 found at low levels on red blood cells and could theoretically result in haemolysis. One subject (in the DPd cohort, Study MMY1001) experienced a Grade 1 TEAE of hemolysis on Study Day 70 which was diagnosed based on the presence of schistocytes on peripheral blood smear. There was no immediate exacerbation of anemia and this TEAE occurred 13 days after blood transfusion and 12 days after daratumumab infusion. No other TEAEs related to hemolysis have been reported.

Interference with blood typing is already included in the Warnings and Precautions section of the daratumumab Product Information, however, no new cases of daratumumab interference with blood typing have been reported in the present pivotal studies.

Vital signs, physical findings, and other observations related to safety

A review of vital signs in the randomized, controlled studies did not identify any safety signals.

Safety in special populations

A separate analysis of TEAEs was performed for the daratumumab groups (DVd, DRd, DPd) combined from all 4 studies to evaluate potential differences in the safety of daratumumab in subgroups of subjects defined by age, gender, race, baseline renal function, baseline hepatic function, and geographic region.

Table 42 Subgroup analyses on Overview of TEAEs; Safety Analysis Set (Studies: MMY3003, MMY3004, MMY1001 and GEN503)

		Dara Combined					
		N	TEAE	Serious TEAE	Grade 3 or 4 TEAE	TD due to TEAE[a]	TEAE with outcome Death[b]
All subjects		664	656 (98.8%)	308 (46.4%)	547 (82.4%)	53 (8.0%)	32 (4.8%)
Age:	18 to < 65 years	336	332 (98.8%)	140 (41.7%)	270 (80.4%)	16 (4.8%)	15 (4.5%)
	65 to < 75 years	269	266 (98.9%)	135 (50.2%)	227 (84.4%)	28 (10.4%)	15 (5.6%)
	>= 75 years	59	58 (98.3%)	33 (55.9%)	50 (84.7%)	9 (15.3%)	2 (3.4%)
Sex:	Male	382	378 (99.0%)	191 (50.0%)	317 (83.0%)	36 (9.4%)	21 (5.5%)
	Female	282	278 (98.6%)	117 (41.5%)	230 (81.6%)	17 (6.0%)	11 (3.9%)
Race:	White	527	519 (98.5%)	253 (48.0%)	430 (81.6%)	45 (8.5%)	28 (5.3%)
	Other	137	137 (100.0%)	55 (40.1%)	117 (85.4%)	8 (5.8%)	4 (2.9%)
Renal Impairment (Creatinine Clearance)	Normal (CrCl >= 90 mL/min)	240	238 (99.2%)	99 (41.3%)	194 (80.8%)	16 (6.7%)	12 (5.0%)
	Mild (CrCl 60 to < 90 mL/min)	249	245 (98.4%)	104 (41.8%)	202 (81.1%)	17 (6.8%)	9 (3.6%)
	Moderate (CrCl 30 to < 60 mL/min)	159	157 (98.7%)	93 (58.5%)	135 (84.9%)	17 (10.7%)	11 (6.9%)
	Severe (CrCl < 30 mL/min)	12	12 (100.0%)	10 (83.3%)	12 (100.0%)	3 (25.0%)	0
Hepatic Function[c]	Normal	570	563 (98.8%)	263 (46.1%)	470 (82.5%)	47 (8.2%)	29 (5.1%)
	Impaired	86	85 (98.8%)	39 (45.3%)	70 (81.4%)	6 (7.0%)	3 (3.5%)
Geographic Region:	West EU+NA+CAN	398	396 (99.5%)	190 (47.7%)	342 (85.9%)	32 (8.0%)	18 (4.5%)
	Other Regions	266	260 (97.7%)	118 (44.4%)	205 (77.1%)	21 (7.9%)	14 (5.3%)

Key: D=Daratumumab, Vd=bortezomib-dexamethasone, Rd=lenalidomide-dexamethasone, Pd=pomalidomide-dexamethasone.
Keys: TEAE = treatment-emergent adverse event. TD = treatment discontinuation.
Note: Percentages are calculated with the number of subjects in each subgroup as denominator.
[a]Treatment discontinuation due to adverse event on the end of treatment CRF page.
[b]TEAE with outcome death on the AE CRF page.
[c]Hepatic function is classified as normal and impaired groups. The impaired group includes subjects of 82 mildly, 3 moderately and 1 severely hepatic impairment per NCI Organ Dysfunction criteria.
West EU+US+CAN includes Belgium, Denmark, Greece, Netherlands, France, Great Britain, Sweden, Italy, Spain, USA, and Canada. Other region includes Australia, Israel, Japan, South Korea, Turkey, Taiwan, Poland, Brazil, Czech Republic, Hungary, Mexico, Russia, and Ukraine.

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Intrinsic Factors

Adverse Events by Age Group

Of the 664 subjects, 336 (51%) were 18 to <65 years of age, 269 (41%) were 65 to<75 years, and 59 (9%) were≥75 years of age. The incidence of TEAEs by age subgroup was similar to the total population. The safety profile observed in elderly subjects was consistent with the expected age-related morbidity in this population. Subjects ≥75 years, had an incidence of deaths due to TEAEs (3.4%) compared to all subjects (4.8%). However, the sample size in this subgroup was too small to make meaningful comparison.

Adverse Events by Sex

Of the 664 subjects treated with the combination regimen with daratumumab, 282 (42%) were female and 382 (58%) were male. The incidence of TEAEs by sex was similar to the overall population.

Adverse Events by Race

Of the 664 subjects treated with the combination regimen with daratumumab, 527 (79%) were White, and 137 (21%) were non-White. The incidence of TEAEs by race was similar to the overall population.

Adverse Events by Baseline Renal Function

240 subjects (36%) had a normal baseline creatinine clearance (CrCl) of ≥90 mL/min, 249 (38%) had a baseline CrCl of 60 to <90 mL/min and 159 (24%) had a baseline CrCl of 30 to <60 mL/min. The incidence of TEAEs in the ≥60 mL/min was similar to the overall population. However subjects with moderate renal impairment with (baseline CrCl of 30 to <60 mL/min) had a higher incidence of serious TEAE, 59% compared to 46% in the overall population, mostly due to Infections and Infestations SOC (31% versus 24% in the overall population). Subjects with severe renal impairment (CrCl of <30 mL/min) were too small in number (n=12) to make a clinically meaningful conclusion.

Adverse Events by Baseline Hepatic Function

Daratumumab being an IgG1κ mAb, is presumably biotransformed in the same manner as any other endogenous IgG, and is subject to similar elimination. Hepatic enzyme-mediated metabolism of intact daratumumab is therefore unlikely to represent major elimination routes. As such, variations in hepatic function are not expected to affect the elimination of daratumumab. 570 (87%) subjects treated with a daratumumab containing regimen had a normal hepatic function at baseline, and 86 (13%) had mildly impaired hepatic function. In general, the incidence of TEAEs by baseline hepatic function was similar to the overall population. No clear pattern in the incidence of TEAEs for subjects with normal versus mildly impaired hepatic function was reported. The differences may be due to the small number of subjects with mild hepatic impairment, precluding any meaningful comparisons.

Extrinsic Factors

Adverse Events by Geographic Region

In general, the incidence of TEAEs by geographic region was similar to the overall population. 398 (60%) of the subjects were from Western Europe, US and Canada, and 40% were from other regions, such as Asia, Australia, Mexico and Eastern Europe.

Overdose

There has been no experience of overdose in clinical studies. Doses up to 24 mg/kg have been administered intravenously in a clinical study (GEN501) without reaching the maximum tolerated dose.

There is no known specific antidote for daratumumab overdose. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment be instituted immediately.

Use in Pregnancy and Lactation

There are no data available on the use of daratumumab in pregnant women and no animal data to assess the potential effects of daratumumab to increase the risk of developmental abnormalities or feto/neonatal toxicities.

Women of childbearing potential using the drug should use effective contraception during and up to 3 months after treatment. The 3-month washout for females is related to the linear terminal half-life of daratumumab in plasma of about 18 days, which can be expected upon complete saturation of target-mediated clearance and with repeated dosing of daratumumab. Theoretically, daratumumab is expected to be eliminated from the body in approximately 5 half-lives (90 days). The recommendation for women to avoid becoming pregnant until 3 months after the last dose of daratumumab is a fairly conservative approach which is supported.

It is not known whether daratumumab is secreted into human or animal milk or affects milk production. There are no studies to assess the effect of daratumumab on the breast-fed infant. Maternal IgG is excreted in human milk; however, published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts.

Drug Abuse

Daratumumab is administered in a controlled setting by healthcare providers. There is no known drug abuse potential with daratumumab.

Withdrawal and Rebound

No clinical studies of the withdrawal or rebound effects of daratumumab have been conducted. Treatment is to be continued until disease progression.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No clinical information is available related to the effect of daratumumab on the ability to drive, operate machinery, or the impairment of mental ability. The effect of daratumumab on the ability to drive or operate machinery or the impairment of mental ability has not been formally studied; however, in the integrated safety population, TEAEs, such as fatigue, that could potentially affect the ability to drive or operate machinery should be considered.

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been performed with daratumumab. It is expected that daratumumab is metabolized in the same manner as any other endogenous immunoglobulin (degraded into small peptides and amino acids via catabolic pathways) and is subject to similar elimination. Renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are therefore unlikely to represent major elimination routes. As such, variations in renal and hepatic function or drug metabolizing enzymes are not expected to affect the elimination of daratumumab. As a monoclonal antibody that binds with high affinity to a unique epitope on CD38, daratumumab is also not anticipated to alter drug metabolizing enzymes.

As part of Study MMY1001, PK profiles of combination agents (bortezomib, pomalidomide, and thalidomide) were assessed and compared to literature values. Pharmacokinetic values for daratumumab are assessed and compared with monotherapy values. Overall, there is no indication of clinically relevant drug-drug interactions between daratumumab and small molecules typically used in treatment of multiple myeloma.

Discontinuation due to adverse events

A summary of the reasons for discontinuation from study treatment is presented in Table 47. A lower percentage of subjects receiving DVd (31%) or DRd (24%) have discontinued treatment compared to those

receiving background therapies alone (Vd: 44%; Rd: 47%). In the DPd cohort, 57% of subjects have discontinued treatment.

Table 43 Summary of Subject Disposition of Study Treatment: Safety Analysis Set (Studies: MMY3003, MMY3004, MMY1001 and GEN503)

	MMY3004		MMY3003+GEN503		MMY1001
	Vd	DVd	Rd	DRd	DPd
Analysis set: safety	237	243	281	318	103
Subjects who had treatment ongoing	20 (8.4%)	169 (69.5%)	149 (53.0%)	241 (75.8%)	44 (42.7%)
Subjects who discontinued treatment	104 (43.9%)	74 (30.5%)	132 (47.0%)	77 (24.2%)	59 (57.3%)
Reason for discontinuation					
Progressive disease	60 (25.3%)	47 (19.3%)	96 (34.2%)	46 (14.5%)	34 (33.0%)
Adverse event	23 (9.7%)	19 (7.8%)	23 (8.2%)	22 (6.9%)	14 (13.6%)
Physician decision	0	0	2 (0.7%)	5 (1.6%)	4 (3.9%)
Death	4 (1.7%)	4 (1.6%)	1 (0.4%)	2 (0.6%)	2 (1.9%)
Non-compliance with study drug[a]	8 (3.4%)	3 (1.2%)	5 (1.8%)	1 (0.3%)	0
Withdrawal by subject	9 (3.8%)	1 (0.4%)	5 (1.8%)	1 (0.3%)	4 (3.9%)
Other	0	0	0	0	1 (1.0%)

Key: D=Daratumumab, Vd=bortezomib-dexamethasone, Rd=lenalidomide-dexamethasone, Pd=pomalidomide-dexamethasone.
Rd is only from MMY3003.
Percentages are calculated with the number of subjects in each group as denominator.
[a]Based on reason 'Subject refused to further study treatment' on 'End of Treatment' CRF page.
Note: MMY3004: Vd arm treated for 8 cycles and DVd arm treated until PD per protocol. Subjects in Vd arm who were treated for 8 cycles are not considered as treatment discontinuation.

[TSIDS01.RTF] [JNJ-54767414\Z_SCS\DBR_MMY_RR_2016\RE_MMY_RR_2016\PROD\TSIDS01.SAS] 01JUN2016, 10:47

Adverse Events Leading to Discontinuation of Treatment

Discontinuation of all study treatment due to TEAEs was low and balanced between treatment groups (Table 48). Across all groups, pneumonia was the most common reason for discontinuation of all study treatment. Discontinuation of daratumumab alone was infrequent (1% to 2%) across all studies.

Table 44 TEAEs leading to discontinuation of Study Treatment of More than 1 Subjec by MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Studies: MMY3003, MMY3004, MMY1001 and GEN503)

	MMY3004		MMY3003+GEN503		MMY1001
	Vd	DVd	Rd	DRd	DPd
Analysis set: safety	237	243	281	318	103
Total number of subjects with TEAE leading to discontinuation of study treatment *	22 (9.3%)	18 (7.4%)	22 (7.8%)	22 (6.9%)	13 (12.6%)
MedDRA system organ class/Preferred term					
Infections And Infestations	5 (2.1%)	6 (2.5%)	5 (1.8%)	8 (2.5%)	5 (4.9%)
Pneumonia	1 (0.4%)	3 (1.2%)	2 (0.7%)	3 (0.9%)	1 (1.0%)
Septic Shock	1 (0.4%)	0	0	2 (0.6%)	0
Gangrene	1 (0.4%)	0	0	0	0
Sepsis	0	1 (0.4%)	1 (0.4%)	0	1 (1.0%)
General Disorders And Administration Site Conditions	2 (0.8%)	0	0	3 (0.9%)	0
General Physical Health Deterioration	1 (0.4%)	0	0	3 (0.9%)	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	0	1 (0.4%)	3 (1.1%)	3 (0.9%)	0
Nervous System Disorders	10 (4.2%)	3 (1.2%)	2 (0.7%)	2 (0.6%)	0
Cerebral Infarction	0	1 (0.4%)	1 (0.4%)	1 (0.3%)	0
Peripheral Sensory Neuropathy	6 (2.5%)	1 (0.4%)	0	0	0
Cardiac Disorders	2 (0.8%)	4 (1.6%)	2 (0.7%)	1 (0.3%)	2 (1.9%)
Cardiac Arrest	1 (0.4%)	1 (0.4%)	1 (0.4%)	0	0
Cardiac Failure Congestive	0	2 (0.8%)	0	0	1 (1.0%)
Renal And Urinary Disorders	0	0	2 (0.7%)	1 (0.3%)	0
Renal Failure	0	0	2 (0.7%)	1 (0.3%)	0
Respiratory, Thoracic And Mediastinal Disorders	1 (0.4%)	5 (2.1%)	5 (1.8%)	1 (0.3%)	4 (3.9%)
Laryngeal Oedema	0	1 (0.4%)	0	1 (0.3%)	0
Dyspnoea	0	1 (0.4%)	0	0	1 (1.0%)
Pulmonary Embolism	1 (0.4%)	0	3 (1.1%)	0	0
Respiratory Failure	0	1 (0.4%)	0	0	1 (1.0%)
Blood And Lymphatic System Disorders	0	0	3 (1.1%)	0	1 (1.0%)
Thrombocytopenia	0	0	1 (0.4%)	0	1 (1.0%)
Vascular Disorders	2 (0.8%)	0	1 (0.4%)	0	1 (1.0%)
Orthostatic Hypotension	2 (0.8%)	0	0	0	0

Key: D=Daratumumab, Vd=bortezomib-dexamethasone, Rd=lenalidomide-dexamethasone, Pd=pomalidomide-dexamethasone.
Keys: TEAE = treatment-emergent adverse event.
Rd is only from MMY3003.
* Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
Note: Adverse events are reported using MedDRA version 18.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.
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Dose modifications due to AEs

Daratumumab dose modifications consisted of dose delays and dose skips. The TEAEs that led to a delay or skip prior to the start of the infusion in 2 or more subjects are summarized in Table 17. For all daratumumab groups combined, the most frequent reasons for interruption of daratumumab dosing were neutropenia and thrombocytopenia.

In the DVd group, 87 subjects (36%) had modifications to daratumumab dosing. The single most common reason for daratumumab dose modification was thrombocytopenia, reported for 28 subjects (12%). Pneumonia was the next most common reason, reported for 11 subjects (5%).

In the DRd group (excluding GEN503 as this information was not collected), 105 subjects (37%) had modifications to daratumumab dosing. The single most common reason for daratumumab dose modification was neutropenia, reported for 29 subjects (10%). Pneumonia was the next most common reason, reported for 10 subjects (4%).

In the DPd cohort, 50 subjects (49%) had modifications to daratumumab dosing. The single most common reason was neutropenia, reported for 24 subjects (23%). Thrombocytopenia was the next most common reason, reported for 9 subjects (9%).

Dose Modification of Background Therapy

A higher proportion of subjects from the DVd group were reported with a TEAE leading to dose modifications (dose delays, dose skipping, schedule change, or dose reduction) of bortezomib (DVd: 64%, Vd: 54%) and dexamethasone (DVd: 46%, Vd: 39%) compared with the Vd group. The most commonly reported TEAE leading to dose modifications was peripheral sensory neuropathy for bortezomib (DVd: 32%, Vd: 23%) and upper respiratory tract infection for dexamethasone (DVd: 3%, Vd: 5%).

In Study MMY3003, a higher proportion of subjects from the DRd group were reported with a TEAE leading to dose modifications (dose delay, dose skip, dose reduction) of lenalidomide (DRd: 71%, Rd: 54%) and dexamethasone (DRd: 58%, Rd: 44%) compared with the Rd group. The most commonly reported TEAE leading to dose modifications was neutropenia for both lenalidomide (DRd: 34%, Rd: 22%) and dexamethasone (DRd: 7%, Rd: 4%).

Seventy-three percent (73%) of subjects experienced TEAEs leading to pomalidomide dose modification (ie, dose delays, dose skipping, dose re-escalation, or dose reduction); the most common reason was neutropenia (48%).

Table 45 TEAEs leading to infusion Modification prior to infusion Start in Two or More subjects by System Organ Class, Prederred Term and Relationship; Safety Analysis Set (Studies MMY3003, MMY3004, MMY1001 and GEN503)

	MMY3004	MMY3003+GEN503	MMY1001	Total
	DVd	DRd	DPd	Dara Combined
Analysis set: safety[a]	243	283	103	629
Total number of subjects with TEAE leading to infusion modification prior to infusion start[b]	87 (35.8%)	105 (37.1%)	50 (48.5%)	242 (38.5%)
MedDRA system organ class / Preferred term				
Infections and infestations	34 (14.0%)	61 (21.6%)	18 (17.5%)	113 (18.0%)
Pneumonia	11 (4.5%)	10 (3.5%)	3 (2.9%)	24 (3.8%)
Upper respiratory tract infection	4 (1.6%)	6 (2.1%)	3 (2.9%)	13 (2.1%)
Bronchitis	5 (2.1%)	5 (1.8%)	0	10 (1.6%)
Influenza	2 (0.8%)	5 (1.8%)	1 (1.0%)	8 (1.3%)
Lower respiratory tract infection	1 (0.4%)	5 (1.8%)	0	6 (1.0%)
Nasopharyngitis	0	5 (1.8%)	0	5 (0.8%)
Respiratory syncytial virus infection	1 (0.4%)	1 (0.4%)	3 (2.9%)	5 (0.8%)
Urinary tract infection	0	4 (1.4%)	1 (1.0%)	5 (0.8%)
Herpes zoster	3 (1.2%)	0	1 (1.0%)	4 (0.6%)
Lung infection	1 (0.4%)	2 (0.7%)	1 (1.0%)	4 (0.6%)
Parainfluenzae virus infection	1 (0.4%)	1 (0.4%)	2 (1.9%)	4 (0.6%)
Pneumonia influenzal	0	3 (1.1%)	0	3 (0.5%)
Sepsis	0	1 (0.4%)	2 (1.9%)	3 (0.5%)
Gastroenteritis	1 (0.4%)	1 (0.4%)	0	2 (0.3%)
Respiratory tract infection	0	2 (0.7%)	0	2 (0.3%)
Rhinitis	1 (0.4%)	1 (0.4%)	0	2 (0.3%)
Sinusitis	1 (0.4%)	1 (0.4%)	0	2 (0.3%)
Blood and lymphatic system disorders	32 (13.2%)	33 (11.7%)	27 (26.2%)	92 (14.6%)
Neutropenia	5 (2.1%)	29 (10.2%)	24 (23.3%)	58 (9.2%)
Thrombocytopenia	28 (11.5%)	5 (1.8%)	9 (8.7%)	42 (6.7%)
Febrile neutropenia	3 (1.2%)	4 (1.4%)	3 (2.9%)	10 (1.6%)
Anaemia	2 (0.8%)	2 (0.7%)	4 (3.9%)	8 (1.3%)
Leukopenia	0	1 (0.4%)	3 (2.9%)	4 (0.6%)
Gastrointestinal disorders	9 (3.7%)	12 (4.2%)	1 (1.0%)	22 (3.5%)
Diarrhoea	5 (2.1%)	7 (2.5%)	1 (1.0%)	13 (2.1%)
Nausea	0	2 (0.7%)	0	2 (0.3%)
Vomiting	0	2 (0.7%)	0	2 (0.3%)

General disorders and administration site conditions	7 (2.9%)	13 (4.6%)	2 (1.9%)	22 (3.5%)
Pyrexia	5 (2.1%)	7 (2.5%)	2 (1.9%)	14 (2.2%)
Asthenia	0	3 (1.1%)	0	3 (0.5%)
Fatigue	1 (0.4%)	2 (0.7%)	0	3 (0.5%)
Influenza like illness	1 (0.4%)	1 (0.4%)	0	2 (0.3%)
Respiratory, thoracic and mediastinal disorders	5 (2.1%)	2 (0.7%)	5 (4.9%)	12 (1.9%)
Dyspnoea	1 (0.4%)	1 (0.4%)	2 (1.9%)	4 (0.6%)
Cough	1 (0.4%)	1 (0.4%)	1 (1.0%)	3 (0.5%)
Investigations	2 (0.8%)	4 (1.4%)	4 (3.9%)	10 (1.6%)
Alanine aminotransferase increased	1 (0.4%)	3 (1.1%)	1 (1.0%)	5 (0.8%)
Aspartate aminotransferase increased	0	2 (0.7%)	2 (1.9%)	4 (0.6%)
Blood alkaline phosphatase increased	0	2 (0.7%)	1 (1.0%)	3 (0.5%)
Blood creatinine increased	1 (0.4%)	0	1 (1.0%)	2 (0.3%)
Gamma-glutamyltransferase increased	1 (0.4%)	1 (0.4%)	0	2 (0.3%)
Nervous system disorders	3 (1.2%)	3 (1.1%)	4 (3.9%)	10 (1.6%)
Peripheral sensory neuropathy	1 (0.4%)	0	1 (1.0%)	2 (0.3%)
Syncope	0	1 (0.4%)	1 (1.0%)	2 (0.3%)
Metabolism and nutrition disorders	2 (0.8%)	2 (0.7%)	3 (2.9%)	7 (1.1%)
Hyperglycaemia	1 (0.4%)	1 (0.4%)	0	2 (0.3%)
Skin and subcutaneous tissue disorders	0	4 (1.4%)	2 (1.9%)	6 (1.0%)
Rash generalised	0	1 (0.4%)	1 (1.0%)	2 (0.3%)
Hepatobiliary disorders	0	2 (0.7%)	2 (1.9%)	4 (0.6%)
Hyperbilirubinaemia	0	1 (0.4%)	2 (1.9%)	3 (0.5%)
Musculoskeletal and connective tissue disorders	2 (0.8%)	2 (0.7%)	0	4 (0.6%)
Renal and urinary disorders	2 (0.8%)	2 (0.7%)	0	4 (0.6%)
Acute kidney injury	2 (0.8%)	1 (0.4%)	0	3 (0.5%)

Key: D=Daratumumab, Vd=bortezomib-dexamethasone, Rd=lenalidomide-dexamethasone, Pd=pomalidomide-dexamethasone.
Keys: TEAE = treatment-emergent adverse event.
[a]GEN503 is excluded from this summary as it did not collect dose delay and dose skip information.
[b]Infusion modification prior to infusion start includes infusion skipping or delay.
Note: Adverse events are reported using MedDRA version 18.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.
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Post marketing experience

A cumulative review was performed on all post-marketing spontaneous cases of daratumumab and all events received by the MAH and entered into global safety database cumulatively through 15 May 2016. The results suggest that the drug's post-marketing safety profile is consistent with the known safety profile of daratumumab as a single agent indicated for the treatment of patients with relapsed and refractory multiple myeloma.

The search of the global safety database retrieved a total of 289 cases. Of these, 266 were further analyzed. Among the 266 cases, 138 were serious and 128 were non serious. Of the cases reporting patient sex, 52% (93/179) concerned males. The patients ranged in age from 38 to 88 years (mean age 64.4 years, median age 65 years). The outcome was non-fatal in majority of the cases (92.1%; 245/266).

Review of the serious cases (n=138), which reported 366 events, revealed that the following 4 events were reported with greatest frequency: IRRs (9.6%; 35/366), dyspnoea (4.4%; 16/366), death (4.1%; 15/366) and decreased platelet count/thrombocytopenia (5.2%; 19/366). In many of the cases, the reported events are consistent with listed events in the company core data sheet for daratumumab.

Of the 138 serious cases reviewed, event outcome was fatal in 21 cases, in 13 cases the cause of death was unspecified and in 8 cases, the fatal MedDRA PTs reported were: death, pancytopenia, plasma cell myeloma, and sepsis (reported twice each); acute respiratory failure, asthenia, cardiac disorder, cardiac failure congestive, central nervous system necrosis, cerebrovascular accident, disease progression, febrile neutropenia, leukocytosis, leukoencephalopathy, metabolic acidosis, plasmablastic lymphoma, tachycardia, and tachypnoea (reported once each).

2.5.1. Discussion on clinical safety

Safety data from a total of 1182 subjects were collected in order to evaluate the safety profile of daratumumab together with standard background therapy, 664 subjects received daratumumab in combination with standard background therapies and 518 subjects received background therapies alone.

The proposed treatment dose applied (16 mg/kg) corresponds to the treatment dose of the majority of subjects included in the studies. Long term data (>6 months) was obtained from 141/243 subjects in the DVd group and 282/318 subjects in the DRd group, including a total of 158 subjects who received treatment for more than a year. The number of exposed subjects and degree of exposure is considered sufficient to evaluate the safety of daratumumab in combination with the background therapies.

The majority of subjects in the studies experienced AEs. Most notably, infusion related reactions were common and justify the recommendation of pre- and post-infusion steroid treatment. Other frequently occurring AEs were fatigue, nausea, anaemia, neutropenia, thrombocytopenia, upper respiratory tract infection, diarrhoea and peripheral sensory neuropathy.

The TEAEs reported for subjects in the daratumumab+ background group were similar to those reported in the background group, and included known toxicities of lenalidomide/bortezomib and those of daratumumab as monotherapy. In the daratumumab+lenalidomide+dexamethssone (DRd and Rd) group, the most commonly reported TEAEs were: neutropenia, diarrhea, fatigue, upper respiratory tract infection, and anemia. Neutropenia was more often observed as a TEAE in the DRd group compared with the Rd group (DRd: 59%; Rd: 43%) particularly in the first 2 cycles of treatment (DRd: 48%; Rd: 26%) and in subjects ≥ 65 years (DRd: 60%, Rd: 41%). This difference could be due to a more frequent dosing of daratumumab treatment during this period. For the daratumumab+bortezimib+dexamethasone (DVd and Vd) group, the most commonly reported TEAEs were: thrombocytopenia, peripheral sensory neuropathy, anemia, and fatigue. Peripheral neuropathy is a well-known adverse effect due to bortezomib, this may also be affected by comorbidities or underlying multiple myeloma.

Grade 3 and 4 adverse events seemed to be higher in the DVd group (76% and versus 62%, respectively). This increase in Grade 3 or 4 TEAEs was mainly due to haematologic TEAEs as thrombocytopenia (45% versus 33%), neutropenia (13% versus 4%) and lymphopenia (10% versus 3%) and was more prominent in early cycles of the treatment. However the incidence of bleeding was low during the study (DVd: 7%; Vd: 4%). The cytopenias are more prominent in the early cycles of treatment.

Infusion-related reactions are usually associated with administration of daratumumab. The TEAE terms used to describe IRRs and the timing of the IRRs with respect to the start of the daratumumab infusion were consistent with the IRRs previously reported for daratumumab in monotherapy studies. Most IRRs were Grade 1 or 2 and were experienced on Day 1 of the first infusion of daratumumab. In the MMY3003 and MMY3004 studies, IRRs were reported in 48% and 45% of subjects respectively in the daratumumab+lenalidomide+dexamethasone (DRd) and the daratumumab+bortezomib+dexamethasone studies (DVd). Few subjects discontinued daratumumab due to IRRs, 1 subject in the DRd group, and 2 in the DVd group.

Infections and infestations, a common problem in the treatment of patients with multiple myeloma, were reported in 83% of subjects in the DRd group vs. 73% in the Rd group, and 68% in the DVd group vs. 53% in the Vd group. However the incidence of grade 3 or 4 infections was the same between the treatment groups, both in the DRd/Rd group (28% and 23% respectively) and in the DVd/Vd groups (21% and 19% respectively). The majority of infections were mild (Grade 1 or 2) and did not require hospitalization. The most common infections were respiratory disorders such as upper respiratory tract infection, bronchitis, sinusitis, or nasopharyngitis, which were common across all regimens.

Daratumumab may increase neutropenia and thrombocytopenia induced by background therapy. Complete blood cell counts should be monitored periodically during treatment according to manufacturer's prescribing information for background therapies. Patients with neutropenia should be monitored for signs of infection. Daratumumab delay may be required to allow recovery of blood cell counts. No dose reduction of daratumumab is recommended. Supportive care with transfusions or growth factors should be considered (SmPC section 4.4). Based on the above, both neutropenia and thrombocytopenia have been classified as important identified risks in the Risk Management Plan (RMP).

Patients treated with daratumumab combination therapy (n = 299) were evaluated for anti-therapeutic antibody responses to daratumumab at multiple time points during treatment and up to 8 weeks following the end of treatment. Following the start of daratumumab treatment, 2 (0.7%) of the combination therapy patients tested positive for anti daratumumab antibodies; 1 of the combination therapy patients developed transient neutralizing antibodies against daratumumab (SmPC section 5.1).

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time. In the event of a planned transfusion blood transfusion centres should be notified of this interference with indirect antiglobulin tests. If an emergency transfusion is required, non-cross matched ABO/RhD compatible RBCs can be given per local blood bank practices (SmPC, sections 4.4 and 4.5). Educational materials will be distributed to Health Care Professionals (HCPs) and blood banks to advise on the risk of and solutions for interference for blood typing. Patient ID cards will be distributed to increase awareness to patients about the interference of blood typing occurring with daratumumab. A survey to measure awareness of blood banks and HCPs on the interference of blood typing is requested and results are expected to be provided in the PSUR (please see RMP section 2.6).

No subjects in DVd, Vd, or DPd groups had an AE of QT prolongation. QT prolongation was reported as an AE for 6 subjects (2%) in the DRd group and 1 subject (0.4%) in the Rd group. QT prolongation has been added as an important potential risk and the secondary objective of study SMM2001 which is a randomised Phase 2 trial to evaluate 3 daratumumab dose schedules in smouldering multiple myeloma, is to determine if daratumumab has an effect on QT interval. The study results are expected to be submitted by the end of 2018 (please see RMP section 2.6).

Discontinuations from treatment (2% to 5%) and deaths (0.8% to 2%) due to infection were rare and balanced between groups.

Pneumonia occurred in 11% to 13% of the study population and was the most commonly reported, severe (Grade 3 or 4) infection (7% to 10%) and also the most commonly reported serious infection (7% to 9%). The occurrence of pneumonia was balanced between treatment groups, and did not result in a high rate of treatment discontinuations (DRd/DVd: 3 subjects in each group, Rd/Vd: 2/1 subjects) or deaths (DRd/DVd: 2/1 subjects, Rd/Vd: 2 subjects in each group). The rate of opportunistic infections across all groups was generally low.

Dose modifications of daratumumab typically were dose delays or skipped doses prior to the start of an infusion. In the DVd group, 36% of subjects had modifications to daratumumab dosing, the 2 most common TEAEs were thrombocytopenia (12%) and pneumonia (5%). In the DRd group 37% of subjects had modifications to daratumumab dosing, the 2 most common TEAEs were neutropenia (10%) and pneumonia (4%).

The tolerability of the DRd combination is supported by the low frequency of study treatment discontinuation due to TEAEs (DRd 7%, Rd 8%) and the DVd combination, DVd 7% and Vd 9% respectively).

Both bortezomib and lenalidomide increase the risk of herpes zoster reactivation, but despite prophylactic antiviral therapy was administered; herpes zoster was reported in some of the subjects. However not all subjects received prophylactic antiviral treatment. The incidence of herpes zoster reactivation was low and balanced between treatment groups. Although small numbers, herpes zoster reactivation was lower in subjects who received prophylactic treatment than in those who did not. This is reflected in the SmPC.

Peripheral neuropathy which is a well-known adverse effect due to bortezomib and also might be due to underlying disease was reported in 46% of the DVd group and 38% in the Vd group. The MAH analysed possible risk factors of peripheral neuropathy, in conclusion, the higher rate of peripheral neuropathy was due to longer exposure to bortezomib, but factors such as prior history of peripheral neuropathy, diabetes mellitus, prior exposure to thalidomide and older age might potentially contribute to the symptoms, although no statistical significant difference was noted.

Overall the frequency of severe AEs is considered acceptable. Of note, 21/138 patients died, and it may be questioned whether this number is higher than expected. It is endorsed, that the patient population was heavily pretreated with refractory/relapsed disease. The MAH has reviewed the post marketing data for the cause of death as reported in spontaneous reports, 18 deaths among 2711 patients/months exposure were reported. A detailed analysis of fatal TEAEs showed that cause of death could be attributed to end stage disease or events associated with the underlying malignant disease, eg. infection and multi-organ failure. Thus the numbers of death are not higher than what could be expected in this clinical setting.

Blood samples from the study participants were analysed for anti-daratumumab antibodies. In 2 out of 298 evaluable patients anti-daratumumab antibodies were detected, however the titer for the positive samples (1:20) demonstrated detection only at the minimum required dilution of the method, and thus was near the lower limit of the antidaratumumab antibody detection method. In order to improve the immunogenicity method's ability to detect anti-daratumumab antibodies in the presence of high trough levels of daratumumab, a study has been requested for which study results are expected by the end of 2018 (please see RMP section 2.6).

No drug-drug interaction studies were performed. However, as daratumumab is an IgG, renal excretion and hepatic enzyme-mediated metabolism is considered unlikely.

2.5.2. Conclusions on clinical safety

Based on data from 664 subjects included in the pivotal and supportive studies, the safety profile is consistent with the known toxicities of the respective background therapies and daratumumab monotherapy. Daratumumab may increase the rate of cytopenias known to be associated with each background therapy (neutropenia with lenalidomide or pomalidomide and thrombocytopenia with bortezomib). However they appeared to be manageable by supportive care and dose modifications, and did not result in an increase in discontinuation of study treatments or deaths. Both neutropenia and thrombocytopenia have been classified as important identified risks in the Risk Management Plan (RMP).

Thus, overall daratumumab in combination with standard background therapies as lenalidomide+dexamethasone and bortezomib+dexamethasone is well tolerated, with a manageable side effect profile.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 2.0 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content, as per PRAC advice:

Safety concerns

Table 46. Summary of Safety Concerns

Important Identified Risks	
	Infusion Related Reactions (IRRs)
	Interference for blood typing (minor antigen) (Positive Indirect Coombs' test)
	Neutropenia
	Thrombocytopenia
Important Potential Risks	
	Infections
	Prolonged decrease in NK cells
	QTc prolongation
	Immunogenicity
	Intravascular haemolysis
Missing Information	
	Use in pregnancy and lactation
	Reproductive and developmental toxicity
	Use in the elderly ≥75 years
	Use in patients with moderate or severe hepatic impairment
	Long term use (>2 years)

Pharmacovigilance plan

Table 47. Summary of the Pharmacovigilance Plan

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Survey of additional risk minimisation measures for interference of blood typing (category 3)	To measure awareness of blood banks and HCPs on the interference of blood typing	Interference for blood typing (minor antigen) (Positive Indirect Coombs' test)	Planned	Protocol to be submitted: 3 months after EC decision Initial evaluation: 18 months following the launch of the product Final Report: Final results will be presented in the next PSUR/PBRER after the survey has been concluded
Trial SMM2001: A randomised Phase 2 trial to evaluate 3 daratumumab dose schedules in smouldering multiple myeloma. (category 3)	As a secondary objective to determine if daratumumab has an effect on QT interval	Effect of daratumumab on QT interval	Started	4th Quarter 2018
Investigate new method for detecting antidrug antibodies (category 3)	Improve the immunogenicity method's ability to detect anti-daratumumab antibodies in the presence of high trough levels of daratumumab	Immunogenicity	Planned	4th Quarter of 2018

Risk minimisation measures

Table 48. Summary table of risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks:		
Infusion Related Reactions (IRRs)	SmPC sections 4.2, 4.4, 4.8	None
Interference for blood typing (minor antigen) (Positive Indirect Coombs' test)	SmPC section 4.4	Educational materials will be distributed to HCPs and blood banks to advise regarding the risk of and solutions for interference for blood typing. As well as patient ID cards will be distributed to increase awareness to patients about the interference of blood typing occurring with daratumumab.
Neutropenia	SmPC sections 4.4 and 4.8	None
Thrombocytopenia	SmPC section 4.4 and 4.8	None
Important potential risks:		
Infections	SmPC section 4.8	None
Prolonged decrease in NK cells	SmPC section 5.1	None
QTc prolongation	SmPC section 5.1	None
Immunogenicity	SmPC section 5.1	None
Intravascular haemolysis	SmPC section 4.8	None
Missing Information:		
Use in pregnancy and lactation	SmPC section 4.6	None
Reproductive and developmental toxicity	SmPC sections 4.6 and 5.3	None
Use in the elderly ≥75 years	SmPC sections 4.2 and 5.2	None
Use in patients with moderate or severe hepatic impairment	SmPC sections 4.2 and 5.2 .	None
Long term use (>2 years)	None proposed.	None

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex

I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC have been updated. Particularly, a new warning with regard to neutropenia/thrombocytopenia induced by background therapy has been added to the product information. The Package Leaflet has been updated accordingly.

Furthermore, Annex II is updated to reflect on the fulfilment of the specific obligations following submission of the final results of studies MMY3003 and MMY3004. As a consequence, the conditional marketing authorisation is switched to a full marketing authorisation (see section 3.7 and section 4).

2.7.1. User consultation

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

- The package leaflet included in this current application has the same format as the one previously tested.
- With the 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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Multiple myeloma is an incurable malignant disorder of the plasma cells, characterised by uncontrolled and progressive proliferation of a plasma cell clone. The median age of patients at diagnosis is 65 years. The abnormal plasma cell proliferation accumulates in the bone marrow, displacing the normal hematopoietic tissue. The plasma cells produce a monoclonal antibody, paraprotein (M-protein and free-light chain), which is an immunoglobulin (Ig) or a fragment of one that has lost its function (Kyle 2009, Palumbo 2011). The normal immunoglobulins (Ig) are compromised leading to increased susceptibility to infections.

3.1.2. Available therapies and unmet medical need

Current treatment options for patients with relapsed or refractory multiple myeloma include combination chemotherapy, proteasome inhibitors (PIs; eg, bortezomib, carfilzomib, ixazomib), immunomodulatory agents (IMiDs; eg, thalidomide, lenalidomide, and pomalidomide), histone deacetylase inhibitors (eg, panobinostat); monoclonal antibodies (mAb) (eg, daratumumab and elotuzumab), high-dose chemotherapy, and autologous stem cell transplantation (ASCT).

3.1.3. Main clinical studies

The clinical package of daratumumab for the treatment of subjects with relapsed or refractory multiple myeloma is primarily supported by data from 2 pivotal phase 3 randomised open-label studies, MMY3003 and MMY3004, where daratumumab is added to one of two established standard of care background

regimens. In the MMY3003 study, the efficacy of daratumumab when combined with lenalidomide and low-dose dexamethasone (DRd) was compared with lenalidomide and low-dose dexamethasone (Rd), and in the MMY3004 study, the efficacy of daratumumab when combined with bortezomib and dexamethasone (DVd) was compared with bortezomib and dexamethasone (Vd). Both studies were performed in patients with relapsed or refractory multiple myeloma, who had received at least one prior therapy.

3.2. Favourable effects

Study MMY3003 (daratumumab in combination with lenalidomide (DRd) compared with Rd):

Treatment with DRd resulted in a 63% reduction in the risk of disease progression or death compared with Rd alone (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001). The median PFS was not reached for the DRd group and was 18.4 months for the Rd group. The PFS results were consistent among all pre-planned sensitivity analyses and across different clinically relevant pre-specified subgroups, such as number and type of prior lines of therapy, staging, cytogenetic risk group, and whether refractory to last treatment.

The ORR was higher in the DRd group, 93% compared with 76% in the Rd group (p<0.0001).

The rate of VGPR or better was 76% in the DRd group compared with 44% in the Rd group (p<0.0001). Subjects in the DRd group had higher rate of CR or better (43%) compared with the Rd group (19%) (p<0.0001).

More subjects were MRD negative at the 10^{-4} threshold who received DRd, 29% compared with those who received Rd, 8% (chi-squared odds ratio 4.85; 95% CI: 2.93, 8.03; p<0.0001).

The 18-month OS rate was 86.1% (95% CI: 79.9, 90.5) in the DRd group and 75.6% (95% CI: 59.8, 85.9) in the Rd group.

Study MMY3004 (daratumumab in combination with bortezomib (DVd) compared with Vd):

Treatment with DVd resulted in a 61% reduction in the risk of disease progression or death compared with Vd (HR=0.39; 95% CI: 0.28, 053; p<0.0001). The median PFS was not reached for the DVd group and was 7.2 months for the Vd group. The PFS result were consistent among all pre-planned sensitivity analyses and across different clinically relevant prespecified subgroups, such as number and type of prior lines of therapy, staging, cytogenetic risk group, and whether refractory to last treatment.

The ORR was higher in the DVd group, 83% compared with 63% in the Vd group (p<0.0001).

The rate of VGPR or better was 59% in the DVd group, compared with 29% in the Vd group (p<0.0001). Subjects in the DVD group had a higher rate of CR or better, 19% vs. 9% in the Vd group (p=0.0012).

More subjects were MRD negative at the 10-4 threshold in the DVd group, 14% compared with 3% in the Vd group (chi-square odds ratio =5.37; 95% CI: 2.33, 12.37; p<0.0001).

The 12-month survival rates were 82% for both treatment groups.

Generally the subgroup analyses and the secondary endpoints support the robustness and clinical meaningfulness of adding daratumumab to standard background therapies as lenalidomide + dexamethasone and bortezomib + dexamethasone.

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties and limitations about favourable effects.

3.4. Unfavourable effects

The safety profile of daratumumab in combination with lenalidomide/dexamethasone and bortezomib/dexamethasone was generally consistent with the known safety profiles of daratumumab and the respective background therapies.

Treatment with daratumumab induced a relatively high incidence of IRRs, 47% subjects experienced an IRR, the majority (approximately 95%) occurred during the first infusion and the incidence is reduced during subsequent cycles of treatment. The majority of IRRs are mild (Grade 1 or 2) and no Grade 4 or 5 IRRs occurred. Both acute and delayed onset infusion-related reactions have been observed and for this reason both pre-and post-infusion treatment with steroids is recommended.

Overall, other frequently occurring AEs were: fatigue, nausea, anaemia, neutropenia, thrombocytopenia, upper respiratory tract infection and diarrhoea.

While the incidence of Grade 3 or 4 TEAEs and serious TEAEs was slightly higher in the daratumumab combination groups, TEAEs were managed by supportive care and dose modifications, and did not result in an increase in discontinuation of study treatments or deaths. Discontinuation of treatment due to TEAEs was low and balanced between treatment groups, the most common cause being infections.

The incidence of death within 30 days of the last dose of study drug was relatively low and balanced between treatment groups, the most common reason was due to infections (1% to 2%).

3.5. Uncertainties and limitations about unfavourable effects

Daratumumab may increase the rate of cytopenias known to be associated with each background therapy (neutropenia with lenalidomide or pomalidomide and thrombocytopenia with bortezomib). However they appeared to be manageable by supportive care and dose modifications, and did not result in an increase in discontinuation of study treatments or deaths. Both neutropenia and thrombocytopenia have been classified as important identified risks in the Risk Management Plan (RMP).

3.6. Effects Table

Table 49. Effects Table for daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	Median time from randomization to progression or death	Months	DRd NE DVd NE	Rd 18.4 (13.9,NE) Vd 7.2 (6.2, 7.9)	HR=0.37; 95% CI: 0.27, 0.52; p<0.0001 HR=0.39; 95% CI: 0.28, 053; p<0.0001	Numbers presented were taken from studies MMY003 and MMY004 (see 'clinical efficacy' section)
Unfavourable Effects						
TEAEs of at least 10% in either treatment group		%	DRd: 98.4 DVd:98.8	Rd:92.5 Vd:95		See 'clinical safety' section

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Infusion Related Reactions	Incidence of grade 3 or 4 events	%	DRd 5.3 DVd 9	NA		
Neutropenia	Incidence of grade 3 or 4 events	%	DRd 52 DVd 12.8	Rd 37 Vd 4.2	Increased rate in lenalidomide combination	
Thrombocytopenia	Incidence of grade 3 or 4 events	%	DRd 13 DVd 45.3	Rd 13 Vd 32.9	Increased rate in bortezomib combination	
Infections	Incidence of grade 3 or 4 events	%	DRd 28 DVd 21.4	Rd 23 Vd 19%		

Abbreviations: Abbreviations: AE: adverse event, CR:Complete response, DRd: daratumumab-lenalidomide-dexamethasone, DVd :daratumumab-bortezomib-dexamethasone, HR: hazard ratio, MRD: minimal residual disease, NE: not evaluable, ORR: overall response rate, PFS: progression-free surviva, PR: Partial response, Rd: lenalidomide-dexamethasone, Scr: Stringent complete response, TEAEs: treatment-emergent adverse events, Vd: bortezomib-dexamethasone, VGPR: Very good partial response

Data cut-off dates: MMY003: 7 March 2016, MMY004: 11 January 2016.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The two pivotal studies demonstrated a positive effect on PFS. This endpoint and the effects observed are considered clinically significant, when compared to background therapies alone. The effects are convincing and supported by secondary endpoints including response rate and MRD negativity. Although mature OS data are still not available it is reasonable to exclude a possible detrimental effect. Overall, the effect observed in PFS is sufficient to establish the efficacy of the combination of daratumumab, lenalidomide and dexamethasone, and of the combination daratumumab, bortezomib, and dexamethasone in the proposed indications.

The safety profile is as expected in the context of the patient population and for standard background anti-myeloma therapies and manageable.

3.7.2. Balance of benefits and risks

The efficacy of daratumumab in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone in the target population is considered clinically relevant and, in the view of the manageable, and consistent with the known safety profile of daratumumab and the two background therapies, the benefits are considered to outweigh the combined risks.

Additional considerations on the benefit-risk balance

The initial marketing authorisation application for Darzalex was based on an ORR of 29% obtained with daratumumab in pivotal study MMY2002. This effect was considered significant and clinically relevant in 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 despite the absence of confirmatory controlled data. Patients were heavily pretreated, and 79.8% and 69.4% had received more than 3 lines of prior therapy in the MMY2002 and GEN501 studies respectively, further 95% and 95.8% respectively were refractory to both PI's and IMiD's. Together with an acceptable safety-profile in patients in the proposed indication, the benefit-risk balance was considered positive. However, there was a need to provide controlled data in a larger target population within the same condition in order to further define the benefit-risk of daratumumab in the initial indication as follows:

- In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3003, a phase III randomised study investigating lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.
- In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3004, a phase III randomised study investigating bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.

With the current application, given the convincing effect and manageable safety profile, comprehensive clinical data has been provided to confirm efficacy and safety of daratumumab in the initial indication. Even if Study MMY 3003 and Study MMY 3004 were conducted in combination, the results are relevant in view of the overlapping populations and the design of the study allows assess the effect of daratumumab in the studied combinations.

In conclusion, the controlled data confirm the efficacy and safety of daratumumab monotherapy, and that the risk-benefit balance of daratumumab in 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 is favourable.

3.8. Conclusions

The overall B/R of daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy is positive.

In conclusion, the controlled data of studies MMY3003 and MMY3004 confirm the efficacy and safety of daratumumab monotherapy, and that the risk-benefit balance of daratumumab in 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 is favourable. The CHMP agreed on the fulfilment of the specific obligations.

4. Recommendations

Similarity with authorised orphan medicinal products

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

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, II and IIIB

Extension of Indication for Darzalex in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC are updated in order to update the information on the target patient population, posology, warnings, interactions, efficacy and pharmacokinetics. A new warning is introduced in section 4.4 regarding neutropenia/thrombocytopenia induced by background therapy.
Furthermore, the CHMP is of the opinion that all specific obligations have been fulfilled following submission of the final results of studies MMY3003 and MMY3004 and in light of the data generated and the evidence of compliance with the specific obligations, the CHMP recommends the granting of a marketing authorisation in accordance with Article 14(1) of Regulation No 726/2004.
The Package Leaflet and Risk Management Plan (RMP version 2.1) are updated in accordance.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

As a result of the fulfilment of the specific obligations, they are removed from the Annex II:

Description	Due date
In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of DARZALEX, the MAH should submit the results of study MMY3003, a phase III randomised study investigating lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.	30 September 2017
In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of DARZALEX, the MAH should submit the results of study MMY3004, a phase III randomised study investigating bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.	31 December 2016

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

This CHMP recommendation is subject to the following conditions, amended to reflect on the deletion of the above table from the Annex II.E:

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Darzalex (daratumumab) in each Member State (MS) the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, aiming at increasing awareness about the Important Identified Risk of "Interference for blood typing (minor antigen) (Positive Indirect Coombs' test)" and providing guidance on how to manage it.

The MAH shall ensure that in each MS where Darzalex (daratumumab) is marketed, all HCPs and patients who are expected to prescribe, dispense and receive this product have access to/are provided with the below.

The HCPs and Blood Banks educational materials, shall contain the following key elements:
- The guide for HCPs and Blood Banks, to advice about the risk of interference for blood typing and how to minimise it;
- The Patient Alert Card.

The Guide for HCP and Blood Banks shall contain the following key elements:
- All patients should be typed and screened prior to start treatment with daratumumab; alternatively, phenotyping may also be considered;
- Daratumumab-mediated positive indirect Coombs test (interfering with cross-matching of blood) may persist for up to 6 months after the last product's infusion, therefore, the HCP should advise the patient to carry the Patient Alert Card until 6 months after the treatment has ended;
- Daratumumab bound to Red Blood Cells (RBCs) may mask the detection of antibodies to minor antigens in the patient's serum;
- The determination of a patient's ABO and Rh blood type are not impacted;
- The interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell Blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, genotyping may also be considered;
- In case of urgent need for transfusion, non-cross matched ABO/RhD compatible RBC units can be administered as per local bank practices;
- In the event of a planned transfusion, the HCPs should notify blood transfusion centres about the interference with indirect antiglobulin tests;
- Reference to the need to consult the Summary of Product Characteristics (SmPC);
- Reference to the need of giving the Patient Alert Card to the patients and to advise them to consult the Package Leaflet (PL).

The Patient Alert Card, shall contain the following key elements:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using Darzalex (daratumumab), and that this treatment is associated with the Important Identified Risk of Interference for blood typing (minor antigen) (Positive Indirect Coombs' test), which might persist for up to 6 months after the last product's infusion, and a clear reference that the patient should continue to carry this card until 6 months after the treatment has ended;
- Contact details of the Darzalex (daratumumab) prescriber;
- Reference to the need to consult the Package Leaflet (PL).

These conditions fully reflect the advice received from the PRAC.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers by consensus that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies (see appendix 2).

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

Extension of Indication for Darzalex in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 5.1 and 5.2 of the SmPC are updated in order to update the information on the target patient population, posology, warnings, interactions, efficacy and pharmacokinetics. A new warning is introduced in section 4.4 regarding neutropenia/thrombocytopenia induced by background therapy.
Furthermore, the CHMP is of the opinion that all specific obligations have been fulfilled following submission of the final results of studies MMY3003 and MMY3004 and in light of the data generated and the evidence of compliance with the specific obligations, the CHMP recommends the granting of a marketing authorisation in accordance with Article 14(1) of Regulation No 726/2004. Annex II is updated to remove the fulfilled specific obligations.
The Package Leaflet and Risk Management Plan (RMP version 2.1) are updated in accordance.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet.

Summary

Please refer to the Scientific Discussion Darzalex EMEA/H/C/004077/II/0002.

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Appendix

CHMP AR on the novelty of the indication/significant clinical benefit in comparison with existing therapies dated 23 February 2017

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 February 2017
EMA/CHMP/112064/2017
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on the significant clinical benefit in comparison with existing therapies in accordance with Article 14(11) of Regulation (EC) No 726/2004

Invented name: Darzalex

International non-proprietary name: Daratumumab

Procedure no.: EMEA/H/C/004077/II/0002

Marketing authorisation holder (MAH): Janssen-Cilag International N.V.

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Send a question via our website www.ema.europa.eu/contact

An agency of the European Union

1. Introduction

In accordance with the provisions of Article 14(11) of Regulation (EC) No 726/2004, Marketing authorisation holder (MAH) Janssen-Cilag International N.V. has applied for an additional one year marketing protection period in the framework of Darzalex procedure (EMEA/H/C/004077/II/0002).

The request was based on the MAH's position that Darzalex represents a significant clinical benefit in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy in comparison with existing therapies.

2. Justification of significant clinical benefit as presented by the MAH

2.1. Demonstration of new therapeutic indication

A conditional marketing authorization was approved by the European Commission on 20 May 2016 for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) and who have demonstrated disease progression on the last therapy.
The Marketing Authorisation Holder (MAH) is now seeking to expand the indication for daratumumab based primarily on data from 2 comparator controlled Phase 3 studies: MMY3003 (daratumumab plus lenalidomide and dexamethasone) and MMY3004 (daratumumab plus bortezomib and dexamethasone). Based on results from these trials, the MAH is seeking to update the indication to include the treatment of subjects with DARZALEX in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone with relapsed or refractory multiple myeloma who have received at least one prior therapy.

In accordance with the reference to Article 14(11) of Regulation (EC) No 726/2004, the applicant wishes to claim an additional one year of marketing protection as the new therapeutic indication for daratumumab (DARZALEX is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy) represents a significant clinical benefit in comparison with existing therapies.

2.2. Details of existing therapies

Please see below

2.3. Significant clinical benefit based on improved efficacy

The treatment of multiple myeloma has emerged covering a number of treatment options, such as proteasome inhibitors (PIs): bortezomib, carfilzomib, ixazomib; immunomodulatory drugs (IMiDs): thalidomide, lenalidomide, and pomalidomide; histone deacetylase (HDAC) inhibitors such as panobinostat, as well as monoclonal antibodies (mAb) such as Elotuzumab.
For the treatment of relapsed or refractory multiple myeloma, strategies involving PIs or IMiDs used in combination with a steroid have become the standard of care treatment because they have demonstrated good clinical efficacy along with acceptable and manageable safety profiles.

Immunomodulatory Agents
Two agents in particular (lenalidomide and pomalidomide), have been used to treat patients with relapsed or refractory multiple myeloma, especially patients who are bortezomib-refractory or intolerant. Progression-free survival from 2 phase 3 trials of lenalidomide and high dose dexamethasone (RD) versus dexamethasone alone (D) demonstrated a PFS of approximately 11 months for RD and 4.7 months for D (Weber et al. 2007). Clinical studies of lenalidomide and low-dose dexamethasone (Rd) compared to RD, showed a survival advantage and a significantly reduced toxicity profile compared with the RD treatment

(Rajkumar et al. 2010). Toxicity associated with the Rd combination are myelosuppression and thromboembolic events, which are usually manageable (Latif et al. 2012). Rd therefore became one of the standard options for patients with multiple myeloma.

Pomalidomide as a single agent has a low anti-myeloma activity, but in combination with dexamethasone (Pd) to patients with relapsed or refractory multiple myeloma (≥2 prior therapies, including lenalidomide andbortezomib), the clinical outcome was improved. The PFS was prolonged, 4.2 months vs. 2.7 months for pomalidomide alone and the response rates were 33% vs 18%, respectively (Richardson 2014). After a median follow-up of 10.0 months in a separate Phase 3 study which compared Pd to high-dose dexamethasone, the median PFS for Pd was 4·0 months versus 1·9 months for highdose dexamethasone (HR=0·48 [95% CI 0·39–0·60]; p<0·0001). (SanMiguel 2013).
Similar to lenalidomide, the manageable toxicity risks of pomalidomide include thromboembolic events and myelosuppression and also neutropenia (including febrile neutropenia) infection, anemia, and thrombocytopenia.

Proteasome Inhibitors
Three agents in particular (bortezomib, carfilzomib and ixazomib), have been used to treat patients with relapsed or refractory multiple myeloma. The bortezomib-dexamethasone (Vd) combination is widely used and has yielded ORRs of 62% to 70% (Dimopoulous 2015, Kropff 2005) compared with 38% to 50% when bortezomib was administered as a single-agent (Jagannath 2004, Orlowski 2007). In a Phase 3 study of Vd versus dexamethasone, the PFS was 6.2 months and 3.5 months respectively.
Retreatment of bortezomib in subjects previously exposed to bortezomib who now have relapsed disease demonstrated a 40% ORR (Petrucci 2013). Toxicities associated with bortezomib use include peripheral neuropathy, hematologic toxicities, diarrhea, fatigue, dyspnea, and zoster reactivation (Merin 2014).

Carfilzomib administered in combination with lenalidomide and dexamethasone (KRd) resulted in significantly improved PFS (26.3 months) compared with Rd alone (17.6 months) (HR=0.69) (Stewart 2015). The ORR was 87% vs 67% in the KRd vs Rd groups, respectively, with 38% and 9% of patients having a CR or better, and 14% and 4% of patients, respectively, having a stringent CR (sCR). Separately, carfilzomib administered in combination with dexamethasone (Kd) resulted in significantly improved PFS (18.7 months) compared with bortezomib and dexamethasone (Vd, 9.4 months) (HR=0.53) (Dimopoulos 2016). The percentage of patients having a CR or better was 11% and 4% in the Kd vs Vd groups, respectively, with 2% of patients in each group having a stringent CR. Hematologic toxicities, pneumonia, hyponatremia, fatigue, hypophosphatemia, infusion reactions, chest pain, and heart failure are common toxicities associated with carfilzomib (Merin 2014). Carfilzomib product labels carry a warning due to risk of cardiac arrest, congestive heart failure, myocardial ischemia, sudden cardiac death and pulmonary hypertension (Kyprolis Product Information).

Ixazomib is an oral PI, when administered in combination with Rd, PFS was 20.6 months compared to 14.7 months when compared with Rd alone [HR=0.74]); ORR was 78% vs 72%, respectively, with 48% and 39% of patients, respectively achieving VGPR or better (Moreau 2016). Hematologic toxicities, fatigue, rash, decreased appetite, diarrhea, and vomiting are common toxicities associated with ixazomib (Merin 2014).

Therapies With Other Mechanisms of Action
Other agents such as Panobinostat, an oral pan-decetylase inhibitor, is a more recent anti-myeloma agent for patients with relapsed or refractory multiple myeloma. Although a positive effect on PFS and OR was demonstrated when combined with Vd, panobinostat is associated with severe and dose limiting toxicities. The drug seems more effective in more heavily pretreated population i.e., patients who have received a median of 2 prior therapies, including treatment with both bortezomib and an IMiD.
Elotuzumab, a monoclonal antibody, is a recent addition to the treatment of multiple myeloma and is indicated in combination with Rd for the treatment of patients who have received 1 to 3 prior therapies. A number of other classes are also available which include HDAC inhibitors, alkylating agents as well as anthracyclines. However, in addition to these existing therapies, there is still a need for more effective treatments with different mechanisms of action that provide alternative treatment options for these patients.

Daratumumab is a first-in-class, human IgG1 mAb with a MoA that is novel and completely distinct from other anti-myeloma treatment available.
Following scientific advice from the CHMP (Procedure: EMEA/H/SA/2456/1/FU/1/2014/PA/II) the applicant has conducted two comparative randomized Phase 3 studies of daratumumab in combination with established standard of care background regimens; either lenalidomide and dexamethasone (Study MMY3003) or bortezomib and dexamethasone (Study MMY3004). The objective of both studies was to compare the efficacy of daratumumab when combined with these background regimens and to assess if the daratumumab based combination would improve clinical outcomes in subjects with multiple myeloma who have previously been treated with at least one prior therapy when compared to the background regimen alone.

The addition of daratumumab to lenalidomide and dexamethasone (Rd) (MMY3003) or to bortezomib and dexamethasone (Vd)(MMY3004), results in an improvement in PFS, with a 63% reduction in the risk of disease progression or death when daratumumab is added to Rd (DRd) compared to Rd in Study MMY3003 (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001). In the MMY3004 study a 61% reduction in the risk of disease progression or death was reported, when daratumumab was added to Vd (DVd) compared with Rd (HR=0.39; 95% CI: 0.28, 053; p<0.0001). In both studies, the benefit was robust and consistent among all subgroups based on gender, race, age, baseline hepatic and renal impairment and geographical regions.
The positive effect was supported by improvements in key secondary endpoints including time-to-progression (TTP), overall response rate (ORR), depth of response as reflected by the rates of a very good partial response (VGPR) or better and complete response (CR) or better, rate of minimal residual disease (MRD) negativity, and duration of response (DOR).
In Study MMY3003, the ORR is significantly higher in subject receiving DRd, as compared to Rd alone (DRd: 93% vs Rd: 76%; p<0.0001). The responses are robust, with higher VGPR or better rates (DRd: 76% vs Rd: 44%) and rate of CR or better (DRd: 43% vs Rd: 19%). In addition, the MRD negativity rate is significantly higher (DRd: 29% vs Rd: 8%).
In Study MMY3004, the ORR is significantly higher in subjects receiving DVd, as compared to Vd alone (DVd: 83% vs Vd: 63%; p<0.0001). The responses are robust with higher VGPR or better rates (DVd: 59% vs Vd: 29%) and rate of CR or better (DVd: 19% vs Vd: 9%). In addition, the MRD negativity rate is significantly higher (DVd: 14% vs Vd: 3%).

In addition the applicant also conducted two Phase 1/2 studies where daratumumab was administered in combination with either pomalidomide and dexamethasone (Pd) (Study MMY1001), or lenalidomide and dexamethasone (Ld) (study GEN503). The primary objective of these studies was to evaluate safety and tolerability, and for the MMY1001 study, also to evaluate the overall response rate.
Adding daratumumab to another immunomodulatory agent (IMiD), pomalidomide, and dexamethasone (Pd) in heavily pretreated subjects in Study MMY1001, results in ORR (59%; 95% CI: 49; 69) CR or better rate (14%), and a median DOR of 13.6 months. Although these data are interesting, they should be interpreted with caution since no comparator was identified.

2.4. Significant clinical benefit based on improved safety

Safety data from a total of 1182 subjects are included in the safety population: 664 subjects received daratumumab in combination with standard background therapy and 518 subjects received background therapies alone.
With the exception of infusion related reactions (IRRs), the safety profiles of daratumumab in combination with Rd, Vd or Pd were similar to those of the background regimens.
Similar to the daratumumab single agent data, IRRs were experienced by approximately half of subjects receiving daratumumab-based regimens (DRd, DVd, DPd). The majority (94%) of IRRs were Grade 1 or 2, with 95% occurring during the first infusion. No Grade 4 or 5 IRRs occurred, and only 5 subjects (0.8%) discontinued treatment due to IRRs.

The incidence of Grade 3 or 4 TEAEs and serious TEAEs was higher in the daratumumab combination groups, the TEAEs could be managed by supportive care and dose modifications, and did not result in an increase in discontinuation of study treatment or deaths.

Daratumumab may increase cytopenias induced by background therapies, with thrombocytopenia being the most common for subjects receiving bortezomib based regimens and neutropenia the most common for subjects receiving lenalidomide- or pomalidomide-based regimens.
Neutropenia, which is a well known effect of lenalidomide and pomalidomide, was reported more frequently in the daratumumab combination groups than in background therapy alone (DRd: 62%; Rd: 43%; DPd: 79%). Most frequently, neutropenia occurred in the initial cycles, it was managed by dose modifications and growth factor use and rarely led to treatment discontinuation (<1%). The incidence of febrile neutropenia was low (≤7%).
Thrombocytopenia, a known effect of bortezomib, was reported by more subjects in the DVd group compared to the Vd group (DVd: 59%; Vd: 44%); however bleeding events were low and the majority were minor (Grade 1 or 2).
Anemia, all grades and Grade 3 or 4, was similar among all treatment groups in the randomized studies (all grades DRd: 31% vs Rd: 35% and DVd: 26% vs Vd: 31%;Grade 3 or 4: DRd: 12% vs Rd: 20% and DVd: 14% vs Vd: 16%).
Although the overall incidence of infections were reported by a higher percentage of subjects in the daratumumab containing groups compared to the respective background therapy, the majority of all infections were mild (Grade 1 or 2) and did not require hospitalization.
The incidence of Grade 3 or 4 infection was similar between the daratumumab combinations and the background therapies (DRd: 27%; Rd: 23%; DVd: 21%; Vd: 9%; DPd: 27%), with the most common being pneumonia.
Discontinuations from treatment (2% to 5%) and deaths (0.8% to 2%) due to infection were low and balanced between groups in the randomized studies.
Second primary malignancies (SPM) were reported at a low frequency in the DRd and DVd groups (<4%); no SPMs were reported in the DPd cohort.
Discontinuation of treatment due to TEAEs was low across all treatment groups (DRd: 7%; Rd: 8%, DVd: 7%; Vd: 9%, DPd: 13%), with the most common reason for discontinuation being infections (2% to 5%). Infections were also the most common treatment emergent adverse events (TEAEs) leading to death (1% to 2%), but TEAEs with an outcome of death were low across all treatment groups (DRd: 4%; Rd: 5%, DVd: 5%; Vd: 6%, DPd: 7%). Subgroup analyses showed generally comparable safety profiles in various subgroups based on age, gender, race, baseline renal function, baseline hepatic function, and geographic region.

2.5. Significant clinical benefit based on major contribution to patient care

Patient-reported outcome concerning functional status and well-being were assessed using 2 PRO measures, the EORTC-QLQ-C30 and the EQ-5D-5L. Compliance was comparable between treatment groups and baseline scores for daratumumab added to the 2 background therapies (DRd and DVd) compared to backbone therapies alone. The PRO results indicated no statistically significant difference between the combination of daratumumab to background therapies (DRd or DVd) and the corresponding background therapies in change from baseline or median time to improvement or worsening in the Global Health Status/QOL subscale of the EORTC-QLQ-C30 or the EQ-5D-5L Utility score or EQ-5D-5L Visual Analog Scale (VAS). When median time to worsening or improvement in the Utility Score or VAS was analysed, no statistically significant differences were observed between DRd and Rd or DVd and Vd.

3. Assessment of the MAH's justification of significant clinical benefit

3.1. Demonstration of new therapeutic indication

CHMP's position:

Daratumumab was previously approved in May 2016 as monotherapy to treat subjects with advanced stage multiple myeloma. The studies (GEN501 and MMY2002) supporting the approved indication included

end-stage refractory subjects who had received 4-5 (median) prior treatments with 69% and 80% of the subjects having > 3 prior therapies in the GEN501 and MMY2002 studies respectively.

The applicant is now extending the indication to include subjects who have less advanced disease and received at least 1 prior treatment, i.e. as second line treatment in multiple myeloma. The proposed additional indication for daratumumab in this application is for the treatment in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, of adult patients with multiple myeloma who have received at least one prior therapy.

The CHMP acknowledges this is a new indication of daratumumab earlier in the treatment pathway of multiple myeloma.

It is also acknowledged that the two randomized studies, MMY3003 and MMY3004, daratumumab added to 2 standard of care background regimens, either lenalidomide and dexamethasone or bortezomib and dexamethasone, show a significant efficacy improvement with an acceptable and manageable safety profile, and that this represents a new indication.

3.2. Details of existing therapies

CHMP's position:

The applicant has satisfactorily reviewed and detailed the characteristics and limitations of existing therapies.

3.3. Significant clinical benefit based on improved efficacy

CHMP's position:

Daratumumab is a novel monoclonal antibody targeting CD38 on multiple myeloma cells inducing tumour cell death through multiple mechanisms of action. The applicant has conducted 2 pivotal comparative phase 3 studies of daratumumab in combination with 1 of 2 well established standard of care background regimens; either lenalidomide and dexamethasone (Study MMY3003) or bortezomib and dexamethasone (Study MMY3004). The objective of both studies was to compare the efficacy of daratumumab when combined with these background regimens and to assess if, through this addition, the daratumumab based combination would improve clinical outcomes in subjects with multiple myeloma who have previously been treated with at least one prior therapy when compared to the background regimen alone.

The clinical trials were well-controlled and had clinically meaningful endpoints. Daratumumab added to Rd (DRd) (study MMY3003) or daratumumab added to Vd (DVd) (Study MMY3004) results in a 63% and 61% reduction in the risk of disease progression or death respectively, when compared with Rd (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001) or Vd (HR=0.39; 95% CI: 0.28, 053; p<0.0001) in subjects with multiple myeloma who received at least 1 prior therapy. In both studies, the PFS results were consistent among all preplanned sensitivity analyses and across different clinically relevant prespecified subgroups, such as number and type of prior lines of therapy, staging, cytogenetic risk group, and whether refractory to last treatment. Further the benefit was robust and consistent among all subgroups based on gender, race, age, baseline hepatic and renal impairment and geographical regions.
The superiority in efficacy is supported by improvements in key secondary endpoints including time-to-progression.
In the Study MMY3003, the ORR is significantly higher in subject receiving DRd, as compared to Rd alone (DRd: 93% vs Rd: 76%; p<0.0001). The responses are deep, with higher VGPR or better rates (DRd: 76% vs Rd: 44%) and in the rate of CR or better (DRd: 43% vs Rd: 19%). In addition, the MRD negativity rate is significantly higher (DRd: 29% vs Rd: 8%). Other phase 3 trials using lenalidomide+dexamethasone (Rd) as background therapy have previously been published. Carfilzomib + Rd vs. Rd alone, elotuzumb + Rd vs. Rd alone and ixazomib + Rd vs. Rd alone (Stewart 2015, Lonial l2015 and Moreau 2016). Although comparison and interpretation with these data should be done with caution, HR for PFS was in the range of 0.69 to 0.74, ie. they showed a reduction in risk of progression or death of 26% to 31%, compared to a 63% reduction in the present MMY3003 study. The ORR results were overall consistent with the PFS results.

In Study MMY3004, the ORR is significantly higher in subjects receiving DVd, as compared to Vd alone (DVd: 83% vs Vd: 63%; p<0.0001). The responses are deep, with higher VGPR or better rates (DVd: 59% vs Vd: 29%) and a rate of CR or better (DVd: 19% vs Vd: 9%). In addition, the MRD negativity rate is significantly higher (DVd: 14% vs Vd: 3%). Similarly phase 3 bortezomib/dexamethasone-controlled studies with panobinostat+Vd and carfilzomib + Vd, along with a phase 2 trial with elotuzumab+Vd have been published (San-Miguel 2014, Dimopoulus 2016 and Jakubowiak 2016). HR for PFS in these studies ranged from 0.53 to 0.72, compared with 0.39 in the daratumumab study, i.e. a reduction in risk of progression or death of 28% to 47%, compared with 61% in the MMY3004 study with daratumumab. Although comparison between studies is difficult, these data indicate a clinical meaningful benefit of daratumumab combinations with RD and Vd.

Existing therapies	Daratumumab and lenalidomide/dexamethasone	Daratumumab and bortezomib/dexamethasone
	Improved efficacy	Improved efficacy
Carfilzomib (Kyprolis)	Yes	Yes
Elotuzumab (Empliciti)	Yes	Yes
Ixazomib (Ninlaro)	Yes	Not applicable (Ninlaro is indicated in combination with lenalidomide and dexamethasone)
Panobinostat (Farydak)	Not applicable (Farydak is indicated in combination with bortezomib and dexamethasone)	Yes

Note: Lenalidomide, thalidomide and pomalidomide are not included in the tables in sections 3.3, 3.4, 3.5 and 4. Thalidomide and pomalidomide are not studied with any of the backbones as in the daratumumab studies (MMY3003 and MMY3004) and therefore the comparison is not relevant. In addition the approved indication for thalidomide is 1st line, and for pomalidomide it is 3rd line. Finally, lenalidomide is part of the backbone in study MMY3003.

Having considered the data submitted by the MAH, the CHMP considers that the claimed indication for Darzalex brings a significant clinical benefit over existing therapies based on an improved efficacy compared to Kyprolis, Empliciti, Ninlaro and Farydak.

3.4. Significant clinical benefit based on improved safety

CHMP's position:

Safety data from large comparative studies is included in the application. A total of 664 subjects received daratumumab in combination with standard background therapy and 518 subjects received background therapies alone.
The safety profiles of daratumumab in combination with Rd, Vd or Pd were similar to those of the background regimens, with the exception of infusion related reactions (IRRs), which were reported by approximately half of subjects receiving daratumumab-based regimens (DRd, DVd, DPd). The majority of IRRs were low grade and occurred mainly during the first infusion, they were manageable and the pre-and post medication as suggested in the product information is endorsed.

The incidence of Grade 3 or 4 TEAEs and serious TEAEs was higher in the daratumumab combination groups, but were managed by supportive care and dose modifications, and did not result in an increase in discontinuation of study treatment or deaths.
Although daratumumab may increase the cytopenias induced by the background therapies, neutropenia was managed by dose modifications and growth factor use and rarely led to treatment discontinuation (<1%). The incidence of febrile neutropenia was low (≤7%), and bleeding due to thrombocytopenia were low and of minor grade. In the clinical setting, cytopenic adverse effects are well known and manageable.

Although the overall incidence of infections were reported by a higher percentage of subjects in the daratumumab containing groups compared to the respective background therapy, the majority of all

infections were mild (Grade 1 or 2) and did not require hospitalization. The incidence of Grade 3 or 4 infection was similar between the daratumumab combinations and the background therapies (DRd: 27%; Rd: 23%; DVd: 21%; Vd:9%; DPd: 27%), with the most common being pneumonia.

Discontinuations from treatment (2% to 5%) and deaths (0.8% to 2%) due to infection were low and balanced between groups in the randomized studies.

In the previously published data using the lenalidomide or bortezomib backbone treatment, common toxicities associated with carfilzomib combinations include except from hematologic toxicities, pneumonia hyponatraemia, fatigue, hypophosphatemia, IRR and especially high grade cardiovascular events. Common toxicities with elotuzumab combinations involved mainly infections, incl. opportunistic infections IRR and new primary malignancies except from the hematologic toxicities. Adverse events due to the ixazomib combination include except from hematologic toxicities, fatigue, rash, decreased appetite, diarrhea and vomiting. Toxicity due to panobinostat combination especially includes high rates of gastrointestinal adverse events and discontinuation of the treatment. Based on the above, it is not possible to agree on the claim for "improved safety" in comparison to existing therapies based on indirect comparisons.

Existing therapies	Daratumumab and lenalidomide/dexamethasone	Daratumumab and bortezomib/dexamethasone
	Improved safety	Improved safety
Carfilzomib (Kyprolis)	Not applicable	Not applicable
Elotuzumab (Empliciti)	Not applicable	Not applicable
Ixazomib (Ninlaro)	Not applicable	Not applicable
Panobinostat (Farydak)	Not applicable	Not applicable

3.5. Significant clinical benefit based on major contribution to patient care

CHMP's position:

It is considered a benefit to patient care, that a novel drug as daratumumab with a completely distinct mechanism of action from any other anti-myeloma treatment has become available to a group of patients with a dismal prognosis. Daratumumab offers no new mode of administration, however the treatment schedule is adapted to 2 standard of care treatments, this is considered relevant to subjects compliance.

Besides from the fact that an increase of PFS together with acceptable and manageable safety profile is considered a benefit to patient care, the applicant also evaluated the functional status and well-being of the subjects. No detrimental effect in median time to improvement or worsening in the global health status was demonstrated between the combination of daratumumab and background therapies (DRd or DVd) and the corresponding background therapies.

The applicant has not focused on this issue which is considered acceptable considering the novel mechanism of action, the overwhelming benefit on efficacy, and the acceptable and manageable adverse events. Combining daratumumab with the 2 standard treatments lenalidomide/dexamethasone or bortezomib/dexamethasone doses not add on any concerns related to patient care.

Existing therapies	Daratumumab and lenalidomide/dexamethasone	Daratumumab and bortezomib/dexamethasone
	Major contribution to patient care	Major contribution to patient care
Carfilzomib (Kyprolis)	Yes	Yes
Elotuzumab (Empliciti)	Yes	Yes

Ixazomib (Ninlaro)	Yes	Yes
Panobinostat (Farydak)	Yes	Yes

4. Conclusion

CHMP's position:

In conclusion, it is agreed, that addition of daratumumab to standard treatment regimens as lenalidomide and dexamethasone or bortezomib and dexamethasone results in a consistent clinical benefit as compared to standard background therapy alone. The superiority in efficacy is further supported by improvements in key secondary endpoints. When compared with historical, published data, the daratumumab based combinations seems to be superior in relation to PFS and ORR, however due to a historical comparison, the results should be interpreted with caution. Concerning the safety profile, the toxicity of daratumumab is consistent with the known toxicities of the individual agents and clinically manageable. Compared to historical, published data, the safety profile of daratumumab combinations seems to be superior to carfilzomib and panobinostat containing regimens, and especially not to be detrimental to other combination. Based on the above, it is not possible to agree on the claim for "improved safety" in comparison to existing therapies based on indirect comparisons. Finally, there is no indication of a detrimental effect on quality of life not in this application or compared to historical data.

Existing therapies	Darzalex		
	Improved efficacy	Improved safety	Major contribution to patient care
Kyprolis	Yes	Not applicable	Yes
Empliciti	Yes	Not applicable	Yes
Ninlaro	Yes	Not applicable	Yes
Farydak	Yes	Not applicable	Yes

Having considered the data submitted by the MAH, the CHMP by consensus considers that the Darzalex in the claimed indication: ''Darzalex in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone,for the treatment of adult patients with multiple myeloma who have received at least one prior therapy''

- brings a significant clinical benefit over existing therapies based on an improved efficacy compared to Kyprolis, Empliciti, Ninlaro and Farydak and major contribution to patient care compared to Kyprolis, Empliciti, Ninlaro and Farydak

5. Recommendation

The CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and the "Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period", and considers by consensus that the Darzalex in the new therapeutic indication brings a significant clinical benefit in comparison to existing therapies.