17 October 2019
EMA/CHMP/622108/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Darzalex

International non-proprietary name: daratumumab

Procedure No. EMEA/H/C/004077/II/0029

Note

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

Table of contents

List of abbreviations

ADR	adverse drug reaction
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CR	complete response
CRAB	calcium elevation, renal insufficiency, anemia, and bone abnormalities
CrCL	creatinine clearance
DILI	drug-induced liver injury
DOR	duration of response
DRd	daratumumab, lenalidomide, and dexamethasone
DVMP	daratumumab, bortezomib, melphalan, and prednisone
ECOG	Eastern Cooperative Oncology Group
ESMO	European Society for Medical Oncology
FISH	fluorescent in situ hybridization
HDT	high-dose chemotherapy
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IRR	infusion-related reaction
ISS	International Staging System
ITT	intent-to-treat
K_m	Michaelis-Menten constant
MoA	mechanism of action
MPT	melphalan, thalidomide, and prednisone
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PFS2	progression-free survival on next line of therapy
PI	proteasome inhibitor
PRO	patient-reported outcome
Q	intercompartmental clearance
Rd	lenalidomide and dexamethasone
sCR	stringent complete response
SD	standard deviation
SOC	system organ class
SPM	secondary primary malignancies

SWOG	Southwest Oncology Group
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
V_1	volume of distribution in the central compartment
V_2	volume of distribution in the peripheral compartment
VAS	Visual Analogue Scale
VGPR	very good partial response
V_{max}	maximum velocity of the nonlinear clearance process
VMP	bortezomib, melphalan, and prednisone

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 22 March 2019 an application for a variation.

The following variation was requested:

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

Extension of indication in combination with lenalidomide and dexamethasone (Rd) for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT) for Darzalex; as a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 6.1 has also been submitted.

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

Darzalex was designated as an orphan medicinal product EU/3/13/1153 on 24 May 2016. 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 P/0264/2017 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The MAH received Protocol Assistance from the CHMP.

Scientific Advice

The MAH received scientific advice from the CHMP in 2014 (EMEA/H/SA/2456/3/2014/PA/III). The CHMP agreed to study design, treatment regimens and endpoints for the pivotal study MMY3008.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Jorge Camarero Jiménez

Timetable	Actual dates
Submission date	22 March 2019
Start of procedure:	27 April 2019
CHMP Co-Rapporteur Assessment Report	3 July 2019
CHMP Rapporteur Assessment Report	21 June 2019
PRAC Rapporteur Assessment Report	21 June 2019
Updated PRAC Rapporteur Assessment Report	4 July 2019
PRAC Outcome	11 July 2019
CHMP members comments	15 July 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	19 July 2019
Request for supplementary information (RSI)	25 July 2019
CHMP Rapporteur Assessment Report	19 September 2019
PRAC Rapporteur Assessment Report	26 September 2019
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	3 October 2019
CHMP members comments	7 October 2019
Updated CHMP Rapporteur Assessment Report	10 October 2019
Opinion	17 October 2019
The CHMP adopted a report on similarity of Darzalex with Imnovid, Farydak, Kyprolis and Ninlaro on 17 October 2019	17 October 2019

2. Scientific discussion

2.1. Introduction

Multiple myeloma, a malignant disorder of the plasma cells characterized by uncontrolled and progressive proliferation of a plasma cell clone, is estimated to represent 0.8% of all cancers worldwide. The proliferation of myeloma cells causes displacement of normal bone marrow haematopoietic precursors and the overproduction of M-proteins. Characteristic hallmarks of multiple myeloma include osteolytic lesions, anaemia, increased susceptibility to infections, hypercalcaemia, renal insufficiency or failure, and neurological complications.

While OS rates for multiple myeloma have improved significantly over the last decade due to the availability of effective new therapies, it remains an incurable disease. Based on the revised International Staging System (R-ISS), the 5-year OS is 82% for R-ISS stage I, 62% for R-ISS stage II and 40% for R-ISS stage III. Median OS time was not reached for patients with R-ISS stage I and was of 83 and 43 months for R-ISS stage II and R-ISS stage III patients, respectively[1]. Patients with newly diagnosed multiple myeloma are typically categorized into 2 subpopulations defined by their age, comorbidity and suitability for intensive treatment. For patients who are considered fit, an induction regimen followed by high-dose chemotherapy (HDT) and ASCT is considered the standard of care according to both US (National Comprehensive Cancer

[1] Palumbo A, Avet-Loiseau H, Oliva S et al. Revised international staging system for multiple myeloma: a report from International Myeloma Working Group. J Clin Oncol 2015; 33: 2863–2869.

Network [NCCN]) and European Society for Medical Oncology [ESMO]) guidelines, and this therapeutic approach is customarily limited to younger patients. For patients considered ineligible for HDT and ASCT due to their age, presence of comorbidities, and/or physical status, the treatment approach often favours longer, less intensive/toxic treatments.

The coexistence of different tumor subclones at baseline displaying different drug sensitivities ultimately contributes to the development of drug resistance and disease progression (Barlogie 2014). Because combination regimens comprised of agents with non-overlapping and synergistic mechanisms of action target multiple pathways in multiple myeloma cells, they are more likely to overcome intratumoral clonal heterogeneity than single agent or doublet approaches. Thus, triple or quadruple drug regimens have become standard of care for newly diagnosed multiple myeloma (Kumar 2018; Moreau 2017).

Elderly patients are generally not considered eligible for HDT and ASCT due to increased comorbidities which increase the risk of complications, morbidity and mortality. This is particularly notable as multiple myeloma is disproportionately detected in older adults, the majority of whom are older than 65 years at the time of diagnosis (median age at diagnosis: 72 years). Furthermore, comorbidities such as renal dysfunction are present at initial diagnosis in a significant proportion of patients with multiple myeloma (12% to 30%).

Daratumumab is a targeted immunotherapy that binds with high affinity to tumor cells that overexpress CD38, a transmembrane glycoprotein. Combining daratumumab with Rd in patients with newly diagnosed multiple myeloma who are not eligible for ASCT is supported by the approved use of Rd for this indication as well as the approved use of DRd in the relapsed/refractory setting.

The current submission is supported by the Phase 3 study MMY3008 where DRd was compared to Rd for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for ASCT.

The following new indication is proposed:

DARZALEX is indicated in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

Study Identification First Subject First Visit/ Completion date (Day Month Year) Study Status	Phase Study Description/Design, Study Population Key Objective(s)	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects in the SCS (by Treatment Group)
Phase 3 Study			
54767414MMY3008 24 September 2018 (cutoff for interim analysis) Ongoing	Phase 3 Open-label, randomized Subjects with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy and ASCT To compare the efficacy (PFS) of DRd compared with Rd and to evaluate safety/tolerability and clinical outcomes of DRd compared with Rd including: TTP, CR rate, MRD negativity rate, OS, and sCR rate (additional objectives are listed in the CSR) (Mod5.3.5.1/MMY3008)	Treatment Group A: • Lenalidomide PO at 25 mg[1] on Days 1-21 of each 28-day cycle, • Dexamethasone PO or IV at 40 mg[2] once a week (Days 1, 8, 15, 22 of each 28-day cycle). Treatment Group B: • Daratumumab IV at 16 mg/kg; once every week for 8 weeks (Cycles 1-2), then, every other week for 16 additional doses (Cycles 3-6), and then, every 4 weeks (Cycle 7 and beyond) until disease progression or unacceptable toxicity. • Lenalidomide PO at 25 mg[1] on Days 1-21 of each 28-day cycle. • Dexamethasone PO or IV at 40 mg[2] once a week (Days 1, 8, 15, 22 of each 28-day cycle).	Rd: 365 DRd: 364

ASCT=autologous stem cell transplant; CR=complete response; CSR=clinical study report; DRd=daratumumab in combination with lenalidomide and dexamethasone; IV=intravenous; MRD=minimal residual disease; OS=overall survival; PFS=progression-free survival; PO=by mouth; Rd=lenalidomide-dexamethasone; sCR=stringent complete response; TTP=time to disease progression

[1] For subjects with a creatinine clearance between 30 and 50 mL/min, the dose of lenalidomide was recommended to be 10 mg every 24 hours.

[2] For subjects >75 years of age or with BMI <18.5, dexamethasone could be administered at a dose of 20 mg weekly.

2.3.2. Pharmacokinetics

Absorption

Absorption data are not available because all studies in this and prior submissions administered daratumumab as an IV infusion.

Distribution

The mean±SD volume of distribution in subjects who received 16 mg/kg was 90.19±43.40 mL/kg after the first dose and 59.51±54.68 mL/kg following repeat dosing (Study GEN501); Japanese subjects receiving 16 mg/kg exhibited a similar volume of distribution of 57.97±3.29 mL/kg (Study MMY1002). As described by the monotherapy PPK model, the estimate for the central volume of distribution is 56.98±18.07 mL/kg. Overall, these data suggest that daratumumab is primarily localized to the vascular system with limited extravascular tissue distribution

Elimination

As shown previously in the monotherapy studies, daratumumab clearance decreased with increasing dose and with multiple doses. After the first infusion, mean clearance decreased from 1.06 mL/h/kg in the 2 mg/kg group to 0.29 mL/h/kg in the 24 mg/kg group; after repeat dosing, clearance decreased from 0.59 mL/h/kg (n=1) in the 2 mg/kg group to 0.16 mL/h/kg in the 24 mg/kg group. Following the first administration at the approved dose of 16 mg/kg, clearance was 0.42±0.42 mL/h/kg and the t1/2 was 216±104 hours (9.0±4.3 days). Following repeated administration of 16 mg/kg, daratumumab clearance decreased to 0.30±0.12 mL/h/kg and t1/2 increased to 255±216 hours (10.6±9.0 days).

Dose proportionality and time dependencies

Dose proportionality

Following the first administration of daratumumab ranging from 0.005 to 24 mg/kg, Cmax increased in an approximately dose-proportional manner for doses ≥1 mg/kg. After repeat dosing, Cmax increased in a greater than dose-proportional manner. AUC also increased in a greater than dose-proportional manner after both the first and last dose. Consistent with the monotherapy data, Cmax following the first infusion increased in approximate proportion to the increasing daratumumab dose of 2 to 16 mg/kg daratumumab and AUClast increased in a greater than dose-proportional manner after the first dose. These findings are consistent with target-mediated clearance.

As reported for monotherapy, mean clearance following the first dose decreased with increasing dose, from 1.50±0.96 mL/h/kg in the 1 mg/kg cohort to 0.29±0.15 mL/h/kg in the 24 mg/kg cohort. This trend for decreasing clearance with increased dose was also evident following repeat dosing, from 6.72±6.18 mL/h/kg in the 0.5 mg/kg cohort to 0.16±0.08 mL/h/kg in the 24 mg/kg cohort. Following the first administration at the approved dose of 16 mg/kg, clearance was 0.32±0.13 mL/h/kg and 0.10 mL/h/kg in the 1 subject with the parameter estimated after repeat dosing.

Time Dependency

Clearance of daratumumab also decreased with multiple doses in the monotherapy studies: after the first infusion, mean clearance decreased from 1.06 mL/h/kg in the 2 mg/kg group to 0.29 mL/h/kg in the 24 mg/kg group; after the last infusion, mean clearance decreased from 0.59 mL/h/kg in the 2 mg/kg group to 0.16 mL/h/kg in the 24 mg/kg group. Following the first administration at the approved dose of 16 mg/kg, clearance was 0.32±0.13 mL/h/kg (mean±SD) and 0.10 mL/h/kg in the 1 subject with the parameter estimated after repeat dosing.

Comparison of DRd Combination in MMY3008 and Previous Monotherapy and Combination Therapies

Comparison of Cmax (Cycle 1 Day 1) and Ctrough during every-2-week (Cycle 6 Day 1) and every-4-week (Cycle 12 Day 1) dosing was made between the DRd dose regimen from Study MMY3008 (once weekly for 8 weeks, every 2 weeks for 16 weeks, every 4 weeks thereafter) and similar dose regimens from the monotherapy Study MMY2002 and combination therapy Studies GEN503, MMY1001, and MMY3003. Concentrations after administration of the first dose (Cycle 1 Day 1) were similar across monotherapy and combination therapies. The maximal trough concentrations of daratumumab were also similar across studies.

Special populations

No special population studies for hepatic or renal dysfunction with daratumumab have been presented in this application.

Pharmacokinetic interaction studies

No dedicated clinical drug-drug interaction studies were presented. Since there is no overlapping pathway of elimination, no interactions are expected between daratumumab and small-molecule drugs including lenalidomide and dexamethasone. This is considered acceptable.

Population Pharmacokinetic Analysis

A pop-PK model of daratumumab was used to describe the PK characteristics of daratumumab following IV administration in combination with Rd and to evaluate the influence of covariates on the exposure of daratumumab in subjects with newly diagnosed MM who are ineligible for ASCT. In addition, the PK of daratumumab combined with Rd (D-Rd) was compared with that of daratumumab monotherapy studies and the previous combination therapy studies.

The pop-PK analysis included combined data from a Phase 3 study (MMY3008) and a Phase 1/2 study (GEN503). GEN503 data were pooled into the analysis dataset to improve the PK parameter estimates because Study GEN503 included a wider dose range (2 to 16 mg/kg) and a more intensive PK sampling scheme. Both Studies MMY3008 and GEN503 shared the same background therapy and similar concentration-time profiles were observed in these 2 studies.

Effects of Covariates

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 a low body weight (<65 kg, n=102) or high body weight (≥85 kg, n=92) compared to those with a normal body weight (65 to 85 kg, n=161).

Age: No clinically important influence of age on the exposure to daratumumab was observed. There was a 9% decrease in exposure to daratumumab in older subjects (age ≥75 years, n=153) compared to younger subjects (age <75 years, n=202).

Sex: No clinically important influence of sex on the exposure to daratumumab was observed. The exposure to daratumumab in males was approximately 1% lower than that in females (n=173).

Race: Because 92% of subjects were White and there were only limited sample sizes in other race categories, the effect of race was evaluated as White (n=325) and Non-white (n=30). No clinically important influence of race on the exposure to daratumumab was observed. The exposure to daratumumab in White subjects was approximately 8% higher than in Non-white subjects.

Region: Approximately 28% of subjects were North American. The effect of region was evaluated in North America (n=98) and other regions (n=257). No clinically important influence of region on the exposure to daratumumab was observed. The exposure to daratumumab in North American subjects was approximately 6% lower than that in subjects from other regions.

Renal Impairment: The effect of renal impairment was evaluated in categories of normal renal function (creatinine clearance [CRCL] ≥90 mL/min, n=60), mild renal impairment (60≤ CRCL <90 mL/min, n=141), moderate renal impairment (30≤ CRCL <60 mL/min, n=147), and severe renal impairment (CRCL <30 mL/min; n=7). No clinically important differences (≤13%) in the exposure to daratumumab were observed between subjects with renal impairment and those with normal renal function.

Hepatic Impairment: No subjects had severe hepatic impairment (TB >3× upper limit of normal [ULN] and any AST). As only 1 subject had moderate hepatic impairment (TB >1.5× to 3.0× ULN, as defined using the National Cancer Institute criteria of hepatic dysfunction), this subject was combined with subjects with mild hepatic impairment (TB 1.0× to 1.5× ULN or AST >ULN) in this analysis. The effect of hepatic impairment was evaluated in categories of normal hepatic function (TB and AST ≤ULN, n=323) and mild/moderate hepatic impairment (n=31). The exposures to daratumumab in subjects with mild/moderate hepatic impairment were similar to those in subjects with normal hepatic function and were consistent with the findings based on previous studies. No clinically important differences in the exposure to daratumumab (-3%) were observed between subjects with hepatic impairment and those with normal hepatic function as found in the monotherapy or the previous combination therapy study populations.

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 6% lower in subjects with abnormal albumin level (<35 g/L; n=142) compared with subjects who had normal albumin level (≥35 g/L; n=213).

Type of Myeloma: No clinically important differences in the exposure to daratumumab were observed between subjects with IgG myeloma and non-IgG myeloma. The exposure to daratumumab was approximately 18% lower in subjects with IgG myeloma (n=232) compared with subjects with non-IgG myeloma (n=123), consistent with previous study results.

ECOG Score: No clinically important differences in the exposure to daratumumab (≤7%) were observed between subjects with ECOG scores of 1 (n=170) or ≥2 (n=59) and those with ECOG scores of 0 (n=126).

Immunogenicity: All immunogenicity-evaluable subjects (n=338) in the PPK analysis were negative for anti-daratumumab antibodies. Immunogenicity-evaluable subjects were defined as subjects who received at least 1 dose of daratumumab and had at least 1 postinfusion sample for detection of anti-daratumumab antibodies.

2.3.3. Pharmacodynamics

Mechanism of action

No new data on the mechanism of action has been presented in this application.

Daratumumab is a human IgG mAb that binds with high affinity to CD38, a transmembrane glycoprotein expressed on tumor cells, and induces tumor cell death through multiple mechanisms of action. These mechanisms of action include several immune-mediated activities, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and direct cytotoxicity by induction of apoptosis by Fc gamma receptor mediated crosslinking of tumor-bound mAbs (Overdijk 2016). Translational biomarker studies of samples from subjects treated with daratumumab in Phase 1 and Phase 2 studies (Studies GEN501 and MMY2002, respectively) have revealed previously unknown immunomodulatory effects of daratumumab (Krejcik 2016). Daratumumab leads to the rapid and sustained elimination of highly immunosuppressive subsets of CD38+ regulatory T cells, CD38+ myeloid-derived suppressor cells, and CD38+ regulatory B cells (Krejcik 2016). The elimination of these immunosuppressive cells, modulation of CD38 enzymatic activity, and destruction of the malignant myeloma cells are thought to lead to the clonal expansion of CD8+ and CD4+ T cells (Chiu 2016). Altogether, daratumumab's converging mechanisms of actions are hypothesized to synergistically lead to the deep responses observed in patients.

Primary and secondary pharmacology

Primary pharmacology

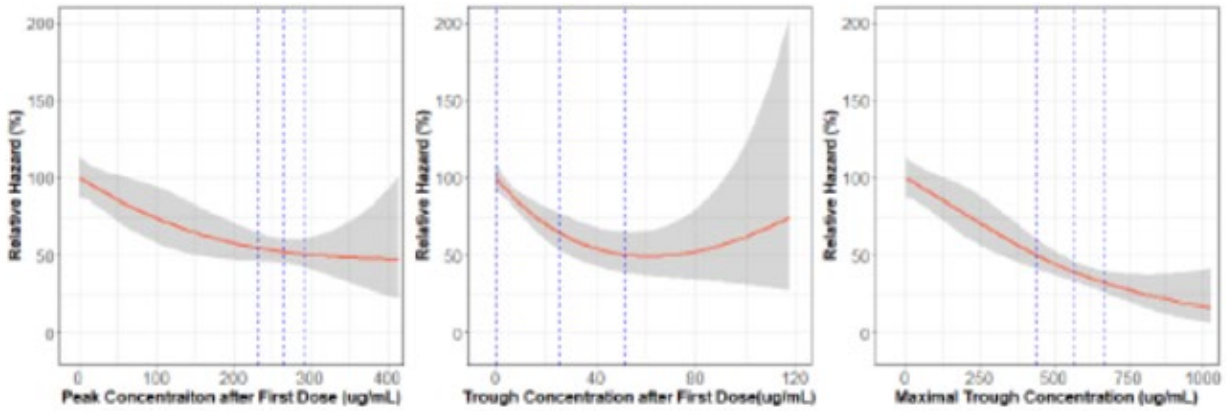
Exploratory Exposure-response Analysis

Exposure-response (E-R) relationships were investigated based on the simulated daratumumab exposure metric data from Study MMY3008 using the pop-PK model. Since all subjects in the D-Rd group received the recommended dose of 16 mg/kg, there is limited exposure variation for daratumumab and, therefore, only exploratory and graphic E-R analyses were performed for selected efficacy endpoints and AEs.

Progression-free Survival

An apparent maximal effect (Emax) relationship was observed between the relative hazard of progression or death and daratumumab systemic exposures. The relative hazard for progression or death decreased rapidly with increasing daratumumab systemic exposure. When the first peak exposures reached the first quartile (Q1) (232 µg/mL), the risk (compared to the control Rd group) was reduced by approximate 50% for PFS, indicating that the maximum effect on PFS had been attained for the majority of the subjects at the 16 mg/kg dose with an acceptable safety profile.

Figure 1: Relative Hazard of PFS at Different Predicted Exposures



Abbreviations: ISS=International Staging System.

Key: The solid red line is the point estimate, and gray shaded areas represent 95% confidence interval. Blue vertical dotted lines separate the quartiles of maximal trough concentration ($C_{trough,max}$), peak and trough concentrations after the first dose ($C_{peak,1st}$ and $C_{trough,1st}$, respectively). The control group in each study was used as the reference (ie, $C_{trough,max}$=0). Hazard ratio and its 95% confidence interval were estimated based on stratified Cox regression models. The stratification factors included ISS staging (I, II, III), region (North America versus other), and age (<75 years versus ≥75 years).

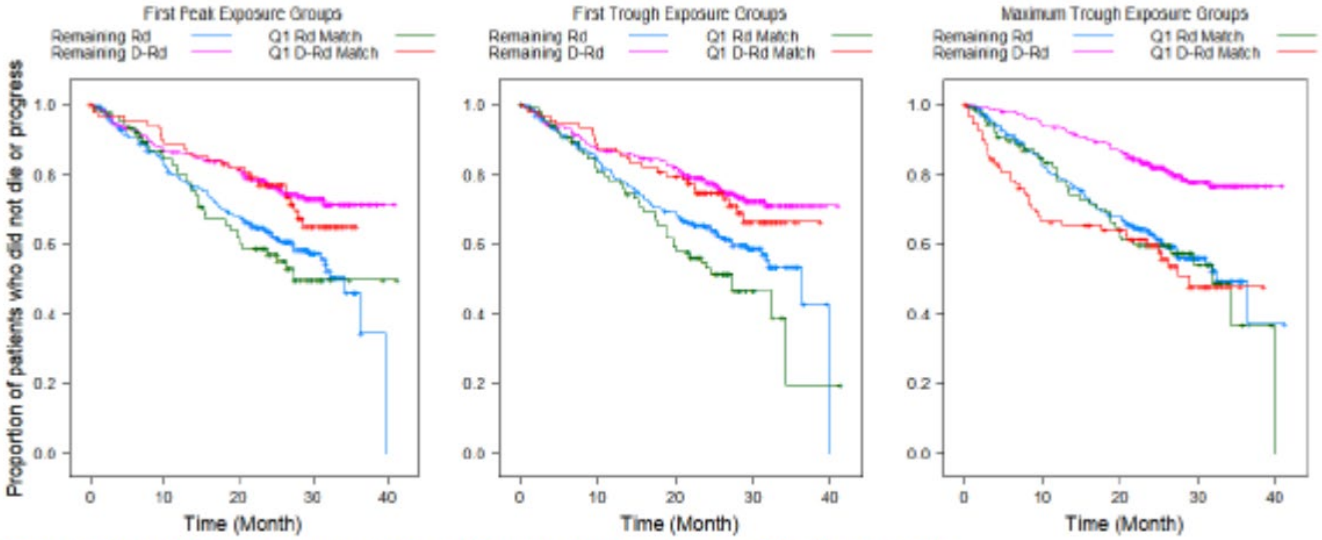
The quartiles for $C_{peak,1st}$ were: 1st quartile (≤232 µg/mL), 2nd quartile (232 to 264 µg/mL), 3rd quartile (264 to 290 µg/mL), and 4th quartile (290 to 415 µg/mL).

The quartiles for $C_{trough,1st}$ were: 1st quartile (≤1.78E-02 µg/mL), 2nd quartile (1.78E-02 to 25.7 µg/mL), 3rd quartile (25.7 to 51.8 µg/mL), and 4th quartile (51.8 to 118 µg/mL).

The quartiles for $C_{trough,max}$ were: 1st quartile (≤439 µg/mL), 2nd quartile (439 to 570 µg/mL), 3rd quartile (570 to 667 µg/mL), and 4th quartile (667 to 1,030 µg/mL).

The improvement in PFS was observed in the majority of the daratumumab-treated subjects (exposure quartiles: Q2-Q4, 75%). In the case-control analysis, the improvement of PFS was apparent in the Q1 DRd match group compared with the Q1 Rd match group for both peak and trough concentrations after the first dose. In addition, the PFS improvement in the Q1 group according to the peak and trough concentration following the first dose appeared comparable to that in the Q2-Q4 groups. The results suggest that, despite trough concentrations following the first dose being close to 0 in Q1 subjects, the PFS improvement in those subjects were similar to that in the Q2-Q4 groups.

Figure 2: **Kaplan-Meier Curves for the Matched Subgroups (PFS)**



Abbreviations: DRd=daratumumab-lenalidomide-dexamethasone; Q1=first quartile; Rd=lenalidomide-dexamethasone.

Note: Maximal trough is the overall maximal trough concentration; First peak is end-of-infusion concentration after the first infusion; First trough is trough concentration after the first infusion.

In summary, the E-R analysis on efficacy data suggests that the maximum drug effect on PFS had been attained for the majority of the subjects at the studied 16 mg/kg dose and it appears that subjects in the DRd arm of Study MMY3008 benefited from the treatment with daratumumab evidenced by a lower relative risk of disease progression/death across the studied concentration range compared with subjects in the Rd arm.

Selected Adverse Events

There was no apparent E-R relationship between Cpeak, 1st and IRR, and between Cpeak max and thrombocytopenia, anemia, neutropenia, lymphopenia, and infections within the studied drug concentration range. The results were consistent with the clinical analysis where the safety profile is similar between the D-Rd and the Rd arms.

Secondary pharmacology

Immunogenicity

No patients developed anti-daratumumab antibodies during Study MMY3008. This confirms previous findings that the risk of immunogenicity for daratumumab is low.

Table 1: **Summary of Antibody to Daratumumab Status; Immune Response-evaluable Population**

	DRd n (%)
Analysis set: immune response-evaluable	338
Subjects with appropriate sample [a]	338
Subjects positive for anti-daratumumab antibodies [b,c]	0
Subjects negative for anti-daratumumab antibodies [b]	338 (100.0%)

Abbreviations: DRd=daratumumab-lenalidomide-dexamethasone.

[a] Subjects with appropriate samples had 1 or more samples obtained after their first daratumumab administration.

[b] Denominator is subjects with appropriate sample.

[c] Includes all subjects who had at least 1 positive sample at any time after start of treatment and baseline positive subjects who had posttreatment sample titers increase at least 2-fold compared to baseline.

2.3.4. Discussion on clinical pharmacology

The clinical pharmacology of daratumumab used as monotherapy is well established. The PK profile for daratumumab when given in combination treatment seems to show a similar pattern to what has been observed in in the monotherapy studies. Clinical pharmacology data for the combination treatment with VMP derive from two clinical studies (MMY3007 and MMY1001) with a total of 353 patients evaluable for PK analyses. Additionally, a pop-PK analysis from Study MMY3008 contributes data. The applied analytical methods for both the statistical analyses and the PK data analysis seem appropriate.

Pharmacokinetics

Overall, there is no new data with regards to the basic pharmacokinetic properties including absorption, distribution, metabolism, elimination and excretion. It is supported that as a mAb, the distribution of daratumumab is primarily localised to the vascular system, and the dose-dependent elimination (nonlinear characteristics) is consistent with target-mediated elimination (where clearance decreases as a function of dose).

The typical pharmacokinetic profile shows similar pattern to what has been observed in in the monotherapy studies. Steady state is reached after approximately 21 weeks (≈5 months) and mean trough concentrations were 375-615 µg/mL. After approximately 1 year, the mean trough concentrations dropped to approximately 250-525 µg/mL. The MAH informs that target saturation >90% is maintained at trough concentrations in the majority (>99%) of the patients following the every 4 week dose regimen.

A logistic regression analysis of overall response rate and predicted maximal pre-infusion (trough) daratumumab concentration showed by the initial (monotherapy) PK analysis, that maximal response rate was obtained with daratumumab concentrations around 300 µg/mL and no additional effect was obtained with higher concentrations. The MAH calculated that 90% of the maximal effect on ORR (EC_{90}^{ORR}) was achieved when Cpre-infusion,max was 274 µg/mL. From the data presented, it appears that mean trough concentrations are well above the thresholds of 274 µg/mL and 300 µg/mL during the initial 4 weeks' dosing period the first 52 weeks but thereafter, pre-infusion values appear to be slightly lower than the thresholds. Mean concentrations are however well above both thresholds at all time points. Thus, when comparing results from the present combination studies (MMY3007 and MMY1001) with the results from the monotherapy studies, similar mean concentrations after first dose and similar pattern for the subsequent cycles are observed. Therefore, it is concluded that the PK data from the two studies including patients treated with the D-VMP combination are comparable with the data reported from the monotherapy studies. This supports the assumption (based on molecular structures of the agents) that there are no interactions with the combination treatment, and it justifies the use of PK-data from the previous registration studies with daratumumab.

The pop-PK analysis was based on 1,635 PK samples from 353 PK-evaluable patients (all receiving daratumumab at 16 mg/kg). Initially, the MAH was asked to to discuss the goodness of fit for the updated population PK as several samples are clustered away from the correlation regression line of the population predictions and the conditional weighted residuals showed samples which lie outside the +/- 5 limits. Eta shrinkage was high for V1 and the visual predictive checks showed that the model poorly captured the data variability. In their response, the MAH agreed that the shrinkage on V1 was fairly high (56%), however, the issue will not be pursued. Thus overall, the goodness-of-fit (GOF) plots presented showed an acceptable symmetrical distribution around the unity line, supporting that the applied model is appropriate and the VPCs for the final updated PPK model are considered acceptable and do not indicate any misspecifications.

The impact of covariate effects was analysed using a forest-plot, showing the relative change to reference individual of each selected covariate on pre-infusion levels (trough concentrations). A change greater than ±20% is considered clinically meaningful. The impact of severe renal impairment versus normal renal function patients leads to change between -30% and 9% change in maximal trough concentrations and patients with higher body-weight (85kg) may show an increase in trough concentrations between 11-27% compared to a 65 kg subject. Based on these results, the impact of high body weight and severe renal impairment on trough concentration levels might be of relevance. The MAH was asked to discuss this issue in more detail. Based on their response, it was concluded that the hazard ratio analysis in over-weight patients demonstrates a slight trend in favour of DRd but the 95% CI includes the unity, demonstrating the

lack of significant effect in this sub-group of population. However, these results seems contradictory with the E-R analysis previously developed, where relative hazard ratio was related to maximal through concentrations, showing that higher through concentrations would lead to a less hazard ratio. The issue will not be pursued. Regarding the patients with severe renal impairment, it is acknowledged that low number of patients with severe renal impairment where recruited in the study and the clinical impact observed in the forest plot could be considered as preliminary.

Pharmacodynamics

No new data related to mechanism of action or QTc evaluation are presented. This is overall acceptable. No patients developed anti-daratumumab antibodies, which is assuring.

It is reassuring that no patients developed anti-daratumumab antibodies during the present Study MMY3008. This confirms previous findings that the risk of immunogenicity for daratumumab is low. The present combination treatment with D-Rd is not expected to increase the risk of immunogenicity. However, in relation to a Post-Authorisation Measure regarding assay and ADA detection, several concerns regard the adequacy of the assay emerged. The Applicant is encouraged to continue immunogenicity surveillance in coming studies. Especially longer-term exposure could add valuable information to better understand ADA response kinetics by capturing more persistent responses, if any, and to rule out impact on efficacy. The impact of ADA on efficacy will be further investigated in samples from previous studies using a highly sensitive assay.

2.3.5. Conclusions on clinical pharmacology

The new analyses presented do not change the current knowledge on PK/PD and immunogenicity of daratumumab.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No dedicated dose-response studies were conducted.

In study MMY3008, daratumumab was administered at 16 mg/kg weekly for 8 weeks (for 8 doses), every 2 weeks for 16 weeks (for 8 doses), then every 4 weeks thereafter, which is the approved dose regimen of daratumumab as monotherapy and in combination therapy with Rd in subjects with RRMM.

2.4.2. Main study

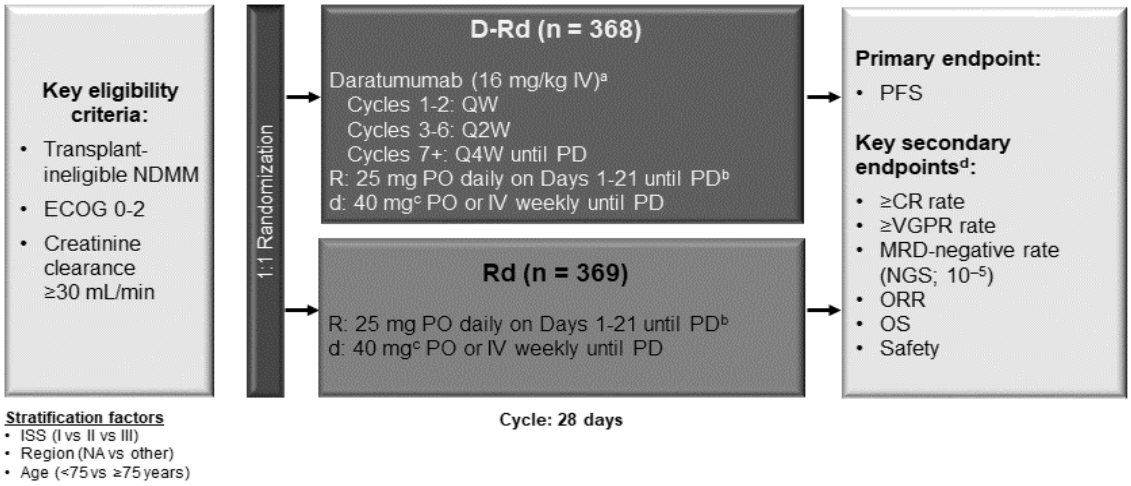
Study MMY3008: Randomized, open-label, active controlled, parallel-group, multicentre study in subjects at least 18 years of age with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy and ASCT

This is a randomized, open-label, active controlled, parallel-group, multicentre study in subjects at least 18 years of age with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and ASCT. Approximately 730 subjects were planned to be enrolled in this study with 365 subjects per treatment arm.

Methods

Figure 3: Schematic Overview of Study MMY3008

Screening within 21 days of randomization



End-of-Treatment Visit (30 days after last dose) → Long Term Follow-up.

BMI=body mass index; CR=complete response; D=daratumumab; d=dexamethasone; ECOG= Eastern Cooperative Oncology Group; ISS=International Staging System; IV=intravenous; MRD= minimal residual disease; n=number; NA=North America; NDMM=newly diagnosed multiple myeloma; NGS=next-generation sequencing; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PO=per os; QW=once weekly; Q2W=once every 2 weeks; Q4W=once every 4 weeks; R=lenalidomide; VGPR=very good partial response

[a] *On days when daratumumab was administered, dexamethasone was administered to patients in the DRd group and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication.*

[b] *For subjects with a creatinine clearance between 30 and 50 mL/min, the dose of lenalidomide was recommended to be 10 mg every 24 hours.*

[c] *For subjects older than 75 years of age or with BMI <18.5, dexamethasone could be administered at a dose of 20 mg weekly.*

[d] *Efficacy endpoints were sequentially tested in the order shown.*

Study participants

Main inclusion criteria for participation in the study were the following:

- Subject must have documented multiple myeloma satisfying the CRAB (calcium elevation, renal insufficiency, anemia and bone abnormalities) criteria, monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy proven plasmacytoma, and measurable disease.
  - Measurable disease, as assessed by central laboratory, defined by any of the following:

    IgG myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or

    IgA, IgM, IgD, or IgE multiple myeloma: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or

    Light chain multiple myeloma without measurable disease in serum or urine: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.
- Newly diagnosed and not considered candidate for high-dose chemotherapy with SCT due to:
  - Being age ≥65 years, OR
  - In subjects <65 years: presence of important comorbid condition(s) likely to have a negative impact on tolerability of high dose chemotherapy with stem cell transplantation. Sponsor review and approval of subjects under 65 years of age is required before randomization.

- Subject must have an ECOG performance status score of 0, 1, or 2

Main exclusion criteria were:

- Subject has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma. Monoclonal gammopathy of undetermined significance is defined by presence of serum M-protein <3 g/dL; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M-protein; and (if determined) proportion of plasma cells in the bone marrow of 10% or less (Kyle 2003).17 Smoldering multiple myeloma is defined as asymptomatic multiple myeloma with absence of related organ or tissue impairment end organ damage (Kyle 2003, Kyle 2007).17,19
- Subject has a diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions.
- Subject has prior or current systemic therapy or SCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for 4 days) of corticosteroids before treatment.

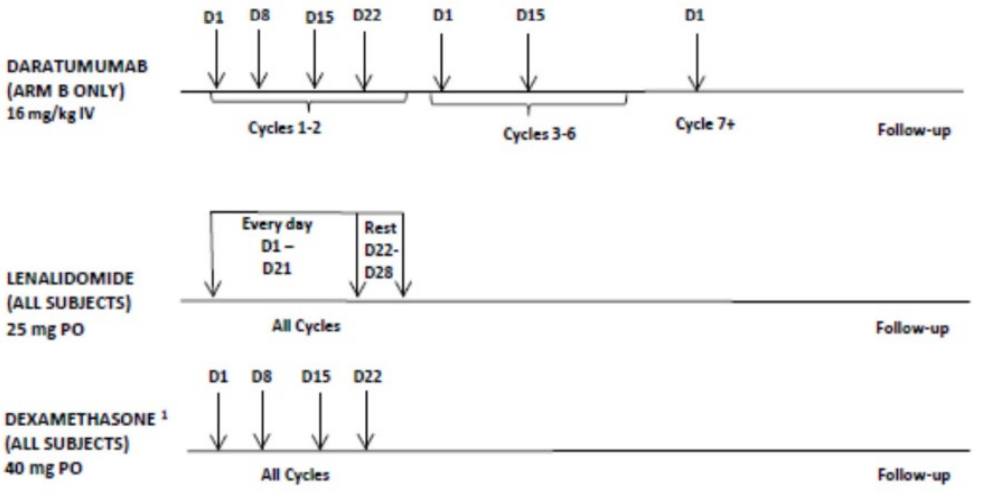
Treatments

- **Treatment Arm A (Rd)**: Lenalidomide was administered at a dose of 25 mg orally on Days 1 through 21 of each 28-day cycle (for subjects with a creatinine clearance [CrCL] between 30 and 50 mL/min, the dose of lenalidomide was to be 10 mg every 24 hours), and dexamethasone was administered at a dose of 40 mg (oral or IV) once a week (for subjects older than 75 years or underweight [body mass index <18.5], the dexamethasone could be administered at a dose of 20 mg weekly). Subjects were to continue lenalidomide and dexamethasone until disease progression or unacceptable toxicity.

- **Treatment Arm B (DRd):** Daratumumab (16 mg/kg IV) was administered weekly for the first 8 weeks (Cycles 1-2) of treatment and then every other week for 16 weeks (Cycles 3-6), then every 4 weeks (from Cycle 7 and beyond). Lenalidomide and dexamethasone were administered as described in Treatment Arm A. Subjects were to continue on DRd until disease progression or unacceptable toxicity.

The Follow-up Phase began once the subject discontinued all study treatments.

Figure 4: **Schematic Overview Study Treatment Administration**



1. On days when daratumumab is administered, dexamethasone will be administered to subjects in Arm B in the clinic and will serve as the treatment dose of steroid as well as the required pre-medication prior to daratumumab infusion.

Objectives

Primary Objective
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 subjects with newly diagnosed multiple myeloma who are not candidates for high dose chemotherapy and autologous stem cell transplant.

Secondary Objectives
- Time to disease progression (TTP)
- Complete response (CR) rate
- Minimal residual disease (MRD) negativity rate
- PFS2 (defined as time from randomization to progression on the next line of therapy or death, whichever comes first)
- Overall survival (OS)
- Time to next treatment
- Stringent CR (sCR) rate
- Overall response rate (partial response [PR] rate or better)
- Proportion of subjects who achieve very good partial response (VGPR) or better
- Time to response
- Duration of response
- To evaluate the clinical efficacy of daratumumab combination with Rd in high-risk molecular subgroups
- To evaluate treatment effects on patient-reported outcomes and heath economic/resource utilization
- To assess the safety and tolerability of daratumumab when administered in combination with Rd.
- To assess the pharmacokinetics of daratumumab in combination with Rd.
- To assess the immunogenicity of daratumumab.

Exploratory Objective
- To explore biomarkers predictive of response or resistance to therapy
- To assess durability of MRD negativity

Outcomes/endpoints

Primary endpoints

The primary endpoint is **PFS**, which is defined as the duration from the date of randomization to either progressive disease, or death, whichever occurs first. PFS was determined by the use of a validated computer algorithm that combines laboratory results (eg, monoclonal [M]-protein level) and applicable imaging and generates the outcome according to IMWG criteria (Durie 2006, Rajkumar 2011). Further, sensitivity analyses of PFS were performed, including those using investigator-determined response.

Secondary endpoints

The secondary efficacy endpoints include:

- **Time to disease progression** (TTP): is defined as the time from the date of randomization to the date of first documented evidence of PD, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the date of the disease evaluation before the start of any subsequent anti-myeloma therapy.

- CR rate, defined as the percentage of subjects achieving CR, as defined:

- Negative immunofixation of serum and urine, and
- Disappearance of any soft tissue plasmacytomas, and

- <5% plasma cells (PCs) in bone marrow
- For those subjects with negative serum M-protein quantitation by electrophoresis (SPEP) and suspected daratumumab interference on immunofixation, a reflex assay using anti-idiotypeantibody will be utilized to confirm daratumumab interference and rule out false positive immunofixation. Patients who have confirmed daratumumab interference, but meet all other clinical criteria for CR or sCR, will be considered CR/sCR.

- MRD negativity rate, defined as the proportion of subjects assessed as MRD negative, at any timepoint after the date of randomization.

- **Progression-free Survival on Next line of Therapy (PFS2),** defined as the time from randomization to progression on the next line of treatment or death, whichever comes first. Disease progression will be based on investigator judgment. For those subjects who are still alive and not yet progressed on the next line of treatment, they will be censored on the last date of follow-up.

- Overall survival (OS), measured from the date of randomization to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.

- **Time to next treatment**, defined as the time from randomization to the start of the next-line treatment.

- **sCR rate**, defined as the percentage of subjects achieving CR in addition to having a normal free light chain (FLC) ratio and an absence of clonal cells in bone marrow by immunohistochemistry, immunofluorescence, 2-4 color flow cytometry

- **Overall response rate (ORR),** defined as the proportion of subjects who achieve PR or better, according to the IMWG criteria, during or after the study treatment.

- **Proportion of subjects who achieve VGPR or better**, defined as the proportion of subjects achieving VGPR and CR (including sCR) according to the IMWG criteria during or after the study treatment at the time of data cutoff.

- **Time to response**, defined as the time between the randomization and the first efficacy evaluation that the subject has met all criteria for PR or better. For subjects without response, data will be censored either at the date of progressive disease or, in the absence of progressive disease, at the last disease evaluation before the start of subsequent anti-myeloma therapy.

- **Duration of response**, calculated from the date of initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease, as defined in the IMWG criteria. For subjects who have not progressed, data will be censored at the last disease evaluation before the start of any subsequent anti-myeloma therapy.

- To evaluate clinical efficacy of DRd in high risk molecular subgroups compared to Rd alone.

- To evaluate the impact of DRd compared to Rd on patient-reported perception of global health.

Sample size

The sample size calculation was based on the assumption that the median PFS for Rd arm is approximately 24 months and the addition of daratumumab would reduce the risk of the disease progression or death by 25%, ie, assuming the hazard ratio (DRd vs Rd) of 0.75, a total of 390 PFS events is needed to achieve a power of 80% to detect this hazard ratio with a log-rank test (two-sided alpha is 0.05).

With a 21-month accrual period and an additional 24-month follow-up, the total sample size needed for the study is approximately 730 (365/arm) subjects.

The sample size calculation has taken into consideration an annual dropout rate of 5%, and the planned interim efficacy analysis used the O'Brien-Fleming alpha spending function. PFS and responses were derived using the same validated computer algorithm as used in previous daratumumab studies.

Randomisation

Subjects were randomly assigned (1:1 ratio) to receive either DRd or Rd stratified by International Staging System (ISS, I vs II vs III), region (North America vs Other), and age (<75 vs ≥75).

Blinding (masking)

As this is an open study, blinding procedures are not applicable.

Statistical methods

Long-term survival follow-up was to continue until 330 deaths had been observed or 7 years after the last subject was randomized, whichever came first. The study was to achieve approximately 80% power to detect a 27% reduction in the risk of death (hazard ratio [HR]=0.73) with a log-rank test (two-sided alpha=0.05).

The primary endpoint of Progression-free survival (PFS) and responses were derived using the validated computer algorithm as used in previous daratumumab studies. For PFS, the primary analysis was to consist of a stratified log rank test for the comparison of the PFS distribution between the 2 treatment arms. The Kaplan-Meier method was to be used to estimate the distribution of overall PFS for each treatment. The treatment effect (hazard ratio) and its two-sided 95% confidence intervals were to be estimated using a stratified Cox regression model with treatment as the sole explanatory variable. Other time-to-event efficacy endpoints, including TTP, PFS2, OS, and time to subsequent anti-myeloma treatment, were to be analysed similarly.

Comparison between the 2 treatment arms of overall response rates, VGPR or better rate, CR or better rate, MRD negativity rate, and other binary endpoints were to be conducted using the stratified Cox regression model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized. Other time-to-event efficacy endpoints, including TTP, PFS2, OS, and time to subsequent anti myeloma treatment, were to be analysed similarly. Duration of response were to be analysed descriptively using the Kaplan-Meier method.

For overall survival, the final analysis will occur after 330 deaths have been observed. Earlier analyses, in which overall survival are analyzed will be considered as interim analyses, and the stopping boundary will be determined using the observed number of deaths at the time of the analyses and a modified linear alpha-spending function per the Lan-DeMets method. At the interim PFS analysis (234 PFS events), a total alpha of 0.0001 (2-sided) will be spent. Cumulative total alpha (2-sided) spent at each subsequent analysis of OS will be the total alpha allocated to OS multiplied by the proportion of the number of deaths observed at the time of the analysis out of the total planned number of deaths (330).

Strong control of familywise Type I error rate will be controlled at a two-sided significance level of 0.05 for the following major secondary endpoints: TTP, CR rate, MRD negativity rate, PFS2 and OS. A hierarchical testing procedure will be used

Interim analyses

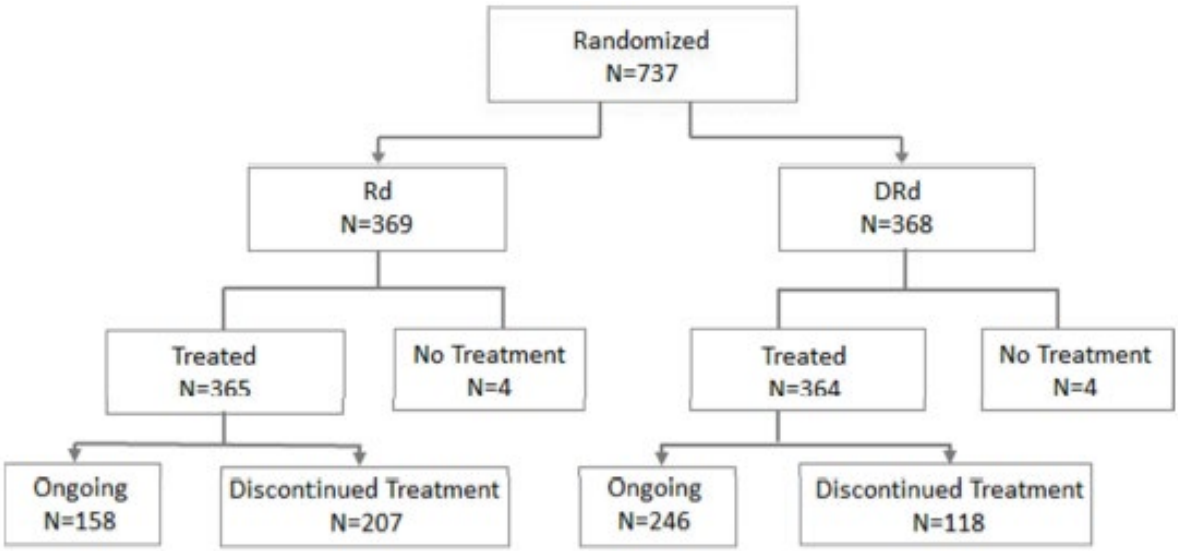
Two interim analyses are planned. The first interim analysis, with a purpose to evaluate safety, will be performed after a total of approximately 100 subjects have been treated for at least 8 weeks or discontinued the study treatment. The second interim analysis will be performed when 234 PFS events, which is 60% of

the total planned events, have been accumulated. The purpose of this interim analysis is to evaluate cumulative interim safety and efficacy data. The significance level at this interim analysis to establish the superiority of DRd over Rd with regard to PFS will be 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. If the experimental arm (DRd) is numerically worse than the control arm in terms of PFS (observed hazard ratio >1 favoring the control arm), then the study may be terminated for futility, with a conditional power of less than 20% under the alternative hypothesis given the observed interim data.

Results

Participant flow

Figure 5: Participant flow Study MMY3008



Source: Table 2

Table 2: Summary of study treatment disposition, Intent-to-treat Analysis Set, Study MMY3008

	Rd n (%)	DRd n (%)	Total n (%)
Analysis set: intent-to-treat	369	368	737
Subjects randomized but not treated [a]	4 (1.1%)	4 (1.1%)	8 (1.1%)
Subjects treated [a]	365 (98.9%)	364 (98.9%)	729 (98.9%)
Subjects who discontinued treatment [b]	207 (56.7%)	118 (32.4%)	325 (44.6%)
Reason for discontinuation [b]			
Progressive disease	87 (23.8%)	53 (14.6%)	140 (19.2%)
Adverse event	59 (16.2%)	27 (7.4%)	86 (11.8%)
Death	16 (4.4%)	21 (5.8%)	37 (5.1%)
Non-compliance with study drug [c]	23 (6.3%)	13 (3.6%)	36 (4.9%)
Physician decision	17 (4.7%)	2 (0.5%)	19 (2.6%)
Lost to follow-up	1 (0.3%)	0	1 (0.1%)
Withdrawal by subject	4 (1.1%)	0	4 (0.5%)
Other	0	2 (0.5%)	2 (0.3%)
Subjects who discontinued study [a]	93 (25.2%)	70 (19.0%)	163 (22.1%)
Reason for discontinuation [a]			
Death	76 (20.6%)	62 (16.8%)	138 (18.7%)
Withdrawal by subject	14 (3.8%)	7 (1.9%)	21 (2.8%)
Lost to follow-up	3 (0.8%)	1 (0.3%)	4 (0.5%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone.
[a] Percentages are based on number of subjects randomized.
[b] Percentages are based on number of subjects treated.
[c] Captured as reason 'Subject refused further study treatment' on 'End of Treatment' CRF page.
[TSIDS01.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\TSIDS01.SAS] 26NOV2018, 18:18

Recruitment

Study Center(s): Austria (4 sites), Australia (9 sites), Belgium (3 sites), Canada (8 sites), Denmark (3 sites), France (45 sites), Germany (14 sites), Ireland (2 sites), Israel (4 sites), Italy (4 sites), Netherlands (3 sites), Sweden (7 sites), United Kingdom (14 sites), United States (56 sites).

Study Period: 10 March 2015 (Date first subject signed informed consent) to 24 September 2018, the data cut-off for the second interim analysis.

Conduct of the study

The original protocol was dated 14 July 2014, and there were 4 global amendments in addition to country specific amendments for the UK, Germany, and France. The rationale for each amendment is summarized below:

Summary of Protocol Amendments for 54767414MMY3008

Amendment INT-1 (29 October 2014; substantial)	• Clarifications were made to MRD monitoring and investigator feedback was incorporated into the protocol.
Amendment INT-1/UK-1 (26 March 2015; substantial)	• Revision made to update the criteria for treatment discontinuation, based on feedback from the UK Medicines and Healthcare Products Regulatory Agency (MHRA).
Amendment DEU-1 (13 April 2015; substantial)	• Revision made to the exclusion criterion for hepatitis, based on feedback from the German PEI on a related ongoing daratumumab protocol.
Amendment INT-2 (26 August 2015; substantial)	• Revisions made to clarify blood typing assessment during the Screening Phase by incorporating Indirect Antiglobulin (Coombs) Testing (IAT) due to the risk of daratumumab interference with blood typing. Also, further defined the exclusion criteria for hepatitis B and C, and HIV.
Amendment INT-2/UK-1 (28 August 2015; substantial)	• Country specific change from UK-1 incorporated into INT-2
Amendment INT-2/FRA-1 (17 February 2016; non-substantial)	• Revisions made to incorporate feedback from the French National Ethics Committee regarding duration of contraceptive use from 4 to 3 months per IB and ICF risk language
Amendment INT-3 (02 November 2016; substantial)	• Revisions were made to the timepoints for the assessment of MRD-negativity to align with newly defined IMWG categories.
Amendment INT-3/UK-1 (14 November 2016; substantial)	• Country specific change from UK-1 incorporated into INT-3
Amendment INT-4 (22 May 2017; substantial)	• Revision made for subjects in the DRd group to continue treatment with lenalidomide and dexamethasone until disease progression or unacceptable toxicity based on continuous lenalidomide treatment emerging as the standard of care and consistent with the approved lenalidomide prescribing information. Previous version had lenalidomide and dexamethasone stopping at 2 years in the DRd group. Two subjects in the DRd group had treatment disruption due to implementing the amendment. One subject had met the 2-year mark while waiting for IRB approval of the amendment and received one month of treatment with daratumumab alone. The second subject signed the ICF for amendment 4 but Rd was discontinued at the 2-year mark in error.
Amendment INT-4.UK-1 (01 June 2017; substantial)	• Country specific change from UK-1 incorporated into INT-4

During the study, issues were identified involving the collection of unscheduled samples for pharmacokinetic, quantitative immunoglobulins, and exploratory peripheral blood MRD testing from study subjects. A corrective action plan was implemented. The non-compliance did not have an impact on the safety, physical, or mental integrity of the study subjects. Some of the unscheduled pharmacokinetic samples were tested but the results were not included in the analysis. Additionally, pharmacokinetic samples not tested will be destroyed. The unscheduled peripheral blood MRD samples were not tested and the samples will be destroyed. The unscheduled quantitative immunoglobulin samples were tested, and the data retained in the database.

Protocol deviations

All protocol deviations of eligibility criteria and those deviations that could impact subject safety or primary endpoints were considered major protocol deviations. Major protocol deviations were reported for 68 subjects (9.2%) across both treatment groups: 25 subjects (6.8%) in the DRd group and 43 subjects (11.7%) in the Rd group. One subject in the DRd group had 2 major protocol deviations (entered but did not satisfy criteria and other [M-protein disease evaluation at screening not within protocol defined window]).

Baseline data

Table 3: Summary of baseline disease characteristics – ITT

	Rd n (%)	DRd n (%)	Total n (%)
Analysis set: intent-to-treat	369	368	737
Age, years			
N	369	368	737
Category, n (%)			
<65	4 (1.1%)	4 (1.1%)	8 (1.1%)
65 - <70	73 (19.8%)	74 (20.1%)	147 (19.9%)
70 - <75	131 (35.5%)	130 (35.3%)	261 (35.4%)
≥75	161 (43.6%)	160 (43.5%)	321 (43.6%)
Mean (SD)	74.2 (5.66)	74.0 (5.44)	74.1 (5.55)
Median	74.0	73.0	73.0
Range	(45; 89)	(50; 90)	(45; 90)
Sex, n (%)			
N	369	368	737
Male	195 (52.8%)	189 (51.4%)	384 (52.1%)
Female	174 (47.2%)	179 (48.6%)	353 (47.9%)
Ethnicity, n (%)			
N	369	368	737
Hispanic or Latino	12 (3.3%)	11 (3.0%)	23 (3.1%)
Not Hispanic or Latino	352 (95.4%)	347 (94.3%)	699 (94.8%)
Unknown	3 (0.8%)	6 (1.6%)	9 (1.2%)
Not Reported	2 (0.5%)	4 (1.1%)	6 (0.8%)
Race, n (%)			
N	369	368	737
White	339 (91.9%)	336 (91.3%)	675 (91.6%)
Black or African American	16 (4.3%)	12 (3.3%)	28 (3.8%)
Asian	2 (0.5%)	3 (0.8%)	5 (0.7%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	1 (0.3%)	0	1 (0.1%)
Other *	6 (1.6%)	6 (1.6%)	12 (1.6%)
Unknown	1 (0.3%)	2 (0.5%)	3 (0.4%)
Not Reported	4 (1.1%)	9 (2.4%)	13 (1.8%)
Weight (kg)			
N	369	368	737
Category, n (%)			
< 50	13 (3.5%)	9 (2.4%)	22 (3.0%)
50 - < 65	93 (25.2%)	96 (26.1%)	189 (25.6%)
65 - < 85	184 (49.9%)	168 (45.7%)	352 (47.8%)
≥ 85	79 (21.4%)	95 (25.8%)	174 (23.6%)
Mean (SD)	74.0 (15.21)	75.1 (16.66)	74.5 (15.95)
Median	72.9	72.1	72.3
Range	(39; 140)	(45; 152)	(39; 152)
Height (cm)			
N	369	368	737
Mean (SD)	166.1 (9.53)	166.2 (9.25)	166.1 (9.39)
Median	166.0	166.0	166.0
Range	(144; 192)	(137; 193)	(137; 193)
Baseline BSA (m^2)			
N	369	368	737
Mean (SD)	1.840 (0.2224)	1.854 (0.2326)	1.847 (0.2275)
Median	1.817	1.830	1.826
Range	(1.27; 2.61)	(1.34; 2.73)	(1.27; 2.73)
Baseline ECOG score, n (%)			
N	369	368	737
0	123 (33.3%)	127 (34.5%)	250 (33.9%)
1	187 (50.7%)	178 (48.4%)	365 (49.5%)
≥2	59 (16.0%)	63 (17.1%)	122 (16.6%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; BSA=Body Surface Area; ECOG=Eastern Cooperative Oncology Group.

* Subjects reporting multiple races are included under other.

Note: Percentages are calculated with the number of subjects in each treatment group with available data as denominator.

[TSIDEM02.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\TSIDEM02.SAS] 26NOV2018, 18:17

Numbers analysed

The primary analysis population was the intent-to-treat (ITT) population, which included all randomized subjects. A summary of all subjects per analysis set is presented in the following Table.

Table 4: Subjects per analysis set

	Rd n	DRd n	Total n
Study population			
Subjects screened			952
Intent-to-treat (ITT)	369	368	737
Per-protocol[a] (PP)	360	359	719
Response-evaluable[b]	356	354	710
Pharmacokinetic evaluable[c]	-	356	356
Immunogenicity evaluable[d]	-	338	338

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone.
[a] Includes subjects who are randomized and meet all eligibility criteria.
[b] Includes 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 one component of study treatment and have adequate post-baseline disease assessments.
[c] Includes subjects assigned to DRd group who received at least 1 administration of daratumumab and have at least 1 pharmacokinetic sample concentration value after the first infusion.
[d] Includes subjects assigned to DRd group who have at least 1 immunogenicity sample obtained after their first daratumumab administration.
Modified from [TSIDS02.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\TSIDS02.SAS] 26NOV2018, 18:18

Outcomes and estimation

Primary Endpoint:

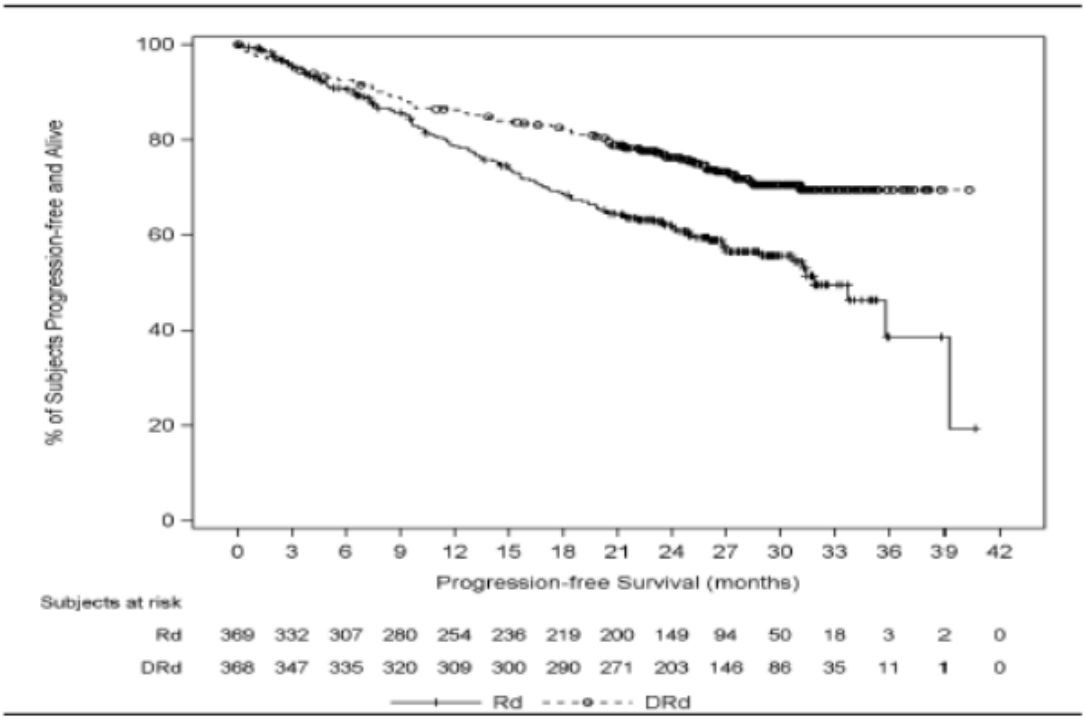
PFS (cut-off 24 September 2018)

Table 5: PFS based on computerised algorithm: ITT

	Rd	DRd
Analysis set: intent-to-treat	369	368
Progression-free survival (PFS)		
Number of events (%)	143 (38.8%)	97 (26.4%)
Number of censored (%)	226 (61.2%)	271 (73.6%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	14.46 (11.56, 16.82)	25.56 (20.53, 31.08)
Median (95% CI)	31.87 (28.94, NE)	NE (NE, NE)
75% quantile (95% CI)	39.23 (35.81, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.56 (0.43, 0.73)
12-month PFS rate % (95% CI)	78.6 (73.8, 82.6)	86.2 (82.2, 89.4)
24-month PFS rate % (95% CI)	62.0 (56.5, 67.1)	76.2 (71.4, 80.4)
36-month PFS rate % (95% CI)	38.5 (23.0, 53.9)	69.5 (63.5, 74.6)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; CI = confidence interval.
[a] p-value is based on the log-rank test stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized.
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized. A hazard ratio <1 indicates an advantage for DRd.
[TEFPFS01.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\TEFPFS01.SAS] 26NOV2018, 19:23

Figure 6: Kaplan-Meier plot for PFS - ITT



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

[GEFPFS01.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\GEFPFS01.SAS] 26NOV2018, 19:52

Table 6: Summary of reasons for Censoring PFS

	Rd n (%)	DRd n (%)
Analysis set: intent-to-treat	369	368
Subjects censored	226 (61.2%)	271 (73.6%)
Reason for censoring[a]		
Study cut-off	178 (78.8%)	256 (94.5%)
Subsequent antimyeloma therapy	34 (15.0%)	12 (4.4%)
Withdrawal of consent to study participation	13 (5.8%)	3 (1.1%)
Lost to follow-up	1 (0.4%)	0
Subjects with progression-free survival event	143 (38.8%)	97 (26.4%)
Subjects with confirmed progressive disease[b,c]	111 (77.6%)	64 (66.0%)
Reason for progressive disease[c]		
Serum M-protein	68 (61.3%)	32 (50.0%)
Urine M-protein	20 (18.0%)	6 (9.4%)
Serum FLC[d]	6 (5.4%)	6 (9.4%)
Bone lesion (increase in size)	11 (9.9%)	5 (7.8%)
Bone lesion (new bone lesion)	17 (15.3%)	11 (17.2%)
Plasmacytomas (increase in size)	0	1 (1.6%)
Plasmacytomas (new plasmacytomas)	7 (6.3%)	7 (10.9%)
Hypercalcemia	3 (2.7%)	1 (1.6%)
Subjects died without confirmed progressive disease[e]	32 (22.4%)	33 (34.0%)
Death due to progressive disease[f]	2 (6.3%)	2 (6.1%)
Other[g]	30 (93.8%)	31 (93.9%)

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

[a] Percentages are based on number of subjects censored in each treatment group.

[b] A subject may show PD based on more than one criterion.

[c, e] Percentages are based on number of subjects with PFS event in each treatment group.

[d] Only applicable to subjects without measurable serum and urine M-protein levels.

[f] Percentages are based on number of subjects with PD event in each treatment group.

[g] Percentages are based on number of subjects with "death without confirmed PD" event in each treatment group.

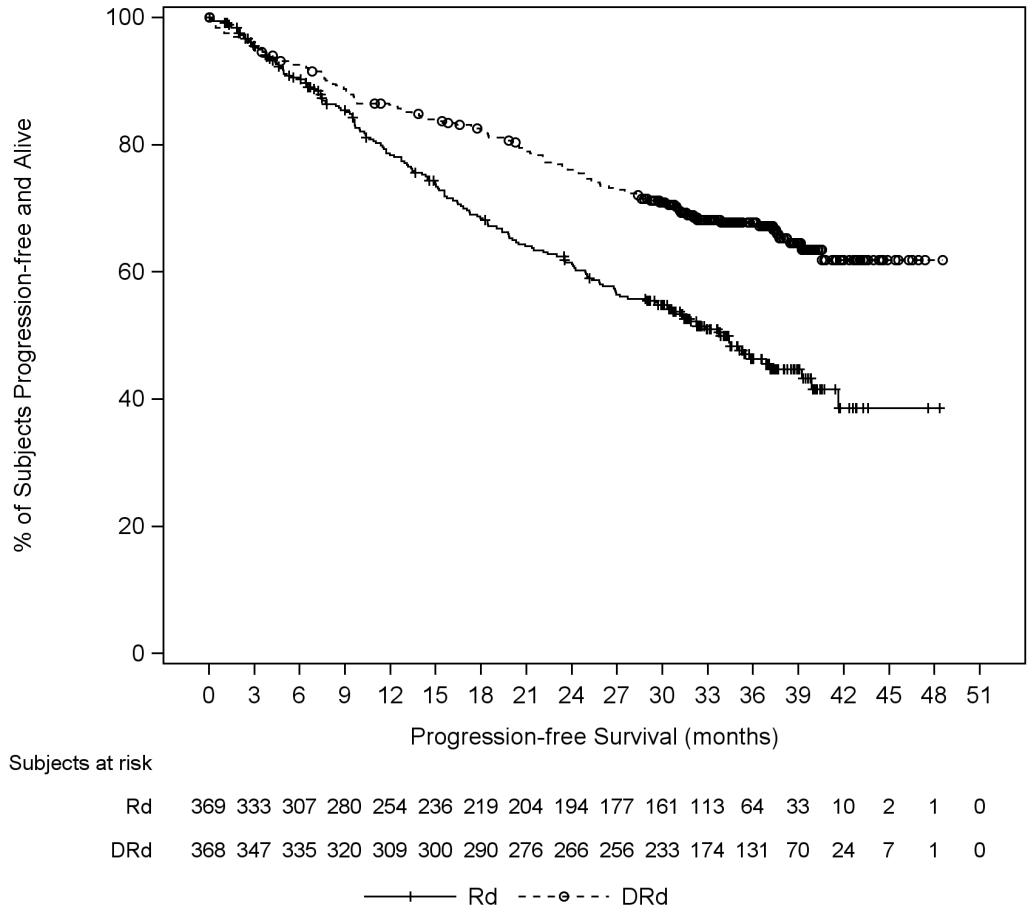
[TEFRFPD01.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\TEFRFPD01.SAS] 26NOV2018, 19:25

Updated PFS (cut-off 10 June 2019)

Table 7: Updated PFS based on computerised algorithm: ITT

	Rd	DRd
Analysis set: intent-to-treat	369	368
Progression-free survival (PFS)		
Number of events (%)	171 (46.3%)	120 (32.6%)
Number of censored (%)	198 (53.7%)	248 (67.4%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	14.32 (11.50, 16.66)	24.94 (20.53, 30.36)
Median (95% CI)	33.84 (28.94, 39.23)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.56 (0.44, 0.71)
12-month PFS rate % (95% CI)	78.4 (73.6, 82.4)	86.2 (82.2, 89.4)
24-month PFS rate % (95% CI)	61.5 (56.0, 66.5)	76.0 (71.2, 80.1)
36-month PFS rate % (95% CI)	46.3 (40.3, 52.1)	67.7 (62.5, 72.4)

Figure 7: Updated Kaplan-Meier plot for PFS - ITT



Secondary Endpoints:

For key secondary endpoints, pre-specified hierarchical testing, along with alpha spending using group sequential methods, was performed to strongly control the family-wise type I error rate at 0.05 (2-sided).

The p-values for CR or better rate, VGPR or better rate, MRD negativity rate, and ORR, all crossed the O'Brien-Fleming stopping boundary of 0.0244 as pre-specified.

Response-related secondary efficacy endpoints

Table 8: Summary of Response related secondary efficacy endpoints - ITT

	Rd	DRd
Overall response (sCR+CR+VGPR+PR)		
n(%)	300 (81.3%)	342 (92.9%)
(95% CI)	(76.9%, 85.1%)	(89.8%, 95.3%)
Odds Ratio (95% CI)		3.05 (1.89, 4.94)
P-value[a]		<0.0001
VGPR or better (sCR+CR+VGPR)		
n(%)	196 (53.1%)	292 (79.3%)
(95% CI)	(47.9%, 58.3%)	(74.8%, 83.4%)
Odds Ratio (95% CI)		3.40 (2.45, 4.72)
P-value[a]		<0.0001
CR or better (sCR+CR)		
n(%)	92 (24.9%)	175 (47.6%)
(95% CI)	(20.6%, 29.7%)	(42.4%, 52.8%)
Odds Ratio (95% CI)		2.72 (1.99, 3.71)
P-value[a]		<0.0001
sCR		
n(%)	46 (12.5%)	112 (30.4%)
(95% CI)	(9.3%, 16.3%)	(25.8%, 35.4%)
Odds Ratio (95% CI)		3.09 (2.11, 4.54)
P-value[a]		<0.0001
MRD negativity rate (10^{-5})		
n(%)	27 (7.3%)	89 (24.2%)
95% CI of MRD negativity rate	(4.9%, 10.5%)	(19.9%, 28.9%)
Odds ratio with 95% CI		4.04 (2.55, 6.39)
P-value[b]		<0.0001

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; CI=confidence interval; CR=complete response; MRD=minimal residual disease; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.
[a] P-value from the Cochran Mantel-Haenszel Chi-Squared test.
[b] P-value from Fisher's exact test.
Note: Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized. An odds ratio > 1 indicates an advantage for DRd.
[TEFRESP01_SCE.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\TEFRESP01_SCE.SAS] 21JAN2019, 09:05

Minimal Residual Disease (MRD)

For the ITT population, the DRd group demonstrated a greater rate of MRD negativity compared with the Rd group. The MRD negativity rate at the sensitivity threshold of 10-5 was more than 3-fold higher in subjects in the DRd group compared with subjects in the Rd group (DRd: 24.2%, Rd: 7.3%; odds ratio=4.04; 95% CI: 2.55, 6.39; p<0.0001).

An important aspect in the assessment of MRD is the identification of tumor sequence from the baseline sample (calibration) that is required to evaluate the residual disease burden at the time of a deep clinical response. The overall calibration success rate was 238 of 267 (91.9%) in subjects with confirmed CR or better response. As an exploratory evaluation, MRD analyses using different thresholds (10-4 and 10-6) were also conducted in the ITT population. The rates of MRD negativity at these threshold levels were also significantly higher for the DRd group compared with the Rd group.

Overall Survival (OS)

Table 9: Summary of Overall Survival (unstratified analysis) - ITT

	Rd	DRd
Analysis set: intent-to-treat	369	368
Overall survival		
Number of events (%)	103 (27.9%)	85 (23.1%)
Number of censored (%)	266 (72.1%)	283 (76.9%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	32.85 (27.60, 37.39)	38.64 (32.85, NE)
Median (95% CI)	NE (47.28, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		0.0775
Hazard ratio (95% CI)[b]		0.77 (0.58, 1.03)
12-month survival rate % (95% CI)	91.3 (87.9, 93.8)	92.6 (89.4, 94.9)
24-month survival rate % (95% CI)	83.4 (79.1, 86.9)	84.3 (80.2, 87.7)
36-month survival rate % (95% CI)	72.4 (67.2, 76.9)	77.3 (72.4, 81.4)
48-month survival rate % (95% CI)	53.4 (31.8, 70.8)	70.5 (62.8, 76.9)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; CI = confidence interval.
[a] p-value is based on the unstratified 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 DRd.
[TEFOS02_9MO.RTF] [JNJ-54767414\MMY3008\DBR_9M_2019\RE_9M_2019\PROD\TEFOS02_9MO.SAS] 17JUL2019, 20:15

PFS2

Table 10

Summary of Progression-free Survival on Next Line of Therapy (PFS2) Based on Investigator Assessment - ITT

	Rd	DRd
Analysis set: intent-to-treat	369	368
Progression-free survival on next line of therapy (PFS2)		
Number of events (%)	121 (32.8%)	96 (26.1%)
Number of censored (%)	248 (67.2%)	272 (73.9%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	26.02 (21.55, 30.19)	34.07 (30.29, 41.03)
Median (95% CI)	47.28 (39.62, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (47.28, NE)	NE (NE, NE)
P-value[a]		0.0079
Hazard ratio (95% CI)[b]		0.69 (0.53, 0.91)
12-month PFS2 rate % (95% CI)	89.5 (85.8, 92.3)	90.7 (87.2, 93.2)
24-month PFS2 rate % (95% CI)	77.7 (72.9, 81.8)	82.5 (78.2, 86.1)
36-month PFS2 rate % (95% CI)	63.8 (58.0, 69.0)	74.3 (69.2, 78.6)
48-month PFS2 rate % (95% CI)	45.2 (24.4, 63.9)	65.4 (56.7, 72.8)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; CI = confidence interval.
[a] p-value is based on the log-rank test stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized.
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized. A hazard ratio < 1 indicates an advantage for DRd.

Time to Disease Progression

Table 11

Summary of Time to Disease Progression - ITT

	Rd	DRd
Analysis set: intent-to-treat	369	368
Time to disease progression[a]		
Number of events (%)	135 (36.6%)	83 (22.6%)
Number of censored (%)	234 (63.4%)	285 (77.4%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	17.25 (14.88, 20.93)	37.36 (26.45, NE)
Median (95% CI)	41.66 (34.50, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[b]		<0.0001
Hazard ratio (95% CI)[c]		0.49 (0.37, 0.64)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; CI = confidence interval.
[a] Time to disease progression is defined as the time from the date of randomization to the date of first observation of PD by IMWG algorithm, or death due to PD (prior to subsequent antimyeloma therapy or withdrawal of consent to study participation).
[b] p-value is based on the log-rank test stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized.
[c] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized. A hazard ratio < 1 indicates an advantage for DRd.

Time to Response

The median time to response was rapid, occurring after 1 month of treatment. Median time to best response was longer in the DRd group (8.82 months) compared with the Rd group (5.29 months). Median time to VGPR or better (2.94 vs 4.62 months) and median time to CR or better (10.35 vs 11.22 months) was shorter for the DRd group versus the Rd group, respectively.

Table 12: Summary of Time to Response

	Rd	DRd
Analysis set: responders (PR or better) in response-evaluable	300	342
Time to first response [a] (months)		
N	300	342
Mean (SD)	1.90 (1.820)	1.54 (1.300)
Median	1.05	1.05
Range	(0.3; 15.3)	(0.2; 12.1)
Time to best response [a] (months)		
N	300	342
Mean (SD)	7.86 (7.153)	10.08 (7.767)
Median	5.29	8.82
Range	(0.9; 29.9)	(0.9; 38.4)
Time to VGPR or better (months)		
N	196	292
Mean (SD)	6.20 (5.455)	4.89 (4.747)
Median	4.62	2.94
Range	(0.9; 27.6)	(0.9; 24.3)
Time to CR or better (months)		
N	92	175
Mean (SD)	12.61 (6.100)	11.95 (6.416)
Median	11.22	10.35
Range	(2.8; 29.9)	(1.0; 35.2)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; PR = partial response.
[a] Response PR or better.
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 one component of study treatment and have adequate post-baseline disease assessments.

Ancillary analyses

Sensitivity analysis

PFS by investigator

Table 13: PFS based on investigator assessment - ITT

	Rd	DRd
Analysis set: intent-to-treat	369	368
Progression-free survival (PFS)		
Number of events (%)	146 (39.6%)	97 (26.4%)
Number of censored (%)	223 (60.4%)	271 (73.6%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	14.09 (11.50, 16.56)	25.86 (20.73, 31.08)
Median (95% CI)	31.41 (26.94, 39.23)	NE (NE, NE)
75% quantile (95% CI)	39.23 (35.81, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.54 (0.42, 0.70)
12-month PFS rate % (95% CI)	78.3 (73.5, 82.3)	86.5 (82.5, 89.6)
24-month PFS rate % (95% CI)	61.5 (55.9, 66.6)	76.5 (71.6, 80.6)
36-month PFS rate % (95% CI)	35.1 (18.6, 52.2)	68.0 (61.6, 73.7)

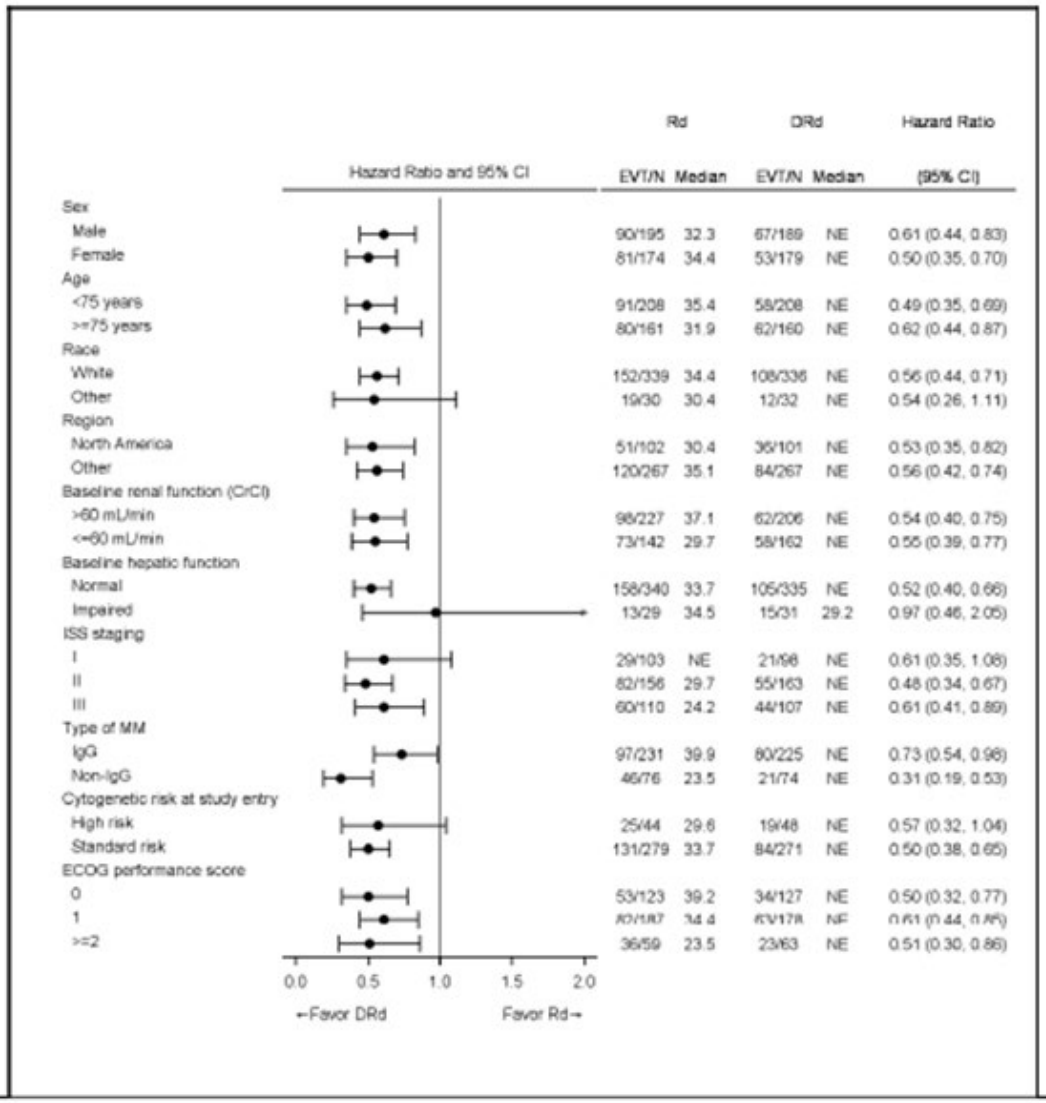
Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; CI = confidence interval.
[a] p-value is based on the log-rank test stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized.
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with ISS staging (I, II, III), region (North America vs. Other), and age (<75 years vs. ≥75 years) as randomized. A hazard ratio <1 indicates an advantage for DRd.
[TEFPFS02.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\TEFPFS02.SAS] 26NOV2018, 19:23

Other sensitivity analyses

A PFS analysis that did not censor data for starting subsequent anti-myeloma therapy, an analysis of PFS that censored for death or progression after more than 1 missed disease evaluation, a PFS analysis evaluating the per-protocol population, and an un-stratified PFS analysis, all showed results consistent with the primary analysis.

Subgroup analyses

Figure 8: **Forrest plot of subgroup analyses of PFS; ITT**



Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; EVT = event.
Note: Impaired baseline hepatic function includes mild (total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5ULN); moderate (1.5×ULN < total bilirubin ≤ 3×ULN); and severe (total bilirubin > 3×ULN).
Note: High risk cytogenetics is defined as positive for any of t (4; 14), t (14; 16), and 17p deletion by FISH or karyotype
Note: Type of MM subgroup analysis is based on subjects with measurable disease in serum.

Summary of main study

The following table summarises 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 14. Summary of Efficacy for Study 54767414MMY3008

Title: A Phase 3 Study Comparing Daratumumab, Lenalidomide, and Dexamethasone (D-Rd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy			
Study identifier	54767414MMY3008		
Design	Phase 3, open-label, multi-center, randomized trial comparing Daratumumab, Lenalidomide, and Dexamethasone (D-Rd) vs Lenalidomide and Dexamethasone (Rd) in Subjects with Previously Untreated Multiple Myeloma who are Ineligible for High Dose Therapy		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Approx. 3.5 years Study initiation date 10 March 2015 Data cut off 24 September 2018 *Ongoing* n/a n/a
Hypothesis	Superiority		
Treatments groups	D-Rd		Daratumumab 16 mg/kg IV (each cycle [C] 28 days) Q 1 week for 8 weeks (C 1-2), Q 2 weeks (C 4-6), Q 4 weeks (C7+), until disease progression or unacceptable toxicity. Rd as below.
	Rd		Lenalidomide 25 mg PO on days 1 through 21 of each 28-day cycle (for subjects with a creatinine clearance between 30 and 50 mL/min, lenalidomide 10 mg PO on days 1 through 21 of each 28-day cycle), and dexamethasone (oral or IV) 40 mg once a week (for subjects older than 75 years or underweight (body mass index [BMI] <18.5), dexamethasone 20 mg weekly) until disease progression or unacceptable toxicity.
Endpoints and definitions	**Primary endpoint**	**Progression free survival (PFS)**	**Progression free survival**, defined as the duration from the date of randomization to either progressive disease, based on computerized algorithm according to IMWG criteria, or death, whichever occurred first.
	Secondary endpoint	**Overall response rate (ORR)**	Proportion of subjects who achieve a partial response (PR) or better (ie., PR, very good partial response, complete response or stringent complete response), based on computerized algorithm according to IMWG.

	Secondary endpoint	**Complete response or better rate (CR or better rate)**	Proportion of subjects with a response of CR or better, based on computerized algorithm according to IMWG.
	Secondary endpoint	**Minimal Residual Disease-negativity rate (MRD-negativity rate)**	Proportion of subjects assessed as MRD negative, at any timepoint after the date of randomization.
	Secondary endpoint	**Overall Survival (OS)**	Overall survival (OS), defined as the duration from the date of randomization to the date of the subject's death.
Database lock	**21 November 2018**		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**Intent to treat (ITT)**		
Descriptive statistics and estimate variability	**Treatment group**	**D-Rd**	**Rd**
	Number of subjects	**368**	**369**
	Primary endpoint: **Median PFS (months)**	NE	31.9
	95% CI	(NE, NE)	(28.9, NE)
	Secondary endpoint: **ORR**	92.9%	81.3%
	95% CI	(89.8%, 95.3%)	(76.9%, 85.1%)
	Secondary endpoint: **CR or better rate**	47.6%	24.9%
	95% CI	(42.4%, 52.8%)	(20.6%, 29.7%)
	Secondary endpoint: **MRD-negativity rate (NGS, 10^{-5})**	24.2%	7.3%
	95% CI	(19.9%, 28.9%)	(4.9%, 10.5%)
	Secondary endpoint: **Median OS (months)**	NE	NE
	95% CI	(NE, NE)	(39.23, NE)
Effect estimate per comparison	Primary endpoint: **PFS**	Comparison groups	D-Rd vs. Rd
		Hazard ratio (HR)	0.56
		95% CI	0.43-0.73
		P-value	<0.0001
	Secondary endpoint: **ORR**	Comparison groups	D-Rd vs. Rd
		Odds ratio	3.05
		95% CI	1.89-4.94
		P-value	<0.0001
	Secondary endpoint: **CR or better rate**	Comparison groups	D-Rd vs. Rd
		Odds ratio	2.72
		95% CI	1.99-3.71
		P-value	<0.0001
	Secondary endpoint: **MRD-negativity rate (NGS, 10^{-5})**	Comparison groups	D-Rd vs. Rd

		Odds ratio	4.04
		95% CI	2.55-6.39
		P-value	<0.0001
	Secondary endpoint: **OS**	Comparison groups	D-Rd vs. Rd
		Hazard ratio	0.78
		95% CI	0.56-1.10
		P-value	0.1528

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH has provided a randomised phase 3, open-label, active controlled, and multicentre study (MMY3008). The incl/excl criteria clearly define a patient population above 18 years, with newly diagnosed MM ineligible for ASCT and with ECOG 0-2. Sections 4.1 and 5.1 of the SmPC clearly reflect the included patient population. The primary endpoint (PFS) is acceptable in this first-line setting. PFS2, CR and OS are important secondary endpoints.

Overall, the study was well-conducted.

Efficacy data and additional analyses

The study met its primary endpoint showing a statistically significant and clinically meaningful difference in PFS in favour of DRd (36-month PFS rate % (95% CI) of 69.5 (63.5, 74.6) in DRd arm vs 38.5 (23.0, 53.9) in Rd arm; median PFS not reached in DRd arm and 31.9 months in the Rd arm; HR (955 CI) = 0.56 (0.43, 0.73), p-value < 0.0001). Several sensitivity analyses have been provided, including PFS by investigator, all showed similar results as the primary analysis. Consistent results were shown across the majority of subgroups. Updated PFS data (cut-off 10th June 2019) with a median follow-up of 36.4 months continue to show statistically significant and clinically meaningful results.

Across all response criteria DRd show statistically significant and clinically relevant results that confirm the primary analysis. The MRD negativity rate is 24.2% vs. 7.3% in favour of DRd.

Overall survival data are still immature. The MAH has committed to present the final clinical study report of study MMY3008 by 4Q2024.

2.4.4. Conclusions on the clinical efficacy

Study MMY3008 was well conducted. The study met its primary endpoint and showed statistically significant and clinically relevant results. The results from secondary endpoints and subgroup analysis are by majority consistent with the primary endpoint.

2.5. Clinical safety

Introduction

Summaries of adverse events and other safety data are based on 729 subjects (DRd: 364 subjects, Rd: 365 subjects) who were randomized, received at least 1 dose of any study treatment and contributed any safety data after the start of study treatment, ie, the Safety Population.

Patient exposure

A summary of treatment cycles received by subjects in both treatment groups is presented below.

As of the clinical cutoff, subjects in the DRd group had received a median of 27 cycles and subjects in the Rd group had received 22 cycles of treatment. In addition, 237 subjects (65.1%) in the DRd group and 157 subjects (43.0%) in the Rd group had received more than 24 cycles of treatment. The median duration of treatment was 25.3 months for the DRd group and 21.3 months for the Rd group. Thirty-five subjects in the DRd group discontinued Rd but continued daratumumab and an additional 25 subjects discontinued lenalidomide but continued daratumumab and dexamethasone. Four subjects in DRd discontinued daratumumab but continued Rd.

Table 15: **Summary of treatment cycles; SAS**

	Rd	DRd
Analysis set: safety	365	364
Distribution of subjects treated in and beyond each cycle, n (%)		
≥ 1 cycle	365 (100.0%)	364 (100.0%)
≥ 2 cycles	348 (95.3%)	355 (97.5%)
≥ 3 cycles	335 (91.8%)	348 (95.6%)
≥ 4 cycles	326 (89.3%)	342 (94.0%)
≥ 5 cycles	318 (87.1%)	339 (93.1%)
≥ 6 cycles	307 (84.1%)	337 (92.6%)
≥ 7 cycles	297 (81.4%)	330 (90.7%)
≥ 13 cycles	252 (69.0%)	306 (84.1%)
≥ 19 cycles	210 (57.5%)	284 (78.0%)
> 24 cycles	157 (43.0%)	237 (65.1%)
> 30 cycles	70 (19.2%)	125 (34.3%)
> 36 cycles	13 (3.6%)	30 (8.2%)
Total number of treatment cycles received, n (%)		
1	17 (4.7%)	9 (2.5%)
2	13 (3.6%)	7 (1.9%)
Cycle 1-2	30 (8.2%)	16 (4.4%)
3	9 (2.5%)	6 (1.6%)
4	8 (2.2%)	3 (0.8%)
5	11 (3.0%)	2 (0.5%)
6	10 (2.7%)	7 (1.9%)
Cycle 3-6	38 (10.4%)	18 (4.9%)
Cycle 7-12	45 (12.3%)	24 (6.6%)
Cycle 13-18	42 (11.5%)	22 (6.0%)
Cycle 19-24	53 (14.5%)	47 (12.9%)
> 24 cycles	157 (43.0%)	237 (65.1%)
> 30 cycles	70 (19.2%)	125 (34.3%)

> 36 cycles	13 (3.6%)	30 (8.2%)
Summary of total number of treatment cycles received		
N	365	364
Mean (SD)	19.8 (11.21)	25.0 (10.28)
Median	22.0	27.0
Range	(1; 43)	(1; 44)

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

[TSIEXP01.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\TSIEXP01.SAS] 26NOV2018, 18:18

Table 16: Summary of relative dose intensity; SAS

	Rd n (%)	DRd n (%)	Total n (%)
Analysis set: safety	365	364	729
Lenalidomide(mg) relative dose intensity (%)			
N	348	339	687
Mean (SD)	83.49 (29.371)	73.56 (29.671)	78.59 (29.913)
Median	91.43	76.22	84.54
Range	(4.8; 234.2)	(7.9; 240.9)	(4.8; 240.9)
Category, n (%)			
<80%	134 (38.5%)	181 (53.4%)	315 (45.9%)
≥80% - ≤120%	200 (57.5%)	149 (44.0%)	349 (50.8%)
>120% *	14 (4.0%)	9 (2.7%)	23 (3.3%)
Dexamethasone(mg) relative dose intensity (%)			
N	365	364	729
Mean (SD)	82.61 (20.345)	78.41 (21.087)	80.51 (20.811)
Median	90.71	84.21	87.44
Range	(18.9; 154.5)	(22.9; 110.7)	(18.9; 154.5)
Daratumumab (mg/kg) relative dose intensity (%)			
N		364	364
Mean (SD)		95.76 (10.452)	95.76 (10.452)
Median		98.36	98.36
Range		(3.2; 107.0)	(3.2; 107.0)
Daratumumab (mg/kg) relative dose intensity (Cycle 1-2, %)			
N		364	364
Mean (SD)		90.74 (13.297)	90.74 (13.297)
Median		91.91	91.91
Range		(3.2; 116.4)	(3.2; 116.4)
Daratumumab (mg/kg) relative dose intensity (Cycle 3-6, %)			
N		345	345
Mean (SD)		99.40 (7.531)	99.40 (7.531)
Median		100.76	100.76
Range		(48.8; 111.7)	(48.8; 111.7)
Daratumumab (mg/kg) relative dose intensity (Cycle ≥7, %)			
N		327	327
Mean (SD)		99.81 (4.015)	99.81 (4.015)
Median		100.00	100.00
Range		(71.2; 110.1)	(71.2; 110.1)

	Rd n (%)	DRd n (%)	Total n (%)
Analysis set: safety	365	364	729
Lenalidomide(mg) relative dose intensity (%)			
N	348	339	687
Mean (SD)	83.49 (29.371)	73.56 (29.671)	78.59 (29.913)
Median	91.43	76.22	84.54
Range	(4.8; 234.2)	(7.9; 240.9)	(4.8; 240.9)
Category, n (%)			
<80%	134 (38.5%)	181 (53.4%)	315 (45.9%)
≥80% - ≤120%	200 (57.5%)	149 (44.0%)	349 (50.8%)
>120% [a]	14 (4.0%)	9 (2.7%)	23 (3.3%)
Dexamethasone(mg) relative dose intensity (%)			
N	365	364	729
Mean (SD)	82.61 (20.345)	78.41 (21.087)	80.51 (20.811)
Median	90.71	84.21	87.44
Range	(18.9; 154.5)	(22.9; 110.7)	(18.9; 154.5)
Daratumumab (mg/kg) relative dose intensity (%)			
N		364	364
Mean (SD)		95.76 (10.452)	95.76 (10.452)
Median		98.36	98.36
Range		(3.2; 107.0)	(3.2; 107.0)
Daratumumab (mg/kg) relative dose intensity (Cycle 1-2, %)			
N		364	364
Mean (SD)		90.74 (13.297)	90.74 (13.297)
Median		91.91	91.91
Range		(3.2; 116.4)	(3.2; 116.4)
Daratumumab (mg/kg) relative dose intensity (Cycle 3-6, %)			
N		345	345
Mean (SD)		99.40 (7.531)	99.40 (7.531)
Median		100.76	100.76
Range		(48.8; 111.7)	(48.8; 111.7)
Daratumumab (mg/kg) relative dose intensity (Cycle ≥7, %)			
N		327	327
Mean (SD)		99.81 (4.015)	99.81 (4.015)
Median		100.00	100.00
Range		(71.2; 110.1)	(71.2; 110.1)

Adverse events

Table 17: Overview of TEAEs; SAS

	Rd n (%)	DRd n (%)
Analysis set: safety	365	364
Any TEAE	362 (99.2%)	364 (100.0%)
Maximum toxicity grade		
Grade 1	6 (1.6%)	0
Grade 2	53 (14.5%)	35 (9.6%)
Grade 3	200 (54.8%)	206 (56.6%)
Grade 4	80 (21.9%)	98 (26.9%)
Grade 5	23 (6.3%)	25 (6.9%)
Any serious TEAE	229 (62.7%)	229 (62.9%)
TEAE leading to discontinuation of lenalidomide	62 (17.0%)	76 (20.9%)
TEAE leading to discontinuation of dexamethasone	95 (26.0%)	88 (24.2%)
TEAE leading to discontinuation of daratumumab	0	30 (8.2%)
TEAE leading to discontinuation of study treatment*	58 (15.9%)	26 (7.1%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
* 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 20.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.
Note: Dexamethasone is for dexamethasone or equivalent.
Modified from [TSFAE01.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\TSFAE01.SAS] 26NOV2018, 18:26

Common AEs

Table 18: Most common (at least 10%) TEAEs

	Rd n (%)	DRd n (%)
Analysis set: safety	365	364
Total number of subjects with TEAE	362 (99.2%)	364 (100.0%)
MedDRA system organ class/preferred term		
Infections and infestations	268 (73.4%)	314 (86.3%)
Bronchitis	74 (20.3%)	106 (29.1%)
Upper respiratory tract infection	52 (14.2%)	83 (22.8%)
Pneumonia	46 (12.6%)	82 (22.5%)
Urinary tract infection	38 (10.4%)	64 (17.6%)
Viral upper respiratory tract infection	46 (12.6%)	56 (15.4%)
Gastrointestinal disorders	290 (79.5%)	311 (85.4%)
Diarrhoea	168 (46.0%)	207 (56.9%)
Constipation	130 (35.6%)	149 (40.9%)
Nausea	84 (23.0%)	115 (31.6%)
Vomiting	45 (12.3%)	61 (16.8%)
Abdominal pain	33 (9.0%)	43 (11.8%)
General disorders and administration site conditions	269 (73.7%)	311 (85.4%)
Fatigue	104 (28.5%)	147 (40.4%)
Oedema peripheral	107 (29.3%)	140 (38.5%)
Asthenia	90 (24.7%)	117 (32.1%)
Pyrexia	65 (17.8%)	84 (23.1%)
Chills	6 (1.6%)	46 (12.6%)
Musculoskeletal and connective tissue disorders	256 (70.1%)	286 (78.6%)
Back pain	96 (26.3%)	123 (33.8%)
Muscle spasms	79 (21.6%)	107 (29.4%)
Arthralgia	64 (17.5%)	70 (19.2%)
Pain in extremity	50 (13.7%)	60 (16.5%)
Musculoskeletal pain	40 (11.0%)	51 (14.0%)
Bone pain	36 (9.9%)	37 (10.2%)
Musculoskeletal chest pain	43 (11.8%)	27 (7.4%)
Blood and lymphatic system disorders	234 (64.1%)	275 (75.5%)
Neutropenia	154 (42.2%)	207 (56.9%)
Anaemia	138 (37.8%)	126 (34.6%)
Leukopenia	34 (9.3%)	68 (18.7%)
Thrombocytopenia	69 (18.9%)	68 (18.7%)
Lymphopenia	45 (12.3%)	66 (18.1%)
Nervous system disorders	234 (64.1%)	260 (71.4%)
Peripheral sensory neuropathy	54 (14.8%)	87 (23.9%)
Dizziness	58 (15.9%)	69 (19.0%)
Headache	39 (10.7%)	69 (19.0%)
Paraesthesia	30 (8.2%)	58 (15.9%)
Tremor	51 (14.0%)	57 (15.7%)
Dysgeusia	35 (9.6%)	40 (11.0%)
Respiratory, thoracic and mediastinal disorders	168 (46.0%)	243 (66.8%)
Dyspnoea	56 (15.3%)	101 (27.7%)
Cough	59 (16.2%)	100 (27.5%)
Metabolism and nutrition disorders	175 (47.9%)	228 (62.6%)
Decreased appetite	55 (15.1%)	80 (22.0%)
Hypokalaemia	61 (16.7%)	75 (20.6%)
Hyperglycaemia	28 (7.7%)	50 (13.7%)
Hypocalcaemia	32 (8.8%)	50 (13.7%)
Skin and subcutaneous tissue disorders	186 (51.0%)	191 (52.5%)
Rash	43 (11.8%)	57 (15.7%)
Psychiatric disorders	191 (52.3%)	179 (49.2%)
Insomnia	107 (29.3%)	109 (29.9%)
Investigations	116 (31.8%)	166 (45.6%)
Weight decreased	63 (17.3%)	101 (27.7%)
Vascular disorders	138 (37.8%)	164 (45.1%)

Hypertension	26 (7.1%)	47 (12.9%)
Eye disorders	123 (33.7%)	115 (31.6%)
Cataract	59 (16.2%)	54 (14.8%)
Cardiac disorders	96 (26.3%)	100 (27.5%)
Atrial fibrillation	37 (10.1%)	23 (6.3%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.
[TSFAE02AA.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\TSFAE02AA.SAS] 26NOV2018, 18:42

Table 19: Grade 3/4 AEs

Table 22: Most Common (at Least 5%) Grade 3 or 4 Treatment-emergent Adverse Events by MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set (Study 54767414MMY3008)

	Rd			DRd		
	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
Analysis set: safety	365			364		
Total number of subjects with toxicity grade 3 or 4 TEAE	301 (82.5%)	204 (55.9%)	97 (26.6%)	327 (89.8%)	210 (57.7%)	117 (32.1%)
MedDRA system organ class/preferred term						
Blood and lymphatic system disorders	189 (51.8%)	142 (38.9%)	47 (12.9%)	224 (61.5%)	152 (41.8%)	72 (19.8%)
Neutropenia	129 (35.3%)	93 (25.5%)	36 (9.9%)	182 (50.0%)	125 (34.3%)	57 (15.7%)
Lymphopenia	39 (10.7%)	35 (9.6%)	4 (1.1%)	55 (15.1%)	42 (11.5%)	13 (3.6%)
Anaemia	72 (19.7%)	72 (19.7%)	0	43 (11.8%)	43 (11.8%)	0
Leukopenia	18 (4.9%)	16 (4.4%)	2 (0.5%)	40 (11.0%)	35 (9.6%)	5 (1.4%)
Thrombocytopenia	32 (8.8%)	23 (6.3%)	9 (2.5%)	27 (7.4%)	20 (5.5%)	7 (1.9%)
Infections and infestations	85 (23.3%)	64 (17.5%)	21 (5.8%)	117 (32.1%)	92 (25.3%)	25 (6.9%)
Pneumonia	29 (7.9%)	24 (6.6%)	5 (1.4%)	50 (13.7%)	45 (12.4%)	5 (1.4%)
Metabolism and nutrition disorders	74 (20.3%)	54 (14.8%)	20 (5.5%)	75 (20.6%)	61 (16.8%)	14 (3.8%)
Hypokalaemia	32 (8.8%)	25 (6.8%)	7 (1.9%)	32 (8.8%)	28 (7.7%)	4 (1.1%)
Hyperglycaemia	14 (3.8%)	12 (3.3%)	2 (0.5%)	26 (7.1%)	22 (6.0%)	4 (1.1%)
Gastrointestinal disorders	50 (13.7%)	45 (12.3%)	5 (1.4%)	60 (16.5%)	53 (14.6%)	7 (1.9%)
Diarrhoea	15 (4.1%)	15 (4.1%)	0	24 (6.6%)	24 (6.6%)	0
General disorders and administration site conditions	49 (13.4%)	44 (12.1%)	5 (1.4%)	58 (15.9%)	57 (15.7%)	1 (0.3%)
Fatigue	14 (3.8%)	14 (3.8%)	0	29 (8.0%)	29 (8.0%)	0
Respiratory, thoracic and mediastinal disorders	35 (9.6%)	29 (7.9%)	6 (1.6%)	46 (12.6%)	40 (11.0%)	6 (1.6%)
Pulmonary embolism	19 (5.2%)	16 (4.4%)	3 (0.8%)	19 (5.2%)	17 (4.7%)	2 (0.5%)
Vascular disorders	29 (7.9%)	26 (7.1%)	3 (0.8%)	45 (12.4%)	41 (11.3%)	4 (1.1%)
Hypertension	13 (3.6%)	13 (3.6%)	0	24 (6.6%)	23 (6.3%)	1 (0.3%)
Eye disorders	34 (9.3%)	34 (9.3%)	0	28 (7.7%)	28 (7.7%)	0
Cataract	29 (7.9%)	29 (7.9%)	0	26 (7.1%)	26 (7.1%)	0

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.
[TSFAE03AA.RTF] [JNJ-54767414\MMY3008\DBR_CSR\RE_CSR\PROD\TSFAE03AA.SAS] 26NOV2018, 18:43

Table 20

Number of Subjects with 1 or More Toxicity Grade 3 or 4 Treatment-emergent Adverse Events with difference of 2% Higher in DRd treatment group, by MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set (Study 54767414MMY3008)

	Rd			DRd		
	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
Analysis set: safety	365			364		
Total number of subjects with toxicity grade 3 or 4 TEAE	301 (82.5%)	204 (55.9%)	97 (26.6%)	327 (89.8%)	210 (57.7%)	117 (32.1%)
MedDRA system organ class/preferred term						
Blood and lymphatic system disorders	189 (51.8%)	142 (38.9%)	47 (12.9%)	224 (61.5%)	152 (41.8%)	72 (19.8%)
Neutropenia	129 (35.3%)	93 (25.5%)	36 (9.9%)	182 (50.0%)	125 (34.3%)	57 (15.7%)
Lymphopenia	39 (10.7%)	35 (9.6%)	4 (1.1%)	55 (15.1%)	42 (11.5%)	13 (3.6%)
Leukopenia	18 (4.9%)	16 (4.4%)	2 (0.5%)	40 (11.0%)	35 (9.6%)	5 (1.4%)
Infections and infestations	85 (23.3%)	64 (17.5%)	21 (5.8%)	117 (32.1%)	92 (25.3%)	25 (6.9%)
Pneumonia	29 (7.9%)	24 (6.6%)	5 (1.4%)	50 (13.7%)	45 (12.4%)	5 (1.4%)
Metabolism and nutrition disorders	74 (20.3%)	54 (14.8%)	20 (5.5%)	75 (20.6%)	61 (16.8%)	14 (3.8%)
Hyperglycaemia	14 (3.8%)	12 (3.3%)	2 (0.5%)	26 (7.1%)	22 (6.0%)	4 (1.1%)
Gastrointestinal disorders	50 (13.7%)	45 (12.3%)	5 (1.4%)	60 (16.5%)	53 (14.6%)	7 (1.9%)
Diarrhoea	15 (4.1%)	15 (4.1%)	0	24 (6.6%)	24 (6.6%)	0
General disorders and administration site conditions	49 (13.4%)	44 (12.1%)	5 (1.4%)	58 (15.9%)	57 (15.7%)	1 (0.3%)
Fatigue	14 (3.8%)	14 (3.8%)	0	29 (8.0%)	29 (8.0%)	0
Respiratory, thoracic and mediastinal disorders	35 (9.6%)	29 (7.9%)	6 (1.6%)	46 (12.6%)	40 (11.0%)	6 (1.6%)
Dyspnoea	4 (1.1%)	4 (1.1%)	0	12 (3.3%)	11 (3.0%)	1 (0.3%)
Vascular disorders	29 (7.9%)	26 (7.1%)	3 (0.8%)	45 (12.4%)	41 (11.3%)	4 (1.1%)
Hypertension	13 (3.6%)	13 (3.6%)	0	24 (6.6%)	23 (6.3%)	1 (0.3%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Drug-related TEAEs

The most frequently reported (≥20%) daratumumab-related TEAE, as assessed by the investigators, was neutropenia (26.4%). The most frequently reported lenalidomide-related TEAEs (≥20% in either treatment group) in the DRd and Rd groups, respectively, were:

- Neutropenia (54.1% and 40.0%)
- Diarrhea (33.5% and 27.7%)
- Fatigue (29.9% and 21.4%)
- Anemia (23.6% and 26.6%)
- Constipation (18.7% and 20.3%)

The most frequently reported dexamethasone-related TEAEs (≥20% in either treatment group) in the DRd and Rd groups, respectively, were:

Insomnia (25.5% and 24.4%)
Peripheral oedema (20.3% and 15.3%).

A majority of Grade 3 or 4 TEAEs assessed as related to study treatment by the investigators were in the Blood and Lymphatic system disorders SOC. The most frequently reported (≥10%) Grade 3 or 4 daratumumab-related TEAE was neutropenia (21.2%). The most frequently reported (≥10% in either

treatment group) Grade 3 or 4 lenalidomide-related TEAEs in the DRd and Rd groups, respectively, were neutropenia (48.1% and 33.7%), anemia (7.1% and 13.7%), and lymphopenia (10.2% and 6.8%).
The most frequently reported Grade 3 or 4 dexamethasone-related TEAE was pneumonia (9.3% in the DRd group and 4.1% in the Rd group).

Serious adverse event/deaths/other significant events

Table 21: **Deaths**

	Rd n (%)	DRd n (%)	Total n (%)
Analysis set: safety	365	364	729
Total number of subjects who died within 60 days of first study treatment dose	7 (1.9%)	10 (2.7%)	17 (2.3%)
Primary cause of death			
Adverse event	6 (1.6%)	9 (2.5%)	15 (2.1%)
Disease progression	0	1 (0.3%)	1 (0.1%)
Other	1 (0.3%)	0	1 (0.1%)
Total number of subjects who died within 30 days of last study treatment dose	24 (6.6%)	25 (6.9%)	49 (6.7%)
Primary cause of death			
Adverse event	22 (6.0%)	23 (6.3%)	45 (6.2%)
Disease progression	1 (0.3%)	1 (0.3%)	2 (0.3%)
Other	1 (0.3%)	1 (0.3%)	2 (0.3%)

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

Table 22: TEAEs with outcome Death

Analysis set: safety	Rd n (%) Total 365	Related to LEN	Related to DEX	DRd n (%) Total 364	Related to DARA	Related to LEN	Related to DEX
Total number of subjects with TEAE with outcome death	23 (6.3%)	7 (1.9%)	6 (1.6%)	25 (6.9%)	5 (1.4%)	10 (2.7%)	3 (0.8%)
MedDRA system organ class/preferred term							
Cardiac disorders	10 (2.7%)	2 (0.5%)	1 (0.3%)	7 (1.9%)	1 (0.3%)	3 (0.8%)	0
Acute myocardial infarction	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0
Arteriosclerosis coronary artery	0	0	0	1 (0.3%)	0	1 (0.3%)	0
Cardiac failure acute	0	0	0	1 (0.3%)	0	1 (0.3%)	0
Cardiac amyloidosis	1 (0.3%)	0	0	0	0	0	0
Cardiac arrest	2 (0.5%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	0	0
Cardiac failure	1 (0.3%)	0	0	1 (0.3%)	0	0	0
Cardiogenic shock	1 (0.3%)	0	0	0	0	0	0
Hypertensive heart disease	0	0	0	1 (0.3%)	0	0	0
Myocardial infarction	3 (0.8%)	1 (0.3%)	0	1 (0.3%)	0	0	0
Myocardial ischaemia	1 (0.3%)	0	0	1 (0.3%)	0	0	0
Infections and infestations	6 (1.6%)	3 (0.8%)	3 (0.8%)	8 (2.2%)	3 (0.8%)	3 (0.8%)	3 (0.8%)
Neutropenic sepsis	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0
Nocardiosis	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Urosepsis	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Klebsiella infection	0	0	0	1 (0.3%)	0	0	0
Lower respiratory tract infection	0	0	0	1 (0.3%)	0	0	0
Pneumonia	3 (0.8%)	2 (0.5%)	2 (0.5%)	2 (0.5%)	0	0	1 (0.3%)
Sepsis	2 (0.5%)	0	0	0	0	0	0
Septic shock	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3%)	0	0	2 (0.5%)	1 (0.3%)	2 (0.5%)	0
Adenocarcinoma gastric	0	0	0	1 (0.3%)	0	1 (0.3%)	0
Diffuse large B-cell lymphoma	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0
Small cell lung cancer	1 (0.3%)	0	0	0	0	0	0
Nervous system disorders	0	0	0	3 (0.8%)	0	2 (0.5%)	0
Cerebrovascular accident	0	0	0	1 (0.3%)	0	1 (0.3%)	0
Haemorrhagic stroke	0	0	0	1 (0.3%)	0	1 (0.3%)	0
Hepatic encephalopathy	0	0	0	1 (0.3%)	0	0	0
Gastrointestinal disorders	2 (0.5%)	0	1 (0.3%)	0	0	0	0
Gastrointestinal haemorrhage	1 (0.3%)	0	1 (0.3%)	0	0	0	0
Pneumoperitoneum	1 (0.3%)	0	0	0	0	0	0
General disorders and administration site conditions	3 (0.8%)	1 (0.3%)	1 (0.3%)	3 (0.8%)	0	0	0
General physical health deterioration	2 (0.5%)	0	0	1 (0.3%)	0	0	0
Multiple organ dysfunction syndrome	0	0	0	1 (0.3%)	0	0	0
Sudden cardiac death	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	0	0	0
Sudden death	0	0	0	1 (0.3%)	0	0	0
Injury, poisoning and procedural complications	0	0	0	2 (0.5%)	0	0	0
Accident	0	0	0	1 (0.3%)	0	0	0
Subdural haematoma	0	0	0	1 (0.3%)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.3%)	1 (0.3%)	0	0	0	0	0
Pulmonary embolism	1 (0.3%)	1 (0.3%)	0	0	0	0	0

There were 3 Grade 5 TEAEs related to nervous system disorder that occurred in DRd subjects.

- One subject was a 79-year-old male with an ongoing medical history including hepatic cirrhosis and increased blood bilirubin levels. Several episodes of hyperammonemia were reported during the study. The investigator considered these events to be not related to any component of study treatment.

On Study Day 416, a Grade 2 serious adverse event (SAE) of hepatic encephalopathy was reported. The investigator considered this event to be doubtfully related to daratumumab and lenalidomide, and not related to dexamethasone. The subject discontinued daratumumab on Study Day 407 and dexamethasone on Study Day 484 and continued lenalidomide monotherapy.

On Study Day 711, which was 304 days after the last daratumumab dose, 227 days after the last dexamethasone dose, and 6 days after the last lenalidomide dose, a Grade 4 SAE of hepatic encephalopathy was also reported. The investigator considered this event to be not related to any component of study treatment.

On Study Day 717, the subject died due to Grade 5 hepatic encephalopathy. No autopsy was performed. The subject had last received the lenalidomide dose on Study Day 705, which was 298 days after the last daratumumab dose.

- A second subject was an 81-year-old male with an ongoing medical history including hypertension, type 1 diabetes mellitus, mitral valve incompetence, ventricular hypertrophy, and tobacco abuse and a prior medical history of infectious pneumonia. The subject was on prophylactic antithrombotic treatment (heparin calcium) from study entry. At diagnosis, 91% of the subject's bone marrow nucleated cells were plasma cells and platelet count at screening (Study Day -3) was 58×10^9/L.

  On Study Day 40, a Grade 3 SAE of pneumonia was reported and the subject was hospitalized. Treatment included amoxicillin/clavulanate (Augmentin), amoxicillin, and levofloxacin. The dose of dexamethasone was reduced to 20 mg from Study Day 50 due to the Grade 3 SAE of pneumonia and a Grade 2 nonserious adverse event of urinary tract infection.

  Since Cycle 1 Day 1, the subject had intermittent Grade 3 thrombocytopenia that worsened to Grade 4 thrombocytopenia on Study Day 45. On Study Day 51, the subject died of Grade 5 hemorrhagic stroke in relation to Grade 4 thrombocytopenia (platelet count was 22×10^9/L). The investigator considered the event of hemorrhagic stroke as probably related to lenalidomide, doubtfully related to daratumumab, and not related to dexamethasone. The subject had last received the lenalidomide dose on Study Day 45, and daratumumab and dexamethasone doses on Study Day 50.

- A third subject was a 76-year-old male with an ongoing medical history including atrial fibrillation and hypertension and prior medical history of coronary arterial stent insertion and myocardial infarction.

  On Study Day 697, the subject underwent spinal surgery. During the hospitalization, the subject developed an arterial embolism of the lower limb and Grade 4 SAEs of atrial fibrillation, cerebrovascular accident, intestinal ischemia, multiple organ dysfunction syndrome, and peripheral ischemia. The investigator considered these events to be possibly related to lenalidomide and not related to daratumumab or prednisolone. On Study Day 710, the subject died due to Grade 5 cerebrovascular accident. An autopsy was not performed. The subject had last received the daratumumab, prednisolone, and lenalidomide dose on Study Days 686, 693, and 696, respectively.

All three subjects had contributing medical histories that predisposed them to the Grade 5 neurological events that occurred and therefore, it is difficult to isolate the impact that treatment had on the fatal neurologic events. The first subject had ongoing hepatic cirrhosis at the time of study entry which worsened while on study, but the subject had not received daratumumab for almost 10 months prior to the fatal event. The second subject had low bone marrow reserve and therefore, thrombocytopenia complicated treatment. The final subject had a history of atrial fibrillation and myocardial infarction prior to developing a post-operative thrombotic event that cascaded to multi-organ dysfunction and a Grade 5 cerebrovascular accident.

Three subjects (0.8%) in the DRd group died due to treatment-emergent hemorrhage or stroke. Two subjects died due to hemorrhagic stroke and cerebrovascular accident. The remaining subject died due to subdural hematoma and is summarized below.

- The subject was a 63-year-old male who had an ongoing medical history of hypertension, type 2 diabetes mellitus chronic obstructive pulmonary disease, chronic kidney disease, depression, and prior medical history of smoking and alcohol use.

On Study Day −10, a Grade 3 SAE of subdural hematoma occurred. On the same day, platelet function lab results showed an abnormal platelet function.

On Study Day 8, accidental head trauma was reported and the SAE of subdural hematoma worsened to Grade 4. The investigator considered this event to be not related to any of the study medications. The subject underwent a craniotomy on Study Day 8 and received a transfusion of 4 units of fresh frozen plasma. The subject died of subdural hemorrhage on Study Day 10. The subject had last received the daratumumab, lenalidomide, and dexamethasone doses on Study Days 1, 7, and 8, respectively.

One subject (0.3%) in the Rd group died due to TEAEs related to hemorrhage or stroke (due to gastrointestinal hemorrhage).

- The subject was an 83-year-old white female who had an ongoing medical history of hypertension, hypercholesterolemia and had a prior medical history of bilateral pulmonary embolism.

  The subject was on prophylactic antithrombotic treatment (tinzaparin sodium) from study entry.

  On Study Day 51, a Grade 4 SAE of gastrointestinal hemorrhage was reported. An upper gastrointestinal endoscopy showed esophagitis and confirmed the diagnosis of gastrointestinal hemorrhage. On the same day, the subject received packed red blood cell transfusion and esomeprazole. The investigator considered the event of gastrointestinal hemorrhage to be doubtfully related to lenalidomide and very likely related to dexamethasone. On Study Day 58, the subject died of the SAE of gastrointestinal hemorrhage. The subject had last received the lenalidomide and dexamethasone dose on Study Days 50 and 51, respectively.

Serious Adverse Events

Table 23: SAEs

	Rd n (%)	DRd n (%)
Analysis set: safety	365	364
Total number of subjects with serious TEAE	229 (62.7%)	229 (62.9%)
MedDRA system organ class/preferred term		
Infections and infestations	79 (21.6%)	120 (33.0%)
Pneumonia	27 (7.4%)	48 (13.2%)
Bronchitis	5 (1.4%)	12 (3.3%)
Influenza	6 (1.6%)	11 (3.0%)
Lower respiratory tract infection	11 (3.0%)	10 (2.7%)
Sepsis	7 (1.9%)	9 (2.5%)
Urinary tract infection	5 (1.4%)	8 (2.2%)
Musculoskeletal and connective tissue disorders	33 (9.0%)	40 (11.0%)
Back pain	8 (2.2%)	12 (3.3%)
Gastrointestinal disorders	35 (9.6%)	39 (10.7%)
Diarrhoea	6 (1.6%)	9 (2.5%)
Cardiac disorders	39 (10.7%)	35 (9.6%)
Atrial fibrillation	12 (3.3%)	8 (2.2%)
Cardiac failure	9 (2.5%)	5 (1.4%)
General disorders and administration site conditions	36 (9.9%)	31 (8.5%)
Pyrexia	11 (3.0%)	16 (4.4%)
General physical health deterioration	10 (2.7%)	2 (0.5%)
Respiratory, thoracic and mediastinal disorders	29 (7.9%)	30 (8.2%)
Pulmonary embolism	14 (3.8%)	11 (3.0%)
Renal and urinary disorders	23 (6.3%)	22 (6.0%)
Acute kidney injury	14 (3.8%)	11 (3.0%)
Vascular disorders	18 (4.9%)	19 (5.2%)
Deep vein thrombosis	8 (2.2%)	5 (1.4%)
Blood and lymphatic system disorders	23 (6.3%)	18 (4.9%)
Febrile neutropenia	9 (2.5%)	9 (2.5%)
Anaemia	12 (3.3%)	6 (1.6%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Adverse Events of Special Interest (AESI)

IRR

Infusion-related reactions (IRRs) associated with daratumumab administration were reported in 149 subjects (40.9%). The most frequently reported (≥5% of subjects) preferred terms for IRRs were dyspnea (9.3%), cough (7.4%), and chills (7.4%). Of the subjects with IRRs, most (139 of 149 subjects) had Grade 1 or 2 events; 2.5% of subjects had Grade 3 IRRs; 1 subject (0.3%) had a Grade 4 IRR; no Grade 5 IRR was reported. One subject discontinued treatment with daratumumab due to IRRs (preferred terms of Grade 4 hypertension and Grade 3 tachycardia, dyspnea, and non-cardiac chest pain).

Most subjects with an IRR experienced the IRR during the first infusion of daratumumab (146 of 149 subjects), a pattern consistent with previous daratumumab studies. Six (1.7%) and 14 subjects (3.9%) had an IRR during the second or subsequent infusions, respectively. Fifteen subjects (4.1%) experienced an IRR in more than 1 infusion.
The median onset time for IRRs was 90 minutes into the first infusion, 111 minutes for the second infusion, and 68.5 minutes for the subsequent infusions, which is consistent with previous daratumumab studies.

Cytopenias

Table 24: Number of Subjects with 1 or more treatment emerged cytopenia AEs

	Rd				DRd			
	All Grades n (%)	Grade 3 or 4 n (%)	Grade 5 n (%)	Leading to Disc. n (%)	All Grades n (%)	Grade 3 or 4 n (%)	Grade 5 n (%)	Leading to Disc. n (%)
Analysis set: safety	365				364			
Subjects with any treatment-emergent cytopenia adverse events	233 (63.8%)	189 (51.8%)	0	4 (1.1%)	273 (75.0%)	220 (60.4%)	1 (0.3%)	2 (0.5%)
MedDRA preferred term								
Neutropenia *	156 (42.7%)	131 (35.9%)	0	1 (0.3%)	208 (57.1%)	182 (50.0%)	1 (0.3%)	1 (0.3%)
Neutropenia	154 (42.2%)	129 (35.3%)	0	1 (0.3%)	207 (56.9%)	182 (50.0%)	0	0
Febrile neutropenia	11 (3.0%)	11 (3.0%)	0	0	11 (3.0%)	11 (3.0%)	0	0
Neutropenic sepsis	0	0	0	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)
Neutropenic infection	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0
Anaemia *	139 (38.1%)	72 (19.7%)	0	1 (0.3%)	127 (34.9%)	43 (11.8%)	0	0
Anaemia	138 (37.8%)	72 (19.7%)	0	1 (0.3%)	126 (34.6%)	43 (11.8%)	0	0
Anaemia macrocytic	2 (0.5%)	1 (0.3%)	0	0	1 (0.3%)	0	0	0
Microcytic anaemia	0	0	0	0	1 (0.3%)	0	0	0
Thrombocytopenia *	69 (18.9%)	32 (8.8%)	0	2 (0.5%)	68 (18.7%)	27 (7.4%)	0	1 (0.3%)
Thrombocytopenia	69 (18.9%)	32 (8.8%)	0	2 (0.5%)	68 (18.7%)	27 (7.4%)	0	1 (0.3%)
Lymphopenia *	45 (12.3%)	39 (10.7%)	0	0	66 (18.1%)	55 (15.1%)	0	0
Lymphopenia	45 (12.3%)	39 (10.7%)	0	0	66 (18.1%)	55 (15.1%)	0	0

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; Disc. = discontinuation; TEAE = treatment-emergent adverse event.
* Preferred term grouping.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages in the total column and toxicity grade columns are calculated with the number of subjects treated in each group as denominator.

Secondary malignancies

Table 25: **Summary of Second Primary Malignancies**

	Rd n (%)	DRd n (%)	Total n (%)
Analysis set: safety	365	364	729
Total number of subjects with second primary malignancies	26 (7.1%)	32 (8.8%)	58 (8.0%)
Cancer type/ dictionary-derived term			
Cutaneous	13 (3.6%)	21 (5.8%)	34 (4.7%)
Basal cell carcinoma	8 (2.2%)	12 (3.3%)	20 (2.7%)
Squamous cell carcinoma of skin	4 (1.1%)	9 (2.5%)	13 (1.8%)
Bowen's disease	1 (0.3%)	3 (0.8%)	4 (0.5%)
Keratoacanthoma	1 (0.3%)	0	1 (0.1%)
Porocarcinoma	0	1 (0.3%)	1 (0.1%)
Invasive Solid Malignancy	11 (3.0%)	10 (2.7%)	21 (2.9%)
Prostate cancer	2 (0.5%)	2 (0.5%)	4 (0.5%)
Adenocarcinoma gastric	1 (0.3%)	1 (0.3%)	2 (0.3%)
Adenocarcinoma of colon	0	1 (0.3%)	1 (0.1%)
Breast cancer	1 (0.3%)	0	1 (0.1%)
Breast neoplasm	0	1 (0.3%)	1 (0.1%)
Colorectal adenocarcinoma	0	1 (0.3%)	1 (0.1%)
Gastrointestinal neoplasm	1 (0.3%)	0	1 (0.1%)
Gastrointestinal stromal tumour	0	1 (0.3%)	1 (0.1%)
Invasive lobular breast carcinoma	0	1 (0.3%)	1 (0.1%)
Leiomyosarcoma	1 (0.3%)	0	1 (0.1%)
Lung neoplasm malignant	1 (0.3%)	0	1 (0.1%)
Meningioma	0	1 (0.3%)	1 (0.1%)
Neuroendocrine carcinoma of the skin	1 (0.3%)	0	1 (0.1%)
Pancreatic carcinoma	1 (0.3%)	0	1 (0.1%)
Pancreatic carcinoma metastatic	0	1 (0.3%)	1 (0.1%)
Small cell lung cancer	1 (0.3%)	0	1 (0.1%)
Transitional cell carcinoma	1 (0.3%)	0	1 (0.1%)
Invasive Hematologic Malignancy	2 (0.5%)	2 (0.5%)	4 (0.5%)
Diffuse large B-cell lymphoma	1 (0.3%)	1 (0.3%)	2 (0.3%)
Mantle cell lymphoma	0	1 (0.3%)	1 (0.1%)
Myelodysplastic syndrome	1 (0.3%)	0	1 (0.1%)

Key: Rd=lenalidomide-dexamethasone; DRd=daratumumab-lenalidomide-dexamethasone

Haemorrhage

The incidence of hemorrhage events (all grades) was balanced across the 2 treatment groups (DRd: 29.4%, Rd: 26.3%) and the majority of events were Grades 1 or 2. One subject in the Rd group discontinued study treatment due to a TEAE of intracranial hemorrhage. Two subjects in the DRd group died due to TEAEs of hemorrhagic stroke and subdural hematoma and 1 subject in the Rd group died due to a TEAE of gastrointestinal hemorrhage.

Four subjects (1.1%) in the DRd group and 1 subject in the Rd group (0.3%) received fresh frozen plasma transfusions. The median time to first onset of hemorrhage events was similar between treatment groups, 31.0 and 29.1 weeks in the DRd and Rd groups, respectively. In both treatment groups, more subjects with hemorrhage events had the first onset during the first (Cycle 1-12) and second (Cycle 13-24) year with fewer first onset events occurring at year 3.

Infections and Infestations

Overall, the incidence of infections and infestations was higher in the DRd group (86.3%) compared to the Rd group (73.4%). The difference was primarily driven by bronchitis (DRd: 29.1%, Rd: 20.3%), upper respiratory tract infection (DRd: 22.8%, Rd: 14.2%), pneumonia (DRd: 22.5%, Rd: 12.6%), and urinary tract infection (DRd: 17.6%, Rd: 10.4%).

The incidence of Grade 3 or 4 infections was higher in the DRd group (32.1%) compared with the Rd group (23.3%). This was largely due to a higher incidence of Grade 3 or 4 pneumonia in the DRd group (13.7%)

compared with the Rd group (7.9%). Additionally, the incidence of serious TEAEs of infection were also higher in the DRd group (33.0%) compared with the Rd group (21.6%). This was also due to a higher incidence of serious TEAEs of pneumonia in the DRd group (13.2%) compared with the Rd group (7.4%). For all other Grade 3 or 4 and serious TEAEs of infection, the difference between treatment groups was <2%.

Although infections were reported by a higher percentage of subjects in the DRd treatment group compared with the Rd treatment group, infections were manageable and rarely led to study discontinuation or death. Discontinuation of study treatments due to infection and infestation TEAEs was low in both groups; DRd group (2 subjects [0.5%]) and Rd group (5 subjects [1.4%]). Deaths due to infection were low and balanced between groups (DRd: 2.2%, Rd: 1.6%).

Among subjects in the DRd group who experienced Grade ≥3 pneumonia, 45 subjects had Grade 3, 5 subjects had Grade 4, and 2 subjects had Grade 5 pneumonia. One subject in the DRd group who died due to hemorrhagic stroke had ongoing Grade 3 pneumonia at the time of death. Among the subjects in the Rd group who experienced Grade ≥3 pneumonia, 24 subjects had Grade 3, 5 subjects had Grade 4, and 3 subjects had Grade 5 pneumonia.

The median time to first onset of treatment emergent infections and infestations was similar between treatment groups, 14.1 weeks and 13.6 weeks in the DRd and Rd groups, respectively.

Viral Infections

The most frequently reported (≥2% in either treatment group) treatment emergent viral infections in the DRd and Rd groups, respectively, were viral upper respiratory infection (15.4% and 12.6%), influenza (9.3% and 5.8%), oral herpes (2.2% and 3.0%), and herpes zoster (1.4% and 3.6%).

The Grade 3 or 4 treatment-emergent viral infections were balanced across treatment groups (12 events in each group). In the DRd group influenza (8 subjects) was the only Grade 3 or 4 viral infection reported in more than 1 subject. In the Rd group influenza (8 subjects) and respiratory syncytial virus infection (2 subjects) were the only Grade 3 or 4 viral infections reported in more than 1 subject. One subject in the Rd group discontinued study treatment due to a TEAE of influenza . The review of TEAE viral infections is limited to those adverse events where a virus was identified and reported; it is possible that some infectious TEAEs are not classified as viral if the pathogen was not identified or reported.

Prophylactic antiviral therapy for herpes infection was administered to 65.2% of subjects in the DRd group and 45.5% of subjects in the Rd group. Systemic antiviral therapy (the majority of which was for prophylactic treatment) was administered to 69.8% of subjects in the DRd group and 52.3% of subjects in the Rd group. The median time to first onset of viral infections was longer in the DRd group (36.8 weeks) compared with the Rd group (32.4 weeks). In both treatment groups, a greater proportion of subjects with viral infections had the first onset during the first year (Cycle 1-12) with fewer first onset events occurring at year 2 or 3.

Hepatitis B Reactivation

No subject in this study had reactivation of hepatitis B. Five subjects (4 in the DRd group and 1 in the Rd group) had baseline serologies consistent with prior exposure to hepatitis B, only 1 subject (DRd group) was HBSAg positive. Three subjects of the 5 subjects received prophylaxis against hepatitis B reactivation with either tenofovir (2 subjects in the DRd group) or lamivudine (1 subject in the Rd group).

Opportunistic Infections

History of herpes virus infections was balanced across treatment groups, 15 subjects in each treatment group (preferred terms of herpes zoster, ophthalmic herpes zoster, oral herpes, genital herpes, herpes simplex).

The most frequently reported (≥2% in either treatment group) opportunistic infections in the DRd and Rd groups, respectively, were oral candidiasis (4.1% and 5.2%), oral herpes (2.2% and 3.0%), and herpes zoster (1.4% and 3.6%). Five Grade 3 or 4 treatment-emergent opportunistic infections (cytomegalovirus viremia, nocardiosis, pneumocystis jirovecii infection, pneumocystis jirovecii pneumonia, and pulmonary mycosis) were reported for subjects in the DRd group and 1 Grade 3 or 4 treatment-emergent opportunistic infection (varicella zoster virus infection) for 1 subject in the Rd group. No individual Grade 3 or 4 opportunistic infection was reported in more than 1 subject. No subject discontinued study treatment due to an opportunistic infection. One subject in the DRd group died due to a TEAE of nocardiosis.

The median time to first onset of opportunistic infections was shorter in the DRd group (14.0 weeks) compared with the Rd group (21.6 weeks). In both treatment groups, most subjects with opportunistic infections had the first onset during the first year (Cycle 1-12) with few first onset events occurring at year 2 or 3.

Tumor Lysis Syndrome

There were no reports of tumor lysis syndrome in either treatment group during the study.

Intravascular Haemolysis

There were no reports of intravascular hemolysis in either treatment group during the study.

Treatment-emergent Interferences for Blood Typing

No subject had treatment-emergent interference for blood typing reported during the study.

Other Adverse Events

Thrombotic Events
The incidence of thrombotic events was balanced between the DRd and Rd groups. The occurrence of events by individual preferred terms were as follows:

- Deep vein thrombosis (DRd: 8.5%; Rd: 9.6%)
- Pulmonary embolism (DRd: 5.2%; Rd: 5.5%)

Prophylactic use of antithrombotic agents was balanced across the 2 treatment groups (DRd: 64.4%, Rd: 66.9%).

Laboratory findings

Table 26: **Haematology**

	Rd						DRd					
		Toxicity Grade, n (%)						Toxicity Grade, n (%)				
	Total	0	1	2	3	4	Total	0	1	2	3	4
Analysis set: safety	365						364					
Hematology												
WBC low (Leukopenia)	364 (99.7%)	38 (10.4%)	123 (33.8%)	113 (31.0%)	74 (20.3%)	16 (4.4%)	362 (99.5%)	15 (4.1%)	78 (21.5%)	141 (39.0%)	109 (30.1%)	19 (5.2%)
Hemoglobin low (Anemia)	363 (99.5%)	9 (2.5%)	108 (29.8%)	157 (43.3%)	89 (24.5%)	0	362 (99.5%)	7 (1.9%)	115 (31.8%)	188 (51.9%)	52 (14.4%)	0
Platelets low (Thrombocytopenia)	363 (99.5%)	125 (34.4%)	169 (46.6%)	29 (8.0%)	27 (7.4%)	13 (3.6%)	362 (99.5%)	95 (26.2%)	208 (57.5%)	28 (7.7%)	21 (5.8%)	10 (2.8%)
Neutrophils low (Neutropenia)	362 (99.2%)	69 (19.1%)	52 (14.4%)	96 (26.5%)	106 (29.3%)	39 (10.8%)	362 (99.5%)	25 (6.9%)	47 (13.0%)	83 (22.9%)	144 (39.8%)	63 (17.4%)
Lymphocytes low (Lymphopenia)	362 (99.2%)	77 (21.3%)	0	129 (35.6%)	135 (37.3%)	21 (5.8%)	362 (99.5%)	51 (14.1%)	0	121 (33.4%)	151 (41.7%)	39 (10.8%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; WBC = White Blood Cell.
Note: The laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03. Grade 0 means normal. Subjects reported as Grade 0 are subjects with normal values or a value in the opposite direction (for laboratory tests with bidirectional toxicities defined).
Note: For each parameter, the total column includes all subjects with available data at both baseline and post-baseline, including those whose toxicity grade did not worsen during treatment; percentages in the total column are calculated with the number of treated subjects in each group as denominator. Percentages for toxicity grade columns are calculated with the number of subjects in the total column as denominator. For each subject and each parameter, the worst toxicity grade is selected.

Table 27: Chemistry

	Rd						DRd					
		Toxicity Grade, n (%)						Toxicity Grade, n (%)				
	Total	0	1	2	3	4	Total	0	1	2	3	4
Analysis set: safety	365						364					
Biochemistry												
ALT high	357 (97.8%)	235 (65.8%)	106 (29.7%)	8 (2.2%)	5 (1.4%)	3 (0.8%)	355 (97.5%)	228 (64.2%)	107 (30.1%)	11 (3.1%)	9 (2.5%)	0
AST high	356 (97.5%)	265 (74.4%)	79 (22.2%)	6 (1.7%)	5 (1.4%)	1 (0.3%)	355 (97.5%)	259 (73.0%)	87 (24.5%)	5 (1.4%)	4 (1.1%)	0
Creatinine high	361 (98.9%)	183 (50.7%)	122 (33.8%)	45 (12.5%)	11 (3.0%)	0	358 (98.4%)	164 (45.8%)	136 (38.0%)	45 (12.6%)	11 (3.1%)	2 (0.6%)
Sodium high (Hypernatremia)	352 (96.4%)	302 (85.8%)	49 (13.9%)	0	1 (0.3%)	0	350 (96.2%)	283 (80.9%)	63 (18.0%)	1 (0.3%)	2 (0.6%)	1 (0.3%)
Sodium low (Hyponatremia)	352 (96.4%)	203 (57.7%)	122 (34.7%)	0	25 (7.1%)	2 (0.6%)	350 (96.2%)	187 (53.4%)	131 (37.4%)	0	30 (8.6%)	2 (0.6%)
Potassium high (Hyperkalemia)	352 (96.4%)	250 (71.0%)	80 (22.7%)	13 (3.7%)	8 (2.3%)	1 (0.3%)	348 (95.6%)	243 (69.8%)	89 (25.6%)	10 (2.9%)	5 (1.4%)	1 (0.3%)
Potassium low (Hypokalemia)	352 (96.4%)	217 (61.6%)	0	94 (26.7%)	32 (9.1%)	9 (2.6%)	348 (95.6%)	196 (56.3%)	0	106 (30.5%)	42 (12.1%)	4 (1.1%)
Bilirubin high	357 (97.8%)	288 (80.7%)	42 (11.8%)	25 (7.0%)	1 (0.3%)	1 (0.3%)	356 (97.8%)	290 (81.5%)	40 (11.2%)	22 (6.2%)	4 (1.1%)	0
Alkaline phosphatase high	356 (97.5%)	210 (59.0%)	139 (39.0%)	6 (1.7%)	1 (0.3%)	0	353 (97.0%)	173 (49.0%)	162 (45.9%)	14 (4.0%)	4 (1.1%)	0
Uric acid high (Hyperuricemia)	344 (94.2%)	267 (77.6%)	68 (19.8%)	0	0	9 (2.6%)	336 (92.3%)	265 (78.9%)	63 (18.8%)	0	0	8 (2.4%)
Corrected calcium high (Hypercalcemia)	362 (99.2%)	257 (71.0%)	88 (24.3%)	8 (2.2%)	3 (0.8%)	6 (1.7%)	358 (98.4%)	277 (77.4%)	71 (19.8%)	4 (1.1%)	4 (1.1%)	2 (0.6%)
Corrected calcium low (Hypocalcemia)	362 (99.2%)	220 (60.8%)	85 (23.5%)	45 (12.4%)	7 (1.9%)	5 (1.4%)	358 (98.4%)	142 (39.7%)	131 (36.6%)	60 (16.8%)	18 (5.0%)	7 (2.0%)
Albumin low (Hypoalbuminemia)	361 (98.9%)	77 (21.3%)	134 (37.1%)	137 (38.0%)	13 (3.6%)	0	358 (98.4%)	65 (18.2%)	135 (37.7%)	145 (40.5%)	13 (3.6%)	0
Glucose high (Hyperglycemia)	353 (96.7%)	325 (92.1%)	0	0	26 (7.4%)	2 (0.6%)	341 (93.7%)	296 (86.8%)	0	0	40 (11.7%)	5 (1.5%)
Glucose low (Hypoglycemia)	353 (96.7%)	265 (75.1%)	81 (22.9%)	5 (1.4%)	1 (0.3%)	1 (0.3%)	341 (93.7%)	266 (78.0%)	63 (18.5%)	10 (2.9%)	1 (0.3%)	1 (0.3%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; ALT = Alanine Aminotransferase; AST = Aspartate Aminotransferase
Note: The laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03. Grade 0 means normal. Subjects reported as Grade 0 are subjects with normal values or a value in the opposite direction (for laboratory tests with bidirectional toxicities defined).
Note: For each parameter, the total column includes all subjects with available data at both baseline and post-baseline, including those whose toxicity grade did not worsen during treatment; percentages in the total column are calculated with the number of treated subjects in each group as denominator. Percentages for toxicity grade columns are calculated with the number of subjects in the total column as denominator. For each subject and each parameter, the worst toxicity grade is selected.

Table 28: Vital signs

	Rd	DRd
Analysis set: safety	365	364
Maximum weight loss from baseline, n (%)		
5 - <10%	92 (25.2%)	105 (28.8%)
10 - <20%	100 (27.4%)	101 (27.7%)
>= 20%	24 (6.6%)	19 (5.2%)

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

Safety in special populations

Table 29: **Age**

Overview of Treatment emergent Adverse Events by Age - SAS

	Rd n (%)			DRd n (%)		
	< 75 years	≥ 75 years	Total	< 75 years	≥ 75 years	Total
Analysis set: safety	206	159	365	207	157	364
Any TEAE	203 (98.5%)	159 (100.0%)	362 (99.2%)	207 (100.0%)	157 (100.0%)	364 (100.0%)
At least one related[a]	192 (93.2%)	153 (96.2%)	345 (94.5%)	205 (99.0%)	156 (99.4%)	361 (99.2%)
Maximum toxicity grade						
Grade 1	5 (2.4%)	1 (0.6%)	6 (1.6%)	0	0	0
Grade 2	37 (18.0%)	16 (10.1%)	53 (14.5%)	27 (13.0%)	8 (5.1%)	35 (9.6%)
Grade 3	113 (54.9%)	87 (54.7%)	200 (54.8%)	119 (57.5%)	87 (55.4%)	206 (56.6%)
Grade 4	38 (18.4%)	42 (26.4%)	80 (21.9%)	51 (24.6%)	47 (29.9%)	98 (26.9%)
Grade 5	10 (4.9%)	13 (8.2%)	23 (6.3%)	10 (4.8%)	15 (9.6%)	25 (6.9%)
Any serious TEAE	117 (56.8%)	112 (70.4%)	229 (62.7%)	126 (60.9%)	103 (65.6%)	229 (62.9%)
At least one related[a]	69 (33.5%)	72 (45.3%)	141 (38.6%)	80 (38.6%)	68 (43.3%)	148 (40.7%)
TEAE leading to discontinuation of lenalidomide	27 (13.1%)	35 (22.0%)	62 (17.0%)	30 (14.5%)	46 (29.3%)	76 (20.9%)
At least one related to lenalidomide	20 (9.7%)	24 (15.1%)	44 (12.1%)	26 (12.6%)	34 (21.7%)	60 (16.5%)
TEAE leading to discontinuation of dexamethasone	45 (21.8%)	50 (31.4%)	95 (26.0%)	46 (22.2%)	42 (26.8%)	88 (24.2%)
At least one related to dexamethasone	22 (10.7%)	26 (16.4%)	48 (13.2%)	40 (19.3%)	22 (14.0%)	62 (17.0%)
TEAE leading to discontinuation of daratumumab	0	0	0	12 (5.8%)	18 (11.5%)	30 (8.2%)
At least one related to daratumumab	0	0	0	8 (3.9%)	7 (4.5%)	15 (4.1%)
TEAE leading to discontinuation of study treatment[b]	25 (12.1%)	33 (20.8%)	58 (15.9%)	10 (4.8%)	16 (10.2%)	26 (7.1%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 3 components of study treatment: lenalidomide, dexamethasone or daratumumab.
[b] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
Note: Dexamethasone is for dexamethasone or equivalent.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator. Percentages of subgroups were calculated with the number of subjects in each subgroup as denominator.

Table 30: Sex

TSFAE01D: Overview of Treatment-emergent Adverse Events by Sex; Safety Analysis Set (Study 54767414MMY3008)

	Rd n (%)			DRd n (%)		
	Male	Female	Total	Male	Female	Total
Analysis set: safety	193	172	365	188	176	364
Any TEAE	190 (98.4%)	172 (100.0%)	362 (99.2%)	188 (100.0%)	176 (100.0%)	364 (100.0%)
At least one related[a]	178 (92.2%)	167 (97.1%)	345 (94.5%)	187 (99.5%)	174 (98.9%)	361 (99.2%)
Maximum toxicity grade						
Grade 1	5 (2.6%)	1 (0.6%)	6 (1.6%)	0	0	0
Grade 2	21 (10.9%)	32 (18.6%)	53 (14.5%)	18 (9.6%)	17 (9.7%)	35 (9.6%)
Grade 3	115 (59.6%)	85 (49.4%)	200 (54.8%)	98 (52.1%)	108 (61.4%)	206 (56.6%)
Grade 4	38 (19.7%)	42 (24.4%)	80 (21.9%)	51 (27.1%)	47 (26.7%)	98 (26.9%)
Grade 5	11 (5.7%)	12 (7.0%)	23 (6.3%)	21 (11.2%)	4 (2.3%)	25 (6.9%)
Any serious TEAE	123 (63.7%)	106 (61.6%)	229 (62.7%)	121 (64.4%)	108 (61.4%)	229 (62.9%)
At least one related[a]	68 (35.2%)	73 (42.4%)	141 (38.6%)	80 (42.6%)	68 (38.6%)	148 (40.7%)
TEAE leading to discontinuation of lenalidomide	30 (15.5%)	32 (18.6%)	62 (17.0%)	40 (21.3%)	36 (20.5%)	76 (20.9%)
At least one related to lenalidomide	18 (9.3%)	26 (15.1%)	44 (12.1%)	28 (14.9%)	32 (18.2%)	60 (16.5%)
TEAE leading to discontinuation of dexamethasone	43 (22.3%)	52 (30.2%)	95 (26.0%)	45 (23.9%)	43 (24.4%)	88 (24.2%)
At least one related to dexamethasone	21 (10.9%)	27 (15.7%)	48 (13.2%)	28 (14.9%)	34 (19.3%)	62 (17.0%)
TEAE leading to discontinuation of daratumumab	0	0	0	15 (8.0%)	15 (8.5%)	30 (8.2%)
At least one related to daratumumab	0	0	0	4 (2.1%)	11 (6.3%)	15 (4.1%)
TEAE leading to discontinuation of study treatment[b]	27 (14.0%)	31 (18.0%)	58 (15.9%)	13 (6.9%)	13 (7.4%)	26 (7.1%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 3 components of study treatment: lenalidomide, dexamethasone or daratumumab.
[b] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
Note: Dexamethasone is for dexamethasone or equivalent.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator. Percentages of subgroups were calculated with the number of subjects in each subgroup as denominator.

Table 31: Race

TSFAE01E: Overview of Treatment-emergent Adverse Events by Race; Safety Analysis Set (Study 54767414MMY3008)

	Rd n (%)			DRd n (%)		
	White	Other*	Total	White	Other*	Total
Analysis set: safety	335	30	365	334	30	364
Any TEAE	332 (99.1%)	30 (100.0%)	362 (99.2%)	334 (100.0%)	30 (100.0%)	364 (100.0%)
At least one related[a]	317 (94.6%)	28 (93.3%)	345 (94.5%)	331 (99.1%)	30 (100.0%)	361 (99.2%)
Maximum toxicity grade						
Grade 1	5 (1.5%)	1 (3.3%)	6 (1.6%)	0	0	0
Grade 2	51 (15.2%)	2 (6.7%)	53 (14.5%)	35 (10.5%)	0	35 (9.6%)
Grade 3	177 (52.8%)	23 (76.7%)	200 (54.8%)	185 (55.4%)	21 (70.0%)	206 (56.6%)
Grade 4	77 (23.0%)	3 (10.0%)	80 (21.9%)	92 (27.5%)	6 (20.0%)	98 (26.9%)
Grade 5	22 (6.6%)	1 (3.3%)	23 (6.3%)	22 (6.6%)	3 (10.0%)	25 (6.9%)
Any serious TEAE	213 (63.6%)	16 (53.3%)	229 (62.7%)	210 (62.9%)	19 (63.3%)	229 (62.9%)
At least one related[a]	133 (39.7%)	8 (26.7%)	141 (38.6%)	132 (39.5%)	16 (53.3%)	148 (40.7%)
TEAE leading to discontinuation of lenalidomide	56 (16.7%)	6 (20.0%)	62 (17.0%)	69 (20.7%)	7 (23.3%)	76 (20.9%)
At least one related to lenalidomide	40 (11.9%)	4 (13.3%)	44 (12.1%)	54 (16.2%)	6 (20.0%)	60 (16.5%)
TEAE leading to discontinuation of dexamethasone	86 (25.7%)	9 (30.0%)	95 (26.0%)	80 (24.0%)	8 (26.7%)	88 (24.2%)
At least one related to dexamethasone	43 (12.8%)	5 (16.7%)	48 (13.2%)	57 (17.1%)	5 (16.7%)	62 (17.0%)
TEAE leading to discontinuation of daratumumab	0	0	0	26 (7.8%)	4 (13.3%)	30 (8.2%)
At least one related to daratumumab	0	0	0	12 (3.6%)	3 (10.0%)	15 (4.1%)
TEAE leading to discontinuation of study treatment[b]	52 (15.5%)	6 (20.0%)	58 (15.9%)	22 (6.6%)	4 (13.3%)	26 (7.1%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 3 components of study treatment: lenalidomide, dexamethasone or daratumumab.
[b] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
Note: Dexamethasone is for dexamethasone or equivalent.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator. Percentages of subgroups were calculated with the number of subjects in each subgroup as denominator.
* Includes subjects with race other than white, unknown or not reported.

Table 32: **Region**

TSFAE01F: Overview of Treatment-emergent Adverse Events by Region; Safety Analysis Set (Study 54767414MMY3008)

	Rd n (%)			DRd n (%)		
	North America	Other	Total	North America	Other	Total
Analysis set: safety	99	266	365	99	265	364
Any TEAE	97 (98.0%)	265 (99.6%)	362 (99.2%)	99 (100.0%)	265 (100.0%)	364 (100.0%)
At least one related[a]	91 (91.9%)	254 (95.5%)	345 (94.5%)	98 (99.0%)	263 (99.2%)	361 (99.2%)
Maximum toxicity grade						
Grade 1	2 (2.0%)	4 (1.5%)	6 (1.6%)	0	0	0
Grade 2	9 (9.1%)	44 (16.5%)	53 (14.5%)	10 (10.1%)	25 (9.4%)	35 (9.6%)
Grade 3	58 (58.6%)	142 (53.4%)	200 (54.8%)	57 (57.6%)	149 (56.2%)	206 (56.6%)
Grade 4	24 (24.2%)	56 (21.1%)	80 (21.9%)	25 (25.3%)	73 (27.5%)	98 (26.9%)
Grade 5	4 (4.0%)	19 (7.1%)	23 (6.3%)	7 (7.1%)	18 (6.8%)	25 (6.9%)
Any serious TEAE	54 (54.5%)	175 (65.8%)	229 (62.7%)	62 (62.6%)	167 (63.0%)	229 (62.9%)
At least one related[a]	26 (26.3%)	115 (43.2%)	141 (38.6%)	40 (40.4%)	108 (40.8%)	148 (40.7%)
TEAE leading to discontinuation of lenalidomide	12 (12.1%)	50 (18.8%)	62 (17.0%)	24 (24.2%)	52 (19.6%)	76 (20.9%)
At least one related to lenalidomide	8 (8.1%)	36 (13.5%)	44 (12.1%)	18 (18.2%)	42 (15.8%)	60 (16.5%)
TEAE leading to discontinuation of dexamethasone	21 (21.2%)	74 (27.8%)	95 (26.0%)	27 (27.3%)	61 (23.0%)	88 (24.2%)
At least one related to dexamethasone	11 (11.1%)	37 (13.9%)	48 (13.2%)	17 (17.2%)	45 (17.0%)	62 (17.0%)
TEAE leading to discontinuation of daratumumab	0	0	0	11 (11.1%)	19 (7.2%)	30 (8.2%)
At least one related to daratumumab	0	0	0	5 (5.1%)	10 (3.8%)	15 (4.1%)
TEAE leading to discontinuation of study treatment[b]	12 (12.1%)	46 (17.3%)	58 (15.9%)	9 (9.1%)	17 (6.4%)	26 (7.1%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 3 components of study treatment: lenalidomide, dexamethasone or daratumumab.
[b] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
Note: Dexamethasone is for dexamethasone or equivalent.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator. Percentages of subgroups were calculated with the number of subjects in each subgroup as denominator.

Table 33: **Baseline renal function**

TSFAE01G: Overview of Treatment-emergent Adverse Events by Baseline Renal (Creatinine Clearance) Function Status; Safety Analysis Set (Study 54767414MMY3008)

	Rd n (%)					DRd n (%)				
	< 30 mL/min	30 to < 60 mL/min	60 to < 90 mL/min	≥ 90 mL/min	Total	< 30 mL/min	30 to < 60 mL/min	60 to < 90 mL/min	≥ 90 mL/min	Total
Analysis set: safety	4	134	167	60	365	7	151	145	61	364
Any TEAE	4 (100.0%)	133 (99.3%)	165 (98.8%)	60 (100.0%)	362 (99.2%)	7 (100.0%)	151 (100.0%)	145 (100.0%)	61 (100.0%)	364 (100.0%)
At least one related[a]	4 (100.0%)	129 (96.3%)	154 (92.2%)	58 (96.7%)	345 (94.5%)	7 (100.0%)	149 (98.7%)	144 (99.3%)	61 (100.0%)	361 (99.2%)
Maximum toxicity grade										
Grade 1	0	1 (0.7%)	4 (2.4%)	1 (1.7%)	6 (1.6%)	0	0	0	0	0
Grade 2	0	15 (11.2%)	29 (17.4%)	9 (15.0%)	53 (14.5%)	0	14 (9.3%)	18 (12.4%)	3 (4.9%)	35 (9.6%)
Grade 3	3 (75.0%)	77 (57.5%)	89 (53.3%)	31 (51.7%)	200 (54.8%)	2 (28.6%)	84 (55.6%)	87 (60.0%)	33 (54.1%)	206 (56.6%)
Grade 4	1 (25.0%)	30 (22.4%)	35 (21.0%)	14 (23.3%)	80 (21.9%)	3 (42.9%)	42 (27.8%)	33 (22.8%)	20 (32.8%)	98 (26.9%)
Grade 5	0	10 (7.5%)	8 (4.8%)	5 (8.3%)	23 (6.3%)	2 (28.6%)	11 (7.3%)	7 (4.8%)	5 (8.2%)	25 (6.9%)
Any serious TEAE	2 (50.0%)	88 (65.7%)	105 (62.9%)	34 (56.7%)	229 (62.7%)	4 (57.1%)	94 (62.3%)	91 (62.8%)	40 (65.6%)	229 (62.9%)
At least one related[a]	2 (50.0%)	59 (44.0%)	62 (37.1%)	18 (30.0%)	141 (38.6%)	3 (42.9%)	59 (39.1%)	56 (38.6%)	30 (49.2%)	148 (40.7%)
TEAE leading to discontinuation of lenalidomide	0	26 (19.4%)	19 (11.4%)	17 (28.3%)	62 (17.0%)	1 (14.3%)	40 (26.5%)	24 (16.6%)	11 (18.0%)	76 (20.9%)
At least one related to lenalidomide	0	19 (14.2%)	12 (7.2%)	13 (21.7%)	44 (12.1%)	0	32 (21.2%)	21 (14.5%)	7 (11.5%)	60 (16.5%)
TEAE leading to discontinuation of dexamethasone	2 (50.0%)	40 (29.9%)	33 (19.8%)	20 (33.3%)	95 (26.0%)	0	37 (24.5%)	39 (26.9%)	12 (19.7%)	88 (24.2%)
At least one related to dexamethasone	1 (25.0%)	22 (16.4%)	20 (12.0%)	5 (8.3%)	48 (13.2%)	0	25 (16.6%)	29 (20.0%)	8 (13.1%)	62 (17.0%)
TEAE leading to discontinuation of daratumumab	0	0	0	0	0	0	14 (9.3%)	10 (6.9%)	6 (9.8%)	30 (8.2%)
At least one related to daratumumab	0	0	0	0	0	0	5 (3.3%)	7 (4.8%)	3 (4.9%)	15 (4.1%)
TEAE leading to discontinuation of study treatment[b]	0	26 (19.4%)	16 (9.6%)	16 (26.7%)	58 (15.9%)	0	12 (7.9%)	10 (6.9%)	4 (6.6%)	26 (7.1%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 3 components of study treatment: lenalidomide, dexamethasone or daratumumab.
[b] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
Note: For the subjects whose baseline renal function (Creatinine Clearance) status less than 30 mL/min, the values on screening visit are greater than 30 mL/min.
Note: Dexamethasone is for dexamethasone or equivalent.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator. Percentages of subgroups were calculated with the number of subjects in each subgroup as denominator.

Table 34: **Baseline hepatic function**

TSFAE01H: Overview of Treatment-emergent Adverse Events by Baseline Hepatic Function Status; Safety Analysis Set (Study 54767414MMY3008)

	Rd n (%)			DRd n (%)		
	Normal	Impaired[b]	Total	Normal	Impaired[b]	Total
Analysis set: safety	336	29	365	332	31	364
Any TEAE	333 (99.1%)	29 (100.0%)	362 (99.2%)	332 (100.0%)	31 (100.0%)	364 (100.0%)
At least one related[a]	317 (94.3%)	28 (96.6%)	345 (94.5%)	329 (99.1%)	31 (100.0%)	361 (99.2%)
Maximum toxicity grade						
Grade 1	6 (1.8%)	0	6 (1.6%)	0	0	0
Grade 2	51 (15.2%)	2 (6.9%)	53 (14.5%)	31 (9.3%)	4 (12.9%)	35 (9.6%)
Grade 3	184 (54.8%)	16 (55.2%)	200 (54.8%)	192 (57.8%)	14 (45.2%)	206 (56.6%)
Grade 4	71 (21.1%)	9 (31.0%)	80 (21.9%)	87 (26.2%)	10 (32.3%)	98 (26.9%)
Grade 5	21 (6.3%)	2 (6.9%)	23 (6.3%)	22 (6.6%)	3 (9.7%)	25 (6.9%)
Any serious TEAE	210 (62.5%)	19 (65.5%)	229 (62.7%)	209 (63.0%)	20 (64.5%)	229 (62.9%)
At least one related[a]	127 (37.8%)	14 (48.3%)	141 (38.6%)	135 (40.7%)	13 (41.9%)	148 (40.7%)
TEAE leading to discontinuation of lenalidomide	55 (16.4%)	7 (24.1%)	62 (17.0%)	65 (19.6%)	11 (35.5%)	76 (20.9%)
At least one related to lenalidomide	40 (11.9%)	4 (13.8%)	44 (12.1%)	53 (16.0%)	7 (22.6%)	60 (16.5%)
TEAE leading to discontinuation of dexamethasone	87 (25.9%)	8 (27.6%)	95 (26.0%)	80 (24.1%)	8 (25.8%)	88 (24.2%)
At least one related to dexamethasone	46 (13.7%)	2 (6.9%)	48 (13.2%)	57 (17.2%)	5 (16.1%)	62 (17.0%)
TEAE leading to discontinuation of daratumumab	0	0	0	23 (6.9%)	7 (22.6%)	30 (8.2%)
At least one related to daratumumab	0	0	0	12 (3.6%)	3 (9.7%)	15 (4.1%)
TEAE leading to discontinuation of study treatment[b]	51 (15.2%)	7 (24.1%)	58 (15.9%)	20 (6.0%)	6 (19.4%)	26 (7.1%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 3 components of study treatment: lenalidomide, dexamethasone or daratumumab.
[b] Includes mild, moderate and severe.
Note: Dexamethasone is for dexamethasone or equivalent.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages in the total column were calculated with the number of subjects in each group as denominator. Percentages of subgroups were calculated with the number of subjects in each subgroup as denominator.

[TSFAE01H.RTF] [JNJ-54767414MMY3008\DBR_CSR\RE_CSR\PROD\TSFAE01H.SAS] 30NOV2018, 18:41

TEAE leading to discontinuation of daratumumab	0	27 (14.2%)
At least one related to daratumumab	0	11 (5.8%)
TEAE leading to discontinuation of study treatment[b]	35 (18.5%)	21 (11.1%)

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
*Subjects considered unfit for transplant includes: subjects <65 years old with significant comorbidity or ECOG PS=2; subjects 65-74 years old with ECOG PS=2; or subjects at least 75 years old.
[a] TEAEs related to at least 1 of the 3 components of study treatment: lenalidomide, dexamethasone or daratumumab.
[b] Includes those subjects indicated as having discontinued treatment due to an adverse event on the end of treatment CRF page.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Discontinuation due to adverse events

Table 35: No of subjects with 1 or more TEAEs leading to Discontinuation with a frequency of at least 1% in either treatment group

	Rd			DRd		
	All Grades n (%)	Grade 3 or 4 n (%)	Grade 5 n (%)	All Grades n (%)	Grade 3 or 4 n (%)	Grade 5 n (%)
Analysis set: safety	365			364		
Total number of subjects with TEAE leading to discontinuation of study treatment*	58 (15.9%)	48 (13.2%)	0	26 (7.1%)	17 (4.7%)	0
MedDRA system organ class/preferred term						
General disorders and administration site conditions	7 (1.9%)	6 (1.6%)	0	5 (1.4%)	1 (0.3%)	0
Fatigue	0	0	0	4 (1.1%)	1 (0.3%)	0
Asthenia	4 (1.1%)	4 (1.1%)	0	1 (0.3%)	0	0

Key: Rd = lenalidomide-dexamethasone; DRd = daratumumab-lenalidomide-dexamethasone; TEAE = treatment-emergent adverse event.
* 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 20.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Post marketing experience

The proposed indication is not marketed.

2.6. Discussion on clinical safety

The evaluation of the DRd safety comes from one single pivotal phase 3 study. Overall, a significant number of patients have been exposed to a sufficient number of cycles of DRd for a substantial period of time. This should enable a thorough safety assessment of DRd.

In general, there are slightly more Grade 4 AEs in the DRd arm, 26.9% vs. 21.9%, and looking at common AEs there seems to be more AEs in the DRd arm across all SOCs. The higher number of AEs in DRd reflects the safety profile of daratumumab.

Overall, there are more Grade 3-4 AEs in the DRd arm. Looking at Grade 3-4 AEs a significant difference is seen in neutropenia, lymphopenia and leukopenia. This is also reflected in Grade 3 pneumonia, 12.4% vs. 6.6% in favour of Rd. There is no difference in terms of Grade 4 pneumonias. The higher risk of neutropenia and infections is known with daratumumab and is clearly reflected in sections 4.4 and 4.8 of the SmPC.

Looking at AEs judged to be drug-related by the investigators, differences were seen in terms of neutropenia, diarrhoea and fatigue.

There is no relevant difference in terms of deaths within 60 days of the first dose and within 30 days of the last dose. Overall, no differences could be seen in total number of deaths, 6.3% vs. 6.9%, Rd and DRd respectively.

Cytopenia is commonly associated with daratumumab, however, more importantly there were no relevant differences between Rd and DRd in terms of febrile neutropenia, neutropenic sepsis or neutropenic infection.

There are no significant differences in terms of Grade 3-4 viral infections. However, viral re-activation is a serious risk in relation to daratumumab. The SmPC clearly reflects that prophylaxis for herpes zoster should be considered. There has been cases of fatal hepatitis B reactivation in other studies. This issue is currently

being addressed in a different procedure (EMEA/H/C/004077/II/0027).Opportunistic infections (Grade 3 or 4) were reported more frequently in the DRd group [5 subjects (cytomegalovirus viremia, nocardiosis, pneumocystis jirovecii infection, pneumocystis jirovecii pneumonia, and pulmonary mycosis)] than in the Rd group (1 subject: varicella zoster virus infection). No individual Grade 3 or 4 opportunistic infection was reported in more than 1 subject. No subject discontinued study treatment due to an opportunistic infection. One subject in the DRd group died due to a TEAE of nocardiosis. The median time to first onset of opportunistic infections was shorter in the DRd group (14 weeks) compared with the Rd group (21.6 weeks). In both treatment groups, most subjects with opportunistic infections had the first onset during the first year (Cycle 1-12) with few first onset events occurring at year 2 or 3.

More patients in the Rd arm discontinued treatment due to AEs, 15.8% vs 7.1%, however, many patients could continue daratumumab monotherapy despite AEs leading to discontinuation of the Rd.

Overall, the observed safety profile is as expected and in line with the safety profile of daratumumab.

2.6.1. Conclusions on clinical safety

Overall, the safety profile of DRd is worse than Rd. The additional toxicity clearly reflects the known safety profile of daratumumab. However, the majority of the AEs are clinically manageable, and no new safety findings were observed during this study.

2.6.2. PSUR cycle

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

2.7. 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 6.2 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 6.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Interference for blood typing (minor antigen) (positive indirect Coombs' test)
Important potential risks	Tumour lysis syndrome Immunogenicity
Missing information	Use in pregnancy and lactation Reproductive and developmental toxicity

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
RRA-19284: Survey of the effectiveness of the DARZALEX® educational materials regarding the minimization of risk of interference of blood typing Ongoing	To assess knowledge and understanding for handling interference with blood typing, in accordance with the educational materials.	Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Final report presented in the next PSUR after survey conclusion	3rd Quarter 2019
Investigate new method for detecting antidrug antibodies Ongoing	Improve the immunogenicity method's ability to detect anti-daratumumab antibodies in the presence of high trough levels of daratumumab.	Immunogenicity	Final report	4th Quarter 2018

Key: PSUR = Periodic Safety Update Report.

Risk minimisation measures

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Routine risk minimization measures: SmPC Section 4.4, which advises that patients should be typed and screened and phenotyping or genotyping be considered prior to starting daratumumab treatment; SmPC Sections 4.4, which advises HCPs to notify blood transfusion centers of this interference with indirect antiglobulin tests in the event of a planned transfusion; SmPC Section 4.4, which recommends that if	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: A guided targeted follow-up questionnaire to collect additional information concerning adverse events associated with interference and transfusion reactions. Additional pharmacovigilance activities:

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	an emergency transfusion is required, non-cross-matched ABO/RhD compatible RBCs can be given per local blood bank practices; SmPC Section 4.5, which recommends to mitigate daratumumab interference by treating reagent RBCs with DTT to disrupt daratumumab binding or other locally validated methods, and that Kell negative units should be supplied after ruling out or identifying alloantibodies using DTT treated RBCs; PL Section 2, which instructs patients to inform the person doing the blood test to match blood type that they are receiving treatment with daratumumab. Additional risk minimization measures: Distribution of educational materials and Patient Alert Cards to HCPs and blood banks as described in the PL, in Annex II, D.	Participation of targeted HCPs and blood banks in a survey to evaluate the effectiveness of educational materials distributed to raise awareness and understanding for handling interference for blood typing in accordance with the educational program. Final report due by 3rd Quarter 2019.
Hepatitis B virus reactivation	Routine risk minimization measures: SmPC Section 4.4 and PL Section 2, which advise HBV screening before initiation of treatment with daratumumab and to monitor for clinical and laboratory signs of HBV reactivation during, and for at least 6 months following the end of daratumumab treatment for patients with evidence of positive HBV serology; SmPC Section 4.4, which advises to manage patients according to current clinical guidelines, and to consider consulting a hepatitis disease expert as clinically indicated; SmPC Section 4.4, which advises to suspend treatment with daratumumab and to institute appropriate treatment in patients who develop reactivation of HBV while on daratumumab. Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV; PL Section 2, which includes a warning to	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	patients with history or current HBV infection. SmPC Section 4.8 and PL Section 4, which lists hepatitis B virus reactivation (hepatitis) as an adverse reaction; Additional risk minimization measures: Distribution of a DHPC to HCPs who prescribe daratumumab.	
Immunogenicity	Routine risk minimization measures: SmPC Section 5.1, which describes results of evaluation and detection of anti-daratumumab antibodies in patients treated with daratumumab alone and patients treated with combination therapies. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: Investigation of a new method for detecting antidrug antibodies to improve the immunogenicity method's ability to detect anti-daratumumab antibodies in the presence of high trough levels of daratumumab. Final report 4th Quarter 2018.
Use in pregnancy and lactation	Routine risk minimization measures: SmPC Section 4.6 and PL Section 2. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Reproductive and developmental toxicity	Routine risk communication: SmPC Section 5.3. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

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

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template, which were accepted by the CHMP.

2.8.1. User consultation

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

The changes to the package leaflet are minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Multiple myeloma (MM) is a malignant clonal plasma cells disorder, that represents approximately a 0.8% of all cancers worldwide (Ferlay 2015). The proliferation of the malignant clonal plasma cells leads to subsequent replacement of normal bone marrow hematopoietic precursors and overproduction of M-proteins, progressive morbidity and eventual mortality. Characteristic MM hallmarks include osteolytic lesions, anaemia (due to bone marrow dysfunction), increased susceptibility to infections (due to immunosuppression), hypercalcemia, renal insufficiency/failure, and neurological complications (Palumbo 2011).

3.1.2. Available therapies and unmet medical need

Patients with newly diagnosed multiple myeloma are typically categorized into 2 subpopulations defined by their age and suitability for intensive treatment. For patients who are considered fit, an induction regimen followed by high-dose chemotherapy (HDT) and ASCT is considered the standard of care. For patients considered ineligible for HDT and ASCT due to their age, presence of comorbidities, and/or physical status, the treatment approach often favors longer, less intensive/toxic treatments, including most commonly a proteasome inhibitor, an immunomodulatory drug, and a corticosteroid in toxicity-adapted fashions.

3.1.3. Main clinical studies

The current submission is based on data from the Phase 3 study, MMY3008 (clinical cut-off, 10 June 2019). This study is a randomized, open-label, active controlled, parallel-group, multicentre study in subjects at least 18 years of age with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy and ASCT, to evaluate the efficacy (PFS) of DRd compared with Rd and to evaluate the safety/tolerability and clinical outcomes of DRd compared to Rd.

3.2. Favourable effects

- The study met is primary endpoint showing a statistically significant and clinically meaningful difference in favour of DRd (median PFS was not reached in DRd, but was 31.9 months in the Rd arm. HR (95% CI) = 0.56 (0.43, 0.73), p-value < 0.0001).

- Secondary endpoints (time to PD, time to subsequent therapy and PFS2) all show consistent favourable effects, confirming the primary analysis.
- Across all response criteria DRd show statistically significant and clinically relevant results that confirm the primary analysis.
- The MRD negativity rate was 24.2% vs. 7.3% at 3 years in favour of DRd.

3.3. Uncertainties and limitations about favourable effects

OS data are immature. The MAH has committed to providing the final CSR post-authorisation.

Additionally, it should be noted that since the response rates in D-Rd are better, with a higher rate of CR and also with a greater depth of response (MRD negativity), continuing with a long-term maintenance treatment with daratumumab could be questioned, especially in those patients who achieve an optimal response. However, addressing this question would require a new clinical study, which is currently out of the scope of this application.

3.4. Unfavourable effects

In general, there are slightly more Grade 4 AEs in the DRd arm, 26.9% vs. 21.9%, and looking at common AEs there seems to be more AEs in the DRd arm across all SOCs. The higher number of AEs in DRd reflects the safety profile of daratumumab.

Looking at Grade 3-4 AEs, a significant increase with daratumumab is seen in neutropenia, lymphopenia and leukopenia. This is also reflected in Grade 3 pneumonia, 12.4% for DRd vs. 6.6% for Rd. There is no difference in terms of Grade 4 pneumonias. The higher risk of neutropenia and infections is known with daratumumab and is reflected in the SmPC.

Cytopenia is commonly associated with daratumumab; however, there were no relevant differences between Rd and DRd in terms of febrile neutropenia, neutropenic sepsis or neutropenic infection.

There are no significant differences in terms of Grade 3-4 viral infections. However, viral re-activation is a serious risk in relation to daratumumab. The SmPC clearly reflects that prophylaxis for herpes zoster should be considered. There have been cases of fatal hepatitis B reactivation in other studies. This issue is currently being addressed in a different procedure (EMEA/H/C/004077/II/0027).

3.5. Uncertainties and limitations about unfavourable effects

There are no major uncertainties or limitations about unfavourable effects.

3.6. Effects Table

Table 36. Effects Table for DARZALEX (daratumumab) in combination with lenalidomide and dexamethasone for the treatment of adult patients with NDMM who are ineligible for autologous stem cell transplant (data cut-off:10 June 2019)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Progression-free survival	months	NE	33.8		
		HR	0.56	1	p-value <0.00001 HR = 0.56 (95% confidence interval (0.44, 0.71))	

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
Grade 4 AEs		%	32.1%	26.6%		
infections		%	87.6%	76.4%		
cytopenia (all grades)		%	77.2%	66.0%		

NE cannot yet be estimated

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In Study MMY3008, DRd now showed clinically relevant improvements in terms of PFS and response rates in patients newly-diagnosed with a multiple myeloma who are ineligible for ASCT. These results are highly relevant in this population with a dismal prognosis. A sCR rate of 30.4% is clinically very encouraging.

Overall, the safety profile of daratumumab in combination with Rd seems generally consistent with the known safety profile of daratumumab and the respective combination agents and it seems to be manageable with dosing modifications, and is reasonably tolerated, as suggested by the relatively low proportion of discontinuations due to AEs.

3.7.2. Balance of benefits and risks

The B/R balance of DRd in the proposed patient population is considered positive, since the demonstrated benefits of DRd for the treatment of adult patients with NDMM that are ineligible for ASCT are considered to outweigh the toxicity of the combination, which is considered generally acceptable and manageable in the current clinical setting.

3.8. Conclusions

The overall B/R of Darzalex in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends 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 in combination with lenalidomide and dexamethasone (Rd) for the treatment of adult

patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT) for Darzalex; as a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP has been updated accordingly (finally agreed version 6.2). Furthermore, the Annex II is brought in line with the latest QRD template version 10.1.

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

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Darzalex is not similar to Imnovid (pomalidomide), Farydak (panabinostat), Kyprolis (carfilzomib) and Ninlaro (ixazomib) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

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 in combination with lenalidomide and dexamethasone (Rd) for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (ASCT) for Darzalex; as a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP has been updated accordingly (finally agreed version 6.2). Furthermore, the Annex II is brought in line with the latest QRD template version 10.1. Furthermore, Annex II is brought in line with the latest QRD template version 10.1.

Summary

Please refer to the Scientific Discussion Darzalex-H-C-4077-II-0029.