26 July 2018
EMA/CHMP/599644/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Darzalex

International non-proprietary name: daratumumab

Procedure No. EMEA/H/C/004077/II/0011

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ASCT	autologous stem cell transplant
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	non-specific linear clearance
CR	complete response
CrCL	creatinine clearance
D-VMP	daratumumab + bortezomib (VELCADE) + melphalan + prednisone
EBMT	European Group for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EMN	European Myeloma Network
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDT	high-dose chemotherapy
HR	hazard ratio
HRQoL	health-related quality of life
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IRR	infusion-related reaction
ISS	International Staging System
ITT	intent-to-treat
IV	Intravenous
mAb	monoclonal antibody
MoA	mechanism of action
MP	melphalan-prednisone
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NGS	next generation sequencing
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PFS2	time from randomization to progression on the next line of therapy or death, whichever comes first
PI	proteasome inhibitor
PRAC	Pharmacovigilance Risk Assessment Committee
PPK	population pharmacokinetics
Rd	lenalidomide + dexamethasone
SC	Subcutaneous
sCR	stringent complete response
SmPC	Summary of Product Characteristics and Package
SOC	System Organ Class
SPM	second primary malignancies
TEAE	treatment emergent adverse event
TLS	tumor lysis syndrome
TTP	time-to-progression
US	United States
VCd	bortezomib (VELCADE) + cyclophosphamide + dexamethasone
VGPR	very good partial response
VMP	bortezomib (VELCADE) + melphalan + 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 21 November 2017 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 to include the combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant for Darzalex; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 3.2 (in version 2 of the RMP template) has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the contact details of the Lithuanian and Slovenian local representatives in the Package Leaflet. Furthermore, the MAH took the opportunity to update Annex II with regards to PSUR requirements.

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 17 July 2013. Darzalex was designated as an orphan medicinal product in the following indication: Treatment of plasma cell myeloma.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0264/2017 on the granting of a product specific waiver for daratumumab (Darzalex) and CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The applicant did seek Protocol Assistance at 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.

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	21 November 2017
Start of procedure:	23 December 2017
CHMP Co-Rapporteur preliminary Assessment Report	16 February 2018
CHMP Rapporteur preliminary Assessment Report	06 February 2018
PRAC Rapporteur preliminary Assessment Report	23 February 2018
PRAC members comments	28 February 2018
PRAC Rapporteur updated Assessment Report	01 March 2018
PRAC Outcome	08 March 2018
CHMP members comments	13 March 2018
Updated CHMP Rapporteurs Joint Assessment Report	15 March 2018
Request for supplementary information (RSI)	22 March 2018
Submission of responses	27 April 2018
Start of procedure	28 May 2018
CHMP Joint Rapporteurs preliminary responses Assessment Report	27 June 2018
PRAC Rapporteur preliminary responses Assessment Report	25 June 2018
PRAC members comments	04 July 2018
PRAC Rapporteur Updated responses Assessment Report	05 July 2018
PRAC RMP advice and assessment overview adopted by PRAC	12 July 2018
CHMP members comments	16 July 2018
Joint CHMP Rapporteurs Updated responses Assessment Report	19 July 2018
Revised Updated Joint CHMP Rapporteurs responses Assessment Report	20 July 2018
CHMP Opinion	26 July 2018
The CHMP adopted a report on similarity of Darzalex with Thalidomide Celgene, Imnovid, Farydak, Kyprolis and Ninlaro on date (Appendix I)	26 July 2018

2. Scientific discussion

2.1. Introduction

Multiple myeloma, a malignant disorder of plasma cells, is characterized by uncontrolled and progressive proliferation of a plasma cell clone. The proliferation of myeloma cells causes displacement of the normal

bone marrow leading to dysfunction in normal hematopoietic tissue and destruction of the normal bone marrow architecture, resulting in progressive morbidity and eventual mortality.

At the time of diagnosis of multiple myeloma, patients are categorized into 2 subpopulations according to co-morbidity, whether suitable for intensive treatment or not. 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 Network [NCCN]; (Kumar 2017) and European (European Society for Medical Oncology [ESMO]; (Moreau 2017) guidelines. For patients considered ineligible for HDT and ASCT due to presence of comorbidities, older age, and/or physical status, the treatment approach often favors 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. Because combination regimens comprised of agents with non-overlapping and synergistic MoAs 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 treatment for newly diagnosed multiple myeloma.

The combination of bortezomib plus melphalan plus prednisone (VMP) is the only Velcade -containing triplet regimen approved in the US and Europe for frontline therapy in patients ineligible for transplant. The combination of lenalidomide plus dexamethasone (Rd) is also approved for use in this population in Europe and the US.

Despite these approved regimens, there remains an unmet need for new therapeutic options for the frontline setting directed at alternative MoAs that can better control the disease and provide deeper, more sustained responses and better long-term outcomes, including maintenance of HRQoL.

Daratumumab is a targeted immunotherapy that binds with high affinity to tumor cells that overexpress CD38, a transmembrane glycoprotein, on multiple myeloma plasma cells. Multiple mechanisms of action (MoA) have been observed for daratumumab, including complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, antibody dependent cellular phagocytosis, and direct cytotoxicity by induction of apoptosis by Fc gamma receptor mediated crosslinking of tumor-bound monoclonal antibodies. Daratumumab leads to the 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 and modulation of CD38 enzymatic activity leads to the increased clonal expansion of CD8+ and CD4+ T cells. Together, daratumumab's cytotoxic and immunomodulatory MoAs are hypothesized to synergistically result in the deep anti-myeloma responses observed in patients.

Support for combining daratumumab with VMP is based on results of an ex vivo flow cytometry-based assay in which daratumumab in combination with VMP significantly enhanced the anti-tumor treatment effect by almost doubling the cell lysis levels in bone marrow mononuclear cell isolates obtained from subjects with multiple myeloma. Daratumumab's cell- and complement-mediated (and potentially direct) cytotoxic effects against multiple myeloma cells, combined with the observed synergy with bortezomib (also in samples from patients refractory to bortezomib), may potentially improve the clinical outcome for patients with multiple myeloma when combined with a bortezomib-based combination regimen.

The current submission supporting the approval of daratumumab for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for ASCT is based on data from the Phase 3 study, MMY3007 (clinical cut-off, 12 June 2017), comparing daratumumab 16 mg/kg administered in combination with VMP to VMP alone. In addition to data from MMY3007, supportive data from a single cohort of 12 subjects with newly diagnosed multiple myeloma ineligible for transplant who were administered D-VMP as part of a Phase 1b study (MMY1001) are described briefly in this Clinical Overview

The following indication is proposed:

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

The recommended dose is 16 mg/kg body weight administered as an intravenous infusion as per the following schedule:

Table 1 dosing schedule in combination with bortezomib, melphalan and prednisone ([VMP]; 6-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 54[a]	every three weeks (total of 16 doses)
Week 55 onwards until disease progression[b]	every four weeks

[a] First dose of the every-3-week dosing schedule is given at Week 7
[b] First dose of the every-4-week dosing schedule is given at Week 55

Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle, followed by **once** weekly at Weeks 1, 2, 4 and 5 for eight more 6-week cycles. For information on the VMP dose and dosing schedule when administered with DARZALEX, see section 5.1.

2.2. Non-clinical aspects

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

2.2.1. Ecotoxicity / environmental risk assessment

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

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 2: Summary of study design elements for studies MMY3007 and MMY1001

Table 1: Summary of Study Design Elements for Studies MMY3007 and MMY1001			
Study Identification/ First Subject First Visit/Clinical Cutoff	**Phase Study Description/Design Study Population/ Efficacy Endpoints**	**Number of Subjects Randomized/Treated**	**Dose Regimen and Duration of Treatment**
Phase 3 Study			
54767414MMY3007 26 Jan 2015 12 Jun 2017 (interim clinical cutoff) Ongoing	Phase 3 Open-label, randomized Subjects with newly diagnosed multiple myeloma who are ineligible for high-dose therapy Primary Endpoint: PFS Key secondary endpoints: ORR, rate of VGPR or better, rate of CR or better, MRD negativity rate, OS Other secondary endpoints: PFS2, sCR, TTP, TTR, DOR, time to subsequent anti-myeloma treatment, and PRO endpoints	Total: 706/700 D-VMP: 350/346 VMP: 356/354	D- VMP treatment group: Daratumumab solution (IV): • 16 mg/kg; once a week for 6 weeks (Cycle 1), • Then every 3 weeks for 16 additional doses (Cycles 2-9, 6-week cycles), and • Every 4 weeks (Cycle 10 and beyond; 4-week cycles) until disease progression or unacceptable toxicity. D-VMP and VMP treatment groups (9 cycles): Subjects in both treatment groups received: • Bortezomib SC 1.3 mg/m^2 twice a week (Weeks 1, 2, 4, and 5) in Cycle 1 followed by once a week (Weeks 1, 2, 4, and 5) in Cycles 2 to 9, • Melphalan PO at 9 mg/m^2 on Day 1 to 4 of each bortezomib cycle, and • Prednisone PO at 60 mg/m^2 on Day 1 to 4 of each bortezomib cycle.
Phase 1b Study (D-VMP Cohort)			
54767414MMY1001 10 Mar 2014 16 Jun 2017 (interim clinical cutoff) Ongoing	Phase 1b Open-label, non-randomized, multicenter D-VMP Cohort: Subjects with newly diagnosed multiple myeloma who are ineligible for high-dose therapy Primary efficacy endpoint: ORR Secondary endpoint: OS	D-VMP Cohort: 12	D-VMP Cohort (9 cycles only) • Daratumumab solution (IV) 16 mg/kg once a week for 6 weeks (Cycle 1), followed by every 3 weeks (Cycle 2-9), • Bortezomib SC 1.3 mg/m^2 twice a week for 6 weeks (Cycle 1), followed by once a week for subsequent cycles (Cycle 2-9), • Melphalan PO (IV on Day 1) at 9 mg/m^2 on Days 1 to 4 of Cycles 1 to 9, and • Prednisone PO at 60 mg/m^2 on Days 1 to 4 of Cycles 1 to 9.

CR=complete response; DOR=duration of response; D-VMP=daratumumab in combination with bortezomib + melphalan + prednisone; IV=intravenous; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival from randomization to next line of subsequent anti-myeloma therapy; PO=oral; PRO=patient reported outcomes; SC=subcutaneous; sCR=stringent complete response; TTP=time to progression; TTR=time to response; VGPR=very good partial response; VMP = bortezomib + melphalan + prednisone.

2.3.2. Pharmacokinetics

The clinical pharmacology of daratumumab has been well characterised and summarised in the initial monotherapy submission. Further, the clinical pharmacology properties of daratumumab in combination treatment with other agents than the Bortezomib-Melphalan-Prednisone (D-VMP) combination were studied in 680 subjects in two Phase 1/2 and two Phase 3 combination studies. An overview of the 2 studies which support the present submission are provided in Table 2. In both of these studies, daratumumab was administered at 16 mg/kg in combination with a background regimen of VMP.

Data from the initial mono- and combination-treatment studies as well as studies 3007 and 1001 and a population PK (Pop-PK) analysis based on these two studies support the PK data of the present application.

Table 3: Combination PK studies

Study Number	Phase	Subject Population	Doses (Number of Subjects Dosed)	Number of Subjects Evaluable for Pharmacokinetic Analysis/Number of Subjects Treated
MMY3007	3	Subjects with newly diagnosed multiple myeloma who are ineligible for high-dose therapy	16 mg/kg (700 subjects): D-VMP: 346 VMP:354	342/346
MMY1001	1b	D-VMP Cohort: Subjects with newly diagnosed multiple myeloma	16 mg/kg (12 subjects in D-VMP cohort)	11/12 in D-VMP cohort
Total Subjects Evaluable for Pharmacokinetic Analysis/Total Subjects Treated				353/358

Key: D-VMP=daratumumab-bortezomib-melphalan-prednisone; VMP=bortezomib-melphalan-prednisone

Absorption, Distribution and Elimination

The absorption, distribution, metabolism, and excretion characteristics of daratumumab are based on PK analysis of full PK profiles available in monotherapy dosing and detailed in the initial submission. These characteristics are summarised below.

Absorption

Absorption data are not available because all studies in this and prior submissions administered daratumumab as an IV infusion. Bioavailability is per definition 100%.

Distribution

Typical IgG1-based monoclonal antibodies (mAbs) are primarily confined to the vascular system (Mascelli 2007). The mean±SD volumen of distribution (Vd) in subjects who received daratumumab 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, monotherapy). As described by the monotherapy Pop-PK model, the estimate for the central volume of distribution is 56.98±18.07 mL/kg. Traditional protein-binding studies using human serum albumin as conducted for small molecules are not applicable to therapeutic biologics (ICH S6 1997).

Elimination (Metabolism and Excretion)

As an IgG1κ mAb, daratumumab is presumably biotransformed in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and is subject to similar elimination (Mascelli 2007; Tabrizi 2006). Renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are therefore unlikely to represent major elimination routes. As such, variations in renal and hepatic function are not expected to affect the elimination of daratumumab.

As shown previously in the monotherapy studies, daratumumab clearance decreased with increasing doses and with multiple doses. After the first full 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 (Study GEN501, monotherapy). Following the first administration at the approved dose of 16 mg/kg, clearance was 0.42±0.42 mL/h/kg and T½ was 216.06±104.04 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 T½ increased to 255.29±216.47 hours (10.6±9.0 days) (Study GEN501, monotherapy).

Preinfusion and postinfusion concentrations were measured in Study MMY3007 (342 patients) and a summary of the daratumumab pre-infusion and post-infusion concentrations in serum is presented in Table 3, and the mean daratumumab peak and trough concentrations are presented in Figure 2. The peak concentration at the end of the first dose was 266.7±86.9 µg/mL. On Cycle 3 Day 1, the day of the ninth overall dose of daratumumab and the start of the second cycle of every-3-week-dosing, the predose trough concentration was 272.5±154.9 µg/mL and Cmax postinfusion was 595.9±204.5 µg/mL. Daratumumab concentrations observed after 3 additional cycles of every 3 week-dosing (Cycle 6 Day 1) were similar to the Cycle 3 Day 1 values, with mean±SD trough and peak concentrations of 297.2±145.8 µg/mL and 636.4±215.9 µg/mL, respectively.

Table 4: Daratumumab concentration (µg/mL); PK set in MMY3007

	Preinfusion	Postinfusion
Analysis set: pharmacokinetic-evaluable[a]		342
Cycle 1, Day 1		
N	334	317
Mean (SD)	2.03 (21.832)	266.72 (86.857)
Coefficient of variation	1076.9%	32.6%
Geometric mean	17.40	250.43
Median	0.00	262.05
Range	(0.0; 314.7)	(0.0; 576.9)
Cycle 3, Day 1		
N	281	285
Mean (SD)	272.46 (154.935)	595.85 (204.519)
Coefficient of variation	56.9%	34.3%
Geometric mean	219.00	559.42
Median	270.73	591.66
Range	(0.0; 818.1)	(150.2; 1256.2)
Cycle 6, Day 1		
N	259	257
Mean (SD)	297.17 (145.796)	636.35 (215.922)
Coefficient of variation	49.1%	33.9%
Geometric mean	254.68	603.67
Median	286.92	618.77
Range	(0.0; 781.8)	(193.2; 2281.7)
End-of-treatment[a]		
N		16
Mean (SD)		126.24 (101.164)
Coefficient of variation		80.1%
Geometric mean		89.63
Median		122.84
Range		(0.0; 367.8)
Posttreatment week 8[a]		
N		7
Mean (SD)		38.87 (38.299)
Coefficient of variation		98.5%
Geometric mean		24.79
Median		32.53
Range		(0.0; 102.9)

Key: SD=standard deviation.

[a] For reporting purpose, data are displayed in the postinfusion column.

Note: Table includes subjects who received at least 1 administration of daratumumab and have at least 1 pharmacokinetic sample concentration value after the first infusion.

Note: Predose samples include those collected at the same time as start of infusion.

Note: Samples with a collection time out of defined windows are excluded.

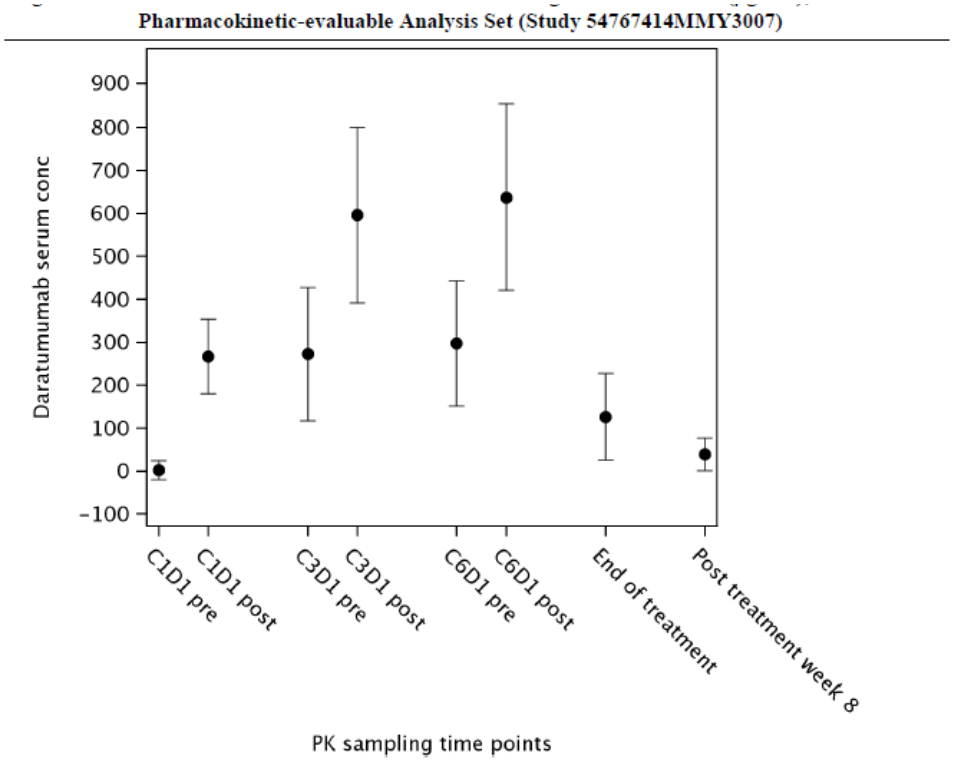


Figure 1: mean daratumumab peak and trough concentrations (µg/mL)

Descriptive statistics for serum daratumumab concentrations by time-point in Study MMY1001 (11 patients) are presented in Table 4. The mean±SD daratumumab concentration at the end of the first dose was 332.2±57.1 µg/mL. Accumulation of daratumumab continued during weekly dosing until Cycle 2 Day 1, when the mean (SD) predose and postdose concentrations reached 588.0±161.4 and 936.0±225.1 µg/mL, respectively. Mean Cmax following the Cycle 2 Day 1 dose was 2.8-fold higher than the Cmax following the first dose. Mean concentrations began to decrease slightly following less frequent daratumumab administration starting in Cycle 2.

Table 5: summary of daratumumab serum concentrations (µg/mL) over time

Pharmacokinetics Evaluable- Daratumumab (Study MMY1001)

	Preinfusion	Postinfusion
Subjects evaluable for daratumumab PK[a]	11	
Cycle 1, Day 1		
N	11	11
Mean (SD)	0.00 (0.000)	332.16 (57.086)
Coefficient of variation	-	17.2%
Geometric mean	-	327.6
Median	0.00	324.72
Range	(0.0; 0.0)	(245.7; 404.5)
Cycle 1, Day 22		
N	8	9
Mean (SD)	319.15 (105.615)	664.85 (122.917)
Coefficient of variation	33.1%	18.5%
Geometric mean	298.46	651.54
Median	339.68	700.72
Range	(116.9; 449.5)	(363.6; 782.1)
Cycle 2, Day 1		
N	10	11
Mean (SD)	587.97 (161.442)	935.95 (225.116)
Coefficient of variation	27.5%	24.1%
Geometric mean	557.73	906.88
Median	607.88	989.35
Range	(199.9; 744.3)	(489.1; 1269.8)
Cycle 3, Day 1		
N	6	8
Mean (SD)	383.24 (178.673)	695.98 (213.037)
Coefficient of variation	46.6%	30.6%
Geometric mean	306.96	662.23
Median	431.84	744.04
Range	(48.2; 534.3)	(344.4; 952.0)
Cycle 4, Day 1		
N	9	8
Mean (SD)	360.45 (141.735)	748.97 (179.887)
Coefficient of variation	39.3%	24.0%
Geometric mean	313.87	724.2
Median	401.38	823.25
Range	(58.7; 517.2)	(368.7; 906.8)

	Preinfusion	Postinfusion
Posttreatment Week 3[b]		
N		1
Mean (SD)		345.16 (-)
Coefficient of variation		-
Geometric mean		345.16
Median		345.16
Range		(345.2; 345.2)
Posttreatment Week 9[b]		
N		5
Mean (SD)		172.53 (86.815)
Coefficient of variation		50.3%
Geometric mean		145.39
Median		216.80
Range		(41.4; 251.0)

Key: D-VMP=daratumumab-bortezomib-melphalan-prednisone; PK = pharmacokinetic; SD=standard deviation
[a] Subjects who had 1 measurable PK concentration posttreatment record.
[b] For reporting purpose, data are displayed in the postinfusion column.
Note: Samples outside of allowed sampling windows are not included. In addition, samples collected after an incomplete dose (less than 80% intended dose was administered) and prior to the next complete dose are not included.

Comparison and Analyses of Results Across Studies

Following the first dose of 16 mg/kg of daratumumab in combination studies of D-VMP, the mean end of infusion concentrations were 266.72 and 332.16 µg/mL for Study MMY3007 and the D-VMP cohort of Study MMY1001, respectively. These results were similar to the mean end of infusion concentration following the first monotherapy dose, which was reported as 312.54 µg/mL.

When co-administered with VMP, daratumumab serum concentrations accumulated after weekly administration in a similar way compared with daratumumab monotherapy and decrease slightly during subsequent less frequent dosing periods. The mean concentration of daratumumab after 6 weekly 16-mg/kg doses (ie, Cycle 2 Day 1 predose) was 587.97 µg/mL in Study MMY1001, which was a 2.8-fold increase in daratumumab peak concentration at the end of 6 weekly doses when compared with the first dose (Study MMY1001). These results were similar to the mean trough concentration after 8 weekly doses in the monotherapy study MMY2002 (573.49 µg/mL), with a 2.9-fold increase in daratumumab peak concentration at the end of 8 weekly doses when compared with the first dose.

Dose proportionality, time dependencies and inter-subject variability

Daratumumab elimination showed nonlinear characteristics: elimination T½ increased with dose while clearance decreased with increasing dose. Clearance also decreased with multiple doses.

Dose Proportionality

Daratumumab elimination showed nonlinear characteristics in the monotherapy studies. Following the first administration of daratumumab ranging from 0.005 to 24 mg/kg, Cmax increased in approximate proportion to daratumumab dose for doses of at least 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, in Study GEN503, Cmax following the first full 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.

As reported for monotherapy, also in the initial combination treatment study (GEN503), mean clearance following the first dose decreased with increasing dose, from 1.5±1.1 mL/h/kg in the 1 mg/kg cohort to 0.3±0.2 mL/h/kg in the 24 mg/kg cohort. This trend for decreasing clearance with increased dose was also evident following repeat dosing, from 6.7±6.2 mL/h/kg in the 0.5-mg/kg cohort to 0.2±0.1 mL/h/kg in the 24 mg/kg cohort. Following the first administration at the approved dose of 16 mg/kg, clearance was 0.3±0.1 mL/h/kg and 0.1 mL/h/kg in the 1 subject with the parameter estimated after repeat dosing. Due to the evident nonlinear PK, statistical assessment of dose proportionality was not performed.

Time Dependency

Clearance of daratumumab in study GEN503 also decreased with multiple doses in the monotherapy studies: after the first full infusion, mean clearance decreased from 1.1 mL/h/kg in the 2 mg/kg group to 0.3 mL/h/kg in the 24 mg/kg group; after the last full infusion, mean clearance decreased from 0.6 mL/h/kg in the 2 mg/kg group to 0.2 mL/h/kg in the 24 mg/kg group. Following the first administration at the approved dose of 16 mg/kg, clearance was 0.3±0.1 mL/h/kg (mean±SD) and 0.1 mL/h/kg in the 1 subject with the parameter estimated after repeat dosing. The trend of decreasing clearance with repeated dosing was also evident in Part 2 of Study GEN501 and Study MMY1002.

Inter-subject variability

In Study MMY3007, inter-subject variability for daratumumab exposure appeared moderate, with a 33% to 34% coefficient of variation for post-infusion concentrations.

Special populations

See under population-PK analysis section.

Pharmacokinetic interaction studies

No dedicated drug-drug interaction studies were performed, and no interactions of daratumumab and small molecule drugs such as bortezomib, melphalan, and prednisone are expected as there is no overlapping pathway of elimination. As reported in a previous submission, analysis of daratumumab and bortezomib concentrations from Study MMY1001 indicated a lack of clinically relevant drug-drug interaction between these molecules.

Population Pharmacokinetic Analysis

Methods for Population Pharmacokinetic Analysis

A Population Pharmacokinetic (PPK) model of daratumumab was developed to describe the PK characteristics of daratumumab in combination with VMP and to evaluate the influence of covariates on the disposition of daratumumab in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant. In addition, PK of daratumumab combined with VMP was compared with that of daratumumab monotherapy studies and the previous combination therapy studies.

The PPK analysis included combined data from a Phase 3 study (MMY3007) and the D-VMP combination arm of a Phase 1b (MMY1001). Serum concentration-time data of daratumumab were used for nonlinear mixed effects modelling using NONMEM® (ICON plc, Version 7.3).

The first-order conditional estimation with the INTERACTION method was used. Due to the lack of overlapping clearance mechanism for daratumumab and co-administered small-molecule combination therapies, no direct impact of the combination therapies on the PK of daratumumab is expected. Therefore, the previously developed base and final PPK models were used to fit the concentration-time data of daratumumab. To compare the effects of covariates on exposure to daratumumab, subgroup analyses were

conducted on predicted exposure metrics derived from simulation of daratumumab PK profiles based on empirical Bayesian estimates of individual PK parameters.

Intrinsic and extrinsic Factors

Body weight, age, sex, race, renal impairment, baseline albumin, hepatic dysfunction categories using the National Cancer Institute (NCI) criteria (based on aspartate aminotransferase [AST] and total bilirubin [TB]), and type of myeloma at baseline (IgG versus non-IgG) were considered as intrinsic factors to be examined for their potential impact on PK of daratumumab. Region of subject enrollment was evaluated as an extrinsic factor in the PPK analysis and Exposure to daratumumab compared between subgroups for baseline disease status (ie, ECOG status at baseline) was evaluated as 'Other factors'.

Cox proportional hazard regression models, implemented in the "survival" package in R (Therneau 2000), were used to explore the relationship between exposure metrics and the relative hazard of progression or death using P-splines. The control group in Study MMY3007 was used as the reference level to calculate the relative hazard.

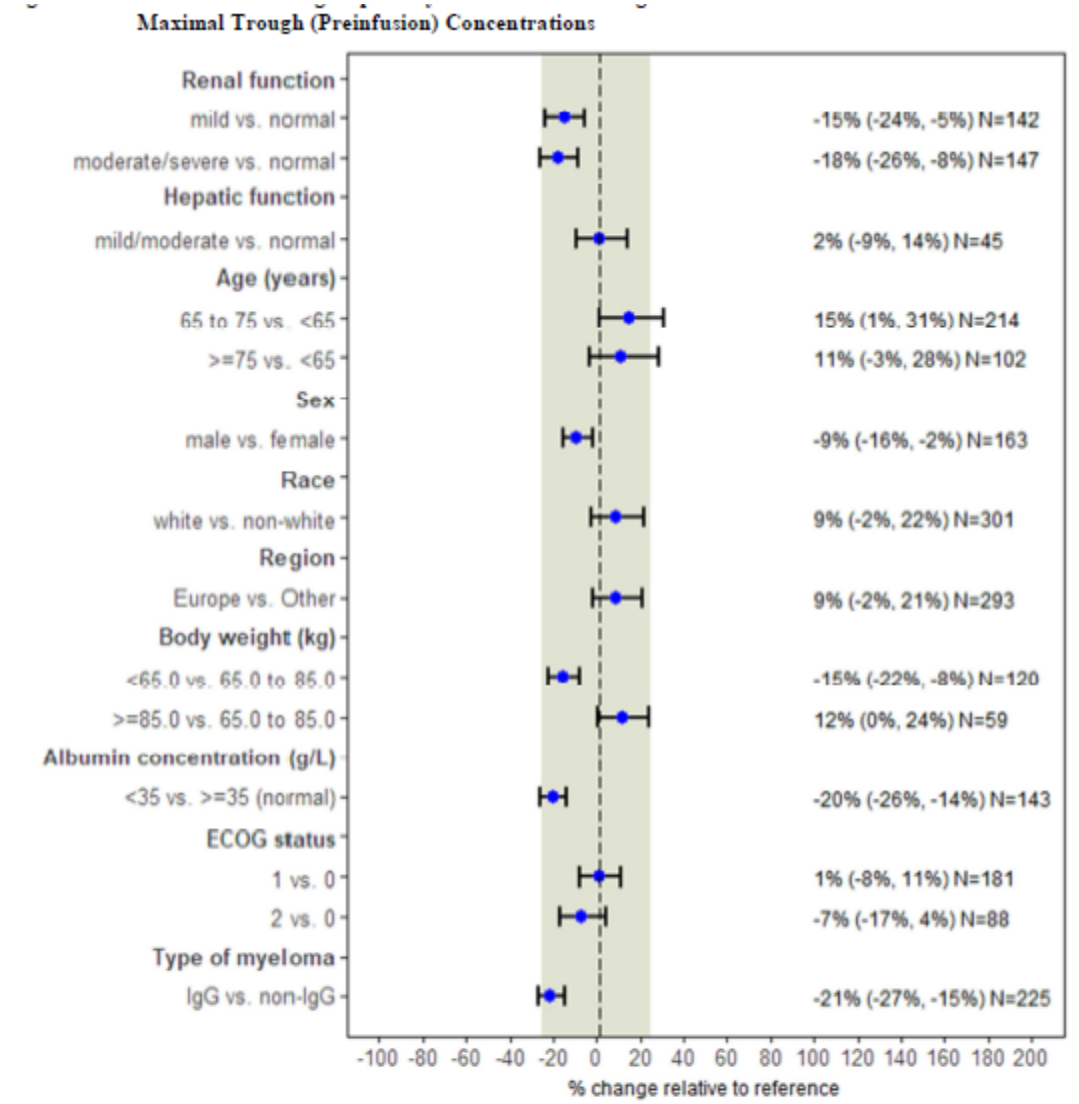
In addition, a matched case-control analysis was conducted to assess the influence of potential imbalances of risk factors among subjects with different exposure quantiles (Yang 2013). The potential of unbalanced distribution of identified covariates (risk factors) among different exposure quantile was examined.

Population Pharmacokinetic Analysis

The PPK analysis was based on 1,635 PK samples from 352 PPK-evaluable subjects with at least 1 evaluable (concentration above the lower limit of quantification) postdose sample. The observed concentration time data of daratumumab were adequately described by a 2-compartment PPK model with parallel linear and nonlinear Michaelis-Menten eliminations. The model was parameterised in terms of non-specific linear clearance (CL), volume of distribution in the central compartment (V1), inter-compartmental clearance (Q), volume of distribution in the peripheral compartment (V2), maximum rate of the saturable target-mediated drug disposition clearance process (Vmax), and daratumumab concentration (Km) associated with half of Vmax. The estimated CL value was similar to the clearance of non-specific endogenous IgG reported in the literature, and the estimated V1 value approached plasma volume. The ratio of the steady-state peak concentration after every 4 week dosing and the peak concentration after the first dose was 2.06±0.61 (mean±SD).

Effects of Covariates

A forest plot was constructed to compare the exposure (maximal trough concentration) of daratumumab in subgroups defined by specific covariates.



ECOG=Eastern Cooperative Oncology Group; IgG=immunoglobulin G.

Key: Solid blue circle represents mean and error bar represents 95% confidence interval. Dashed line represents no change at 0%. Numbers represent percent change, confidence interval, and number of subjects in the comparison groups. Gray shaded region represents ±25% from reference value.

Note: Analyses assumed that all subjects in Studies MMY1001 and MMY3007 received 16 mg/kg weekly for 6 weeks (6 doses), every 3 weeks for 48 weeks (16 doses), and then every 4 weeks thereafter. Maximal trough (preinfusion) concentration was derived as the trough concentration of the first dose of the every 3 dosing period.

The number of subjects in the reference group for each covariate: normal renal function (N=62); normal hepatic function (N=304); age <65 yr (N=36); female (N=189); Non-white (N=51); other region (N=59); body weight 65.0 to 85.0 kg (N=172); normal albumin concentration (N=209); ECOG=0 (N=83); non-IgG myeloma (N=127).

Only 2 subjects had moderate hepatic impairment, and 2 subjects had severe renal impairment. These subjects are combined with subjects with mild hepatic impairment and moderate renal impairment, respectively, in this analysis.

Figure 2: Forest plot of subgroup analyses on % change vs ref predicted max trough

Body Weight: When daratumumab was administered on a mg/kg basis, no clinically important differences (ie, ≤15%) in the exposure to daratumumab were observed in subjects with a low (<65 kg, n=120) or high (>85 kg, n=59) body weight compared to those with a normal body weight (65 to 85 kg, n=172). The CL and V1 of daratumumab significantly increased with increasing body weight. The difference in exposure had minimal impact on target saturation.

Age: No clinically important influence of age on the exposure to daratumumab was observed. The difference in exposure was within 15% between younger (age <65 years, n=36) and older subjects (65 years ≤ age <75 years, n=214; and age ≥75 years, n=102).

Sex: No clinically important influence of sex on the exposure to daratumumab was observed. The difference in exposure was approximately 9% between males (n=163) and females (n=189), although V1 of daratumumab in female subjects was approximately 13% lower than that of male subjects.

Race: Because 85% of subjects were White and there were only limited sample sizes in other race categories, the effect of race was evaluated as White (n=301) and Non-white (n=51). No clinically important influence of race on the exposure to daratumumab was observed. The difference in exposure was approximately 9% between White and Non-white subjects.

Region: The majority (83%) of subjects were from the European Union (EU). The effect of region was evaluated in EU (n=293) and Other (n=59). The difference in exposure was approximately 9% between EU and Other.

Renal Impairment: As only 2 subjects had severe renal impairment (creatinine clearance [CRCL] <30 mL/min), they were combined with subjects with moderate renal impairment (30≤ CRCL <60 mL/min) in this analysis. The effect of renal impairment was evaluated in categories of normal renal function (CRCL ≥90 mL/min, n=62), mild renal impairment (60≤ CRCL <90 mL/min, n=142), and moderate/severe renal impairment (n=147). No clinically important differences (≤18%) in the exposure to daratumumab were observed between subjects with renal impairment and those with normal renal function.

Hepatic Impairment: As only 2 subjects had moderate hepatic impairment (TB >1.5× to 3.0× upper limit of normal [ULN] as defined using the NCI criteria of hepatic dysfunction) and no subjects had severe hepatic impairment (TB >3× ULN and any AST), the 2 subjects with moderate hepatic impairment were 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=304) and mild/moderate hepatic impairment (n=45). The exposures in subjects with mild/moderate hepatic impairment were similar with subjects who had normal hepatic function and consistent with the findings based on previous studies. No clinically important differences in the exposure to daratumumab 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 (low) albumin and those with normal albumin level. The exposure to daratumumab was 20% lower in subjects with abnormal (low) albumin level (<35 g/L; n=143) compared with subjects who had normal albumin level (≥35 g/L; n=209). The difference in exposure had minimal impact on target saturation.

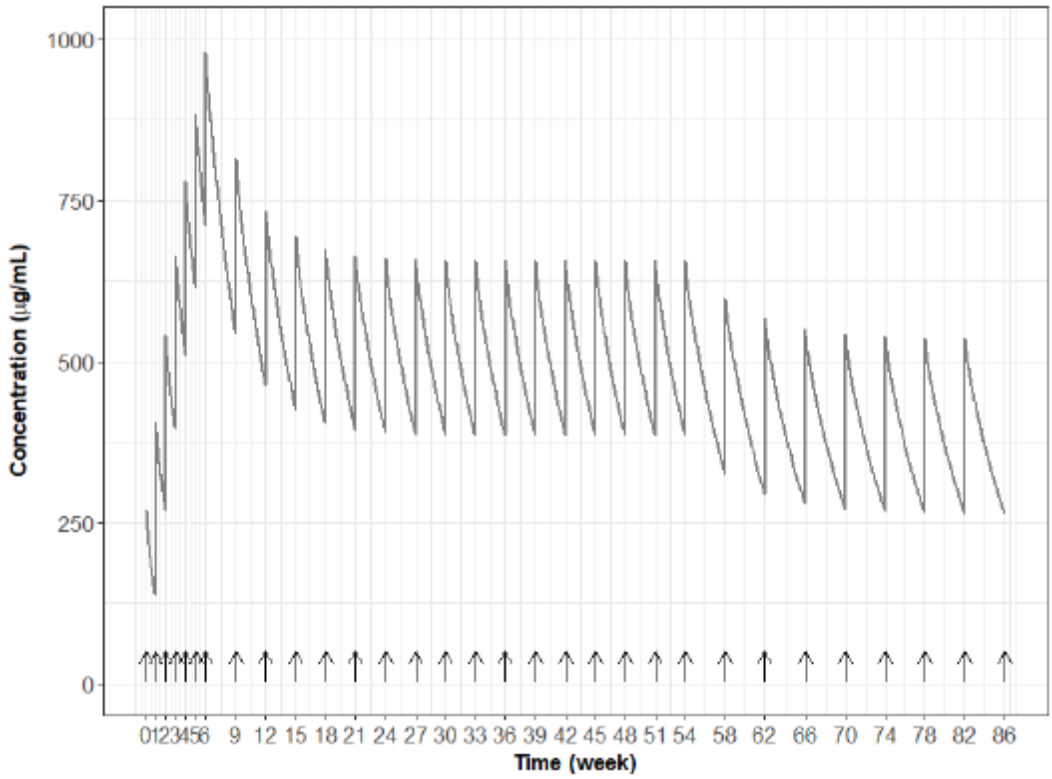
Type of Myeloma: No clinically important differences in the exposure to daratumumab were observed between subjects with IgG myeloma and non-IgG myeloma. The exposure to daratumumab was approximately 20% lower in the IgG multiple myeloma subjects (n=225) compared to the non-IgG subjects (n=127). The difference in exposure had minimal impact on target saturation.

Immunogenicity: No immunogenicity-evaluable subjects (n=119) in the PPK analysis were positive for ADA to daratumumab.

ECOG Score: No clinically important differences in the exposure to daratumumab (≤7%) were observed between subjects with ECOG scores of 1 (n=181) or 2 (n=88) and those with ECOG scores of 0 (n=83).

Similar to what was observed in data from previous studies of monotherapy, apparent steady state seems to be reached at approximately 5 months. The ratio of the steady-state peak after every 4 week dosing and the peak after the first dose was 2.06±0.61 (mean±SD). Target saturation >90% is maintained at trough concentrations in the majority (>99%) of the subjects following the every 4 week dose regimen.

Figure 3: **Typical Pharmacokinetic Profile of Daratumumab for 16 mg/kg Once Weekly for 6 Weeks (6 Doses), Followed by Once Every 3 Weeks for 48 Weeks (16 Doses), and Once Every 4 Weeks Thereafter (8 Doses)**



Key: Black arrows represent dosing events.
Note: Weeks refer to elapsed time.
Source: Mod5.3.3.5/FLMM/POPPK/Fig7

Figure 3

Comparison of PK between D-VMP Combination and Previous Monotherapy and Combination Therapies:

In general, the maximal trough concentration of daratumumab was similar following the D-VMP dose regimen and the approved dose regimen (16 mg/kg weekly for 8 weeks followed by every 2 weeks for 16 weeks, then every 4 weeks thereafter) in previous monotherapy and combination therapy studies. The model-derived T½ associated with the CL of daratumumab was approximately 22.1±9.7 (mean±SD) days, comparable to the T½ of 18±9 (mean±SD) days derived from the monotherapy data and the T½ of 23.3±11.8 (mean±SD) days derived from previous combination therapies. Similar to what was observed in previous studies, apparent steady state seemed to be reached at approximately 5 months. The covariate effects estimated based on the Phase 3 study MMY3007 were similar to those estimated in the previous model based on the monotherapy studies or the previous combination therapy studies. Consistent with the findings in previous studies, none of the investigated intrinsic and extrinsic factors had clinically important effects on the exposure to daratumumab as all the covariate effects were within approximately 20% with minimal impact on target saturation due to the estimated small binding affinity (Km=0.93 µg/mL). Therefore, no dose adjustment is recommended based on these factors.

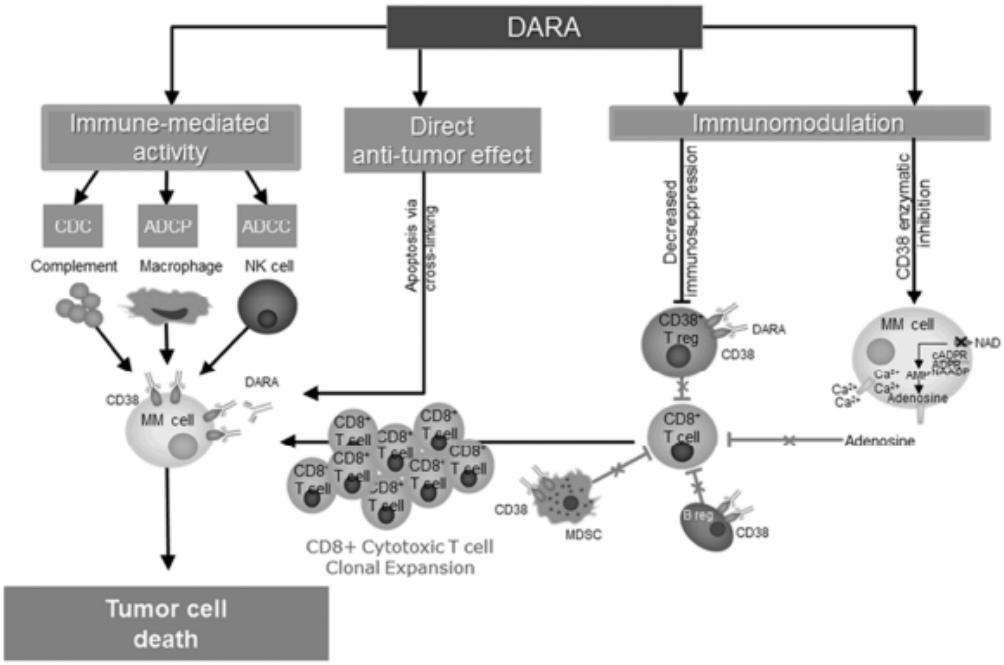
Exploratory Exposure-Response Relationships: Exposure-Response (E-R) relationships were investigated based on the data from Study MMY3007. Since all subjects in MMY3007 (daratumumab group) received the recommended dose of 16 mg/kg, there is limited exposure variation to evaluate the E-R relationship and, therefore, only exploratory and graphic E-R analyses were performed for selected efficacy endpoints and AEs.

2.3.3. Pharmacodynamics

Mechanism of action

Daratumumab is a human IgG mAb immunotherapy that binds with high affinity to CD38, a transmembrane glycoprotein expressed on tumour cells, and induces tumour cell death through multiple mechanisms of action. These mechanisms of action include several immune-mediated activities, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and direct cytotoxicity by induction of apoptosis by Fc gamma receptor mediated crosslinking of tumour-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 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 hypothesised to synergistically lead to the deep responses observed in patients. A summary of daratumumab's novel, converging mechanism of action is presented in Figure 1.

Figure 1: Daratumumab Mechanisms of Action



ADCC=antibody-dependent cellular cytotoxicity; ADCP=antibody-dependent cellular phagocytosis; CDC=complement-dependent cytotoxicity

Figure 4: mechanism of action

Primary and secondary pharmacology

Pharmacodynamic assessments were not included in Studies MMY3007 and MMY1001 (D-VMP arm).

The monotherapy submission and the RRMM submission reported decreases in NK cells in peripheral blood and bone marrow following treatment with daratumumab monotherapy and in combination with other treatment regimens. No new PD data are available.

Immunogenicity

A summary of anti-daratumumab antibody status for Study MMY3007 and the D-VMP cohort of Study MMY1001 are shown in Table 6 and Table 7, respectively. Of the 119 subjects (including 6 subjects from Study MMY1001) who were treated with D-VMP and had samples appropriate for immunogenicity evaluation, 0 (0%) were positive for anti-daratumumab antibodies.

In monotherapy studies, none (0%) of the 199 subjects evaluable for immunogenicity were positive for antibodies to daratumumab. In the 4 combination studies in the RRMM submission, 2 (0.7%) of the 298 evaluable subjects (including the 6 subjects in the MMY1001 D-VMP cohort) were positive for antibodies to daratumumab. These results consistently indicate a low risk of immunogenicity with daratumumab.

QTc Evaluation

The evaluation of QTc intervals versus serum concentrations of daratumumab has been provided in the monotherapy submission and revealed that daratumumab has no effect on electrocardiographic (ECG) parameters. No additional ECG interval data for analysis of QT were collected in Studies MMY3007 or MMY1001 (D-VMP cohort).

Neutralising Anti-daratumumab Antibodies

No patients treated D-VMP in Study MMY3007 or in the D-VMP cohort of Study MMY1001 at the time of the cut-off were positive for anti-daratumumab antibodies; therefore, the presence of neutralising antibodies was not assessed.

2.3.4. PK/PD modelling

See Results from the population PK analyses presented above.

2.3.5. Discussion on clinical pharmacology

The PK profile for daratumumab when given in combination treatment seems to show 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. However, in the Exploratory-Response (E-R) analysis, a potential confounding between post-treatment drug effects and maximal trough concentration was observed in the D-VMP treated newly diagnosed MM subjects. This potential confounding effect has not been observed in previous E-R analyses in monotherapy or in previous authorised combinations. The MAH pointed out the fact of being D-VMP population included in the current analysis a first line treatment population as the potential reason. The populations included in the previous submissions were exposed to at least 1 prior line of multiple myeloma treatment and there is a potential that the prior treatments made this relationship less apparent in those exposure-response analyses. Additionally, the MAH plans to continue to monitor this confounding in future studies for untreated patients with multiple myeloma. This is considered acceptable. The MAH clarified the range of exposure cover by every quartile in the Kaplan-Meier Curves (Progression-free survival) in the E-R analysis of the combination D-VMP

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 present data presented in Figure 3, 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 seems to be comparable with the data reported from the monotherapy studies. This may support 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 PPK analysis was based on 1,635 PK samples from 353 PK-evaluable patients (all receiving daratumumab at 16 mg/kg). Several covariates were investigated in the PPK analysis. Consistent with the results from the initial (mono- and combination-therapy) PPK analyses, results from the present PPK analysis show that albumin level, type of myeloma and body weight were the covariates with the highest impact on the PK values. Further, in the present analysis, (numeric) differences were also observed for gender and renal function. As there is no reason to believe that the gender and/or renal function should influence the PK of daratumumab when used in the D-VMP combination treatment, these findings are mostly expected to be a random finding. Nonetheless, for a proper comparison of estimates CL between the previous submitted PPK models and the current one, the MAH was asked to discuss this further. The MAH discussed the relevance of deleting covariate FORM in the previous submitted PPK models. Covariate FORM was used to evaluate the potential differences in clearance (CL) between Phase 2 pre-change and Phase 3 post-change drug products. However, only Phase 3 post-change drug product was used in Study MMY3007 and in the D-VMP arm of Study MMY1001. Therefore, it is not possible to include covariate FORM and estimate its effects in this model. Additionally, it was justified that use of covariate FORM is the only reason for the differences observed on estimates CL between previous submitted models and table with the comparison included in the PPK report submitted with the current variation. Of note, the differences are not expected to be of clinical relevance and currently no dose-adjustments are considered necessary.

With regards to the pharmacodynamics, no new data related to mechanism of action or QTc evaluation are presented. This is acceptable; an ongoing trial SMM2001 will investigate further this identified risk (see RMP).

No patients developed anti-daratumumab antibodies, which is assuring. A study aiming to improve the immunogenicity method's ability to detect anti-daratumumab antibodies in the presence of high trough levels of daratumumab is ongoing (see RMP).

2.3.6. 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 MMY3007, daratumumab was administered at 16 mg/kg as per the daratumumab prescribing information, but the dosing schedule was modified to match the 6-week cycle length for VMP: 16 mg/kg IV weekly for 6 weeks, then every 3 weeks for 48 weeks (Cycle 2 to 9), and then every 4 weeks thereafter (post-VMP Treatment Phase) until documented progression, unacceptable toxicity, or study end.

2.4.2. Main study(ies)

Study MMY 3007

The phase 3 pivotal study MMY 3007 is a randomized, open-label, parallel-group, controlled multicentre study to compare the efficacy of daratumumab when combined with VMP (D-VMP) to that of VMP in terms of PFS in subjects at least 18 years of age with previously untreated multiple myeloma who are ineligible for high-dose therapy. A target of up to 700 subjects were planned to be enrolled in this study, with 350 subjects planned per treatment arm.

Methods

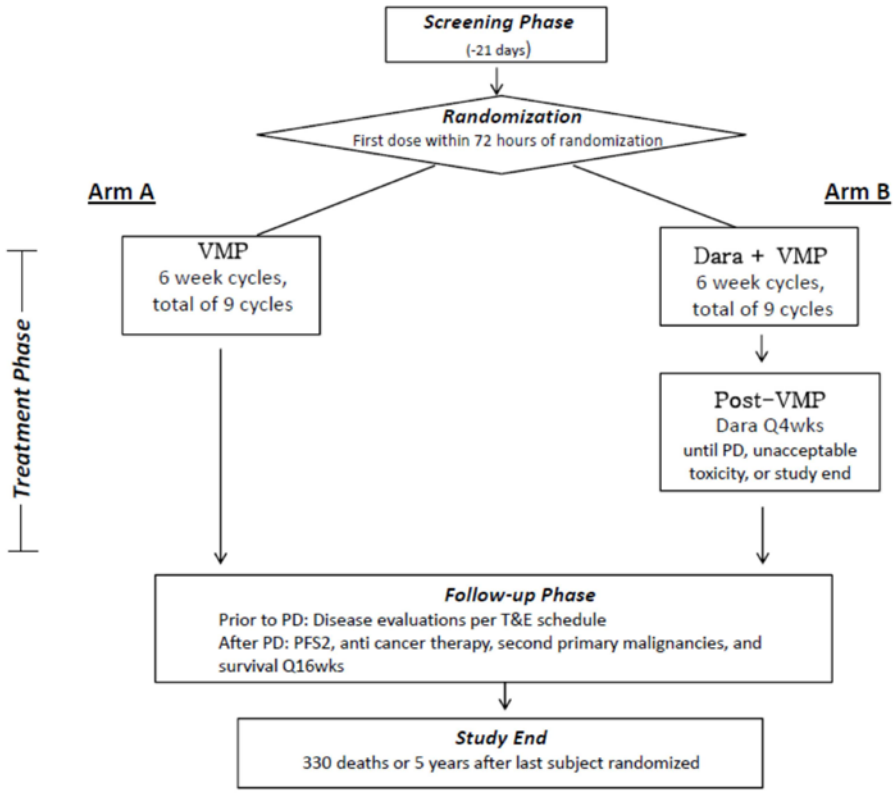


Figure 5

Study participants

Inclusion Criteria

Key eligibility criteria for inclusion in the study were as follows:

1. Subject had to be at least 18 years of age.
2. Subject had to have documented multiple myeloma as defined by the criteria below:
3. Diagnostic criteria of calcium elevation, renal insufficiency, anemia, and bone abnormalities (CRAB)
4. Monoclonal plasma cells in the bone marrow >= 10% at some point in their disease history or presence of a biopsy proven plasmacytoma.
5. Measurable disease at Screening as defined by any of the following:
   - IgG multiple myeloma: Serum monoclonal paraprotein (M-protein) level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
   - IgA, IgD, IgE, IgM multiple myeloma: serum M-protein level ≥0.5 g/dL or urine M-protein level ≥200 mg/24 hours; or

- Light chain multiple myeloma without measurable disease in the serum or the urine: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.

6. Newly diagnosed and not considered candidate for high-dose chemotherapy with ASCT 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 of these comorbid conditions and approval is required before randomization.
7. Subject must have had an ECOG Performance Status score of 0, 1, or 2.

Exclusion Criteria

Subjects were not to be enrolled into the study if it was determined upon pre-study examination that:

1. Subject had a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma.
2. Subject had 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.
3. Subject had prior or current systemic therapy or ASCT for multiple myeloma, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment.
4. Subject had peripheral neuropathy or neuropathic pain Grade 2 or higher, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.
5. Subject had plasma cell leukemia (according to WHO criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of ≥2×109/L) or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)

Treatments

The administration schedule for study treatments is described in the protocol. Subjects were to receive VMP for a maximum of 9 cycles. For subjects randomized into Treatment Arm B, daratumumab was to be given until disease progression, unacceptable toxicity, or other reasons.

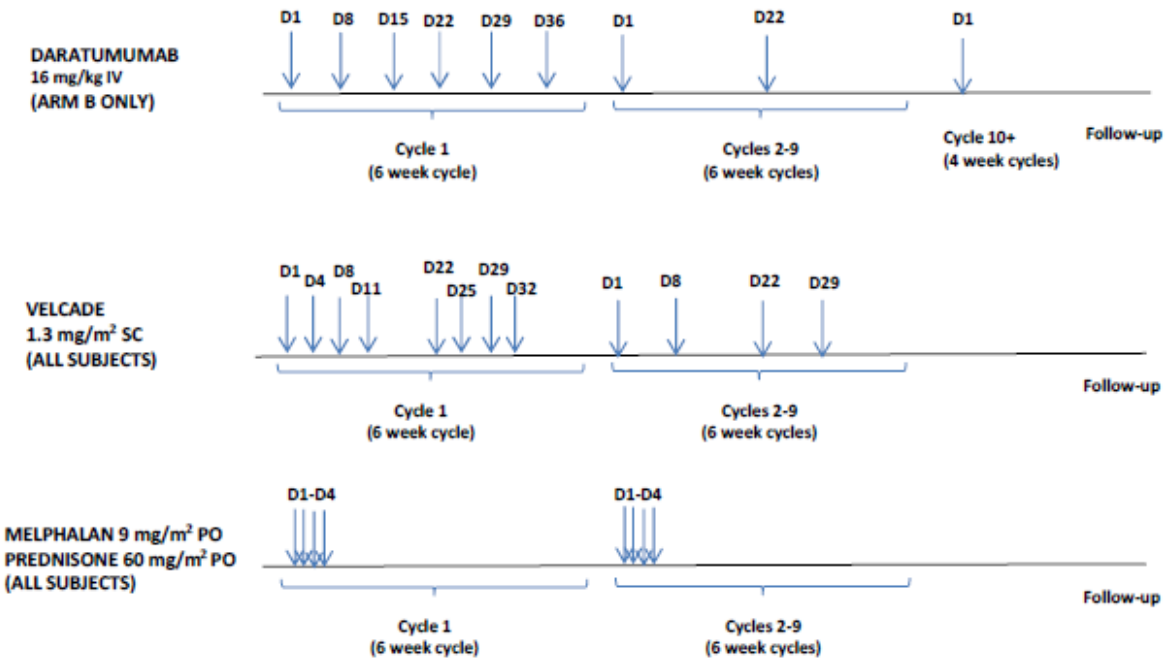


Figure 6: Treatment administration

Daratumumab Administration

For subjects assigned to Arm B (D-VMP), daratumumab (16 mg/kg) was administered by IV infusion initially once every week for 6 weeks (Cycle 1; 1 VELCADE cycle); then once every 3 weeks for an additional 16 doses (Cycles 2-9); then once every 4 weeks thereafter (post-VMP Treatment Phase), until documented progression, unacceptable toxicity, or study end. The daratumumab dosing schedule was minimally adjusted to accommodate the standard VMP 6-week cycle. Each subject's dose of daratumumab was calculated based on the subject's weight rounded to the nearest kilogram. The dose did not need to be recalculated for weight changes that were <10% from baseline.

For all daratumumab infusions, subjects received pre-infusion and post-infusion medications (as needed) to reduce the risk of infusion-related reactions. Details on the toxicity management and guidelines for the prevention and management of infusion reactions including pre-infusion medications and post-infusion medications are provided in the protocol. Subjects who needed to discontinue treatment with any one component of study treatment (bortezomib, melphalan, prednisone, or daratumumab) were permitted to continue to receive treatment with the other components of study treatment, as assigned.

Bortezomib Administration

For both treatment groups, bortezomib was administered at a dose of 1.3 mg/m2 as a SC injection twice weekly (Weeks 1, 2, 4, and 5) for one 6-week cycle (Cycle 1; 8 doses per cycle) followed by once weekly (Weeks 1, 2, 4, and 5) administrations for eight 6-week cycles (Cycles 2 to 9; 4 doses per cycle). Dose adjustments were to be based on the highest grade of toxicity that was ascribed to bortezomib (Appendix 1). The rationale for weekly dosing of bortezomib after Cycle 1 is provided.

Melphalan and Prednisone Administration

Melphalan was administered at 9 mg/m2 and prednisone was administered at 60 mg/m2 on Day 1 to 4 of each bortezomib cycle. Both melphalan and prednisone were administered orally. For subjects randomized to Treatment Arm B, 20mg dexamethasone was substituted for the planned dose of prednisone on Day 1 of each cycle. In this setting, dexamethasone was utilized as the treatment dose of steroid for that particular day, as well as the required pre-medication prior to daratumumab infusion. Melphalan and prednisone could be reduced, or the treatment schedule could be modified for the management of the study treatment-related toxicities (Appendix 1).

Assessment of tumour response and disease progression was conducted in accordance with the International Myeloma Working Group (IMWG) response criteria. An assessment of MRD was conducted on bone marrow samples. Safety evaluations included adverse event monitoring, physical examinations, electrocardiogram (ECG) monitoring, clinical laboratory parameters (hematology and chemistry), vital sign measurements, and Eastern Cooperative Oncology Group (ECOG) performance status. Blood samples were drawn for assessment of pharmacokinetic parameters and immunogenicity.

Objectives

Primary Objective

To compare the efficacy of daratumumab (PFS) when combined with VMP (D-VMP) to that of VMP in previously untreated multiple myeloma subjects who are ineligible for high dose therapy.

Secondary Objectives

To determine if the addition of daratumumab to VMP would improve clinical outcome as measured by:

- ORR (partial response [PR] or better)
- Very good partial response (VGPR) or better rate

- Complete response (CR) or better rate
- Minimal residual disease (MRD) negativity rate
- OS
- Progression-free survival 2 (PFS2)
- Time to disease progression (TTP)
- Time to response
- Duration of response (DOR)
- Time to next treatment
- To assess patient reported outcomes and heath economic/resource utilization.
- To determine the pharmacokinetics and immunogenicity of daratumumab.
- To assess the safety and tolerability of daratumumab when administered in combination with VMP.
- To evaluate clinical efficacy of daratumumab when added to VMP in high risk molecular subgroups.

Exploratory Objectives

- To explore biomarkers predictive of response and resistance to therapy.
- To assess durability of MRD negativity.

Outcomes / endpoints

Table 6: Key efficacy endpoints for study MMY3007

Endpoint	Definition
Primary Endpoint	
PFS	Duration from the date of randomization to either progressive disease, according to the IMWG response criteria, or death, whichever occurs first. PFS is based on a computerized algorithm.
Secondary Efficacy Endpoints in Hierarchical Testing	
ORR	Proportion of subjects who achieve a PR or better (ie, PR, VGPR, CR, or sCR) based on the computerized algorithm, according to IMWG response criteria, during or after the study treatment but before the start of subsequent anti-myeloma therapy.
Rate of VGPR or better	Proportion of subjects with a response of VGPR or better (ie, VGPR, CR, or sCR) based on the computerized algorithm, according to IMWG response criteria, during or after the study treatment but before the start of subsequent anti-myeloma therapy.
Rate of CR or better	Proportion of subjects with a response of CR or better (ie, CR or sCR) based on the computerized algorithm, according to IMWG response criteria, during or after the study treatment but before the start of subsequent anti-myeloma therapy.
MRD negativity rate	Proportion of subjects who had a negative MRD assessment (at the 10^{-5} threshold) at any timepoint after randomization (and before disease progression the start of subsequent anti-myeloma therapy) by bone marrow aspirate. MRD was evaluated using a validated NGS assay (clonoSEQ®, Version 2.0). A 510(K) application is currently under review by the US, Food and Drug Administration and calibration rates of over 90% have been obtained using the assay on NDMM samples from Study MY3007.
OS	Time from the date of randomization to the date of death due to any cause.
Other Secondary Endpoints (Not in Hierarchical Testing)	
PFS2	Duration from randomization to progression on the next line of subsequent anti-myeloma therapy or death due to any cause (before the start of the second subsequent anti-myeloma treatment), whichever comes first.
TTP	Time between the date of randomization and the date of first documented evidence of confirmed PD, according to IMWG response criteria, or death due to progressive disease, whichever occurs first.
TTR	For subjects with a PR or better as their best response, time to response (ie, time to first response) was defined as time between the date of randomization and the first efficacy evaluation at which the subject met all criteria for PR or better based on the computerized algorithm.
DOR	Only for subjects with a confirmed response (PR or better), time between first documentation of response and disease progression based on the computerized algorithm, according to IMWG response criteria, or death due to PD, whichever occurs first.
Time to subsequent anti-myeloma treatment	Time from randomization to the start of subsequent anti-myeloma treatment.
Functional status and well-being (PRO)	Change in functioning, symptoms, and health-related quality of life assessed using the EORTC-QLQ-C30 and the EQ-5D-5L.

CR=complete response; DOR=duration of response; EORTC-QLQ-C30=European Organization for Research and Treatment of Cancer - Quality of Life Questionnaire - Core Questionnaire; EQ-5D-5L=EuroQol 5-dimension Questionnaire; IMWG=International Myeloma Working Group; MRD=minimal residual disease; NDMM=newly diagnosed multiple myeloma; NGS=next-generation sequencing; ORR=overall response rate; OS=overall survival; PD=progressive disease; PFS=progression-free survival; PFS2=progression-free survival on the next line of therapy; PR=partial response; PRO=patient report outcome; sCR=stringent complete response; TTP=time to disease progression; TTR=time to response; US=United States; VGPR=very good partial response.

If the primary efficacy endpoint (PFS) was statistically significant, several secondary endpoints would be sequentially tested, as indicated inTable 2: ORR, VGPR and CR were calculated using a computerized algorithm, according to IMWG response criteria. For the evaluation of MRD by bone marrow aspirate, the threshold value of 10^{-5} was used to evaluate MRD negativity status. Relapse from CR by positive immunofixation or trace amount of M-protein was not considered to be progressive disease and was not included in the PFS calculation.

Sample size

The sample size calculation was based on the assumption that the median PFS for the VMP group in this study was estimated to be approximately 21 months, and that the addition of daratumumab would reduce the risk of the disease progression or death by 27.6%, i.e., assuming the hazard ratio (D-VMP vs VMP) of 0.724, which translates to a median PFS of 29 months for the D-VMP arm. A total of 360 PFS events would be needed to achieve a power of 85% to detect this hazard ratio with a log-rank test (two-sided alpha is 0.05). With a 20-month accrual period and an additional 21-month follow-up, the total sample size needed for the study was approximately 700 (350/treatment group) subjects. The sample size calculation has taken into consideration an annual dropout rate of 5%.

Long-term survival follow-up was to continue until 330 deaths had been observed or 5 years after the last subject was randomized, whichever came first. This study was to achieve approximately 80% power to detect a 27% reduction in the risk of death (HR=0.73) with a logrank test (two-sided alpha=0.05) if 330 death events were observed at the study end.

Randomisation

Central randomization was implemented in this study. Subjects were randomly assigned to 1 of 2 treatment groups based on a computer-generated randomization schedule prepared before the study was under the supervision of the sponsor. Eligible subjects were stratified by ISS (I, II, or III) at screening (based on central laboratory results), region (Europe vs Other), and age (<75 vs≥75), and then randomized to treatment in a 1:1 ratio to either Treatment Arm A (VMP alone) or Treatment Arm B (D-VMP). The interactive web response system (IWRS) was to assign a unique treatment code, which dictated the treatment assignment and matching study treatment for the subject.

Blinding (masking)

As this was an open-label study, blinding procedures were not applicable.

Statistical methods

Primary and Secondary Endpoints

The primary efficacy endpoint of this study is PFS. The null hypothesis is that there is no difference in PFS between the combination D-VMP and VMP alone in subjects with newly diagnosed multiple myeloma who are ineligible for high dose chemotherapy. The secondary endpoints such as TTP, ORR, VGPR or better rate, CR or better rate, MRD negativity rate, PFS2, time to response, duration of response and OS will be evaluated as well.

In general, continuous variables were summarized using descriptive statistics such as mean, standard deviation (SD), median and range. Categorical variables were summarized using frequency and percentage. For time-to-event variables, which were defined as from the date of randomization to the date of the event, the Kaplan-Meier method was used for descriptive summaries. The primary treatment comparison of the distribution of overall PFS will be based on a stratified log-rank test. Hazard ratio and its 95% confidence interval were estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable. Stratification factors used in the analyses include ISS staging (I, II, III), region (Europe vs other), and age (<75 years vs ≥75 years).

All statistical hypothesis tests and 95% confidence intervals presented were 2-sided. The primary hypothesis is to be tested at the 0.05 significance level (overall).

If the primary endpoint of PFS is statistically significant, secondary endpoints will be sequentially tested, each with an overall two-sided alpha of 0.05, by utilizing a hierarchical testing approach to control Type I error rate. The statistical methods used and hierarchical order for the secondary endpoints are listed in Table below.

Analyses of demographics, baseline characteristics, and efficacy endpoints were primarily analyzed using the intent-to-treat population (ITT), defined as subjects who have been randomly assigned to the D-VMP or VMP group.

Table 7: Statistical Methods for Key Efficacy Endpoints.

Endpoint	Statistical Methods
Primary Endpoint	
PFS	Kaplan-Meier method, stratified log-rank test, stratified Cox's regression model. Stratification for primary analysis: ISS staging (I, II, or III), region (Europe vs. Other), and age (<75 years vs. ≥75 years)
Secondary Endpoints in Hierarchical Testing	
ORR	CMH test controlled for 3 stratification factors: ISS staging (I, II, or III), region (Europe vs. Other), and age (<75 years vs. ≥75 years). Descriptive statistics for sCR (ie, N and percentage of subjects achieving sCR and corresponding 95% exact confidence interval)
Rate of VGPR or better	
Rate of CR or better	
MRD negativity rate	Fisher's exact test controlled for 3 stratification factors: ISS staging (I, II, or III), region (Europe vs. Other), and age (<75 years vs. ≥75 years)
OS	Kaplan-Meier method, unstratified Cox's regression model for the second interim analysis
Other Secondary Endpoints (Not in Hierarchical Testing)	
PFS2	Kaplan-Meier method, stratified log-rank test, stratified Cox's regression model
TTP	Kaplan-Meier method, stratified log-rank test, stratified Cox's regression model
TTR	Descriptive statistics (ie, n, mean, SD, median, and range)
DOR	Kaplan-Meier method
Time to subsequent anti-myeloma therapy	Kaplan-Meier method, stratified log-rank test, stratified Cox's regression model
Functional status and well-being	Descriptive statistics (ie, N, mean, SD, median, change from baseline). Distribution based method to define improvement and worsening in scores. Kaplan-Meier method used for time to worsening. Mixed effects model with repeated measures for change from baseline.

CMH=Cochran-Mantel-Haenszel; CR=complete response; DOR=duration of response; ISS=International Staging System; MRD=minimal residual disease; ORR=overall response rate; OS=overall survival; PFS=progression-free survival; PFS2=progression-free survival on the next line of therapy; sCR=stringent complete response; TTP=time to progression; TTR=time to response; VGPR=very good partial response.

Censoring rules for PFS

PFS is defined as the duration from the date of randomization to either progressive disease, according to the IMWG response criteria, or death, whichever occurs first.

Subjects who start subsequent antimyeloma therapies for multiple myeloma without disease progression were censored at the last disease assessment before the start of subsequent therapies. Subjects who withdrew consent from the study before disease progression were censored at the last disease assessment. Subjects who were lost to follow-up were censored at the last disease assessment before subjects were lost to follow-up. Subjects who have not progressed and were still alive at the cutoff date for analysis were censored at the last disease assessment. Subjects without any postbaseline disease assessment were censored at the randomization. Reasons for censoring were summarized for the ITT population.

Interim Analyses

Two interim analyses were planned for this study. The first interim analysis, with a purpose to evaluate safety, was performed after a total of approximately 100 subjects have been treated for at least 2 cycles or discontinued the study treatment. The second interim analysis was planned to be performed when 216 PFS events (60% of the total events) have been accumulated. The purpose of the second interim analysis was to evaluate cumulative interim safety and efficacy data. The primary PFS analysis was planned to occur when

approximately 360 PFS events have been observed if the second interim analysis does not result in an early stop due to efficacy or futility. The end of the study will occur when 330 subjects have died, or 5 years after the last subject is randomized.

The exact significance level at the second interim analysis is to be determined by the observed number of events per the O'Brien-Fleming alpha spending function for PFS, ORR, VGPR or better rate, CR or better rate and MRD negativity rate. For OS, a modified linear alpha spending function will be used. The alpha level for the first look at OS was 0.0001. If the null hypothesis for an endpoint is rejected at the second IA, it will remain rejected and will not be re-tested.

The results presented here correspond to the second interim analysis (231 PFS events, approx. 64 % of total planned PFS events). An Independent Data Monitoring Committee (IDMC) was commissioned to review efficacy and safety results at the planned interim analyses. The primary PFS analysis was skipped since the second IA was positive.

Sensitivity Analysis and subgroups analysis for PFS

The following sensitivity analyses were planned for PFS:

- Progressive disease based on investigator assessment
- Not Censored for Start of Subsequent Antimyeloma Therapies
- Censored for Death/PD after Missing More Than One Disease Evaluation
- Analysis of PFS using the per-protocol population
- Analysis using unstratified log rank rest and Cox Regression Model

Subgroup analyses for PFS were also performed and included age, sex, race, geographic region, ISS staging, renal function, hepatic function, type of multiple myeloma, cytogenetic risk and baseline Eastern Cooperative Oncology Group (ECOG) performance status score.

Results

Participant flow

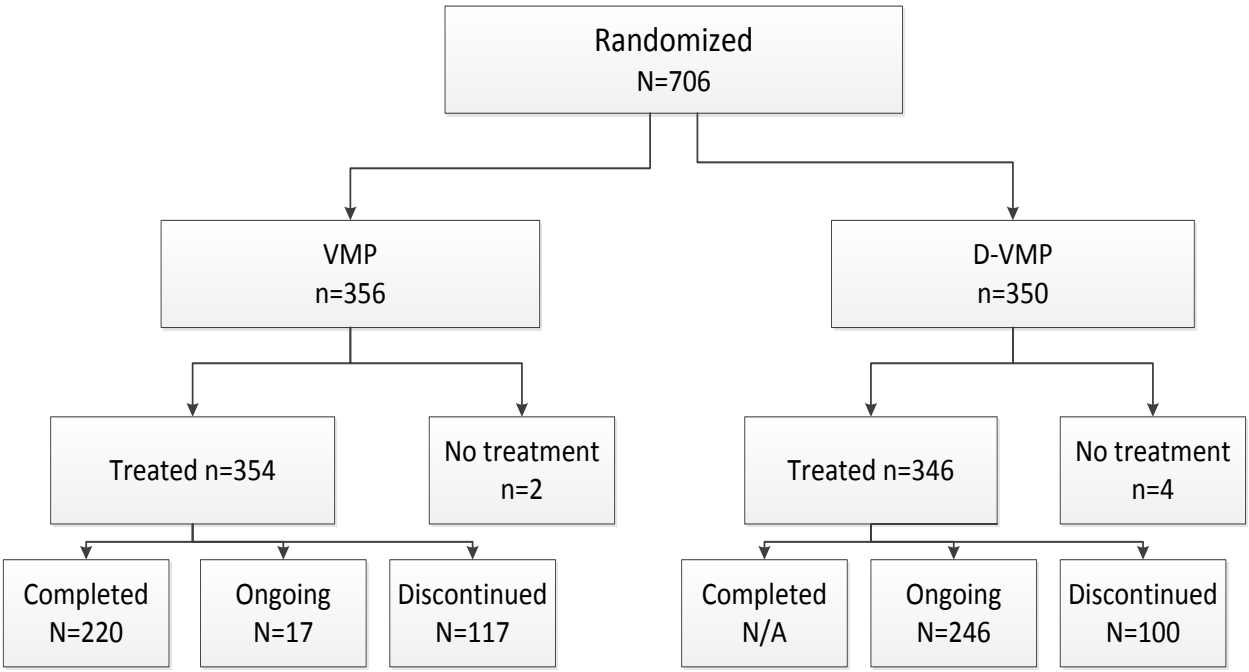


Figure 7: Participant flow

Table 8: Summary of study treatment disposition by cycle (SAS) in MMY3007

	VMP	D-VMP		
	Total	Cycles 1-9	Cycles 10+	Total
	n (%)	n (%)	n (%)	n (%)
Analysis set: safety	354			346
Subjects who completed study treatment	220 (62.1%)	N/A	N/A	N/A
Subjects still on study treatment	17 (4.8%)	17 (4.9%)	229 (66.2%)	246 (71.1%)
Subjects who discontinued study treatment	117 (33.1%)	67 (19.4%)	33 (9.5%)	100 (28.9%)
Reason for discontinuation				
Progressive disease	47 (13.3%)	23 (6.6%)	30 (8.7%)	53 (15.3%)
Adverse event	33 (9.3%)	17 (4.9%)	0	17 (4.9%)
Death	8 (2.3%)	11 (3.2%)	2 (0.6%)	13 (3.8%)
Non-compliance with study drug [a]	15 (4.2%)	10 (2.9%)	1 (0.3%)	11 (3.2%)
Withdrawal by subject	6 (1.7%)	2 (0.6%)	0	2 (0.6%)
Physician decision	7 (2.0%)	0	0	0
Other	1 (0.3%)	4 (1.2%)	0	4 (1.2%)

Key: VMP = bortezomib-melphalan-prednisone; D-VMP = daratumumab-bortezomib-melphalan-prednisone.

Recruitment

Study Center(s): Argentina (3 sites), Australia (6 sites), Belgium (6 sites), Brazil (6 sites), Bulgaria (7 sites), Croatia (2 sites), Czech Republic (5 sites), Georgia (3 sites), Germany (2 sites), Greece (5 sites), Hungary (5 sites), Italy (12 sites), Japan (17 sites), Korea (7 sites), Macedonia (3 sites), Poland (10 sites), Portugal

(2 sites), Romania (4 sites), Russian Federation (10 sites), Serbia (4 sites), Spain (18 sites), Turkey (7 sites), Ukraine (7 sites), United Kingdom (8 sites), United States of America (3 sites).

Study Period: The first subject was randomized on 09 Feb 2015; the data cut-off date for the second interim analysis was 12 Jun 2017. As of this date, 706 subjects from 162 centers in 25 countries were randomized into Study MMY3007, with 350 subjects randomized to the D-VMP group and 356 subjects randomized to the VMP group. The Study is ongoing. Treatment groups were distributed similarly by region. The majority (83%) of subjects were enrolled at sites in Europe, with most subjects from Spain (15%), Poland (9%), Italy (8%), Czech Republic (7%), Ukraine (7%), and the Russian Federation (6%). Seventeen percent of subjects were enrolled in countries outside Europe, with most of those subjects from Japan (7%) and the Republic of Korea (6%); 6 subjects (<1%) were enrolled in the United States.

To control for any variation in transplant ineligibility criteria among countries or regions, subjects were considered transplant-ineligible if they were age ≥65 years; if <65 years old, subjects had to have important comorbid conditions deemed likely to have a negative impact on tolerability to the high dose chemotherapy used in ASCT. Age was the main transplant ineligibility criterion for 649 subjects (92%), and comorbidity accounted for 56 (8%) subjects; 1 subject did not have an age or comorbidity factor, however, bortezomib and transplant were not available as treatment options for this subject. This was reported as a major protocol deviation.

Conduct of the study

Protocol amendments

The original protocol was dated 26 June 2014, and there were 6 amendments (2 country– specific) to the protocol.

Key changes are summarized below:

Table 9: Summary of protocol amendments

Summary of Protocol Amendments for 54767414MMY3007	
Amendment 1 (24 November 2014; substantial)	• Clarifications were made to the inclusion/exclusion criteria to align with other daratumumab protocols, and investigator feedback was incorporated into the protocol.
Amendment INT-1/ITA-1 (04 May 2015; substantial)	• To address a request from the Italian Health Authority, the Safety Evaluations section was updated to implement routine monitoring of electrolytes.
Amendment 2 (05 November 2015; substantial)	• Text was revised to provide updated guidance with respect to bortezomib dose modifications (per the Summary of Product Characteristics [SmPC] and United Sates Package Insert [USPI]) and to align with the VELCADE label regarding dose modifications, to incorporate investigator feedback into the protocol, and to revise operational aspects of the study and provide clarifications on study procedures.
Amendment 3 (26 July 2016; non- substantial)	• Clarification was made regarding collection of sodium and potassium levels as part of the chemistry panel for safety analysis.
Amendment 4 (11 November 2016; substantial)	• Timepoints for collection of bone marrow for MRD assessment were revised in order to align the protocol with the new categories of MRD-negativity defined by the IMWG.
Amendment 4/JPN-1 (06 March 2017; non-substantial)	• Changes were made to clarify that the Anticipated Event language is not applicable specifically for sites in Japan.

Protocol Deviations

All protocol deviations of eligibility criteria and those deviations that could impact subject safety or study endpoints were considered major protocol deviations. Major protocol deviations were reported for 81

subjects (12%) across both treatment groups: 36 subjects (10%) in the D-VMP group and 45 subjects (13%) in the VMP group.

Table 10: Summary of major protocol deviations – ITT

	VMP n (%)	D-VMP n (%)	Total n (%)
Analysis set: intent-to-treat	356	350	706
Total number of subjects with major protocol deviation	45 (12.6%)	36 (10.3%)	81 (11.5%)
Type of major protocol deviation			
Developed withdrawal criteria but not withdrawn	0	1 (0.3%)	1 (0.1%)
Efficacy assessment deviation	19 (5.3%)	6 (1.7%)	25 (3.5%)
Entered but did not satisfy criteria	6 (1.7%)	6 (1.7%)	12 (1.7%)
Received a disallowed concomitant treatment	11 (3.1%)	11 (3.1%)	22 (3.1%)
Received wrong treatment or incorrect dose	8 (2.2%)	9 (2.6%)	17 (2.4%)
Safety assessment deviation	6 (1.7%)	5 (1.4%)	11 (1.6%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.

In the D-VMP group, of the 6 subjects with efficacy assessment deviations, 5 received subsequent anticancer therapy before confirmation of disease progression, and 1 was missing an efficacy assessment prior to confirmation of disease progression. Eleven (11) subjects received a disallowed concomitant treatment (systemic corticosteroids >10mg prednisone per day or equivalent). Nine (9) subjects received the wrong treatment or incorrect dose. For 5 subjects, study treatment was not administered according to the protocol schedule (1 of these subjects also had a deviation for treatment modification during an adverse event); 2 additional subjects had a deviation for treatment not modified during an adverse event; 1 subject received an incorrect duration and volume of daratumumab infusion; 1 subject received an incorrect dose of bortezomib; and 1 subject received chlorambucil instead of melphalan). Six (6) subjects entered but did not satisfy criteria; 3 of these subjects had known chronic obstructive pulmonary disease or persistent asthma, 2 subjects had prior or current systemic therapy for multiple myeloma, and

1 subject had incomplete screening procedures. Safety assessment deviation was reported for 5 subjects, all with incomplete screening procedures. One subject developed withdrawal criteria, but did not discontinue from treatment.

In the VMP group, of the 19 subjects with efficacy assessment deviations, 16 received subsequent anticancer therapy before confirmation of disease progression (2 of these subjects also had a deviation for receiving systemic corticosteroids >10mg prednisone per day or equivalent), and 3 were missing an efficacy assessment prior to confirmation of disease progression. Eleven (11) subjects received a disallowed concomitant treatment, 10 received systemic corticosteroids >10 mg prednisone per day or equivalent, and 1 received a strong cyp3a4 inducer while using bortezomib. Eight (8) subjects received wrong treatment or incorrect dose. For 2 subjects, study treatment was not administered according to the protocol schedule, 4 subjects had a deviation for treatment not modified during an adverse event, 1 subject received an incorrect dose of bortezomib, and 1 subject received chlorambucil instead of melphalan. Six (6) subjects entered but did not satisfy criteria; 4 of these subjects did not have pre-treatment laboratory values meeting the protocol-specified criteria, 1 subject was not newly-diagnosed or a candidate for high-dose chemotherapy, and 1 subject had prior or current systemic therapy for multiple myeloma. A safety assessment deviation was reported for 6 subjects, all with incomplete screening procedures.

A per protocol analysis that removed subjects (6 subjects in the D-VMP group and 5 subjects in the VMP group) with deviations due to not meeting inclusion/exclusion from the ITT population was used as a

sensitivity analysis for PFS, and the results were consistent with the primary PFS analysis. Protocol deviations did not have a significant impact on the overall study results.

Baseline disease characteristics

Table 11: Summary of baseline disease characteristics – ITT

	VMP	D-VMP	Total
Analysis set: intent-to-treat	356	350	706
Type of myeloma by immunofixation or serum FLC assay, n (%)			
N	356	350	706
IgG	229 (64.3%)	224 (64.0%)	453 (64.2%)
IgA	82 (23.0%)	73 (20.9%)	155 (22.0%)
IgM	1 (0.3%)	1 (0.3%)	2 (0.3%)
IgD	2 (0.6%)	7 (2.0%)	9 (1.3%)
IgE	0	0	0
Light chain	33 (9.3%)	36 (10.3%)	69 (9.8%)
Kappa	17 (4.8%)	23 (6.6%)	40 (5.7%)
Lambda	16 (4.5%)	13 (3.7%)	29 (4.1%)
Biclonal	4 (1.1%)	5 (1.4%)	9 (1.3%)
Negative immunofixation	5 (1.4%)	4 (1.1%)	9 (1.3%)
Type of measurable disease [a], n (%)			
N	356	350	706
Serum only			
IgG	140 (39.3%)	143 (40.9%)	283 (40.1%)
IgA	53 (14.9%)	49 (14.0%)	102 (14.4%)
Other [b]	3 (0.8%)	6 (1.7%)	9 (1.3%)
Serum and urine	105 (29.5%)	91 (26.0%)	196 (27.8%)
Urine only	37 (10.4%)	43 (12.3%)	80 (11.3%)
Serum FLC	18 (5.1%)	18 (5.1%)	36 (5.1%)
ISS staging [c], n (%)			
N	356	350	706
I	67 (18.8%)	69 (19.7%)	136 (19.3%)
II	160 (44.9%)	139 (39.7%)	299 (42.4%)
III	129 (36.2%)	142 (40.6%)	271 (38.4%)
Time from MM diagnosis to randomization (months)			
N	356	350	706
Mean (SD)	1.27 (1.737)	1.09 (1.056)	1.18 (1.442)
Median	0.82	0.76	0.79
Range	(0.1; 25.3)	(0.1; 11.4)	(0.1; 25.3)
Number of lytic bone lesions, n (%)			
N	356	350	706
None	83 (23.3%)	71 (20.3%)	154 (21.8%)
1-3	79 (22.2%)	81 (23.1%)	160 (22.7%)
4-10	71 (19.9%)	64 (18.3%)	135 (19.1%)
More than 10	123 (34.6%)	134 (38.3%)	257 (36.4%)
Presence of diffuse myeloma-related osteopenia, n (%)			
N	356	349	705
Yes	160 (44.9%)	177 (50.7%)	337 (47.8%)
No	196 (55.1%)	172 (49.3%)	368 (52.2%)
Number of extramedullary plasmacytomas, n (%)			
N	356	350	706
0	336 (94.4%)	334 (95.4%)	670 (94.9%)
≥1	20 (5.6%)	16 (4.6%)	36 (5.1%)

Presence of evaluable bone marrow assessment, n (%)			
N	356	350	706
Yes	356 (100.0%)	350 (100.0%)	706 (100.0%)
No	0	0	0
% Plasma cells, bone marrow biopsy/aspirate, n (%)			
N	356	350	706
<10	3 (0.8%)	13 (3.7%)	16 (2.3%)
10-30	140 (39.3%)	126 (36.0%)	266 (37.7%)
>30	213 (59.8%)	211 (60.3%)	424 (60.1%)
% Plasma cells, bone marrow biopsy, n (%)			
N	158	147	305
<10	4 (2.5%)	5 (3.4%)	9 (3.0%)
10-30	43 (27.2%)	35 (23.8%)	78 (25.6%)
>30	111 (70.3%)	107 (72.8%)	218 (71.5%)
% Plasma cells, bone marrow aspirate, n (%)			
N	318	326	644
<10	13 (4.1%)	21 (6.4%)	34 (5.3%)
10-30	157 (49.4%)	146 (44.8%)	303 (47.0%)
>30	148 (46.5%)	159 (48.8%)	307 (47.7%)
Cytogenetic risk [d], n (%)			
N	302	314	616
Standard risk	257 (85.1%)	261 (83.1%)	518 (84.1%)
High risk[e]	45 (14.9%)	53 (16.9%)	98 (15.9%)
del(17p)	27 (8.9%)	29 (9.2%)	56 (9.1%)
t(4;14)	17 (5.6%)	25 (8.0%)	42 (6.8%)
t(14;16)	6 (2.0%)	6 (1.9%)	12 (1.9%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: FLC = free light chain; ISS = International Staging System; MM = multiple myeloma; NE = not evaluable.
[a] Includes subjects without measurable disease in serum and urine.
[b] Includes IgD, IgM, IgE and biclonal.
[c] ISS staging is derived based on the combination of serum β2-microglobulin and albumin.
[d] Cytogenetic risk is based on FISH or karyotype testing.
[e] Subject may have had at least one high-risk abnormality [del17p, t(4;14) or t(14;16)].

Table 12: Summary of IMWG revised ISS staging in MM – ITT

	VMP n (%)	D-VMP n (%)
Analysis set: intent-to-treat	356	350
IMWG Revised ISS Staging[a]		
N	331	333
I	38 (11.5%)	47 (14.1%)
II	247 (74.6%)	226 (67.9%)
III	46 (13.9%)	60 (18.0%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: IMWG=International Myeloma Working Group; ISS=International Staging System.
[a] Determination is based on three factors: International Staging System (ISS); presence of chromosomal abnormalities of t(4; 14), t(14; 16), or del17p by FISH or Karyotype testing and serum lactate dehydrogenase (LDH) at baseline.

Numbers analysed

Table 13: Subjects per analysis set

	VMP n	D-VMP n	Total n
Study population			
Subjects screened			887
Intent-to-treat (ITT)	356	350	706
Safety	354	346	700
Per-protocol[a] (PP)	351	344	695
Response-evaluable[b]	341	337	678
Pharmacokinetic evaluable[c]	-	342	342
Immunogenicity evaluable[d]	-	113	113

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
[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 D-VMP 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 D-VMP group who have at least 1 immunogenicity sample obtained after their first daratumumab administration.

Outcomes and estimation

Primary endpoint: PFS

Table 14: PFS based on computerised algorithm: ITT

	VMP	D-VMP
Analysis set: intent-to-treat	356	350
Progression-free survival (PFS)		
Number of events (%)	143 (40.2%)	88 (25.1%)
Number of censored (%)	213 (59.8%)	262 (74.9%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	12.98 (9.92, 13.83)	16.36 (14.52, 18.23)
Median (95% CI)	18.14 (16.53, 19.91)	NE (NE, NE)
75% quantile (95% CI)	NE (22.67, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.50 (0.38, 0.65)
12-month PFS rate % (95% CI)	76.0 (71.0, 80.2)	86.7 (82.6, 89.9)
18-month PFS rate % (95% CI)	50.2 (43.2, 56.7)	71.6 (65.5, 76.8)
24-month PFS rate % (95% CI)	30.9 (18.4, 44.3)	61.7 (53.3, 69.1)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test stratified with ISS staging (I, II, III), region (Europe 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 (Europe vs. Other), and age (<75 years vs. ≥75 years) as randomized. A hazard ratio <1 indicates an advantage for D-VMP.

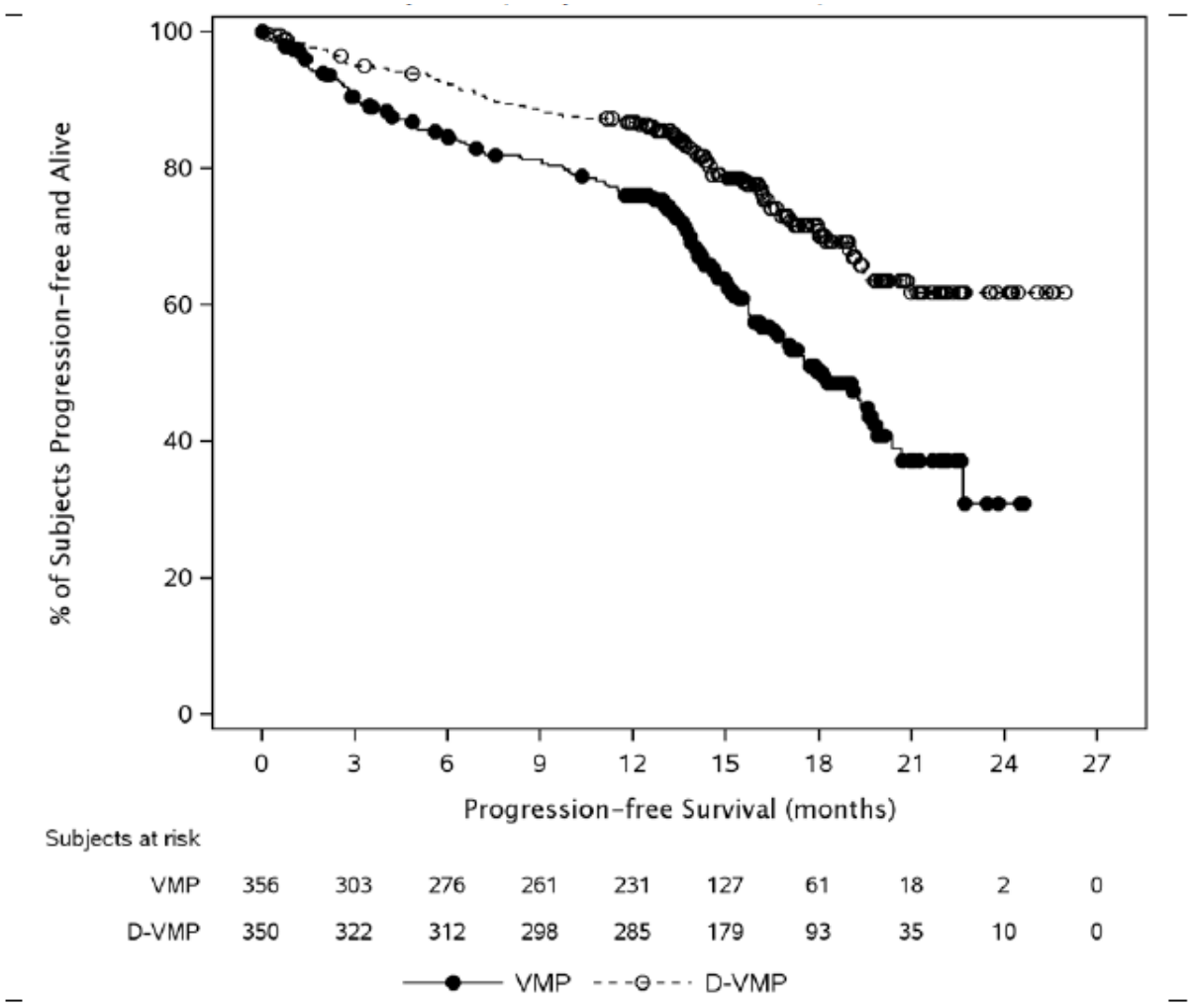


Figure 8: Kaplan-Meier plot for PFS - ITT

Table 15: Summary of reasons for Censoring PFS

	VMP n (%)	D-VMP n (%)
Analysis set: intent-to-treat	356	350
Subjects censored	213 (59.8%)	262 (74.9%)
Reason for censoring[a]		
Study cut-off	174 (81.7%)	246 (93.9%)
Subsequent antimyeloma therapy	17 (8.0%)	5 (1.9%)
Randomized but not treated	2 (0.9%)	4 (1.5%)
Withdrawal of consent to study participation	9 (4.2%)	4 (1.5%)
Subject refusal of further disease assessment or not compliant with disease assessment schedule after treatment discontinuation	8 (3.8%)	3 (1.1%)
Lost to follow-up	2 (0.9%)	0
Physician decision	1 (0.5%)	0
Subjects with progression-free survival event	143 (40.2%)	88 (25.1%)
Subjects with progressive disease[b,c]	118 (82.5%)	63 (71.6%)
Reason for progressive disease[f]		
Serum M-protein	84 (71.2%)	43 (68.3%)
Urine M-protein	17 (14.4%)	6 (9.5%)
Serum FLC[d]	6 (5.1%)	1 (1.6%)
Bone lesion (increase in size)	6 (5.1%)	4 (6.3%)
Bone lesion (new bone lesion)	6 (5.1%)	4 (6.3%)
Plasmacytomas (increase in size)	2 (1.7%)	3 (4.8%)
Plasmacytomas (new plasmacytomas)	4 (3.4%)	11 (17.5%)
Hypercalcemia	0	0
Subjects died without progressive disease[e]	25 (17.5%)	25 (28.4%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
[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.
Note: Subjects in "Study cut-off" category are still at risk.

Secondary endpoints: ORR, VGPR and CR

Table 16: Summary of overall best confirmed response - ITT

	VMP		D-VMP			
	n (%)	95% CI for %	n (%)	95% CI for %	Odds Ratio (95% CI)[a]	P-value[b]
Analysis set: intent-to-treat	356		350			
Response category						
Stringent complete response (sCR)	25 (7.0%)	(4.6%, 10.2%)	63 (18.0%)	(14.1%, 22.4%)		
Complete response (CR)	62 (17.4%)	(13.6%, 21.8%)	86 (24.6%)	(20.2%, 29.4%)		
Very good partial response (VGPR)	90 (25.3%)	(20.8%, 30.1%)	100 (28.6%)	(23.9%, 33.6%)		
Partial response (PR)	86 (24.2%)	(19.8%, 28.9%)	69 (19.7%)	(15.7%, 24.3%)		
Stable disease (SD)	76 (21.3%)	(17.2%, 26.0%)	20 (5.7%)	(3.5%, 8.7%)		
Progressive disease (PD)	2 (0.6%)	(0.1%, 2.0%)	0	(NE, NE)		
Not evaluable (NE)	15 (4.2%)	(2.4%, 6.9%)	12 (3.4%)	(1.8%, 5.9%)		
Overall response (sCR+CR+VGPR+PR)	263 (73.9%)	(69.0%, 78.4%)	318 (90.9%)	(87.3%, 93.7%)	3.55 (2.30, 5.49)	<0.0001
VGPR or better (sCR + CR + VGPR)	177 (49.7%)	(44.4%, 55.0%)	249 (71.1%)	(66.1%, 75.8%)	2.50 (1.83, 3.41)	<0.0001
CR or better (sCR + CR)	87 (24.4%)	(20.1%, 29.2%)	149 (42.6%)	(37.3%, 47.9%)	2.31 (1.67, 3.20)	<0.0001

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: CI = confidence interval.
[a] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: ISS staging (I, II, III), region (Europe vs. Other), and age (<75 years vs. ≥75 years) as randomized. An odds ratio > 1 indicates an advantage for D-VMP.
[b] P-value from the Cochran Mantel-Haenszel Chi-Squared test.
Note: Response was assessed by computerized algorithm, based on International Uniform Response Criteria Consensus Recommendations.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Table 17: summary of best confirmed response within 12 months and Overall (ITT)

	VMP		D-VMP	
	Within 12 months[a]	Overall	Within 12 months[a]	Overall
Analysis set: intent-to-treat		356		350
Response category				
Overall response (sCR+CR+VGPR+PR)	262 (73.6%)	263 (73.9%)	314 (89.7%)	318 (90.9%)
VGPR or better (sCR + CR + VGPR)	176 (49.4%)	177 (49.7%)	245 (70.0%)	249 (71.1%)
CR or better (sCR + CR)	74 (20.8%)	87 (24.4%)	119 (34.0%)	149 (42.6%)

Key: VMP = bortezomib-melphalan-prednisone; D-VMP = daratumumab-bortezomib-melphalan-prednisone.
[a] Best response within 12 months from the date of first dose of study treatment or randomization.
Note: Response was assessed by computerized algorithm, based on International Uniform Response Criteria Consensus Recommendations.

Table 18: Summary of Overall best confirmed response based on Investigator's assessment in ITT

	VMP		D-VMP			
	n (%)	95% CI for %	n (%)	95% CI for %	Odds Ratio (95% CI)[a]	P-value[b]
Analysis set: intent-to-treat	356		350			
Response category						
Stringent complete response (sCR)	33 (9.3%)	(6.5%, 12.8%)	71 (20.3%)	(16.2%, 24.9%)		
Complete response (CR)	54 (15.2%)	(11.6%, 19.3%)	74 (21.1%)	(17.0%, 25.8%)		
Very good partial response (VGPR)	84 (23.6%)	(19.3%, 28.4%)	104 (29.7%)	(25.0%, 34.8%)		
Partial response (PR)	97 (27.2%)	(22.7%, 32.2%)	69 (19.7%)	(15.7%, 24.3%)		
Stable disease (SD)	71 (19.9%)	(15.9%, 24.5%)	19 (5.4%)	(3.3%, 8.3%)		
Progressive disease (PD)	2 (0.6%)	(0.1%, 2.0%)	0	(NE, NE)		
Not evaluable (NE)	15 (4.2%)	(2.4%, 6.9%)	13 (3.7%)	(2.0%, 6.3%)		
Overall response (sCR+CR+VGPR+PR)	268 (75.3%)	(70.5%, 79.7%)	318 (90.9%)	(87.3%, 93.7%)	3.33 (2.14, 5.18)	<0.0001
VGPR or better (sCR + CR + VGPR)	171 (48.0%)	(42.7%, 53.4%)	249 (71.1%)	(66.1%, 75.8%)	2.67 (1.95, 3.64)	<0.0001
CR or better (sCR + CR)	87 (24.4%)	(20.1%, 29.2%)	145 (41.4%)	(36.2%, 46.8%)	2.20 (1.59, 3.04)	<0.0001

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: CI = confidence interval.
[a] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: ISS staging (I, II, III), region (Europe vs. Other), and age (<75 years vs. ≥75 years) as randomized. An odds ratio > 1 indicates an advantage for D-VMP.
[b] P-value from the Cochran Mantel-Haenszel Chi-Squared test.
Note: Response was assessed by investigators, based on International Uniform Response Criteria Consensus Recommendations.

Secondary endpoint: MRD

Table 19: Summary of MRD negativity rate at 10-5 in bone marrow; ITT

	VMP	D-VMP
Analysis set: intent-to-treat	356	350
MRD negativity rate (10^{-5})	22 (6.2%)	78 (22.3%)
95% CI[a] of MRD negativity rate	(3.9%, 9.2%)	(18.0%, 27.0%)
Odds ratio with 95% CI[b]		4.36 (2.64, 7.21)
P-value[c]		<0.0001

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: CI = confidence interval.
[a] Exact 95% confidence interval.
[b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors are: ISS staging (I, II, III), region (Europe vs. Other), and age (<75 years vs. ≥75 years) as randomized. An odds ratio > 1 indicates an advantage for D-VMP.
[c] P-value from Fisher's exact test.
Note: MRD negativity status is based on post-randomization assessment.

Secondary endpoint: OS

With a median overall follow-up of 16.5 months, the OS data were not yet mature.

Table 20: Summary of OS - ITT

	VMP	D-VMP
Analysis set: intent-to-treat	356	350
Overall survival		
Number of events (%)	48 (13.5%)	45 (12.9%)
Number of censored (%)	308 (86.5%)	305 (87.1%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	NE (19.68, NE)	NE (20.30, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		0.6691
Hazard ratio (95% CI)[b]		0.92 (0.61, 1.37)
12-month survival rate % (95% CI)	91.1 (87.6, 93.6)	93.0 (89.8, 95.3)
24-month survival rate % (95% CI)	79.8 (72.5, 85.3)	80.1 (72.7, 85.6)
36-month survival rate % (95% CI)	NE (NE, NE)	NE (NE, NE)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: 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 D-VMP.

Secondary endpoint: PFS2

Similar to OS, PFS2 data were not yet mature. Forty-four subjects (13%) in the D-VMP group and 50 subjects (14%) in the VMP group had a PFS2 event. The HR for this PFS2 analysis was 0.82 (95% CI: 0.55, 1.24; p=0.3510).

Table 21: Summary of PFS2

TEFPFS2A: Summary of Progression-free Survival on Next Line of Therapy (PFS2 Un-stratified) Based on Investigator Assessment; Intent-to-treat Analysis Set (Study 54767414MMY3007)		
	VMP	D-VMP
Analysis set: intent-to-treat	356	350
Progression-free survival on next line of therapy (PFS2)		
Number of events (%)	50 (14.0%)	44 (12.6%)
Number of censored (%)	306 (86.0%)	306 (87.4%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	NE (19.42, NE)	NE (20.30, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		0.3510
Hazard ratio (95% CI)[b]		0.82 (0.55, 1.24)
12-month PFS2 rate % (95% CI)	89.2 (85.4, 92.1)	92.6 (89.3, 95.0)
18-month PFS2 rate % (95% CI)	85.0 (80.2, 88.7)	86.4 (81.4, 90.1)
24-month PFS2 rate % (95% CI)	79.4 (72.4, 84.8)	75.3 (61.1, 84.9)

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

[TEFPFS2A.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TEFPFS2A.SAS] 28AUG2017, 05:59

Secondary endpoint: Time to disease progression (TTP)

Table 22: Summary of TTP

TEFTTP01: Summary of Time to Disease Progression Based on Computerized Algorithm; Intent-to-treat Analysis Set (Study 54767414MMY3007)		
	VMP	D-VMP
Analysis set: intent-to-treat	356	350
Time to disease progression		
Number of events (%)	120 (33.7%)	63 (18.0%)
Number of censored (%)	236 (66.3%)	287 (82.0%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	13.77 (12.68, 14.55)	18.99 (16.39, NE)
Median (95% CI)	19.35 (17.38, 22.67)	NE (NE, NE)
75% quantile (95% CI)	NE (22.67, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.41 (0.30, 0.56)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test stratified with ISS staging (I, II, III), region (Europe 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 (Europe vs. Other), and age (<75 years vs. ≥75 years) as randomized. A hazard ratio < 1 indicates an advantage for D-VMP.

[TEFTTP01.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TEFTTP01.SAS] 28AUG2017, 04:34

Secondary endpoint: Time to response (TTR)

Table 23: Descriptive summary of TTR

	VMP	D-VMP
Analysis set: responders (PR or better) in response-evaluable analysis set	263	318
Time to first response[a] (months)		
N	263	318
Mean (SD)	1.73 (1.884)	1.46 (1.936)
Median	0.82	0.79
Range	(0.7; 12.6)	(0.4; 15.5)
Time to VGPR or better (months)		
N	177	249
Mean (SD)	3.55 (2.871)	3.43 (3.004)
Median	2.83	2.20
Range	(0.7; 12.6)	(0.7; 19.2)
Time to CR or better (months)		
N	87	149
Mean (SD)	8.09 (3.920)	8.49 (4.047)
Median	7.46	8.31
Range	(0.7; 20.5)	(1.9; 21.0)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
[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.

Secondary endpoint: DOR

Table 24: Summary of DOR; Responders (PR or better) in response- evaluable Analysis set

	VMP	D-VMP
Analysis set: responders (PR or better) in response-evaluable analysis set	263	318
Duration of response		
Number of events (%)	71 (27.0%)	56 (17.6%)
Number of censored (%)	192 (73.0%)	262 (82.4%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	14.1 (12.5, 15.9)	18.4 (16.4, NE)
Median (95% CI)	21.3 (18.4, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: CI = confidence interval; PR = Partial response; NE = Not estimable.
Note: Number of events refers to number of responders (PR or better) who developed disease progression or died due to disease progression.
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.

Secondary endpoint: Time to next treatment (TTNT)

Table 25: Summary of time to subsequent treatment anti-myeloma therapy; ITT

	VMP	D-VMP
Analysis set: intent-to-treat	356	350
Time to subsequent anti-myeloma treatment		
Number of events (%)	93 (26.1%)	50 (14.3%)
Number of censored (%)	263 (73.9%)	300 (85.7%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	16.2 (14.1, 17.6)	20.8 (19.4, NE)
Median (95% CI)	NE (21.4, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.48 (0.34, 0.67)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test stratified with ISS staging (I, II, III), region (Europe 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 (Europe vs. Other), and age (<75 years vs. ≥75 years) as randomized. A hazard ratio < 1 indicates an advantage for D-VMP.
Note: Number of events refers to number of subjects who started subsequent antimyeloma therapy or died due to progressive disease, whichever occurs first.

Secondary endpoint: HRQoL

Compliance with EORTC QLQ-C30 and EQ-5D-5L assessments was comparable between treatment groups. The compliance rates at baseline were 90% and 90% in the D-VMP group and 91% and 92% in the VMP group, for the EQ-5D-5L and EORTC QLQ-C30, respectively. Through month 12, compliance was greater than 70% for the EQ-5D-5L and EORTC QLQ-C30 in both the D-VMP and VMP groups. It should be noted that 6 subjects were randomized and not treated (4 in D-VMP group and 2 in VMP group) and therefore did not contribute PRO data.

The functional status and well-being results from patient reported outcome (PRO) endpoints, including the cancer-specific EORTC-QLQ-C30 and the general health EQ-5D-5L, indicated that improvements in health-related quality of life in subjects who remained in the study in both the D-VMP and VMP groups were maintained.

EORTC-QLQ-C30

Global Health Status Subscale

Baseline scores on the Global Health Status (GHS) subscale were comparable between treatment groups. There was a statistically significant difference in the mean change from baseline at Month 3 for the EORTC QLQ-C30 GHS, in favor of D-VMP treatment (LS mean change; VMP: 4.1 [95% CI: 1.8, 6.5], D-VMP: 7.6 [95% CI: 5.3, 9.8]; [p=0.0265]), though no adjustment was made for multiplicity. There were no statistically significant differences in least square mean changes from baseline between the VMP and D-VMP groups for month 6 through month 18; HRQOL improvements were comparable between treatment groups.

The median time to improvement was 3.06 months for the D-VMP group and 3.75 months for the VMP group) for the GHS subscale. While there was no statistically significant difference in the GHS subscale median time to worsening between treatment groups, there was a 4.8-month difference with a longer time to worsening with D-VMP treatment (23.56 months for the D-VMP group and 18.76 months for the VMP group; HR=0.80 (95%CI: 0.60, 1.08) [p=0.1438]).

Functional and Symptom Subscales

The other subscales of the EORTC-QLQ-C30 included: functional scales (physical, role, cognitive, emotional, and social), symptom scales (fatigue, pain, and nausea and vomiting) and single-item symptom scores for the following: dyspnea, loss of appetite, sleep disturbance, constipation, diarrhea, and financial difficulties. Baseline scores on all subscales were comparable between treatment groups. For the functional scales (physical, role, cognitive, emotional, and social), and symptom scales (fatigue, pain, and nausea and vomiting), least square mean changes from baseline were not statistically significant different between treatment groups.

EQ-5D-5L

Baseline scores on the EQ-5D-5L utility score and EQ-5D-5L VAS were comparable between treatment groups. There was a statistically significant difference in the mean change from baseline at Month 3 for the EQ-5D-5L VAS, in favor of D-VMP treatment (LS mean change; VMP: 3.7 [95% CI: 1.7, 5.7], D-VMP: 6.8 [95% CI: 4.9, 8.7]; [p=0.0151]) though no adjustment was made for multiplicity. No statistically significant differences between treatment groups were observed in least square mean changes from baseline for the EQ-5D-5L utility value; utility improvement was comparable over the treatment period. For the median time to improvement, the utility value median was 2.89 months for the D-VMP group and 2.99 months for the VMP group, and the VAS median was 2.96 months for the D-VMP group and 4.19 months for the VMP group. Median time to worsening in utility and VAS scores was not evaluable at the clinical cutoff of 16.5 months.

Ancillary analyses

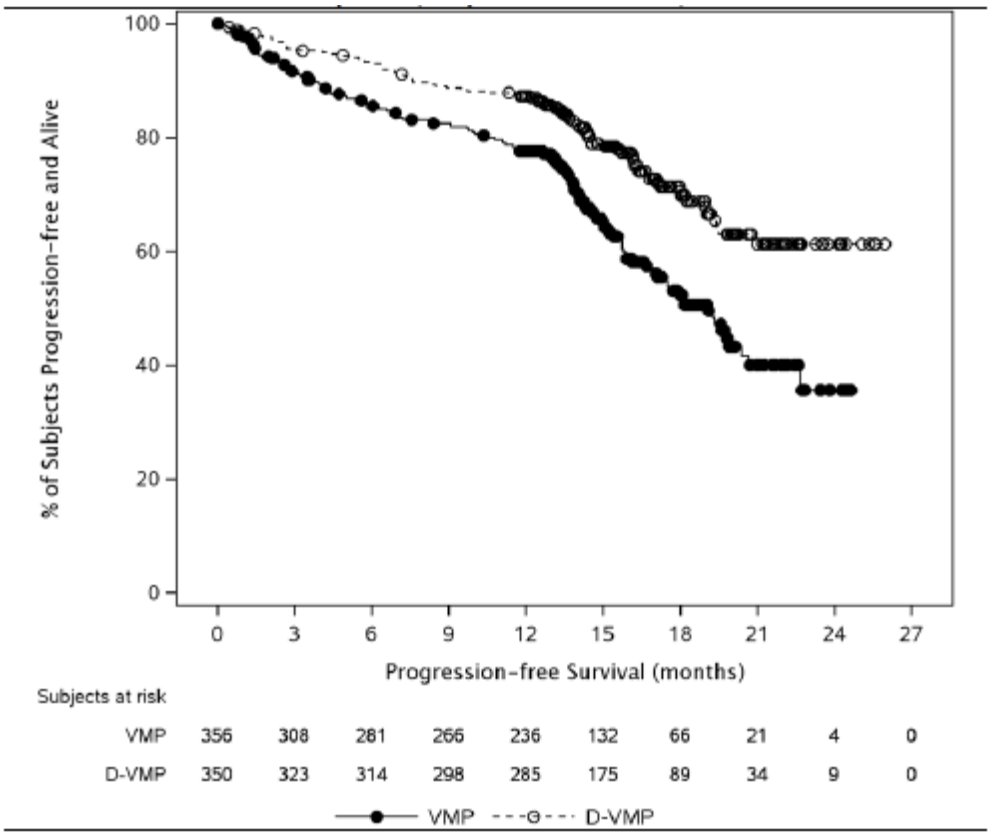
Sensitivity analysis of PFS by INV

A sensitivity analysis using disease progression assessed by the investigator showed consistency with the primary results. By investigator assessment, 88 subjects (25%) in the D-VMP group and 137 subjects (39%) in the VMP group progressed or died. As seen in the primary analysis, there was a statistically significant improvement in PFS for subjects in the D-VMP group compared with VMP group (HR=0.53; 95% CI: 0.40, 0.69; p<0.0001). Reasons for censoring of data from the investigator assessment were also consistent with that in the primary analysis.

Table 26: Summary of PFS based on investigator's assessment; ITT

	VMP	D-VMP
Analysis set: intent-to-treat	356	350
Progression-free survival (PFS)		
Number of events (%)	137 (38.5%)	88 (25.1%)
Number of censored (%)	219 (61.5%)	262 (74.9%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	13.37 (10.81, 13.90)	16.36 (14.52, 18.23)
Median (95% CI)	19.12 (16.85, 20.37)	NE (NE, NE)
75% quantile (95% CI)	NE (22.67, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.53 (0.40, 0.69)
12-month PFS rate % (95% CI)	77.5 (72.6, 81.6)	87.3 (83.2, 90.4)
18-month PFS rate % (95% CI)	52.3 (45.3, 58.8)	71.4 (65.2, 76.6)
24-month PFS rate % (95% CI)	35.5 (24.5, 46.7)	61.3 (52.7, 68.7)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: CI = confidence interval.
[a] p-value is based on the log-rank test stratified with ISS staging (I, II, III), region (Europe 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 (Europe vs. Other), and age (<75 years vs. ≥75 years) as randomized. A hazard ratio <1 indicates an advantage for D-VMP.



Key: VMP=bortezomib-melphalan-prednisone;
D-VMP=daratumumab-bortezomib-melphalan-prednisone.

Figure 9: K-M plot for PFS based on investigator's assessment; ITT

Table 27: summary of reasons for censoring of PFS based on investigator assessment; ITT

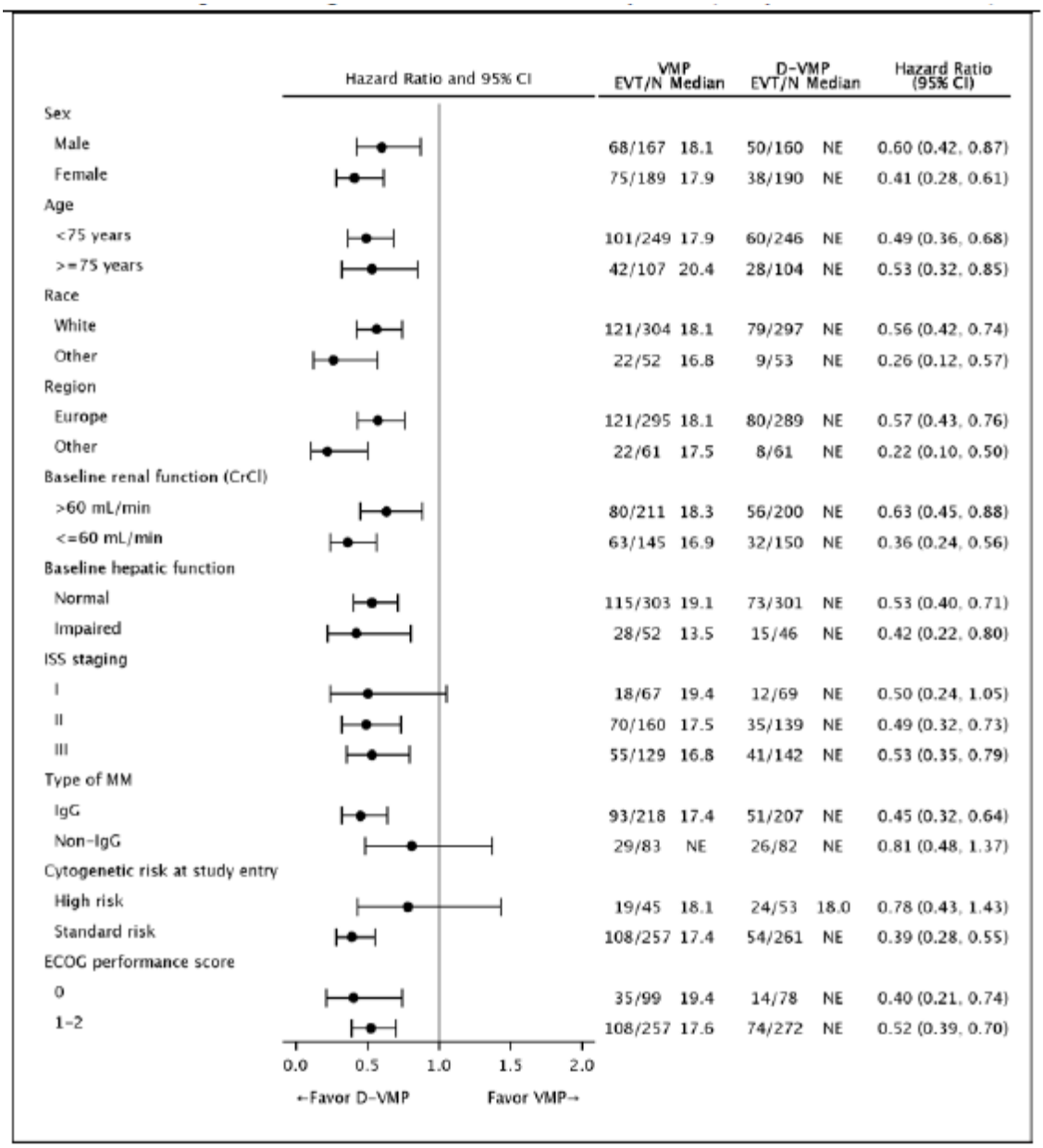
	VMP n (%)	D-VMP n (%)
Analysis set: intent-to-treat	356	350
Subjects censored	219 (61.5%)	262 (74.9%)
Reason for censoring[a]		
Study cut-off	180 (82.2%)	246 (93.9%)
Subsequent antimyeloma therapy	16 (7.3%)	5 (1.9%)
Randomized but not treated	2 (0.9%)	4 (1.5%)
Withdrawal of consent to study participation	10 (4.6%)	4 (1.5%)
Subject refusal of further disease assessment or not compliant with disease assessment schedule after treatment discontinuation	8 (3.7%)	3 (1.1%)
Lost to follow-up	2 (0.9%)	0
Physician decision	1 (0.5%)	0
Subjects with progression-free survival event	137 (38.5%)	88 (25.1%)
Subjects with progressive disease[b,c]	112 (81.8%)	63 (71.6%)
Reason for progressive disease[f]		
Serum M-protein	80 (71.4%)	41 (65.1%)
Urine M-protein	15 (13.4%)	5 (7.9%)
Serum FLC[d]	4 (3.6%)	1 (1.6%)
Bone marrow plasma cell	0	0
Bone lesion (increase in size)	6 (5.4%)	3 (4.8%)
Bone lesion (new bone lesion)	4 (3.6%)	3 (4.8%)
Plasmacytomas (increase in size)	3 (2.7%)	2 (3.2%)
Plasmacytomas (new plasmacytomas)	5 (4.5%)	12 (19.0%)
Hypercalcemia	1 (0.9%)	0
Subjects died without progressive disease[e]	25 (18.2%)	25 (28.4%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
[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.
Note: Subjects in "Study cut-off" category are still at risk.
[TEFRFPD02.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TEFRFPD02.SAS] 29AUG2017, 10:22

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 unstratified PFS analysis, all showed results consistent with the primary analysis.

Subgroups analysis of PFS



Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Impaired baseline hepatic function includes mild (total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5×ULN); moderate (1.5×ULN < total bilirubin ≤ 3×ULN); and severe (total bilirubin > 3×ULN).
High risk cytogenetics is defined as: 1) by FISH testing: t (4; 14), t (14; 16), and 17p deletion; or 2) by Karyotype testing: t (4; 14), 17p deletion.
Note: Type of MM subgroup analysis is based on subjects with measurable disease in serum.

Figure 10: Forest plot of subgroup analyses of PFS; ITT

Outcomes and estimation

Summary of main study(ies)

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

Table 28: Summary of Efficacy for trial MMY3007

Title: Open-label, Multi-center, randomized Study of Darzalex (daratumumab) in combination with bortezomib, melphalan and prednisone (D-VMP) versus VMP alone, for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant			
Study identifier	MMY3007		
Design	Phase 3, open-label, multi-center, randomised trial		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		approx. 2.5 years, study initiation date 26 jan 2015, data cut off 12 june 2017, ongoing.
Hypothesis	Superiority		
Treatments groups	D-VMP		Daratumumab 16 mg/kg IV, Q week for 6 weeks (C 1), Q 3 weeks (C 2-9, 6 weeks cycles), Q 4 weeks (C 10 -, 4 weeks cycles) until PD or unacceptable toxicity. VMP
	VMP		VMP: subjects in both treatment groups. Bortezomib sc, 1.3 mg/m^2 x2 weekly (W 1,2,4 and 5) in C1, x1 weekly (W 1,2,4 and5) in C 2-9. Melphalan po, 9mg/m^2 day 1-4 of each bortezomib cycle. Prednisone po 60 mg/ m^2 day 1-4 of each bortezomib cycle.
Endpoints and definitions	Primary endpoint	PFS	Progression free survival, defined as the duration from the date of randomization to either progressive disease, according to IMWG response criteria, or death, whichever occurs first.
	ORR	Overall response rate	Proportion of subjects who achieve a PR or better (ie., PR, VGPR, CR or sCR), based on computerized algorithm, according to IMWG
	CR or better	CR and sCR	Proportion of subjects with a response of CR or better, based on computerized algorithm, according to IMWG
Database	12 june 2017		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	<Intent to treat>		
Descriptive Statistics and estimate variability	Treatment group	D-VMP	VMP
	Number of subject	350	356
	PFS, months	NE	18.14

	95% CI		(16.53 , 19.91)	NE
	ORR	90.9%	73.9%	
		(87.3,93.7)	(69,78.4)	
	CR or better (CR + sCR)	42.6% /37.3, 47.9)	24.4% (20.1,29.2)	

Effect estimate per comparison	Primary endpoint PFS	Comparison groups	D-VMP vs. VMP
		Hazard ratio (HR)	0.50
		95% CI	(0.38, 0.65)
		P-value	<0.0001
		Odds ratio	3.33
		95% CI	(2.14,5.18)
		P-value	<0.0001
	Secondary endpoint: CR or better	Comparison groups	D-VMP vs. VMP
		Odds ratio	2.31
		95% CI	(1.67, 3.2)
		P-value	<0.0001

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

Not applicable

Clinical studies in special populations

Specific clinical studies in special populations were not submitted.

Supportive study(ies)

The MAH has provided data from additional 12 patients from a phase 1 study (not shown here). These data are considered too limited to provide any added value and were not considered for this assessment.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH has provided one pivotal phase 3 study, MMY3007, and one small phase 1b supportive study to support the proposed new indication. The pivotal study is a randomised, multicentre and international study, including approximately 700 patients. The incl/excl. criteria define a newly diagnosed MM population that are ineligible for ASCT. The proposed new indication reflects these criteria. The majority of the patients have IgG myeloma, ISS stage II, and no extramedullary plasmacytomas.

Patients were randomised 1:1 to VMP or D+VMP, and patients randomised to D+VMP will continue Dara Q 4wks post-VMP until PD, unacceptable toxicity, or study end.

The objectives are clearly described. The primary objective is to compare efficacy in terms of PFS between VMP and D-VMP.

The MAH has applied few and clinically meaningful stratification factors. With regard to sample size; the power and alpha are as to be expected for a phase III study. With regard to statistics, two interim analyses (IA's) were planned for the primary endpoint. The first IA was planned in order to assess safety. The second IA was planned when approximately 60% of PFS events had occurred. The MAH has applied an alpha spending function to control the alpha, which is agreed. The MAH has applied a hierarchical testing for the testing of secondary endpoints. This is also acknowledged.

In Study MMY3007, daratumumab was administered at 16 mg/kg as per the daratumumab prescribing information, but the dosing schedule was modified to match the 6-week cycle length for VMP: 16 mg/kg IV weekly for 6 weeks, then every 3 weeks for 48 weeks (Cycle 2 to 9), and then every 4 weeks thereafter (post-VMP Treatment Phase) until documented progression, unacceptable toxicity, or study end. CD38, the target for daratumumab, is expressed on NK cells and clinical data has shown NK cell suppression to be a marker of target drug activity. Clinical pharmacokinetic data have shown the 16 mg/kg dose to be the lowest dose that results in nearly complete target suppression at all time points. This dose and schedule continuously suppressed NK cells throughout dosing.

The baseline demographics are overall well-balanced between the two treatment arms. The majority of patient are white, with a median age of 71 years. However, there were 12 more patients below 65 years in the D-VMP arm, while there were slightly more patients above 65 in the VMP arm. The medical history of patients < 65 years was analysed, showing 53% in the D-VMP arm having an ECOG PS score of 2 vs. 33% in the VMP arm. Those with PS score of 1 had medical comorbidities such as cardiac, respiratory, central nervous disorders or others rendering them transplant-ineligible.

Overall, the pivotal study is well conducted.

Efficacy data and additional analyses

The study met its primary endpoint at the planned second interim analysis showing both a statistically significant and clinically highly relevant difference in terms of PFS. The MAH updated data with clinical cut off of 12 October 2017, approximately 4 months after the primary cut-off. The median PFS for the updated data was 19.29 months in the VMP group vs. not reached in D-VMP group (HR=0.46; 95% CI: 0.36, 0.60; p<0.0001) compared to 18.14 in the VMP arm and not yet reached in the D-VMP arm (HR=0.50; 95% CI: 0.38, 0.65; p< 0.0001) in the original analyses. Thus, updated data were consistent with the primary analyses. OS data are still not yet mature. It is noted, that 16% had a high-risk cytogenetic abnormality, ie. the results may be biased by relatively few high-risk patients. The risk of disease progression is reduced by 54%. The updated data are reflected in the SmPC section 5.1.

Re-randomization was not performed by start of the maintenance treatment phase with daratumumab monotherapy. However, the CHMP (SAWP) accepted the proposed study design. Nonetheless, it is not possible to disentangle the effect of the maintenance therapy with daratumumab monotherapy from the combination treatment. This also in view of the apparent dropping of the PFS curves after stopping of the VMP combination. Data regarding durability of MRD would be able to give some insights on this issue. However, there is limited data on durability of MRD negativity, only few patients had MRD assessments performed. MRD analysis using other thresholds (10-4 and 10-6) showed similar results, which from a clinical perspective is encouraging. In order to further substantiate the contribution of daratumumab maintenance therapy, the MAH has analysed PFS for the first 12 months on treatment and after 12 months. Median PFS was only reached for the VMP arm after 12 months. Although data were not mature, PFS was consistent both before and after 12 months, (HR=0.51; 95% CI: 0.35, 0.74; and HR=0.48; 95% CI: 0.33, 0.71 respectively), in favour of the D-VMP arm. Despite small numbers, more patients in the D-VMP arm compared with the VMP arm achieved CR or better (9% vs. 4%).

With regard to the secondary endpoints ORR, VGPR and CR, they are all in line with the primary endpoint, showing statistically highly significant differences in favour of Dara. There is almost a doubling in CR or better (24.4% vs. 42.6%), which is relevant from a clinical perspective. The ORR is 90.9% in the D-VMP arm compared with 73.9% in the VMP arm. The effect of D-VMP was observed during the first 12 months with a CR rate of 34% and 21% respectively for the D-VMP and the VMP group. Overall, these results show an added benefit of Dara in combination with VMP in newly diagnosed patients with multiple myeloma, who are ineligible for autologous stem cell transplant. The MRD negativity rate is 22.3% vs. 6.2% in the D-VMP and VMP arms respectively, demonstrating a deep effect of D-VMP as compared with VMP in Multiple Myeloma.

It is not possible to disentangle the effect of the maintenance therapy with daratumumab monotherapy from the combination treatment. This also in view of the apparent dropping of the PFS curves after stopping of the VMP combination. The data on durability of MRD negativity are limited, only few patients had MRD assessments performed, but initial data showed a positive effect in the D-VMP arm, which from a clinical perspective is encouraging. In order to further substantiate the contribution of daratumumab maintenance therapy, the MAH has analysed PFS for the first 12 months on treatment and after 12 months. Median PFS was only reached for the VMP arm after 12 months. Although data were not mature, PFS was consistent both before and after 12 months, (HR=0.51; 95% CI: 0.35, 0.74; and HR=0.48; 95% CI: 0.33, 0.71 respectively), in favour of the D-VMP arm. Despite small numbers, more patients in the D-VMP arm compared with the VMP arm achieved CR or better (9% vs. 4%).

The other secondary endpoints, OS, PFS2, TTP, DOR, and TTNT are all in line with the primary endpoint, but data are immature. OS data are not expected to be mature for the time being. The MAH has committed to provide updated data post-approval. For the remaining secondary endpoint, the updated data were consistent with the primary analyses. Final Clinical Study Report will be provided post – approval. The MAH will also provide the updated analyses of biomarkers predictive of response and resistance to therapy post-approval. These analyses will be performed after the study is unblinded and correlated with clinical responses.

There is an unmet need in patients that are ineligible for ASCT. These patients have different options for treatment, and one of the options is VMP. However, regardless of treatment regimen, the patients will relapse. Thus, there is an unmet medical need and prolongation of PFS is clinically meaningful, both from a patient and physicians perspective. Several clinically meaningful secondary objectives are defined, including ORR, PFS2, and OS.

It is acknowledged that the MAH has adhered to the CHMP scientific advice, however, the management of this patient population has changed over the last couple of years. Therefore there are concerns related to the generalizability of the efficacy results to the target population in clinical practice, given that nowadays in many centers across the EU, comorborbidity and physiological age are more important factors to consider if a patient is “ineligible" for high dose chemotherapy and ASCT. The MAH has presented the efficacy results for the subset of patients considered ineligible to high dose QT + SCT according to current practice guidelines, i.e. 270 out of 356 (76%) patients in the VMP study group and 273 out of 350 (79%) patients in D-VMP study group. Results for this subset of patients are fully consistent to those seen for the overall studied population, which is reassuring. The main results for this subgroup of patients are reflected in Section 5.1 of the SmPC.

The subgroup analysis shows results that are consistent with the primary endpoint, however, some subgroups include few patient, which is reflected in the wide confidence interval. The MAH has analysed PFS when patients younger than 65 years were excluded. The results were consistent with the original analysis, which is reassuring. Subgroup analyses of PFS by age group were also consistent with the original PFS analysis, but due to small numbers, the results should be interpreted with caution. Thus the effect of D+VMP is considered similar across all stratification factors. Furthermore, the subgroup analysis by ECOG PS at baseline is difficult to interpretate, given that results in the group with the worst status (ECOG PS 2) might be diluted by the results in the more represented group of patients with an ECOG PS=1. This is a relevant

aspect to determine whether a given patient is candidate to ASCT or not. The MAH has analysed the 3 categories of ECOG PS. They show rather consistent results with a trend for lower ORR and PFS results in both study groups in patients with poorer PS and a trend for a lower magnitude of benefit vs the SOC in same patient subgroups. Nevertheless, based on these results the benefit of D-VMP over VMP in terms of PFS and ORR can be concluded across the 3 groups of patients.

The MAH has presented the efficacy results for the subset of patients considered ineligible to high dose chemotherapy + SCT according to current practice guidelines, either due to older age (at least 70 years), comorbidities or ECOG PS=2, i.e. 270 out of 356 (76%) patients in the VMP study group and 273 out of 350 (79%) patients in D-VMP study group. Sensitivity analyses showed the PFS result (HR=0.56; 95% CI: 0.42, 0.75) and the depth of response (overall response rate [ORR]: 90% in D-VMP group vs 74% in VMP group; very good partial response [VGPR] or better rate: 71% in D-VMP group vs 51% in VMP group); and complete response (CR) or better rate: 42% in D-VMP group vs 26% in VMP group). These results are fully consistent to those seen for the overall studied population, which is reassuring.

2.4.4. Conclusions on the clinical efficacy

Study MMY3007 comparing VMP to Dara+VMP is a well-conducted phase III study, demonstrating the added value of Dara in combination with VMP. PFS was significantly prolonged, and median PFS has not yet been reached in the D-VMP arm. The risk of disease progression is reduced by 54%, which is considered encouraging from a clinical point of view. 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 700 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. Based on the study design, subjects in the VMP group were treated for a maximum of 9 cycles of VMP and subsequently entered into a Follow-up phase. In the D-VMP group, subjects were treated for 9 cycles of D-VMP combination treatment and subsequently continued daratumumab monotherapy until disease progression. The median exposure for the D-VMP group was 12 cycles, whereas the median exposure for the VMP group was 9 cycles.

Patient exposure

A summary of treatment cycles received by subjects in both treatment groups is presented below. According to the protocol, after completing nine 6-week cycles, subjects in the D-VMP group were to receive daratumumab 16 mg/kg monotherapy every 4 weeks. Subjects randomized to the VMP group were to be treated for 9 cycles and then enter a follow-up observation phase until disease progression. Eighty-two percent (82%) of subjects in the D-VMP group and 68% of subjects in the VMP group received up to 9 cycles of treatment (including subjects who received any dose of study treatment in Cycle 9). As of the clinical cut-off, subjects in the D-VMP group received a median of 12 cycles and subjects in the VMP group received a median of 9 cycles. The median duration of treatment was 14.74 months for the D-VMP group and 11.99 months for the VMP group.

Table 29: Summary of treatment cycles; SAS

	VMP n (%)	D-VMP n (%)
Analysis set: safety	354	346
Distribution of subjects treated in & beyond each cycle		
≥ 1 cycle	354 (100.0%)	346 (100.0%)
≥ 2 cycles	330 (93.2%)	330 (95.4%)
≥ 3 cycles	308 (87.0%)	325 (93.9%)
≥ 4 cycles	294 (83.1%)	320 (92.5%)
≥ 5 cycles	281 (79.4%)	313 (90.5%)
≥ 6 cycles	269 (76.0%)	302 (87.3%)
≥ 7 cycles	256 (72.3%)	299 (86.4%)
≥ 8 cycles	250 (70.6%)	293 (84.7%)
≥ 9 cycles	240 (67.8%)	285 (82.4%)
10+ cycles	0	262 (75.7%)
Total number of treatment cycles received		
1	24 (6.8%)	16 (4.6%)
2	22 (6.2%)	5 (1.4%)
3	14 (4.0%)	5 (1.4%)
4	13 (3.7%)	7 (2.0%)
5	12 (3.4%)	11 (3.2%)
6	13 (3.7%)	3 (0.9%)
7	6 (1.7%)	6 (1.7%)
8	10 (2.8%)	8 (2.3%)
9	240 (67.8%)	23 (6.6%)
Cycle 2-9	330 (93.2%)	68 (19.7%)
10+	0	262 (75.7%)
Summary of total number of treatment cycles received		
N	354	346
Mean (SD)	7.3 (2.79)	12.2 (5.08)
Median	9.0	12.0
Range	(1; 9)	(1; 24)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Note: Percentages are calculated with the number of subjects in each treatment group as denominator.

Table 30: summary of relative dose intensity; SAS

	VMP	D-VMP
Analysis set: safety	354	346
Bortezomib (mg/m²) relative dose intensity (%)		
N	354	345
Mean (SD)	88.51 (13.869)	88.29 (15.593)
Median	93.88	95.61
Range	(26.2; 110.6)	(12.1; 106.3)
Bortezomib (mg/m²) relative dose intensity (Cycle 1, %)		
N	354	345
Mean (SD)	93.50 (11.349)	91.52 (15.164)
Median	98.37	98.18
Range	(37.7; 110.6)	(12.1; 106.3)
Bortezomib (mg/m²) relative dose intensity (Cycles 2-9, %)		
N	329	329
Mean (SD)	86.35 (17.430)	87.82 (17.147)
Median	94.40	96.15
Range	(7.4; 105.8)	(9.1; 106.3)
Melphalan (mg/m²) relative dose intensity (%)		
N	353	344
Mean (SD)	92.88 (12.434)	93.08 (12.360)
Median	96.82	96.68
Range	(37.2; 119.6)	(26.0; 142.5)
Prednisone equivalent[a] (mg/m²) relative dose intensity (%)		
N	353	346
Mean (SD)	97.29 (9.167)	97.40 (8.952)
Median	98.84	99.07
Range	(35.3; 185.7)	(24.4; 129.8)
Daratumumab (mg/kg) relative dose intensity (%)		
N	0	346
Mean (SD)	-	93.34 (16.356)
Median	-	98.78
Range	-	(1.3; 106.3)
Daratumumab (mg/kg) relative dose intensity (Cycle 1, %)		
N	0	346
Mean (SD)	-	90.45 (18.920)
Median	-	99.84
Range	-	(2.5; 106.3)
Daratumumab (mg/kg) relative dose intensity (Cycles 2-9, %)		
N	0	325
Mean (SD)	-	97.45 (6.924)
Median	-	100.00
Range	-	(50.0; 111.3)
Daratumumab (mg/kg) relative dose intensity (Cycles 10+, %)		
N	0	262
Mean (SD)	-	100.00 (4.985)
Median	-	100.00
Range	-	(33.3; 113.8)

Adverse events

Table 31: Overview of TEAEs; SAS

	VMP n (%)	D-VMP n (%)
Analysis set: safety	354	346
Any TEAE	342 (96.6%)	334 (96.5%)
At least one related[a]	302 (85.3%)	307 (88.7%)
At least one related to bortezomib	284 (80.2%)	262 (75.7%)
At least one related to melphalan	232 (65.5%)	223 (64.5%)
At least one related to steroids[b]	145 (41.0%)	166 (48.0%)
At least one related to daratumumab	0	206 (59.5%)
Maximum toxicity grade	342 (96.6%)	334 (96.5%)
Grade 1	11 (3.1%)	12 (3.5%)
Grade 2	55 (15.5%)	50 (14.5%)
Grade 3	180 (50.8%)	182 (52.6%)
Grade 4	77 (21.8%)	71 (20.5%)
Grade 5	19 (5.4%)	19 (5.5%)
Any serious TEAE	115 (32.5%)	144 (41.6%)
At least one related[a]	54 (15.3%)	65 (18.8%)
At least one related to bortezomib	43 (12.1%)	41 (11.8%)
At least one related to melphalan	32 (9.0%)	32 (9.2%)
At least one related to steroids[b]	19 (5.4%)	29 (8.4%)
At least one related to daratumumab	0	42 (12.1%)
TEAE leading to discontinuation of bortezomib	39 (11.0%)	27 (7.8%)
At least one related to bortezomib	25 (7.1%)	15 (4.3%)
TEAE leading to discontinuation of melphalan	37 (10.5%)	18 (5.2%)
At least one related to melphalan	9 (2.5%)	3 (0.9%)
TEAE leading to discontinuation of steroids[b]	32 (9.0%)	19 (5.5%)
At least one related to steroids[b]	4 (1.1%)	5 (1.4%)
TEAE leading to discontinuation of daratumumab	0	23 (6.6%)
At least one related to daratumumab	0	9 (2.6%)
Death due to AEs	19 (5.4%)	19 (5.5%)
At least one related to bortezomib	1 (0.3%)	2 (0.6%)
At least one related to melphalan	1 (0.3%)	3 (0.9%)
At least one related to steroids[b]	0	3 (0.9%)
At least one related to daratumumab	0	1 (0.3%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 4 components of study treatment: bortezomib, melphalan, steroids, daratumumab.
[b] Prednisone or prednisolone for VMP group; for D-VMP group, other corticosteroids (i.e. dexamethasone, methylprednisolone, hydrocortisone, betamethasone) may have been used as substitutes.
Note: Adverse events are reported using MedDRA version 20.0.

Common AEs

Table 32: Most common (at least 10%) TEAEs

Table 25: Most Common (At Least 10%) Treatment-emergent Adverse Events by MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414MMY3007)

	VMP n (%)	D-VMP n (%)
Analysis set: safety	354	346
Total number of subjects with TEAE	342 (96.6%)	334 (96.5%)
MedDRA system organ class / preferred term		
Blood and lymphatic system disorders	269 (76.0%)	254 (73.4%)
Neutropenia	186 (52.5%)	172 (49.7%)
Thrombocytopenia	190 (53.7%)	169 (48.8%)
Anaemia	133 (37.6%)	97 (28.0%)
Leukopenia	53 (15.0%)	46 (13.3%)
Lymphopenia	36 (10.2%)	37 (10.7%)
Infections and infestations	170 (48.0%)	231 (66.8%)
Upper respiratory tract infection	49 (13.8%)	91 (26.3%)
Pneumonia	17 (4.8%)	53 (15.3%)
Bronchitis	27 (7.6%)	50 (14.5%)
General disorders and administration site conditions	184 (52.0%)	194 (56.1%)
Pyrexia	74 (20.9%)	80 (23.1%)
Oedema peripheral	39 (11.0%)	62 (17.9%)
Fatigue	51 (14.4%)	48 (13.9%)
Asthenia	42 (11.9%)	40 (11.6%)
Gastrointestinal disorders	192 (54.2%)	191 (55.2%)
Diarrhoea	87 (24.6%)	82 (23.7%)
Nausea	76 (21.5%)	72 (20.8%)
Constipation	65 (18.4%)	63 (18.2%)
Vomiting	55 (15.5%)	59 (17.1%)
Nervous system disorders	180 (50.8%)	164 (47.4%)
Peripheral sensory neuropathy	121 (34.2%)	98 (28.3%)
Musculoskeletal and connective tissue disorders	116 (32.8%)	134 (38.7%)
Back pain	42 (11.9%)	48 (13.9%)
Respiratory, thoracic and mediastinal disorders	74 (20.9%)	132 (38.2%)
Cough	27 (7.6%)	52 (15.0%)
Dyspnoea	16 (4.5%)	43 (12.4%)
Metabolism and nutrition disorders	125 (35.3%)	125 (36.1%)
Decreased appetite	46 (13.0%)	40 (11.6%)
Skin and subcutaneous tissue disorders	97 (27.4%)	83 (24.0%)
Rash	39 (11.0%)	29 (8.4%)
Vascular disorders	52 (14.7%)	80 (23.1%)
Hypertension	11 (3.1%)	35 (10.1%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: 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.
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Table 33: Grade 3 / 4 AEs

Table 26: 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 54767414MMY3007)

	VMP			D-VMP		
	Total n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)	Grade 3 n (%)	Grade 4 n (%)
Analysis set: safety	354			346		
Total number of subjects with toxicity grade 3 or 4 TEAE	273 (77.1%)	184 (52.0%)	89 (25.1%)	268 (77.5%)	187 (54.0%)	81 (23.4%)
MedDRA system organ class / preferred term						
Blood and lymphatic system disorders	219 (61.9%)	145 (41.0%)	74 (20.9%)	209 (60.4%)	149 (43.1%)	60 (17.3%)
Neutropenia	137 (38.7%)	104 (29.4%)	33 (9.3%)	138 (39.9%)	106 (30.6%)	32 (9.2%)
Thrombocytopenia	133 (37.6%)	82 (23.2%)	51 (14.4%)	119 (34.4%)	84 (24.3%)	35 (10.1%)
Anaemia	70 (19.8%)	67 (18.9%)	3 (0.8%)	55 (15.9%)	53 (15.3%)	2 (0.6%)
Leukopenia	30 (8.5%)	23 (6.5%)	7 (2.0%)	28 (8.1%)	22 (6.4%)	6 (1.7%)
Lymphopenia	22 (6.2%)	13 (3.7%)	9 (2.5%)	26 (7.5%)	18 (5.2%)	8 (2.3%)
Infections and infestations	52 (14.7%)	46 (13.0%)	6 (1.7%)	80 (23.1%)	73 (21.1%)	7 (2.0%)
Pneumonia	14 (4.0%)	13 (3.7%)	1 (0.3%)	39 (11.3%)	38 (11.0%)	1 (0.3%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: TEAE = treatment-emergent adverse event.
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.
[TSFAE03AA.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFAE03AA.SAS] 28AUG2017, 04:34

Adverse Events of Special Interest (AESI):

Infusion-related Reactions

Infusion-related reactions (IRRs) associated with daratumumab administration were reported in 96 subjects (28%). Most (95%) treatment-emergent IRRs were Grade 1 or 2; 4% of subjects had Grade 3 IRRs, and 1% of subjects (2 subjects) had Grade 4 IRRs; no Grade 5 IRR was reported. The most frequently reported TEAE terms (reported in >5%) used to describe IRRs were dyspnea (7%) and chills (6%). Subject narratives are provided for subjects who had Grade 3 or higher IRRs.

Table 34: IRRs

TSFAE06A: Number of Subjects with 1 or More Treatment-emergent Infusion Related Reactions by MedDRA System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set (Study 54767414MMY3007)

	D-VMP			
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Analysis set: safety	346			
Total number of subjects with infusion related reactions	96 (27.7%)	15 (4.3%)	2 (0.6%)	0
Total number of subjects with infusion related reactions in more than 1 infusion	14 (4.0%)			
MedDRA system organ class / preferred term				
Respiratory, thoracic and mediastinal disorders	51 (14.7%)	11 (3.2%)	2 (0.6%)	0
Dyspnoea	25 (7.2%)	6 (1.7%)	2 (0.6%)	0
Bronchospasm	10 (2.9%)	3 (0.9%)	0	0
Cough	8 (2.3%)	0	0	0
Throat irritation	6 (1.7%)	0	0	0
Hypoxia	4 (1.2%)	3 (0.9%)	0	0
Nasal congestion	4 (1.2%)	0	0	0
Wheezing	4 (1.2%)	0	1 (0.3%)	0
Sneezing	2 (0.6%)	0	0	0
Tachypnoea	2 (0.6%)	0	1 (0.3%)	0
Dysphonia	1 (0.3%)	0	0	0
Laryngospasm	1 (0.3%)	0	0	0
Pharyngeal paraesthesia	1 (0.3%)	0	0	0
Pulmonary oedema	1 (0.3%)	0	0	0
Throat tightness	1 (0.3%)	0	0	0
General disorders and administration site conditions	31 (9.0%)	1 (0.3%)	0	0
Chills	22 (6.4%)	0	0	0
Pyrexia	13 (3.8%)	0	0	0
Chest discomfort	1 (0.3%)	0	0	0
Injection site erythema	1 (0.3%)	0	0	0
Malaise	1 (0.3%)	1 (0.3%)	0	0
Non-cardiac chest pain	1 (0.3%)	0	0	0
Pain	1 (0.3%)	0	0	0
Vascular disorders	24 (6.9%)	5 (1.4%)	1 (0.3%)	0
Hypertension	16 (4.6%)	5 (1.4%)	1 (0.3%)	0
Hypotension	8 (2.3%)	0	0	0
Skin and subcutaneous tissue disorders	14 (4.0%)	2 (0.6%)	0	0
Rash	4 (1.2%)	0	0	0
Hyperhidrosis	3 (0.9%)	2 (0.6%)	0	0
Pruritus	3 (0.9%)	0	0	0
Rash erythematous	2 (0.6%)	0	0	0
Erythema	1 (0.3%)	0	0	0
Skin reaction	1 (0.3%)	0	0	0
Urticaria	1 (0.3%)	0	0	0
Gastrointestinal disorders	12 (3.5%)	1 (0.3%)	0	0
Nausea	8 (2.3%)	0	0	0
Vomiting	6 (1.7%)	0	0	0
Abdominal pain	2 (0.6%)	1 (0.3%)	0	0
Diarrhoea	1 (0.3%)	0	0	0
Nervous system disorders	12 (3.5%)	0	0	0
Tremor	6 (1.7%)	0	0	0
Headache	5 (1.4%)	0	0	0
Dizziness postural	1 (0.3%)	0	0	0

Table 35: Cytopenia

Table 31: Number of Subjects with 1 or More Treatment-emergent Cytopenia Adverse Events by MedDRA Preferred Term and Maximum Toxicity Grade; Safety Analysis Set (Study 54767414MMY3007)								
	VMP				D-VMP			
	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	354				346			
Subjects with any treatment-emergent cytopenia adverse events	268 (75.7%)	218 (61.6%)	0	1 (0.3%)	253 (73.1%)	207 (59.8%)	0	2 (0.6%)
MedDRA preferred term								
Neutropenia [a]	188 (53.1%)	140 (39.5%)	0	0	174 (50.3%)	139 (40.2%)	0	0
Neutropenia	186 (52.5%)	137 (38.7%)	0	0	172 (49.7%)	138 (39.9%)	0	0
Febrile neutropenia	10 (2.8%)	8 (2.3%)	0	0	5 (1.4%)	4 (1.2%)	0	0
Neutropenic infection	1 (0.3%)	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0	0
Thrombocytopenia [a]	190 (53.7%)	133 (37.6%)	0	1 (0.3%)	169 (48.8%)	119 (34.4%)	0	1 (0.3%)
Thrombocytopenia	190 (53.7%)	133 (37.6%)	0	1 (0.3%)	169 (48.8%)	119 (34.4%)	0	1 (0.3%)
Anaemia [a]	133 (37.6%)	70 (19.8%)	0	1 (0.3%)	97 (28.0%)	55 (15.9%)	0	1 (0.3%)
Anaemia	133 (37.6%)	70 (19.8%)	0	1 (0.3%)	97 (28.0%)	55 (15.9%)	0	1 (0.3%)
Lymphopenia [a]	36 (10.2%)	22 (6.2%)	0	0	37 (10.7%)	26 (7.5%)	0	0
Lymphopenia	36 (10.2%)	22 (6.2%)	0	0	37 (10.7%)	26 (7.5%)	0	0

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: Disc.= discontinuation; TEAE = treatment-emergent adverse event.
[a] 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.
[TSFAE28.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFAE28.SAS] 28AUG2017, 04:34

Table 36: Haemorrhage

TSFAE29: Number of Subjects with 1 or More Treatment-emergent Hemorrhage Events by MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414MMY3007)	VMP		D-VMP	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Analysis set: safety	354		346	
Total number of subjects with treatment-emergent hemorrhage events	39 (11.0%)	6 (1.7%)	53 (15.3%)	9 (2.6%)
MedDRA system organ class / preferred term				
Gastrointestinal disorders	10 (2.8%)	5 (1.4%)	15 (4.3%)	4 (1.2%)
Gastrointestinal haemorrhage	0	0	3 (0.9%)	2 (0.6%)
Melaena	1 (0.3%)	0	3 (0.9%)	0
Anal haemorrhage	0	0	2 (0.6%)	0
Haemorrhoidal haemorrhage	0	0	2 (0.6%)	1 (0.3%)
Rectal haemorrhage	1 (0.3%)	1 (0.3%)	2 (0.6%)	1 (0.3%)
Gingival bleeding	2 (0.6%)	1 (0.3%)	1 (0.3%)	0
Haematochezia	0	0	1 (0.3%)	0
Intra-abdominal haematoma	1 (0.3%)	0	1 (0.3%)	0
Mouth haemorrhage	1 (0.3%)	0	1 (0.3%)	0
Gastric haemorrhage	1 (0.3%)	1 (0.3%)	0	0
Haematemesis	2 (0.6%)	1 (0.3%)	0	0
Oesophagitis haemorrhagic	1 (0.3%)	1 (0.3%)	0	0
Injury, poisoning and procedural complications	3 (0.8%)	0	14 (4.0%)	2 (0.6%)
Contusion	2 (0.6%)	0	7 (2.0%)	0
Bone contusion	0	0	1 (0.3%)	0
Periorbital haematoma	0	0	1 (0.3%)	0
Post procedural haemorrhage	0	0	1 (0.3%)	1 (0.3%)
Subarachnoid haemorrhage	0	0	1 (0.3%)	0
Subcutaneous haematoma	0	0	1 (0.3%)	0
Traumatic haemorrhage	0	0	1 (0.3%)	1 (0.3%)
Wound haemorrhage	0	0	1 (0.3%)	0
Eye contusion	1 (0.3%)	0	0	0
Respiratory, thoracic and mediastinal disorders	9 (2.5%)	1 (0.3%)	10 (2.9%)	1 (0.3%)
Epistaxis	7 (2.0%)	0	8 (2.3%)	1 (0.3%)
Haemoptysis	2 (0.6%)	1 (0.3%)	1 (0.3%)	0
Nasal septum haematoma	0	0	1 (0.3%)	0
Eye disorders	1 (0.3%)	0	8 (2.3%)	1 (0.3%)
Conjunctival haemorrhage	0	0	4 (1.2%)	1 (0.3%)
Eye haemorrhage	0	0	2 (0.6%)	0
Eyelid haematoma	0	0	1 (0.3%)	0
Intraocular haematoma	0	0	1 (0.3%)	0
Retinal haemorrhage	1 (0.3%)	0	0	0
Skin and subcutaneous tissue disorders	6 (1.7%)	0	4 (1.2%)	0
Ecchymosis	2 (0.6%)	0	2 (0.6%)	0
Petechiae	2 (0.6%)	0	1 (0.3%)	0
Skin haemorrhage	1 (0.3%)	0	1 (0.3%)	0
Haemorrhage subcutaneous	1 (0.3%)	0	0	0
Renal and urinary disorders	3 (0.8%)	0	3 (0.9%)	0
Haematuria	2 (0.6%)	0	3 (0.9%)	0
Cystitis haemorrhagic	1 (0.3%)	0	0	0
Vascular disorders	6 (1.7%)	0	3 (0.9%)	0
Haematoma	6 (1.7%)	0	3 (0.9%)	0
Musculoskeletal and connective tissue disorders	0	0	2 (0.6%)	0
Muscle haemorrhage	0	0	2 (0.6%)	0
Blood and lymphatic system disorders	0	0	1 (0.3%)	0
Disseminated intravascular coagulation	0	0	1 (0.3%)	0
General disorders and administration site conditions	1 (0.3%)	0	1 (0.3%)	0

Infections and infestations

Overall, the rates of infections and infestations were higher in the D-VMP (67%) compared to the VMP (48%) group. This was primarily driven by upper respiratory tract infections (D-VMP group: 26%; VMP group: 14%), pneumonia (D-VMP group: 15%; VMP group: 5%) and bronchitis (D-VMP group: 15%; VMP group: 8%). However, discontinuation of study treatments due to infection and infestation TEAEs was low and balanced between the two groups, reported in 3 subjects (0.9%) in the D-VMP group and 5 subjects (1.4%) in the VMP group), and 1 subject in each group discontinued treatment due to pneumonia.

Table 37: Second primary malignancies

Table 32: Summary of Second Primary Malignancies; Safety Analysis Set (Study 54767414MMY3007)			
	VMP n (%)	D-VMP n (%)	Total n (%)
Analysis set: safety	354	346	700
Total number of subjects with second primary malignancies	9 (2.5%)	8 (2.3%)	17 (2.4%)
Cancer type/ dictionary-derived term			
Non-cutaneous/invasive	5 (1.4%)	5 (1.4%)	10 (1.4%)
Adenocarcinoma of colon	2 (0.6%)	1 (0.3%)	3 (0.4%)
Renal cell carcinoma	0	2 (0.6%)	2 (0.3%)
Adenocarcinoma gastric	1 (0.3%)	0	1 (0.1%)
Bile duct cancer	0	1 (0.3%)	1 (0.1%)
Breast cancer	1 (0.3%)	0	1 (0.1%)
Oesophageal adenocarcinoma	0	1 (0.3%)	1 (0.1%)
Rectal adenocarcinoma	1 (0.3%)	0	1 (0.1%)
Cutaneous/non-invasive	2 (0.6%)	3 (0.9%)	5 (0.7%)
Basal cell carcinoma	2 (0.6%)	1 (0.3%)	3 (0.4%)
Squamous cell carcinoma of skin	0	2 (0.6%)	2 (0.3%)
Hematologic malignancies	2 (0.6%)	0	2 (0.3%)
Acute myeloid leukaemia	1 (0.3%)	0	1 (0.1%)
Myelodysplastic syndrome	1 (0.3%)	0	1 (0.1%)

Key: VMP = bortezomib-melphalan-prednisone; D-VMP = daratumumab-bortezomib-melphalan-prednisone.
[TSFSPM01.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFSPM01.SAS] 28AUG2017, 04:34

Table 38: Tumor lysis syndrome (TLS)

Table 33: Summary of Subjects with Treatment-emergent Tumor Lysis Syndrome; Safety Analysis Set (Study 54767414MMY3007)						
Subject ID; Age/Sex; Treatment	Study Day of AE Onset/AE Duration (days)	Toxicity Grade	SAE	Lab values at diagnosis (lab values at baseline)	Outcome	Assessment
66/M; VMP	11/34	3	No	Uric acid 5.6 (6.3) mg/dL Potassium 5.4 (4.1) mmol/dL Corrected Calcium 8.5 (9.6) mg/dL Creatinine 1.2 (0.8) mg/dL	RECOVERED/ RESOLVED	Nonserious grade 3 AE, did not meet Cairo-Bishop criteria for TLS, daratumumab not given
72/M; VMP	13/12	5	Yes	Uric acid 11.2 (5.8) mg/dL Phosphorus 17.4 mg/dL Potassium 4.0 (2.6) mmol/L Corrected Calcium 2.3 (2.6) mmol/dL Creatinine 1.6 (0.8) mg/dL	FATAL	Met criteria for TLS, daratumumab not given
56/F; D-VMP	2/1	5	Yes	Uric acid 292 (268) µmol/L Phosphorus 2.33 mmol/L Potassium 3.3 mmol/L Corrected Calcium 1.98 mmol/L Creatinine 240 (147) µmol/L	FATAL	Did not meet Cairo-Bishop criteria for TLS, investigator determined TLS not related to daratumumab and bortezomib, probably related to melphalan and dexamethasone; autopsy determined cause of death was neoplasm progression
80/M; D-VMP	2/30	3	No	Uric acid 3.5 (3.7) mg/dL Potassium 4.4 (4.6) mmol/L Corrected Calcium 8.5 (8.1) mg/dL Creatinine 0.6 (0.7) mg/dL	RECOVERED/ RESOLVED	Nonserious grade 3 AE, did not meet Cairo-Bishop criteria for TLS, investigator acknowledged TLS diagnosis was not supported by any abnormal laboratory values meeting TLS criteria. Subject eventually died of acute respiratory failure.

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: AE = Adverse event; SAE = Serious adverse event.
Note: Cairo-Bishop criteria for tumor lysis syndrome: two or more changes within three days before or seven days after cytotoxic therapy; Uric acid ≥476 µmol/L, Potassium ≥6.0 mmol/L, Phosphorus ≥2.1 mmol/L, Calcium ≤1.75 mmol/L, or change from baseline exceeding 25%.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Outcome of recovered/resolved could mean the toxicity grade changed.

Table 39: Intravascular haemolysis

Table 34: Listing of Treatment-emergent Intravascular Hemolysis; Safety Analysis Set (Study 54767414MMY3007)

Treatment Group	Subject ID	Adverse Event (MedDRA Preferred Term [Verbatim])	Study Day of AE Onset/AE Duration (days)	SAE?	Toxicity Grade	Relationship to[a]				Action Taken with[b]				Outcome	Transfusion[e]/ Study Day
						Dara[c]	Bor[c]	Mel[c]	Stero-ids[c,d]	Dara[c]	Bor[c]	Mel[c]	Stero-ids[c,d]		
VMP	1	Haemolysis [DRUG-INDUCED HEMOLYSIS RELATED TO DISULONE]	247/17	No	2	NR	NR	NR	NR	NA	DNC	DNC	DNC	RECOVERED/ RESOLVED	PACKED RED BLOOD CELLS TRANSFUSION/233 PACKED RED BLOOD CELLS TRANSFUSION/247
D-VMP	2	Haemolysis [HAEMOLYSIS]	3/271	No	1	VL	NR	NR	NR	DNC	DNC	DNC	DNC	RECOVERED/ RESOLVED	
	3	Haemolysis [HAEMOLYSIS]	36/49	No	2	Prob.	NR	NR	NR	DNC	DNC	DNC	DNC	RECOVERED/ RESOLVED	PACKED RED BLOOD CELLS TRANSFUSION/35

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: SAE = Serious adverse event.
[a] Key: NR = Not Related; DO = Doubtful; Poss. = Possible; Prob. = Probable; VL = Very Likely.
[b] Key: DI = Drug Interrupted; DNC = Dose Not Changed; DR = Dose Reduced; DW = Drug Withdrawn; NA = Not Applicable; UN = Unknown.
[c] Key: Dara = daratumumab; Bor = bortezomib; Mel = melphalan; Steroids = prednisone or equivalent.
[d] Prednisone or prednisolone for VMP group; for D-VMP group, other corticosteroids (i.e. dexamethasone, methylprednisolone, hydrocortisone, betamethasone) may have been used as substitutes.
[e] Transfusions of whole blood or packed red blood cells on or within 1 month prior to the start of the intravascular hemolysis event are listed.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Outcome of recovered/resolved could mean the toxicity grade changed.
[LSFAE09.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/LSFAE09.SAS] 30AUG2017, 01:27

Treatment-emergent Interferences for Blood Typing

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

Other AEs of interest

Table 40: Peripheral neuropathies

Table 35: Number of Subjects with 1 or More Treatment-emergent Peripheral Neuropathy by MedDRA High Level Term and Preferred Term; Safety Analysis Set (Study 54767414MMY3007)

	VMP		D-VMP	
	All Grades n (%)	Grade 3 or 4 n (%)	All Grades n (%)	Grade 3 or 4 n (%)
Analysis set: safety	354		346	
Total number of subjects with treatment emergent peripheral neuropathy	132 (37.3%)	18 (5.1%)	110 (31.8%)	10 (2.9%)
MedDRA high level term/preferred term				
Peripheral neuropathies NEC	132 (37.3%)	18 (5.1%)	110 (31.8%)	10 (2.9%)
Peripheral sensory neuropathy	121 (34.2%)	14 (4.0%)	98 (28.3%)	5 (1.4%)
Peripheral sensorimotor neuropathy	8 (2.3%)	3 (0.8%)	9 (2.6%)	4 (1.2%)
Neuropathy peripheral	2 (0.6%)	1 (0.3%)	3 (0.9%)	0
Peripheral motor neuropathy	4 (1.1%)	0	3 (0.9%)	1 (0.3%)
Axonal neuropathy	0	0	1 (0.3%)	0

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: 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.
[TSFAE27.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFAE27.SAS] 28AUG2017, 05:51

Serious adverse event / deaths / other significant events

Table 41: Deaths

Table 27: Summary of Death and Cause of Death; Safety Analysis Set (Study 54767414MMY3007)	VMP n (%)	D-VMP n (%)	Total n (%)
Analysis set: safety	354	346	700
Total number of subject who died during study	48 (13.6%)	45 (13.0%)	93 (13.3%)
Total number of subjects who died within 30 days of last study treatment dose	16 (4.5%)	14 (4.0%)	30 (4.3%)
Primary cause of death			
Adverse event	16 (4.5%)	12 (3.5%)	28 (4.0%)
At least one related[a]	1 (0.3%)	3 (0.9%)	4 (0.6%)
AE(s) unrelated	15 (4.2%)	9 (2.6%)	24 (3.4%)
Disease progression	0	2 (0.6%)	2 (0.3%)
Other	0	0	0
Total number of subjects who died within 60 days of first study treatment dose	13 (3.7%)	9 (2.6%)	22 (3.1%)
Primary cause of death			
Adverse event	13 (3.7%)	8 (2.3%)	21 (3.0%)
At least one related[a]	2 (0.6%)	3 (0.9%)	5 (0.7%)
AE(s) unrelated	11 (3.1%)	5 (1.4%)	16 (2.3%)
Disease progression	0	0	0
Other	0	1 (0.3%)	1 (0.1%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
[a] Includes adverse events that were related to at least 1 of the 4 components of study treatment: bortezomib, melphalan, steroids or daratumumab.

Modified from [TSFDTH01.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFDTH01.SAS] 28AUG2017, 04:34

Table 42: TEAEs with outcome Death

Table 28: Number of Subjects with a Treatment-emergent Adverse Event with Outcome Death by MedDRA Preferred Term and Relationship; Safety Analysis Set (Study 54767414MMY3007)

	VMP n (%)				D-VMP n (%)				
	Total	Related to Bor	Related to Mel	Related to Steroids	Total	Related to Dara	Related to Bor	Related to Mel	Related to Steroids
Analysis set: safety	354				346				
Total number of subjects with TEAE with outcome death	19 (5.4%)	1 (0.3%)	1 (0.3%)	0	19 (5.5%)	1 (0.3%)	2 (0.6%)	3 (0.9%)	3 (0.9%)
MedDRA preferred term									
Death	2 (0.6%)	0	0	0	2 (0.6%)	0	0	0	0
Pneumonia	0	0	0	0	2 (0.6%)	0	0	1 (0.3%)	0
Acute myocardial infarction	0	0	0	0	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)
Acute respiratory distress syndrome	0	0	0	0	1 (0.3%)	0	0	0	0
Acute respiratory failure	0	0	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Bile duct cancer	0	0	0	0	1 (0.3%)	0	0	0	0
Cardiac arrest	2 (0.6%)	0	0	0	1 (0.3%)	0	0	0	0
Cardiac failure acute	0	0	0	0	1 (0.3%)	0	0	0	0
Cardiovascular insufficiency	0	0	0	0	1 (0.3%)	0	0	0	0
Depression	0	0	0	0	1 (0.3%)	0	0	0	0
Haemorrhage intracranial	0	0	0	0	1 (0.3%)	0	0	0	0
Ischaemic stroke	0	0	0	0	1 (0.3%)	0	0	0	0
Parkinson's disease	0	0	0	0	1 (0.3%)	0	0	0	0
Peritonitis	0	0	0	0	1 (0.3%)	0	0	0	0
Septic shock	1 (0.3%)	0	0	0	1 (0.3%)	0	0	0	0
Tumour lysis syndrome	1 (0.3%)	0	0	0	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)
Upper respiratory tract infection	0	0	0	0	1 (0.3%)	0	0	0	0
Acute kidney injury	1 (0.3%)	0	0	0	0	0	0	0	0
Adenocarcinoma of colon	1 (0.3%)	0	0	0	0	0	0	0	0
Anuria	1 (0.3%)	0	0	0	0	0	0	0	0
Candida sepsis	1 (0.3%)	0	0	0	0	0	0	0	0
Cardiac failure	1 (0.3%)	0	0	0	0	0	0	0	0
Cardio-respiratory arrest	1 (0.3%)	0	0	0	0	0	0	0	0
Cerebral infarction	1 (0.3%)	0	0	0	0	0	0	0	0
Obstructive airways disorder	1 (0.3%)	0	0	0	0	0	0	0	0
Pneumonia bacterial	1 (0.3%)	0	1 (0.3%)	0	0	0	0	0	0
Pneumothorax spontaneous	1 (0.3%)	0	0	0	0	0	0	0	0
Pulmonary embolism	1 (0.3%)	1 (0.3%)	0	0	0	0	0	0	0
Sepsis	1 (0.3%)	0	0	0	0	0	0	0	0
Traumatic shock	1 (0.3%)	0	0	0	0	0	0	0	0

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: TEAE = treatment-emergent adverse event. Bor = bortezomib; Mel = melphalan; Steroids = prednisone or equivalent; Dara = daratumumab.
Note: Adverse events are reported using MedDRA version 20.0.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Table 43: SAEs

Table 29: Most Common (At Least 2%) Treatment-emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414MMY3007)

	VMP n (%)	D-VMP n (%)
Analysis set: safety	354	346
Total number of subjects with serious TEAE	115 (32.5%)	144 (41.6%)
MedDRA system organ class / preferred term		
Infections and infestations	42 (11.9%)	80 (23.1%)
Pneumonia	11 (3.1%)	35 (10.1%)
Bronchitis	2 (0.6%)	8 (2.3%)
Lower respiratory tract infection	3 (0.8%)	8 (2.3%)
Upper respiratory tract infection	3 (0.8%)	7 (2.0%)
Cardiac disorders	15 (4.2%)	18 (5.2%)
Cardiac failure	7 (2.0%)	1 (0.3%)
Blood and lymphatic system disorders	21 (5.9%)	15 (4.3%)
Anaemia	9 (2.5%)	6 (1.7%)
Febrile neutropenia	7 (2.0%)	2 (0.6%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: 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.
[TSFAE05AA.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFAE05AA.SAS] 28AUG2017, 04:34

Laboratory findings

Table 44: Haematology

Table 37: Summary of Worst Toxicity Grade During Treatment in Hematology and Biochemistry; Safety Analysis Set (Study 54767414MMY3007)

	VMP Toxicity Grade, n (%)						D-VMP Toxicity Grade, n (%)					
	Total	0	1	2	3	4	Total	0	1	2	3	4
Analysis set: safety	354						346					
Hematology												
WBC low (Leukopenia)	352 (99.4%)	12 (3.4%)	70 (19.9%)	136 (38.6%)	111 (31.5%)	23 (6.5%)	345 (99.7%)	8 (2.3%)	67 (19.4%)	122 (35.4%)	127 (36.8%)	21 (6.1%)
Hemoglobin low (Anemia)	352 (99.4%)	3 (0.9%)	98 (27.8%)	170 (48.3%)	81 (23.0%)	0	345 (99.7%)	10 (2.9%)	108 (31.3%)	156 (45.2%)	71 (20.6%)	0
Platelets low (Thrombocytopenia)	352 (99.4%)	32 (9.1%)	116 (33.0%)	57 (16.2%)	91 (25.9%)	56 (15.9%)	345 (99.7%)	29 (8.4%)	108 (31.3%)	77 (22.3%)	92 (26.7%)	39 (11.3%)
Neutrophils low (Neutropenia)	352 (99.4%)	41 (11.6%)	51 (14.5%)	110 (31.3%)	112 (31.8%)	38 (10.8%)	345 (99.7%)	37 (10.7%)	54 (15.7%)	102 (29.6%)	118 (34.2%)	34 (9.9%)
Lymphocytes low (Lymphopenia)	352 (99.4%)	50 (14.2%)	0	110 (31.3%)	158 (44.9%)	34 (9.7%)	345 (99.7%)	43 (12.5%)	0	96 (27.8%)	162 (47.0%)	44 (12.8%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: 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.
Modified from [TSFLAB02.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFLAB02.SAS] 28AUG2017, 05:51

Table 45: Chemistry

Table 38: Summary of Worst Toxicity Grade During Treatment in Hematology and Biochemistry; Safety Analysis Set (Study 54767414MMY3007)

	VMP Toxicity Grade, n (%)						D-VMP Toxicity Grade, n (%)					
	Total	0	1	2	3	4	Total	0	1	2	3	4
Analysis set: safety	354						346					
Biochemistry												
ALT high	343 (96.9%)	226 (65.9%)	101 (29.4%)	10 (2.9%)	4 (1.2%)	2 (0.6%)	341 (98.6%)	231 (67.7%)	95 (27.9%)	5 (1.5%)	10 (2.9%)	0
AST high	343 (96.9%)	221 (64.4%)	106 (30.9%)	10 (2.9%)	4 (1.2%)	2 (0.6%)	341 (98.6%)	236 (69.2%)	89 (26.1%)	7 (2.1%)	6 (1.8%)	3 (0.9%)
Creatinine high	343 (96.9%)	194 (56.6%)	102 (29.7%)	38 (11.1%)	5 (1.5%)	4 (1.2%)	343 (99.1%)	199 (58.0%)	109 (31.8%)	33 (9.6%)	2 (0.6%)	0
Sodium high (Hypernatremia)	251 (70.9%)	215 (85.7%)	33 (13.1%)	1 (0.4%)	1 (0.4%)	1 (0.4%)	253 (73.1%)	205 (81.0%)	42 (16.6%)	5 (2.0%)	1 (0.4%)	0
Sodium low (Hyponatremia)	251 (70.9%)	151 (60.2%)	80 (31.9%)	0	16 (6.4%)	4 (1.6%)	253 (73.1%)	159 (62.8%)	68 (26.9%)	0	24 (9.5%)	2 (0.8%)
Potassium high (Hyperkalemia)	251 (70.9%)	198 (78.9%)	29 (11.6%)	16 (6.4%)	6 (2.4%)	2 (0.8%)	252 (72.8%)	200 (79.4%)	27 (10.7%)	18 (7.1%)	5 (2.0%)	2 (0.8%)
Potassium low (Hypokalemia)	251 (70.9%)	187 (74.5%)	0	55 (21.9%)	7 (2.8%)	2 (0.8%)	252 (72.8%)	178 (70.6%)	0	64 (25.4%)	7 (2.8%)	3 (1.2%)
Bilirubin high	343 (96.9%)	289 (84.3%)	32 (9.3%)	17 (5.0%)	5 (1.5%)	0	338 (97.7%)	293 (86.7%)	32 (9.5%)	11 (3.3%)	2 (0.6%)	0
Alkaline phosphatase high	341 (96.3%)	165 (48.4%)	150 (44.0%)	16 (4.7%)	10 (2.9%)	0	340 (98.3%)	127 (37.4%)	181 (53.2%)	30 (8.8%)	2 (0.6%)	0
Uric acid high (Hyperuricemia)	340 (96.0%)	240 (70.6%)	87 (25.6%)	0	0	13 (3.8%)	335 (96.8%)	244 (72.8%)	84 (25.1%)	0	0	7 (2.1%)
Corrected calcium high (Hypercalcemia)	346 (97.7%)	268 (77.5%)	65 (18.8%)	6 (1.7%)	5 (1.4%)	2 (0.6%)	344 (99.4%)	275 (79.9%)	60 (17.4%)	6 (1.7%)	3 (0.9%)	0
Corrected calcium low (Hypocalcemia)	346 (97.7%)	223 (64.5%)	87 (25.1%)	25 (7.2%)	7 (2.0%)	4 (1.2%)	344 (99.4%)	181 (52.6%)	104 (30.2%)	47 (13.7%)	6 (1.7%)	6 (1.7%)
Albumin low (Hypoalbuminemia)	345 (97.5%)	167 (48.4%)	95 (27.5%)	79 (22.9%)	4 (1.2%)	0	343 (99.1%)	151 (44.0%)	103 (30.0%)	81 (23.6%)	8 (2.3%)	0
Glucose high (Hyperglycemia)	264 (74.6%)	80 (30.3%)	126 (47.7%)	44 (16.7%)	14 (5.3%)	0	280 (80.9%)	87 (31.1%)	142 (50.7%)	35 (12.5%)	16 (5.7%)	0
Glucose low (Hypoglycemia)	340 (96.0%)	278 (81.8%)	48 (14.1%)	12 (3.5%)	2 (0.6%)	0	341 (98.6%)	289 (84.8%)	40 (11.7%)	11 (3.2%)	0	1 (0.3%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: AST = Aspartate Aminotransferase; ALT = Alanine 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.
Modified from [TSFLAB02.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFLAB02.SAS] 28AUG2017, 05:51

Table 46: Vital signs

TSIVIS01: Summary of Vital Signs Values at Baseline; Intent-to-treat Analysis Set (Study 54767414MMY3007)			
	VMP	D-VMP	Total
Analysis set: intent-to-treat	356	350	706
Height (cm)			
N	356	350	706
Mean (SD)	163.3 (10.16)	162.7 (9.65)	163.0 (9.91)
Median	163.0	162.4	163.0
Range	(125; 190)	(137; 186)	(125; 190)
Weight (kg)			
N	356	350	706
Mean (SD)	71.89 (14.691)	70.82 (14.728)	71.36 (14.709)
Median	71.00	69.00	70.00
Range	(30.1; 115.0)	(38.5; 142.0)	(30.1; 142.0)
Temperature (C)			
N	356	347	703
Mean (SD)	36.45 (0.373)	36.47 (0.442)	36.46 (0.408)
Median	36.50	36.50	36.50
Range	(34.7; 38.3)	(34.7; 39.7)	(34.7; 39.7)
Diastolic Blood Pressure (mmHg)			
N	356	349	705
Mean (SD)	76.3 (9.78)	77.0 (9.25)	76.6 (9.52)
Median	79.0	80.0	80.0
Range	(49; 114)	(50; 100)	(49; 114)
Systolic Blood Pressure (mmHg)			
N	356	349	705
Mean (SD)	131.6 (16.19)	132.5 (15.79)	132.0 (15.99)
Median	130.0	130.0	130.0
Range	(95; 215)	(86; 187)	(86; 215)
Pulse Rate (BEATS/MIN)			
N	356	349	705
Mean (SD)	76.4 (10.54)	76.6 (10.83)	76.5 (10.68)
Median	76.0	76.0	76.0
Range	(49; 116)	(30; 112)	(30; 116)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
[TSIVIS01.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSIVIS01.SAS] 28AUG2017, 05:51

ECG

TSFECG01: Summary of Baseline and Post-baseline 12-Lead ECG Results; Safety Analysis Set (Study 54767414MMY3007)

	VMP n (%)	D-VMP n (%)
Analysis set: safety	354	346
12-lead ECG overall interpretation		
Baseline		
N	352	346
Normal	195 (55.4%)	195 (56.4%)
Abnormal, clinically insignificant	155 (44.0%)	148 (42.8%)
Abnormal, clinically significant	2 (0.6%)	3 (0.9%)
Not evaluable	0	0
Cycle 3 Day 1 Post-infusion		
N	263	283
Normal	155 (58.9%)	177 (62.5%)
Abnormal, clinically insignificant	106 (40.3%)	103 (36.4%)
Abnormal, clinically significant	2 (0.8%)	3 (1.1%)
Not evaluable	0	0
Cycle 6 Day 1 Post-infusion		
N	247	272
Normal	146 (59.1%)	164 (60.3%)
Abnormal, clinically insignificant	96 (38.9%)	106 (39.0%)
Abnormal, clinically significant	5 (2.0%)	2 (0.7%)
Not evaluable	0	0
End-of-treatment		
N	257	61
Normal	142 (55.3%)	32 (52.5%)
Abnormal, clinically insignificant	113 (44.0%)	29 (47.5%)
Abnormal, clinically significant	2 (0.8%)	0
Not evaluable	0	0

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Note: Percentages are calculated with the number of subjects in each group with available data as denominator.
[TSFECG01.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFECG01.SAS] 28AUG2017, 12:53

Safety in special populations

Table 47: Age

Table 36: Overview of Treatment-emergent Adverse Events by Age; Safety Analysis Set (Study 54767414MMY3007)

	VMP n (%)				D-VMP n (%)			
	<65 years	65- < 75 years	>=75 years	Total	<65 years	65- < 75 years	>=75 years	Total
Analysis set: safety	24	224	106	354	36	208	102	346
Any TEAE	21 (87.5%)	215 (96.0%)	106 (100.0%)	342 (96.6%)	31 (86.1%)	203 (97.6%)	100 (98.0%)	334 (96.5%)
Maximum toxicity grade								
Grade 1	0	7 (3.1%)	4 (3.8%)	11 (3.1%)	2 (5.6%)	8 (3.8%)	2 (2.0%)	12 (3.5%)
Grade 2	5 (20.8%)	38 (17.0%)	12 (11.3%)	55 (15.5%)	5 (13.9%)	38 (18.3%)	7 (6.9%)	50 (14.5%)
Grade 3	10 (41.7%)	112 (50.0%)	58 (54.7%)	180 (50.8%)	19 (52.8%)	114 (54.8%)	49 (48.0%)	182 (52.6%)
Grade 4	5 (20.8%)	47 (21.0%)	25 (23.6%)	77 (21.8%)	2 (5.6%)	36 (17.3%)	33 (32.4%)	71 (20.5%)
Grade 5	1 (4.2%)	11 (4.9%)	7 (6.6%)	19 (5.4%)	3 (8.3%)	7 (3.4%)	9 (8.8%)	19 (5.5%)
Any serious TEAE	6 (25.0%)	65 (29.0%)	44 (41.5%)	115 (32.5%)	10 (27.8%)	79 (38.0%)	55 (53.9%)	144 (41.6%)
TEAE leading to discontinuation of bortezomib	1 (4.2%)	18 (8.0%)	20 (18.9%)	39 (11.0%)	1 (2.8%)	14 (6.7%)	12 (11.8%)	27 (7.8%)
TEAE leading to discontinuation of melphalan	1 (4.2%)	19 (8.5%)	17 (16.0%)	37 (10.5%)	1 (2.8%)	10 (4.8%)	7 (6.9%)	18 (5.2%)
TEAE leading to discontinuation of steroids[a]	1 (4.2%)	15 (6.7%)	16 (15.1%)	32 (9.0%)	1 (2.8%)	10 (4.8%)	8 (7.8%)	19 (5.5%)
TEAE leading to discontinuation of daratumumab	0	0	0	0	1 (2.8%)	9 (4.3%)	13 (12.7%)	23 (6.6%)
Death due to AEs	1 (4.2%)	11 (4.9%)	7 (6.6%)	19 (5.4%)	3 (8.3%)	7 (3.4%)	9 (8.8%)	19 (5.5%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: TEAE = treatment-emergent adverse event.
[a] Prednisone or prednisolone for VMP group; for D-VMP group, other corticosteroids (i.e. dexamethasone, methylprednisolone, hydrocortisone, betamethasone) may have been used as substitutes.
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.
Modified from TSFAE01C.RTF [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFAE01C.SAS] 28AUG2017, 12:53

Table 48: Sex

TSFAE01D: Overview of Treatment-emergent Adverse Events by Sex; Safety Analysis Set (Study 54767414MMY3007)

	VMP n (%)			D-VMP n (%)		
	Male	Female	Total	Male	Female	Total
Analysis set: safety	166	188	354	159	187	346
Any TEAE	159 (95.8%)	183 (97.3%)	342 (96.6%)	151 (95.0%)	183 (97.9%)	334 (96.5%)
At least one related[a]	139 (83.7%)	163 (86.7%)	302 (85.3%)	139 (87.4%)	168 (89.8%)	307 (88.7%)
At least one related to bortezomib	131 (78.9%)	153 (81.4%)	284 (80.2%)	111 (69.8%)	151 (80.7%)	262 (75.7%)
At least one related to melphalan	102 (61.4%)	130 (69.1%)	232 (65.5%)	95 (59.7%)	128 (68.4%)	223 (64.5%)
At least one related to steroids[b]	58 (34.9%)	87 (46.3%)	145 (41.0%)	73 (45.9%)	93 (49.7%)	166 (48.0%)
At least one related to daratumumab	0	0	0	94 (59.1%)	112 (59.9%)	206 (59.5%)
Maximum toxicity grade						
Grade 1	5 (3.0%)	6 (3.2%)	11 (3.1%)	6 (3.8%)	6 (3.2%)	12 (3.5%)
Grade 2	30 (18.1%)	25 (13.3%)	55 (15.5%)	24 (15.1%)	26 (13.9%)	50 (14.5%)
Grade 3	81 (48.8%)	99 (52.7%)	180 (50.8%)	87 (54.7%)	95 (50.8%)	182 (52.6%)
Grade 4	30 (18.1%)	47 (25.0%)	77 (21.8%)	22 (13.8%)	49 (26.2%)	71 (20.5%)
Grade 5	13 (7.8%)	6 (3.2%)	19 (5.4%)	12 (7.5%)	7 (3.7%)	19 (5.5%)
Any serious TEAE	52 (31.3%)	63 (33.5%)	115 (32.5%)	71 (44.7%)	73 (39.0%)	144 (41.6%)
At least one related[a]	24 (14.5%)	30 (16.0%)	54 (15.3%)	28 (17.6%)	37 (19.8%)	65 (18.8%)
At least one related to bortezomib	22 (13.3%)	21 (11.2%)	43 (12.1%)	20 (12.6%)	21 (11.2%)	41 (11.8%)
At least one related to melphalan	12 (7.2%)	20 (10.6%)	32 (9.0%)	14 (8.8%)	18 (9.6%)	32 (9.2%)
At least one related to steroids[b]	5 (3.0%)	14 (7.4%)	19 (5.4%)	14 (8.8%)	15 (8.0%)	29 (8.4%)
At least one related to daratumumab	0	0	0	20 (12.6%)	22 (11.8%)	42 (12.1%)
TEAE leading to discontinuation of bortezomib	25 (15.1%)	14 (7.4%)	39 (11.0%)	12 (7.5%)	15 (8.0%)	27 (7.8%)
At least one related to bortezomib	16 (9.6%)	9 (4.8%)	25 (7.1%)	7 (4.4%)	8 (4.3%)	15 (4.3%)
TEAE leading to discontinuation of melphalan	20 (12.0%)	17 (9.0%)	37 (10.5%)	7 (4.4%)	11 (5.9%)	18 (5.2%)
At least one related to melphalan	2 (1.2%)	7 (3.7%)	9 (2.5%)	1 (0.6%)	2 (1.1%)	3 (0.9%)
TEAE leading to discontinuation of steroids[b]	19 (11.4%)	13 (6.9%)	32 (9.0%)	8 (5.0%)	11 (5.9%)	19 (5.5%)
At least one related to steroids[b]	2 (1.2%)	2 (1.1%)	4 (1.1%)	3 (1.9%)	2 (1.1%)	5 (1.4%)
TEAE leading to discontinuation of daratumumab	0	0	0	10 (6.3%)	13 (7.0%)	23 (6.6%)
At least one related to daratumumab	0	0	0	4 (2.5%)	5 (2.7%)	9 (2.6%)
Death due to AEs	13 (7.8%)	6 (3.2%)	19 (5.4%)	12 (7.5%)	7 (3.7%)	19 (5.5%)
At least one related to bortezomib	1 (0.6%)	0	1 (0.3%)	2 (1.3%)	0	2 (0.6%)
At least one related to melphalan	0	1 (0.5%)	1 (0.3%)	2 (1.3%)	1 (0.5%)	3 (0.9%)
At least one related to steroids[b]	0	0	0	2 (1.3%)	1 (0.5%)	3 (0.9%)
At least one related to daratumumab	0	0	0	1 (0.6%)	0	1 (0.3%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 4 components of study treatment: bortezomib, melphalan, steriods, daratumunab.
[b] Prednisone or prednisolone for VMP group; for D-VMP group, other corticosteroids (i.e. dexamethasone, methylprednisolone, hydrocortisone, betamethasone) may have been used as substitutes.
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.

[TSFAE01D.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFAE01D.SAS] 28AUG2017, 12:53

Race

The majority of subjects in the study were white (293 subjects [85%] in the D-VMP group and 302 subjects [85%] in the VMP group). Due to the small number of subjects in the study with race of "Other" (53 subjects in the D-VMP group and 52 subjects in the VMP group), limited interpretation of safety data categorized by race can be performed.

Table 49: Region

TSFAE01F: Overview of Treatment-emergent Adverse Events by Region; Safety Analysis Set (Study 54767414MMY3007)

	VMP n (%)			D-VMP n (%)		
	Europe [a]	Other	Total	Europe [a]	Other	Total
Analysis set: safety	293	61	354	286	60	346
Any TEAE	282 (96.2%)	60 (98.4%)	342 (96.6%)	274 (95.8%)	60 (100.0%)	334 (96.5%)
At least one related[b]	246 (84.0%)	56 (91.8%)	302 (85.3%)	247 (86.4%)	60 (100.0%)	307 (88.7%)
At least one related to bortezomib	229 (78.2%)	55 (90.2%)	284 (80.2%)	206 (72.0%)	56 (93.3%)	262 (75.7%)
At least one related to melphalan	186 (63.5%)	46 (75.4%)	232 (65.5%)	176 (61.5%)	47 (78.3%)	223 (64.5%)
At least one related to steroids[c]	106 (36.2%)	39 (63.9%)	145 (41.0%)	122 (42.7%)	44 (73.3%)	166 (48.0%)
At least one related to daratumumab	0	0	0	152 (53.1%)	54 (90.0%)	206 (59.5%)
Maximum toxicity grade						
Grade 1	8 (2.7%)	3 (4.9%)	11 (3.1%)	11 (3.8%)	1 (1.7%)	12 (3.5%)
Grade 2	51 (17.4%)	4 (6.6%)	55 (15.5%)	49 (17.1%)	1 (1.7%)	50 (14.5%)
Grade 3	149 (50.9%)	31 (50.8%)	180 (50.8%)	150 (52.4%)	32 (53.3%)	182 (52.6%)
Grade 4	58 (19.8%)	19 (31.1%)	77 (21.8%)	46 (16.1%)	25 (41.7%)	71 (20.5%)
Grade 5	16 (5.5%)	3 (4.9%)	19 (5.4%)	18 (6.3%)	1 (1.7%)	19 (5.5%)
Any serious TEAE	90 (30.7%)	25 (41.0%)	115 (32.5%)	117 (40.9%)	27 (45.0%)	144 (41.6%)
At least one related[b]	37 (12.6%)	17 (27.9%)	54 (15.3%)	47 (16.4%)	18 (30.0%)	65 (18.8%)
At least one related to bortezomib	26 (8.9%)	17 (27.9%)	43 (12.1%)	29 (10.1%)	12 (20.0%)	41 (11.8%)
At least one related to melphalan	22 (7.5%)	10 (16.4%)	32 (9.0%)	23 (8.0%)	9 (15.0%)	32 (9.2%)
At least one related to steroids[c]	12 (4.1%)	7 (11.5%)	19 (5.4%)	18 (6.3%)	11 (18.3%)	29 (8.4%)
At least one related to daratumumab	0	0	0	29 (10.1%)	13 (21.7%)	42 (12.1%)
TEAE leading to discontinuation of bortezomib	27 (9.2%)	12 (19.7%)	39 (11.0%)	23 (8.0%)	4 (6.7%)	27 (7.8%)
At least one related to bortezomib	14 (4.8%)	11 (18.0%)	25 (7.1%)	13 (4.5%)	2 (3.3%)	15 (4.3%)
TEAE leading to discontinuation of melphalan	25 (8.5%)	12 (19.7%)	37 (10.5%)	15 (5.2%)	3 (5.0%)	18 (5.2%)
At least one related to melphalan	7 (2.4%)	2 (3.3%)	9 (2.5%)	2 (0.7%)	1 (1.7%)	3 (0.9%)
TEAE leading to discontinuation of steroids[c]	21 (7.2%)	11 (18.0%)	32 (9.0%)	16 (5.6%)	3 (5.0%)	19 (5.5%)
At least one related to steroids[c]	3 (1.0%)	1 (1.6%)	4 (1.1%)	4 (1.4%)	1 (1.7%)	5 (1.4%)
TEAE leading to discontinuation of daratumumab	0	0	0	18 (6.3%)	5 (8.3%)	23 (6.6%)
At least one related to daratumumab	0	0	0	7 (2.4%)	2 (3.3%)	9 (2.6%)
Death due to AEs	16 (5.5%)	3 (4.9%)	19 (5.4%)	18 (6.3%)	1 (1.7%)	19 (5.5%)
At least one related to bortezomib	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	1 (1.7%)	2 (0.6%)
At least one related to melphalan	1 (0.3%)	0	1 (0.3%)	2 (0.7%)	1 (1.7%)	3 (0.9%)
At least one related to steroids[c]	0	0	0	2 (0.7%)	1 (1.7%)	3 (0.9%)
At least one related to daratumumab	0	0	0	0	1 (1.7%)	1 (0.3%)

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: TEAE = treatment-emergent adverse event.
[a] Includes Turkey and Russian Federation (stratified as OTHER at the randomization).
[b] TEAEs related to at least 1 of the 4 components of study treatment: bortezomib, melphalan, steriods, daratumunab.
[c] Prednisone or prednisolone for VMP group; for D-VMP group, other corticosteroids (i.e. dexamethasone, methylprednisolone, hydrocortisone, betamethasone) may have been used as substitutes.
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.

[TSFAE01F.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFAE01F.SAS] 28AUG2017, 12:53

Table 50: Baseline renal function

TSFAE01G: Overview of Treatment-emergent Adverse Events by Baseline Renal Function (Creatinine Clearance) Status; Safety Analysis Set (Study 54767414MMY3007)

	VMP n (%)					D-VMP 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	7	137	149	61	354	2	144	140	60	346
Any TEAE	7 (100.0%)	135 (98.5%)	142 (95.3%)	58 (95.1%)	342 (96.6%)	2 (100.0%)	139 (96.5%)	138 (98.6%)	55 (91.7%)	334 (96.5%)
At least one related[a]	5 (71.4%)	122 (89.1%)	124 (83.2%)	51 (83.6%)	302 (85.3%)	2 (100.0%)	130 (90.3%)	124 (88.6%)	51 (85.0%)	307 (88.7%)
At least one related to bortezomib	5 (71.4%)	118 (86.1%)	117 (78.5%)	44 (72.1%)	284 (80.2%)	1 (50.0%)	111 (77.1%)	107 (76.4%)	43 (71.7%)	262 (75.7%)
At least one related to melphalan	3 (42.9%)	100 (73.0%)	97 (65.1%)	32 (52.5%)	232 (65.5%)	1 (50.0%)	101 (70.1%)	85 (60.7%)	36 (60.0%)	223 (64.5%)
At least one related to steroids[b]	3 (42.9%)	63 (46.0%)	59 (39.6%)	20 (32.8%)	145 (41.0%)	2 (100.0%)	69 (47.9%)	70 (50.0%)	25 (41.7%)	166 (48.0%)
At least one related to daratumumab	0	0	0	0	0	1 (50.0%)	87 (60.4%)	81 (57.9%)	37 (61.7%)	206 (59.5%)
Maximum toxicity grade										
Grade 1	0	4 (2.9%)	4 (2.7%)	3 (4.9%)	11 (3.1%)	0	5 (3.5%)	4 (2.9%)	3 (5.0%)	12 (3.5%)
Grade 2	0	18 (13.1%)	27 (18.1%)	10 (16.4%)	55 (15.5%)	0	15 (10.4%)	29 (20.7%)	6 (10.0%)	50 (14.5%)
Grade 3	4 (57.1%)	70 (51.1%)	76 (51.0%)	30 (49.2%)	180 (50.8%)	1 (50.0%)	74 (51.4%)	69 (49.3%)	38 (63.3%)	182 (52.6%)
Grade 4	1 (14.3%)	35 (25.5%)	29 (19.5%)	12 (19.7%)	77 (21.8%)	0	35 (24.3%)	29 (20.7%)	7 (11.7%)	71 (20.5%)
Grade 5	2 (28.6%)	8 (5.8%)	6 (4.0%)	3 (4.9%)	19 (5.4%)	1 (50.0%)	10 (6.9%)	7 (5.0%)	1 (1.7%)	19 (5.5%)
Any serious TEAE	4 (57.1%)	59 (43.1%)	36 (24.2%)	16 (26.2%)	115 (32.5%)	2 (100.0%)	62 (43.1%)	61 (43.6%)	19 (31.7%)	144 (41.6%)
At least one related[a]	0	32 (23.4%)	14 (9.4%)	8 (13.1%)	54 (15.3%)	1 (50.0%)	34 (23.6%)	22 (15.7%)	8 (13.3%)	65 (18.8%)
At least one related to bortezomib	0	29 (21.2%)	10 (6.7%)	4 (6.6%)	43 (12.1%)	1 (50.0%)	21 (14.6%)	13 (9.3%)	6 (10.0%)	41 (11.8%)
At least one related to melphalan	0	23 (16.8%)	4 (2.7%)	5 (8.2%)	32 (9.0%)	0	18 (12.5%)	9 (6.4%)	5 (8.3%)	32 (9.2%)
At least one related to steroids[b]	0	11 (8.0%)	4 (2.7%)	4 (6.6%)	19 (5.4%)	0	16 (11.1%)	10 (7.1%)	3 (5.0%)	29 (8.4%)
At least one related to daratumumab	0	0	0	0	0	0	21 (14.6%)	15 (10.7%)	6 (10.0%)	42 (12.1%)
TEAE leading to discontinuation of bortezomib	1 (14.3%)	18 (13.1%)	13 (8.7%)	7 (11.5%)	39 (11.0%)	1 (50.0%)	13 (9.0%)	11 (7.9%)	2 (3.3%)	27 (7.8%)
At least one related to bortezomib	1 (14.3%)	14 (10.2%)	8 (5.4%)	2 (3.3%)	25 (7.1%)	0	8 (5.6%)	6 (4.3%)	1 (1.7%)	15 (4.3%)
TEAE leading to discontinuation of melphalan	2 (28.6%)	17 (12.4%)	12 (8.1%)	6 (9.8%)	37 (10.5%)	1 (50.0%)	8 (5.6%)	8 (5.7%)	1 (1.7%)	18 (5.2%)
At least one related to melphalan	2 (28.6%)	4 (2.9%)	1 (0.7%)	2 (3.3%)	9 (2.5%)	0	2 (1.4%)	1 (0.7%)	0	3 (0.9%)
TEAE leading to discontinuation of steroids[b]	1 (14.3%)	15 (10.9%)	11 (7.4%)	5 (8.2%)	32 (9.0%)	1 (50.0%)	8 (5.6%)	9 (6.4%)	1 (1.7%)	19 (5.5%)
At least one related to steroids[b]	0	3 (2.2%)	1 (0.7%)	0	4 (1.1%)	0	3 (2.1%)	2 (1.4%)	0	5 (1.4%)
TEAE leading to discontinuation of daratumumab	0	0	0	0	0	1 (50.0%)	9 (6.3%)	11 (7.9%)	2 (3.3%)	23 (6.6%)
At least one related to daratumumab	0	0	0	0	0	0	3 (2.1%)	6 (4.3%)	0	9 (2.6%)
Death due to AEs	2 (28.6%)	8 (5.8%)	6 (4.0%)	3 (4.9%)	19 (5.4%)	1 (50.0%)	10 (6.9%)	7 (5.0%)	1 (1.7%)	19 (5.5%)
At least one related to bortezomib	0	1 (0.7%)	0	0	1 (0.3%)	0	2 (1.4%)	0	0	2 (0.6%)
At least one related to melphalan	0	0	0	1 (1.6%)	1 (0.3%)	0	2 (1.4%)	0	1 (1.7%)	3 (0.9%)
At least one related to steroids[b]	0	0	0	0	0	0	3 (2.1%)	0	0	3 (0.9%)
At least one related to daratumumab	0	0	0	0	0	0	1 (0.7%)	0	0	1 (0.3%)

Table 51: ECOG

TSFECOG02: Shift Summary of Baseline versus on Treatment and Worst Score During Treatment in ECOG Performance Score; Safety Analysis Set (Study 54767414MMY3007)

	VMP Baseline				D-VMP Baseline			
	0	1	2	Total	0	1	2	Total
ECOG Performance Score								
Month 3								
0	74	20	5	99	62	17	10	89
1	12	119	29	160	12	146	44	202
2	5	10	33	48	0	4	23	27
3	0	0	0	0	0	0	3	3
4	0	0	0	0	0	1	0	1
5	0	0	0	0	0	0	0	0
Total	91	149	67	307	74	168	80	322
Month 6								
0	70	24	7	101	61	29	12	102
1	12	108	32	152	12	130	49	191
2	1	8	20	29	0	2	12	14
3	1	0	0	1	0	0	3	3
4	0	0	0	0	0	1	0	1
5	0	0	1	1	0	0	0	0
Total	84	140	60	284	73	162	76	311
Month 9								
0	62	25	7	94	59	27	15	101
1	15	97	30	142	12	124	44	180
2	1	7	16	24	0	4	10	14
3	0	0	0	0	0	0	2	2
4	0	0	0	0	0	1	0	1
5	0	0	0	0	0	0	0	0
Total	78	129	53	260	71	156	71	298
Month 12								
0	56	24	9	89	57	24	15	96
1	16	79	27	122	10	108	39	157
2	1	4	10	15	1	4	8	13
3	0	0	0	0	0	0	1	1
4	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
Total	73	107	46	226	68	136	63	267
Month 18								
0	17	8	4	29	21	16	8	45
1	4	32	8	44	7	39	19	65
2	0	1	3	4	0	2	4	6
3	0	0	0	0	0	1	0	1
4	0	0	1	1	0	1	0	1
5	0	0	0	0	0	0	0	0
Total	21	41	16	78	28	59	31	118
Month 24								
0	3	2	1	6	1	3	0	4
1	1	2	0	3	1	5	0	6
2	0	0	0	0	0	1	0	1
3	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0
Total	4	4	1	9	2	9	0	11
Worst ECOG Score								
0	60	12	3	75	48	14	7	69
1	25	124	29	178	25	141	46	212
2	5	16	33	54	1	13	23	37
3	1	0	0	1	0	1	5	6
4	0	0	1	1	0	1	0	1
5	0	0	1	1	0	0	0	0
Total	91	152	67	310	74	170	81	325

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.

[TSFECOG02.RTF] [/SAS/3699/54767414MMY3007/FILES/RE/IA2/PROGRAMS/TSFECOG02.SAS] 28AUG2017, 05:59

Safety related to drug-drug interactions and other interactions

No dedicated drug-drug interaction studies were performed, and no interactions of daratumumab and small molecule drugs such as bortezomib, melphalan, and prednisone are expected as there is no overlapping pathway of elimination. In Study MMY3003, 286 patients were treated with daratumumab in combination with lenalidomide and dexamethasone (DRd), and in Study MMY3004, 251 patients were treated with

daratumumab in combination bortezomib and dexamethasone (DVd). No signs of drug-drug interaction with daratumumab were identified, and combination therapy with lenalidomide and dexamethasone, or bortezomib and dexamethasone, are approved indications for daratumumab.

Discontinuation due to adverse events

Table 52: No. of subjects with 1 or more TEAEs leading to Discontinuation with a frequency of at least 1% in either treatment group

	VMP			D-VMP		
	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	354			346		
Total number of subjects with TEAE leading to discontinuation of study treatment[a]	32 (9.0%)	17 (4.8%)	4 (1.1%)	17 (4.9%)	15 (4.3%)	1 (0.3%)
MedDRA system organ class / preferred term						
Nervous system disorders	13 (3.7%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	0
Peripheral sensory neuropathy	6 (1.7%)	1 (0.3%)	0	0	0	0

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: TEAE = treatment-emergent adverse event.
[a] 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.

Table 53: No. of subjects with 1 or more TEAEs leading to Discontinuation

	VMP			D-VMP		
	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	354			346		
Total number of subjects with TEAE leading to discontinuation of study treatment[a]	32 (9.0%)	17 (4.8%)	4 (1.1%)	17 (4.9%)	15 (4.3%)	1 (0.3%)
MedDRA system organ class / preferred term						
Infections and infestations	5 (1.4%)	3 (0.8%)	1 (0.3%)	3 (0.9%)	3 (0.9%)	0
Upper respiratory tract infection	0	0	0	2 (0.6%)	2 (0.6%)	0
Pneumonia	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0
Enterococcal bacteraemia	1 (0.3%)	1 (0.3%)	0	0	0	0
Pelvic infection	1 (0.3%)	1 (0.3%)	0	0	0	0
Pneumonia bacterial	1 (0.3%)	0	1 (0.3%)	0	0	0
Tuberculous pleurisy	1 (0.3%)	1 (0.3%)	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3%)	1 (0.3%)	0	3 (0.9%)	2 (0.6%)	1 (0.3%)
Bile duct cancer	0	0	0	1 (0.3%)	0	1 (0.3%)
Oesophageal adenocarcinoma	0	0	0	1 (0.3%)	1 (0.3%)	0
Renal cell carcinoma	0	0	0	1 (0.3%)	1 (0.3%)	0
Adenocarcinoma of colon	1 (0.3%)	1 (0.3%)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	4 (1.1%)	1 (0.3%)	1 (0.3%)	3 (0.9%)	2 (0.6%)	0
Acute respiratory failure	0	0	0	1 (0.3%)	1 (0.3%)	0
Dyspnoea	0	0	0	1 (0.3%)	1 (0.3%)	0
Pneumonitis	0	0	0	1 (0.3%)	0	0
Tachypnoea	0	0	0	1 (0.3%)	1 (0.3%)	0
Wheezing	0	0	0	1 (0.3%)	1 (0.3%)	0
Epistaxis	1 (0.3%)	0	0	0	0	0
Interstitial lung disease	1 (0.3%)	0	0	0	0	0
Pneumothorax spontaneous	1 (0.3%)	1 (0.3%)	0	0	0	0
Pulmonary embolism	1 (0.3%)	0	1 (0.3%)	0	0	0
Blood and lymphatic system disorders	1 (0.3%)	1 (0.3%)	0	2 (0.6%)	2 (0.6%)	0
Anaemia	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0
Thrombocytopenia	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0
Cardiac disorders	0	0	0	1 (0.3%)	1 (0.3%)	0
Cardiac failure acute	0	0	0	1 (0.3%)	1 (0.3%)	0
Gastrointestinal disorders	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0
Rectal haemorrhage	0	0	0	1 (0.3%)	1 (0.3%)	0
Vomiting	1 (0.3%)	1 (0.3%)	0	0	0	0
General disorders and administration site conditions	4 (1.1%)	4 (1.1%)	0	1 (0.3%)	1 (0.3%)	0
Fatigue	2 (0.6%)	2 (0.6%)	0	1 (0.3%)	1 (0.3%)	0
Generalised oedema	1 (0.3%)	1 (0.3%)	0	0	0	0
Malaise	1 (0.3%)	0	0	0	0	0
Multiple organ dysfunction syndrome	1 (0.3%)	1 (0.3%)	0	0	0	0
Investigations	0	0	0	1 (0.3%)	1 (0.3%)	0
Oxygen saturation decreased	0	0	0	1 (0.3%)	1 (0.3%)	0
Metabolism and nutrition disorders	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	0
Marasmus	0	0	0	1 (0.3%)	1 (0.3%)	0

Tumour lysis syndrome	1 (0.3%)	0	1 (0.3%)	0	0	0
Nervous system disorders	13 (3.7%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	0
Parkinson's disease	0	0	0	1 (0.3%)	1 (0.3%)	0
Ataxia	1 (0.3%)	1 (0.3%)	0	0	0	0
Cerebral infarction	1 (0.3%)	0	1 (0.3%)	0	0	0
Ischaemic stroke	1 (0.3%)	0	0	0	0	0
Neuralgia	2 (0.6%)	0	0	0	0	0
Paraesthesia	1 (0.3%)	0	0	0	0	0
Peripheral motor neuropathy	1 (0.3%)	0	0	0	0	0
Peripheral sensory neuropathy	6 (1.7%)	1 (0.3%)	0	0	0	0
Psychiatric disorders	0	0	0	1 (0.3%)	1 (0.3%)	0
Agitation	0	0	0	1 (0.3%)	1 (0.3%)	0
Vascular disorders	0	0	0	1 (0.3%)	1 (0.3%)	0
Hypovolaemic shock	0	0	0	1 (0.3%)	1 (0.3%)	0
Injury, poisoning and procedural complications	1 (0.3%)	1 (0.3%)	0	0	0	0
Femur fracture	1 (0.3%)	1 (0.3%)	0	0	0	0
Renal and urinary disorders	2 (0.6%)	2 (0.6%)	0	0	0	0
Acute kidney injury	1 (0.3%)	1 (0.3%)	0	0	0	0
Chronic kidney disease	1 (0.3%)	1 (0.3%)	0	0	0	0
Skin and subcutaneous tissue disorders	2 (0.6%)	1 (0.3%)	0	0	0	0
Erythema multiforme	1 (0.3%)	1 (0.3%)	0	0	0	0
Rash generalised	1 (0.3%)	0	0	0	0	0

Key: VMP=bortezomib-melphalan-prednisone; D-VMP=daratumumab-bortezomib-melphalan-prednisone.
Key: TEAE = treatment-emergent adverse event.
[a] 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.

Dose modifications

A higher proportion of subjects in the D-VMP group (70%) had a TEAE leading to treatment cycle delays or dose modifications for any study drug (ie, dose delays, dose skipping, schedule change or dose reduction) compared with the VMP group (63%). Of note, dose reductions to daratumumab were not allowed, thus subjects could only delay or skip daratumumab. In addition, a higher proportion of subjects in the D-VMP group (49%) had a Grade 3 or 4 TEAE leading to treatment cycle delays or dose modifications for any study drug compared with the VMP group (40%). The most common (>5% in either group) TEAEs leading to treatment cycle delays or dose modifications in the D-VMP and VMP groups, respectively, were thrombocytopenia (20% and 16%), neutropenia (17% and 16%), peripheral sensory neuropathy (15% and 18%), pneumonia (11% and 3%), upper respiratory tract infection (10% and 4%), bronchitis (8% and 3%), neuralgia (6% and 4%), and diarrhea (reported in 5% of subjects in both groups).

A similar proportion of subjects in the D-VMP group (57%) and VMP group (56%) had a TEAE leading to dose modifications of bortezomib. The most commonly reported (>5% in either group) TEAEs leading to dose modifications of bortezomib in the D-VMP and VMP groups, respectively, were peripheral sensory neuropathy (15% and 18%), thrombocytopenia (12% and 12%), neutropenia (10% and 11%), pneumonia (7% and 2%), neuralgia (6% and 3%), and upper respiratory tract infection (6% and 3%). A similar proportion of subjects in the D-VMP group (22%) had a TEAE leading to dose modifications of melphalan compared with the VMP group (23%).

The most commonly reported (>5% in either group) TEAEs leading to dose modifications of melphalan treatment in the D-VMP and VMP groups, respectively, were thrombocytopenia (11% and 8%), and neutropenia (7% and 9%).

A similar proportion of subjects in the D-VMP group (8%) had a TEAE leading to dose modifications of steroids compared with the VMP group (7%). No TEAEs were reported for more than 2% for either group.

Forty percent (40%) of subjects in the D-VMP group had a TEAE leading to dose modifications of daratumumab; 31% had a Grade 3 or 4 TEAE leading to dose modifications of daratumumab. The most common (>5%) TEAEs leading to dose modifications of daratumumab were thrombocytopenia (12%), neutropenia (11%), and pneumonia (7%).

Post marketing experience

The proposed indication is not marketed.

2.5.1. Discussion on clinical safety

The majority of patients experienced an AE, however the question is whether the pattern of AEs change as a function of time. The MAH has analysed TEAEs in the D-VMP group during the first part of the study compared with the second (maintenance phase) part of the study. The major difference in TEAEs between the two treatment groups in the first 9 cycles was more infections and infestations, especially pneumonia in the D-VMP group compared with the VMP group. After cycle 9, ie during daratumumab monotherapy, 46% of the patients had a reported TEAE of new onset, the most frequent being upper respiratory tract infection (6%). Other TEAEs occurred at a low frequency (<5%) and no new TEAE with a high frequency was reported during daratumumab monotherapy.

The most common AEs are related to blood and lymphatic disorders, infections, GI disorders, peripheral neuropathy, hypertension, musculoskeletal system, decreased appetite and respiratory system. Main differences in disfavour of D+VMP are seen with regard to upper respiratory tract infections, pneumonia, bronchitis, cough, dyspnoea and hypertension. This reflects the known safety profile of Dara and VMP. Infections and infestations (including pneumonia and upper respiratory tract infection), cough, hypertension and dyspnoea are very common in patients being treated with Dara. Hypertension, cough, bronchitis and dyspnoea are related to IRR that are observed in approximately 50% of patients treated with Dara.

The most common Grade 3/4 AEs were as expected in this group of patients, neutropenia, thrombocytopenia, anaemia and pneumonia. Except for pneumonia, the addition of Dara to VMP did not result in clinically relevant difference between the two treatment arms. This is reassuring. As mentioned before, pneumonia is a very common AE related to Dara, however, this AE is manageable in the clinical setting with antibiotics, etc.

Not surprisingly, IRRs are very common and well known in patients treated with Dara and in the D+VMP arm. The majority of the events are Grade 1 or 2, no Grade 5 AEs were reported. The SmPC gives clear precautionary measures in order to minimise the risk of IRRs.

Even though the thrombocytopenia is very common, the incidence of haemorrhage is low in both treatment arms, but slightly higher in the D+VMP arm. However, the majority of the events are Grade 1-2, and the incidence of Grade 4 AEs is similar between the two treatment arms. Contusions seems to be relatively more common in the D+VMP arm, but these events were found to be related to the chemotherapy, no action was taken and they all resolved spontaneously.

Peripheral neuropathy is a debilitating AE related to bortezomib. However, the weekly administration of bortezomib leads to better tolerance. The incidence of Grade 3/4 peripheral neuropathy is low in both treatment arms, but considerable lower in the D+VMP arm. This is reassuring. Nonetheless, bortezomib was discontinued in 8% vs. 11% of the subjects in D+VMP and VMP respectively.

The majority of the patients that died, did so during the study. Overall, the number of subjects that died during the study, within 30 days of last dose and within 60 day of the first 60 days, is similar between the two treatment groups. However, there are some discrepancies between the number of Grade 5 AEs (reported on table 5 of the SCS) and deaths within 30 days from the last study dose (reported on tables 10 and 11 of the

SCS), with a total of 8 more deaths reported as grade 5 AEs. The MAH has clarified, that most of the events were found to be related to the chemotherapy, no action was taken and they all resolved spontaneously.

SAE are more frequent in the D+VMP arm, 41.6% vs. 32.5%. The main difference is driven by infections and infestations. As discussed previously, this reflects the known safety profile of Dara and VMP. Infections and infestations (including pneumonia and upper respiratory tract infection), cough, hypertension and dyspnoea are very common in patients being treated with Dara. However, most events were clinically manageable and thereby avoiding discontinuation from study treatment.

Overall, abnormal chemistry values of Grade 3 or 4 were low in both treatment arms, except for hypernatremia and hyperglycaemia. These AEs are easily manageable in the clinical setting. With regard to liver parameters, 2 patients in the D-VMP arm and 4 patients in the VMP arm met the criteria for Hy's law. None of the patients required dose modifications or interruption of the treatment. They all had medical comorbidities, which most likely contributed to the laboratory abnormalities.

Apart from slightly more Grade 4 AEs in females, no relevant differences were observed with regard to age, sex, region or race. Patients with impaired renal and hepatic function had, not surprisingly, slightly more AEs and discontinuations in both treatment arms.

Although numbers censored in each group are small, it is noted, that 12 (19%) had a new plasmacytoma in the D-VMP arm compared to 5 (4.5%) in the VMP group. The MAH found no scientific explanation to this difference.

Overall, discontinuation rates are low in both treatment arms, however, a difference in favour of D+VMP is observed. This is reassuring and seems to reflect the fact that the combination of Dara and VMP is well-tolerated and that the observed AEs are manageable in the clinical setting with supportive therapy and dose modifications, which were more common in the D+VMP arm. There is no clear pattern in the AEs leading to discontinuation.

Finallly, but yet most importantly, as previously discussed in relation to the assessment of efficacy, the study population may not be considered representative of a population "ineligible for ASCT" in most EU countries according to current standards.

The MAH has provided an update with 4 additional months of follow-up (data cut-off date 12 October, 2017). At that time, 66.2% of subjects in the D-VMP were still receiving treatment, while all subjects in the VMP group had either completed or discontinue treatment. Only 1 additional subject died during the updated safety follow-up, due to the exacerbation of heart failure. This Grade 5 AE was considered as unrelated to study treatment (event narrative provided, not shown in this AR).

Overall, the type and frequency of events occurred during the additional 4 months of follow-up did not change from those reported in the initial follow-up period and no new signals or alarming findings were identified.

The MAH has not provided the information broken down as requested (subgroup 1. patients ≥70 years old; subgroup 2. patients between the ages of 65 and 70, with important co-morbidities and/or a poor performance status (i.e., ECOG 2)), but pooled according to their definition of subjects unfit for transplant (subjects <65 years old with significant co-morbidity or ECOG PS Score=2; or subjects 65-69 years old with ECOG PS=2; or subjects at least 70 years old. Overall, the safety findings do not substantially differ from those in the control group. However, slightly higher frequencies (e.g., serious AEs, certain SOCs) are observed when compared to the overall population. In light of the efficacy data available, separate safety data on population subsets considered of special interest due to their vulnerability to added toxicity (e.g., those with ECOG PS score =2) are deemed critical for the B/R discussion and for the individualized prescribing decision**.**

No subject had treatment-emergent interference for blood typing reported during the study. A survey of the effectiveness of the educational materials regarding the minimization of risk of interference of blood typing is ongoing (see RMP).

Overall, the observed safety profile is as expected and in line with the safety profile of Dara and VMP. Discontinuation rate is low, reflecting the fact that AEs are manageable in the clinical setting with supportive therapy and dose modification. The provided safety update is consistent with the primary analyses.

2.5.2. Conclusions on clinical safety

The addition of daratumumab to VMP is well-tolerated. The observed safety profile is as expected and in line with the safety profile of daratumumab and VMP.

2.5.3. PSUR cycle

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

2.6. Risk management plan

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

The PRAC considered that the risk management plan version 3.1 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the Risk Management Plan version 3.2 with the following content (new text marked as underlined, deletions marked as strikethrough):

Safety concerns

Summary of safety concerns	
Important identified risks	~~Infusion Related Reactions (IRRs)~~ Interference for blood typing (minor antigen) (Positive Indirect Coombs' test) ~~Neutropenia~~ ~~Thrombocytopenia~~
Important potential risks	~~Infections~~ ~~Prolonged decrease in NK cells~~ Tumour lysis syndrome QTc prolongation Immunogenicity ~~Intravascular haemolysis~~
Missing information	Use in pregnancy and lactation Reproductive and developmental toxicity

Summary of safety concerns	
	~~Use in the elderly ≥ 75 years~~ ~~Use in patients with moderate or severe hepatic impairment~~ Long term use (> 2 years)

Pharmacovigilance plan

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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
Trial SMM2001: A randomised Phase 2 trial to evaluate 3 daratumumab dose schedules in smouldering multiple myeloma. Ongoing	As a secondary objective to determine if daratumumab has an effect on QT interval	QTc prolongation	Trial completion	3rd Quarter 2018
			Final report	4th Quarter 2018
Investigate new method for detecting antidrug antibodies Planned	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

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
~~Infusion Related Reactions~~	~~Routine risk minimisation measures:~~ • ~~SmPC Section 4.2 and 4.4, where advice is given regarding administration of pre-medication with antihistamines, antipyretics and corticosteroids prior to daratumumab infusion to reduce the risk of infusion related reactions, for monitoring throughout the infusion and the post-infusion period, and administration of post-infusion medication with oral corticosteroids to reduce the risk of delayed infusion related reactions. These sections also describe treatment measures to manage infusion related reactions.~~ • ~~Patient Leaflet Section 4, where information on signs and symptoms of infusion related reactions are described for patients.~~ ~~Additional risk minimisation measures:~~ • ~~None.~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:~~ • ~~None.~~ ~~Additional pharmacovigilance activities:~~ • ~~None.~~
Interference for blood typing (minor antigen) (Positive Indirect Coombs' test)	Routine risk minimisation 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 Health Care Professionals to notify blood transfusion centres of this interference with indirect antiglobulin tests in the event of a planned transfusion, • Patient Leaflet 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 minimisation measures: • Distribution of educational materials and Patient Alert Cards to Health Care Professionals and Blood banks as described in the Patient Leaflet, in Annex II, D.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • A guided targeted follow-up questionnaire to collect additional information concerning adverse events associated with interference and transfusion reactions. Additional pharmacovigilance activities: • 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 programme.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
~~Neutropenia~~	~~Routine risk minimisation measures:~~ • ~~SmPC Section 4.4, where advice is given to periodically monitor complete blood cell counts during daratumumab treatment, to monitor patients with neutropenia for signs of infection, to delay daratumumab administration if required to allow recovery of blood cell counts, and to consider supportive care with growth factors.~~ • ~~Patient Leaflet Section 4, where patients are informed that daratumumab can decrease white blood cell counts and instructs patients to inform their healthcare provider if they develop fever.~~ ~~Additional risk minimisation measures:~~ • ~~None.~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:~~ • ~~None.~~ ~~Additional pharmacovigilance activities:~~ • ~~None.~~
~~Thrombocytopenia~~	~~Routine risk minimisation measures:~~ • ~~SmPC Section 4.4, where advice is given to periodically monitor complete blood cell counts during daratumumab treatment, to delay daratumumab administration if required to allow recovery of blood cell counts, and to consider supportive care with transfusions.~~ • ~~Patient Leaflet Section 4, where patients are informed that daratumumab can lower platelet counts and instructs patients to inform their healthcare provider if they have signs of bruising or bleeding.~~ ~~Additional risk minimisation measures:~~ • ~~None.~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:~~ • ~~None.~~ ~~Additional pharmacovigilance activities:~~ • ~~None.~~
~~Infections~~	~~Routine risk minimisation measures:~~ • ~~SmPC Section 4.8, where information is given regarding infections reported with daratumumab combination and background therapies.~~ • ~~Patient Leaflet Section 4, where patients are informed regarding possible side effects including infections of airways, such as nose, sinuses, or throat.~~ ~~Additional risk minimisation measures:~~ • ~~None.~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:~~ • ~~None.~~ ~~Additional pharmacovigilance activities:~~ • ~~None.~~

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
~~Prolonged decrease in NK cells~~	~~Routine risk minimisation measures:~~ • ~~SmPC Section 5.1, where information is given on the potential for decrease in natural killer cells during treatment with daratumumab.~~ ~~Additional risk minimisation measures:~~ • ~~None.~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:~~ • ~~None.~~ ~~Additional pharmacovigilance activities:~~ • ~~None.~~
Tumour lysis syndrome	Routine risk minimisation measures: • None. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
QTc prolongation	Routine risk minimisation measures: • SmPC Section 5.1, where information is given on results of a study that indicated no large increase in mean QTcF interval following daratumumab infusions. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • A QTc substudy of a trial to evaluate daratumumab dose schedules in patients with smouldering multiple myeloma for assessment of pharmacokinetic and biomarker parameters to determine if daratumumab has an effect on QT prolongation.
Immunogenicity	Routine risk minimisation 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 minimisation 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.
~~Intravascular haemolysis~~	~~Routine risk minimisation measures:~~ • ~~SmPC Section 4.8, which advises that there is a theoretical risk of haemolysis.~~ ~~Additional risk minimisation measures:~~ ~~None.~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:~~ • ~~None.~~ ~~Additional pharmacovigilance activities:~~ • ~~None.~~

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnancy and lactation	Routine risk minimisation measures: • SmPC Section 4.6 and PL Section 2 Other routine risk minimisation measures beyond the Product Information: 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 Other routine risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
~~Use in elderly ≥75 years~~	~~Routine risk communication:~~ • ~~SmPC Sections 4.2 and 5.2~~ ~~Other routine risk minimisation measures beyond the Product Information:~~ ~~None.~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:~~ • ~~None.~~ ~~Additional pharmacovigilance activities:~~ • ~~None.~~
~~Use in patients with moderate or severe hepatic impairment~~	~~Routine risk communication:~~ • ~~SmPC Sections 4.2 and 5.2~~ ~~Other routine risk minimisation measures beyond the Product Information:~~ ~~None.~~	~~Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:~~ • ~~None.~~ ~~Additional pharmacovigilance activities:~~ • ~~None.~~
Long term use (>2 years)	Routine risk communication: • None Other routine risk minimisation measures beyond the Product Information: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of Lithuania and Slovenia.

2.7.1. User consultation

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

Full user testing in compliance with the above mentioned legislative requirements was recently performed (n= 20 participants) on the package leaflet developed for DARZALEX for the initial Marketing Authorisation

Application, which received a positive opinion on 1st April 2016 by the Committee for Medicinal Products for Human Use and a European Commission decision on 20th May 2016.

The package leaflet has been updated since the initial authorisation as part of a Type II variation to extend the indication, however, minimal changes were introduced and the proposed changes reflected language and a format that was consistent with previously approved leaflet.

With the currently proposed indication extension, minimal changes have been introduced to the package leaflet and the proposed changes reflect language and a format that is consistent with that in the currently approved leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The treatment of patients with newly diagnosed multiple myeloma - who are considered ineligible for HDT and ASCT due to their age, presence of comorbidities, and/or physical status.

3.1.2. Available therapies and unmet medical need

The combination of bortezomib plus melphalan plus prednisone (VMP) is a standard triplet regimen approved in the US and Europe for frontline therapy in patients ineligible for transplant. The combination of lenalidomide plus dexamethasone (Rd) is also approved for use in this population in Europe and the US.

Despite these approved regimens, there remains an unmet need for new therapeutic options for the frontline setting directed at alternative MoAs that can better control the disease and provide deeper, more sustained responses and better long-term outcomes.

3.1.3. Main clinical studies

The current submission supporting the approval of daratumumab for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for ASCT is based on data from the Phase 3 study, MMY3007 (clinical cut-off, 12 June 2017), comparing daratumumab 16 mg/kg administered in combination with VMP to VMP alone.

3.2. Favourable effects

Study MMY3007 showed both a statistically significant and clinically highly relevant difference in terms of PFS. The updated median PFS is 19.29 months in the VMP arm and not yet reached in the D-VMP arm. The updated HR is HR=0.46; 95% CI: 0.36, 0.60; p<0.0001. The risk of disease progression is reduced by 54%.

Secondary endpoints are all in line with the primary endpoint, showing statistically highly significant differences in favour of daratumumab. There is almost a doubling in CR or better (24.4% vs. 42.6%), which is very encouraging from a clinical perspective. The ORR is 90.9% in the D-VMP arm compared with 73.9% in the VMP arm. Overall, these results clearly show the added benefit of Dara in combination with VMP in this patient population. The MRD negativity rate is 22.3% vs. 6.2% in the D-VMP and VMP arms respectively. This demonstrates a deep and profound effect of Dara+VMP, indicating a more durable response. Data on durability of MRD negativity are sparce, the MAH will however continue to evaluate MRD according to the MMY3007 protocol.

Results for the secondary endpoints, PFS2, TTP, DOR, and TTNT were updated with additional + 4 months since database cut-off were consistent with the primary analyses, although data are still not mature.

3.3. Uncertainties and limitations about favourable effects

There are no uncertainties about the favourable effects.

The final OS analysis will be provided post-approval as a Post-Authorisation Measure (LEG) by December 2021, together with updated PFS, PFS2, TTP, DOR and durability of MRD negativity data post-approval. Further, the MAH will provide the updated analyses of biomarkers predictive of response and resistance to therapy post-approval as a Post-Authorisation Measure (LEG) by June 2022.

3.4. Unfavourable effects

The majority of patients experienced an AE. The major difference in TEAEs between the two treatment groups in the first 9 cycles was more infections and infestations, especially pneumonia in the D-VMP group compared with the VMP group. After cycle 9, ie. during daratumumab monotherapy, 46% of the patients had a reported TEAE of new onset, the most frequent being upper respiratory tract infection (6%). Other TEAEs occurred at a low frequency (<5%) and no new TEAE with a high frequency was reported during daratumumab monotherapy.

The MAH has provided an update with 4 additional months of follow-up (data cut-off date 12 October, 2017). At that time, 66.2% of subjects in the D-VMP were still receiving treatment, while all subjects in the VMP group had either completed or discontinue treatment. Overall, the type and frequency of events occurred during the additional 4 months of follow-up did not change from those reported in the initial follow-up period and no new signals were identified.

The interference with blood typing test (indirect Coombs test) at an earlier disease stage has previously been discussed. The MAH has analysed the available post-marketing data, and very few cases of interference of blood typing (an important identified risk) or haemolysis (an important potential risk) have been reported, which is reassuring. Data on these risks are included as part of the routine Pharmacovigilance activities, since both risks are currently included in the RMP. In addition, the MAH is assessing the effectiveness of the implemented mitigation measures via a survey (PASS).

The safety profile in patients considered unfit for transplant, was in general consistent with that of the overall study population, no signal or alarming data were observed.

3.5. Uncertainties and limitations about unfavourable effects

There were no uncertainties in the knowledge about the unfavourable effects.

3.6. Effects Table

Effect	Short description	Unit	D+VMP	VMP	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS		months	NE	18.14	HR = 0.50, p<0.0001	
ORR		N(%)	318(90.9%)	263(73.9%)	Odds ratio = 3.55, p<0.0001	
VGPR or better		N(%)	249(71.1%)	177(49.7%)	Odds ratio = 2.50, p<0.0001	
CR or better		N(%)	149(42.6%)	87(24.4%)	Odds ratio = 2.31, p<0.0001	
Unfavourable Effects						
SAEs		N(%)	144(41.6%)	115(32.5%)		
Upper respiratory tract infections		N(%)	91(26.3%)	49(13.8%)		
Pneumonia		N(%)	53(15.3%)	17(4.8%)		
Bronchitis		N(%)	50(14.5%)	27(7.6%)		
Cough		N(%)	52(15.0%)	27(7.6%)		
Dyspnoea		N(%)	43(12.4%)	16(4.5%)		
Hypertension		N(%)	35(10.1%)	11 (3.1%)		
IRR associated with dara		N(%)	96(27.7%)	N/A		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Study MMY3007 comparing VMP to Dara+VMP is a well-designed and well-conducted phase III study, convincingly demonstrating the added value of Dara in combination with VMP. PFS was significantly prolonged, and median PFS has not yet been reached in the D-VMP arm. The risk of disease progression is reduced by 54%, which is considered clinically encouraging. The results from secondary endpoints and subgroup analyses are all consistent with the primary endpoint. The MRD negativity rate of 22.3% vs. 6.2% in the D-VMP and VMP arms respectively is interesting, demonstrating a deep and more sustainable response of the Dara-VMP treatment.

However, this comes at the cost of an increased risk of SAE, especially pneumonia. Infections and infestations (including pneumonia and upper respiratory tract infection), cough, hypertension and dyspnea are very common in patients being treated with Dara. Most events were clinically manageable with supportive therapy and thereby avoiding discontinuation from study treatment.

Overall, the addition of Dara to VMP is well tolerated. The observed safety profile is as expected and in line with the safety profile of Dara and VMP. The safety profile for patients considered unfit for transplant is consistent with that of the overall study population. Discontinuation rate is low, reflecting the fact that AEs are overall manageable in the clinical setting with supportive therapy and dose modification.

The benefits of daratumamab in combination with VMP seem to outweigh the risks.

3.7.2. Balance of benefits and risks

The Benefit-risk balance of daratumumab in combination with VMP in patients with newly diagnosed MM, who are ineligible for ASCT, is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall B/R of Darzalex in combination with bortezomib, melphalan and prednisone 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 and IIIB

Extension of Indication to include the combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant for Darzalex; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP version 3.2 (in version 2 of the RMP template) has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the contact details of the Lithuanian and Slovenian local representatives in the Package Leaflet. Furthermore, the MAH took the opportunity to update Annex II with regards to PSUR requirements.

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

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk management plan (RMP)

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

An updated RMP should be submitted:

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

Additional risk minimisation measures

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

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

The HCPs and Blood Banks educational materials, shall contain the following key elements:

The guide for HCPs and Blood Banks, to advice about the risk of interference for blood typing and how to minimise it;

The Patient Alert Card.

The Guide for HCP and Blood Banks shall contain the following key elements:

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

Package Leaflet (PL).

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

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

Similarity with authorised orphan medicinal products

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

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 to include the combination with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant for Darzalex; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. The RMP is updated to version 3.2 (in version 2 of the RMP template). In addition, the Marketing authorisation holder took the opportunity to update Annex II with regards to PSUR requirements and to update the contact details of the Lithuanian and Slovenian local representatives in the Package Leaflet.

Summary

Please refer to the Scientific Discussion – Darzalex II-11.