

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 120 mg/ml S.C

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 mL vial of solution for injection contains 1,800 mg of daratumumab (120 mg daratumumab per mL).

Daratumumab is a human monoclonal IgG1κ antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

Excipients with known effect
Each 15 mL vial of solution for injection contains 735.1 mg of sorbitol (E420).
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection, S.C.

The solution is clear to opalescent, colourless to yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

DARZALEX subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified.

DARZALEX should be administered by a healthcare professional, and the first dose should be administered in an environment where resuscitation facilities are available. It is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and dose is being given to the patient as prescribed.

For patients currently receiving daratumumab intravenous formulation, DARZALEX solution for subcutaneous injection may be used as an alternative to the intravenous daratumumab formulation starting at the next scheduled dose.

Pre- and post-injection medicinal products should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. See below "Recommended concomitant medicinal products" and section 4.4.

Posology

Dosing schedule in combination with lenalidomide (4-week cycle regimen) and as monotherapy
The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 1.

Table 1: DARZALEX dosing schedule in combination with lenalidomide (4-week cycle dosing regimen) and monotherapy

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24 ^a	every two weeks (total of 8 doses)
Week 25 onwards until disease progression ^b	every four weeks

- ^a First dose of the every-2-week dosing schedule is given at Week 9
- ^b First dose of the every-4-week dosing schedule is given at Week 25

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle regimens)
The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 2.

Table 2: DARZALEX 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 solution for subcutaneous injection, see section 5.1.

Dosing schedule in combination with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT)
The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 3.

Table 3: DARZALEX dosing schedule in combination with bortezomib, thalidomide and dexamethasone (IVTd); 4-week cycle dosing regimen)

Treatment phase	Weeks	Schedule
Induction	Weeks 1 to 8	weekly (total of 8 doses)
	Weeks 9 to 16 ^a	every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 1 to 8 ^b	every two weeks (total of 4 doses)

- ^a First dose of the every-2-week dosing schedule is given at Week 9

- ^b First dose of the every-2-week dosing schedule is given at Week 1 upon re-initiation of treatment following ASCT

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib (3-week cycle regimen)
The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 4.

Table 4: DARZALEX dosing schedule in combination with bortezomib (3-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24 ^a	every three weeks (total of 5 doses)
Week 25 onwards until disease progression ^b	every four weeks

- ^a First dose of the every-3-week dosing schedule is given at Week 10
- ^b First dose of the every-4-week dosing schedule is given at Week 25

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Missed dose

If a planned dose of DARZALEX is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

Dose modifications

No dose reductions of DARZALEX are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity (see section 4.4). For information concerning medicinal products given in combination with DARZALEX, see corresponding Summary of Product Characteristics.

In clinical studies, no modification to rate or dose of DARZALEX solution for subcutaneous injection was required to manage IRRs.

Recommended concomitant medicinal products

Pre-injection medicinal product

Pre-injection medicinal products (oral or intravenous) should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every administration of DARZALEX solution for subcutaneous injection as follows:

- Corticosteroid (long-acting or intermediate-acting)
 - Monotherapy:
 - Methylprednisolone 100 mg, or equivalent. Following the second injection, the dose of corticosteroid may be reduced to methylprednisolone 60 mg.
 - Combination therapy:
 - Dexamethasone 20 mg (or equivalent), administered prior to every DARZALEX solution for subcutaneous injection. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-injection medicinal product on DARZALEX administration days (see section 5.1). Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX administration days when patients have received dexamethasone (or equivalent) as a pre-injection medicinal product.
- Antipyretics (paracetamol 650 to 1,000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Post-injection medicinal product

Post-injection medicinal products should be administered to reduce the risk of delayed IRRs as follows:

- Monotherapy:
 - Oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) should be administered on each of the two days following all injections (beginning the day after the injection).
- Combination therapy:
 - Consider administering low-dose oral methylprednisolone (≤20 mg) or equivalent dose of post-injection medicinal products including short and long-acting specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX injection, additional post-injection medicinal products may not be needed (see section 5.1).

If the patient experiences no major IRRs after the first three injections, post-injection corticosteroids (excluding any background regimen corticosteroids) may be discontinued.

Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-injection medicinal products including short and long-acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four injections, if the patient experiences no major IRRs, these inhaled post-injection medicinal products may be discontinued at the discretion of the physician.

Prophylaxis for herpes zoster virus reactivation

Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation.

Special populations

Renal impairment

No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses no dosage adjustment is necessary for patients with renal impairment (see section 5.2).

Hepatic impairment

No formal studies of daratumumab in patients with hepatic impairment have been conducted. The serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see section 4.5). This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Elderly

No dose adjustments are considered necessary (see section 5.2).

Paediatric population

DARZALEX is not indicated for children and adolescents under 18 years old. The safety and efficacy of DARZALEX in children aged below 18 years of age have not been established.

Body weight (>120 kg)

Limited number of patients with body weight >120 kg have been studied using flat-dose (1,800 mg) DARZALEX solution for subcutaneous injection and efficacy in these patients has not been established. No dose adjustment based on body weight can currently be recommended (see sections 4.4 and 5.2).

Method of administration

DARZALEX subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified. See section 6.6 for special precautions prior to administration.

To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.

Inject 15 mL DARZALEX solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject DARZALEX solution for subcutaneous injection at other sites of the body as no data are available.

Injection sites should be rotated for successive injections.

DARZALEX solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.

Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

During treatment with DARZALEX solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as DARZALEX.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the trade name of the administered product should be clearly recorded.

It is recommended to record the batch number as well.

Infusion-related reactions

DARZALEX solution for subcutaneous injection can cause severe and/or serious IRRs, including anaphylactic reactions. In clinical studies, approximately 11% (52/490) of patients experienced an IRR. Most IRRs occurred following the first injection and were Grade 1-2. IRRs occurring with subsequent injections were seen in less than 1% of patients (see section 4.8).

The median time to onset of IRRs following DARZALEX injection was 3.7 hours (range 0.15-83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in less than 1% of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension and tachycardia (see section 4.8).

Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored and counselled regarding IRRs, especially during and following the first and second injections. If an anaphylactic reaction or life-threatening (Grade 4) reactions occur, appropriate emergency care should be initiated immediately. DARZALEX therapy should be discontinued immediately and permanently (see sections 4.2 and 4.3).

To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following DARZALEX injection (see section 4.2). Patients with a history of chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g. short- and long-acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease (see section 4.2).

Neutropenia/Thrombocytopenia

DARZALEX may increase neutropenia and thrombocytopenia induced by background therapy (see section 4.8).

Complete blood cell counts should be monitored periodically during treatment according to manufacturer's prescribing information for background therapies. Patients with neutropenia should be monitored for signs of infection. DARZALEX delay may be required to allow recovery of blood cell counts. In lower body weight patients receiving DARZALEX subcutaneous formulation, higher rates of neutropenia were observed; however, this was not associated with higher rates of serious infections. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions or growth factors.

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab administration. It should be recognised that daratumumab bound to RBCs may

mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time.

In the event of a planned transfusion blood transfusion centres should be notified of this interference with indirect antiglobulin tests (see section 4.5). If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

With the exception of IRRs (see Table 5 below), the safety profile of DARZALEX subcutaneous formulation (evaluated in 260 and 258 patients treated with the subcutaneous and intravenous formulations respectively) from the Phase III study MMY3012 was similar to the known safety profile of the intravenous formulation. Neutropenia is the only adverse reaction reported at ≥ 5% higher frequency for DARZALEX subcutaneous formulation compared to intravenous daratumumab (Grade 3 or 4: 13% vs 8%, respectively).

Tabulated list of adverse reactions

Table 5 summarises the adverse reactions that occurred in patients receiving DARZALEX subcutaneous formulation or intravenous formulation of daratumumab. The data reflects exposure to DARZALEX subcutaneous formulation (1,800 mg) in 490 patients with multiple myeloma (MM) including 260 patients from a Phase III active-controlled trial (Study MMY3012) who received DARZALEX solution for subcutaneous injection as monotherapy and three open-label, clinical studies in which patients received DARZALEX solution for subcutaneous injection either as monotherapy (N=31, MMY1004 and MMY1008) and MMY2040 in which patients received DARZALEX solution for subcutaneous injection in combination with either bortezomib, melphalan and prednisone (D-VMP; n=67), lenalidomide and dexamethasone (D-Rd, n=65) or bortezomib, lenalidomide and dexamethasone (D-VRd, n=67).

The safety data also reflects exposure to intravenous daratumumab (16 mg/kg) in 2324 patients with multiple myeloma including 1910 patients who received intravenous daratumumab in combination with background regimens and 414 patients who received intravenous daratumumab as monotherapy. Post-marketing adverse reactions are also included.

Excipients
This medicinal product contains sorbitol (E420). Patients with rare hereditary fructose intolerance (HFI) should not take this medicinal product (see section 2).

This medicinal product also contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

As an IgG1κ monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug-metabolising enzymes are not expected to affect the elimination of daratumumab. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolising enzymes.

Clinical pharmacokinetic assessments with daratumumab and lenalidomide, pomalidomide, thalidomide, bortezomib, melphalan, prednisone, carfilzomib and dexamethasone indicated no clinically-relevant drug-drug interaction between daratumumab and these small molecule medicinal products.

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching (see section 4.4). Daratumumab 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, phenotyping or genotyping may also be considered (see section 4.4).

Interference with serum protein electrophoresis and immunofixation tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a validated daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception

Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment.

Pregnancy

There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. If the patient becomes pregnant while taking this medicine, the patient should be informed of the potential risk to the fetus.

Breast-feeding

It is not known whether daratumumab is excreted into human or animal milk. Maternal IgG is excreted in human milk, but does not enter the neonatal and newborn/infant circulations in substantial amounts as they are degraded in the gastrointestinal tract and not absorbed.

The effect of daratumumab on newborns/infants is unknown. A decision should be made whether to discontinue breast-feeding or to discontinue DARZALEX therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available to determine potential effects of daratumumab on fertility in males or females (see section 5.3).

4.7 Effects on ability to drive and use machines

DARZALEX has no known effects on the ability to drive and use machines. However, fatigue has been reported in patients taking daratumumab and this should be taken into account when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions of any grade (≥20 % patients) with daratumumab (either intravenous or subcutaneous formulations) were administered either as monotherapy or combination treatment were IRRs, fatigue, nausea, diarrhoea, constipation, pyrexia, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, sepsis, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation.

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Gastrointestinal disorders	Diarrhoea	Very Common	29%	3%
	Constipation	Very Common	28%	1%
	Nausea	Very Common	23%	1% [#]
	Vomiting	Very Common	14%	1% [#]
	Pancreatitis ^a	Common	1%	<1%
Skin and subcutaneous tissue disorders	Rash	Common	9%	<1% [#]
	Pruritus	Common	5%	<1% [#]
Musculoskeletal and connective tissue disorders	Back pain	Very Common	17%	2%
	Muscle spasms	Very Common	12%	<1% [#]
	Arthralgia	Very Common	10%	1% [#]
	Musculoskeletal chest pain	Common	6%	<1% [#]
General disorders and administration site conditions	Fatigue	Common	23%	3%
	Oedema peripheral ^a	Very Common	22%	1%
	Pyrexia	Very Common	22%	1%
	Asthenia	Very Common	18%	2%
	Chills	Common	9%	<1% [#]
	Injection site erythema ^a	Common	4%	0
	Injection site reactions ^{c,d,e}	Common	8%	0
	Infusion-related reactions ^f			
Injury, poisoning and procedural complications	Daratumumab intravenous ^g	Very Common	39%	5%
	Daratumumab subcutaneous ^h	Very Common	11%	1% [#]

Clinical experience with daratumumab concentrate for solution for infusion (intravenous formulation)

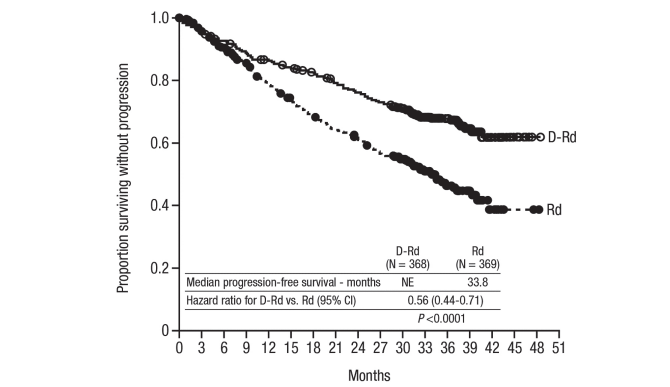
Newly diagnosed multiple myeloma
Combination treatment with lenalidomide and dexamethasone in patients ineligible for autologous stem cell transplant:

Study MMY3008, an open-label, randomised, active-controlled Phase III study, compared treatment with intravenous daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with newly diagnosed multiple myeloma. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On intravenous daratumumab infusion days, the dexamethasone dose was given as a pre-infusion medicinal product. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 737 patients were randomised: 368 to the DRd arm and 369 to the Rd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 73 (range: 45-90) years, with 44% of the patients >75 years of age. The majority were white (92%), male (52%), 34% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 49.5% had an ECOG performance score of 1 and 17% had an ECOG performance score of ≥2. Twenty-seven percent had International Staging System (ISS) Stage I, 43% had ISS Stage II and 29% had ISS Stage III disease. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

Study MMY3008 showed an improvement in Progression Free Survival (PFS) in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (hazard ratio [HR]=0.56; 95% CI: 0.43, 0.73; p<0.0001), representing 44% reduction in the risk of disease progression or death in patients treated with DRd. Results of an updated PFS analysis approximately 9 months after the original clinical cutoff, continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was not reached in the DRd arm and was 33.8 months in the Rd arm (HR=0.56; 95% CI: 0.44, 0.71; p<0.0001).

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3008



Additional efficacy results from Study MMY3008 are presented in Table 8 below.

Table 8: Additional efficacy results from Study MMY3008 ^a			
	DRd (n=368)	Rd (n=369)	
Overall response (sCR+CR+VGPR+PR) n(%) ^a	342 (92.9%)	300 (81.3%)	
p-value ^b	<0.0001		
Stringent complete response (sCR)	112 (30.4%)	46 (12.5%)	
Complete response (CR)	63 (17.1%)	46 (12.5%)	
Very good partial response (VGPR)	117 (31.8%)	104 (28.2%)	
Partial response (PR)	50 (13.6%)	104 (28.2%)	
CR or better (sCR + CR)	175 (47.6%)	92 (24.9%)	
p-value ^b	<0.0001		
VGPR or better (sCR + CR + VGPR)	292 (79.3%)	196 (53.1%)	
p-value ^b	<0.0001		
MRD negativity rate ^{a,c} n(%)	89 (24.2%)	27 (7.3%)	
95% CI (%)	19.9% (28.9%)	4.9% (10.5%)	
Odds ratio with 95% CI ^d	4.04 (2.55, 6.39)		
p-value ^e	<0.0001		

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval

^a Based on intent-to-treat population
^b p-value from Cochran Mantel-Haenszel Chi-Squared test
^c Based on threshold of 10⁻⁵
^d Mantel-Haenszel estimate of the odds ratio for un-stratified tables is used. An odds ratio >1 indicates an advantage for DRd.
^e p-value from Fisher's exact test.

In responders, the median time to response was 1.05 months (range: 0.2 to 12.1 months) in the DRd group and 1.05 to 15.3 months (range: 0.2 to 15.3 months) in the Rd group. The median duration of response had not been reached in the DRd group and was 34.7 months (95% CI: 30.8, not estimable) in the Rd group.

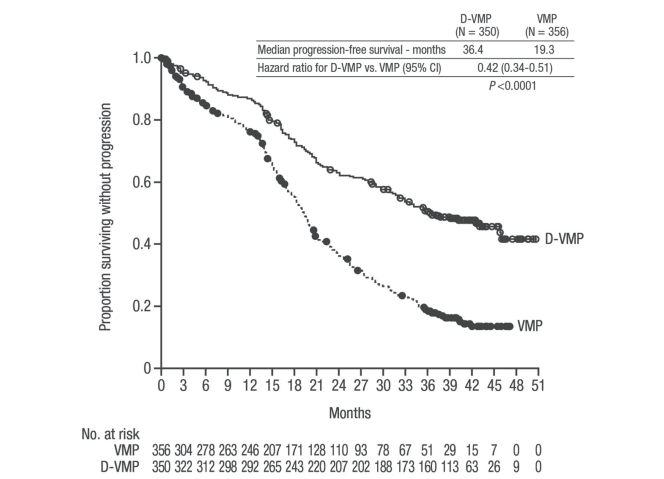
Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant:

Study MMY3007, an open-label, randomised, active-controlled Phase III study, compared treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m² body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m², and prednisone at 60 mg/m² were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). Intravenous daratumumab treatment was continued until disease progression or unacceptable toxicity.

A total of 706 patients were randomised: 350 to the D-VMP arm and 356 to the VMP arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 71 (range: 40-93) years, with 30% of the patients >75 years of age. The majority were white (85%), female (54%), 25% had an ECOG performance score of 0, 50% had an ECOG performance score of 1 and 25% had an ECOG performance score of 2. Patients had IgG/IgA/Light chain myeloma in 64%/22%/10% of instances, 19% had ISS Stage I, 42% had ISS Stage II, 38% had ISS Stage III disease and 84% had standard risk cytogenetics. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

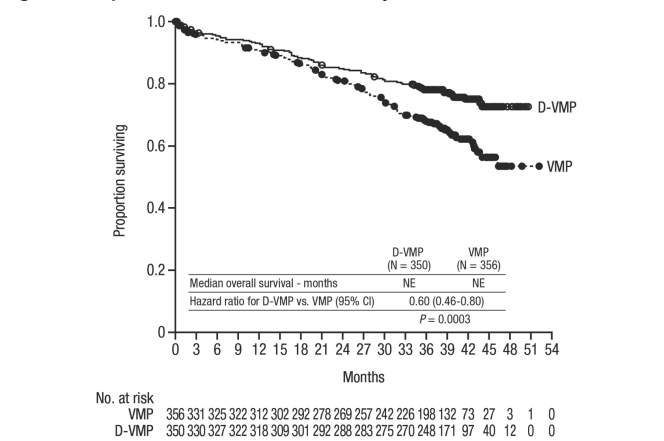
With a median follow-up of 16.5 months, the primary analysis of PFS in Study MMY3007 showed an improvement in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (HR=0.55; 95% CI: 0.38, 0.65; p<0.0001). Results of an updated PFS analysis after a median follow-up of 40 months continued to show an improvement in PFS for patients in the D-VMP arm compared with the VMP arm. Median PFS was 36.4 months in the D-VMP arm and 19.3 months in the VMP arm (HR=0.42; 95% CI: 0.34, 0.51; p<0.0001), representing a 58% reduction in the risk of disease progression or death in patients treated with D-VMP.

Figure 2: Kaplan-Meier Curve of PFS in Study MMY3007



After a median follow-up of 40 months, D-VMP has shown an overall survival (OS) advantage over the VMP arm (HR=0.60; 95% CI: 0.46, 0.80; p=0.0003), representing a 40% reduction in the risk of death in patients treated in the D-VMP arm. Median OS was not reached for either arm.

Figure 3: Kaplan-Meier Curve of OS in Study MMY3007



Additional efficacy results from Study MMY3007 are presented in Table 9 below.

Table 9: Additional efficacy results from Study MMY3007 ^a		
	D-VMP (n=350)	VMP (n=356)
Overall response (sCR+CR+VGPR+PR) n(%) ^a	318 (90.9)	263 (73.9)
p-value ^b	<0.0001	
Stringent complete response (sCR) n(%)	63 (18.0)	25 (7.0)
Complete response (CR) n(%)	86 (24.6)	62 (17.4)
Very good partial response (VGPR) n(%)	100 (28.6)	90 (25.3)
Partial response (PR) n(%)	69 (19.7)	86 (24.2)
MRD negativity rate (95% CI) ^c (%)	22.3 (18.0, 27.0)	6.2 (3.9, 9.2)
Odds ratio with 95% CI ^d	4.36 (2.64, 7.21)	
p-value ^e	<0.0001	

DRd=daratumumab-lenalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; MRD=minimal residual disease; CI=confidence interval

^a Based on intent-to-treat population
^b p-value from Cochran Mantel-Haenszel Chi-Squared test
^c Based on threshold of 10⁻⁵
^d Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. Results of a PFS analysis by censoring patients who were randomised to daratumumab maintenance in the second randomisation, at the date of the second randomisation showed HR=0.50; 95% CI: 0.34, 0.75; p=0.0005.

D-VMP=daratumumab-bortezomib-melphalan-prednisone; VMP=bortezomib-melphalan-prednisone; MRD=minimal residual disease; CI=confidence interval

^a Based on intent-to-treat population
^b p-value from Cochran Mantel-Haenszel Chi-Squared test
^c Based on threshold of 10⁻⁵
^d Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio >1 indicates an advantage for D-VMP.
^e p-value from Fisher's exact test.

In responders, the median time to response was 0.79 months (range: 0.4 to 15.3 months) in the D-VMP group and 0.82 months (range: 0.7 to 12.6 months) in the VMP group. The median duration of response had not been reached in the D-VMP group and was 21.3 months (range: 18.4, not estimable) in the VMP group. A subgroup analysis was performed on patients at least 70 years old, or those 65-69 years old with ECOG performance score of 2, or aged less than 65 years of age with significant comorbidity or ECOG performance score of 2 (D-VMP: n=273; VMP: n=270). The efficacy results in this subgroup were consistent with the overall population. In this subgroup, median PFS was not reached in the D-VMP group and was 17.9 months in the VMP group (HR=0.56; 95% CI: 0.42, 0.75; p<0.0001). The overall response rate was 90% in the D-VMP group and 74% in the VMP group (VGPR rate: 29% in D-VMP group and 26% in VMP group; CR: 22% in D-VMP group and 18% in VMP group; sCR rate: 20% in D-VMP group and 7% in VMP group). The safety results of this subgroup were consistent with the overall population. Furthermore, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89; VMP: n=84), was also consistent with the overall population.

Combination treatment with bortezomib, thalidomide and dexamethasone (VTD) in patients eligible for autologous stem cell transplant (ASCT):
Study MMY3006 is a 2 Part, open-label, randomised, active-controlled Phase III study. Part 1 compared induction and consolidation treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib, thalidomide and dexamethasone (D-VTD) to treatment with bortezomib, thalidomide and dexamethasone (VTD) in patients with newly diagnosed multiple myeloma eligible for ASCT. The consolidation phase of treatment began a minimum of 30 days post-ASCT, when the patient had recovered sufficiently, and engraftment was complete. In Part 2, subjects with at least a partial response (PR) by Day 100 post-transplant were re-randomised in a 1:1 ratio to daratumumab maintenance or observation only. Only results from Part 1 are described hereafter.

Bortezomib was administered by subcutaneous injection or intravenous injection at a dose of 1.3 mg/m² body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 28 day (4-week) induction treatment cycles (Cycles 1-4) and two consolidation cycles (Cycles 5 and 6) following ASCT after Cycle 4. Thalidomide was administered orally at 100 mg daily during the six bortezomib cycles. Dexamethasone (oral or intravenous) was administered at 40 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23 of Cycles 1 and 2, and at 40 mg on Days 1-2 and 20 mg on subsequent dosing days (Days 8, 9, 15, 16) of Cycles 3-4. Dexamethasone 20 mg was administered on Days 1, 2, 8, 9, 15, 16 in Cycles 5 and 6. On the days of intravenous daratumumab infusion, the dexamethasone dose was administered intravenously as a pre-infusion medicinal product. Dose adjustments for bortezomib, thalidomide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 1085 patients were randomised: 543 to the D-VTD arm and 542 to the VTD arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 58 (range: 22 to 65) years. All patients were ≤65 years: 43% were in the age group ≥60-65 years, 41% were in the age group ≥50-60 years and 16% below age of 50 years. The majority were male (59%), 48% had an ECOG performance score of 0, 42% had an ECOG performance score of 1 and 10% had an ECOG performance score of 2. Forty percent had International Staging System (ISS) Stage I, 45% had ISS Stage II and 15% had ISS Stage III disease.

Efficacy was evaluated by the stringent Complete Response (sCR) rate at Day 100 post-transplant and Progression free survival (PFS).

Table 10: Efficacy results from Study MMY3006^a

	D-VTD (n=543)	VTD (n=542)	P value ^b
Response assessment Day 100 post-transplant			
Stringent Complete Response (sCR)	157 (28.9%)	110 (20.3%)	0.0010
CR or better (sCR+CR)	211 (38.9%)	141 (26.0%)	<0.0001
Very Good Partial Response or better (sCR+CR+VGPR)	453 (83.4%)	423 (78.0%)	
MRD negativity ^{c,d} n(%)	346 (63.7%)	236 (43.5%)	<0.0001
95% CI (%)	(59.5%, 67.8%)	(39.3%, 47.8%)	
Odds ratio with 95% CI ^e	2.27 (1.78, 2.90)		
MRD negativity in combination with CR or better ^c n(%)	183 (33.7%)	108 (19.9%)	<0.0001
95% CI (%)	(29.7%, 37.9%)	(16.6%, 23.5%)	
Odds ratio with 95% CI ^e	2.06 (1.56, 2.72)		

D-VTD=daratumumab-bortezomib-thalidomide-dexamethasone; VTD=bortezomib-thalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval

^a Based on intent-to-treat population
^b p-value from Cochran Mantel-Haenszel Chi-Squared test
^c Based on threshold of 10⁻⁵
^d Regardless of response per IMWG
^e Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. Results of a PFS analysis by censoring patients who were randomised to daratumumab maintenance in the second randomisation, at the date of the second randomisation showed HR=0.50; 95% CI: 0.34, 0.75; p=0.0005.

Relapsed/Refractory multiple myeloma

Monotherapy

The clinical efficacy and safety of intravenous daratumumab monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma whose prior therapy included a proteasome inhibitor and an immunomodulatory agent

and who had demonstrated disease progression on the last therapy, was demonstrated in two open-label studies.

In Study MMY2002, 106 patients with relapsed and refractory multiple myeloma received 16 mg/kg intravenous daratumumab until disease progression. The median patient age was 63.5 years (range, 31 to 84 years), 11% of patients were ≥75 years of age, 49% were male and 79% were Caucasian. Patients had received a median of 5 prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation (ASCT). Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%). At baseline, 97% of patients were refractory to the last line of treatment, 96% were refractory to both, a proteasome inhibitor (PI) and immunomodulatory agent (IMiD), 77% were refractory to alkylating agents, 63% were refractory to pomalidomide and 48% of patients were refractory to carfilzomib.

Efficacy results of the pre-planned interim analysis based on Independent Review Committee (IRC) assessment are presented in Table 11 below.

Table 11: IRC assessed efficacy results for study MMY2002

Efficacy endpoint	Intravenous daratumumab 16 mg/kg N=106
Overall response rate ¹ (ORR: sCR+CR+VGPR+PR) [n (%)]	31 (29.2)
95% CI (%)	(20.8, 38.9)
Stringent complete response (sCR) [n (%)]	3 (2.8)
Complete response (CR) [n]	0
Very good partial response (VGPR) [n (%)]	10 (9.4)
Partial response (PR) [n (%)]	18 (17.0)
Clinical Benefit Rate (ORR+MR) [n (%)]	36 (34.0)
Median Duration of Response [months (95% CI)]	7.4 (5.5, NE)
Median Time to Response [months (range)]	1 (0.9; 5.6)

¹ Primary efficacy endpoint (International Myeloma Working Group criteria)
CI=confidence interval; NE=not estimable; MR=minimal response

Overall response rate (ORR) in MMY2002 was similar regardless of type of prior anti-myeloma therapy.

At a survival update with a median duration of follow-up of 14.7 months, median Overall Survival (OS) was 17.5 months (95% CI:13.7, not estimable). In Study GEN501, 42 patients with relapsed and refractory multiple myeloma received 16 mg/kg intravenous daratumumab until disease progression. The median patient age was 64 years (range, 44 to 76 years), 64% were male and 76% were Caucasian. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent of patients had received prior ASCT. Prior therapies included bortezomib (100%), lenalidomide (95%), pomalidomide (36%) and carfilzomib (19%). At baseline, 76% of patients were refractory to the last line of treatment, 64% were refractory to both a PI and IMiD, 60% were refractory to alkylating agents, 36% were refractory to pomalidomide and 17% were refractory to carfilzomib.

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.
^a p-value from Cochran Mantel-Haenszel Chi-Squared test
^b Based on Intent-to-treat population and threshold of 10⁻⁵
^c Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DRd.
^d p-value is from a Fisher's exact test.

Pre-planned interim analysis showed that treatment with daratumumab at 16 mg/kg led to a 36% ORR with 5% CR and 5% VGPR. The median time to response was 1 (range: 0.5 to 3.2) month. The median duration of response was not reached (95% CI: 5.6 months, not estimable).

At a survival update with a median duration of follow-up of 15.2 months, median OS was not reached (95% CI: 19.9 months, not estimable), with 74% of subjects still alive.

Combination treatment with lenalidomide:

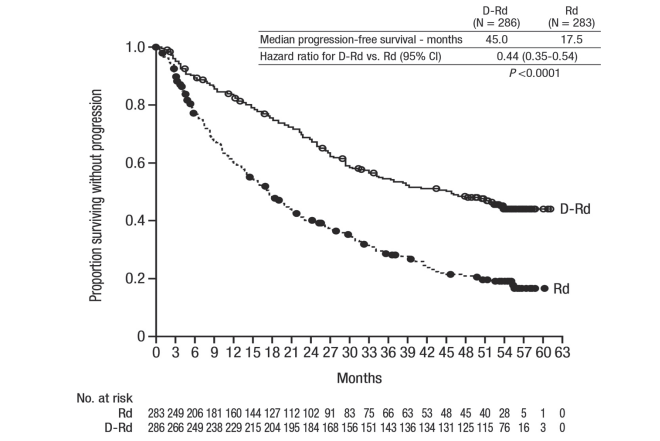
Study MMY3003, an open-label, randomised, active-controlled Phase III trial, compared treatment with intravenous daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose dexamethasone at 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On intravenous daratumumab infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medicinal product and the remainder given the day after the infusion. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomised; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the intravenous daratumumab and the control arm. The median patient age was 65 years (range 34 to 89 years) and 11% were ≥75 years. The majority of patients (86%) received a prior PI, 55% of patients had received a prior IMiD, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior PI and IMiD. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of patients were refractory to a PI only, and 21% were refractory to bortezomib. Patients refractory to lenalidomide were excluded from the study.

With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001). Results of an updated PFS analysis after a median follow-up of 50 months continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was 45.0 months in the DRd arm and 17.5 months in the Rd arm (HR=0.44; 95% CI: 0.35, 0.54; p<0.0001), representing a 56% reduction in the risk of disease progression or death in patients treated with DRd (see Figure 4).

Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant:

Figure 4: Kaplan-Meier Curve of PFS in Study MMY3003



Additional efficacy results from Study MMY3003 are presented in Table 12 below.

Table 12: Additional efficacy results from Study MMY3003		
Response evaluable patient number	DRd (n=281)	Rd (n=276)
Overall response (sCR+CR+VGPR+PR) n(%)	261 (92.9)	211 (76.4)
p-value ^a	<0.0001	
Stringent complete response (sCR)	51 (18.1)	20 (7.2)
Complete response (CR)	70 (24.9)	33 (12.0)
Very good partial response (VGPR)	92 (32.7)	69 (25.0)
Partial response (PR)	48 (17.1)	89 (32.2)
Median Time to Response [months (95% CI)]	1.0 (1.0, 1.1)	1.3 (1.1, 1.9)
Median Duration of Response [months (95% CI)]	NE (NE, NE)	17.4 (17.4, NE)
MRD negative rate (95% CI) ^b (%)	21.0 (16.4, 26.2)	2.8 (1.2, 5.5)
Odds ratio with 95% CI ^c	9.31 (4.31, 20.09)	
p-value ^d	<0.0001	

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

^a p-value from Cochran Mantel-Haenszel Chi-Squared test
^b Based on Intent-to-treat population and threshold of 10⁻⁵
^c Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DRd.
^d p-value is from a Fisher's exact test.

Median OS was not reached for either treatment group. With an overall median follow-up of 13.5 months, the hazard ratio for OS was 0.64 (95% CI: 0.40, 1.01; p=0.0534).

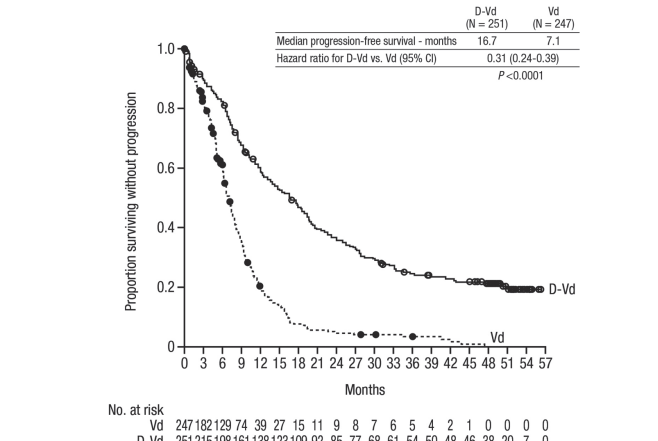
Combination treatment with bortezomib:

Study MMY3004, an open-label, randomised, active-controlled Phase III trial, compared treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib and dexamethasone (DvD), to treatment with bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Bortezomib was administered by subcutaneous injection or intravenous infusion at a dose of 1.3 mg/m² body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle) or a reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of intravenous daratumumab infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medicinal product. Intravenous daratumumab treatment was continued until disease progression or unacceptable toxicity.

A total of 498 patients were randomised; 251 to the DvD arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the intravenous daratumumab and the control arm. The median patient age was 64 years (range 30 to 88 years) and 12% were ≥75 years. Sixty-nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76% of patients received an IMiD (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment. Thirty-three percent (33%) of patients were refractory to an IMiD only, and 28% were refractory to lenalidomide. Patients refractory to bortezomib were excluded from the study.

With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the DvD arm as compared to the Vd arm; the median PFS had not been reached in the DvD arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.55]; p-value=0.0001). Results of an updated PFS analysis after a median follow-up of 50 months continued to show an improvement in PFS for patients in the DvD arm compared with the Vd arm. Median PFS was 45.0 months in the DvD arm and 17.5 months in the Vd arm (HR [95% CI]: 0.31 [0.24, 0.39]; p-value<0.0001), representing a 69% reduction in the risk of disease progression or death in patients treated with DvD versus Vd (see Figure 5).

Figure 5: Kaplan-Meier Curve of PFS in Study MMY3004



Additional efficacy results from Study MMY3004 are presented in Table 13 below.

Table 13: Additional efficacy results from Study MMY3004		
Response evaluable patient number	DvD (n=240)	Vd (n=234)
Overall response (sCR+CR+VGPR+PR) n(%)	199 (82.9)	148 (63.2)
p-value ^a	<0.0001	
Stringent complete response (sCR)	11 (4.6)	5 (2.1)
Complete response (CR)	35 (14.6)	16 (6.8)
Very good partial response (VGPR)	96 (40.0)	47 (20.1