Daratumumab Concentrate for Solution for Infusion

DARZALEX®

DOSAGE FORMS AND STRENGTHS

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology. DARZALEX is available as a colorless to yellow preservative free liquid concentrate for intravenous infusion after dilution.

Each mL contains 20 mg daratumumab.

- 5 mL vial: Each single-use vial contains 100 mg of daratumumab.
- 20 mL vial: Each single-use vial contains 400 mg of daratumumab.

For excipients, see List of Excipients.

CLINICAL INFORMATION INDICATIONS

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.

DOSAGE AND ADMINISTRATION

DARZALEX should be administered by a healthcare professional, with immediate access to emergency equipment and appropriate medical support to manage infusion-related reactions (IRRs) if they occur.

Pre- and post-infusion medications should be administered (see Recommended concomitant medications below).

Dosage – Adults (≥18 years) Recommended dose

The DARZALEX dosing schedule in Table 1 is for combination therapy with 4-week cycle regimens (e.g. lenalidomide, pomalidomide) and for monotherapy as follows:

- combination therapy with lenalidomide and low-dose dexamethasone for patients with newly diagnosed multiple myeloma ineligible for autologous stem cell transplant (ASCT)
- combination therapy with lenalidomide for patients with relapsed/refractory multiple myeloma
- monotherapy for patients with relapsed/refractory multiple myeloma

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Table 5):

Table 1. Dosing schedule for DARZALEX monotherapy and in combination with 4-week cycle dosing regimens

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 dosing instructions for medicinal products administered with DARZALEX, see Clinical Studies and manufacturer's prescribing information.

The DARZALEX dosing schedule in Table 2 is for combination therapy with bortezomib, melphalan and prednisone (6-week cycle regimen) for patients with newly diagnosed multiple myeloma ineligible for ASCT.

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Table 5):

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, see *Clinical Studies.*

The DARZALEX dosing schedule in Table 3 is for combination therapy with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for ASCT.

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Table 5):

Table 3: DARZALEX dosing schedule in combination with bortezomib, thalidomide and dexamethasone ([VTd]; 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 dosing instructions of medicinal products administered with DARZALEX, see Clinical Studies and manufacturer's prescribing information.

The DARZALEX dosing schedule in Table 4 is for combination therapy with 3-week cycle regimens (e.g. bortezomib) for patients with relapsed/refractory multiple myeloma.

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Table 5):

Table 4: Dosing schedule for DARZALEX with 3-week cycle dosing regimens

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 dosing instructions for medicinal products administered with DARZALEX see *Clinical Studies* and manufacturer's prescribing information.

Missed dose (s)
If a planned dose of DARZALEX is missed, administer the dose as soon as possible and adjust the dosing schedule 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 hematological toxicity (see Warnings and Precautions). For information concerning medicinal products given in combination with DARZALEX, see manufacturer's prescribing information.

Recommended concomitant medications
Pre-infusion medication
Administer the following pre-infusion medications to reduce the risk of IRRs to all patients 1-3 hours prior to every infusion of DARZALEX:

- Corticosteroid (long-acting or intermediate-acting) Monotherapy:

  Methylprednisolone 100 mg, or equivalent, administered intravenously. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg). Combination therapy:
  Administer 20 mg dexamethasone (or equivalent) prior to every DARZALEX infusion. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on DARZALEX infusion days (see *Clinical Studies*).

  Dexamethasone is given intravenously prior to the first DARZALEX infusion and oral administration may be considered prior to subsequent infusions. Additional background-regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX infusion days when patients have received dexamethasone as a pre-medication.

- Antipyretics (oral paracetamol/acetaminophen 650 to 1000 mg).

- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Post-infusion medication

Administer post-infusion medication to reduce the risk of delayed infusion-related reactions as follows:

Monotherapy:

Administer oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) on each of the 2 days following all DARZALEX infusions (beginning the day after the infusion).

Combination therapy:

Consider administering low-dose oral methylprednisolone (≤ 20 mg) or equivalent the day after the DARZALEX infusion.

However, if a background regimen-specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX infusion, additional post-infusion medications may not be needed (see *Clinical Studies*).

Additionally, for patients with a history of chronic obstructive pulmonary disease, consider the use of post-infusion medications including short and long acting bronchodilators, and inhaled corticosteroids. Following the first four infusions, if the patient experiences no major IRRs, these inhaled post-infusion medications 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
Pediatrics (17 years of age and younger)
The safety and efficacy of DARZALEX have not been established in pediatric patients.

Elderly (65 years of age and older)
No dose adjustments are considered necessary in elderly patients (see Pharmacokinetic Properties, *Adverse Reactions*).

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 Pharmacokinetic Properties).

Hepatic impairment
No formal studies of daratumumab in patients with hepatic impairment have been conducted. Changes in hepatic function are unlikely to have any effect on the elimination of daratumumab since IgG1 molecules such as daratumumab are not metabolized through hepatic pathways. Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment (see Pharmacokinetic Properties).

Administration
DARZALEX is administered as an intravenous infusion following dilution with 0.9% Sodium Chloride. For instructions on dilution of the medicinal product before administration, see Instructions for Use and Handling and Disposal.

Following dilution the DARZALEX infusion should be intravenously administered at the appropriate initial infusion rate, presented in Table 5 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively, see Table 5 below.

Table 5: Infusion rates for DARZALEX (16 mg/kg) administration

	Dilution Volume	Initial Rate (first hour)	Rate Increment[a]	Maximum Rate
Week 1 Infusion				
Option 1 (Single dose infusion)				
Week 1 Day 1 (16 mg/kg)	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Option 2 (Split dose infusion)				
Week 1 Day 1 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 1 Day 2 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 2 (16 mg/kg) infusion[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent (Week 3 onwards, 16 mg/kg) infusions[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Consider incremental escalation of the infusion rate only in the absence of infusion reactions.

[b] Dilution volume of 500 mL for the 16 mg/kg dose should be used only if there were no infusion reactions the previous week. Otherwise, use a dilution volume of 1000 mL.

[c] Use a modified initial rate (100 mL/hour) for subsequent infusions (i.e. Week 3 onwards) only if there were no infusion reactions during the previous infusion. Otherwise, continue to use instructions indicated in the table for the Week 2 infusion rate.

Management of infusion-related reactions
Administer pre-infusion medications to reduce the risk of IRRs prior to treatment with DARZALEX.

For IRRs of any grade/severity, immediately interrupt the DARZALEX infusion and manage symptoms.

Management of IRRs may further require reduction in the rate of infusion, or treatment discontinuation of DARZALEX as outlined below (see also Warnings and Precautions).

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the IRR occurred. If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (Table 5).
- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as appropriate (Table 5). Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue DARZALEX upon the third occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life-threatening): Permanently discontinue DARZALEX treatment.

CONTRAINDICATIONS
Patients with a history of severe hypersensitivity to daratumumab or any of the excipients.

WARNINGS AND PRECAUTIONS

Infusion–related reactions
DARZALEX can cause serious IRRs, including anaphylactic reactions. These reactions can be life-threatening and fatal outcomes have been reported.

Monitor patients throughout the infusion and the post-infusion period.

In clinical trials, IRRs were reported in approximately half of all patients treated with DARZALEX.
The majority of IRRs occurred at the first infusion and were Grade 1-2. Four percent of patients had an IRR at more than one infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, and hypertension, laryngeal edema pulmonary edema, myocardial infarction, and ocular adverse reactions (including choroidal effusion, acute myopia and acute angle closure glaucoma). Signs and symptoms may include respiratory symptoms, such as nasal congestion, cough, throat irritation, as well as chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus, hypotension and blurred vision (see Adverse Reactions). Fatal IRRs were not reported in these trials.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with DARZALEX. Interrupt DARZALEX infusion for IRRs of any severity and institute medical management/supportive treatment as needed. For patients with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion. If an anaphylactic reaction or life-threatening (Grade 4) IRR occurs, permanently discontinue administration of DARZALEX and institute appropriate emergency care (see Dosage and Administration).

To reduce the risk of delayed IRRs, administer oral corticosteroids to all patients following all DARZALEX infusions. Additionally consider the use of post-infusion medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur. If ocular symptoms occur, interrupt DARZALEX infusion and seek immediate ophthalmologic evaluation prior to restarting DARZALEX (see Dosage and Administration).

Neutropenia/Thrombocytopenia

DARZALEX may increase neutropenia and thrombocytopenia induced by background therapy (see Adverse Reactions).

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX dose delay may be required to allow recovery of blood cell counts. 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 infusion. It should be recognized 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.

Type and screen patients prior to starting DARZALEX.

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

Hepatitis B Virus (HBV) reactivation

Hepatitis B virus (HBV) reactivation, in some cases fatal, has been reported in patients treated with DARZALEX. HBV screening should be performed in all patients before initiation of treatment with DARZALEX.

For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of DARZALEX treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated.

In patients who develop reactivation of HBV while on DARZALEX, suspend treatment with DARZALEX and any concomitant steroids, chemotherapy, and institute appropriate treatment. Resumption of DARZALEX treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

INTERACTIONS

No drug-drug interaction studies have been performed.

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

Effects of DARZALEX on laboratory tests

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. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or genotyping. 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.

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 (CRs) by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response (VGPR), 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 CR (see Clinical Studies).

PREGNANCY, BREAST-FEEDING AND FERTILITY

Pregnancy

There are no human or animal data to assess the risk of DARZALEX use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore, DARZALEX 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 drug, the patient should be informed of the potential risk to the fetus.

To avoid exposure to the fetus, women of reproductive potential should use effective contraception during and for 3 months after cessation of DARZALEX treatment.

Breast-feeding

It is not known whether daratumumab is excreted into human or animal milk or affects milk production. There are no studies to assess the effect of daratumumab on the breast-fed infant.

Maternal IgG is excreted in human milk, but does not enter the neonatal and infant circulations in substantial amounts as they are degraded in the gastrointestinal tract and not absorbed. Because the risks of DARZALEX to the infant from oral ingestion are unknown, a decision should be made whether to discontinue breast-feeding, or 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

DARZALEX has no or negligible influence 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.

ADVERSE REACTIONS

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of daratumumab based on the comprehensive assessment of the available adverse event information. A causal relationship with daratumumab cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety data described below reflect exposure to DARZALEX (16 mg/kg) in 2066 patients with multiple myeloma including 1910 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy.

The most frequent adverse reactions (≥20%) were IRRs, fatigue, nausea, diarrhea, constipation, pyrexia, dyspnea, cough, neutropenia, thrombocytopenia, anemia, edema peripheral, asthenia, peripheral sensory neuropathy, and upper respiratory tract infection. Serious adverse reactions were sepsis, pneumonia, bronchitis, upper respiratory tract infection, pulmonary edema, influenza, pyrexia, dehydration, diarrhea, atrial fibrillation. Table 6 summarizes the adverse reactions that occurred in patients receiving DARZALEX.

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000) and very rare (< 1/10000). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 6: Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg

System Organ Class	Adverse reaction	Frequency	Incidence (%)	
			Any Grade	Grade 3-4
Infections and infestations	Upper respiratory tract infection[+]	Very Common	46	4
	Pneumonia[+]		19	11
	Bronchitis[+]		17	2
	Urinary tract infection	Common	8	1
	Sepsis[+]		4	4
	Cytomegalovirus infection[+]		1	<1*
Blood and lymphatic system disorders	Neutropenia[+]	Very Common	44	39
	Thrombocytopenia+		31	19
	Anemia[+]		27	12
	Lymphopenia[+]		14	11
	Leukopenia[+]		12	6
Immune system disorders	Hypogammaglobulinemia[+i]	Common	3	<1*
Metabolism and nutrition disorders	Decreased appetite	Very Common	12	1
	Hypokalemia[+]		10	3
	Hyperglycemia	Common	7	3
	Hypocalcemia		6	1
	Dehydration		3	1*
Psychiatric disorders	Insomnia	Very Common	16	1*
Nervous system disorders	Peripheral neuropathy[+]	Very Common	35	4
	Headache		12	<1*
	Paresthesia		11	<1
	Dizziness		10	<1*
	Syncope	Common	2	2*
Cardiac disorders	Atrial fibrillation	Common	4	1
Vascular disorders	Hypertension[+]	Very Common	10	5
Respiratory, thoracic and mediastinal disorders	Cough[+]	Very Common	25	<1*
	Dyspnea[+]		21	3
	Pulmonary edema[+]	Common	1	<1
Gastrointestinal disorders	Constipation	Very Common	33	1
	Diarrhea		32	4
	Nausea		26	2*
	Vomiting		16	1*
	Abdominal Pain[+]		14	1
	Pancreatitis[+]	Common	1	1
Skin and subcutaneous tissue disorders	Rash	Very Common	13	1*
	Pruritus	Common	7	<1*
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[+]	Very Common	37	4

	Arthralgia		14	1
	Muscle spasms		14	<1*
General disorders and administration site conditions	Edema peripheral+	Very Common	27	1
	Fatigue		26	4
	Pyrexia		23	2
	Asthenia		21	2
	Chills	Common	9	<1*
Injury, poisoning and procedural complications	Infusion-related reaction#	Very Common	40	4

+ Indicates grouping of terms
* No grade 4
\# Infusion-related reaction includes terms determined by investigators to be related to infusion, see below

Infusion-related reactions
In clinical trials (monotherapy and combination treatments; N=2066) the incidence of any grade infusion-related reactions was 37% with the first (16 mg/kg, Week 1) infusion of DARZALEX, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion reaction at Week 2 or subsequent infusions.

The median time to onset of a reaction was 1.5 hours (range: 0 to 72.8 hours). The incidence of infusion modifications due to reactions was 36%. Median durations of 16 mg/kg infusions for the 1st, 2nd and subsequent infusions were approximately 7, 4 and 3 hours respectively.

Severe infusion-related reactions included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension. Other adverse infusion-related reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea (*see* Warnings and Precautions).

When DARZALEX dosing was interrupted in the setting of ASCT (Study MMY3006) for a median of 3.75 (range: 2.4; 6.9) months, upon re-initiation of DARZALEX the incidence of IRRs was 11% at first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption due to ASCT. IRRs occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3/4:<1%) with those reported in previous studies at Week 2 or subsequent infusions.

In study MMY1001, patients receiving daratumumab combination treatment (n=97) were administered the first 16 mg/kg daratumumab dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of infusions were 4.2 h for Week 1-Day 1, 4.2 h for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Infections
In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported as follows: Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 28%, Rd: 23%; DPd: 28%; DKd[a]: 36%, Kd[a]: 27%; DKd[b]: 21%
[a]where carfilzomib 20/56 mg/m^2 was administered twice-weekly
[b]where carfilzomib 20/70 mg/m^2 was administered once-weekly

Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; DVTd: 22%, VTd: 20%. Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections (occurred in 1-4% of patients) Fatal infections were primarily due to pneumonia and sepsis.

In patients receiving DARZALEX combination therapy, fatal infections (Grade 5) were reported as follows: Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%; DKd[a]: 5%, Kd[a]: 3%; DKd[b]: 0%

[a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly

[b] where carfilzomib 20/70 mg/m^2 was administered once-weekly

Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

Other special population

Of the 2459 patients who received DARZALEX at the recommended dose, 38% were 65 to 75 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients (see *Adverse Reactions*, *Clinical Studies*). Among patients with relapsed and refractory multiple myeloma (n=1213), the most common serious adverse reactions that occurred more frequently in elderly (≥65 years of age) were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the most common serious adverse reaction that occurred more frequently in elderly (≥75 years of age) was pneumonia.

Postmarketing data

Adverse reactions identified during postmarketing experience with daratumumab are included in Table 7. The frequencies are provided according to the following convention:

Very common	≥1/10
Common	≥1/100 to <1/10
Uncommon	≥1/1000 to <1/100
Rare	≥1/10000 to <1/1000
Very rare	<1/10000, including isolated reports
Not known	frequency cannot be estimated from the available data

In Table 7, adverse reactions are presented by frequency category based on spontaneous reporting rates.

Table 7: Postmarketing Adverse Reactions identified with daratumumab

System Organ Class Adverse Reaction	**Frequency Category based on Spontaneous Reporting Rate**	**Frequency Category based on Incidence in Clinical trial**
Immune System disorders Anaphylactic reaction	Rare	Not known
Infections and Infestations COVID-19 Hepatitis B virus reactivation	Uncommon Rare	Not Known Uncommon

OVERDOSE

Symptoms and signs

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

Treatment

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01FC01

Mechanism of action

Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of cells in a variety of hematological malignancies, including multiple myeloma

tumor cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signaling and enzymatic activity.

Daratumumab has been shown to potently inhibit the in vivo growth of CD38-expressing tumor cells. Based on in vitro studies, daratumumab may utilize multiple effector functions, resulting in immune mediated tumor cell death. These studies suggest that daratumumab can induce tumor cell lysis through complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP) in malignancies expressing CD38. A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+T_{regs}) and B cells (CD38+B_{regs}) are decreased by daratumumab. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with DARZALEX treatment in peripheral whole blood and bone marrow. T-cell receptor DNA sequencing verified that T-cell clonality was increased with DARZALEX treatment, indicating immune modulatory effects that may contribute to clinical response.

Daratumumab induced apoptosis *in vitro* after Fc mediated cross-linking. In addition, daratumumab modulated CD38 enzymatic activity, inhibiting the cyclase enzyme activity and stimulating the hydrolase activity. The significance of these *in vitro* effects in a clinical setting, and the implications on tumor growth, are not well- understood.

Pharmacodynamic effects

Natural killer (NK) cell and T-cell count
NK cells are known to express high levels of CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+$CD56^{dim}$) NK cells in peripheral whole blood and bone marrow were observed with DARZALEX treatment. However, baseline levels of NK cells did not show an association with clinical response.

Immunogenicity
In multiple myeloma patients treated with DARZALEX in monotherapy and combination clinical trials, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies.

Immunogenicity data are highly dependent on the sensitivity and specificity of the test methods used. Additionally, the observed incidence of a positive result in a test method may be influenced by several factors, including sample handling, timing of sample collection, drug interference, concomitant medication and the underlying disease. Therefore, comparison of the incidence of antibodies to daratumumab with the incidence of antibodies to other products may be misleading.

Clinical studies

Newly Diagnosed Multiple Myeloma

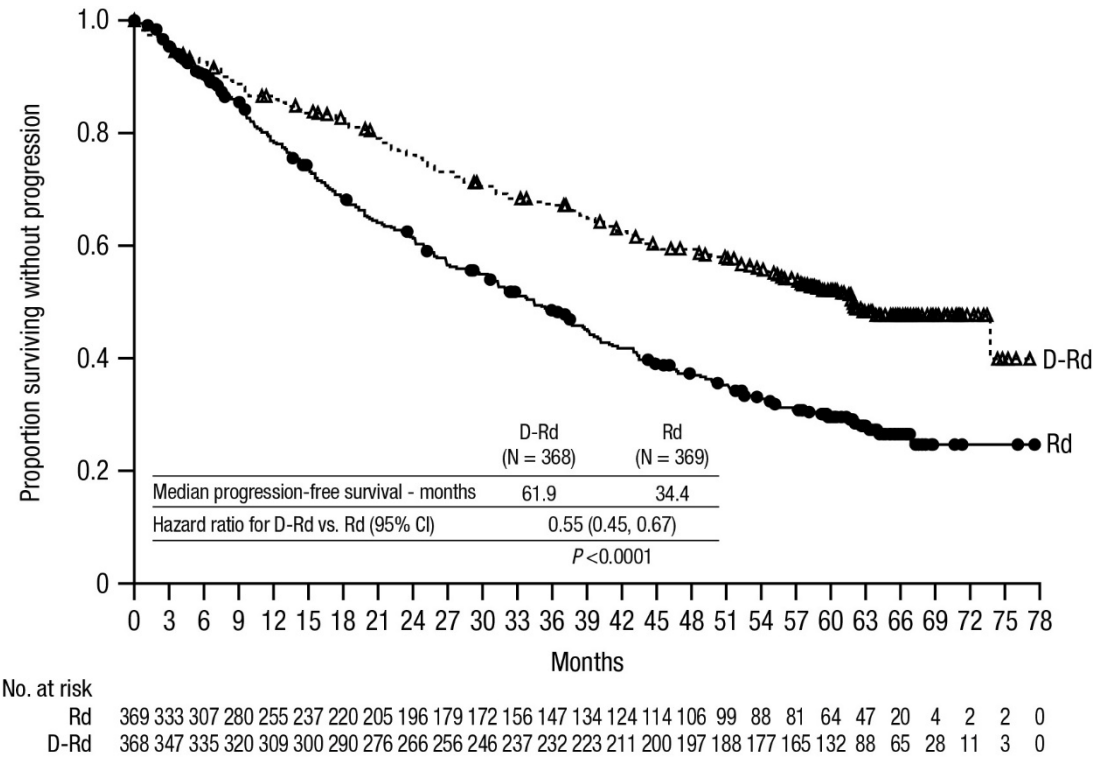
Combination treatment with lenalidomide and dexamethasone in patients ineligible for autologous stem cell transplant
Study MMY3008 an open-label, randomized, active-controlled Phase 3 study, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to 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 DARZALEX infusion days, the dexamethasone dose was given as a pre-infusion medication. 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 randomized: 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, 50% 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 and overall survival (OS).

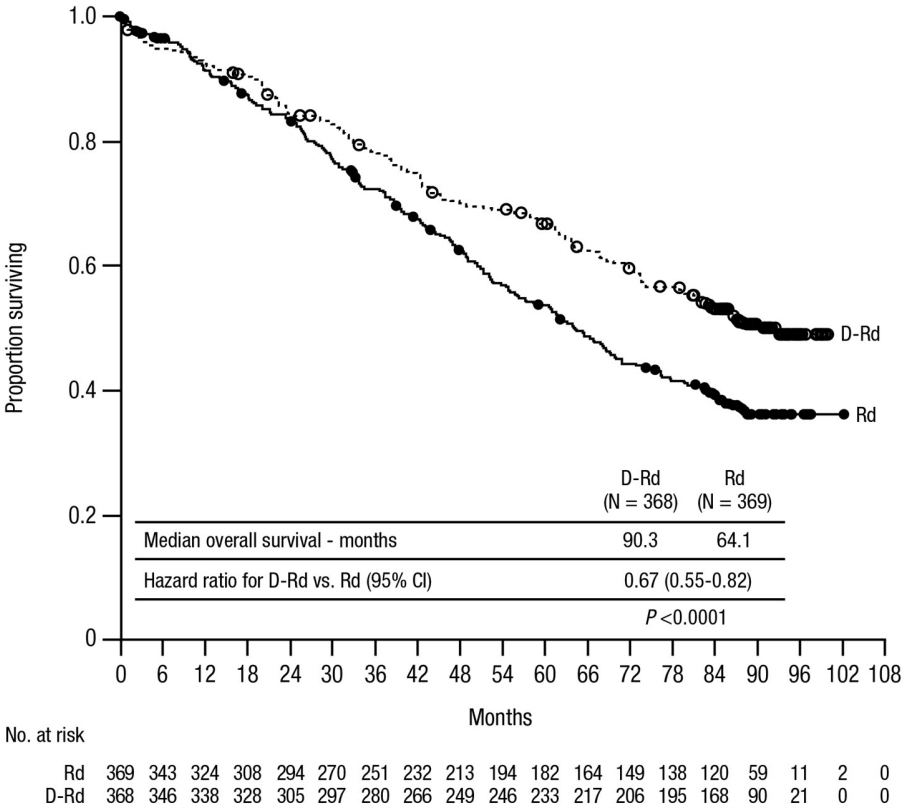
With a median follow-up of 28 months, the primary analysis of PFS in study MMY3008 demonstrated an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (hazard ratio [HR]=0.56; 95% CI: 0.43, 0.73; p<0.0001), representing 44% reduction in the risk of disease progression or death in patients treated with DRd. Results of an updated PFS analysis after a median follow-up of 64 months continued to show an improvement in PFS for patients in the DRd arm compared with the Rd am. Median PFS was 61.9 monthsin the DRd arm and 34.4 months in the Rd arm (HR=0.55; 95% CI: 0.45, 0.67; p<0.0001), representing a 45% reduction in the risk of disease progression or death in patients treated with DRd.

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



After a median follow-up of 56 months, DRd has shown an OS advantage over the Rd arm (HR=0.68; 95% CI: 0.53, 0.86; p=0.0013), representing a 32% reduction in the risk of death in patients treated in the DRd arm. After a median follow-up of 89 months, the median OS was 90.3 months (95% CI: 80.8, NE) in the DRd arm and 64.1 months (95% CI: 56, 70.8) in the Rd arm.. The 84 -month survival rate was 53% (95% CI: 48, 58) in the DRd arm and was 39% (95% CI: 34, 45) in the Rd arm.

Figure 2: Kaplan-Meier Curve of OS in Study MMY3008



Additional efficacy results from Study MMY3008 are presented in the table below.

Table 8: Additional efficacy results from Study MMY3008

	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 months (range: 0.3 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.

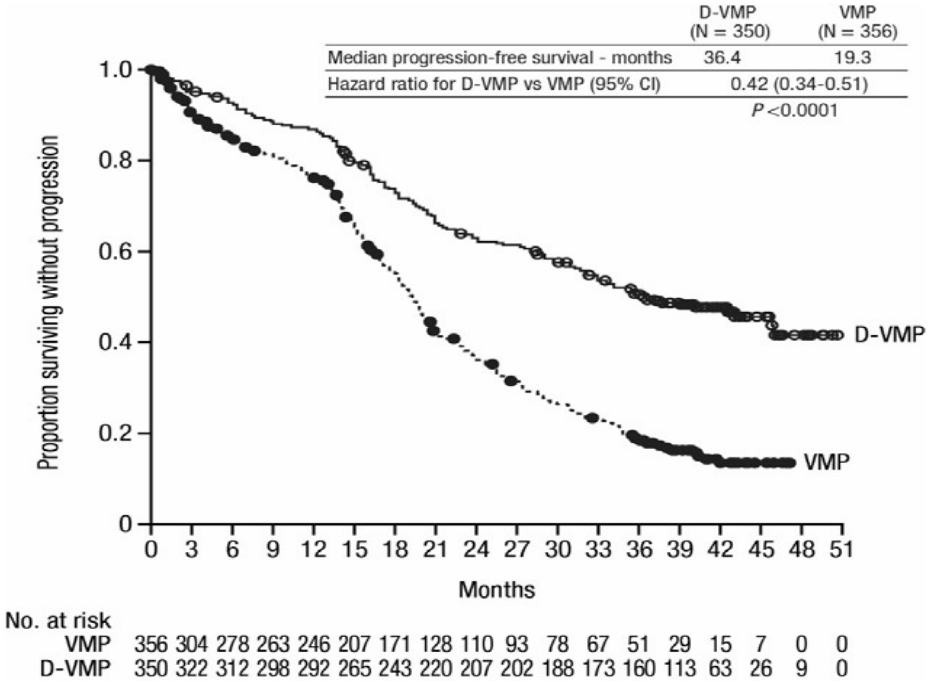
Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant

Study MMY3007, an open-label, randomized, active-controlled Phase 3 study, compared treatment with DARZALEX 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 (SC) injection at a dose of 1.3 mg/m^2 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/m^2, and prednisone at 60 mg/m^2 were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). DARZALEX treatment was continued until disease progression or unacceptable toxicity.

A total of 706 patients were randomized: 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 and 38% had ISS Stage III disease. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

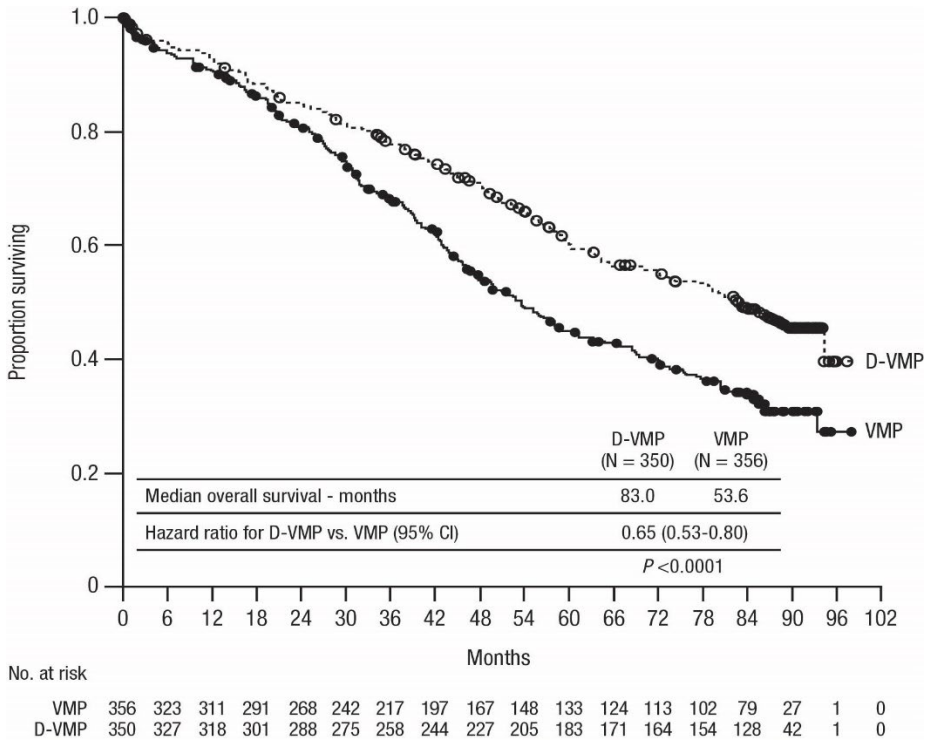
With a median follow-up of 16.5 months, the primary analysis of PFS in study MMY3007 demonstrated an improvement in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (HR=0.5; 95% CI: 0.38, 0.65; p<0.0001), representing 50% reduction in the risk of disease progression or death in patients treated with D-VMP. 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 3: 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. After a median follow-up of 87 months, the median OS was 83 months (95% CI: 72.5, NE) in the D-VMP arm and 53.6 months (95% CI: 46.3, 60.9) in the VMP arm.

Figure 4: Kaplan-Meier Curve of OS in Study MMY3007



Additional efficacy results from Study MMY3007 are presented in the table below.

Table 9: Additional efficacy results from Study MMY3007

	D-VMP (n=350)	VMP (n=356)
Overall response (sCR+CR+VGPR+PR) [n(%)]	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 negative rate (95% CI)[c] (%)	22.3 (18.0, 27.0)	6.2 (3.9, 9.2)
Odds ratio with 95% CI[d] p-value[e]	4.36 (2.64, 7.21)	
	<0.0001	

D-VMP = daratumumab-bortezomib-melphalan-prednisone; VMP = bortezomib-melphalan- prednisone; MRD = minimal residual disease; CI = confidence interval; NE = not estimable. [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] A 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 15.5 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.

Combination with bortezomib, thalidomide and dexamethasone in patients eligible for autologous stem cell transplant (ASCT)

Study MMY3006, an open-label, randomized, active-controlled Phase 3 study compared induction and consolidation treatment with DARZALEX 16 mg/kg in combination with bortezomib, thalidomide and dexamethasone (DVTd) 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.

Bortezomib was administered by subcutaneous (SC) injection or intravenous (IV) injection at a dose of 1.3 mg/m^2 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 DARZALEX infusion, the dexamethasone dose was administered intravenously as a pre-infusion medication. Dose adjustments for bortezomib, thalidomide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 1085 patients were randomized: 543 to the DVTd 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). 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 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.

Table 10: Efficacy results from Study MMY3006[a]

	DVTd (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] n(%)	346 (63.7%)	236 (43.5%)	<0.0001
95% CI (%)	(59.5%, 67.8%)	(39.3%, 47.8%)	
Odds ratio with 95% CI[d]	2.27 (1.78, 2.90)		
MRD negativity[e] n(%)	183 (33.7%)	108 (19.9%)	<0.0001
95% CI (%)	(29.7%, 37.9%)	(16.6%, 23.5%)	
Odds ratio with 95% CI[d]	2.06 (1.56, 2.72)		

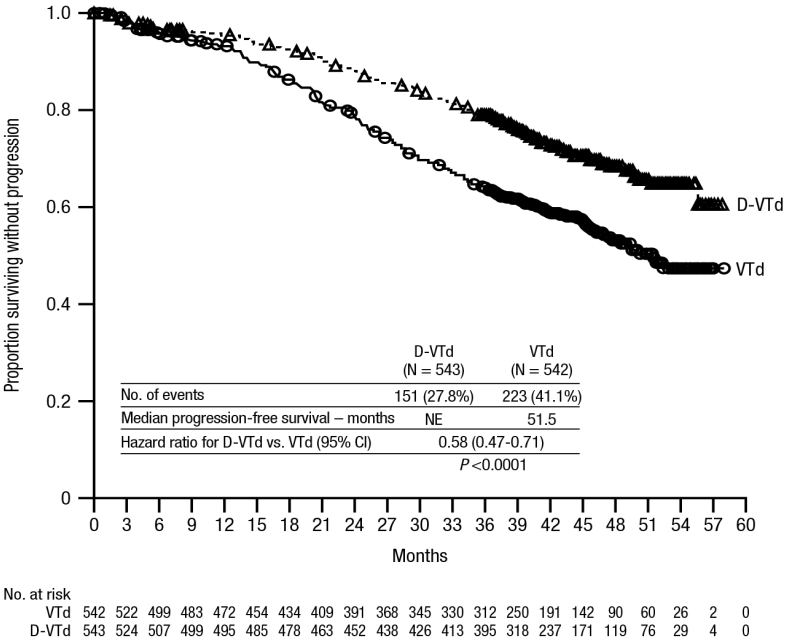
D-VTd=daratumumab-bortezomib-thalidomide-dexamethasone; VTd=bortezomib-thalidomide-dexamethasone;
MRD=minimal residual disease; CI=confidence interval

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 Mantel-Haenszel estimate of the common odds ratio for stratified tables is used.
e Only includes patients who achieved MRD negativity (threshold of 10^{-5}) and CR or better

With a median follow-up of 18.8 months, the primary analysis of PFS in study MMY3006 demonstrated an improvement in PFS in the DVTd arm as compared to the VTd arm; the median PFS had not been reached

in either arm. Treatment with DVTd resulted in a reduction in the risk of progression or death by 53% compared to VTd alone (HR=0.47; 95% CI: 0.33, 0.67; p<0.0001). Results of an updated PFS analysis after a median follow-up of 44.5 months continued to show an improvement in PFS for patients in the DVTd arm compared with the VTd arm. Median PFS was not reached in the DVTd arm and was 51.5 months in the VTd arm (HR=0.58; 95% CI: 0.47, 0.71; p<0.0001), representing a 42% reduction in the risk of disease progression or death in patients treated with DVTd.

Figure 5: Kaplan-Meier Curve of PFS in Study MMY3006



Relapsed/Refractory Multiple Myeloma

Combination treatment with lenalidomide and dexamethasone

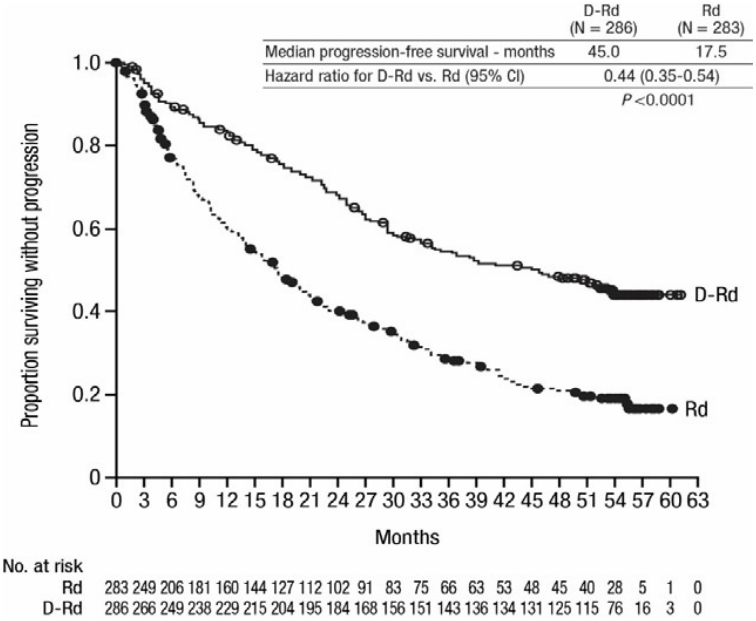
Study MMY3003, an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with multiple myeloma who had received at least 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 oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. 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 569 patients were randomized; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 65 years (range 34 to 89 years), 11% were ≥ 75 years, 59% were male; 69% Caucasian, 18% Asian, and 3% African American. Patients had received a median of 1 prior line of therapy. Sixty -three percent (63%) of patients had received prior autologous stem cell transplantation (ASCT). The majority of patients (86%) received a prior proteasome inhibitor (PI), 55% of patients had received a prior immunomodulatory agent (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. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

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

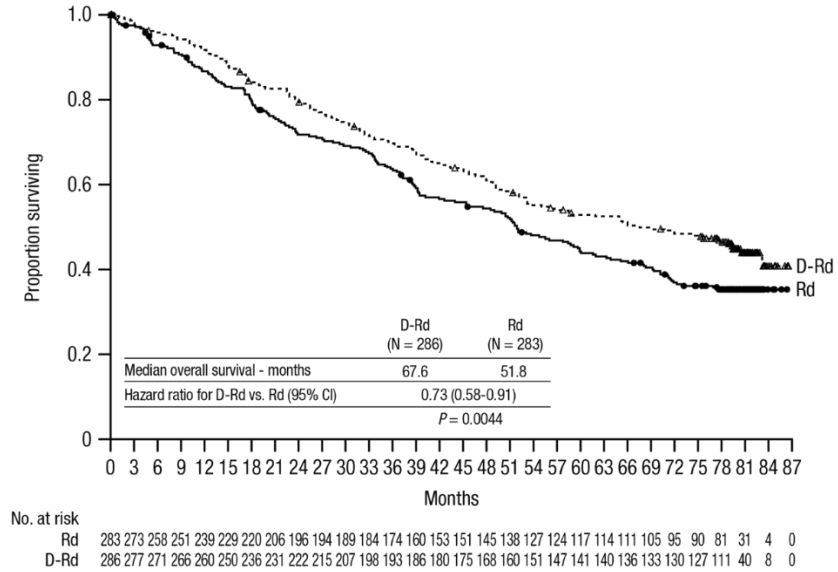
DRd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001) representing 63% reduction in the risk of disease progression or death in patients treated with DRd. Results of an updated PFS analysis after a median follow-up of 55 months continued to show an improvement in PFS for patients 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.

Figure 6: Kaplan-Meier Curve of PFS in Study MMY3003



After a median follow-up of 80 months, DRd has shown an OS advantage over the Rd arm (HR=0.73; 95% CI: 0.58, 0.91; p=0.0044), representing a 27% reduction in the risk of death in patients treated in the DRd arm. The median OS was 67.6 months in the DRd arm and 51.8 months in the Rd arm. The 78-month survival rate was 47% (95% CI: 41, 52) in the DRd arm and was 35% (95% CI: 30, 41) in the Rd arm.

Figure 7: Kaplan-Meier Curve of OS in Study MMY3003



Additional efficacy results from Study MMY3003 are presented in the table below.

Table 11: Additional efficacy results from Study MMY3003

Response evaluable patient number	DRd (n=281)	Rd (n=276)
Overall response (sCR+CR+VGPR+PR) n(%) p-value[a]	261 (92.9) <0.0001	211 (76.4)
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^{-4}

[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 Fisher's exact test.

Combination treatment with bortezomib and dexamethasone

Study MMY3004, an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with multiple myeloma who had received at least one prior therapy.

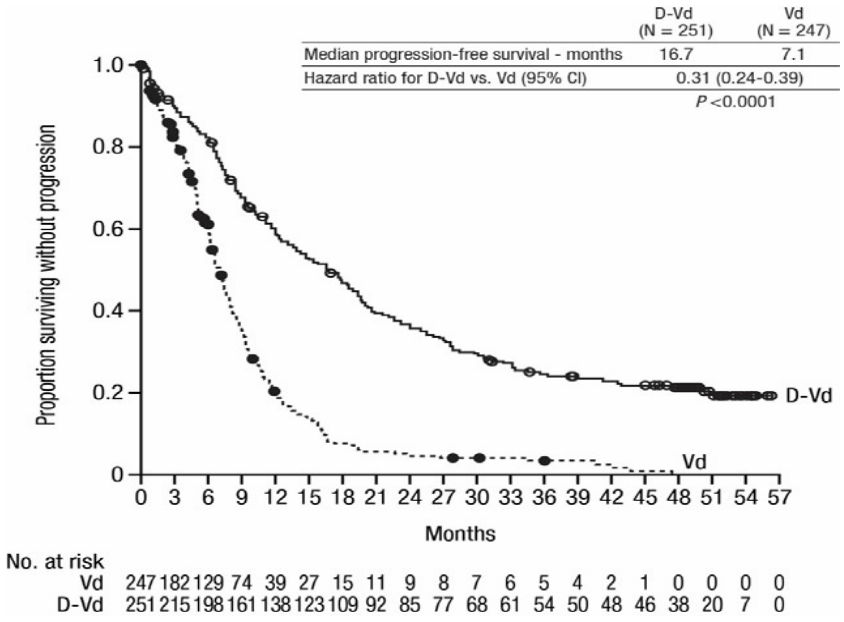
Bortezomib was administered by SC injection or IV injection at a dose of 1.3 mg/m^2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of the 8 bortezomib cycles (80 mg/week for two out of three weeks of each 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 DARZALEX infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Bortezomib and dexamethasone were given for 8 three-week cycles in both treatment arms; whereas DARZALEX was given until treatment progression. However, dexamethasone 20 mg was continued as a DARZALEX pre-infusion medication in the DVd arm. Dose adjustments for bortezomib and dexamethasone were applied according to manufacturer's prescribing information.

A total of 498 patients were randomized; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 64 years (range 30 to 88 years); 12% were ≥ 75 years, 57% were male; 87% Caucasian, 5% Asian and 4% African American. Patients had received a median of 2 prior lines of therapy and 61% of patients had received prior autologous stem cell transplantation (ASCT). 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 and the proportions of patients refractory to any specific prior therapy were well balanced between the treatment groups. Thirty-three percent (33%) of patients were refractory to an IMiD only, and 28% were refractory to lenalidomide. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated

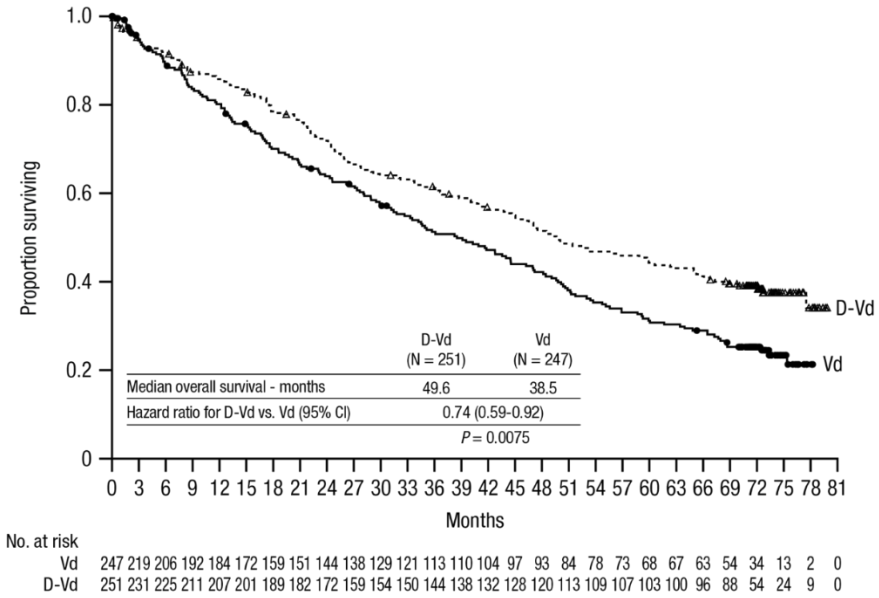
an improvement in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p- value < 0.0001), representing a 61% reduction in the risk of disease progression or death for patients treated with DVd versus Vd. 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 16.7 months in the DVd arm and 7.1 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.

Figure 8: Kaplan-Meier Curve of PFS in Study MMY3004



After a median follow-up of 73 months, DVd has shown an OS advantage over the Vd arm (HR=0.74; 95% CI: 0.59, 0.92; p=0.0075), representing a 26% reduction in the risk of death in patients treated in the DVd arm. The median OS was 49.6 months in the DVd arm and 38.5 months in the Vd arm. The 72-month survival rate was 39% (95% CI: 33, 45) in the DVd arm and was 25% (95% CI: 20, 31) in the Vd arm.

Figure 9: Kaplan-Meier Curve of OS in Study MMY3004



Additional efficacy results from Study MMY3004 are presented in the table below.

Table 12: Additional efficacy results from Study MMY3004

Response evaluable patient number	DVd (n=240)	Vd (n=234)
Overall response (sCR+CR+VGPR+PR) n(%) P-value[a]	199 (82.9) <0.0001	148 (63.2)
Stringent complete response (sCR) Complete response (CR) Very good partial response (VGPR) Partial response (PR)	11 (4.6) 35 (14.6) 96 (40.0) 57 (23.8)	5 (2.1) 16 (6.8) 47 (20.1) 80 (34.2)
Median Time to Response [months (range)]	0.9 (0.8, 1.4)	1.6 (1.5, 2.1)
Median Duration of Response [months (95% CI)]	NE (11.5, NE)	7.9 (6.7, 11.3)
MRD negative rate (95% CI)[b] (%)	8.8 (5.6, 13.0)	1.2 (0.3, 3.5)
Odds ratio with 95% CI[c]	9.04 (2.53, 32.21)	
P-value[d]	0.0001	

DVd = daratumumab- bortezomib-dexamethasone; Vd = bortezomib-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^{-4}

c Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio > 1 indicates an advantage for DVd.

d p-value is from Fischer's exact test

Monotherapy

The clinical efficacy and safety of DARZALEX monotherapy for the treatment of patients with relapsed and refractory multiple myeloma whose prior therapy included a proteasome inhibitor and an immunomodulatory agent, was demonstrated in two open-label studies.

In Study MMY2002, 106 patients with relapsed and refractory multiple myeloma received 16 mg/kg DARZALEX until disease progression. The median patient age was 63.5 years (range, 31 to 84 years), 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, 95% were refractory to both, a PI and IMiD, 77% were refractory to alkylating agents, 63% were refractory to pomalidomide and 48% of patients were refractory to carfilzomib.

Efficacy results based on Independent Review Committee (IRC) assessment are presented in the table below.

Table 13. IRC assessed efficacy results for study MMY2002

Efficacy Endpoint	**DARZALEX 16 mg/kg N=106**
Overall response rate[1] (ORR: sCR+CR+VGPR+PR) [n (%)] 95% CI (%)	31 (29.2) (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. With a median duration of follow-up of 9 months, median OS was not reached. The 12-month OS rate was 65% (95% CI: 51.2, 75.5).

In Study GEN501, 42 patients with relapsed and refractory multiple myeloma received 16 mg/kg DARZALEX 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.

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). With a median duration of follow-up of 10 months, median OS was not reached. The 12-month OS rate was 77% (95% CI: 58.0, 88.2).

PHARMACOKINETIC PROPERTIES

The pharmacokinetics (PK) of daratumumab following intravenous administration of DARZALEX monotherapy were evaluated in patients with relapsed and refractory multiple myeloma at dose levels from 0.1 mg/kg to 24 mg/kg. A population PK model of daratumumab was developed to describe the PK characteristics of daratumumab and to evaluate the influence of covariates on the disposition of daratumumab in patients with multiple myeloma. The population PK analysis included 223 patients receiving DARZALEX monotherapy in two clinical trials (150 subjects received 16 mg/kg).

In the 1- to 24 mg/kg cohorts, peak serum concentrations (C_{max}) after the first dose increased in approximate proportion to dose and volume of distribution was consistent with initial distribution into the plasma compartment. Increases in AUC were more than dose-proportional and clearance (CL) decreased with increasing dose. These observations suggest CD38 may become saturated at higher doses, after which the impact of target binding clearance is minimized and the clearance of daratumumab approximates the linear clearance of endogenous IgG1. Clearance also decreased with multiple doses, which may be related to tumor burden decreases.

Terminal half-life increases with increasing dose and with repeated dosing. The mean (standard deviation [SD]) estimated terminal half-life of daratumumab following the first 16 mg/kg dose was 9 (4.3) days. Based on population PK analysis, the mean (SD) half-life associated with non-specific linear elimination was approximately 18 (9) days; this is the terminal half-life that can be expected upon complete saturation of target mediated clearance and repeat dosing of daratumumab.

At the end of weekly dosing for the recommended monotherapy schedule and dose of 16 mg/kg, the mean (SD) serum C_{max} value was 915 (410.3) micrograms/mL, approximately 2.9-fold higher than following the first infusion. The mean (SD) predose (trough) serum concentration at the end of weekly dosing was 573 (331.5) micrograms/mL.

Based on the population PK analysis of DARZALEX monotherapy, daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion), and the mean (SD) ratio of C_{max} at steady-state to C_{max} after the first dose was 1.6 (0.5). The mean (SD) central volume of distribution is 56.98 (18.07) mL/kg.

Four additional population PK analyses were conducted in patients with multiple myeloma that received daratumumab in various combination therapies (N=1765). Daratumumab concentration-time profiles were similar following the monotherapy and combination therapies. The mean estimated terminal half-life associated with linear clearance in combination therapy was approximately 15-24 days.

Based on population PK analysis body weight was identified as a statistically significant covariate for daratumumab clearance. Therefore, body weight based dosing is an appropriate dosing strategy for the multiple myeloma patients.

Simulation of daratumumab pharmacokinetics was conducted for all recommended dosing schedules using individual PK parameters of patients with multiple myeloma (n=1309). The simulation results confirmed that the split and single dosing for the first dose should provide similar PK, with the exception of the PK profile in the first day of the treatment.

Special populations Age and gender
Based on population PK analyses in patients receiving monotherapy or various combination therapies, age (range: 31-93 years) had no clinically important effect on the PK of daratumumab, and the exposure of daratumumab was similar between younger (aged <65 years, n=706) and older (aged ≥65 to <75 years n=913; aged ≥75 years, n=369) patients.

Gender did not affect exposure of daratumumab to a clinically relevant degree in population PK analyses.

Renal impairment
No formal studies of DARZALEX in patients with renal impairment have been conducted. Population PK analyses were performed based on pre-existing renal function data in patients receiving daratumumab monotherapy or various combination therapies, including 592 patients with normal renal function (creatinine clearance [CRCL] ≥90 mL/min), 757 with mild renal impairment (CRCL <90 and ≥60 mL/min), 604 with moderate renal impairment (CRCL <60 and ≥30 mL/min), and 34 with severe renal impairment or end stage renal disease (CRCL <30 mL/min). No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function.

Hepatic impairment
No formal studies of DARZALEX in patients with hepatic impairment have been conducted. Population PK analyses were performed in patients receiving daratumumab monotherapy or various combination therapies, including 1742 patients with normal hepatic function (total bilirubin [TB] and aspartate aminotransferase [AST]≤ upper limit of normal [ULN]), 224 with mild hepatic impairment (TB 1.0× to 1.5× ULN or AST>ULN) and 10 patients with moderate (TB >1.5× to 3.0× ULN; n=9) or severe (TB >3.0× ULN; n=1) hepatic impairment. No clinically important differences in the exposure to daratumumab were observed between patients with hepatic impairment and those with normal hepatic function.

Race
Based on the population PK analyses in patients receiving either daratumumab monotherapy or various combination therapies, the exposure to daratumumab was similar between white (n=1662) and non-white (n=326) subjects.

NON-CLINICAL INFORMATION

CARCINOGENICITY AND MUTAGENICITY
No animal studies have been performed to establish the carcinogenic potential of daratumumab. Routine genotoxicity and carcinogenicity studies are generally not applicable to biologic pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material.

REPRODUCTIVE TOXICOLOGY
No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development.

FERTILITY
No animal studies have been performed to determine potential effects on fertility in males or females.

PHARMACEUTICAL INFORMATION LIST OF EXCIPIENTS
- Glacial acetic acid
- Mannitol
- Polysorbate 20
- Sodium acetate trihydrate
- Sodium chloride
- Water for injection

INCOMPATIBILITIES
This medicinal product must not be mixed with other medicinal products except those mentioned in Instructions for Use and Handling and Disposal.

SHELF LIFE
Unopened vials:
24 months

After dilution:
Since daratumumab solutions do not contain a preservative, unless the method of opening/ dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, the solution may be stored in a refrigerator at 2°C-8°C (36°F–46°F) for up to 24 hours prior to use. followed by 15 hours (including infusion time) at room temperature 15°C–25°C (59°F–77°F) and room light. If stored in the refrigerator, allow the solution to come to room temperature before administration.

STORAGE CONDITIONS
Store unopened vials at 2°C–8°C.
Do not freeze.
Do not shake.
Keep the vial in the outer carton box in order to protect from light. Keep out of the sight and reach of children.
For storage conditions of the diluted medicinal product, see *Shelf-life.*

INSTRUCTIONS FOR USE AND HANDLING AND DISPOSAL
Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg), total volume (mL) of DARZALEX solution required and the number of DARZALEX vials needed based on patient weight.
- Check that the DARZALEX solution is colorless to yellow. Do not use if opaque particles, discoloration or other foreign particles are present.
- Using aseptic technique, remove a volume of 0.9% Sodium Chloride from the infusion bag/container that is equal to the required volume of DARZALEX solution.
- Withdraw the necessary amount of DARZALEX solution and dilute to the appropriate volume by adding to an infusion bag/container containing 0.9% Sodium Chloride (see Dosage and Administration). Infusion bags/containers must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.
- Gently invert the bag/container to mix the solution. Do not shake or freeze.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discoloration or foreign particles are observed.
- Since DARZALEX does not contain a preservative, diluted solutions should be administered within 15 hours (including infusion time) at room temperature 15°C-25°C (59°F–77°F) and in room light.
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions 2°C – 8°C (36°F–46°F) and protected from light. Do not freeze. If stored in the refrigerator, allow the solution to come to room temperature before administration.
- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.
- Do not infuse DARZALEX concomitantly in the same intravenous line with other agents.
- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.

PATIENT COUNSELING INFORMATION

Infusion Reactions
Advise patients to seek immediate medical attention for any of the following signs and symptoms of infusion reactions:

itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing *(see Warnings and Precautions and Adverse Reactions)*.

Neutropenia
Advise patients that if they have a fever, they should contact their healthcare professional *(see Warnings and Precautions and Adverse Reactions)*.

Thrombocytopenia
Advise patients to inform their healthcare professional if they notice signs of bruising or bleeding *(see Warnings and Precautions and Adverse Reactions)*.

Interference with Laboratory Tests
Advise patients to inform healthcare providers including blood transfusion centers/personnel that they are taking DARZALEX, in the event of a planned transfusion *(see* Effects of DARZALEX on laboratory tests).

Advise patients that DARZALEX can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response *(see* Effects of DARZALEX on laboratory tests).

Hepatitis B Virus (HBV) Reactivation:
Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX could cause hepatitis B virus to become active again (*see Adverse Reactions)*.

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