DARZALEX®
Daratumumab.
Concentrate for solution for infusion

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
DARZALEX is indicated as monotherapy for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and an immunomodulatory agent.
DARZALEX is indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior therapy.
DARZALEX is indicated in combination with lenalidomide and dexamethasone, or bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

Posology and method of administration
DARZALEX should be administered by a healthcare professional, in an environment where resuscitation facilities are available.

Pre- and post-infusion medications should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. See below "Recommended concomitant medications", "Management of infusion-related reactions" and *Warnings and Precautions*.

Posology
Dosing schedule in combination with lenalidomide and dexamethasone (4-week cycle regimen) and for monotherapy
The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 1.

Table 1: DARZALEX dosing schedule in combination with lenalidomide and dexamethasone (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, see section Pharmacodynamic properties and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle regimens)
The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion 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 (daratumumab only)

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

Dosing schedule in combination with bortezomib (3-week cycle regimen)
The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 3.

Table 3: 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, see section Pharmacodynamic properties and the corresponding Summary of Product Characteristics.

Infusion rates
Following dilution the DARZALEX infusion should be intravenously administered at the initial infusion rate presented in Table 4 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 4 below.

Table 4: Infusion rates for DARZALEX administration

	Dilution Volume	**Initial Rate (first hour)**	**Rate Increments [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 (16mg/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] incremental escalation of the infusion rate should be considered in the absence of infusion reactions.
[b] A dilution volume of 500 mL for the 16 mg/kg should be used only if there were no IRRs the previous week. Otherwise, use a dilution volume of 1000 mL.
[c] A modified initial rate (100 mL/hour) for subsequent infusions (i.e. Week 3 onwards) should only be used only if there were no IRRs during the previous infusion. Otherwise, continue to use instructions indicated in the table for the Week 2 infusion rate.

Management of infusion-related reactions
Pre-infusion medications should be administered to reduce the risk of infusion-related reactions (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 *Warnings and Precautions*).

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, the infusion should be resumed 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 be resumed at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (Table 1).
- Grade 3 (severe): Once reaction symptoms resolve, restarting of the infusion may be considered at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, infusion rate escalation may be resumed at increments and intervals as appropriate (Table 4). The procedure above should be repeated 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.

Missed dose (s)
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 *Warnings and Precautions*). For information concerning medicinal products given in combination with DARZALEX, see corresponding Summary of Product Characteristics.

Recommended concomitant medications
Pre-infusion medication
Pre-infusion medications should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every infusion of DARZALEX as follows:

- 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:
  Dexamethasone 20mg, administered prior to every DARZALEX infusion (see *Pharmacodynamic Properties*). 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 650 to 1,000 mg)
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Post-infusion medication
Post-infusion medications should be administered to reduce the risk of delayed infusion-related reactions 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 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) is administered the day after the DARZALEX infusion, additional postinfusion medications may not be needed (see *Pharmacodynamic Properties*).

Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-infusion medications including short and long acting bronchodilators, and inhaled corticosteroids should be considered. 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
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.
Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment (see *Pharmacokinetic Properties*).

Elderly
No dose adjustments are considered necessary in elderly patients (see *Pharmacokinetic Properties, Adverse Reactions*).

Paediatric population
The safety and efficacy of DARZALEX in children aged below 18 years of age have not been established.
No data are available (see *Pharmacodynamic Properties*).

Method of administration
DARZALEX is for intravenous use. It is administered as an intravenous infusion following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. For instructions on dilution of the medicinal product before administration, see *Instructions for Use and Handling and Disposal*.

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, IRR 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.

Interference with determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, 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.

Excipients

Each 5 mL and 20 mL vial of DARZALEX contains 0.4 mmol and 1.6 mmol (9.3 mg and 37.3 mg) sodium, respectively. This should be taken into consideration by patients on a controlled sodium diet.

Interactions

No drug-drug interaction studies have been performed.

Clinical pharmacokinetic assessments of daratumumab in combination with bortezomib 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 complete response (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 up to 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 2459 patients with multiple myeloma including 2303 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy.

Newly Diagnosed Multiple Myeloma

Combination treatment with lenalidomide and dexamethasone (DRd)

Adverse reactions described in the table below reflect exposure to DARZALEX for a median treatment duration of 25.3 months (range: 0.1 to 40.44 months) for the daratumumab-lenalidomide-dexamethasone (DRd) group and median treatment duration of 21.3 months (range: 0.03 to 40.64 months) for the lenalidomide-dexamethasone group (Rd) in a Phase 3 active-controlled study (Study MMY3008). The most frequent (≥20%) adverse reactions were infusion reactions, diarrhea, constipation, nausea, peripheral edema, fatigue, back pain, asthenia, pyrexia, upper respiratory tract infection. bronchitis, pneumonia, decreased appetite, muscle spasms, peripheral sensory neuropathy, dyspnea and cough. Serious adverse reactions with a 2% greater incidence in the DRd arm compared to the Rd arm were dehydration (DRd 2% vs Rd <1%), bronchitis (DRd 4% vs Rd 2%) and pneumonia (DRd 15% vs Rd 8%).

Table 5: Adverse reactions reported in Study MMY3008*

System Organ Class	DRd (N=364)	Rd (N=365)

Adverse Reaction	Any Grade (%)	Grade 3 (%)	Grade 4 (%)	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Infusion reactions[a]	41	2	<1	0	0	0
Gastrointestinal disorders						
Diarrhea	57	7	0	46	4	0
Constipation	41	1	<1	36	<1	0
Nausea	32	1	0	23	1	0
Vomiting	17	1	0	12	<1	0
General disorders and administration site conditions						
Peripheral edema[b]	41	2	0	33	1	0
Fatigue	40	8	0	28	4	0
Back pain	34	3	<1	26	3	<1
Asthenia	32	4	0	25	3	<1
Pyrexia	23	2	0	18	2	0
Chills	13	0	0	2	0	0
Infections and infestations						
Upper respiratory tract infection[c]	52	2	<1	36	2	<1
Bronchitis[d]	29	3	0	21	1	0
Pneumonia[e]	26	14	1	14	7	1
Urinary tract infection	18	2	0	10	2	0
Metabolism and nutrition disorders						
Decreased appetite	22	1	0	15	<1	<1
Hyperglycemia	14	6	1	8	3	1
Hypocalcemia	14	1	<1	9	1	1
Musculoskeletal and connective tissue disorders						
Muscle spasms	29	1	0	22	1	0
Nervous system disorders						
Peripheral sensory neuropathy	24	1	0	15	0	0
Headache	19	1	0	11	0	0
Paresthesia	16	0	0	8	0	0
Respiratory, thoracic and mediastinal disorders						
Dyspnea[f]	32	3	<1	20	1	0
Cough[g]	30	<1	0	18	0	0
Vascular disorders						
Hypertension[h]	13	6	<1	7	4	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion-related Reactions below

[b] Generalized edema, Gravitational edema, Edema, Edema peripheral, Peripheral swelling

[c] Acute sinusitis, Bacterial rhinitis, Laryngitis, Metapneumovirus infection, Nasopharyngitis, Oropharyngeal candidiasis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Tonsillitis, Tracheitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection

[d] Bronchiolitis, Bronchitis, Bronchitis viral, Respiratory syncytial virus bronchiolitis, Tracheobronchitis

[e] Atypical pneumonia, Bronchopulmonary aspergillosis, Lung infection, Pneumocystis jirovecii infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia pneumococcal, Pneumonia viral, Pulmonary mycosis

[f] Dyspnea, Dyspnea exertional

[g] Cough, Productive cough

[h] Blood pressure increased, Hypertension

* Note: Adverse reactions that occurred in ≥ 10% of patients and with at least a 5% frequency greater in the DRd arm are listed. Hematology laboratory related toxicities were excluded and reported separately in the table below.

Laboratory abnormalities worsening during treatment from baseline listed in the table below.

Table 6: Treatment-emergent hematology laboratory abnormalities in Study MMY3008

	DRd (N=364) %			Rd (N=365) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	47	13	0	57	24	0
Thrombocytopenia	67	6	3	58	7	4
Leukopenia	90	30	5	82	20	4
Neutropenia	91	39	17	77	28	11
Lymphopenia	84	41	11	75	36	6

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

Combination treatment with bortezomib, melphalan and prednisone

Adverse reactions described in the table below reflect exposure to DARZALEX for a median treatment duration of 14.7 months (range: 0 to 25.8 months) for the daratumumab, bortezomib, melphalan and prednisone (D-VMP) group, and median treatment duration of 12 months (range: 0.1 to 14.9 months) for the VMP group in a Phase 3 active-controlled study (Study MMY3007). The most frequent adverse reactions (≥20%) were infusion reactions, upper respiratory tract infection and edema peripheral. Serious adverse reactions with at least a 2% greater incidence in the D-VMP arm compared to the VMP arm were pneumonia (D-VMP 11% vs VMP 4%), upper respiratory tract infection (D-VMP 5% vs VMP 1%), and pulmonary edema (D-VMP 2% vs VMP 0%).

Table 7: Adverse reactions reported in Study MMY3007*

System Organ Class Adverse Reaction	**D-VMP (N=346)**			**VMP (N=354)**		
	Any Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**	**Any Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Infusion reactions[a]	28	4	1	0	0	0
General disorders and administration site conditions						
Edema peripheral[b]	21	1	< 1	14	1	0
Infections and infestations						
Upper respiratory tract infection[b]	48	5	0	28	3	0
Pneumonia[b]	16	12	< 1	6	5	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[b]	16	< 1	0	8	< 1	0
Dyspnea[b]	13	2	1	5	1	0
Pulmonary edema[b]	2	1	< 1	< 1	< 1	0
Vascular disorders						
Hypertension[b]	10	4	< 1	3	2	0

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

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion-related Reactions below.

[b] Indicates grouping of preferred terms

*Note: Adverse reactions that occurred in ≥10% of patients and with at least a 5% frequency greater in the D-VMP arm are listed. In addition, serious adverse reactions are listed if there was at least a 2% greater incidence in the D-VMP arm compared to the VMP arm.

Hematology laboratory related toxicities were excluded and reported separately in the table below

Laboratory abnormalities worsening during treatment from baseline listed in the table below.

Table 8: Treatment-emergent hematology laboratory abnormalities in Study MMY3007

	D-VMP (N=346) %			**VMP (N=354) %**		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Anemia	47	18	0	50	21	0
Thrombocytopenia	88	27	11	88	26	16
Neutropenia	86	34	10	87	32	11
Lymphopenia	85	46	12	83	44	9

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

Relapsed/Refractory Multiple Myeloma

Combination treatment with lenalidomide and dexamethasone

Adverse reactions described in the table below reflect exposure to DARZALEX for a median treatment duration of 13.1 months (range: 0 to 20.7 months) for the daratumumab-lenalidomide-dexamethasone (DRd) group and median treatment duration of 12.3 months (range: 0.2 to 20.1 months) for the lenalidomide-dexamethasone group (Rd) in a Phase 3 active-controlled study (Study MMY3003). The most frequent adverse reactions were infusion reactions, diarrhea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnea. Serious adverse reactions were pneumonia, upper respiratory tract infection, influenza and pyrexia. Adverse reactions resulted in discontinuations for 7% (n=19) of patients in the DRd arm versus 8% (n=22) in the Rd arm.

Table 9: Adverse reactions reported in Study MMY3003*

System Organ Class Adverse Reaction	**DRd (N=283)**			**Rd (N=281)**		
	Any Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**	**Any Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Infusion reactions[a]	48	5	0	0	0	0
Gastrointestinal disorders						
Diarrhea	43	5	0	25	3	0

Nausea	24	1	0	14	0	0
Vomiting	17	1	0	5	1	0
General disorders and administration site conditions						
Fatigue	35	6	< 1	28	2	0
Pyrexia	20	2	0	11	1	0
Infections and infestations						
Influenza	7	3	0	5	1	0
Pneumonia[b]	19	10	2	15	7	2
Upper respiratory tract infection[b]	65	6	< 1	51	4	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	26	1	0	19	2	0
Nervous system disorders						
Headache	13	0	0	7	0	0
Respiratory, thoracic and mediastinal disorders						
Cough[b]	30	0	0	15	0	0
Dyspnea	21	3	< 1	12	1	0

Key: D=daratumumab, Rd=lenalidomide-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion-related Reactions below

[b] Indicates grouping of preferred terms

* Note: Adverse reactions that occurred in ≥ 10% of patients and with at least a 5% frequency greater in the DRd arm are listed. In addition, serious adverse events are listed if there was at least a 2% greater incidence in the DRd arm compared to the Rd arm.

Hematology laboratory related toxicities were excluded and reported separately in the table below

Laboratory abnormalities worsening during treatment from baseline are listed in the table below.

Table 10: Treatment-emergent hematology laboratory abnormalities

	Study MMY3003					
	DRd (N=283) %			**Rd (N=281) %**		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Anemia	52	13	0	57	19	0
Thrombocytopenia	73	7	6	67	10	5
Neutropenia	92	36	17	87	32	8
Lymphopenia	95	42	10	87	32	6

Key: D=Daratumumab, Rd=lenalidomide-dexamethasone.

Combination treatment with bortezomib and dexamethasone

Adverse reactions described in Table 7 reflect exposure to DARZALEX for a median treatment duration of 6.5 months (range: 0 to 14.8 months) for the daratumumab-bortezomib-dexamethasone (DVd) group and median treatment duration of 5.2 months (range: 0.2 to 8.0 months) for the bortezomib group (Vd) in a Phase 3 active-controlled study (Study MMY3004). The most frequent adverse reactions (>20%) were infusion reactions, diarrhea, peripheral edema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnea. Serious adverse reactions included diarrhea, upper respiratory tract infection and atrial fibrillation. Adverse reactions resulted in discontinuations for 7% (n=18) of patients in the DVd arm versus 9% (n=22) in the Vd arm.

Table 11: Adverse reactions reported in Study MMY3004*

System Organ Class Adverse Reaction	**DVd (N=243)**			**Vd (N=237)**		
	Any Grade (%)	**Grade 3 (%)**	**Grade 4 (%)**	**Any Grade (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Infusion reactions[a]	45	9	0	0	0	0
Cardiac disorders						
Atrial fibrillation	5	1	1	2	1	0
Gastrointestinal disorders						
Diarrhea	32	3	< 1	22	1	0
Vomiting	11	0	0	4	0	0
General disorders and administration site conditions						
Edema peripheral[b]	22	1	0	13	0	0
Pyrexia	16	1	0	11	1	0
Infections and infestations						
Upper respiratory tract infection[b]	44	6	0	30	3	< 1
Nervous system disorders						

Peripheral sensory neuropathy	47	5	0	38	6	< 1
Respiratory, thoracic and mediastinal disorders						
Cough[b]	27	0	0	14	0	0
Dyspnea[b]	21	4	0	11	1	0

Key: D=daratumumab, Vd=bortezomib-dexamethasone.

[a] Infusion reaction includes terms determined by investigators to be related to infusion, see section on Infusion-related Reactions below

[b] Indicates grouping of preferred terms

*Note: Adverse reactions that occurred in ≥ 10% of patients and with at least a 5% frequency greater in the DVd arm are listed. In addition, serious adverse events are listed if there was at least a 2% greater incidence in the DVd arm compared to the Rd arm. Hematology laboratory related toxicities were excluded and reported separately in table below.

Laboratory abnormalities worsening during treatment are listed in table below.

Table 12: Treatment-emergent hematology laboratory abnormalities

	Study MMY3004					
	DVd (N=243) %			**Vd (N=237) %**		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Anemia	48	13	0	56	14	0
Thrombocytopenia	90	28	19	85	22	13
Neutropenia	58	12	3	40	5	<1
Lymphopenia	89	41	7	81	24	3

Key: D=Daratumumab, Vd=bortezomib-dexamethasone.

Monotherapy

The data described below reflect exposure to DARZALEX in three pooled open-label clinical studies that included 156 patients with relapsed and refractory multiple myeloma treated with DARZALEX at 16 mg/kg. The median duration of DARZALEX treatment was 3.3 months, with the longest duration of treatment being 14.2 months. Adverse reactions occurring at a rate of ≥ 10% are presented in table below. The most frequently reported adverse reactions (≥ 20%) were IRRs, fatigue, nausea, back pain, anemia, neutropenia and thrombocytopenia. Four percent of patients discontinued DARZALEX treatment due to adverse reactions, none of which were considered drug related.

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).

Table 13: Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg

System Organ Class	**Adverse Reaction**	**Frequency (all Grades)**	**Incidence (%)**	
			All Grades	**Grade 3-4**
Infections and infestations	Upper respiratory tract infection	Very Common	17	1*
	Nasopharyngitis		12	0
	Pneumonia**		10	6*
Blood and lymphatic system disorders	Anemia	Very Common	25	17*
	Neutropenia		22	12
	Thrombocytopenia		20	14
Metabolism and nutrition disorders	Decreased appetite	Very Common	15	1*
Respiratory, thoracic and mediastinal disorders	Cough	Very Common	14	0
Gastrointestinal disorders	Nausea	Very Common	21	0
	Diarrhea		15	0
	Constipation		14	0
Musculoskeletal and connective tissue disorders	Back pain	Very Common	20	2*
	Arthralgia		16	0
	Pain in extremity		15	1*
	Musculoskeletal chest pain		10	1*
General disorders and administration site conditions	Fatigue	Very Common	37	2*
	Pyrexia		17	1*
Injury, poisoning and procedural complications	Infusion-related reaction***	Very Common	51	4*

* No Grade 4

** Pneumonia also includes the terms pneumonia streptococcal and lobar pneumonia

*** Infusion-related reactions include but are not limited to, the following multiple adverse reaction terms: nasal congestion, cough, chills, allergic rhinitis, throat irritation, dyspnea, nausea (all ≥ 5%), bronchospasm (2.6%), hypertension (1.9%) and hypoxia (1.3%).

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 with second 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).

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%.
Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%.
Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In the 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%.
Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%.

Adverse Reactions identified from other clinical trials
Sepsis

Other adverse reactions
Other adverse reactions reported in patients treated with daratumumab in clinical trials are listed in Table 14.

Table 14: Other adverse reactions reported in patients treated with daratumumab in clinical trials

System Organ Class Adverse Reaction (%)
Infections and infestations
Cytomegalovirus infection[a] (≤1%)
Immune system disorders
Hypogammaglobulinemia[b] (3%)
Metabolism and nutrition disorders
Hypokalemia (10%)
Psychiatric disorders
Insomnia (17%)
Nervous system disorders
Dizziness (9%)
Syncope (3%)
Gastrointestinal disorders
Abdominal pain[c] (14%)
Pancreatitis[d] (1%)
Skin and subcutaneous and connective tissue disorders
Rash (12%)
Pruritus (6%)
Musculoskeletal and connective tissue disorders
Musculoskeletal pain[e] (35%)
Arthralgia (14%)

a. Cytomegalovirus chorioretinitis, Cytomegalovirus enteritis, Cytomegalovirus enterocolitis, Cytomegalovirus gastroenteritis, Cytomegalovirus infection, Cytomegalovirus esophagitis, Cytomegalovirus viremia, Pneumonia cytomegaloviral.
b. Hypogammaglobulinemia, Blood immunoglobulin G decreased. Immunoglobulins decreased.
c. Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal tenderness.
d. Pancreatitis, Pancreatitis acute, Pancreatitis chronic, Hyperamylasemia, Obstructive pancreatitis, Lipase increased.
e. Back pain, Flank pain, Groin pain, Musculoskeletal chest pain, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity.

Other special population
The incidence of serious adverse reactions was higher in older than in younger patients. 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 11. 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 15, adverse reactions are presented by frequency category based on spontaneous reporting rates, as well as frequency category based on precise incidence in a clinical trial, when known.

Table 15: 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	Uncommon	Not known
Hepatitis B virus reactivation	Rare	Uncommon

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor, dan Zat Adiktif
Badan Pengawas Obat dan Makanan Republik Indonesia
Address: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id/

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.

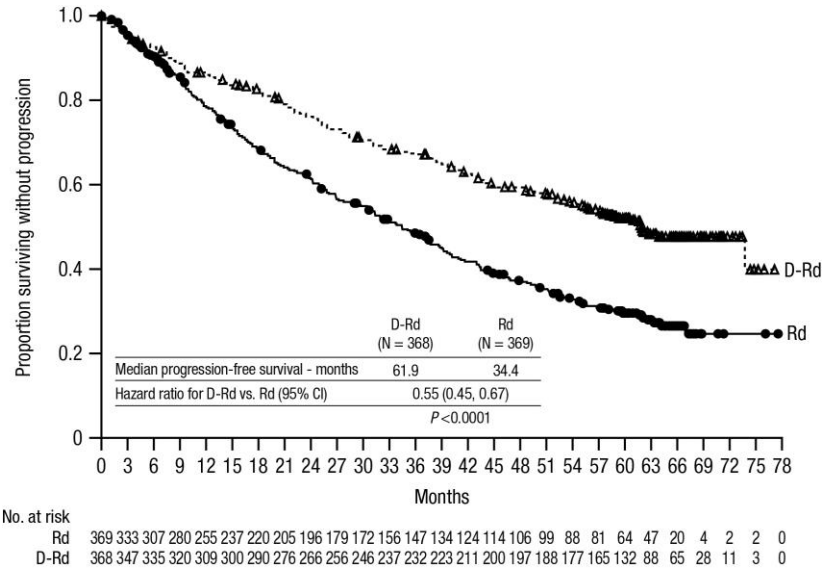
Pharmacodynamic effects

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 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 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 months in 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.

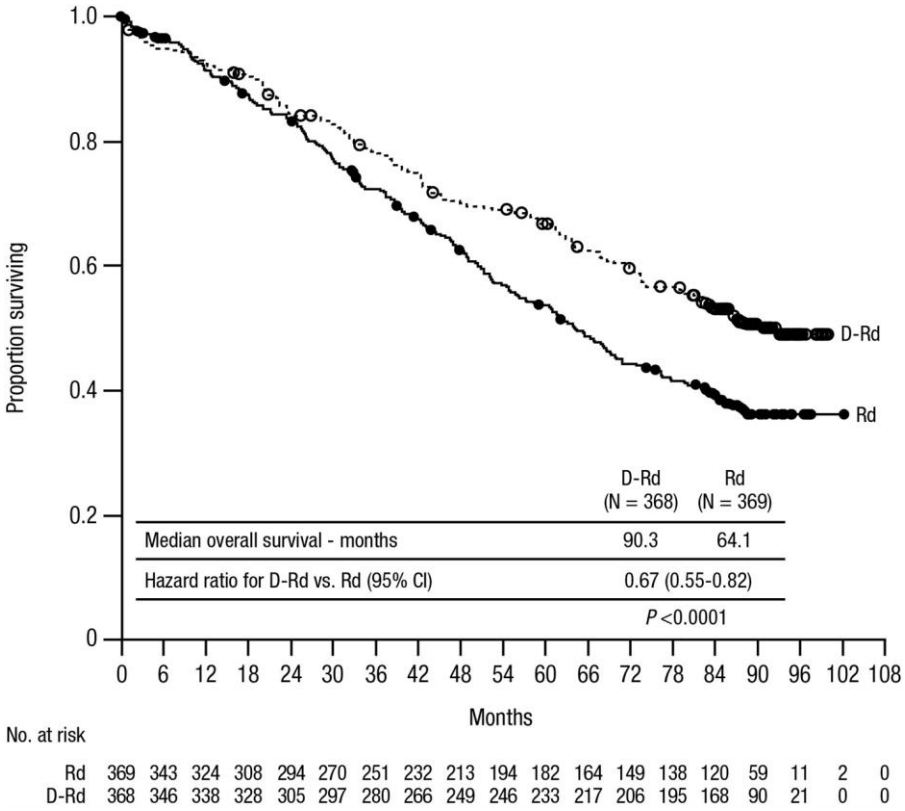
Figure 1: Kaplan-Meier Curve of PFS in Study MMY3008



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 was90.3 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 16: 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 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.

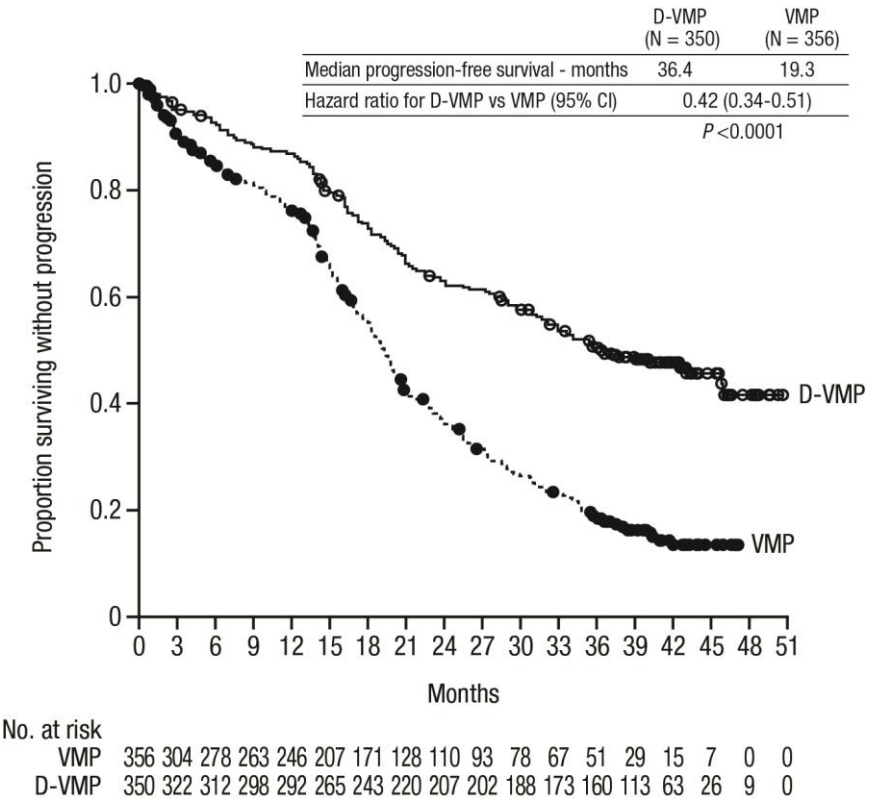
Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant

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).

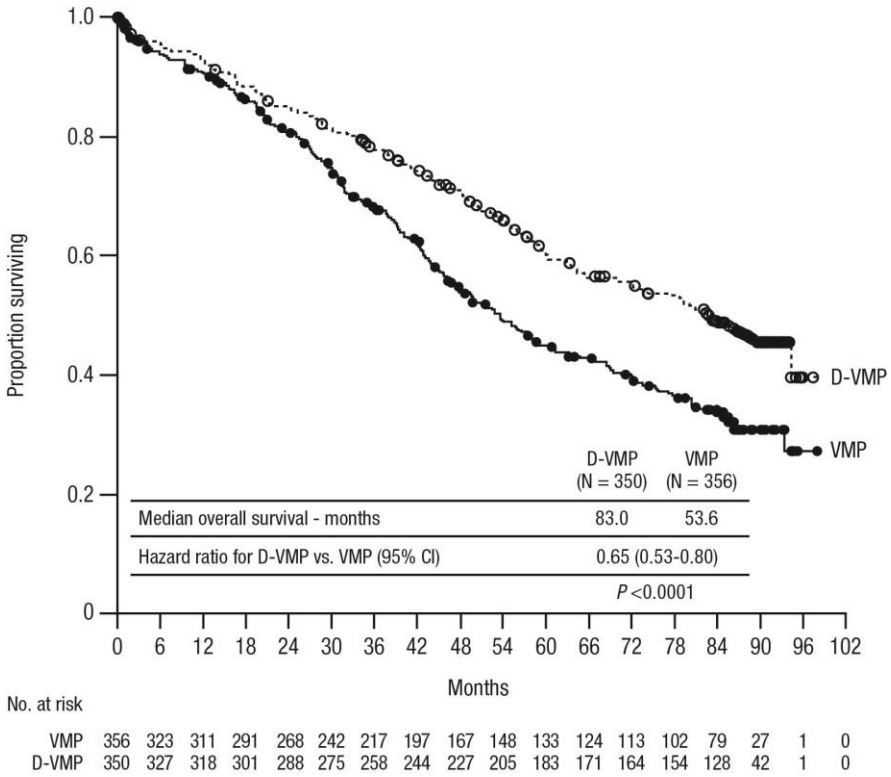
With a median follow-up of 16.5 months, the primary analysis of PFS in study MMY3007 demonstrated an improvement in PFS in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (HR=0.5; 95% CI: 0.38, 0.65; p<0.0001), representing 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 17: Additional efficacy results from Study MMY3007[a]

	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]	4.36 (2.64, 7.21)	
p-value[e]	<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.

Relapsed/Refractory Multiple Myeloma

Combination treatment with lenalidomide and dexamethasone

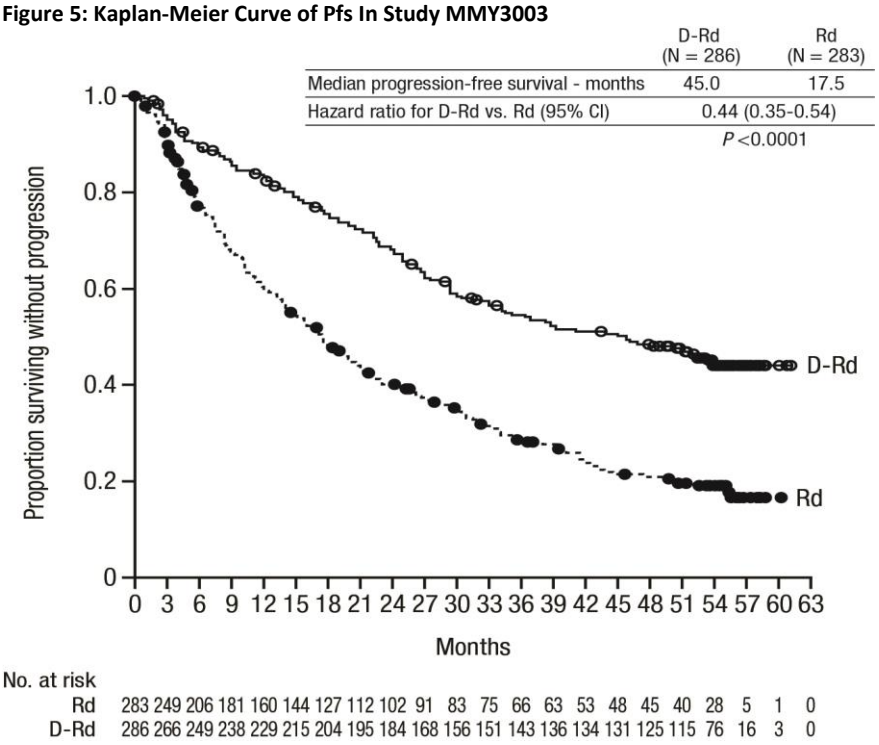
Study MMY3003, an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma 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 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. 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).

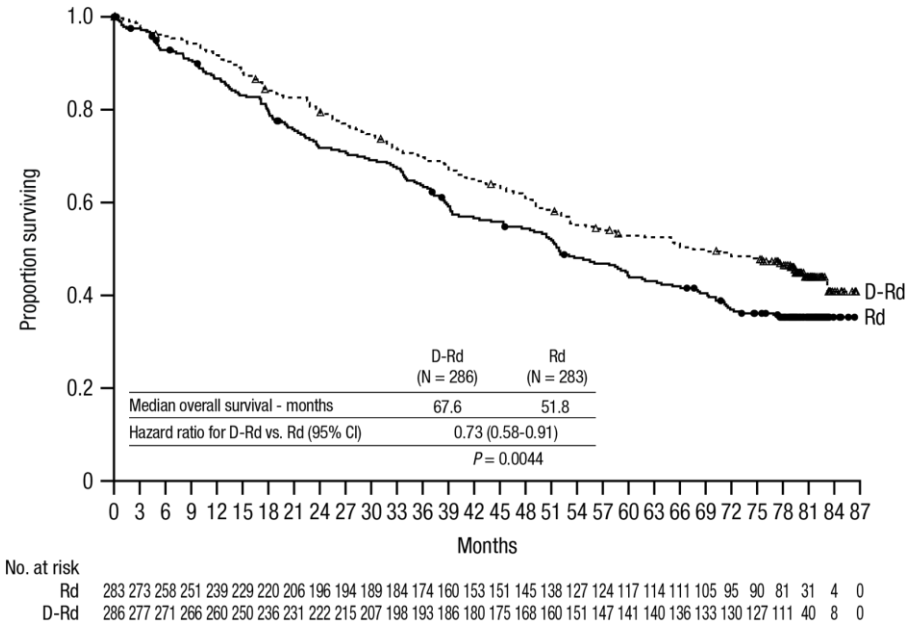
With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001) representing 63% reduction 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 5: 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 6: Kaplan-Meier Curve of OS in Study MMY3003



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

Table 18: 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^{-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 Fisher's exact test.

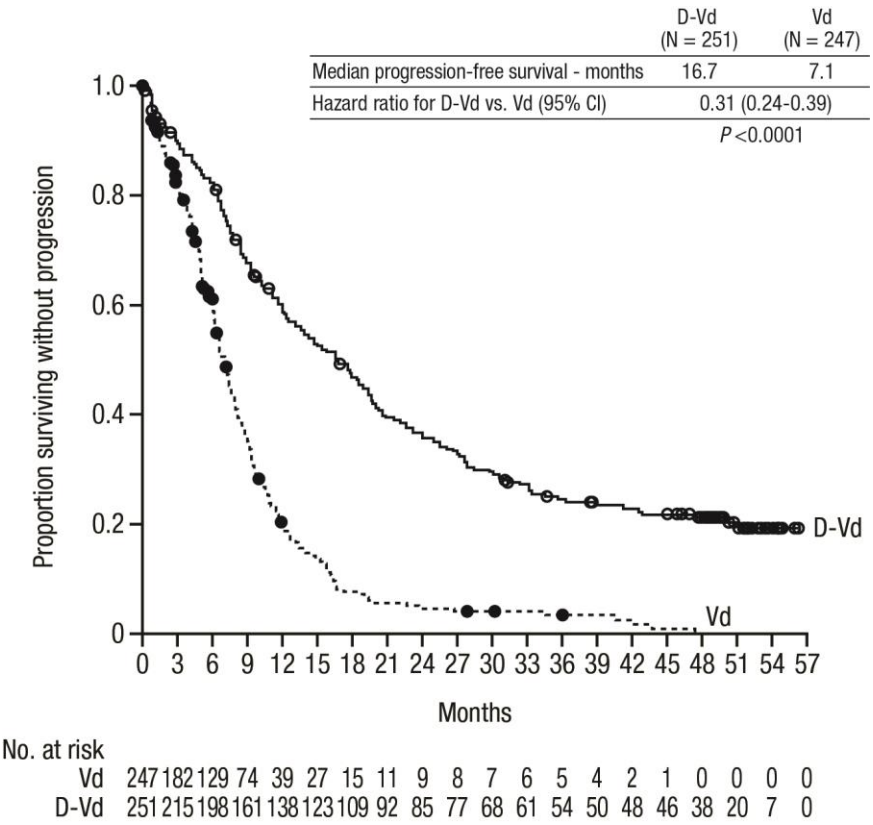
Combination treatment with bortezomib and dexamethasone

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).

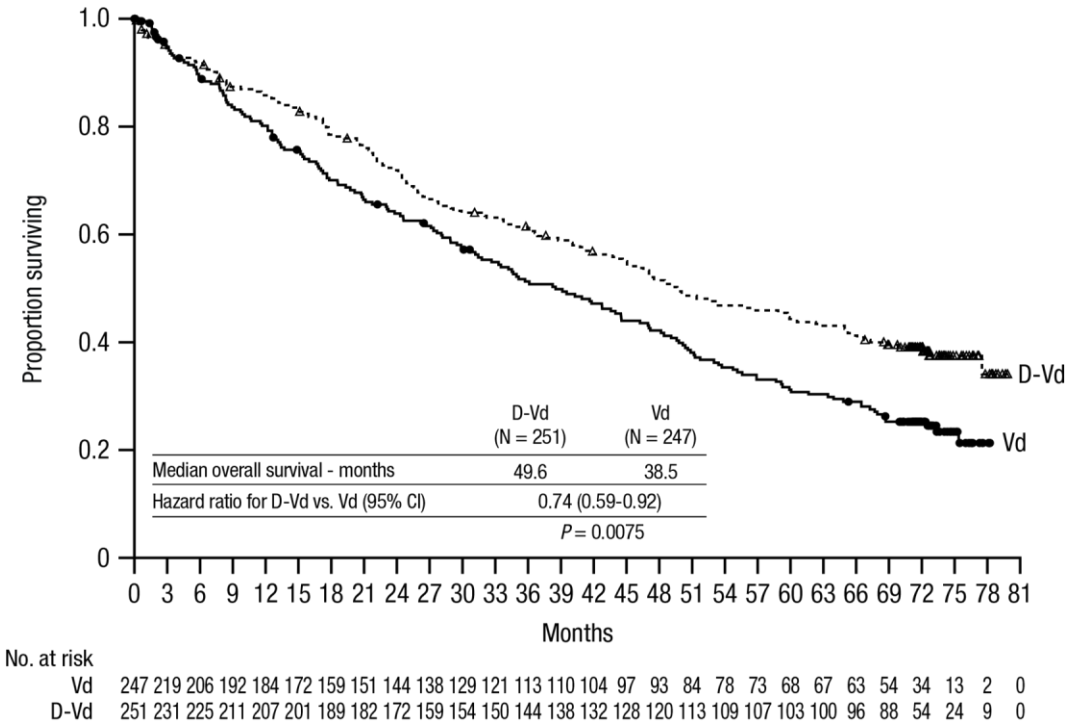
With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value < 0.0001), representing 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 7: 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 8: Kaplan-Meier Curve of OS in Study MMY3004



Additional efficacy results from study MMY3004 are presented table below.

Table 19: 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)	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)
Partial response (PR)	57 (23.8)	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^{-5}

[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 Fisher'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 table below.

Table 20: 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 Overall Survival (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) plasma 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.

Three additional population PK analyses were conducted in patients with multiple myeloma that received daratumumab in various combination therapies (N=1390). 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 15-23 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=518) and older (aged ≥65 to <75 years n=761; aged ≥75◦years, n=334) 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 analysis were performed based on pre-existing renal function data in patients receiving daratumumab monotherapy or various combination therapies, including 441 patients with normal renal function (creatinine clearance [CRCL] ≥90 mL/min), 621 with mild renal impairment (CRCL <90 and ≥60 mL/min), 523 with moderate renal impairment (CRCL <60 and ≥30 mL/min), and 27 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 1404 patients with normal hepatic function (total bilirubin [TB] and aspartate aminotransferase [AST] ≤ upper limit of normal [ULN]) 189 with mild hepatic impairment (TB 1.0× to 1.5× ULN or AST>ULN) and 8 patients with moderate (TB >1.5× to 3.0× ULN; n=7), 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=1371) and non-white (n=242) 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 for up to 24 hours prior to use, followed by 15 hours (including infusion time) at room temperature

15°C–25°C and room light. If stored in the refrigerator, allow the solution to come to room temperature before administration.

Storage Conditions
Keep out of the sight and reach of children.
For storage conditions of the diluted medicinal product, see *Shelf-life.*

Nature and Contents of Container
For 100 mg presentation:
The product is supplied as a sterile, 20 mg/mL liquid concentrate for infusion. Each vial contains 100 mg of daratumumab in a 5 mL nominal fill volume and an excess volume of at least 0.21 mL. A 6R Type 1 glass vial with an elastomeric closure and an aluminum seal with a flip-off cap

For 400 mg presentation:
The product is supplied as a sterile, 20 mg/mL liquid concentrate for infusion. Each vial contains 400 mg of daratumumab in a 20 mL nominal fill volume and an excess volume of at least 0.35 mL. A 25R Type 1 glass vial with an elastomeric closure and an aluminum seal with a flip-off cap

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 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 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.

HOW SUPPLIED
Darzalex Concentrate for solution for infusion
Box, 1 vial @ 100mg/5mL
Reg. No.: DKI2060001549A1

Darzalex Concentrate for solution for infusion
Box, 1 vial @ 400mg/20mL
Reg. No.: DKI2060001549A1

FIRST AUTHORISATION DATE
20 MARCH 2019

HARUS DENGAN RESEP DOKTER

Manufactured by Cilag AG, Schaffhausen, Switzerland
Registered by PT Integrated Healthcare Indonesia, Jakarta – Indonesia
For adverse event and product quality complaint please contact drugsafety@jacid.jnj.com or Phone (021) 2935-3935

Based on CCDS v.21 16Nov23 + v.23 19Jun24 + v.24 03Oct24+TD BPOM 8Apr25

INFORMASI PRODUK UNTUK PASIEN

DARZALEX 100mg/5mL dan 400mg/20mL konsentrat untuk larutan untuk injeksi
daratumumab

Baca semua informasi produk ini secara seksama sebelum Anda mulai menggunakan obat ini.
- Simpan informasi produk ini. Anda mungkin perlu untuk membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau perawat Anda.

Apa yang ada dalam informasi produk ini

1. Apakah DARZALEX itu dan digunakan untuk apa

Apakah DARZALEX itu?
DARZALEX mengandung zat aktif 'daratumumab'. Obat ini termasuk ke dalam kelompok obat yang disebut "antibodi monoklonal". Salah satu cara kerja antibodi monoklonal adalah dengan menempelkan diri pada sel kanker tertentu di tubuh Anda, sehingga sistem kekebalan tubuh Anda dapat menghancurkannya.

DARZALEX digunakan pada orang dewasa (18 tahun keatas) yang memiliki sejenis kanker yang disebut "*multiple myeloma*". Kanker ini merupakan kanker sumsum tulang. DARZALEX digunakan jika kanker Anda tidak membaik setelah mendapatkan pengobatan lainnya.

DARZALEX digunakan sebagai agen tunggal dalam pengobatan multiple myeloma yang telah menerima tiga lini terapi sebelumnya. Darzalex juga digunakan dalam kombinasi dengan **lenalidomide dan dexamethasone** atau bortezomib dan dexamethasone pada pasien *multiple myeloma* refrakter atau kambuh yang telah menerima sekurang-kurangnya satu terapi. Darzalex juga digunakan dalam kombinasi dengan lenalidomide dan dexamethasone atau bortezomib, melphalan dan prednisone pada pasien multiple myeloma baru yang tidak memenuhi syarat untuk transplantasi *stem cell*.

2. Apa saja yang perlu Anda ketahui sebelum menggunakan DARZALEX

Anda tidak boleh diberikan DARZALEX:
- Jika sebelumnya Anda pernah mengalami reaksi alergi parah terhadap daratumumab atau bahan lain dari obat ini

Peringatan dan Perhatian
Bicaralah dengan dokter, atau perawat Anda sebelum menggunakan DARZALEX:

<u>Reaksi terkait pemberian infus</u>
Sebelum dan sesudah setiap pemberian infus DARZALEX, Anda akan diberi obat-obatan untuk membantu mengurangi kemungkinan adanya reaksi dari pemberian infus (lihat "Obat-obatan yang diberikan selama pengobatan dengan DARZALEX " pada bagian 3). Reaksi ini bisa terjadi selama pemberian infus atau dalam 3 hari setelah pemberian infus.

Dalam beberapa kasus, Anda mungkin memiliki reaksi alergi yang parah termasuk bengkak pada wajah, bibir, mulut, lidah atau tenggorokan, sulit menelan atau bernapas atau ruam gatal (biduran). Beberapa reaksi alergi serius dan reaksi terkait infus berat lainnya telah mengakibatkan kematian.

Beritahu segera dokter atau perawat Anda jika Anda mendapatkan reaksi terkait pemberian infus seperti yang tercantum di bagian 4.

Jika Anda mengalami reaksi terkait pemberian infus, Anda mungkin memerlukan obat-obatan lain, atau infus mungkin perlu diperlambat atau dihentikan. Bila reaksi ini hilang, atau menjadi lebih baik pemberian infus bisa dimulai lagi.
Reaksi ini sering terjadi pada pemberian infus pertama. Jika Anda pernah mengalami reaksi ini sebelumnya kemungkinan Anda tidak akan mengalaminya lagi. Dokter Anda mungkin memutuskan untuk tidak menggunakan DARZALEX jika Anda memiliki reaksi terkait infus yang berat.

Transfusi darah
Jika Anda memerlukan transfusi darah, Anda akan menjalani tes darah terlebih dulu untuk menyesuaikan dengan tipe darah Anda. DARZALEX bisa mempengaruhi hasil dari tes darah ini. Beritahu pada petugas yang melakukan tes bahwa Anda sedang menggunakan DARZALEX.

Penurunan jumlah sel darah
DARZALEX dapat menurunkan jumlah hitung sel darah putih yang berfungsi membantu melawan infeksi, dan sel darah yang disebut platelet yang berfungsi membantu menggumpalkan darah. Beritahu penyedia layanan kesehatan Anda jika Anda mengalami demam atau memiliki tanda-tanda memar atau pendarahan.

Hepatitis B
Beri tahu dokter Anda jika Anda pernah atau mungkin sekarang memiliki infeksi hepatitis B, karena DARZALEX dapat menyebabkan virus hepatitis B menjadi aktif kembali. Dokter Anda akan memeriksa tanda-tanda infeksi ini sebelum, selama, dan beberapa saat setelah perawatan dengan DARZALEX. Beri tahu dokter Anda segera jika Anda mengalami kelelahan yang semakin memburuk atau kulit Anda atau bagian mata Anda yang putih menguning.

Beberapa tes laboratotium
DARZALEX dapat mempengaruhi hasil dari beberapa pemeriksaan laboratorium yaitu Coombs test (uji untuk anemia karena penyakit autoimun) dan uji untuk mengetahui respon terhadap pengobatan myeloma. Konsultasikan dengan dokter apabila Anda akan menjalani pemeriksaan laboratorium.

Anak-anak dan remaja
Jangan berikan DARZALEX pada anak-anak atau remaja di bawah usia 18 tahun. Hal ini dikarenakan belum diketahui bagaimana obat tersebut akan mempengaruhi mereka.

Obat-obatan lain dan DARZALEX
Beritahu penyedia layanan kesehatan Anda tentang semua obat yang Anda minum, termasuk obat resep dan obat bebas, vitamin, dan suplemen herbal.

Kehamilan
Bicarakan dengan dokter atau perawat Anda sebelum Anda diberi DARZALEX jika Anda sedang hamil, atau berpikir mungkin hamil atau berencana untuk hamil.
Jika Anda hamil saat menjalani pengobatan ini, segera beritahu dokter atau perawat Anda. Anda dan dokter Anda akan memutuskan apakah manfaat pengobatan ini lebih besar daripada risiko pada bayi Anda.

Kontrasepsi
Wanita yang sedang diberikan DARZALEX harus menggunakan kontrasepsi yang efektif selama pengobatan dan selama 3 bulan setelah pengobatan.

Menyusui
Anda dan dokter Anda akan memutuskan apakah manfaat menyusui lebih besar daripada risiko pada bayi Anda. Karena obat ini bisa masuk ke dalam air susu ibu dan belum diketahui bagaimana obat tersebut akan mempengaruhi bayi.

DARZALEX mengandung sodium

Setiap 5 ml DARZALEX mengandung 0,4 mmol (9,3mg) sodium atau garam. Konsultasikan kepada dokter bila Anda sedang menjalani terapi rendah garam.

Mengemudi dan menggunakan mesin
Anda mungkin akan merasa letih setelah menggunakan DARZALEX yang dapat mempengaruhi kemampuan Anda untuk mengemudi atau menggunakan peralatan mesin.

3. Bagaimana DARZALEX diberikan

Bagaimana obat ini diberikan
DARZALEX akan diberikan kepada Anda oleh dokter atau perawat. Obat ini diberikan selama beberapa jam secara suntikan ke dalam pembuluh darah ("infus intravena").

Berapa banyak diberikan
Dokter Anda akan menentukan dosis dan jadwal DARZALEX yang tepat untuk Anda. Dosis DARZALEX akan tergantung pada berat badan Anda. Dosis awal DARZALEX yang biasa adalah 16 mg per kg berat badan.
DARZALEX dapat diberikan sendiri atau bersamaan dengan obat-obatan lain yang digunakan untuk mengobati multiple myeloma.

Jika diberikan sendiri, DARZALEX dapat diberikan:
- seminggu sekali untuk 8 minggu pertama
- kemudian setiap 2 minggu sekali selama 16 minggu
- kemudian setiap 4 minggu setelah itu selama kondisi Anda tidak memburuk

Jika DARZALEX diberikan bersama dengan obat-obatan lain dokter Anda dapat mengubah waktu antar dosis dan juga berapa banyak pengobatan yang akan Anda terima.
Pada minggu pertama, dokter Anda mungkin memberi Anda dosis DARZALEX yang dibagi selama dua hari berturut-turut.

Obat-obatan yang diberikan selama pengobatan dengan DARZALEX
Anda mungkin diberi obat untuk menurunkan kemungkinan terkena herpes zoster (*shingles*).

Sebelum setiap pemberian infus DARZALEX, Anda akan diberi obat-obatan yang membantu mengurangi kemungkinan reaksi terkait pemberian infus. Obat-obatan tersebut termasuk:
- Obat untuk reaksi alergi (anti histamin)
- Obat untuk peradangan (kortikosteroid)
- Obat-obatan untuk demam (seperti parasetamol/asetaminofen).

Setelah setiap pemberian infus DARZALEX, Anda akan diberi obat-obatan secara oral (seperti kortikosteroid) untuk menurunkan kemungkinan reaksi terkait infus.

Pasien dengan masalah pernafasan
Jika Anda memiliki masalah pernapasan, seperti asma atau Penyakit Paru Obstruktif Kronik (PPOK), Anda akan diberi obat yang dihirup untuk membantu masalah pernapasan Anda:
- Obat-obatan untuk membantu saluran udara di paru-paru tetap terbuka (bronkodilator)
- Obat-obatan untuk menurunkan pembengkakan dan iritasi di paru-paru Anda (kortikosteroid)

Jika Anda diberi DARZALEX lebih dari yang seharusnya
Obat ini akan diberikan oleh dokter atau perawat Anda. Jika pada kejadian yang sangat jarang terjadi Anda diberi dosis terlalu banyak (overdosis), dokter Anda akan memeriksa Anda untuk melihat efek samping yang mungkin terjadi.

Jika Anda melupakan jadwal Anda untuk mendapatkan DARZALEX
Hal ini sangat penting untuk menjalani seluruh jadwal pengobatan Anda untuk memastikan pengobatan Anda barhasil. Jika Anda melewatkan jadwal Anda, sesegera mungkin menggantinya.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau perawat Anda.

4. Efek samping

Seperti semua obat lainnya, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mengalaminya.

Reaksi terkait infus
Beritahu dokter atau perawat Anda segera jika Anda mendapatkan tanda-tanda reaksi terkait pemberian infus berikut selama atau dalam 3 hari setelah pemberian infus. Anda mungkin memerlukan obat-obatan lain, atau pemberian infus mungkin perlu diperlambat atau dihentikan.

Reaksi ini sangat umum (dapat dialami lebih dari 1 dari 10 orang):
- menggigil
- sakit tenggorokan, batuk
- mual
- muntah
- hidung gatal, berair atau tersumbat
- merasa sesak napas atau masalah pernafasan lainnya

Gejala umum lainnya (mempengaruhi hingga 1 dari 10 orang) yaitu:
- ketidaknyamanan pada dada
- pusing atau kepala terasa ringan (hipotensi)
- gatal
- mengi

Jarang (mempengaruhi 1 dari 1000 orang):
- reaksi alergi yang parah termasuk bengkak pada wajah, bibir, mulut, lidah atau tenggorokan, sulit menelan atau bernapas atau ruam gatal (biduran).
- Nyeri dada
- Sakit pada mata
- Penglihatan kabur

Jika Anda mengalami salah satu dari reaksi terkait pemberian infus di atas, segera beritahu dokter atau perawat Anda.

Efek samping lainnya
Sangat umum (dapat dialami lebih dari 1 dari 10 orang):
- demam
- merasa sangat lelah
- diare
- sakit perut
- konstipasi
- penurunan nafsu makan
- kesulitan tidur
- sakit kepala
- merasa pusing
- kerusakan syaraf yang dapat menyebabkan kesemutan, mati rasa atau nyeri
- tekanan darah tinggi
- ruam kulit
- kejang otot
- bengkak pada tangan, pergelangan kaki atau kaki
- merasa lemah
- nyeri otot dan sendi (termasuk nyeri tulang belakang dan nyeri otot dada

- infeksi paru-paru (pneumonia)
- bronkitis
- infeksi saluran udara - seperti hidung, sinus atau tenggorokan
- jumlah hitung sel darah merah rendah yang membawa oksigen dalam darah (anemia)
- jumlah hitung sel darah putih yang membantu melawan infeksi yang rendah (neutropenia, limfopenia, leukopenia)
- *trombositopenia* yaitu jumlah trombosit (jenis sel darah yang membantu proses penggumpalan darah) yang rendah.
- hypokalemia yaitu jumlah potassium dalam darah yang rendah
- perasaan yang tidak biasa pada kulit (seperti perasaan kesemutan atau sensasi serangga merayap pada kulit)

Umum (dapat dialami hingga 1 dari 10 orang):
- detak jantung tidak teratur (fibrilasi atrium)
- cairan yang tertimbun di paru-paru yang membuat Anda sesak napas
- infeksi saluran kemih
- infeksi yang parah di seluruh tubuh (sepsis)
- dehidrasi
- pingsan
- menggigil
- kadar gula yang tinggi dalam darah
- kadar kalsium yang rendah dalam darah
- Level yang rendah pada antibodi yang disebut 'imunoglobulin' di dalam darah yang membantu melawan infeksi (hipogammaglobulinemia)
- radang pankreas
- gatal
- salah satu jenis dari infeksi virus herpes (infeksi cytomegalovirus)

Tidak umum (dapat dialami hingga 1 dari 100 orang)
- radang hati/liver (hepatitis)
- COVID-19

Beritahukan ke dokter / perawat / apoteker apabila Anda mengalami efek samping setelah mendapatkan obat ini.

5. Bagaimana cara menyimpan DARZALEX

Simpan dalam suhu 2^0C - 8^0C dan terlindung dari cahaya
Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

6. Isi kemasan dan informasi lainnya

Apa isi DARZALEX
Zat aktif dari DARZALEX adalah daratumumab.

Bahan kandungan lainnya adalah asam asetat glasial, mannitol, polysorbat 20, sodium asetat trihidrat, sodium klorida dan air untuk injeksi.

Tiap 5mL konsentrat vial mengandung 100mg daratumumab (20mg/mL).
Tiap 20mL konsentrat vial mengandung 400mg daratumumab (20mg/mL).

Seperti apa DARZALEX dan isi kemasannya
DARZALEX tersedia dalam bentuk konsentrat tidak berwarna hingga kekuningan untuk pemberian infus secara intravena setelah pengenceran.

DARZALEX dikemas dalam kemasan karton berisi 1 gelas vial.

Batas kadaluarsa obat: 24 bulan.

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HARUS DENGAN RESEP DOKTER

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Didaftarkan oleh:
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Untuk pelaporan efek samping dan keluhan kualitas produk, dapat menghubungi drugsafety@jacid.jnj.com atau telp. (021) 2935-3935

Informasi berikut ditujukan untuk profesional kesehatan saja:

Produk obat ini hanya untuk penggunaan tunggal.

Siapkan larutan infus dengan menggunakan teknik aseptik sebagai berikut:

- Hitung dosis (mg), total volume (mL) larutan DARZALEX yang dibutuhkan dan jumlah botol DARZALEX yang dibutuhkan berdasarkan berat badan pasien.
- Periksa apakah larutan DARZALEX tidak berwarna hingga berwarna kekuningan. Jangan gunakan jika partikel buram, perubahan warna atau terdapat partikel asing lainnya ada.
- Menggunakan teknik aseptik, kelurkan 0,9% Sodium Chloride dari kantong infus / kontainer yang sama dengan volume DARZALEX yang dibutuhkan.
- Ambil sejumlah larutan DARZALEX yang diperlukan dan encerkan ke volume yang sesuai dengan menambahkan ke kantong infus / wadah yang mengandung 0,9% Sodium Chloride. Kantung / wadah infus harus dibuat dari campuran polivinilklorida (PVC), polipropilen (PP), polietilen (PE) atau poliolefin (PP + PE). Encerkan di bawah kondisi aseptik yang tepat. Buang bagian yang tidak terpakai yang tertinggal di botol.
- Balikkan wadah untuk pencampuran larutan. Jangan di kocok atau dibekukan.
- Periksa partikulat dan perubahan warna produk obat secara visual sebelum pemberian. Larutan yang diencerkan dapat sangat kecil, tembus ke partikel protein putih, karena daratumumab adalah protein. Jangan gunakan jika partikel tampak buram, berubah warna atau terdapat partikel asing.
- Karena DARZALEX tidak mengandung larutan pengawet, larutan harus diberikan dalam waktu 15 jam (termasuk waktu infus) pada suhu kamar 15°C-25°C dan dalam cahaya ruangan.
- Jika tidak digunakan segera, larutan yang diencerkan dapat disimpan sebelum pemberian sampai 24 jam dalam suhu 2°C - 8°C dan terlindung dari cahaya. Jangan dibekukan.
- Berikan larutan yang telah diencerkan dengan infus secara intravena menggunakan set infus yang dilengkapi dengan regulator aliran dan dengan filter polieterulfon pengikat polieterulfon, steril, non-pirogenik, rendah protein, (ukuran pori 0,22 atau 0,2 mikrometer). Perlengkapan poliuretan (PU), polibutadiena (PBD), PVC, PP atau PE harus digunakan.
- Jangan suntikan DARZALEX bersamaan dengan jalur intravena yang sama dengan produk lainnya.
- Jangan menyimpan bagian yang tidak terpakai dari larutan infus untuk digunakan kembali. Produk atau bahan limbah yang tidak terpakai harus dibuang sesuai dengan persyaratan yang berlaku.

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