DARZALEX®

daratumumab concentrated solution for infusion

AUSTRALIAN PRODUCT INFORMATION

1. NAME OF THE MEDICINE

Daratumumab.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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.

For a full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

DARZALEX concentrated solution for infusion is supplied as a colourless to yellow preservative free liquid concentrate for intravenous infusion after dilution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

DARZALEX is indicated for the treatment of patients:

- with newly diagnosed multiple myeloma:
  - who are eligible for autologous stem cell transplant. For use in combination with:
    - bortezomib, thalidomide, and dexamethasone.
  - who are ineligible for autologous stem cell transplant. For use in combination with:
    - bortezomib, melphalan and prednisone, or
    - lenalidomide and dexamethasone.
- with relapsed or refractory multiple myeloma who have received:
  - at least one prior therapy. For use in combination with:
    - bortezomib and dexamethasone, or
    - lenalidomide and dexamethasone.
    - carfilzomib and dexamethasone
  - at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are refractory to both a PI and an immunomodulatory agent. For use as:
    - monotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Before DARZALEX therapy is commenced, clinicians should arrange for extended red cell phenotyping of patients (see section 4.4 Special warnings and precautions for use, Effects on laboratory tests).

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

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

Substitution by any other biological medicinal product requires the consent of the prescribing physician.

Dosage – Adults (≥ 18 years)

Recommended dose

DARZALEX with VTd combination therapy (4-week cycle dosing regimen)

The DARZALEX dosing schedule in Table 1 is for combination therapy with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for ASCT.

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Administration: Table 6):

Table 1: DARZALEX dosing schedule in combination with bortezomib, thalidomide and dexamethasone ([DVTd]; 4-week cycle dosing regimen)

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

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

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

Bortezomib is administered by subcutaneous (SC) injection or intravenous (IV) injection at a dose of 1.3 mg/m^2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 28-day (4-week) induction treatment cycles (Cycles 1-4) and two consolidation cycles (Cycles 5 and 6) following ASCT after Cycle 4.

DARZALEX with VMP combination therapy (6-week cycle dosing regimen)

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

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Administration: Table 6):

Table 2: DARZALEX dosing schedule in combination with bortezomib, melphalan and prednisone ([DVMP]; 6-week cycle dosing regimen)

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

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

Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (8 doses), followed by **once** weekly at Weeks 1, 2, 4 and 5 for eight additional 6-week cycles (32 additional doses for a total of 40 doses). For information on the VMP dose and dosing schedule when administered with DARZALEX, see section 5.1 Pharmacodynamic properties, Clinical trials.

DARZALEX with Vd combination therapy (3-week cycle dosing regimen)

The DARZALEX dosing schedule in Table 3 is for combination therapy with 3-week cycle regimen (bortezomib and dexamethasone) for patients with relapsed/refractory multiple myeloma.

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Administration: Table 6):

Table 3: DARZALEX dosing schedule in combination with bortezomib and dexamethasone ([DVd]; 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 dosing instructions for medicinal products administered with DARZALEX see section 5.1 Pharmacodynamic properties, Clinical trials and manufacturer's Product Information.

DARZALEX with Rd, Kd combination therapy or DARZALEX monotherapy (4-week cycle dosing regimens)

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

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

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule (infusion rates presented in Administration: Table 6):

Table 4: DARZALEX dosing schedule in combination with lenalidomide and low-dose dexamethasone or monotherapy ([DRd] or monotherapy; 4-week cycle dosing regimens)

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

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

For dosing instructions of medicinal products administered with DARZALEX, see section 5.1 Pharmacodynamic properties, Clinical trials and manufacturer's Product Information.

Table 5: DARZALEX dosing schedule in combination with carfilzomib and dexamethasone ([DKd], 4-week cycle dosing regimens)

Weeks	DARZALEX Dose[c]	Schedule
Week 1	8 mg/kg	days 1 and 2 (total 2 doses)
Weeks 2 to 8	16 mg/kg	weekly (total of 7 doses)
Weeks 9 to 24[a]	16 mg/kg	every two weeks (total of 8 doses)
Week 25 onwards until disease progression[b]	16 mg/kg	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
[c] Based on actual body weight

Recommended concomitant medications

Pre-infusion medication

It is important to administer the following pre-infusion medications to reduce the risk of IRRs (**including fatal IRRs**) to all patients 1-3 hours prior to every infusion of DARZALEX:

- Corticosteroid (long-acting or intermediate-acting)

  Monotherapy:

  Methylprednisolone 100 mg, or equivalent, administered intravenously. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg).

  Combination therapy:

  Administer 20 mg dexamethasone (or equivalent) prior to every DARZALEX infusion.

  When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on DARZALEX infusion days (see section 5.1 Pharmacodynamic properties, Clinical trials).

  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 500 to 1000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Post-infusion medication

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

Monotherapy:

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

Combination therapy:

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

However, if a background regimen-specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX infusion, additional post-infusion medications may not be needed (see section 5.1 Pharmacodynamic properties, Clinical trials).

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

Prophylaxis for herpes zoster virus reactivation

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

Management of infusion-related reactions

It is important to administer pre-infusion medications to reduce the risk of IRRs (**including fatal IRRs**) prior to treatment with DARZALEX.

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

Management of IRRs may further require reduction in the rate of infusion, or treatment discontinuation of DARZALEX as outlined below (see also section 4.4 Special warnings and precautions for use).

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the IRR occurred. If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (see Administration: Table 6).
- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as appropriate (see Administration: Table 6). Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue DARZALEX upon the third occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life threatening): Permanently discontinue DARZALEX treatment.

Missed dose(s)

If a planned dose of DARZALEX is missed, administer the dose as soon as possible and adjust the dosing schedule accordingly, maintaining the treatment interval.

Dose modifications

No dose reductions of DARZALEX are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity (see section 4.4 Special warnings and precautions for use). For information concerning medicinal products given in combination with DARZALEX, see manufacturer's Product Information.

Special populations

Paediatrics (17 years of age and younger)

The safety and efficacy of DARZALEX have not been established in paediatric patients.

Elderly (65 years of age and older)

No dose adjustments are considered necessary in elderly patients (see section 5.2 Pharmacokinetic properties, section 4.8 Adverse effects).

Renal impairment

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

Hepatic impairment

No formal studies of daratumumab in patients with hepatic impairment have been conducted. Changes in hepatic function are unlikely to have any effect on the elimination of daratumumab since IgG1 molecules such as daratumumab are not metabolised through hepatic pathways. Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment) (see section 5.2 Pharmacokinetic properties).

Administration

DARZALEX is administered as an intravenous infusion following dilution with 0.9% Sodium Chloride. For instructions on dilution of the medicinal product before administration, see Instructions for use and handling and section 6.6 Special precautions for disposal.

Following dilution the DARZALEX infusion should be intravenously administered at the appropriate initial infusion rate presented in Table 6 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 6 below.

Table 6: Infusion rates for DARZALEX (16 mg/kg) administration

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

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

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

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

Instructions for use and handling

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 colourless 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 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.
- 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 micrometre). 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.

4.3 CONTRAINDICATIONS

Patients with a history of severe hypersensitivity (eg anaphylactic reaction) to daratumumab, or to any of the excipients.

Before starting therapy, refer to the Product Information for medicinal products used in combination with DARZALEX.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Before starting combination therapy, also refer to the Product Information for relevant other medicines (bortezomib, lenalidomide, thalidomide, dexamethasone, as appropriate).

Patients receiving DARZALEX in combination with lenalidomide and dexamethasone or thalidomide and dexamethasone should adhere to the pregnancy prevention programmes of lenalidomide or thalidomide (see also section 4.6 Fertility, pregnancy and lactation).

Infusion–related reactions

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

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

In clinical trials, IRRs were reported in approximately half of all patients treated with DARZALEX.

The majority of IRRs occurred at the first infusion and were Grade 1-2. Four percent of patients had an IRR at more than one infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension, laryngeal oedema, pulmonary oedema, 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 section 4.8 Adverse effects (Undesirable effects)). Fatal IRRs were not reported in these trials.

Pre-medicate patients with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs (**including fatal IRRs**) prior to treatment with DARZALEX (see section 4.2 Dose and method of administration). 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 section 4.2 Dose and method of 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 section 4.2 Dose and method of administration).

Neutropenia/thrombocytopenia

DARZALEX increases the incidence of neutropenia (including febrile neutropenia) and the incidence of thrombocytopenia.

Monitor complete blood cell counts periodically during treatment. This should be done as per clinical judgment but not less frequently than 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.

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.Use in the elderly

No overall differences in safety or effectiveness were observed between older (≥ 65 years) and younger patients.

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

Paediatric use

The safety and efficacy of DARZALEX have not been established in paediatric patients.

Effect on laboratory tests

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

Type and screen patients prior to starting DARZALEX.

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

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 Interactions with other medicines and other forms of interactions). This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug-drug interaction studies have been performed.

Clinical pharmacokinetic assessments of daratumumab in combination with lenalidomide, pomalidomide, thalidomide, 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 (see section 4.4 Special warnings and precautions for use, Effects on laboratory tests).

Interference with serum protein electrophoresis and immunofixation tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, consider other methods to evaluate the depth of response.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No data are available to determine potential effects of daratumumab on fertility in males or females.

Use in pregnancy – Pregnancy Category C

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 foetus. 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 foetus, women of reproductive potential should use effective contraception during and for 3 months after cessation of DARZALEX treatment. However, when DARZALEX is used in combination with lenalidomide and dexamethasone, or thalidomide and dexamethasone, patients must also follow advice about use in pregnancy of those products – see below.

Use of DARZALEX with lenalidomide or thalidomide

Lenalidomide and thalidomide (both Pregnancy Category X) are associated with risk of foetal harm, including severe life-threatening human birth defects. Refer to the lenalidomide and thalidomide PI for additional information. Patients receiving DARZALEX in combination with lenalidomide and dexamethasone, or thalidomide and dexamethasone, should adhere to the pregnancy prevention programme of these medicines.

Use in lactation

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.

4.7 EFFECT 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.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

<u>Combination treatment with bortezomib, thalidomide and dexamethasone (DVTd)</u>

Adverse reactions described in the table below reflect exposure to DARZALEX up to day 100 post-transplant in a Phase 3 active-controlled study, Study MMY3006 (see section 5.1 Pharmacodynamic properties, Clinical Studies). The median duration of induction/ASCT/consolidation treatment was 8.9 (range: 7.0 to 12.0) months for the DVTd group and 8.7 (range: 6.4 to 11.5) months for the VTd group. The most frequent adverse reactions (>20%) were infusion reactions, nausea, pyrexia, upper respiratory tract infection and bronchitis. Serious adverse reactions with a 2% greater incidence in the DVTd arm compared to the VTd arm were bronchitis (DVTd 2% vs VTd <1%) and pneumonia (DVTd 6% vs VTd 4%).

Table 7: Adverse reactions reported in Study MMY3006*

System Organ Class Adverse Reaction	DVTd (N=536)			VTd (N=538)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Infusion reactions[a]	35	3	<1	0	0	0
Gastrointestinal disorders						
Nausea	30	4	0	24	2	<1
Vomiting	16	2	0	10	2	0
General disorders and administration site conditions						
Pyrexia	26	2	<1	21	2	0
Infections and infestations						
Upper respiratory tract infection[b]	27	1	0	17	1	0
Bronchitis[c]	20	1	0	13	1	0
Respiratory, thoracic and mediastinal disorders						
Cough[d]	17	0	0	9	0	0
Vascular disorders						
Hypertension	10	4	0	5	2	0

Key: D=daratumumab, VTd=bortezomib-thalidomide -dexamethasone.

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

[b] Laryngitis, Laryngitis viral, 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

[c] Bronchiolitis, Bronchitis, Bronchitis chronic, Respiratory syncytial virus bronchitis, Tracheobronchitis

[d] Cough, Productive cough

*Note: Adverse reactions that occurred in ≥ 10% of patients and with at least a 5% frequency greater in the DVTd arm are listed.

Haematology 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 haematology laboratory abnormalities in Study MMY3006

	DVTd (N=536) %			VTd (N=538) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anemia	36	4	0	35	5	0
Thrombocytopenia	81	9	5	58	8	3
Leukopenia	82	14	10	57	6	9
Neutropenia	63	19	14	41	10	9
Lymphopenia	95	44	15	91	37	10

Key: D=daratumumab, VTd=bortezomib-thalidomide -dexamethasone.

Combination treatment with bortezomib, melphalan and prednisone (DVMP)

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 (DVMP) 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 oedema peripheral. Serious adverse reactions with at least a 2% greater incidence in the DVMP arm compared to the VMP arm were pneumonia (DVMP 11% vs VMP 4%), upper respiratory tract infection (DVMP 5% vs VMP 1%), and pulmonary oedema (DVMP 2% vs VMP 0%).

Table 9: Adverse reactions reported in Study MMY3007*

System Organ Class Adverse Reaction	DVMP (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						
Oedema 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
Dyspnoea[b]	13	2	1	5	1	0
Pulmonary oedema[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 action 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 DVMP arm are listed. In addition, serious adverse reactions are listed if there was at least a 2% greater incidence in the DVMP arm compared to the VMP arm.

Haematology 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 10: Treatment-emergent haematology laboratory abnormalities in Study MMY3007

	DVMP (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

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, diarrhoea, constipation, nausea, peripheral oedema, fatigue, back pain, asthenia, pyrexia, upper respiratory tract infection, bronchitis, pneumonia, decreased appetite, muscle spasms, peripheral sensory neuropathy, dyspnoea 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 11: Adverse reactions reported in Study MMY3008*

System Organ Class Adverse Reaction	DRd (N=364)			Rd (N=365)		
	Any Grade (%)	Grade 3 (%)	Grade 4 (%)	Any Grade (%)	Grade 3 (%)	Grade 4 (%)
Infusion reactions[a]	41	2	<1	0	0	0
Gastrointestinal disorders						
Diarrhoea	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 oedema[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						
Dyspnoea[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] Generalised oedema, Gravitational oedema, Oedema, Oedema 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] Dyspnoea, Dyspnoea 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. Haematology 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 12: Treatment-emergent haematology 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.

Relapsed/refractory multiple myeloma

Combination treatment with bortezomib and dexamethasone (DVd)

Adverse reactions described in Table 13 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-dexamethasone group (Vd) in a Phase 3 active-controlled study (Study MMY3004). The most frequent adverse reactions (>20%) were infusion reactions, diarrhoea, peripheral oedema, upper respiratory tract infection, peripheral sensory neuropathy, cough and dyspnoea. Serious adverse reactions included diarrhoea, 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 13: 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						
Diarrhoea	32	3	< 1	22	1	0
Vomiting	11	0	0	4	0	0
General disorders and administration site conditions						
Oedema 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
Dyspnoea[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. Haematology laboratory related toxicities were excluded and reported separately in the table below.

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

Table 14: Treatment-emergent haematology laboratory abnormalities

	Study MMY3004					
	DVd (N=243) %			Vd (N=237) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anaemia	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.

Combination treatment with lenalidomide and dexamethasone (DRd)

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) 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, diarrhoea, nausea, fatigue, pyrexia, upper respiratory tract infection, muscle spasms, cough and dyspnoea. 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 15: 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						
Diarrhoea	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
Dyspnoea	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 description of 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.

Haematology 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 16: Treatment-emergent haematology laboratory abnormalities

	Study MMY3003					
	DRd (N=283) %			Rd (N=281) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Anaemia	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 twice-weekly (20/56 mg/m^2) carfilzomib and dexamethasone (DKd)

Adverse reactions described in the table below reflect exposure to DARZALEX for a median treatment duration of 16.1 months (range: 0.1 to 23.7 months) for the daratumumab-carfilzomib-dexamethasone (DKd) group and median treatment duration of 9.3 months (range: 0.1 to 22.4 months) for the carfilzomib-dexamethasone group (Kd) in a Phase 3 active-controlled study (Study 20160275 (CANDOR). The most frequent (≥20%) adverse reactions were infusion reactions, diarrhea, fatigue, upper respiratory tract infection, and pneumonia. Serious adverse reactions with a 2% greater incidence in the DKd arm compared to the Kd arm were pneumonia (DKd 14% vs Kd 11%), sepsis (DKd 6% vs Kd 3%), influenza (DKd 4% vs Kd 1%), pyrexia (DKd 4% vs Kd 2%), bronchitis (DKd 2% vs Kd 0%), and diarrhea (DKd 2% vs Kd 0%). Fatal events within 30 days of treatment cessation, regardless of causality, were reported in 10% of all patients treated with DKd versus 5% of patients treated with Kd and the most common cause was infection. Within the DKd group, fatal events occurred in 14% of the patients ≥65 years and 6% of the patients <65 years (see *Infections, Other special population* below).

Infusion related reactions that occurred on the same date or next date of any daratumumab dosing was 18% in the DKd arm and on the same date or next date of first daratumumab dosing was 12% in the DKd arm. Infusion related reactions that occurred on the same date of any carfilzomib dosing was 41% in the DKd arm compared to 28% in the Kd arm and on the same date of first carfilzomib dosing was 13% in the DKd arm compared to 1% in the Kd arm.

Table 17: Adverse reactions reported in Study 20160275 (CANDOR)*

System Organ Class Adverse Reaction	DKd (N=308) %			Kd (N=153) %		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
Gastrointestinal disorders						
Diarrhea	31	4	0	14	1	0
Nausea	18	0	0	13	1	0
General disorders and administration site conditions						
Fatigue	24	7	<1	18	5	0
Infections and infestations						
Upper respiratory tract infection[a]	51	6	<1	39	4	0
Pneumonia[b]	22	12	3	16	10	1
Bronchitis[c]	19	3	0	12	1	0
Musculoskeletal and connective tissue disorders						
Back pain	16	2	0	10	1	1
Psychiatric disorders						
Insomnia	18	4	0	11	2	0

Key: D=Daratumumab; Kd=carfilzomib-dexamethasone

[a] Acute sinusitis, Laryngitis, 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, Upper respiratory tract infection bacterial, Viral upper respiratory tract infection

[b] Atypical pneumonia, Lung infection, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia bacterial, Pneumonia cytomegaloviral, Pneumonia mycoplasmal, Pneumonia respiratory syncytial viral, Pneumonia viral

[c] Bronchiolitis, Bronchitis, Bronchitis viral, Tracheobronchitis

*Note: Adverse reactions that occurred in ≥ 10% of patients and with at least a 5% frequency greater in the DKd arm are listed. Haematology 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 18: Treatment-emergent haematology laboratory abnormalities in Study 20160275 (CANDOR)

	DKd (N=308) %			Kd (N=153) %		
	Any Grade	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
Anemia	61	9	0	69	11	0
Thrombocytopenia	77	15	4	58	7	3
Leukopenia	66	17	1	59	8	1
Neutropenia	46	9	1	35	7	1
Lymphopenia	89	48	8	71	31	4

Key: D=Daratumumab; Kd=carfilzomib-dexamethasone.

Combination treatment with once-weekly carfilzomib (20/70 mg/m^2) and dexamethasone (DKd)

Adverse reactions described in table below reflect exposure to DARZALEX carfilzomib and dexamethasone (DKd) for a median treatment duration of 19.8 months (range: 0.3 to 34.5 months) in Study MMY1001. Fatal events within 30 days of treatment cessation, regardless of causality, were reported in 4% of all patients treated with DKd.

Table 19: Adverse reactions reported in Study MMY1001

System Organ Class Adverse Reaction	DKd (N=85)%		
	Any Grade	**Grade 3**	**Grade 4**
Infusion reactions[a]	44	2	0
Gastrointestinal disorders			
Nausea	42	1	0
Diarrhea	38	2	0
General disorders and administration site conditions			
Fatigue	17	4	0
Infections and infestations			
Upper respiratory tract infection[b]	69	5	0
Bronchitis[c]	20	0	0
Pneumonia[d]	12	5	2
Musculoskeletal and connective tissue disorders			
Back pain	25	0	0
Psychiatric disorders			
Insomnia	33	5	0

Key: D=Daratumumab; Kd=carfilzomib-dexamethasone

[a] Includes terms determined by investigators to be related to infusion.

[b] Acute sinusitis, Metapneumovirus infection, Nasopharyngitis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinusitis, Upper respiratory tract infection, Viral pharyngitis, Viral rhinitis, Viral upper respiratory tract infection

[c] Bronchiolitis, Bronchitis, Bronchitis viral

[d] Bronchopulmonary aspergillosis, Pneumonia, Pneumonia aspiration, Pneumonia haemophilus

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

Table 20: Treatment-emergent haematology laboratory abnormalities in Study MMY1001

	DKd (N=85)%		
	Any Grade	**Grade 3**	**Grade 4**
Anemia	60	19	0
Thrombocytopenia	85	22	11
Leukopenia	75	27	2
Neutropenia	64	19	1
Lymphopenia	89	40	15

Key: D=Daratumumab, Kd= carfilzomib-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 the table below. The most frequently reported adverse reactions (≥ 20%) were IRRs, fatigue, nausea, back pain, anaemia, 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 21: 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	Anaemia	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
	Diarrhoea		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, dyspnoea, 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 IRRs was 37% with the first (16 mg/kg, Week 1) infusion of DARZALEX, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion reaction at Week 2 or subsequent infusions.

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

Severe IRRs included bronchospasm, dyspnoea, laryngeal oedema, pulmonary oedema, hypoxia, and hypertension. Other adverse infusion-related reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea (see section 4.4 Special warnings and precautions for use).

In patients with newly diagnosed multiple myeloma, 5 subjects (1.4%) in the DVMP group (Study MMY3007), 3 subjects (0.6%) in the DVTd group (Study MMY3006) and 1 subject (0.7%) in the DRd group (Study MMY3008) discontinued DARZALEX due to IRRs. In combination studies in relapsed/refractory multiple myeloma, 5 subjects (0.8%) discontinued DARZALEX treatment due to IRRs. In the monotherapy study, no subject treated with 16 mg/kg DARZALEX discontinued treatment due to an IRR.

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

In study MMY1001, patients receiving daratumumab combination treatment (n=97) were administered the first 16 mg/kg daratumumab dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade IRRs was 42%, with 36% of patients experiencing IRRs 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 hours for Week 1-Day 1, 4.2 hours for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Infections

In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported as follows:

Relapsed/refractory patient studies: DVd: 21%, Vd: 19%, DRd: 28%, Rd: 23%; DPd: 28%; DKd[a]: 36%, Kd[a]: 27%; DKd[b]: 21%.

[a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly
[b] where carfilzomib 20/70 mg/m^2 was administered once-weekly

Newly diagnosed patient studies: DVMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; DVTd: 22%, VTd: 20%.

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In 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%; DPd: 2%; DKd[a]: 5%, Kd[a]: 3%; DKd[b]: 0%

[a] where carfilzomib 20/56 mg/m^2 was administered twice-weekly
[b] where carfilzomib 20/70 mg/m^2 was administered once-weekly

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

Other Adverse Reactions

Other adverse reactions reported in patients treated with daratumumab in clinical trials are listed in Table 22.

Table 22: Other adverse reactions reported in patients treated with daratumumab in clinical trials

System Organ Class	Adverse Reaction
Infections and infestations	Cytomegalovirus infection[a] (<1%), Hepatitis B virus reactivation (< 1%)
Immune system disorders	Hypogammaglobulinemia[b] (3%)
Metabolism and nutrition disorders	Hypokalaemia (10%)
Psychiatric disorders	Insomnia (17%)
Nervous system disorders	Dizziness (9%), Syncope (3%)
Gastrointestinal disorders	Abdominal pain[c] (14%), Pancreatitis[d] (1%)
Skin and subcutaneous 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

Of the 2459 patients who received DARZALEX at the recommended dose, 38% were 65 to 75 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients (see section 5.1 Pharmacodynamic properties, Clinical trials). 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 DARZALEX are included in Table 23. 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 23, 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 23: Postmarketing adverse reactions identified with daratumumab

System Organ Class Adverse Reaction	Frequency Category based on Spontaneous Reporting Rate
Immune System disorders	
Anaphylactic reaction	Rare
Infections and Infestations	
COVID-19	Uncommon
Hepatitis B virus reactivation	Rare

Reporting suspected adverse reactions

Reporting suspected adverse reactions after registration 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 at https://www.tga.gov.au/reporting-problems.

4.9 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.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMICS PROPERTIES

Pharmacotherapeutic group: 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 haematological malignancies, including multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.

Daratumumab has been shown to inhibit the *in vivo* growth of CD38-expressing tumour cells. Based on *in vitro* studies, daratumumab may utilise multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour 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 tumour 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. A total of 6/1713 subjects tested (0.4%) were positive for anti-daratumumab antibodies in combined and monotherapy daratumumab IV studies. Of these 6, 4 tested positive for neutralising 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.

Cardiac electrophysiology

Daratumumab as a large protein has a low likelihood of direct ion channel interactions. The effect of daratumumab on the QTc interval was evaluated in an open-label study for 83 patients (Study GEN501) with relapsed and refractory multiple myeloma following daratumumab infusions (4 to 24 mg/kg). Linear mixed PK-PD analyses indicated no large increase in mean QTcF interval (i.e., greater than 20ms) at daratumumab C_{max}. The mean time-averaged QTcF interval increase was 10.1 ms (n=3) and 4.3 ms (n=42) in the 16 mg/kg cohorts from these analyses.

Clinical trials

Newly diagnosed multiple myeloma

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

Study MMY3006, an open-label, randomised, active-controlled Phase 3 study compared induction and consolidation treatment with DARZALEX 16 mg/kg in combination with bortezomib, thalidomide and dexamethasone (DVTd) to treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients with newly diagnosed multiple myeloma eligible for ASCT. The consolidation phase of treatment began a minimum of 30 days post-ASCT, when the patient had recovered sufficiently, and engraftment was complete.

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

Table 24: Dosage regimen in treatment with bortezomib, thalidomide and dexamethasone

	Induction Phase		**Consolidation Phase**
	Weeks 1-8	**Weeks 9-16**	**Weeks 1-8 (starting minimum of 30 days post-transplant)**
Daratumumab	16 mg/kg IV Weekly for two 4-week induction cycles (total of 8 doses)	16 mg/kg IV Every 2 weeks for two 4-week induction cycles (total of 4 doses)	16 mg/kg IV Every 2 weeks for two 4-week consolidation cycles (total of 4 doses)
Bortezomib	1.3 mg/m^2 SC[a] Days 1, 4, 8, 11 in each of the four 4-week cycles (total of 16 doses)		1.3 mg/m^2 SC[a] Days 1, 4, 8, 11 of the two 4-week cycles (total of 8 doses)
Thalidomide	100 mg oral Daily in each cycle		
Dexamethasone[b, c]	40 mg oral or IV Days 1, 2, 8, 9, 15, 16, 22, 23	40 mg oral or IV Days 1, 2 and 20 mg oral or IV Days 8, 9, 15, 16	20 mg oral or IV Days 1, 2, 8, 9, 15, 16

[a] Bortezomib was administered SC; or IV if injection site reactions were encountered.
[b] Dexamethasone reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5
[c] On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication.

A total of 1085 patients were randomised: 543 to the DVTd arm and 542 to the VTd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 58 (range: 22 to 65 years). The majority were male (59%), 48% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 42% had an ECOG performance score of 1 and 10% had an ECOG performance score of 2. Forty percent had ISS Stage I, 45% had ISS Stage II and 15% had ISS Stage III disease.

Efficacy was evaluated by the stringent Complete Response (sCR) rate at Day 100 post-transplant.

Table 25: Efficacy results from Study MMY3006[a]

	DVTd (n=543)	**VTd (n=542)**	**Odds Ratio (95% CI)[b]**	**P value[c]**
Response assessment Day 100 post-transplant				
Stringent Complete Response (sCR)	157 (28.9%)	110 (20.3%)	1.60 (1.21, 2.12)	0.0010
CR or better (sCR+CR)	211 (38.9%)	141 (26.0%)	1.82 (1.40, 2.36)	<0.0001

Very Good Partial Response or better (sCR+CR+VGPR)	453 (83.4%)	423 (78.0%)	1.41 (1.04, 1.92)	
MRD negativity[d] n(%)	346 (63.7%)	236 (43.5%)	2.27 (1.78, 2.90)	<0.0001
95% CI (%)	(59.5%, 67.8%)	(39.3%, 47.8%)		
MRD negativity[e] n(%)	183 (33.7%)	108 (19.9%)	2.06 (1.56, 2.72)	<0.0001
95% CI (%)	(29.7%, 37.9%)	(16.6%, 23.5%)		

DVTd=daratumumab-bortezomib-thalidomide-dexamethasone; VTd=bortezomib-thalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval; HR = Hazard Ratio

[a] Based on intent-to-treat population

[b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used.

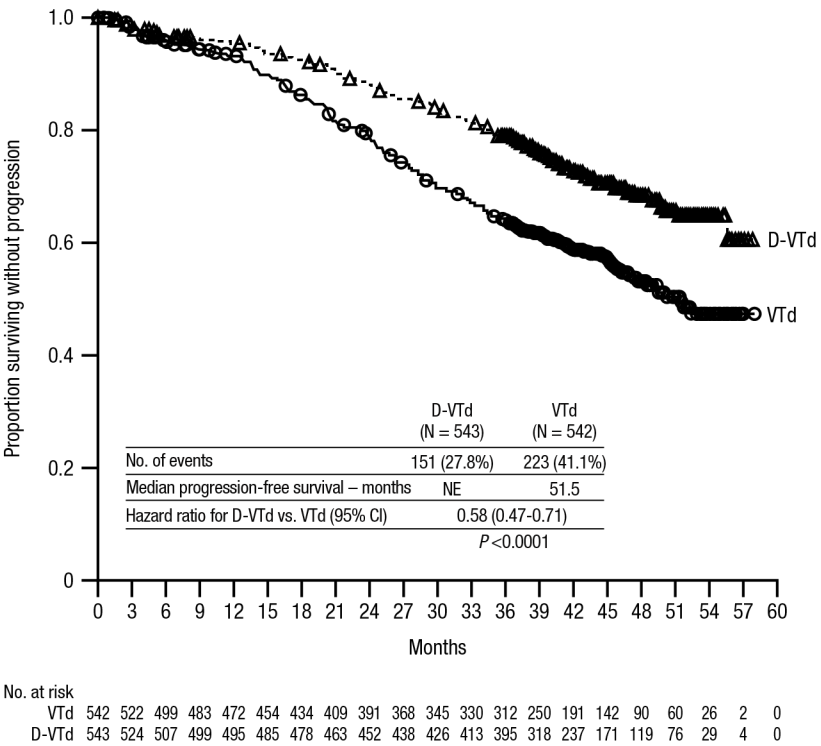
[c] p-value from Cochran Mantel-Haenszel Chi-Squared test.

[d] Based on threshold of 10^{-5}

[e] Only includes patients who achieved MRD negativity (threshold of 10^{-5}) and CR or better

With a median follow-up of 18.8 months, the primary analysis of PFS in study MMY3006 demonstrated an improvement in Progression Free Survival (PFS) in the DVTd arm as compared to the VTd arm; the median PFS had not been reached in either arm. Treatment with DVTd resulted in a reduction in the risk of progression or death by 53% compared to VTd alone (HR=0.47; 95% CI: 0.33, 0.67; p<0.0001). Results of an updated PFS analysis after a median follow-up of 44.5 months showed that median PFS was not reached in the DVTd arm and was 51.5 months in the VTd arm (HR=0.58; 95% CI: 0.47, 0.71; p<0.0001).

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3006



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

Study MMY3007, an open-label, randomised, active-controlled Phase 3 study, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib, melphalan and prednisone (DVMP), 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 additional 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.

Table 26: Dosage regimen in combination treatment with bortezomib, melphalan and prednisone

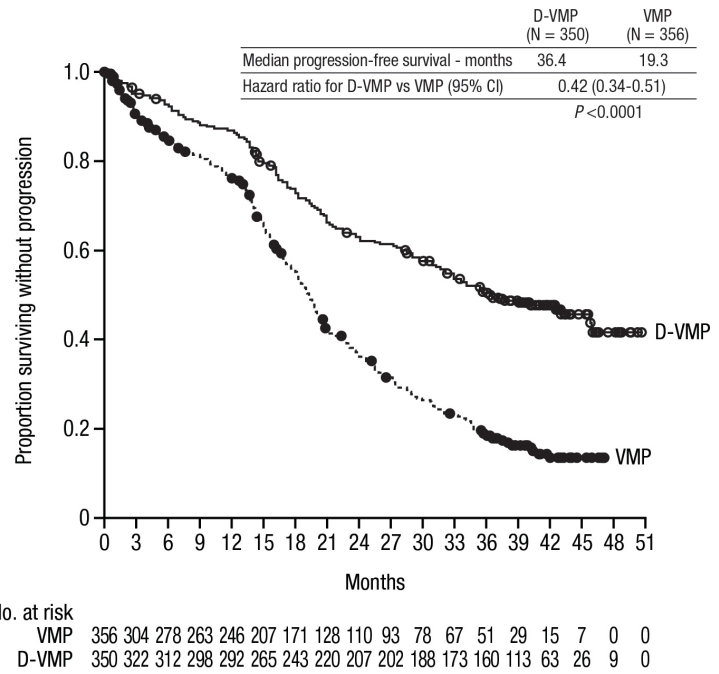
	Weeks 1-6	Weeks 7-54	Weeks 55 onwards until disease progression
Daratumumab	16 mg/kg IV Weekly (total of 6 doses)	16 mg/kg IV Every 3 weeks (total of 16 doses)[a]	16 mg/kg IV Every 4 weeks[b]
Bortezomib	1.3 mg/m^2 SC Twice weekly Weeks 1, 2, 4 and 5 of the first 6-week cycle	1.3 mg/m^2 SC Once weekly Weeks 1, 2, 4 and 5 of each repeated 6- week cycle	-
Melphalan	9 mg/m^2 oral Days 1-4 of each repeated 6- week cycle		-
Prednisone	60 mg/m^2 oral Days 1-4 of each repeated 6- week cycle		-

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

A total of 706 patients were randomised: 350 to the DVMP 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% and 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.

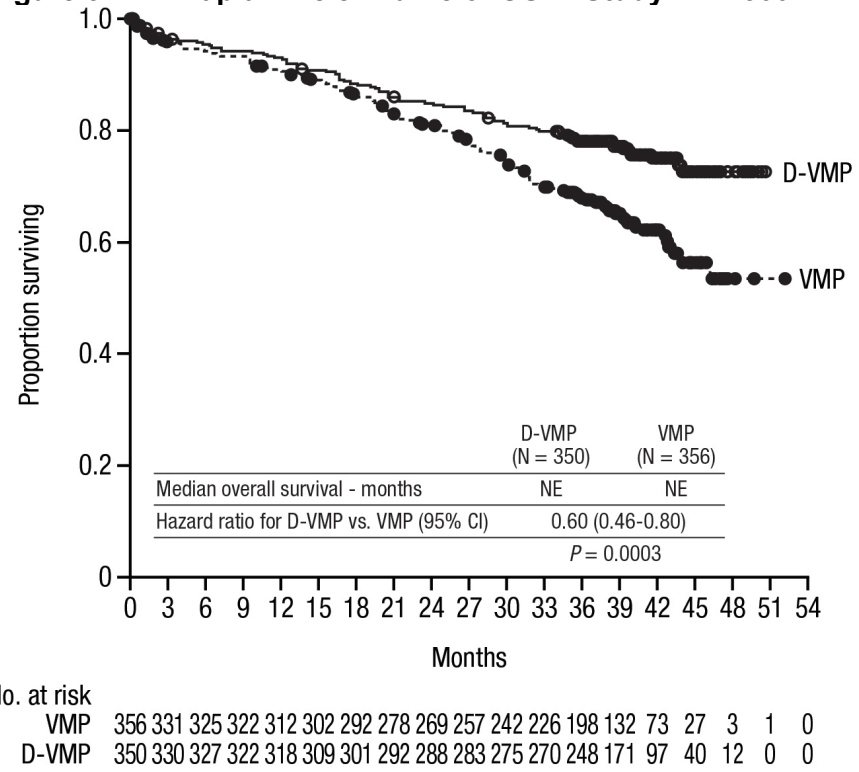
With a median follow-up of 16.5 months, the primary analysis of PFS in study MMY3007 demonstrated an improvement in the DVMP arm as compared to the VMP arm; the median PFS had not been reached in the DVMP arm and was 18.1 months in the VMP arm (HR=0.5; 95% CI: 0.38, 0.65; p<0.0001), representing 50% reduction in the risk of disease progression or death in patients treated with DVMP. 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 (95% CI: 32.1, 45.9) in the DVMP arm and 19.3 months (95% CI: 18.0, 20.4) in the VMP arm.

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



After a median follow-up of 40 months, an improvement in overall survival (OS) was demonstrated for the DVMP arm (83 deaths, 23.7%) as compared to the VMP arm (126 deaths, 35.6%) (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 DVMP arm. Median OS was not reached for either arm.

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



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

Table 27: Additional efficacy results from Study MMY3007[a]

	DVMP (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	

DVMP = 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 DVMP.

[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 DVMP 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 DVMP group and was 21.3 months (range: 18.4, not estimable) in the VMP group.

Combination treatment with lenalidomide and dexamethasone in patients ineligible for autologous stem cell transplant

Study MMY3008 an open-label, randomised, 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 Product Information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

Table 28: Dosage regimen in combination treatment with lenalidomide and dexamethasone

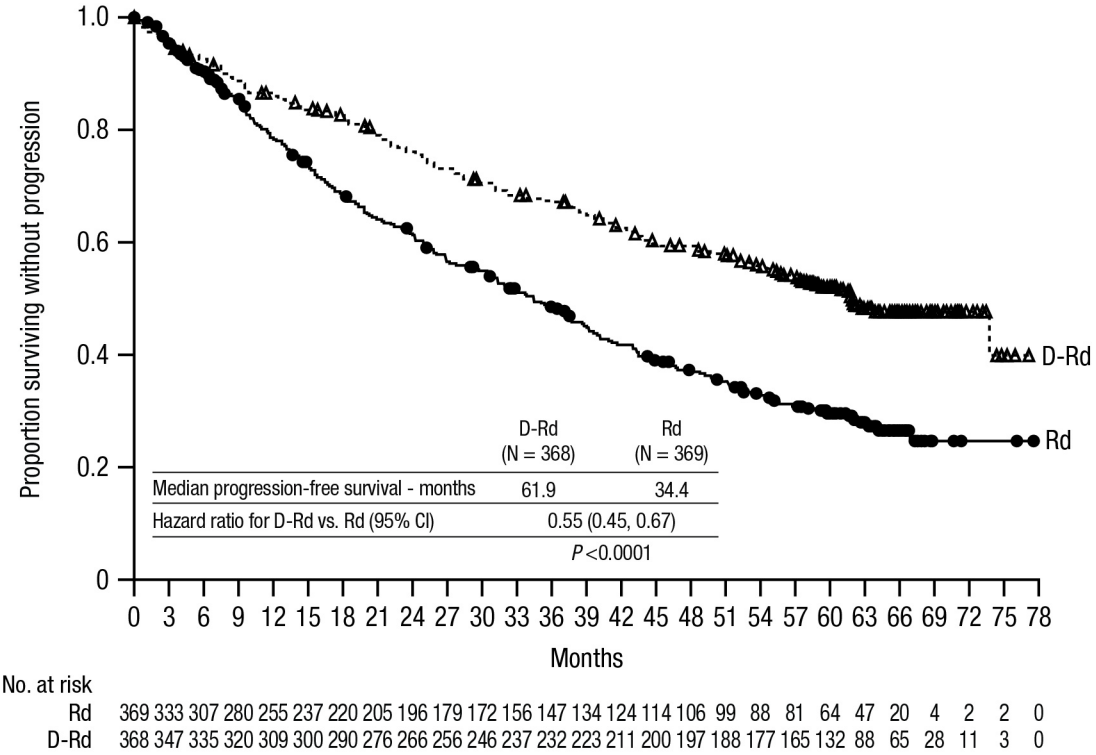
	Weeks 1-8	**Weeks 9-24**	**Weeks ≥ 25**
Daratumumab	16 mg/kg IV Weekly for two 4-week cycles (total of 8 doses)	16 mg/kg IV Every 2 weeks for four 4-week cycles (total of 8 doses)	16 mg/kg IV Every 4 weeks
Lenalidomide	25 mg oral, once daily Days 1-21 of each repeated 28 day [4-week] cycles		
Dexamethasone[a, b]	40 mg oral or IV Weekly		

[a] Dexamethasone reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5
[b] On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication.

A total of 737 patients were randomised: 368 to the DRd arm and 369 to the Rd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 73 (range: 45-90) years, with 44% of the patients ≥75 years of age. The majority were white (92%), male (52%), 34% had an ECOG performance score of 0, 50% had an ECOG performance score of 1 and 17% had an ECOG performance score of ≥2. Twenty-seven percent had International Staging System (ISS) Stage I, 43% had ISS Stage II and 29% had ISS Stage III disease. Efficacy was evaluated by progression free survival (PFS) based on IMWG criteria

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 arm. Median PFS was 61.9 months in the DRd arm and 34.4 months (95% CI, 29.6, 39.2) 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 with DRd.

Figure 4: Kaplan-Meier Curve of PFS in Study MMY3008

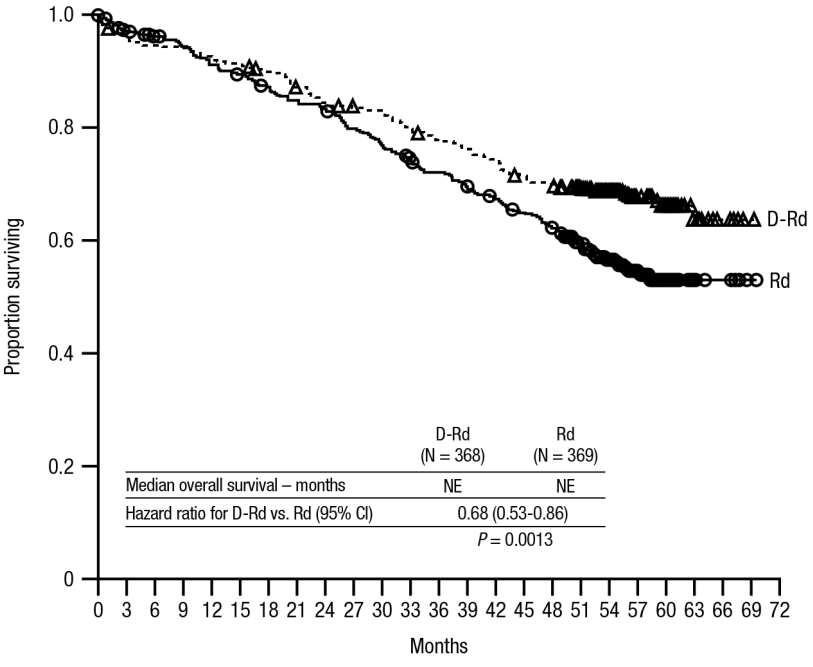


No. at risk

Rd	369	333	307	280	255	237	220	205	196	179	172	156	147	134	124	114	106	99	88	81	64	47	20	4	2	2	0
D-Rd	368	347	335	320	309	300	290	276	266	256	246	237	232	223	211	200	197	188	177	165	132	88	65	28	11	3	0

After a median follow-up of 56 months, an improvement in OS was demonstrated for the DRd arm (117 deaths, 31.8%) as compared to the Rd arm (156 deaths, 42.3%) (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. Median OS was not reached for either arm. The 60 month survival rate was 66% (95% CI: 61, 71) in the DRd arm and was 53% (95% CI: 47, 59) in the Rd arm.

Figure 5: Kaplan-Meier Curve of OS in Study MMY3008



No. at risk

Rd	369	351	343	336	324	317	308	300	294	281	270	258	251	241	232	223	213	183	134	85	42	14	5	1	0
D-Rd	368	350	346	344	338	334	328	316	305	302	297	286	280	273	266	255	249	228	170	118	63	22	6	1	0

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

Table 29: 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.

Relapsed/refractory multiple myeloma

Combination treatment with bortezomib and dexamethasone

Study MMY3004, an open-label, randomised, 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. DARZALEX was continued until disease progression or unacceptable toxicity. Patients refractory to bortezomib were excluded from the study. Dose adjustments for bortezomib and dexamethasone were applied according to manufacturer's Product Information.

Table 30: Dosage regimen in combination treatment with bortezomib

	Weeks 1-9	**Weeks 10-24**	**Weeks ≥ 25**
Daratumumab	16 mg/kg IV Weekly	16 mg/kg IV Every 3 weeks	16 mg/kg IV Every 4 weeks
Bortezomib	1.3 mg/m^2 SC or IV Days 1,4,8,11 of each repeated 21 day [3 week] cycle		-
Dexamethasone[a, b]	20 mg oral or IV once daily Days 1, 2, 4, 5, 8, 9, 11, 12 of each repeated 21 day [3 week] cycle (ie 80 mg/week for two out of three weeks of each of the bortezomib cycle)		20 mg oral or IV (given as daratumumab pre-infusion medication)

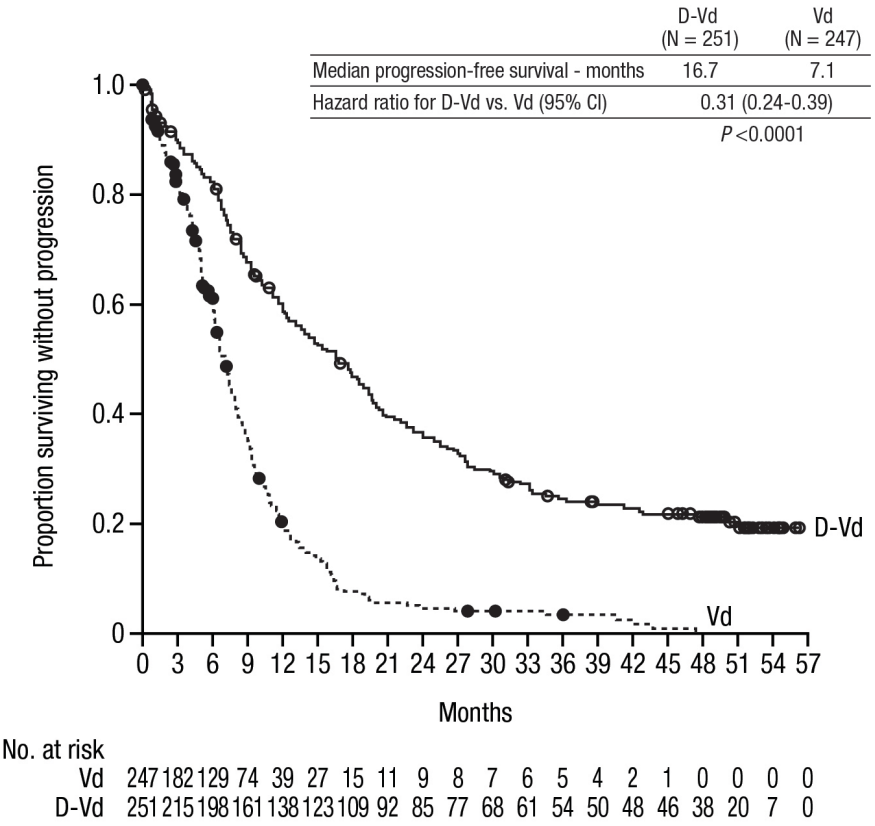
[a] Dexamethasone reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy.

[b] 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.

A total of 498 patients were randomised; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the 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

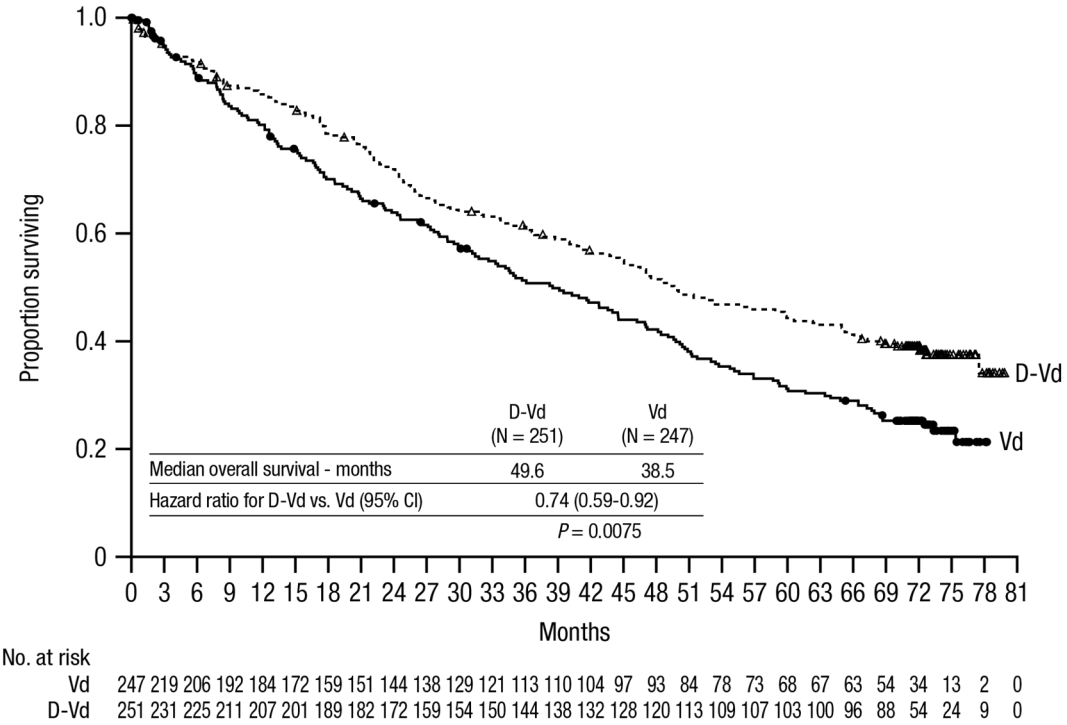
With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value < 0.0001), representing 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 (95% CI: 13.1, 19.4) in the DVd arm and 7.1 months (95% CI: 6.2. 7.7) 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 6: Kaplan-Meier Curve of PFS in Study MMY3004



After a median follow-up of 73 months, an improvement in OS was demonstrated for the DVd arm (148 deaths, 59.0%) as compared to the Vd arm (171 deaths, 69.2%) (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 (95% CI: 42.2, 62.3) in the DVd arm and 38.5 months (95% CI: 31.2, 46.2) 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 7: Kaplan-Meier Curve of OS in Study MMY3004



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

Table 31: 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 Fischer's exact test

Combination treatment with lenalidomide and dexamethasone

Study MMY3003, an open-label, randomised, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with multiple myeloma who had received at least one prior therapy.

Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's Product Information. Treatment was continued in both arms until disease progression or unacceptable toxicity. Patients refractory to lenalidomide were excluded from the study.

Table 32: Dosage regimen in combination treatment with lenalidomide

	Weeks 1-8	**Weeks 9-24**	**Weeks ≥ 25**
Daratumumab	16 mg/kg IV Weekly for two 4-week cycles (total of 8 doses)	16 mg/kg IV Every 2 weeks for four 4-week cycles (total of 8 doses)	16 mg/kg IV Every 4 weeks
Lenalidomide	25 mg oral, once daily Days 1-21 of each repeated 28 day [4 week] cycle		
Dexamethasone[a, b]	40 mg oral or IV Weekly		

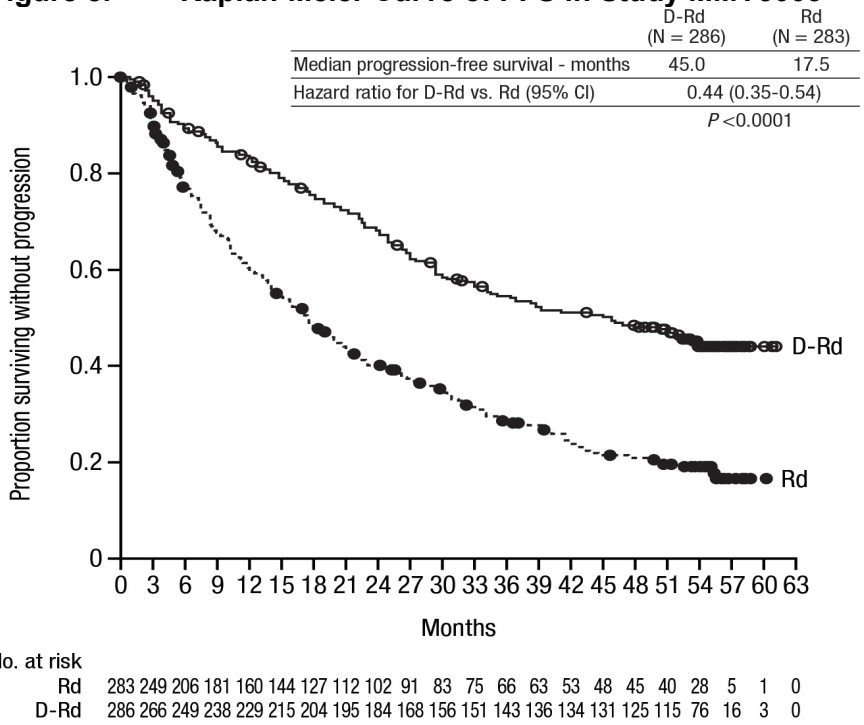
[a] Dexamethasone reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5

[b] On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication.

A total of 569 patients were randomised; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the 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

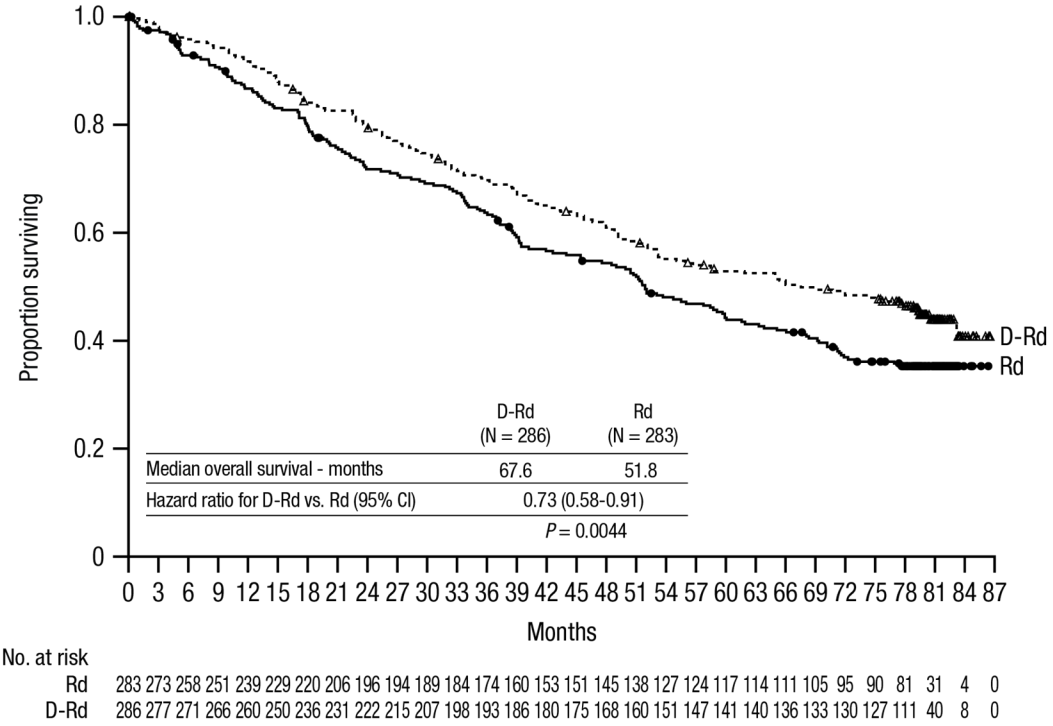
With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (HR = 0.37; 95% CI: 0.27, 0.52; p<0.0001) representing 63% reduction in the risk of disease progression or death in patients treated with DRd (Figure 8). 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 (95% CI: 34.1, 53.9) in the DRd arm and 17.5 months (95% CI: 13.9, 20.8) 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 8: Kaplan-Meier Curve of PFS in Study MMY3003



After a median follow-up of 80 months, an improvement in OS was demonstrated for the DRd arm (153 deaths, 53.5%) as compared to the Rd arm (175 deaths, 61.8%) (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 (95% CI: 53.1, 80.5) in the DRd arm and 51.8 months (95% CI: 44.0, 60.0) 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 9: Kaplan-Meier Curve of OS in Study MMY3003



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

Table 33: Additional efficacy results from Study MMY3003

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

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

[a] p-value from Cochran Mantel-Haenszel Chi-Squared test.

[b] Based on Intent-to-treat population and threshold of 10^{-5}

[c] Mantel Haenszel estimate of the common odds ratio is used. An odds ratio > 1 indicates an advantage for DRd.

[d] p-value is from Fisher's exact test.

Combination treatment with twice-weekly (20/56 mg/m^2) carfilzomib and dexamethasone

Study 20160275 (CANDOR), an open-label, randomised, active-controlled Phase 3 trial, compared treatment with DARZALEX in combination with carfilzomib and dexamethasone (DKd) to treatment with carfilzomib and dexamethasone (Kd) in patients with multiple myeloma who had received at least one to three prior lines of therapy.

DARZALEX was administered intravenously at a dose of 8 mg/kg in Cycle 1 on Days 1 and 2, Thereafter, DARZALEX was administered intravenously at a dose of 16mg/kg on Days 8, 15 and 22 of Cycle 1; Days 1, 8, 15 and 22 of Cycle 2; Days 1 and 15 of Cycle 3 to 6; and Day 1 of each 28-day cycle until disease progression.

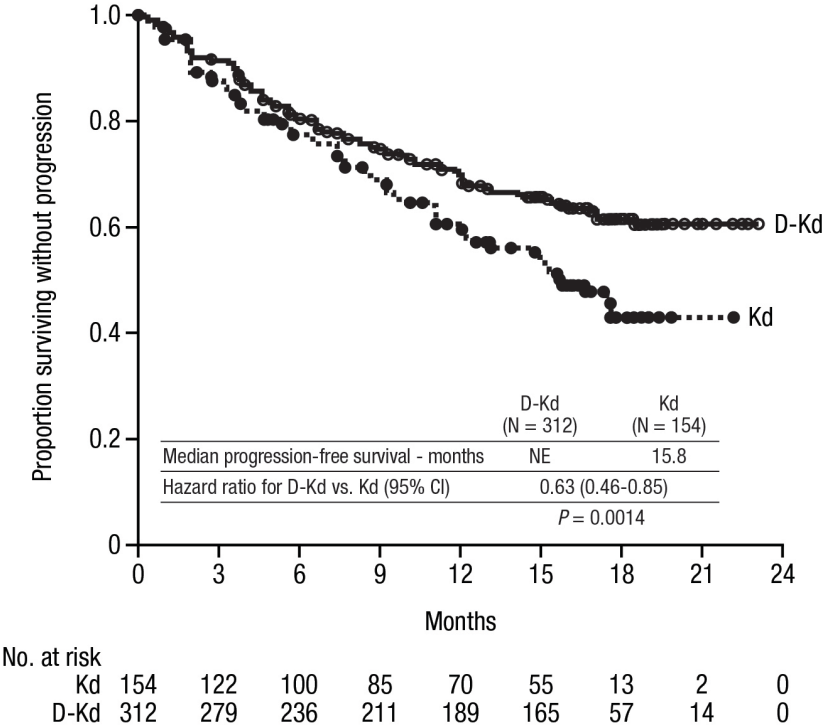
Carfilzomib was administered as IV infusion twice weekly on Days 1, 2, 8, 9, 15, and 16 of repeated 28-day [4-week] treatment cycles. Carfilzomib dose was 20 mg/m^2 on Cycle 1 Days 1 and 2 and 56 mg/m^2 beginning on Cycle 1 Day 8 and thereafter.

Dexamethasone was administered orally or by IV infusion at a total dose of 40 mg weekly. Dexamethasone was administered as an IV infusion on carfilzomib and/or DARZALEX IV infusion days. On the days of DARZALEX and/or carfilzomib infusion, 20 mg of the dexamethasone dose was administered via IV as a pre-infusion medication. The remaining 20 mg of dexamethasone was administered via IV on successive day of carfilzomib and/or DARZALEX infusions. For patients >75 years on a reduced total dexamethasone dose of 20 mg, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Dose adjustments for carfilzomib 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 466 patients were randomised; 312 to the DKd arm and 154 to the Kd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 64 years (range 29 to 84 years), 9% were ≥75 years, 58% were male; 79% Caucasian, 14% Asian, and 2% African American. Patients had received a median of 2 prior lines of therapy and 58% of patients had received prior autologous stem cell transplantation (ASCT). The majority of patients (92%) received a prior PI and of those 34% were refractory to PI including regimen. Fourty-two percent (42%) of patients had received prior lenalidomide and of those, 33% were refractory to a lenalidomide containing regimen.

Efficacy was evaluated by PFS based on IMWG criteria. Study 20160275 (CANDOR) demonstrated an improvement in PFS in the DKd arm as compared to the Kd arm; the median PFS had not been reached in the DKd arm and was 15.8 months in the Kd arm (hazard ratio [HR]=0.630; 95% CI: 0.464, 0.854; p=0.0014), representing 37% reduction in the risk of disease progression or death for patients treated with DKd versus Kd. PFS improvement observed in the ITT population was also observed in lenalidomide refractory patients.

Figure 10: Kaplan-Meier Curve of PFS in Study 20160275 (CANDOR)



After a median follow-up of 17.1 months, 95 deaths were observed [N=59 (19%) in the DKd group and N=36 (23%) in the Kd group]. Overall survival (OS) data were not mature, however, there was a trend toward longer OS in the DKd arm compared with the Kd arm (HR=0.745; 95% CI: 0.491, 1.131; p=0.0836).

Additional efficacy results from Study 20160275 (CANDOR) are presented in table below.

Table 34: Additional efficacy results from Study 20160275 (CANDOR)

	DKd (N=312)	**Kd (N=154)**
Overall response (sCR+CR+VGPR+PR) n(%)[a, b]	263 (84.3%)	115 (74.7%)
p-value[c]	0.0040	
Complete response (CR)[d]	89 (28.5%)	16 (10.4%)
MRD [-] CR[e]	43 (13.8%)	5 (3.2%)
Very good partial response (VGPR)	127 (40.7%)	59 (38.3%)
Partial response (PR)	47 (15.1%)	40 (26.0%)
MRD [-] CR rate at 12 months n(%)[a, b, e]	39 (12.5%)	2 (1.3%)
95% CI (%)	(9.0, 16.7)	(0.2, 4.6)
p-value[c]	<0.0001	

DKd = daratumumab-carfilzomib-dexamethasone; Kd =carfilzomib-dexamethasone; MRD [-] CR=minimal residual disease; CI=confidence interval

[a] Based on intent-to-treat population
[b] Responses based on the IRC assessments
[c] p-value from the stratified Cochran Mantel-Haenszel Chi-Squared test
[d] sCR could not be differentiated due to lack of kappa/lambda ration by IHC
[e] MRD[-]CR (at a 10^{-5} level) is defined as achievement of CR per IMWG-URC and MRD[-] status as assessed by the next-generation sequencing assay (ClonoSEQ)

In responders, the median time to response was 1 month (range: 1 to 14 months) in the DKd group and 1 month (range: 1 to 10 months) in the Kd group. The median duration of response had not been reached in the DKd group and was 16.6 months (95% CI: 13.9, not estimable) in the Kd group.

Limited data are available in patients ≥ 75 years of age. A total of 43 patients ≥ 75 years of age were enrolled in Study 20160275 (CANDOR) (25 and 18 patients in the DKd and Kd groups, respectively). A HR of 1.459 (95% CI: 0.504, 4.223) in PFS was observed. The risk of fatal treatment emergent adverse events was higher among patients ≥ 65 years of age. DKd should be used with caution in patients ≥ 75 years of age after careful consideration of the potential benefit/risk on an individual basis.

Combination treatment with once-weekly (20/70 mg/m^2) carfilzomib and dexamethasone

Study MMY1001 was an open-label trial in which 85 patients with multiple myeloma who had received at least one prior therapy, received DARZALEX in combination with carfilzomib and low-dose dexamethasone until disease progression.

Ten patients were administered DARZALEX 16 mg/kg intravenously on Cycle 1, Day 1 and the remaining patients were administered DARZALEX 8 mg/kg intravenously on Cycle 1, Days 1 and 2. Thereafter DARZALEX 16 mg/kg was administered intravenously on Days 8, 15, and 22 of Cycle 1; Days 1, 8, 15 and 22 of Cycle 2; Days 1 and 15 of Cycle 3 to 6; and then Day 1 of each remaining 28-day cycle.

Carfilzomib was administered as IV infusion once weekly at a dose of 20 mg/m^2 on Cycle 1 Day 1 and escalated to dose of 70 mg/m^2 on Cycle 1 Days 8 and 15, and Days 1, 8, and 15 of subsequent cycles.

Dexamethasone was given at total dose of 40 mg (patients ≤75 years) or 20 mg (patients >75 years) per week. For first DARZALEX split-dose, dexamethasone was administered on Day 1 and Day 2 before the DARZALEX infusions. During other DARZALEX infusion weeks, dexamethasone was administered on infusion days at a dose of 20 mg before the DARZALEX infusion and 20 mg the day after the DARZALEX infusion.

The median patient age was 66 years (range: 38 to 85 years) with 9% of patients ≥75 years of age. Patients in the study had received a median of 2 prior lines of therapy. Seventy-three percent (73%) of patients had received prior ASCT. All patients received prior bortezomib, and 95% of patients received prior lenalidomide. Sixty percent (60%) of patients were refractory to lenalidomide and 29% of patients were refractory to both a PI an IMiD.

Efficacy results were based on overall response rate using IMWG criteria (see Table 35).

Table 35: Efficacy results for MMY1001 (DKd arm)

	N=85
Overall response rate (ORR) 95% CI (%)	69 (81.2%) (71.2, 88.8)
Stringent complete response (sCR)	18 (21.2%)
Complete response (CR)	12 (14.1%)
Very good partial response (VGPR)	28 (32.9%)
Partial response (PR)	11 (12.9%)

ORR = sCR+CR+VGPR+PR
CI = Confidence Interval

Monotherapy

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

In Study MMY2002, 106 patients with relapsed and refractory multiple myeloma received 16 mg/kg DARZALEX until disease progression. The median patient age was 63.5 years (range, 31 to 84 years), 49% were male and 79% were Caucasian. Patients had received a median of 5 prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation (ASCT). Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%). At baseline, 97% of patients were refractory to the last line of treatment, 95% were refractory to both, a PI and IMiD, 77% were refractory to alkylating agents, 63% were refractory to pomalidomide and 48% of patients were refractory to carfilzomib.

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

Table 36: 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. At a survival update with a median duration of follow up of 14.7 months, median OS was 17.5 months (95% CI:13.7, not estimable).
In Study GEN501, 42 patients with relapsed and refractory multiple myeloma received 16 mg/kg 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.

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

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

5.2 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 minimised and the clearance of daratumumab approximates the linear clearance of endogenous IgG1. Clearance also decreased with multiple doses, which may be related to tumour burden decreases.

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

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

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

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 15-23days.

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.

Additional information on 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, age; ≥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 analyses 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), 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Routine genotoxicity studies are generally not applicable to biologic pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material.

Carcinogenicity

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

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

glacial acetic acid
mannitol
polysorbate 20
sodium acetate trihydrate
sodium chloride
water for injections

6.2 INCOMPATIBILITIES

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 SHELF-LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened vials

Store in a refrigerator (2°C–8°C).

Do not freeze.

Store in the original package in order to protect from light.

After dilution

DARZALEX contains no antimicrobial preservative. To reduce microbiological hazard, use as soon as possible after dilution. If not used immediately, the solution may be stored in a refrigerator protected from light 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.

6.5 NATURE AND CONTENTS OF CONTAINER

DARZALEX is available in cartons containing 1 vial:

- 5 mL concentrate in a Type 1 glass vial with an elastomeric closure and an aluminium seal with an aqua flip-off button containing 100 mg of daratumumab.
- 20 mL concentrate in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a purple flip-off button containing 400 mg of daratumumab.

Product is for single use in one patient only.

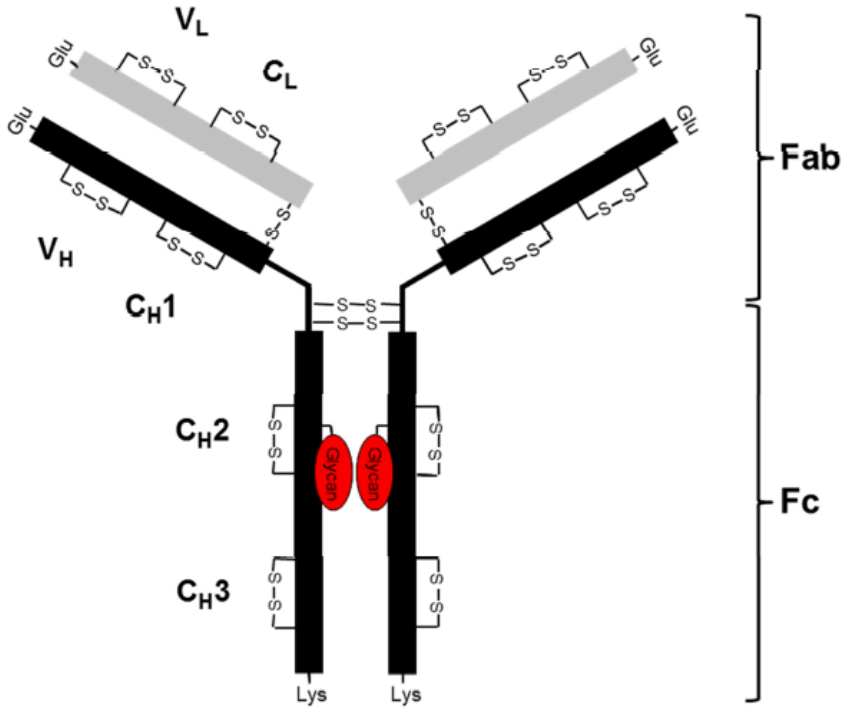
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure

Figure 11: General structure of daratumumab



CAS Registry Number: 945721-28-8

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8. SPONSOR

JANSSEN-CILAG Pty Ltd

1-5 Khartoum Road
Macquarie Park NSW 2113
Australia
Telephone: 1800 226 334

9. DATE OF FIRST APPROVAL

17 July 2017

10. DATE OF REVISION

27 February 2025

Summary table of changes

Section	Summary of changes
4.8	ADR updates to Table 22