

## Consensus

# Best Practice for the Administration of Daratumumab in Multiple Myeloma: Australian Myeloma Nurse Expert Opinion

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## ABSTRACT

Patients with multiple myeloma (MM) are typically of an advanced age and may have significant co-existing medical conditions. They have often had multiple lines of therapy and as such experience disease-related effects alongside associated treatment toxicities. Daratumumab is a monoclonal antibody approved for the treatment of MM in the relapsed/refractory setting. Clinical studies found that daratumumab showed good tolerability as a monotherapy and in combination with current standard therapies. However, the administration of daratumumab does require specific management considerations. It is administered as an intravenous infusion and infusion-related reactions (IRRs) may occur. Daratumumab also interferes with

routine blood transfusion tests, giving false positives for the indirect antiglobulin test. This article highlights key nursing care considerations and practical management aspects to improve the treatment experience of patients receiving daratumumab infusions. Pretreatment aspects, patient education, pre- and post-medication, daratumumab administration, and the management of IRRs are discussed. An IRR management sheet that could be used by nurses and a patient information sheet are located at the end of this article.

**Key words:** Daratumumab, infusion-related reaction, multiple myeloma

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## Introduction

Multiple myeloma (MM) is a malignant disorder of the plasma cells that often leads to damage and weakening of the bone, compromised immunity, cytopenia, and damage to the kidneys and other organs.<sup>[1]</sup> It is the second-most common hematologic malignancy and accounts for as many as 2% of deaths from all cancers.<sup>[2]</sup> In Australia, in 2013, the age-adjusted incidence for MM was 6.3/100,000 with 1,637 cases diagnosed.<sup>[3]</sup> The incidence of MM is higher among men than among women and predominately affects patients aged 65 years or older.<sup>[3]</sup> While MM remains an incurable cancer, life expectancy has improved significantly due to routine use of new targeted therapies.<sup>[3,4]</sup> In Australia, there has been at least a 21% increase in the 5-year overall survival (OS) rate from the years 1984–1988 to 2009–2013.<sup>[3]</sup>

The advanced age of the majority of patients with MM often means that patients present with significant coexisting medical conditions, such as renal impairment, diabetes, and pulmonary and cardiac diseases that may adversely impact outcomes. Management of these comorbidities plays a key role in optimizing the efficacy of treatment.<sup>[5]</sup> Furthermore, for patients to benefit from improved OS, they are required to adhere to increasing lines of multi-agent therapy over longer periods of time.<sup>[6]</sup> Most patients have had several lines of therapy and experience disease-related effects alongside associated treatment toxicities, such as cytopenia, infection, thromboembolism, peripheral neuropathy, gastrointestinal effects, and even second primary malignancies.<sup>[7,8]</sup>

The diagnosis of a chronic cancer such as MM with the resultant disease and treatment-related effects has an adverse impact on a patient's health-related quality of life (HRQoL).<sup>[6,9-12]</sup> Health professionals caring for those with MM should be mindful of the chronic and complex nature of MM, and the individual impact on each patient, when optimizing treatment delivery and best supportive care. The goals of therapy remain to control the disease, maximize the patient's HRQoL, and prolong survival.<sup>[13]</sup>

The incorporation of proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs) into the standard of care is currently one of the most effective approaches for patients with newly diagnosed MM. As there is no curative treatment, MM inevitably relapses and several lines of therapy are typically required.<sup>[1]</sup> For patients who are refractory to PI and IMiD drugs, the prognosis can be poor with a median OS of only 9 months.<sup>[14]</sup> Drugs currently approved for use in Australia for the treatment of MM are outlined in Table 1.

### Daratumumab overview

Novel agents such as daratumumab have recently been approved for use in the relapsed/refractory (RR)

**Table 1: Commonly used drugs currently approved for use in Australia for the treatment of multiple myeloma<sup>[13]</sup>**

Class of drug	Drug name
PIs	Bortezomib
	Carfilzomib
	Ixazomib*
IMiDs	Thalidomide
	Lenalidomide
	Pomalidomide
Cytotoxic agents	Cyclophosphamide
	Melphalan
	Combination chemotherapy, for example, DT/DV-PACE <sup>[15,16]</sup>
Corticosteroids	Dexamethasone
	Prednisolone/prednisone
mAbs	Daratumumab*
	Elotuzumab*

\*Not listed on PBS at the time of publication. DT-PACE: Dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide, DV-PACE: Dexamethasone, bortezomib, cisplatin, doxorubicin, cyclophosphamide, and etoposide, PIs: Proteasome inhibitors, IMiDs: Immunomodulatory drugs, mAbs: Monoclonal antibodies, PBS: Pharmaceutical Benefits Scheme

setting. Daratumumab is a human IgG $\kappa$  monoclonal antibody that targets CD38, which is highly expressed on myeloma cells. Daratumumab has direct and indirect antitumor activity and diverse mechanisms of action including induction of apoptosis, immune-mediated actions, and immunomodulatory functions.<sup>[17]</sup> In heavily pretreated patients with relapsed or RR MM, single-agent daratumumab was associated with an overall response rate of 31% and a median OS of 20.1 months.<sup>[18]</sup>

Clinical trials evaluating the combination of daratumumab with PIs and IMiDs in patients with relapsed or RR MM demonstrated that adding daratumumab improved progression-free survival (PFS) while maintaining an acceptable safety profile. The CASTOR phase III clinical trial randomized 498 patients who had received a median of two prior lines of therapy to daratumumab therapy in combination with bortezomib and dexamethasone or bortezomib and dexamethasone alone. Addition of daratumumab resulted in significant improvement in PFS compared to bortezomib and dexamethasone alone at a prespecified interim analysis.<sup>[17]</sup> After a median follow-up period of 7.4 months, the median PFS was not reached in the daratumumab group (95% confidence interval [CI]: 12.3 to could not be estimated) and was 7.2 months (95% CI: 6.2–7.9 months) in the control group. The hazard ratio (HR) for progression or death for daratumumab versus control was 0.39 (95% CI: 0.28–0.53,  $P < 0.001$ ), crossing the prespecified stopping boundary. Based on the results of the interim analysis, the Independent Data and Safety Monitoring Committee recommended that the trial be unblinded early. Additional PFS data have been published recently and, after a median follow-up of 19.4 months, the median PFS for the daratumumab group was

16.7 months compared to 7.1 months in the control group (HR: 0.31, 95% CI: 0.24–0.39).<sup>[19]</sup>

The POLLUX phase III clinical trial randomized 569 patients who had received a median of one prior line of therapy to daratumumab plus lenalidomide and dexamethasone or lenalidomide and dexamethasone. At a median follow-up of 13.5 months in a prespecified interim analysis, the median PFS for the daratumumab group was not reached (95% CI: could not be estimated) as compared with 18.4 months (95% CI: 13.9 to could not be estimated) in the control group. The HR for disease progression or death in the daratumumab group versus the control group was 0.37 (95% CI: 0.27–0.52,  $P < 0.001$ ).<sup>[20]</sup> More recent data showed that after a median follow-up of 25.4 months, PFS was significantly prolonged with the daratumumab group compared to the control group (not reached versus 17.5 months, HR: 0.41, 95% CI: 0.31–0.53,  $P < 0.0001$ ).<sup>[21]</sup>

Daratumumab was approved for use by the Food and Drug Administration in the United States in 2015 and by the Therapeutic Goods Administration in Australia in 2017. In Australia, it is indicated as a monotherapy for the treatment of patients with MM who have received at least three prior lines of therapy including a PI and an IMiD or who are refractory to both a PI and an IMiD. Daratumumab is also approved for use in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with MM who have received at least one prior therapy.<sup>[22]</sup> The cost of daratumumab therapy is currently not subsidized by the Australian government through the Pharmaceutical Benefits Scheme (PBS). This would normally preclude a drug from becoming “standard of care” until such a time that successful PBS listing has been granted.

Clinical studies found that daratumumab showed good tolerability as a monotherapy and in combination with current standard therapies. However, the administration of daratumumab does require specific management considerations.<sup>[14]</sup> Daratumumab is delivered as an intravenous (IV) infusion, and infusion-related reactions (IRRs), common to all monoclonal antibodies (mAbs), may occur. Most infusion reactions related to mAbs are caused by cytokine release. The symptoms are generally mild to moderate in severity and usually occur within the first couple of hours, most often with the first infusion, and the symptoms appear to subside with each subsequent dose. Cytokine release reactions may be managed by short-term cessation of the monoclonal antibody infusion, with supportive measures such as administration of oxygen, corticosteroids, bronchodilators and histamine blockers, and restarting the infusion at a slower rate.<sup>[23]</sup>

Anaphylactic reactions to mAbs are rare but are reported occasionally.<sup>[23]</sup> Differentiation of a cytokine release syndrome from anaphylactic reaction can be difficult to determine in the early stages. A true anaphylactic reaction usually has a rapid onset within the first few minutes of infusion. Cytokine release reactions are more commonly within 30–120 min of infusion. Initial management of an anaphylactic reaction is the same as an IRR resulting from cytokine release reactions. Accurate documentation of the onset of symptoms is vital to assist in diagnosis. An anaphylactic reaction is more likely to have respiratory symptoms, hypotension, and/or cutaneous symptoms and will require early administration of epinephrine to avoid clinical deterioration.<sup>[23]</sup>

IRRs were reported in approximately half of all patients treated with daratumumab, with most occurring during the first infusion. The occurrence of IRRs can be influenced by the infusion rate<sup>[24]</sup> and the median time to onset of a reaction was 1.4 h.<sup>[22]</sup> In clinical trials (monotherapy and combination treatments;  $n = 820$ ), 46% of patients experienced IRRs with the first infusion, 2% with the second infusion, and 3% with subsequent infusions. The incidence of infusion interruptions was 42%. Less than 1% of patients had a Grade 3 infusion reaction with second or subsequent infusions. No Grade 4 or 5 infusion reactions occurred [Table 2 for definition of IRR grades].<sup>[22]</sup> The IRRs seen were generally mild and discontinuations due to IRRs were rare. In clinical trials of daratumumab monotherapy, no discontinuations or life-threatening IRRs were observed.<sup>[24]</sup> In combination studies, only five patients (0.8%) discontinued daratumumab treatment due to IRRs.<sup>[22]</sup> There was a lower incidence of IRRs (27.7%) in the ALCYONE trial,<sup>[26]</sup> which randomized 706 patients with newly diagnosed MM to bortezomib, melphalan, and prednisone alone or with daratumumab. The reason for the lower incidence of IRRs in this study is not clear.

Daratumumab IRRs are characterized by nasal congestion, throat irritation, cough, as well as chills,

**Table 2: Grading of infusion-related reactions according to the National Cancer Institute common terminology criteria for adverse events<sup>[25]</sup>**

Grade	Definition
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medication indicated for $\leq 24$ h
3	Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae
4	Life-threatening consequences; urgent intervention indicated
5	Death

NSAIDs: Nonsteroidal anti-inflammatory drugs, IV: Intravenous

vomiting, and nausea. Severe (grade 3) IRRs included bronchospasm, dyspnea, laryngeal edema, pulmonary edema, hypoxia, and hypertension.<sup>[22]</sup>

In addition to IRRs, the most commonly reported adverse effects (AEs) ( $\geq 20\%$ ) are fatigue, nausea, back pain, anemia, neutropenia, and thrombocytopenia. Table 3<sup>[22]</sup> lists adverse reactions that occurred at a rate of  $\geq 10\%$  for patients treated with daratumumab monotherapy during three open-label clinical studies. When daratumumab is used in combination with other active MM agents, then the adverse reaction profile can change. Common adverse reactions for combination therapies during clinical studies were thrombocytopenia for daratumumab with bortezomib and neutropenia for daratumumab with lenalidomide. Diarrhea was also common with both regimens.<sup>[22]</sup>

Another important aspect of daratumumab administration is the interference of daratumumab with routine blood transfusion laboratory tests. Daratumumab does not interfere with ABO/RhD typing, but does give false-positive results for the indirect antiglobulin test (IAT; Coombs test), which is used for the detection of irregular blood group antibodies.<sup>[27,28]</sup> As a result, it is important that blood typing is done prior to administration of daratumumab and that health-care providers, pathology departments, and blood banks are aware that the patient is receiving daratumumab therapy. Patients should be supplied with an identification card providing their blood type and explaining that they are receiving daratumumab.

Daratumumab can also affect the determination of complete response and disease progression in some patients with IgG kappa myeloma protein. This is because daratumumab is a human IgG kappa monoclonal antibody

that can be detected on the serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous monoclonal immunoglobulins (M-protein), leading to false-positive assay results.<sup>[14,22]</sup>

Current standard therapies for MM (PIs, IMiDs, corticosteroids, and alkylating agents) use multiple administration modalities. For example, bortezomib (PI) can be administered intravenously but, more commonly, subcutaneously, and lenalidomide (IMiD) is administered orally. A trained health professional must deliver all daratumumab infusions. Based on experience from clinical trials, the median duration of the first infusion is 7 h (minimum 6.5 h). This does not include premedication or monitoring times and it will take longer if the patient experiences IRRs. As a result, it is important to provide relevant information about daratumumab treatment to patients. This should include its route of administration, hospital visits required, and concomitant medications, so patient expectations can be managed around the schedule of treatment and potential associated IRRs. This article outlines some key nursing care considerations and practical management aspects to help prevent and successfully manage IRRs and to improve the treatment experience of patients receiving daratumumab infusions.

## Daratumumab Administration

The following nursing considerations and practical approaches are based on clinical experience gained from a variety of centers across Australia in the public and private sectors and the recommendations for daratumumab administration from the pharmaceutical

**Table 3: Adverse reactions in multiple myeloma patients treated with daratumumab monotherapy (16 mg/kg)<sup>[22]</sup>**

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

\*No Grade 4, <sup>f</sup>Pneumonia also includes the terms pneumonia streptococcal and lobar pneumonia, <sup>g</sup>Infusion-related reactions include, but are not limited to, the following multiple adverse reaction terms: Nasal congestion, cough, chills, allergic rhinitis, throat irritation, dyspnea, nausea (all $\geq 5\%$ ), bronchospasm (2.6%), hypertension (1.9%), and hypoxia (1.3%)

manufacturer (Janssen-Cilag). A checklist outlining the key aspects of daratumumab administration is given in Figure 1.

### Pretreatment preparations

#### Patient preassessment (up to 2 weeks prior to starting treatment)

There are a range of patient assessments that need to be performed before starting treatment with daratumumab. Patients should be assessed 1–2 weeks prior to treatment for the following:

#### Vein assessment for peripheral intravenous cannula

Daratumumab is administered as an IV infusion; therefore, it is important to establish that the patient has suitable IV access for frequent insertions of peripheral IV cannulas (PIVCs) and subsequent infusions. If PIVC is not feasible, then alternative venous access will be required. Alternative access devices may include a central venous access device such as a peripherally inserted central catheter, implantable venous port, or tunneled or nontunneled central venous catheter.

#### History of respiratory diseases

Special care needs to be taken for patients with chronic obstructive pulmonary disease (COPD) or chronic asthma. Forced expiratory volume in 1 s (FEV<sub>1</sub>) testing may be required in patients if COPD is suspected. Patients who use inhaled bronchodilators for mild asthma should be advised to bring inhalers with them for the first infusion. For patients with a history of COPD or severe persistent asthma, post-infusion medications such as antihistamines, short- and long-acting bronchodilators, and inhaled corticosteroids should be considered.<sup>[14]</sup>

#### Patient weight

Daratumumab is prescribed by patient's body weight; an accurate baseline weight must be recorded. Weight measurements should be made before each infusion administration and the dose of daratumumab adjusted if there is a 10% change from baseline weight or in accordance with institutional guidelines.

#### Patients should be assessed 1–3 days prior to treatment for the following

##### Pre-existing conditions and comorbidities

Daratumumab is currently approved for use in Australia in patients with relapsed or refractory MM. Therefore, establishing pre-existing disease or treatment-related side effects prior to commencement of daratumumab therapy will ensure accurate assessment of new symptoms or worsening pre-existing symptoms. Common disease or treatment effects may include peripheral neuropathy,

#### Pre-treatment preparations

- Assess patient's veins for peripheral intravenous catheters (PIVC)
- Organize CVAD if PIVC not appropriate
- Assess patient's history of respiratory disease. Carry out forced expiratory volume in one second (FEV<sub>1</sub>) testing if chronic obstructive pulmonary disease (COPD) is suspected.
- Record patient weight
- Establish patient pre-existing conditions and comorbidities
- Ensure patient has had blood typing and has wallet card/medic bracelet with blood profile
- Insert alert into patient medical notes regarding impact of daratumumab on blood typing
- Ensure blood bank has been notified
- Ensure patient has received key information about daratumumab, infusion related reactions (IRRs), pre and post medications and duration and sequencing of treatment
- Check that the patient has completed the consent form
- Check that someone is able to bring the patient to and from the hospital on the day of treatment (for the first cycle of treatment)
- Check that a 10 hour out-patient hematology day therapy chair (and in-patient bed if first infusion) has been booked early in the day and is in a visible location
- Check that all medications have been charted
- Check that pharmacy has reviewed the treatment schedule as per local policy/protocol
- Educate any staff who have not had prior experience with administration of daratumumab

#### Day of treatment

- Check patient medical records and confirm consistent with treatment orders
- Check baseline blood tests have been undertaken
- Check that medication for IRRs is charted and close at hand
- Check that the patient has acquired post-infusion medications
- Carry out patient baseline observations
- Notify the pharmacy and determine the time for daratumumab availability
- Educate patient about pre-medication and IRRs
- Administer pre-medications 1 to 3 hours before daratumumab administration
- Place a sign in a visible location showing the appropriate daratumumab administration start time
- Check contact details of carer, plan for transport home

#### Daratumumab administration

- Make all attending healthcare professionals aware if a patient is undergoing their first infusion and ensure the patient is within a direct line of sight
- Ensure clear daratumumab administration guidelines and infusion rates are readily available
- Ensure that clear IRR assessment and management guidelines are readily available
- Document start time of daratumumab administration
- Record the time, grade and symptoms of any IRRs along with any interventions including timing and response
- Ensure pharmacist/prescriber is aware of any IRRs so that the next dose can be made up appropriately

#### Completion and discharge

- Document the time that the infusion of daratumumab was completed
- Ensure that the patient remains for 2 hours after completion of first treatment
- Cancel in-patient bed if not required after 2 hour observation period
- Explain the post-infusion medication schedule to the patient
- Discuss the possibility of delayed IRRs with the patient, what to look for and who to contact
- Re-emphasize that the patient must carry the blood type wallet card/medic alert bracelet for 6 months after completion of daratumumab
- Ensure that the patient has relevant contact details, check next medical, blood typing and pathology appointments
- Explain subsequent dosing schedule and length of subsequent infusions.

**Figure 1:** Checklist for nurses for the preparation and administration of daratumumab

cytopenia, thrombotic events, gastrointestinal effects, and other comorbidities of older age such as cardiac or respiratory disease or diabetes.

**Blood typing**

Daratumumab gives false-positive results for the IAT; Coombs test. Patients should obtain a baseline red blood cell phenotype 1–3 days prior to starting daratumumab therapy so that blood provided for transfusion is of the correct phenotype. Genotyping may be considered if phenotyping is not possible due to recent transfusion, or if the patient has a positive direct antiglobulin test, or if suitable phenotyping reagents are not available.<sup>[28]</sup> Patients should be supplied with a transfusion card to indicate that they are receiving daratumumab and carry this card throughout the treatment period and for at least 6 months after the treatment ends.<sup>[14,28]</sup> The card should also specify the blood profile (ABO, Rh, and IAT) determined before the first infusion of daratumumab, along with information for health-care providers and blood transfusion departments about the interference of daratumumab with the IAT test. Alternatively, the patient could wear a medic alert bracelet. Patient records should also include an alert that daratumumab treatment may result in a false-positive IAT.

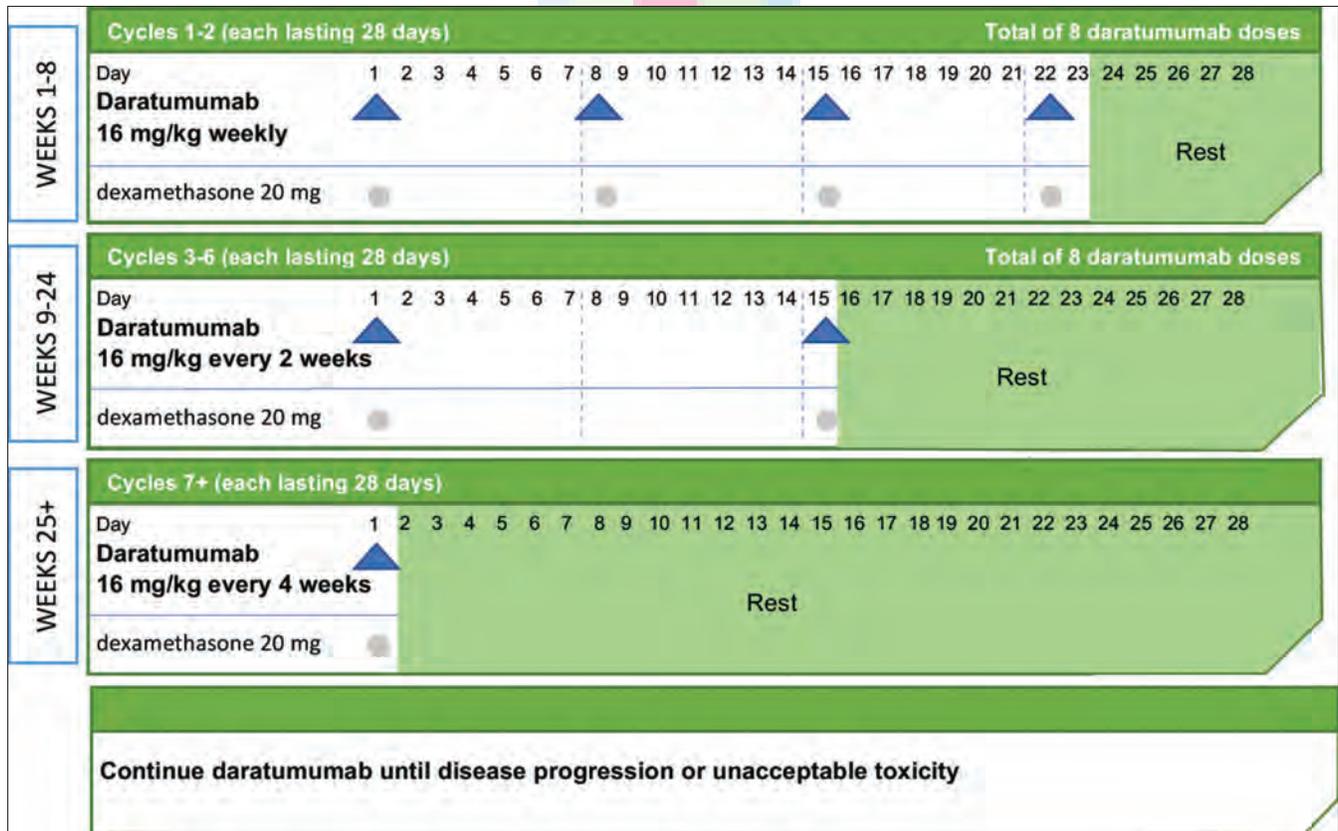
**Patient education (1–3 days prior to starting treatment)**

Health-related information promotes self-care, informs treatment decisions, and improves effectiveness of clinical care.<sup>[29,30]</sup> The treating team need to ensure that they give the patient and their family the relevant information and opportunity to ask questions about daratumumab,

including treatment schedule and likely duration, AEs, and infusion reactions. Patients should be provided with written information to support their learning and understanding. These could be in the form of local information fact sheets, or those provided by third parties such as patient advocacy groups or NPS Medicine Wise or the manufacturer. There is a page at the end of this article that lists key information about the administration of daratumumab that could be given to patients. Patients and their families, where possible, should be provided with time and support to process and understand the information provided, to ask questions, and to facilitate an informed decision. There are various aspects of daratumumab treatment outlined below that need to be explained to the patient.

**Duration and frequency of treatment**

It is important that the sequencing and duration of the treatment is explained. Many patients will have had previous MM treatments that have been administered orally, intravenously, or subcutaneously and need to be made aware of the relatively long infusion time for daratumumab, particularly for the first infusion. Daratumumab monotherapy is administered weekly during the first 8 weeks, every 2 weeks for the following 16 weeks, and monthly thereafter [Figure 2]. The first infusion has a median duration of 7 h, with a median duration of second



**Figure 2:** Dosing schedule for daratumumab monotherapy. On daratumumab infusion days, 20 mg of dexamethasone is given as a pre-infusion medication<sup>[22]</sup>

and subsequent infusions of 4.3 and 3.5 h, respectively.<sup>[22]</sup> This infusion time does not include the time required for premedications or first dose post-infusion monitoring, and the infusion may take longer if there are IRRs. Suggest that the patient brings something to keep them entertained during the infusion time, for example, a book or some music. Having a support person to help with transport to and from the hospital, especially if lengthy infusions are required, can help cut down on associated parking costs.

After the first infusion, it is recommended that the patient waits for 2 h in the unit so that they can be observed for IRRs before they are discharged from the hospital. Ensure that the patient understands that they may need to be admitted to hospital to complete the infusion if an IRR occurs and should be advised to bring an overnight bag with necessities.

#### *Infusion-related reactions*

Patients should be reassured that most IRRs are mild in severity and are manageable. The importance of pre- and post-medications for controlling and limiting IRRs should be explained and written information should be provided on when and how to use them. Check that the patient has a “toolbox” at home for management of IRRs that should include supportive medications such as anti-nausea tablets, anti-diarrheal, antacid/proton pump inhibitors, and thermometer etc. and understands how to contact the treatment center in and out of hours should they experience difficulty.

#### *Combination therapy*

Patients receiving combination therapy should also be given information about the additional medication. Provide patients with written medication schedules, especially if they are receiving daratumumab in combination with other concomitant supportive medication.

#### *Blood typing*

Explain why blood typing is required prior to daratumumab administration and check that the patient has a blood type wallet card or medic alert bracelet. Explain that this should be carried by the patient for up to 6 months after daratumumab treatment is completed.

#### *Supportive care and patient consent form*

Explain to the patient that some of the pre-medications, and daratumumab itself, may cause drowsiness and it is recommended for the first cycle (4 weeks) of treatment that someone brings them to and collects them from the hospital on the day of treatment. Ensure that there are appropriate post-infusion care and support arrangements in place. Ensure that the patient has completed patient consent forms in accordance with local policy, and a patient

assessment questionnaire, as per local assessment practice, for example, pre-treatment symptom assessment, HRQoL, or other patient-reported outcome measures (PROMs).

#### ***Scheduling and capacity management for treatment centers (1–2 weeks prior to starting treatment)***

The first administration of daratumumab can take as long as 10 h (including pre-medication and post-infusion monitoring); therefore, it is necessary to establish if this can be supported in the day unit. The treatment time may be longer than 10 h if there are IRRs. It is recommended that an inpatient bed as well as an outpatient hematology day therapy chair is booked for the first infusion. The hematology day therapy chair needs to be booked so that treatment can start as early as possible in the day. The location of the chair, particularly for the first infusion, is an important consideration; it must be within the line of sight with resuscitation equipment readily accessible.

All medications should be charted including pre- and post-medications and medications to treat IRRs. A review of medication for the treatment schedule should be conducted by the pharmacist as per local policy/protocol. Ensure all paperwork is ready for the treatment to go ahead. Ensure that the pharmacist understands that daratumumab should not be reconstituted until they are notified on the day of infusion that the infusion will proceed. In centers that undertake nurse reconstitution of mAbs, clarification that the patient will proceed with the infusion and the required timing must be ascertained prior to reconstitution.

#### ***Education of relevant hematology oncology staff***

Educate any staff who have not had previous experience using daratumumab and consider mentoring by an experienced nurse for the first infusion. Provide staff with relevant supportive information such as local unit daratumumab administration policy and guidelines, an administration checklist [Figure 1], grading and management of IRRs, and patient treatment schedules. Ensure that the staff are clear about the scheduling order if using a combination of drugs. Figures 2-4 show the dosage regimen for daratumumab monotherapy and in combination with lenalidomide or bortezomib.<sup>[22]</sup>

#### ***Daratumumab treatment***

##### ***Medical records***

Refer to patient medical records for the latest medical/nursing patient care plan and confirm that these are consistent with treatment orders. Check that the patient has obtained the relevant post-infusion supportive medication. Carry out patient baseline observations. Notify the pharmacy and determine the time for daratumumab availability.

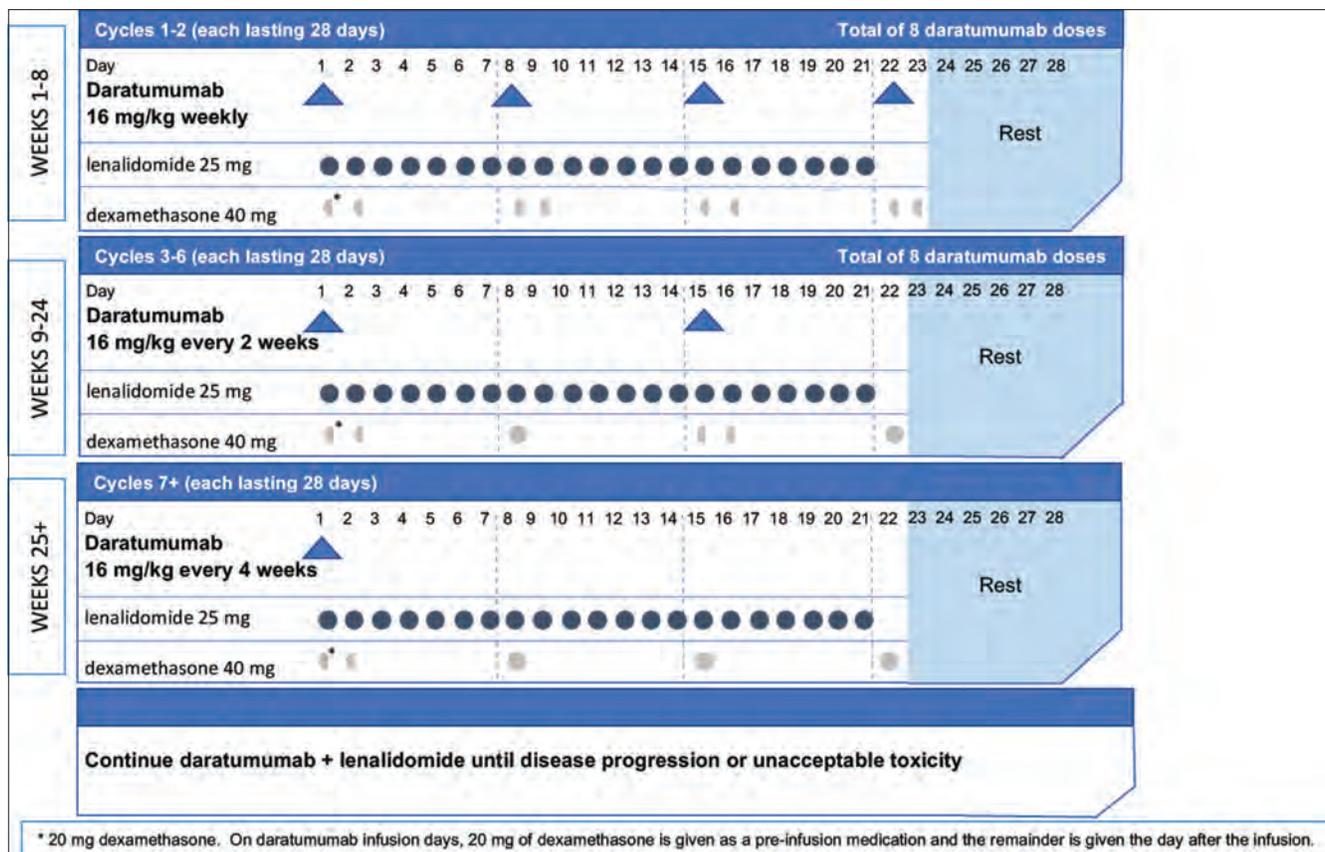


Figure 3: Dosing schedule for daratumumab in combination with lenalidomide<sup>[22]</sup>

### Blood test monitoring

Check baseline blood test results before administration of daratumumab. Monitor blood testing within a treatment cycle according to local policy.

### Patient education

Ensure that the patient has an orientation of the day unit and explain the schedule for the day. Discuss why the pre-medication is being used and that IRRs may occur when daratumumab is administered and ensure that any patient allergies are known and do not contraindicate planned treatment. Reassure the patient that the IRRs are generally mild and occur most frequently during the first infusion. Tell the patient what they should look out for and when to alert the nurse. Explain that a health-care professional will be monitoring the patient during the infusion. Explain that if the patient experiences an IRR, daratumumab treatment may be paused. The earlier an IRR is detected, the shorter the delay to the dose. Earlier detection may reduce the severity of the symptoms and therefore increase the likelihood that the infusion can proceed.

### Pre-medication

To prevent the occurrence of IRRs with daratumumab, the following preinfusion medications must be administered

approximately 1 h and no longer than 3 h prior to every daratumumab infusion.<sup>[22]</sup>

- Corticosteroid

Monotherapy:

Dexamethasone 20 mg should be administered intravenously or an equivalent intermediate- or long-acting corticosteroid for the first two infusions, and 12 mg (oral or IV) dexamethasone thereafter in the absence of IRRs in the first two infusions.

Combination therapy:

Administer 20 mg (oral or IV) dexamethasone prior to every daratumumab infusion.

- Oral antipyretics (paracetamol 500–1000 mg)
- Oral or IV antihistamine (loratadine 10 mg or equivalent).

There is also some evidence that the use of montelukast (a leukotriene receptor antagonist) may also be effective as a preinfusion medication for IRRs.<sup>[30]</sup>

Place a sign on the IV stand or in a visible location showing the start time for appropriate administration of daratumumab. It is important that daratumumab treatment is not started too soon after the administration of premedications as this may increase the risk of an IRR.<sup>[31]</sup>

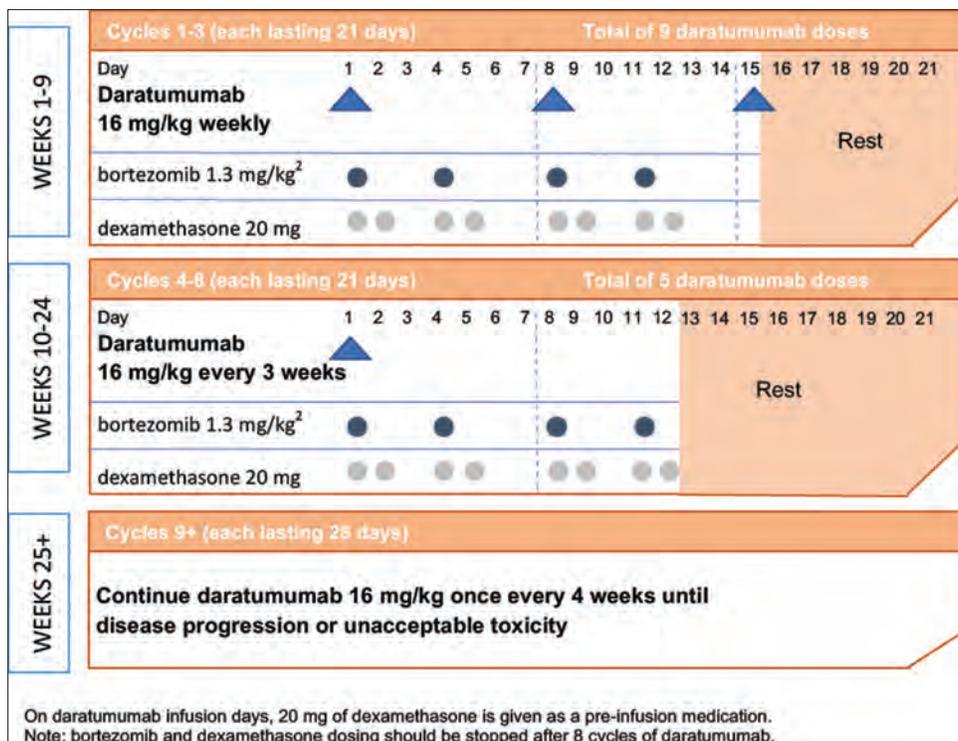


Figure 4: Dosing schedule for daratumumab in combination with bortezomib.<sup>[22]</sup>

### Administration of daratumumab

Ensure that there are clear daratumumab administration guidelines readily available [Table 4]. Daratumumab is administered as an IV infusion, through a well-functioning IV catheter using an infusion set with a flow regulator to control the infusion rate. The infusion solution must be filtered using an inline, sterile, nonpyrogenic, low protein-binding polyethersulfone filter (0.2 µm) during the infusion. If not used immediately, the diluted solution can be stored for up to 24 h at refrigerated conditions (2°C–8°C) and protected from light. Allow the solution to come to room temperature and use immediately as the daratumumab solution does not contain a preservative. The diluted solution should be used within 15 h at room temperature (15°C–25°C) and in room light. Do not infuse daratumumab concomitantly in the same IV line with other agents. Do not store any unused portion of the infusion solution for reuse.<sup>[14,22]</sup>

Following dilution, the daratumumab infusion should be intravenously administered at the appropriate infusion rate which is described below and presented in Table 4.<sup>[22]</sup> Start the administration of daratumumab and document the start time. Remind the patient about potential IRRs. The median time to onset of a reaction is 1.4 h,<sup>[22]</sup> but can occur at any time throughout the infusion. Be aware that there will be a delay before the active drug reaches the patient as it needs to flow from the infusion bag through the tubing to the cannula and patient. All attending health-care professionals

Table 4: Infusion rates for daratumumab administration

First infusion (total volume to be infused: 1000 mL)		Second infusion (total volume to be infused: 500 mL)		Subsequent infusion (total volume to be infused: 500 mL)	
Time (min)	mL/h	Time (min)	mL/h	Time (min)	mL/h
0-60	50	0-60	50	0-60	100
61-120	100	61-120	100	61-120	150
121-180	150	121-180	150	121-180	200
181-240	200	181-	200	181-	200
241-300	200				
301-360	200				
361	200				

Consider incremental escalation of the infusion rate only in the absence of infusion reactions. Median time for the first infusion is 7 h. The median time for the second infusion is 4.3 h. The median time for subsequent infusions is 3.5 h. Adapted from Janssen Darzalex® (daratumumab) patient information<sup>[22]</sup>

should be made aware when a patient is undergoing their first infusion due to the higher risk of an IRR during the first exposure. First time patients should be kept within direct line of sight during initial infusion commencement. An increase in flow rate can also result in IRRs and so it is important that patients are also carefully observed at each increment of flow rate.

### First infusion

Daratumumab is to be diluted in normal saline (NS) to a total volume of 1000 mL by withdrawing a volume of NS equivalent to the volume of daratumumab to be added, prior to adding daratumumab. The infusion should be administered at an initial rate of 50 mL/h. In the absence

of IRRs/hypersensitivity, the rate of the infusion can be escalated in increments of 50 mL/h every 60 min in the first 3 h to a maximum rate of 200 mL/h.

#### Second infusion

If the first infusion of daratumumab was well tolerated by the patient (absence of IRRs with severity NCI CTCAE Grade 2 or above during the first 3 h), then the second infusion will be diluted in 500 mL of NS and administered at an initial rate of 50 mL/h and increased by 50 mL/h increments at 60 min intervals, as tolerated, to a maximum rate of 200 mL/h. If the previous infusion was not well tolerated, then instructions for the first infusion should be used.

#### Subsequent infusions

If the first two infusions of daratumumab were well tolerated by the patient (defined by an absence of IRRs with severity Grade 2 or above during a final infusion rate of  $\geq 100$  mL/h), then subsequent infusions will be diluted in 500 mL of NS and administered at an initial rate of 100 mL/h and increased by 50 mL/h increments at 60 min intervals, as tolerated, to a maximum rate of 200 mL/h. If the previous infusion was not well tolerated, then instructions for the second infusion will be used.

#### Hypertension and hypotension

Hypertension is common in patients with MM and hypertension can occur as an IRR.<sup>[22]</sup> Take regular blood pressure measurements during daratumumab administration. Hypotension is less common but can also occur.

#### Infusion-related reaction and adverse effect management

If IRRs occur despite the implementation of premedications, it is crucial to stop the daratumumab infusion immediately, even if only mild symptoms are detected. The infusion should be stopped until symptoms have resolved. Ensure that clear IRR assessment and management guidelines are readily available.

Tables 2 and 5 outline the grading and infusion administration recommendations for IRRs.<sup>[22,25]</sup> (See Appendix) It is critical to obtain clear and accurate documentation for any IRRs, as this information will enable the clinician to decide whether rechallenge is feasible and safe.<sup>[23]</sup> Nurses must record the time that the IRR occurred and the grade and symptoms of the reaction along with any interventions including timing and response.

The administration of another dose of an antihistamine can be considered; this may shorten the time to restart the infusion and may also result in faster resolution of the symptoms.<sup>[14]</sup> Other medications can be given at the clinician's discretion, for example, non-steroidal anti-inflammatory drugs, narcotics, or IV fluids. Oxygen can

**Table 5: Administration guidelines for infusion commencement after infusion-related reactions<sup>[22]</sup>**

Grade	Management of IRR
Grade 1-2 (mild to moderate)	Once reaction symptoms resolve, the infusion should be resumed at no more than half the rate at which the IRR occurred If the patient does not experience any further IRR symptoms, infusion rate escalation may be resumed at increments and intervals as appropriate up to the maximum rate of 200 mL/h
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, infusion rate escalation may be resumed at increments and intervals as appropriate  The procedure above should be repeated in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction
Grade 4 (life-threatening)	Permanently discontinue daratumumab treatment

IRR: Infusion-related reaction

also be given. It may be worthwhile to have an IRR pack readily available which holds appropriate medication to treat the reactions. Every IRR and every patient is different and it is important to be able to consult a clinician.

Once the symptoms have been resolved, the infusion may be restarted at no more than half the rate during which the IRR occurred. Document the time of symptom resolution and the time and description of infusion commencement. There is an infusion record page at the end of this article that could be used to document key infusion aspects including IRRs. The pharmacist/prescriber must be made aware that an IRR occurred so that the next dose of daratumumab is made up appropriately.

#### Completion of daratumumab treatment and discharge

Document the time that the infusion was completed. If there were IRRs, document the type, grade, and management of the reaction as this will determine the delivery of the second infusion. For the first infusion, the patient should wait for 2 h after the infusion is complete to monitor for late-onset IRRs. The patient is then discharged to home or admitted to a ward with post-infusion medications. We suggest that the booked inpatient bed should not be released until it is confirmed that it is not needed at the end of the 2 h observation period.

#### Post-infusion medications

Oral corticosteroids should be administered to prevent the occurrence of delayed IRRs:<sup>[14,22]</sup>

- Patients receiving daratumumab monotherapy
  - Oral corticosteroid (4 mg dexamethasone or equivalent) should be administered on each of the 2 days following all daratumumab infusions (beginning the day after the infusion).

Patients receiving combination therapy:

- Consider administering  $\leq 4$  mg dexamethasone (or equivalent) the day after daratumumab infusion. However, if a background regimen-specific corticosteroid (e.g. dexamethasone) is administered the day after the daratumumab infusion, additional post-infusion medications may not be needed.

Patients with a history of obstructive pulmonary disease require careful observation and may need additional post-infusion medication, including short- and long-acting bronchodilators and inhaled corticosteroids. These inhaled post-medications may be discontinued after the first four infusions if the patient has not experienced any major IRRs.<sup>[14]</sup>

Patients with MM have an increased risk of developing viral infections, including herpes zoster.<sup>[8,9]</sup> For patients receiving daratumumab, it is recommended that herpes zoster prophylaxis be considered for the prevention of herpes zoster virus reactivation.<sup>[22]</sup> Antiviral prophylaxis should be initiated within 1 week after starting daratumumab and continued for 3 months following completion of treatment.

#### Patient education

Nursing staff need to emphasize the key messages about post-infusion medications, and ensure that the patients and their family members/carers understand the possibility of delayed IRRs and know what symptoms should be reported. Re-emphasize that the patient must carry the blood type wallet card for 6 months following the completion of daratumumab therapy. Nurses should ensure that the patient has the relevant contact details, follow-up medical appointments, blood typing alert card, and any pathology forms required prior to the next infusion. Explain the subsequent dosing schedule and length of the second and subsequent infusions to the patient.

#### Conclusion

Daratumumab is a novel and promising medication for the treatment of patients with RR MM. Ongoing trials are also assessing its safety and efficacy in newly diagnosed patients. The risk of IRRs with daratumumab infusion is well established, and our clinical experience to date is consistent with other findings that the IRRs are largely mild in severity and are manageable. It is important that health-care professionals ensure that patients starting daratumumab are made aware of the duration and scheduling of treatment so that patient expectations can be managed. The practical guidelines outlined in this article will help nurses involved in the administration of daratumumab to improve the treatment experience of patients with MM.

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#### Conflicts of interest

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## Appendix<sup>[22]</sup>

### DARATUMUMAB INFUSION RECORD

FAMILY NAME	MRN
GIVEN NAME	<input type="checkbox"/> Male <input type="checkbox"/> Female
D.O.B.	Tel.
ADDRESS	

Premedication	
Medication details	Time administered

Has the patient experienced any reactions to daratumumab previously?  
YES /NO /NA

### Daratumumab Administration

Date:	Infusion No.:	Total Infusion Volume:	Start Time*:	Finish Time:	
First and Second Infusion			Third and Subsequent Infusions		
Time	Infusion Rate	Signature	Time	Infusion Rate	Signature
	50ml/hr			100 ml/hr	
	100ml/hr			150 ml/hr	
	150 ml/hr			200 ml/hr	
	200 ml/hr				

\*1-3 hours after pre-medication

### IRR Management

	Time infusion stopped	Infusion rate	IRR Grade	Symptoms/Timing of symptom onset	Intervention, timing and patient response	Time of symptom resolution	Time infusion restarted
1							
2							
3							
4							

### Infusion completion\*

Any IRRs	Yes/No	If yes inform pharmacy/prescriber
Patient discharged		
Check that patient has relevant information and post infusion medications**		
Signature		

\*If first infusion then patient is to remain in unit for 2 hours after completion of treatment in order to monitor for late onset IRRs

\*\*Thermometer, dexamethasone. Consider need for: antihistamine, bronchodilators, inhaled steroids

## INFUSION RATES FOR DARATUMUMAB ADMINISTRATION

FIRST INFUSION (Total vol. to be infused 1000ml)		SECOND INFUSION (Total vol. to be infused 500ml)*		SUBSEQUENT INFUSION (Total vol. to be infused 500ml)*	
Time (minutes)	ml/hr	Time (minutes)	ml/hr	Time (minutes)	ml/hr
0-60	50	0-60	50	0-60	100
61-120	100	61-120	100	61-120	150
121-180	150	121-180	150	121-180	200
181-240	200	181-	200	181-	200
241-300	200				
301-360	200				
361-	200				

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

\*Decrease in volume of second and consequent infusion only in absence of infusion reactions

Median time for the first infusion is 7 hours, for the second infusion is 4.3 hours and for subsequent infusions is 3.5 hours.

## GRADING OF INFUSION RELATED REACTIONS<sup>[25]</sup>

Grade	Definition
1	Mild transient reaction; infusion interruption not indicated; intervention not indicated
2	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medication indicated for less than or equal to 24 hours
3	Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae
4	Life-threatening consequences; urgent intervention indicated

## ADMINISTRATION GUIDELINES FOR INFUSION RECOMMENCEMENT AFTER INFUSION RELATED REACTIONS

Grade	Management of IRR
Grade 1-2 (mild to moderate)	Once reaction symptoms resolve, the infusion should be resumed at no more than half the rate at which the IRR occurred.  If the patient does not experience any further IRR symptoms, infusion rate escalation may be resumed at increments and intervals as appropriate up to the maximum rate of 200 ml/hour
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, infusion rate escalation may be resumed at increments and intervals as appropriate.  The procedure above should be repeated in the event of recurrence of Grade 3 symptoms. <u>Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction</u>
Grade 4 (life-threatening)	Permanently discontinue daratumumab treatment

## Patient Information for Daratumumab Infusion\*

(\*Information only to be given to patients who have been prescribed daratumumab)

**What is daratumumab?** Daratumumab is a monoclonal antibody that works in several ways. One way this monoclonal antibody works is by attaching itself to multiple myeloma cells in your body and directly killing them, and/or allowing your immune system to destroy them.

-Depending on where you are in your treatment journey, your doctor may discuss treatment with daratumumab on its own or in combination with other therapy. Your doctor will decide what dose you will receive and the time between doses.

-Daratumumab is administered by a healthcare professional as an intravenous (IV) infusion into your vein in your arm.

### Before treatment:

-The first infusion appointment will take a total of about 10 hours and future infusions will be 3-5 hours. Make sure you bring something with you such as a book, music etc. to keep you occupied.

-A health care provider will administer medicines before each dose of daratumumab to help reduce the risk of infusion related reactions (IRRs). This includes an antihistamine which can make some people feel drowsy. It is a good idea to have someone to bring you to and from the hospital for the first few doses.

### During Treatment:

-Daratumumab will be given intravenously by a health care provider (HCP). Be mindful about how you feel during the infusion and tell your HCP if you think you are having a reaction or about any discomfort you experience as you may be having an infusion related reaction.

-A HCP will monitor you during your infusion. If you do have a reaction the infusion may be paused.

### Common symptoms of infusion related reactions may include:

- Shortness of breath or trouble breathing
- Dizziness or light-headedness (low blood pressure)
- Cough
- Wheezing
- Throat tightness
- Runny or stuffy nose
- Headache
- Itching
- Nausea
- Vomiting
- Chills
- Fever

### After treatment:

-You may be given medicines to lower the chance of delayed infusion related reactions.

-Make sure you talk with your HCP about when you will receive your next infusions and make sure you come for all your infusions and follow up appointments.

-Carry your blood type identification card with you. If you need a blood transfusion it is important to know you have had daratumumab.

### Hospital Contact Details:

Further information about your condition or treatment can be obtained from your healthcare professional.

Daratumumab is manufactured by Janssen-Cilag Pty Ltd, 1-5 Khartoum Rd, Macquarie Park, NSW 2113, Australia