Thames Valley
Strategic Clinical Network

DARATUMUMAB WITH POMALIDOMIDE AND DEXAMETHASONE

INDICATION

Relapsed/refractory multiple myeloma

This combination is not funded by NHS England. Individual funding must be agreed prior to initiation

Key prescribing points:

- Subcutaneous route of administration of daratumumab uses fixed dosing and is the standard of care for patients.
- The intravenous route of administration uses weight-based dosing (Refer to Appendix 1) and can be used in specific clinical scenarios if required, at the clinician discretion.

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&E
   - LFTs
   - Calcium
   - Albumin
   - Uric acid
   - CRP
   - Baseline random blood glucose level
   - Virology: EBV, CMV, Hep B, Hep C, HIV serology
   - Consider annual flu and pneumococcal vaccination pre therapy
   - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins.
   - Serum free light chain assay (Freelite)
   - β_2 microglobulin
   - LDH
   - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury Disctrict Hospita
Salisbury
Wiltshire, SP2 8BJ

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- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- **Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that patient is due to commence Daratumumab. Patient will require red cell phenotyping as cross match fails due to binding of Daratumumab to red cells.**
- Imaging as per NICE/network guidance and clinical presentation

Additional Investigations

- Plasma viscosity if hyperviscosity suspected
- If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology

2. Counselling about risks in pregnancy - There are no human data to inform a risk with use of daratumumab during pregnancy. However, Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment.
3. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given.
4. Fertility - all patients should be offered fertility advice, as appropriate.
5. Hydration - fluid intake of at least 3 litres /day should be attempted.
6. Document patient's height and weight, dose on actual body weight.
7. Document patient's performance status.
8. Treatment must be agreed at the relevant MDT.

REGIMENSPECIFIC PRE-ASSESMENT

1. Ensure patients are given a Patient ID Card for daratumumab and are instructed to carry this for 6 months after stopping treatment.
2. Advise patients to inform their other HCPs that they have received daratumumab, particularly before a transfusion and to show their patient ID card to healthcare professionals that treat them.
3. Obtain written consent for the treatment including signing Celgene Pregnancy Prevention Programme forms.

DRUG REGIMEN

Cycles 1 &2	**Pre-meds**	Montelukast 10mg PO on **(cycle 1 only)** Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 20mg PO (with first daratumumab dose, then can be reduced to 12mg from the second dose onwards)	To be given 1 hour prior to daratumumab Days 1, 8, 15 and 22
	Daratumumab	1800mg (fixed dose) subcutaneously over 3-5 minutes	Days 1, 8, 15 and 22
	Post-infusion	Dexamethasone 4mg mg PO	Days 2,3, 9,10,16,17, 23 and 24 i.e. For two days starting the day after daratumumab to reduce the risk of delayed reactions
	Pomalidomide	4mg PO daily on days 1-21	NOCTE
	Weekly dexamethasone	If >75 years: 20mg total (including dexamethasone pre-med on daratumumab days)	Days 1, 8, 15 and 22
		If ≤75 years: 40mg total (including dexamethasone pre-med on daratumumab days)	Days 1, 8, 15 and 22

Cycles 3 to 6	**Pre-meds**	Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 12mg PO	To be given 1 hour prior to daratumumab Days 1 and 15
	Daratumumab	1800mg (fixed dose) subcutaneously over 3-5 minutes	Days 1 and 15
	Post-infusion	Dexamethasone 4mg PO	Days 2, 3, 16 and 17 i.e. For two days starting the day after daratumumab to reduce the risk of delayed reactions
	Pomalidomide	4mg PO daily on days 1-21	NOCTE
	Weekly dexamethasone	If >75 years: 20mg total (including dexamethasone pre-med on daratumumab days)	Days 1, 8, 15 and 22
		If ≤75 years: 40mg total (including dexamethasone pre-med on daratumumab days)	Days 1, 8, 15 and 22

Cycle 7 onwards	**Pre-meds**	Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 12mg PO	To be given 1 hour prior to daratumumab Days 1 only
	Daratumumab	1800mg (fixed dose) subcutaneously over 3-5 minutes	Days 1 only
	Post-infusion	Dexamethasone 4mg PO	Day 2 and 3 i.e. For two days starting the day after daratumumab to reduce the risk of delayed reactions
	Pomalidomide	4mg PO daily on days 1-21	NOCTE
	Weekly dexamethasone	If > 75 years: 20mg total (including dexamethasone pre-med on daratumumab days)	Days 1, 8, 15 and 22
		If ≤75 years: 40mg total (including dexamethasone pre-med	

		on daratumumab days)	

Additional Post-medications: the use of post-infusion medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur. 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.

CYCLE FREQUENCY
The cycle is repeated every 28 days until disease progression.

DOSE MODIFICATIONS

Haematological

Daratumumab:

No dose adjustments are made for daratumumab

Pomalidomide:

To initiate a new cycle of pomalidomide, ANC ≥ 1.0 x 10^9/L and Platelets ≥ 50 x 10^9/L

Toxicity	Dose Modification
Neutropenia:	
ANC < 0.5 x 10^9/L OR Febrile Neutropenia and ANC < 1.0 x 10^9/L. When ANC return to ≥1 x 10^9/l	Interrupt Pomalidomide, monitor FBC weekly Resume Pomalidomide at 3 mg OD
For each subsequent drop ANC < 0.5 x 10^9/L When ANC ≥ 1.0 x 10^9/L	Interrupt Pomalidomide Resume pomalidomide treatment at one dose level lower than the previous dose.
Thrombocytopenia:	
Platelets < 25 x 10^9/L When Platelets ≥ 50 x 10^9/L	Interrupt Pomalidomide, monitor FBC weekly Resume pomalidomide treatment at one dose level lower than previous dose.
For each subsequent drop Platelets < 25 x 10^9/L When Platelets ≥ 50 x 10^9/L	Interrupt Pomalidomide Resume pomalidomide treatment at one dose level lower than the previous dose.

If toxicities occur after dose reductions to 1 mg, then discontinue Pomalidomide.

Weekly injections of G-CSF can be administered to keep maintain dose intensity (aim to keep neutrophil counts >1.0)

Pomalidomide dosing levels:

Dose level	Oral pomalidomide dose
Starting dose	4mg
Dose level -1	3mg
Dose level -1	2mg
Dose level -1	1mg

Non-Haematological

Daratumumab:

For the management of infusion-related reactions please see section below "Managing Infusion-related reactions".

Pomalidomide

Toxicity	Dose Modification
-Grade 3 or 4 -When resolved to Grade ≤ 2	-Interrupt pomalidomide - Resume pomalidomide treatment at one dose level lower than the previous dose.
-Skin rash G2 or G3 -Skin rash G4 (exfoliative/bullous rash)	-Interrupt or discontinue pomalidomide -Discontinue pomalidomide
Angioedema (all grades)	Discontinue pomalidomide

Renal and Hepatic Impairment

Daratumumab

Renal	Hepatic
No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population PK analyses no dosage adjustment is necessary for patients with renal impairment	No formal studies of daratumumab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment

Pomalidomide

Renal	Hepatic
No dose adjustment required in renal	Avoid if serum bilirubin > 34 umol/L

impairment On haemodialysis days, patients should take pomalidomide following haemodialysis	Careful monitoring is required in hepatic impairment

INVESTIGATIONS – during treatment

- FBC, U&Es, LFTs, Ca^{++}, glucose – every 3 - 4 weeks.
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of treatment and for 3 months afterwards.
- Prophylactic fluconazole 50mg OD.
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Proton pump inhibitor or H2 antagonist at clinician's discretion on days of steroids
- Thromboprophylaxis/anticoagulation see VTE section below.
- Bone protection as per NSSG Bone Protection protocol MM.

EMETIC RISK

Low risk

EXTRAVASATION RISK

Neutral

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Daratumumab:

- **<u>Interference with Serological Testing</u>**
  Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Daratumumab bound to RBCs masks 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.

I. **Blood Transfusion must be notified of this interference with serological testing and Blood Bank must be notified that a patient has received daratumumab.**

II. **Patients must be typed and screened prior to starting daratumumab.**

III. **Important information on safety and risk minimisation of Daratumumab and interference with Blood Compatability Testing can be found of the summary of product characteristics on the following links:**

http://www.medicines.org.uk/emc/RMM.539.pdf
http://www.medicines.org.uk/emc/RMM.545.pdf

IV. Ensure patients are given a Patient ID Card for daratumumab and are instructed to carry this for 6 months after stopping treatment.

V. Ask patients to tell their other HCPs that they have received daratumumab, particularly before a transfusion and to show their patient ID card to healthcare professionals that treat them.

- **Interference with Determination of Complete Response**

  Daratumumab is a human IgG kappa monoclonal antibody detectable on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in all patients with IgG kappa myeloma. On an adhoc basis DIRA assay (removes interference) can be organised through Janssen if required.

- **Risk of reactivation of hepatitis B virus (MHRA 2019):**

  Hepatitis B virus reactivation has been reported in patients treated with daratumumab, including several fatal cases worldwide

  All patients must be screened for hepatitis B virus before initiation of daratumumab; patients with unknown serology who are already on treatment should also be screened

  Monitoring is required for patients with positive serology for clinical and laboratory signs of hepatitis B reactivation during treatment, and for at least 6 months following the end of daratumumab treatment

  Patients with positive serology need to be advised to seek medical help immediately if they experience signs and symptoms suggestive of hepatitis B virus reactivation

  Treatment with daratumumab should be stopped in patients with hepatitis B virus reactivation; appropriate treatment needs to be instituted in consultation with experts in the treatment of hepatitis B virus infection; consult with experts before resuming daratumumab in patients with adequately controlled viral reactivation

  Suspected adverse drug reactions associated with daratumumab need to be reported to the

Yellow Card Scheme

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

- **Infusion reactions with subcutaneous daratumumab:**

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

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

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

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

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

  Managing Infusion related reactions from intravenous daraumumab:
  Please consult Appendix 1 of this document

- **Other common adverse effects:** Fatigue, allergic rhinitis, pyrexia, nasopharyngitis, URTI, cough, GI disorders (nausea, constipation, diarrhoea), headache, neutropenia and hypertension have also been reported. The most common serious adverse reactions were pneumonia, and pyrexia.

Pomalidomide:

- Venous thromboembolism (VTE): There is an increased risk of thrombosis with lenalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:

  1. Prophylactic low-molecular weight heparin OR

2. Prophylactic NOAC e.g. apixaban 2.5mg bd (check product specific information)

Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for higher-risk patients with additional risk factors.

If VTE occurs, lenalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.

- Fatigue, dizziness and confusion
- Peripheral neuropathy, diarrhea/constipation, pneumonia, peripheral oedema.
- Risks of cardiac failure, interstitial lung disease and hepatotoxicity: There is a published MHRA drug alert (2015) on pomalidomide and risks of cardiac failure, interstitial lung disease and hepatotoxicity. See weblink: https://www.gov.uk/drug-safety-update/pomalidomide-imnovid-risks-of-cardiac-failure-interstitial-lung-disease-and-hepatotoxicity.

TREATMENT RELATED MORTALITY

<5%

REFERENCES

1. Ajai Chari, Attaya Suvannasankha, Joseph W. Fay, Bertrand Arnulf, Jonathan L. Kaufman, Jainulabdeen J. Ifthikharuddin, Brendan M. Weiss, Amrita Krishnan, Suzanne Lentzsch, Raymond Comenzo, Jianping Wang, Kerri Nottage, Christopher Chiu, Nushmia Z. Khokhar, Tahamtan Ahmadi, and Sagar Lonial (2017). Daratumumab Plus Pomalidomide and Dexamethasone in Relapsed and/or Refractory Multiple Myeloma. *Blood,* 13 (8): 974-981
2. Darzalex ® (Daratumumab), eMC UK Summary of Product Characteristics for Janssen,02 July 2019
3. Darzalex ® 1800mg solution for SC injection, eMC UK Summary of Product Characteristics for Janssen,28 July 2020
4. Imnovid® (Pomalidomide), eMC UK Summary of Product Characteristics for Janssen,02 May 2019
5. MHRA drug alert 2019: https://www.gov.uk/drug-safety-update/daratumumab-darzalex-risk-of-reactivation-of-hepatitis-b-virus

Name	Revision	Date	Version	Review date
Faouzi Djebbari (Haematology Pharmacist)	New protocol	September 2019	1.0	September 2020
Faouzi Djebbari (Haematology Pharmacist)	Addition of MHRA drug alert	October 2019	1.1	June 2020
NSSG Myeloma Group	Addition of SC option for daratumumab	Aug 2020	1.2	June 2021
Quality manager	Nursing care plan added	May 2021	1.3	June 21

REVIEW

Appendix 1: intravenous daratumumab:

There may be a need to arrange patient admission with the first infusion of intravenous daratumumab, where an extended duration of infusion is anticipated due to potential infusion-related reactions. Some day units are able to accommodate Cycle 1 Day 1, thus avoiding admission. Alternatively, to facilitate administration in the outpatient setting, 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

From cycle 2 onwards, patients may qualify for rapid rate intravenous infusion. See MM.48 (Daratumumab Rapid Rate Infusion) for further information.

DRUG REGIMEN

Cycles 1 &2	**Pre-meds**[b]	Paracetamol 1g PO, Montelukast 10mg PO on **(cycle 1 only)** Chlorphenamine 10 mg IV, Dexamethasone 20mg IV bolus or PO (give IV prior to the first infusion) (can be reduced to 12mg IV bolus or PO following the second infusion)	To be given 1 hour prior to daratumumab infusion
	Daratumumab[a]	16mg/kg Intravenous infusion	Days 1, 8, 15 and 22
	Post-infusion[c]	Dexamethasone 4mg mg PO	Days 2,3, 9,10,16,17, 23 and 24 i.e. For two days starting the day after daratumumab infusion to reduce the risk of delayed infusion reactions
	Pomalidomide	4mg PO daily on days 1-21	NOCTE
	Weekly dexamethasone	If >75 years: 20mg total (including dexamethasone pre-med on daratumumab days)	Days 1, 8, 15 and 22
		If ≤75 years: 40mg total (including dexamethasone pre-med on daratumumab days)	Days 1, 8, 15 and 22
	Pre-meds	Paracetamol 1g PO, Chlorphenamine 10 mg IV, Dexamethasone 12mg IV bolus or PO	To be given 1 hour prior to daratumumab infusion
	Daratumumab	16mg/kg Intravenous infusion	Days 1 and 15

Cycles 3 to 6			
	Post-infusion	Dexamethasone 4mg PO	Days 2, 3, 16 and 17 i.e. For two days starting the day after daratumumab infusion to reduce the risk of delayed infusion reactions
	Pomalidomide	4mg PO daily on days 1-21	NOCTE
	Weekly dexamethasone	If >75 years: 20mg total (including dexamethasone pre-med on daratumumab days)	Days 1, 8, 15 and 22
		If ≤75 years: 40mg total (including dexamethasone pre-med on daratumumab days)	Days 1, 8, 15 and 22
Cycle 7 onwards	**Pre-meds**	Paracetamol 1g PO, Chlorphenamine 10 mg IV, Dexamethasone 12mg IV bolus or PO	To be given 1 hour prior to daratumumab infusion
	Daratumumab	16mg/kg Intravenous infusion	Day 1 only
	Post-infusion	Dexamethasone 4mg PO	Day 2 and 3 i.e. For two days starting the day after daratumumab infusion to reduce the risk of delayed infusion reactions
	Pomalidomide	4mg PO daily on days 1-21	NOCTE
	Weekly dexamethasone	If > 75 years: 20mg total (including dexamethasone pre-med on daratumumab days)	Days 1, 8, 15 and 22
		If ≤75 years: 40mg total (including dexamethasone pre-med on daratumumab days)	

[a]: On the first week of cycle 1, there is an option to administer daratumumab as a split dose at 8mg/kg intravenous infusion, on days 1 and 2 of the first week

[b]: If daratumumab on the first week of therapy is administered as a split dose (8mg/kg days 1 and 2), the same pre-meds given on day 1 must also be given on day 2. Dexamethasone dose given as part of pre-meds on days 1 and 2 of the first week must be kept at 20mg

[c]:If daratumumab on the first week of therapy is administered as a split dose (8mg/kg days 1 and

2), post-infusion dexamethasone must be given at 4mg on day 3 only

Additional Post-medications: the use of post-infusion medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur. 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.

Split dosing of the first dose of daratumumab:

On the first week of cycle 1, there is an option to administer daratumumab as a split dose at 8mg/kg intravenous infusion, on days 1 and 2 of the first week
If daratumumab on the first week of therapy is administered as a split dose (8mg/kg days 1 and 2), the same pre-meds given on day 1 must also be given on day 2. Dexamethasone dose given as part of pre-meds on days 1 and 2 of the first week must be kept at 20mg

Additional Post-medications:

The use of post-infusion medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur. 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.

INFUSION RATES

Administer via an infusion set equipped with a 0.2 µm in-line filter at the appropriate infusion rate. Consider incremental escalation of the infusion rate only in the absence of infusion reactions with the previous infusion.

	Dilution volume (Sodium chloride 0.9%)	**Initial rate (first hour)**	**Rate increment** [a]	**Maximum rate**
First week[a]	Option 1 (full dosing 16mg/kg) C1D1; 1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
	Option 2 (split dosing 8mg/kg) C1D1: 500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
	Option 2 (split dosing 8mg/kg) C1D2: 500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second week[b]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour

Third and subsequent weeks[c]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions. **There is an option to administer daratumumab as a split dose at 8mg/kg intravenous infusion, on days 1 and 2 of the first week**
[b] A dilution volume of 500 mL should be used only if there were no ≥ Grade 1 IRRs during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.
[c] A modified initial rate for subsequent infusions (i.e. third infusion onwards) should only be used only if there were no ≥ Grade 1 IRRs during a final infusion rate of ≥ 100 mL/hr in the first two infusions. Otherwise, use instructions for the second infusion.

Notes:

1. For guidance on infusion rates **in the case of infusion related reactions**. See the managing infusion reactions section below.
2. From *cycle* 2 onwards, patients may qualify for rapid rate infusion. See MM.48 (Daratumumab Rapid Rate Infusion) for further information. Rapid Rate infusion is currently unlicensed.

Infusion-related reactions:

- Daratumumab can cause severe infusion-related reactions (IRR). Approximately half of all patients treated have experienced a reaction, the majority of IRRs occur at the first infusion. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing daratumumab. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion.
- Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, and hypertension. Signs and symptoms may include respiratory symptoms, such as cough, wheezing, larynx and throat tightness and irritation, laryngeal oedema, pulmonary oedema, nasal congestion, and allergic rhinitis. Less common symptoms were hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, and chills.
- Pre-meds must be given 1 hour before the infusion. Patients must be monitored during the entire infusion.
- To reduce the risk of delayed infusion reactions, corticosteroids are given to all patients on the first and second day after all infusions
- Patients with a history of obstructive pulmonary disorders may require additional post-infusion medications to manage respiratory complications. Consider prescribing short-and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders**.**
- **<u>Managing Infusion related reactions</u>**
  For infusion reactions of any grade/severity, immediately interrupt the infusion and manage symptoms. The infusion rate should be reduced when re-starting the infusion as outlined

below. Management of infusion reactions may further require treatment discontinuation as outlined below.

IRR grade	Recommendation
Grade 1-2 (mild to moderate)	Once symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate up to the maximum rate of 200 mL/hour.
Grade 3 (severe)	Once 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. Permanently discontinue treatment upon the third occurrence of a Grade 3 or greater reaction.
Grade 4 (life threatening)	Permanently discontinue treatment.

Nursing Care Plan: Daratumumab with Pomalidomide and Dexamethasone

Indication: Relapsed/refractory Myeloma.

Frequency: Cycles are repeated every 28 days until disease progression.

Alopecia: No.

On cycle 1 day 1 send phenotyping bloods to the Transfusion Lab prior to Daratumumab infusion – send 3x EDTA tubes, all labelled with Safe Tx in a cross match sample bag, marked for the attention of a BMS 7. These bloods can be signed for on Aria once the sample has been sent. Please call the transfusion lab to let them know that phenotyping bloods are being sent because the patient is going to commence Daratumumab. Patient will require red cell phenotyping as cross match fails due to binding of Daratumumab to red cells.

DARATUMUMAB: Monoclonal human antibody.

Administration: Sub cutaneous injection in the abdomen, approximately 7.5cm either side of the naval. Daratumumab is not approved to be given in any other injection sites.

IV infusion is available in a small minority of circumstances; SC administration is the standard of care.

Cycles 1-2 Daratumumab given on days 1, 8, 15 and 22.

Cycles 3-6 Daratumumab given on day 1 and 15.

Cycle 7 onwards Daratumumab given on day 1 (28 day cycle).

Emetic risk: Minimal.

Classification of extravasation: Neutral.

Side effects: Fatigue, bone marrow depression, thrombocytopenia, risk of infection, diarrhoea, constipation, anaemia.

Dosing reactions: Cough, fever, nasal irritation, wheezing, bronchospasm, hypotension, laryngeal and facial oedema, and urticaria/itching, anaphylaxis.

Reactions rarely occur after the first dose. **Patients are required to remain on the unit for 4 hours following Daratumumab injection on C1D1**. No observation period is necessary for subsequent injections.

Premeds are given 1-3 hours prior to Daratumumab, patients usually take these in advance from their TTO's after C1D1.

POMALIDOMIDE: Immunomodulator and angiogenesis inhibitor.

Administered orally at night on **days 1-21 of all cycles.**

Emetic risk: Low

Side effects: VTE, fatigue, dizziness and confusion, peripheral neuropathy, diarrhoea/constipation, pneumonia, peripheral oedema. Risks of cardiac failure, interstitial lung disease and hepatotoxicity.

DEXAMETHASONE: corticosteroid tablets

Administered orally on the day of each Daratumumab dose and 2 days after. Taken with or after food preferably at breakfast.

Dexamathasone also acts as a premed and needs to be given at least 1 hour pre Daratumumab.

Side effects: restlessness, insomnia, mood changes, gastritis, hyperglycaemia, increased appetite, fluid retention, weight gain, immunosuppression.

Regime Specific Considerations

- Bloods are required (including glucose) at the start of each cycle. Patients with unstable blood counts may require more frequent monitoring.
- Pregnancy test for pre-menopausal women under the age of 55 before the start of each cycle.
- Advise patients to maintain a fluid intake of 2-3 litres and avoid dehydration through the prompt management of diarrhoea and nausea/vomiting.
- Assess for presence of peripheral neuropathy before starting treatment and **prior to the start of each cycle.**
- Ensure patients have been given a Patient ID Card for Daratumumab and are instructed to carry this for 6 months after stopping treatment; please check with Myeloma CNS team.
- Inject the SC dose of Daratumumab (15 mL) into the abdomen approximately 7.5 cm to the right or left of the navel over 5 minutes. Rotate injection sites for each dose. If the patient experiences pain or discomfort the injection can be paused. If necessary the remainder of the injection can be given on the other side of the abdomen.
- Advise patients to maintain fluid intake of 2-3 litres a day and avoid dehydration through the prompt management of diarrhoea and nausea/vomiting.
- **IV Daratumumab only** - administer via an infusion set equipped with a 0.2 µm in-line filter at the appropriate infusion rate. Rapid rate can be given from cycle 2 as long as there has been no reaction to the previous dose and this was given in 500mls rather than 1 litre of fluid. Montelukast needs to be given before the first rapid rate infusion.
- Montelukast is given as a premed pre SC/IV Daratumumab on C1 only.