DARATUMUMAB WITH BORTEZOMIB AND DEXAMETHASONE (DVd)

INDICATION[a]

Relapsed multiple myeloma in adults who have received only one prior line of therapy[b] which included treatment with lenalidomide, or lenalidomide is unsuitable for 2nd line therapy [NICE TA897].

[a] This indication is not funded for amyloidosis patients (except for patients who have a proven diagnosis of myeloma with an associated diagnosis of amyloidosis)

[b] Exception permitted for patients who commenced the interim COVID-19 option of ixazomib, lenalidomide and dexamethasone as second line therapy.

Patients should not have received previous treatment with Daratumumab or an anti-CD38 antibody unless they have been previously treated with daratumumab in which case the patient must have received the daratumumab as part of induction therapy pre-transplant and must have responded to that daratumumab-containing combination [Blueteq criteria].

Blueteq approval required.

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

Ensure all the following staging investigations are done:

- FBC & film
- Clotting screen
- U&Es, LFTs, Calcium
- Albumin
- Uric acid
- ECG & Transthoracic echocardiogram to assess LV function if clinically indicated.
- Virology: HIV, Hepatitis B (including core antibody), and Hepatitis C
- Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
- Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
- Serum free light chain assay (Freelite)
- Transfusion assays add
- β_2 microglobulin
- 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 Genetics Laboratory (address below).
- Imaging as per NICE/network guidance and clinical presentation
- Bone marrow aspirate and trephine (with immunophenotyping for kappa/lambda if appropriate)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury Disctrict Hospital

Salisbury
Wiltshire
SP2 8BJ

Additional investigations:

1. Plasma viscosity if hyperviscosity suspected.
2. 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.
3. Fertility - all patients should be offered fertility advice, as appropriate.
4. Hydration - fluid intake of at least 3 litres /day should be attempted.
5. Document patient's height and weight, dose on actual body weight.
6. Document patient's performance status
7. Treatment must be agreed at the relevant MDT.
8. Annual flu vaccination, Covid-19 vaccination/boosters and pneumococcal vaccination (5 yearly boosters) pre-treatment.

REGIMEN SPECIFIC PRE-ASSESMENT

1. 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 after the first trimester of pregnancy. Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment.
2. Evaluate for presence of neuropathy prior to starting bortezomib. This is usually done by clinical assessment although nerve conduction studies may be useful in occasional patients to document the extent of neurological damage prior to treatment with bortezomib. Baseline clinical assessment must be documented in the notes before the first dose of bortezomib is prescribed.
3. Baseline lying and standing blood pressure should be recorded.
4. **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.**

DRUG REGIMEN

Note there are 2 schedules described for cycles 1 – 8 of treatment, of which the twice weekly schedule includes 32 total doses of bortezomib and weekly schedule 24 doses.

1. **ONCE weekly bortezomib**
2. **TWICE weekly bortezomib**

Switching between regimens mid-treatment to manage toxicity can cause confusion if the correct aria regimen is not activated. Note the once weekly regimen is set up as a non-pathway regimen and you will be requested to justify the reasoning for switching, of which Grade 2 or 3 neuropathy is an option.

The subcutaneous route of administration is routinely recommended. IV infusion remains an option for specific clinical scenarios (see Appendix 1).

Please always prescribe with the correct aria regimen, especially where decisions to adjust schedule mid-treatment to avoid prescribing/dosing errors.

1. ONCE weekly bortezomib

Consider if poor performance status, existing neuropathy or Grade 2/3 neuropathy during treatment.

Dexamethasone serves several functions in this protocol; it is used as the steroid component of the triple combination regime and has dual function as prophylaxis against immediate and delayed daratumumab infusion reactions when administered pre- and 24 hours post-injection.

Cycles 1 to 3 – 21-day cycle

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Cycle 1 only - Montelukast 10mg Chlorphenamine 4mg Dexamethasone 20mg	1, 8 and 15	Oral 1 hour prior to daratumumab
Daratumumab	1800mg fixed dose	1, 8 and 15	Subcutaneous
Bortezomib	1.3 mg/m^2	1, 8 and 15	Subcutaneous
Dexamethasone	20 mg once daily	2, 9 and 16	Oral With food, in morning

Cycles 4 to 8 – 21-day cycle

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Chlorphenamine 4mg Dexamethasone 12-20mg	1	Oral 1 hour prior to daratumumab
Daratumumab	1800mg fixed dose	1	Subcutaneous
Bortezomib	1.3 mg/m^2	1, 8 and 15	Subcutaneous
Dexamethasone	20mg once daily	2, 8, 9, 15 and 16	Oral With food, in morning

Cycles 9 onwards – 28-day cycle

N.B. This component will need to be prescribed as a new regimen (Daratumumab SC Bortezomib Dexamethasone (cycle 9 onwards)) on aria.

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Chlorphenamine 4mg Dexamethasone 12mg	1	Oral 1 hour prior to daratumumab
Daratumumab	1800mg fixed dose	1	Subcutaneous

Dexamethasone	4mg once daily	2 and 3	Oral With food, in morning

2. TWICE weekly bortezomib

Dexamethasone serves several functions in this protocol; it is used as the steroid component of the triple combination regime and has dual function as prophylaxis against immediate and delayed daratumumab infusion reactions when administered pre- and 24 hours post-injection.

Cycles 1 to 3 – 21-day cycle

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Cycle 1 only - Montelukast 10mg Chlorphenamine 4mg Dexamethasone 20mg	1, 8 and 15	Oral 1 hour prior to daratumumab
Daratumumab	1800mg fixed dose	1, 8 and 15	Subcutaneous
Bortezomib	1.3 mg/m^2	1, 4, 8 and 11	Subcutaneous
Dexamethasone	20 mg once daily	2, 4, 5, 9, 11, 12	Oral With food, in morning
Dexamethasone	4 mg once daily	16, 17	Oral With food, in morning

Cycles 4 to 8 – 21-day cycle

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Chlorphenamine 4mg Dexamethasone 20mg	1	Oral 1 hour prior to daratumumab
Daratumumab	1800mg fixed dose	1	Subcutaneous
Bortezomib	1.3 mg/m^2	1, 4, 8 and 11	Subcutaneous
Dexamethasone	20 mg once daily	2, 4, 5, 8, 9, 11, 12	Oral With food, in morning

Cycles 9 onwards – 28-day cycle

N.B. This component will need to be prescribed as a new regimen (Daratumumab SC Bortezomib Dexamethasone (cycle 9 onwards)) on aria.

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Chlorphenamine 4mg Dexamethasone 12mg	1	Oral 1 hour prior to daratumumab
Daratumumab	1800mg fixed dose	1	Subcutaneous
Dexamethasone	4mg once daily	2 and 3	Oral With food, in morning

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CYCLE FREQUENCY

Cycles 1 to 8 - every 21 days

Cycles 9 onwards (maintenance) - every 28 days until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS

Haematological toxicity:

Daratumumab	• No dose reduction. • Consider dose delay in G3 thrombocytopenia with bleeding, or G4 haematological toxicity to allow count recovery. • Monitor neutropenic patients for signs of infection.
Bortezomib	• G4 haematological toxicity – withhold treatment. • Once resolved, re-initiate at 25% reduced dose (e.g., 1.3 mg/m^2 → 1.0 mg/m^2; 1.0 mg/m^2 → 0.7 mg/m^2). • If the toxicity is not resolved or if it recurs at the lowest dose, discontinue unless benefit outweighs risk.

Non-Haematological toxicity* (for PN, renal and hepatic see specific section):

Daratumumab	• Monitor patients for signs of infection.
Bortezomib	• Any G3 toxicity – discuss with consultant if necessary to withhold treatment. • Once resolved, re-initiate at 25% reduction (1.3 mg/m^2 reduced to 1.0 mg/m^2; 1.0 mg/m^2 reduced to 0.7 mg/m^2). If the toxicity is not resolved or if it recurs at the lowest dose, discontinue unless benefit outweighs risk.

*Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Peripheral neuropathy:

Patients with pre-existing severe neuropathy may be treated with bortezomib only after careful risk/benefit assessment.

	Severity (CTCAE Grade)	Recommendation
Bortezomib	Grade 1 with no pain or loss of function	No adjustment.
	Grade 1 with pain or Grade 2	Reduce to 1.0 mg/m^2 or change treatment schedule to 1.3mg/m^2 once per week if patient currently on twice weekly.
	Grade 2 with pain or Grade 3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7 mg/m^2 once weekly.
	Grade 4 and/or severe autonomic neuropathy	Discontinue

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.

Bortezomib	
Renal	**Hepatic**
No dose reduction necessary. For dialysis patients, bortezomib should be given after dialysis. It is unclear whether baseline kidney dysfunction influences the risk of bortezomib-related renal adverse events.	Bilirubin 1.0 - 1.5 x ULN: No dose reduction required. Bilirubin > 1.5 x ULN: Reduce to 0.7 mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m^2 or further reduction to 0.5 mg/m^2 in subsequent cycles based on tolerability.

INVESTIGATIONS – during treatment

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle
- FBC, U&Es, LFTs, Ca^{++}, glucose – every 3 - 4 weeks.
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle of bortezomib.
- Blood pressure (consider checking for postural drop if symptomatic)
- Ig's, paraprotein, usually monthly after first 2 months, Freelite assay if appropriate.
- Consider bone marrow assessment after four cycles for non-secretory Myeloma.
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance.

CONCURRENT MEDICATIONS

- ***Cycle 1 only -*** allopurinol 300 mg daily for 7 days.
- Aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of therapy and for 3 months after the completion of bortezomib.
- Fluconazole 50mg OD.
- H2 antagonist or proton pump inhibitor at clinician's discretion.
- Consider co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- For patients deemed at very high risk of infections only: Consider prophylactic levofloxacin 500mg OD for 12 weeks (cycles 1-4). Beware that levofloxacin and other Fluoroquinolones can cause disabling and potentially long-lasting or irreversible side effects and their risks/benefits should be considered before use. See MHRA warning here. Adjust dose for renal function.
- Bone protection as per NSSG Bone Protection protocol MM.3
- Consider use of loperamide if required for the management of transient diarrhoea.

INTERACTIONS

Patients on bortezomib should be closely monitored if taking concurrent CYP3A4 inhibitors (e.g., ketoconazole, ritonavir), or CYP3A4-inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, and St John's Wort).

Use caution with medicines that may worsen symptoms of postural hypotension e.g., diuretics, blood pressure medication etc.

EMETIC RISK

Low risk.

EXTRAVASATION RISK

Daratumumab - Neutral

Bortezomib - Irritant

ADVERSE EFFECTS/REGIEMN SPECIFIC COMPLICATIONS

The most common adverse events are thrombocytopenia, neutropenia, anaemia, upper respiratory tract infections, pneumonia, diarrhoea, peripheral neuropathy, fatigue, cough, constipation and infusion reactions.

Interference with serological testing

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 dose. 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 Lab 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 Compatibility Testing can be found on the summary of product characteristics (www.medicines.org.uk)

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.

Risk of reactivation of hepatitis B virus (MHRA alert 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.

Infusion reactions with subcutaneous injection:

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.

Peripheral neuropathy:

Patients should be advised to report pain, hypersensitivity, prickling, numbness, and paraesthesia. If these occur, consider dose reduction. Consider use of amitriptyline, gabapentin/pregabalin and pain team referral. Local neuropathy assessment tools should be utilised. *Use caution in patients with existing peripheral neuropathy.*

Dizziness and orthostatic hypotension:

Patients should be advised that Bortezomib may cause orthostatic hypotension and that they should sit upright for a few minutes prior to standing up from a recumbent position. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells. *Caution in patients with history of syncope*, *receiving medications associated with hypotension and patients who are dehydrated.*

Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of fludrocortisone and/or sympathomimetics. Patients who experience dizziness or low blood pressure may benefit from 500ml intravenous 0.9% sodium chloride with each dose of bortezomib.

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.

Other side effects:
Fatigue, allergic rhinitis, pyrexia, nasopharyngitis, URTI, cough, GI disorders (nausea, constipation, diarrhoea), headache, neutropenia and hypertension have also been reported.

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REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche Cancer Pharmacist	New protocol	Dec ‘17	1.0	Dec ‘19
Network Protocol Review	Investigations. Concurrent medication. Adverse events	Jun ’18	1.1	June 2020
Faouzi Djebbari Haematology Pharmacist	CDF approval, daratumumab split dosing, infusion table, references	April ‘19	2.0	June 2020
Network Protocol Review 2019	Update of indications, regimen-specific pre-assessment, drug regimen, infusion rates, concurrent medication, adverse effects and references	Jun ‘19	2.1	June 2020
Faouzi Djebbari Haematology Pharmacist	Addition of MHRA drug alert	Oct ’19	2.2	June 2020
Faouzi Djebbari Haematology Pharmacist	Addition of SC daratumumab option during the COVID-19 pandemic	May ‘20	2.4	June 2021
Faouzi Djebbari Haematology Pharmacist	Time of pre-meds updated	June ‘20	2.5	June 2021
Faouzi Djebbari Haematology Pharmacist	Significant update with standard SC daratumumab	June ‘20	3.0	June 2021
NSSG Myeloma Group	Annual myeloma protocol review and update	Oct ‘20	3.1	June 2021
NSSG Myeloma Group	Update to name of weekly schedule	Jan ‘21	3.2	June 2021
Quality Manager	Nursing care plan added	May ’21	3.3	June 2021
NSSG Myeloma Group	2021 Annual Protocol Review	June ’21	3.4	June 2022
NSSG Myeloma Group	Updated concurrent medication section	Nov ‘22	3.5	June 2023
NSSG Myeloma Group	NICE TA publication. Major formatting update. Minor corrections.	June ‘23	4.0	June 2025

APPENDIX 1:

DARATUMUMAB (IV)

Cycle 1, first dose logistics:

Consider arranging inpatient admission for the first infusion of intravenous daratumumab as long infusion timeframe is anticipated due to infusion-related reactions.

Some day treatment units can accommodate the first dose, thus avoiding admission – check locally. To help facilitate administration in the outpatient setting, the first prescribed dose may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively

In this regimen post-daratumumab dexamethasone is used for prevention of delayed infusion reactions. On daratumumab weeks, pre- and post- infusion dexamethasone also being used as the weekly steroid component of the triple combination regimen.

In the absence of infusion reactions dexamethasone may be reduced in the elderly, or in those with poor steroid tolerance.

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.

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

Cycles 1 to 3 – 21-day cycle

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Cycle 1 only - Montelukast 10mg Chlorphenamine 4mg Dexamethasone 20mg	1, 8 and 15	Oral 1 hour prior to daratumumab
Daratumumab	16 mg/Kg	1, 8 and 15	Intravenous Infusion
Bortezomib*	1.3 mg/m^2	1, 4, 8 and 11	Subcutaneous
Dexamethasone	20 mg once daily	2, 4, 5, 9, 11, 12	Oral With food, in morning
Dexamethasone	4 mg once daily	16, 17	Oral With food, in morning

Cycles 4 to 8 – 21-day cycle

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Chlorphenamine 4mg Dexamethasone 20mg	1	Oral 1 hour prior to daratumumab

Daratumumab	16 mg/Kg	1	Intravenous Infusion
Bortezomib*	1.3 mg/m^2	1, 4, 8 and 11	Subcutaneous
Dexamethasone	20 mg once daily	2, 4, 5, 8, 9, 11, 12	Oral With food, in morning

Cycles 9 onwards – 28-day cycle

N.B. This component will need to be prescribed as a new regimen (Daratumumab SC Bortezomib Dexamethasone (cycle 9 onwards)) on aria.

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Chlorphenamine 4mg Dexamethasone 12mg	1	Oral 1 hour prior to daratumumab
Daratumumab	16 mg/Kg	1	Intravenous infusion
Dexamethasone	4mg once daily	2 and 3	Oral With food, in morning

*Bortezomib can also be administered weekly on days 1, 8 and 15 in a 21-day cycle, in selected patients where twice-weekly schedule is not appropriate

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INFUSION RATES

Administer via an infusion set equipped with a 0.2 micron 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**	**Maximum rate**
First infusion	Option 1: Full dose of 16mg/Kg on C1D1 1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
	Option 2: Split dose of 8mg/Kg on **C1D1** 500mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
	Option 2: Split dose of 8mg/Kg on **C1D2** 500mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

[a] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion. Otherwise use instructions for the first infusion.

[b] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥ 100mL/hr in the first two infusions. Otherwise use instructions for the second infusion.

For guidance on infusion rates **in the case of infusion related reactions**. See the managing infusion reactions section below.

INFUSION REACTIONS

Daratumumab can cause severe infusion-related reactions (IRR). Approximately half of all patients treated have experienced a reaction, most during 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**.**

Managing Infusion related reactions

For infusion reactions of any grade/severity, immediately interrupt the infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or 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 a maximum rate of 200mL/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 Velcade and Dexamethasone (DVD)

Indication: Relapsed Myeloma.

Frequency: Cycles 1-8 are 21 day cycles, cycle 9 onwards 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 1-3 Daratumumab given on days 1, 8, 15.

Cycles 4-8 Daratumumab given on day 1.

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.

BORTEZOMIB (VELCADE): Proteasome inhibitor

Administered subcutaneously on **days 1, 8 and 15 on cycles 1-8**. Minimum of 72 hours required between doses (twice weekly velcade on days 1, 4, 8 and 11 can also be used).

Emetic risk: Low.

Classification of extravasation: irritant

Side effects: tachycardia, diarrhoea, constipation, anorexia, nausea/vomiting, thrombocytopenia, neutropenia, peripheral neuropathy (sensory and motor), headache, rash, fatigue, postural hypotension, dizziness, shingles, inflammation at injection site, infections, bone marrow depression.

DEXAMETHASONE: corticosteroid tablets

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

Dexamethasone 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

- Lying and standing Blood pressure to be recorded pre cycle 1, advise patients that velcade can cause orthostatic hypotension and counsel them to sit upright for a moment before standing from a sitting/lying position.
- Bloods are required (including glucose) at the start of each cycle. Patients with unstable blood counts (specifically low platelets, see protocol) 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.