

DARATUMUMAB WITH BORTEZOMIB AND DEXAMETHASONE (DVd)

INDICATION

Relapsed multiple myeloma in patients who have received one prior therapy, and are not refractory to bortezomib.

This regimen is funded via **CDF interim Funding. Requires Blueteq approval**

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&Es
 - LFTs
 - Calcium
 - Albumin
 - Uric acid
 - CRP
 - Baseline random blood glucose level
 - ECG & Transthoracic echocardiogram to assess LV function if clinically indicated
 - Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
 - Consider annual flu and pneumococcal vaccination pre therapy
 - Calculated creatinine clearance (CrCl), urine/ creatinine ratio, light chain (Bence Jones)
 - 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 Genetics Laboratory

Salisbury NHS Foundation Trust

Salisbury District hospital

Salisbury, Wilts, 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
- Bone marrow aspirate and trephine (and immunophenotype if appropriate)

Additional investigations:

1. Plasma viscosity if hyperviscosity suspected
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 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.
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. Obtain written consent for the treatment.
4. Fertility - all relevant patients should be offered fertility advice as appropriate.
5. Hydration - ensure fluid intake of at least 3 litres per day.
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

REGIMEN SPECIFIC PRE-ASSESSMENT

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. 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.

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METHOD OF SUBCUTANEOUS DARATUMUMAB ADMINISTRATION:

Inject the subcutaneous dose (15 mL) into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject the dose at other sites of the body as no data are available.

Injection sites should be rotated for successive injections. The subcutaneous dose should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.

Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

DRUG REGIMEN

Key prescribing point:

- For Cycles 1-8, There are two different dosing schedules of DVd, select the correct one on ARIA:
 - **Schedule A:** using bortezomib ONCE weekly in selected patients where twice-weekly schedule is not appropriate. ARIA name→Daratumumab SC Bortezomib Dexamethasone (weekly) (cycle 1-8 only) (21 day).
 - **Schedule B:** using bortezomib TWICE a week (standard dosing). ARIA name→Daratumumab SC Bortezomib Dexamethasone (cycle 1 to 8 only) (21 day).
- From Cycle 9-onwards:
 - This is set up as a separate regimen on Aria. Please ensure that patients who completed 8 cycles are switched on ARIA to the (cycle 9 onwards) regimen. ARIA name→ Daratumumab SC Bortezomib Dexamethasone (cycle 9 onwards) (28 day).

Schedule A: DVd with bortezomib ONCE WEEKLY dosing schedule (Weekly regimen)

Cycles 1 -3

Daratumumab	Pre-meds: 1 hour prior to injection Montelukast 10mg PO on (cycle 1 only) , Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 20mg* PO	Days 1*, 8*, 15*
	Daratumumab 1800mg (fixed dose) subcutaneously over 3-5 minutes	Days 1, 8, 15
	<u>Post-med:</u> Dexamethasone PO*	See below under dexamethasone
Bortezomib	1.3 mg/m ² ONCE weekly given as SC bolus	Days 1, 8 and 15

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Dexamethasone	20mg PO once daily on the day of and day after bortezomib injection	Days 2**, 9** and 16**
	<p>Note: on daratumumab weeks, pre- and post-daratumumab dexamethasone is also being used as the steroid component of the triple combination regime. i.e.:</p> <p>*On Days 1, 8 and 15, dexamethasone is given as a pre-med 1 hour prior to daratumumab to reduce the risk of IRRs.</p> <p>**On Days 2, 9 and 16, dexamethasone is also used as post-med the day after daratumumab to reduce the risk of delayed IRRs</p>	
Cycle frequency: 21- day cycles		

Cycles 4 to 8

Daratumumab	<p><u>Pre-meds:</u> 1 hour prior to injection Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 12-20mg * PO</p> <p>Daratumumab 1800mg (fixed dose) subcutaneously over 3-5 minutes</p> <p><u>Post-med:</u> Dexamethasone 20mg PO*</p>	<p>Day 1*</p> <p>Day 1</p> <p>See below under dexamethasone</p>
	Bortezomib	1.3 mg/m ² ONCE weekly given as SC bolus
Dexamethasone	20mg PO once daily on the day of and day after bortezomib injection	Days 2**, 8, 9, 15 and 16
	<p>*On day 1, dexamethasone is given as pre-med 1 hour prior to daratumumab to reduce the risk of IRRs.</p> <p>**On day 2, dexamethasone is also used as post-med the day after daratumumab to reduce the risk of delayed IRRs</p>	
Cycle frequency: 21- day cycles		

Schedule B: DVd with bortezomib TWICE A WEEK dosing schedule
Cycles 1 to 3

Daratumumab	<p>Pre-meds: 1 hour prior to injection Montelukast 10mg PO on (cycle 1 only), Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 20mg PO*</p> <p>Daratumumab 1800mg (fixed dose) subcutaneously over 3-5 minutes</p> <p>Post-med : Dexamethasone PO</p>	Days 1*, 8*, 15*
Bortezomib	1.3 mg/m ² TWICE a week given as SC bolus	Days 1,4,8 and 11
Dexamethasone	20mg PO	Days 2**, 4, 5, 9**, 11, 12
	4mg PO once daily as post-med for 2 days after daratumumab to reduce the risk of delayed IRRs	Days 16**,17**
	Note: on daratumumab weeks, pre- and post-daratumumab dexamethasone is also being used as the steroid component of the triple combination regime. i.e.:	
	*On Days 1,8 and 15, , dexamethasone is given as pre-med 1 hour prior to daratumumab to reduce the risk of IRRs.	
	**On days 2, 9, 16 and 17 dexamethasone is also used as post-med the day after daratumumab to reduce the risk of delayed IRRs.	
Cycle frequency: 21- day cycles		

Cycles 4 to 8

Daratumumab	<p>Pre-meds: 1 hour prior to injection Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 20mg * PO</p> <p>Daratumumab 1800mg (fixed dose) subcutaneously over 3-5 minutes</p> <p>Post-med : Dexamethasone 20mg PO*</p>	Day 1*
		Day 1
		See below under dexamethasone
Bortezomib**	1.3 mg/m ² TWICE a week given as SC bolus	Days 1,4,8 and 11
Dexamethasone	20mg PO once daily on the day of and day after bortezomib injection	Days 2**, 4, 5, 8, 9, 11 and 12
	*On day 1, dexamethasone is given as pre-med 1 hour prior to daratumumab to reduce the risk of IRRs.	
	** On day 2, dexamethasone is also used as post-med the day after daratumumab to reduce the risk of delayed IRRs.	
Cycle frequency: 21- day cycles		

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Cycle 9- Onwards

Daratumumab	<u>Pre-meds:</u> 1 hour prior to daratumumab Paracetamol 1g PO, Chlorphenamine 4mg PO Dexamethasone 12mg PO	Day 1
	Daratumumab subcutaneously at 1800mg fixed dose over 3-5 minutes	Day 1
	<u>Post-med:</u> Dexamethasone 4mg PO	Days 2 and 3 i.e. for two days starting the day after daratumumab to reduce the risk of delayed infusion reactions
Cycle frequency: 28- day cycles		

CYCLE FREQUENCY

Cycles 1 to 8 are 21-day cycles, cycle 9-onwards are repeated every 28 days until disease progression or unacceptable toxicity.

Additional Post-medications:

The use of post-daratumumab 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 doses, if the patient experiences no major IRRs, these inhaled post-infusion medications may be discontinued at the discretion of the physician.

DOSE MODIFICATIONS

Haematological Toxicity:

Daratumumab: no dose reductions of daratumumab are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of G4 haematological toxicity or G3 or higher thrombocytopenia with bleeding. Patients with neutropenia should be monitored for signs of infection. Daratumumab delay may be required to allow recovery of blood cell counts. In lower body weight patients receiving daratumumab subcutaneous formulation, higher rates of neutropenia were observed; however, this was not associated with higher rates of serious infections.

Bortezomib: withhold at G3 non-haem or G4 haem toxicities. Once resolved, re-initiate at 25% reduced dose (1.3 mg/m² reduced to 1.0 mg/m²; 1.0 mg/m² reduced to 0.7 mg/m²). If the toxicity is not resolved or if it recurs at the lowest dose, discontinue unless the benefit outweighs risk.

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Peripheral neuropathy

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

Grading of neuropathy	Dose modification
G1 with no pain or loss of function	None
G1 with pain or G2	Reduce to 1.0 mg/m ² or change treatment schedule to 1.3 mg/m ² once per week if patient currently on twice weekly
G2 with pain or G3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves, re-initiate treatment at 0.7 mg/m ² once per week.
G4 and/or severe autonomic neuropathy	Discontinue

Hepatic/Renal Impairment

Bortezomib

Renal	Hepatic
Clinical decision if GFR < 20ml/min In dialysis patients, give after dialysis	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 dose reduction to 0.5 mg/m ² in subsequent cycles based on patient tolerability.

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

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

- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the

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duration of therapy and for 3 months after the completion of bortezomib

- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Consider prophylactic levofloxacin 500mg od for 12 weeks (cycles 1-4), at clinician discretion, only in patients deemed at high risk of infections. Adjust dose for renal function
- Prophylactic fluconazole 50mg OD.
- Proton pump inhibitor or H2 antagonist at clinician’s discretion.
- Bone protection as per NSSG Bone Protection protocol MM.3
- Consider use of loperamide if required for the management of transient diarrhoea.

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

EMETIC RISK

Low risk.

EXTRAVASATION RISK

Neutral: daratumumab
Irritant: bortezomib

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 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>

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- 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.
 - **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.
 - **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.
 - **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

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

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.
- Painful neuropathy: Patients should be advised to report pain hypersensitivity prickling, numbness and paraesthesia. If these occur see above dose reductions and consider use of anti-neuropathic medication (e.g. gabapentin). Neuropathy assessment tools are available. 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. Caution in patients with history of syncope, receiving medications associated with hypotension and patients who are dehydrated. Patients who experience dizziness or low blood pressure may benefit from 500 ml intravenous 0.9% sodium chloride with each bortezomib dose.

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REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche (Cancer Pharmacist)	New protocol	December 2017	1.0	December 2019
Network Protocol Review	Investigations. Concurrent medication. Adverse events	June 2018	1.1	June 2020
Faouzi Djebbari (Haematology Pharmacist)	CDF approval, daratumumab split dosing, infusion table, references	April 2019	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	June 2019	2.1	June 2020
Faouzi Djebbari (Haematology Pharmacist)	Addition of MHRA drug alert	October 2019	2.2	June 2020
Faouzi Djebbari (Haematology Pharmacist)	Addition of SC daratumumab option during the COVID-19 pandemic	May 2020	2.4	June 2021
Faouzi Djebbari (Haematology Pharmacist)	Time of pre-meds updated	June 2020	2.5	June 2021
Faouzi Djebbari (Haematology Pharmacist)	Significant update with standard SC daratumumab	June 2020	3.0	June 2021
NSSG Myeloma Group	Annual myeloma protocol review and update	Oct 2020	3.1	June 2021
NSSG Myeloma Group	Update to name of weekly schedule	Jan 2021	3.2	June 2021
Quality Manager	Nursing care plan added	May 2021	3.3	June 2021
NSSG Myeloma Group	2021 Annual Protocol Review	June 2021	3.4	June 2022
NSSG Myeloma Group	Updated concurrent medication section	Nov 2022	3.5	June 2023

Appendix 1: intravenous daratumumab:

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There may be a need to arrange for 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 -3

Daratumumab	Pre-meds: 1 hour prior to infusion Montelukast 10mg PO on (cycle 1 only) , Paracetamol 1g PO, Chlorphenamine 10 mg IV Dexamethasone 20mg* IV bolus or PO (give IV prior to the first infusion)	Days 1, 8, 15
	Daratumumab 16mg/kg Intravenous infusion, <u>Post-infusion:</u> Dexamethasone PO*	Days 1, 8, 15 20mg days 2, 9, and 4mg days 16 and 17 i.e. The day after daratumumab to reduce the risk of delayed infusion reactions*
*Note: on daratumumab weeks, Pre- and post-daratumumab dexamethasone is also being used as the steroid component of the triple combination regime.		
Bortezomib**	1.3 mg/m ² given as SC bolus as standard	Days 1,4,8 and 11
Dexamethasone	20mg PO once daily	Days 4,5,11 and 12
Cycle frequency: 21- day cycles		

**Considering bortezomib weekly on days 1, 8 and 15 in a 21 days cycle in patients where twice-weekly is not appropriate

Cycles 4 to 8

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Daratumumab	<u>Pre-meds:</u> 1 hour prior to infusion Paracetamol 1g PO, Chlorphenamine 10 mg IV Dexamethasone 20mg * IV bolus or PO	Day 1
	Daratumumab 16mg/kg Intravenous infusion <u>Post-infusion:</u> Dexamethasone 20mg PO*	Day 1 Day 2 i.e. The day after daratumumab to reduce the risk of delayed infusion reactions*
*Note: On Days 1 and 2, pre- and post- daratumumab dexamethasone also being used as the steroid component of the triple combination regime.		
Bortezomib**	1.3 mg/m ² given as SC bolus as standard	Days 1,4,8 and 11
Dexamethasone	20mg PO once daily	Days 4,5, 8,9, 11 and 12
Cycle frequency: 21- day cycles		

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

Cycle 9- Onwards

Daratumumab	<u>Pre-meds:</u> 1 hour prior to infusion Paracetamol 1g PO, Chlorphenamine 10 mg IV Dexamethasone 12mg IV bolus or PO	Day 1
	Daratumumab 16mg/kg Intravenous infusion <u>Post-infusion:</u> Dexamethasone 4mg PO	Day 1 Days 2 and 3 i.e. for two days starting the day after daratumumab to reduce the risk of delayed infusion reactions
Cycle frequency: 28- day cycles		

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

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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:

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

This is a controlled document and therefore must not be changed

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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. 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 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.

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