DARATUMUMAB WITH BORTEZOMIB, LENALIDOMIDE AND DEXAMETHASONE (DVRd) FOR TRANSPLANT INELIGIBLE PATIENTS

INDICATION

Treatment of newly diagnosed myeloma patients, who are not eligible for haematopoietic stem cell transplantation – **Blueteq required** – [NICE TA1170].

Patients that commenced induction therapy with the combination of daratumumab plus bortezomib, thalidomide and dexamethasone (DVTd) with the intention of proceeding to a stem cell transplant but have since become **ineligible for transplantation**, despite responding to DVTd. **Blueteq Required - Exceptional use criteria (Blueteq form – point 3)**

N.B. Patients who have NOT responded to DVTd are not eligible to switch to DVRd.

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
   - Virology: HIV, Hepatitis B (including core antibody), and Hepatitis C. CMV and EBV serology at the clinician's discretion.
   - ECG & Transthoracic echocardiogram to assess LV function if clinically indicated.
   - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
   - Serum free light chain assay
   - β2 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 (address below).
   - 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.

- Whole body 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 District Hospital,
Salisbury NHS Foundation Trust
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-ASSESSMENT

1. Evaluate for presence of neuropathy. 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.
2. The conditions of the Lenalidomide Pregnancy Prevention Programme (PPP) must be fulfilled for all male and female patients.
3. Clinical assessment of thrombo-embolic risk.
4. Baseline lying and standing blood pressure should be recorded prior to administration of cycle 1.

DRUG REGIMEN

Initiation phase: Contains 32 doses of Bortezomib. Please note that some patients may stop Bortezomib sooner or may have Bortezomib doses omitted due to peripheral neuropathy or other toxicities.

Dexamethasone doses were based on the Cepheus clinical trial (see references). Changes were made to decrease adverse events from long-term steroids and improve dexamethasone tolerability. Doses of dexamethasone may be reduced further in elderly patients and those with poor steroid tolerance.

The treatment schedule below was adapted from the Cepheus and Perseus clinical trials (see references). The Cepheus trial had an initiation phase of 24 weeks, while the regimen below contains an initiation phase of 32 weeks, to allow for 32 doses of Bortezomib.

Cycles 1 & 2 (28-day duration)

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Cycle 1 only – Montelukast 10mg Chlorphenamine 4mg Dexamethasone 20mg	1, 8, 15 & 22	Oral 1h prior to Daratumumab
Daratumumab	1800mg fixed dose	1, 8, 15 & 22	Subcutaneous
Bortezomib	1.3mg/m^2	1, 8, 15 & 22	Subcutaneous
Dexamethasone	20mg OD	2, 9, 16 & 23	Oral With food, in morning
Lenalidomide	25mg (starting dose) OD	1 to 21	Oral Take at night

Cycles 3 to 8 (28-day duration)

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Chlorphenamine 4mg Dexamethasone 20mg	1	Oral 1h prior to Daratumumab
Daratumumab	1800mg fixed dose	1	Subcutaneous
Bortezomib	1.3mg/m^2	1, 8, 15 & 22	Subcutaneous
Dexamethasone	20mg OD	2, 9, 16 & 23	Oral With food, in morning
Lenalidomide	25mg (starting dose) OD	1 to 21	Oral Take at night

Continuous phase

Cycle 9 onwards (28-day duration)

Drug	Dose	Days	Administration
Daratumumab pre-medication	Paracetamol 1g Chlorphenamine 4mg Dexamethasone 20mg	1	Oral 1h prior to Daratumumab
Daratumumab	1800mg fixed dose	1	Subcutaneous
Dexamethasone	20mg OD	2, 8, 9, 15, 16, 22 & 23	Oral With food, in morning
Lenalidomide	25mg (starting dose) OD	1 to 21	Oral Take at night

Additional post-dose medications:

Consider additional medications (e.g., inhaled corticosteroids, short and long acting bronchodilators) for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications.

Following the first three doses, if the patient experiences no major IRRs, these inhaled post daratumumab medications may be discontinued.

CYCLE FREQUENCY

Cycles 1 to 8: every 28 days
Cycles 9 onwards: every 28 days until disease progression or unacceptable toxicity

---

DOSE MODIFICATIONS

Prior to initiating a new cycle of therapy on cycles 1 to 8:
A new cycle should not be started if absolute neutrophil count (ANC) < 1.0 x 10^9/L and/or platelet counts are < 70 x 10^9/L and/or haemoglobin < 75g/L.

Prior to initiating a new cycle of therapy on cycles 9 onwards:
A new cycle should not be started if absolute neutrophil count (ANC) < 1.0 x 10^9/L and/or platelet counts are < 50 x 10^9/L and/or haemoglobin < 75g/L.

Lenalidomide dose levels:

Starting dose	25mg
Dose level -1	20mg
Dose level -2	15mg
Dose level -3	10mg
Dose level -4	5mg
Dose level -5	Further dose reductions are not recommended

Bortezomib dose levels:

Starting dose	1.3mg/m^2
Dose level -1	1mg/m^2
Dose level -2	0.7mg/m^2
Dose level -3	Discontinue Bortezomib

Haematological toxicity

Neutropenia guidance for Lenalidomide and Bortezomib:

Toxicity	Recommended course
First episode of grade 3 Neutropenia (Neut < 1.0 x 10^9/L)	Hold treatment with Lenalidomide until recovery to baseline or grade 2. Upon recovery, maintain lenalidomide at the current dose level if no other haematological toxicities are present **OR** reduce lenalidomide by one dose level if other haematological toxicities are present. Maintain Bortezomib at the same dose level. Consider starting treatment with G-CSF.
Recurrent episode of grade 3 Neutropenia (Neut < 1.0 x 10^9)	Hold treatment with Lenalidomide until recovery to baseline or grade 2. Upon recovery reduce lenalidomide by one dose level.

Grade 4 Neutropenia (Neutrophils < 50 x 10^9/L) or Neutropenia with Fever (≥38.5°C)	Withold treatment with all drugs until recovery to grade 2 or baseline. Upon recovery, maintain lenalidomide at the current dose level if no other haematological toxicities are present **OR** reduce lenalidomide by one dose level if other haematological toxicities are present. Maintain Bortezomib at the same dose level. If recurrent episode, reduce Lenalidomide and Bortezomib by one dose level.

Thrombocytopenia guidance for Lenalidomide and Bortezomib:

Toxicity	Recommended course
Platelets <50 x 10^9/L without bleeding	Interrupt Lenalidomide. Continue Bortezomib at the same dose level.
When platelets return to ≥75 x 10^9/L	Resume Lenalidomide at one dose level lower.
Platelets < 25 x 10^9/L or grade 3 or 4 thrombocytopenia with bleeding	Interrupt treatment with all drugs until recovery to grade 2 or baseline. Upon recovery reduce Bortezomib and Lenalidomide by one dose level.

Haematological toxicity for Daratumumab: dose changes are not recommended. Daratumumab dose can be delayed if needed.

Toxicity	Recommended course
Grade 4 haematological toxicity (any except lymphopenia)	Withold Daratumumab. Restart Daratumumab once toxicity has recovered to grade 2 or baseline.
Grade 3 thrombocytopenia with bleeding	
Febrile neutropenia	
Neutropenia with infection	

Non-Haematological toxicity

Peripheral neuropathy caused by Bortezomib:

Severity of Neuropathy	Dose modification
Grade 1 (asymptomatic, loss of deep tendon reflexes or paresthesia) with no pain or loss of function	None
Grade 1 with pain or Grade 2 (moderate symptoms or limiting instrumental activities of daily living)	Reduce Bortezomib to 1mg/m^2 once weekly
Grade 2 with pain or Grade 3 (severe symptoms or limiting self-care or instrumental activities of daily living)	Withhold bortezomib treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate bortezomib treatment and reduce dose to 0.7 mg/m^2 once weekly.
Grade 4 (life-threatening consequences, urgent intervention indicated) and/or severe autonomic neuropathy	Discontinue Bortezomib

Renal & 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 is necessary** for patients with hepatic impairment

Bortezomib

Renal	Hepatic
No dose reduction necessary For dialysis patients, bortezomib should be given after dialysis.	Bili > 1.5 x ULN: reduce to 0.7 mg/m2 in the first treatment cycle. Consider dose escalation to 1.0 mg/m2 or further dose reduction to 0.5 mg/m2 in subsequent cycles based on patient tolerability.

Lenalidomide

Renal		Hepatic
CrCl 30 – 49ml/min CrCl < 30ml/min, no dialysis CrCl < 30ml/min, requiring dialysis	10mg once daily* 15mg every other day** 5mg once daily***	No formal studies No specific dose recommendations
*Can increase to 15mg once daily if no response and patient tolerating **Can increase to 10mg once daily if no response and patient tolerating ***On dialysis day, administer dose after dyalisis		

INVESTIGATIONS

Repeat at the start of each treatment cycle.

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC, U&Es, LFTs, Ca^{2+}, glucose
- Ig's, paraprotein, serum free light chains
- Clinical assessment of neuropathy should be undertaken and documented prior to each cycle.
- Blood pressure (consider checking for postural drop if symptomatic)
- Consider bone marrow assessment / PET scan 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 300mg daily for 7 days
- Aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl <10ml/min)
- Famotidine 40mg OD (if already established on a PPI consider switching patient to Famotidine if possible). Consider stopping Famotidine when steroid course is completed.
- Fluconazole 50mg OD. Consider stopping when steroid course is completed.

- Apixaban 2.5mg BD should be used as standard thromboprophylaxis (unless other risk factors or drug interactions present, always clinically assess) - see Thromboprophylaxis information in adverse effects section below.
- Consider co-trimoxazole 480mg to 960mg OD on M/W/F.
- **For patients newly diagnosed and deemed at very high risk of infections only:** Consider prophylactic levofloxacin 500mg OD for 12 weeks (cycles 1-3). Beware that the MHRA discourages prophylactic use of fluoroquinolones since levofloxacin and other Fluoroquinolones can cause disabling and potentially long-lasting or irreversible side effects. The risk/benefit ratio should be carefully considered before use. See MHRA warning here. Adjust dose for renal function.
- Bone protection as per NSSG Bone Protection protocol MM.3
    - Note patients will need dental review prior to any bisphosphonate treatment.

As and when required:

- Onset of diarrhoea: Consider offering prophylactic loperamide PRN 4mg stat at first loose stool, then 2mg PRN every 4 hours up to maximum of 16mg in 24 hours.

- Suspicion of bile salt malabsorption with lenalidomide: Consider colestyramine sachets 4g once daily initially (may need to increase to 2-3 times a day) or colesevelam 2g OD (may need to increase to 2-3 times a day) – unlicensed indication. Colestyramine and Colesevalam may delay or reduce the absorption of other drugs. Administer other medicines 1h before or 6h after Colestyramine and administer Colesevalam 4h before or after other medication.

EMETIC RISK

Low risk.

EXTRAVASATION RISK

Bortezomib – irritant
Daratumumab - neutral

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The most frequent adverse events of any grade in the Cepheus study were: infection (91.9%), diarrhoea (56.9%), peripheral neuropathy (55.8%), neutropenia (55.8%), thrombocytopenia (46.7%), peripheral oedema (42.1%), upper respiratory tract infection (39.6%), constipation (38.1), anaemia (37.1%), fatigue (32%), hypokalaemia (29.4%), pneumonia (24.4%), urinary tract infection (20.8%). The most common adverse events of grade 3 of 4 were neutropenia (44.2%) and thrombocytopenia (28.4%).

Risk of reactivation of hepatitis B virus (MHRA alert 2019)

Hepatitis B virus reactivation has been reported in patients treated with immunosuppressive agents, anti-CD38 antibodies and proteosome inhibitors, which all carry a moderate risk of hepatitis B reactivation.

All patients must be screened for hepatitis B virus before initiation of daratumumab, bortezomib and lenalidomide. Patients with unknown serology who are already on treatment should also be screened.

Guidance on Hepatitis B reactivation during immunosuppressive SACT can be found from the following entities:

- National Institute for Health and Care Excellence (Clinical guidelines [CG165])
- European Association for the Study of the Liver (EASL HBV guideline 2017)
- American Society of Clinical Oncology (Huang et al, Journal of Clinical Oncology 2020)
- UK Chemotherapy board

Local Hepatitis B reactivation policy should be followed. Consider consulting the local Viral Hepatitis team for advice.

Please consult local Hepatitis B reactivation policy for further details on monitoring, choice of antiviral prophylaxis, dose and duration of prophylactic treatment.

Myelosuppression

Including neutropenia and thrombocytopenia which may require dose interruptions and reductions. Monitor patients with neutropenia for signs of infection. Patients should be advised to monitor themselves for bleeding or bruising, especially if prophylactic VTE treatments are concomitantly administered. Follow dose modifications for haematological toxicity as per section above.

1- DARATUMUMAB-RELATED:

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.

- ✓ **Blood Transfusion must be notified of this interference with serological testing and Blood Bank must be notified that a patient has received daratumumab.**
- ✓ **Patients must be screened prior to starting daratumumab.**
- ✓ **Important information on safety and risk minimisation of Daratumumab and interference with Blood Compatibility Testing can be found of the summary of product characteristics (www.medicines.org.uk)**
- ✓ **Ensure patients are given a Patient ID Card for daratumumab and are instructed to carry this for 6 months after stopping treatment.**
- ✓ **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.

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 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) symptoms 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.

2- LENALIDOMIDE-RELATED

Teratogenicity

The risk management programme should be observed - see risk management materials on www.medicines.org.uk. The concomitant use of an effective method of contraception is mandatory in all female patients of childbearing potential. Male patients should also use a condom when having sexual intercourse with women of childbearing potential. **Prescribing and dispensing of lenalidomide must be in line with the pregnancy prevention programme.**

Diarrhoea

Diarrhoea was reported in 56.9% of patients. Patients may require use of antidiarrheal medication and supportive care. Bile salt malabsorption occurs in a small percentage of patients on lenalidomide. Consider dietary adjustments with low fat meal intake and prescribing bile acid sequestrants (cholestyramine).

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:

- **Prophylactic Apixaban 2.5mg BD (check product specific information) should be used as standard thromboprophylaxis**
- Prophylactic low-molecular weight heparin is an alternative if Apixaban is not indicated.
- If the patient is already established on an alternative DOAC change to Apixaban is not required (always clinically assess).

Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is not a preference 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 local guidelines.

Drowsiness, somnolence and sedation

Take the dose at night time. Lenalidomide may potentiate the drowsiness caused by alcohol and other sedative medication. If affected, patients should be instructed not to drive cars, use machinery or perform hazardous tasks whilst taking lenalidomide.

Rash

Antihistamines and topical corticosteroids can often be used to treat limited, localized, treatment-related rash, but lenalidomide interruption or discontinuation should be considered for grade 2/3 rash. Re-challenge with lenalidomide is reasonable in patients who do not have a severe rash and will often allow continued treatment. Lenalidomide must be discontinued for angioedema, grade 4 rash, and exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis are suspected, and should not be resumed after discontinuation for these reactions

Secondary malignancies

There is an MHRA alert on an increased risk of secondary malignancies in three large trials of lenalidomide treatment. The MHRA recommend vigilance in reporting such events promptly. Quoted incidence is 3 to 4% per annum.

Hypothyroidism

Hypothyroidism has been reported in patients on lenalidomide. Baseline assessment of thyroid function and ongoing monitoring is recommended.

Other warnings

Due to the teratogenocity of lenalidomide, patients should be informed not to donate blood or semen during or within 8 weeks of stopping lenalidomide treatment.

3 – BORTEZOMIB-RELATED

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.

4 – DEXAMETHASONE-RELATED

Mood changes, restlessness, withdrawal effects, insomnia, gastritis, fluid retention, weight gain, hyperglycaemia, glucose intolerance.

TREATMENT RELATED MORTALITY

<5%

REFERENCES

1. Darzalex ® (Daratumumab), eMC UK Summary of Product Characteristics for Janssen, Apr 2026
2. Bortezomib (Velcade®) eMC UK Summary of Product Characteristics, Janssen, September 2024
3. Lenalidomide, Thornton & Ross eMC UK Summary of Product Characteristics, Thornton & Ross, January 2025
4. Dexamethasone, Aspen eMC UK Summary of Product Characteristics, Aspen, April 2026
5. NICE TA10726, technology appraisal guidance, 24 June 2026
6. Usmani SZ, Facon T, Hungria V, Weisel KC, Mateos MV, San-Miguel J, et al. Daratumumab plus bortezomib, lenalidomide and dexamethasone for transplant-ineligible or transplant deferred newly diagnosed multiple myeloma: the randomized phase 3 CEPHEUS trial. Nat Med. 2025;31(4):1350-1365.
7. Sonneveld P, Brojil A, Gay F, Mina R, Dimopoulos MA, Moreau P, et al. Daratumumab, bortezomib, lenalidomide and dexamethasone for transplant eligible patients with newly diagnosed multiple myeloma (PERSEUS). N Engl J Med. 2024;390(5):301-313.

REVIEW

Name	Revision	Date	Version	Review date
Jaimal Kothari, Myeloma Consultant Lead Ana Rita Gomes, Advanced Cancer Pharmacist	New protocol	July 2026	1.0	July 2028