# Daratumumab, Bortezomib, Thalidomide and Dexamethasone – D-VTd (Myeloma)

## Indication

Induction and consolidation therapy for newly diagnosed transplant-eligible multiple myeloma patients with performance status ≤2.

NICE TA763.

## ICD-10 codes

Codes with a prefix C90

## Regimen details

**Cycles 1 & 2 (28 day)**

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1,8,15 and 22 | Daratumumab | 1800mg | SC bolus |
| 1,4,8 and 11 | Bortezomib[#] | 1.3mg/m$^2$ | SC bolus |
| 1-28 (continuously) | Thalidomide | 100mg ON | PO |
| 1+2, 8+9, 15+16, 22+23 | Dexamethasone | 40mg OM * | PO |

**Cycles 3-4 (28 day)**

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1 and 15 | Daratumumab | 1800mg | SC bolus |
| 1,4,8 and 11 | Bortezomib[#] | 1.3mg/m$^2$ | SC bolus |
| 1-28 (continuously) | Thalidomide | 100mg ON | PO |
| 1+2 | Dexamethasone | 40mg OM | PO |
| 8, 9, 15 and 16 | Dexamethasone | 20mg OM* | PO |

**Cycles 5-6 (28 day) - after ASCT**

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1 and 15 | Daratumumab | 1800mg | SC bolus |
| 1,4,8 and 11 | Bortezomib[#] | 1.3mg/m$^2$ | SC bolus |
| 1-28 (continuously) | Thalidomide | 100mg ON | PO |
| 1,2, 8, 9, 15 and 16 | Dexamethasone | 20mg OM* | PO |

[#]If twice weekly administration is not tolerated, bortezomib can be given once a week on days 1,8,15 and 22 (unlicensed)

*This is the total dose of dexamethasone per day. If a patient is receiving daratumumab on that day, they should receive this dose as premedication.

## Cycle frequency

28 days

## Number of cycles

6 cycles total
The regimen consists of 4 cycles daratumumab-VTD then autologous stem cell transplant (ASCT) followed by 2 cycles of daratumumab-VTD as consolidation therapy.

## Administration

**Daratumumab**
Inject 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 into 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.

Patients should be observed for at least 6 hours after the end of the SC injection following the first dose (or as per local policy) and, if deemed necessary, after subsequent injections.

**Bortezomib**
Administration by subcutaneous bolus injection into the thigh or abdomen. Rotate sites, avoid injecting into the same site in the same cycle e.g., alternate between right and left abdomen, and right and left thigh. Avoid site used for daratumumab administration on days when both drugs are administered.
Patient should be encouraged to drink 2 – 3 litres over the 24 hours after each dose of bortezomib in the first cycle, to reduce the risk of tumour lysis syndrome. **At least 72 hours must elapse between doses of bortezomib.** If a planned dose of bortezomib is delayed, adjust the dosing schedule accordingly, to maintain the treatment interval.

**Thalidomide**
Available in 50mg capsules. Capsules should be swallowed whole at bedtime to avoid daytime sedation. Patients should be advised not to drive or operate machinery for 8 hours after each dose.

Women of childbearing potential must have a **NEGATIVE PREGANANCY TEST** within 72 hours before starting thalidomide therapy, then once a month during treatment, continuing until one month after stopping treatment (every 2 weeks if irregular periods). If a woman thinks she may be pregnant she must stop taking thalidomide immediately.

**Dexamethasone**
Tablets should be taken in the morning, with or immediately after food.

## Pre-medication

1-3 hours prior to daratumumab subcutaneous injection:
Paracetamol 500mg-1g PO,
Chlorphenamine 10mg IV or 4mg PO,
Dexamethasone PO – dose dependent on cycle/day of treatment, see regimen details above
Hydration fluids may be required, ensure a fluid intake of at least 3 litres/day on treatment days in cycle 1
Consider montelukast 10mg PO administered >30 mins prior to first infusion and subsequent infusions in cycle 1.

## Emetogenicity

This regimen has low emetic potential

## Additional supportive medication

Allopurinol 300 mg OD (100mg OD if CrCl < 20mL/min) for days 1-7 in cycle 1.
Prophylactic aciclovir for the duration of treatment and for 3 months afterwards.
Consider prophylactic co-trimoxazole.
Consider levofloxacin 500mg OD (reduced dose if CrCl <50ml/min – see SPC) for 12 weeks (cycles 1-3)
Prophylactic antifungals as per local policy.
Proton pump inhibitor or H2 antagonist.
Loperamide if required.
Laxative as required for thalidomide induced constipation.
Bisphosphonates as per local protocol.
Thromboprophylaxis as per local protocol.

## Extravasation

Bortezomib is irritant (Group3 ).
Daratumumab is neutral (Group 1).

## Investigations – pre first cycle

| Investigation | Validity period |
|---|---|
| FBC | 14 days |
| Group and Save | Inform transfusion laboratory that patient is due to commence daratumumab |
| U+Es including creatinine | 14 days |
| LFTs | 14 days |
| Calcium | 14 days |
| Glucose | 14 days |
| Hepatitis B/C & HIV screening | 14 days |
| Pregnancy test (if female of childbearing potential) | 72 hours |

**Other investigations:**
It is advisable to assess the following before starting treatment and during treatment as clinically indicated:
Plasma viscosity
Uric acid
β2 microglobulin
Serum protein electrophoresis and immunofixation for quantification of serum monoclonal (M) protein and immunoglobulins
Serum free light chain assay Urine collection for light chain excretion
Consider bone marrow aspirate and trephine (with immunophenotype) and myeloma FISH
Whole body CT, MRI, PET-CT or skeletal survey as clinically indicated
MRI whole spine if suspicion of spinal cord compression
Pulmonary function
Consider baseline echocardiogram (risk of bortezomib-induced cardiomyopathy).

## Investigations – pre subsequent cycles

| Investigation | Validity period |
|---|---|
| FBC | 72 hours |
| U+Es including creatinine | 72 hours |
| LFTs | 72 hours |
| Pregnancy test (if female of childbearing potential) | 72 hours |
| Calcium | As clinically indicated |
| Glucose | As clinically indicated |

Immunoglobulins, M protein quantification; serum free light chain assay as clinically indicated.

## Standard limits for administration to go ahead

If blood test results not within range, authorisation to administer **must** be given by prescriber/ consultant

| **Investigation** | **Limit** |
|---|---|
| Neutrophils | ≥ 1.0 x $10^9$/L |
| Platelets | ≥ 70 x $10^9$/L |
| Creatinine Clearance | ≥ 20ml/min |
| Bilirubin | < 1.5 x ULN |
| AST/ALT | ≤ ULN |

## Dose modifications

Doses of bortezomib are modified according to the following table:

| | |
|---|---|
| Full dose | 1.3mg/$m^2$ |
| First dose reduction | 1.0mg/$m^2$ |
| Second dose reduction | 0.7mg/$m^2$ |

- **Haematological toxicity**

To commence a new cycle, platelets should be ≥ 70 x $10^9$/L and neutrophils ≥ 1.0 x $10^9$/L

Daratumumab: no specific modifications or dose reductions are advised. Dose delays maybe considered to allow recovery of blood counts.

Bortezomib: withhold subsequent doses at onset of grade 4 haematological toxicity (platelets < 25 x $10^9$/L or neutrophils < 0.5 x $10^9$/L). Once toxicity has resolved, re-initiate at next dose reduction level. If the toxicity is not resolved or if it recurs at the lowest dose, discontinue unless benefit outweighs risk.

If cytopenia considered to be disease related, treatment may be given at consultant discretion.

- **Renal impairment**

Daratumumab: No dose adjustment necessary.

Bortezomib: Consider dose reduction if CrCl <20ml/min
For patients on dialysis, bortezomib should be given after the dialysis procedure as dialysis may reduce bortezomib concentration.

Thalidomide: No specific dose recommendations available. Closely monitor for adverse effects in severe renal impairment

- **Hepatic impairment**

Daratumumab: no dose modifications are required in mild or moderate hepatic impairment (bilirubin ≤3 x ULN or AST/ALT ≤ULN or Child Pugh A or B). Daratumumab has not been studied in severe hepatic impairment (bilirubin > 3 × ULN and any elevation of AST/ALT or Child Pugh C) – use with caution.

Bortezomib: If bilirubin > 1.5 x ULN consider starting dose of 0.7mg/$m^2$ for cycle 1. For subsequent cycles consider increasing dose to 1mg/$m^2$ or reducing dose to 0.5mg/$m^2$ according to tolerability.

Thalidomide: No specific dose recommendations available. Closely monitor for adverse effects in severe hepatic impairment.

- **Neurotoxicity**

| Neuropathy grade | Bortezomib dose |
|---|---|
| Grade 1 with no pain | 100% |
| Grade 1 with pain or grade 2 but not interfering with daily living | 1.0mg/m$^2$ or switch to once weekly dosing schedule |
| Grade 2 with pain or grade 3 | Withhold until symptoms resolved. Restart at 0.7mg/m$^2$ |
| Grade 4 | Discontinue |

Thalidomide-related peripheral neuropathy:
Grade 2: reduce the dose of thalidomide by 50%
Grade 3: discontinue thalidomide until recovered to ≤ grade 1, then restart with a 50% dose reduction. Discontinue treatment if symptoms do not improve to ≤ grade 1 or for Grade 4 toxicity.

### Daratumumab Treatment reactions

Daratumumab can cause severe infusion reactions. Approximately half of all patients receiving IV treatment experienced a reaction, mostly during the first infusion however infusion reactions can also occur with subsequent infusions. For SC dosing the incidence was much lower, around 2% with a median onset of 3.5 hours.
Severe adverse reactions have occurred, including bronchospasm, hypoxia, dyspnoea, and hypertension. Signs and symptoms may include 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-medications must be given at least 1 hour before the dose. Patients receiving SC treatment should be monitored for 6 hours following the first dose. Monitoring following subsequent SC doses is at the clinician discretion.
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/injection related reactions (IRR)

For infusion/injection reactions of any grade/severity, immediately interrupt the infusion and manage symptoms. Management of infusion/injection reactions may further require reduction in the rate of infusion, or treatment discontinuation as outlined in the SPC

### Other toxicities

Bortezomib: Any other ≥ grade 3 non-haematological toxicity withhold bortezomib until recovered to ≤ grade 1. Recommence with dose reduction of one level.

If severe steroid-related side effects develop, consider dose reduction to 20mg weekly or discontinue. However, a minimum of 12mg is required before each daratumumab dose

Venous thromboembolism (VTE) associated with thalidomide should be treated with full dose anticoagulation.

## Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**
  Thromboembolism
  Tumour lysis syndrome
  Orthostatic hypotension
  Painful peripheral neuropathy
  Cardiac toxicity
  Stevens-Johnson syndrome
  Myelosuppression
  Teratogenicity

- **Frequently occurring side effects**
  Myelosuppression
  Constipation, diarrhoea
  Nausea and vomiting
  Fatigue, somnolence
  Peripheral neuropathy
  Headache

- **Other side effects**
  Atrial fibrillation
  Peripheral oedema
  Allergic rhinitis, nasopharyngitis,
  Pyrexia
  Dyspnoea
  Orthostatic hypotension
  URTI, pneumonia, cough
  Hypertension
  Hyperglycaemia
  Cutaneous reactions

## Significant drug interactions – for full details consult product literature/ reference texts

**Daratumumab**: no interaction studies have been performed.

**Bortezomib:**
**Antihypertensives**: Risk of additive hypotensive effect. Close monitoring of BP is required.
**Oral antidiabetic agents:** Hyper- and hypoglycaemia has been reported. Close monitoring of blood glucose is required.
**Ciclosporin:** increased risk of severe neuropathy: avoid concomitant use.
**High dose vitamin C:** reduced efficacy of bortezomib: avoid concomitant use.
**Cytochrome P34A inhibitors** (ketoconazole and other azole antifungals, clarithromycin, erythromycin) may increase bortezomib levels: avoid concomitant use. Cytochrome P34A inducers (rifampicin, carbamazepine, phenytoin, St John's Wort) may reduce bortezomib levels: avoid concomitant use.

**Thalidomide:**
Hormonal contraceptives: may increase risk of thrombo-embolic disease
Sedative medication: may enhance sedative effect

## Additional comments

**Interference with Blood Transfusion Serological Testing**

Daratumumab binds to CD38 on red blood cells (RBCs) and may result 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 upon.

- The blood transfusion laboratory must be notified of this interference with serological testing and notified that a patient has received daratumumab.
- Patients must have a Blood Group and Antibody screen prior to starting daratumumab.
- Patient will require red cell phenotyping/genotyping.
- Ensure patients are given a Patient Alert Card for daratumumab and are instructed to carry this for 6 months after stopping treatment and show the card to healthcare professionals that treat them.
- Counsel patients to tell their other health care professionals that they received daratumumab, particularly before a transfusion.

**Interference with determination of monoclonal protein concentration**

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 on the determination of complete response and of disease progression in all patients with IgG kappa myeloma.

**Thalidomide teratogenicity**

Women of childbearing potential and males must use contraception as outlined by a MHRA approved Risk Management Program. See pregnancy prevention protocol for full details. Patients should be informed not to donate blood or semen during or within 8 weeks of stopping thalidomide treatment.

## References


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