DARATUMUMAB WITH BORTEZOMIB AND DEXAMETHASONE

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

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)
   - \( \beta_2 \) 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

   - 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.
Additional investigations:

- Plasma viscosity if hyperviscosity suspected
- Imaging as per NICE/network guidance and clinical presentation
- Bone marrow aspirate and trephine (and immunophenotype if appropriate)
- Bone marrow aspirate and trephine (and immunophenotype if appropriate)

REGIMEN SPECIFIC PRE-ASSESSMENT

1. You may have to arrange for patient admission with the first infusion of daratumumab, where an extended duration of infusion is anticipated due to prior 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.
2. Ensure patients are given a Patient ID Card for daratumumab and are instructed to carry this for 6 months after stopping treatment.
3. 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.
4. From cycle 2 onwards, patients may qualify for rapid rate infusion. See MM.48 (Daratumumab Rapid Rate Infusion) for further information.
5. 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.
6. Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1.
## DRUG REGIMEN

### Cycles 1 - 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Time</th>
</tr>
</thead>
</table>
| **Daratumumab** | Pre-meds: 30 minutes 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)  
**Daratumumab** 16mg/kg Intravenous infusion.  
**Post-infusion:** **Dexamethasone** PO* | Days 1, 8, 15  
20mg days 2, 9, and 4mg days 16 and 17  
i.e. The day after daratumumab infusion to reduce the risk of delayed infusion reactions*  
*Note: on daratumumab weeks Pre- and post- infusion dexamethasone is also being used as the steroid component of the triple combination regime. |
| **Bortezomib** | 1.3 mg/m² given as SC bolus as standard                                                                                                            | Days 1, 4, 8 and 11                                                   |
| **Dexamethasone** | 20mg PO once daily  
(The dose may be reduced in the elderly or if steroid-related side effects develop)                                                          | 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 who experienced neuropathy or those with pre-existing neuropathy**

### Cycles 4 to 8

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Time</th>
</tr>
</thead>
</table>
| **Daratumumab** | Pre-meds: 30 minutes prior to infusion Paracetamol 1g PO, Chlorphenamine 10 mg IV, **Dexamethasone** 20mg* IV bolus or PO  
**Daratumumab** 16mg/kg Intravenous infusion.  
**Post-infusion:** **Dexamethasone** 20mg PO* | Day 1  
Day 1  
Day 2  
i.e. The day after daratumumab infusion to reduce the risk of delayed infusion reactions*  
*Note: On Days 1 and 2, pre- and post- infusion dexamethasone also being used as the steroid component of the triple combination regime. |
| **Bortezomib** | 1.3 mg/m² given as SC bolus as standard                                                                                                            | Days 1, 4, 8 and 11                                                   |
| **Dexamethasone** | 20mg PO once daily  
(The dose may be reduced in the elderly or if steroid-related side effects develop)                                                          | 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**

### Cycle 9- Onwards

<table>
<thead>
<tr>
<th>Daratumumab</th>
<th>Pre-meds: 30 minutes prior to infusion</th>
<th>Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paracetamol 1g PO, Chlorphenamine 10 mg IV, Dexamethasone 12mg IV bolus or PO</td>
<td></td>
</tr>
<tr>
<td>Daratumumab</td>
<td>16mg/kg Intravenous infusion.</td>
<td>Day 1</td>
</tr>
<tr>
<td>Post-infusion: Dexamethasone 4mg PO</td>
<td>Days 2 and 3 i.e. for two days starting the day after daratumumab infusion to reduce the risk of delayed infusion reactions</td>
<td></td>
</tr>
</tbody>
</table>

**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 pre- and post-infusion medication:

For patients with a history of chronic obstructive pulmonary disease, the use of post-infusion medications including short and long acting bronchodilators, and inhaled corticosteroids should be considered. 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.
DARATUMUMAB 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.

<table>
<thead>
<tr>
<th></th>
<th>Dilution volume (Sodium chloride 0.9%)</th>
<th>Initial rate (first hour)</th>
<th>Rate increment a</th>
<th>Maximum rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First week</strong>a</td>
<td>Option 1 (full dosing 16mg/kg)</td>
<td>50 mL/hour</td>
<td>50 mL/hour every hour</td>
<td>200 mL/hour</td>
</tr>
<tr>
<td></td>
<td>C1D1: 1000 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Option 2 (split dosing 8mg/kg)</td>
<td>50 mL/hour</td>
<td>50 mL/hour every hour</td>
<td>200 mL/hour</td>
</tr>
<tr>
<td></td>
<td>C1D1: 500 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Option 2 (split dosing 8mg/kg)</td>
<td>50 mL/hour</td>
<td>50 mL/hour every hour</td>
<td>200 mL/hour</td>
</tr>
<tr>
<td></td>
<td>C1D2: 500 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Second week</strong>b</td>
<td>500 mL</td>
<td>50 mL/hour</td>
<td>50 mL/hour every hour</td>
<td>200 mL/hour</td>
</tr>
<tr>
<td><strong>Third and subsequent weeks</strong>c</td>
<td>500 mL</td>
<td>100 mL/hour</td>
<td>50 mL/hour every hour</td>
<td>200 mL/hour</td>
</tr>
</tbody>
</table>

a Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions. **There is an option to administer daratumumab as a split dose at 8mg/kg intravenous infusion, on days 1 and 2 of the first week**

b A dilution volume of 500 mL should be used only if there were no ≥ Grade 1 IRRs during the first 3 hours of the first infusion. Otherwise, continue to use a dilution volume of 1000 mL and instructions for the first infusion.

c A modified initial rate for subsequent infusions (i.e. third infusion onwards) should only be used only if there were no ≥ Grade 1 IRRs during a final infusion rate of ≥ 100 mL/hr in the first two infusions. Otherwise, use instructions for the second infusion.

Notes:
1. For guidance on infusion rates in the case of infusion related reactions. See the managing infusion reactions section below.
2. Rapid Rate infusion – from Cycle 2 onwards, see MM.48.

**CYCLE FREQUENCY**

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

Prescribing point: please note that cycles (1-8) and cycles (9-onwards) are set up as separate regimens on Aria. Please ensure that patients who completed 8 cycles are switched on ARIA to the (cycle 9 onwards) regimen.
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.

**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 benefit outweighs risk.

**Peripheral neuropathy**

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

<table>
<thead>
<tr>
<th>Grading of neuropathy</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1 with no pain or loss of function</td>
<td>None</td>
</tr>
<tr>
<td>G1 with pain or G2</td>
<td>Reduce to 1.0 mg/m² or Change treatment schedule to 1.3 mg/m² once per week</td>
</tr>
<tr>
<td>G2 with pain or G3</td>
<td>Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7 mg/m² once per week.</td>
</tr>
<tr>
<td>G4 and/or severe autonomic neuropathy</td>
<td>Discontinue</td>
</tr>
</tbody>
</table>

**Hepatic/Renal Impairment**

**Bortezomib**

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical decision if GFR &lt; 20ml/min</td>
<td>Bili &gt; 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.</td>
</tr>
</tbody>
</table>

**Daratumumab:**

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td>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</td>
</tr>
</tbody>
</table>

This is a controlled document and therefore must not be changed
NVESTIGATIONS – 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 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.
- 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, carabamazepine, phenytoin, phenobarbital, and St John’s wort).

EMETIC RISK

Low risk.

EXTRAVASATION RISK

Neutral

ADVERSE EFFECTS/REGIMEN 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 infusion. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient’s serum. The determination of a patient’s ABO and Rh blood type are not impacted.
I. Blood Transfusion must be notified of this interference with serological testing and Blood Bank must be notified that a patient has received daratumumab.

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

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

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

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

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

- **Interference with Determination of Complete Response**
  Daratumumab is a human IgG kappa monoclonal antibody detectable on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and of disease progression in all patients with IgG kappa myeloma.

- **Infusion reactions**
  Daratumumab can cause severe infusion-related reactions (IRRs). Approximately half of all patients treated have experienced a reaction, the majority of IRRs occur 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. The infusion rate should be reduced when re-starting the infusion as outlined below Management of infusion reactions may further treatment discontinuation as outlined below.
<table>
<thead>
<tr>
<th>IRR grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-2 (mild to moderate)</td>
<td>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.</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>Once reaction 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.</td>
</tr>
<tr>
<td>Grade 4 (life threatening)</td>
<td>Permanently discontinue treatment.</td>
</tr>
</tbody>
</table>

- **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.

**REFERENCES**

2. Velcade® Bortezomib eMC UK Summary of Product Characteristics, Janssen, Feb 2019
3. Darzalex® (Daratumumab), eMC UK Summary of Product Characteristics for Janssen, Jan 2019

**REVIEW**

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
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<tbody>
<tr>
<td>Nadjoua Maouche</td>
<td>New protocol</td>
<td>December 2017</td>
<td>1.0</td>
<td>December 2019</td>
</tr>
<tr>
<td>(Cancer Pharmacist)</td>
<td></td>
<td></td>
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<tr>
<td>Faouzi Djebbari</td>
<td>CDF approval, daratumumab split dosing, infusion table, references</td>
<td>April 2019</td>
<td>2.0</td>
<td>June 2020</td>
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<tr>
<td>(Haematology Pharmacist)</td>
<td></td>
<td></td>
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<tr>
<td>Network Protocol Review 2019</td>
<td>Update of indications, regimen-specific pre-assessment, drug regimen, infusion rates, concurrent medication, adverse effects and references</td>
<td>June 2019</td>
<td>2.1</td>
<td>June 2020</td>
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<tr>
<td>Faouzi Djebbari</td>
<td>Addition of MHRA drug alert</td>
<td>October 2019</td>
<td>2.2</td>
<td>June 2020</td>
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<td>(Haematology Pharmacist)</td>
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