DARATUMUMAB WITH BORTEZOMIB AND DEXAMETHASONE

INDICATION

Relapsed multiple myeloma in patients who received one prior therapy

This regimen is funded via CDF interim Funding. Requires Blueteq Application

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)
   - 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.
   - Imaging as per NICE/network guidance and clinical presentation
   - Bone marrow aspirate and trephine (and immunophenotype if appropriate)
Additional investigations:
- 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. 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.
8. Treatment must be agreed at the relevant MDT

REGIMEN SPECIFIC PRE-ASSESMENT
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.
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. 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.
5. 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>Pre-meds: 1 hour prior to infusion</th>
<th>Post-infusion: Dexamethasone PO*</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daratumumab</td>
<td>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)</td>
<td></td>
<td>Days 1, 8, 15</td>
</tr>
<tr>
<td></td>
<td>Daratumumab 16mg/kg Intravenous infusion.</td>
<td></td>
<td>Days 1, 8, 15</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 20mg* IV bolus or PO</td>
<td></td>
<td>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*</td>
</tr>
<tr>
<td></td>
<td>*Note: on daratumumab weeks Pre- and post-infusion dexamethasone is also being used as the steroid component of the triple combination regime.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib**</td>
<td>1.3 mg/m² given as SC bolus as standard</td>
<td></td>
<td>Days 1,4,8 and 11</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>20mg PO once daily</td>
<td></td>
<td>Days 4,5,11 and 12</td>
</tr>
<tr>
<td></td>
<td>(The dose may be reduced in the elderly or if steroid-related side effects develop)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cycle frequency: 21- day cycles</strong></td>
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</tr>
</tbody>
</table>

**Bortezomib can also be administered weekly on days 1, 8 and 15 in a 21 days cycle**

#### Cycles 4 to 8

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pre-meds: 1 hour prior to infusion</th>
<th>Post-infusion: Dexamethasone PO*</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daratumumab</td>
<td>Paracetamol 1g PO, Chlorphenamine 10 mg IV, Dexamethasone 20mg * IV bolus or PO</td>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td></td>
<td>Daratumumab 16mg/kg Intravenous infusion.</td>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone 20mg PO*</td>
<td></td>
<td>Day 2</td>
</tr>
<tr>
<td></td>
<td>*Note: On Days 1 and 2, pre- and post- infusion dexamethasone also being used as the steroid component of the triple combination regime.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bortezomib**</td>
<td>1.3 mg/m² given as SC bolus as standard</td>
<td></td>
<td>Days 1,4,8 and 11</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>20mg PO once daily</td>
<td></td>
<td>Days 4,5, 8,9, 11 and 12</td>
</tr>
<tr>
<td></td>
<td>(The dose may be reduced in the elderly or if steroid-related side effects develop)</td>
<td></td>
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<td></td>
<td></td>
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</tbody>
</table>
**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: 1 hour 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>Day 1</td>
</tr>
<tr>
<td></td>
<td>Daratumumab 16mg/kg Intravenous infusion.</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>
</tr>
<tr>
<td></td>
<td>Post-infusion: Dexamethasone 4mg PO</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.
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>Dilution volume (Sodium chloride 0.9%)</th>
<th>Initial rate (first hour)</th>
<th>Rate increment</th>
<th>Maximum rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First weeka</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>C1D1: 1000 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>C1D1: 500 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<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>C1D2: 500 mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second weekb</td>
<td>500 mL</td>
<td>50 mL/hour every hour</td>
<td>200 mL/hour</td>
</tr>
<tr>
<td>Third and subsequent weeksc</td>
<td>500 mL</td>
<td>100 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.

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

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>

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)
- 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>
</table>

This is a controlled document and therefore must not be changed
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 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.

Grade 4 (life threatening)  Permanently discontinue treatment.

- **Contraception**
  To avoid exposure to the fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of daratumumab treatment.

- **Other 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 Amitriptyline, Gabapentin and Pain Team referral. Neuropathy assessment tools are available in DTU. 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 ® Borrezomib 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>
</tr>
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<tbody>
<tr>
<td>Nadjoua Maouche (Cancer Pharmacist)</td>
<td>New protocol</td>
<td>December 2017</td>
<td>1.0</td>
<td>December 2019</td>
</tr>
<tr>
<td></td>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Faouzi Djebbari (Haematology Pharmacist)</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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MM.47
DaraVelDex

Authorised by Myeloma lead Dr. Karthik Ramasamy

April 2019

V. 2.0