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| **Indication** | Relapsed transplant ineligible multiple myeloma in patients who have received one prior line of treatment.<br>The patient must have not received previous treatment with daratumumab, or an anti-CD38 antibody, unless they have been previously treated with daratumumab as part of induction therapy pre-transplant and responded to daratumumab.<br><br>Patients who commenced on the Interim COVID option of ixazomib with lenalidomide and dexamethasone (Blueteq form code IXA2CV) as a second line therapy instead of daratumumab bortezomib and dexamethasone during the COVID19 pandemic to avoid hospital admissions can be granted an exception to the 1 prior line of therapy rule.<br><br>NB Daratumumab in this indication is not funded for amyloidosis patients (with the exception of patients who have a proven diagnosis of myeloma and also have an associated diagnosis of amyloidosis) |
| **Treatment Intent** | Disease modification |
| **Frequency and number of cycles** | Every 21 days cycle 1 to 8, then every 28 days from cycle 9.<br><br>Bortezomib and dexamethasone (except when dexamethasone is given as pre-medication before daratumumab) should be stopped after 8 cycles.<br><br>Continue daratumumab until progressive disease or unacceptable toxicity or patient choice, whichever occurs first.<br>Bortezomib and dexamethasone treatment can be continued in the event daratumumab is permanently discontinued (due to toxicity).<br><br>A formal medical review **MUST** occur by the end of the first 6 weeks of treatment to establish whether treatment should continue. |
| **Monitoring Parameters pre-treatment** | • **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion.<br>• Consider flu and pneumococcal vaccination pre-therapy.<br>• Monitor FBC before each cycle and on Day 8 and Day 15 of cycle 1-3 and on Day 1 and Day 8 of cycles 4-8.<br>From cycle 9 monitor FBC on day 1 of each cycle. Proceed when neutrophils > 0.5 x $10^9$/L and platelets > 25 x $10^9$/L.<br>• U&Es & LFTs at each cycle.<br>• BP baseline and if clinically indicated thereafter.<br>• Lung function assessment required in patients with pre-existing respiratory disease (COPD, asthma) and heavy smokers. Clinician to decide if further imaging required in patients with additional co-morbidities.<br>• Blood glucose every cycle.<br>• ECG baseline and if clinically indicated thereafter.<br>• Ensure patient is well hydrated (drinking ~3L/day) prior to treatment.<br>• Limited data of daratumumab sc in patients >120kg, give at clinician's discretion. |

- **Dose reduction:**
  - Dose reductions of daratumumab are not recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity.
  - Dexamethasone: Dose reduction may be considered in patients who are >75 years, patients who have a BMI <18.5, patients with poorly controlled diabetes mellitus or who have had prior intolerance/adverse event (AE) to steroid therapy.
  - Bortezomib: If Hb < 65g/l transfuse patient and restart treatment when Hb >65g/l. Bortezomib should be withheld for any grade 3 non-haematological (see below for guidance on managing neuropathic toxicities) or Grade 4 haematological toxicities (neutrophils < 0.5 x $10^9$/L or platelets < 25 x $10^9$/L); once toxicity has settled reinitiate at 75%, (i.e. 1.3mg/$m^2$ → 1.0mg/$m^2$ → 0.7mg/$m^2$).
    For Neuropathic Pain and or Peripheral Sensory or Motor Neuropathy dose reductions see table 1.
- **Hepatic Impairment:**
  - Daratumumab: No dose adjustments necessary.
  - Bortezomib: Consider dose reduction in moderate/severe hepatic impairment (Bilirubin >1.5xULN), reduce Bortezomib 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.
- **Renal Impairment:**
  - Daratumumab: No dose adjustments necessary.
  - Bortezomib: CrCl < 20ml/min discuss with consultant.
- **Daratumumab injection related reactions (IRRs**):
  - Daratumumab can cause severe injection reactions which may result in admission to hospital. Pre-meds must be given 1-3 hours before the injection.
  - Patients should be pre-medicated with chlorphenamine, dexamethasone and paracetamol as well as monitored (vital signs before and after the injection) 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. Patients should be observed for 6 hours post the 1st injection, 2 hours after 2nd dose and then 15 minutes observation after subsequent doses.
  - 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 disease to manage respiratory complications should they occur.
  - **From cycle 9 only**: If the patient experiences no major IRRs post injection corticosteroids may be discontinued at the clinician's discretion. This ONLY applies to monotherapy.
- **Administration of daratumumab sc:**
  - Inject 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 at other sites of the body as no data are available. Injection sites should be rotated for successive injections.
  - Daratumumab solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.

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| | ○ 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.<br>○ During treatment with daratumumab solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as daratumumab.<br>• **Interference with tests (refer to company risk materials):** Daratumumab binds to CD38 on red blood cells and results in a positive Indirect Antiglobulin Test (Coombs test) which may persist for up to 6 months after the last infusion. Send a blood sample for group/ direct antiglobulin/phenotype testing prior to treatment. Daratumumab may be detected on SPE and IFE assays resulting in false positive results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses.<br>• **Caution with Bortezomib:**<br>○ Use with caution in patients with pre-existing heart disease or with high risk factors.<br>○ Patients should be advised to report any new or worsening respiratory symptoms.<br>○ Bortezomib can affect the ability to drive and use machines. If patients experience fatigue/dizziness or blurred vision they should not drive.<br>○ At least 72 hours must elapse between consecutive Bortezomib doses.<br>• **Common drug interactions: (for comprehensive list refer to BNF/SPC)**<br>The concomitant use of bortezomib with strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital and St. John's Wort) is not recommended, as efficacy may be reduced. CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) should be used with caution and patients monitored for toxicity.<br>• **Contraception:** To avoid exposure to the foetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of daratumumab treatment.<br>• **Missed dose:** If a planned dose of daratumumab is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval. |
| **References** | KMCC protocol HAEM-MYEL-041 V2 CDF list V1.261 |

NB For funding information, refer to CDF and NICE Drugs Funding List

**Table 1: Dose modification of bortezomib for neuropathic toxicities**

| **Severity of Peripheral Neuropathy Signs and Symptoms*** | **Modification of Dose and Regimen** |
|---|---|
| Grade 1 (asymptomatic; loss of deep tendon reflexes or paraesthesia) without pain or loss of function | No Action |
| Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities of Daily Living (ADL)**) | Reduce bortezomib to 1 mg/m2 |
| Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care ADL ***) | Withhold bortezomib therapy until toxicity resolves. When toxicity resolves, reinitiate with a reduced dose of bortezomib at 0.7 mg/m2 once per week |
| Grade 4 (life-threatening consequences; urgent intervention indicated) | Discontinue bortezomib |
| *Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0 **Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money etc; ***Self care<br>ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. | |

**Cycle 1-3: cycle length 21 days**

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---|---|---|---|
| 1 | Dexamethasone | 20mg | PO | stat | To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack) |
| | Paracetamol | 1gm | PO | stat | |
| | Chlorphenamine | 4mg | PO | stat | |
| | Montelukast **Cycle 1 only** | 10mg | PO | stat | |
| | **DARATUMUMAB** | **1800mg** | SC | bolus | Inject 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 at other sites of the body as no data are available. Injection sites should be rotated for successive injections |
| | **BORTEZOMIB** | **1.3mg/m²** | SC | bolus | |
| 4 | **BORTEZOMIB** | **1.3mg/m²** | SC | bolus | |
| 8 | Dexamethasone | 20mg | PO | stat | To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack) |
| | Paracetamol | 1gm | PO | stat | |
| | Chlorphenamine | 4mg | PO | stat | |
| | **DARATUMUMAB** | **1800mg** | SC | bolus | Inject 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 at other sites of the body as no data are available. Injection sites should be rotated for successive injections |
| | **BORTEZOMIB** | **1.3mg/m²** | SC | bolus | |
| 11 | **BORTEZOMIB** | **1.3mg/m²** | SC | bolus | |
| 15 | Dexamethasone | 20mg | PO | stat | To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack) |
| | Paracetamol | 1gm | PO | stat | |
| | Chlorphenamine | 4mg | PO | stat | |
| | **DARATUMUMAB** | **1800mg** | SC | bolus | Inject 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 at other sites of the body as no data are available. Injection sites should be rotated for successive injections |

**TTOs cycle 1-3 only**

| TTO | Drug | Dose | Route | Directions |
|---|---|---|---|---|
| Day 1 | Dexamethasone | 20mg | PO | OM on days 2, 4, 5, 9, 11, 12 and 16.<br>(Where appropriate dose must be taken prior to bortezomib injection i.e. on days where bortezomib alone is administered) |
| | Aciclovir | 400mg | PO | BD continuously (plus 3 more months after completion of last treatment dose) |
| | Co-trimoxazole | 480mg | PO | TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last treatment dose) |
| | Allopurinol | 300mg | PO | OD and review after 4 weeks. Prescribe continuing supply if required from cycle 2 onwards. |
| | Omeprazole | 20mg | PO | OD |
| | Metoclopramide | 10mg | PO | Take 10mg TDS for 3 days after bortezomib then up to TDS when required. Do not take for more than 5 days continuously.<br><br>On Cycle 1 only, then prescribe as required |
| | Loperamide | 2mg | PO | Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day).<br><br>Dispense on Cycle 1 only, and then prescribe as required. |
| | **Consider the use of prophylactic anti-fungals** | | | |
| | **Pre Med TTO packs to be dispensed.** | | | |

**Cycle 4-8: repeat every 21 days**

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---|---|---|---|
| 1 | Dexamethasone | 20mg | PO | stat | To be administered 1-3 hours prior to daratumumab. (dispensed as TTO pack) |
| | Paracetamol | 1gm | PO | stat | |
| | Chlorphenamine | 4mg | PO | stat | |
| | **DARATUMUMAB** | **1800mg** | SC | bolus | Inject 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 at other sites of the body as no data are available.<br>Injection sites should be rotated for successive injections |
| | **BORTEZOMIB** | **1.3mg/m$^2$** | SC | bolus | |
| 4 | **BORTEZOMIB** | **1.3mg/m$^2$** | SC | bolus | |
| 8 | **BORTEZOMIB** | **1.3mg/m$^2$** | SC | bolus | |
| 11 | **BORTEZOMIB** | **1.3mg/m$^2$** | SC | bolus | |

**TTOs cycle 4-8**

| TTO | Drug | Dose | Route | Directions |
|---|---|---|---|---|
| Day 1 | Dexamethasone | 20mg | PO | OM on days 2,4,5,8,9,11 and 12<br>(Where appropriate dose must be taken prior to bortezomib injection ie on days where bortezomib alone is administered) |
| | Aciclovir | 400mg | PO | BD continuously (plus 3 more months after completion of last treatment dose) |
| | Co-trimoxazole | 480mg | PO | TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last treatment dose) |
| | Omeprazole | 20mg | PO | OD |
| | Metoclopramide | 10mg | PO | Take 10mg TDS for 3 days after bortezomib then up to TDS when required<br>Do not take for more than 5 days continuously.<br>On Cycle 1 only, then prescribe as required |
| | Loperamide | 2mg | PO | Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day).<br>Dispense on Cycle 1 only, and then prescribe as required. |
| | **Consider the use of prophylactic anti-fungals** | | | |
| | **Pre Med TTO packs to be dispensed.** | | | |

**Cycle 9 onwards repeat every 28 days**

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---|---|---|---|
| 1 | Dexamethasone | 12mg | PO | stat | To be administered 1-3 hours prior to daratumumab.<br>NB review dose of dexamethasone and increase back to 20mg where clinically indicated.<br>(dispensed as TTO pack) |
| | Paracetamol | 1gm | PO | stat | |
| | Chlorphenamine | 4mg | PO | stat | |
| | **DARATUMUMAB** | **1800mg** | SC | bolus | Over 3-5minutes<br>Inject 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 at other sites of the body as no data are available.<br>Injection sites should be rotated for successive injections |

**TTOs cycle 9 onwards**

| TTO | Drug | Dose | Route | Directions |
|---|---|---|---|---|
| Day 1 | Dexamethasone | 4mg | PO | To be taken in the morning for 2 days starting the day after daratumumab treatment.<br>NB if no major IRR after sc daratumumab, this can be stopped (notes above) |
| | Aciclovir | 400mg | PO | BD continuously (plus 3 more months after completion of last treatment dose) |
| | Co-trimoxazole | 480mg | PO | TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last treatment dose) |
| | Metoclopramide | 10mg | PO | Take 10mg up to TDS when required. Do not take for more than 5 days continuously.<br><br>On Cycle 1 only, then prescribe as required |
| | Loperamide | 2mg | PO | Take two capsules (4mg) after first loose stool, then one capsule (2mg) after each loose stool when required. (Maximum 16mg per day).<br><br>Dispense on Cycle 1 only, and then prescribe as required. |
| | **Consider the use of prophylactic anti-fungals** | | | |
| | **Pre Med TTO packs to be dispensed.** | | | |