PANOBINOSTAT / BORTEZOMIB (VELCADE) / DEXAMETHASONE (PanBorDex)

INDICATION

Relapsed or relapsed and refractory multiple myeloma in patients who have received at least 2 prior lines of therapy including bortezomib and an immunomodulatory agent (NICE TA380).

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&Es
   - LFTs
   - Calcium
   - Uric acid
   - CRP
   - Virology: HIV, Hepatitis B (including core antibody), and Hepatitis C
   - Calculated creatinine clearance (CrCl), urine protein/creatinine ratio
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
   - Serum free light chain assay (Freelite)
   - Hevylite analysis (if paraprotein level difficult to quantify)
   - Albumin & β2 microglobulin for ISS staging
   - 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.
   - Group and save
   - 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 NHS Foundation Trust
Salisbury District Hospital
Salisbury
Wiltshire
SP2 8BJ
ADDITIONAL INVESTIGATIONS

- Plasma viscosity if hyperviscosity suspected.

2. If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology.
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.
4. Fertility - all patients should be offered fertility advice, as appropriate.
5. Hydration - fluid intake of at least 3 litres /day should be attempted.
7. Treatment must be agreed at the relevant MDT.

REGIMENT SPECIFIC PRE-ASSESSMENT

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.

Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1. ECG must be performed prior to the start of therapy and repeated periodically every cycle during treatment as clinically indicated. QTcF must be <480 msec prior to initiation of treatment with panobinostat.

**DRUG REGIMEN:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bortezomib</strong></td>
<td>1.3 mg/m² given as SC bolus Days 1, 4, 8 and 11 as per SPC</td>
</tr>
<tr>
<td></td>
<td>We recommend Frequency is reduced to weekly, to days 1, 8, 15</td>
</tr>
<tr>
<td></td>
<td>From cycle 9, reduce to days 1 and 8.</td>
</tr>
<tr>
<td><strong>WITH</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Dexamethasone</strong></td>
<td>20 mg PO once daily</td>
</tr>
<tr>
<td></td>
<td>On the day of and day after each Bortezomib dose. This will usually be days 1,</td>
</tr>
<tr>
<td></td>
<td>2, 4, 5, 8, 9, 11 &amp; 12 For weekly bortezomib patients, this will be</td>
</tr>
<tr>
<td></td>
<td>on days 1, 2, 8, 9, 15 and 16.</td>
</tr>
<tr>
<td></td>
<td>From cycle 9, reduce to days 1, 2, 8, and 9.</td>
</tr>
<tr>
<td><strong>WITH</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Panobinostat</strong></td>
<td>20 mg PO</td>
</tr>
<tr>
<td></td>
<td>Days 1, 3, 5, 8, 10 and 12. Consider dosing twice a week on days 1,5,8 and 12</td>
</tr>
</tbody>
</table>

At least 72 hours should elapse between consecutive doses of Bortezomib. Panobinostat is available as 10mg, 15mg and 20mg strength capsules.
CYCLE FREQUENCY
Repeat every 21 days, continue until signs of disease progression or unacceptable toxicity for up to 8 treatment cycles. In patients showing clinical benefit, treatment can continue for an additional 8 cycles (total 16 cycles).

CONTRAINDICATIONS
- Pregnant or breast-feeding women – absolute contraindication.
- Acute diffuse infiltrative pulmonary and pericardial disease.
- Patients with known sensitivity to bortezomib, boron or mannitol.
- Refer to the NPS treatment plan document for full details of contraindications and exclusion criteria.

INVESTIGATIONS (prior to the beginning of each treatment cycle)
- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC (weekly)
- U&E, LFTs, adjusted calcium, and magnesium
- ECG must be performed prior to the start of therapy and repeated periodically every cycle during treatment as clinically indicated. QTcF must be <480 msec prior to initiation of treatment with panobinostat.
- 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, Freelite assay.
- Consider repeat BM aspirate and trephine after 3 cycles in non-secretory myeloma and check result prior to starting cycle #5.
- Random blood glucose/blood sugar

DOSE MODIFICATIONS

Haematological toxicity
Baseline platelet count must be at least 100x 10⁹/L and baseline absolute neutrophil count (ANC) must be at least 1.0 x 10⁹/L. If the counts are lower due to heavy marrow burden patient can be started on this protocol but FBC should be monitored weekly (or more often as clinically indicated) during treatment.

Dosing levels of panobinostat and bortezomib:

<table>
<thead>
<tr>
<th></th>
<th>Initial dose</th>
<th>Dose Level -1</th>
<th>Dose Level - 2</th>
<th>Then</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panobinostat</td>
<td>20mg</td>
<td>15mg</td>
<td>10mg</td>
<td>discontinue</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3mg/m²</td>
<td>1.0mg/m²</td>
<td>0.7 mg/m²</td>
<td>discontinue</td>
</tr>
</tbody>
</table>
# Thrombocytopenia:

<table>
<thead>
<tr>
<th>Thrombocytopenia grade on day of treatment</th>
<th>Modification of panobinostat starting dose</th>
<th>Panobinostat dose on recovery to grade 2 thrombocytopenia ($\geq 50 \times 10^9/l$)</th>
<th>Modification of bortezomib starting dose</th>
<th>Bortezomib dose on recovery to grade 2 thrombocytopenia ($\geq 50 \times 10^9/l$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 Platelets $&lt; 50 \times 10^9/l$ with bleeding</td>
<td>Omit dose</td>
<td>Resume at reduced dose</td>
<td>Omit dose</td>
<td>Resume at same dose</td>
</tr>
<tr>
<td>Grade 4 Platelets $&lt; 25 \times 10^9/l$</td>
<td>Omit dose</td>
<td>Resume at reduced dose</td>
<td>Omit dose</td>
<td>Resume at reduced dose</td>
</tr>
</tbody>
</table>

# Neutropenia:

Support with GCSF can be considered as per local policy

<table>
<thead>
<tr>
<th>Neutropenia grade on day of treatment</th>
<th>Modification of panobinostat starting dose</th>
<th>Panobinostat dose on recovery to grade 2 neutropenia ($&lt;1.5-1.0 \times 10^9/l$)</th>
<th>Modification of bortezomib starting dose</th>
<th>Bortezomib dose on recovery to grade 2 neutropenia ($&lt;1.5-1.0 \times 10^9/l$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 neutropenia ($&lt;1.0-0.5 \times 10^9/l$)</td>
<td>Omit dose</td>
<td>Resume at same dose</td>
<td>Omit dose</td>
<td>Resume at same dose</td>
</tr>
<tr>
<td>Grade 4 neutropenia ($&lt;0.5 \times 10^9/l$) or febrile neutropenia ($&lt;1.0 \times 10^9/l$ and fever $\geq 38.5^\circ C$)</td>
<td>Omit dose</td>
<td>Resume at reduced dose</td>
<td>Omit dose</td>
<td>Resume at same dose</td>
</tr>
</tbody>
</table>

# Diarrhoea:

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>Grade on day of treatment</th>
<th>Modification of panobinostat starting dose</th>
<th>Panobinostat dose on recovery to $\leq$ grade 1</th>
<th>Modification of bortezomib starting dose</th>
<th>Bortezomib dose on recovery to $\leq$ grade 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>Grade 2 despite anti-diarrhoeal medicinal product</td>
<td>Omit dose</td>
<td>Resume at the same dose</td>
<td>Omit dose</td>
<td>Resume at reduced dose or change to once weekly</td>
</tr>
<tr>
<td></td>
<td>Grade 3 despite anti-diarrhoeal medicinal product</td>
<td>Omit dose</td>
<td>Resume at reduced dose</td>
<td>Omit dose</td>
<td>Resume at reduced dose or with the same dose but with a once-weekly schedule</td>
</tr>
<tr>
<td></td>
<td>Grade 4 despite anti-diarrhoeal medicinal product</td>
<td>Permanently discontinue</td>
<td>Permanently discontinue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Nausea and vomiting:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Grade 1 &amp; 2</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panobinostat</td>
<td>Maintain dose level</td>
<td>Discontinue until resolves to ≤ grade 1 then restart reduced by one dose level</td>
</tr>
</tbody>
</table>

Bortezomib-related neuropathy:

<table>
<thead>
<tr>
<th>Severity of neuropathy</th>
<th>Posology 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</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>

Renal and hepatic impairment:

Panobinostat:

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>- No dose reductions are required in mild to severe renal impairment. - No studies were conducted in end stage renal failure patients. Avoid use in these patients</td>
<td>Mild (Bili ≤1.0 x ULN and ALT/AST &gt;ULN) or (Bili &gt;1.0 x ULN and ≤1.5 x ULN and any ALT/AST): Start at reduced dose 15 mg in 1st cycle. Consider dose escalation up to 20 mg in subsequent cycles if tolerated. Moderate (Bili &gt;1.5 x ULN and ≤3.0 x ULN and any ALT/AST): Start at reduced dose 10 mg in the 1st cycle. Consider dose escalation up to 15 mg in subsequent cycles if tolerated</td>
</tr>
</tbody>
</table>

Bortezomib:

<table>
<thead>
<tr>
<th>Renal</th>
<th>Hepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>- For dialysis patients, bortezomib should be given after dialysis</td>
<td>Bili &gt; 1.5x 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>

QTc prolongation

Patients must have QTcF < 480 msec prior to initiating treatment with panobinostat. If during treatment, the QTcF increases to ≥480 msec, treatment must be interrupted and any electrolyte abnormalities must be corrected, adjust dosing as follows:

- Omit, if QTcF is ≥480 msec or above 60 msec from baseline.
- If resolved within 7 days, resume at prior dose if first occurrence or at reduced dose if QT prolongation is recurrent.
- If unresolved within 7 days, treatment should be discontinued.
- If any QTcF value is above 500 msec, permanently discontinue panobinostat.
EMETIC RISK

Moderately emetogenic.
Avoid anti-emetics which cause QTC prolongation e.g. ondasetron, metoclopramide.

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only.
- Prophylactic aciclovir 200 mg bd to tid for the duration of treatment and 3 months post therapy.
- Bone protection as per NSSG Bone Protection protocol MM.3
- Proton Pump Inhibitor or H2 antagonist at clinician’s discretion.
- Consider prophylactic co-trimoxazole, particularly if heavily pre-treated or previous autograft.
- Loperamide 4mg stat then 2mg prn every 4 hours up to maximum of 16mg in 24 hours should be prescribed readily available for patient to start at the first episode of diarrhoea.
- Antiemetic: cyclizine. Avoid drugs which can cause QTc prolongation

DRUG INTERACTIONS
(Consult pharmacist or Refer to SmPC for further details on drug interactions)

CYP3A4 inhibitors/inducers:
In patients who take concomitant medicinal products which are strong CYP3A and/or P-gp inhibitors, including, but not limited to, ketoconazole, itraconazole, voriconazole, ritonavir, saquinavir, telithromycin, posaconazole and nefazodone, the dose of panobinostat should be reduced to 10 mg. If continuous treatment with a strong CYP3A4 inhibitor is required, a dose escalation from 10 mg to 15 mg panobinostat may be considered based on patient tolerability.

- Drugs that may cause QTc prolongation or induce torsades de pointes should be avoided.
- Patients should be cautioned about the use of concomitant medications that may be associated with peripheral neuropathy (such as amiodarone, antivirals, isoniazid, nitrofurantoin or statins), or with a decrease in blood pressure.
- Patients on bortezomib should be closely monitored if on CYP3A4-inhibitors (e.g. ketoconazole, ritonavir). The concomitant use of bortezomib with strong CYP3A4-inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, and St John’s wort) is not recommended as efficacy may be reduced.
- Strong CYP3A inducers should be avoided with Panobinostat. Reduce the starting dose of Panobinostat to 10mg when co-administered with strong CYP3A inhibitors.
- Patients on oral hypoglycaemic may require close monitoring of blood sugar levels.
### ADVERSE EFFECTS/REGIMEN COMPLICATIONS

**WARNING ABOUT PANOBINOSTAT: FATAL AND SERIOUS TOXICITIES:**

**SEVERE DIARRHEA AND CARDIAC TOXICITIES**

Severe diarrhoea occurred in 25% of panobinostat treated patients. Monitor for symptoms, institute anti-diarrheal treatment, interrupt panobinostat and then reduce dose or discontinue it.

Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred in patients receiving panobinostat. Arrhythmias may be exacerbated by electrolyte abnormalities. Obtain ECG and electrolytes at baseline and periodically during treatment as clinically indicated.

- **Diarrhoea**: Severe diarrhoea occurred in 25% of treated patients. Monitor for symptoms, institute anti-diarrheal treatment, interrupt panobinostat and then reduce dose or discontinue it.
- **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 for use of bortezomib in patients with existing peripheral neuropathy (>Grade 2).
- **Cardiac adverse effects**: Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred in patients receiving panobinostat. Arrhythmias may be exacerbated by electrolyte abnormalities. Obtain ECG and electrolytes at baseline and periodically during treatment as clinically indicated.
- **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. Management of orthostatic/postural hypotension may include adjustment of antihypertensive medicinal products, rehydration or administration of mineralocorticosteroids and/or sympathomimetics. Patients should be instructed to seek medical advice if they experience symptoms of dizziness, light-headedness or fainting spells. Patients who experience dizziness or low blood pressure may benefit from 500 ml intravenous 0.9% sodium chloride with each bortezomib dose.
- **Herpes zoster virus reactivation, progressive multifocal leukoencephalopathy (PML)**

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**TREATMENT RELATED MORTALITY**

5%

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**REFERENCES**


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**REVIEW**

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nadjoua Maouche Pharmacist</td>
<td>Indication, Drug regime, Investigations, Dose modification, Adverse effects, contraindication removed</td>
<td>May 2016</td>
<td>2.0</td>
<td>May 2018</td>
</tr>
<tr>
<td>Faouzi Djebbari (Haematology Pharmacist)</td>
<td>Updated dose modifications, renal and hepatic impairment, concurrent medication, drug interactions and references</td>
<td>July 2017</td>
<td>2.1</td>
<td>May 2018</td>
</tr>
</tbody>
</table>