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| **Indication** | Treatment option for adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent.<br>Funded only when used as combination regimen |
| **Treatment Intent** | Complete/ Partial Remission |
| **Frequency and number of cycles** | Repeat every 28 days<br>Maximum of 16 cycles |
| **Monitoring Parameters pre-treatment** | • **Virology screen: Hepatitis B & C, HIV (Hepatitis B includes HBVsAg and HBVcAb)**<br>• **ECG prior to start of therapy and before day 1 of each cycle** – QTcF must be </= 480msec prior to initiation of treatment with panobinostat. Omit dose if QTcF is >/= 480 msec or above 60 msec from baseline.<br>• If QT prolongation is resolved within 7 days, resume treatment at prior dose for initial occurrence or at reduced dose if QT prolongation is recurrent. If QT prolongation is unresolved within 7 days, OR if any QTcF value is above 500 msec, panobinostat should be permanently discontinued.<br>• FBC before every cycle (1-16) and on days 8, 15 and 22 for cycles 1 to 8 and on day 15 of cycles 9 to 16.<br>• U&Es/LFTs before each cycle. Any abnormal serum potassium, magnesium or phosphorus values should be corrected prior to initiation of panobinostat.<br>• Regular monitoring of blood glucose is considered good practice but optional<br>• Thyroid function should be monitored before cycle 1 and then as clinically indicated.<br>• A baseline ECHO or MUGA scan should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. ECHO/MUGA should be repeated if there is suspicion of cardiac toxicity at any point during treatment.<br>• At least 72 hours must elapse between consecutive Bortezomib doses.<br>• Review after cycle 4 for response.<br>• Consider PCP prophylaxis/ antiviral/ antifungal therapy if lymphocyte count <1.0 x $10^9$/L<br>• **Renal Impairment:**<br>  ○ **Bortezomib** should be used with caution in patients with CrCl < 20ml/min not undergoing dialysis; however, no specific dosing recommendations have been made. Since dialysis may reduce bortezomib concentrations, bortezomib should be administered after the dialysis procedure.<br>  ○ **Panobinostat**, no dose reduction in renal impairment is required for panobinostat. Panobinostat has not been studied in patients with end stage renal disease or patients on dialysis.<br>• **Hepatic Impairment:**<br>  ○ **Bortezomib:** In moderate hepatic impairment (>1.5 ULN Bilirubin & any AST) reduce to 0.7 mg/$m^2$ in the first treatment cycle. Consider dose escalation to 1.0 mg/$m^2$ or further dose reduction to 0.5 mg/$m^2$ in subsequent cycles based on tolerability.<br>  ○ **Panobinostat:** In mild hepatic impairment (</=1xULN bilirubin & AST >ULN **or** >1xULN to </=1.5xULN bilirubin & any AST) reduce dose to 15mg for cycle 1. Consider dose escalation up to 20mg in subsequent cycles based on patient tolerability.<br>In moderate impairment (>1.5 to 3 x ULN Bilirubin & any AST) reduce panobinostat dose to 10mg for cycle 1. Consider dose escalation up to 15mg in subsequent cycles based on patient tolerability.<br>  ○ This regimen is contraindicated in severe hepatic impairment. |

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| | • **Dose modifications**<br>**Haematological Toxicity: Day 1**: Proceed when neutrophils >/= 1.0 x $10^9$/L **and** platelets >/= 100x $10^9$/L. If neutrophils <1.0 x $10^9$/L **or** platelets <100 x$10^9$/L delay on a weekly basis until recovery of toxicity.<br>**Days 8, 15 and 22 see table 1.**<br>• **Non-Haematological Toxicity:**<br>• Gastrointestinal toxicity: see table 2<br>• Neuropathic pain and/or peripheral neuropathy: see table 3<br>• If a dose reduction of panobinostat is required, reduce in increments of 5mg. The dose should not be reduced below 10mg.<br>• For any other >/= Grade 3 non-haematological toxicities considered to be related to bortezomib therapy then this should be withheld until symptoms of the toxicity have resolved to </= Grade 2. Bortezomib may then be reinitiated at a dose reduced by one dose level (from 1.3mg/$m^2$ to 1mg/$m^2$, or from 1mg/$m^2$ to 0.7mg/$m^2$).<br>• **Doses reduced for toxicity should not be re-escalated.**<br>• **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:**<br>• Patients on continuous concomitant strong CYP3A and/or Pgp inhibitors should have the dose of panobinostat reduced to 10mg. This can be escalated to 15mg, based on tolerability.<br>• Avoid star fruit, grapefruit, grapefruit juice, pomegranate and pomegranate juice as these are known to inhibit P450 3A enzymes and increase the bioavailability of panobinostat.<br>• Concomitant use of strong CYP3A4 inducers including but not limited to carbamazepine, phenobarbital, phenytoin, rifampicin and St John's Wort should be avoided as the efficacy of panobinostat may be reduced.<br>• Patients should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir).<br>• 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.<br>• **Missed dose:** Omitted doses of bortezomib should not subsequently be made up. If a dose of panobinostat is missed, if within 12 hours of schedule dose it should be taken if more than 12 hours omit dose and continue with next scheduled dose.<br>• **For oral self-administration:** refer to local Trust policy on oral anti-cancer medicines and supply Patient Information Leaflet and Cancerbackup information sheet. |
| **References** | https://www.medicines.org.uk/emc<br>https://www.medicinescomplete.com/#/content/bnf/_515336032#content%2Fbnf%2F_515336032%23pot-medicines<br>KMCC protocol HAEM-MYEL-021 C1-8 V2 ACN protocol V1 |

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

**Table 1 Day 8, 15 and 22 haematological toxicity:**

| **Platelets (x $10^9$/L)** | **Modification of panobinostat dose** | **Modification of bortezomib dose** |
|---|---|---|
| >/= 50 | 100 % dose | 100 % dose |
| < 50 with bleeding | Withhold until platelet recovery ≥ 50 x $10^9$/L, resume at reduced dose.<br>Reduce by 5mg (panobinostat dose should not be reduced below 10mg). | Omit dose.<br>Once platelets recover ≥ 50 x $10^9$/L:<br>For first occurrence: resume bortezomib at same dose.<br>For second occurrence: resume bortezomib at reduced dose (from 1.3mg/$m^2$ to 1mg/$m^2$, or from 1mg/$m^2$ to 0.7mg/$m^2$). |
| < 25 | Withhold until platelet recovery ≥ 50 x $10^9$/L, resume at reduced dose.<br>Reduce by 5mg (panobinostat dose should not be reduced below 10mg). | Omit dose.<br>Once platelets recover ≥ 50 x $10^9$/L:<br>For first occurrence: resume bortezomib at same dose.<br>For second occurrence: resume bortezomib at reduced dose (from 1.3mg/$m^2$ to 1mg/$m^2$, or from 1mg/$m^2$ to 0.7mg/$m^2$). |
| **Neutrophils (x $10^9$/L)** | **Modification of panobinostat dose** | **Modification of bortezomib dose** |
| >/= 1.0 | 100% dose | 100% dose |
| 0.5-0.9 | Withhold until neutrophil recovery ≥ 1.0 x $10^9$/L, resume at same dose.<br>Reduce by 5mg (panobinostat dose should not be reduced below 10mg). | Omit dose.<br>Once neutrophils recover ≥ 1.0 x $10^9$/L,<br>resume bortezomib at same dose. |
| < 0.5 | Withhold until neutrophil recovery ≥ 1.0 x $10^9$/L, resume at reduced dose.<br>Reduce by 5mg (panobinostat dose should not be reduced below 10mg). | Omit dose.<br>Once neutrophils recover ≥ 1.0 x $10^9$/L,<br>resume bortezomib at same dose. |

**Table 2 Gastrointestinal toxicity**

| | **Panobinostat** dose | **Bortezomib** dose |
|---|---|---|
| Grade 2 diarrhoea | Omit until recovery to</= Grade 1, resume at same dose. | Omit until recovery to </=Grade 1, resume at reduced dose. |
| Grade 3 diarrhoea, nausea or vomiting | Omit until recovery to ≤ Grade 1, reduce by 5mg (panobinostat dose should not be reduced below 10mg). | Omit until recovery to </= Grade 1, resume at reduced dose. |
| Grade 4 | Permanently discontinue | Permanently discontinue |

**Table 3 Neuropathic pain and/or peripheral neuropathy**

| **NCI CTCAE Grade** | **Bortezomib dose** |
|---|---|
| Grade 1 (asymptomatic; loss of deep tendon reflexes or paraesthesia) with no pain or loss of function | No action |
| Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental activities of daily living such as preparing meals, shopping for groceries or clothes, using telephone, managing money, etc) | Reduce to 1mg/$m^2$ |
| Grade 2 with pain or Grade 3 (severe symptoms; limiting self-care activities of daily living such as bathing, dressing and undressing, feeding self, using the toilet, taking medicinal products, and not bedridden) | Withhold bortezomib treatment until symptoms of toxicity have resolved.<br>When toxicity resolves, re-initiate bortezomib treatment and reduce dose to 0.7mg/$m^2$ once per week. |
| Grade 4 (life threatening consequences; urgent intervention indicated) and/or severe autonomic neuropathy | Discontinue bortezomib |

**Repeat every 28 days: Cycle 1-8**

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---|---|---|---|
| Day 1,8,15 and 22 | **BORTEZOMIB** | **1.3mg/$m^2$** | SC | stat | |
| TTO | Drug | Dose | Route | Directions | |
| Day 1 | **DEXAMETHASONE** | 20mg | PO | OM days 1,8,15 and 22 | |
| | **PANOBINOSTAT** | 20mg | PO | OM days 1,3,5,15,17 and 19<br>(available as 20mg, 15mg & 10mg capsules) | |
| | Metoclopramide | 10mg | PO | Up to TDS PRN<br>Do not take for more than 5 days continuously. | |
| | Omeprazole | 20mg | PO | OM | |
| | Loperamide | 2mg | PO | Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified. | |
| | Aciclovir | 400mg | PO | BD | |
| | Allopurinol | 100mg-300mg | PO | OD for 3 weeks **Cycle 1 only.** | |

**Cycle 9 to 16**

| Day | Drug | Dose | Route | Infusion Duration | Administration |
|---|---|---|---|---|---|
| Day 1 and 15 | **BORTEZOMIB** | **1.3mg/m$^2$** | SC | STAT | |
| TTO | Drug | Dose | Route | Directions | |
| | **DEXAMETHASONE** | 20mg | PO | OM days 1 and 15 | |
| | **PANOBINOSTAT** | 20mg | PO | OM days 1,3,5,15,17 and 19 (available as 20mg, 15mg & 10mg capsules) | |
| | Metoclopramide | 10mg | PO | Up to TDS PRN Do not take for more than 5 days continuously. | |
| | Omeprazole | 20mg | PO | OM | |
| | Loperamide | 2mg | PO | Take 4mg (2 capsules) initially, then 2mg (1 capsule) after each loose stool when required. Maximum 16mg (8 capsules) a day. Dispense 30 capsules on cycle 1 then only if specified. | |
| | Aciclovir | 400mg | PO | BD | |