PANOBINOSTAT & BORTEZOMIB

An option for treating adult patients with relapsed and/or refractory multiple myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent
NICE approved January 2016

Drugs/Dosage:

Cycles 1 – 8 (3-week cycles)*:

Bortezomib (2.5mg/ml)	1.3mg/m^2	s/c bolus on Day 1, Day 4, Day 8 and Day 11 (at least 72 hours between doses)
Dexamethasone	20mg	po once daily on Days 1+2, 4+5, 8+9, 11+12
Panobinostat	20mg	po once daily on Days 1, 3, 5, 8, 10 & 12

then, for patients showing clinical benefit:

Cycles 9 – 16 (3-week cycles):

Bortezomib (2.5mg/ml)	1.3mg/m^2	s/c bolus on Day 1 and Day 8
Dexamethasone	20mg	po once daily on Days 1+2, 8+9
Panobinostat	20mg	po once daily on Days 1, 3, 5, 8, 10 & 12

**Alternative schedule for patients aged > 75 years, depending on their general PS and co-morbidities (3-week cycle):*

Bortezomib (2.5mg/ml)	1.3mg/m^2	s/c bolus on Day 1 and Day 8
Dexamethasone	20mg	po once daily on Day 1 and Day 8
Panobinostat	15mg	po once daily on Days 1, 3, 5, 8, 10 & 12 of Cycle 1, and if tolerated, escalate to 20mg dose on Cycle 2

Other Drugs:

Allopurinol, dose according to renal function – review after the 1st cycle.
Omeprazole 20mg od (or ranitidine) is recommended whilst treating with steroids.
Fluconazole 100mg po od as antifungal prophylaxis
Aciclovir 400mg po bd
Consider PCP prophylaxis – prescribe according to unit practice/protocol.
Ensure patient has a supply of loperamide, for panobinostat-associated diarrhoea

Frequency:

3 weekly cycle for 8 cycles
Then a further 8 cycles, with once weekly bortezomib and dexamethasone, may be given to patients showing clinical benefit after the first 8 cycles.
Funding is for combination treatment, so if a patient needs to permanently discontinue one of the agents, then the other agent should also be discontinued.

Administration:

Bortezomib given by subcutaneous bolus injection into the thigh or abdomen.
Rotate sites: avoid injecting into the same site in the same cycle, e.g. alternate between right and left abdomen, and right and left thigh.
Patient should be encouraged to drink 2 – 3 litres over the 24 hours after each dose of bortezomib in the first cycle, to reduce the risk of tumour lysis syndrome.
Panobinostat is available as 10mg, 15mg and 20mg capsules, and should be swallowed whole with water, with or without food. If a dose is missed, it can be taken up to 12 hours after the specified dose time.
Grapefruit, grapefruit juice, pomegranates, pomegranate juice and star fruit should all be avoided while on panobinostat.
Dexamethasone is to be taken in the morning with or after food.

Reason for Update: frequency of FBC monitoring updated; thrombocytopenia table clarified	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 2	Date: 27.11.17
Supersedes: Version 1	Review date: December 2019
Prepared by: S Taylor	Checked by: C Tucker

Main Toxicities: *panobinostat side effects:* myelosuppression, with thrombocytopenia of particular concern; diarrhoea; prolonged QT_c interval; raised LFTs; hypothyroidism
bortezomib side effects: myelosuppression (thrombocytopenia common but recovers rapidly; neutropenia usually less severe); postural hypotension; rash; GI toxicity; peripheral neuropathy (use with caution in patients with pre-existing neuropathy); exacerbation / development of heart failure (monitor patients with risk factors or pre-existing heart disease closely); injection site reactions; *steroid side effects*

Anti- emetics: moderately emetogenic (but anti-emetic doses of dexamethasone not required)
For s/c route of bortezomib, avoid inserting a cannula: oral metoclopramide to be taken before each bortezomib dose, and then tds as required.
Severe nausea has been reported with panobinostat, but domperidone or ondansetron should be used with caution, due to their effect on QT interval.

Regular Investigations:		
	FBC	Day 1 & Day 8* of Cycles 1 & 2, then see below**
	U&Es & LFTs	Day 1
	Mg^{2+}	as indicated, especially in patients with diarrhoea
	MUGA/echo	only if concerned
	Blood pressure, lying and standing	Day 1 (& with every dose if sensori-motor problems)
	Paraprotein and/or serum free light chains	Day 1
	ECG, including QT_c	baseline, after one cycle, then periodically during treatment only if any concerns
	Blood glucose and blood pressure	see Comments
	Thyroid function	as clinically indicated

**If there is any clinical concern, arrange for FBC on Day 4 & 11 as well;*
SPC advice is to monitor patients aged > 65 years twice weekly – and monitoring of blood counts should also be considered during the "rest period" e.g. on days 15 and/or 18, especially in patients ≥ 65 years and patients with a baseline platelet count below 150 x 10^9/l.
*** For patients with stable blood counts after 2 cycles and no clinical concerns, then FBC monitoring may be reduced to Day 1 only of each cycle,* ***only with approval from the patient's haematology Consultant.***

Comments: Blood glucose and blood pressure monitoring to be tailored according to individual patient needs, while on high dose dexamethasone.

The IV route (IV bolus over 3 – 5 seconds) for bortezomib may be substituted if the s/c route is considered inappropriate (eg ITU patient), although note that this is associated with an increased incidence and severity of neuropathy-related toxicities. Also note that aseptics need to be informed of the change in route, as the formulation is different.

Loperamide should be started at the first sign of abdominal cramping, loose stools or diarrhoea.

Interactions: Reduce panobinostat dose to 10mg if patient requires a concomitant strong CYP3A4 inhibitor and / or Pgp inhibitor (e.g. itraconazole, voriconazole, ritonavir, saquinavir, clarithromycin, posaconazole).
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.
Panobinostat should be avoided in patients with any hepatic impairment and receiving a strong CYP3A4 inhibitor.

Concomitant use of strong enzyme inducers (e.g. carbamazepine, phenytoin, St John's wort) with panobinostat should be avoided, as this may increase the risk of therapeutic failure. Women using hormonal contraceptives should additionally use a barrier method of contraception.

Dose Modifications

Haematological Toxicity:

Before Cycle 1, and before Day 1 of subsequent cycles:
Proceed only if platelets ≥ 100 x 10^9/L and neutrophils ≥ 1.0 x 10^9/L

If platelet count falls to < 50 x 10^9/l, monitor the platelet counts at least twice weekly until recovered to > 50 x 10^9/l. Platelet transfusions may be required.

Treatment may need to be discontinued if thrombocytopenia does not improve despite the dose modifications described below and/or the patient requires repeated platelet transfusions. N.B. Panobinostat should be reduced in 5mg steps, but should not be reduced below 10mg.

Dose modifications for thrombocytopenia:

Platelet count (x 10^9/l) on day of treatment	**Panobinostat**	**Bortezomib**
Platelets < 50 with bleeding, *or* Platelets < 25	Omit dose (delay if Day 1 of cycle). Once platelets ≥ 50 x 10^9/l (≥ 100 x 10^9/l if Day 1 of cycle), resume with a **5mg dose reduction.**	Omit dose (delay if Day 1 of cycle), and only resume once platelets ≥ 50 x 10^9/l (≥ 100 x 10^9/l if Day 1 of cycle). If only 1 dose omitted, resume at same dose. But if more than 1 dose omitted, resume with reduced dose.

Dose modifications for neutropenia:

Neutrophil count (x 10^9/l) on day of treatment	**Panobinostat**	**Bortezomib**
< 1.0 – 0.5	Omit dose. Once neutrophils ≥ 1.0 x 10^9/l, resume at the same dose.	Omit dose. Once neutrophils ≥ 1.0 x 10^9/l, resume at the same dose.
< 0.5, or < 1.0 with temp ≥38.5^{o}C	Omit dose. Once neutrophils ≥ 1.0 x 10^9/l, resume with a **5mg dose reduction.**	

Diarrhoea:

Grade of diarrhoea, despite loperamide	**Action**
Grade 2	Interrupt treatment until resolved to Grade 0-1, then resume with panobinostat at the same dose; and bortezomib at a reduced dose or change to once weekly.
Grade 3	Interrupt treatment until resolved to Grade 0-1, then resume panobinostat **with a 5mg dose reduction;** and bortezomib at a reduced dose, or changed to once weekly.
Grade 4	Discontinue panobinostat and bortezomib permanently

QTc prolongation: QTc must be < 480 msec before initiating treatment.
Ensure abnormal electrolytes (K^+, Mg^{2+} and PO_4) are corrected prior to initiation of treatment.

In the event of QT prolongation after treatment has started:

- Omit panobinostat if QTc ≥ 480 msec, or above 60 msec from baseline reading.
- 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 QT_c > 500 msec, treatment should be discontinued.

Steroid Side Effects: If severe steroid-related side effects develop, withhold further dexamethasone until resolved to Grade 2 or less. Then re-start with a 50% dose reduction.

Sensory and Motor Neuropathy: Symptoms include numbness, tingling, burning, cramps, dysaesthesias.
This dose reduction schedule applies to new neuropathy symptoms (excludes pre-existing stable neuropathy):

Dose level	Dose of bortezomib (mg/m^2)
0	1.3
- 1	1.0
- 2	0.7

Severity of peripheral neuropathy	Modification of dose and regimen
Grade 1 (paraesthesia and/or loss of reflexes) with no pain or loss of function	For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule: no action, or reduce dose to 1.0mg/m^2
Grade 1 with pain or Grade 2 (interfering with function but not the activities of daily living)	Withhold bortezomib treatment until symptoms resolved to Grade 1. Treat with appropriate anti-neuropathic agents. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule, reduce dose to next level down.
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib treatment until symptoms resolved to Grade 1. Treat with appropriate anti-neuropathic agents. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule and maintain same dose. For patients on weekly schedule, reduce dose to next level down.
Grade 4 (sensory neuropathy which is disabling or motor neuropathy which is life-threatening or leads to paralysis)	Discontinue bortezomib

Autonomic neuropathy, diarrhoea and hypotension: This can come on insidiously and careful questioning of patients for symptoms of postural dizziness and unsteadiness is essential. The majority of patients on anti-hypertensive treatment will need their medication adjusting. Any patient who develops signs/symptoms of sensori-motor neuropathy should have lying and standing BP measurements at *each* dose of bortezomib, not just on day 1, even if asymptomatic.

Severity of autonomic neuropathy	Modification of dose and regimen
Grade 1: Occasional dizziness on standing (<3x/week)	No action
Grade 2: Regular dizziness on standing with no postural drop, or Grade 2 diarrhoea	Withhold bortezomib treatment until symptoms resolved to Grade 1. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule, reduce dose to next level down (1.3mg/m^2 to 1.0mg/m^2; 1.0mg/m^2 to 0.7mg/m^2)
Grade 3: Postural drop of ≥20mm Hg with or without dizziness. Dizziness interfering with activities of daily living, or Grade 3 diarrhoea	Withhold bortezomib treatment until symptoms resolved to Grade 1. When toxicity resolves, re-initiate bortezomib treatment as follows: For patients on bi-weekly schedule, change to weekly schedule at same dose. For patients on weekly schedule, reduce dose to next level down (1.3mg/m^2 to 1.0mg/m^2; 1.0mg/m^2 to 0.7mg/m^2)
Grade 4: Syncopal episodes or other autonomic disturbance e.g. > Grade 3 diarrhoea	Discontinue bortezomib

Other Toxicities:

If any other Grade 3 or 4 non-haematological toxicities due to bortezomib occur, bortezomib should be withheld.
Once recovered, bortezomib may be re-introduced with a 25% dose reduction.

If Grade 3 nausea or Grade 3 - 4 vomiting, despite anti-emetic usage, panobinostat should be temporarily discontinued. On recovery to Grade 1, it may be resumed with a 5mg dose reduction.

If any other panobinostat-related Grade 3 or 4 toxicities, or Grade 2 recurrence, omit panobinostat until recovery to Grade ≤1, and then resume treatment at a reduced dose.
If any Grade 3 - 4 toxicity recurrence, a further panobinostat dose reduction may be considered once resolved to Grade <1.

Bortezomib injection site reactions (up to 5cm in diameter) are generally Grade 1 (red, dry or itchy) and last 3 – 5 days. Symptoms may be routinely managed with aloe vera gel, or other moisturisers.

Renal Impairment:

Consider a dose reduction of bortezomib if CrCl < 20ml/min.
For patients on dialysis, bortezomib should be given after the dialysis procedure, as dialysis may reduce bortezomib concentrations.
Panobinostat dose adjustments are not necessary in patients with mild to severe renal impairment, although it has not been used in patients on dialysis or with end-stage renal disease.

Hepatic Impairment:

Grade of hepatic impairment	Panobinostat start dose	Bortezomib start dose
Mild: Bilirubin >1.0 – 1.5 x ULN and any AST ***or*** AST > ULN	Start at 15mg dose for the first cycle, then increase to 20mg dose for subsequent cycles, based on tolerability	No modification
Moderate: Bilirubin >1.5 – 3 x ULN and any AST	Start at 10mg dose for the first cycle, then increase to 15mg dose for subsequent cycles, based on tolerability	Reduce dose to 0.7mg/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 patient tolerability.
Severe	This regimen is contra-indicated	

Patient Information: Macmillan leaflet for Bortezomib; (no leaflet currently available for panobinostat)

References: San-Miguel, J et al ; Lancet 2014 ; 15 (11) : 1195 - 1206