PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Panobinostat, Bortezomib and Dexamethasone Multiple Myeloma

PROTOCOL REF: MPHAPBDMM
(Version No. 1.0)

Approved for use in:

NICE TA380

- Relapsed/refractory multiple myeloma adult patients who have received at least 2 prior lines of therapy (including bortezomib and an immunomodulatory agent)

Dosage:

Cycles 1-8

Drug	Dose	Route	Frequency
Panobinostat	**20mg**	Oral	Days 1, 3, 5, 8, 10 and 12
Bortezomib	**1.3mg/m^2**	Subcutaneous	Days 1, 4, 8 and 11
Dexamethasone	**20mg**	Oral	Days 1, 2, 4, 5, 8, 9, 11 and 12

Cycles 9-16

Drug	Dose	Route	Frequency
Panobinostat	**20mg**	Oral	Days 1, 3, 5, 8, 10 and 12
Bortezomib	**1.3mg/m^2**	Subcutaneous	Days 1 and 8
Dexamethasone	**20mg**	Oral	Days 1, 2, 8 and 9

Cycle **every 21 days** for a maximum of **16 cycles**

- At least 72 hours should elapse between administrations of bortezomib
- Patients should start with the licensed twice weekly dose of bortezomib, but at consultant discretion can be given weekly bortezomib if not tolerating treatment
- For patients >75 years of age, depending on the patient's general condition and concomitant diseases the following adjustments can be made at clinician discretion. Panobinostat may be started at a dose of 10 to 15 mg, and if tolerated in the first cycle escalated to 20 mg in the second cycle. Bortezomib may be started at 1.3 mg/m^2 once weekly on days 1 and 8, and dexamethasone at 20 mg on days 1 and 8.

Review for ongoing clinical benefit after 8 cycles- if ongoing benefits continue to a maximum of 16 cycles.

Administration (+/- Counselling Points):

- Dexamethasone tablets should be taken in the morning after food.
- Patients should be instructed to avoid star fruit, grapefruit, grapefruit juice, pomegranates and pomegranate juice due to interaction with panobinostat.
- Women of childbearing potential should use effective contraception during and for 3 months after treatment finishes. Hormonal methods may be affected by treatment and therefore additional barrier methods should also be used.

Emetogenic risk

Moderately emetogenic.

Supportive treatments:

- Metoclopramide PO 10mg TDS PRN
- Allopurinol PO 100mg or 300mg OD (depending on renal function) for first cycle only
- Omeprazole PO 20mg OD – to review each cycle
- Aciclovir PO 400mg BD for the duration of treatment
- Co-trimoxazole PO 480mg OD for the duration of treatment
- Loperamide PO 2mg PRN (Max 16mg in 24 hours)

Dosing in renal and hepatic impairment:

Renal	
Panobinostat	No dose reductions necessary. Note limited data on use in end-stage renal disease and dialysis patients.
Bortezomib	No dose reductions necessary if eGFR >20ml/min Unknown PK data in patients with severe renal impairment not undergoing dialysis Dialysis may reduce bortezomib concentrations and therefore should be administered after dialysis

Hepatic			
Panobinostat			
Grade of hepatic impairment	**Bilirubin level**	**AST levels**	**Modification of starting dose**
Mild	≤1.0 x ULN	>ULN	Reduce dose to 15mg panobinostat for the first cycle. (A dose escalation from 15mg to 20mg may be considered in subsequent cycles based on patient tolerability).
	>1.0x to 1.5x ULN	Any	
Moderate	>1.5x to 3x ULN	Any	Reduce dose to 10mg panobinostat for the first cycle. (A dose escalation from 10mg to 15mg may be considered in subsequent cycles based on patient tolerability).
Severe	>3x ULN	Any	Avoid due to limited safety data in this population.

Hepatic			
Bortezomib Metabolized by liver enzymes and therefore dose reductions required in moderate to severe impairment.			
Grade of hepatic impairment	**Bilirubin level**	**AST levels**	**Modification of starting dose**
Moderate	>1.5x to 3x ULN	Any	Reduce bortezomib to 0.7mg/m^2 in the first treatment cycle. Consider dose escalation to 1.0mg/m^2 or further dose reduction to 0.5mg/m^2 in subsequent cycles based on patient tolerability
Severe	>3x ULN	Any	

Interactions:

Bortezomib:

- Patients on bortezomib should be closely monitored if on a potent CYP3A4-inhibitors (e.g. ketoconazole, ritonavir), or a strong CYP3A4-inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, and St John's wort).

Panobinostat:

- In patients who take concomitant medicinal products which are strong CYP3A and/or Pgp inhibitors, including, but not limited to, ketoconazole, itraconazole, voriconazole, ritonavir, saquinavir, telithromycin, posaconazole and nefazodone, the dose of panobinostat should be reduced
- Patients should be instructed to avoid star fruit, grapefruit, grapefruit juice, pomegranates and pomegranate juice, as these are known to inhibit cytochrome P450 3A enzymes and may increase the bioavailability of panobinostat.
- The concomitant use of strong CYP3A4 inducers including, but not limited to, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin and St. John's Wort (Hypericum perforatum), should be avoided.
- Avoid panobinostat use in patients who are taking CYP2D6 substrates with a narrow therapeutic index (including, but not limited to, pimozide). When co-administered with sensitive CYP2D6 substrates (e.g. atomoxetine, dextromethorphan, metoprolol, nebivolol, perphenazine and pimozide), dose titrate individual CYP2D6 substrates based on tolerability and frequently monitor patients for adverse reactions.
- Due to risk of QT prolongation co-administration with other medications known to prolong QT should be avoided or used with caution.

Dexamethasone:

- Dexamethasone is a moderate inducer of CYP3A4. Co-administration of dexamethasone with other drugs that are metabolised by CYP3A4 (e.g. indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentrations.

- Concomitant treatment with CYP3A4 inhibitors may increase the risk of systemic side effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects in which case patients should be monitored for systemic corticosteroid side effects.

Please refer to the relevant SPC for more drug-drug interaction information.

Bortezomib: https://www.medicines.org.uk/emc/product/10201/smpc#gref

Panobinostat: https://www.medicines.org.uk/emc/product/12138/smpc#gref

Dexamethasone: https://www.medicines.org.uk/emc/product/5411/smpc#gref

Treatment schedule:

Cycle 1-8 only

Day	Drug	Dose	Route
1	Panobinostat	**20mg**	PO
	Dexamethasone	**20mg**	PO
	Bortezomib	**1.3mg/m^2**	SC
2	Dexamethasone	**20mg**	PO
3	Panobinostat	**20mg**	PO
4	Bortezomib	**1.3mg/m^2**	SC
	Dexamethasone	**20mg**	PO
5	Panobinostat	**20mg**	PO
	Dexamethasone	**20mg**	PO
8	Panobinostat	**20mg**	PO
	Bortezomib	**1.3mg/m^2**	SC
	Dexamethasone	**20mg**	PO
9	Dexamethasone	**20mg**	PO
10	Panobinostat	**20mg**	PO
11	Bortezomib	**1.3mg/m^2**	SC
	Dexamethasone	**20mg**	PO
12	Panobinostat	**20mg**	PO
	Dexamethasone	**20mg**	PO

Cycle 9-16 only

Day	Drug	Dose	Route
1	Panobinostat	**20mg**	PO
	Dexamethasone	**20mg**	PO
	Bortezomib	**1.3mg/m^2**	SC
2	Dexamethasone	**20mg**	PO
3	Panobinostat	**20mg**	PO
5	Panobinostat	**20mg**	PO
8	Panobinostat	**20mg**	PO
	Bortezomib	**1.3mg/m^2**	SC
	Dexamethasone	**20mg**	PO
9	Dexamethasone	**20mg**	PO
10	Panobinostat	**20mg**	PO
12	Panobinostat	**20mg**	PO

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea

Bortezomib

Serious adverse reactions uncommonly reported during treatment with bortezomib include cardiac failure, tumour lysis syndrome, pulmonary hypertension, posterior reversible encephalopathy syndrome, acute diffuse infiltrative pulmonary disorders and rarely autonomic neuropathy.

The most commonly reported adverse reactions during treatment with bortezomib are nausea, diarrhoea, constipation, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, peripheral neuropathy (including sensory), headache, paraesthesia, decreased appetite, dyspnoea, rash, herpes zoster and myalgia.

Panobinostat

The most commonly reported adverse reactions during treatment with panobinostat are nausea, diarrhoea, vomiting, fatigue, pyrexia, thrombocytopenia, anaemia, neutropenia, QT prolongation.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2+	Ongoing
Informed Consent	x			
Clinical Assessment	x	x	x	
SACT Assessment (to include PS and toxicities)	x	x	x	
FBC	x	x	x	
U&E & LFTs & Calcium profile	x	x	x	
ECG* (See page 10 for further information)	x	x	x	Repeated periodically every cycle during treatment as clinically indicated.
CrCl (Cockcroft and Gault)	x			
Bone profile	x			As clinically indicated
Blood glucose and HbA1c	x			As clinically indicated
Hep B core antibody and surface antigens & Hep C & HIV 1+2	x			
Serum Igs/electrophoresis/serum free light chains (if indicated)	x	x	x	
Neurological assessment (for neuropathy) – performed at medical review	x	x		
Blood pressure measurement	x	x	x	Lying and standing blood pressure prior to cycle 1
Height	x			
Weight	x	x	x	
Imaging as per NICE/network guidance and clinical indication	x			To restage as indicated
Pregnancy test	x			If appropriate
Thyroid function (free T4 and TSH)	x			As clinically indicated

*In the event of long QT interval prior to initiation of panobinostat (QTcF ≥480 msec at baseline), the start of treatment should be delayed until pre-dose average QTcF has returned to <480 msec

<u>Note:</u> It is important ECG completed prior to the start of therapy and repeated periodically before each treatment cycle.

Dose Modifications and Toxicity Management:

Dose step reductions:

	Panobinostat	Bortezomib
Starting dose	20mg	1.3mg/m^2
Dose level 1	15mg	1.0 mg/m^2
Dose level 2	10mg	0.7 mg/m^2

Note: Dose reduction for both panobinostat and bortezomib can be managed independently.

Haematological toxicity:

Proceed on day 1 if:

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Thrombocytopenia

Platelets	Recommended action	
Grade 3 Fall to < 50 x 10^9/L with bleeding	First occurrence	Omit panobinostat and once platelets recovered to ≥50 x 10^9/L resume at **reduced** dose
		Omit bortezomib and once platelets recovered to ≥50 x 10^9/L resume at the same dose
	Second or subsequent occurrences	Omit panobinostat and once platelets recovered to ≥50 x 10^9/L resume at **reduced** dose
		Omit bortezomib and once platelets recovered to ≥50 x 10^9/L resume at a **reduced** dose
Grade 4 Fall to <25 x 10^9/L	First occurrence	Omit panobinostat and once platelets recovered to ≥50 x 10^9/L resume at **reduced** dose
		Omit bortezomib and once platelets recovered to ≥50 x 10^9/L resume at the same dose
	Second or subsequent occurrences	Omit panobinostat and once platelets recovered to ≥50 x 10^9/L resume at **reduced** dose
		Omit bortezomib and once platelets recovered to ≥50 x 10^9/L resume at a **reduced** dose

Neutropenia

Platelets	Recommended action
Grade 3 Fall to 0.5-1 x 10^9/L	Omit panobinostat and once neutrophils >1 x 10^9/L resume at the same dose.
	Omit bortezomib and once neutrophils >1 x 10^9/L resume at the same dose.
Grade 4 Fall to < 0.5 x 10^9/L or febrile neutropenia (fever ≥38.5°C and neuts <1).	Omit panobinostat and once neutrophils >1 x 10^9/L resume at the **reduced** dose.
	Omit bortezomib and once neutrophils >1 x 10^9/L resume at the same dose.

Note: G-CSF treatment may be considered for prolonged neutropenia.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Panobinostat

Toxicity	Recommended action	
Diarrhoea	Grade 2 despite anti-diarrhoeal medication	Omit dose of panobinostat and once recovers to ≤grade 1 resume at the same dose
		Omit dose of bortezomib and once recovers to ≤grade 1 resume at the **reduced** dose or change to once weekly
	Grade 3 despite anti-diarrhoea medication	Omit dose of panobinostat and once recovers to ≤grade 1 resume at a **reduced** dose
		Omit dose of bortezomib and once recovers to ≤grade 1 resume at the **reduced** dose or with the same dose but with a once-weekly scheduling.
	Grade 4 despite anti-diarrhoeal medication	Permanently discontinue treatment

QT prolongation	QTc ≥480msec or >60msec from baseline	Omit dose of panobinostat. If QTc prolongation resolved within 7 days, resume treatment at prior dose for initial occurrence or reduced dose if QT prolongation is recurrent. If QTc is not resolved within 7 days treatment should be discontinued.
	QTC >500msec	Permanently discontinue treatment
Other	• CTC grade 2 toxicity recurrence or CTC grades 3 and 4 - omit the dose until recovery to CTC grade ≤1 and resume treatment at a reduced dose. • CTC grade 3 or 4 toxicity recurrence - a further dose reduction may be considered once the adverse event has resolved to CTC grade ≤1.	

Bortezomib

Grading of neuropathy	Recommended action
Grade 1 with no pain or loss of function	None
Grade 1 with pain or Grade 2	Reduce to 1.0 mg/m^2 or Change treatment schedule to 1.3 mg/m^2 once per week
Grade 2 with pain or Grade 3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7 mg/m^2 once per week.
Grade 4 and/or severe autonomic neuropathy	Discontinue

References:

1. Summary of Product Characteristics, Farydak®, Panobinostat, Novartis, last updated 21st March 2021 https://www.medicines.org.uk/emc [accessed on 8th February 2023]
2. NICE TA 380 – Panobinostat for treating multiple myeloma after at least 2 previous treatments. Published: 27th January 2016. www.nice,org.uk [accessed on 8th February 2023]
3. Summary of Product Characteristics, Velcade® Bortezomib, Thornton & Ross Ltd., Last updated 9th August 2022 http://www.medicines.org.uk [accessed on 8th February 2023]
4. Summary of Product Characteristics, Dexamethasone tablet 2mg, Aspen, last updated 14th August 2022 https://www.medicines.org.uk/emc [accessed on 8th February 2023]

Circulation/Dissemination

Date added into Q-Pulse	9th June 2023
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Version History

Date	Vesion	Author name and designation	Summary of main changes
April 2023	1.0	**Tom Sanders (Advanced Pharmacist Haematology**	**New protocol**