PANOBINOSTAT (Farydak®) + BORTEZOMIB (Velcade®) + DEXAMETHASONE (FVD)

(NICE TA380 January 2016)

INDICATION: Panobinostat (Farydak®) in combination with bortezomib (Velcade®) and dexamethasone is recommended as an option for patients with relapsed myeloma who have received at least 2 prior regimens including bortezomib and an immunomodulatory agent.

Prior to commencement

- Patients must have an ECOG performance status of 0, 1 or 2.
- Patients must have evidence of progressive myeloma on or after the most recent treatment regime as defined by IMWG criteria.
- Panobinostat clearance does not appear to be affected by age, gender, race or body surface area. Patients with mild or moderate hepatic impairment should receive a reduced starting dose of panobinostat. Renal impairment does not affect panobinostat clearance, though its use in patients with end-stage renal failure or those on dialysis has not been investigated.
- Baseline ECG – the QT interval must be < 480 msec prior to panobinostat therapy (see below)
- Beware concomitant use of strong CYP3A inhibitors (e.g. ketoconazole). Consider reducing panobinostat dose (see below). Caution must also be taken regarding concomitant use of drugs which could prolong the QT interval. Ondansetron can prolong the QT interval so should only be used in cases of severe emesis not responsive to other anti-emetics.
- Panobinostat can be associated with diarrhoea, fatigue, anaemia, thrombocytopenia. (see below)
- Bortezomib can be associated with neuropathy and thrombocytopenia. (see below)
- Consent for course.

Prior to each cycle

- Women of childbearing potential must have a negative pregnancy test at screening and men who are sexually active with a woman of childbearing potential must agree to use barrier methods of contraception
- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- Check FBC (prior to each dose of bortezomib – i.e. twice weekly during first 2 weeks of a cycle on days 1, 4, 8, 11 and also day 15 and/or 18 in patients >65 years or platelets less than 150), U&Es, magnesium, phosphate, LFTs. Discuss with consultant if renal or hepatic function have changed significantly.
- ECG after first cycle and periodically if any concerns (see below)

Dosing for cycles 1 - 8 is as below (1 cycle = 3 weeks):

Panobinostat	20 mg	oral	days 1, 3, 5, 8, 10 & 12 (e.g. Mon, Wed, Fri for 2 weeks then 1 week off)
Bortezomib	1.3 mg/m^2	s/c	days 1, 4, 8 & 11 (e.g. Mon, Thurs, for 2 weeks then 1 week off)
Dexamethasone	20mg	oral	days 1, 2, 4, 5, 8, 9, 11 & 12 (e.g. Mon, Tues, Thurs, Fri for 2 weeks then 1 week off)

Dosing for cycles 9 – 16 is as below (1 cycle = 3 weeks):

Panobinostat	20mg	oral days 1, 3, 5, 8, 10 & 12 (same as previous dosing: e.g. Mon, Wed, Fri for 2 weeks then 1 week off)
Bortezomib	1.3 mg/m^2	s/c days 1 & 8 (i.e. weekly for 2 weeks, then 1 week off)
Dexamethasone	20mg	oral days 1, 2, 8 & 9 (e.g. Mon, Tues for 2 weeks, then 1 week off)

Complete 16 cycles in total

*Panobinostat should be taken at the same time each scheduled day; if a dose is missed it can be taken up to 12 hours later

Anti-emetic prophylaxis	Metoclopramide
Other medications	Allopurinol 300mg od (100mg if Cr.Cl <20ml/min) for cycle 1
	Acyclovir 400mg bd
	Loperamide prn

Panobinostat toxicities

Oral panobinostat is a potent non-selective histone deacetylase inhibitor and the first in class to show clear benefit in patients with relapsed or refractory myeloma. Actions include blockade of the aggresome pathway, a protein degradation process similar to the proteasome pathway, which may explain its synergistic activity in combination with bortezomib, as well as why the combination appears to be effective in patients refractory to bortezomib alone due to panobinostat's ability to block a potential resistance mechanism. Patients must be advised to avoid star fruit, grapefruit or pomegranate in any form. Toxicities include:

- Thrombocytopenia, anaemia, neutropenia, haemorrhage, infection
- Diarrhoea, abdominal discomfort or bloating, nausea, constipation, dyspepsia
- Prolonged QT interval
- Transient elevations in liver aminotransferases and bilirubin
- Hypothyroidism, fatigue

Bortezomib Toxicities

Bortezomib is a first in class proteasome inhibitor, with reduced toxicity when given subcutaneously rather than IV. Toxicities include:

- Peripheral neuropathy (may be painful)
- Fluid retention & cardiac failure
- Thrombocytopenia, neutropenic sepsis
- Fatigue, malaise, weakness
- Nausea
- Diarrhoea, constipation, ileus
- Hypotension

Dose modifications – panobinostat is reduced in increments of 5mg, bortezomib in increments of 0.3mg/m^2. Minimum dose of panobinostat is 10mg, bortezomib 0.7mg/m^2 (or 0.5mg/m^2 in liver impairment). In the event of discontinuation, both drugs must be discontinued, continuing on single agent treatment is not permitted

Dose modification for neutropenia (unless due to disease)

Neutrophils 0.5 - 1	Omit treatment, resume both panobinostat and bortezomib at same dose when neutrophils > 1
Neutrophils < 0.5 or febrile neutropenia	Omit treatment, resume panobinostat at reduced dose but bortezomib at same dose when resolved

Dose modification for thrombocytopenia (unless due to disease)

Platelets < 50 with bleeding or platelets < 25	Omit treatment, resume panobinostat at reduced dose but bortezomib at same dose when platelets > 50. If thrombocytopenia recurs then resume bortezomib at reduced dose when platelets > 50.

Dose modifications for peripheral neuropathy

• Grade 1 (but no pain) i.e loss of tendon reflexes or paraesthesiae but not interfering with function	No change
• Grade 1 with pain or Grade 2, i.e objective sensory loss or paraesthesia interfering with function but not activities of daily living	Reduce bortezomib to 1.0mg/m^2
• Grade 2 with pain or Grade 3, i.e sensory loss or paraesthesia interfering with activities of daily living	Withhold until symptoms resolve, then restart bortezomib at 0.7mg/m^2 at <u>once</u> a week. If symptoms fail to resolve within 2 weeks – stop treatment
• Grade 4, i.e permanent sensory loss that interferes with function	Discontinue treatment (bortezomib and panobinostat)

Modification for renal dysfunction

- If < 30ml/min *discuss with consultant*. Note that the incidence of serious adverse effects increases with mild-moderate renal impairment. Patients have been treated safely when the creatinine clearance is<30ml/min and on dialysis but monitor carefully for toxicities if renal function is impaired. Give after dialysis. No dose adjustment is necessary for panobinostat although it has not been used in patients on dialysis or with end stage renal disease

Modification for liver dysfunction

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

Dose modification for diarrhoea

Grade 2 despite anti-diarrhoeal medication	Omit treatment, resume at same dose of panobinostat and reduced dose of bortezomib (or the same dose given weekly) when resolved
Grade 3 despite anti-diarrhoeal medication	Omit treatment, resume at reduced dose (or the same dose of bortezomib but given weekly)
Grade 4 despite anti-diarrhoeal medication	Discontinue treatment

QTc prolongation

If a prolonged QT interval is found on ECG prior to initiation of panobinostat (QTcF ≥ 480ms or above 60ms from baseline), the start of therapy should be delayed until pre-dose average QTcF has returned to <480 msec and abnormal serum potassium, magnesium or phosphorus values corrected. In the event of QT prolongation during treatment:

- The dose should be omitted if the QTcF is ≥ 480ms or above 60ms from baseline.
- If the 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, treatment should be discontinued.
- If any QTcF value is above 500 msec, panobinstat should be permanently discontinued

References: San-Miguel JF, Hungria VTM, Yoon S-S et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicenter randomized double-blind phase 3 trial. Lancet Oncol, 2014; 15(11): 1195-1206. (PANORAMA-1 trial)

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