Selinexor, Bortezomib and Dexamethasone (Multiple Myeloma)

Please note this protocol has been produced in a new format that is currently being piloted. Any feedback on this new format should be sent to SSGMeetings@uhbw.nhs.uk

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Indication

Transplant ineligible patients with multiple myeloma who have had 1 line of treatment and are refractory to both daratumumab and lenalidomide or who have had 2 lines of treatment and are refractory to lenalidomide.

(NICE TA 974)

Response Rates

Phase III BOSTON trial (Note: includes patients on 2nd, 3rd and 4th line treatment)

- Selinexor, bortezomib, dexamethasone (SVd, n= 195) vs bortezomib and dexamethasone (Vd, n= 207)
- ORR: SVd 76.4% vs Vd 62.3%
- PFS: SVd 13.93 months vs Vd 9.46 months. HR 0.7

2nd line subgroup analysis:

- PFS: SVd 21 months vs Vd 11 months HR 0.62

3rd line subgroup analysis:

- No statistically significant difference in PFS

Treatment related mortality

2%

Regimen details

Days	Drug	Dose	Route
1, 8, 15, 22 and 29	Selinexor	100mg*	Oral
1, 8, 15 and 22	Bortezomib	1.3mg/m^2	SC injection
1+2, 8+9, 15+16, 22+23, 29+30	Dexamethasone	20mg	Oral

* NB. Max dose is 70mg/m^2 so if surface area < 1.43m^2 reduce starting dose to 80mg

Cycle frequency
35 days

Number of cycles
Until disease progression or unacceptable toxicity

Pre-medication
Antiemetics as outlined below.

Supportive medication
Allopurinol 300mg OD (100mg OD if CrCl<20ml/min) for days 1-7 in cycle 1.
Prophylactic aciclovir for the duration of treatment and for 3 months afterwards
Consider prophylactic co-trimoxazole
Consider levofloxacin 500mg OD (reduced dose if CrCl < 50ml/min – see SPC) for first 12 weeks.
Consider prophylactic antifungals as per local policy
Proton pump inhibitor or H2 antagonist
Bisphosphonates as per local policy.

Emetogenicity
This regimen has moderate emetic potential – refer to local policy
Dual therapy is recommended:

- ondansetron 8mg 30-60 minutes before Selinexor with a second dose 8 hours after Selinexor administration, then 8mg BD for 2-3 days following each Selinexor dose
- plus metoclopramide 10mg TDS starting 30-60 minutes prior to Selinexor and continuing TDS for 2-3 days following each Selinexor administration.

Consider escalation, if needed, to include:

- haloperidol 1.5mg ON or olanzapine 2.5-5mg ON
- aprepitant 125mg D1 and 80mg D2 & 3. Reduce dexamethasone doses to 10mg on days of aprepitant administration due to CYPA3A4 interaction.

Administration

Selinexor
Selinexor is available as 20mg film coated tablets.
Selinexor may be administered with or without food. Tablets should be swallowed whole with water and must not be crushed, chewed, broken or divided to prevent risk of skin irritation from the active substance. If a patient misses a dose of selinexor, or vomits after taking a dose, the dose should not be repeated and the dose should be taken as usual on the next regularly scheduled day.

Bortezomib
Administration 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. **At least 72 hours must elapse between doses of bortezomib.** If a planned dose of bortezomib is delayed, adjust the dosing schedule accordingly, to maintain the treatment interval.

Dexamethasone
Tablets should be taken in the morning, with or immediately after food.

Extravasation
N/A

Mandatory investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U&Es (including creatinine)	14 days
LFTs	14 days
Bone profile (Calcium, phosphate, magnesium)	14 days
Virology (Hep B/C, HIV)	3 months (or as per local policy)

Additional investigations advised pre-first cycle

- HbA1C
- β2 microglobulin
- CRP
- LDH
- Serum free light chains (SFLC)/Paraprotein (PP)/Immunoglobulins (Igs)
- Urine protein/creatinine ratio
- Neuropathy assessment
- Baseline lying and standing blood pressure

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours*
U&Es (including creatinine)	7 days
LFTs	7 days
Bone profile (Calcium, phosphate, magnesium)	7 days

* Weekly FBC is recommended for the first cycle.

Additional investigations advised pre subsequent cycles

- SFLC, PP, Igs – results are not required prior to administration of cycle

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer must be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Haemoglobin	≥ 80g/L
Creatinine Clearance	≥ 15ml/min
Bilirubin	< 1.5 x ULN
AST/ALT	≤ ULN
Sodium	> 130 mmol/L

Dose modifications

Selinexor:

Dose level	Dose
Starting dose	100mg once weekly
First dose reduction	80mg once weekly
Second dose reduction	60mg once weekly
Third dose reduction	40mg once weekly

If symptoms do not resolve on lowest dose level, treatment should be discontinued.

Bortezomib:

Dose level	Dose
Full dose	1.3mg/m^2
First dose reduction	1.0mg/m^2
Second dose reduction	0.7mg/m^2

Haematological toxicity

Bortezomib: Interrupt dosing for Grade 4 toxicity (neutrophils < 0.5 x 10^9/L or platelets < 25 x 10^9/L). Bortezomib may be reintroduced at next dose reduction level once toxicity has resolved (neutrophils > 1.0 x 10^9/L and platelets > 70 x 10^9/L).

Selinexor:

Thrombocytopenia:

Platelet count	Action
25 - 74 x 10^9/L	Reduce selinexor by one dose level continuing usual dosing schedule
25 – 74 x 10^9/L *with* concurrent bleeding	Interrupt selinexor until platelets > 50 x 10^9/L Restart selinexor at next dose reduction level after bleeding has resolved
< 25 x 10^9/L	Interrupt selinexor Monitor until platelet count returns to ≥ 50 x 10^9/L, restart selinexor at next dose reduction level

Neutropenia:

Neutrophil count	Action
0.5 – 1 x 10^9/L *without* fever	Reduce selinexor by one dose level continuing usual dosing schedule
< 0.5 x 10^9/L OR Febrile neutropenia	Interrupt selinexor Monitor until neutrophil count returns to ≥ 1.0 x 10^9/L, restart Selinexor at next dose reduction level

Anaemia:

Haemoglobin/Anaemia	Action
< 80g/L	Reduce selinexor by one dose level continuing usual dosing schedule Administer blood transfusions/other supportive treatments as per local guidelines
Life threatening consequences (urgent intervention indicated)	Interrupt selinexor Administer blood transfusions/other supportive treatments as per local guidelines Monitor until haemoglobin returns to 80g/L, restart selinexor at next dose reduction level

If cytopenia considered to be disease related, treatment may be given at consultant discretion.

Renal impairment

Selinexor: No dose adjustment is required in mild, moderate or severe impairment. There is no data available in end stage renal disease or haemodialysis.
Bortezomib: no dose adjustment is required.

Hepatic impairment

Selinexor: No dose adjustment is required in mild hepatic impairment (bilirubin < 1.5 x ULN with any ALT). There is insufficient data for patients with moderate or severe hepatic impairment (bilirubin > 1.5 x ULN with any ALT).
Bortezomib: If bilirubin > 1.5 x ULN consider starting dose of 0.7mg/m^2 for cycle 1. For subsequent cycles consider increasing dose to 1mg/m^2 or reducing to 0.5mg/m^2 according to tolerability.

Other toxicities

Selinexor:

Toxicity	Definition	Action/Dose adjustment
Hyponatraemia	Sodium ≤ 130 mmol/L	Interrupt selinexor and provide supportive care Monitor until sodium > 130mmol/L Restart selinexor at 1 level dose reduction
Fatigue	Grade 2 for > 7 days OR Grade 3	Interrupt selinexor Monitor until fatigue returns to Grade 1 or baseline Restart selinexor at 1 level dose reduction
Nausea and Vomiting	Grade 1 or 2	Continue selinexor and initiate additional antiemetic therapy
	Grade ≥ 3	Interrupt selinexor and initiate additional antiemetic therapy Monitor until nausea or vomiting returns to Grade 2 or baseline Restart selinexor at 1 level dose reduction

Toxicity	Definition	Action/Dose adjustment
Diarrhoea	Grade 2	1st occurrence: continue selinexor and initiate anti-diarrhoeal 2nd occurrence: reduce selinexor by one dose level and initiate anti-diarrhoeal
	Grade ≥ 3	Interrupt selinexor and initiate anti-diarrhoeal Monitor until diarrhoea returns to Grade 2 or lower Restart Selinexor at 1 level dose reduction
Weight loss/ Anorexia	Weight loss of 10-20% OR Anorexia associated with significant weight loss or malnutrition	Interrupt selinexor and provide supportive care Monitor until weight returns to 90% of baseline weight Restart selinexor at 1 level dose reduction
Ocular adverse events	Grade 2 (excluding cataract)	Perform ophthalmologic evaluation Interrupt selinexor and provide supportive care Monitor until ocular symptoms resolve to Grade 1 or baseline Restart selinexor at 1 dose level reduction
	Grade ≥ 3 (excluding cataract)	Permanently discontinue selinexor.
Any other non-haematological adverse events	Grade 3 or 4	Interrupt selinexor Monitor until resolved to ≤ Grade 2 Restart selinexor at 1 level dose reduction

Bortezomib:

Neuropathy:

Neuropathy grade	Action and bortezomib dose
Grade 1 with no pain	100%
Grade 1 with pain or grade 2 but not interfering with daily living	Reduce to 1.0mg/m^2
Grade 2 with pain or grade 3	Withhold until symptoms resolved. Restart at 0.7mg/m^2
Grade 4	Discontinue

Any other ≥ grade 3 non-haematological toxicity withhold bortezomib until recovered to ≤ grade 1. Recommence with dose reduction of one level.

Side Effects

BOSTON study:

Toxicity		Any grade (%)	Grade 3 or 4 (%)
Haematological	Thrombocytopenia	60	39
	Anaemia	36	16
	Neutropenia	15	9
	Fatigue	42	13
	Nausea	50	8
	Diarrhoea	32	6
	Peripheral neuropathy	32	5
	Decreased appetite	35	4
	Weight loss	26	2
	Asthenia	25	8
	Cataract	22	9
	Vomiting	21	4

Specific drug related side effects:

Selinexor – refer to SPC for full details

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Thrombocytopenia, anaemia, neutropenia,	Tumour lysis syndrome	
Hyponatraemia		
Ocular toxicity, cataracts		
Nausea, vomiting, diarrhoea		
Fatigue, asthenia		
Weight loss		

- **Hyponatraemia**

Hyponatraemia was reported with an incidence ranging from 7-47% in trials. 19% of patients across the studies experienced ≥ grade 3 hyponatraemia (120-<130 mmol/L) though this was largely asymptomatic with <5% cases associated with neurological manifestations. Hyponatraemia is usually transient and highly responsive to dose reduction and sodium supplementation.

- **Nausea and vomiting**

Nausea and vomiting are more commonly experienced during the first few cycles of therapy and can improve over time. Effective prophylaxis with dual antiemetics is recommended in all patients or the first 2 cycles of treatment. Antiemetics may be tapered after cycle 2 if tolerance improves.

Bortezomib – refer to SPC for full details

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Thrombocytopenia, neutropenia, anaemia	Infections	Posterior Reversible Encephalopathy Syndrome
Peripheral sensory neuropathy	Motor neuropathy	Pneumonitis, acute respiratory distress syndrome
Orthostatic hypotension	Rash	Stevens-Johnson syndrome, toxic epidermal necrolysis
Fatigue, asthenia		
Nausea, vomiting		Hepatitis, hepatic failure
Diarrhoea, constipation		Heart failure

- **Peripheral neuropathy**

Patients should be advised to report pain, hypersensitivity, prickling, burning sensation, numbness and paraesthesia. If these occur see above dose reductions for bortezomib and consider use of amitriptyline or gabapentin. Caution in patients with existing peripheral neuropathy.

- **Dizziness/Orthostatic hypotension**

Patients should be advised that bortezomib may cause orthostatic hypotension and they they should sit upright for a few minutes prior to standing up from a recumbent position. Caution is advised when treating patients with a history of syncope receiving medications known to be associated with hypotension or in those who are dehydrated. Management of orthostatic hypotension may include adjustment of antihypertensives, rehydration or administration of mineralocorticosteroids and/or sympathomimetics.

Dexamethasone

Common (>10%)	**Uncommon (1-10%)**	**Rare (<1%)**
*High blood sugars	Blurred vision	Headache
Insomnia	Cataracts	Heart failure
Mood disturbance (depression, anxiety, euphoria)	Osteopenia	
Fluid retention	Acne	
Gastro-oesophageal reflux disease (GORD)	Abnormal fat deposits	
Increased appetite		

*pre-treatment HBA1C levels should be checked with monitoring for treatment emergent hyperglycaemia when HBA1C levels are >42mmol/mol. Patients with known diabetes/borderline diabetes should be referred to their diabetic nurse for close monitoring upon commencing dexamethasone

Additional information

Women of childbearing potential and male patients of reproductive potential should be advised to use effective contraception measures during treatment with Selinexor and for at least 1 week following the last dose.

Significant drug interactions – for full details consult product literature/ reference texts

Selinexor:
Strong CYP3A4 inducers: may lead to lower exposure of selinexor.

Bortezomib:
Antihypertensives: Risk of additive hypotensive effect. Close monitoring of BP is required.
Oral antidiabetic agents: Hyper- and hypoglycaemia has been reported. Close monitoring of blood glucose is required.
Ciclosporin: increased risk of severe neuropathy: avoid concomitant use.
High dose vitamin C: reduced efficacy of bortezomib: avoid concomitant use.
Cytochrome P34A inhibitors (ketoconazole and other azole antifungals, clarithromycin, erythromycin) may increase bortezomib levels: avoid concomitant use. Cytochrome P34A inducers (rifampicin, carbamazepine, phenytoin, St John's Wort) may reduce bortezomib levels: avoid concomitant use.

References

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Version	Issue date	Review date	Revision	Written/Checked/Authorised
1	July 2024	July 2027	New protocol	Written/Reviewed: Dr A Whiteway (Consultant Haematologist, North Bristol NHS Trust), B Bagnall (Haematology Pharmacist, North Bristol NHS Trust) Checked: Kate Gregory (Lead pharmacist for SACT protocols, SWAG Cancer Alliance) Authorised: Dr J Braybrooke (UHBW NHS Trust and SWAG Cancer Alliance)