Selinexor 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

Relapsed or refractory multiple myeloma after 4 or more treatments and is refractory to at least 2 proteasome inhibitors, 2 immunomodulatory agents and an anti-CD38 monoclonal antibody.

(NICE TA970)

Response Rates

Phase IIb single-arm STORM trial

- ORR: 39% - minimal response or better, 26% partial response or better.
- PFS: 3.7 months

Treatment related mortality

1-2%

Regimen details

Days	Drug	Dose	Route
1 and 3 of each week	Selinexor	80mg	Oral
1 and 3 of each week	Dexamethasone	20mg	Oral

Cycle frequency
28 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.
Prophylactic antifungals as per local policy
Proton pump inhibitor or H2 antagonist
Bisphosphonates as per local policy.

Emetogenicity
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.

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

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)	

* 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

Dose level	Dose
Starting dose	80mg on days 1 and 3 of each week (160mg per week)
First dose reduction	100mg once weekly
Second dose reduction	80mg once weekly
Third dose reduction	60mg once weekly

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

Haematological toxicity

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

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

Hepatic impairment

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).

Other toxicities

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
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

Side Effects

STORM trial:

Toxicity		Any grade (%)	Grade 3 or 4 (%)
Haematological	Thrombocytopenia	73	58
	Anaemia	67	44
	Neutropenia	40	21
	Leukopenia	33	14
	Lymphopenia	16	11
Non-haematological	Fatigue	73	25
	Nausea	72	10
	Decreased appetite	56	5
	Decreased weight	50	1
	Diarrhoea	46	7
	Vomiting	38	3
	Hyponatraemia	37	22
	Upper respiratory tract infection	23	2
	Constipation	22	2
	Dyspnoea	22	4

Specific drug related side effects:

Selinexor

Common (>10%)	Uncommon (1-10%)	Rare (<1%)
Thrombocytopenia, anaemia, neutropenia, febrile 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.

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	
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

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

References

- Summary of Product Characteristics: Selinexor (Nexpovio) accessed 30 May 2024 via www.medicines.org.uk
- National Institute for Health and Care Excellence TA970. Accessed 30 May 2024 via www.nice.org.uk
- Chari, A. et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. N Engl J Med 2019;381:727-738
- Gavriatopoulou, M. et al. Integrated safety profile of Selinexor in multiple myeloma: experience from 437 patients enrolled in clinical trials. *Leukemia* 2020 34:2430-2440

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 (Consultant Oncologist, UHBW NHS Trust and SWAG Cancer Alliance)