SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

IXAZOMIB, LENALIDOMIDE & DEXAMETHASONE (IRD) Multiple Myeloma

PROTOCOL REF: MPHAILDHA
(Version No. 1.1)

Approved for use in:

- Patients with multiple myeloma who have received 2 or 3 prior lines of therapy ***(i.e. 3rd or 4th line treatment only)*** and is neither refractory to previous proteasome-inhibitor based or lenalidomide-based treatment at any line of therapy.

Blueteq registration required

Dosage:

Drug	Dose	Route	Frequency
Ixazomib	**4mg ONCE weekly**	PO	Day, 1, 8 and 15
Lenalidomide	**25mg ONCE daily**	PO	Day 1 to 21
Dexamethasone	**40mg ONCE weekly***	PO	Days 1, 8, 15 and 22

*Differing doses and frequencies of dexamethasone may be used at the discretion of the prescriber. Prescribers should carefully evaluate which dose of dexamethasone to use, considering the condition and disease status of the patient.

Cycle length: every 28 days. Continue until disease progressions or intolerance.

Administration:

- Lenalidomide capsules should be taken orally at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.

- Ixazomib capsules should be taken orally at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be taken at least 1 hour before or at least 2 hours after food, and swallowed whole with a glass of water.
- If a dose of lenalidomide is missed and <12hours late the missed dose should be taken. Missed doses >12hours should be omitted and the next dose taken as scheduled.
- If a dose of ixazomib is missed and the next dose is due in <72 hours do NOT take an additional dose. If the next dose of ixazomib is due in ≥72 hours the missed dose can be taken.
- If a patient vomits after taking a dose of lenalidomide / ixazomib, the patient should not repeat the dose and should resume dosing at the time of the next scheduled dose.
- Dexamethasone tablets should be taken in the morning after food.
- The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the pregnancy prevention programme (with lenalidomide) and provide patients with appropriate patient educational brochure and patient card.

Pregnancy Prevention Programme:

Due to the increased risk of birth defects associated fetal exposure to lenalidomide the following should be adhered to:

- A Treatment Initiation Form (TIF) must be completed prior to treatment initiation with lenalidomide
- A Prescription Authorisation Form (PAF) must be completed by the prescriber for each supply of lenalidomide. This must be approved by a pharmacist when verifying each prescription and confirmation of dispensing completed by the relevant dispensing pharmacy. Supply must be completed within 7 days of the prescription generation.
- A maximum of 3 months can be supplied for men or women of non-child bearing potential
- A maximum of 1 month can be supplied for women of child bearing potential. A negative pregnancy test must be confirmed within 3 days of prescription generation.

Emetogenic risk:

Low risk

Supportive treatments:

- Allopurinol 300mg daily for 28 days (cycle one only)
- Aciclovir 400mg twice daily
- Co-trimoxazole 480mg once daily
- Nystatin 1mL QDS **OR** Fluconazole 50mg daily for antifungal prophylaxis (if higher doses of steroids being used, review each cycle)
- Omeprazole 20mg once daily - review each cycle
- Ondansetron 4-8mg TDS PRN for 5-7 days, usually prescribed for cycle 1 only
- VTE prophylaxis:
    - Dalteparin 5,000 units subcutaneous injection daily (or alternative prophylactic LMWH)
    - Therapeutic dose LMWH in high risk patients. Patients may continue previously established DOAC treatment or be switched to a LMWH.
    - Aspirin 75mg daily (for those patients who decline LMWHs or for those deemed to be low risk on long term treatment)

Dosing in renal and hepatic impairment:

Renal Dose Modifications		
	Creatinine Clearance (mL/min)	**Dose Adjustment**
Lenalidomide	30 – 50	10mg once daily*
	<30 not requiring dialysis	15mg alternate days
	End stage renal disease (<30)	5mg once daily
Ixazomib	<30	3mg weekly (not dialyzable so give without regards to timing of dialysis)

*The dose may be escalated to 15mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment

Hepatic Dose Modifications	
Lenalidomide	Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

Ixazomib	Bilirubin >1.5 xULN – reduce to 3mg weekly

Interactions:

Ixazomib:

- **Strong CYP3A inducers**- may reduce the efficacy of ixazomib, therefore the concomitant use of strong CYP3A inducers such as carbamazepine, phenytoin, rifampicin and St. John's Wort, should be avoided. Closely monitor patients for disease control if co-administration with a strong CYP3A inducer cannot be avoided.
- **Oral contraceptives**- efficacy of these may be reduced. Women should be advised to use additional contraceptive measures.

Lenalidomide:

- Agents that may increase the risk of thrombosis, such as HRT should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone.
- **Digoxin** – concomitant administration with lenalidomide increased plasma exposure of digoxin, monitoring of the digoxin concentration is advised during lenalidomide treatment.
- **Statins** – there is an increased risk of rhabdomyolysis when statins are administered with lenalidomide. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Please refer to the SPC for full list of interactions and further information.

Main toxicities:

Lenalidomide
Infection, anaemia, thrombocytopenia, neutropenia, hypokalaemia, paraesthesia, peripheral neuropathy, pulmonary embolism, DVT, cough, dyspnea, diarrhea, constipation, nausea, abdominal pain, vomiting, deranged LFTs, rash, dry skin, myalgia, fatigue
Ixazomib
Infections, anaemia, neutropenia, thrombocytopenia, peripheral neuropathy, herpes zoster infection, diarrhoea, constipation, nausea, vomiting, rash, back pain, peripheral oedema, eye disorders such as conjunctivitis, cataracts, blurred vision and dry eyes.

Investigations and treatment plan:

	Pre	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 1 day 15	Cycle 1 day 22	Cycle 2	Cycle 3 onwards	Ongoing
Informed Consent	X							
Clinical Assessment	X	X				X	X	Prior to every cycle
SACT Assessment	X	X				X	X	Prior to every cycle
Celgene Pregnancy Prevention Program Consent	X							
Celgene prescription authorization form		X	X	X	X	X	X	
On Treatment Review (OTR)			X	X	X			
FBC	X	X	X	X	X	X	X	Prior to every cycle
U&E & LFTs, CrCl (Cockcroft and Gault)	X	X				X	X	Prior to every cycle
Bone profile	X							As clinically indicated
Blood glucose and HbA1c	X							Repeat as clinically indicated
Virology screen HepB and C/HIV	X							
Dental assessment	X							As clinically indicated
Serum Igs/electrophoresis/serum free light chains (if indicated)	X	X				X	X	Prior to every cycle
Neurological assessment (for neuropathy)	X	X				X	X	Prior to every cycle
Imaging as per NICE/network guidance and clinical indication	X							To restage as indicated
Pregnancy test	X							If clinically indicated
Thyroid function test	X							If clinically indicated
Height	X							
Weight	X	X	X	X	X	X	X	

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle can proceed if:

ANC is ≥ 1.0 x 10^9/L	Platelets ≥ 75 x 10^9/L

Dose step reductions

Dose Levels	Ixazomib	Lenalidomide
Starting dose	4mg	25mg
Dose level 1	3mg	15mg
Dose level 2	2.3mg	10mg
Dose level 3	Discontinue	5mg

Dose reduction for both products can be managed independently.

Dexamethasone dose may be reduced at the prescriber's discretion dependent on patient's tolerability.

An alternating dose modification approach is recommended for ixazomib and lenalidomide for overlapping toxicities of thrombocytopenia, neutropenia and rash. For these toxicities, the first dose modification step is to withhold/reduce lenalidomide.

Thrombocytopenia

When platelets	Recommended course	
Fall to < 30 x 10^9/L	First occurrence	Withhold ixazomib and lenalidomide until platelet count ≥30 x 10^9/L Following recovering, resume lenalidomide at the next lower dose and resume ixazomib at its most recent dose.
	Second and subsequent occurrences	Withhold ixazomib and lenalidomide until platelet count ≥30 x 10^9/L Following recovering resume ixazomib at the next lower dose and resume lenalidomide at current dose. For additional occurrences, alternate dose modification of lenalidomide and ixazomib.

Neutropenia:

When neutrophils	Recommended course	
Fall to < 0.5 x 10^9/L	First occurrence	Withhold Ixazomib and lenalidomide until neutrophil counts ≥0.5 x 10^9/L. Consider adding G-CSF. Following recovering, resume lenalidomide at the next lower dose and resume ixazomib at its most recent dose.
	Second and subsequent occurrences	Withhold ixazomib and lenalidomide until platelet count >30 x 10^9/L Following recovering resume ixazomib at the next lower dose and resume lenalidomide at current dose. For additional occurrences, alternate dose modification of lenalidomide and ixazomib.

Non- Haematological toxicity:

Non-haematologic toxicities should, at the physician's discretion, generally be recovered to patient's baseline condition or ≤ Grade 1

Toxicity		Recommended course	
Skin Rash	Grade 2 or 3	First Occurrence	Withhold lenalidomide until rash recovers to ≤Grade 1. Following recovery, resume lenalidomide at the next lower dose.
		Second and subsequent occurrences	Withhold ixazomib and lenalidomide until rash recovers to ≤Grade 1. Following recovery, resume ixazomib at the next lower dose and resume lenalidomide at its most recent dose. For additional occurrences, alternate dose modification of lenalidomide and ixazomib.
	Grade 4	Discontinue treatment regimen	
Peripheral Neuropathy	Grade 1 +pain or Grade 2	Withhold Ixazomib until peripheral neuropathy recovers to ≤Grade 1 without pain or patient's baseline. Following recovery, resume ixazomib at its most recent dose	
	Grade 2+pain or Grade 3	Withhold ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or ≤Grade 1 prior to resuming ixazomib.	

		Following recovery, resume ixazomib at the next lower dose.
	Grade 4	Discontinue treatment permanently.
Other	Lenalid-omide	For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion.
	Ixazomib	Withhold ixazomib. Toxicities should, at the physician's discretion, generally recover to patient's baseline condition or at most Grade 1 prior to resuming ixazomib. If attributable to ixazomib, resume ixazomib at the next lower dose following recovery.

References:

1. Summary of Product Characteristics, Revlimid®, Lenalidomide, Celgene, last updated 23rd May 2019 [accessed on 10th May 2023] https://www.medicines.org.uk/emc
2. Summary of Product Characeteristics, Ninlaro®, Ixazomib, Takeda UK, last updated 3rd October 2019 [accessed on 10th May 2023]
3. Summary of Product Characteristics, Dexamethasone tablet 2mg, Aspen, last updated 26th January 2018 [accessed on 10th May 2023] https://www.medicines.org.uk/emc
4. NICE TA870 – Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma. Published: Feb 2023 www.nice.org.uk [accessed on 10th May 2023]

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
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Version History

		Author name and designation	Summary of main changes
			To be completed by author
Sept 2019	1.0	**Kelly-Marie Crampton**	**New protocol**
June 2023	1.1	**Jennifer Gibson (Principal Pharmacist Haematology)**	**Transferred to new template. Updated peripheral neuropathy dose modification section. Rationalised indication list. Added main toxicity section and Pregnancy Prevention Program Section**