Systemic Anti Cancer Therapy Protocol

Isatuximab with Pomalidomide and Dexamethasone Multiple Myeloma

PROTOCOL REF: MPHAIPDHA
(Version No: 1.0)

Approved for use in:

Isatuximab is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma if:

- They have received exactly **3 previous lines of therapies** (that have included at least 2 consecutive cycles of lenalidomide, and at least 2 consecutive cycles of a proteasome inhibitor)
- They have demonstrated disease progression on the last therapy
- They have either not have received any previous therapy with an anti-CD38 antibody (eg daratumumab) or did **not progress within 60 days** of the last infusion of an anti-CD38 antibody treatment
- They have not received prior treatment with pomalidomide

Blueteq registration is required.

Dosage:

Drug	Dose	Route	Frequency
Isatuximab	**10mg/kg**	IV infusion	*Cycle 1*: Days 1, 8, 15 and 22 *Cycle 2 onwards*: Days 1 and 15
Pomalidomide	**4mg**	Oral	Days 1 to 21
Dexamethasone	**40mg** (or 20mg if ≥75 years old)	Oral	Days 1, 8, 15 and 22

Cycle Length: 28 days

Treatment to continue until disease progression or unacceptable toxicities

Administration:

- Pomalidomide tablets should be taken at the same time each day. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole with water.
- If a dose of pomalidomide is missed omit dose and continue with next scheduled dose.
- It is recommended to press only one end of the capsule of pomalidomide to remove it from the blister thereby reducing the risk of capsule deformation or breakage.
- 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 pomalidomide) and provide patients with appropriate patient educational brochure and patient card.
- Oral dexamethasone must be taken 15-60 minutes prior to isatuximab
- See infusion rate table for administration details

Anti-emetic risk:

Mildly emetogenic

Supportive treatments:

Pre-infusion medications (given 15-60 minutes prior to isatuximab):-

- Paracetamol PO 1g
- Chlorphenamine IV 10mg
- Omeprazole PO 20mg
- Dexamethasone PO 40mg (or 20mg if ≥ 75 years old) – this is the treatment dose but should also be given as the pre medication.

Patients who do not experience an infusion reaction upon their first 4 administrations of Isatuximab may have their need for subsequent premedication reconsidered.

Supportive meds:-

- Allopurinol PO 300mg daily (cycle 1 only)
- Omeprazole PO 20mg daily

- Aciclovir PO 400mg twice daily
- Co-trimoxazole PO 480mg daily
- Anticoagulation – options include prophylactic dose of low molecular weight heparin (LWMH), treatment dose of LMWH in high risk patients. For patients established on DOACs, patients may continue DOAC treatment or be switched to a LMWH. For those patients who decline LMWHs or for those deemed to be low risk on long term treatment – there is the option to be converted to aspirin after having LMWH in the first 6-12 months.
- Consider Nystatin 1ml four times a day or Fluconazole 50mg daily
- Chlorhexidine mouthwash 10ml twice a day

Extravasation risk:

Isatuximab is a monoclonal antibody therefore there are no specific recommendations – treat symptomatically.

Refer to the Trust guidance for the prevention and management of extravasation

Interactions:

Pomalidomide

If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, reduce the dose of pomalidomide by 50%.

Isatuximab

Interference with serological testing

Because CD38 protein is expressed on the surface of red blood cells, isatuximab, an anti-CD38 antibody, may interfere with blood bank serologic tests with potential false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches in patients treated with isatuximab.

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Isatuximab may be incidentally detected by serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the monitoring of M-protein and could interfere with

accurate response classification based on International Myeloma Working Group (IMWG) criteria.

Recommendations

To avoid potential problems with RBC transfusion, patients being treated with isatuximab should have blood type and screen tests performed prior to the first isatuximab infusion. Phenotyping may be considered prior to starting isatuximab treatment as per local practice. If treatment with isatuximab has already started, the blood bank should be informed that the patient is receiving isatuximab and isatuximab interference with blood compatibility testing can be resolved using dithiothreitol (DTT)-treated RBCs. If an emergency transfusion is required, noncross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices.

Treatment schedule:

Cycle 1

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**40mg** (or 20mg if ≥75 years old)	**PO**	15-60 minutes pre -isatuximab
	Paracetamol	**1g**	**PO**	
	Omeprazole	**20mg**	**PO**	
	Chlorphenamine	**10mg**	**IV**	15-60 minutes pre -isatuximab Bolus dose over 3 to 5 minutes
	Pomalidomide	**4mg**	**PO**	In the evening
	Isatuximab	**10mg/kg**	**IV**	In 250mls NaCl 0.9% (See below for infusion rate)
2 to 7	**Pomalidomide**	**4mg**	**PO**	In the evening
8	**Dexamethasone**	**40mg** (or 20mg if ≥75 years old)	**PO**	15-60 minutes pre -isatuximab
	Paracetamol	**1g**	**PO**	
	Omeprazole	**20mg**	**PO**	
	Chlorphenamine	**10mg**	**IV**	15-60 minutes pre -isatuximab Bolus dose over 3 to 5 minutes
	Pomalidomide	**4mg**	**PO**	In the evening
	Isatuximab	**10mg/kg**	**IV**	In 250mls NaCl 0.9% (See below for infusion rate)

9 to 14	**Pomalidomide**	**4mg**	**PO**	In the evening
15	**Dexamethasone**	**40mg** (or 20mg if ≥75 years old)	**PO**	15-60 minutes pre -isatuximab
	Paracetamol	**1g**	**PO**	
	Omeprazole	**20mg**	**PO**	
	Chlorphenamine	**10mg**	**IV**	15-60 minutes pre -isatuximab Bolus dose over 3 to 5 minutes
	Pomalidomide	**4mg**	**PO**	In the evening
	Isatuximab	**10mg/kg**	**IV**	In 250mls NaCl 0.9% (See below for infusion rate)
16 to 21	**Pomalidomide**	**4mg**	**PO**	In the evening
22	**Dexamethasone**	**40mg** (or 20mg if ≥75 years old)	**PO**	15-60 minutes pre -isatuximab
	Paracetamol	**1g**	**PO**	
	Omeprazole	**20mg**	**PO**	
	Chlorphenamine	**10mg**	**IV**	15-60 minutes pre -isatuximab Bolus dose over 3 to 5 minutes
	Isatuximab	**10mg/kg**	**IV**	In 250mls NaCl 0.9% (See below for infusion rate)

Cycle 2 onwards

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**40mg** (or 20mg if ≥75 years old)	**PO**	15-60 minutes pre -isatuximab
	Paracetamol	**1g**	**PO**	
	Omeprazole	**20mg**	**PO**	
	Chlorphenamine	**10mg**	**IV**	15-60 minutes pre -isatuximab Bolus dose over 3 to 5 minutes
	Pomalidomide	**4mg**	**PO**	In the evening
	Isatuximab	**10mg/kg**	**IV**	In 250mls NaCl 0.9% (See below for infusion rate)
2 to 7	**Pomalidomide**	**4mg**	**PO**	In the evening
8	**Pomalidomide**	**4mg**	**PO**	In the evening
	Dexamethasone	**40mg** (or 20mg if ≥75	**PO**	

		years old)		
9 to 14	**Pomalidomide**	**4mg**	**PO**	In the evening
15	**Dexamethasone**	**40mg** (or 20mg if ≥75 years old)	**PO**	15-60 minutes pre -isatuximab
	Paracetamol	**1g**	**PO**	
	Omeprazole	**20mg**	**PO**	
	Chlorphenamine	**10mg**	**IV**	15-60 minutes pre -isatuximab Bolus dose over 3 to 5 minutes
	Pomalidomide	**4mg**	**PO**	In the evening
	Isatuximab	**10mg/kg**	**IV**	In 250mls NaCl 0.9% (See below for infusion rate)
16 to 21	**Pomalidomide**	**4mg**	**PO**	In the evening
22	**Dexamethasone**	**40mg** (or 20mg if ≥75 years old)	**PO**	

Infusion rates for Isatuximab:

NB all doses of isatuximab are diluted in 250ml of sodium chloride 0.9%

	Dilution volume	***Initial rate***	***Absence of infusion reactions***	***Rate increment***	***Maximum rate***
First infusion	250mL	25mL/hr	For 60 minutes	25mL/hr every 30 minutes	150mL/hr
Second infusion	250mL	50mL/hr	For 30 minutes	50mL/hr for 30 minutes then increase by 100mL/hr every 30 minutes	200mL/hr
Subsequent infusions	250mL	200mL/hr	_____	_____	200mL/hr

- Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions
- In patients who experience Grade 2 (moderate) infusion reactions, a temporary interruption in the infusion should be considered and additional symptomatic medicinal products can be administered. After improvement to grade ≤1 (mild), isatuximab infusion may be resumed at half of the initial infusion rate under close monitoring and supportive care, as needed. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown above.
- If symptoms do not resolve rapidly or do not improve to Grade ≤1 after interruption of isatuximab infusion, recur after initial improvement with appropriate medicinal products, or require hospitalization or are life-threatening (Grade ≥3), treatment with isatuximab should be permanently discontinued and additional supportive therapy should be administered, as needed.

Investigations and treatment plan:

	Pre	Cycle 1	Before each dose of Isatuximab	Cycle 2+ day 1	Cycle 2+ day 8	Ongoing
Informed Consent	X					
Clinical Assessment	X	X		X		
SACT Assessment (including toxicity assessment and PS)		X	X	X	X	
Blood pressure/ Pulse/ Temperature/ Respiratory rate		X	X	X	X	Continuously monitored during Isatuximab infusion
FBC	X	X		X		
U&E and LFTs, bone profile	X	X		X		Prior to every cycle
CrCl	X	X		X		Prior to every cycle
HbA1C	X					Repeat as clinically indicated
B2Microglobulin	X					
Serum Igs/electrophoresis/serum free light chains (if indicated)	X	X		X		Prior to every cycle
Red cell phenotype (notify transfusion lab)	X					
Hepatitis B/C serology	X					
Pregnancy test	X					As clinically indicated
Neurological assessment (for neuropathy)		X		X		
Height recorded	X					

Weight recorded	X	X		X		Prior to every cycle
Imaging as per NICE/network guidance and clinical indication	X					To restage as indicated
Dental assessment	X					As clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Isatuximab

Proceed if:-

ANC ≥ 0.5 x 10^9/L

If stopped, restart isatuximab when ANC ≥ 1.0 x 10^9/L.

Pomalidomide

Proceed if:-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 50 x 10^9/L

Toxicity	**Dose modification**
Neutropenia ANC < 0.5 x 10^9/L or febrile neutropenia (fever ≥38.5°C and ANC <1 x 10^9/L)	Interrupt pomalidomide treatment for remainder of cycle. Follow FBC weekly.
ANC return to ≥ 1 x 10^9/L	Resume pomalidomide treatment at one dose level lower than previous dose.
For each subsequent drop < 0.5 x 10^9/L	Interrupt pomalidomide treatment.
ANC return to ≥ 1 x 10^9/L	Resume pomalidomide treatment at one dose level lower than the previous dose.
Thrombocytopenia Platelet count < 25 x 10^9/L	Interrupt pomalidomide treatment for remainder of cycle. Follow FBC weekly.
Platelet count return to ≥ 50 x 10^9/L	Resume pomalidomide treatment at one dose level lower than previous dose.
For each subsequent drop < 25 x 10^9/L	Interrupt pomalidomide treatment.
Platelet count return to ≥ 50 x 10^9/L	Resume pomalidomide treatment at one dose level lower than the previous dose.

Dose level	**Oral pomalidomide dose**
Starting dose	4 mg
Dose level -1	3 mg
Dose level -2	2 mg
Dose level -3	1 mg

Non-haematological toxicity:

Nausea, vomiting, diarrhoea and infusion related reactions

Pomalidomide

Toxicity	Dose Modification
Any grade 3 or 4 toxicity (except those listed below) When resolved to Grade ≤ 2	Interrupt pomalidomide Resume pomalidomide treatment at one dose level lower than the previous dose
Skin rash G2 or G3 Skin rash G4 (exfoliative/bullous rash)	Interrupt or discontinue pomalidomide Discontinue pomalidomide
Angioedema (all grades)	Discontinue pomalidomide

Dosing in renal and hepatic impairment

Isatuximab

Renal	Hepatic
Limited evidence but no dose adjustment required	Limited evidence but no dose adjustment required

Pomalidomide

Renal	Hepatic
No dose adjustment required for renal dysfunction. On haemodialysis days, patients should take pomalidomide following haemodialysis.	Limited evidence but no dose adjustment required (patients with serum total bilirubin > 1.5 x ULN were excluded from clinical trial)

References:

1. Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory multiple myeloma (TA658), NICE 2020
2. Summary of Product Characteristics, Imnovid®, pomalidomide, Celgene Ltd, accessed November 2020 www.medicines.org.uk
3. Summary of Product Characteristics, Sarclisa®, isatuximab, Sanofi Genzyme, accessed November 2020 www.medicines.org.uk
4. Michel Attal, Paul G Richardson, S Vincent Rajkumar, Jesus San-Miguel, Meral Beksac, Ivan Spicka, Xavier Leleu, Fredrik Schjesvold, Philippe Moreau, Meletios

A Dimopoulos, Jeffrey Shang-Yi Huang, Jiri Minarik, Michele Cavo, H Miles Prince, Sandrine Macé, Kathryn P Corzo, Frank Campana, Solenn Le-Guennec, Franck Dubin, Kenneth C Anderson, on behalf of the ICARIA-MM study group† (2019). Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet, 394 (10214): 2096-2107