

BC Cancer Protocol Summary for Therapy of Multiple Myeloma using Pomalidomide, Dexamethasone and Isatuximab with or without Cyclophosphamide

Protocol Code

UMYISAPOMD

Tumour Group

Myeloma

Contact Physician

Dr. Christopher Venner

ELIGIBILITY:

Patients must have:

- Relapsed/refractory multiple myeloma,
- Previously received prior therapy that has included lenalidomide and a proteasome inhibitor (may have been discontinued due to progression or intolerance), and
- A BC Cancer “Compassionate Access Program” request approval prior to treatment

Registration of the prescribing physician and patient with the RevAid Program (www.RevAid.ca) is required.

Notes:

- Patients on active treatment with UMYPOMDEX who do not have proven progression may switch to UMYISAPOMD if all other eligibility criteria are met
- Patients are eligible for only one line of anti-CD38 monoclonal antibody therapy (e.g. daratumumab or isatuximab). Re-use of anti CD-38 monoclonal antibody therapy can only be considered if not refractory to use in a prior line.
- Cyclophosphamide may be added per physician discretion to increase response

EXCLUSIONS:

Patients must not:

- Have prior progression on daratumumab-containing regimen,
- Have known hypersensitivity to pomalidomide, or
- Be pregnant or lactating

CAUTIONS:

- Platelet count less than $30 \times 10^9/L$
- ANC less than $1.0 \times 10^9/L$. Consider giving filgrastim
- Previous hypersensitivity to lenalidomide or thalidomide

TESTS:

- Baseline (required before first treatment): Red Blood Cell phenotype and Group and Screen pre-isatuximab (mark on requisition "patient to start isatuximab")
- Baseline (required before first treatment): CBC & Diff, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose. If female of child-bearing potential (FCBP): Confirm negative pregnancy test results via a quantitative beta-hCG blood test obtained 7 to 14 days and 24 hours prior to initial prescription.
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): serum protein electrophoresis **and** serum free light chain levels, immunoglobulin panel (IgA, IgG, IgM), HCAb, HBsAg, HBsAb, HBcoreAb, TSH, beta-2 microglobulin
- Every 4 weeks (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis **and** serum free light chain levels
- Every 4 weeks (optional, results not mandatory but encouraged prior to each cycle): urine protein electrophoresis, immunoglobulin panel (IgA, IgG, IgM), beta-2 microglobulin
- Every 4 weeks: CBC & Diff, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose; if female of childbearing potential: quantitative beta-hCG blood test
- Days 8, 15, 22: (optional if pre-cycle cytopenias, hypercalcemia, hepatic or renal dysfunction, or steroid-induced diabetes is a concern. Results do not have to be available to proceed with treatment. Provider to review results, no dose modifications indicated for mid-cycle bloodwork): CBC & Diff, creatinine, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, random glucose
- Every three months (required for pomalidomide, but results do not have to be available to proceed with treatment): TSH
- If female of childbearing potential: Every week for 4 weeks during cycle 1: quantitative beta-hCG blood test. Provider responsible for checking results.
- If clinically indicated: HBV viral load (see protocol [SCHBV](#))

PREMEDICATIONS:

30 minutes prior to isatuximab infusion:

- dexamethasone* (see Treatment table, below)
- acetaminophen 650 mg PO prior to each isatuximab infusion, and then Q4H PRN during the IV infusion if the infusion exceeds 4 hours.
- loratadine 10 mg PO (preferred) or diphenhydramine 50 mg PO/IV prior to each isatuximab, then:
 - If using loratadine: give diphenhydramine 50 mg IV Q4H PRN allergic reaction
 - If using diphenhydramine: repeat diphenhydramine 50 mg IV Q4H PRN allergic reaction
- Optional, recommended prior to first dose of isatuximab, and prior to subsequent doses for patients who experience reaction: famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible with diphenhydramine, if using)
- montelukast 10 mg PO prior to **each** isatuximab **dose in Cycle 1**, then **optional for Cycle 2 onwards**
- **If no reaction after 4 consecutive doses of isatuximab, may discontinue acetaminophen, loratadine/diphenhydramine, famotidine and montelukast.**
Dexamethasone continues per Treatment table, below

- * predniSONE may be used instead of dexamethasone as the therapeutic steroid. A minimum of 100 mg of predniSONE prior to each isatuximab dose is recommended for cycle 1. After cycle 1, a lower dose of predniSONE may be administered prior to each isatuximab dose.
- If there is a contraindication to high-dose steroid, a minimum of 100 mg hydrocortisone is required prior to each isatuximab dose for cycle 1 to prevent infusion related reactions with isatuximab. See OTHER OPTIONS FOR STEROID DOSING, below.
- The therapeutic dose of steroid is used as the premedication steroid to reduce the risk of reactions. The therapeutic steroid dose should be administered prior to isatuximab.

SUPPORTIVE MEDICATIONS:

- Very high risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, follow hepatitis B prophylaxis as per SCHBV.
- Antiviral prophylaxis against reactivation of varicella-zoster virus (VZV) is recommended prior to initiating isatuximab. Patients should take valACYclovir 500 mg PO daily.
- Oral proton-pump inhibitor or H₂ antagonist for the duration of treatment with dexamethasone may be considered
- ASA (enteric coated), warfarin, direct oral anticoagulant (DOAC) or low molecular weight heparin (LMWH) daily continuing for the duration of treatment with pomalidomide.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
dexamethasone	40 mg* once weekly on Days 1, 8, 15, and 22	PO (preferred, or IV) <ul style="list-style-type: none"> ▪ Give 30 minutes prior to isatuximab ▪ Patient to self-administer on days without isatuximab. Morning may be preferred.
isatuximab	Cycle 1: 10 mg/kg on Days 1, 8, 15, and 22 Cycle 2 and subsequent: 10 mg/kg on Days 1 and 15	IV in 250 mL NS (use 0.2 micron in-line filter) If reaction** at any time during infusion, follow instructions per <u>SCDRUGRX</u>
		Cycle 1 Day 1: Start at 25 mL/hour; if no reactions after 60 minutes, increase rate by 25 mL/hour every 30 minutes until maximum 150 mL/hour
		Cycle 1 Day 8: if no reaction to Cycle 1 Day 1, or reaction is Grade 2*** or less: Start at 50 mL/hour; if no reaction after 30 minutes, increase rate by 50 mL/hour for 30 minutes, then by 100 mL/hour until maximum 200 mL/hour OR If reaction on Cycle 1 Day 1 is Grade 3*** : Start at 25 mL/hour; if no reactions** after 60 minutes, increase by 25 mL/hour every 30 minutes until maximum 150 mL/hour (slow infusion)
		Cycle 1 Day 15 and Day 22 and subsequent infusions: if no reaction to previous infusion, or reaction is Grade 2*** or less: Infuse over 30 minutes OR If reaction in previous infusion is Grade 3*** : Start at 100 mL/hour; if no reactions** after 60 minutes, increase by 50 mL/hour every 60 minutes until maximum 200 mL/hour (slow infusion)
pomalidomide	4 mg once daily on Days 1 to 21	PO, in the evening may be preferred
OPTIONAL cyclophosphamide*	500 mg once weekly on Days 1, 8, 15, and 22 OR 50 mg once every 2 days	PO, in the morning may be preferred

* Dexamethasone dose may vary dependent on tolerability and co-morbidities. For older patients i.e. 75 years of age or older, the starting dose of dexamethasone should be 20 mg PO weekly. See also: Other options for steroid dosing, below

** If BP falls to less than 80/50 mmHg or pulse increases to greater than 120 or if flushing, dyspnea, chills, rash, pruritus, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort occurs, stop isatuximab infusion and page physician. See Infusion Reaction section in protocol for when to resume infusion and rate.

*** For grading of infusion-related reaction, see Appendix: Infusion Related Reaction.

‡ cyclophosphamide may be added per physician discretion to increase response.

Repeat every 28 days until progression or unacceptable toxicity.

- If a dose of pomalidomide is missed, take the next dose at the same usual time.
- If pomalidomide is resumed mid-cycle after being held for toxicity:
 - Stop on Day 21 as scheduled
 - Maintain at least 7 days rest before resuming next cycle

For additional information on isatuximab infusion rates, see Appendix: Isatuximab infusion rate titration table.

Vitals monitoring and Observation:

Isatuximab:

For infusion on [Cycle 1, Day 1](#):

- Vital signs immediately before the start of the infusion, then every 30 minutes x 4, then every 1 to 2 hours until the end of the infusion. Vital signs post infusion at 30 minutes after the end of the infusion. Patient may leave when infusion is complete and patient is stable for 30 minutes.

For subsequent infusions i.e. [Cycle 1, Day 8 and beyond](#):

- Vital signs immediately before the start and at the end of the infusion, and as needed. [Vital signs not required after 4 treatments with no infusion reaction](#). Patient may leave when infusion is complete.

OTHER OPTIONS FOR STEROID DOSING

- Can be used (but may result in lower efficacy). Dose must be adjusted based upon toxicity and patient tolerance. Some examples included below:

Option A:

dexamethasone 20 mg PO once weekly (or dexamethasone 4 to 40 mg PO once weekly based on toxicity and patient tolerance)

Option B:

predniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance. (e.g. predniSONE 10 to 100 mg PO once weekly)

Option C:

No dexamethasone or predniSONE. High-dose steroids may need to be avoided in certain patients who are intolerant or have difficulty with side-effects. It is expected that the response will be inferior than without high-dose steroids. High-dose steroids may be added for non-response. In cycle 1, hydrocortisone 100 mg IV should be considered prior to each isatuximab dose for prevention of IRR with isatuximab.

DOSE MODIFICATIONS:

Isatuximab Dose Modifications: No specific dose modifications for isatuximab. Manage adverse reactions with treatment delays as indicated.

Pomalidomide Dose Modifications: Use one of the 1 mg, 2 mg, 3 mg or 4 mg capsules for dosing. Currently there is no evidence to support the use of other dosing regimens (i.e., there is no clinical reason or research available to support the use of a combination of pomalidomide capsules for dosing, however the use of such dosing does have significant budgetary implications).

Pomalidomide Dose Levels:

Dose Level 0	Dose Level -1	Dose Level -2	Dose Level -3
4 mg	3 mg	2 mg	1 mg

1. Infusion-related reactions (IRRs): Isatuximab

- Refer to [SCDRUGRX](#) protocol for management guidelines

Rate Adjustment for Isatuximab Infusion-Related Reactions:

Infusion reactions	Rate Adjustment
If BP falls to less than 80/50 mmHg or pulse increases to greater than 120 or if flushing, dyspnea, chills, rash, pruritus, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort, stop infusion and page physician	<p>Initial occurrence: After recovery of symptoms, restart infusion at HALF the rate at which the infusion reactions occurred. If symptoms do not recur after 30 minutes, continue with escalation of infusion rates as per Treatment table, above.</p> <p>Subsequent occurrence: If the infusion must be stopped a second time, restart after recovery of symptoms, at HALF the rate at which the infusion reactions occurred and continue at that rate without further escalation</p>

Infusion Rate when resuming isatuximab infusion after Grade 1 or greater symptoms are resolved:

Infusion Rate when Reaction Occurred (mL/hour)	Maximum Infusion Rate when Resuming Infusion (mL/hour)
25	13
50	25
75	38
100	50
125	63
150	75
175	88
200	100

2. Hematological (based on pre-cycle labwork):

ANC (x 10 ⁹ /L) on Day 1		Platelets (x 10 ⁹ /L) on Day 1	Pomalidomide Dose	Isatuximab Dose	Cyclophosphamide Dose (if using)
Greater than or equal to 1.0	and	Greater than or equal to 50	100%	100%	100%
0.5 to 0.99 [†]	or	30 to 49	Notify provider. Proceed but at next lower dose level, above.	100%	Delay until recovery
less than 0.5 or febrile neutropenia (ANC less than 1.0 with oral temperature greater than or equal to 38.0° Celsius)	or	less than 30*	Hold pomalidomide until ANC greater than or equal to 1.0 and platelets greater than or equal to 30, then restart at next lower dose level, above.		

* follow hematology weekly and consider arrangements for transfusion support as required.

† Consider weekly filgrastim if clinically indicated and filgrastim is available. Filgrastim is not covered as a benefit drug by BC Cancer.

3. Hepatic Impairment:

Hepatic impairment	Pomalidomide Dose	Isatuximab Dose	Cyclophosphamide (if using)
Mild or moderate (Child-Pugh Class A or B)	3 mg	No adjustment required	No adjustment required
Severe (Child-Pugh Class C)	2 mg		

Pomalidomide is metabolized in the liver.

4. Renal Impairment: pomalidomide and isatuximab

Estimated GFR (eGFR) or Creatinine clearance (mL/min)	Pomalidomide Dose	Isatuximab Dose
Less than 30	3 mg* *For patients on hemodialysis, on hemodialysis days, take pomalidomide following hemodialysis	100% No adjustment required in mild to severe renal impairment. No data in patients requiring hemodialysis

Pomalidomide and its metabolites are excreted by the kidneys.

Renal Impairment: cyclophosphamide

- Renal failure: dose reduction is necessary per table, below. Physician may consider giving full dose of cyclophosphamide irrespective of renal function if deemed to be of benefit.
- For patients on hemodialysis, give dose after dialysis.

Creatinine clearance (mL/min)	Cyclophosphamide Dose
Greater than or equal to 10	100 %
Less than 10	75 %

Calculated creatinine clearance = $\frac{N \times (140 - \text{Age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromols/L)}}$

N = 1.04 (Females) and 1.23 (Males)

PRECAUTIONS:

- Infusion-related reactions** to isatuximab are reported in up to 46% of patients. Most IRRs occur during the first cycle of isatuximab treatment, with the majority of reactions resolving on the same day. Symptoms include hypertension, dyspnea, bronchospasm, tachycardia, cough, dyspnea, nasal congestion, vomiting, nausea, and chills. To minimize the risk and severity of reaction, premedication with an antipyretic, H2 antagonist, antihistamine, and corticosteroid is recommended. When dexamethasone is prescribed as part of combination therapy, additional dexamethasone premedication may not be required. Permanently discontinue isatuximab if a Grade 4 or higher infusion-related reaction occurs, or if symptoms do not improve or recur after infusion interruption. For management of infusion-related reactions, see BC Cancer Protocol [SCDRUGRX](#): Management of Infusion-Related Reactions to Systemic Therapy Agents.

2. **Teratogenicity:** If pomalidomide is taken during pregnancy, it may cause severe birth defects or death to the fetus. Pomalidomide should never be used by females who are pregnant or who could become pregnant while taking the drug. Even a single dose taken by a pregnant woman may cause birth defects.
3. **Venous thrombosis/embolism:** Pomalidomide with dexamethasone is known to increase the risk for thromboembolic disease. **ASA 81 mg** oral daily should be considered in all patients. For those with higher risk of thrombo-embolic disease, full anti-coagulation should be considered.
4. **Interference with cross-matching and red blood cell antibody screening** occurs due to drug binding to CD38 on red blood cells (RBC) resulting in a positive Indirect Antiglobulin Test (Coombs test). This interference may persist for up to 6 months post last isatuximab treatment. Inform blood bank that a patient has received isatuximab. Type and screen patients prior to starting isatuximab.
5. **Interference with determination of myeloma response** as isatuximab (a human IgG kappa monoclonal antibody) may be detected on serum protein electrophoresis and immunofixation assays which monitor for endogenous M-protein. Interference with these assays by isatuximab may affect the determination of complete response and disease progression in some patients with IgG kappa myeloma protein.
6. **Hematologic** toxicities including neutropenia, febrile neutropenia, thrombocytopenia, lymphocytopenia and anemia are reported during treatment with isatuximab. Infections including upper respiratory tract infections, pneumonia, and urinary tract infections are reported and occur even in the absence of neutropenia. Patients with neutropenia should be closely monitored for signs of infection and promptly treated.
7. **Second Primary Malignancies (SPM)** are reported with increased incidence for patients being treated with isatuximab, pomalidomide and dexamethasone over patients taking pomalidomide and dexamethasone without isatuximab. Malignancies include skin and solid tumour cancers. Monitor for development of second primary malignancies.
8. **Hepatitis B Reactivation:** See [SCHBV protocol](#) for more details.
9. **Need for irradiated blood products:** Patients receiving an autotransplant require irradiated blood products from 7 days prior to collection to 3 months post transplant (6 months if total body irradiation conditioning) to eliminate the risk of potentially life-threatening transfusion-related graft-versus-host-disease. All other myeloma patients do not require irradiated blood products.

Call Dr. Christopher Venner or tumour group delegate at 604-877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Attal M, Richardson PG, Rajkumar SV, et al; ICARIA-MM study group. 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*. 2019 Dec 7;394(10214):2096-2107.
2. CADTH Reimbursement Review. Provisional Funding Algorithm. Multiple Myeloma. November 2022.
3. Isatuximab (Sarclisa) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies 2021.

Appendix:

Isatuximab Infusion Rate Titration Table

Isatuximab –UMYISAPOMD

Cycle 1 Day 1:

Isatuximab 10 mg/kg in 250 mL NS Total Volume – refer to Pharmacy Label		
TITRATION RATE	DURATION	VOLUME TO BE INFUSED (VTBI)
25 mL/h	60 minutes	25 mL
50 mL/h	30 minutes	25 mL
75 mL/h	30 minutes	38 mL
100 mL/h	30 minutes	50 mL
125 mL/h	30 minutes	63 mL
150 mL/h	To Be Determined*	To Be Determined*

*Refer to Total Volume on Pharmacy label and adjust duration and VTBI as needed

Cycle 1 Day 8:

Isatuximab 10 mg/kg in 250 mL NS Total Volume – refer to Pharmacy Label		
TITRATION RATE	DURATION	VOLUME TO BE INFUSED (VTBI)
50 mL/h	30 minutes	25 mL
100 mL/h	30 minutes	50 mL
200 mL/h	To Be Determined*	To Be Determined*

*Refer to Total Volume on Pharmacy label and adjust duration and VTBI as needed

Cycle 1 Day 8 (Slow infusion):

Isatuximab 10 mg/kg in 250 mL NS Total Volume – refer to Pharmacy Label		
TITRATION RATE	DURATION	VOLUME TO BE INFUSED (VTBI)
25 mL/h	60 minutes	25 mL
50 mL/h	30 minutes	25 mL
75 mL/h	30 minutes	38 mL
100 mL/h	30 minutes	50 mL
125 mL/h	30 minutes	63 mL
150 mL/h	To Be Determined*	To Be Determined*

*Refer to Total Volume on Pharmacy label and adjust duration and VTBI as needed

Cycle 1 Day 15 and onwards:

Isatuximab 10 mg/kg in 250 mL NS Total Volume – refer to Pharmacy Label	
DURATION	VOLUME TO BE INFUSED (VTBI)
30 minutes	250 ml*

*Refer to Total Volume on Pharmacy label and adjust VTBI as needed

Cycle 1 Day 15 and onwards (Slow infusion):

Isatuximab 10 mg/kg in 250 mL NS Total Volume – refer to Pharmacy Label		
TITRATION RATE	DURATION	VOLUME TO BE INFUSED (VTBI)
100 mL/h	60 minutes	100 mL
150 mL/h	60 minutes	150 mL
200 mL/h	To Be Determined*	To Be Determined*

*Refer to Total Volume on Pharmacy label and adjust duration and VTBI as needed

Appendix: Infusion Related Reaction

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, iv fluids); prophylactic medications indicated for less than or equal to 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and /or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death

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