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

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|---|---|
| ***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, platelets, 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, 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, platelets, 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, platelets, 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.

**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 isatuximab for cycle 1, Day 1, then consider discontinuing if no infusion reactions
- **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:**

- If HBsAg or HBcoreAb positive, start hepatitis B prophylaxis as per current guidelines.
- 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 $H_2$ 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)<br>▪ Give 30 minutes prior to isatuximab<br>▪ Patient to self-administer on days without isatuximab. Morning may be preferred. |
| isatuximab | Cycle 1:<br>10 mg/kg on Days 1, 8, 15, and 22<br><br>Cycle 2 and subsequent**:**<br>10 mg/kg on Days 1 and 15 | IV in 250 mL NS<br>(use 0.2 micron in-line filter)<br><br>If reaction** at any time during infusion, follow instructions per SCDRUGRX |
| | | **Cycle 1 Day 1:**<br><br>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:<br>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<br>OR<br>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 at 200 mL/hour<br>OR<br><br>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**<br>cyclophosphamide¥ | 500 mg once weekly on Days 1, 8, 15, and 22<br>*OR*<br>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. 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. 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:

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| **Option A:**<br>dexamethasone 20 mg PO once weekly (or dexamethasone 4 to 40 mg PO once weekly based on toxicity and patient tolerance) |
| **Option B:**<br>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:**<br>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 | **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.<br><br>**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 |

**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*<br>*For patients on hemodialysis, on hemodialysis days, take pomalidomide following hemodialysis | 100%<br>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 = $\frac{N \times (140 - Age) \times weight\ (kg)}{Serum\ Creatinine\ (micromols/L)}$

N = 1.04 (Females) and 1.23 (Males)

**PRECAUTIONS:**

1. **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**: All myeloma patients should be tested for both HBsAg and HBcAb. If either test is positive, such patients should be treated with hepatitis B prophylaxis according to current guidelines. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every three months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
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<br>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<br>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<br>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<br>Total Volume – refer to Pharmacy Label | | |
|---|---|---|
| **TITRATION RATE** | **DURATION** | **VOLUME TO BE INFUSED (VTBI)** |
| **200 mL/h** | **75 minutes*** | **250 ml*** |

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

**Cycle 1 Day 15 and onwards (Slow infusion):**

| **Isatuximab** 10 mg/kg in 250 mL NS<br>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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