BC Cancer Protocol Summary for Treatment of Previously Untreated Multiple Myeloma and Not Eligible for Stem Cell Transplant Using Bortezomib, Lenalidomide and Dexamethasone

Protocol Code	***UMYBLDF***
Tumour Group	***Lymphoma, Leukemia/BMT***
Contact Physicians	***Dr. Jesse Shustik*** ***Dr. Kevin Song***
Contact Pharmacist	***Louisa Pang***

ELIGIBILITY:

- Patients with newly diagnosed multiple myeloma as per the updated International Myeloma Working Group criteria, who are ineligible for stem cell transplant
- Life expectancy of greater than 3 months
- A BC Cancer "Compassionate Access Program" request with appropriate clinical information for each patient must be approved prior to treatment
- Registration of the prescribing physician and patient with the RevAid Program (www.RevAid.ca)

EXCLUSIONS:

- Pregnant or lactating women
- Absolute neutrophil count (ANC) less than 1.0 x 10^9/L may be considered a relative contraindication
- Platelet count less than 50 x 10^9/L may be considered a relative contraindication
- Total bilirubin greater than or equal to 1.5 x upper limit of normal
- Known hypersensitivity to lenalidomide or pomalidomide or thalidomide
- Patients who are being considered for stem cell transplant. Lenalidomide can cause difficulty with peripheral blood stem cell collection.

TESTS:

- Baseline (required before first treatment): CBC and differential, platelets, creatinine, LFTs (bilirubin, ALT). 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/or*** serum free light chain levels, HBsAg, HBcoreAb, TSH, calcium
- Every 2 weeks (for lenalidomide) during the first 4 cycles then may reduce frequency to every four weeks: CBC and differential, platelets, creatinine, calcium

- Every three months (required for lenalidomide, 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
- Before day 1: CBC and differential, platelets, creatinine, bilirubin, ALT; if female of childbearing potential: quantitative beta-hCG blood test
- Before day 1 (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis ***and/or*** serum free light chain levels, and calcium.
- **Cycles 1 to 8 only**: If CBC prior to day 1 show ANC less than 1.5 x 10^9/L or platelets less than 75 x 10^9/L, then:
    - Before day 8 and 15 (**for bortezomib only**): CBC and differential
- If clinically indicated: skeletal survey X-rays (at least annually)

PREMEDICATIONS:

None

SUPPORTIVE MEDICATIONS:

- Oral proton-pump inhibitor or H_2 antagonist for the duration of treatment with dexamethasone or prednisone may be considered
- ASA (enteric coated), warfarin, direct oral anticoagulant (DOAC) PO or low molecular weight heparin (LMWH) SC daily continuing for the duration of treatment with lenalidomide
- If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily for the duration of chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive
- Antiviral prophylaxis is recommended prior to initiating bortezomib for patients who have a history of varicella zoster virus (VZV) infection (chicken pox and shingles). Patients should take valACYclovir 500 mg PO daily while taking bortezomib and for 4 weeks after its discontinuation

TREATMENT:

1 cycle = 28 days. Treat until progression or unacceptable toxicity

Drug	Dose	BC Cancer Administration Guideline
bortezomib	**Cycles 1 to 8 only** 1.3 mg/m^2 on days 1, 8, and 15	SC (abdomen or thigh)[¥]
lenalidomide	25 mg once daily for 21 days (d1-21)	PO, in the evening may be preferred
dexamethasone	*40 mg once daily on days 1, 8, 15 and 22	PO, in the morning may be preferred

[¥]back of the arm can also be considered as a third option, after abdomen or thigh

* Dose may vary dependent on tolerability and co-morbidities

- Patients over 75 years of age: consider using dexamethasone 20 mg
- predniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance.

OTHER OPTIONS FOR DEXAMETHASONE DOSING

Option A: Oral dexamethasone 20 or 40 mg daily on days 1-4, 9-12, 17-20 x 4 cycles; then 20 or 40 mg daily on days 1-4 only for subsequent cycles. The dose should be adjusted based upon toxicity and patient tolerance. (e.g. dexamethasone 4 - 40 mg PO once weekly)
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 – 100 mg PO once weekly)
Option C: No dexamethasone. Dexamethasone 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 using lenalidomide alone. Dexamethasone may be added for non-response.

DOSE MODIFICATIONS:

I. LENALIDOMIDE DOSE MODIFICATIONS:

Fatigue may respond to dose reduction

NB: Use one of the 25 mg, 20 mg, 15 mg, 10 mg, 5 mg or 2.5 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 lenalidomide capsules for dosing, however the use of such dosing does have significant budgetary implications).

Dexamethasone should continue to be taken even if Lenalidomide is held due to a dose limiting toxicity.

Dose Levels	Lenalidomide on Days 1–21 of Every 28-Day Cycle
Standard dose	25 mg/d on Days 1-21
Dose level -1	20 mg/d on Days 1-21
Dose level -2	15 mg/d on Days 1-21
Dose level -3	10 mg/d on Days 1-21
Dose level -4	5 mg/d on Days 1-21
Dose level -5	2.5 mg/d on Days 1-21

1. Hematological

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	1st Event Dose	2nd Event Dose	3rd Event Dose	4th Event Dose or subsequent
Greater than or equal to 1.0	and	Greater than or equal to 50	100%	100%	100%	100%
0.5 to less than 1.0	or	25 to less than 50	Delay* then 100%	Delay* then 100%	Delay* then 100%	Delay* then 100%
Less than 0.5†,‡ or febrile neutropenia	or	Less than 25	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by One dose level when dosing resumed at next cycle Do not dose below 2.5 mg

* Delay until ANC greater than or equal to 1.0 x 10^9/L and platelets greater than or equal to 50 x 10^9/L

† Consider filgrastim if clinically indicated and filgrastim is available

‡ If neutropenia is isolated without other toxicity and filgrastim treatments continue, may consider continuing with no dose reduction. Filgrastim is not covered as a benefit drug by the BC Cancer.

Note: Bloodwork monitored every 2 weeks for the first 4 cycles

Day 15 bloodwork for Cycle 1-4 will be monitored by the physician and physician will be responsible to check and advise patient on dose adjustment, as per suggested guidelines above.

For females of child-bearing potential on weekly pregnancy test during cycle 1, physician will be responsible for checking results

2. Renal dysfunction:

Estimated GFR (eGFR)* or Creatinine clearance (mL/min)	Lenalidomide Dose
Greater than or equal to 60	25 mg daily†
30-59	10 mg daily†‡
Less than 30, not requiring dialysis	15 mg every other day for 21 days, then rest for 7 days (i.e. 28-day cycle)

*As reported in patient's laboratory report
†Dosing for 21 days (d 1-21) of each 28-day cycle
‡Dose can be escalated to 15 mg after 2 cycles if patient is not responding to treatment and is tolerating the drug; may consider escalating to 25 mg if patient continues to tolerate the drug

3. Non-hematological/Non-renal

Toxicity	1st occurrence	2nd occurrence	3rd occurrence	4th or subsequent occurrence
Grade 3 or greater exfoliative rash, SJS, TEN	Discontinue			
Pneumonitis	For suspected pneumonitis, hold and investigate; discontinue if confirmed			
Grade 3-4 (any other toxicity)	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by one dose level when dosing resumed at next cycle	Delay* then decrease by one dose level when dosing resumed at next cycle Do not dose below 2.5 mg

*Stop treatment immediately and delay until toxicity resolved to grade 0-2

II. BORTEZOMIB DOSE MODIFCATIONS:

1. Hematological for labs on days 1, 8 and 15:

ANC ($x10^9$/L)	Platelets ($x10^9$/L)	Dose (bortezomib)
greater than or equal to 0.5	And greater than or equal to 50	100%
less than 0.5	Or less than 50	Delay until recovery checking CBC weekly; consider reducing dose to the next lower level*

*(bortezomib dose levels; 1.3 mg/m^2, 1.0 mg/m^2, 0.7 mg/m^2)

2. Peripheral Neuropathy:

Severity of Peripheral Neuropathy Signs and Symptoms	Dose (bortezomib)
Grade 1 (paresthesia and/or loss of reflexes) without pain or loss of function	100%
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce dose to 1 mg/m^2
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Delay until recovery. When resolved, reduce dose to 0.7 mg/m^2
Grade 4 (permanent sensory loss that interferes with function)	Discontinue treatment

3. Hepatic Impairment:

	Bilirubin	ALT	Bortezomib Dose
Mild	less than or equal to 1.0 x upper limit of normal	greater than the upper limit of normal	100%
	greater than 1.0-1.5 x upper limit of normal	Any	100%
Moderate	greater than 1.5-3 x upper limit of normal	Any	▪ Reduce dose to 0.7 mg/m^2 in the first cycle. ▪ Consider dose escalation to 1 mg/m^2 *or* further dose reduction to 0.5 mg/m^2 in subsequent cycles based on patient tolerability.
Severe	greater than 3 x upper limit of normal	Any	

4. Renal dysfunction:

No dose reduction is necessary for renal failure. For patients on hemodialysis, give dose after dialysis.

5. Diarrhea:

Diarrhea grading system

Grade 1	Grade 2	Grade 3	Grade 4
Increase of less than 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 – 6 stools per day over baseline; IV fluids indicated for less than 24 hrs; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of greater than 7 stools per day over baseline; incontinence; IV fluids for greater than 24 hrs; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g., hemodynamic collapse)

Treatment of Diarrhea during cycle		
At first loose stool:	Start loperamide 2 mg po q 2 h while awake and q 4 h while sleeping. Continue around the clock until 12 h diarrhea free	• If *diarrhea free greater than 12 h*, stop loperamide. If new episode, retreat with loperamide. • If *grade 3* diarrhea or diarrhea accompanied by *mucus or dehydration, hold doses of Bortezomib* (if applicable) and hydrate.

Diarrhea management: Next Cycle Dosing

Delay next cycle until diarrhea has resolved (less than 2 watery bowel movements / day)

Severity of diarrhea with *last* cycle:	Bortezomib dose *this* cycle
less than or equal to grade 2	no change from previous cycle
greater than or equal to grade 3 or associated with mucus or dehydration	Reduce dose to 80% of that used in the last course (if two dose reductions have already occurred further treatment with Bortezomib must be individualized and should only continue if a clearly useful clinical response in the myeloma has occurred)

PRECAUTIONS:

1. **Teratogenicity**: If lenalidomide is taken during pregnancy, it may cause severe birth defects or death to the fetus. Lenalidomide 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.
2. **Hepatotoxicity:** Hepatic failure, including fatal cases, has been reported in multiple myeloma patients treated with lenalidomide in combination with dexamethasone during post-marketing. The mechanism of severe drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes and concomitant medications may be risk factors. Stop lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.
3. **Hypothyroidism:** The use of lenalidomide may result in hypothyroidism. Thyroid function tests should be repeated every 3 months. Treatment with thyroid replacement should be considered even for subclinical hypothyroidism. Lenalidomide can be continued if hypothyroidism can be easily managed.
4. **Venous thrombosis/embolism:** Lenalidomide 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 thromboembolic disease full anti-coagulation should be considered.
5. **Hepatitis B Reactivation**: All myeloma patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamiVUDine during chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two 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.
6. **Skin Rashes**: Lenalidomide may cause skin rashes although in general it is not severe. Minor rashes can be treated with diphenhydramine and/or steroid creams and lenalidomide can be continued. Moderate rashes may require holding lenalidomide until resolution of the rash. For more severe rashes (greater than or equal to Grade 3: severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering greater than or equal to 50% BSA) lenalidomide should be discontinued.
7. **Second Primary Malignancies (SPM)**: In clinical trials of newly diagnosed multiple myeloma patients, for those receiving lenalidomide with dexamethasone, the hematological SPM incidence rate (0.14 per 100 person-years) was not increased as compared to patients on thalidomide in combination with melphalan and prednisone (0.91 per 100 person-years). The risk of occurrence of SPM must be taken into account before initiating treatment with lenalidomide. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of second primary malignancies and institute treatment as indicated.
8. **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.
9. **Green tea avoidance.** Some of the components in green tea and preparations made from green tea block the activity of bortezomib in *in vitro* experiments. Green tea or preparations made from green tea should be avoided by patients taking bortezomib.

10. **H. zoster (shingles) prophylaxis:** Antiviral prophylaxis is recommended prior to initiating bortezomib for patients who are VZV seropositive. Patients should take valACYclovir 500 mg PO daily while taking bortezomib and for 4 weeks after its discontinuation. Of note, VZV serology if often not reliable, even in patients previously exposed. Most clinicians choose to prescribe valACYclovir without testing for VZV serology.

Call Dr. Jesse Shustik, Dr. Kevin Song (Leukemia/BMT), Dr. Laurie Sehn (Lymphoma) or tumour group delegate with any problems or questions regarding this treatment program. (Leukemia/BMT at (604) 875-4863 or after hours (604) 875-4111; Lymphoma at (604) 877-6000 or 1-800-663-3333)

References:

1. O'Donnell E *et al.* A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. *Br J Haematol* 2018; 182:222-230.

2. Durie B *et al*. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet* 2017; 389:519-527.

3.Teva Canada. Bortezomib product monograph. Toronto, Ontario; 26 May 2016