BC Cancer Protocol Summary for the Treatment of Previously Untreated Light Chain Amyloidosis and Not Eligible for Stem Cell Transplant using Daratumumab, Cyclophosphamide, Bortezomib and Dexamethasone

Protocol Code	*LYDARCBDF*
Tumour Group	*Lymphoma*
Contact Physicians	*Dr. Christopher Venner* *Dr. Jesse Shustik* *Dr. Kevin Song*

ELIGIBILITY:

Patients must have:
- Newly diagnosed light chain (AL) amyloidosis
    - With disease involving at least one organ system and
- Ineligibility for stem cell transplant or not being offered as part of initial treatment

Note:
- Patients who are currently on first-line therapy started prior to, or have completed first-line therapy within 3 months of, 1 Sep 2022 may switch to LYDARCBDF if they have not experienced progression and meet other eligibility criteria

EXCLUSIONS:
- Prior treatment for AL amyloidosis or multiple myeloma
- Previous or current diagnosis of multiple myeloma

CAUTIONS:
- Neutrophils of 1.0 x 10^9/L or less. Consider giving filgrastim
- Platelet count of 30 x 10^9/L or less,
- AST or ALT 2.5 times greater than upper limit of normal, or total bilirubin greater than or equal to 1.5 x upper limit of normal

TESTS:
- Baseline (required before first treatment): Red Blood Cell phenotype and Group and Screen pre-daratumumab (mark on requisition ”patient to start daratumumab”)
- Baseline (required before first treatment): CBC & Diff, platelets, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose
- Baseline (required, but results do not have to be available to proceed with treatment; results must be checked before proceeding with further treatment): serum protein electrophoresis and serum free light chain level, immunoglobulin panel (IgA, IgG, IgM), HCAb, HBsAg,

HBcoreAb, beta-2 microglobulin, troponin I cardiac high sensitivity, NT-pro BNP, albumin creatinine ratio urine, urine protein electrophoresis
- Every 4 weeks (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis and free light chain levels, troponin I cardiac high sensitivity, NT-pro BNP, albumin creatinine ratio urine
- Every 4 weeks (optional, results not mandatory but encouraged prior to each cycle): immunoglobulin panel (IgA, IgG, IgM), urine electrophoresis, beta-2 microglobulin
- Every 4 weeks: CBC & Diff, platelets, creatinine, urea, sodium, potassium, total bilirubin, ALT, alkaline phosphatase, calcium, albumin, LDH, random glucose
- Days 8, 15, 22: (optional if pre-cycle cytopenias hypercalcemia, hepatic or renal dysfunction, or steroid-induced diabetes 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

PREMEDICATIONS:

Prior to daratumumab administration:
- acetaminophen 650 mg PO prior to each daratumumab . Then repeat acetaminophen Q4H PRN
- loratadine 10 mg PO (preferred) or diphenhydrAMINE 50 mg PO/IV prior to each daratumumab, 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.
- montelukast 10 mg PO prior to daratumumab for cycle 1, Day 1, then consider discontinuing if no reaction
- dexamethasone 20 to 40 mg PO prior to daratumumab for cycle 1 only. (The therapeutic dose of dexamethasone is used as the premedication steroid to reduce the risk of reactions). After cycle 1, steroids are not required as a premedication as the risk of administration reactions is significantly reduced after the third dose of daratumumab.[15] The therapeutic dexamethasone dose (if ordered) should be administered prior to daratumumab.
    - predniSONE may be used instead of dexamethasone as the therapeutic steroid. A minimum of 100 mg of predniSONE is required for cycle 1. After cycle 1, a lower dose of predniSONE may be used and administered prior to daratumumab

  Note: A minimum of 20 mg of dexamethasone (or 100 mg of predniSONE) is not needed prior to each daratumumab treatment after cycle 1

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 daratumumab. Patients should take valACYclovir 500 mg PO daily
- Oral proton-pump inhibitor or H_2 antagonist for the duration of treatment with dexamethasone or predniSONE may be considered

TREATMENT:

1 cycle = 28 days. Treat until progression or a maximum of 24 cycles

Insert a peripheral IV and saline lock for Cycle 1 Day 1 only for subcutaneous daratumumab, for use in the event of a hypersensitivity reaction.

Drug	Dose	BC Cancer Administration Guideline
dexamethasone	Cycle 1 to 6: 40 mg* once weekly on Days 1, 8, 15 and 22 For patients greater than 75 years of age (or younger than 75 years of age at MD's discretion), use dexamethasone 20 mg or lower	PO prior to daratumumab, and on the weeks when daratumumab is not given, taken in the morning
cyclophosphamide	Cycle 1 to 6: 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
bortezomib≠	Cycle 1 to 6: 1.3 mg/m^2 (may start with 1.5 mg/m^2) once weekly on Days 1, 8, 15, 22	subcutaneous (abdomen or thigh)
daratumumab	Cycles 1 and 2: 1800 mg (fixed dose in 15 mL) on Days 1, 8, 15 and 22 Cycles 3 to 6: 1800 mg (fixed dose in 15 mL) on Days 1 and 15 Cycles 7 and subsequent: 1800 mg (fixed dose in 15 mL) on Day 1	subcutaneous over 5 minutes in the abdomen Observe¥ for 1 hour after administration on Day 1 of Cycle 1. Observation not required for subsequent doses, except at physician discretion

*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. The risk of administration reactions is significantly reduced after the third dose of daratumumab; therefore, premedication with steroids is not required after cycle 1.[15]

≠On days when both subcutaneous daratumumab and bortezomib is administered, give bortezomib before subcutaneous daratumumab.

¥ Observe patient for 1 hour after injection on Cycle 1 Day 1 only. If dyspnea, chills, rash, fever, pruritis, vomiting, chest pain, throat tightness, cough, wheezing, or any other new acute discomfort occurs, page physician. Observation after subsequent doses at physician discretion only.

Vitals monitoring:

Vital signs immediately prior to the injection, at the end of the injection, and at the end of observation period for first injection only (Cycle 1 Day 1), and as needed.

POST TREATMENT MEDICATIONS:

Patients with a higher risk of respiratory complications (e.g., patients with chronic obstructive pulmonary disease (COPD) who have a forced expiratory volume in 1 second of less than 80%; patients with asthma) should be treated with post-injection medication consisting of an antihistamine (diphenhydramine) on the first and second days after all injections, short acting adrenergic receptor agonist (salbutamol inhaler) and control medications for lung disease (e.g., inhaled corticosteroids +/- long-acting β2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators +/- inhaled corticosteroids for patients with COPD.

OTHER OPTIONS FOR STEROID DOSING

- Can be used (but may result in lower efficacy). Dose should 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/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 with 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 daratumumab dose for prevention of IRR.

DOSE MODIFICATIONS:

Bortezomib dose levels:

Dose Level 0	Dose level -1	Dose level -2	Dose level -3	Dose level -4
1.5 mg/m^2	1.3 mg/m^2	1 mg/m^2	0.7 mg/m^2	0.5 mg/m^2

1. Hematological (based on pre-cycle lab work):

ANC (x10^9/L) On Day 1		**Platelets (x10^9/L)** On Day 1	**Bortezomib Dose**	**Daratumumab Dose**	**Cyclophosphamide Dose**
Greater than or equal to 0.5	and	Greater than or equal to 50	Maintain dose level	100%	100%
0.5 to 0.99	and	30 to 49	Notify provider. Proceed but consider dose reduction by one dose level for low platelets.	100%	Delay until recovery
Less than 0.5†	or	Less than 30*	May proceed but consider decrease by one dose level if felt to be treatment related.		
Reoccurrence of less than 0.5†	or	Reoccurrence of less than 30*	For recurrence of ANC less than 0.5, may proceed but consider decrease by one dose level if felt to be treatment related Delay until platelets greater than or equal to 30, then consider decreasing by one dose level		

*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.

2. Hepatic Impairment:

	Total bilirubin	ALT or AST	Bortezomib Dose	Daratumumab Dose	Cyclophosphamide Dose
Mild	less than or equal to 1 x ULN	greater than ULN	100%	100 %	100 %
	greater than 1 to 1.5 x ULN	Any	100%		
Moderate	greater than 1.5 to 3 x ULN	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 ULN	Any			

3. Renal Failure:

Bortezomib and Daratumumab:

Estimated GFR (eGFR)* or Creatinine clearance (mL/min)	Bortezomib Dose	Daratumumab Dose
Greater than or equal to 60	100% For patients on hemodialysis, give dose after dialysis.	100% For patients on hemodialysis, give dose after dialysis.
30 to 59		
Less than 30, not requiring dialysis		

Cyclophosphamide:

- 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 = $\frac{N \times (140 - Age) \times weight\ (kg)}{Serum\ Creatinine\ (micromol/L)}$

N = 1.04 (Females) and 1.23 (Males)

4. Peripheral Neuropathy: bortezomib

Severity of Peripheral Neuropathy Signs and Symptoms	Bortezomib Dose
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 weekly
Grade 4 (permanent sensory loss that interferes with function)	Discontinue treatment

5. Diarrhea management with bortezomib:

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 24hrs; 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 q2h while awake and q4h 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 or consider once a week dosing. (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)

6. Infusion reactions

There are no modifications required to subcutaneous daratumumab for any current or previous infusion/administration reaction(s).

See BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Chemotherapeutic Agents – SCDRUGRX.

PRECAUTIONS:

1. **Infusion/administration reactions** occur in approximately 15% of patients after subcutaneous injection and can be serious including bronchospasm, hypoxia and hypertension. These usually occur with the first dose and rarely after subsequent infusions. Nearly all reactions occurred shortly after completing the subcutaneous injection. Other signs and symptoms include cough, wheezing, larynx and throat tightness/irritation, laryngeal edema, pulmonary edema, nasal congestion, and allergic rhinitis. Less commonly reported symptoms include hypotension, headache, urticarial rash, pruritus, nausea, vomiting, and chills. **Premedication** with antihistamines, antipyretics, and corticosteroids is required; stop infusion for any infusion reactions and manage as appropriate. Administer in a facility with immediate access to resuscitative measures (e.g., glucocorticoids, epinephrine, bronchodilators, and/or oxygen). Consider administration of oral corticosteroids on the second day after administration to reduce the risk of delayed infusion reactions. Consider short- and long-acting bronchodilators and inhaled corticosteroids for patients with obstructive pulmonary disorders; monitor closely. See BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Chemotherapeutic Agents – SCDRUGRX.
2. **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 daratumumab treatment. Inform blood bank that a patient has received daratumumab. Type and screen patients prior to starting daratumumab.
3. **Interference with determination of myeloma response** as daratumumab (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 daratumumab may affect the determination of complete response and disease progression in some patients with IgG kappa myeloma protein.
4. **Hepatitis B Reactivation**: All 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.
5. **Live vaccines**: Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.

6. **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.

7. **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.
8. **Diarrhea management with bortezomib:** see diarrhea management in bortezomib dose modification section.
9. **Peripheral Neuropathy:** occurs in 36–37% of patients receiving IV bortezomib with 8–14% resulting in grade 3–4 severity of symptoms. This is a common and often dose limiting side effect. Administration of bortezomib via the subcutaneous route instead of IV push significantly reduces the occurrence of peripheral neuropathy.

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. Kastritis E, Palladini G, Minnema MC, et al. Daratumumab-based treatment for immunoglobulin light-chain amyloidosis. N Engl J Med 2021;385:46-58.
2. Roussel M, Merlini G, Chevret S, et al. A prospective phase 2 trial of daratumumab in patients with previously treated systemic light-chain amyloidosis. Blood 2020; 135(18):1531-1540.
3. Sanchorawala V, Sarosiek S, Schulman A, et al. Safety, tolerability, and response rates of daratumumab in relapsed AL amyloidosis: results of a phase 2 study. Blood 2020; 135(18):1541-1547.
4. Janssen Inc. DARZALEX® SC product monograph. Toronto, Ontario; 29 July 2020.
5. Nahi H, Usmani SZ, Mateos MV et al. Corticosteroid tapering in patients (Pts) with relapsed or refractory multiple myeloma (RRMM) receiving subcutaneous daratumumab (DARA SC): Part 3 of the open-label, multicenter, phase Ib PAVO Study. ASCO Virtual Poster Presentation 2020, Abstract 8537.

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 (eg. 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**

CTCAE v5.0-Nov.27, 2017