

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

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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

CAUTION:

- Neutrophils of $1.0 \times 10^9/L$ or less (consider giving filgrastim),
- Platelet count of $75 \times 10^9/L$ or less,
- Hemoglobin level of 75 g/L or less,
- AST or ALT level of 2.5 times greater than the ULN, or
- Bilirubin of 1.5 or greater than the ULN

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, sodium, potassium, creatinine, calcium, ALT, serum bilirubin, alkaline phosphatase, albumin
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with further treatment): HBsAg, HBcoreAb, serum protein electrophoresis, serum free light chain level, immunoglobulin panel, troponin I cardiac high sensitivity, NT-pro BNP, albumin creatinine ratio urine, urine protein electrophoresis, beta 2 microglobulin

Cycles 1 to 6

- Day 1: CBC & diff, platelets, sodium, potassium, creatinine, calcium, ALT, serum bilirubin, alkaline phosphatase, albumin
- Day 1: (required, but results do not have to be available to proceed with treatment): serum protein electrophoresis, free light chain levels, troponin I cardiac high sensitivity, NT-pro BNP, albumin creatinine ratio urine, urine protein electrophoresis
- Day 1: (optional, results do not have to be available to proceed with treatment): immunoglobulin panel (IgA, IgG, IgM)
- Day 15: CBC & diff, platelets. If clinically indicated, sodium, potassium, creatinine, ALT, serum bilirubin

Cycle 7 and subsequent

- Day 1: CBC & diff, platelets, sodium, potassium, creatinine, calcium, ALT, serum bilirubin, alkaline phosphatase, albumin
- Day 1: (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, urine protein electrophoresis
- Day 1: (optional, results do not have to be available to proceed with treatment): immunoglobulin panel (IgA, IgG, IgM)

Cycles 1 to 6 (for bortezomib only)

- If CBC prior to day 1 show ANC less than $1.5 \times 10^9/L$ or platelets less than $100 \times 10^9/L$ then:
 - Before day 8, 15, 22 CBC and differential

PREMEDICATIONS:

Prior to daratumumab administration:

- acetaminophen 650 mg PO prior to each daratumumab . Then repeat acetaminophen Q4H PRN
- loratadine 10 mg PO 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 infusion or injection reactions
- 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 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. (Complete special authority form)
- If Varicella-zoster Virus (VZV) seropositive, start valACYClovir 500 mg PO daily and continue for entire duration of bortezomib and/or daratumumab and for 4 weeks after discontinuation.
- Oral proton-pump inhibitor or H₂ antagonist for the duration of treatment with dexamethasone 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*	<u>Cycle 1 to 6:</u> 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**	<u>Cycle 1 to 6:</u> 300 mg/m ^{2***} once weekly on days 1, 8, 15, 22 (maximum dose 500 mg)	PO
bortezomib[‡]	<u>Cycle 1 to 6:</u> 1.3 mg/m ² once weekly on days 1, 8, 15, 22	subcutaneous (abdomen or thigh)
daratumumab	<u>Cycles 1 and 2:</u> 1800 mg (fixed dose in 15 mL) on days 1, 8, 15 and 22 <u>Cycles 3 to 6:</u> 1800 mg (fixed dose in 15 mL) on days 1 and 15 <u>Cycles 7 and subsequent:</u> 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

*Therapeutic dose of dexamethasone is used as the premedication steroid to reduce the risk of administration reactions. PredniSONE may be substituted for dexamethasone as the therapeutic steroid per physician preference. A minimum of 20 mg dexamethasone or 100 mg predniSONE is required for cycle 1 only to prevent infusion reactions. 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

**If neutropenia is a concern consider a dose reduction of cyclophosphamide

***round dose to the nearest 25 mg

‡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-infusion medication consisting of an antihistamine (diphenhydramine) on the first and second days after all infusions, short acting adrenergic receptor agonist (salbutamol inhaler) and control medications for lung disease (e.g., inhaled corticosteroids +/- long-acting β 2 adrenergic receptor agonists for patients with asthma; long-acting bronchodilators +/- inhaled corticosteroids for patients with COPD).

OTHER OPTIONS FOR STEROID DOSING

Option A: Oral dexamethasone 20 mg once weekly on days 1, 8, 15 and 22
Option B: predniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance.
Option C: No steroid. 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 using bortezomib alone. Hydrocortisone 100 mg IV should be given as a pre-medication prior to daratumumab in these cases to mitigate infusion reactions for Cycle 1 (see premedications). Steroids may be added for sub-optimal response.

DOSE MODIFICATIONS:

I. CYCLOPHOSPHAMIDE DOSE MODIFICATIONS:

1. Hematological, for low counts due to treatment, not disease

For cyclophosphamide lab on day 1 only

ANC (x10 ⁹ /L)	Platelets (x10 ⁹ /L)	Dose (cyclophosphamide)
greater or equal to 1.0	greater than or equal to 80	100%
less than 1.0	less than 80	Consider delay until recovery checking CBC weekly

2. Hepatic Impairment:

For cyclophosphamide, no dose reduction is necessary for hepatic impairment.

3. Renal Failure:

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

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

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

N = 1.04 (Females) and 1.23 (Males)

II. BORTEZOMIB DOSE MODIFICATIONS:

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

1. Hematological*:

ANC (x10 ⁹ /L)	Platelets (x10 ⁹ /L)	Bortezomib Dose
greater than or equal to 0.5	And greater than or equal to 30	100%
less than 0.5	Or less than 30	Consider delay until recovery checking CBC weekly or consider omit; reduce dose to 1 mg/m ²
reoccurrence of less than 0.5	reoccurrence of less than 30	Consider delay until recovery checking CBC weekly or consider omit; further reduce dose to 0.7 mg/m ²

*Modify on day 1 only. MD may delay or consider omitting on other days.

2. Peripheral Neuropathy:

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

3. Hepatic Impairment:

	Bilirubin	ALT or AST	Bortezomib Dose
Mild	less than or equal to 1 x ULN	greater than ULN	100%
	greater than 1 – 1.5 x ULN	Any	100%
Moderate	greater than 1.5-3 x ULN	Any	<ul style="list-style-type: none"> ▪ Reduce dose to 0.7 mg/m² in the first cycle. ▪ Consider dose escalation to 1 mg/m² <u>or</u> further dose reduction to 0.5 mg/m² in subsequent cycles based on patient tolerability.
Severe	greater than 3 x ULN	Any	

4. Renal Failure:

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

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	<ul style="list-style-type: none"> • If <u>diarrhea free greater than 12 h</u>, stop loperamide. If new episode, retreat with loperamide. • If <u>grade 3</u> diarrhea or diarrhea accompanied by <u>mucus or dehydration</u>, <u>hold doses of Bortezomib</u> (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 <u>last</u> cycle:	Bortezomib dose <u>this</u> 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)

III. DARATUMUMAB DOSE MODIFICATIONS:

1. 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.

2. Hematological†, for low counts due to treatment, not disease

ANC(x10 ⁹ /L)		Platelets (x10 ⁹ /L)	daratumumab
Greater than or equal to 1.0	and	Greater than or equal to 50	100 %
Less than 1.0	and/or	Less than 50	Delay until recovery

†Modify on day 1 only. MD may delay or consider omitting on other days.

Consider holding bortezomib and cyclophosphamide if daratumumab is delayed for cytopenias. Dexamethasone does NOT need to be held.

3. Renal Failure:

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

IV. STEROID DOSE MODIFICATIONS

Dexamethasone (or predniSONE) does NOT need to be held when cyclophosphamide, bortezomib or daratumumab are held.

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 lymphoma 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 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.
5. **VZV prophylaxis:** Antiviral prophylaxis is recommended prior to initiating daratumumab and/or bortezomib for patients who are VZV seropositive. Patients should take valacyclovir 500 mg PO daily while taking daratumumab and for 4 weeks after its discontinuation. Of note, VZV serology is often not reliable, even in patients previously exposed. Most clinicians choose to prescribe valacyclovir without testing for VZV serology.
6. **Live vaccines:** Patients with any history of lymphoid cancers including myeloma should not be given live vaccines.
7. **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. .
8. **Green tea avoidance:** Some of the components in green tea and preparations made from green tea block the activity of bortezomib in vitro experiments. Green tea or preparations made from green tea should be avoided by patients taking bortezomib.
9. **Diarrhea management with bortezomib:** see diarrhea management in bortezomib dose modification section.
10. **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 Dr. Jesse Shustik (Lymphoma), or Dr. Kevin Song (Leukemia/BMT), or tumour group delegate with any problems or questions regarding this treatment program. (Lymphoma at (604) 877-6000 or 1-800-663-3333; Leukemia/BMT at (604) 875-4863 or after hours (604) 875-4111)

References:

1. Kastiris 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	<u>Death</u>

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