BC Cancer Protocol Summary for Treatment of Hodgkin Lymphoma with DOXOrubicin, vinBLAStine, Dacarbazine and Nivolumab

***Protocol Code**:* *LYAVDNIV*

***Tumour Group**:* *Lymphoma*

***Contact Physician**:* *Dr. Kerry Savage*

ELIGIBILITY:
Patients must have:

- 12 years of age or older,
- Previously untreated stage IIB to IV classical Hodgkin lymphoma, OR
- Previously untreated bulky stage II classical Hodgkin lymphoma defined as tumour mass greater than or equal to 10cm

Patients should have:

- No significant active autoimmune disease
- Adequate hematologic, renal and hepatic function

Note: Patients started on LYAVDBV or LYABVD prior to Dec 1 may transition to LYAVDNIV provided that:

1. No more than 3 cycles have been administered
2. Disease progression has not occurred
3. LYAVDNIV eligibility criteria is met

CAUTIONS:

- Patients with long term immunosuppressive therapy or systemic corticosteroids (requiring more than 10 mg predniSONE/day or equivalent)

TESTS:

- Baseline: CBC & Diff, total bilirubin, ALT, alkaline phosphatase, LDH, creatinine, sodium, potassium, TSH, morning serum cortisol, chest x-ray
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBcoreAb, HBsAb
- Baseline, if clinically indicated: BNP, ECG, MUGA or echocardiogram
- Before each treatment: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH
- If clinically indicated: chest x-ray, morning serum cortisol, lipase, serum or urine HCG (required for woman of child bearing potential if pregnancy suspected), Free T3 and Free T4, serum ACTH levels, testosterone, estradiol, FSH, LH, random glucose, ECG, MUGA, echocardiogram, C-reactive protein, creatine kinase, troponin, BNP, HBV viral load (see protocol SCHBV)
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional).

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- If prior infusion reactions to nivolumab:
  - diphenhydrAMINE 50 mg PO 30 minutes prior to nivolumab
  - acetaminophen 325 to 975 mg PO 30 minutes prior to nivolumab
  - hydrocortisone 25 mg IV 30 minutes prior to nivolumab
- If past etoposide drug reactions:
  - hydrocortisone 100 mg IV prior to etoposide
  - diphenhydrAMINE 50 mg IV prior to etoposide

SUPPORTIVE MEDICATIONS:

- High risk of hepatitis B reactivation. If HBsAg or HBcoreAb positive, start hepatitis B prophylaxis as per BC Cancer Protocol Summary for Hepatitis B Virus Reactivation (SCHBV).
- Primary prophylaxis with filgrastim is not mandatory but should be considered in those 60 years of age or older.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
DOXOrubicin	25 mg/m^2 on Days 1 and 15	IV push
vinBLAStine	6 mg/m^2 on Days 1 and 15	IV in 50 mL NS over 15 minutes
dacarbazine	375 mg/m^2 on Days 1 and 15	IV in 500 mL NS or D5W over 1 to 2 hours
nivolumab	3 mg/kg* on Days 1 and 15 (maximum 240mg)	IV in 50 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter

*Select dose band per Dose Banding Table (appendix).

- Each cycle is 28 days.
- Treatment duration: until disease progression or intolerable toxicity, to a maximum of 6 cycles.

DOSE MODIFICATIONS:

1. **Nivolumab:** No specific dose modifications. Toxicity managed by treatment delay and other measures (see SCIMMUNE protocol for management of immune-mediated adverse reactions to checkpoint inhibitors immunotherapy).

2. **Hematological**:

ANC (x 10^9/L)	Dose Modification
greater than or equal to 0.6	100 %
less than 0.6	100 % plus filgrastim 5 mcg/kg* SC daily x 5 days starting on day 7 and day 21

The patient should be treated with Filgrastim (G-CSF) in doses sufficient to allow full dose treatment on schedule using the above dose modifications. Note: this guideline applies only if the treatment is potentially curative and after experience with one or more cycles of treatment indicate Filgrastim (G-CSF) is required. (See Pharmacare guidelines). Consider G-CSF prophylaxis in patients ≥ 60 years of age.

*Filgrastim 300 mcg: up to 75 kg
480 mcg: 76 kg to 110 kg
600 mcg: greater than 110 kg

Transfuse as needed to keep hemoglobin greater than 90 g/L, platelets greater than 20 x 10^9/L

3. Peripheral Neuropathy: for vinBLAStine

Toxicity	vinBLAStine Dose Modification
Dysesthesias, areflexia only	100%
Abnormal buttoning, writing	67%
Motor neuropathy, moderate	50%
Motor neuropathy, severe	Omit

4. Hepatotoxicity: For DOXOrubicin

Total bilirubin (micromol/L)	Dose Modification
2 to 35	100%
35 to 85	50%
greater than 85	Omit DOXOrubicin. Substitute cyclophosphamide 375 mg/m^2

Note: This adjustment is only necessary for the initial treatment. After the hyperbilirubinemia has resolved adjustment is only necessary if overt jaundice re-occurs. Serum bilirubin does not need to be requested before each treatment.

Hepatotoxicity: For vinBLAStine

Total bilirubin (micromol/L)	Dose Modification
Less than 25	100%
25 to 50	50%
Greater than 50	25%

4. **Cardiotoxicity**: DOXOrubicin only
   DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. When DOXOrubicin cannot be used due to proven cardiac dysfunction, each dose of DOXOrubicin can be replaced by etoposide 25 mg/m^2 IV on the first day (use non-DEHP bag and tubing with 0.2 micron in-line filter), 50 mg/m^2 PO on the second and third days. Cardiac assessment is recommended if patient has received greater than or equal to 300 mg/m2 of DOXOrubicin (BC Cancer Drug Manual). Work-up may include an assessment of cardiac ejection fraction, and cardiac oncology referral if necessary. NOTE: When doxorubicin is replaced with etoposide, administer etoposide IV in place of doxorubicin (follow same sequence).

5. **Dacarbazine unavailability**: Occasionally dacarbazine becomes unavailable due to manufacturing or other problems. If this occurs**,** and only if dacarbazine is completely unavailable, the Lymphoma Tumour Group recommends that Compassionate Access Program (CAP) approval be sought for cyclophosphamide 375 mg/m^2 to be substituted for each dose of the dacarbazine until the supply is renewed. There are no direct data that this substitution is equally effective, however, cyclophosphamide is an effective drug for Hodgkin's lymphoma, works via the same class of mechanisms (alkylation), causes the same minimal level of myelosuppression at this dose and is not sterilizing for men or women at this dose. When used at this dose no adjustment for myelosuppression is required.

PRECAUTIONS:

1. **Serious immune-mediated reactions**: these can be severe to fatal and usually occur during the nivolumab treatment course. They may include enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathy, as well as toxicities in other organ systems. Early diagnosis and appropriate management are essential to minimize life-threatening complications (see SCIMMUNE protocol for management of immune-mediated adverse reactions to checkpoint inhibitors immunotherapy).
2. **Infusion-related reactions:** isolated cases of severe reaction have been reported. In case of a severe reaction, nivolumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab with close monitoring. Premedications with acetaminophen and anti-histamine may be considered if there is a history of reaction. If applicable, monitor etoposide infusion for the first 15 minutes for signs of hypotension. Refer to BC Cancer Infusion-Related Reactions Guidelines.
3. **Neutropenia**: fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. Cardiac assessment is recommended if patient has received greater than or equal to 300 mg/m^2 of DOXOrubicin. (BC Cancer Drug Manual). Work-up may include an assessment of cardiac ejection fraction, and cardiac oncology referral if necessary.
5. **Extravasation**: DOXOrubicin and vinBLAStine cause pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
6. **Peripheral neuropathy:** vinBLAStine can cause peripheral sensory neuropathy. Cases of peripheral motor neuropathy have also been reported. VinBLAStine can also cause autonomic neuropathy. Monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness and institute dose modifications accordingly.
7. **Hepatitis B Reactivation**: See SCHBV protocol for more details.

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

References:

1. Nivolumab CDA-AMC Canada's Drug Agency Reimbursement Recommendation. Canadian Journal of Health Technologies. Aug 2025; 5(8) 1-11.
2. Herrera AF, LeBlanc M, Castellino SM et al. Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma. N Engl J Med 2024; 391: 1379-89.

Appendix. Dose Bands

NIVOLUMAB DOSE BANDING TABLE (1-3mg/kg capped at 240 mg)

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 36		**Pharmacy prepares specific dose**
43.5	51.49	**48**
51.5	60.49	**56**
60.5	69.49	**66**
69.5	77.49	**74**
77.5	87.49	**80**
88.5	95.49	**90**
95.5	109.49	**100**
109.5	131.49	**120**
131.5	153.49	**140**
153.5	175.49	**160**
175.5	197.49	**180**
197.5	219.49	**200**
219.5	239.49	**220**
239.5	240	**240**