BC Cancer Protocol Summary for Alternative Treatment of Microsatellite Instability-High or Mismatch Repair Deficient Endometrial Cancer using Dostarlimab with PACLitaxel NAB and CARBOplatin

***Protocol Code*:** *UGOEAVDPNC*

***Tumour Group*:** *Gynecology*

***Contact Physician*:** *Dr. Aalok Kumar*

ELIGIBILITY:

Patients must have:

- Previous severe hypersensitivity reaction or anaphylaxis to PACLitaxel that is not manageable despite use of premedications, or
- Previous moderate PACLitaxel hypersensitivity reaction that cannot be managed by premedications due to a strong contraindication to high dose steroids, such as poorly controlled diabetes, and
- Eligible for UGOEAVDCAT
  and
- BC Cancer "Compassionate Access Program" request approval prior to treatment

Patients should have:

- Good performance status
- Adequate hepatic and renal function
- Access to a treatment center with expertise to manage immune-mediated adverse reactions of dostarlimab

Note:

- At time of subsequent disease progression, dostarlimab retreatment (with or without chemotherapy) is allowed for an additional one year of therapy if:
  - Patients have completed 3 years of therapy without progression
  - Patients have stopped dostarlimab due to toxicity (not progression)

EXCLUSIONS:

Patients must not have:

- Severe hepatic dysfunction contraindicating PACLitaxel NAB

CAUTIONS:

- Greater than or equal to Grade 2 sensory or motor neuropathy
- Active, known or suspected autoimmune disease
- Patients with long term immunosuppressive therapy or systemic corticosteroids (requiring more than 10 mg predniSONE/day or equivalent)

TESTS:

- Baseline: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, TSH, random glucose, morning serum cortisol, chest x-ray or CT chest if not previously done
- Baseline, if clinically indicated: GGT, total protein, albumin, lipase, creatine kinase, serum or urine HCG (required for women of childbearing potential if pregnancy suspected), free T3 and free T4, serum ACTH levels, testosterone, estradiol, FSH, LH, CA 125, CA 15-3, CA 19-9, ECG
- Prior to each treatment: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, TSH
- If clinically indicated: GGT, total protein, albumin, morning serum cortisol, lipase, random glucose, creatine kinase, serum or urine HCG (required for women of childbearing potential if pregnancy suspected), free T3 and free T4, serum ACTH levels, testosterone, estradiol, FSH, LH, CA 125, CA 15-3, CA 19-9, ECG, chest x-ray
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional)

PREMEDICATIONS:

Cycle 1 to 6:

- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)
- If prior infusion reactions to dostarlimab: diphenhydrAMINE 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

Cycle 7 to 23:

- Antiemetics are not usually required
- If required, antiemetic protocol for low emetogenicity (see SCNAUSEA)
- If prior infusion reactions to dostarlimab: diphenhydrAMINE 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

TREATMENT:

Cycles 1 to 6:

Drug	Dose	BC Cancer Administration Guideline
dostarlimab	500 mg	IV in 100 mL NS over 30 minutes using a 0.2 micron in-line filter*
PACLitaxel NAB	260 mg/m^2	IV over 30 minutes**
CARBOplatin	Dose = AUC 5 or 6*** x (GFR + 25)	IV in 100 to 250 mL NS over 30 minutes

* use separate infusion line and filter for each drug

** in empty sterile bags and tubing with 15 micron filter; no specific material required for bag or tubing

*** use AUC of 6; if extensive prior radiation therapy, use AUC of 5

Measured GFR (e.g. nuclear renogram) is preferred whenever feasible, *particularly* in circumstances of co-morbidity that could affect renal function (third-space fluid accumulations, hypoproteinemia, potentially inadequate fluid intake, etc.). The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR; the estimated GFR reported by the lab or calculated using the Cockcroft-Gault equation should be capped at 125 mL/min when it is used to calculate the initial CARBOplatin dose. When a nuclear renogram is available, this clearance would take precedence.

Cockcroft-Gault Formula

$$\text{GFR} = \frac{1.04 \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

Note: The *same* method of estimation should be used throughout the treatment course (i.e. if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).

Repeat every 3 weeks for 6 cycles, then:

Cycle 7 to 23:

- Cycle 7 starts 3 weeks after Cycle 6

Drug	Dose	BC Cancer Administration Guideline
dostarlimab	1000 mg	IV in 100 mL NS over 30 minutes using a 0.2 micron in-line filter

Repeat every 6 weeks to a maximum of 23 cycles (approximately 3 years of total dostarlimab treatment) or until disease progression or toxicity.

DOSE MODIFICATIONS:

- No specific dose modifications for dostarlimab. Toxicity managed by treatment delay and other measures (see SCIMMUNE protocol for management of immune-mediated adverse reactions to checkpoint inhibitors immunotherapy, http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf).

1. Infusion-related reactions to dostarlimab:

- Refer to SCDRUGRX for management guidelines

Grade	Management
1	▪ See SCDRUGRX
2	▪ Stop infusion and manage per SCDRUGRX ▪ If resolution within 1 hour of stopping, restart at 50% infusion rate ▪ If no resolution within 1 hour, do not restart infusion. Premedicate for next scheduled dose (see Premedications, above)
3 or 4	▪ Stop infusion and manage per SCDRUGRX ▪ Discontinue dostarlimab treatment

2. Hematology:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Doses (PACLitaxel NAB and CARBOplatin)
Greater than or equal to 1.0	and	Greater than or equal to 100	Proceed at same doses
Less than 1.0	or	Less than 100	Delay until recovery

Febrile Neutropenia:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Doses (PACLitaxel NAB and CARBOplatin)
Febrile neutropenia at any time	and	Any	Delay until recovery, then reduce subsequent doses to 80%

3. Sensory Neuropathy: PACLitaxel NAB

Grade	Toxicity	Dose – 1st Occurrence	Dose – 2nd Occurrence
1	Asymptomatic; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	Maintain dose	Maintain dose
2	Sensory alteration or paresthesia (including tingling) but not interfering with function, but not interfering with ADL	Maintain dose	Maintain dose
3	Sensory alteration or paresthesia interfering with ADL	Hold treatment until resolved to Grade 2, then reduce dose to 85%**	Hold treatment until resolved to Grade 2, then reduce dose to 70%**
4	Disabling	Hold treatment until resolved to Grade 2, then reduce dose to 85%**	Hold treatment until resolved to Grade 2, then reduce dose to 70%** or discontinue further therapy

** Dose reductions should be maintained for subsequent cycles and not re-escalated.

4. Hepatic dysfunction: PACLitaxel NAB

ALT or AST		Total bilirubin	PACLitaxel NAB
Less than or equal to 10 x ULN	and	Greater than 1 to less than or equal to 1.5 x ULN	100%
Less than or equal to 10 x ULN	and/or	Greater than 1.5 to less than or equal to 5 x ULN	80%*
Greater than 10 x ULN	or	Greater than 5 x ULN	Hold

* may re-escalate dose if hepatic function normalizes and reduced dose is tolerated for at least 2 cycles

5. **Arthralgia and/or myalgia:** If arthralgia and/or myalgia of Grade 2 (moderate) or higher is not relieved by adequate doses of NSAIDs or acetaminophen with codeine (e.g., TYLENOL #3®), a limited number of studies report a possible therapeutic benefit using:
   - predniSONE 10 mg PO bid x 5 days starting 24 hours post-PACLitaxel NAB
   - gabapentin 300 mg PO on day before chemotherapy, 300 mg bid on treatment day, then 300 mg tid x 5-15 days (based on duration of arthromyalgia)

   If arthralgia and/or myalgia persist, reduce subsequent PACLitaxel NAB doses to 85%

6. **Renal dysfunction**: If significant increase (greater than 20% or rises above the upper limit of normal) in creatinine, recheck/recalculate GFR and recalculate CARBOplatin dose using new GFR. No modification is required for PACLitaxel NAB in mild to moderate renal impairment. PACLitaxel NAB has not been studied in patients with creatinine clearance less than 30 mL/min.

PRECAUTIONS:

1. **Serious immune-mediated reactions to dostarlimab**: can be severe to fatal and usually occur during the treatment course, but may develop months after discontinuation of dostarlimab. They may include colitis, endocrinopathies including hypothyroidism, hyperthyroidism, thyroiditis, hypophysitis, type 1 diabetes mellitus, nephritis, hepatitis, immune-mediated skin reactions including cases of Stevens-Johnson syndrome or toxic epidermal necrolysis, myocarditis, neuropathy, pneumonitis, 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:** are rarely reported with dostarlimab but may be severe. See Dose Modifications, above, and SCDRUGRX: Management of Infusion-Related Reactions to Systemic Therapy Agents.
3. An albumin form of PACLitaxel may substantially affect a drug's functional properties relative to those of drug in solution. **Do not** substitute with or for other PACLitaxel formulations.
4. **Extravasation:** PACLitaxel NAB causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
5. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
6. **Drug interactions:** PACLitaxel NAB is metabolized by CYP2C8 and CYP3A4; caution should be exercised when administering with drugs which are CYP2C8 or CYP3A4 inducers or inhibitors.
7. **Cardiac toxicity** has been reported rarely while patients receive PACLitaxel NAB. Severe cardiovascular events (3%), including chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension.

8. **Theoretical risk of viral disease transmission**, due to human albumin component, is extremely remote.

Call Dr. Aalok Kumar or tumour group delegate at (604) 930-2098 or 1-800-523-2885 with any problems or questions regarding this treatment program.

References:

1. Mirza MR, Chase DM, Slomovitz BM, et al; RUBY Investigators. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023 Jun 8;388(23):2145-2158.
2. Dostarlimab (Jemperli) CADTH [Canada's Drug Agency (CDA-AMC)] Reimbursement Recommendation. Canadian Journal of Health Technologies May 2024; 4(5): 1-25.
3. CADTH [Canada's Drug Agency (CDA-AMC)] Reimbursement Review. Provisional Funding Algorithm. Endometrial Cancer. June 2024.