

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

Protocol Code: GOEAVDCAT

Tumour Group: Gynecology

Contact Physician: GO Systemic Therapy

ELIGIBILITY:

Patients must have:

- Advanced or metastatic endometrial cancer,
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), tested on primary or metastatic tumour,
- Not amenable to curative intent treatment, and
- At least one of the following criteria:
 - De novo Stage III or IV, previously untreated,
 - First recurrence and no prior systemic treatment in advanced setting,
 - Previously treated in neoadjuvant or adjuvant setting and first recurrence a minimum of 6 months after completion of 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

Notes:

- Patients on active treatment with GOENDAVCAT without progression may switch to UGOEAVDCAT if all other eligibility criteria are met
- 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:

- Active central nervous system (CNS) metastases. Treated or stable CNS metastases are eligible
- AST and/or ALT greater than 10 times the upper limit of normal (ULN), or
- Total bilirubin greater than 5 x ULN

CAUTIONS:

- Pre-existing motor or sensory neuropathy greater than Grade 2
- 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: lipase, 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, CEA, LDH, GGT, magnesium, calcium, BNP, troponin, ECG, echocardiogram
- Prior to each treatment: CBC & Diff, creatinine, ALT, alkaline phosphatase, total bilirubin, sodium, potassium, TSH
- If clinically indicated: morning serum cortisol, lipase, random glucose, LDH, GGT, magnesium, calcium, troponin, 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, CEA, ECG, chest x-ray
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (optional)

PREMEDICATIONS:

Cycles 1 to 6:

- If no prior infusion reactions to dostarlimab: administer premedications as sequenced below
45 minutes prior to PACLitaxel:
 - dexamethasone 20 mg IV in 50 mL NS over 15 minutes30 minutes prior to PACLitaxel:
 - diphenhydrAMINE 50 mg IV in 50 mL NS 50 over 15 minutes and famotidine 20 mg IV in 100 mL NS over 15 minutes (Y-site compatible)
- If prior infusion reactions to dostarlimab: administer PACLitaxel premedications prior to dostarlimab
45 minutes prior to dostarlimab:
 - dexamethasone 20 mg IV in 50 mL NS over 15 minutes30 minutes prior to dostarlimab:
 - diphenhydrAMINE 50 mg IV in 50 mL NS over 15 minutes and famotidine 20 mg IV in 100 mL NS over 15 minutes (Y-site compatible)acetaminophen 325 to 975 mg PO prior to dostarlimab
- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)

Cycle 7 to 29:

- 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	175 mg/m ² **	IV in 250 to 500 mL NS over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter*)
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

** Conservative PACLitaxel dosing (i.e., 155 mg/m² or 135 mg/m²) with escalation up to 175 mg/m² if tolerated may be considered in the following cases: ECOG greater than or equal to 2, existing or potential myelosuppression; existing or potential arthralgia and myalgia; prior radiotherapy, particularly to the pelvic region; reduced bone marrow capacity

*** 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 29:

- 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).

1. Infusion-related reactions to dostarlimab:

- Refer to SCDRUGRX for management guidelines

Grade	Management
1	<ul style="list-style-type: none"> ▪ See <u>SCDRUGRX</u>
2	<ul style="list-style-type: none"> ▪ Stop infusion and manage per <u>SCDRUGRX</u> ▪ 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	<ul style="list-style-type: none"> ▪ Stop infusion and manage per <u>SCDRUGRX</u> ▪ Discontinue dostarlimab treatment

2. Hematology:

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

- 3. Arthralgia and/or myalgia:** If arthralgia and/or myalgia from PACLitaxel of Grade 2 (moderate) or higher was not adequately relieved by 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 for 5 days starting 24 hours post-PACLitaxel
 - gabapentin 300 mg PO on day before chemotherapy, 300 mg BID on treatment day, then 300 mg TID for 5 to 15 days (based on duration of arthromyalgia)
- If arthralgia and/or myalgia persists, reduce subsequent PACLitaxel doses to 135 mg/m²
- 4. Neuropathy:** Dose modification or discontinuation may be required (see BC Cancer Drug Manual).
- 5. 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.

6. Hepatic dysfunction: reduce PACLitaxel dose:

ALT		Total bilirubin	Dose (mg/m ²)
Less than 10 x ULN	and	Less than or equal to 1.25 x ULN	175
Less than 10 x ULN	and	1.26 to 2 x ULN	135
Less than 10 x ULN	and	2.01 to 5 x ULN	90
Greater than or equal to 10 x ULN	and/ or	Greater than 5 x ULN	Not recommended

ULN = upper limit of normal

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. **Hypersensitivity to PACLitaxel:** Reactions are common. See BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Chemotherapeutic Agents – SCDRUGRX.

<u>Mild</u> symptoms (e.g. mild flushing, rash, pruritus)	complete PACLitaxel infusion. Supervise at bedside no treatment required
<u>moderate</u> symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	stop PACLitaxel infusion give IV diphenhydrAMINE 25 to 50 mg and hydrocortisone IV 100 mg after recovery of symptoms resume PACLitaxel infusion at 20 mL/hr for 5 minutes, 30 mL/hr for 5 minutes, 40 mL/hr for 5 minutes, then 60 mL/hr for 5 minutes. If no reaction, increase to full rate. if reaction recurs, discontinue PACLitaxel therapy
<u>severe</u> symptoms (i.e. <u>one</u> or more of respiratory distress requiring treatment, generalised urticaria, angioedema, hypotension requiring therapy)	stop PACLitaxel infusion give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated discontinue PACLitaxel therapy

4. **Extravasation:** PACLitaxel 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 is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Contact the GO Systemic Therapy physician at your regional cancer centre or the GO Systemic Therapy Chair 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.