Regimen Monograph

A - Regimen Name

CRBPPACL+DOST Regimen

Paclitaxel-Carboplatin-Dostarlimab

DOST(MNT) Regimen

Dostarlimab (Maintenance)

Disease Site

Gynecologic
Endometrial

Intent

Adjuvant
Curative
Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For treatment of primary advanced or first recurrent endometrial cancer

- Refer to the NDFP form for funding details in dMMR or MSI-H endometrial cancer.
- Patients who do not meet the NDFP eligibility criteria may be eligible for compassionate drug access.

Supplementary Public Funding	**dostarlimab** New Drug Funding Program (Dostarlimab - Primary Advanced or Recurrent MSI-H or dMMR Endometrial Cancer)

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B - Drug Regimen

Cycles 1 to 6:

dostarlimab	500 mg	IV	Day 1, q 3 weeks
PACLitaxel	175 mg /m²	IV	Day 1, q 3 weeks
CARBOplatin	AUC 5*	IV	Day 1, q 3 weeks

*Adjust Carboplatin dose to AUC target (using Calvert formula) as outlined in "Other Notes" section.

Then,

DOST(MNT)^:

dostarlimab	1000 mg	IV	Day 1, q 6 weeks

^ starting 3 weeks after the last dose of CRBPPACL+DOST

Administer dostarlimab prior to the chemotherapy when given on the same day.

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C - Cycle Frequency

Every 3 weeks for 6 cycles, unless disease progression or unacceptable toxicity.

After completion of CRBPPACL+DOST, continue with dostarlimab maintenance DOST(MNT) **every 6 weeks** for up to 3 years, unless disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate + NK1 antagonist (Carboplatin AUC ≥ 5)

Minimal (dostarlimab maintenance)

- Also refer to CCO Antiemetic Summary

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Pre-medications (prophylaxis for infusion reaction):

Dostarlimab:

- Routine pre-medication is not recommended.
- May consider antipyretic and H1-receptor antagonist in patients who experienced a grade 2 infusion reaction.

Note: Pre-medication for chemotherapy was administered after dostarlimab in the RUBY trial.

Paclitaxel*:

- Dexamethasone 20 mg PO 12-and 6-hours OR Dexamethasone 20 mg IV 30 minutes pre-infusion†
- Diphenhydramine 25-50 mg IV/PO 30-60 minutes pre-infusion
- Ranitidine 50 mg IV OR Famotidine 20 mg IV 30-60 minutes pre-infusion

* Consider **discontinuing** pre-medications for paclitaxel if there was no IR in the first 2 doses.

† Oral and IV dexamethasone are both effective at reducing overall IR rates. Some evidence suggests that oral dexamethasone may be more effective for reducing severe reactions; however, adverse effects and compliance remain a concern.

Carboplatin:

- There is insufficient evidence that routine prophylaxis with pre-medications reduce infusion reaction (IR) rates.
- Corticosteroids and H1-receptor antagonists ± H2-receptor antagonists **may** reduce IR rates for some patients (e.g. gynecological patients with a platinum-free interval (PFI) >12 months or a history of drug allergy who are receiving carboplatin starting from the 7th cycle) but no optimal pre-medication regimen has been established.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Patients should have MSI-H or dMMR tumour status confirmed by a validated test prior to starting treatment.

Avoid the use of corticosteroids or immunosuppressants before starting treatment.

Dosage with toxicity

Dose reductions are not recommended for dostarlimab. Doses may be delayed or discontinued based on toxicity. Refer to dostarlimab drug monograph(s) for additional details on immune-related adverse effects (irAEs).

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions of Immune-related toxicities and their management.

Suggested Dose Levels for Paclitaxel:

Dose Level	Paclitaxel (mg/m^2)
0	175
-1	135
-2	110

Dose modifications for Carboplatin & Paclitaxel:

Worst Toxicity (Counts x 10^9/L)	Carboplatin	Paclitaxel
ANC < 1.5 for > 7 days	Hold[1]; No change upon restart	Hold[1], then Consider adding G-CSF and continue current dose, if appropriate OR ↓ 1 dose level
ANC < 0.5 for ≥ 7 days or Febrile Neutropenia	Hold[1]; ↓ 1 AUC upon restart	Hold[1], then Consider adding G-CSF and continue current dose, if appropriate OR ↓ 1 dose level
Platelets < 25 or Thrombocytopenic bleeding	Hold[1]; ↓ 1 AUC upon restart	Hold[1]; ↓ 1 dose level upon restart
Grade 2 neuropathy	No change	Omit or consider ↓ 1 dose level
Grade 3 neuropathy	No change	Omit or ↓ 1 dose level
Other Grade 3 non-hematologic toxicity	Hold[1]; ↓ 1 AUC upon restart	Hold[1]; ↓ 1 dose level upon restart
Grade 4 non-hematologic toxicity	Discontinue	Discontinue
Any grade cystoid macular edema	No change	Discontinue

[1]Do not start new cycle until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L, and non-hematological toxicities have recovered to ≤ grade 2.

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Carboplatin & Paclitaxel:

Grade	Management	Re-challenge	
	Carboplatin / Paclitaxel	**Carboplatin#**	**Paclitaxel**
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • After symptom resolution, restart with pre-medications ± reduced infusion rate.	• Consider pre-medications* and infusing at a reduced infusion rate prior to re-challenge. • May consider adding oral montelukast ± oral acetylsalicylic acid.	• Consider re-challenge with pre-medications and at a reduced infusion rate. • After 2 subsequent IRs, consider replacing with a different taxane. Give intensified pre-medications and reduce the infusion rate. • May consider adding oral montelukast ± oral acetylsalicylic acid.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary. • There is insufficient evidence to recommend substitution with another taxane at re-challenge. • High cross-reactivity rates have been reported.

#There is evidence that re-challenging with **cisplatin** after carboplatin reaction can be a viable option; however, exact cross reactivity between platinum agents is not known, but can be as high as 25%.

*Up to 50% of patients can experience recurrent reactions during re-challenge **despite** using pre-medications (e.g. corticosteroid and H1/H2-receptor antagonist).

Dostarlimab:

Grade	Management	Re-challenge
1	• Continue infusion if appropriate • Manage the symptoms.	• N/A
2	• Stop the infusion • Manage the symptoms. **Restart:** • After symptom resolution, may restart at 50% of the infusion rate (if resolved within 1 hour of stopping) or restart with pre-medications.	• Re-challenge with close monitoring and pre-medications (antipyretic and H1-receptor antagonist). • If Gr. 2 recurs with adequate pre-medication, permanently discontinue (do not re-challenge).
3 or 4	• Stop treatment • Aggressively manage the symptoms.	• Discontinue permanently (do not re-challenge).

Hepatic Impairment

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions for immune-related hepatic toxicity management.

For paclitaxel, caution and dose reduction are advised in patients with moderate to severe hepatic impairment. Patients receiving paclitaxel with hepatic impairment may be at risk of toxicity, especially severe myelosuppression.

Suggested dose modifications are:

Bilirubin		AST/ALT	Dostarlimab (% usual dose)	PACLitaxel (% usual dose)	CARBOplatin (% usual dose)
≤1.25 x ULN	And	2-10 x ULN	No change	75%	No change
1.26 to 2.5 x ULN	And	<10x ULN	Caution; limited data	40%	
2.6 to 4 x	And	<10x ULN	Caution; no data	25%	

ULN					
>4 x ULN	And/Or	≥10 x ULN		Consider risk-benefit or Omit	

Renal Impairment

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions for immune-related renal toxicity management

Creatinine Clearance (mL/min)	Dostarlimab	PACLitaxel	CARBOplatin
≥ 30 to 50	No change	No change	Use Calvert formula*
20 to < 30	Limited data		
≥ 15 and < 20			Discontinue
< 15	No data		

*Refer to "Other Notes" section.

Dosage in the Elderly

No adjustment required but elderly patients are more at risk for severe toxicity. Caution should be exercised and dose reduction considered for carboplatin as elderly patients may have reduced renal function, more severe myelosuppression and neuropathy. There is limited data with dostarlimab in patients ≥ 75 years of age.

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F - Adverse Effects

Refer to dostarlimab, PACLitaxel, CARBOplatin drug monograph(s) for additional details of adverse effects.

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Alopecia (rarely permanent) • Peripheral neuropathy (may be severe) • Myelosuppression ± infection, bleeding (may be severe) • Musculoskeletal pain • Nausea, vomiting	• Hypersensitivity • Diarrhea (may be severe) • Rash, pruritus • Abnormal electrolyte(s) • Nephrotoxicity (may be severe) • Fatigue	• Hypothyroidism • Hypertension • Edema • Mucositis • ↑ LFTs • Hearing impairment • ECG changes	• Arrhythmia, cardiotoxicity • Adrenal insufficiency • Arterial/ venous thromboembolism • Infusion related or injection site reaction • Autonomic neuropathy • Encephalitis, encephalopathy • Eye disorders (cystoid macular edema, optic nerve disorder, optic neuritis, keratitis) • GI obstruction / perforation • Hemolytic uremic syndrome • Hepatitis • Hypophysitis • Hyperthyroidism • Pancreatitis • Radiation recall reaction • Secondary malignancy • Seizure • SJS, TEN

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G - Interactions

Refer to dostarlimab, PACLitaxel, CARBOplatin drug monograph(s) for additional details.

- Monitor INR in patients receiving warfarin and carboplatin concomitantly; warfarin dosage adjustment may be required.
- Monitor closely with nephrotoxic and ototoxic drugs (ie. aminoglycosides) given concomitantly with carboplatin due to additive effects.
- Monitor closely with phenytoin; phenytoin dose adjustment may be required while receiving paclitaxel and carboplatin.
- Avoid if possible, or caution with radiation while receiving paclitaxel; may increase the risk of radiation pneumonitis.

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H - Drug Administration and Special Precautions

Refer to dostarlimab, PACLitaxel, CARBOplatin drug monograph(s) for additional details.

Administration

PACLitaxel:

- In order to minimize patients' exposure to DEHP leaching from PVC bags or sets, use polyolefin or polypropylene infusion bags and polyethylene-lined administration sets (with an in-line filter no greater than 0.22 microns).
- Dilute in 500-1000 mL Normal Saline or 5% Dextrose, in a final concentration of 0.3-1.2 mg/mL and infuse over 3 hours.
- Extended infusion of paclitaxel is not recommended as primary prophylaxis to reduce paclitaxel IRs.
- Excessive shaking, agitation, or vibration may induce precipitation and should be avoided
- Precipitation may rarely occur with infusions longer than 3 hours.

CARBOplatin:

- Mix in 100mL to 250mL bag (5% Dextrose or Normal Saline); infuse IV over 15 to 60 minutes.
- There is insufficient evidence that routine prophylaxis with extended infusion reduces IR rates.
- Incompatible with sets, needles or syringes containing aluminum – leads to precipitation and loss of potency.
- Protect from light.

Dostarlimab:

- Dilute in a 0.9% sodium chloride or D5W IV infusion bag.
- Final drug concentration after dilution should be between 2 mg/mL and 10 mg/mL.
- Gently invert infusion bag to mix. Do not shake.
- Infuse IV over 30 minutes, using a 0.2 or 0.22 micron in-line filter.
- Administer dostarlimab prior to the chemotherapy when given on the same day.
- Do not administer as IV push or bolus.
- Do not co-administer with other drugs through the same line.
- Compatible with polyvinyl chloride (PVC), platinum cured silicon or polypropylene (PP) infusion sets, fittings made from PVC or polycarbonate, and polyethersulfone (PES) in-line filters.
- Store unopened vials refrigerated (2°C to 8°C) and protect from light. Do not freeze.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications

- Patients with a history of severe hypersensitivity reactions to platinum-containing compounds, dostarlimab, paclitaxel or other drugs formulated in Cremophor EL (polyethoxylated castor oil)
- Patients with pre-existing severe renal impairment
- Patients with severe myelosuppression or bleeding tumours

Warnings / Precautions

- Patients who have received extensive prior treatment, have poor performance status and those over 65 years of age
- Patients with abnormal renal function or who are receiving concomitant nephrotoxic drugs
- Patients who have previously experienced severe or life-threatening skin reactions on prior

treatment with immune-stimulatory anticancer agents.

- Dostarlimab may cause serious immune-mediated reactions affecting multiple organ systems, including GI, hepatic, renal, respiratory, endocrine and others. Use with caution and monitor closely in patients with pre-existing conditions such as colitis, hepatic impairment, respiratory or endocrine disorders, such as hypo or hyperthyroidism or diabetes mellitus.

- Paclitaxel contains ethanol, and is administered with agents such as antihistamines which cause drowsiness. Patients should be cautioned regarding driving and the use of machinery.

- Patients with conditions such as serious active infection (HIV, hep B or C), active autoimmune disease, conditions that require systemic immunosuppressive therapy and a history of interstitial lung disease were excluded from dostarlimab clinical studies.

- Avoid live vaccines. Reduced immunogenicity may occur with the use of inactivated vaccines.

Pregnancy / Lactation

- This regimen is **not recommended** for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.

- Breastfeeding is **not recommended** during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).

- Fertility Effects:
  - Carboplatin: Unknown
  - Paclitaxel: Probable
  - Dostarlimab: Unknown

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

- CBC; Baseline and before each cycle
- Liver function tests; Baseline and before each cycle
- Renal function tests, including urine protein and electrolytes; Baseline and before each cycle
- Blood pressure and pulse; During paclitaxel infusion
- Continuous cardiac monitoring; during subsequent infusions in patients who developed serious conduction abnormalities
- Thyroid function tests; Baseline and as clinically indicated
- Blood glucose; Baseline and as clinically indicated
- Clinical toxicity assessment for thromboembolism, bleeding, infection, hypersensitivity, injection site reaction, GI effects, ototoxicity, rash, musculoskeletal, neurologic, respiratory, endocrine, cardiac and ophthalmic effects; At each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- INR; baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit

CRBPPACL+DOST	5-6 hours

Pharmacy Workload **(average time per visit)**

CRBPPACL+DOST	30.383 minutes
DOST(MNT)	19.75 minutes

Nursing Workload **(average time per visit)**

CRBPPACL+DOST	59.833 minutes
DOST(MNT)	40.75 minutes

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K - References

Carboplatin drug monograph, Ontario Health (Cancer Care Ontario).

Dostarlimab drug monograph, Ontario Health (Cancer Care Ontario).

Jemperli dostarlimab for injection Product Monograph. GlaxoSmithKline Inc. Mississauga, Ontario; July 2024.

Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023 Jun 8;388(23):2145-58.

Paclitaxel drug monograph, Ontario Health (Cancer Care Ontario).

Protocol for: Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023 Jun 8;388(23):2145-58.

May 2025 Updated Rationale and Uses section to add: Patients who do not meet the NDFP eligibility criteria may be eligible for compassionate drug access.

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L - Other Notes

Calvert Formula

DOSE (mg) = target AUC X (GFR + 25)

- AUC = product of serum concentration (mg/mL) and time (min)
- GFR (glomerular filtration rate) expressed as measured Creatinine Clearance or estimated from Serum Creatinine (by Cockcroft and Gault method or Jelliffe method)

(Calvert AH, Newell DR, Gumbrell LA, et al, Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol, 1989; 7: 1748-1756)

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to

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Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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