BC Cancer Protocol for Primary Treatment of Squamous, Adenocarcinoma, or Adenosquamous Cancer of the Cervix with CARBOplatin, PACLitaxel, and Pembrolizumab

Protocol Code	*UGOCXCATP*
Tumour Group	*Gynecology*
Contact Physician	*Dr. Yvette Drew*

ELIGIBILITY:

Patients must have:
- Squamous, adenocarcinoma, or adenosquamous carcinoma of the cervix,
- Persistent, recurrent, or metastatic disease,
- PD-L1 expression with combined positive score (CPS) greater than or equal to 1,
- No amenability to curative-intent treatment,
- No prior chemotherapy in the advanced setting (except chemotherapy as part of combined modality therapy with curative intent), and
- BC Cancer Compassionate Access Program (CAP) approval.

Patients should have:
- ECOG 0 to 2,
- Adequate baseline hematological, hepatic and renal function, and
- Access to a treatment centre with expertise in managing immunotherapy mediated toxicities of pembrolizumab.

Notes:
- At time of subsequent disease progression, retreatment with GOCXCATP is allowed for an additional 18 cycles of pembrolizumab for 3-weekly dosing or 9 cycles for 6-weekly dosing (or a combination of both) including doses given as GOCXBP and GOCXBP6 if:
    - Patients have completed 2 years without progression
    - Patients have stopped GOCXCATP for reasons other than progression (e.g. toxicity or complete response)
- Patients on active treatment with GOCXCAT and do not have proven progression may switch to GOCXCATP if all other eligibility criteria are met

EXCLUSIONS:
Patients must not have:
- Unstable or symptomatic central nervous system metastases,
- Any small cell component,
- Neutrophils less than 1 x 10^9/L,
- Initiation of single-agent pembrolizumab monotherapy without chemotherapy, or
- Cancer of the vagina or vulva

CAUTIONS:

- Active, known, or suspected autoimmune disease,
- Patients with long term immunosuppressive therapy or systemic corticosteroids (requiring more than 10 mg predniSONE/day or equivalent), or
- Pre-existing motor or sensory neuropathy greater than grade 2.

TESTS:

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

PREMEDICATIONS:

PACLitaxel must not be started unless the following drugs have been given:

- **If no prior infusion reactions to pembrolizumab:** administer premedications as sequenced below.
  45 minutes prior to PACLitaxel:
  - dexamethasone 20 mg IV in 50 mL NS over 15 minutes

  30 minutes prior to PACLitaxel:
  - diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

- **If prior infusion reactions to pembrolizumab**: administer PACLitaxel premedications prior to pembrolizumab.
  45 minutes prior to pembrolizumab:
  - dexamethasone 20 mg IV in 50 mL NS over 15 minutes

  30 minutes prior to pembrolizumab:
  - diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

  acetaminophen 325 to 975 mg PO prior to pembrolizumab

- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)

TREATMENT

Drug	Starting Dose	BC Cancer Administration Guideline
pembrolizumab	2 mg/kg (maximum 200 mg)	IV in 50 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 x (GFR +25)	IV in 100 to 250 mL NS over 30 minutes

*Use a separate infusion line and filter for each drug

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).

- Each cycle is 21 days (3 weeks).
- Chemotherapy treatment: usual duration of chemotherapy is 6 cycles. Patients with ongoing benefit may continue beyond 6 cycles per discretion of treating physician
- Pembrolizumab duration:
    - Initial pembrolizumab therapy: maximum of 36 cycles for 3-weekly dosing or 18 cycles for 6-weekly dosing (or a combination of both) or 2 years of treatment, including doses given as GOCXBP and GOCXBP6
    - Retreatment may be permitted (see eligibility)
- If patients are intolerant of the chemotherapy after at least 1 cycle, pembrolizumab can be continued as above
- For continuation of treatment with maintenance pembrolizumab without chemotherapy, see protocol GOCXBP or GOCXBP6.

DOSE MODIFICATIONS:

1. **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)**	**PACLitaxel Dose**	**CARBOplatin Dose**
Febrile neutropenia at any time	and	any	Delay until recovery, then reduce subsequent doses to 80%	Delay until recovery, then reduce subsequent doses to 80%

2. **Other Toxicities:** No specific dose modifications for pembrolizumab. 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**)**

3. **Arthralgia and/or myalgia**: If arthralgia and/or myalgia from PACLitaxel 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
   - gabapentin 300 mg PO on day before chemotherapy, 300 mg bid on treatment day, then 300 mg tid x 7 to 10 days
   - If arthralgia and/or myalgia persists, reduce subsequent PACLitaxel doses to 135 mg/m^2.
4. **Neuropathy**: Dose modification or discontinuation may be required (see BC Cancer Drug Manual).
5. **Renal dysfunction**: If significant increase (greater than 20%) in creatinine, repeat nuclear renogram (if available) and recalculate CARBOplatin dose using new GFR.
6. **Hepatic dysfunction**: Dose reduction may be required for PACLitaxel (see BC Cancer Drug Manual)

PRECAUTIONS:

1. **Serious immune-mediated reactions to pembrolizumab**: these can be severe to fatal and usually occur during the 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,** http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf)
2. **Infusion-related reactions:** isolated cases of severe reaction have been reported. In case of a severe reaction, pembrolizumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive pembrolizumab with close monitoring. Premedications with acetaminophen and anti-histamine may be considered if there is a history of reaction.

3. **Hypersensitivity:** Reactions are common with PACLitaxel. See BC Cancer Hypersensitivity Guidelines.

mild symptoms (e.g. mild flushing, rash, pruritus)	• complete PACLitaxel infusion. • Supervise at bedside • no treatment required
moderate symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension	• stop PACLitaxel infusion • give IV diphenhydrAMINE 25 to 50 mg and IV 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
severe symptoms (i.e. *one* or more of respiratory distress requiring treatment, generalized 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.

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

References:

1. Vasey PA. Role of docetaxel in the treatment of newly diagnosed advanced ovarian cancer. J Clin Oncol 2003;21(90100):136s-44s.
2. Moore DH, McQuellon RP, Blessing JA, et al. A randomized phase III study of cisplatin versus cisplatin plus paclitaxel in stage IVB, recurrent or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. Proc Am Soc Clin Oncol 2001;20:(abstract 801).
3. Benedetti Panici P, Bellati F, Plotti F, et al. Neoadjuvant chemotherapy followed by radical surgery in patients affected by vaginal carcinoma. Gynecol Oncol. 2008;111(2):307-311.
4. Raspagliesi F, Zanaboni F, Martinelli F, Scasso S, Laufer J, Ditto A. Role of paclitaxel and cisplatin as the neoadjuvant treatment for locally advanced squamous cell carcinoma of the vulva. J Gynecol Oncol. 2014;25(1):22-29.
5. Colombo N, Dubot C, Lorusso D, et al; KEYNOTE-826 Investigators. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer. N Engl J Med. 2021 Nov 11;385(20):1856-1867.