# BC Cancer Protocol for Alternative Treatment of Squamous, Adenocarcinoma, or Adenosquamous Cancer of the Cervix with CARBOplatin, PACLitaxel NAB (ABRAXANE), and Pembrolizumab

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| ***Protocol Code*** | *GOCXCPNP* |
| ***Tumour Group*** | *Gynecology* |
| ***Contact Physician*** | *Dr. Aalok Kumar* |

**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, and
- 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
- Been treated with and eligible for UGOCXCATP

Note:
- BC Cancer Compassionate Access Program (CAP) approval is not required to switch between UGOCXCATP and this protocol if above criteria are met.

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 GOCXCPNP 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 GOCXCPNP for reasons other than progression (e.g. toxicity or complete response)

**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,
- Cancer of the vagina or vulva, or
- Severe hepatic dysfunction contraindicating PACLitaxel NAB

**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, random 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, random 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**:

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

**TREATMENT:**

| Drug | 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 NAB (ABRAXANE) | 260 mg/m$^2$ | IV over 30 minutes** |
| 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
** in empty sterile bags and tubing with **15** micron filter; no specific material required for bag or tubing

*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 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)** | **PACLitaxel NAB 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. **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.

3. **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

4. **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)

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 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. 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. 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.