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

Protocol Code	*GOCXCPNBP*
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 UGOCXCATBP

Note:
- BC Cancer Compassionate Access Program (CAP) approval is not required to switch between UGOCXCATBP 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 GOCXCPNBP 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 GOCXCPNBP for reasons other than progression (e.g. toxicity or complete response)

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EXCLUSIONS:

Patients must not have:

- Unstable or symptomatic central nervous system metastases,
- Any small cell component,
- Neutrophils less than 1.0 x 10^9/L,
- Initiation of single-agent pembrolizumab or bevacizumab monotherapy without chemotherapy,
- Cancer of the vagina or vulva,
- Major surgery within 4 weeks,
- Uncontrolled hypertension,
- Prior bevacizumab,
- Severe hepatic dysfunction contraindicating PACLitaxel NAB, or
- Bleeding diathesis

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)
- Pre-existing motor or sensory neuropathy greater than Grade 2
- Uncontrolled arterial or venous thromboembolism
- MI or CVA within 4 months
- Avoid NSAIDS and ASA if possible

TESTS:

- Baseline: CBC and differential, platelets, creatinine, ALT, total bilirubin, alkaline phosphatase, sodium, potassium, TSH, random glucose, dipstick or laboratory urinalysis for protein, blood pressure (BP) measurement, 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, dipstick or laboratory urinalysis for protein, blood pressure measurement
- 24 hour urine for protein if occurrence of proteinuria (dipstick urinalysis shows 2+ or 3+ or laboratory urinalysis for protein is greater than or equal to 1 g/L)
- Blood pressure measurement to be taken pre- and post-dose in first three cycles, and then pre-dose only in subsequent cycles
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR at the beginning of each cycle
- Weight at baseline and every scheduled physician’s visit
- 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).

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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
bevacizumab	15 mg/kg***	IV in 100 to 250 mL NS over 30 minutes to 1 hour†

* 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
*** bevacizumab dose does not need to be recalculated after Cycle 1 even if weight changes

† first infusion over 60 minutes; subsequent infusions over 30 minutes. Observe for fever, chills, rash, pruritus, urticaria, or angioedema and stop infusion and contact the physician if any of these occur. Infusion reactions should be treated according to severity. If the bevacizumab infusion is restarted then it should be given at an initial rate to complete after 60 minutes or longer.

If acute hypertension (increase in BP measurement of greater than 20 mmHg diastolic or greater than 150/100 if previously within normal limits) occurs during bevacizumab infusion – stop treatment. Resume at half the original rate of infusion if blood pressure has returned to pretreatment range within one hour. If blood pressure does not return to pretreatment range within one hour – hold bevacizumab; subsequent infusions of bevacizumab should be given over 3 hours. Acute hypertension that is symptomatic (e.g., onset of headaches or change in level of consciousness) or BP measurement of greater than 180/110 that does not improve within one hour of stopping bevacizumab is an urgent situation that requires treatment.

Use only normal saline for line priming and flushing.

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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 with or without bevacizumab can be continued as above
- Bevacizumab treatment: to progression or intolerance
- For continuation of treatment with maintenance pembrolizumab with or without bevacizumab without chemotherapy, see protocol GOCXBP or GOCXBP6.

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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%

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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)

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5. Proteinuria:

There are 3 different measures of proteinuria that may be used to assess the need for modification of bevacizumab therapy – urine dipstick analysis (measured in + values), laboratory urinalysis for protein (measured in g/L) and 24-hour urine collections for protein (measured in g/24 hours)

Urine dipstick analysis or laboratory urinalysis for protein should be performed at baseline and then prior to each cycle:

Degree of Proteinuria	Bevacizumab Dose
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. ***Adjust bevacizumab treatment based on the table below.***
If urine dipstick shows 4+ at baseline or during treatment	Withhold bevacizumab and proceed with 24 hour urine collection

24-Hour Urine Total Protein (g/24 hours)	Bevacizumab Dose
less than or equal to 2	100%
greater than 2 to 4	Hold dose and recheck 24-hour urine every 2 weeks. When less than or equal to 2 g/24 hour, resume therapy at **10 mg/kg**
greater than 4	Withhold/Discontinue bevacizumab

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6. **Hypertension:**

Blood Pressure (mmHg)	Bevacizumab Dose
less than or equal to 150/100	100%
greater than 150/100 asymptomatic	100% Notify physician and start or adjust antihypertensive therapy***
hypertensive crisis	discontinue therapy

- Antihypertensive therapy may include hydrochlorothiazide 12.5 to 25 mg PO once daily, ramipril (ALTACE®) 2.5 to 5 mg PO once daily, or amlodipine (NORVASC®) 5 to 10 mg PO once daily.

****Any patients presenting with chest pain, significant leg swelling, shortness of breath, new severe headaches or new neurologic symptoms, must be re-assessed by a physician before receiving further bevacizumab infusions.***

7. **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%
8. **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.

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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. **Gastrointestinal perforations and wound dehiscence:** Can be fatal. Typical presentation is reported as abdominal pain. Bevacizumab should be discontinued in patients with gastrointestinal perforation or wound dehiscence.
7. **Hemorrhage:** Bevacizumab has been associated with hemorrhage. Cases of CNS hemorrhage, some with fatal outcome, have been observed. Patients should be monitored for signs and symptoms of CNS bleeding. If Grade 3/4 hemorrhage occurs, discontinue bevacizumab. Patients with significant bleeding diatheses should not receive bevacizumab. Platelet inhibitory medications such as NSAIDS (including ASA at doses greater than 325 mg/day) should be discontinued prior to institution of bevacizumab. COX-2 inhibitors are permissible.
8. **Thrombosis:** A history of arterial thromboembolic events or age greater than 65 years is associated with an increased risk of arterial thromboembolic events with bevacizumab. If Grade 3 thromboembolic event or incidentally discovered pulmonary embolus arises, hold bevacizumab for 2 weeks, then consider resumption of bevacizumab if risks of tumour-related hemorrhage are judged low AND the patient is on a stable dose of anticoagulant. If a second Grade 3 thrombosis occurs, or if a Grade 4 thrombosis occurs, discontinue bevacizumab. Patients on warfarin should have INR checked frequently, at least once every 2-3 weeks, while receiving bevacizumab.
9. **Proteinuria:** Has been seen in all clinical trials with bevacizumab to date and is likely dose-dependent. If proteinuria of greater than or equal to 2 g/24 h persists for more than 3 months, consider further investigations - possibly a renal biopsy.

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10. **Hypertension:** Has been seen in all clinical trials with bevacizumab to date and is likely dose-dependent. The most commonly used therapies are calcium channel blockers, ACE inhibitors and diuretics. Blood pressure should be monitored through routine vital signs evaluations. If hypertension is poorly controlled with adequate medication, discontinue bevacizumab.
11. **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** Rarely, patients being treated with bevacizumab may develop seizures, headache, altered mental status, visual disturbances, with or without associated hypertension consistent with RPLS. May be reversible if recognized and treated promptly.
12. **Congestive Heart Failure**: Has been reported in up to 3.5% of patients treated with bevacizumab. Most patients showed improvement in symptoms and/or LVEF following appropriate medical therapy.
13. **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.
14. **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.
15. **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:

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7. 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.
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