BC Cancer Protocol for Maintenance Therapy of Squamous, Adenocarcinoma, or Adenosquamous Cancer of the Cervix with 6-Weekly Pembrolizumab with or without Bevacizumab

Protocol Code	*GOCXBP6*
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, and
- Eligible for and completed chemotherapy portion of UGOCXCATP, UGOCXCATBP, GOCXCPNBP, or GOCXCPNP with no disease progression.

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

Note: BC Cancer Compassionate Access Program (CAP) approval is not required to switch between GOCXBP and GOCXBP6

EXCLUSIONS:

Patients must not have:
- Unstable or symptomatic central nervous system metastases,
- Any small cell component, or
- Cancer of the vagina or vulva, and

If using bevacizumab, patients must not have:
- Major surgery within 4 weeks,
- Uncontrolled hypertension, 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), or
- If using bevacizumab, caution if:
    - uncontrolled arterial or venous thromboembolism, or
    - MI or CVA within 4 months.

  Avoid NSAIDS and ASA if possible.

TESTS:

- **Baseline and prior to each treatment:** CBC and differential, platelets, creatinine, ALT, total bilirubin, alkaline phosphatase, sodium, potassium, TSH
- 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, 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)

Additional tests if using bevacizumab:

- **Additional baseline if using bevacizumab**: Dipstick or laboratory urinalysis for protein, blood pressure (BP) measurement
- **Prior to each treatment of bevacizumab:** 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 pre-bevacizumab, or follows monitoring established for patient from prior UGOCXCATP, UGOCXCATBP, GOCXCPNBP, or GOCXCPNP treatment

PREMEDICATIONS:

- Antiemetics are not usually required
- If required, antiemetic protocol for low emetogenicity (see 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	4 mg/kg (maximum 400 mg) on Day 1	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter

If using bevacizumab:

Drug	Dose	BC Cancer Administration Guideline
bevacizumab	15 mg/kg* on Days 1 and 22	IV in 100 to 250 mL NS over 30 minutes**

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

****** Patients may have received and tolerated first infusion from UGOCXCATBP or GOCXCPNBP. 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 of 60 minutes or longer.

If acute hypertension (increase in BP measurement of greater than 20 mm Hg 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 returns 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.

Each cycle is 42 days (6 weeks)

- Pembrolizumab treatment 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 with chemotherapy UGOCXCATP, UGOCXCATBP, GOCXCPNBP, or GOCXCPNP
    - Retreatment may be allowed, see protocol UGOCXCATP, UGOCXCATBP GOCXCPNBP, or GOCXCPNP
- Bevacizumab treatment duration: to progression or intolerance

DOSE MODIFICATIONS:

1. **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

2. **Hypertension:**

Blood Pressure (mm Hg)	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 25mg PO once daily, ramipril (ALTACE®) 2.5 to 5 mg PO once daily, or amlodipine (NORVASC®) 5 to 10mg 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.***

3. **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**)**

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. **Gastrointestinal perforations and wound dehiscence**: Can be fatal. Typical presentation is reported as abdominal pain associated with symptoms such as

constipation and vomiting. Bevacizumab should be discontinued in patients with gastrointestinal perforation or wound dehiscence requiring medical intervention.

4. **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.
5. **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.
6. **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 hr persists for more than 3 months, consider further investigations - possibly a renal biopsy.
7. **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.
8. **Reversible Posterior Leukoencephalopathy Syndrome**: 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.
9. **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.

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:

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.