

BC Cancer Protocol Summary for Primary Treatment of Invasive Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer with High Risk Of Relapse Using Bevacizumab, CARBOplatin and PACLitaxel

Protocol Code

GOOVCATB

Tumour Group

Gynecologic Oncology

Contact Physician

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ELIGIBILITY:

- Invasive epithelial ovarian, fallopian tube or primary peritoneal cancer
- High risk of relapse (stage III sub-optimally debulked [> 1 cm of residual disease], stage III unresectable, or stage IV disease)
- No interval debulking surgery planned
- *Note: Use of bevacizumab in first-line setting precludes its use in subsequent lines of treatment*

EXCLUSIONS:

- Received prior bevacizumab
- neutrophils less than $1 \times 10^9/L$
- AST and/or ALT greater than 10 times the upper limit of normal
- total bilirubin greater than 128 micromol/L
- performance status greater than ECOG 3
- major surgery within 4 weeks
- uncontrolled hypertension
- pregnancy or breastfeeding
- bleeding diathesis
- history of bowel obstruction or unresolved bowel obstruction (*see note in Precautions section, below*)

RELATIVE CONTRAINDICATIONS:

- 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
- at risk of bowel obstruction (*see note in Precautions section, below*)

TESTS:

- **Baseline:** CBC & diff, platelets, creatinine, liver function tests (including bilirubin, ALT, alkaline phosphatase, GGT, LDH), sodium, potassium, dipstick or laboratory urinalysis for protein, blood pressure (BP) measurement, imaging as appropriate, tumor markers (CA 15-3, CA 125, CA 19-9) as appropriate
- Day 14 in first cycle (and in subsequent cycle if dose modification made): CBC & diff, platelets.
- **Before each treatment (Induction):** CBC & diff, creatinine, dipstick or laboratory urinalysis for protein, blood pressure measurement; if clinically indicated: any initially elevated tumor marker (CA 15-3, CA 125, CA 19-9), bilirubin, alkaline phosphatase, GGT, ALT, LDH, total protein, albumin
- **Before each treatment (Maintenance bevacizumab):** Dipstick or laboratory urinalysis for protein, blood pressure measurement; if clinically indicated: any initially elevated tumor marker (CA 15-3, CA 125, CA 19-9), CBC & diff, platelet, creatinine, bilirubin, alkaline phosphatase, GGT, ALT, LDH, total protein, albumin
- 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-bevacizumab in first three cycles, and then pre-dose only subsequently

- For patients on warfarin, weekly INR until stable warfarin dose established, then INR at the beginning of each cycle

PREMEDICATIONS:

- **PACLitaxel must not be started unless the following drugs have been given:**
 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)
- Antiemetic protocol for highly emetogenic chemotherapy protocols (see [SCNAUSEA](#))
- None required for maintenance bevacizumab

TREATMENT:

Induction:

- Give PACLitaxel first
- Bevacizumab begins cycle 2
- Use only normal saline for line priming and flushing.

Drug	Starting Dose	BC Cancer Administration Guideline
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** x (GFR + 25)	IV in 100 to 250 mL NS over 30 minutes
bevacizumab	7.5 mg/kg***	IV in 100 mL NS over 15 minutes to 1 hour****

Repeat every 21 days for 6 cycles. May extend to 9 cycles if the patient has not achieved a complete response but is continuing to respond.

* Conservative dosing (i.e., 155 mg/m² or 135 mg/m²) may be considered in the following cases: ECOG greater than 2, existing or potential myelosuppression; existing or potential arthralgia and myalgia; prior radiotherapy, particularly to the pelvic region; reduced bone marrow capacity. An initial dose of 135 mg/m² is recommended in patients greater than 75 years of age, with escalation to 155 mg/m² and then 175 mg/m² if tolerated.

** Use AUC of 6; if prior pelvic radiation therapy, use AUC of 5.

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

**** first infusion over 60 minutes; subsequent infusions over 15 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.

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.

Cockcroft-Gault Formula

$$\text{GFR} = \frac{1.04 \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

Maintenance bevacizumab: additional 12 cycles

Drug	Starting Dose	BC Cancer Administration Guideline
bevacizumab	7.5 mg/Kg ^{***}	IV in 100 mL NS over 15 minutes ^{****}

Repeat every 21 days up to a maximum of 12 cycles. (Total bevacizumab up to maximum 17 doses)

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

^{****} 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.

DOSE MODIFICATIONS:

1. Hematological:

a) on treatment day:

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Doses (both drugs)
greater than or equal to 1.0	and	greater than or equal to 100	treat as per nadir
less than 1.0	or	less than 100	delay until recovery

b) at nadir:

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	PACLitaxel	CARBOplatin
greater than or equal to 0.5	and	greater than or equal to 75	100%	100%
less than 0.5	and	less than or equal to 75	80%	80%
less than 0.5	and	greater than or equal to 75	80%	100%
greater than or equal to 0.5	and	less than or equal to 75	100%	80%
Febrile neutropenia at any time			80%	80%

Note: If dose has been reduced, dose increase/re-escalation for good nadir counts is not recommended.

2. 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	
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 7.5 mg/kg
greater than 4	Withhold/Discontinue bevacizumab

3. 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.**

- Arthralgia and/or myalgia:** The following regimen may be useful in preventing arthralgias/myalgias: 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/m².
- Neuropathy:** Dose modification or discontinuation may be required (see BC Cancer Drug Manual).
- Renal dysfunction:** If significant increase (greater than 20%) in creatinine, recalculate CARBOplatin dose using new GFR.
- Hepatic dysfunction:** Dose reduction may be required for PACLitaxel (see BC Cancer Drug Manual)

NB – In the setting of severe side effects that cannot be modified consider switching drugs i.e., CARBOplatin to CISplatin; PACLitaxel to DOCEtaxel, DOXOrubicin pegylated liposomal, or gemcitabine.

PRECAUTIONS:

- Bowel-related Toxicities:** Use of bevacizumab carries a risk of bowel perforation and other serious bowel problems. In the AURELIA study, the bowel-related exclusion criteria were: history of bowel obstruction (including subocclusive disease) related to underlying disease, a history of abdominal fistula, GI perforation or intra-abdominal abscess, evidence of rectosigmoid involvement by pelvic examination, bowel involvement on CT imaging, or clinical symptoms of bowel obstruction.

2. Hypersensitivity: Reactions are common. See BC Cancer Hypersensitivity Guidelines

<i>mild</i> symptoms (e.g. mild flushing, rash, pruritus)	<ul style="list-style-type: none"> ▪ complete PACLitaxel infusion. Supervise at bedside ▪ no treatment required
<i>moderate</i> symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	<ul style="list-style-type: none"> ▪ 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
<i>severe</i> symptoms (i.e. <i>one</i> or more of respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy)	<ul style="list-style-type: none"> ▪ stop PACLitaxel infusion ▪ give iv antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated ▪ discontinue PACLitaxel therapy

If significant or unmanageable hypersensitivity to CARBOplatin occurs, consider substituting CISplatin 70 mg/m².

3. **Extravasation:** PACLitaxel causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
4. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **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.
6. **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.
7. **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.
8. **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.
9. **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.

10. Reversible Posterior Leukoencephalopathy Syndrome (RPLS): Rarely, patients 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.

11. 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. Jenny Ko or tumour group delegate at (604) 851-4710 or 1-877-547-3777 with any problems or questions regarding this treatment program.

References:

1. Perren TJ, Swart AM, Pfisterer J, et al. A phase 3 trial of bevacizumab in ovarian cancer. *The New England Journal of Medicine*. 2011;365(26):2484-2496.
2. Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *The Lancet Oncology*. 2015;16(8):928-936.