BC Cancer Protocol Summary for Alternative Treatment of Gynecological Malignancies using Bevacizumab, CARBOplatin and PACLitaxel NAB (ABRAXANE)

Protocol Code	*GOCABRBEV*
Tumour Group	*Gynecologic Oncology*
Contact Physician	*Dr. Theresa Chan*

ELIGIBILITY:

- Previous severe hypersensitivity reaction or anaphylaxis to PACLitaxel that is not manageable despite use of premedications
- 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
- Eligible for the following protocols:
  - GOOVCATB
  - GOCXCATB

EXCLUSIONS:

- Platinum resistant/refractory disease
- Disease progression on prior taxane therapy
- Severe hepatic dysfunction contraindicating PACLitaxel NAB
- Greater than or equal to grade 2 sensory or motor neuropathy
- Received prior bevacizumab
- Major surgery within 4 weeks
- Uncontrolled hypertension
- Bleeding diathesis
- History of bowel obstruction or unresolved bowel obstruction *(see note in Precautions section, below)*

TESTS:

- **Baseline:** CBC & diff, platelets, creatinine, bilirubin, ALT, alk phos, LDH, sodium, potassium, dipstick or laboratory urinalysis for protein, blood pressure (BP) measurement, imaging as appropriate, tumour markers as appropriate, camera nuclear renogram for GFR (optional)
- Day 14 of first cycle (optional, if not done with prior regimen) and subsequent cycles (if a dose modification has been made): CBC & diff, platelets.
- **Before each treatment:** CBC & diff, creatinine, dipstick or laboratory urinalysis for protein, blood pressure measurement, any initially elevated tumour marker
- **If clinically indicated:** bilirubin, alk phos, GGT, ALT, LDH, albumin, total protein
- 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:

- Antiemetic protocol for moderate emetogenic chemotherapy protocols (see SCNAUSEA)

TREATMENT:

Induction:

- Give PACLitaxel NAB first
- Bevacizumab begins cycle 2 of platinum therapy for ovarian cancer.

Drug	Dose	BC Cancer Administration Guideline
PACLitaxel NAB (ABRAXANE)	260 mg/m²	IV over 30 minutes*
CARBOplatin	Dose = AUC** x (GFR +25)	IV in 100 to 250 mL NS over 30 minutes
bevacizumab	For ovarian cancer: 7.5 mg/kg *** **OR** for cervical cancer: 15 mg/kg ***	IV in 100 mL NS over 15 minutes to 1 hour**** IV in 100 to 250 mL NS over 30 minutes to 1 hour****

Repeat every 21 days to complete total number of cycles in original bevacizumab, CARBOplatin and PACLitaxel protocol. For maintenance bevacizumab in ovarian cancer, continue treatment using GOOVCATB.

*in empty sterile bags and tubing with 15 micron filter; no specific material required for bag or tubing

**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 or 30 minutes depending on the dose, as above. 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.

Measured GFR (e.g. nuclear renogram) is preferred in circumstances of co-morbidity that could affect renal function (third-space fluid accumulations, hypoproteinemia, potentially inadequate fluid intake, age greater than 70, 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

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

Recalculate GFR if creatinine increases by greater than 20% or rises above the upper limit of normal.

DOSE MODIFICATIONS:

1. **Hematological:** PACLitaxel NAB and CARBOplatin

a) on treatment day:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Doses (both drugs)
greater than or equal to 1.5	and	greater than or equal to 100	Treat as per nadir (if applicable); otherwise, proceed at same doses
less than 1.5	or	less than 100	Delay until recovery. If 2nd delay, use filgrastim (G-CSF) or dose reduction.

b) at nadir (until nadir pattern established):

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

* % of previous cycle's dose, at physician's discretion. If dose is changed, subsequent nadir counts must be checked.

** 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 standard dosing
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 hydrochlorthiazide 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.***

4. **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.

5. **Hepatic dysfunction**: PACLitaxel NAB

ALT or AST		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

6. **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%

7. **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. 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.

2. **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.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
4. **Extravasation**: PACLitaxel NAB causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
5. **Hypersensitivity:** Reactions to CARBOplatin may occur. Refer to BC Cancer Hypersensitivity Guidelines.
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.
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 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. **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.
13. **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.
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. Theresa Chan 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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6. Dizon DS, Schwartz J, Rojan A, et al. Cross-sensitivity between paclitaxel and docetaxel in a women's cancers program. Gyencol Oncol. 2006;100:149-51.
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8. Celgene Inc. ABRAXANE® product monograph. Mississauga, Ontario; 31 August 2018