BC Cancer Protocol Summary for Primary Treatment of No Visible Residual (Moderate-High Risk) Invasive Epithelial Ovarian, Fallopian Tube and Primary Peritoneal Cancer Using CARBOplatin and PACLitaxel

***Protocol Code**:*	*GOOVCATM*
***Tumour Group**:*	*Gynecology*
***Contact Physicians**:*	*Dr. Anna Tinker*

ELIGIBILITY:
- invasive epithelial ovarian, fallopian tube and primary peritoneal cancer, with no *visible* residual tumour, or borderline with invasive implants
- FIGO Ia: Grade 2 or 3
- FIGO Ib: Grade 2 or 3
- FIGO Ic, II, or III: any Grade

EXCLUSIONS:
- visible residual tumour (use GOOVCATX or GOOVCADX)
- AST and/or ALT greater than 10 times the Upper Limit of Normal (ULN)
- total bilirubin greater than 128 micromol/L

RELATIVE CONTRAINDICATIONS:
- pre-existing motor or sensory neuropathy greater than grade 2
- performance status greater than ECOG 3

TESTS:
- Baseline: CBC & diff, platelets, creatinine, tumour marker (CA 125, CA 15-3, CA 19-9), ALT, Alk Phos, bilirubin (if abnormal liver function is a potential concern), camera nuclear renogram for GFR (optional)
- Day 14 (and Day 21 if using 4 week interval) of first cycle (and in subsequent cycle(s) if a dose modification has been made): CBC & diff, platelets. No need for interim count check once safe nadir pattern has been established.
- Before each treatment: CBC & diff, creatinine, any initially elevated tumour marker,
- If clinically indicated: bilirubin, Alk Phos, GGT, ALT, LDH, protein level, albumin.

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)

TREATMENT (give PACLitaxel first):

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

* Conservative dosing (i.e., 155 mg/m^2 or 135 mg/m^2) 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/m^2 is recommended in patients greater than 75 years of age, with escalation to 155 mg/m^2 and then 175 mg/m^2 if tolerated.

** use AUC of 6; if extensive prior radiation therapy, use AUC of 5

Repeat every 21-28 days for: (a) 3 cycles, if to be followed by radiation therapy; or
(b) 6 cycles, if radiation therapy is not planned (papillary serous histology or contraindication to use of irradiation)

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, at a point of (optional) checking, creatinine increases by greater than 20% or rises above the upper limit of normal.

DOSE MODIFICATIONS:

1. **Hematology:**

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 (if applicable); otherwise, proceed at same doses
less than 1.0	or	less than 100	Delay until recovery. If using 21-day interval, switch to 28-day interval. If 2nd delay, use G-CSF or dose reduction.

* If ANC greater than 0.8 and monocytes greater than or equal to 20%, neutrophil count recovery is likely imminent. Continuation without delay may occur at physician's discretion.

b) at nadir (until nadir pattern established):

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

2. **Arthralgia and/or myalgia**: If arthralgia and/or myalgia of grade 2 (moderate) or higher was not adequately relieved by 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
   - gabapentin 300 mg PO on day before chemotherapy, 300 mg bid on treatment day, then 300 mg tid x 5 to 15 days days (based on duration of arthromyalgia)

   If arthralgia and/or myalgia persists, reduce subsequent PACLitaxel doses to 135 mg/m^2 or switch taxane to DOCEtaxel (GOOVCADM)

3. **Neuropathy**: Dose modification or discontinuation may be required (see BC Cancer Drug Manual).

4. **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.

5. **Hepatic dysfunction**: Dose reduction may be required for PACLItaxel.

ALT		Bilirubin	Dose
less than 10 x ULN	and	less than or equal to 1.25 x ULN	175 mg/m^2
less than 10 x ULN	and	1.26-2 x ULN	135 mg/m^2
less than 10 x ULN	and	2.01-5 x ULN	90 mg/m^2
greater than or equal to 10 x ULN	and/or	greater than 5 x ULN	not recommended

PRECAUTIONS:

1. **Hypersensitivity**: Reactions to PACLitaxel are common. See BC Cancer Hypersensitivity Guidelines

Mild symptoms (e.g. mild flushing, rash, pruritus)	▪ complete PACLitaxel infusion. Supervise at bedside ▪ no treatment required
moderate symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension	▪ stop PACLitaxel infusion ▪ give IV diphenhydrAMINE 25 to 50 mg and hydrocortisone IV 100 mg ▪ after recovery of symptoms resume PACLitaxel infusion at 20 mL/h for 5 minutes, 30 mL/h for 5 minutes, 40 mL/h for 5 minutes, then 60 mL/h for 5 minutes. If no reaction, increase to full rate. ▪ if reaction recurs, discontinue PACLitaxel therapy
severe symptoms (i.e. *one* or more of respiratory distress requiring treatment, generalised urticaria, angioedema, hypotension requiring therapy)	▪ stop PACLitaxel infusion ▪ give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated ▪ discontinue PACLitaxel therapy

2. **Extravasation**: PACLitaxel causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.

3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.

4. **Drug Interactions**: PACLitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Call Dr. Anna Tinker or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.