BC Cancer Protocol Summary for NEOAdjuvant Therapy for Triple Negative Breast Cancer using Pembrolizumab, Weekly CARBOplatin and Weekly PACLitaxel, Followed by DOXOrubicin and Cyclophosphamide

***Protocol Code**:*	*BRPCWTAC*
***Tumour Group**:*	*Breast*
***Contact Physician**:*	*Dr. Nathalie LeVasseur*

ELIGIBILITY:

Patients must have:
- Previously untreated triple negative breast cancer (ER, PR and HER2 negative based on ASCO/CAP guidelines*), and
- Clinical stage IIA or greater disease

  * Patients are considered triple negative if ER and PR Allred score 0 to 2 out of 8, and/or immunohistochemistry (IHC) score is 0. All other cases require approval via BC Cancer Compassionate Access Program (CAP)

Patients should have:
- ECOG 0 to 2
- Adequate baseline hematological, hepatic and renal function
- Access to a treatment center with expertise to manage immune-mediated adverse reactions of pembrolizumab

Notes:
- Patients who were started on neoadjuvant treatment with BRLACTWAC or BRLACTWACG prior to 1 Feb 2023 and have not received surgery yet, may switch to BRPCWTAC if all other eligibility criteria are met
- PD-L1 status not required
- See protocol BRAJPEM for single-agent pembrolizumab while surgical resection is pending

EXCLUSIONS:

Patients must not have:
- Stage I disease
- Metastatic disease
- Severe cardiovascular disease with LVEF less than 45%

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)

TESTS:

- Baseline: CBC & Diff, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, morning serum cortisol, creatine kinase, appropriate imaging (at least a baseline CXR if no baseline chest CT or PET)
- Before each cycle: CBC & Diff, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH
- Cycles 1 to 4: Prior to treatment on day 8 and 15: CBC & Diff, platelets, creatinine
- If clinically indicated: chest x-ray, morning serum cortisol, creatine kinase, lipase, GGT, serum or urine HCG (required for woman of child bearing potential if pregnancy suspected), Free T3 and Free T4, serum ACTH levels, testosterone, estradiol, FSH, LH, random glucose, ECG
- Post neoadjuvant treatment, just prior to surgery: morning serum cortisol is recommended
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional).

PREMEDICATIONS:

- **For the 4 cycles (=12 weeks) of PACLitaxel: PACLitaxel must not be started unless the following drugs have been given**:
  - 45 minutes prior to PACLitaxel: dexamethasone 10 mg IV in 50 mL NS over 15 minutes
  - 30 minutes prior to PACLitaxel: diphenhydrAMINE 25 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)
- **NOTE**: If no PACLitaxel infusion reactions occur, no premedications may be needed for subsequent PACLitaxel doses and may be omitted at physician's discretion.
- **NOTE:** If no infusion reactions occur, dexamethasone 8 mg PO may be given on Days 1, 8, and 15 of each cycle (day of CARBOplatin treatment) in place of the regimen in the first bullet point above.
- If infusion reactions occur, premedications for re-challenge include dexamethasone 20 mg PO given 12 hours and 6 hours prior to treatment, plus IV premedications given 30 minutes prior to PACLitaxel: dexamethasone 20 mg, diphenhydrAMINE 50 mg, and H_2-antagonist (e.g., famotidine 20 mg).
- For CARBOplatin: Antiemetic protocol for moderate emetogenic chemotherapy (see protocol SCNAUSEA)
- **For the 4 cycles of DOXOrubicin and cyclophosphamide**: 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; or administer PACLitaxel premedications prior to pembrolizumab.

TREATMENT:

- Cycles 1 to 4: Four consecutive cycles of pembrolizumab, PACLitaxel and CARBOplatin

Drug	Dose	BC Cancer Administration Guideline
pembrolizumab	2 mg/kg (maximum 200 mg) on Day 1	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter*
PACLitaxel	80 mg/m^2 on Days 1, 8 and 15	IV in 100 to 500 mL NS over 1 hour (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter)
CARBOplatin	AUC 1.5 x (GFR + 25) on Days 1, 8, and 15	IV in 50 to 250 mL NS over 30 minutes

* Use a separate infusion line and filter for each drug

- Cycle length = 3 weeks, repeat every 21 days for 4 cycles (= 12 weeks total), followed by
- Cycles 5 to 8: Four consecutive cycles of pembrolizumab, DOXOrubicin and cyclophosphamide
- Cycle 5 to start on week 13

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
DOXOrubicin	60 mg/m²	IV push
cyclophosphamide	600 mg/m²	IV in 100 to 250 mL NS over 20 min to 1 hour

- Repeat every 21 days for 4 cycles
- Note: single-agent pembrolizumab to be given every 3 weeks for nine more doses post-operatively (to a total of 17 doses, see protocol BRAJPEM). If there is a delay between completion of NEOadjuvant chemotherapy and surgery, continue with pembrolizumab per protocol BRAJPEM.

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).

DOSE MODIFICATIONS:

1. For pembrolizumab:

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)

1. Hematological

For cycles of PACLitaxel and CARBOplatin only:

- Applicable for all days of treatment (i.e. Days 1, 8, and 15 for PACLitaxel and CARBOplatin)

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose (both drugs)
Greater than or equal to 1.5	and	Greater than or equal to 90	100%
1.0 to less than 1.5*	or	70 to less than 90	75%
Less than 1.0	or	Less than 70	Delay** and reduce next dose level or add filgrastim

* if ANC 1.0 to less than 1.5 and patient fit and well can consider full dose of PACLitaxel 80 mg/m^2 at discretion of physician

For cycles of DOXOrubicin and cyclophosphamide only:

ANC (x10^9/L)		Platelets (x10^9/L)	Dose (both drugs)
Greater than or equal to 1.5	and	Greater than or equal to 90	100%
1.0 to less than 1.5	or	70 to less than 90	75%
Less than 1.0	or	Less than 70	Delay or add filgrastim

2. Non-Hematological Toxicity

Grade	Dose
Grade 2 motor or sensory neuropathy	Decrease dose of PACLitaxel by 10 mg/m^2
All other clinically significant grade 2 non-hematological toxicity	Hold treatment until toxicity resolved to less than or equal grade 1 Decrease subsequent doses by 10 mg/m^2
Greater than or equal to Grade 3	Discontinue treatment

3. **Hepatic dysfunction**:

For Cycles 1 to 4: Reduce PACLitaxel dose:

ALT		Total bilirubin	Dose (mg/m^2)
less than 3 x ULN	and	less than or equal to 1.25 x ULN	80
less than 3 x ULN	and	1.26 to 2 x ULN	60
less than 3 x ULN	and	2.01 to 3 x ULN	40
greater than or equal to 3 x ULN	and/ or	greater than 3 x ULN	not recommended

ULN = upper limit of normal

For Cycles 5 to 8: Dose modifications required for DOXOrubicin. Refer to BC Cancer Drug manual.

4. **Renal dysfunction:** Use nuclear renogram or predictive formula to calculate cycle 1 dose, as detailed above. Consider re-calculation of dose if serum creatinine changes ± 20% from baseline. Dose modification may be required for Cyclophosphamide. Refer to BC Cancer Drug Manual.

5. Arthralgia and/or myalgia: If arthralgia and/or myalgia from PACLitaxel 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:
   - 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 persist, reduce subsequent PACLitaxel doses to 65mg/m^2.

6. Neuropathy: Dose modification or discontinuation may be required (see BC Cancer Drug Manual).
7. **Gastrointestinal toxicity:** If greater than or equal to grade 3 mucositis occurs, PACLitaxel and CARBOplatin should be withheld until resolution to less than or equal to grade 1, then reinstituted at 80% of previous dose.

PRECAUTIONS:

1. **Infusion-related reactions**: Reactions to PACLitaxel are common. See BC Cancer SCDRUGRX.

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 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**: DOXOrubicin and PACLitaxel cause pain and 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. **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)
5. **Pembrolizumab 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.

Call Dr. Nathalie LeVasseur or tumour group delegate at (604) 930-2098 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References

1. Schmid P, Cortes J, Pusztai L, et al. KEYNOTE-522 Investigators. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020 Feb 27;382(9):810-821.