BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Pembrolizumab with PACLitaxel

***Protocol Code**:* *BRAVPP*

***Tumour Group**:* *Breast*

***Contact Physician**:* *Dr. Nathalie LeVasseur*

ELIGIBILITY:

Patients must have:

- Locally recurrent unresectable or metastatic breast cancer,
- Triple negative (ER, PR and HER2 negative based on ASCO/CAP guidelines*),
- Previously untreated in the metastatic setting, and
- PD-L1 expression with combined positive score (CPS) greater than or equal to 10

  * 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 0-2,
- Adequate hematological, hepatic and renal function,
- Asymptomatic/stable brain metastases (if applicable), and
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of pembrolizumab

Notes:

- Patients are eligible to receive any of the following, but not their sequential use:
  - Pembrolizumab with PACLitaxel (BRAVPP),
  - Pembrolizumab with PACLitaxel NAB (ABRAXANE) (BRAVPPN), or
  - Pembrolizumab with gemcitabine and CARBOplatin (BRAVPGC)
- Patients on active first-line treatment responding to BRAVTW, BRAVABR, BRAVTAX, or BRAVDOC are eligible to switch to BRAVPP or BRAVPPN if all other eligibility criteria are met.
- Patients are eligible if greater than or equal to 6 months since completion of prior neoadjuvant or adjuvant chemotherapy.
- Patients are eligible if greater than or equal to 6 months since completion of neoadjuvant or adjuvant immunotherapy.
- At time of subsequent disease progression, pembrolizumab retreatment (with chemotherapy per BRAVPP or without chemotherapy per BRAVPEM or BRAVPEM6) is allowed for an additional 1 year of therapy if:
  - Patients have completed 2 years of therapy without progression
  - Patients have stopped pembrolizumab for reasons other than progression (e.g. toxicity or complete response)
  - Additional CAP approval not required for retreatment

EXCLUSIONS:
Patients must not have:
- Relapsed on *or* within *6 months* of completing neoadjuvant or adjuvant chemotherapy, or
- Relapsed on *or* within *6 months* of completing neoadjuvant or adjuvant pembrolizumab.

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, random glucose, appropriate imaging (at least a baseline CXR if no baseline chest CT or PET)
- Before each treatment:
  - Day 1 – CBC & Diff, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH
  - Day 8 and 15 – CBC & Diff, platelets
- If clinically indicated: chest x-ray, morning serum cortisol, creatine kinase, lipase, random glucose, serum or urine HCG (required for women of child bearing potential if pregnancy suspected), free T3 and free T4, serum ACTH levels, estradiol, FSH, LH, ECG, CA15-3
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional).

PREMEDICATIONS:

- **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.
- 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). If no infusion reactions occur, standard premedications (see above) will be used for subsequent PACLitaxel doses.
- Additional antiemetics not usually required (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:

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*)

* Use a separate infusion line and filter for each drug

- Each cycle is 21 days (3 weeks)
- Duration of treatment
  - Chemotherapy: until disease progression.
  - Pembrolizumab**:** maximum of 36 cycles or 2 years of treatment, including doses given as BRAVPEM and BRAVPEM6, or until disease progression.
  - If chemotherapy is discontinued, transition to protocol BRAVPEM or BRAVPEM6 for single-agent pembrolizumab.
- Retreatment may be allowed (refer to eligibility)

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)

2. Hematological

For PACLitaxel:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose	Dose after Neutropenic Sepsis on PACLitaxel
Greater than or equal to 1.0	and	Greater than or equal to 90	80 mg/m^2	65 mg/m^2
Less than 1.0	or	Less than 90	Contact Physician: Delay treatment. Physician may choose to reduce next dose to 65 mg/m^2	delay

3. **Non-Hematological Toxicity**

For PACLitaxel:

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

4. **Hepatic dysfunction**:

For PACLitaxel:

ALT or AST		Total bilirubin	Dose (mg/m^2)
less than 10 x ULN	and	less than or equal to 1.25 x ULN	80
less than 10 x ULN	and	1.26 to 2 x ULN	60
less than 10 x ULN	and	2.01 to 5 x ULN	40
greater than or equal to 10 x ULN	and/ or	greater than 5 x ULN	not recommended

ULN = upper limit of normal

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 for 7 to 10 days

   If arthralgia and/or myalgia persist, reduce subsequent PACLitaxel doses to 65 mg/m^2.

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**: 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. **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. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020;396(10265):1817-1828.
2. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP Guideline Update. J Clin Oncol 2020;38(12):1346-1366.