BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Pembrolizumab and PACLitaxel NAB (ABRAXANE)

***Protocol Code**:* *BRAVPPN*

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

***Contact Physician**:* *Dr. Stephen Chia*
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 to 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 prior neoadjuvant or adjuvant immunotherapy.
- At time of subsequent disease progression, pembrolizumab retreatment (with chemotherapy per BRAVPPN 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.
- Severe hepatic dysfunction contraindicating PACLitaxel NAB (ABRAXANE)

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)
- Greater than or equal to grade 2 sensory or motor neuropathy

TESTS:

- Baseline: CBC & Diff, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, GGT, 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: CBC & Diff, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH
- If clinically indicated: chest x-ray, morning serum cortisol, creatine kinase, lipase, GGT, urea, 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:

- Additional anti-emetics not usually required.
- **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 pembrolizumab.

TREATMENT:

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*
PACLitaxel NAB (ABRAXANE)	260 mg/m^2	IV over 30 minutes**

* use separate infusion line and filter for each drug

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

- 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 NAB (ABRAXANE) only:

ANC ($x 10^9$/L)		**Platelets ($x 10^9$/L)**	**Dose of PACLitaxel NAB (ABRAXANE)**
greater than or equal to 1.5	and	greater than or equal to 100	100% (260 mg/m^2)
1.0 to less than 1.5	and	greater than or equal to 100	**220 mg/m^2**
less than 1.0	or	less than 100	Delay until: • ANC greater than or equal to 1.5, and • Platelets greater than or equal to 100 Then consider giving **220 mg/m^2**

	1st Occurrence	**2nd Occurrence**
Febrile neutropenia	Delay until: • ANC greater than or equal to 1.5 x 10^9/L, and • Platelets greater than or equal to 100 x 10^9/L Then reduce dose to **220 mg/m^{2*}**	Delay until: • ANC greater than or equal to 1.5 x 10^9/L, and • Platelets greater than or equal to 100 x 10^9/L Then reduce dose to **180 mg/m^{2*}**

* Maintain dose reductions for subsequent cycles and do not re-escalate

3. Hepatic Dysfunctions

ALT or AST		Total bilirubin	PACLitaxel NAB (ABRAXANE)
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

4. Sensory Neuropathy

For PACLitaxel NAB (ABRAXANE)

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 until resolved to grade 2, then reduce dose to 220 mg/m^{2*}	Hold until resolved to grade 2, then reduce dose to 180 mg/m^{2*}
4	Disabling	Hold until resolved to grade 2, then reduce dose to 220 mg/m^{2*}	Hold until resolved to grade 2, then reduce dose to 180 mg/m^{2*} or discontinue

* Maintain dose reductions for subsequent cycles and do not re-escalate

5. Arthralgia and/or myalgia: If arthralgia and/or myalgia from PACLitaxel NAB (ABRAXANE) 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 for 7 to 10 days

If arthralgia and/or myalgia persist, reduce subsequent PACLitaxel NAB doses to 220 mg/m^2.

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. **Extravasation**: PACLitaxel NAB (ABRAXANE) 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.
6. **Renal Dysfunction:** No adjustment required for PACLitaxel NAB (ABRAXANE) in mild to moderate renal impairment. PACLitaxel NAB has not been studied in patients with creatinine clearance less than 30 mL/min.
7. **Drug Interactions**: PACLitaxel NAB (ABRAXANE) is metabolized by CYP2C8 and CYP3A4; caution should be exercised when administering with drugs which are CYP2C8 or CYP3A4 inducers or inhibitors.
8. **Cardiac toxicity** has been reported rarely while patients receive PACLitaxel NAB (ABRAXANE). Severe cardiovascular events (3%), including chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension.
9. Theoretical risk of viral disease transmission, due to human albumin component in PACLitaxel NAB (ABRAXANE), is extremely remote.

Call Dr. Stephen Chia, Dr. Nathalie LeVasseur or tumour group delegate at 604-877-6000 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.