BC Cancer Protocol Summary for Palliative Therapy for Metastatic Breast Cancer using Pembrolizumab, Gemcitabine, and CARBOplatin

Protocol Code	*BRAVPGC*
Tumour Group	*Breast*
Contact Physician	*Dr. Stephen Chia*
	Dr. Nathalie LeVasseur

ELIGIBILITY:

Patients must have:

- Locally recurrent unresectable or metastatic breast triple negative breast cancer*,
- Previously untreated in the metastatic setting, and
- PD-L1 expression with combined positive score (CPS) greater than or equal to 10

* Patients are eligible if:

1. HER2 negative:
   - HER2 IHC 0 to 1, or
   - HER2 IHC 2 with FISH negative,

   and
2. ER negative:
   - Less than 1% of ER positive cells, and
   - ER Allred score 0 to 2 out of 8

- Regardless of PR results
- All other cases including ER-low requests 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 BRAVGEMP are eligible to switch to BRAVPGC 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 BRAVPGC 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, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, morning serum cortisol, creatine kinase, random glucose, creatine kinase appropriate imaging (at least a baseline CXR if no baseline chest CT or PET)
- Baseline, if clinically indicated: lipase, BNP, troponin, ECG, echocardiogram
- Before each treatment:
  - Day 1 – CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatine kinase
  - Day 8 – CBC & Diff, creatinine
- If clinically indicated: chest x-ray, morning serum cortisol, 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, troponin
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional).

PREMEDICATIONS:

- Antiemetic protocol for moderately 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 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
gemcitabine	1000 mg/m^2/day on Days 1 and 8 (total dose per cycle = 2000 mg/m^2)	IV in 250 mL NS over 30 minutes
CARBOplatin	Dose = AUC 2 x (GFR + 25) on Days 1 and 8	IV in 50 to 250 mL NS over 30 minutes

- 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)

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)

2. Hematology:

For gemcitabine and CARBOplatin Day 1 of each cycle

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
greater than or equal to 1.0	and	greater than or equal to 100	100%
0.5 to less than 1.0	or	75 to less than 100	75%
less than 0.5	or	less than 75	**Delay**

For gemcitabine and CARBOplatin Day 8 of each cycle

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose**
greater than or equal to 1.0	and	greater than or equal to 100	100%
0.5 to less than 1.0	or	75 to less than 100	75%
less than 0.5	or	less than 75	**Omit**
****Dose adjustment only for the day of treatment the CBC is drawn**			

3. **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.

For gemcitabine only:

Grade	Stomatitis	Diarrhea	Dose
1	Painless ulcers, erythema or mild soreness	Increase of 2 to 3 stools/day	100%
2	Painful erythema, edema, or ulcers but can eat	Increase of 4 to 6 stools, or nocturnal stools	Omit until toxicity resolved then resume at 100%
3	Painful erythema, edema, or ulcers and cannot eat	Increase of 7 to 9 stools/day or incontinence, malabsorption	Omit until toxicity resolved then resume at 75%
4	Mucosal necrosis, requires parenteral support	Increase of greater than or equal to 10 stools/day or grossly bloody diarrhea requiring parenteral support	Omit until toxicity resolved then resume at 50%

PRECAUTIONS:

1. **Serious immune-mediated reactions**: can be severe to fatal and usually occur during the treatment course with pembrolizumab, but may develop months after discontinuation of therapy. They may include enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathy, pneumonitis, 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).
2. **Infusion-related reactions:** isolated cases of severe infusion reactions have been reported with pembrolizumab. Discontinue pembrolizumab with severe reactions (Grade 3 or 4). Patients with mild or moderate infusion reactions may receive pembrolizumab with close monitoring and use of premedication.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Renal Dysfunction**: Irreversible renal failure associated with hemolytic uremic syndrome may occur with gemcitabine use (rare). Use caution with pre-existing renal dysfunction.
5. **Pulmonary Toxicity**: Acute shortness of breath may occur with gemcitabine use. Discontinue treatment if drug-induced pneumonitis is suspected.

6. **Possible interaction with warfarin** has been reported and may occur at any time. Close monitoring is recommended (monitor INR weekly during gemcitabine therapy and for 1 to 2 months after discontinuing gemcitabine treatment).

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.