BC Cancer Protocol Summary for the Treatment of Unresectable or Metastatic Melanoma Using Pembrolizumab

Protocol Code	*SMAVPEM*
Tumour Group	*Skin and Melanoma*
Contact Physician	*Dr. Vanessa Bernstein*

ELIGIBILITY:

Patients must have:
- Unresectable stage 3 or stage 4 metastatic melanoma,
- Ipilimumab naïve, regardless of BRAF V600 mutation status, and
- No prior systemic therapy for advanced disease with the exception of BRAF and/or MEK inhibitors for BRAF mutant metastatic melanoma

Note:
- Patients are eligible to receive pembrolizumab or nivolumab but not sequential use of these agents
- CAP approval not required to switch between SMAVPEM and SMAVPEM6

Patients should have:
- ECOG 0 – 1,
- Adequate hepatic and renal function, and
- access to a treatment centre with expertise to manage immune-mediated adverse reactions of pembrolizumab

EXCLUSIONS:

- Active central nervous system metastases (should be asymptomatic and/or stable),
- Relapsed on or within 6 months of completing adjuvant anti-PD1 therapy,
- Caution with concurrent autoimmune disease, or
- Use with caution in patients with long term immunosuppressive therapy or systemic corticosteroids (Requiring more than 10 mg predniSONE/day or equivalent)

TESTS:

- Baseline: CBC and differentials, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, serum morning cortisol, chest x-ray
- Before each treatment: CBC and differentials, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH
- If clinically indicated: chest x-ray, morning serum cortisol, lipase, glucose, seum 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, ECG

- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional).

PREMEDICATIONS:

- Antiemetics are not usually required.
- Antiemetic protocol for low emetogenicity (see SCNAUSEA).
- If prior infusion reactions to pembrolizumab: diphenhydrAMINE 50 mg PO, acetaminophen 325 mg to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

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

- Repeat every 3 weeks until disease progression, unacceptable toxicity, or a maximum of 2 years of treatment

DOSE MODIFICATIONS:

No specific dose modifications. 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**).**

PRECAUTIONS:

- **Serious immune-mediated reactions**: 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).
- **Infusion-related reactions:** isolated cases of severe reaction have been reported. In case of a severe reaction (Grade 3 or 4), pembrolizumab infusion should be permanently 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. Vanessa Bernstein or tumour group delegate at 250-519-5570 or 1-800-670-3322 with any problems or questions regarding this treatment program.

References:

1. Robert C, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Eng J Med 2015;372:2521-32.
2. Robert C, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014; 384: 1109–17.
3. Ribas A, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015; 16: 908–18.
4. Pan-Canadian Oncology Drug Review. Expert Review Committee final recommendation of pembrolizumab. (KEYTRUDA) for the treatment of patients with unresectable or metastatic melanoma. 16 November 2015.
5. Merck Canada: KEYTRUDA (pembrolizumab) product monograph. Kirkland, Quebec: 15 April 2016.
6. Postow M, Wolchok J. Toxicities associated with checkpoint inhibitor immunotherapy. UpToDate revised November 2015. Accessed: www.uptodate.com, May 2016.
7. Weber JS, et al. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 2016;21:1-11.