BC Cancer Protocol Summary for the Adjuvant Treatment of Resected Stage IIB to IV NED Melanoma Using 6-Weekly Pembrolizumab

Protocol Code	*SMAJPEM6*
Tumour Group	*Skin and Melanoma*
Contact Physician	*Dr. Vanessa Bernstein*

ELIGIBILITY:

Patients must have:

- Completely resected cutaneous or mucosal* melanoma,
  - Stage IIB (pT3bN0 or pT4aN0) or stage IIC (pT4bN0), or
  - Stage IIIA to IV NED (AJCC 8th edition). Disease metastasized to the regional nodes (if stage IIIA and only one node involved then metastatic deposit ≥ 1 mm), in-transit metastases or distant metastases must be completely surgically resected,
- Pembrolizumab initiated within 12 weeks of surgery,
- No prior systemic therapy for melanoma, and
- Brain metastases must be completely resected (or definitively treated with stereotactic radiation)

* Eligible if mucosal melanoma stage IIIA to IV NED.

Patients should have:

- Adequate baseline hematological, hepatic and renal function
- Access to a treatment centre with expertise in managing immunotherapy mediated toxicities of pembrolizumab

Note:

- Patients may have subsequent checkpoint inhibitors for advanced disease if last adjuvant pembrolizumab dose was > 6 months.
- CAP approval is not required to switch between 3-weekly and 6-weekly dosing of pembrolizumab.
- Patients with stage IIIA to IV NED resected melanoma (but not patients with stage IIB or stage IIC resected melanoma):
  - Can receive one year of either adjuvant nivolumab, pembrolizumab OR combination daBRAFenib/trametinib. Patients with BRAF mutated melanoma who are unable to tolerate up to a 3-month trial of combination daBRAFenib/trametinib due to toxicities can apply for adjuvant pembrolizumab and complete a total of one year of therapy. A switch to combination cobimetinib/vemURAFenib is not funded.
- Patients with stage IIB or stage IIC disease are only eligible for 1 year of adjuvant pembrolizumab

EXCLUSIONS:

Patients must not have:

- Uveal or ocular melanoma,
- Concurrent treatment for melanoma (this protocol is monotherapy only), or
- Stage II mucosal melanoma

CAUTIONS:
- Concurrent 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, appropriate imaging (at least a baseline CXR if no baseline chest CT)
- Baseline, if clinically indicated: BNP, troponin, ECG, echocardiogram
- Before each treatment: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatine kinase
- If clinically indicated: chest x-ray, morning serum cortisol, lipase, 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, glucose, troponin, 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 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
pembrolizumab	4 mg/kg (maximum 400 mg)	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter

- Repeat **every 6 weeks** for 9 cycles* maximum (approximately 1 year), unless disease progression or unacceptable toxicity.
  *Includes doses given as SMAJPEM

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, 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. Vanessa Bernstein or tumour group delegate at 250-519-5500 or 1-800-670-3322 with any problems or questions regarding this treatment program.

References:

1. Eggermont *et. al.* Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. N Engl J Med 2018; 378:1789-1801
2. Merck Canada Inc.: KEYTRUDA (pembrolizumab) product monograph. Kirkland, Quebec: 20 September 2019.
3. Pan-Canadian Oncology Drug Review. Expert Review Committee final recommendation on pembrolizumab (Keytruda) for the adjuvant treatment of patients with stage IIIA (limited to lymph node metastasis of > 1 mm) to stage IIID (8th edition of the American Joint Committee on Cancer [AJCC] staging system) cutaneous melanoma. 1 August 2019.
4. Merck Sharp & Dohme Corp, New Jersey, USA, Inc. US Prescribing Information for Keytruda®. June 2020.
5. Luke JJ, Ascierto PA, Carlino MS, et al. KEYNOTE-716: Phase III study of adjuvant pembrolizumab v ersus placebo in resected high-risk stage II melanoma. Future Oncol. 2020 Jan;16(3):4429-4438.