BC Cancer Protocol Summary for the Neoadjuvant-Adjuvant Treatment of Stage IIIB to IV Melanoma Using Pembrolizumab

Protocol Code	*SMNAPEM*
Tumour Group	*Skin and Melanoma*
Contact Physicians	*Dr. Vanessa Bernstein* *Dr. Alison Weppler*

ELIGIBILITY:

Patients must have:

- Resectable cutaneous, acral or mucosal melanoma,
- Clinically detectable nodal disease at presentation or limited resectable metastatic disease at presentation [i.e., stage IIIB to IIID or oligometastatic stage IV (M1a, M1b and M1c) per AJCC 8th edition], and
- Be planned for standard curative intent resection

Patients should have:

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

Notes:

- Three cycles of pembrolizumab should be administered pre-operatively (neoadjuvant treatment phase), unless patient needs to go to surgery early for clinical reasons
- CAP approval is not required to switch between 3-weekly and 6-weekly dosing of pembrolizumab post-operatively (adjuvant treatment phase). Do not switch to 6-weekly dosing during neoadjuvant treatment phase
- Patients may have subsequent checkpoint inhibitors for advanced disease if last adjuvant pembrolizumab dose was > 6 months prior

EXCLUSIONS:

Patients must not have:

- Uveal or ocular melanoma

CAUTIONS:

- Concurrent autoimmune disease
- Patients with long term immunosuppressive therapy or systemic corticosteroids (requiring more than 10 mg predniSONE/day or equivalent)

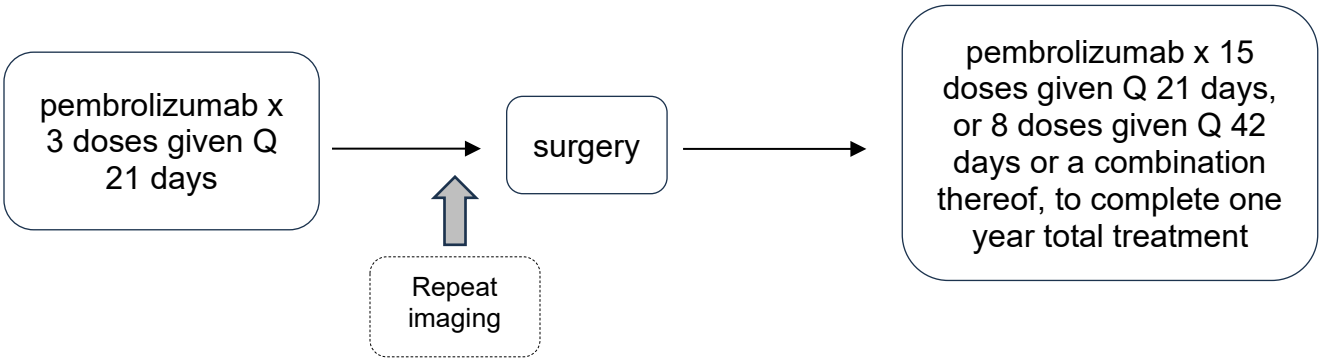
TESTS:

- 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
- Cycles 1 to 3, before each treatment: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatine kinase, random glucose, morning serum cortisol
- Cycles 4 onward, before each treatment: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatine kinase, random glucose
- If clinically indicated: chest x-ray, morning serum cortisol, lipase, serum or urine HCG (required for woman of childbearing potential if pregnancy suspected), Free T3 and Free T4, serum ACTH levels, testosterone, estradiol, FSH, LH, troponin, ECG
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional).

PREMEDICATIONS:

- Antiemetics are not usually required.
- If antiemetics needed, use 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 Schema:



TREATMENT:

Neoadjuvant Phase:

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

- Each cycle is **3 weeks** (21 days)
- Neoadjuvant phase: Give 3 cycles pre-operatively, then
- After Cycle 3, prior to surgery the following are required:
  - Morning serum cortisol
  - Repeat imaging (CT or PET)

then

Adjuvant Phase:

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

- Each cycle is **3 weeks** (21 days)
- Give for a maximum of 15 cycles* post-operatively, unless disease progression or unacceptable toxicity
  * or equivalent, including cycles given on 6-weekly schedule

OR

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

- Each cycle is **6 weeks** (42 days)
- Give for a maximum of 8 cycles* post-operatively, unless disease progression or unacceptable toxicity.
  * or equivalent, including cycles given on 3-weekly schedule

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)

PRECAUTIONS:

- **Serious immune-mediated reactions**: these can be severe to fatal and usually occur during the treatment course, but can have delayed presentations even after treatment completion. They may include myocarditis, enterocolitis, intestinal perforation or hemorrhage, hepatitis, pneumonitis, dermatitis, neuropathy, endocrinopathies (e.g., adrenal insufficiency, type 1 diabetes mellitus, hypo/hyperthyroidism), 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)**
- **Infusion-related reactions:** isolated cases of severe reactions 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 and premedications with acetaminophen and antihistamine. Additional premedication with steroids and a slower infusion rate may be considered for subsequent doses.

Call Dr. Alison Weppler or tumour group delegate at 604-877-6050 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Patel SP, Othus M, Chen Y, et al. Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma. N Engl J Med. 2023 Mar 2;388(9):813-823.
2. Pembrolizumab (Keytruda) CADTH [Canada's Drug Agency (CDA-AMC)] Reimbursement Recommendation. Canadian Journal of Health Technologies, Aug 2024