BC Cancer Protocol Summary for the Adjuvant Treatment of Resected Stage III - IV NED Melanoma Using 4-Weekly Nivolumab

Protocol Code	*SMAJNIV4*
Tumour Group	*Skin and Melanoma*
Contact Physician	*Dr. Vanessa Bernstein*

ELIGIBILITY:

Patients must have:

- Cutaneous or mucosal melanoma 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.
- Brain metastases must be completely resected (or definitively treated with stereotactic radiation)

Patients should have:

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

Note:

- Patients 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 switch to adjuvant nivolumab or pembrolizumab and complete a total of one year of therapy. A switch to combination vemURAFenib/cobimetinib or encorafenib/binimetinib is not funded.
- Patients may have subsequent checkpoint inhibitors for advanced disease if last adjuvant nivolumab dose was > 6 months (except combination ipilimumab with nivolumab using SMAVIPNI or SMAVALIPNI protocols, which do not restrict > 6 months eligibility).
- CAP approval is not required to switch between 2-weekly and 4-weekly dosing of nivolumab (except patients previously treated with SMNAIPNI).
- Patients with a pathological partial or nonresponse (>10% residual viable tumour) after previous neoadjuvant treatment with SMNAIPNI are eligible for 11 cycles of treatment at 4-weekly dosing (CAP approval is required for 2-weekly dosing option).

EXCLUSIONS:

Patients must not have:

- Uveal or ocular melanoma
- Achieved a major pathological response (≤10% residual viable tumour) after previous neoadjuvant SMNAIPNI

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, 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 nivolumab: 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
nivolumab	6 mg/kg (maximum 480 mg)	IV in 50 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter

- Repeat **every 4 weeks** for 52 weeks* (13 cycles), unless disease progression or unacceptable toxicity. *Includes doses given as SMAJNIV to total 52 weeks treatment
- Patients previously treated with neoadjuvant combination ipilimumab and nivolumab SMNAIPNI: Repeat **every 4 weeks** for 11 cycles, unless disease progression or unacceptable toxicity.

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. 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**).
- **Infusion-related reactions:** isolated cases of severe reaction have been reported. In case of a severe reaction, nivolumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab 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. Weber J, *et. al.* Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma N Engl J Med 2017;377:1824-1835
2. Bristol-Myers Squibb: OPDIVO® (nivolumab) product monograph. Montreal, Quebec: 13 March 2019.
3. Weber JS, et al. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 2016;21:1-11.