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

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

ELIGIBILITY:

Patients must have:

- Unresectable or metastatic melanoma in patients who are previously untreated, 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 or nivolumab but not sequential use of these agents
- CAP approval not required to switch between SMAVNIV and SMAVNIV4

Patients should have:

- Good performance status,
- Adequate hepatic and renal function, and
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of nivolumab

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 & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, morning serum cortisol, chest x-ray
- Before each treatment: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH
- 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, 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	3 mg/kg (maximum 240 mg)	IV in 50 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter

- Repeat **every 2 weeks** until disease progression or unacceptable toxicity
- If pseudo progression on imaging is suspected, may continue treatment for another 6 weeks. Discontinue treatment if confirmatory progression on subsequent scan (6-10 weeks)

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, 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 250-519-5570 or 1-800-670-3322 with any problems or questions regarding this treatment program.

References:

1. Robert C, et al. Nivolumab in previously untreated melanoma without *BRAF* mutation. N Engl J Med 2015;372:320-30.
2. Larkin J, et al.Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23-34.
3. Topalian S, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014;32:1020-30.
4. Weber J, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16:75-84.
5. Bristol-Myers Squibb: OPDIVO (nivolumab) product monograph. Montreal, Quebec: 26 October 2016.
6. Bristol-Myers Squibb: OPDIVO prescribing information. Princeton, NJ: November 2016.
7. Weber JS, et al. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 2016;21:1-11.
8. Waterhouse D, Horn L, Reynolds C, et al. Safety profile of nivolumab administered as 30-min infusion: analysis of data from CheckMate 153. Cancer Chemother Pharmacol 2018;81:679-86.