BC Cancer Protocol Summary for the Treatment of Unresectable or Metastatic Melanoma using Alternative Dosing Regimen of Ipilimumab and Nivolumab

Protocol Code	*SMAVALIPNI*
Tumour Group	*Skin and Melanoma*
Contact Physician	*Dr. Kerry Savage*

ELIGIBILITY:

Patients must have:
- Unresectable stage III or stage IV melanoma,
- Not deemed suitable for SMAVIPNI by the treating medical oncologist, and
- No prior systemic therapy for advanced disease, except:
  - Prior treatment with BRAF and/or MEK inhibitors for BRAF mutant metastatic melanoma
  - Prior treatment with tebentafusp for HLA-A*02:01-positive unresectable or metastatic uveal melanoma

Patients should have:
- Adequate hepatic and renal function
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of immunotherapy checkpoint inhibitors

Notes:
- Patients who received prior adjuvant immunotherapy are eligible if there was a disease-free interval of 6 months or greater
- Patients may not switch from nivolumab to pembrolizumab in the maintenance phase

EXCLUSIONS:

Patients must not have:
- Progression on anti-PD-1 monotherapy for advanced disease or within 6 months of completing adjuvant anti-PD1 therapy
- Prior treatment with combination immunotherapy for advanced disease
- Retreatment with ipilimumab and nivolumab (SMAVIPNI or SMAVALIPNI) upon disease relapse
- Active central nervous system metastases (unless asymptomatic and/or stable)

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, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, glucose, TSH, creatine kinase (CK), morning serum cortisol, chest x-ray (if no baseline chest CT)
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBcoreAb
- Note: tuberculin skin test recommended
- Before each treatment: CBC & Diff, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatine kinase (CK), glucose
- 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 induction phase with ipilimumab and nivolumab. Optional when patients are on nivolumab

PREMEDICATIONS:

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

TREATMENT:

Induction Phase

Drug	Dose	BC Cancer Administration Guideline
nivolumab	3 mg/kg	IV in 50 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter*
ipilimumab	1 mg/kg	IV in 25 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter*

*Use a separate infusion line and filter for each drug

- Repeat **every 3 weeks** for 4 cycles

Maintenance Phase

Drug	2-Weekly 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

- Start 3 weeks after last induction phase dose and 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)

OR

Drug	4-Weekly 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

- Start 6 weeks after last induction phase dose and repeat **every 4 weeks** until disease progression or unacceptable toxicity
- If pseudo progression on imaging is suspected, may continue treatment for another 8 weeks. Discontinue treatment if confirmatory progression on subsequent scan (8-12 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:

1. **Serious immune-mediated reactions**: can be severe to fatal and usually occur during the treatment course, but may develop months after discontinuation of therapy. They may include enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathy, pneumonitis, 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).
2. **Infusion-related reactions:** isolated cases of severe reaction have been reported.

In case of a severe reaction, ipilimumab and/or nivolumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab and/or nivolumab with close monitoring. Premedications with acetaminophen and anti-histamine may be considered.

Call Dr. Kerry Savage or tumour group delegate at 604-877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

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4. Momtaz P, Park V, Panageas KS, et al. Safety of infusing ipilimumab over 30 minutes. J Clin Oncol (ePub 29 June 2015).
5. Bristol-Myers Squibb: OPDIVO (nivolumab) product monograph. Montreal, Quebec: 15 November 2018.
6. Bristol-Myers Squibb: OPDIVO prescribing information. Princeton, NJ: November 2016.
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9. 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.
10. Lebbé C, Meyer N, Mortier L, et al. Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial. J Clin Oncol. 2019 Apr 10;37(11):867-875.
11. Lebbé C, Meyer N, Mortier L, et al. Two dosing regimens of nivolumab (NIVO) plus ipilimumab (IPI) for advanced (adv) melanoma: Three-year results of CheckMate 511. J Clin Oncol. 2021 May 20;39 (15 suppl): 9516-9516.