BC Cancer Protocol Summary for the Treatment of Unresectable or Metastatic Melanoma using Nivolumab-relatlimab

Protocol Code	*USMAVNIVRE*
Tumour Group	*Skin and Melanoma*
Contact Physician	*Dr. Alison Weppler*

ELIGIBILITY:

Patients must have:

- Unresectable stage III or stage IV melanoma,
- No prior systemic therapy for advanced disease with the exception of BRAF and/or MEK inhibitors for BRAF mutant metastatic melanoma, and
- BC Cancer "Compassionate Access Program" request approval prior to treatment

Patients should have:

- Good performance status,
- 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 neoadjuvant or adjuvant immunotherapy are eligible if there was a disease-free interval of 6 months or greater
- In the advanced setting, patients are eligible to receive pembrolizumab, nivolumab, nivolumab-relatlimab, or combination ipilimumab with nivolumab, but not sequential use of these agents. Switching for intolerance is permitted.

EXCLUSIONS:

Patients must not have:

- Progression on anti-PD-1 therapy for advanced disease or be within 6 months of completing neoadjuvant or adjuvant anti-PD1 therapy,
- Active central nervous system metastases (unless asymptomatic and/or stable),
- Uveal 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, random glucose, TSH, creatine kinase, troponin, morning serum cortisol, chest x-ray (if no baseline chest CT)
- Baseline, if clinically indicated: BNP, ECG, echocardiogram
- 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, HBsAb, HBcoreAb
- Before each treatment: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatine kinase, random glucose, morning serum cortisol
- If clinically indicated: chest x-ray, 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 prior infusion reactions to nivolumab-relatlimab: diphenhydrAMINE 50 mg PO and acetaminophen 325 to 975 mg PO 30 minutes prior to treatment. If necessary, hydrocortisone 25 mg IV 30 minutes prior to treatment can be added

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
nivolumab-relatlimab	480 mg-160 mg	IV in 100 mL* NS over 30 minutes using a 0.2 micron in-line filter

* For adult patients with body weight less than 40 kg, use 50 mL NS

- Repeat **every 4 weeks** until clinical 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)
- If intolerant of nivolumab-relatlimab combination, patients may switch to nivolumab monotherapy per provider discretion (see SMAVNIV, SMAVNIV4)

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 myocarditis, enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathies (i.e. Type 1 diabetes mellitus/diabetic ketoacidosis, hypophysitis/adrenal insufficiency), 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).
2. **Infusion-related reactions:** infusion-related reactions can range from mild to isolated cases of severe reactions. Symptoms may include chills, shaking, itching, rash, flushing, dyspnea, dizziness, and fever. Refer to BC Cancer SCDRUGRX. In the case of a severe reaction, nivolumab-relatlimab infusion should be discontinued. In the case of a moderate reaction, after treatment interruption and management, infusion should be restarted when symptoms resolved, at 50% of the original infusion rate. Patients may receive subsequent nivolumab-relatlimab with close monitoring and premedication with acetaminophen and antihistamine. Additional premedication with steroids may be considered. Consider capping infusion rate at 50% for subsequent treatments.

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. Tawbi HA, Schadendorf D, Lipson EJ, et al.; RELATIVITY-047 Investigators. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med. 2022 Jan 6;386(1):24-34.
2. Nivolumab and Relatlimab (Opdualag) CADTH [Canada's Drug Agency (CDA-AMC)] Reimbursement Recommendation. Canadian Journal of Health Technologies Feb 2024; 4(2): 1-31.
3. CADTH [Canada's Drug Agency (CDA-AMC)] Reimbursement Review. Provisional Funding Algorithm. Cutaneous melanoma Aug 2024.