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

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

ELIGIBILITY:

Patients must have:

- Unresectable stage III or stage IV melanoma
- At least one prior systemic therapy (Note: this may include pembrolizumab, nivolumab, or nivolumab-relatlimab)

Patients should have:

- Adequate hepatic and renal function,
- Life expectancy of at least 4 months, and
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of ipilimumab.

EXCLUSIONS:

Patients must not have:

- 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, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, serum morning cortisol, creatine kinase
- Baseline if clinically indicated: BNP, troponin, ECG, echocardiogram
- Before each treatment: CBC & Diff, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatine kinase
- If clinically indicated: morning serum cortisol, lipase, glucose, 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 but recommended).

PREMEDICATIONS:

- Antiemetics are not usually required.
- Antiemetic protocol for low emetogenicity (see SCNAUSEA).
- If prior infusion reactions to ipilimumab: 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
ipilimumab	3 mg/kg IV every 3 weeks	IV in 50 to 250 mL NS over 30 minutes using a 0.2 micron in-line filter

- Repeat every 3 weeks for 4 cycles
- If stable disease (more than 3 months) or complete / partial response, consider repeating treatment course (re-induction) at disease progression

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

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. Jeffrey S, et al. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30:2691-7.
2. Bristol-Myers Squibb: YERVOY (ipilimumab): Serious and fatal immune-mediated adverse reactions - YERVOY Risk Evaluation and Mitigation Strategy (REMS). http://www.yervoy.com/hcp/rems.aspx (Accessed in October, 2012)
3. Pan-Canadian Oncology Drug Review. Expert Review Committee final recommendation for ipilimumab (Yervoy) for advanced melanoma. 18 April 2012.
4. Pan-Canadian Oncology Drug Review. Final clinical guidance report for ipilimumab (Yervoy) for advanced melanoma. 18 April 2012
5. Bristol-Myers Squibb: YERVOY (ipilimumab) product monograph. Montreal, Quebec: 4 Dec 2018.
6. Robert C, et al. Ipilimumab plus darcarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517-26.
7. Sosman JA. Ipilimumab (anti-CTLA-4) immunotherapy in advanced melanoma. UpToDate. (Accessed on December 13, 2011)
8. Iddawela M, et al. Ipilimumab-induced thrombocytopenia in patient with metastatic melanoma. J Oncol Pharm Pract 2011;18(2):287-92.
9. Bristol-Myers Squibb Clinical Protocol CA184045(05a), A Multicenter Treatment Protocol for Expanded Access Use of Ipilimumab (BMS-734016) Monotherapy in Subjects with Unresectable Stage III or Stage IV Melanoma. June 20, 2011
10. Hodi FS, et al. Improved survival with Ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.
11. Akhtari M, et al. Neutropenia in a patient treated with ipilimumab (anti-CTLA-4 antibody). J Immunother 2009;32(3):322-4.
12. Bristol-Myers Squibb Pharma: YERVOY (ipilimumab) summary of product characteristics. Uxbridge, United Kingdom: 2 July 2012.
13. Danielli R, Ridolfi R, Chiarion-Sileni V, et al. Ipilimumab in pretreated patients with metastatic uveal melanoma: safety and clinical efficacy. Cancer Immunol Immunother 2012;61:41–8.
14. Maio1 M, Chairion Sileni V, Pilla L, et al. Efficacy and safety of ipilimumab in patients with pretreated, ocular melanoma: experience from Italian clinics participating in the European Expanded Access Programme (EAP). ESMO 2012 abstract 2844.
15. Khattak MA, Fisher R, Hughes P, et al. Ipilimumab activity in advanced uveal melanoma. Melanoma Res 2013;23:79–81.
16. Rubin, K. Managing immune-related adverse events to ipilimumab: a nurse's guide. Clin J Oncol Nurs 2012; 16(2):E69-E75.
17. Momtaz P, Park V, Panageas KS, et al. Safety of infusing ipilimumab over 30 minutes. J Clin Oncol (ePub 29 June 2015).
18. Weber JS, et al. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 2016;21:1-11.