BC Cancer Protocol Summary for the Treatment of Malignant Mesothelioma using Ipilimumab and 3-Weekly Nivolumab

Protocol Code	*LUMMIPNI3*
Tumour Group	*Lung*
Contact Physician	*Dr. Sophie Sun*

ELIGIBILITY:

Patients must have:
- Previously untreated and unresectable malignant pleural mesothelioma

Note:
- Patients who were started on first-line platinum doublet therapy prior to 1 May 2022 and are still receiving platinum doublet may switch to LUMMIPNI3 if they have not experienced progression and meet other eligibility criteria
- CAP approval is not required to switch between LUMMIPNI3 and LUMMIPNI

Patients should have:
- Good performance status (ECOG 0-2),
- Adequate hepatic and renal function,
- Asymptomatic/stable brain metastases (if applicable), and
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of checkpoint inhibitors

CAUTION:

- Active, known or suspected autoimmune disease
- 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, glucose, TSH, morning serum cortisol, chest x-ray
- 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
- Baseline (optional): C-reactive protein and albumin (results do not have to be available to proceed with first treatment)
- Note: tuberculin skin test strongly recommended

- Before each treatment: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatine kinase, 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 treatment (optional).

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:

Drug	Dose	BC Cancer Administration Guideline
nivolumab	4.5 mg/kg on Days 1 and 22 (maximum 360 mg)	IV in 50 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter*
ipilimumab	1 mg/kg on Day 1	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 6 weeks** until disease progression, unacceptable toxicity, or a maximum of 17 cycles or 2 years of treatment.

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**: 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).
- **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. Sophie Sun or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Bristol-Myers Squibb: OPDIVO (nivolumab) product monograph. Montreal, Quebec: 2 June 2022.
2. Bristol-Myers Squibb: YERVOY (ipilimumab) product monograph. Montreal, Quebec: 3 March 2022**.**
3. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicenter, randomized, open-label, phase 3 trial. Lancet 2021; 397:375-86.
4. Momtaz P, Park V, Panageas KS, et al. Safety of infusing ipilimumab over 30 minutes. J Clin Oncol 2015; 33(30): 3454-3458
5. 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.
6. Weber JS, et al. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 2016; 21(30):1-11.
7. CADTH Canadian Drug Expert Committee. Reimbursement Recommendation: Nivolumab in combination with ipilimumab (Opdivo-Yervoy); Indication: Treatment of adult patients with unresectable malignant pleural mesothelioma who have not received prior systemic therapy for malignant pleural mesothelioma. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; August 2021.