

BC Cancer Protocol Summary for Maintenance Therapy of Advanced Non-Squamous Non-Small Cell Lung Cancer with Pemetrexed and Pembrolizumab

Protocol Code LUAVPPMBM

Tumour Group Lung

Contact Physician Dr. Sophie Sun

ELIGIBILITY:

- Advanced non-small cell lung cancer
- Restricted to disease of non-squamous cell histology without sensitizing EGFR, ROS1 or ALK mutations
- No disease progression after 4 cycles of LUAVPPMBM
- Maintenance treatment to be started 21 to 42 days after final cycle of LUAVPPMBM
- ECOG 0-2 at the start of maintenance
- Adequate hepatic and renal function
- Asymptomatic/stable brain metastases (if applicable)
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of pembrolizumab
- NOTE:
 - Use of first-line/maintenance pembrolizumab precludes the use of nivolumab and atezolizumab as any subsequent line of therapy in the same patient

EXCLUSIONS:

- ECOG performance status > 2
- Active, known or suspected autoimmune disease
- 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
- Weekly: CBC & differential, platelets during cycles 1 and 2; may be omitted in subsequent cycles
- If clinically indicated: chest x-ray, morning serum cortisol, lipase, glucose, serum or urine HCG (required for women 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:

- **Vitamin supplementation mandatory** starting at least 7 days prior to the first cycle, and to continue while on treatment, until 21 days after last pemetrexed dose:
 - folic acid 0.4 mg PO daily
 - vitamin B12 1000 mcg IM every 9 weeks
- **Prophylaxis for skin rash:** dexamethasone 4 mg PO BID for 3 days beginning the day before pemetrexed. (May proceed with treatment even if patient has not taken the pre-treatment dexamethasone doses. Instruct patient to begin immediately)
- Antiemetic protocol for low emetogenic chemotherapy (see SCNAUSEA)
- **If prior infusion reactions to pembrolizumab:** 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
pembrolizumab	2 mg/kg (maximum 200 mg)	IV in 50 mL NS over 30 minutes Using a 0.2 micron in-line filter Keep final concentration to 1 to 10 mg/mL
pemetrexed	500 mg/m ²	IV in 100 mL NS over 10 minutes

- **Repeat every 3 weeks until disease progression, unacceptable toxicity or a maximum of 2 years of treatment (including doses given as LUAVPPMB)**
- **If intolerant to maintenance pemetrexed, may continue maintenance therapy with single-agent pembrolizumab. See LUAVPMBM or LUAVPMBM6.**

DOSE MODIFICATIONS:

No specific dose modifications for pembrolizumab. 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).

For pemetrexed:

1. HEMATOLOGY

Based on day 1 counts:

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Pemetrexed Dose
greater than or equal to 1.5	and	greater than or equal to 100	100%
less than 1.5	or	less than 100	Delay

Based on nadir counts:

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Pemetrexed Dose
greater than or equal to 0.5	and	greater than or equal to 50	100%
less than 0.5	and	greater than or equal to 50	75%
any	and	less than 50	50%

2. RENAL DYSFUNCTION

Calculated Cr Clearance (mL/min)	Pemetrexed Dose
greater than or equal to 45	100%
less than 45	Delay

3. MUCOSITIS

For next cycle:

Mucositis Grade	Pemetrexed dose
0-2	100%
3-4	50% previous dose*
*Discontinue treatment after two dose reductions	

4. OTHER TOXICITIES:

- For any other grade 3 or higher toxicity, delay treatment until toxicity resolves, then resume with 25% dose decrease if considered appropriate to resume by attending oncologist

PRECAUTIONS:

1. **Serious immune-mediated reactions:** can be severe to fatal and usually occur during the treatment course with pembrolizumab, 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 infusion reactions have been reported with pembrolizumab. Discontinue pembrolizumab with severe reactions (Grade 3 or 4). Patients with mild or moderate infusion reactions may receive pembrolizumab with close monitoring and use of premedication.
3. **Vitamin supplements:** appropriate prescription of folic acid and vitamin B12 is essential. The incidence of adverse events such as febrile neutropenia related to pemetrexed is higher without vitamin supplementation.
4. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **NSAIDs:** Concurrent nonsteroidal anti-inflammatory agents should be avoided as they may decrease the renal clearance of pemetrexed.

Contact 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. Langer CJ, Gadgeel SM, Borghaei H, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. *Lancet Oncol.* 2016;17(11):1497-1508.
2. Merck Canada: KEYTRUDA (pembrolizumab) product monograph. Kirkland, Quebec: 20 July 2017.
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4. Borghaei H, Langer CJ, Gadgeel S, et al. 24-month overall survival from KEYNOTE-021 Cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced non-small cell lung cancer. *J Thorac Oncol.* 2019;14(1):124-129.
5. Gandhi L, Rodrigues-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small cell lung cancer. *N Engl J Med.* 2018;378(22):2078-2092.
6. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 2009;374:1432-40.