

BC Cancer Protocol Summary for First-Line Treatment of Advanced Non-Squamous Non-Small Cell Lung Cancer with Platinum, Pemetrexed and Pembrolizumab

Protocol Code

ULUAVPPMB

Tumour Group

Lung

Contact Physician

Dr. Sophie Sun

ELIGIBILITY:

- Previously untreated advanced non-small cell lung cancer
- Restricted to disease of non-squamous cell histology without sensitizing EGFR, ROS or ALK mutations
- ECOG 0-2
- 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
- *BC Cancer Compassionate Access Program (CAP) approval must be obtained*
- Patients on active treatment responding to LUAVPP (< 4 cycles) may be eligible to switch to ULUAVPPMB. *CAP approval must be obtained.*
- NOTE:
 - Patients on active treatment with maintenance pemetrexed or single-agent pembrolizumab are not eligible to switch to ULUAVPPMB
 - Use of first-line pembrolizumab precludes the use of nivolumab and atezolizumab as any subsequent line of therapy in the same patient

EXCLUSIONS:

- Patients who have relapsed on or within *6 months* of completing adjuvant durvalumab
- Patients who have relapsed within *12 months* of completing adjuvant platinum chemotherapy
- 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
 - C-reactive protein and albumin (optional, and results do not have to be available to proceed with first treatment)

- **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 highly 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* |
| CISplatin | 75 mg/m ² | IV in 500 mL NS over 1 hour† |

* Pemetrexed may be given anytime during the pre-hydration period⁶

† Pre- and post-hydration protocol for high-dose CISplatin required according to institutional guidelines (eg, prehydration with 1 L NS over 1 hour, CISplatin in 500 mL NS with potassium chloride 20 mEq, magnesium sulfate 1 g and mannitol 30 g)

- **Repeat every 3 weeks x 4 cycles**
- **Maintenance treatment to begin 21 to 42 days after last cycle; see LUAVPPMBM**

DOSE MODIFICATIONS:

1. HEMATOLOGY

Based on day 1 counts:

| ANC (x 10 ⁹ /L) | | Platelets (x 10 ⁹ /L) | 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 (for pemetrexed only):

| 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) | CISplatin Dose | Pemetrexed Dose |
|----------------------------------|---|--|
| greater than or equal to 60 | 100% | 100% |
| 45 to less than 60 | 80% CISplatin or use CARBOplatin option | 100% |
| less than 45 | Hold | Hold regardless of type of platinum |

3. MUCOSITIS

For next cycle:

| Mucositis Grade | CISplatin dose | Pemetrexed dose |
|---|----------------|--------------------|
| 0-2 | 100% | 100% |
| 3-4 | 100% | 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
- 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).

Alternatively, CARBOplatin may be used instead of CISplatin:

| 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 |
| CARBOplatin | Dose = AUC 5 x (GFR ⁺⁺ +25) | IV in 250 mL NS over 30 minutes |

⁺⁺ GFR may be determined by nuclear renogram or estimated by the Cockcroft formula, at the discretion of the attending physician:

$$\text{GFR} = \frac{N \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{Serum creatinine (micromol/L)}} \quad N = 1.04 \text{ (women) or } 1.23 \text{ (men)}$$

The estimated GFR should be capped at 125 mL/min when it is used to calculate the initial CARBOplatin dose. When a nuclear renogram is available, this clearance would take precedence.

- **Repeat every 3 weeks x 4 cycles**
- **Maintenance treatment to begin 21 to 42 days after last cycle; see LUAVPPMBM**

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.
6. **Renal Toxicity:** nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Use caution with pre-existing renal dysfunction.
7. **Neurotoxicity:** CISplatin is neurotoxic and may have to be discontinued if functionally important neuropathy develops. Particular caution must be used in individuals with existing neuropathy.
8. **Ototoxicity:** CISplatin is ototoxic and its use must be cautioned in individuals with existing hearing loss.

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.
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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.
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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.