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

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

ELIGIBILITY:

- Previously untreated advanced non-small cell lung cancer and use of ULUAVPCPMB is not recommended
- Restricted to disease of *squamous* cell histology
- 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 platinum doublet chemotherapy (< 4 cycles) may be eligible to switch to ULUAVPGPMB. *CAP approval must be obtained.*
- NOTE:
    - Patients on active treatment with single-agent pembrolizumab are not eligible to switch to ULUAVPGPMB
    - 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, camera nuclear renogram for GFR (if available)
    - C-reactive protein and albumin (optional, and results do not have to be available to proceed with first treatment)

- Before each treatment:
    - Day 1 – CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH
    - Day 8 – CBC & differential, platelets, creatinine
- 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:

- Antiemetic protocol for high 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 on day 1 (maximum 200 mg)	IV in 50 mL NS over 30 minutes Using a 0.2 micron in-line filter
gemcitabine	1250 mg/m^2/day on days 1 and 8 (total dose per cycle = 2500 mg/m^2)	IV in 250 mL NS over 30 minutes
CISplatin	75 mg/m^2/day on day 1	IV in 500 mL NS over 1 hour*

* 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 LUAVPMBM or LUAVPMBM6**

DOSE MODIFICATIONS:

1. HEMATOLOGY

For gemcitabine day 1 of each cycle

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
greater than or equal to 1.0	and	greater than or equal to 100	100%
0.5 to less than 1.0	or	75 to less than 100	75%
less than 0.5	or	less than 75	**Delay***
**** Platinum also delayed***			

For gemcitabine day 8 of each cycle

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose**
greater than or equal to 1.0	and	greater than or equal to 100	100%
0.5 to less than 1.0	or	75 to less than 100	75%
less than 0.5	or	less than 75	**Omit**
****Dose adjustment only for the day of treatment the CBC is drawn**			

2. RENAL DYSFUNCTION

Calculated Cr Clearance (mL/min)	CISplatin dose	Gemcitabine dose
greater than or equal to 60	100%	100%
45 to less than 60	80% CISplatin or go to CARBOplatin option (same prehydration as 75 mg/m^2 dose)	100%
less than 45	Hold CISplatin or delay with additional IV fluids or go to CARBOplatin option	75%
less than 30	Omit	Omit

3. **OTHER TOXICITIES**:

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 gemcitabine only:

Grade	Stomatitis	Diarrhea	Dose
1	Painless ulcers, erythema or mild soreness	Increase of 2 to 3 stools/day	100%
2	Painful erythema, edema, or ulcers but can eat	Increase of 4 to 6 stools, or nocturnal stools	Omit until toxicity resolved then resume at 100%
3	Painful erythema, edema, or ulcers and cannot eat	Increase of 7 to 9 stools/day or incontinence, malabsorption	Omit until toxicity resolved then resume at 75%
4	Mucosal necrosis, requires parenteral support	Increase of greater than or equal to 10 stools/day or grossly bloody diarrhea requiring parenteral support	Omit until toxicity resolved then resume at 50%

Alternatively, CARBOplatin may be used instead of CISplatin:

Drug	Dose	BC Cancer Administration Guideline
pembrolizumab	2 mg/kg on day 1 (maximum 200 mg)	IV in 50 mL NS over 30 minutes Using a 0.2 micron in-line filter
When CARBOplatin is used, gemcitabine dose should be reduced to 1000 mg/m^2:		
gemcitabine	1000 mg/m^2/day on days 1 and 8 (total dose per cycle = 2000 mg/m^2)	IV in 250 mL NS over 30 minutes
CARBOplatin	AUC 5 or 6 on day 1 Dose = AUC x (GFR* + 25)	IV in 100 to 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:

$$\text{GFR} = \frac{N \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

N = 1.04 (women) or 1.23 (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 LUAVPMBM or LUAVPMBM6**

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. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Renal Toxicity**: nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Use caution with pre-existing renal dysfunction.
5. **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.
6. **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. Merck Canada: KEYTRUDA (pembrolizumab) product monograph. Kirkland, Quebec: 20 July 2017.
2. Postow M, Wolchok J. Toxicities Associated With Checkpoint Inhibitor Immunotherapy. UpToDate revised 2015. Accessed: www.uptodate.com, May 2016.
3. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small cell lung cancer. N Engl J Med. 2016;375(19):1823-1833.
4. Paz-Ares L, Luft A, Vincente D, et al. Pembrolizumab plus chemotherapy for squamous non-small cell lung cancer. N Engl J Med. 2018;379(21):2040-51.
5. 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.