BC Cancer Protocol Summary for First-Line Treatment of Advanced Squamous Cell Carcinoma of the Head and Neck with PACLitaxel, CARBOplatin and Pembrolizumab

Protocol Code	*HNAVPCPMB*
Tumour Group	*Head and Neck*
Contact Physician	*Dr. Cheryl Ho*

ELIGIBILITY:

Patients must have:

- Previously untreated recurrent or metastatic squamous cell carcinoma of the head and neck including primary unknown not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy)
    - Prior neoadjuvant, radiosensitizing or adjuvant systemic therapy in the curative setting permitted if completed greater than 6 months prior

Note: Patients on active treatment responding to first-line platinum-based chemotherapy (less than 4 cycles) may be eligible to switch to HNAVPCPMB. *CAP approval must be obtained.*

Patient should have:

- ECOG 0-2
- Adequate hematologic, hepatic and renal function
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of pembrolizumab

EXCLUSIONS:

- Nasopharyngeal carcinoma, or non-squamous histologies
- Recurrent disease within 6 months of curative neoadjuvant or adjuvant platinum-based therapy
- Symptomatic central nervous system metastases
- Cautions with concurrent autoimmune disease, known active hepatitis B, C or HIV
- 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 & Diff, creatinine, ALT, total bilirubin, alkaline phosphatase, LDH, GGT, albumin, sodium, potassium, TSH, morning serum cortisol, chest x-ray
- Before each treatment: CBC & Diff, creatinine, ALT, total bilirubin, alkaline phosphatase, LDH, sodium, potassium, TSH
- If clinically indicated: morning serum cortisol, chest x-ray, 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:

PACLitaxel must not be started unless the following drugs have been given:

- **If no prior infusion reactions to pembrolizumab:** administer premedications as sequenced below
  45 minutes prior to PACLitaxel:
  - dexamethasone 20 mg IV in 50 mL NS over 15 minutes

  30 minutes prior to PACLitaxel:
  - diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

- **If prior infusion reactions to pembrolizumab**: administer PACLitaxel premedications prior to pembrolizumab
  45 minutes prior to pembrolizumab:
  - dexamethasone 20 mg IV in 50 mL NS over 15 minutes

  30 minutes prior to pembrolizumab:
  - diphenhydrAMINE 50 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)
  - acetaminophen 325 to 975 mg PO prior to pembrolizumab

- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA protocol).

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*
PACLitaxel	175 mg/m^2	IV in 250 to 500 mL NS over 3 hours use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter*
CARBOplatin	AUC 5 or 6 Dose = AUC x (GFR** + 25)	IV in 100 to 250 mL NS over 30 minutes

* use separate infusion line and filter for each drug

- **Repeat every 21 days x 4 to 6 cycles**
- **Maintenance pembrolizumab treatment to begin 21 days after last cycle; see HNAVPMBM or HNAVPMBM6**

*GFR preferably from nuclear renogram, if not possible use:

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

Recalculate GFR if creatinine increases by greater than 20% or rises above the upper limit of normal.

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).

1. HEMATOLOGY

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%
less than 1.0	or	less than 100	**Delay until recovery**

2. **Arthralgia and/or myalgia**: If arthralgia and/or myalgia of grade 2 (moderate) or higher is not relieved by adequate doses of NSAIDs or acetaminophen with codeine (e.g., TYLENOL #3®), a limited number of studies report a possible therapeutic benefit using:
   - predniSONE 10 mg PO bid x 5 days starting 24 hours post-PACLitaxel
   - gabapentin 300 mg PO on day before chemotherapy, 300 mg bid on treatment day, then 300 mg tid x 7 to 10 days
   - If arthralgia and/or myalgia persists, reduce subsequent PACLItaxel doses to 150 mg/m^2.
3. **Neuropathy**: Dose modification or discontinuation may be required (see BC Cancer Drug Manual).
4. **Renal dysfunction**: If significant increase (greater than 20%) in creatinine, repeat nuclear renogram (if available) and recalculate CARBOplatin dose using new GFR.
5. **Hepatic dysfunction**: Dose reduction may be required for PACLitaxel (see BC Cancer Drug Manual)

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. **Hypersensitivity**: Reactions are common with PACLitaxel. See BC Cancer Hypersensitivity Guidelines.

mild symptoms (e.g. mild flushing, rash, pruritus)	▪ complete PACLitaxel infusion. Supervise at bedside ▪ no treatment required
moderate symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension	▪ stop PACLitaxel infusion ▪ give IV diphenhydrAMINE 25-50 mg and IV hydrocortisone IV 100 mg ▪ after recovery of symptoms resume PACLitaxel infusion at 20 mL/hr for 5 minutes, 30 mL/hr for 5 minutes, 40 mL/hr for 5 minutes, then 60 mL/hr for 5 minutes. If no reaction, increase to full rate. ▪ if reaction recurs, discontinue PACLitaxel therapy
severe symptoms (i.e. *one* or more of respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy)	▪ stop PACLitaxel infusion ▪ give IV antihistamine and steroid as above. Add epinephhrine or bronchodilators if indicated ▪ discontinue PACLitaxel therapy

4. **Extravasation**: PACLitaxel causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.

5. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.

Contact Dr. Cheryl Ho or tumour group delegate at (604) 877-6000 or 1-800-523-2885 with any problems or questions regarding this treatment program.

REFERENCES:

1. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 2019;394:1915-28.