BC Cancer Protocol Summary for First-Line Treatment of Advanced Squamous Cell Carcinoma of the Head and Neck using Platinum, Fluorouracil and Pembrolizumab

***Protocol Code**:*	*HNAVPFPMB*
***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 HNAVPFPMB. *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 & differential, platelets, creatinine, ALT, bilirubin, alkaline phosphatase, LDH, sodium, potassium, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine), TSH, morning serum cortisol, chest x-ray
- Before each treatment: CBC & differential, platelets, creatinine, ALT, 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:

- With CISplatin: antiemetic protocol for Highly emetogenic chemotherapy (see protocol SCNAUSEA).
- With CARBOplatin: antiemetic protocol for Moderately emetogenic chemotherapy (see SCNAUSEA protocol).
- **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
CISplatin	75 mg/m^2	IV in 500 mL NS with potassium chloride 20 mEq, magnesium sulphate 1 g, Mannitol 30 g over 1 hour*
fluorouracil	1000 mg/m^2/day for 4 days (total dose = 4000 mg/m^2 over 96 h)	IV in D5W to a total volume of 480 mL by continuous infusion at 5 mL/h via appropriate infusor device
*Prehydrate with NS 1000 mL over 1 hour		

Alternatively, CARBOplatin may be used instead of CISplatin:

DRUG	DOSE	BC Cancer Administration Guidelines
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
CARBOplatin	AUC 5 Dose = AUC x (GFR* + 25)	IV in 100 to 250 mL NS over 30 minutes
fluorouracil	1000 mg/m^2/day for 4 days (total dose = 4000 mg/m^2 over 96 h)	IV in D5W to a total volume of 480 mL by continuous infusion at 5 mL/h via appropriate infusor device

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

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

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.

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

DOSE MODIFICATIONS:

Fluorouracil Dosing Based on DPYD Activity Score (DPYD-AS)
Refer to "Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)" on www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.

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-protocolssite/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 100	100%
less than 1.0	or	less than 100	**Delay**

2. **Renal Dysfunction**: for CISplatin

Calculated Cr Clearance (mL/min)	CISplatin dose
greater than or equal to 60	100%
45 to less than 60	80% CISplatin
less than 45	Hold CISplatin or delay with additional IV fluids or go to CARBOplatin option (see above).

4. Neurotoxicity:

- Tinnitus, mild high frequency hearing loss, and delayed peripheral neuropathy may occur secondary to CISplatin. The latter are generally reversible with time. If clinically significant hearing loss or functionally significant peripheral neuropathy occurs, discontinue CISplatin only.
- CNS toxicity due to fluorouracil is infrequent, but would necessitate cessation of treatment

3. GI Toxicity:

- see next table for toxicity grading criteria for diarrhea, nausea and vomiting, and stomatitis

Toxicity Grade	1st Event fluorouracil dose	2nd Event fluorouracil dose	3rd Event fluorouracil dose	4th Event fluorouracil dose
0-1	100%	100%	100%	100%
2	delay* then 100%	delay* then 75%	delay* then 50%	discontinue
3	delay* then 75%	delay* then 50%	discontinue	discontinue
4	discontinue or delay* then 50%	discontinue	discontinue	discontinue

Grade	Diarrhea	Nausea and Vomiting	Stomatitis
0-1	Increase of 2-3 stools/day or nocturnal stools	1 vomit/day but can eat	Painless ulcers, erythema or mild soreness
2	Increase of 4-6 stools/day or nocturnal stools	2-5 vomits/day; intake decreased but can eat	Painful erythema, edema or ulcers but can eat
3	Increase of 7-9 stools/day or incontinence, malabsorption	6-10 vomits/day and cannot eat	Painful erythema, edema or ulcers and cannot eat
4	Increase of 10 or more stools/day or grossly bloody diarrhea; may require parenteral support; dehydration	10 vomits or more per day or requires parenteral support; dehydration	Mucosal necrosis, requires parenteral support

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-protocolssite/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. **Diarrhea**: Patients should report mild diarrhea that persists over 24 hours or moderate diarrhea (4 stools or more per day above normal, or a moderate increase in ostomy output). Mild diarrhea can be treated with loperamide (eg. IMODIUM®) following the manufacturer's directions or per the BC Cancer Guidelines for Management of Chemotherapy-Induced Diarrhea. Note that diarrhea may result in increased INR and the risk of bleeding in patients on warfarin
5. **Dihydropyrimidine dehydrogenase (DPD) deficiency** may result in severe and unexpected toxicity – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population.
6. **Renal toxicity** may occur with a salt and water losing nephropathy. Patients should be encouraged to maintain good oral hydration.
7. **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil or capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.
8. **Possible drug interactions with fluorouracil and warfarin, phenytoin and fosphenytoin** have been reported and may occur at any time. Close monitoring is recommended (eg, for warfarin, monitor INR weekly during fluorouracil therapy and for 1 month after stopping fluorouracil).

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.