BC Cancer Protocol Summary for Palliative Therapy for Unresectable, Platinum-refractory, Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck Using Nivolumab

Protocol Code: UHNAVNIV
Tumour Group: Head and Neck
Contact Physician: Dr. Cheryl Ho

ELIGIBILITY:
- Histologically confirmed recurrent or metastatic SCCHN (oral cavity, oropharynx, pharynx, larynx, primary unknown), stage III/IV and not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy)
- Patients have received at least 1 prior line of platinum chemotherapy in the neoadjuvant, adjuvant, concurrent, or metastatic setting
- ECOG 0-2
- Adequate hepatic and renal function
- Patients may be PDL1 positive or negative
- Patients may be p16 positive or negative
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of nivolumab
- A BC Cancer “Compassionate Access Program” request with appropriate clinical information for each patient must be approved prior to treatment

EXCLUSIONS:
- Recurrent or metastatic cancers of the salivary gland, nasopharyngeal carcinoma, or non-squamous histologies
- Active central nervous system metastases (should be asymptomatic and/or stable)
- Active autoimmune disease, active hepatitis B, C or HIV (HCV antibody or negative HCV RNA permitted)
- 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, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, random glucose, TSH
- Before each treatment: CBC/differential, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, glucose
- If clinically indicated: chest x-ray, free T3 and free T4, morning serum cortisol, lipase, serum ACTH levels, FSH, LH, testosterone, estradiol
- Weekly telephone assessment for signs and symptoms of side effects while on treatment (optional but recommended).
PREMEDICATIONS:

- Antiemetic protocol for low emetogenic chemotherapy protocols (see SCNAUSEA). Antiemetics are not usually required.

TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
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<tbody>
<tr>
<td>nivolumab</td>
<td>3 mg/kg (maximum 240 mg)</td>
<td>IV in 100* mL NS over 30 minutes using a 0.2 or 0.22 micron in-line filter</td>
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*keep final concentration to 1 to 10 mg/mL

Repeat every 2 weeks until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS:

No specific dose modifications. Toxicity managed by treatment delay and other measures (see Appendix for Immune-mediated Adverse Reaction Management Guide).

PRECAUTIONS:

- **Serious immune-mediated reactions**: these can be severe to fatal and usually occur during the treatment course. They may include enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathy, as well as toxicities in other organ systems. Early diagnosis and appropriate management are essential to minimize life-threatening complications (see Appendix for Immune-mediated Adverse Reaction Management Guide).

- **Infusion-related reactions**: isolated cases of severe reaction have been reported. In case of a severe reaction (Grade 3 or 4), nivolumab infusion should be permanently discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab with close monitoring. Premedications with acetaminophen and antihistamine may be considered if there is a history of reaction.

Call Dr. Cheryl Ho or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

2. Gillison ML, Blumenschein G, Fayette J, et al. Phase III, open-label, randomized study of Nivolumab (nivo) vs investigator’s choice (IC) for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): CheckMate-141. ASCO Meeting Abstracts 34:6009, May 2016.
**Appendix. Immune-mediated adverse reaction management guide**

**Pneumonitis**

**Grade 1**
Radiographic changes only
- Physician notified of assessment
- Consider withholding nivolumab
- Monitor every 2 to 3 days
- Consider pulmonary and infectious disease consultation

Reassess at least every 3 weeks
- If improved
  - Resume nivolumab (if withheld) when stable
- If worsens
  - Treat as Grade 2 or Grades 3 or 4

**Grade 2**
Mild to moderate symptoms, worsens from baseline
- Physician notified and collaborative symptom management initiated
- **Withhold nivolumab**
- Consider high resolution CT scan
- Monitor daily
- predniSONE 1 to 2 mg/kg/day PO
- Patient education of steroid use
- Pulmonary and infectious disease consultation
- Consider bronchoscopy, lung biopsy
- Book nursing follow up call as needed

Reassess every 1 to 3 days
- If improved to baseline
  - Taper steroid over at least 1 month
    - BEFORE resuming nivolumab
- If persists or worsens after 2 weeks
  - Treat as Grades 3 or 4

**Grade 3 or 4**
Severe symptoms, new or worsening hypoxia, life-threatening
- Hospitalize
- **Discontinue nivolumab**
- Monitor daily
- predniSONE 1 to 2 mg/kg/day PO
- Patient education of steroid use
- Pulmonary and infectious disease consultation
- Consider bronchoscopy, lung biopsy
- Upon discharge, book nursing follow up call as needed

If improved to baseline
- Taper steroid over at least 1 month
- If persists or worsens after 2 days
  - Consider non-steroid immunosuppressive agents

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Enterocolitis

**Grade 1**
Diarrhea of less than 4 stools per day over baseline; asymptomatic colitis

- Physician notified of assessment
- Nursing management per BC Cancer Symptom Management Guidelines: Cancer-Related Diarrhea
- Antidiarrheal treatment
- Book nursing follow up call for next business day and/or create care plan if BC Cancer nurse unable to follow up

**Grade 2**
Diarrhea of 4 to 6 stools per day over baseline, IV fluids less than 24 h, normal daily activities, abdominal pain, mucus or blood in stool,

- Physician notified and collaborative symptom management initiated
- **Withhold nivolumab**
- Antidiarrheal treatment
- If persists beyond 3-5 days or recur, start prednisone 0.5 to 1 mg/kg/day PO
- Patient education of steroid use
- Nursing management per BC Cancer Symptom Management Guidelines: Cancer-Related Diarrhea
- Book nursing follow up call as needed

**Grade 3 or 4**
Grade 3: diarrhea of 7 or more stools per day over baseline, incontinence, IV fluids for 24 h or more, impaired daily activities; colitis with severe abdominal pain, requiring medical interventions, peritoneal signs of bowel perforation
Grade 4: life-threatening colitis, perforation

- **Physician notified and collaborative symptom management initiated**
- **Withhold (if Grade 3) or discontinue (if Grade 4 or persistent Grade 3) nivolumab**
- Gastroenterology consultation
- Rule out bowel perforation; if bowel perforation is present, DO NOT administer corticosteroids
- Consider endoscopic evaluation
- prednisone 1 to 2 mg/kg/day PO
- Patient education of steroid use
- Nursing management per BC Cancer Symptom Management Guidelines: Cancer-Related Diarrhea
- Book nursing follow up call as needed

**Improvement to Grade 1 or less**
- Resume nivolumab
- If steroid used, taper over at least 1 month BEFORE resuming nivolumab
- Patient education of steroid tapering per physician order

**Improvement to Grade 1 or less**
- Taper prednisone over at least 1 month before resuming nivolumab
- Patient education of steroid tapering per physician order

If no response within 5 days or recur
- Consider treatment with infliximab; if refractory to infliximab, consider mycophenolate
- Continually evaluate for evidence of gastrointestinal perforation or peritonitis
- Consider repeat endoscopy

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**Liver**

**Monitoring**
Abnormal liver function test, jaundice, tiredness

**Grade 2**
AST or ALT 3 to less than 5 X ULN
or
Total bilirubin 1.5 to 3 X ULN

- Physician notified and collaborative symptom management initiated
- Withhold nivolumab
- Rule out infectious or malignant causes or obstruction
- Increase LFTs monitoring to every 3 days until resolution
- predniSONE 1 to 2 mg/kg/day PO
- Patient education on steroid use
- Book future nursing follow up call as needed

**If AST/ALT 3 × ULN or lower and bilirubin 1.5 × ULN or lower, or return to baseline**
- Resume nivolumab
- If steroid used, taper over at least 1 month BEFORE resuming nivolumab
- Patient education of steroid tapering per physician order

**Grades 3 or 4**
AST or ALT more than 5 X ULN
or
Total bilirubin more than 3 X ULN
or
AST or ALT increases ≥50% baseline and lasts ≥1 week in patients with liver metastasis who begin treatment with Grade 2 elevation of AST or ALT

- Physician notified and collaborative symptom management initiated
- Discontinue nivolumab
- Rule out infectious or malignant causes or obstruction
- Increase LFTs monitoring to every 1 to 2 days until resolution
- Gastroenterology consultation
- predniSONE 1 to 2 mg/kg/day PO
- Patient education on steroid use
- Book future nursing follow up call as needed

**If LFTs return to Grade 2 or less**
- Taper predniSONE over at least 1 month

**For persistent Grades 3 or 4 for more than 3 to 5 days, worsens, or recurs:**
- Consider non-steroid immunosuppressive agents (e.g., mycophenolate)
Renal

Monitoring
Increase in serum creatinine, decreased urine output, hematuria, edema

Grade 1
Creatinine >1 - 1.5 x ULN
- Creatinine weekly

When return to baseline
- Resume routine creatinine

Grade 2
Creatinine >1.5 - 3.0 x ULN
- Physician notified and collaborative symptom management initiated
- Withhold nivolumab
- Nephrology consultation
- Creatinine every 2 to 3 days
- predniSONE 0.5 to 1 mg/kg/day PO
- Patient education on steroid use
- Consider renal biopsy
- Book future nursing follow up call as needed

If improved to Grade 1
- Taper steroid over at least 1 month
- BEFORE resuming nivolumab and routine creatinine
If persists for more than 7 days or worsens
- Treat as Grade 4

Grade 3
Creatinine >3.0 - 6.0 x ULN
Grade 4 >6.0 x ULN
- Physician notified and collaborative symptom management initiated
- Discontinue nivolumab
- Nephrology consultation
- Creatinine daily
- predniSONE 1 to 2 mg/kg/day PO
- Patient education on steroid use
- Consider renal biopsy
- Book future nursing follow up call as needed

If improved to Grade 1
- Taper steroid over at least 1 month

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Endocrine

Monitoring
Persistent or unusual headaches, extreme tiredness, weight gain or loss, mood or behaviour changes (e.g., decreased libido, irritability, forgetfulness) dizziness or fainting, hair loss, feeling cold, constipation, voice gets deeper

Symptomatic endocrinopathy

- Physician notified and collaborative symptom management initiated
- Continue nivolumab if hypothyroidism or hyperthyroidism
- Withhold nivolumab if other endocrinopathies with abnormal lab or pituitary scan
- Evaluate endocrine function
- Endocrinology consultation
- Consider pituitary scan
- Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan
- Appropriate hormone replacement if symptomatic with abnormal lab or pituitary scan

If improved with or without hormone replacement:
- Resume nivolumab

Continue standard monitoring
- Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

Suspicion of adrenal crisis

- Physician notified and collaborative symptom management initiated
- Rule out sepsis
- Withhold nivolumab
- Evaluate endocrine function
- Endocrinology consultation
- Consider pituitary scan
- Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan
- Endocrinology consult
- Stress dose of IV steroids with mineralocorticoid activity
- IV fluids

When adrenal crisis ruled out:
- Treat as symptomatic endocrinopathy
Other immune-mediated or treatment-related adverse reactions

If severe or clinically significant:
- Withhold (Grade 3) or permanently discontinue nivolumab (Grade 4)
- prednisone 1 to 2 mg/kg/day PO
- Corticosteroid eye drops for uveitis
- Consider referring to a specialist

1. **Eye**: uveitis
2. **Gastrointestinal**: pancreatitis
3. **Musculoskeletal**: myositis
4. **Skin**: severe skin reactions