BC Cancer Protocol Summary for First-Line Treatment of Advanced Squamous Non-Small Cell Lung Cancer with PACLitaxel, CARBOplatin, Ipilimumab and Nivolumab

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

ELIGIBILITY:

Patients must have:

- Advanced non-small cell lung cancer,
- Disease of *squamous* cell histology, and
- No prior treatment in advanced setting

Note:

- Patients on active treatment responding to platinum doublet chemotherapy (< 4 cycles) may be eligible to switch to LUAVPCIPNI. *CAP approval must be obtained.*
- Patients on active treatment with single-agent pembrolizumab are not eligible to switch to LUAVPCIPNI
- Patients who received first-line combination nivolumab and ipilimumab are not eligible for subsequent line of therapy using pembrolizumab, atezolizumab, or single agent nivolumab.

Patients should have:

- ECOG 0-2,
- Adequate hepatic and renal function,
- Asymptomatic/stable brain metastases (if applicable), and
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of checkpoint inhibitors

EXCLUSIONS:

Patients must not have:

- Relapsed on *or* within *6 months* of completing adjuvant durvalumab or atezolizumab, or
- Relapsed within *12 months* of completing adjuvant platinum chemotherapy

CAUTIONS:

- Active, known or suspected autoimmune disease
- 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, glucose, TSH, morning serum cortisol, chest x-ray, camera nuclear renogram for GFR (if available)
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBcoreAb
- Baseline (optional): C-reactive protein and albumin (results do not have to be available to proceed with first treatment)
- Note: tuberculin skin test strongly recommended
- Before each treatment: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatine kinase, glucose
- If clinically indicated: chest x-ray, morning serum cortisol, lipase, 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:

Cycles 1 and 2:

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

- **If no prior infusion reactions to nivolumab or ipilimumab:** 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 nivolumab or ipilimumab**: administer PACLitaxel premedications prior to nivolumab
  45 minutes prior to nivolumab:
  - dexamethasone 20 mg IV in 50 mL NS over 15 minutes

  30 minutes prior to nivolumab:
  - 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 nivolumab
- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)

Subsequent cycles:

- Antiemetics are not usually required.
- **If prior infusion reactions to ipilimumab or nivolumab:** diphenhydrAMINE 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

TREATMENT:

Cycle 1:

Drug	Dose	BC Cancer Administration Guideline
nivolumab	4.5 mg/kg (maximum 360 mg)	IV in 50 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter*
ipilimumab	1 mg/kg	IV in 25 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter*
PACLitaxel	200 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 a separate infusion line and filter for each drug

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

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

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.

Cycle 2: (to be given 3 weeks after Cycle 1)

Drug	Dose	BC Cancer Administration Guideline
nivolumab	4.5 mg/kg (maximum 360 mg)	IV in 50 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter*
PACLitaxel	200 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 a separate infusion line and filter for each drug

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

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

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.

Cycle 3 onwards: (to begin 3 weeks after Cycle 2)

Drug	Dose	BC Cancer Administration Guideline
nivolumab	4.5 mg/kg on Days 1 and 22 (maximum 360 mg)	IV in 50 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter*
ipilimumab	1 mg/kg on Day 1	IV in 25 to 100 mL NS over 30 minutes using a 0.2 micron in-line filter*

* Use a separate infusion line and filter for each drug

Repeat **every 6 weeks** until disease progression, unacceptable toxicity, or a maximum of 2 years of treatment (maximum 17 total doses of ipilimumab and 34 total doses of nivolumab).

DOSE MODIFICATIONS:

1. HEMATOLOGY (Cycles 1 and 2):

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. **Other toxicities**: No specific dose modifications for ipilimumab or nivolumab. 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).

3. **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 175 mg/m^2.
4. **Neuropathy**: Dose modification or discontinuation may be required (see BC Cancer Drug Manual).
5. **Renal dysfunction**: If significant increase (greater than 20%) in creatinine, repeat nuclear renogram (if available) and recalculate CARBOplatin dose using new GFR.
6. **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, 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 reaction have been reported. In case of a severe reaction, ipilimumab and/or nivolumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab and/or nivolumab with close monitoring. Premedications with acetaminophen and anti-histamine may be considered.

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. 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. Bristol-Myers Squibb: OPDIVO (nivolumab) product monograph. Montreal, Quebec: 1 December 2021.
2. Bristol-Myers Squibb: YERVOY (ipilimumab) product monograph. Montreal, Quebec: 26 April 2021.
3. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomized, open-label, phase 3 trial. Lancet Oncol 2021; 22:198-211.
4. Momtaz P, Park V, Panageas KS, et al. Safety of infusing ipilimumab over 30 minutes. J Clin Oncol 2015; 33(30): 3454-3458
5. Waterhouse D, Horn L, Reynolds C, et al. Safety profile of nivolumab administered as 30-min infusion: analysis of data from CheckMate 153. Cancer Chemother Pharmacol 2018; 81: 679-86.
6. Weber JS, et al. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 2016; 21(30):1-11.