BC Cancer Protocol Summary for Neoadjuvant Treatment of Non-Small Cell Lung Cancer with Nivolumab, CARBOplatin and PACLitaxel

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

ELIGIBILITY:

Patients must have:
- Previously untreated resectable non-small cell lung cancer (NSCLC),
- Tumour ≥ 4 cm or node positive, M0,
- Any histology *except* large cell neuroendocrine carcinoma, and

Patients should have:
- Good performance status,
- Adequate hematologic, hepatic and renal function, and
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of checkpoint inhibitors

Notes:
- PD-L1 status not required
- Patients are eligible for subsequent:
  - Adjuvant chemotherapy and/or radiation
  - Checkpoint inhibitors in the advanced setting, provided the last dose of immunotherapy was greater than 6 months prior, and no progression occurred during treatment
- Patients are not eligible for subsequent adjuvant atezolizumab

EXCLUSIONS:

Patients must not have:
- Known EGFR or ALK mutation
- Large cell neuroendocrine carcinoma,
- Unresectable or metastatic disease

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 & Diff, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, random glucose, TSH, morning serum cortisol, chest x-ray
- 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
- Before each treatment: CBC & Diff, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatine kinase, random 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:

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

- **If no prior infusion reactions to nivolumab:** 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**: 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)

TREATMENT:

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 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

Cockcroft formula:

$$\text{GFR} = \frac{\text{N x (140 – age in years) x wt (kg)}}{\text{serum creatinine (micromol/L)}}$$ N = 1.23 male, 1.04 female

** The estimated GFR calculated using the Cockcroft-Gault equation 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** for up to 3 cycles.
- If patients are intolerant of the chemotherapy after at least 1 cycle, nivolumab can be continued as above

DOSE MODIFICATIONS:

1. **Hematological:**

ANC (x 10^9/L)		Platelets (x 10^9/L)	PACLitaxel and CARBOplatin Dose
Greater than or equal to 1.5	and	Greater than or equal to 100	100%
1.0 to less than 1.5	or	75 to less than 100	75%
Less than 1.0	or	Less than 100	**Delay***

2. **Other toxicities**:

- No specific dose modifications for 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. **Hypersensitivity**: Reactions are common to PACLitaxel. See BC Cancer Protocol Summary for Management of Infusion-Related Reactions to Systemic Therapy Agents, SCDRUGRX.

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. **Arthralgia and/or myalgia**: If arthralgia and/or myalgia from PACLitaxel 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 7-10 days
5. **Neuropathy**: Dose modification or discontinuation may be required (see BC Cancer Drug Manual).
6. **Renal dysfunction**: If significant increase (greater than 20%) in creatinine, repeat nuclear renogram (if available) and recalculate CARBOplatin dose using new GFR.
7. **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, nivolumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab with close monitoring. Premedications with acetaminophen and anti-histamine may be considered.
3. **Extravasation**: PACLitaxel causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
4. **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. Forde PM, Spicer J, Lu S, et al; CheckMate 816 Investigators. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med. 2022 May 26;386(21):1973-1985.
2. Nivolumab (Opdivo) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies 2023; 3(4):1-24.