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

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

ELIGIBILITY:

Patients must have:

- Advanced non-small cell lung cancer,
- Tumour with *non-squamous* cell histology and without sensitizing EGFR, ROS or ALK mutations, and
- No prior treatment in advanced setting

Note:

- Patients on active treatment responding to LUAVPP (< 4 cycles) may be eligible to switch to LUAVPPIPNI. *CAP approval must be obtained.*
- Patients on active treatment with maintenance pemetrexed or single agent pembrolizumab are not eligible to switch to LUAVPPIPNI
- 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
- 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
- Weekly: CBC & differential, platelets during cycles 1 and 2; may be omitted in subsequent cycles
- 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:

- **Vitamin supplementation mandatory** starting at least 7 days prior to the first cycle, and to continue while on treatment, until 21 days after last pemetrexed dose:
  - folic acid 0.4 mg PO daily
  - vitamin B12 1000 mcg IM every 9 weeks
- Prophylaxis for skin rash: dexamethasone 8 to 12 mg PO prior to treatment, then 4 mg PO every 12 hours for 4 doses.
- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)
- **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

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*†
pemetrexed	500 mg/m^2	IV in 100 mL NS over 10 minutes†
CISplatin	75 mg/m^2	IV in 500 mL NS over 1 hour‡

* Use a separate infusion line and filter for each drug
† Nivolumab, ipilimumab and pemetrexed may be given during the pre-hydration period[6]
‡ Pre- and post-hydration protocol for high-dose CISplatin required according to institutional guidelines (eg, prehydration with 1 L NS over 1 hour, CISplatin in 500 mL NS with potassium chloride 20 mEq, magnesium sulfate 1 g and mannitol 30 g)

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†
pemetrexed	500 mg/m^2	IV in 100 mL NS over 10 minutes†
CISplatin	75 mg/m^2	IV in 500 mL NS over 1 hour‡

† Nivolumab and pemetrexed may be given during the pre-hydration period[6]
‡ Pre- and post-hydration protocol for high-dose CISplatin required according to institutional guidelines (eg, prehydration with 1 L NS over 1 hour, CISplatin in 500 mL NS with potassium chloride 20 mEq, magnesium sulfate 1 g and mannitol 30 g)

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):

***Based on day 1 counts*:**

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
greater than or equal to 1.5	and	greater than or equal to 100	100%
less than 1.5	or	less than 100	**Delay**

***Based on nadir counts (for pemetrexed only)*:**

ANC (x 10^9/L)		Platelets (x 10^9/L)	Pemetrexed Dose
greater than or equal to 0.5	and	greater than or equal to 50	100%
less than 0.5	and	greater than or equal to 50	75%
any	and	less than 50	50%

2. RENAL DYSFUNCTION

Calculated CrCl (mL/min)	CISplatin Dose	Pemetrexed Dose
greater than or equal to 60	100%	100%
45 to less than 60	80% CISplatin or use CARBOplatin option	100%
less than 45	**Hold**	**Hold** regardless of type of platinum

3. MUCOSITIS

For next cycle:

Mucositis Grade	CISplatin dose	Pemetrexed dose
0-2	100%	100%
3-4	100%	50% previous dose*
***Discontinue treatment after two dose reductions**		

4. OTHER TOXICITIES:

- For any other grade 3 or higher toxicity, delay treatment until toxicity resolves, then resume with 25% dose decrease if considered appropriate to resume by attending oncologist
- 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).

Alternatively, CARBOplatin may be used instead of CISplatin for Cycles 1 and 2:

Drug	Dose	BC Cancer Administration Guideline
CARBOplatin	Dose = AUC 5 x (GFR¥ +25)	IV in 100 to 250 mL NS over 30 minutes

¥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.

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. **Vitamin supplements**: appropriate prescription of folic acid and vitamin B12 is essential. The incidence of adverse events such as febrile neutropenia related to pemetrexed is higher without vitamin supplementation.
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **NSAIDs**: Concurrent nonsteroidal anti-inflammatory agents should be avoided as they may decrease the renal clearance of pemetrexed.
6. **Renal Toxicity**: nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Use caution with pre-existing renal dysfunction.
7. **Neurotoxicity**: CISplatin is neurotoxic and may have to be discontinued if functionally important neuropathy develops. Particular caution must be used in individuals with existing neuropathy.
8. **Ototoxicity**: CISplatin is ototoxic and its use must be cautioned in individuals with existing hearing loss.

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. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432-40.
7. Weber JS, et al. Management of adverse events following treatment with anti-programmed death-1 agents. Oncologist 2016; 21(30):1-11.