BC Cancer Protocol Summary for Neoadjuvant Treatment of Non-Squamous Non-Small Cell Lung Cancer with Nivolumab, Pemetrexed and Platinum

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

ELIGIBILITY:

Patients must have:
- Previously untreated resectable non-small cell lung cancer (NSCLC),
- Tumour size 4 cm or greater or node positive, M0,
- Non-squamous histology, and
- No EGFR or ALK mutation

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:
- 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, 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, 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 childbearing 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:

- **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 nivolumab:** 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
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 60 minutes†
† pre- and post-hydration protocol for high-dose CISplatin required according to institutional guidelines (e.g., prehydration with 1000 mL NS over 60 minutes, CISplatin in 500 mL NS with potassium chloride 20 mmol, magnesium sulfate 1 g and mannitol 30 g)		

*select dose per Dose Banding Table (appendix).

** nivolumab and pemetrexed may be given during the pre-hydration period

- 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:

***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**

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 to 2	100%	100%
3 to 4	100%	50% previous dose*
***Discontinue treatment after two dose reductions**		

4. 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).

Alternatively, CARBOplatin may be used instead of CISplatin:

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:

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

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.

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).**
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 antihistamine 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. 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.

Appendix. Dose Bands

NIVOLUMAB DOSE BANDING TABLE (4.5 mg/kg capped at 360 mg)

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 170		**Pharmacy prepares specific dose**
170	191.49	**180**
191.5	219.49	**200**
219.5	239.49	**220**
239.5	259.49	**240**
259.5	279.49	**260**
279.5	298.49	**280**
298.5	319.49	**300**
319.5	349.49	**320**
349.5	360	**360**