BC Cancer Protocol Summary for First-Line Treatment of Advanced Non-Small Cell Lung Cancer with Platinum, Gemcitabine and Cemiplimab

Protocol Code	*LUAVPGCEM*
Tumour Group	*Lung*
Contact Physician	*Lung Systemic Therapy*

ELIGIBILITY:

Patients must have:

- Stage IIIB or IIIC non-small cell lung cancer (NSCLC) not amenable to curative intent therapy, or stage IV NSCLC, where use of LUAVPCCEM is not recommended, and
- No prior treatment in advanced setting

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 cemiplimab.

Note:

- Use of first-line cemiplimab precludes the use of nivolumab, pembrolizumab and atezolizumab as any subsequent line of therapy
- At time of subsequent progression, retreatment (with or without chemotherapy) is permitted for an additional 1 year (17 cycles) if:
  - Patient completed 108 weeks (36 cycles) of therapy without progression, or
  - Patient stopped treatment due to toxicity (not progression)
  - CAP approval not required for retreatment

EXCLUSIONS:

Patients must not have:

- Presence of EGFR, ALK or ROS1 mutations
- Progression on or within 6 months of completing adjuvant or neoadjuvant treatment
- Active central nervous system metastases (unless asymptomatic and/or stable)

CAUTIONS:

- Concurrent autoimmune disease
- Patients with long term immunosuppressive therapy or systemic corticosteroids (requiring more than 10 mg predniSONE/day or equivalent)
- Received prior treatment with idelalisib, regardless of indication

TESTS:

- Baseline: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, morning serum cortisol
- Baseline, if clinically indicated: BNP, troponin, creatine kinase, ECG, echocardiogram, chest x-ray
- Before each treatment:
    - Day 1 – CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH
    - Day 8 – CBC & Diff, creatinine
- 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, random glucose, troponin, creatine kinase, ECG
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (optional).

PREMEDICATIONS:

Cycles 1 to 6:

- Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)
- If prior infusion reactions to cemiplimab: diphenhydrAMINE 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

Cycle 7 onwards:

- Antiemetics are not usually required.
- If prior infusion reaction to cemiplimab: diphenhydrAMINE 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

TREATMENT:

Cycles 1 to 6:

Drug	Dose	BC Cancer Administration Guideline
cemiplimab	350 mg on Day 1	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter
gemcitabine	1000 mg/m^2/day on Days 1 and 8 (total dose per cycle = 2000 mg/m^2)	IV in 250 mL NS over 30 minutes
CISplatin	75 mg/m^2/day on Day 1	IV in 500 mL NS over 1 hour*

* 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)

- Repeat every 3 weeks for up to 6 cycles, then proceed to maintenance treatment (cycle 7 onwards).

Cycle 7 onwards:

Drug	Dose	BC Cancer Administration Guideline
cemiplimab	350 mg	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter

- Repeat every 3 weeks until disease progression, unacceptable toxicity, or a maximum of 108 weeks (36 cycles total including those given with chemotherapy), whichever comes first.
- Retreatment may be allowed (refer to Eligibility section, above).

DOSE MODIFICATIONS:

1. **For cemiplimab:**
   No specific dose modifications for cemiplimab. Toxicity managed by treatment delay and other measures (see SCIMMUNE protocol for management of immune-mediated adverse reactions to checkpoint inhibitor immunotherapy).

2. **Hematology:**

For gemcitabine day 1 of each cycle

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%
0.5 to less than 1.0	or	75 to less than 100	75%
Less than 0.5	or	Less than 75	Delay*
* Platinum also delayed			

For gemcitabine day 8 of each cycle

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%
0.5 to less than 1.0	or	75 to less than 100	75%
Less than 0.5	or	Less than 75	Omit
**Dose adjustment only for the day of treatment the CBC is drawn			

3. Renal Dysfunction:

Calculated Creatinine Clearance (mL/min)	CISplatin Dose	Gemcitabine Dose
Greater than or equal to 60	100%	100%
45 to less than 60	80% CISplatin or go to CARBOplatin option (same prehydration as 75 mg/m^2 dose)	100%
Less than 45	Hold CISplatin or delay with additional IV fluids or go to CARBOplatin option	75%
Less than 30	Omit	Omit

Alternatively, CARBOplatin may be used instead of CISplatin:

Drug	Dose	BC Cancer Administration Guideline
cemiplimab	350 mg on Day 1	IV in 50 mL NS over 30 minutes using a 0.2 micron in-line filter
gemcitabine	1000 mg/m^2/day on Days 1 and 8 (total dose per cycle = 2000 mg/m^2)	IV in 250 mL NS over 30 minutes
CARBOplatin	Dose = AUC 5 x (GFR* + 25) on Day 1	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:

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

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.

- Repeat every 3 weeks for up to 6 cycles, then proceed to maintenance treatment (cycle 7 onwards).

4. **Other Toxicities**:

For gemcitabine only:

Grade	Stomatitis	Diarrhea	Dose
1	Painless ulcers, erythema or mild soreness	Increase of 2 to 3 stools/day	100%
2	Painful erythema, edema, or ulcers but can eat	Increase of 4 to 6 stools, or nocturnal stools	Omit until toxicity resolved then resume at 100%
3	Painful erythema, edema, or ulcers and cannot eat	Increase of 7 to 9 stools/day or incontinence, malabsorption	Omit until toxicity resolved then resume at 75%
4	Mucosal necrosis, requires parenteral support	Increase of greater than or equal to 10 stools/day or grossly bloody diarrhea requiring parenteral support	Omit until toxicity resolved then resume at 50%

PRECAUTIONS:

1. **Serious immune-mediated reactions**: can be severe to fatal and usually occur during the treatment course with cemiplimab,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 infusion reactions have been reported with cemiplimab. Discontinue cemiplimab with severe reactions (Grade 3 or 4). Patients with mild or moderate infusion reactions may receive cemiplimab with close monitoring, reduced rates of administration and use of premedication.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Renal Toxicity**: nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Use caution with pre-existing renal dysfunction.
5. **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.

6. **Ototoxicity**: CISplatin is ototoxic and its use must be cautioned in individuals with existing hearing loss.

Contact the LU Systemic Therapy physician at your regional cancer centre or LU Systemic Therapy Chair with any problems or questions regarding this treatment program.

REFERENCES:

1. Gogishvili M, Melkadze T, Makharadze T, et al. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. Nat Med. 2022 Nov;28(11):2374-2380.
2. Cemiplimab (Libtayo) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies, May 2024; 4(5).