BC Cancer Protocol Summary for Treatment of Extensive Stage Small Cell Lung Cancer (SCLC) with Durvalumab, Platinum and Etoposide

Protocol Code	*LUSCDURPE*
Tumour Group	*Lung*
Contact Physician	*Dr. Christopher Lee*

ELIGIBILITY:

Patients must have:

- Previously untreated extensive stage small cell lung cancer (ES-SCLC)

Patients should have

- ECOG 0 to 2
- Adequate bone marrow, hepatic and renal function
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of durvalumab

Note:

- Patients on active treatment with LUSCPE (less than 4 cycles) and do not have proven progression may switch to LUSCDURPE if all other eligibility criteria are met
- Patients previously treated with combined modality therapy for limited stage disease are eligible for LUSCDURPE if relapse occurs greater than 6 months after previous treatment
- Patients are eligible to receive either LUSCDURPE or LUSCATPE, but not both

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 AND MONITORING:

- Baseline: CBC & differential, platelets, creatinine, calcium, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, morning serum cortisol, chest x-ray
    - C-reactive protein and albumin (optional, and results do not have to be available to proceed with first treatment)
- Before each cycle: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH
- If clinically indicated: chest x-ray, ECG, morning serum cortisol, lipase, glucose, calcium, 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
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (optional)

PREMEDICATIONS:

For cycles 1 to 4:

- Antiemetic protocol for moderately emetogenic chemotherapy as long as CISplatin dose is not greater than or equal to 50 mg. If CISplatin is greater than or equal to 50 mg, or if giving CARBOplatin, use antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- hydrocortisone & diphenhydrAMINE for history of hypersensitivity to etoposide
- If prior infusion reactions to durvalumab: diphenhydrAMINE 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

For cycles 5 and beyond:

- Antiemetics are not usually required
- Antiemetic protocol for low emetogenicity (see SCNAUSEA)
- If prior infusion reactions to durvalumab: diphenhydrAMINE 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

TREATMENT:

Cycles 1 to 4:

Drug	Dose	BC Cancer Administration Guideline
durvalumab	20 mg/kg on Day 1 (maximum 1500 mg)	IV in 100 mL NS over 60 minutes using a 0.2 micron in-line filter*
CISplatin	25 mg/m^2/day on Days 1 to 3	IV in 100 to 250 mL NS over 30 minutes
etoposide	100 mg/m^2/day on Days 1 to 3	IV in 250 to 1000 mL NS over 45 minutes to 1 hour 30 minutes (use non-DEHP equipment with 0.2 micron in-line filter*)

* Use a separate infusion line and filter for each drug

In cases of CISplatin toxicity or poorly functioning patients or Age greater than 75:

Drug	Dose	BC Cancer Administration Guideline
CARBOplatin	AUC 5 on Day 1 only Dose = AUC x (GFR** +25)	IV in 100 to 250 mL NS over 30 minutes.

**GFR preferably from nuclear renogram, if not possible use:

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

N = 1.04 (women) or 1.23 (men)

The estimated GFR 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 x 4 cycles,** followed by

Cycle 5 onwards: (to start 3 weeks after cycle 4)

Drug	Dose	BC Cancer Administration Guideline
durvalumab	20 mg/kg (maximum 1500 mg)	IV in 100 mL NS over 60 minutes using a 0.2 micron in-line filter

- **Repeat every 4 weeks** until disease progression or unacceptable toxicity

DOSE MODIFICATIONS:

Durvalumab:

No specific dose modifications. Toxicity managed by treatment delay and other measures (see SCIMMUNE for management of immune-mediated adverse reactions to checkpoint inhibitor immunotherapy: http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf).

1. **Hematology:** for etoposide

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%
1.0 to less than 1.5	or	75 to less than 100	75%
less than 1.0	or	less than 75	**Delay**

2. **Hepatic dysfunction:** for etoposide

Bilirubin (micromol/L)	Dose	
less than 25	100%	100 mg/m^2/day x 3 days
25 to 50	50%	50 mg/m^2/day x 3 days
51 to 85	25%	25 mg/m^2/day x 3 days
greater than 85	**Delay**	

3. **Renal dysfunction:**

For CISplatin

Calculated Cr Clearance (mL/min)	Dose
greater than or equal to 60	100%
45 to less than 60	80% CISplatin or go to CARBOplatin option
less than 45	Hold CISplatin or delay with additional IV fluids or go to CARBOplatin option

For etoposide

Initial dose modification to 75% should be considered if creatinine clearance is less than 30 mL/min. Subsequent dosing should be based on patient tolerance and clinical effect.

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 for management of immune-mediated adverse reactions to checkpoint inhibitor immunotherapy: http://www.bccancer.bc.ca/chemotherapy-protocols-site/Documents/Supportive%20Care/SCIMMUNE_Protocol.pdf).
2. **Infusion-related reactions:** isolated cases of severe infusion reactions have been reported. For mild or moderate infusion reactions, decrease the infusion rate to 50% or temporarily interrupt infusion until the reaction has resolved. Consider premedication for subsequent infusions. Permanently discontinue durvalumab for severe reactions.
3. **Hypersensitivity:** Monitor infusion of etoposide for the first 15 minutes for signs of hypotension. Hypersensitivity reactions have also been reported for CISplatin. Refer to BC Cancer Hypersensitivity Guidelines.
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Infections:** severe infections such as sepsis, necrotizing fasciitis, and osteomyelitis have been reported. Treat suspected or confirmed infections as indicated. Withhold durvalumab for severe infections.
6. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.

Contact Dr. Christopher Lee or tumour group delegate at (604) 930-2098 or 1-800-523-2885 with any problems or questions regarding this treatment program.

REFERENCES:

1. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum–etoposide versus platinum–etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019;394(10212):1929-1939.