

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

Protocol Code

LUAVPPDT

Tumour Group

Lung

Contact Physician

LU Systemic Therapy

ELIGIBILITY:

Patients must have:

- Advanced non-small cell lung cancer not amenable to curative intent treatment,
- Disease of non-squamous cell histology,
- No sensitizing EGFR mutation or ALK genomic tumour aberrations,
- No prior treatment in advanced setting

Patients should have:

- Good performance status,
- Adequate hepatic and renal function,
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of durvalumab and tremelimumab

Notes:

- Patients on active treatment with other immunotherapy-containing regimen may be able to switch only in the event of a severe infusion reaction. *CAP approval must be obtained.*

EXCLUSIONS:

Patients must not have:

- Untreated/unstable CNS or leptomeningeal metastases
- Relapsed on or within 6 months of completing neoadjuvant or adjuvant immunotherapy and/or 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 & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, morning serum cortisol, chest x-ray
- Before each treatment: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH
- If clinically indicated: chest x-ray, morning serum cortisol, lipase, random glucose, 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 of pemetrexed, 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
- Cycles 1 to 4:
 - Antiemetic protocol for highly emetogenic chemotherapy (see SCNAUSEA)
 - Prophylaxis for skin rash: dexamethasone 8 to 12 mg PO prior to pemetrexed, then 4 mg PO every 12 hours for 4 doses.
- Cycles 5 onward:
 - Antiemetic protocol for low emetogenic chemotherapy (see SCNAUSEA)
 - Prophylaxis for skin rash: dexamethasone 4 mg PO BID for 3 days beginning the day before pemetrexed. (May proceed with treatment even if patient has not taken the pre-treatment dexamethasone doses. Instruct patient to begin immediately)
- If prior infusion reactions to durvalumab and tremelimumab: diphenhydramine 50 mg PO, acetaminophen 325 to 975 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

TREATMENT:

Cycle 1 to 4: 1 cycle = 21 days

Drug	Dose	BC Cancer Administration Guideline
tremelimumab	75 mg	IV in 50 mL NS over 60 minutes Using a 0.2 micron in-line filter*
durvalumab	20 mg/kg** (maximum 1500 mg)	IV in 100 mL NS over 60 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†

*Use a separate infusion line and filter for each drug

**Select dose per Dose Banding Table (appendix)

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

Vital Sign Monitoring and Observation:

For Cycle 1 and first re-treatment dose of tremelimumab and durvalumab:

- Vital signs immediately before the start of tremelimumab infusion, at 30 minutes into the infusion (halfway through infusion), at end of infusion, and as clinically indicated.
- Patients to be observed for one hour after the end of tremelimumab infusion for signs of infusion-related reaction (IRR). Signs may include chills, itching, rash, flushing, shortness of breath, wheezing, dizziness, fever, facial swelling or back/neck pain
- No observation required with subsequent infusions if no infusion-related reaction with Cycle 1

Repeat every 21 days for 4 cycles, then proceed to Cycle 5

Cycle 5: starts 21 days 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
pemetrexed	500 mg/m ²	IV in 100 mL NS over 10 minutes

Cycle 6: starts 28 days after Cycle 5

Drug	Dose	BC Cancer Administration Guideline
tremelimumab	75 mg	IV in 50 mL NS over 60 minutes Using a 0.2 micron in-line filter**
durvalumab	20 mg/kg* (maximum 1500 mg)	IV in 100 mL NS over 60 minutes Using a 0.2 micron in-line filter**
pemetrexed	500 mg/m ²	IV in 100 mL NS over 10 minutes

Cycle 7 onward: starts 28 days after Cycle 6

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
pemetrexed	500 mg/m ²	IV in 100 mL NS over 10 minutes

*Select dose per Dose Banding Table (appendix)

**Use a separate infusion line and filter for each drug

- Repeat every 28 days until disease progression or intolerable toxicity.

Optional retreatment with tremelimumab with durvalumab:

At physician discretion, patients may be retreated with 4 doses of tremelimumab in combination with durvalumab if they previously completed the 5 cycles of the combination of durvalumab and tremelimumab, and have progressive disease during the durvalumab monotherapy portion of the regimen. The retreatment doses will be given every 28 days. A maximum of 4 retreatment doses of tremelimumab per patient will be funded.

DOSE MODIFICATIONS:

For durvalumab and tremelimumab:

No specific dose modifications for durvalumab and tremelimumab. Toxicity managed by treatment delay and other measures (see SCIMMUNE protocol for management of immune-mediated adverse reactions to checkpoint inhibitors immunotherapy).

For pemetrexed and CISplatin:

1. Hematology:

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:

Creatinine Clearance (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

Alternatively, CARBOplatin may be used instead of CISplatin:

Drug	Dose	BC Cancer Administration Guideline
CARBOplatin	Dose = AUC 5 x (GFR ^{††} + 25) on Day 1	IV in 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:

$$\text{GFR} = \frac{N \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{Serum creatinine (micromol/L)}} \quad N = 1.04 \text{ (women) or } 1.23 \text{ (men)}$$

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 4 cycles (Cycles 1 to 4).

3. Mucositis:

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:

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.

PRECAUTIONS:

- 1. Serious immune-mediated reactions:** can be severe to fatal and usually occur during the treatment course with durvalumab and tremelimumab, 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 to durvalumab and tremelimumab:** 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 tremelimumab and/or durvalumab for severe reactions.
- 3. Infections:** severe infections such as sepsis, necrotizing fasciitis, and osteomyelitis have been reported during durvalumab treatment. Infections such as influenza, pneumonia and upper respiratory tract infections have been reported in patients treated with tremelimumab. Treat suspected or confirmed infections as indicated. Withhold tremelimumab and durvalumab for severe infections.
- 4. Vitamin supplements:** appropriate prescription of folic acid and vitamin B12 is essential during pemetrexed treatment. The incidence of adverse events such as febrile neutropenia related to pemetrexed is higher without vitamin supplementation.
- 5. Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
- 6. NSAIDs:** Concurrent nonsteroidal anti-inflammatory agents should be avoided as they may decrease the renal clearance of pemetrexed.
- 7. Renal Toxicity:** nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Use caution with pre-existing renal dysfunction.

8. **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.
9. **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 the LU Systemic Therapy Chair with any problems or questions regarding this treatment program.

REFERENCES:

1. Johnson M, Co, BC, Luft A et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. J Clin Oncol 2023; 41(6): 1213-1227.
2. Durvalumab (Imfinzi) and Tremelimumab (Imjudo) CADTH [Canada's Drug Agency (CDA-AMC)] Reimbursement Recommendation. Canadian Journal of Health Technologies June 2025; 5(6): 1-30.

Appendix. Dose Bands

DURVALUMAB DOSE BANDING TABLE (20 mg/kg capped at 1500 mg)

Ordered Dose (mg)		Rounded dose (mg)
From:	To:	
Less than 369		Pharmacy prepares specific dose
369	440.49	400
440.5	475.49	450
475.5	555.49	500
555.5	666.49	600
666.5	777.49	700
777.5	888.49	800
888.5	999.49	900
999.5	1099.49	1000
1099.5	1199.49	1100
1199.5	1299.49	1200
1299.5	1399.49	1300
1399.5	1499.49	1400
1499.5	1500	1500