BC Cancer Protocol Summary for First-Line Treatment of Advanced Non-Small Cell Lung Cancer (NSCLC) with CARBOplatin, Pemetrexed and Amivantamab

***Protocol Code**:* *ULUAVPPAF*

***Tumour Group**:* *Lung*

***Contact Physician**:* *LU Systemic Therapy*

ELIGIBILITY:
Patient must have:
- Locally advanced (not amenable to curative therapy) or metastatic NSCLC with non-squamous histology,
- EGFR mutation-positive tumour with exon 20 insertion mutation confirmed by an accredited laboratory,
- BC Cancer "Compassionate Access Program" request approval prior to treatment

Patient should have:
- Good performance status
- Adequate hematologic, renal and liver function
- Asymptomatic/stable brain metastases (if applicable)

Note:
- Patients who started alternate first-line treatment prior to 1 April 2026 may switch to ULUAVPPAF provided there is no evidence of progression
- Patients who previously received neoadjuvant and/or adjuvant therapy are eligible for treatment, provided progression occurred at least 6 months following treatment completion
- Patients who started alternate therapies prior to confirmation of exon 20 insertion mutation may switch to ULUAVPPAF once their mutation status is confirmed

EXCLUSIONS:
- Prior systemic treatment for locally advanced or metastatic disease
- Squamous-cell histology
- Unstable CNS metastases
- Active interstitial lung disease

CAUTIONS:
- History of interstitial lung disease

TESTS:
- Baseline: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, GGT albumin, sodium, potassium, magnesium, random glucose
- Prior to each cycle: CBC & Diff, creatinine, total bilirubin, ALT
- If clinically indicated, prior to Cycle 1 Days 8 and 15:: CBC & Diff, creatinine, total bilirubin, ALT
- If clinically indicated: alkaline phosphatase, LDH, GGT, albumin, sodium, potassium, magnesium random glucose

PREMEDICATIONS:

- For Cycles 1 to 4: antiemetic protocol for highly emetogenic chemotherapy for CARBOplatin (see protocol SCNAUSEA)
- For Cycle 5 and onwards: antiemetics are not usually required. If required, antiemetic protocol for low emetogenicity (see protocol SCNAUSEA)
- Dexamethasone 8 mg PO BID for 4 doses, starting two days prior to Cycle 1 Day 1
- 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 to 1 mg PO once daily
  - vitamin B12 1000 mcg IM every 9 weeks
- Prophylaxis for skin rash:
  - Cycle 1: not needed due to dexamethasone being given as amivantamab premedication
  - Cycle 2 and onward: dexamethasone 8 to 12 mg PO prior to pemetrexed (may be omitted when dexamethasone is given as premedication), then 4 mg PO every 12 hours for 4 doses.
- Amivantamab-specific premedications (see table below)

Amivantamab Premedications:

Cycle and Day of Treatment	Medication	Dose	Administration
Cycle 1 Day 1	dexamethasone	20 mg	IV 60 to 120 minutes prior to amivantamab
	dexamethasone	8 mg	PO 60 minutes prior to treatment*
	diphenhydrAMINE	50 mg	IV 50 mL NS over 15 min (Y-site compatible with famotidine) 30 minutes prior to amivantamab
	famotidine	20 mg	IV in 100 mL NS over 15 min (Y-site compatible with diphenhydrAMINE) 30 minutes prior to amivantamab
	acetaminophen	650 to 975 mg	PO 30 to 60 minutes prior to amivantamab
Cycle 1 Day 2	dexamethasone	10 mg	IV 45 to 60 minutes prior to amivantamab
	diphenhydrAMINE	50 mg	IV 50 mL NS over 15 min (Y-site compatible with famotidine) 30 minutes prior to amivantamab
	famotidine	20 mg	IV in 100 mL NS over 15 min (Y-site compatible with diphenhydrAMINE) 30 minutes prior to amivantamab
	acetaminophen	650 to 975 mg	PO 30 to 60 minutes prior to amivantamab
Cycle 1 Day 8 and onward	dexamethasone (optional**)	10 mg	IV 45 to 60 minutes prior to amivantamab
	diphenhydrAMINE	50 mg	IV 50 mL NS over 15 min (Y-site compatible with famotidine) 30 minutes prior to amivantamab
	famotidine (optional)	20 mg	IV in 100 mL NS over 15 min (Y-site compatible with diphenhydrAMINE) 30 minutes prior to amivantamab
	acetaminophen	650 to 975 mg	PO 30 to 60 minutes prior to amivantamab

*If not already given as part of antiemetic regimen

**Cycle 1 Day 8 and onward, if prior infusion reaction to amivantamab: dexamethasone 10 mg IV to 60 minutes prior to treatment on subsequent treatment days

- After prolonged dose interruptions of amivantamab, restart the premedications upon reinitiation of treatment

SUPPORTIVE MEDICATIONS:

- To reduce the risk and severity of skin and nail infections:
  - doxycycline or minocycline PO 100 mg BID for 12 weeks starting on Cycle 1 Day 1
  - following completion of oral antibiotic therapy, start clindamycin 1% topical lotion to scalp daily for 9 months
  - non-comedogenic moisturizer on the face and whole body while on treatment
  - chlorhexidine 4% soap daily for hands and feet while on treatment

TREATMENT: 1 cycle = 21 days

Cycle 1:

For patients with body weight **less than 80 kg at baseline**

Drug	Dose	BC Cancer Administration Guideline
pemetrexed	500 mg/m^2 on Day 1	IV in 100 mL NS over 10 minutes
CARBOplatin	AUC 5 x (GFR* + 25) on Day 1	IV in 100 to 250 mL NS over 30 minutes
amivantamab	350 mg on Day 1	IV in 250 mL NS** (use 0.2 micron in-line filter) Start infusion at 50 mL/hour. If no reactions after 2 hours, increase rate to 75 mL/hour
	1050 mg on Day 2	IV in 250 mL NS** (use 0.2 micron in-line filter) Start infusion at 33 mL/hour. If no reactions after 2 hours, increase rate to 50 mL/hour
	1400 mg on Day 8	IV in 250 mL NS** (use 0.2 micron in-line filter) Infuse at 65 mL/hour
	1400 mg on Day 15	IV in 250 mL NS** (use 0.2 micron in-line filter) Infuse at 85 mL/hour

OR

For patients with body weight **greater than or equal to 80 kg at baseline**

Drug	Dose	BC Cancer Administration Guideline
pemetrexed	500 mg/m^2 on Day 1	IV in 100 mL NS over 10 minutes
CARBOplatin	AUC 5 x (GFR* + 25) on Day 1	IV in 100 to 250 mL NS over 30 minutes
amivantamab	350 mg on Day 1	IV in 250 mL NS** (use 0.2 micron in-line filter) Start infusion at 50 mL/hour. If no reactions after 2 hours, increase rate to 75 mL/hour
	1400 mg on Day 2	IV in 250 mL NS** (use 0.2 micron in-line filter) Start infusion at 25 mL/hour. If no reactions after 2 hours, increase rate to 50 mL/hour
	1750 mg on Day 8	IV in 250 mL NS** (use 0.2 micron in-line filter) Infuse at 65 mL/hour
	1750 mg on Day 15	IV in 250 mL NS** (use 0.2 micron in-line filter) Infuse at 85 mL/hour

**amivantamab should be administered via a peripheral line for all Cycle 1 doses to minimize drug exposure in the event of an infusion-related reaction.

Monitoring on Cycle 1 Days 1 and 2: vital signs at start of infusion and at increment change.

Cycle 2: all drugs administered on Day 1

Drug	Dose	BC Cancer Administration Guideline
pemetrexed	500 mg/m^2	IV in 100 mL NS over 10 minutes
CARBOplatin	AUC 5 x (GFR* + 25)	IV in 100 to 250 mL NS over 30 minutes
amivantamab	Less than 80 kg at baseline: 1400 mg **OR** Greater than or equal to 80 kg at baseline: 1750 mg	IV in 250 mL NS (use 0.2 micron in-line filter) Infuse at 125 mL/hour

Cycles 3 and 4: all drugs administered on Day 1

Drug	Dose	BC Cancer Administration Guideline
pemetrexed	500 mg/m^2	IV in 100 mL NS over 10 minutes
CARBOplatin	AUC 5 x (GFR* + 25)	IV in 100 to 250 mL NS over 30 minutes
amivantamab	Less than 80 kg at baseline: 1750 mg **OR** Greater than or equal to 80 kg at baseline: 2100 mg	IV in 250 mL NS (use 0.2 micron in-line filter) Infuse at 125 mL/hour

Cycle 5 and onward: all drugs administered on Day 1

Drug	Dose	BC Cancer Administration Guideline
pemetrexed	500 mg/m^2	IV in 100 mL NS over 10 minutes
amivantamab	Less than 80 kg at baseline: 1750 mg **OR** Greater than or equal to 80 kg at baseline: 2100 mg	IV in 250 mL NS (use 0.2 micron in-line filter) Infuse at 125 mL/hour

*GFR may be determined by nuclear renogram or estimated by the Cockcroft formula, at the discretion of the attending physician:

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

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 21 days until disease progression or intolerable toxicity.

DOSE MODIFICATIONS:

For amivantamab: Dose adjustments are not required for body weight changes from baseline.

Dose at Toxicity Occurrence	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
1050 mg	700 mg	350 mg	Discontinue amivantamab
1400 mg	1050 mg	700 mg	
1750 mg	1400 mg	1050 mg	
2100 mg	1750 mg	1400 mg	

1. **Hematologic Toxicity:** for Day 1*

ANC (x 10^9/L)		Platelets (x 10^9/L)	Management
Greater than or equal to 1.5	and	Greater than or equal to 100	100%
Less than 1.5	or	Less than 100	Delay

*dose modification for hematologic toxicity is not required for Days 2, 8 and 15 in Cycle 1

2. **Renal Dysfunction:**

Creatinine Clearance (mL/min)	Pemetrexed Dose
Greater than or equal to 60	100%
45 to less than 60	100%
Less than 45	Hold

For CARBOplatin: If significant increase in creatinine (greater than 20% or rises above the upper limit of normal), recheck/recalculate GFR and recalculate CARBOplatin dose using new GFR.

For amivantamab: No dosage adjustment is necessary for creatinine clearance greater than or equal to 30 mL/min. If creatinine clearance is less than 30 mL/min, contact the physician, as there is no data available on use below this threshold.

3. **Hepatic Dysfunction:** amivantamab dose adjustment is not required when total bilirubin is less than or equal to 1.5 times the upper limit of normal. If total bilirubin is greater than 1.5 times the upper limit of normal, contact the physician, as there is no data available on use below this threshold.

4. **Infusion-related reactions to amivantamab:** Refer to SCDRUGRX for management guidelines

Severity	Management
Grade 1 to 3	▪ Stop infusion at first sign of infusion and manage per SCDRUGRX ▪ Upon resolution of symptoms, resume infusion at 50% of the rate at time of reaction ▪ If there are no additional symptoms after 5 minutes, increase the infusion rate to 75% of the rate at time of reaction for 5 minutes, then increase to 100% and continue with infusion rate escalation as per Treatment section above. ▪ Premedicate for next scheduled dose (see Premedications above)
Recurrent Grade 3 or any Grade 4	▪ Stop infusion and manage per SCDRUGRX ▪ Permanently discontinue amivantamab

5. **Skin and Nail Toxicity:**

Severity	Management
Grade 1	▪ Initiate supportive care and reassess after 2 weeks
Grade 2	▪ Initiate supportive care and reassess after 2 weeks ▪ If no improvement after 2 weeks, consider reducing amivantamab dose
Grade 3	▪ Initiate supportive care and withhold amivantamab until toxicity recovers to Grade 2 or lower ▪ Upon recovery, resume amivantamab at reduced dose ▪ If no improvement within 2 weeks, permanently discontinue amivantamab
Grade 4 and severe bullous, blistering, or exfoliating skin conditions	▪ Permanently discontinue amivantamab

- Supportive care may include topical corticosteroids, and topical and/or oral antibiotics
- For Grade 3 or poorly tolerated Grade 2 events, add systemic antibiotics and steroids, and consider dermatologic consultation
- Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist.

6. **Interstitial Lung Disease (ILD)/Pneumonitis:** Withhold amivantamab for suspected ILD/pneumonitis of any grade. If ILD/pneumonitis is confirmed, permanently discontinue amivantamab.

7. **Other Toxicity:**

Severity	Drug	Management
Grade 3	amivantamab	▪ Withhold until toxicity improved to Grade 1 or baseline ▪ If recovery occurs within 1 week, resume at same dose ▪ If recovery takes longer than 1 week, resume at reduced dose ▪ Permanently discontinue amivantamab if recovery does not occur within 4 weeks
	pemetrexed and CARBOplatin	▪ Withhold until toxicity resolves, then resume with 25% dose decrease at discretion of treating physician
Grade 4	amivantamab	▪ Withhold amivantamab until toxicity improved to Grade 1 or baseline ▪ If recovery occurs within 4 weeks, resume at reduced dose ▪ Permanently discontinue amivantamab if recovery does not occur within 4 weeks or for recurrent Grade 4 reactions
	pemetrexed and CARBOplatin	▪ Withhold until toxicity resolves, then resume with 25% dose decrease at discretion of treating physician

8. **Mucositis**

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

PRECAUTIONS:

1. **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.
2. **NSAIDs**: Concurrent nonsteroidal anti-inflammatory agents should be avoided as they may decrease the renal clearance of pemetrexed.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Infusion-Related Reactions** including dyspnea, flushing, fever, chills, nausea, chest discomfort and vomiting are reported with amivantamab and occur most commonly with the first infusion. The incidence of infusion-related reactions decreases with subsequent doses. Patients should be premedicated with antihistamines and antipyretics routinely. Glucocorticoids are required in Cycle 1 Days 1 and 2, and for subsequent treatments if there was a prior infusion related reaction. Amivantamab should be administered via a peripheral line for all Cycle 1 doses to minimize drug exposure in the event of an infusion-related reaction. If peripheral access is limiting, earlier use of a central line may be considered after Cycle 1 Day 8, if deemed medically acceptable. For management of infusion-related reactions, refer to BC Cancer Protocol SCDRUGRX
5. **Interstitial Lung Disease (ILD)/Pneumonitis** may occur in patients treated with amivantamab. Use caution in patients with history or ILD or pneumonitis. Monitor patients for signs and symptoms such as dyspnea, cough and fever, interrupt treatment for suspected ILD and investigate promptly. If ILD is confirmed, permanently discontinue amivantamab.

6. **Ophthalmologic toxicity** due to amivantamab may present as dry eye symptoms, blurred vision, keratitis, ocular itching or uveitis. Ophthalmology referral is recommended for patients with worsening eye symptoms. Management may include withholding amivantamab, dose reduction or discontinuation.
7. **Skin and Nail Toxicity:** has been reported, including rash, dermatitis acneiform, pruritus, dry skin, and toxic epidermal necrolysis. Prophylactic measures such as use of topical antibiotics, oral antibiotics, topical antiseptic solution, and ceramide-based moisturizers are recommended to reduce severity of skin reactions. Sun exposure should be limited during treatment with amivantamab and for 2 months following treatment. Use protective clothing and broad-spectrum UVA/UVB sunscreen if sun exposure cannot be avoided. Skin reactions are managed based on the severity of the reaction, by withholding amivantamab, dose reduction, or permanent discontinuation. Topical/oral steroids or antibiotics may be required to treat infections. Dermatology consultation is recommended for patients presenting with severe rash or rash with an atypical appearance or distribution, and patients whose skin reaction fails to show improvement within 2 weeks.

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

REFERENCES:

1. Zhou C, Tang KJ, Cho BC et al. Amivantamab Plus Chemotherapy in NSCLC with EGFR Exon 20 Insertions. N Engl J Med Nov 2023; 389: 2039-51.
2. Amivantamab (RYBREVANT) Canada's Drug Agency (CDA-AMC) Reimbursement Recommendation. Canadian Journal of Health Technologies. January 2025; 5(1): 1-27.