

BC Cancer Protocol Summary for First Line Treatment of Advanced Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Non-Small Cell Lung Cancer (NSCLC) with Amivantamab and Lazertinib

Protocol Code:

LUAVAMLA

Tumour Group:

Lung

Contact Physician:

LU Systemic Therapy

ELIGIBILITY:

Patient must have:

- Previously untreated, newly diagnosed locally advanced or metastatic NSCLC not amenable to curative surgery or chemoradiation,
- Tumour with EGFR exon 19 deletions or exon 21 L858R substitution mutations confirmed by an accredited laboratory

Patient should have:

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

Note:

- Patients are eligible for either LUAVAMLA, LUAVPPOSI or LUAVOSIF, but not sequential use of these treatments. Switching for intolerance is funded, provided that the toxicity is not considered related to the EGFR inhibitor component and only in the absence of disease progression

EXCLUSIONS:

Patient must not have:

- Untreated/unstable CNS metastases
- Prior systemic treatment for advanced disease
- Prior progression on or within 6 months of completing neoadjuvant or adjuvant therapy
- Active interstitial lung disease (ILD) or history of ILD

TESTS:

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

PREMEDICATIONS:

- 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

Cycle and Day of Treatment	Premedication	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 amivantamab
	diphenhydrAMINE	50 mg	IV in 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 in 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 in 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

*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 treatment 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 100 mg PO 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

- Prophylactic anticoagulation for the first 4 cycles:
 - Use a direct oral anticoagulant (e.g. apixaban, rivaroxaban) or a low molecular weight heparin (e.g. dalteparin). Select agent based on patient-specific factors.
 - Avoid vitamin K antagonists (e.g. warfarin) due to instability, susceptibility to drug interactions, and narrow therapeutic index.
 - May extend prophylaxis beyond 4 months based on patient factors and clinician judgment.

TREATMENT: 1 cycle = 28 days

Cycle 1:

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

Drug	Dose	BC Cancer Administration Guideline
lazertinib	240 mg once daily	PO*
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
	700 mg on Day 2	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 8	IV in 250 mL NS** (use 0.2 micron in-line filter) Infuse at 85 mL/hour
	1050 mg on Day 15	IV in 250 mL NS** (use 0.2 micron in-line filter) Infuse at 125 mL/hour
	1050 mg on Day 22	

OR

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

Drug	Dose	BC Cancer Administration Guideline
lazertinib	240 mg once daily	PO*
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 35 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
	1400 mg on Day 22	IV in 250 mL NS** (use 0.2 micron in-line filter) Infuse at 125 mL/hour

*When lazertinib and amivantamab are administered on the same day, lazertinib is recommended to be taken any time before amivantamab

**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 and onward:

Drug	Dose	BC Cancer Administration Guideline
lazertinib	240 mg once daily	PO*
amivantamab	Less than 80 kg at baseline: 1050 mg on Days 1 and 15 OR Greater than or equal to 80 kg at baseline: 1400 mg on Days 1 and 15	IV in 250 mL NS (use 0.2 micron in-line filter) Infuse at 125 mL/hour

*When lazertinib and amivantamab are administered on the same day, lazertinib is recommended to be taken any time before amivantamab

- Repeat every 28 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	1 st Dose Reduction	2 nd Dose Reduction	3 rd Dose Reduction
1050 mg	700 mg	350 mg	Discontinue amivantamab
1400 mg	1050 mg	700 mg	

For lazertinib:

Initial Dose	1 st Dose Reduction	2 nd Dose Reduction	3 rd Dose Reduction
240 mg	160 mg	80 mg	Discontinue lazertinib

1. Infusion-Related Reactions to amivantamab: Refer to SCDRUGRX for management guidelines

Severity	Management
Grade 1 to 3	- Stop infusion at first sign of reaction and manage per <u>SCDRUGRX</u> - 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 <u>SCDRUGRX</u> - Permanently discontinue amivantamab

2. 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, reduce amivantamab dose and continue lazertinib at same dose - Continue to reassess every 2 weeks, and if no improvement, reduce lazertinib dose until improvement to less than or equal to Grade 1
Grade 3	- Initiate supportive care and withhold both lazertinib and amivantamab until toxicity recovers to less than or equal to Grade 2 - Upon recovery: - lazertinib: may resume treatment at same dose, but consider dose reduction - amivantamab: resume at next lower dose level - If no improvement within 2 weeks, permanently discontinue both drugs
Grade 4 and severe bullous, blistering, or exfoliating skin conditions	- Permanently discontinue amivantamab - Withhold lazertinib until improvement to less than or equal to Grade 2 or baseline, then may resume lazertinib at same dose or consider dose reduction

- Supportive care may include topical corticosteroids, and topical and/or oral antibiotics (also see Supportive Medications for prevention, above)
- 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.

3. Interstitial Lung Disease (ILD)/Pneumonitis: Withhold treatment for suspected ILD/pneumonitis of any grade. If ILD/pneumonitis is confirmed, permanently discontinue treatment with both drugs.

4. Venous Thromboembolic Events (VTE):

Severity	Management
Grade 2 or 3	- Withhold both lazertinib and amivantamab - Administer anticoagulant treatment as clinically indicated - Once anticoagulant treatment has been initiated, may resume treatment with both lazertinib and amivantamab at the same dose, at the discretion of the treatment provider
Recurrent Grade 2 or 3 despite therapeutic level of anticoagulation	- Withhold lazertinib and permanently discontinue amivantamab - Administer anticoagulant treatment as clinically indicated - Once anticoagulant treatment has been initiated, may resume treatment with lazertinib at same dose, at the discretion of the treatment provider
Grade 4	

5. **Symptomatic Congestive Heart Failure:** Discontinue lazertinib for any symptomatic congestive heart failure, regardless of severity.

6. Other Toxicity:

Severity	Management
Grade 3	- Withhold both drugs until toxicity improves to Grade 1 or baseline - If recovery occurs within 1 week: - lazertinib: may resume at same dose if restarting lazertinib alone, or consider dose reduction if restarting with amivantamab - amivantamab: resume at same dose - If recovery takes longer than 1 week: - lazertinib: may resume at same dose if restarting lazertinib alone, or consider dose reduction if restarting with amivantamab - amivantamab: resume at reduced dose - If recovery does not occur within 4 weeks: - amivantamab: permanently discontinue - lazertinib: consider permanently discontinuing
Grade 4	- Withhold both drugs until toxicity improves to Grade 1 or baseline - If recovery occurs within 4 weeks, resume both lazertinib and amivantamab at next lower dose level - Permanently discontinue both lazertinib and amivantamab if recovery does not occur within 4 weeks
Recurrent Grade 4	Permanently discontinue both lazertinib and amivantamab

PRECAUTIONS:

1. **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

2. **Interstitial Lung Disease (ILD)/Pneumonitis** may occur in patients treated with lazertinib and 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 both lazertinib and amivantamab.
3. **Ophthalmologic toxicity** due to lazertinib and 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 treatment, dose reduction or treatment discontinuation.
4. **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 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 treatment, dose reduction, or permanent treatment 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.
5. **Left Ventricular Dysfunction and Cardiomyopathy:** Left ventricular ejection fraction (LVEF) reductions of more than 10 percentage points and a drop below the lower limit of normal have been reported, however a causal relationship has not been established. Assess electrolyte levels prior to treatment and correct any abnormalities prior to initiating treatment with lazertinib and amivantamab. Initiate close cardiac monitoring in patients with cardiac risk factors and those who develop cardiac signs and symptoms during treatment.
6. **Venous thromboembolic events** such as deep vein thrombosis and pulmonary embolism have been reported. Fatal events have occurred. Events typically occur in the first four months of treatment and anticoagulant prophylaxis is strongly recommended during this timeframe. If clinically indicated, prophylactic anticoagulants may be continued beyond four months at the discretion of the treating physician. Management of thromboembolic events may include treatment interruption, and anticoagulant treatment. See BC Cancer Drug Manual for more details.

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. Cho BC, Lu S, Felip E et al. Amivantamab plus Lazertinib in Previously Untreated EGFR-Mutated Advanced NSCLC. N Engl J Med 2024;391:1486-1498.
2. Yang JCH, Lu S, Hayashi H et al. Overall Survival with Amivantamab-Lazertinib in EGFR-Mutated Advanced NSCLC. N Engl J Med 2025;393:1681-1693.
3. Lazertinib and Amivantamab (LAZCLUZE and RYBREVANT) Canada's Drug Agency (CDA-AMC) Reimbursement Recommendation. Canadian Journal of Health Technologies. July 2025; 5(7): 1-30.