BC Cancer Protocol Summary for Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Lorlatinib

Protocol Code: *LUAVLOR*

Tumour Group: *Lung*

Contact Physician: *Dr. Sophie Sun*

ELIGIBILITY:

Patients must have:

- Locally advanced or metastatic non-small cell lung cancer,
- No prior systemic treatment, and
- Laboratory confirmed anaplastic lymphoma kinase (ALK)-positive tumour defined as either IHC 3+, FISH positive, or positive by molecular testing (next-generation sequencing)

Patients should have:

- ECOG 0 to 2,
- Adequately controlled blood pressure

Notes:

- Patients are eligible to receive one of: lorlatinib, alectinib, crizotinib or brigatinib in the first-line setting. Switching for intolerance is permitted. Switching after progression is not funded
- Sequential ALK targeted therapies are not funded after first-line lorlatinib

EXCLUSIONS:

Patients must not have:

- Progression during treatment on previous ALK-targeted tyrosine kinase inhibitor
- Severe acute or chronic medical or psychiatric conditions (including recent or active suicidal ideation or behaviour)

TESTS:

- Baseline: alkaline phosphatase, ALT, total bilirubin, LDH, creatinine, sodium, potassium, fasting glucose, total cholesterol, triglycerides, lipase, ECG, blood pressure
- Baseline if clinically indicated (optional, and results do not have to be available to proceed with first treatment): CBC & Diff, platelets, C-reactive protein, albumin
- During treatment:
  - Total cholesterol, triglycerides after 2 weeks of treatment
  - Monthly for first 3 months of treatment, and at each physician visit thereafter: total cholesterol, triglycerides, ALT, total bilirubin, alkaline phosphatase, LDH, ECG, blood pressure
  - If clinically indicated: CBC & Diff, platelets, fasting glucose, hemoglobin A1C, creatine kinase, LDL, HDL, calcium, albumin, GGT, lipase, creatinine, sodium, potassium, magnesium, urea, chest radiograph for monitoring of dyspnea to rule out development of pneumonitis

PREMEDICATIONS:

- no premedications needed

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
lorlatinib	100 mg once daily	PO

Continuously until disease progression or unacceptable toxicity.

- Careful re-evaluation after initiation of therapy is essential as lorlatinib should be continued *only if* tumour regression continues or the disease is stable and cancer-related symptoms have improved. Continued lorlatinib for "psychological" palliation in the face of progressive disease is inappropriate.

DOSE MODICATIONS:

- Lorlatinib dose levels:

Dose level 0	Dose level -1	Dose level -2
100 mg PO once daily	75 mg PO once daily	50 mg PO once daily

1. **Hypercholesterolemia or hypertriglyceridemia:**

Grade	Elevation (mmol/L)	Lorlatinib dose
1	Total cholesterol greater than ULN to 7.75 or Triglycerides 1.71 to 3.42	▪ 100% ▪ Initiate or adjust lipid-lowering therapy
2	Total cholesterol 7.76 to 10.34 or Triglycerides 3.43 to 5.7	
3	Total cholesterol 10.35 to 12.92 or Triglycerides 5.71 to 11.4	▪ 100% ▪ Initiate or adjust lipid-lowering therapy, or change to new lipid-lowering therapy
4	Total cholesterol greater than 12.92 or Triglycerides greater than 11.4	▪ Hold lorlatinib until total cholesterol 12.92 or less, and triglycerides 11.4 or less ▪ First occurrence: maximize lipid-lowering therapy, then restart at 100% ▪ If recurrent, maximize lipid-lowering therapy, then restart but at next lower dose level

2. **Central nervous system effects:**
   - Including seizures, psychotic effects, changes in cognitive function, mood (including suicidal ideation), speech, mental status, sleep

Grade	Severity	Lorlatinib dose
1	Mild	▪ Continue at the same dose, or hold until recovery to baseline, then restart at same dose or reduce to next lower dose
2	Moderate	▪ Hold until less than or equal to Grade 1, then restart at next lower dose
3	Severe	
4	Life-threatening/Urgent intervention indicated	▪ Discontinue

3. **Hypertension:**
   - May require antihypertensive treatment initiation or adjustment

Grade	Severity (mmHg)	Lorlatinib dose
3	Systolic 160 or greater or diastolic 100 or greater; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	▪ First occurrence: Hold until systolic less than 140 and diastolic less than 90, then restart at same dose ▪ Recurrent: Hold until systolic less than 140 and diastolic less than 90, then restart at next lower dose ▪ Discontinue if blood pressure cannot be adequately controlled
4	Life-threatening consequences, urgent intervention indicated	▪ First occurrence: Hold until systolic less than 140 and diastolic less than 90, then restart at reduced dose or discontinue ▪ Recurrent: Discontinue

4. **Hyperglycemia:**

Grade	Severity (mmol/L, fasting measurement)	Lorlatinib dose
3	Greater than 13.9 despite optimal anti-hyperglycemic treatment	▪ Hold until adequately controlled, then restart at next lower dose ▪ Discontinue if blood sugar cannot be adequately controlled
4	Life-threatening consequences, urgent intervention indicated	

5. **PR interval prolongation/atrioventricular (AV) block:**

- Assess concomitant medications and electrolyte imbalance that may prolong PR interval
- Monitor ECG/symptoms potentially related to AV block closely

Event	Lorlatinib dose	
	Asymptomatic	**Symptomatic***
First-degree AV block	▪ Continue at same dose	▪ Hold until symptoms resolve, then restart at same dose or one dose level lower
Second-degree AV block	▪ Hold ▪ If subsequent ECG does not show second-degree AV block, restart at same dose or one dose level lower	▪ Hold ▪ Refer for cardiac observation and monitoring ▪ Consider pacemaker if persistent ▪ If resolution of second-degree AV block and symptoms resolved, restart at reduced dose
Complete AV block	▪ Hold ▪ Refer for cardiac observation and monitoring ▪ Temporary pacemaker placement may be indicated ▪ If no resolution, placement of a permanent pacemaker may be considered ▪ If pacemaker placed, may restart at previous dose ▪ If no pacemaker placed but symptoms resolve and PR interval is less than 200 msec, restart at one dose level lower	

* Symptoms may include: Dyspnea, malaise, lightheadedness, chest pain, syncope

5. **Renal impairment:**

Creatinine Clearance (mL/min)	Lorlatinib Dose
30 or higher	100%
15 to less than 30	Dose level -1

6. **Drug Interactions:**
   - Lorlatinib dose adjustment may be required for concomitant administration with other medications
   - Discontinuation of CYP3A inhibitors or inducers may alter lorlatinib levels and may necessitate dose adjustment
   - Avoid concurrent administration with medications that prolong PR interval. See BC Cancer Drug Manual

PRECAUTIONS:

1. **Hyperlipidemia** is common with lorlatinib, with patients commonly requiring initiation of lipid-lowering medications. Interruption or adjustment of lorlatinib dose in addition to treatment for hyperlipidemia may be required. See Dose Modifications.
2. **Interstitial lung disease (ILD)/pneumonitis** can occur during treatment with lorlatinib. Monitor for symptoms such as dyspnea, cough, or fever. Hold lorlatinib and investigate symptoms immediately. Discontinue for any Grade ILD/pneumonitis.
3. **Central nervous system (CNS) and psychiatric effects** including seizures, psychotic effects, changes in cognitive function, mood (including suicidal ideation), speech, mental status, sleep have been observed in patients taking lorlatinib. Ability to drive or operate machinery may be compromised. Discontinuation of lorlatinib is recommended for Grade 4 CNS effect. Dose modification may be required if less than Grade 4. See Dose Modifications, above.
4. **Hypertension** can occur in patients taking lorlatinib. Pre-existing hypertension should be adequately controlled prior to initiation of lorlatinib. It is recommended that patients monitor their blood pressure regularly (home measurements, GP's office, etc.) and keep a journal of their blood pressure measurements that can be submitted to the physician at the next appointment. Temporary suspension of lorlatinib is recommended for patients with severe hypertension (greater than 160 mmHg systolic or greater than 100 mmHg diastolic). Treatment with lorlatinib may be resumed at a reduced dose once hypertension is controlled. See Dose Modifications, above.
5. **Atrioventricular (AV) block and PR interval prolongation** are reported in patients taking lorlatinib. Symptoms may include dizziness, syncope, or slow heart rhythm. Correct electrolyte abnormalities prior to treatment and monitor ECG and electrolytes as indicated in patients with known risk factors. Dose interruption and modification may be required, see Dose Modifications. Cardiology consult may be required. Use with caution when used concomitantly with other drugs that prolong PR interval or disrupt electrolyte levels. See BC Cancer Drug Manual.
6. **Hyperglycemia** has occurred in patients taking lorlatinib. Dose interruption, reduction, or discontinuation may be required. See Dose Modifications.
7. **Peripheral neuropathy** can occur during treatment with lorlatinib. Dose adjustment per physician discretion may be considered.
8. **Peripheral edema** is associated with lorlatinib use. Leg elevations, exercise as tolerated and limiting dietary salt may be of benefit. Dose adjustment per physician discretion may be considered.

9. **Hepatic impairment** is likely to increase lorlatinib plasma concentrations. No dose adjustment is necessary for mild hepatic impairment. Lorlatinib has not been studied in moderate or severe hepatic impairment.
10. **Hepatotoxicity** with increased liver transaminases may occur during treatment. Severe hepatotoxicity has occurred during concomitant administration of lorlatinib with a strong CYP3A inducer. See BC Cancer Drug Manual.
11. **Renal impairment:** No dose adjustments are required for mild or moderate renal impairment. Dose reduction is required for patients with severe renal impairment. See dose adjustment table above. Lorlatinib has not been studied in patients requiring hemodialysis.
12. **Increases in lipase** are reported during lorlatinib use. Dose modification may be indicated per physician discretion.
13. **Vision problems** including diplopia, photophobia, blurred vision, and floaters can occur during treatment with lorlatinib. Patients should be assessed for changes in vision.
14. **Musculoskeletal**: Myalgia can occur and may be associated with elevated creatine kinase. Management of symptoms may require dose interruption of modification.

Call Dr. Sophie Sun or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions relating to this treatment program.

References:

1. Shaw AT, Bauer TM, de Marinis F, et al; CROWN Trial Investigators. First-Line Lorlatinib or Crizotinib in Advanced *ALK*-Positive Lung Cancer. N Engl J Med. 2020 Nov 19;383(21):2018-2029
2. Bauer TM, Felip E, Solomon BJ, et al. Clinical Management of Adverse Events Associated with Lorlatinib. Oncologist. 2019 Aug;24(8):1103-1110
3. Lorlatinib (Lorbrena) CADTH Reimbursement Recommendation. Canadian Journal of Health Technologies April 2022; 2(4):1-21.
4. CADTH Reimbursement Review. Provisional Funding Algorithm. Anaplastic Lymphoma Kinase–Positive Non–Small Cell Lung Cancer. May 2022.