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

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

ELIGIBILITY:

Patients must have:

- Advanced non-small cell lung cancer,
- Laboratory confirmed anaplastic lymphoma kinase (ALK)-positive tumour, defined as either IHC 3+, FISH positive, or positive by molecular testing (next-generation sequencing), and
- Disease progression on crizotinib, or intolerance to crizotinib

Patients should have:

- ECOG 0 to 2

Note:

- Sequential ALK targeted therapies (e.g., crizotinib, ceritinib) are ***not*** funded after first-line alectinib,brigatinib, or lorlatinib

EXCLUSIONS:

Patients must not have:

- Congenital long QT syndrome or a persistent corrected electrocardiogram interval (QTc) of ≥ 500 msec
- Progression during treatment on previous ALK-targeted tyrosine kinase inhibitor

TESTS:

- Baseline: alkaline phosphatase, ALT, total bilirubin, LDH, creatinine, sodium, potassium, lipase, fasting glucose
  - C-reactive protein and albumin (optional, and results do not have to be available to proceed with first treatment)
- During treatment: alkaline phosphatase, ALT, total bilirubin, and LDH should be checked two weeks after starting ceritinib and at each subsequent visit
- As required: creatinine, lipase and glucose if baseline abnormalities or if clinically indicated otherwise; ECG, sodium, potassium, heart rate and blood pressure to monitor for cardiotoxicity; chest X-ray and scans to monitor index lesions; chest radiograph for monitoring of dyspnea to rule out development of pneumonitis

PREMEDICATIONS:

- no premedications required

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
ceritinib	450 mg once daily	PO with food

Dose reduction:
Dose level -1: 300 mg once daily
Dose level -2: 150 mg once daily

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

DOSE MODICATIONS:

1. **Hepatic Dysfunction:**

ALT or AST elevation to > 5.0 x ULN with bilirubin ≤1.5 x ULN	Withhold until recovery of AST/ALT to ≤ 3.0 x ULN or baseline, then resume at 300 mg daily
ALT or AST elevation to > 3.0 x ULN and concurrent bilirubin elevation to > 2 x ULN (in absence of cholestasis or hemolysis)	Permanently discontinue

2. **Pneumonitis:** permanently discontinue ceritinib for development of any grade of treatment-related pneumonitis.
3. **QTc Prolongation:** treatment interruption and subsequent dose reduction required for QTc > 500 msec.
4. **Bradycardia:** for symptomatic, non-life threatening bradycardia, withhold treatment until asymptomatic or heart rate increases to > 60 bpm. Evaluate contributing concomitant medications and consider dose reduction when treatment resumes.
5. **Gastrointestinal toxicity:** treatment interruption and subsequent dose reduction required for grade 3 toxicity.
6. **Hyperglycemia:** treatment interruption and subsequent dose reduction required for persistent glucose levels > 13.9 mmol/L despite optimal anti-hyperglycemic therapy.
7. **Pancreatic toxicity:** treatment interruption and subsequent dose reduction required for lipase/amylase > 2 x ULN.

PRECAUTIONS:

1. **Cardiotoxicity**: QT interval prolongation and symptomatic bradycardia have been observed in patients treated with ceritinib. Ceritinib should be administered with caution in patients with pre-existing or those predisposed to QTc prolongation, or those who are taking medications that are known to prolong the QT interval. Caution should be exercised in patients with a low heart rate at baseline (<60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular block, ischemic heart disease, or congestive heart failure. Concomitant medications that result in a decrease in heart rate should be avoided if possible during treatment with ceritinib. Heart rate and blood pressure should be monitored regularly.
2. **Hyperglycemia**: ceritinib has been associated with hyperglycemia, with the risk being higher in patients with diabetes mellitus and/or concurrent steroid use. Fasting serum glucose should be periodically monitored if clinically indicated and anti-hyperglycemic medications initiated/optimized as required.
3. **Respiratory**: ceritinib has been associated with severe, life-threatening or fatal treatment-related pneumonitis. Patients should be regularly monitored for pulmonary symptoms indicative of pneumonitis.
4. **Pancreatic Toxicity**: pancreatitis, including one fatality, has been reported in less than 1% of patients receiving ceritinib in clinical studies. Monitor lipase and amylase and observe patients closely for signs and symptoms of pancreatitis.
5. **Drug interactions**: ceritinib is primarily metabolized via CYP3A. The concurrent use of strong CYP3A inhibitors may increase ceritinib plasma concentration and should be avoided. The concurrent use of strong CYP3A inducers may decrease ceritinib plasma concentration and should be avoided.
6. **Hepatic Impairment**: as ceritinib is eliminated primarily via the liver, patients with hepatic impairment may have increased exposure. Use caution in patients with moderate to severe hepatic impairment.
7. **Hepatotoxicity**: drug-induced hepatotoxicity has occurred in patients treated with ceritinib. The majority of cases are manageable and reversible with treatment interruption and/or dose reduction. Transaminases and bilirubin should be monitored regularly with more frequent testing following elevations.
8. **Gastrointestinal toxicity**: gastrointestinal toxicity occurred in 98% of patients, with a median time onset of 4-8 days. Symptoms are managed with antidiarrheal agents, antinauseants, and fluid replacement as required.

Contact Dr. Christopher Lee or tumour group delegate at (604) 930-4064 or 1-800-663-3333 with any problems or questions relating to this treatment program.

References:

1. Novartis Pharmaceuticals Canada Inc. ZYKADIA® product monograph. Dorval, Quebec; 31 August 2016.
2. Shaw AT, Kim DW, Mehra et al. Certinib in ALK-rearranged non-small cell lung cancer. N Engl J Med. 2014; 370 (13): 1189.
3. G Scagliotti, TM Kim, L Crino et al. Certinib vs chemotherapy (CT) in patients (pts) with advanced anaplastic lymphoma kinase (ALK)-rearranged (ALK+) non-small cell lung cancer (NSCLC) previously treated with CT and crizotinib (CRZ): results from the confirmatory phase 3 ASCEND-5 study.
4. De Castro Jr G, Tan DS, Crino L et al. First-line Ceritinib Versus Chemotherapy in Patients with ALK-rearranged (ALK+) NSCLC: A Randomized, Phase 3 Study (ASCEND-4) WCLC. 2016; PL03.0.
5. Novartis Pharmaceuticals Corporation. ZYKADIA® full prescribing information. East Hanover, NJ, USA; June 2017.
6. Novartis Pharmaceuticals Canada Inc. ZYKADIA® product monograph. Dorval, Quebec; 6 January 2020.
7. Cho BC, Obermannova R, Bearz A et al. Efficacy and safety of ceritinib (450 mg/d or 600 mg/d) with food versus 750 mg/d fasted in patients with ALK receptor tyrosine kinase (ALK)-positive NSCLC: primary efficacy results from the ASCEND-8 study. Journal of Thoracic Oncology. 2019; 14(7): 1255-1265.
8. Cho BC, Kim D-W, Bearz, A et al. ASCEND-8: A randomized phase 1 study of ceritinib, 450mg or 600mg, taken with a low-fat meal versus 750mg in fasted state in patients with ALK-rearranged metastatic NSCLC. Journal of Thoracic Oncology. 2017; 12(9): 1357-1367.