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

Protocol Code:	*LUAVALE*
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
- One of the following indications:
  - First-line monotherapy. Patients are eligible to receive one of: alectinib, lorlatinib, crizotinib or brigatinib. Switching for intolerance is permitted. OR
  - Second-line monotherapy for disease progression on crizotinib, or in patients with intolerance to crizotinib

Patients should have:

- ECOG 0 to 2

EXCLUSIONS:

Patients must not have:

- ROS1 mutation
- Baseline symptomatic bradycardia or QTc interval greater than 470 msec
- Severe renal impairment with CrCl less than 30 mL/min
- Progression during treatment on previous ALK-targeted tyrosine kinase inhibitor other than crizotinib

TESTS:

- Baseline: alkaline phosphatase, ALT, total bilirubin, LDH, heart rate, blood pressure
  - 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 monitored every 2 weeks for the first three months of treatment, and at each subsequent visit thereafter
  - CPK levels should be monitored every 2 weeks for the first month of treatment and as clinically indicated thereafter
- As required: calcium, potassium, ECG, heart rate and blood pressure to monitor for cardiotoxicity; creatinine; CPK; chest radiograph for monitoring of dyspnea to rule out development of pneumonitis; chest X-ray and scans to monitor index lesions.

- **PREMEDICATIONS:**
- no premedications needed

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
alectinib	600 mg twice daily	PO

Hepatic Impairment: *in patients with underlying severe hepatic impairment the recommended starting dose is 450 mg PO twice daily*

Dose reduction*:*
Dose level -1: 450 mg twice daily
Dose level -2: 300 mg twice daily

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

DOSE MODICATIONS:

1. **Hepatic Dysfunction:**

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

2. **Renal dysfunction:** treatment interruption and subsequent dose reduction is required for development of grade 3 renal impairment. Permanently discontinue for development of grade 4 renal impairment. Refer to BC Cancer Drug Manual.
3. **Bradycardia:** for symptomatic, non-life threatening bradycardia, withhold treatment until asymptomatic or heart rate increases to ≥ 60 bpm. Permanently discontinue for recurrent life-threatening bradycardia or life-threatening bradycardia which occurs in the absence of concurrent bradycardic/hypotensive medications. Refer to BC Cancer Drug Manual.
4. **Myalgia/CPK Elevation:** treatment interruption may be required for symptom management or for elevation of CPK to > 5 x ULN. Refer to BC Cancer Drug Manual.
5. **Pneumonitis:** permanently discontinue alectinib for development of any grade of treatment-related pneumonitis.
6. **Gastrointestinal perforation:** permanently discontinue alectinib for development of gastrointestinal perforation.

PRECAUTIONS:

1. **Cardiotoxicity**: Bradycardia, both symptomatic and asymptomatic, has been observed in patients treated with alectinib. Heart rate and blood pressure should be monitored regularly during treatment and co-administration of medications that lower heart rate should be avoided to the extent possible. If avoidance is not possible, patients should be closely monitored. Caution should be exercised in patients with a lower baseline heart rate, history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure. Cardiology consult may be required.
2. **Gastrointestinal Perforation**: Gastrointestinal perforation with fatal outcome, has occurred in <1% of patients treatment with alectinib. Exercise caution in patients at increased risk for gastrointestinal perforation – concomitant use of medications with risk of gastrointestinal perforation, history of diverticulitis, metastases to the gastrointestinal tract. Alectinib should be permanently discontinued in patients who develop gastrointestinal perforation.
3. **Respiratory**: Alectinib has been associated with cases of ILD/pneumonitis. Patients should be regularly monitored throughout treatment for pulmonary symptoms indicative of pneumonitis.
4. **Hepatic Impairment**: Patients with underlying *severe* hepatic impairment should receive a dose reduction of alectinib. Dose adjustment is not required for patients with underlying mild or moderate hepatic impairment. However, for <u>all</u> patients with hepatic impairment, appropriate monitoring is advised.
5. **Hepatotoxicity**: Bilirubin and transaminase elevations have been reported and generally occur within the first three months of treatment. Elevations are usually reversible with treatment interruption/dose reduction. However, biopsy confirmed *drug-induced liver injury* has occurred in some patients. Monitor liver function regularly during treatment and increase test frequency if clinically indicated.
6. **Musculoskeletal**: Myalgia can sometimes be severe and may be associated with elevated *creatine phosphokinase (CPK)*. Management of symptoms may require alectinib dose modification or temporary discontinuation of treatment.
7. **Photosensitivity**: Photosensitivity has been reported. Prolonged sun exposure should be avoided. If exposure is unavoidable, broad-spectrum sun screen and lip balm of at least SPF 50 should be used during treatment and for seven days after discontinuation of treatment.
8. **Vision disorders**: Diplopia, blurry vision, vitreous floaters, asthenopia, and reduced visual acuity have all been reported. Patients experiencing vision disorders should be cautious when driving or operating machinery.

Call Dr. Christopher Lee 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. Hoffman-La Roche Ltd. Alectinib (ALECENSARO®) product monograph. Mississauga, Ontario: 27 September 2016.
2. Peters S, Camidge R, Shaw A et al. Alectinib vs Crizotinib in Untreated ALK-Positive Non-Small Cell Lung Cancer. NEJM 2017; 377: 829-38.
3. Hida T, Nokihara H, Kondo M, et al. Alectinib vs Criztonib in Patients with ALK-Positive Non-Small Cell Lung Cancer (J-ALEX): an open-label, randomized phase 3 trial. Lancet 2017 July; 390(10089): 29-39.