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

Protocol Code: *LUAVCRIZ*

Tumour Group: *Lung*

Contact Physician: *Dr. Christopher Lee*

ELIGIBILITY:

- Advanced non-small cell lung cancer
- Laboratory confirmed anaplastic lymphoma kinase (ALK)-positive tumour defined as either IHC 3+ or FISH positive
- ECOG 0-2
- Second-line monotherapy for disease progression after prior platinum-based chemotherapy
- NOTE: Patients must have ***progressive disease*** on or after first-line therapy
- *NOTE*:
    - Sequential ALK targeted therapies (e.g., crizotinib, ceritinib) is ***not*** funded after first-line alectinib or brigatinib

EXCLUSIONS:

- Congenital long QT syndrome or a persistent corrected electrocardiogram interval (QTc) of ≥ 500 msec

TESTS:

- Baseline: CBC & Diff, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, calcium, magnesium, sodium, potassium, ECG
- Baseline, if clinically indicated: C-reactive protein and albumin
- Cycles 1 and 2, every 2 weeks: CBC & Diff, alkaline phosphatase, ALT, total bilirubin and LDH
- Cycles 3 onwards, prior to each visit: CBC & Diff, alkaline phosphatase, ALT, total bilirubin and LDH
- If clinically indicated: ECG, calcium, magnesium, sodium, potassium, creatinine, heart rate, blood pressure, chest X-ray, CT chest

PREMEDICATIONS:

- no premedications needed

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
crizotinib	250 mg twice daily	PO

Dose reduction:

Dose level -1: 200 mg twice daily

Dose level -2: 250 mg once daily

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

DOSE MODICATIONS:

1. Hematological:

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
greater than or equal to 1.0	and	greater than or equal to 50	250 mg twice daily
0.5 to less than 1.0	or	25 to less than 50	Withhold until recovery, then resume at same dose schedule
less than 0.5	or	less than 25	Withhold until recovery, then resume at 200 mg twice daily[a]

[a] In case of recurrence, withhold until recovery, then resume at 250 mg once daily. Permanently discontinue in case of Grade 4 recurrence (ANC< 0.5 or Platelets <25).

2. **Hepatic Dysfunction:**

Baseline bilirubin > 1.5 x ULN and ≤ 3 x ULN (with any ALT or AST)	Reduce starting dose to dose level -1 (200 mg twice daily)
Baseline bilirubin > 3 x ULN (with any ALT or AST)	Reduce starting dose to dose level -2 (250 mg once daily)
ALT elevation to > 5.0 x ULN with bilirubin ≤1.5 x ULN	Withhold until recovery of ALT to ≤ 3.0 x ULN or baseline, then resume at the next lower dose[a]
ALT elevation to > 3.0 x ULN and concurrent bilirubin elevation to > 1.5 x ULN	Permanently discontinue

[a] In case of recurrence, withhold until recovery to Grade <1 or baseline, then resume at 250 mg once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence. For patients treated with 250 mg once daily or whose dose was reduced to 250 mg once daily, discontinue during evaluation.

3. **Pneumonitis:** permanently discontinue crizotinib for development of any grade of treatment-related pneumonitis
4. **Renal dysfunction:** for severe impairment (CrCl < 30mL/min), not requiring dialysis, reduce dose to 50% (250mg once daily)
5. **QTc Prolongation:** treatment interruption and subsequent dose reduction is required for QTc ≥ 500 msec. Refer to the BC Cancer Drug Manual.
6. **Bradycardia:** for symptomatic, non-life threatening bradycardia, withhold treatment until asymptomatic or heart rate increases to > 60 bpm. Consider dose reduction when treatment resumes. Refer to the BC Cancer Drug Manual.
7. **Severe visual loss:** discontinue crizotinib for new onset of severe visual loss.

PRECAUTIONS:

1. **Cardiotoxicity**: QT interval prolongation and symptomatic bradycardia have been observed in patients treated with crizotinib. Crizotinib 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 crizotinib. Heart rate and blood pressure should be monitored regularly.

2. **Respiratory**: Crizotinib has been associated with severe, life-threatening or fatal treatment-related pneumonitis. These cases occurred within 2 months after the initiation of treatment. Patients should be regularly monitored for pulmonary symptoms indicative of pneumonitis.
3. **Vision disorders**: diplopia, photopsia, blurred vision, and vitreous floaters were frequently reported by patients treated with crizotinib. Ophthalmological evaluation should be considered if vision disorder persists or worsens in severity. Patient's ability to drive or operate machinery may be compromised.
4. **Drug interactions**: Crizotinib is a substrate and inhibitor of CYP3A. The concurrent use of strong CYP3A inhibitors may increase crizotinib plasma concentration and should be avoided. The concurrent use of strong CYP3A inducers may decrease crizotinib plasma concentration and should be avoided.
5. **Hepatic Impairment**: Crizotinib is extensively metabolized in the liver and hepatic impairment may result in higher plasma concentrations. Treatment with crizotinib should be used with caution in patients with hepatic impairment.
6. **Crizotinib-Induced hepatotoxicity**: Drug-induced hepatotoxicity, including hepatic failure, with fatal outcome has occurred in <1% of patients treatment with crizotinib.

Call Dr. Christopher Lee or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Pfizer Canada Inc. Crizotinib (XALKORI®) product monograph. Kirkland, Quebec: Pfizer Canada Inc; 23 November 2012.
2. Shaw T, Kim DW, Nakagawa K. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013; 368:2385-94.
3. Lexi-Drugs® (database on the Internet). Crizotinib. Lexi-Comp Inc., 17 December 2013. Available at http://online.lexi.com. Accessed 13 February, 2014.