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

EXCLUSIONS:
- Congenital long QT syndrome or a persistent corrected electrocardiogram interval (QTc) of ≥ 500 msec
- Baseline AST or ALT > 2.5 x ULN or, > 5 x ULN if due to underlying malignancy, or with total bilirubin > 1.5 x ULN

TESTS:
- Baseline: CBC & differential, platelets, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium
  - C-reactive protein and albumin (optional, and results do not have to be available to proceed with first treatment)
- During treatment: CBC & differential, platelets, alkaline phosphatase, ALT, total bilirubin and LDH should be checked two weeks after starting crizotinib and at each subsequent visit
- As required: 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 needed

TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>crizotinib</td>
<td>250 mg twice daily</td>
<td>PO</td>
</tr>
</tbody>
</table>

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 MODIFICATIONS:

1. Hematological:

<table>
<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose</th>
</tr>
</thead>
</table>
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 oncedaily. Permanently discontinue in case of Grade 4 recurrence (ANC < 0.5 or Platelets <25).

2. 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 200 mg twice daily^a |

ALT or AST 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 (AST/ALT ≤ 3.0 x ULN), then resume at 250 mg once daily. Permanently discontinue in case of further Grade 3 or 4 recurrence.

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.

**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:**