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

Protocol Code:	*LUAVBRI*
Tumour Group:	*Lung*
Contact Physician:	*Dr. Barb Melosky*

ELIGIBILITY:

Patients must have:

- Stage IIIB or IV non-small cell lung cancer,
- Laboratory confirmed anaplastic lymphoma kinase (ALK)-positive tumour defined as either IHC 3+ or FISH positive, and
- No prior systemic therapy

Patients should have:

- ECOG performance status 0-2

Note:

- Patients who are currently on first-line crizotinib (LUAVCRIZF) started prior to 1 Jun 2022 may switch to LUAVBRI if they have not experienced progression and meet other eligibility criteria
- Sequential ALK targeted therapy (e.g., crizotinib, alectinib, ceritinib) is ***not*** funded after first-line brigatinib

CAUTION:

- Patients with low heart rate at baseline (< 60 bpm), history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular block, ischemic heart disease, or congestive heart failure
- Most pulmonary adverse reactions are observed within the first 7 days of treatment initiation and usually within the first 24 to 48 hours; if possible, patients should start treatment early in the week, preferably on a Monday.

TESTS:

- **Baseline**: creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, creatine phosphokinase, lipase, fasting glucose, heart rate, blood pressure
  - CBC and differential, sodium, potassium, magnesium, CEA, 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, LDH every 2 weeks for 3 cycles
- **During treatment**: alkaline phosphatase, ALT, total bilirubin, LDH, creatine phosphokinase, lipase, heart rate, blood pressure at each visit

- **If clinically indicated:** CBC and differential, sodium, potassium, magnesium, CEA, fasting glucose, creatinine; 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:

Drug	Dose	BC Cancer Administration Guideline
brigatinib	180 mg once daily Starting dose = 90 mg PO once daily for 7 days; if tolerated†, increase to 180 mg PO once daily thereafter	PO

† Prescriber to assess patient

For treatment interruptions of 14 days or longer (for reasons other than adverse reactions), resume treatment at the starting dose of 90 mg PO once daily for 7 days before increasing to the previously tolerated dose

Dose reduction:

Dose level -1: 120 mg once daily

Dose level -2: 90 mg once daily

Dose level -3: 60 mg once daily

Permanently discontinue treatment if patients are unable to tolerate 60 mg PO once daily dosing.

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

DOSE MODICATIONS:

1. Hepatic Dysfunction:

Severe hepatic impairment (Child-Pugh class C)	Reduce one dose level
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 the next lower dose level
ALT elevation to > 3.0 x ULN and concurrent bilirubin elevation to > 2 x ULN in the absence of cholestasis or hemolysis	Permanently discontinue

2. **Renal dysfunction:** if severe renal impairment (CrCl < 30 mL/min), reduce starting brigatinib dose by approximately 50% (i.e., from 180 mg to 90 mg, or from 90 mg to 60 mg).

3. **Interstitial Lung Disease (ILD)/Pneumonitis:** for development of grade 1 or 2 ILD/pneumonitis, withhold brigatinib until recovery to baseline; dose reduction may be required once treatment resumes. Permanently discontinue brigatinib for development of Grade 3 or 4 ILD/pneumonitis or for *recurrence* of ILD/pneumonitis.

4. **Hypertension:** for severe hypertension, brigatinib should be withheld until recovery to Grade 1 or to baseline. Dose modification may be required when treatment resumes.

5. **Bradycardia:** for symptomatic, non-life threatening bradycardia, withhold treatment until asymptomatic or heart rate increases to > 60 bpm. Dose modification may be required when treatment resumes.

6. **Visual disturbances:** withhold brigatinib in patients with new or worsening visual symptoms of Grade 2 or greater severity. Dose reduction is recommended upon recovery to Grade 1 or baseline. Permanently discontinue treatment for development of Grade 4 visual disturbances.

7. **Creatine phosphokinase:**

Grade 3 or 4 elevation (> 5 x ULN) with Grade ≥ 2 muscle pain or weakness	Withhold brigatinib until recovery to Grade ≤ 1 (≤ 2.5 x ULN) or baseline, then resume at prior dose. Recurrence: withhold brigatinib until recovery to Grade ≤ 1 (≤ 2.5 x ULN) or baseline, then resume at next lower dose.

8. **Pancreatic Enzymes Lipase/Amylase:**

Grade 3 elevation (> 2 x ULN)	Withhold brigatinib until recovery to Grade ≤ 1 (≤ 1.5 x ULN) or baseline, then resume at prior dose. Recurrence: withhold brigatinib until recovery to Grade ≤ 1 (≤ 1.5 x ULN) or baseline, then resume at next lower dose.
Grade 4 elevation (> 5 x ULN)	Withhold brigatinib until recovery to Grade ≤ 1 (≤ 1.5 x ULN) or baseline, then resume at next lower dose.

9. **Hyperglycemia:** if adequate hyperglycemic control cannot be achieved with optimal medical management, withhold brigatinib. Upon recovery, resume treatment at the next lower dose. Permanent treatment discontinuation may be required.

10. **Drug interactions – CYP 3A4 *inhibitors*:** brigatinib is a substrate of CYP 3A4. The concomitant use of moderate or strong CYP 3A4 inhibitors should be avoided. If concomitant use of moderate CYP 3A4 inhibitors cannot be avoided, reduce brigatinib dose by one dose level. If concomitant use of strong CYP 3A4 inhibitors cannot be avoided, reduce brigatinib dose by approximately 50%, from 180 mg to 90 mg, or from 90 mg to 60 mg. After discontinuation of the moderate or strong inhibitor, brigatinib may resumed at the prior dose.

11. **Drug interactions – CYP 3A4 *inducers*:** brigatinib is a substrate of CYP 3A4. The concomitant use of moderate or strong CYP 3A4 inducers should be avoided. If concomitant use of *moderate* CYP 3A4 inducers cannot be avoided, brigatinib dose increase is recommended. Increase dose in 30 mg increments after 7 days of treatment at the current dose as tolerated, up to a maximum of twice the brigatinib dose that was tolerated prior to initiating the inducer. After discontinuation of the inducer, brigatinib may be resumed at the prior dose.

PRECAUTIONS:

1. **Respiratory**: Pulmonary adverse reactions have been reported, including severe, life-threatening, and fatal reactions and those with features consistent with ILD/pneumonitis. The etiology of pulmonary reactions is not known. Increased age and recent prior treatment with crizotinib (within 7 days) may be independent risk factors. Most reactions are observed within the first 7 days of treatment initiation and usually within the first 24-48 hours. Reactions have also been reported when treatment was resumed following dose interruption. Therefore, monitoring for new or worsening respiratory symptoms during these periods is important. Pneumonitis can also occur later in treatment (median onset of 150 days). Any evidence of pneumonitis should be promptly investigated.
2. **Bradycardia**: Bradycardia, sinus bradycardia, and prolongation of the PR interval has occurred in patients treated with brigatinib. Heart rate and blood pressure should be monitored regularly. Use caution in patients with a low heart rate at baseline (< 60 bpm), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular block, ischemic heart disease, or congestive heart failure. Concomitant medications that decrease heart rate or prolong PR interval should be avoided to the extent possible.
3. **Hypertension**: Hypertension, including grade 3 hypertension and hypertensive retinopathy, have been reported. Ensure blood pressure is controlled prior to treatment and monitor blood pressure regularly during treatment. Hypertension should be treated according to standard guidelines to control blood pressure. Dose interruption and/or reduction may be required for severe hypertension.
4. **Musculoskelatal**: Elevations in creatine phosphokinase have occurred in up to 75% of patients and should be monitored regularly. Median time to onset is 27 days. Patients should be advised to report any unexplained muscle pain, tenderness, or weakness.
5. **Visual Disturbances**: Visual disturbances such as blurred vision, photophobia, photopsia, diplopia, and reduced visual acuity may occur. Severe reactions such as grade 3 macular edema and cataract have been reported. Obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of grade 2 or greater severity. Ability to drive or operate machinery may be compromised.
6. **Photosensitivity**: Photosensitivity to sunlight has been reported, although severe reactions are not common. To prevent reactions, patients should avoid prolonged sun exposure during treatment with brigatinib and for 5 days after the last dose. Use of broad spectrum UVA/UVB sunscreen and lip protection with at least SPF 30 are recommended.

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

References:

1. Takeda Canada Inc. Brigatinib (ALUNBRIG®) product monograph. Toronto, Ontario; 2 March 2021.
2. Cambridge DR, Kim HR, Ahn MJ, et al. Brigatinib versus crizotinib for ALK-positive non-small cell lung cancer. N Engl J Med 370: 21; 2018.