BC Cancer Protocol Summary for First-Line Treatment of Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Osimertinib

Protocol Code: *LUAVOSIF*

Tumour Group: *Lung*

Contact Physician: *Dr. Thuan Do*

ELIGIBILITY:

Patients must have:

- Previously untreated locally advanced or metastatic non-small cell lung cancer and
- EGFR mutation-positive tumour with exon 19 deletion or L858R mutation confirmed by accredited laboratory
  - T790M mutation – use LUAVOSI
  - Other mutations – requires BC Cancer Compassionate Access Program (CAP) approval

Patients should have:

- ECOG 0-2

EXCLUSIONS:

- Congenital long QT syndrome or a persistent corrected QT interval (QTc) of ≥ 470 msec

TESTS:

- Baseline: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, calcium, potassium, magnesium, and ECG
  - 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, potassium, calcium and magnesium at each subsequent visit
- As required:
  - CBC & differential, platelets
  - MUGA scan or echocardiogram – if clinically indicated, monitoring of LVEF is recommended at baseline and at 12-week intervals
  - periodic ECG monitoring for QTc prolongation
  - creatinine if clinically indicated
  - chest x-ray and scans to monitor index lesions
  - chest x-ray for monitoring of dyspnea to rule out development of pneumonitis

PREMEDICATIONS:

- no premedications required

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
osimertinib	80 mg once daily	PO

- For patients with difficulty swallowing, or for nasogastric tube administration, please refer to the BC Cancer Drug Manual osimertinib drug monograph

Dose reduction:
Dose level -1: 40 mg once daily

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

DOSE MODICATIONS:

1. **Renal Impairment:** dose modification is not required in patients with mild or moderate renal impairment. Safety and efficacy has not been established in patients with end-stage renal disease (CrCl < 15 mL/min) or on dialysis.
2. **Hepatic Impairment:** dose modification is not required in patients with mild hepatic impairment. Safety and efficacy has not been established in patients with moderate or severe hepatic impairment.
3. **Interstitial Lung Disease (ILD):** permanently discontinue osimertinib for development of any grade of treatment-related ILD/pneumonitis.
4. **QT Prolongation:** treatment interruption and subsequent dose reduction is required for development of QTc prolongation (QTc > 500 msec on at least two separate ECGs).
5. **Left Ventricular Dysfunction/Cardiomyopathy:** treatment interruption is recommended for asymptomatic, absolute decreases in LVEF of 10% from baseline and LVEF below 50%. If *symptomatic* congestive heart failure occurs at any time, treatment should be permanently discontinued.

PRECAUTIONS:

1. **Cardiomyopathy**: congestive heart failure, pulmonary edema, and decreased ejection fraction have been observed in patients treated with osimertinib. Fatal cardiomyopathy has been reported. LVEF should be assessed regularly during treatment, particularly in patients with known cardiac risk factors, and in patients who develop treatment-related cardiac symptoms.
2. **QT Interval Prolongation**: osimertinib is associated with concentration-dependent QT interval prolongation. Monitor ECG at baseline and correct electrolyte abnormalities prior to treatment. Continued monitoring of ECG and

electrolytes is recommended during treatment, particularly in patients with predisposing conditions, and in those receiving concomitant drugs known to prolong the QT interval.

3. **Respiratory**: osimertinib has been associated with severe, life-threatening or fatal treatment-related interstitial lung disease/pneumonitis. Patients should be regularly monitored for pulmonary symptoms indicative of pneumonitis.
4. **Ocular Disorders:** osimertinib has been associated with keratitis, conjunctivitis, blepharitis, and dry eye. Ophthalmologic consultation should be considered for associated symptoms. Contact lens use is known to be an independent risk factor for ocular toxicity, including keratitis. Caution should be exercised when driving or operating machinery.
5. **Drug interactions**: concurrent use of strong CYP3A inducers should be avoided. If possible, concurrent therapy with drugs that prolong the QTc interval or disrupt electrolyte levels should also be avoided.
6. **Skin toxicity**: rash, including dermatitis acneiform, drug eruption, folliculitis, rash erythematous and maculopapular are common. They appear on the face, scalp, “v”-shaped area of the chest, upper trunk and less frequently on the extremities, lower back, abdomen and buttocks. Severe rashes may require dose interruption and modification.
7. **Paronychia**: osimertinib is associated with paronychia, which typically occurs later in treatment (e.g., 4-8 weeks) and can cause severe pain. Preventative measures and good skin care may help to reduce the frequency and severity of symptoms.

Contact Dr. Thuan Do or tumour group delegate at (604) 930-2098 or 1-800-663-3333 with any problems or questions relating to this treatment program.

References:

1. AstraZeneca Canada Inc. TAGRISSO® product monograph. Mississauga, Ontario; 19 January 2018.
2. AstraZeneca Pharmaceuticals LP. TAGRISSO® full prescribing information. Wilmington, DE, USA; August 2018.
3. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small Cell Lung Cancer. N Engl J Med, 2018.
4. Goss G, Tsai CM, Shepherd FA, et al. Osimertinib for pretreated EGFR Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol 2016; 17: 1643-1652.