

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

Protocol Code: LUAVAFAT

Tumour Group: Lung

Contact Physician: Dr. Christopher Lee

ELIGIBILITY:

- Advanced non-small cell lung cancer unsuitable for definitive local therapy
- EGFR mutation-positive tumour confirmed by an accredited laboratory
- Ambulatory performance status
- NOTE:
 - Use of first-line AFatinib to progression precludes the use of both gefitinib and erlotinib as any subsequent line of therapy in the same patient
- NOTE:
 - Consideration should be given to a standard platinum-based doublet as second-line therapy after progression or failure with AFatinib

EXCLUSIONS:

- AFatinib has not been studied in patients with severe hepatic impairment (Child Pugh C)
- **AFatinib is not recommended in patients with CrCl < 15 mL/min or in patients on dialysis**
- Patients with significant or recent gastrointestinal disorders with diarrhea as a major symptom (e.g., Crohn's disease, malabsorption or severe diarrhea of any etiology) should not be treated with AFatinib

TESTS:

- Baseline: creatinine, alkaline phosphatase, ALT, total bilirubin and LDH
 - If required, MUGA scan or echocardiogram
 - 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 checked two weeks after starting AFatinib and at each subsequent visit
- For patients with pre-existing liver disease or concomitant hepatotoxic medications, hepatic function should be closely monitored throughout treatment
- As required:
 - chest X-ray and scans to monitor index lesions
 - chest radiographs for monitoring of dyspnea to rule out development of interstitial pneumonitis
 - creatinine, sodium and potassium for patients at risk of dehydration
 - cardiac monitoring (including assessment of LVEF) for patients with cardiac risk factors

PREMEDICATIONS:

- At physician's discretion, prophylaxis for rash: minocycline 100 mg PO BID.

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
AFAtinib	40 mg	PO daily until progression*

* To be taken on an empty stomach, at least 1 hour before or 3 hours after a meal

- Dose reduction:**
 - Dose level -1: 30 mg daily
 - Dose level -2: 20 mg daily
- Careful re-evaluation after initiation of therapy is essential as AFAtinib should be continued *only if* tumour regression continues or the disease is stable and cancer-related symptoms have improved. Continued AFAtinib for "psychological" palliation in the face of progressive disease is inappropriate.

DOSE MODIFICATIONS:

- Rash/skin toxicity:** If prolonged or severe, may require treatment interruption and/or dose reduction.
- Diarrhea:** treatment interruption is recommended for grade 3 diarrhea or grade 2 diarrhea lasting ≥ 48 hours despite adequate antidiarrheal treatment. Upon recovery, resume treatment at a reduced dose level. Refer to the BC Cancer Drug Manual for detailed management recommendations.
- Renal impairment:** renal impairment increases exposure to AFAtinib. Patients with moderate renal impairment (CrCl between 30-50 mL/min) may be at an increased risk of adverse events and should be closely monitored. **Patients with severe renal impairment (CrCl 15 – 29 mL/min), should receive a reduced starting dose of 30mg PO daily.** Discontinue treatment if CrCl is < 15 mL/min.
- Elevated liver enzymes:** no guidelines for dose modification for mild to moderate hepatic impairment; AFAtinib is not recommended in patients with severe hepatic impairment. Dose interruption may be necessary in patients who develop worsening of liver function. In patients who develop severe hepatic impairment, treatment should be discontinued.

PRECAUTIONS:

- Skin toxicity:** rash, erythema and acneiform rash are very common. In general, rash manifests as a mild or moderate erythematous and acneiform rash, which may occur or worsen in areas exposed to sun. Interrupt or discontinue treatment if severe bullous, blistering or exfoliating conditions develop as **rare** cases **suggestive** of Stevens-Johnson syndrome **and toxic epidermal necrolysis** have been reported.
- Diarrhea:** diarrhea is very common and can result in acute renal insufficiency, dehydration and severe electrolyte imbalance. Onset of diarrhea is within the first 2 weeks of treatment, with grade 3 diarrhea occurring most frequently within the first 6 weeks. Close monitoring and proactive treatment is essential. Antidiarrheal agents should be readily available to

patients so that treatment can be initiated at first onset. Refer to the BC Cancer Drug Manual for detailed management recommendations.

3. **Ocular disorders:** symptoms such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. For any diagnosis of ulcerative keratitis, treatment should be interrupted or discontinued.
4. **Interstitial lung disease (ILD):** ILD or ILD-like events, including fatalities, have been reported. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever) should be performed to exclude ILD.
5. **Cardiac toxicity:** decreased LVEF has been reported. If patients develop cardiac signs/symptoms during treatment, a cardiac consultation as well as treatment interruption/discontinuation should be considered.
6. **Gastrointestinal Perforation:** Gastrointestinal perforation has been reported, and approximately one-third of cases have been fatal. Patients with history of gastrointestinal ulceration or underlying diverticular disease, bowel metastases or those on concomitant medications such as anti-angiogenic agents/steroids/NSAIDs are at increased risk; however, in some cases, patients have had no known predisposing risk factors. Permanently discontinue AFatinib following development of gastrointestinal perforation
7. **Drug interactions:** AFatinib is a substrate of P-glycoprotein (P-gp). Strong inhibitors of P-gp, if administered prior to AFatinib, may lead to increased exposure to AFatinib and should be used with caution.

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

REFERENCES:

1. Boehringer Ingelheim (Canada) Ltd. Afatinib (GIOTRIF®) product monograph. Burlington, Ontario: Boehringer Ingelheim Ltd; 31 July 2014.
2. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3327–34.
3. Wu YL, Zhou C, Hu HP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014;15:213–22.