



Positive Quality Intervention: Non-Small Cell Lung Cancer (NSCLC): Overview of EGFR Inhibitors

Description of PQI: For patients with Non-Small Cell Lung Cancer (NSCLC) that have sensitizing epidermal growth factor receptor (EGFR) mutations (most commonly exon 19 deletions or exon 21 L858R mutations) appropriate for first-line treatment with an EGFR inhibitor, osimertinib (Tagrisso) has a clear progression free survival (PFS) benefit compared to chemotherapy and has been recently recommended as a preferred first line agent according to the NCCN guidelines. If another EGFR inhibitor is being prescribed for a patient with a sensitizing EGFR mutation, the pharmacist will contact the Physician to determine why the current therapy was chosen.

Background: All EGFR inhibitors have demonstrated significant improvement in PFS when compared to standard chemotherapy in patients with positive sensitizing EGFR mutations. Moreover, in both LUX-Lung 3 and LUX-Lung 6 trials, specifically in patients with del 19 EGFR mutations, afatinib has demonstrated a statistically significant improvement in median overall survival (OS) when compared to cisplatin/pemetrexed (33.3 months versus 21.1 months) and tocicplatin/gemcitabine (31.4 months versus 18.4 months) respectively.. Consequently, all EGFR inhibitors have been recommended as category 1 first line treatment options for patients with positive sensitizing EGFR mutations. More recently, in the FLAURA clinical trial, osimertinib was compared to standard therapy with gefitinib or erlotinib in previously untreated patients who had exon 19 deletion or exon 21 L858R EGFR mutation. The median progression free survival was 18.9 months with osimertinib compared to 10.2 months with gefitinib or erlotinib ($p < 0.001$). Additionally, the median duration of response was significantly improved and less grade 3 or more adverse events were reported with osimertinib compared to gefitinib or erlotinib. This trial led to listing osimertinib as a preferred category 1 agent in the NCCN guidelines.

PQI process: Using the practice's EMR

- Identify newly diagnosed metastatic NSCLC patients Stage IIIB/IV adenocarcinoma
- Confirm that EGFR mutational testing was done

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- If not done, document reason why EGFR mutational testing was not done
- If results are pending, what is the plan?
 - Wait and start EGFR inhibitor if positive
 - Wait and start chemotherapy if negative
 - Begin chemotherapy regardless of result
- If EGFR mutational testing was done, document whether it was positive or negative
 - If negative, no further information is required
 - Documentation of choice of chemotherapy
- If EGFR mutation is positive, document the type of mutation: del 19 (exon19), L858R (exon21) or other
- Document 1 of the following 6 treatment choices:
 - Afatinib (Gilotrif)
 - Dacomitinib (Vizimpro)
 - Erlotinib (Tarceva)
 - Gefitinib (Iressa)
 - Osimertinib (Tagrisso)
 - Chemotherapy

Document the starting dose and schedule of the first three choices

- Document reason why any other dose/schedule is given than what is indicated
- Document if a starter kit was given

If chemotherapy was chosen, document the reason why it was selected.

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Dosing: Osimertinib 80mg orally once daily (*Tablet can be dissolved in water for patients with difficulty swallowing*)

Adverse Events: Most common adverse events were diarrhea 58% (Grade ≥ 3 : 2.2%), rash 58% (Grade ≥ 3 : 1.1%), dry skin 36% (Grade ≥ 3 : 0.4%), nail toxicity 35% (Grade ≥ 3 : 0.4%), stomatitis 29% (Grade ≥ 3 : 0.7%), and decreased appetite 20% (Grade ≥ 3 : 2.5%).

Keratitis and potentially fatal cardiomyopathy have also been reported.

Dosing Modifications: Dose modifications have occurred in 2.9% of patients treated with osimertinib in the FLAURA trial mostly due to QTc prolongation, diarrhea, or lymphopenia.

- Permanent discontinuation was reported in 13% of the cases mostly due to interstitial lung disease (ILD) or pneumonitis.
- If QTc ≥ 500 msec on at least two ECGs, osimertinib should be held till QTc is back to baseline or is less than 481 msec and then resumed at 40 mg daily.
- For any \geq grade 3 adverse event, osimertinib should be held for up to 3 weeks and then resumed at either 80 mg or 40 mg daily if the event improves to \leq grade 2.
- Osimertinib should be permanently discontinued in the events of ILD/pneumonitis, symptomatic congestive heart failure, QTc prolongation in association with life-threatening arrhythmia, and any grade ≥ 3 adverse reaction that does not improve within 3 weeks of holding osimertinib.
- Osimertinib should be dosed at 160mg daily during the concomitant administration of a strong CYP3A4 inducer and for 3 weeks after discontinuation of the latter.

Dose modification reference: Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. *N Engl J Med* 2018; 378:113-125.

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Labs:

- Periodic electrocardiogram and electrolytes in patients with a history of cardiac disease
- or in those who are on other medications that can cause QTc interval prolongation
- Periodic left ventricular ejection fraction in patients with cardiac risk factors
- Pregnancy test in females of childbearing potential prior to initiating therapy

Patient Centered Activities

- Provide Oncology Chemotherapy Education (OCE) sheet
- Supply Anti Diarrheal agents
- Supply Moisturizing cream
- Supply Sun Screen

Additional Indication: For the treatment of metastatic NSCLC patients who have a positive EGFR T790M mutation and whose disease has progressed on or after first-line therapy with an EGFR inhibitor

- In the AURA 3 trial, patients with a positive T790M mutation who have previously progressed on erlotinib, gefitinib, or afatinib experienced significant improvement in PFS with osimertinib as compared to pemetrexed and platinum combination (10.1 months versus 4.4 months).

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