# Best Initial Treatment Strategies for *EGFR*-Mutant Lung Cancer

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Abstract

*EGFR* activating mutations were described in lung cancer over a decade ago, and in that time, targeted therapy with epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs) have become the treatment of choice as first-line therapy. Targeted therapy improves responses and progression-free survival when compared with chemotherapy in these patients with advanced disease. Despite improvements in outcomes, resistance develops and the majority of patients experience tumor progression and are not cured. The introduction of third-generation *EGFR* TKIs that effectively block activating mutations and the T790M resistance mutation while sparing wild-type *EGFR* has led to improved outcomes following the development of resistance. The future of *EGFR* therapy will explore the use of these agents and combinations to potentially delay or eliminate resistance to increase efficacy and ultimately survival. This review will focus on current therapies used in the first-line setting for advanced *EGFR* mutation positive non–small cell lung cancer (NSCLC) followed by emerging data that may lead to a transition in the choice for initial therapy in these patients.

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## Introduction

Lung cancer is the leading cause of cancer related mortality worldwide in both men and women.[1] Patients with advanced epidermal growth factor receptor (EGFR) mutated non–small-cell lung cancer (NSCLC) treated with tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib, and afatinib, show improved progression-free survival (PFS) compared with standard chemotherapy as first-line therapy.[2-5] Unfortunately, patients develop resistance through multiple routes, including acquired *EGFR* mutations such as T790M.[6] In order to combat this resistance, second- and third-generation *EGFR* TKIs have been developed. In order to prevent or delay the development of resistance, multiple strategies have been investigated, such as the combination of high-dose pulses with low-dose continuous *EGFR* TKI therapy or co-targeting bypass signaling pathways as in the combined inhibition of both *EGFR* and MET.[7] The development of third-generation TKIs has improved patient outcomes; however, therapeutic resistance still occurs. As the options for therapy increase, the available data should be considered in choosing a frontline treatment.

## Current Options for First-Line Therapy

*EGFR* TKIs have been established as frontline therapy for patients with metastatic *EGFR* mutant lung. Differentiating between these treatment options requires an evaluation of the studies that have been performed.

The IPASS trial led the field, and was a randomized, phase 3 trial that compared gefitinib to carboplatin and paclitaxel in 1217 previously untreated never or light ex-smokers with advanced NSCLC, but did not require *EGFR* mutation. The primary endpoint was PFS, and at 12 months, the PFS was 24.9% with gefitinib and 6.7% with carboplatin/paclitaxel. In the subgroup of patients with an *EGFR* mutation, PFS was significantly longer among those who received gefitinib.[2] Importantly, those without *EGFR* mutation had improved PFS with chemotherapy, highlighting the importance of molecularly testing for activating *EGFR* mutations.

A randomized, phase 3 trial compared gefitinib versus carboplatin/paclitaxel in previously untreated patients with *EGFR*-mutated metastatic NSCLC.[8] Analysis of the first 200 patients revealed that PFS was significantly longer in patients in the gefitinib group resulting in early termination. The gefitinib group had a median PFS of 10.8 versus 5.4 months in the chemotherapy group and a higher response rate of 73.7% versus 30.7%.

A third study comparing gefitinib and cisplatin plus docetaxel had similar results.[9] This randomized, phase 3 study involved 177 previously untreated patients diagnosed with stage IIIB/IV NSCLC or postoperative recurrence with *EGFR* mutations and evaluated PFS as the primary endpoint. The gefitinib group had significantly longer median PFS compared with the cisplatin plus docetaxel group (9.2 versus 6.3 months).

A randomized, phase 3 trial compared erlotinib with carbo-

platin/gemcitabine in 165 patients with stage IIIB/IV NSCLC and *EGFR* mutations.[5] The analysis of PFS included 82 patients in the erlotinib group and 72 in the chemotherapy group. Median PFS was significantly longer in the patients treated with erlotinib than those treated with chemotherapy (13.1 versus 4.6 months).

The EURTAC trial compared erlotinib versus platinum-based chemotherapy for first-line treatment of patients with advanced NSCLC with *EGFR* mutations in a randomized, phase 3 trial.[10] In that study, 86 patients received erlotinib and 87 received standard chemotherapy. The preplanned interim analysis showed the study met its primary endpoint and enrollment was stopped. The median PFS in the erlotinib group was 9.7 months compared with 5.2 months in the chemotherapy group.

The LUX-Lung 3 study was a randomized, phase 3 trial that compared afatinib to pemetrexed/cisplatin in previously untreated EGFR-positive stage IIIB/IV NSCLC patients.[3] The study enrolled 345 patients who were randomly assigned in a 2:1 ratio and stratified by *EGFR* mutation (exon 19 deletion, L858R, or other). The median PFS was 11.1 months for the afatinib group and 6.9 months for the chemotherapy group. Median PFS among patients with exon 19 deletions and L858R deletions was 13.6 months for afatinib and 6.9 months for chemotherapy.

The LUX-Lung 6 trial randomized 364 patients with previously untreated *EGFR* mutation positive stage IIIB/IV NSCLC to receive either afatinib (242 patients) or gemcitabine-cisplatin (122 patients) a 2:1 ratio and stratified patients by *EGFR* mutation (exon 19 deletion, L858R, or other).[4] Median PFS in the afatinib group was 11.0 months and 5.6 months in the gemcitabine-cisplatin group.

A pooled analysis of LUX-Lung 3[3] and LUX-Lung 6[4] included 631 of the 709 patients randomized and evaluated overall survival (OS) in patients with exon 19 (n = 355) and exon 21 mutations (n = 276).[11] OS was significantly longer in the del19-positive tumors in the afatinib group than in the chemotherapy group (31.7 versus 20.7 months). There were no significant differences by treatment group for patients with *EGFR* L858R-positive tumors. This study showed that OS was improved for patients with del19 *EGFR* mutations in the afatinib group.[11]

The LUX-Lung 7 trial was a randomized phase 2B trial that compared first-line treatment with either afatinib or gefitinib in patients with *EGFR*-mutated stage IIIB/IV NSCLC.[12] In the study, 160 patients received afatinib and 159 patients received gefitinib until disease progression. PFS was 11.0 months with afatinib and 10.9 months with gefitinib and median time to treatment failure was 13.7 months with afatinib and 11.5 months with gefitinib, and the results were statistically significant. Furthermore, survival was increased with afatinib at 27.9 versus 24.5 months, but the result was not significant.[13]

The current frontline options with afatinib, erlotinib, and gefitinib offer improved outcomes over standard chemotherapy in *EGFR*-mutant NSCLC patients. Toxicities are manageable and most commonly include rash, and skin toxicity, and diarrhea.[2-5] Despite the benefit to patients, progression invariably occurs so we must consider novel strategies that might increase survival.

### Emerging Frontline Options

Enhancing outcomes for patients may require combination therapy or new generation inhibitors that can prevent or overcome resistance mechanisms. The strategies with early results include combination erlotinib and bevacizumab, afatinib and cetuximab, and osimertinib as first-line therapy for *EGFR*-mutant NSCLC, and other agents and combinations are under investigation.

A randomized, phase 2 study in 154 patients with stage IIIB/IV or recurrent non-squamous NSCLC with *EGFR* mutations and no previous therapy for advanced disease compared erlotinib alone versus erlotinib plus bevacizumab.[14] The median PFS was 16.0 months in the erlotinib plus bevacizumab group and 9.7 months in the erlotinib alone group. Additional studies are ongoing to confirm these results and assess toxicities.

Osimertinib, a third-generation EGFR TKI, is approved as treatment for patients with *EGFR* TKI resistance due to emergence of the T790M mutation, and demonstrated over 50% objective response rate (ORR).[15] With the hypothesis that early treatment with osimertinib can prevent the emergence of T790M as a mechanism of resistance and improve PFS, cohorts were studied using osimertinib as first-line therapy. Sixty patients from 2 phase 1 expansion cohorts of the original AURA trial received either 80 mg per day (n = 30) or 160 mg per day (30 patients) of osimertinib as first-line therapy. The ORR was 77%. Median PFS was 19.3 months for the 160 mg dose, and has not yet been reached for the 80 mg dose.[16] This early data are promising, and a phase 3 trial (FLAURA) is evaluating the efficacy of osimertinib in treatment-naïve *EGFR* mutation positive NSCLC patients (NCT02296125).

Afatinib plus cetuximab demonstrated clinical activity in *EGFR*-mutated lung cancers with acquired resistance compared with gefitinib or erlotinib, both with and without T790M mutations in a phase 1b study.[17] This combination is now being studied as a frontline therapy for *EGFR*-mutant NSCLC (NCT02438722).

Central nervous system (CNS) metastases, including leptomeningeal carcinomatosis, are a challenge in patients with *EGFR* mutation positive lung cancer. Progression within the brain often occurs in the absence of systemic tumor growth due to inadequate drug concentration in the CNS. Pulse dose erlotinib has been shown to be tolerated while increasing penetration into the brain.[18,19] A phase 1 study evaluated twice weekly pulse dose erlotinib at 1200-mg days 1 and 2 followed by 50 mg on

days 3 to 7 in treatment-naïve NSCLC patients with *EGFR* mutations.[20] The study demonstrated similar survival and responses seen in phase 3 trials, but of the 34 patients enrolled, none had progression in an untreated metastasis or developed new CNS metastases while on study. Additional trials evaluating activity of next-generation *EGFR* inhibitors in patients with CNS metastases are planned.

## Future Directions

The use of *EGFR* TKIs is effective, but patients develop resistance, most commonly due to T790M. Molecular analysis of circulating tumor cells or cell-free DNA may provide a strategy for monitoring changes in tumor genotypes and the development of drug resistant mutations during treatment. One study found that the T790M was detectable in pretreatment tumor biopsies and circulating tumor cells during treatment and that T790M mutations were associated with reduced PFS (7.7 versus 16.5 months), and an increase in the number of cells with T790M mutations correlated with disease progression.[21]

A number trials investigating *EGFR* TKIs in the frontline setting are ongoing and the results are forthcoming. These trials will help clarify the optimal use of TKIs in *EGFR* mutation positive NSCLC, and future studies will address the question of proper sequencing of therapy to provide the best outcomes for patients. The timing of third-generation EGFR inhibitors, such as earlier use of osimertinib will likely lead to new mechanisms of resistance, the emergence of the C797S *EGFR* mutation is one example.[22] Additional studies to understand these mechanisms and therapies to overcome resistance will be needed.

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