Epidermal Growth Factor Receptor Mutated Advanced Non–Small Cell Lung Cancer: A Changing Treatment Paradigm

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KEYWORDS

• Non–small cell lung cancer • Epidermal growth factor receptor (EGFR)
• Tyrosine kinase inhibitors (TKI) • TKI resistance • Osimertinib • Gefitinib • Erlotinib
• Afatinib

KEY POINTS

- Activating mutations in the epidermal growth factor receptor (EGFR) are present in approximately 15% of patients with lung adenocarcinoma in the United States.
- EGFR tyrosine kinase inhibitors (TKIs) are associated with high response rate and progression-free survival for patients with non–small cell lung cancer with this genotype.
- Gefitinib, erlotinib, and afatinib are the 3 approved 1st line TKIs for EGFR mutated non-small cell lung cancer (NSCLC).
- Understanding resistance mechanisms has led to the identification of a secondary mutational target, T790M, in more than half of patients, for which osimertinib, a third-generation TKI, has been developed and approved. Other resistance mechanisms besides T790M seem to be more complex because of tumor heterogeneity and multiple overlapping pathways, requiring better methods for detection and monitoring.
- This article reviews the current treatments, resistance mechanisms, and strategies to overcome resistance.

INTRODUCTION

Discovery of epidermal growth factor receptor (EGFR) sensitizing mutations in 2004 changed the treatment paradigm for advanced non–small cell lung cancer (NSCLC).[1,2] At that time, combination chemotherapy resulted in modest improvements in patient outcomes and had reached a therapeutic plateau with a median survival of approximately 8 to 10 months.[3–5] Although most patients present with advanced stage

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disease, one study of the National Cancer Database showed that 25% of all patients diagnosed with stage IV NSCLC from 2000 to 2008 did not receive any cancer-directed treatment.[6] Many of these patients who are diagnosed at a median age of 70 years have multiple comorbidities or reduced functional status and are not offered therapy because of concerns that they will not tolerate it in light of its limited benefits.

The molecular characterization of NSCLC has provided novel therapeutic targets that are amenable to targeted therapies. The development of EGFR tyrosine kinase inhibitors (TKIs) resulted from the observation that malignant cells overexpress EGFR compared with benign neighboring cells.[7] Activation of EGFR on the cell surface was found to be associated with cell proliferation, angiogenesis, invasion, metastasis, and an ability to escape apoptosis.[8] However, only 10% to 20% of unselected patients responded to EGFR TKIs after chemotherapy in initial studies.[9,10] Of these patients, east Asians, women, and never smokers with adenocarcinoma were more likely to achieve partial response with EGFR inhibitor therapy.[10,11] It was later elucidated that ~80% to 90% of these responses were related to the 2 most common activating mutations: exon 19 deletion (del 19) and exon 21 L858R point mutation, which affect the ATP (Adenosine triphosphate) EGFR binding sites.[12] Although EGFR mutated NSCLCs are exquisitely sensitive to TKIs and have led to improvements in progression-free survival (PFS) compared with standard first-line chemotherapy, patients inevitably progress.[13–19] Several resistance mechanisms have been identified, with the most common being the emergence of secondary T790M mutations and bypass pathways. In an effort to overcome resistance, second-generation/third-generation TKIs have been developed and have led to the US Food and Drug Administration (FDA) approval of the first T790M-targeted TKI, osimertinib. However, as understanding of the complexity of resistance mechanisms improves, so does the need for better techniques to detect clinically relevant targets and to treat them. This article discusses the evidence to support current clinical recommendations for EGFR mutated advanced NSCLC, emerging resistance mechanisms, and strategies to treat them.

CHARACTERISTICS OF EPIDERMAL GROWTH FACTOR RECEPTOR MUTATED SUBSETS

Adenocarcinoma of the lung is the most common subtype, representing about 50% of all NSCLCs. The US Lung Cancer Mutation Consortium showed that 64% of these patients have an oncogenic mutation, most of which are mutually exclusive.[20] EGFR represents the second most common mutation at ~15% after Kirsten rat sarcoma (KRAS), but it is the most clinically relevant because of the availability of FDA-approved targeted drugs.[21] In Asians, EGFR mutations are even more common and represent 30% to 40% of the population.[22,23] EGFR mutated NSCLC represents 40% to 60% of never smokers and 15% to 30% of former or current smokers.[22,24,25] Less than 5% of squamous cell cancers have EGFR mutations, which are more common in adenosquamous carcinomas.[21,26] Therefore, all patients with nonsquamous cancers, and never/light smokers, should have molecular profiling.

EGFR mutations are located in exons 18 to 21, which encode the ATP binding site of the tyrosine kinase domain. At present, 2 reversible ATP competitive TKIs (gefitinib, erlotinib) and 1 irreversible TKI (afatinib) are approved in the first-line setting to treat EGFR mutated NSCLC. However, not all mutations seem to have the same sensitivity to TKIs. Patients with del 19 treated with EGFR TKIs seem to have a better outcome compared with those with exon 21 mutation.[17–19,27–29] Some of the other less common EGFR mutations also seem susceptible to EGFR TKIs. The most prevalent of these rarer mutations include exon 18 (G719X), exon 19 insertions, exon 20 insertions (20 ins), de novo exon 20 T790M, exon 20 Ser768I, exon 21 (L861Q), and combined