Making progress in epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer by surpassing resistance: third-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs)

Giannis Mountzios

Department of Medical Oncology, University of Athens School of Medicine, Athens, Greece

Correspondence to: Dr. Giannis Mountzios. Riga Ferraiou 38, Neo Psyxiko, Athens, Greece. Email: gmountzios@gmail.com.

Abstract: Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) represent the standard of care for advanced non-small cell lung cancer (NSCLC) patients whose tumours harbor an activating EGFR mutation. Unfortunately, resistance to first- and second-generation EGFR-TKIs inevitably occurs in all patients with EGFR-mutant disease approximately within a year of treatment. At least half of these cases are attributed to the emergence of a secondary mutation in exon 20 of the EGFR gene, namely the T790M mutation. Third-generation EGFR-TKIs, including osimertinib and rociletinib, target this epigenic mutation, thus re-sensitizing cancer cells to EGFR-TKI inhibition. Osimertinib to date represents the standard of care in EGFR-mutant tumors after failure of first-line EGFR-TKIs by over-performing platinum-based chemotherapy in the recently reported AURA-3 randomized phase III clinical trial. The aim of this review is to describe the different treatment strategies that have been developed to reverse resistance to first- and second-line EGFR-TKIs, the corresponding mechanisms of resistance and the development of novel-generation EGFR-TKIs. We also discuss the challenge posed by the implementation of third-generation EGFR-TKIs earlier in the course of the disease in first-line treatment of EGFR-mutant NSCLC.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR) mutation; EGFR-tyrosine kinase inhibitor (EGFR-TKI); gefitinib; erlotinib; afatinib; osimertinib; T790M

Submitted Aug 04, 2017. Accepted for publication Sep 26, 2017.
doi: 10.21037/atm.2017.10.04
View this article at: http://dx.doi.org/10.21037/atm.2017.10.04

Introduction

Lung cancer remains the most common cause of cancer-related death in both genders (1) and a major challenge for the global health system. Non-small cell lung cancer (NSCLC), the most common type, is a heterogeneous disease with distinct biological characteristics fostering tumor progression and metastasis among the several histological subtypes of the disease. Activating epidermal growth factor receptor (*EGFR*) gene mutations have been identified as the major genetic event driving tumor progression in approximately 10–15% of patients with NSCLC, depending on gender, smoking habits and ethnicity. EGFR-mutant NSCLC represents a typical example of "oncogene addiction" that can be treated by molecular agents that specifically target the constitutive activation of EGFR (2-4).

Since the discovery of small molecules that inhibit the activation of the intracellular domain of EGFR, that functions as a tyrosine kinase, there has been substantial improvement in our understanding of the molecular biology of *EGFR*-mutant NSCLC. The presence of activating EGFR mutations remains the most robust predictor of response to the first-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs) gefitinib and erlotinib and to the second-generation counterparts including afatinib and dacomitinib. Second-generation EGFR-TKIs differ from their first-generation siblings in the sense that they confer irreversible inhibition of the EGFR tyrosine kinase domain. Numerous randomized phase III trials have altogether concluded that gefitinib, erlotinib and afatinib produce a

higher response rate (RR), longer progression-free survival (PFS), and are less toxic than standard platinum-based doublet chemotherapy when given to untreated advanced NSCLC with an activating EGFR mutation (EGFR+) (2-10). Based on these data, EGFR-TKIs are currently recommended by international guidelines as first-line treatment in patients with advanced *EGFR*-mutant NSCLC based on the high level of existing evidence (11,12).

Unfortunately, the majority of patients who experience an initial response to treatment, will progress within a median of 10–12 months of initial treatment and several mechanisms of acquired resistance to first-generation EGFR-TKIs have been reported (13). In more than half of the cases, the identified resistance mechanism is the emergence of a unique missense mutation within exon 20, the so-called T790M mutation, which leads to the substitution of threonine by methionine at position 790 (14,15). The specific locus encodes part of the kinase domain of the receptor, resulting in increased affinity for ATP in comparison with reversible EGFR-TKIs, like gefitinib and erlotinib (16-18). This results in competitive replacement of the drug by ATP in the binding pocket, rendering thus the tumor resistant to inhibition by reversible EGF. Herein, we describe the different treatment strategies that have been developed to obviate failure of first-line EGFR-TKIs, the recent introduction of novel EGFR inhibitors that target the resistance mutation T790M and the challenges posed by the third-generation EGFR-TKIs earlier in the course of the disease in first-line treatment of *EGFR*-mutant NSCLC.

Mechanisms of progression to first- and second-generation EGFR-TKIs and ways to overcome resistance

The emergence of the secondary (epigenic) T790M mutation, as described above, accounts for the majority of cases of failure to treatment with first- and second-generation EGFR-TKIs. c-MET is also considered a promising oncogenic driver in NSCLC. MET activation including gene mutation, amplification and protein overexpression, all of these are potential therapeutic targets and are associated with poor prognosis. Clinical evidence suggests a role for MET activation as both a primary oncogenic driver in subsets of lung cancer, and as a secondary driver of acquired resistance to EGFR-TKIs.

Not all *EGFR*-mutant NSCLC cases progress in the same way: one of the common ways is oligoprogressive disease. Although no universally accepted definition exists to date, oligoprogressive disease usually refers to locoregional or systematic disease progressing slowly but remaining asymptomatic—or mildly symptomatic—in most of the patients. This slow evolution rate of oligoprogressive disease implies that driver oncogene addiction is still present and amenable to treatment, suggesting that a combination of continuous blockade of the driver oncogene with local treatment—either surgery or radiotherapy or stereotactic radiotherapy might be effective and beneficial for these patients. Isolated central nervous system (CNS) metastasis is a frequent event of progression in EGFR positive NSCLC that does not always mean that systemic acquired resistance has been developed and thus continuation of EGFR-TKI oncogene addiction remains a potentially beneficial therapeutic option.

Another important aspect to address, is whether the EGFR-TKI should be used together with chemotherapy due to preclinical studies suggesting a potential benefit from this combinatorial approach, notwithstanding the observed disease flare on discontinuation of the EGFR-TKI (19). This option has been clearly abandoned after the results of the IMPRESS trial, which randomized 265 patients who failed first-line gefitinib to receive either gefitinib plus cisplatin-pemetrexed or placebo plus cisplatin-pemetrexed (20). The study did not show any statistical difference between the two arms in terms of RR (31% *vs.* 34%), nor for PFS [5.4 months for both arms; hazard ratio (HR), 0.86; P=0.27]. Surprisingly, a trend for better overall survival (OS) in favor of cisplatin-pemetrexed chemotherapy alone was observed (17.2 *vs.* 14.8 months; HR, 1.62; P=0.029). In an update at WCLC 2015, T790M status from plasma sample was known for 247 patients, of which 57.5% were T790M positive. Median PFS for the T790M positive subgroup was 4.6 and 5.3 months for Gefitinib and placebo, respectively (HR, 0.97; P=0.88), whereas the corresponding medians for the T790M negative cohort were 6.7 and 5.4 months for gefitinib and placebo, respectively (HR, 0.67; P=0.075) (21), suggesting a small incremental benefit of gefitinib continuation only in T790M negative patients.

Another appealing strategy to overcome resistance is by combining dual inhibition of the extracellular and intracellular domains of the receptor. Preclinical models showed that concurrent administration of afatinib with the monoclonal antibody against EGFR cetuximab, but not each one of the drugs separately, could be effective in EGFR T790M positive tumors with emergent resistance

to erlotinib (22). However, in a subsequent phase I/II study, no benefit of combining erlotinib with cetuximab in patients with acquired resistance to erlotinib was shown (23). Nevertheless, a study combining afatinib with cetuximab conducted in patients with secondary resistance either erlotinib or gefitinib, reported a 30% RR and a median PFS of 4.7 months (24). Responses were seen not only in patients with *EGFR* T790M positive, but also among those without the *EGFR* T790M substitution. Unfortunately, high incidence of adverse events (AEs), particularly rash and diarrhoea, represents a worrisome limitation for the clinical implementation of this combination. Additionally, recent data came to show that some patients who develop resistance to third-generation EGFR-TKIs may be sensitive to cetuximab (25).

In particular cases, change of the first-line EGFR-TKI to a second-generation one might represent an alternative; Second-generation EGFR-TKIs, such as afatinib, dacomitinib, and neratinib, differ from first-line in the sense that they exert an irreversible inhibition of the ATP-binding pocket domain, as mentioned above. These drugs can also target other human epidermal growth factor receptor (HER)-family members, like HER2. The larger drawback that has hampered the clinical development of these agents so far, has been the fact that they do not target effectively the T790M mutation, which accounts for at least half of the resistant cases and this represents a major limitation for these agents. It was in this context that the third-generation EGFR-TKIs, have been developed.

Targeting the T790M mutation

Osimertinib (Tagrisso®, AstraZeneca) is an oral, selective third-generation EGFR-TKI inhibitor, which is active against the T790 mutation (26). The phase I trial of Osimertinib in patients with inoperable lung cancer that progressed after treatment on first-line TKIs combined dose escalation cohorts with gradually increasing doses of the agent (20, 40, 80, 160 and 240 mg) and expansion cohorts (27). Of note, among 31 patients who were enrolled in the dose escalation and 222 in the expansion cohort, 62% exhibited the EGFR T790M mutation. Osimertinib was so well-tolerated and with no dose limiting toxicities, that a maximum tolerable dose (MTD) was not defined. The most common AEs were diarrhoea (47%), rash (40%), nausea (22%) and anorexia (21%). Almost one third (32%) of patients experienced a grade III or higher event but the discontinuation rate due to an AE was as low as 6%. There were six events of potential drug-associated pneumonitis that resolved after treatment discontinuation and seven fatal events but without a clear association with the drug. More than half of the patients experienced an objective response (51%) with a disease control rate (DCR) reaching 84%. Of note, among patients with a T790M mutation, the odds ratio (OR) was 61% with an impressive DCR of 95% whereas in the T790M negative patients corresponding numbers were 21% and 61%, respectively, suggesting that osimertinib also possesses off-target efficacy. The median PFS was 9.6 and 2.8 months for the T790 positive and T790M negative population, respectively.

The encouraging results of the early clinical trials with osimertinib prompted the design of a large phase III clinical trial in the second-line setting, exclusively in T790M mutation-positive patients, after failure of first- or second-generation EGFR-TKIs. In this randomized, international, phase 3 trial (AURA 3) (28), overall 419 patients with T790M-positive advanced non-small cell lung cancer, who had disease progression after first-line EGFR-TKI therapy, were assigned in a 2:1 ratio to receive either oral osimertinib (at a dose of 80 mg once daily) or intravenous pemetrexed (500 mg per square meter of body-surface area) plus either carboplatin [target area under the curve (AUC), 5] or cisplatin (75 mg per square meter) every 3 weeks for up to 6 cycles; maintenance pemetrexed was allowed. The primary end point, which was investigator-assessed PFS, was significantly longer with osimertinib than with platinum therapy plus pemetrexed [10.1 *vs.* 4.4 months; HR, 0.30; 95% confidence interval (CI), 0.23–0.41; P<0.001], as well as the objective RR was significantly better with osimertinib (71%; 95% CI, 65–76%) than with platinum therapy plus pemetrexed (31%; 95% CI, 24–40%) (OR for objective response, 5.39; 95% CI, 3.47–8.48; P<0.001). Notably, among 144 patients with metastases to the CNS, the median duration of PFS was longer among patients receiving osimertinib than among those receiving platinum therapy plus pemetrexed (8.5 *vs.* 4.2 months; HR, 0.32; 95% CI, 0.21–0.49). Osimertinib was also better tolerated, as the proportion of patients with AEs of grade 3 or higher was lower with osimertinib (23%) than with platinum therapy plus pemetrexed (47%). These results led to the approval of osimertinib for the treatment of patients with T790M-positive, EGFR-mutant advanced NSCLC after failure of initial EGFR-TKI treatment, in both the United States and the European Union.

A randomized phase III trial (FLAURA, NCT02296125) is currently evaluating osimertinib *vs.* standard EGFR-TKI

treatment (erlotinib or gefitinib) in the first-line setting of patients whose tumors harbor the T790M mutation, and results are eagerly awaited, probably within 2017. These results will help to clarify the landscape in the first-line setting, by determining whether initial treatment with osimertinib is preferable to first-generation EGFR-TKIs.

Critical aspects and future perspectives

Inevitably, the success of the first-generation EGFR-TKIs is hampered by the emergence of resistance to treatment and subsequent disease progression. One important challenge is when is the optimal timing to switch to second-line therapy: for the subset of patients with slow or asymptomatic progression, continuing the same EGFR-TKI and combining with localized treatment (surgery, radiotherapy) is feasible and may confer additional survival advantage (the case of oligoprogression). Moreover, due to the improved clinical outcomes of patients with *EGFR*-mutant NSCLC, a constantly increasing clinical scenario is that of intracranial disease progression or progression within the CNS, with parallel control of systemic disease: in that case, local ablative therapy combined with cranial or CNS radiotherapy, alongside with continuation of the same molecular agent, may provide disease control for a clinically meaningful period of time.

Undoubtedly, among the various mechanisms of resistance described, the T790M mutation is currently the most clinically significant and exploitable. The so called "third-generation" EGFR-TKIs have shown substantial clinical activity in this setting and moreover with a favorable toxicity profile. As a consequence, the novel treatment algorithm for patients with EGFR positive NSCLC who progress on a first- or second-generation EGFR-TKI necessitates to perform a second biopsy to identify potential mechanisms of resistance. The aforementioned AURA 3 trial elucidated the landscape in the second-line setting, by demonstrating that in *EGFR*-mutant patients progressing after first-line treatments with EGFR-TKIs, osimertinib significantly improved PFS, as compared to platinum chemotherapy combined with pemetrexed. In addition, the FLAURA trial will determine whether the latter should outplace the former as front-line therapy for *EGFR*-mutant NSCLC. Another important question remaining to be addressed is whether the combination of EGFR-TKIs with immune checkpoint inhibitors may improve outcomes in *EGFR*-mutant NSCLC, and this now represents an intense area of research in order to elucidate the optimal timing and sequence of these agents.

Another important aspect of resistance to EGFR-TKIs is that it has conferred a major impact in translational medicine with molecular analysis of tumor biopsies being mandatory not only after diagnosis but also serially upon disease progression. Crucial elements of this strategy remain to be clarified, regarding the optimal timing of the second biopsy and the best site of progressive disease to biopsy, in order to obviate intratumoral molecular heterogeneity. For this reason, "liquid biopsies", either by terms of circulating tumor cells or by terms of circulating tumor DNA, has become increasingly important, in an effort to obviate molecular heterogeneity by captivating the clone that is more likely responsible for metastatic seeding. Of course, this approach is preferable in the sense that it is less invasive and far easier to repeat serially, even in a frail patient, as it requires just a blood sample.

Conclusively, it is without doubt that *EGFR*-mutant NSCLC remains a very challenging area of intensive research, in an effort to reverse resistance to EGFR-TKIs, by taking advantage of the ongoing phenomenon of "oncogene addiction". Moreover, the emergence of resistance and the clinical development of novel-generation EGFR-TKIs that target these resistant clones remain an ideal "prototype" for the study of molecular biology of cancer and ways to circumvent resistance to initial treatment, which may offer significant lessons to other areas of molecular oncology.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29.
2. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
3. Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. J Clin

Oncol 2012;30:1122-8.
4. Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). Ann Oncol 2013;24:54-9.
5. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.
6. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8.
7. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
8. 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.
9. Wu YL, Zhou C, Hu CP, 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.
10. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
11. Masters GA, Temin S, Azzoli CG, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2015;33:3488-515.
12. Reck M, Popat S, Reinmuth N, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii27-39.
13. Cortot AB, Jänne PA. Molecular mechanisms of resistance in epidermal growth factor receptor-mutant lung adenocarcinomas. Eur Respir Rev 2014;23:356-66.
14. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res 2013;19:2240-7.
15. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 2011;3:75ra26.
16. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med 2005;2:e73.
17. Yun CH, Mengwasser KE, Toms AV, et al. The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. Proc Natl Acad Sci U S A 2008;105:2070-5.
18. Matikas A, Mistriotis D, Georgoulias V, et al. Current and Future Approaches in the Management of Non-Small-Cell Lung Cancer Patients With Resistance to EGFR TKIs. Clin Lung Cancer 2015;16:252-61.
19. Chmielecki J, Foo J, Oxnard GR, et al. Optimization of dosing for EGFR-mutant non-small cell lung cancer with evolutionary cancer modeling. Sci Transl Med 2011;3:90ra59.
20. Soria JC, Wu YL, Nakagawa K, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol 2015;16:990-8.
21. Soria JC, Wu YL, Nakagawa K, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. Lancet Oncol 2015;16:990-8.
22. Regales L, Gong Y, Shen R, et al. Dual targeting of EGFR can overcome a major drug resistance mutation in mouse models of EGFR mutant lung cancer. J Clin Invest 2009;119:3000-10.
23. Janjigian YY, Azzoli CG, Krug LM, et al. Phase I/II trial of cetuximab and erlotinib in patients with lung adenocarcinoma and acquired resistance to erlotinib. Clin Cancer Res 2011;17:2521-7.
24. Janjigian YY, Smit EF, Groen HJ, et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. Cancer Discov 2014;4:1036-45.
25. Ercan D, Choi HG, Yun CH, et al. EGFR Mutations and Resistance to Irreversible Pyrimidine-Based EGFR Inhibitors. Clin Cancer Res 2015;21:3913-23.
26. Herbst RS, O'Neill VJ, Fehrenbacher L, et al. Phase

II study of efficacy and safety of bevacizumab in combination with chemotherapy or erlotinib compared with chemotherapy alone for treatment of recurrent or refractory non small-cell lung cancer. J Clin Oncol 2007;25:4743-50.
27. Jänne PA, Yang JC, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med 2015;372:1689-99.
28. Ramalingam SS, Yang JC, Lee CK et al. AZD9291, a mutant-selective EGFR inhibitor, as first-line treatment for EGFR mutation-positive advanced non-small cell lung cancer (NSCLC): Results from a phase 1 expansion cohort. J Clin Oncol 2015;33:abstr 8000.

Cite this article as: Mountzios G. Making progress in epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer by surpassing resistance: third-generation EGFR tyrosine kinase inhibitors (EGFR-TKIs). Ann Transl Med 2018;6(8):140. doi: 10.21037/atm.2017.10.04

