

Treating *EGFR* mutation resistance in non-small cell lung cancer – role of osimertinib

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Abstract: The discovery of mutations in *EGFR* significantly changed the treatment paradigm of patients with *EGFR*-mutant non-small cell lung cancer (NSCLC), a particular group of patients with different clinical characteristics and outcome to *EGFR*-wild-type patients. In these patients, the treatment of choice as first-line therapy is first- or second-generation *EGFR*-tyrosine kinase inhibitors (*EGFR*-TKIs), such as gefitinib, erlotinib, or afatinib. Inevitably, after the initial response, all patients become refractory to these drugs. The most common mechanism of acquired resistance to *EGFR*-TKIs is the development of a second mutation in exon 20 of *EGFR* (*T790M*). Osimertinib is a third-generation *EGFR*-TKI designed for overcoming *T790M*-mediated resistance. Based on the results of efficacy and tolerability of Phase II and Phase III studies, osimertinib has been approved for treatment of advanced *EGFR*^{T790M+} mutation NSCLC following progression on a prior *EGFR*-TKI. Occurrence of acquired resistance to osimertinib represents an urgent need for additional strategies including combination with other agents, such as other targeted therapies or checkpoint inhibitors, or development of new and more potent compounds.

Keywords: *EGFR*-mutant non-small-cell Lung cancer, acquired resistance, *T790M* mutation, third generation *EGFR*-TKI, osimertinib

Introduction

Lung cancer is the second most commonly diagnosed cancer and the main cause of cancer-related mortality in both men and women. Non-small cell lung cancer (NSCLC) represents ~85% of lung cancer cases and it presents as metastatic disease in over half of all cases. In the last few years, treatment of NSCLC has radically changed after the discovery that inhibition by target agents of molecular drivers, such as *EGFR*, could be effective in reducing tumor burden. The prevalence of *EGFR* mutations in adenocarcinoma is 10% of Western and up to 50% of Asian patients. It is well known that *EGFR* mutations are more frequently observed in Asiatic than in Caucasian patients, in female, in never smokers, and mainly in adenocarcinomas, with deletion in exon 19 or point mutation in exon 21 (L858R) as the most common (>90%) types. Nine randomized Phase III clinical trials (OPTIMAL, First Signal, IPASS, WJTOG 3405, NEJSG 002, EURTAC, ENSURE, LUX-3, LUX-6) demonstrated that, in patients harboring classical *EGFR* mutations, *EGFR*-tyrosine kinase inhibitors (*EGFR*-TKIs) such as erlotinib, gefitinib, or afatinib are superior to the standard platinum-based chemotherapy in terms of response rate, progression-free survival (PFS), toxicity profile, and quality of life (Table 1). In up to 60%–80% of patients treated with an *EGFR*-TKI, there is a meaningful tumor regression, but inevitably, after a median time of 9–12

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Table 1 Studies of EGFR-TKIs versus chemotherapy as first-line therapy in EGFR^{mut+} NSCLC

Study	EGFR-TKI	n	Median PFS in TKI arm (months)	P-value	HR
OPTIMAL ⁵¹	Erlotinib	154	13.7	<0.0001	0.16
First signal ⁵²	Gefitinib	42	8.4	0.084	0.48
IPASS ⁵³	Gefitinib	261	9.5	<0.0001	0.36
WJTOG 3405 ⁵⁴	Gefitinib	177	9.2	<0.001	0.42
NEJSG 002 ⁵⁵	Gefitinib	200	10.8	<0.001	0.36
EURTAC ⁵⁶	Erlotinib	174	10.4	<0.0001	0.42
ENSURE ⁵⁷	Erlotinib	217	11.0	0.0001	0.34
LUX-3 ⁵⁸	Afatinib	308	11.1	0.001	0.58
LUX-6 ⁵⁹	Afatinib	364	11.0	<0.0001	0.28

Abbreviations: EGFR-TKI, epidermal growth factor-tyrosine kinase inhibitor; HR, hazard ratio; PFS, progression-free survival.

months, all patients develop acquired resistance and become refractory.^{1–5} Among the different mechanisms of acquired resistance, a secondary mutation, *T790M*, in the exon 20 of the *EGFR* gene is the most frequent event, occurring in ~50%–60% of cases. At the present time, only one agent has been US Food and Drug Administration (FDA) approved for treatment of *EGFR*^{T790M+} patients. Phase II studies and more recently a large Phase III trial demonstrated that osimertinib (Tagrisso, AstraZeneca, London, UK) is active in *EGFR*-TKI-pretreated, *EGFR*^{T790M+} patients, representing today the best option in the acquired resistance setting.^{5–8}

Resistance to EGFR-TKIs

According to Jackman's criteria, resistant patients should have the following features:

1. Previously received treatment with a single-agent EGFR-TKI;
2. Either or both the following elements: a tumor harboring an *EGFR* mutation known to be associated with drug sensitivity (ie, *G719X*, exon 19 deletion, *L858R*, *L861Q*) or objective clinical benefit from treatment with an EGFR-TKI (documented partial or complete response [CR] according to RECIST or WHO criteria) or significant and durable (≥ 6 months) clinical benefits (stable disease [SD] as defined by RECIST or WHO) after initiation of an EGFR-TKI.

The following criteria are additional: systemic progression while on continuous treatment with an EGFR-TKI within the last 30 days and no intervening systemic therapy between cessation of EGFR-TKIs and new therapy.⁹ Acquired resistance to EGFR-TKIs can be target dependent, if it is characterized by the development of a second mutation in *EGFR* sequence,

or target independent, if it is a consequence of the activation of alternative pathways.⁴ The most frequent mechanism of acquired resistance (up to 60% of cases) is target dependent and consists of the emergence of the *T790M* mutation, a characteristic point mutation in exon 20 of the *EGFR* gene. Target-independent mechanisms include *MET* amplification (4%), human EGFR type 2 (*HER2*) amplification (8%–13%), *PIK3CA* mutation (2%), *BRAF* mutation (1%), histological transformation from NSCLC to SCLC (6%), or epithelial–mesenchymal transition (1%–2%).^{2,4} In 18% of the cases, the mechanism of acquired resistance is unknown (Figure 1). Histological and biological review of tissue samples, taken after the development of acquired resistance, demonstrated that, in some cases, these mechanisms overlap and are not mutually exclusive.¹⁰

The complexity of resistance mechanisms highlights the importance of repeating a tumor biopsy at the time of disease progression. Moreover, availability of new agents specifically effective only in the presence of *EGFR*^{T790M} mutation explains why tumor re-biopsy is now entering into clinical practice. Unfortunately, in lung cancer patients, repeating tumor biopsy is not feasible in the majority of cases mainly because of the risk related to a new biopsy in a difficult-to-access disease or patient refusal. Therefore, during the last few years, much interest is growing around the possibility to assess the mutational status on circulating tumor DNA (ctDNA). The so-called “liquid biopsy,” which involves isolating ctDNA in plasma or other biologic fluids, including urine, presents several advantages including the fact that it is

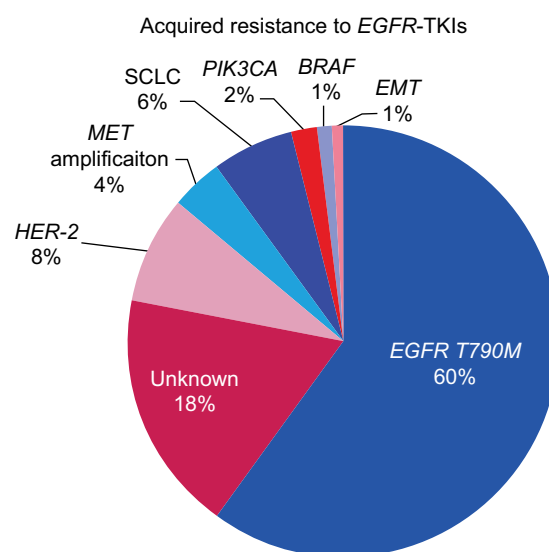


Figure 1 Mechanisms responsible for acquired resistance to EGFR-TKIs. **Abbreviations:** EGFR-TKI, epidermal growth factor-tyrosine kinase inhibitor; EMT, epithelial to mesenchymal transition; SCLC, histological transformation to small cell lung cancer.

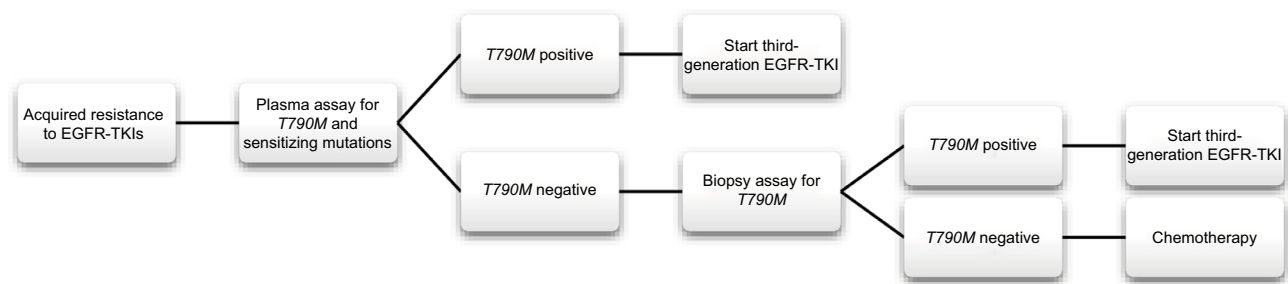


Figure 2 Flowchart for plasma and tumor genotyping for *T790M* testing.
Abbreviations: EGFR-TKI, epidermal growth factor-tyrosine kinase inhibitor.

easy to perform, rapid, and repeatable, overcoming the problem of tumor heterogeneity.^{11,12} The only relevant limitation is represented by the relatively low sensitivity (60%–80%). Sensitivity is also influenced by the type of mutation and tumor burden, with patients with low tumor burden at a high risk of a false-negative result. Therefore, in clinical practice, liquid biopsy is now recommended as the first test to offer to the patient, with tumor biopsy recommended only in the case of a negative result (Figure 2).¹³

Pharmacodynamic

The *T790M* mutation consists of the substitution of threonine at the “gatekeeper” amino acid 790 by methionine. This mutation makes the receptor refractory to the inhibition by reversible EGFR-TKIs through both steric hindrance and increased ATP affinity (its natural substrate). Osimertinib is an oral, irreversible, third-generation TKI targeting *T790M* and EGFR-TKI-sensitizing mutation sparing the activity of wild-type *EGFR*. First-generation reversible TKIs (erlotinib and gefitinib) are ineffective at targeting *T790M*, while they strongly inhibit wild-type *EGFR* cell lines with similar potency to sensitizing mutant *EGFR*. Second-generation irreversible TKIs (afatinib and dacomitinib) show activity against *T790M* in vitro, but concentrations required to overcome *T790M* activity preclinically are not achievable in humans due to non-selective inhibition of wild-type *EGFR* which is associated with significant toxicity.¹⁴ The good safety profile and the tolerability of osimertinib are related to the selective inhibition of *T790M* and *EGFR*-sensitizing mutation. 1) Osimertinib is less potent at inhibiting phosphorylation of EGFR in wild-type cell lines. It is associated with lower skin and gastrointestinal toxicity.

Clinical trials

AURA⁵ was a Phase I study assessing the safety, tolerability, and efficacy of osimertinib. Eligible patients had a locally advanced or metastatic NSCLC, had a known

EGFR-TKI-sensitizing mutation or a prior clinical benefit from treatment with EGFR-TKI, and had a radiologically documented disease progression while receiving such treatment. This study included dose-escalation and dose-expansion cohorts. In the dose-escalation cohorts, patients received a single dose of osimertinib. The first dose tested was 20 mg daily. Each subsequent dose represented a 100% increase from the previous dose, with the exception of the final dose escalation, which was from 160 mg once daily to 240 mg once daily. In the dose-escalation cohorts, pre-treatment *EGFR**T790M* testing was optional, while in the dose-expansion cohorts, a new tumor biopsy was required after disease progression on the most recent regimen. Testing for *EGFR T790M* was performed in a central laboratory or in a local laboratory followed by confirmation in a central laboratory. The objective response rate (ORR) for the entire population was 51% and the disease control rate (DCR) (CR plus partial response plus SD) was 84%. In patients harboring the *T790M* mutation, the ORR was 61% and the DCR was 95%. There was activity in the *T790M*-negative patients with an ORR of 21% and DCR of 61%. In *EGFR*^{*T790M*+} patients, the median PFS was 9.6 months and in *EGFR*^{*T790M*-} patients, it was 2.8 months. The most common adverse events (AEs) were diarrhea (47%), rash (40%), nausea (22%), and anorexia (21%). Grade 3 or higher AEs were observed in 32% of patients, with AEs leading to dose reduction in 7% of patients and AEs leading to drug discontinuation in 6% of patients.^{5,15} The optimal dose to obtain the best efficacy with the lower risk of toxicity is 80 mg once daily.

AURA ex,⁶ a Phase II extension cohort of the Phase I trial, evaluated the efficacy, tolerability, and safety of osimertinib at a dose of 80 mg once daily in the *EGFR*^{*T790M*+} patients progressing after EGFR-TKI treatment. Similar to the results from the Phase I trial, the ORR was 61% with a DCR of 91%. Osimertinib was well tolerated with drug-related grade ≥ 3 AEs reported in 12% of the patients and a discontinuation rate of 4%. These promising results were confirmed also in AURA

2 study,⁷ a Phase II, single-arm trial conducted in *EGFR*^{T790M+}, which showed an ORR of 71%, with a DCR of 92% and a median PFS of 6.8 months.^{6,7} In a combined analysis of 411 patients in both Phase II trials (AURA ex and AURA 2), the most commonly reported all-grade AEs were diarrhea (42%), rash (41%), dry skin (31%), nail toxicity (25%), eye disorders (18%), nausea (17%), decreased appetite (16%), and constipation (15%). These events were primary grade 1/2, with a low rate of grade ≥ 3 AEs. The most common grade ≥ 3 AEs were pneumonia (2%) and pulmonary embolism (2%). Across both studies, dose reductions as a result of AEs were needed for 4.4% of patients. The most frequently reported AEs that led to a dose reduction or interruption were QTc prolongation (2%) and neutropenia (2%). Other AEs resulting in treatment discontinuation were interstitial lung disease (ILD) or pneumonitis (2%) and cerebrovascular accident (1%). Fatal AEs occurred in 3.2% of patients and consisted of four cases of pneumonitis, which were attributed to osimertinib.^{6,7} Since in AURA and AURA 2 trials brain metastases were assessed as non-target lesions, there were no measurements of metastatic brain lesion diameter. Therefore, it was not possible to calculate an ORR or DCR for central nervous system (CNS) disease. In these studies, the proportion of patients with the CNS as the first site of progression was 12%.¹⁶ Omuro et al reported that the incidence of the CNS as an initial failure site reached 33% in EGFR-TKI responders with advanced NSCLC.¹⁷ Approximately half of patients with *EGFR*-positive metastatic NSCLC treated with first-line chemotherapy develop CNS disease relapse, and the low rate of primary CNS relapse in AURA and AURA 2 trials may suggest a CNS antitumor activity¹⁶ of osimertinib. The mechanism underlying the relationship between clinical benefit from EGFR-TKIs and CNS metastasis may involve several causal factors. Prolonged survival through the use of EGFR-TKIs may coincide with a substantial risk of developing CNS metastasis, as the cranial event occurs in a relatively late phase of the disease. The high frequency of *EGFR* mutations in brain metastases of lung adenocarcinoma suggests an intrinsic brain tropism of these tumors. Incomplete drug penetration of the brain–blood barrier may account for the increased incidence of CNS metastasis. Metastatic CNS clones may possess an inherited resistance to EGFR-TKIs, or they may acquire earlier drug resistance during EGFR-TKI therapy.^{17,47} Noteworthy, first-generation EGFR-TKIs hardly penetrate across the blood–brain barrier at the recommended doses.¹⁸ Based on the data from Phase II studies (AURA extension⁶ and AURA 2⁷), osimertinib was approved by FDA, in November 2015, and by European Medicines Agency, in

April 2016, for patients with advanced *EGFR*^{T790M+} NSCLC following progression on a prior EGFR-TKI.

AURA 3,⁸ published on December 2016, is a Phase III trial comparing osimertinib with platinum-based doublet chemotherapy in patients with *EGFR*^{T790M+} advanced NSCLC after first-line EGFR-TKI therapy. Patients were randomly assigned to received oral osimertinib (80 mg once daily) or intravenous pemetrexed (500 mg/m²) plus either carboplatin area under the curve (AUC) 5 or cisplatin (75 mg/m²). The median PFS was significantly longer with osimertinib than with platinum-based chemotherapy (10.1 months vs 4.4 months). This benefit was observed across all predefined subgroups also among patients with stable, asymptomatic CNS metastases (8.5 months vs 4.2 months), supporting preclinical and clinical data suggesting that osimertinib may be an EGFR-TKI with improved brain exposure.¹⁹ The ORR was significantly better with osimertinib than with platinum-based chemotherapy (71% vs 31%). The good clinical profile of osimertinib was confirmed also in AURA 3 trial: the proportion of patients with grade 3 AEs was 23% in the osimertinib group and 47% in the chemotherapy group. Osimertinib was associated with a lower rate of AEs leading to permanent discontinuation.⁸

Leptomeningeal metastasis is another detrimental complication of advanced *EGFR* mutation-positive NSCLC. A Phase I study (BLOOM study NCT02228369) is ongoing to test osimertinib monotherapy at 160 mg once daily against brain and leptomeningeal metastasis. Preliminary data demonstrated encouraging results in terms of safety and efficacy.²⁰

According to the clinical activity and tolerability, osimertinib is being tested in other Phase III studies. In FLAURA Phase III trial (NCT02296125), treatment-naïve patients with locally advanced or metastatic *EGFR* mutant NSCLC were randomly assigned to receive osimertinib (80 mg qd, orally) or standard of care EGFR-TKI (gefitinib 250 mg qd, orally, or erlotinib 150 mg qd, orally).²¹

Combination treatment is another strategy to improve the efficacy and antitumor activity. TATTON trial (NCT02143466) is a multi-arm, Phase Ib trial investigating osimertinib 80 mg once daily in combination with durvalumab (anti-PD-L1 monoclonal antibody) or with savolitinib (*MET* inhibitor) or with selumetinib (MEK 1/2 inhibitor) in patients with advanced *EGFR*-mutant lung cancer. Primary objectives were safety and tolerability and the secondary objective was clinical activity of the combinations. An increase in ILD events was observed with the combination of osimertinib plus durvalumab. Therefore, enrollment in the osimertinib plus durvalumab combination arm has been suspended.²² Other trials assessing the combination treatment are ongoing: osimertinib

plus necitumumab (NCT02496663), plus ramucirumab (NCT02789345), or plus bevacizumab (NCT02803203). In addition to metastatic disease, osimertinib is being tested in the adjuvant setting (ADAURA study, NCT02511106).²³

Currently, osimertinib is the only EGFR-TKI approved for patients with metastatic *EGFR*^{T790M+} NSCLC. Rociletinib (Clovis) is another third-generation EGFR-TKI designed to inhibit both *T790M* and *EGFR*-activating mutations while sparing wild-type *EGFR*. Rociletinib has been investigated in *EGFR*-mutant patients who progressed after at least one line of EGFR-TKI treatment (TIGER X Phase I/II trial), in first-line setting versus erlotinib in *EGFR*-mutated patients (TIGER 1 Phase II/III trial), and in second-line post-standard EGFR-TKI treatment (TIGER 2 Phase II trial) versus chemotherapy in patients who have progressed after standard EGFR-TKI and after platinum-based doublet chemotherapy.² Despite initial promising results, Clovis has stopped the clinical development of rociletinib because of updated data revealing lower response rates than initially reported, a negative vote from the FDA's Oncologic Drugs Advisory Committee (ODAC), and FDA approval of osimertinib, rociletinib's main competitor in the setting.^{24,25} Further third-generation EGFR-TKIs in clinical development are HM61713, ASP8273, EGF816, and PF-06747775.²⁶

Immune checkpoint inhibitors and EGFR-TKIs

Recent data showed that nivolumab (Checkmate 057²⁷ and Checkmate 017²⁸), pembrolizumab (Keynote 010²⁹), and atezolizumab (POPLAR³⁰ and recently OAK³¹ study) are superior to docetaxel in second-line setting and pembrolizumab (Keynote-024³²) also improve survival versus platinum-based chemotherapy in PD-L1-positive untreated NSCLC. As shown in these studies, among *EGFR*-mutant patients, the efficacy of checkpoint inhibitors was lower than that in wild-type population probably because of the low level of mutational load in *EGFR*-mutant tumors. *EGFR*-mutant NSCLC expresses higher PD-L1 levels than wild-type, while gefitinib can reduce the PD-L1 expression, suggesting that combined strategies of EGFR-TKI and immunotherapy may be an interesting approach.³³ While promising results come from a combination of nivolumab plus erlotinib in *EGFR*-mutant advanced NSCLC with acquired resistance to EGFR-TKI³⁴ and from pembrolizumab plus gefitinib in heavily pretreated (up to four prior therapies) *EGFR*-mutant NSCLC,³⁵ association treatment with osimertinib showed significant toxicity. In the Phase I TATTON trial (NCT02143466) and in Phase III CAURAL

trial (NCT02143466), the combination of osimertinib and durvalumab (anti-PD-L1 monoclonal antibody) in patients with *EGFR*-mutant NSCLC with acquired resistance to EGFR-TKI and *T790M* positivity showed a high incidence of ILD.^{22,23} However further Phase I/II combination trials of checkpoint inhibitors are ongoing in EGFR-TKI-naïve and pretreated patients (NCT02013219: erlotinib plus atezolizumab, NCT02364609: afatinib plus pembrolizumab).³⁶ Several clinical studies are underway to assess new immunotherapy strategies in different settings.³⁷ A combination of ipilimumab and nivolumab has been tested as first-line treatment in advanced NSCLC with interesting ORR.⁴⁸ Durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA4) showed clinical activity in relapsed NSCLC.⁴⁹ Many studies are ongoing to test new targets for immunotherapy such as inhibitory molecules (indoleamine-dioxygenase, adenosine, TIM-3, LAG-3) or stimulatory molecules (OX40, CD40, CD27), new peptide vaccines targeting novel antitumor antigens, alternative checkpoint inhibitors, chimeric antigen receptor T cells (CAR-T), histone deacetylase (HDAC) inhibitors, and DNA hypomethylating agents target epigenetics for tumor growth suppression.⁵⁰ Immune checkpoint inhibitors have been approved for therapy of a variety of advanced cancers, and they also can be considered for combination therapy to overcome the acquired resistance to EGFR-TKIs.³⁷

Clinical strategies beyond EGFR-TKI progression

The standard of care for patients with acquired resistance to EGFR-TKIs is rapidly changing after the development of third-generation *EGFR*-TKIs targeting both *T790M* and *EGFR*-TKI-sensitizing mutation. Osimertinib is the new standard of care in patients with metastatic *EGFR*^{T790M+} NSCLC after progression on erlotinib, gefitinib, or afatinib. A second-line platinum-based doublet chemotherapy remains the standard of care in patients without *T790M* mutation or other targetable resistance mechanism especially in the case of dramatic progression.^{3,36} EGFR-TKIs should be interrupted during chemotherapy, although some clones of *EGFR*-mutant NSCLC maintain dependence on *EGFR* signaling after the development of acquired resistance. IMPRESS study is a randomized Phase III trial comparing maintenance gefitinib combined with pemetrexed and cisplatin versus chemotherapy alone in patients with acquired resistance to gefitinib. No difference in PFS was reported in both the arms (median PFS 5.4 months in both the groups). Combination treatment showed a detrimental effect on the overall survival compared with chemotherapy alone. Patients without *T790M* mutation

had a non-significant benefit with combination treatment (PFS 6.7 vs 5.4 months).³⁸ For patients with oligometastatic progression, local therapies such as radiotherapy, surgery, and stereotactic ablative radiotherapy in conjunction with continued *EGFR*-TKI can extend disease control by over 6 months.³⁹ Finally, patients with indolent, asymptomatic progression, and good performance status may continue to be treated with *EGFR*-TKI beyond RECIST progression if there is no evidence of deterioration or intolerable toxicity (Figure 3). These strategies are supported by the risk of disease flare after *EGFR*-TKI cessation, considering that some clones remain sensitive to *EGFR* inhibition after the acquired resistance.^{3,36} Second-generation irreversible TKIs failed to overcome *T790M*-mediated resistance because concentrations at which they overcome *T790M* activity preclinically are not achievable in humans due to dose-limiting toxicity related to non-selective inhibition of wild-type *EGFR*.⁴⁰ Vertical inhibition, the simultaneous inhibition of both extracellular and intracellular receptor domains with the combination of cetuximab and Afatinib, in a Phase Ib clinical trial demonstrated promising results, but the high rate of toxicity limited its use in clinical practice.⁴¹

Acquired resistance to a *T790M*-specific *EGFR* inhibitor

The main mechanism of resistance to osimertinib and to all third-generation irreversible *EGFR* inhibitors⁴² is the acquisition of missense mutation *EGFR C797S* in exon 20 which consist of the substitution of cysteine with serine at the amino acid position 797 within the kinase-binding site. Osimertinib loses the ability to form covalent bond with *EGFR* at the position of cysteine residue.¹² *EGFR C797S* arise in approximately one-third of patients treated with osimertinib¹¹ over a period of 9–13 months.⁴² In preclinical models, the configuration of *T790M* and *C797S* mutation

affects how cells respond to therapy. If the two mutations are in *trans* (on different alleles), cells are resistant to third-generation *EGFR*-TKIs, but a combination of first-generation TKIs can restore *EGFR* inhibition. If the two mutations are in *cis* (on the same allele), cells are refractory to any *EGFR*-TKIs.^{12,23} In a case report of a patient with an *EGFR*-mutant lung cancer, next-generation sequencing (NGS) techniques were performed on three biopsy specimens obtained before treatment with erlotinib, after acquired resistance to erlotinib, and after acquired resistance to AZD9291. The original sensitizing *EGFR* mutation was present in all tumor samples. Under the selective pressure of *EGFR*-TKIs, the tumor developed secondary (*T790M*) and tertiary (*C797S*) mutations to maintain *EGFR* signaling.⁴³ A subsequent study collected plasma samples from 15 patients who received osimertinib therapy and had preexisting plasma *EGFR^{T790M}*. A total of 40% of patients had *EGFR^{del19/T790M/C797S}*, 33% of patients had *EGFR^{T790M}* alone, and *EGFR^{T790M}* was no longer detectable in 27% of patients.⁴⁴ Interestingly, in patients with chronic lymphocytic leukemia treated with ibrutinib, (Bruton tyrosine kinase [BTK] inhibitor), mutations have been detected in C481 (C481S), the analogous cysteine residue to C797 in *EGFR*, suggesting that mutations in this conserved residue may be a common mechanism of acquired resistance to covalent kinase inhibitors.⁴⁵ Additional mechanisms of resistance to osimertinib in patients negative for *C797S* include *HER-2* or *MET* amplification, loss of *T790M* mutation,⁴⁶ *EGFR L718Q*, *EGFR L798I*, *KRAS G12S*.⁴² In addition to acquired mutations and gene amplifications, phenotype transformation represents a distinct mechanism of resistance. Adenocarcinoma turns into small cell lung cancer with *RB1* inactivation as the defining features.⁴² The genomic heterogeneity associated with resistance to *EGFR*-TKIs in NSCLC requires the development of target therapy to overcome *C797S* resistance and combination therapies

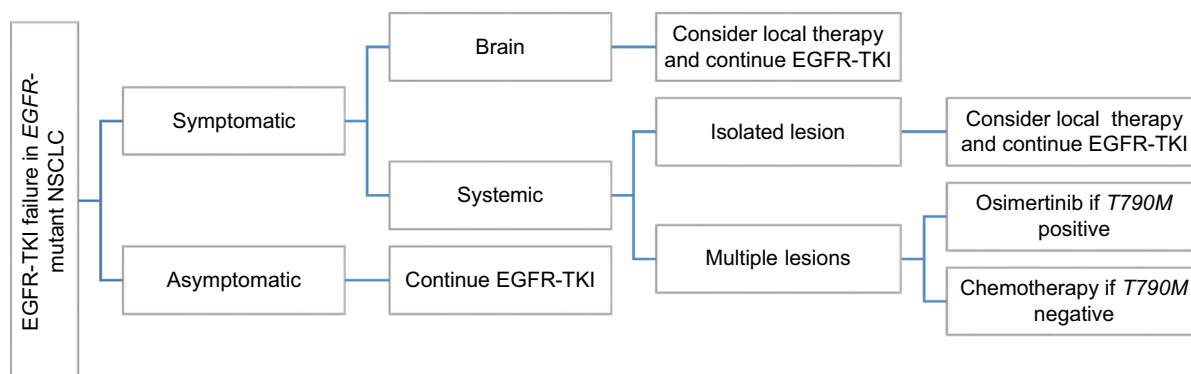


Figure 3 Algorithm for treatment after acquired resistance in *EGFR*-mutant NSCLC.

Abbreviations: *EGFR*-TKI, epidermal growth factor-tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

that can inhibit the emergence of multiple resistance mechanisms.⁴⁴ EAI045 is the first allosteric TKI purposefully designed to overcome *T790M* and *EGFR C797S* mutations. In a genetically engineered mouse model of *L858R/T790M* mutant-driven lung cancer, EAI045 was tested alone and in combination with cetuximab. While the allosteric inhibitor was ineffective alone due to receptor dimerization, the combination of EAI045 and cetuximab showed significant tumor regression. Clinical trials are required to assess these results in patients with advanced NSCLC.⁴²

Conclusion

Acquired resistance is one of the most significant limitations in lung cancer treatment. Despite an initial benefit to target therapies, all patients become refractory. Identification of mechanisms involved in drug resistance is essential to tailor the best treatment strategy for each patient. This is the reason why identification of biomarkers should be encouraged and appropriate tissue sample or plasma assay is essential for biological characterization. Failure of currently available targeted therapies suggests that a single agent may be not sufficient to overcome drug resistance. New strategies, including combination treatment, are currently under investigation to identify new opportunities of treatment.

Disclosure

The authors report no conflicts of interest in this work.

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