CASE REPORT

Overcoming Resistance to Osimertinib by T790M Loss and C797S Acquisition Using Gefitinib in a Patient With *EGFR*-Mutant NSCLC: A Case Report

Diego Enrico, MD,[a,b,*] Florencia Tsou, MD,[a,b] Greta Catani, MD,[c] Carmen Pupareli, MD,[a] María Romina Girotti, PhD,[d] David Esteban Ulloa Alvarez, MD,[e] Federico Waisberg, MD,[b,c] Andrés Rodríguez, MD,[b,c] Roxana Reyes, MD,[f] Matías Chacón, MD,[b,c] Noemí Reguart, MD, PhD,[f,g,h] Claudio Martín, MD[a,b]

[a]*Thoracic Oncology Unit, Department of Medical Oncology, Alexander Fleming Cancer institute, Buenos Aires, Argentina*
[b]*Clinical Research Unit, Department of Medical Oncology, Alexander Fleming Cancer Institute, Buenos Aires, Argentina*
[c]*Department of Medical Oncology, Alexander Fleming Cancer Institute, Buenos Aires, Argentina*
[d]*Universidad Argentina de la Empresa (UADE), Buenos Aires, Argentina*
[e]*Department of Radiology, Alexander Fleming Cancer Institute, Buenos Aires, Argentina*
[f]*Thoracic Oncology Unit, Department of Medical Oncology, Hospital Clinic, Barcelona, Spain*
[g]*Translational Genomics and Targeted Therapies in Solid Tumors, IDIBAPS, Barcelona, Spain*
[h]*Department of Medicine, University of Barcelona, Barcelona, Spain*

Received 25 September 2022; revised 26 December 2022; accepted 27 December 2022
Available online - 28 December 2022

ABSTRACT

Limited strategies are available at disease progression on osimertinib for patients with *EGFR*-mutant NSCLC. The emergence of the on-target *EGFR* C797S mutation has been described as one of the most common mechanisms of resistance. In addition, loss of the *EGFR* T790M mutation has been mainly investigated as a resistance phenomenon to second-line osimertinib exposure. Remarkably, by studying the molecular profile at progression, it has been reported that the presence of the *EGFR*-sensitizing mutation, concurrently with the T790M, and C797S resulted in resistance to the current available *EGFR* tyrosine kinase inhibitors. Here, we report the first clinical evidence of gefitinib efficacy at *EGFR* exon 19 deletion/C797S mutation/T790M loss–mediated resistance to first-line osimertinib. Our findings highlight that dynamic genetic monitoring is a crucial approach in the evolution of *EGFR*-mutant NSCLC to understand the acquired molecular mechanisms for driving the best treatment strategy.

Keywords: EGFR; T790M loss; Osimertinib; C797S; Gefitinib; Case report

Introduction

Tyrosine kinase inhibitors (TKIs) against the EGFR have become the standard treatment for patients with NSCLC harboring *EGFR* mutations. The third-generation EGFR TKI, osimertinib, was found to have substantial efficacy in tumors with both *EGFR*-sensitizing and *EGFR* T790M-resistant mutations.[1] Nevertheless, despite the long-term effectiveness of this drug, the unavoidable

***Corresponding author.**

***Disclosure:** Dr. Reguart reports receiving personal fees from Merck Sharp & Dohme, Novartis, Pfizer, Roche, Amgen, Sanofi, Bayer, Takeda, Novartis, and AstraZeneca; and grants from Merck Sharp & Dohme outside of the submitted work. Dr. Martín has received honoraria as a speaker for Boehringer Ingelheim and AstraZeneca, and for advisory role for Roche, Bristol Myers Squibb, and Merck Sharp & Dohme not related to this work. The remaining authors declare no conflict of interest.*

Address for correspondence: Diego Enrico, MD, Thoracic Oncology Unit, Department of Medical Oncology, Alexander Fleming Cancer Institute, 1180 Crámer, Buenos Aires (1426), Argentina. E-mail: denrico@alexanderfleming.org

Cite this article as: Enrico D, Tsou F, Catani G, et al. Overcoming resistance to osimertinib by T790M loss and C797S acquisition using gefitinib in a patient with *EGFR*-mutant NSCLC: a case report. *JTO Clin Res Rep*. 2023;4:100456.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2022.100456

clinical disease progression is led by the development of the complex and heterogeneous mechanisms of acquired resistance, such as on-target *EGFR* mutations, including the most common *EGFR* C797S, bypass pathway activation, and histologic transformation.[2] Of note, loss of the *EGFR* T790M mutation has also been investigated primarily as a resistance phenomenon to second-line osimertinib therapy.[2]

Under these circumstances, limited strategies are available at disease progression on osimertinib, and the clinical efficacy of previous generation EGFR TKIs, at osimertinib resistance, has been scarcely reported in preclinical models and limited clinical cases.[3–7] Here, we report the first case of a patient with an *EGFR* exon 19 deletion and the novo T790M-mutant NSCLC that progressed to first-line osimertinib by emerging C797S mutation concurrently with T790M loss and subsequently responded to gefitinib.

Case Presentation

A 66-year-old former smoker man was diagnosed with having metastatic lung adenocarcinoma. Results of a bronchoscopy tissue biopsy and the real-time polymerase chain reaction (PCR) assay (AmoyDx EGFR 29 Mutations Detection Kit, Amoy Diagnostics) revealed an *EGFR* exon 19 deletion concurrently with de novo T790M mutation at baseline (Fig. 1). Computed tomography scan revealed a 36-mm solid lesion with irregular borders in the right upper lobe, associated with interstitial thickening of nodular reticular appearance and multiple bilateral lung nodules. In this context, the patient started first-line osimertinib 80 mg daily reaching a partial response. He developed an oligoprogression in the right hilar lesion and enlargement of a subcarinal mediastinal lymph node with a median progression-free survival (PFS) on osimertinib of 21 months (Fig. 1). At this time, a liquid biopsy using the FoundationOne Liquid CDx multigene platform (Roche Foundation Medicine) did not reveal any potential mechanism of resistance. Thus, the patient received intensity-modulated radiotherapy at 5000 cGy (200 cGy daily) on the progressive lesions and continued osimertinib beyond progression. At 29 months from therapy initiation, he presented multiple sites of disease progression by enlargement of the right upper lobe lesion, hilar lesion, mediastinal nodes, the appearance of atelectasis in the right lower lobe, and retroperitoneal nodes. Under this circumstance, a bronchoscopy was required and a tissue biopsy was obtained from the hilar mass progression site. Evaluation by next-generation sequencing using the Oncomine Focus Assay panel found the truncal *EGFR* Glu746_Ala750delins (variant allele frequency [VAF]: 35.18%) and identified the emergence of the resistance *EGFR* C797S mutation (VAF: 17.04%) concurrently with *PIK3CA* H1047L (VAF 47.96%) and *CTNNB1* S45P (VAF: 26.15%). Notably, the T790M mutation was not detected (Fig. 1). Given this resistance landscape, and after the recommendation of our institutional molecular tumor board, the patient received gefitinib 250 mg once daily. Of note, at 2 months of treatment, a computed tomography scan revealed a

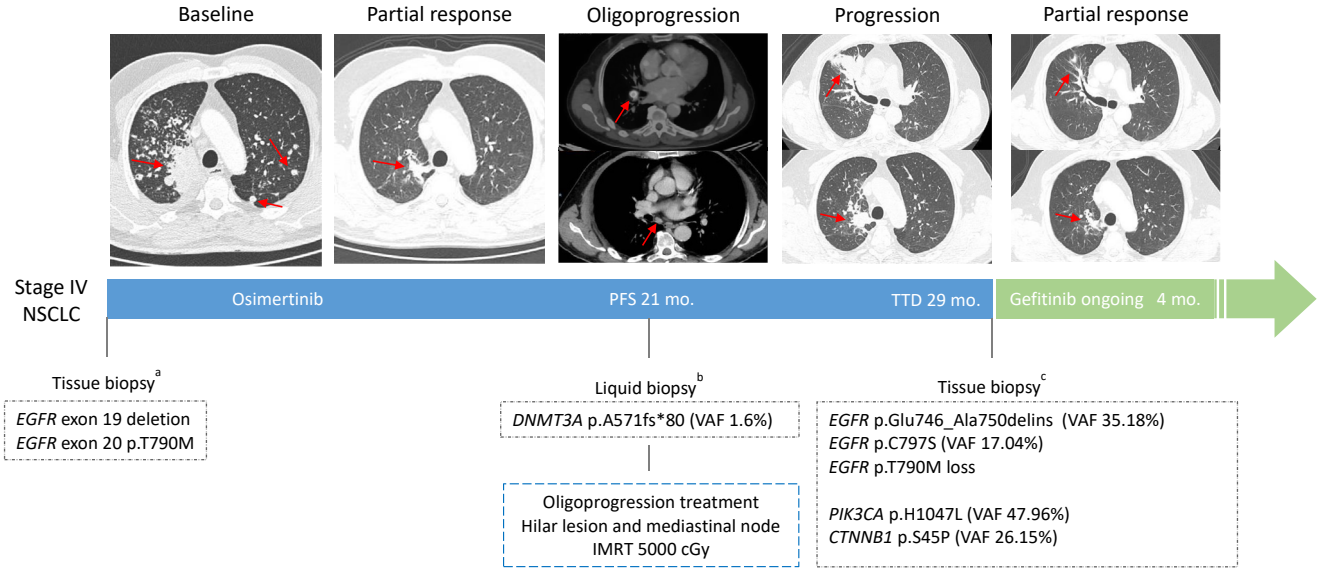

Figure 1. The dynamic lung lesion evolution. (*A*) Bronchoscopy tissue biopsy. Real-time PCR assay (AmoyDx EGFR 29 Mutations Detection Kit). (*B*) FoundationOne Liquid CDx platform. (*C*) Bronchoscopy and biopsy of tissue from the site of progression (hilar lesion). Oncomine Focus Assay (Thermo Fisher Scientific). cGy, centigray; IMRT, intensity-modulated radiotherapy; PFS, progression-free survival; TTD, time-to-treatment discontinuation; VAF, variant allele frequency.

remarkable reduction of the hilar lesion and mediastinal and retroperitoneal nodes and resolution of right lower lobe atelectasis, all together categorized as a partial response. The patient continued on well-tolerated gefitinib therapy until the cutoff day with a consistent efficacy after 4 months without disease progression.

The patient provided written informed consent for specimen collection, genetic analysis, and informed consent for research and publishing purposes.

Discussion

Acquired resistance and progression to EGFR TKIs represent the rule in *EGFR*-mutant NSCLC. The most common resistance mechanism to first- and second-generation EGFR TKIs results from the development of the acquired "gatekeeper" T790M mutation in *EGFR* exon 20, which sterically hinders the binding of first- and second-generation TKIs to the adenosine triphosphate (ATP) binding site of EGFR.[2] Nevertheless, pretreatment de novo T790M mutation can also be detected, and its rate depends on the population analyzed and the detection sensitivity of the technology used. By conventional methods, the frequency reported is between 1% and 8% of all EGFR-mutant NSCLCs, although using PCR ultrasensitive methods the prevalence can increase to 34% to 80%.[8] Nevertheless, the exact frequency of de novo T790M mutation remains controversial.

Of note, osimertinib selectively targets activating *EGFR* mutations, including the T790M resistance mutation, through the formation of a covalent bond to the C797 residue in the ATP binding site of mutant *EGFR*. Hence, osimertinib is the only third-generation EGFR TKI approved for T790M-positive patients.[2] Nevertheless, in patients with *EGFR*-sensitive mutant NSCLC, it has not been prospectively studied if the novo T790M coffers less efficacy to first-line osimertinib compared with patients without this particular mutation. Among seven NSCLC tumors with the novo T790M and L858R mutations in the cohort of treatment-naive patients of the AURA study, osimertinib was reported to have partial response in six cases (86%) and a duration of response ranging from 6.9 to 27.7 months.[9] In addition, Panda et al.[10] retrospectively reported a median PFS of 19.8 months among 14 patients with de novo T790M-mutated NSCLC treated with first-line osimertinib, which is consistent with the 21 months of PFS found in our case. In this scenario, the current AZENT phase 2 ongoing trial (NCT028425) is evaluating the efficacy of first-line osimertinib in patients with NSCLC with T790M mutations at diagnosis. Although the resistance landscape at osimertinib progression is being widely studied, the resistant mechanisms of tumors harboring the *EGFR* sensitivity mutation concurrently with de novo T709M at baseline have not yet been studied.[2]

In contrast, T790M loss represents a resistance mechanism found in approximately 50% to 60% of patients at second-line osimertinib progression. Notably, this phenomenon was found to be associated with early progression to osimertinib, possibly associated with the emergence of competing resistance mechanisms such as *KRAS* mutations, *MET* amplification, small–cell transformation, and gene fusions.[11] Nevertheless, loss of de novo T790M at first-line osimertinib progression, as was found in our case, is scarcely studied.

Importantly, the most common on-target mechanism of resistance to osimertinib is the acquisition of the C797S mutation, which has been reported in 10% to 26% and 7% of patients after second- and first-line osimertinib treatment, respectively.[2,12] The substitution of cysteine by serine at codon 797 in the *EGFR* at the ATP binding site results in the loss of the covalent bond residue between osimertinib and the mutant *EGFR*, conferring also cross-resistance to other irreversible third-generation TKIs, but not to first- or second-generation EGFR TKI.[2] This biological concept is being clinically studied in group A of the ongoing phase 2 ORCHARD trial (NCT03944772).

In the case that C797S emerges in the context of T790M, different therapeutic strategies have been proposed according to the allelic setting in which C797S is acquired. If C797S mutations are in trans, cells can be targeted with both first- and third-generation EGFR TKIs to hit both alleles, respectively, whereas when C797S are in cis, cells are resistant to all available TKIs, requiring new fourth-generation TKIs to reverse the primary sensitivity to EGFR inhibition.[2,13] Conversely, loss of T790M but maintenance of the original sensitive *EGFR* mutation can be therapeutically targeted with the reintroduction of first-generation TKIs even in the setting of the tertiary C797S mutation. This assumption is mainly based on preclinical models revealing gefitinib and afatinib antitumor activity because the original binding pocket is unaffected.[3] Of note, no efficacy of third-generation EGFR TKIs was observed in these models.

To our knowledge, this is the first case to report an acquired *EGFR* C797S mutation and loss of T790M-mediated resistance to first-line osimertinib in a patient with NSCLC and de novo T790M who responded to gefitinib. Comparably, other cases have reported activity of first- and second-generation EGFR TKIs in patients with acquired resistance to osimertinib in second line. Chic et al.[14] reported effective rechallenge with the first-generation TKI gefitinib in a patient with second-line osimertinib resistance mediated by acquisition of C797S and loss of T790M. Likewise, other authors have reported responses to second-generation afatinib and dacomitinib monotherapy in patients with acquired resistance to second-line osimertinib mediated by the

tertiary L718Q/V mutation and loss of T790M.[4–7,15] Our case presents the singularity that osimertinib resistance arose in the context of a de novo T790M-mutation and its loss, together with the acquisition of C797S, which could be confirmed from serial biopsies taken from progression sites.

Finally, some limitations should be highlighted. First, a clonality analysis evaluating whether de novo T790M and *EGFR* exon 19 deletion occurred in the same clone would give a deeper understanding of the resistant intrinsic mechanism. Second, the lack of next-generation sequencing analysis at baseline did not allow us to define the gain-of-function *PIK3CA* p.H1047L oncogenic mutation as a confirmed acquired resistance to osimertinib. Of note, activation of PI3K/AKT/mTOR pathway has been described as one of the main off-target resistance mechanisms to EGFR TKIs.[2]

Conclusions

Therapeutic individualization in patients with *EGFR* resistance mutations is a necessity given the complexity and heterogeneity underlying resistances. Dynamic genetic monitoring is crucial to identify acquired resistance mechanisms to drive the best treatment strategy.

CRediT Authorship Contribution Statement

Diego Enrico, Florencia Tsou, Claudio Martín: Conceptualization, Methodology.

Diego Enrico, Florencia Tsou, Greta Catani, Federico Waisberg, Claudio Martín: Data curation, Writing—original draft preparation.

Diego Enrico, Florencia Tsou: Visualization, Investigation.

Diego Enrico, Noemí Reguart, **Claudio Martín**: Supervision.

Diego Enrico, Florencia Tsou, Greta Catani, Carmen Pupareli, María Romina Girotti, David Esteban Ulloa Alvarez, Federico Waisberg, Andrés Rodríguez, Roxana Reyes, Matías Chacón, Noemí Reguart, Claudio Martín: Validation, Writing—reviewing and editing.

Acknowledgments

This patient gave his informed written consent for the unidentified data to be disclosed and published in any scientific journal for educational purposes. This work received no specific funding.

References

1. Lee CS, Milone M, Seetharamu N. Osimertinib in EGFR-mutated lung cancer: a review of the existing and emerging clinical data. *Onco Targets Ther*. 2021;14:4579–4597.
2. Leonetti A, Sharma S, Minari R, Perego P, Giovannetti E, Tiseo M. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. *Br J Cancer*. 2019;121:725–737.
3. Ercan D, Choi HG, Yun C-H, et al. EGFR mutations and resistance to Irreversible pyrimidine based EGFR inhibitors. *Clin Cancer Res*. 2015;21:3913–3923.
4. Fang W, Gan J, Huang Y, Zhou H, Zhang L. Acquired EGFR L718V mutation and loss of T790M-mediated resistance to osimertinib in a patient with NSCLC who responded to afatinib. *J Thorac Oncol*. 2019;14:e274–e275.
5. Yang X, Huang C, Chen R, Zhao J. Resolving resistance to osimertinib therapy with afatinib in an NSCLC patient with EGFR L718Q mutation. *Clin Lung Cancer*. 2020;21:e258–e260.
6. Liu Y, Li Y, Ou Q, et al. Acquired EGFR L718V mutation mediates resistance to osimertinib in non-small cell lung cancer but retains sensitivity to afatinib. *Lung Cancer*. 2018;118:1–5.
7. Shen Q, Qu J, Chen Z, Zhou J. Case report: dacomitinib overcomes osimertinib resistance in NSCLC patient harboring L718Q mutation: a case report. *Front Oncol*. 2021;11:760097.
8. Lee SH, Kim EY, Kim A, Chang YS. Clinical implication and usefulness of de novo EGFR T790M mutation in lung adenocarcinoma with EGFR-tyrosine kinase inhibitor sensitizing mutation. *Cancer Biol Ther*. 2020;21:741–748.
9. Ramalingam SS, Yang JCH, Lee CK, et al. Osimertinib as first-line treatment of EGFR mutation–positive advanced non–small-cell lung cancer. *J Clin Oncol*. 2018;36:841–849.
10. Panda GS, Noronha V, Shah D, et al. Treatment pattern and outcomes in de novo T790M-mutated non-small cell lung cancer. *Ecancermedicalscience*. 2022;16:1385.
11. Oxnard GR, Hu Y, Mileham KF, et al. Assessment of resistance mechanisms and clinical implications in patients with EGFR T790M-positive lung cancer and acquired resistance to osimertinib. *JAMA Oncol*. 2018;4:1527–1534.
12. Papadimitrakopoulou VA, Wu YL, Han JY, et al. LBA51Analysis of resistance mechanisms to osimertinib in patients with EGFR T790M advanced NSCLC from the AURA3 study. *Ann Oncol*. 2018;29(suppl 8):VIII741.
13. Arulananda S, Do H, Musafer A, Mitchell P, Dobrovic A, John T. Combination osimertinib and gefitinib in C797S and T790M EGFR-mutated non-small cell lung cancer. *J Thorac Oncol*. 2017;12:1728–1732.
14. Chic N, Mayo-de-las-Casas C, Reguart N. Successful treatment with gefitinib in advanced non-small cell lung cancer after acquired resistance to osimertinib. *J Thorac Oncol*. 2017;12:e78–e80.
15. Liu J, Jin B, Su H, Qu X, Liu Y. Afatinib helped overcome subsequent resistance to osimertinib in a patient with NSCLC having leptomeningeal metastasis baring acquired EGFR L718Q mutation: a case report. *BMC Cancer*. 2019;19:702.