Clinical Oncology: Case Reports

Case Report

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# Acquired MET Exon 14 Skipping Mutation and Complex Mutations in EGFR-Mutated Lung Adenocarcinoma: A Case Report

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## Abstract

We report an EGFR NSCLC patient with progression disease to Osimertinib due to *METΔex14* mutation. As exon 21 *L858R* substitution was still detected, the patient was treated with the combination of Osimertinib and Capmatinib. After 3 months, radiological progression disease and *C797S* and *V802F* as new on target mutations were detected, so Gefitinib was administered in monotherapy, with patient exitus due to neumothorax secondary to massive cavitation of his lung cancer 3 months later.

**Keywords:** Osimertinib; Capmatinib; MET exon 14 skipping; C797S mutation; Case report

## Introduction

Activating mutations in Epidermal Growth Factor Receptor (EGFR) gene cause 10% to 20% of Non-Small Cell Lung Cancer (NSCLC); and approximately in 90% of this cases, exon 19 deletions and exon 21 *L858R* substitutions are detected [1,2].

Those aberrations are succesfully targeteated with EGFR Tirosin Quinase Inhibitors (EGFR-TKI). However, acquired resistance due to heterogeneous mechanisms is inevitable [3]. The escape tumoral strategy can be on-target, like EGFR *C797S* or *V802F* mutations; and off-target, like MET dysregulation [3].

We present an EGFR mutant lung adenocarcinoma with long-term survivorship thanks to personalized medicine. Among other particularities, this case is unique due to anomalous resistance mechanisms, such as MET exon 14 skipping mutation (*METΔex14*), and the highly-personalized sequence of target therapies used.

## Case Presentation

A fragile 80 years old patient with hypertension, diabetes and mild renal failure with pleuritic pain, asthenia and dyspnea is diagnosed by CT guided biopsy of a lung adenocarcinoma with liver and bone metastasis, with EGFR exon 21 *L858R* substitution (cobas®EGFR PCR test).

Our patient receives Osimertinib 80 mg every 24 hours, with excellent tolerance and partial response, until radiological progression 13 months later. However, due to clinical benefit, the patient continues therapy 5 months more until deterioration due to bone pain and asthenia. Them, a new biopsy guided by Endobronchial Ultrasound (EBUS) was performed, and AmoyDx® Pan Lung Cancer PCR Panel detects the primary mutation (*L858R* of exon 21), and *METΔex14* as off-target escape mechanism. The limited tumour specimen does not allow additional molecular studies, so Capmatinib (400 mg every 12 hours) is added to Osimertinib.

During the combination treatment, the patient presents grade 1 asthenia, peripheral edema, and worsening of his renal impairment, requiring discontinuation of Capmatinib on one occasion.

Finally, disease progression is confirmed 3 months later, requiring hospital admission due to dyspnea and pain. Meanwhile, a liquid biopsy (GUARDANT 360®) detects the new EGFR complex mutation *C797S* and *V802F*, as well as exon 21 *L858R* substitution.

In this context, the patient starts Gefinitib 250 mg every 24 hours, presenting a clinical improvement, without pain and toxicities; until admission 3 months later due to a massive necrosis and cavitation of the pulmonar mass, with secondary hydropneumothorax (Figure 1), which finally causes patient exitus, despite of urgent chest drainage.

## Discussion

*METΔex14* is detected in 3% to 4% and MET amplification in 1 to 6% of NSCLC at debut and in 5% to 50% of EGFR mutant NSCLC as resistance mechanism [3, 4]. In both cases, Capmatinib, a selective inhibitor of MET receptor, has shown substantial antitumour activity in "GEOMETRY mono-1" clinical trial.

Furthermore, the promising combination of Osimertinib and Capmatinib is being tested in the on-going trial GEOMETRY-E. In the literature, few cases of this association has been presented, especially with METΔex14 as escape mechanism [5]. We decided to offer this novel combination due to the previous tolerance to Osimertinib and the risk of hyperprogression if inhibiting MET receptor exclusively when *L858R* mutation is still detected.

*C797S* mutation is poorly characterized yet, but it is estimated to happen in up to 26% of NSCLCs after EGFR-TKI treatment. *CT97S* mutation is maybe the main mechanism of escape to Osimertinib (7% in FLAURA study, 15% in real world data), and the second to 1º and 2º generation EGFR-TKI [6]. To date, no standard treatment has been defined but there is preclinical and clinical data supporting treatment with 1st and 2nd generation EGFR-TKI. In this setting, we decide to change Osimertinib therapy to Gefinitib, and Capmatinib disruption is supported in our case due to progression, bad tolerance and no detection of *METΔex14* in liquid biopsy. With Gefinitib, the patient presents few months of general improvement, but massive necrosis causes ultimately its death, even when the cavitation of the tumour could have been secondary to EGFR-TKI response.

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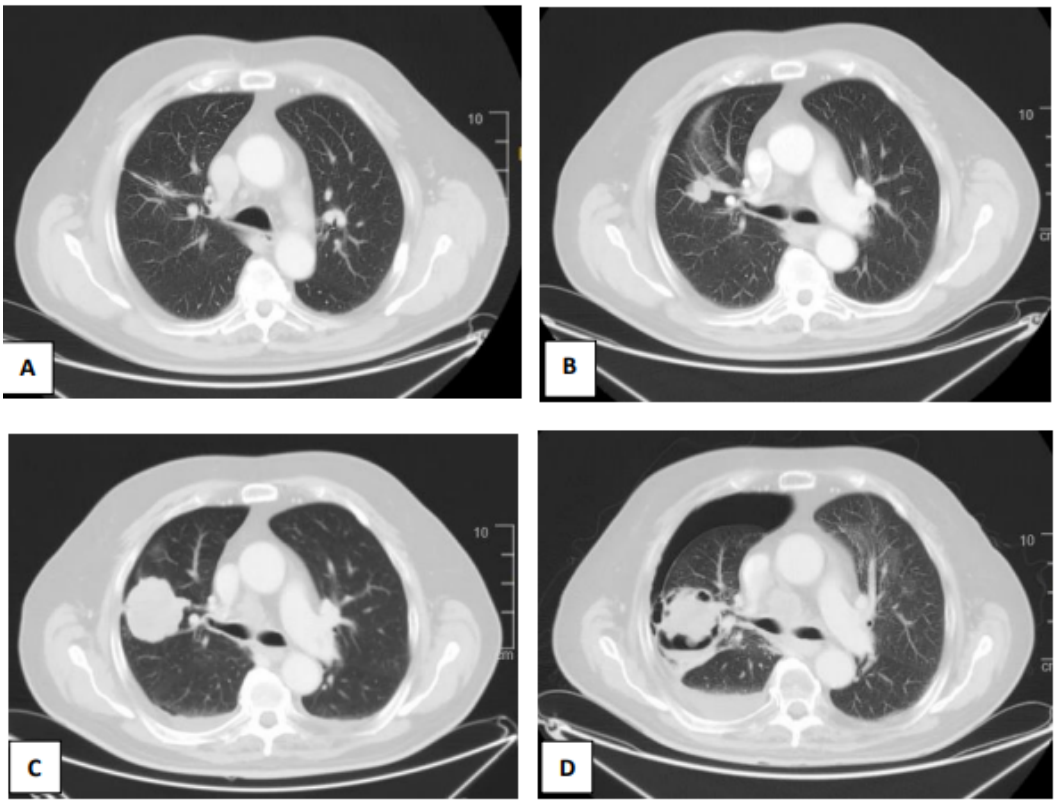


**Figure 1:** CT scans of the pulmonar mass. (A) spiculated left lung nodule at baseline. (B) Proggressive disease after 13 months of response to Osimertinib. (C) Proggresion of a Solid mass after Osimertinib and Capmatinib treatment. (D) massive cavitation with secondary hydroneumothorax during Gefitinib Treatment.

**Table 1:** squema of treatments administered, with molecular findings and the specific response to each line.

| Treatment | Best response | Molecular results | Sample | Sample and molecular analysis |
|---|---|---|---|---|
| **Osimertinib** | Partial disease | EGFR exon 21 *L858R* substitution | Tumor | Cobas®EGFR PCR test |
| **Osimertinib + Capmatinib** | Progressive disease | EGFR exon 21 *L858R* substitution | Tumor | **AmoyDx® Pan Lung Cancer PCR Panel** |
| | | *METΔex14* | | |
| **Gefitinib** | Proggressive disease | EGFR complex mutation *C797S* and *V802F* | Plasma | GUARDANT 360® |
| | | EGFR exon 21 *L858R* substitution | | |

## Conclusion

The unquestionable consolidation of Osimertinib in 1st line of EGFR NSCLC after FLAURA trial has generated a delicate scenario when finally progression disease take place. Time and clinical trial results are needed to reach consolidated scientific evidence, but meanwhile oncologist must take hard therapeutical decisions due to novel mutations mechanism and new agents.

Meanwhile biomarked-directed clinical trial with multiarm designs as ORCHARD are still recruiting, data of case reports is especially interesting. In this scenario, we report a rare case of a patient with EGFR NSCLC with adquired resistance due to *METΔex14* treated with Capmatinib and Osimertinib in combination, and posterior C797S mutation treated with Gefinitib (Table 1). To our knowledge, this could be the first report of this sequence of mutations and treatments

## Conficts of interests

There are not research supports or conflicts o f i nterest r elated t o this publication.

## Ethics Statement

We confirm that the patients gave informed consent to publish his clinical and radiological images.

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