

## Case Report

# Long-term efficacy of osimertinib in *de novo* exon 19 deletion with T790M in an epidermal growth factor receptor mutated lung cancer patient in India

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## ABSTRACT

Primary epidermal growth factor receptor (EGFR) T790M mutation is infrequently identified in previously untreated non-small cell lung cancer (NSCLC) patients. There is variation in the frequency of *de novo* T790M mutations depending on the population examined and the technology used for mutation detection. According to direct sequencing, 0.4–3% of all NSCLCs and 1–8% of all EGFR-mutant NSCLCs show primary T790M mutation. This mutation always coexists with a sensitizing EGFR mutation and is more commonly present along with exon 21 L858R mutation and infrequently with exon 19 deletion. Osimertinib, an oral irreversible third-generation EGFR tyrosine kinase inhibitor, is selective for both, EGFR sensitizing mutations and T790M resistance mutation. AURA trial has confirmed the effectiveness of osimertinib in patients with T790M mutation. The median progression-free survival is better in primary T790M as compared to the acquired mutation in a previously treated NSCLC. The overall survival with osimertinib is still 38.6 months only. Even after good response in both primary and acquired T790M mutation, there is disease progression and shifting to chemotherapy is required. We present an interesting case of a 60-year-old non-smoker female deriving benefit from a single agent osimertinib with a rare combination of mutation at presentation even after 6 years of initiation of therapy.

**Keywords:** Epidermal growth factor receptor mutation, Epidermal growth factor receptor tyrosine kinase inhibitors, Adenocarcinoma lung, Durable response

## INTRODUCTION

Around 85% of lung cancer cases are non-small cell lung cancer (NSCLC). Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) have revolutionized the treatment of EGFR mutant NSCLC, and all three generations of EGFR are widely used in the treatment.

Based on the results of the Soria *et al.*<sup>[1]</sup> study in October 2017, osimertinib is recommended as a first-line treatment for patients with advanced NSCLC with EGFR mutations and was listed as a category I recommendation by the National Comprehensive Cancer Network guidelines in 2019.

Osimertinib is effective against both exon 20 resistant T790M and EGFR sensitizing mutation. The occurrence of primary T790M ranges between 1% and 38%<sup>[2]</sup> and is commonly associated with exon 21 L858R mutation and less frequently with exon 19 deletion.<sup>[3]</sup> However, disease progression occurs even with osimertinib with progression-free survival (PFS) of 18.9 months only.<sup>[1]</sup>

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We present an interesting case of a 60-year-old non-smoker female deriving benefit from a single agent third-generation EGFR-TKI with a rare combination of mutation at presentation, even after 6 years of initiation of therapy.

## CASE REPORT

A 60-year-old hypertensive female reported to us in November 2016, with complaints of persistent cough and right-sided neck swelling for 1 year. All routine investigations were done which were within normal limits.

On physical examination, no pallor, icterus, or organomegaly were noted but the right-sided level IB cervical and the right supraclavicular lymph nodes were palpable.

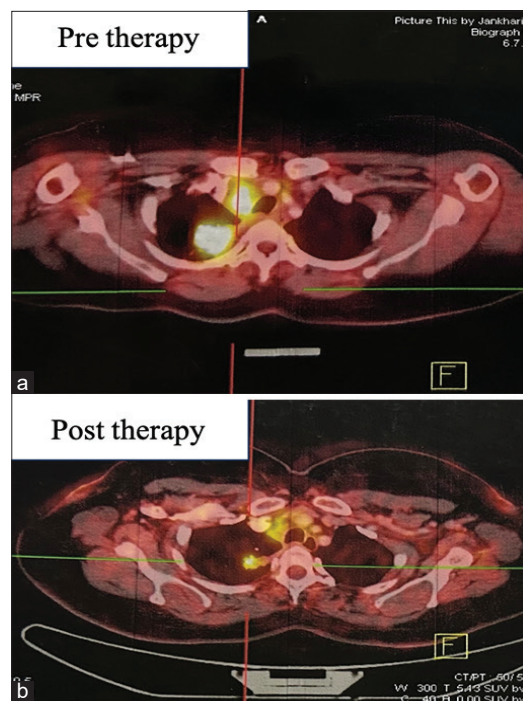
A right supraclavicular lymph node wedge biopsy was done. The biopsy revealed metastatic adenocarcinoma with lung primary as the cells showed positivity for thyroid transcription factor 1 (TTF-1) and Napsin A. This confirmed the diagnosis of metastatic adenocarcinoma lung. The tissue sample was also sent for molecular studies.

To evaluate the extent of the disease, a positron emission tomography and computed tomography (PET-CT) scan was done. The PET-CT scan showed a heterogeneously enhancing soft-tissue mass with spiculated margins in the apico-posterior segment of the right upper lobe, measuring  $4.1 \times 3.5$  cm, abutting the overlying costal and mediastinal pleura. Multiple enlarged the right supraclavicular, bilateral high paratracheal, right pre- and para-tracheal, left paraaortic, pre-carinal, subcarinal, and common iliac lymph nodes showed an increase in metabolic activity [Figure 1a].

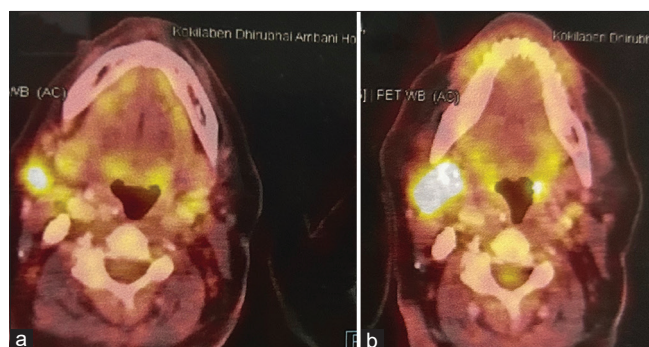
Surgery was ruled out due to the advanced nature of the disease. Pending the results of the molecular studies, the patient was started on an injection of pemetrexed and carboplatin once every 21 days.

The interim PET-CT done post 4 cycles of chemotherapy showed a good response with a reduction in size and activity at the primary site and the multiple involved lymph nodes [Figure 1b]. The results of molecular studies were ready by this time. There was a mutation seen in exon 19 (c.2239\_2250 del) along with exon 20 (c.2369C > T), also called T790M mutation. The patient was advised tablet osimertinib based on the above results. Due to the unavailability of osimertinib in India at that time, she was continued on pemetrexed and carboplatin.

Post-completion of 6 cycles of pemetrexed and carboplatin, the PET-CT scan continued to show a good response. Thus, the patient was started on maintenance pemetrexed every 21 days. Post 6 cycles of maintenance, the PET-CT scan showed an increase in the activity of the submandibular and the right supraclavicular lymph nodes suggestive



**Figure 1:** (a) A heterogeneously enhancing soft-tissue mass in the apico-posterior segment of the right upper lobe, measuring  $4.1 \times 3.5$  cm along with multiple enlarged surrounding lymph nodes. (b) Reduction in the size of the primary and the lymph nodes post chemotherapy.



**Figure 2:** (a) Reduction in the activity and size of the submandibular lymph node post 6 cycles of pemetrexed and carboplatin. (b) Increase in the activity and size of the submandibular lymph node post 4 cycles of maintenance pemetrexed.

of progressive disease [Figure 2a and b]. By this time, osimertinib was available in India. Thus, the patient was started on the tablet osimertinib 80 mg once a day in July 2017. The PET-CT scan done post 3 months with osimertinib showed a reduction in size and activity of submandibular and the right supraclavicular lymph nodes.

She continued on tablet osimertinib from July 2017 to date with only slight darkening of the skin of the face and the hand with no other toxicities. She has been on regular follow-ups since 2017 and has had no relapse or intolerable toxicities in these 6 years.

## DISCUSSION

The incidence of *EGFR* (exons 18–21) mutation in the Indian population is 23%. *EGFR* exon 19 deletion and exon 21 mutation together constitute >90% of the *EGFR*-positive cases.<sup>[4]</sup> There is variation in the incidence of primary T790M NSCLC ranging between 1% and 38% and it depends on the detection method applied and the study population.<sup>[2]</sup> In a study conducted by Panda *et al.*, the incidence is 2.59% in the Indian population.<sup>[5]</sup>

In a study conducted by Wang *et al.*, the frequency of primary T790M with exon 19 deletion was 11% as compared to L858R (45%). Our patient had co-existence of primary T790M with exon 19 deletion.<sup>[6]</sup>

Osimertinib is an oral, third-generation *EGFR*-TKI inhibitor, that has an excellent inhibitory effect on the T790M mutation, especially with the central nervous system metastasis.<sup>[6]</sup> Patients with NSCLC who have progressed to T790M mutation after treatment with *EGFR*-TKIs, show excellent response to osimertinib.<sup>[7]</sup> The AURA3 study showed an overall response rate of 71% and PFS of 10.1 months in treating T790M mutant NSCLC patients compared to chemotherapy.<sup>[8]</sup> The median overall survival (OS) was 38.6 months with osimertinib in the study conducted by Ramalingam *et al.*<sup>[9]</sup>

Meanwhile, for TKI-naïve patients with sensitive *EGFR* mutations, the median PFS of osimertinib was 22.1 months.<sup>[10]</sup> However, limited data are available regarding the effectiveness of osimertinib in patients with primary T790M mutation. Many case reports have indicated that such patients tend to respond well to osimertinib. The median PFS of 8 months was highlighted for four primary T790M mutant patients who received osimertinib in a study conducted in China.<sup>[11]</sup> Wang *et al.* reported patients with primary T790M mutation responded well to osimertinib and had a median PFS of 17.0 months, which was significantly longer in comparison to 10.0 months for patients with acquired T790M mutation. However, the median OS of acquired T790M mutation patients was significantly longer as compared to that of primary T790M mutation patients who received osimertinib.<sup>[6]</sup>

Osimertinib can affect both T790M and 19del/21L858R positions in primary T790M mutant patients. Thus, this high affinity of osimertinib to both sites of *EGFR* mutations accounts for a good response to the therapy. However, in patients with acquired T790M mutation, the selection of first TKIs could result in the inhibition or activation of certain signaling pathways in upstream or downstream of *EGFR* or the upregulated or downregulated expression of

certain proteins, which causes differential response to the osimertinib treatment.<sup>[12]</sup>

Preliminary data suggest that first-line osimertinib resistance mechanisms are similar to those seen in patients with the T790M mutation receiving osimertinib as a second-line therapy. The most common resistance mechanisms include the C797S mutation in exon 20 (7%) and *MET* amplification (15%). *HER2* amplification, *BRAF*, *KRAS*, *PIK3CA*, or rare *EGFR* secondary mutations, also lead to resistance development. The other mutations include M766Q, S768I, and L718V in exon 20 along with the loss of T790M mutation due to prolonged treatment with osimertinib.<sup>[13,14]</sup> In the study conducted by Wang *et al.*, there was rapid progression seen in the patient of primary T790M after the development of osimertinib resistance and died after 2–3 cycles of chemotherapy. However, the patient with acquired T790M had multiple therapy options before and after osimertinib.<sup>[6]</sup>

To conclude, our patient with both exon 19 and exon 20 T790M mutation since presentation was started on tablet osimertinib in 2017. The patient is still continuing to derive the benefit without any relapse, intolerable toxicities, or development of resistance mechanisms. To the best of our knowledge, this is the first longest PFS case from India (non-oriental ethnicity).

## CONCLUSION

Our study reiterates the benefit of osimertinib as first-line therapy in primary exon 20 T790M mutations with PFS of around 6 years with limited toxicity and the absence of resistance to the treatment.

### Ethical approval

The research/study complied with the Helsinki Declaration of 1964.

### Declaration of patient consent

Patient consent not required as patients identity is not disclosed or compromised.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The author(s) confirms that there was no use of artificial intelligence (AI)-assisted technology for assisting in the

writing or editing of the manuscript and no images were manipulated using AI.

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