Salford City Publishers

Journal of Lung Cancer Case Reports

**Case Report** | Vol 1 Iss 1

# Sustained Clinical Response to Third-Generation EGFR TKI Osimertinib in Advanced Non-Small Cell Lung Cancer Harboring an Uncommon Exon 21 L861Q Mutation: A Case Report

**Giuseppe Marino[1*], Francesca Romano[1], Luca Esposito[2] and Sofia Ferrari[1]**

[1]Department of Medical Oncology, Sapienza University of Rome, Sant'Andrea Hospital, Rome, Italy

[2]Division of Respiratory Diseases, University of Padua Medical Center, Padua, Italy

[*]**Corresponding author:** Giuseppe Marino, Department of Medical Oncology, Sapienza University of Rome, Sant'Andrea Hospital, Rome, Italy. E-mail: giuseppe.marino@aosp.bo.it

**Received:** June 23, 2026; **Accepted:** July 12, 2026; **Published:** July 25, 2026

## Abstract

Epidermal growth factor receptor (EGFR) mutations are major driver oncogenes in non-small cell lung cancer (NSCLC). While classical mutations account for the vast majority of cases, uncommon EGFR mutations such as exon 21 L861Q represent a clinically heterogeneous subgroup with historically variable responsiveness to targeted therapies. Here, we report a 68-year-old non-smoking female who presented with progressive cough and dyspnea and was diagnosed with Stage IVA lung adenocarcinoma. Targeted next-generation sequencing (NGS) of biopsy tissue revealed an isolated uncommon EGFR L861Q point mutation without concurrent classical mutations or resistance markers. The patient was initiated on first-line oral osimertinib at 80 mg once daily, achieving a rapid partial response with over 60% tumor regression at 8 weeks alongside complete symptomatic relief. The patient maintained continuous, durable disease control for 18 months with excellent functional status and minimal treatment-related toxicity. This case highlights the high therapeutic efficacy and favorable safety profile of third-generation EGFR TKIs like osimertinib in NSCLC harboring uncommon EGFR L861Q mutations, underscoring the vital role of broad molecular profiling in guiding precision oncology decisions.

**Keywords:** Non-small cell lung cancer (NSCLC); EGFR Exon 21 L861Q mutation; Osimertinib; Targeted therapy

## Introduction

The introduction of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) has transformed the treatment landscape for advanced non-small cell lung cancer (NSCLC). Standard targeted regimens are primarily calibrated for "classical" sensitizing alterations—namely, exon 19 in-frame deletions and exon 21 L858R point mutations—which account for the vast majority of EGFR-mutated NSCLCs [1].

Uncommon EGFR mutations (exons 18–21) constitute 10–15% of all EGFR alterations. Among these, the exon 21 L861Q substitution accounts for approximately 2–3%. Historically, first-generation reversible TKIs (erlotinib, gefitinib) demonstrated limited activity against L861Q variants, yielding lower objective response rates (ORR) and shorter progression-free survival (PFS) compared to classical mutations. While second-generation irreversible TKIs (e.g., afatinib) earned regulatory approval for uncommon mutations based on prospective subset analyses, off-target wild-type EGFR inhibition frequently causes dose-limiting toxicities like severe diarrhea and mucocutaneous reactions [2,3].

Osimertinib, a potent third-generation irreversible EGFR-TKI, selectively targets both EGFR-sensitizing and T790M resistance mutations while sparing wild-type EGFR. Emerging clinical trial data suggest osimertinib offers robust intracranial and systemic activity with superior tolerability in uncommon mutations. Here, we present a case of advanced lung adenocarcinoma with an isolated EGFR L861Q mutation achieving a durable clinical response to first-line osimertinib.

## Case Presentation

A 68-year-old female never-smoker presented with a 2-month history of dry cough, mild exertional dyspnea, and an unintended 4 kg weight loss. She had no prior personal or family history of thoracic malignancy. Physical examination demonstrated clear breath sounds bilaterally and an Eastern Cooperative Oncology Group (ECOG) performance status of 1.

Laboratory Testing: Serum carcinoembryonic antigen (CEA) was elevated at 34.2 ng/mL (reference: <5.0 ng/mL). Complete blood count and hepatic/renal metabolic panels were within normal ranges.

Radiological Imaging: Contrast-enhanced thoracic CT demonstrated a 3.5 × 2.8 cm soft-tissue mass in the right middle lobe, associated with ipsilateral subcarinal lymphadenopathy (station 7) and multiple small contralateral parenchymal nodules. Brain MRI excluded central nervous system (CNS) metastatic disease [4]. Whole-body 18F-FDG PET-CT confirmed hypermetabolic uptake in the primary pulmonary lesion (SUVmax 9.4) and mediastinal nodes without distant abdominal or skeletal metastases.

A CT-guided core-needle biopsy of the right middle lobe mass was performed:
Histopathology: Hematoxylin and eosin staining revealed malignant acinar structures infiltrating lung parenchyma. Immunohistochemistry (IHC) was strongly positive for TTF-1 and Napsin A, confirming primary lung adenocarcinoma.

Next-Generation Sequencing (NGS): Hybridization capture-based targeted NGS identified a single nucleotide variant in exon 21 of the EGFR gene: p.L861Q (c.2582T>A) with a variant allele frequency (VAF) of 28.4%. No concurrent EGFR exon 19, exon 20 insertion, L858R, T790M, or TP53 mutations were detected.

Treatment Management and Clinical Course
The patient was diagnosed with Stage IVA (cT2aN2M1a) Lung Adenocarcinoma.
Given the favorable safety profile and demonstrated activity of third-generation TKIs, she was started on first-line osimertinib 80 mg orally once daily. Treatment was well-tolerated, with only Grade 1 dry skin and mild paronychia managed conservatively [5-8].

Response Assessment: Follow-up CT scans at 8 weeks showed a partial response (RECIST 1.1), with the primary right middle lobe mass regressing from 3.5 cm to 1.3 cm (>60% reduction) and near-complete resolution of bilateral pulmonary nodules [9]. Serum CEA normalized to 3.1 ng/mL.

Long-Term Outcome: Repeat imaging every 3 months confirmed ongoing disease control. At the 18-month follow-up, the patient remained progression-free on continuous osimertinib monotherapy with excellent functional performance (Figure 1 and 2).

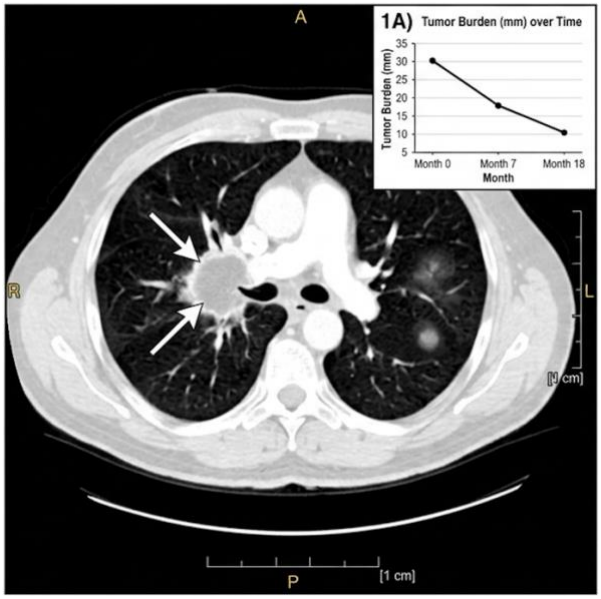


**Figure 1:** Baseline CT and Post-Treatment Response. (A) Baseline CT and Prigrt Pulmonary Thorax.

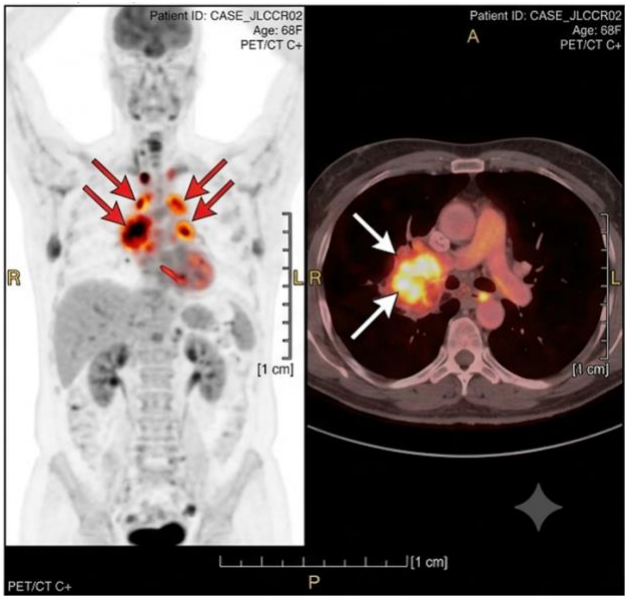


**Figure 2:** PET-CT Staging at Diagnosis. (2A) FDG- PET Scan (MIP) (2B) Exact localization at PET/CT.

## Discussion

Uncommon EGFR mutations pose a distinct therapeutic challenge due to their structural heterogeneity and variable binding affinities for different TKI generations. The L861Q mutation involves a leucine-to-glutamine substitution at amino acid position 861 within the activation loop (A-loop) of the kinase domain, destabilizing the inactive conformation and resulting in constitutive kinase activation.

While second-generation TKIs like afatinib demonstrated efficacy in L861Q mutant tumors in post-hoc analyses of the LUX-Lung trials (ORR ~56%, median PFS 8.2 months), side effects often necessitate dose reductions.

Osimertinib's unique structural design provides high selectivity for mutant EGFR over wild-type receptors. In prospective evaluation (such as the UNICORN trial and KCSG-LU15-09 trial), osimertinib demonstrated compelling antitumor activity in patients with L861Q mutations, with response rates reaching 78% and median PFS exceeding 15 months in L861Q sub-cohorts. Furthermore, osimertinib's superior blood-brain barrier penetration provides crucial protection against CNS recurrence, a frequent site of progression in advanced NSCLC.

This case illustrates that first-line osimertinib can achieve a durable systemic response exceeding 18 months in patients with isolated EGFR L861Q mutations, supporting its role as an effective, highly tolerable targeted option.

## Conclusion

Patients with advanced NSCLC harboring uncommon EGFR alterations, such as exon 21 L861Q, benefit substantially from comprehensive molecular profiling using broad NGS panels. First-line osimertinib represents an efficacious, well-tolerated therapeutic strategy for EGFR L861Q-mutated NSCLC, yielding prolonged disease control and high quality of life.

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