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CASE REPORT

# Immunotherapy Rechallenge of Advanced NSCLC with Acquired EGFR T790M Mutation after EGFR-TKI Therapy: A Case Report

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**Abstract:** Lung adenocarcinoma remains a leading cause of cancer mortality globally. While immune checkpoint inhibitors (ICIs) have improved outcomes in advanced non-small cell lung cancer (NSCLC), their efficacy in patients with acquired epidermal growth factor receptor (EGFR) T790M mutations following multiline therapy is poorly defined. This case report describes a 52-year-old Asian female never-smoker diagnosed with stage IIIA lung adenocarcinoma. She underwent lobectomy and received multiple lines of therapy. Initial genetic testing showed no EGFR T790M mutation, but subsequent testing after multiline treatment confirmed its acquired presence. Following multiline therapeutic failure, the patient received immunotherapy with cadonilimab (a PD-1/CTLA-4 bispecific antibody). This intervention resulted in disease control, and the patient achieved 9.4 months of progression free survival (PFS). This case suggests that immunotherapy with cadonilimab could be a potential consideration for advanced NSCLC harboring acquired EGFR T790M mutation post-multiline therapy.

**Keywords:** non-small cell lung cancer, cadonilimab, case report, immunotherapy, EGFR

## Introduction

Lung cancer imposes a substantial global health burden, predominantly driven by non-small cell lung cancer (NSCLC).[1] The management of advanced NSCLC harboring epidermal growth factor receptor (EGFR) mutations is centered on tyrosine kinase inhibitors (TKIs), yet the invariable development of acquired resistance, most commonly the EGFR T790M mutation, presents a major therapeutic challenge.[2–4] Although chemotherapy remains a standard option, its efficacy is often limited by tolerance issues and modest survival benefits in this heavily pretreated population.[5]

Immunotherapy has emerged as a transformative modality, yet its efficacy in EGFR-mutant NSCLC post-TKI resistance remains incompletely characterized.[6] This creates a profound therapeutic dilemma, particularly for patients who have exhausted TKI options and subsequently progress on conventional immunotherapy. Novel strategies are urgently needed to overcome this immune resistance. Emerging evidence highlights the potential of bispecific immune checkpoint inhibitors, such as cadonilimab, which simultaneously targets programmed death receptor-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4).[7–9] The COMPASSION-03 trial revealed cadonilimab's favorable safety profile and clinically meaningful antitumor activity in advanced solid malignancies, providing a rationale for its investigation in challenging settings.[8]

The optimal therapeutic strategy following resistance to TKI remains undefined. We herein detail the clinical course of a stage IIIA NSCLC patient with acquired EGFR T790M mutation who achieved sustained disease control on cadonilimab after multiline therapy failure. This case report adheres to the AME (Academic Medical Education) Case Report reporting checklist.

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## Case Presentation

A 51-year-old non-smoking female presented in June 2015 with a 5-month history of chronic productive cough. Chest radiography identified a 3.0 cm × 3.5 cm lesion in the left lower lobe, highly suggestive of adenocarcinoma. The patient subsequently underwent radical resection of left lower lung cancer. Postoperative pathology confirmed stage pT2N2M0 adenocarcinoma with lymph node metastases (stations 7, 10, and 11). Genetic testing revealed an EGFR exon 19 deletion (Ex19del) with a variant allele frequency of 43.08%; the T790M mutation was absent. (Figure 1A) Adjuvant therapy with gefitinib was initiated.

After 16 months of sustained response, disease progression was evidenced by mediastinal lymph node enlargement. She subsequently received pemetrexed chemotherapy until further progression in March 2018. (Figure 1B) A repeat biopsy at this time confirmed the persistence of the EGFR exon 19 deletion. (Figure 1A) This finding guided the initiation of the second-line EGFR TKI, icotinib. The patient derived clinical benefit for 18 months until October 2019, when a biopsy of a newly enlarged cervical lymph node confirmed metastatic adenocarcinoma. Notably, biomarker profiling of this lesion revealed a tumor proportion score (TPS) for PD-L1 of 1–4%, MicroSatellite Instability-Low (MSI-L) and a low tumor mutational burden (TMB), collectively characterizing an immune-resistant phenotype (Figure 1A).

Given the lack of a targetable resistance mechanism, therapy was switched to a combination of icotinib and anlotinib. This regimen stabilized the disease for 12 months. In October 2020, the emergence of the EGFR T790M mutation was detected. This finding provided a rationale for transitioning therapy to osimertinib, a third-generation EGFR-TKI targeting the T790M mutation. Unfortunately, the patient progressed rapidly within three months, developing new lung nodules and pleural effusion. (Figure 2) confirming progressive disease (PD) according to the Response Evaluation Criteria in Solid Tumors (RECIST) scoring criteria. The treatment regimen and subsequent patient outcomes are outlined in Table 1.

With limited options after exhaustion of targeted therapies, the patient underwent treatment combining sintilimab (an anti-PD-1 agent), bevacizumab (an anti-VEGF agent), and chemotherapy in February 2021. She experienced fourth-degree myelosuppression necessitating chemotherapy discontinuation, but was maintained on sintilimab and bevacizumab for 39 cycles, achieving a prolonged period of disease control.

Ultimately, progression occurred in July 2023 with widespread lymph node metastases. A brief attempt with furmonertinib was ineffective. By October 2023, the patient presented with a dramatic clinical deterioration featuring extensive right-sided chest wall involvement (edema, skin thickening, pectoralis major muscle swelling), subcutaneous edema, and significant pleural effusions, alongside a steep rise in CEA. (Figure 3) A biopsy of the right breast confirmed invasive ductal carcinoma. Given the multi-refractory status, salvage immunotherapy with cadonilimab (a PD-1/CTLA-4 bispecific antibody) was initiated. During the treatment course, the patient developed grade 4 myelosuppression. This adverse event was effectively managed with supportive measures, including administration of granulocyte colony-stimulating factor (G-CSF), resulting in full hematologic recovery. A follow-up CT scan in January 2024 demonstrated a notable partial response: reduction in lymph node size, resolution of right pectoralis major muscle edema, and improved breast swelling. (Figure 3) The patient achieved a progression free survival (PFS) of 9.4 months following cadonilimab treatment, along with a marked radiographic partial response (PR).

## Discussion

This case report provides the first detailed description of an EGFR T790M-mutated advanced NSCLC patient who had undergone multiple lines of therapy, including resistance to a PD-1 inhibitor, and subsequently achieved a PR following treatment with cadonilimab, a PD-1/CTLA-4 bispecific antibody. This finding challenges the current clinical practice of excluding EGFR-mutated patients from immunotherapy and suggests a potential therapeutic strategy for this "immune-cold" subgroup, which is associated with an extremely poor prognosis.

Although immunotherapy has become a standard of care for advanced NSCLC without driver mutations, EGFR-mutant populations generally derive limited benefit.[10–12] The underlying mechanisms involve multiple factors, including low TMB, low PD-L1 expression, and an immunosuppressive tumor microenvironment (TME) mediated by the EGFR signaling pathway itself. The molecular profile of this patient typifies an immune-cold phenotype.[13] Despite these

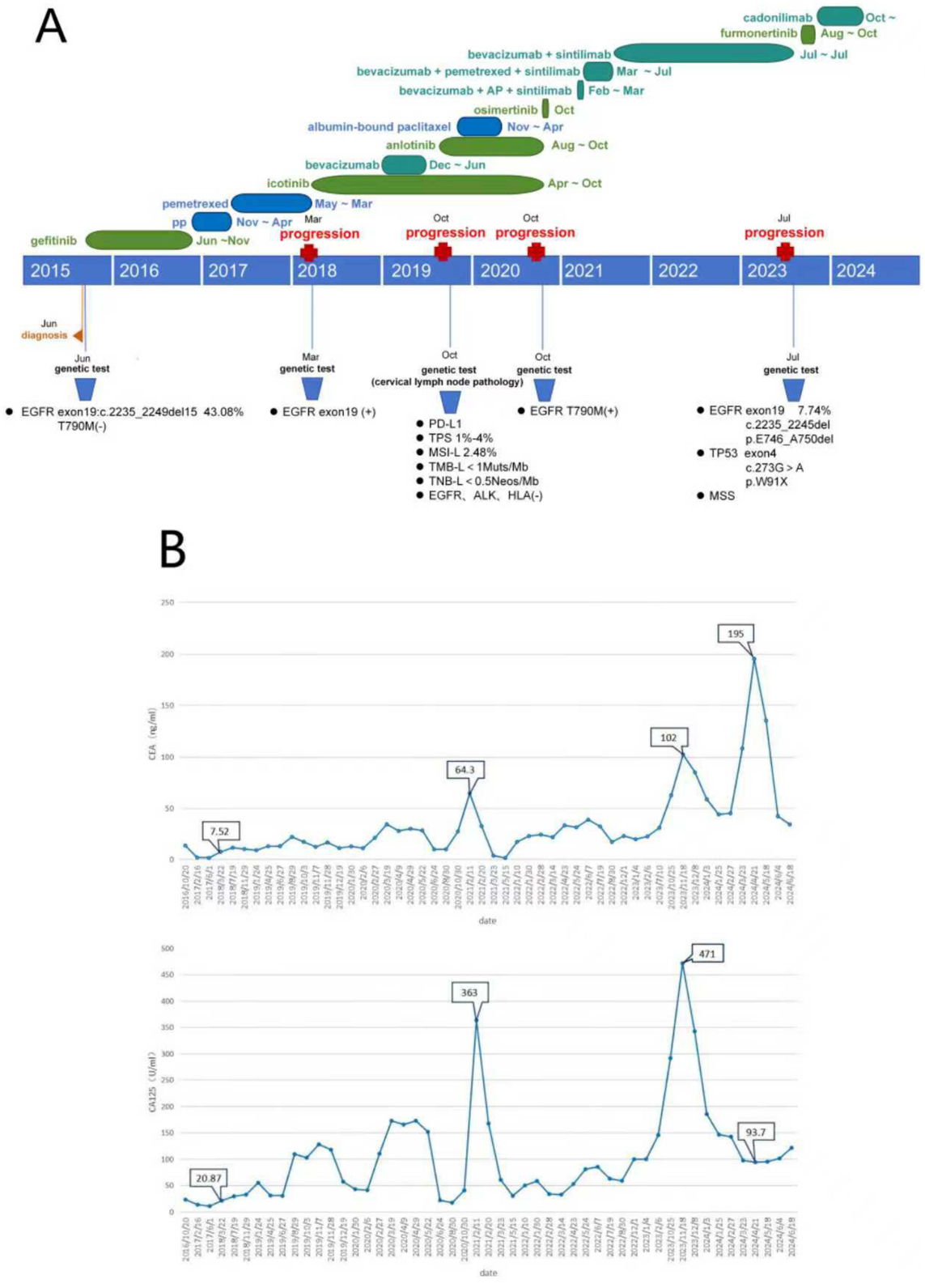


**Figure 1** Treatment regimen, serum testing, and immunohistochemical results of the patient. (**A**) Treatment plan received by the patient. (**B**) the tumor indicators over time. AP, pemetrexed + cisplatin.

**Abbreviations**: CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

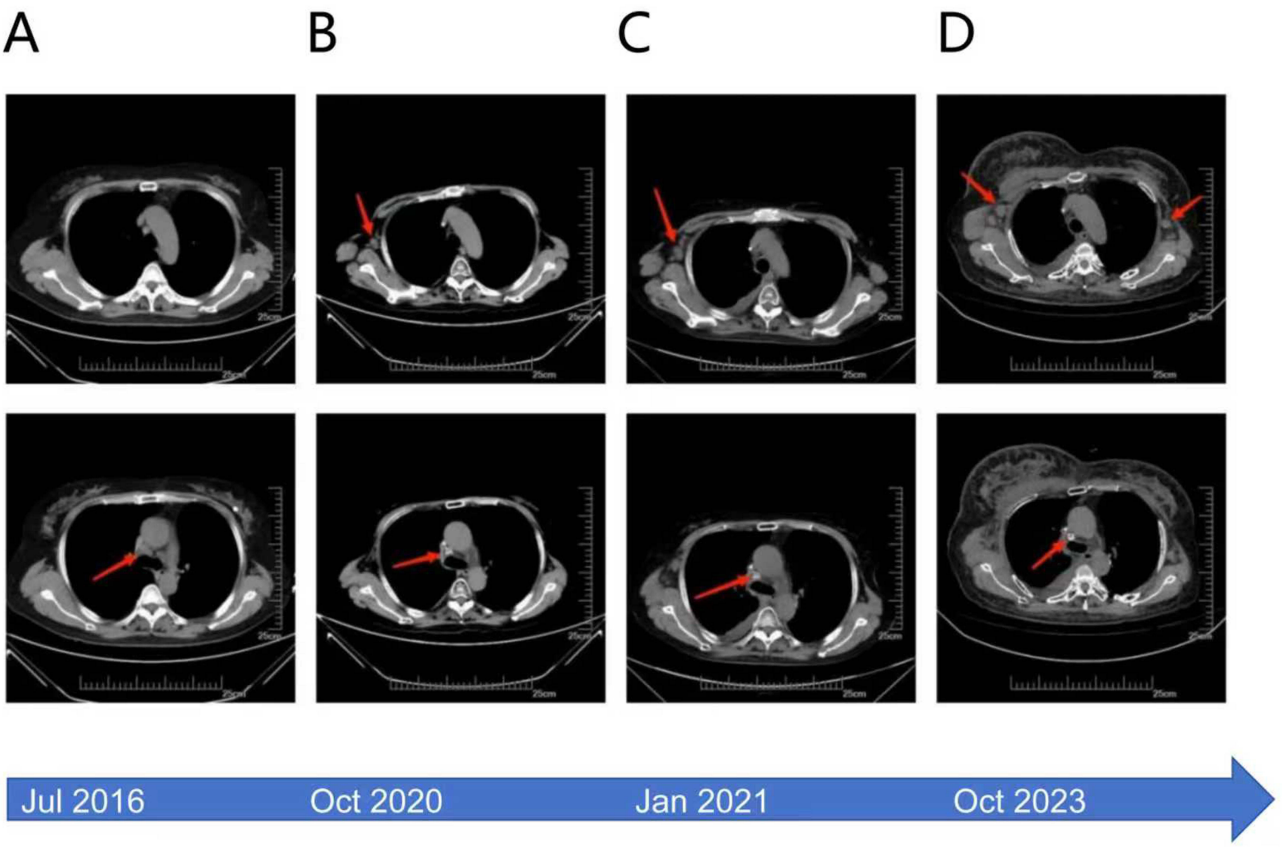


**Figure 2** Computed tomography (CT) images were obtained during the patient's treatment course. (**A**) CT scan showed enlarged lymph nodes in the mediastinum (indicated by red arrows). (**B**) After baseline treatment, new enlarged axillary lymph nodes were observed on CT scan (highlighted with red arrows). (**C**) Following osimertinib treatment, CT scan revealed disease progression (PD), as marked by red arrows. (**D**) After furmonertinib treatment, CT scan demonstrated increased size and number of bilateral axillary lymph nodes (denoted by red arrows).
**Abbreviation**: PD, progressive disease.

unfavorable features, the patient unexpectedly achieved prolonged disease stabilization (SD) lasting 29 months after treatment with sintilimab (an anti-PD-1 antibody) combined with bevacizumab (an anti-VEGF antibody), far exceeding the PFS typically reported with osimertinib monotherapy or combination of immunotherapy and antiangiogenic therapy.[14,15] This sustained clinical benefit may be attributed to the positive modulation of the TME by the combination therapy, such as through vascular normalization and enhanced T-cell infiltration, thereby partially overcoming intrinsic

**Table 1** Timeline of Treatments Received by the Patient and the Subsequent Outcome

| Timeperiod | Treatment | Therapeutic Action | Result |
|---|---|---|---|
| Jun 2015 ~Nov 2016 | Gefitinib | Targeted therapy | PD |
| Nov 2016 ~ Apr 2017 | Pemetrexed + cisplatin | Chemotherapy | SD |
| May 2017 ~ Mar 2018 | Pemetrexed | chEmotherapy | PD |
| Apr 2018 ~ Oct 2020 | Icotinib | Targeted therapy | PD |
| Dec 2018 ~ Jun 2019 | Bevacizumab | Antiangiogenic therapy | PD |
| Aug 2019 ~ Oct 2020 | Anlotinib | Targeted therapy | PD |
| Nov 2019 ~ Apr 2020 | Albumin-bound paclitaxel + anlotinib | Chemotherapy + targeted therapy | PD |
| Oct 2020 ~ Nov 2020 | Osimertinib | Targeted therapy | PD |
| Feb 2021 ~ Mar 2021 | Bevacizumab + AP + sintilimab | Antiangiogenic therapy+chemotherapy+immunotherapy | SD |
| Mar 2021 ~ Jul 2021 | Bevacizumab + pemetrexed + sintilimab | Antiangiogenic therapy+chemotherapy+immunotherapy | SD |
| Jul 2021 ~ Jul 2023 | Bevacizumab + sintilimab | Antiangiogenic therapy+immunotherapy | PD |
| Aug 2023 ~ Oct 2023 | Furmonertinib | Targeted therapy | PD |
| Oct 2023 ~ | Cadonilimab | Immunotherapy | PR |

**Abbreviations**: PD, Progressive Disease; SD, Stable Disease; PR, Partial Response.

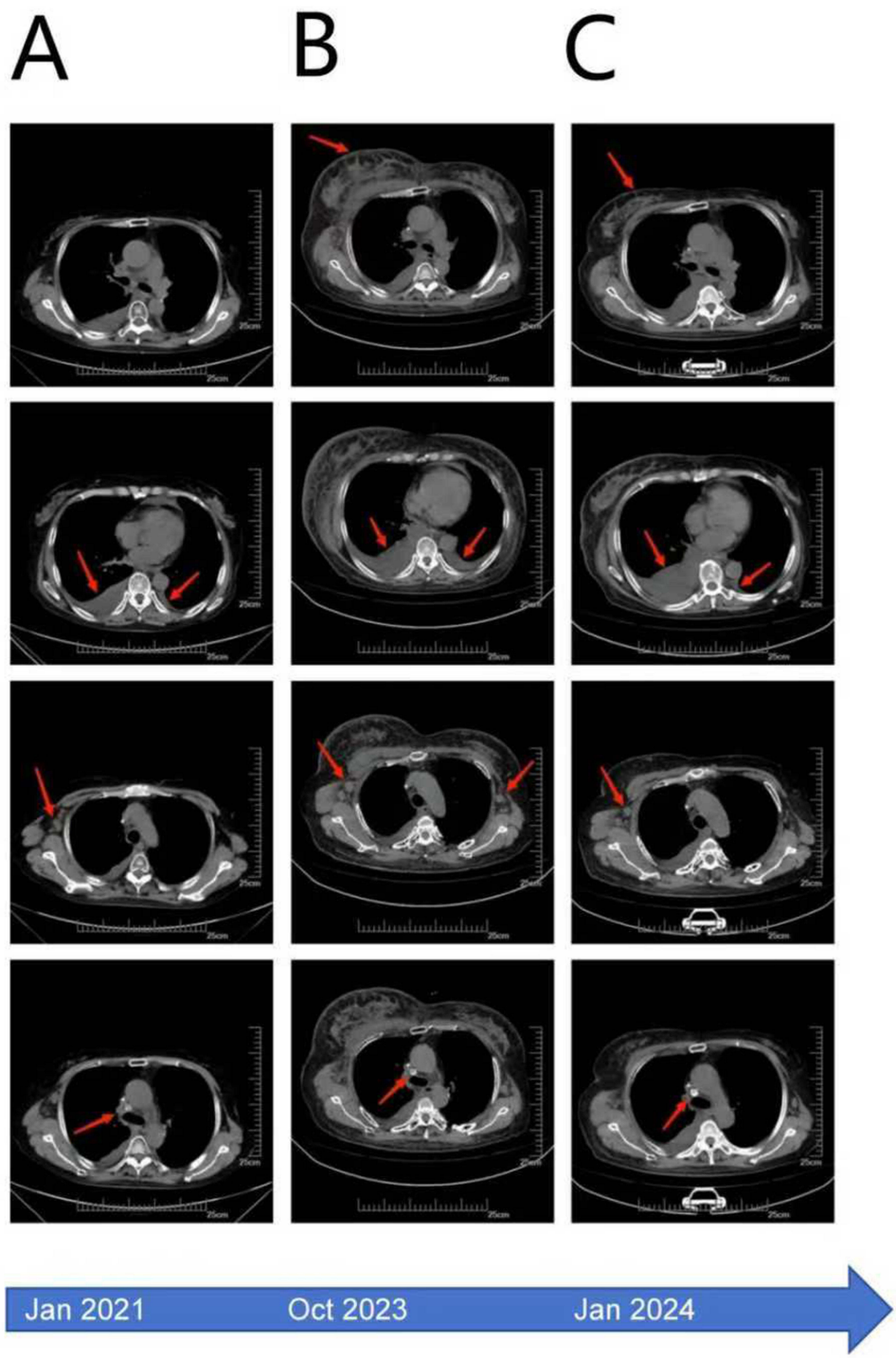


**Figure 3** (**A**) Prior to immunotherapy, CT scan showed enlarged axillary and mediastinal lymph nodes (indicated by red arrows), as well as new bilateral pleural effusion. (**B**) After 39 cycles of immunotherapy, CT scan revealed disease progression (PD), with red arrows highlighting the newly emergent or significantly progressed lesions. (**C**) Following 3 cycles of bispecific antibody immunotherapy, CT scan demonstrated a partial response (PR), where red arrows point to the notably reduced lesions.
**Abbreviation**: PR, partial response.

immune resistance.[16] This finding aligns with a recent meta-analysis by Yi Zhao et al, which established the combination of an ICI, an antiangiogenic agent, and chemotherapy as the optimal therapeutic strategy for patients with advanced EGFR-mutant NSCLC following progression on EGFR TKIs.[17] Nevertheless, this regimen ultimately also resulted in acquired resistance.


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The most significant finding of this case lies in the success of cadonilimab after multiple prior lines of therapy. At a critical juncture when the patient developed resistance to both osimertinib and the combination of immunotherapy and antiangiogenic therapy, accompanied by rapid systemic progression, switching to cadonilimab rapidly induced PFS of 9.4 months.

The mechanism of action may involve simultaneous blockade of both PD-1 and CTLA-4, two key immune checkpoints, resulting in synergistic immune activation.[18] CTLA-4 inhibition promotes T-cell priming and expansion in lymph nodes, while PD-1 inhibition primarily reverses T-cell exhaustion within the TME.[19] This dual blockade strategy may more effectively counteract the profound immunosuppressive state induced by EGFR mutation and repeated prior therapies, providing a strong rationale for overcoming immune resistance. The therapeutic landscape of bispecific antibodies in NSCLC is rapidly evolving, with several novel agents targeting distinct immune pathways under investigation. For instance, Ivonescimab is a bispecific antibody against PD-1 and vascular endothelial growth factor. A recent Phase III trial (HARMONi) demonstrated that median PFS was significantly longer with ivonescimab than with pembrolizumab (11.1 vs 5.8 months).[20] A recent Phase III study demonstrated that combination CTLA-4 and PD-L1 inhibition in previously treated advanced NSCLC improved median overall survival to 11.5 months compared with standard therapy.[21] A 6-month period of SD was achieved with cadonilimab in another case report.[22] Our case demonstrates that the patient achieved a PFS of 9.4 months following cadonilimab treatment.

This study has several limitations. First, this is only a single case report. The efficacy and durability of cadonilimab require validation in prospective large-scale cohort studies. Furthermore, bispecific antibodies carry distinct safety concerns. The patient developed grade 4 myelosuppression. This occurrence underscores the necessity for vigilant monitoring and proactive management in patients receiving such therapies.[19,23] The patient received an extensive sequence of treatments, each of which may have subtly altered the tumor biology and contributed to the subsequent response.

## Conclusion

The case presented in our study demonstrates that a combination of anti-angiogenesis and immunotherapy holds promise as an effective therapeutic approach for advanced lung cancer, particularly in cases of drug resistance and disease progression. Additionally, cadonilimab shows potential as a novel clinical option for lung adenocarcinoma with EGFR T790M mutation and breast metastasis. Nonetheless, Future efforts should focus on prospective clinical trials that incorporate correlative translational analyses to identify predictive biomarkers of response and resistance.

## Ethical Statement

The study involving humans, and publication of the case details, was approved by The Second Affiliated Hospital of Soochow University. The study was conducted in accordance with the local legislation and institutional requirements.

## Consent to Publish

Written informed consent for publication of any potentially identifiable images or data was obtained from the patient's next of kin following the patient's passing. As the patient was deceased, consent could not be obtained directly from her.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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