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CASE REPORT

# Response to Osimertinib Observed in Meningeal-Metastatic NSCLC with EGFR A763V Mutation: A Case Report and Literature Review

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**Abstract:** Here, we report a case of a male patient who was initially diagnosed with stage IV driver gene-negative lung adenocarcinoma and received immune checkpoint inhibitors plus chemotherapy as first-line therapy. The patient progressed to meningeal metastasis and harbored an *EGFR* exon20 p.A763V mutation. A double dose of Osimertinib was recommended and the patient achieved a PFS of 10 months. This report offers evidence that Osimertinib may serve as a treatment option for patients with *EGFR* exon20 p.A763V mutation. In addition, dynamic spatiotemporal heterogeneity of lung cancer cells should be considered when treating patients with *EGFR*-positive NSCLC.

**Keywords:** case report, lung adenocarcinoma, meningeal metastasis, *EGFR* exon20 p.A763V mutation, osimertinib

## Introduction

Over the last 20 years, tremendous progress has been made in the development of new targeted anticancer agents, especially epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC). *EGFR* mutations include classic exon19 deletions (19del) and exon21 p.L858R point mutations, which collectively represent 80–90% of all mutations.[1] Patients harboring these mutations exhibit an excellent clinical response to EGFR-TKIs.

In addition to canonical mutations, mutations in exon 20 are among the most prevalent in NSCLC. An exon 20 insertion mutation, known as *EGFR* ex20ins, typically occurs within the N-terminal region of the EGFR tyrosine kinase domain, following the regulatory C-helix. Besides *EGFR* ex20ins, there are some point mutations in exon 20, such as p.T790M, p.S768I, and p.C797S. The p.T790M mutation is the most common type of mutation responsible for acquired drug resistance in the first and second generations of EGFR-TKIs.[2] The p.S768I mutation is considered resistant to first- and third-generation EGFR-TKIs.[3] The p.C797S mutation is one of the primary causes of drug resistance to the third-generation EGFR-TKI Osimertinib.[4]

Although there have already been reports of lung cancer patients harboring the *EGFR* exon20 p.A763_Y764insFQEA mutation treated with EGFR-TKIs including Osimertinib,[5,6] few reports have focused on the point mutation at codon763 in exon 20, and its therapeutic value remains to be elucidated. Here, we present a rare case of a lung cancer patient who progressed to meningeal metastasis, harboring the *EGFR* exon20 p.A763V mutation, and achieved progression-free survival (PFS) of 10 months with treatment with Osimertinib.

## Case Report

A 47-year-old non-smoking male was admitted to the Department of Pulmonary Oncology because of the discovery of a nodule in the inferior lobe of the left lung during a physical checkup in May 2020. Positron emission tomography-

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computed tomography (PET-CT) revealed a significant nodule measuring 14×10 mm with a lobulated shape, margin spicules, and pleural indentation, which presented a high maximum standard unit value (SUVmax) of 8.2. A slightly increased radiotracer uptake, with SUVmax from 2.9 to 4.5 suggested metastases in the left supraclavicular, mediastinal, and bilateral hilar lymph nodes. Multiple small nodules in both lungs and the interlobar pleura, and multiple bone destruction were also considered metastases (Figure 1). CT-guided lung biopsy was performed, and the pathology revealed poorly differentiated adenocarcinoma (Figure 2). Immunohistochemistry showed positive staining for napsin A, thyroid transcription factor 1 (TTF-1), and cytokeratin 7 (CK7) and negative staining for P40, synaptophysin (Syn), CD56, Chromogranin A (CgA), and cytokeratin 5/6 (CK5/6) with a proliferation index of 30%. A hybridization capture-based next-generation sequencing (NGS) yielded negative results.

Four cycles of programmed cell death ligand 1 (PD-1) inhibitor (camrelizumab) plus chemotherapy (cisplatin and pemetrexed) were administered and the patient achieved partial response according to the immune-modified response evaluation criteria in solid tumor (iRECIST). Subsequently, a PD-1 inhibitor (camrelizumab) plus pemetrexed was used as maintenance therapy. In March 2021, the patient experienced occasional dizziness and underwent brain magnetic resonance imaging (MRI). Multiple brain metastases were observed (Figure 3A–C). The patient underwent whole-brain radiotherapy at a dose of 30Gy in 10 fractions. A routine follow-up MRI of the brain confirmed shrinkage of all tumors (Figure 3D–F). The patient continued to receive a PD-1 inhibitor (camrelizumab) and pemetrexed. In December 2021, brain MRI surveillance confirmed the progression of one intracranial metastasis in the left frontal region, and stereotactic radiation therapy with a dose of 24Gy in three fractions was delivered and the patient continued to receive a PD-1

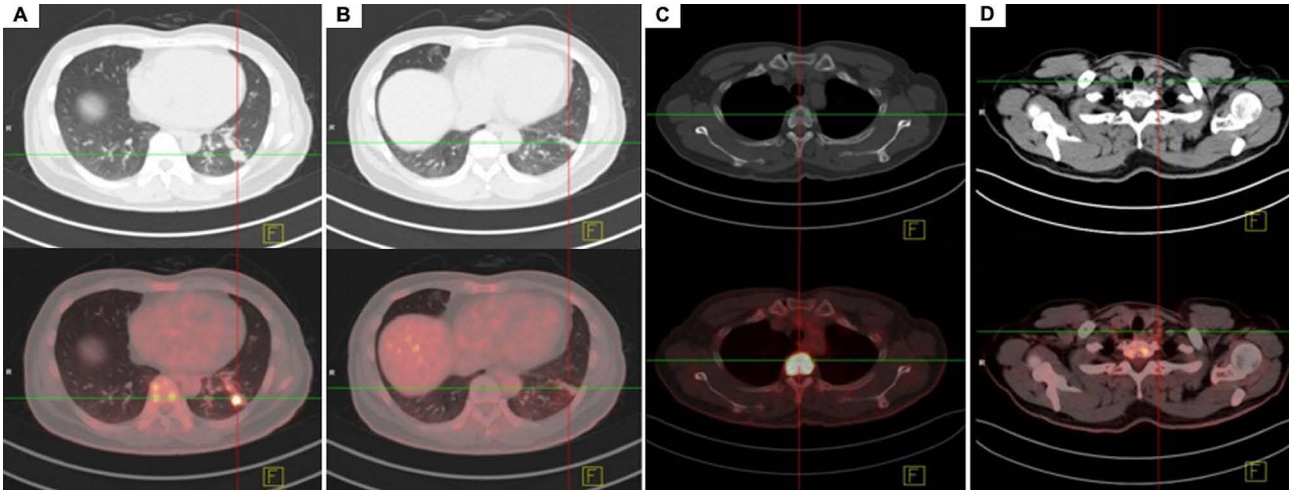


**Figure 1** Positron emission tomography-computed tomography of the patient at the time of diagnosis. PET-CT scan revealed an increased radiotracer uptake of a significant nodule in left lower lobe of lung (**A**), a small nodule in the pleura of interlobar fissure (**B**), bone destruction of thoracic vertebra (**C**) and left supraclavicular lymph node (**D**).

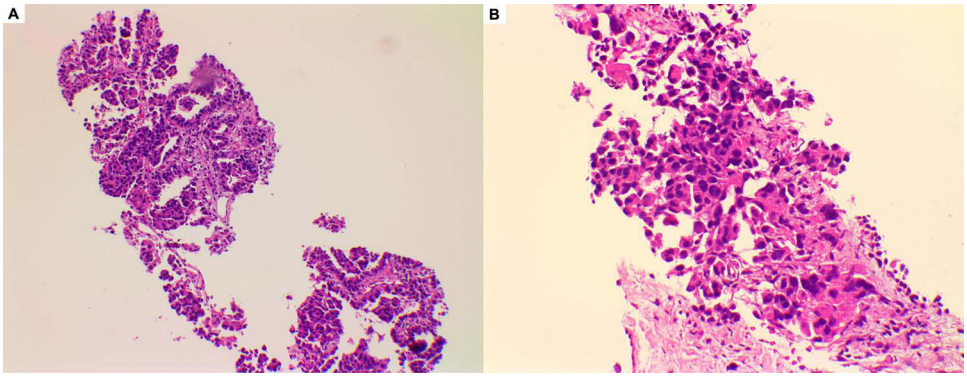


**Figure 2** Pathologic examination of poorly differentiated adenocarcinoma (Hematoxylin and Eosin Stain, Original Magnification 100× for (**A**) and 200× for (**B**)).

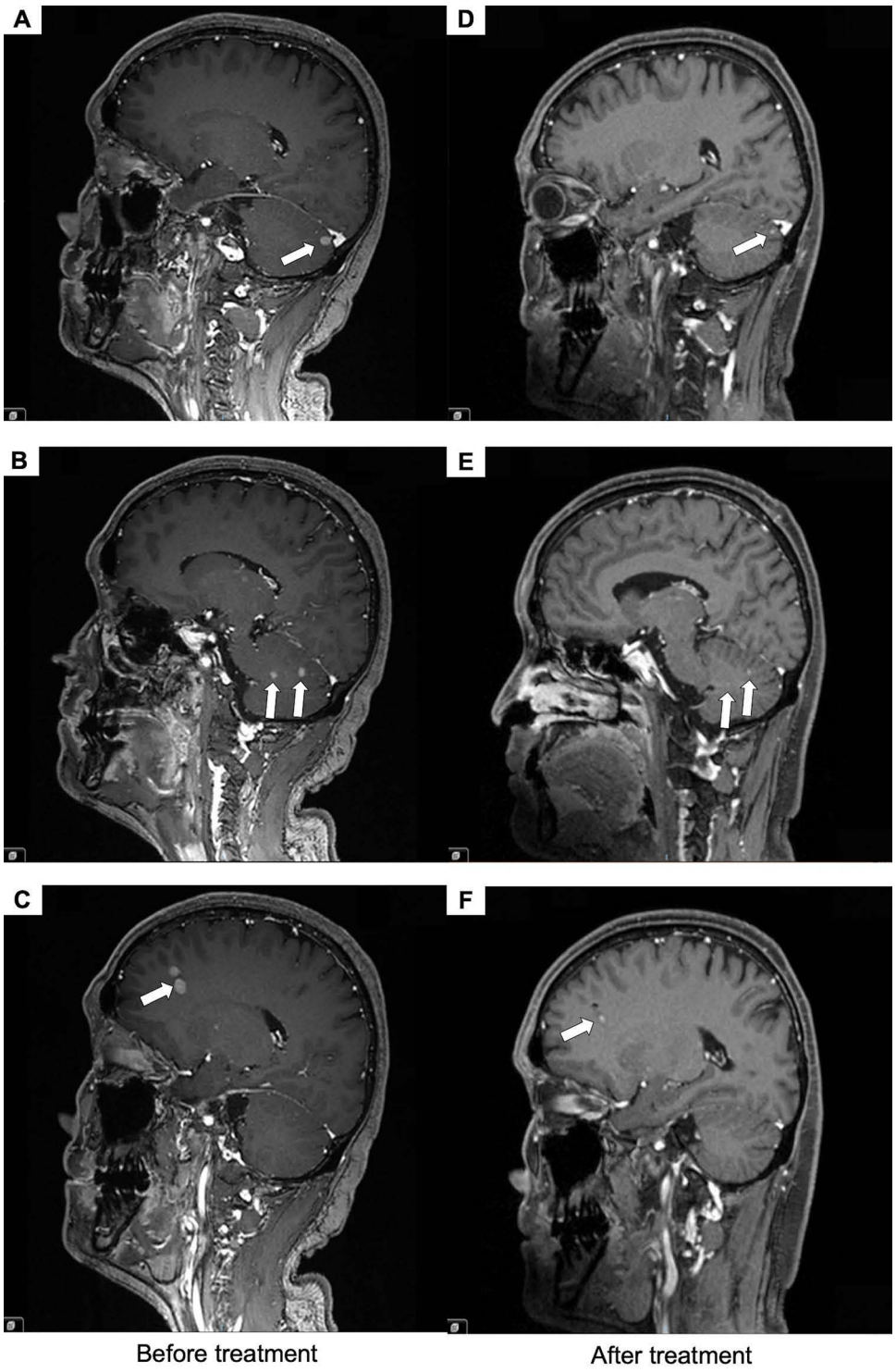


**Figure 3** Brain Imaging before and after treatment on the T1-Weighted Image (Sagittal View). The magnetic resonance imaging scan showed multiple brain metastases (indicated with white arrow) localized in the cerebellum (**A** and **B**) and the frontal lobe (**C**). A whole brain radiation therapy brought about shrinkage of all tumors (indicated with white arrow) (**D**–**F**).

inhibitor (camrelizumab) and pemetrexed. In March 2022, the patient was admitted to the hospital with symptoms of dyskinesia in both lower extremities, urinary incontinence, and difficulty in defecation. Whole-spine MRI confirmed severe spinal cord compression at T2 to T4 (Figure 4). The patient refused to undergo surgery, and radiotherapy with a dose of 20 Gy in five fractions on T2-T4 was performed.


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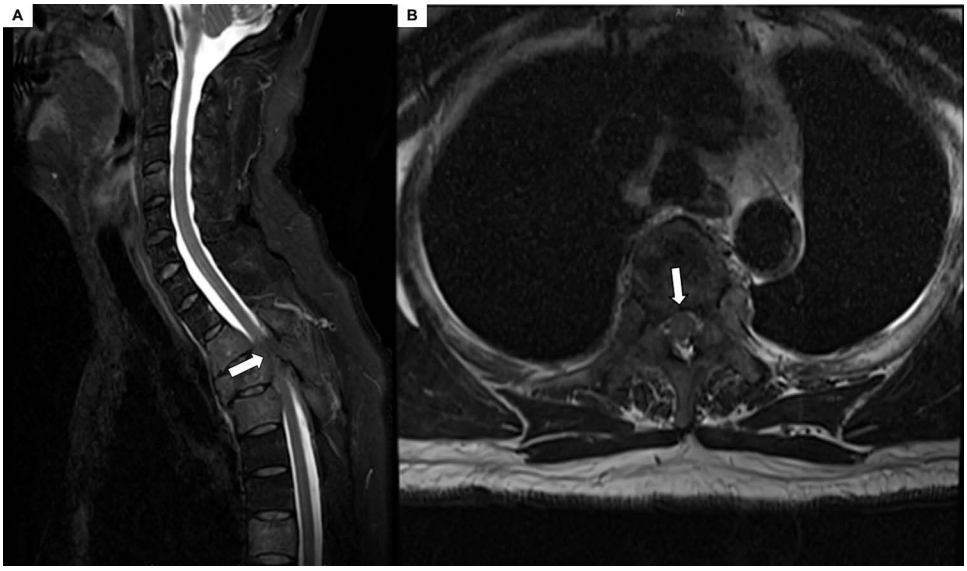


**Figure 4** Thoracic cord compression at T2 to T4 on the T2-weighted image (Transverse/Sagittal View). A whole-spine MRI revealed a thoracic spinal stenosis at T2 to T4 (**A**) (indicated with white arrow) and obliteration of cerebrospinal fluid signal surrounding spinal cord due to the posterior retropulsion of vertebral wall (**B**) (indicated with white arrow).

A shift from PD-1 inhibitor (camrelizumab) plus pemetrexed to bevacizumab plus docetaxel for subsequent systemic therapy had occurred. All symptoms were relieved after radiotherapy and two cycles of bevacizumab plus docetaxel. The patient continued to receive bevacizumab plus docetaxel as a maintenance therapy.

In January 2023, routine clinical surveillance revealed new metastases in the liver and bone and the progression of intracranial metastases. A novel multitarget TKI (anlotinib) that inhibits vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor(FGFR), and c-Kit was prescribed at an oral dose of 10 mg daily as a third-line therapy. After three months of treatment, the patient experienced blurred speech, headaches and dizziness, the deterioration of symptoms prompted us to seek a new treatment. Two cycles of gemcitabine plus bevacizumab were administered as the fourth-line therapy.

However, the patient was admitted to the hospital with limb weakness, memory loss, dizziness, and poor spirits in June 2023. Brain magnetic resonance imaging (MRI) revealed progression of multiple intracranial metastases and mild meningeal enhancement in the medulla oblongata (Figure 5A). A lumbar puncture was performed and tumor cells were found in the cerebrospinal fluid (Figure 5B and C). The same targeted NGS was performed on tumor cells in the cerebrospinal fluid and whole-blood samples. The *EGFR* exon20 p.A763V mutation was detected in the tumor cells in the cerebrospinal fluid. The patient declined chemotherapy and radiotherapy due to fear of side effects. Based on the fact that Chou et al had reported a case of an 80-year-old female with NSCLC who harbored the *EGFR* exon20 p.A763V mutation and achieved a PFS of 1.9 months with treatment of gefitinib, and the theory that most *EGFR* exon20 point mutations were viewed as αC-helix compressing (PACC) mutations which showed good sensitivity to EGFR-TKIs, Osimertinib was recommended on account of patient's poor performance status.[7,8] According to the preclinical data from the BLOOM study suggesting that a higher exposure may provide a good penetration into the CNS, patient was recommended with a double dosage of Osimertinib 160 mg orally once daily.[9] Two weeks of Osimertinib treatment greatly ameliorated the motion function of both lower extremities, and significantly improved the patient's physical and neurologic performance. In December 2023, a follow-up examination showed that the patient had achieved stable disease (Figure 6), and carcinoembryonic antigen (CEA) were tested to monitor tumor growth and response to Osimertinib (Figure 7). In April 2024, a brain MRI revealed that the nodule in the left frontal lobe was slightly larger than before, and abdominal computed tomography revealed new metastases in the left liver, all of which suggested progressive disease. The patient thought that his physical condition had not deteriorated too much and refused to take a biopsy of liver metastases for targeted NGS, and chose to continue taking a double dose of Osimertinib.

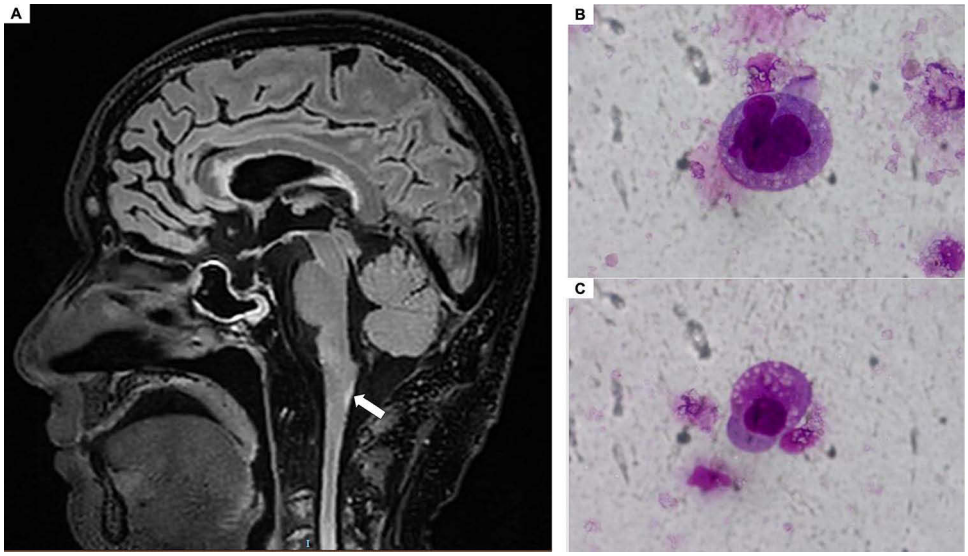


**Figure 5** MRI of the brain on the T2-FLAIR sequence (Sagittal View) and the lung cancer cells in the cerebrospinal fluid under the microscope. The MRI scan on the T2-FLAIR sequence showed mild meningeal enhancement at the level of medulla oblongata (**A**) (indicated with white arrow). Bright-field microscope images of the lung cancer cells in the cerebrospinal fluid (**B** and **C**) (Original magnification 400×).

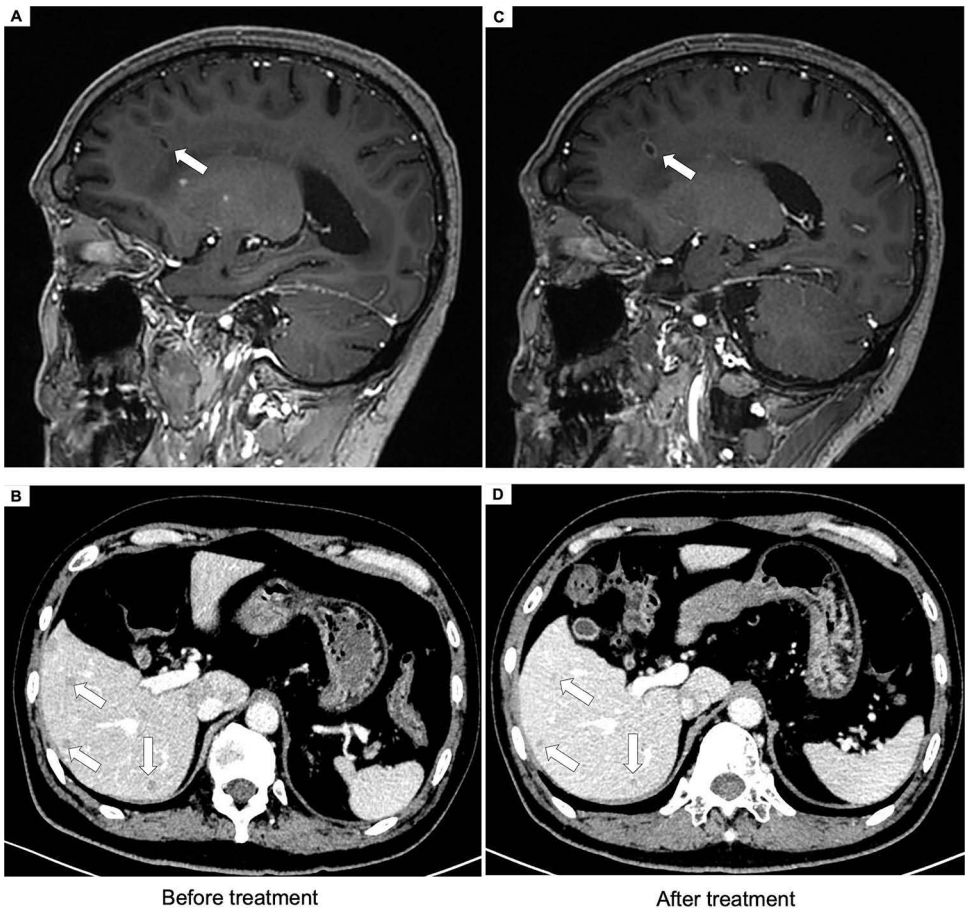


**Figure 6** MRI of the brain on the T1 weighted sequence (Sagittal View) and CT imaging of the liver before and after the treatment of double dosage of Osimertinib. The MRI scan of the brain showed that the lesion in the frontal lobe remained stable (**A** and **C**) (indicated with white arrow). The treatment of double dosage of Osimertinib brought about shrinkage of all metastases in the liver (indicated with white arrow) (**B** and **D**).


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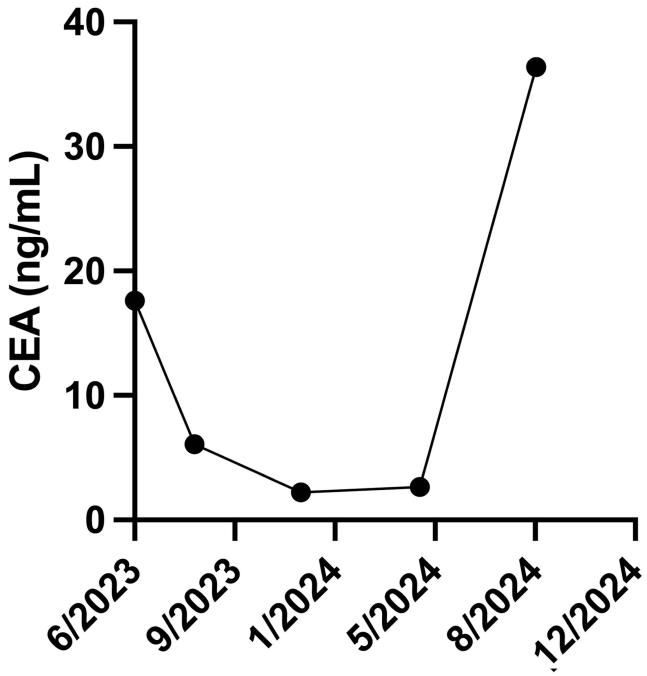


**Figure 7** The course of carcinoembryonic antigen (CEA) under the treatment of Osimertinib. The reference range of CEA was set between 0 and 5 nanograms per milliliter (ng/mL).

In August 2024, the patient was admitted to the hospital due to lightheadedness and imaging reexamination indicated significant progression of brain and liver metastases. We strongly recommended liver biopsy and attempted to clarify the mechanism of resistance to targeted agents. However, considering the high risk of this surgery, his family refused a biopsy. The same targeted NGS of whole-blood samples was performed, and the test did not identify any valuable mutations. Radiotherapy with a dose of 40Gy in 5 fractions was administered for liver metastases. Subsequently, the patient was prescribed a PD-1 inhibitor (sintilimab) in combination with temozolomide. Unfortunately, the patient passed away by the end of October 2024.

## Discussion

Here, we present the case of a male patient with lung adenocarcinoma with multiple metastases whose overall survival had reached 54 months. During treatment, the patient progressed to meningeal metastasis, and the *EGFR* exon20 p. A763V mutation was detected in the tumor cells in the cerebrospinal fluid. The patient was prescribed a double dose of Osimertinib, and achieved a PFS of 10 months.

*EGFR* exon20 encodes amino acids (AA) 762–823, which contain two important regions spanning AA762–775: the regulatory αC-helix domain (AA762–766) and the adjacent loop that follows it (AA767–775), which are further classified into two molecular subtypes: near-loop region (AA767–772) and far-loop region (AA773–775).[10] *EGFR* exon20 mutations exhibit significant heterogeneity in their molecular structure, biological characteristics, and response to EGFR-TKIs. The exon 20 insertion mutation, known as *EGFR* ex20ins, which is predominantly found in younger females, non-smokers, and lung adenocarcinoma patients, is characterized by in-frame insertions and/or duplications of 3–21 base pairs, typically occurring between AA762–775.[11] Most *EGFR* ex20ins have been reported to occur between AA767-775 in the loop region, whereas less than 10% of ex20ins occur within the C-helix. This alteration in exon20 lead to a significant shift in the α-C helix and phosphate-binding loop (P-loop) into the drug-binding pocket, leading to prominent steric hindrance and hampering its binding to targeted agents.[12] The most common subtypes of *EGFR* ex20ins were A767_V769dup and S768_D770dup, which together represented nearly 50% of all EGFR ex20ins mutations.[13] Most patients with *EGFR* ex20ins tend to be less responsive to classical EGFR-TKIs, with an ORR of approximately 10% and PFS of less than 3 months.[11]

Apart from *EGFR* ex20ins, a point mutation in *EGFR* exon20 is another type of mutation that is characterized by the substitution of another amino acid at codon 762–823. The *EGFR* exon20 point mutation is structurally different from the EGFR ex20ins mutation, and, owing to its rarity, few reports have shed light on the therapeutic potential of EGFR-TKIs in patients with this mutation.[14]

Robichaux et al classified EGFR mutations into four distinct subgroups using a structure-based approach: classical-like mutations, T790M-like mutations, exon20 loop insertions and, and PACC mutations.[8] Exon20 insertions in the αC-helix were regarded as classical-like mutations, and the remainder of exon20 insertions occurring in the C-terminal loop of the αC-helix were classified as exon20 loop insertions, and most exon20 point mutations were viewed as PACC mutations, which showed higher selectivity and efficacy for second-generation TKIs than first- and third-generation TKIs. However, point mutations occurring in exon20 show great diversity, and even those occurring in the regulatory αC-helix domain (AA762–766) present different responses to EGFR-TKIs.

Chou et al reported the case of an 80-year-old female non-smoker with squamous cell lung cancer. This patient, harboring the *EGFR* exon20 p.A763V mutation, received gefitinib as a first-line therapy and achieved a PFS of 1.9 months.[7] The poor prognosis of this patient corresponds to the point of view mentioned above that most exon20 point mutations are insensitive to first-generation EGFR-TKIs. However, the poor performance status of this patient at the time of diagnosis limited the efficacy of EGFR-TKIs and affected prognosis. Therefore, we attempted to identify other point mutations occurring between AA762 and AA766 and elucidate the similarities and differences between them.

Lee et al performed an N-ethyl-N-nitrosourea mutagenesis screening of *EGFR* exon20 insertion–mutant cells and found that the *EGFR* exon20 p.E762K mutation conferred resistance to osimertinib.[15] Pennycuick et al reported a non-squamous NSCLC patient carrying the *EGFR* exon20 p.Y764S mutation who received EGFR-TKIs and achieved stable disease for only 3 weeks.[16]

Chou et al also reported the case of a 52-year-old woman with lung adenocarcinoma and *EGFR* exon20 p.V765A mutation who received gefitinib as second-line therapy and achieved a partial response with a PFS of 3.9 months.[7] Hsieh et al reported three lung adenocarcinoma patients with the *EGFR* exon20 p.V765M mutation who had received gefitinib as later-line treatment. Those three patients achieved a partial response, the durations of treatment were 9.47 months, 14.5 months, 15.3 months and the corresponding survivals were 9.5 months, 15.5months, 16 months. However, these patients were found to bear three other mutations, p.L798H, p.K806E, and p.L814P, making it difficult to evaluate the response of gefitinib to these compound mutations and decide which one plays a dominant role in it.[17]

The *EGFR* exon20 p.T766M mutation at the entrance of the ATP-binding site has been reported to play a dominant role in acquired resistance to first-generation ATP-competing TKIs, and the primary mechanism is the increased affinity for ATP relative to EGFR inhibitors. This resistance to first-generation ATP-competing TKIs can be countered by third-generation EGFR-TKIs such as Osimertinib.[18]

*EGFR* exon20 p.M766Q mutation was found to be a driving factor for osimertinib resistance in an *EGFR* p.L858R/p.T790M-mutant lung adenocarcinoma patient. Homology modelling with p.T790M and p.M766Q double mutants revealed that p.M766Q seems to push p.T790M forward into the inhibitor-binding site, thereby weakening osimertinib binding.[19]

The different responses and corresponding mechanisms of these point mutations have also prompted us to find a resemblance between point mutations and insertions occurring near the codon763 and p.A763_Y764insFQEA is the most common and thoroughly studied insertion. Yasuda et al proved that p.A763_Y764insFQEA is an insertion into the αC-helix, which resembles classic mutations such as p.L858R and 19del, and shows significant sensitivity to all classes of EGFR-TKIs. This is because the insertion of FQEA shifts the C-helix and changes the length of the β3-αC loop, resulting in I759A replacement, which leads to catalytic activation.[20]

In addition, the absence of the *EGFR* mutation at the time of diagnosis and the discordance of *EGFR* mutation between cancer cells in the cerebrospinal fluid and peripheral blood raise the question about the spatial and temporal genetic heterogeneity of lung cancer cells. Ogata et al reported that a 64-year-old woman with advanced lung adenocarcinoma had tested negative for *EGFR* mutation using the specimen from pulmonary tumor at initial diagnosis, a rebiopsy for pulmonary tumor was conducted after five years of treatment and a *EGFR* gene test for this specimen exhibited 19del and p.L858R mutations.[21] Since the NGS testing we used was based on the same platform, the presence of the *EGFR* exon20 p.A763V mutation was much more like the result of temporal heterogeneity driven by multiple

factors including intrinsic genomic evolution, tumour cell-microenvironment interactions and selection pressure exerted by anticancer treatment like radiotherapy, targeted therapy and cytotoxic chemotherapy.[22,23]

The discordance of *EGFR* mutation between cancer cells in the cerebrospinal fluid and peripheral blood is another interesting phenomenon. Several independent studies had showed discordance in the *EGFR* gene status of the primary tumor and corresponding metastatic tumor.[24–26] Lee et al had undergone a systematic review and found that the overall discordance rate in *EGFR* mutation was low at 10.36%, the *EGFR* discordance rate was statistically significantly higher in CNS (17.26%) compared with lung/pleural metastases (8.17%).[27] This discordance can be explained by both clonal selection and parallel development models. The former now pays more attention to the microenvironments of the tumor and can be affected by extracellular matrix interactions, cell-to-cell interactions, or nutrient and oxygen status of the cells.[28] In this case, the discordance may be due to the fact that the *EGFR* mutant cancer cells dominate in CNS, while *EGFR*-negative cancer cells gain advantage in peripheral blood. Besides, in order to avoid pseudo-heterogeneity, quality control of the sample, standardization of sequencing analysis, or higher-end sequencing technology like single-cell sequencing will help us to obtain reproducible results important for diagnostic practise and tumor therapeutics.

## Conclusions

In summary, our case shows a male lung adenocarcinoma patient with meningeal metastasis harboring the *EGFR* exon20 p.A763V mutation who had received treatment with Osimertinib and achieved a PFS of 10 months. This report offers evidence that Osimertinib may serve as a treatment option for patients with *EGFR* exon20 p.A763V mutation. In addition, dynamic spatiotemporal heterogeneity of lung cancer cells should be considered when treating patients with *EGFR*-positive NSCLC.

## Data Sharing Statement

Please contact the corresponding author for data requests.

## Ethics Approval and Informed Consent

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2024). Institutional approval was not required to publish the case details. Written informed consent was obtained from the patient's wife for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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The authors thank the patient's wife for her signed agreement to publish this report. All the authors have read and approved the final manuscript.

## 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. All authors gave final approval of the version to be published, have agreed on the journal to which the article has been submitted and have agreed to be accountable for all aspects of the work.

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## Disclosure

The authors have stated that they have no conflicts of interest in this work.

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