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LETTER TO THE EDITOR Open Access

Sunvozertinib overcoming resistance to afatinib and osimertinib in lung adenocarcinoma harboring an EGFR exon 18 DelE709_T710insD mutation

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To the editor,

Epidermal growth factor receptor (EGFR) exon 18 mutations are relatively infrequent, representing 4.1% of total EGFR mutations [1], among which delE709_T710insD mutation accounts for about 0.16% [2] in non-small cell lung cancer (NSCLC). Although no specific targeted therapies have been clinically approved for delE709_T710insD mutation, afatinib has demmonstrated clinical benefits in certain cases. However, the therapeutic landscape following afatinib resistance remains inadequately supported by clinical evidence.

The patient's diagnostic and treatment history was summarized in Figure 1A. In April 2023, a 43-year-old male presented to our institution with a 3-month history of right-sided shoulder pain. He has a smoking history of 2.5 pack-years for almost 10 years. A chest computed tomography (CT) scan revealed a 3.2×2.5 cm mass in the right lower lobe of the lung, accompanied by enlarged mediastinal lymph nodes in the 4R region and the right hilum and diffuse multiple lung metastases (Figure 1B). Magnetic resonance imaging (MRI) of the brain disclosed multifocal lesions with marked edema (Figure 1B), while an isotope bone scan showed multiple bone metastases. Bronchoscopic biopsy pathology confirmed a diagnosis of invasive mucinous adenocarcinoma. Consequently, the patient was diagnosed with right lung adenocarcinoma with multiple metastases, classified as cT2aN2aM1c, stage IV. Subsequently, circulating tumor DNA (ctDNA) next-generation sequencing [GeneseeqPrime® pan-cancer gene panel (437 genes)] identified an EGFR exon 18 DelE709_T710insD mutation along with TP53, FGFR2, JAK3 and TAP1 mutations, and a moderate tumor mutational burden (TMB) of 6.2 mutations per megabase (Mb). Utilizing the PD-L1 22C3 pharmDx kit (Dako, Carpinteria, CA, USA) for PD-L1 immunohistochemical staining, the assessment disclosed a PD-L1 tumor proportion score (TPS) of 60%. At the onset of treatment, the patient received afatinib (40 mg orally daily) and achieved a partial response (PR) (Figure 1C). After five months, MRI showed new intracranial lesions (Figure 1D). In September 2023, whole-brain radiotherapy (WBRT, 3000 cGy in 10 fractions) was administered for the intracranial progression. The patient was immediately followed by targeted therapy with osimertinib at 80 mg orally daily. Nevertheless, one month later, a re-evaluation suggested enlargement and increase of both intracranial and pulmonary lesions (Figure 1E). After detailed communication with the radiologist to rule out the influence of potential inflammatory effects of radiotherapy, we concluded that the disease had progressed. Then, a chemo-immunotherapy and anti-angiogenic agents was initiated, consisting of pemetrexed (500 mg/m^2), carboplatin (area under curve [AUC] of 5), bevacizumab

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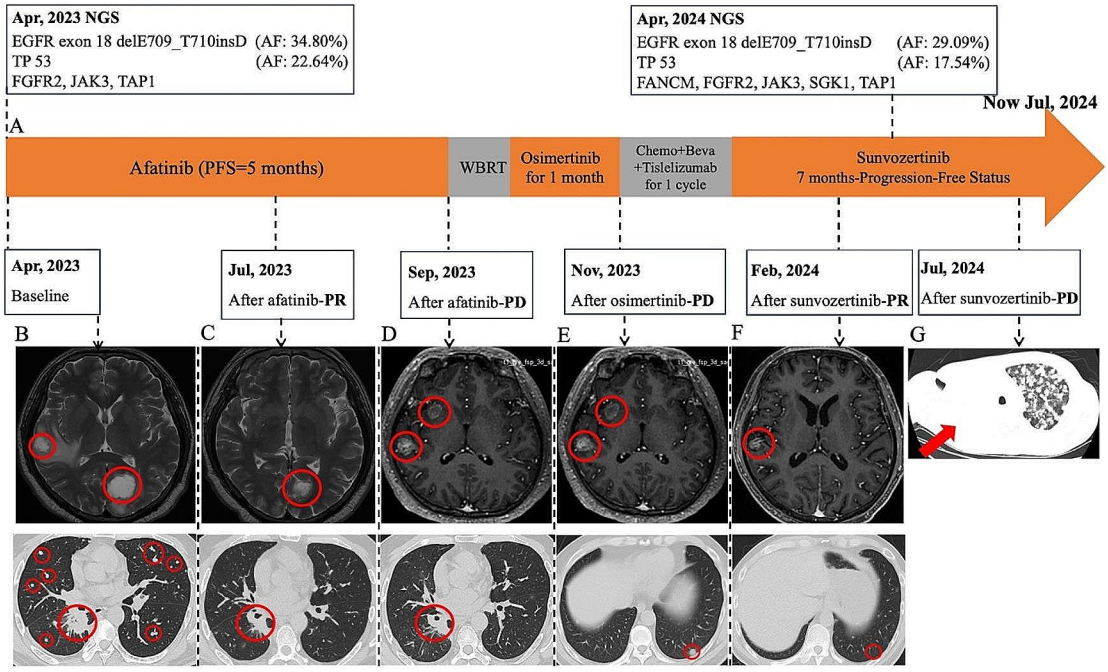

Fig. 1 The timeline of the patient's treatment history and the response of the tumor lesions. (**A**) the timeline of treatments; (**B–G**) Computed tomography (CT) images and brain magnetic resonance imaging (MRI) of the patient's nodules

(7.5 mg/kg) and tislelizumab. However, the patient experienced severe toxicities, including grade IV myelosuppression, weight loss, and generalized pruritic rash, leading to discontinuation of this regimen. Blood carcinoembryonic antigen (CEA) was elevated to 90.04 ng/mL than before (33.27 ng/mL), but the patient refused imaging examination. The patient was unable to tolerate systemic therapy because of worsening cough, headache and dizziness, and concurrent with a drop in his performance status (PS) to a score of 3. Considering the absence of other suitable targeted drugs for EGFR Exon 18 DelE709_T710insD mutation and the remarkable efficacy of the Sunvozertinib in patients with EGFR exon20 insertion mutations, the patient was finally treated with Sunvozertinib in December 2023 after informed consent was obtained. Two months later, a re-assessment showed positive results of this treatment strategy: intracranial metastases, right lower lobe mass with varying degrees of shrinkage (Figure 1F), and significant reduction of dizziness and headache symptoms (PS=1), consequently, the overall response was reclassified as a PR. In July 2024, the patient presented with severe chest tightness, which was confirmed by a chest CT, revealing that the patient had developed a large right-sided pleural effusion (Figure 1G), and a cranial MRI with no significant changes. The patient's progression free survival (PFS) has lasted more than 7 months.

Sunvozertinib has not only shown remarkable efficacy in patients with EGFR exon20 insertion mutations but also preliminary therapeutic potential in the setting of EGFR-TKI resistance [3, 4]. Herein, for the first time, we present a case of an advanced NSCLC patient harboring the EGFR exon 18 delE709_T710insD mutation. Despite secondary resistance to afatinib as well as primary resistance to osimertinib, the patient manifested a striking clinical and radiological response when treated with half-dose sunvozertinib, effectively managing brain metastases and culminating in disease remission. Thus, EGFR exon 18 delE709_T710insD mutation may represent a rare yet potentially actionable sunvozertinib-responsive alteration in NSCLC. And this case provides new real-world clinical insights into the management plans for NSCLC patients carrying the EGFR exon 18 delE709_T710insD mutation. According to the MARIPOSA study [5], the use of dual-targeted combination regimen to help counteract the unfavourable prognosis of EGFR and TP53 co-mutations in advanced NSCLC patients may improve the efficacy of Sunvozertinib. Finally, we recognise the fact that we did not have pre-treatment imaging of Sunvozertinib to absolutely confirm its efficacy is a limitation of this study.

Abbreviations

NGS	Next-generation sequencing
AF	Allelic fraction
WBRT	Whole Brain Radiation Therapy

Chemo	Chemotherpy
Beva	Bevacizumab
PR	Partial response
PD	Progressive disease

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Not applicable.

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Kaibo Ding prepared the manuscript; Zhongsheng Peng and Dujiang Liu collected the data; Yanjun Xu reviewed the manuscript.

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Declarations

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Not applicable.

Consent for publication
The patient gave his written consent to this publication.

Competing interests
The authors declare no conflicts of interest.

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References

1. Forbes SA, et al. COSMIC: somatic cancer genetics at high-resolution. Nucleic Acids Res. 2017;45:D777–83.
2. Wu JY, et al. Effectiveness of tyrosine kinase inhibitors on uncommon E709X epidermal growth factor receptor mutations in non-small-cell lung cancer. Onco Targets Ther. 2016;9:6137–45.
3. Wang M, et al. Sunvozertinib for patients in China with platinum-pretreated locally advanced or metastatic non-small-cell lung cancer and EGFR exon 20 insertion mutation (WU-KONG6): single-arm, open-label, multicentre, phase 2 trial. Lancet Respir Med. 2024;12:217–24.
4. Yang JC-H, Wen-Tsung Huang YX et al. Anti-tumor activity of sunvozertinib in NSCLC with EGFR sensitizing mutations after failure of EGFR TKI treatment. J Clin Oncol. 2023;41.
5. Felip E et al. Amivantamab plus Lazertinib versus osimertinib in first-line EGFR-mutant advanced non-small-cell lung cancer with biomarkers of high-risk disease: a secondary analysis from MARIPOSA. Ann Oncol. 2024.

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