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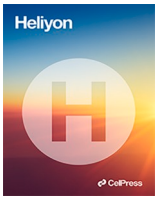

Case report

Successful therapy of a critically ill non-small cell lung cancer patient with compound mutations in *EGFR* G719X and S768I genes using furmonertinib: A case report

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ABSTRACT

Background: Somatic mutations in epidermal growth factor receptor (*EGFR*) genes, such as G719X and S768I, and tyrosine kinase inhibitors (TKIs) have been confirmed to be promising for developing new targeted therapies against advanced non-small-cell lung cancer (NSCLC). The G719X and S768I mutations are uncommon and often occur in the form of compound mutations. However, the efficacy of furmonertinib in patients with these uncommon compound mutations has not yet been elucidated.

Case presentation: In this study, the G719X/S768I compound mutations were detected in a critically ill NSCLC patient. This patient received furmonertinib for 14 months and successfully responded to the treatment. The present case report highlights the ideal clinical response, with ongoing follow-up.

Conclusion: We report the successful treatment of a critically ill NSCLC patient carrying rare compound *EGFR* G719X and S768I mutations using furmonertinib. To the best of our knowledge, this is the first reported case of a successful furmonertinib treatment of compound *EGFR* G719X and S768I mutations. Furmonertinib, a third-generation *EGFR*-TKI, may be effective in controlling the *EGFR* G719X and S768I compound mutations in NSCLC.

1. Introduction

Considered a major malignancy, lung cancer is a threat to human health owing to its high mortality and is on top of the non-gender-specific death-cause cancer list. Almost 85% of the various types of lung cancers are categorised as non-small cell lung cancers (NSCLC), which can be driven by different genes, including the epidermal growth factor receptor (*EGFR*) [1]. The two most common mutations in NSCLC are exon 19 deletion and exon 21 L858R point mutations. These classical mutations account for approximately 90% of all *EGFR* mutations in NSCLC. The remaining 10% of *EGFR* mutations include rare mutations such as exon 18 point mutations (G719X), exon 20 insertion mutations (20 ins), and exon 20 point mutations (S768I) [2,3]. The frequency of *EGFR* compound mutations vary among studies and populations, with previous studies indicating an incidence rate of approximately 4%–26% among Asians and 5%–7% among Caucasians with *EGFR* mutation-positive NSCLC [4]. The low incidence of such rare *EGFR* mutations has led to unclear clinical characteristics in this group of patients and their outcomes following *EGFR*-tyrosine kinase inhibitor (TKI) therapy. The present study investigated a clinical case in which a patient with critical NSCLC carrying the G719X and S768I compound

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mutations was treated with furmonertinib and achieved effective remission.

2. Case presentation

A 56-year-old Chinese Han male was admitted to our hospital on August 25, 2021 with a claim of 'chest distress for more than 6 months, with symptoms worsening within the last 2 weeks'. The patient, in good health, reported no smoking history but had a 10-year history of exposure to second-hand smoke. In addition, the patient reported no history of familial genetic diseases or infections. The patient developed chest distress with cough and white sputum without any obvious cause in January 2021. The patient had no uncomfortable symptoms such as chills, fever, dizziness, headache, palpitations, or chest pain. He did not visit the hospital or take any medications. On August 11, 2021, the patient noted a deterioration in symptoms, with an increased frequency of attacks following physical activity. He visited the Respiratory clinic of our hospital and underwent chest computed tomography (CT) on 23 August 2021, which revealed multiple nodules, plaques, and masses in both lungs, pericardial cavity effusion, and minor bilateral pleural effusion (Fig. 1). Bronchoscopy performed on August 25, 2021 suggested congestion and hypertrophy of the bronchial mucosa, and no obvious neoplastic formation was observed within the field of view. In addition, tissue biopsies were performed on the right upper lobe, right middle lobe, basal and dorsal segments of the right lower lobe, left upper lobe, and basal and dorsal segments of the left lower lobe of the lungs (Fig. 2a). The patient's pulse oxygen level dropped to 70% during the biopsy. No obvious signs of embolism were observed in the main pulmonary artery or its larger branch lumen during subsequent enhanced CT of the chest. The physical examination indicated a temperature of 36.7 °C; heart rate, 120 beats/min; respiratory rate, 32 breaths/min; and blood pressure, 132/65 mmHg (1 mmHg = 0.133 kPa). The patient was conscious, with diminished respiratory sounds in both lungs and audible wet rales. In addition, the patient exhibited a normal cardiac rhythm, and no pathological murmur was detected in either of the lower extremities.

Routine tests were performed after hospital admission. Routine blood, urine, and faecal examinations indicated normal conditions. The biochemical, electrolyte, coagulation functions and autoantibody tests revealed no significant abnormalities. The patient's tumour marker indices were as follows: CEA: 77.7 ng/mL (0–5 ng/mL); CYFRA211: 7.76 ng/mL (0–3.3 ng/mL); NSE: 17.6 ng/mL (0–17 ng/mL); CA125: 191 U/mL (0–35 U/mL); and D-dimer: 2.08 μg/ml (0–0.5 μg/ml). The autoantibody test showed the anti-Scl-70 antibody to be weakly positive (±). The immunohistochemical outcomes of bronchoscopy biopsy were performed on 2 September 2021 and included CK7 (+), NapsinA (+), TTF1 (+), CK20 (−), CDX2 (−), P504S (foci +), PSA (−), Ki-67 (+10%), CK5/6 (−), P63 (−), CD117 (), and PD-L1 (−) (Fig. 2b). Gene detection results (ADx-ARMS and RT-PCR) suggested mutations in *EGFR* exons 18 (G719X) and 20 (S768I). No mutations were detected in *ALK*, *ROS1*, *RET*, *KRAS*, *NRAS*, *BRAF*, *PIK3CA*, *HER-2*, and *MET* (Fig. 2c). Whole-body bone imaging performed on 6 September 2021 indicated regional bone lesions in the left maxillofacial region, as well as on the left sides of the atlas, 9th posterior spine, and ischium. This raises the possibility of metastatic bone tumours. Cranial magnetic resonance imaging (MRI) performed on 7 September 2021 revealed multiple abnormal signal foci located in the left frontoparietal lobe, left occipital lobe, and right temporal lobe, indicating a metastatic tumour accompanied by haemorrhage. In addition, abnormal signal foci in the left septal and maxillary sinuses with bone destruction in the anterior wall of the left maxillary sinus suggested a metastatic tumour. Moreover, cranial MRI suggested paranasal sinusitis and mild bilateral mastoiditis.

The patient was treated with cisplatin (60 mg, d1 and d2) + albumin paclitaxel (200 mg, d1 and d8) from 4 September 2021. On 10

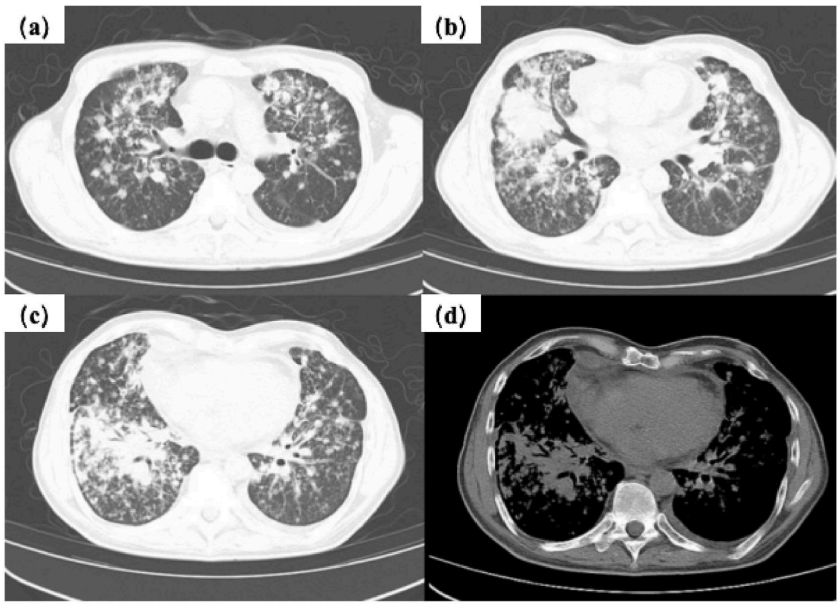

Fig. 1. Chest CT(23 August 2021) suggested multiple nodules, plagues, and masses in both lungs and pericardial cavity effusion. A small amount of effusion in both pleural cavities was observed. a-c) Chest CT of the lung window; d) Chest CT of the mediastinum window.

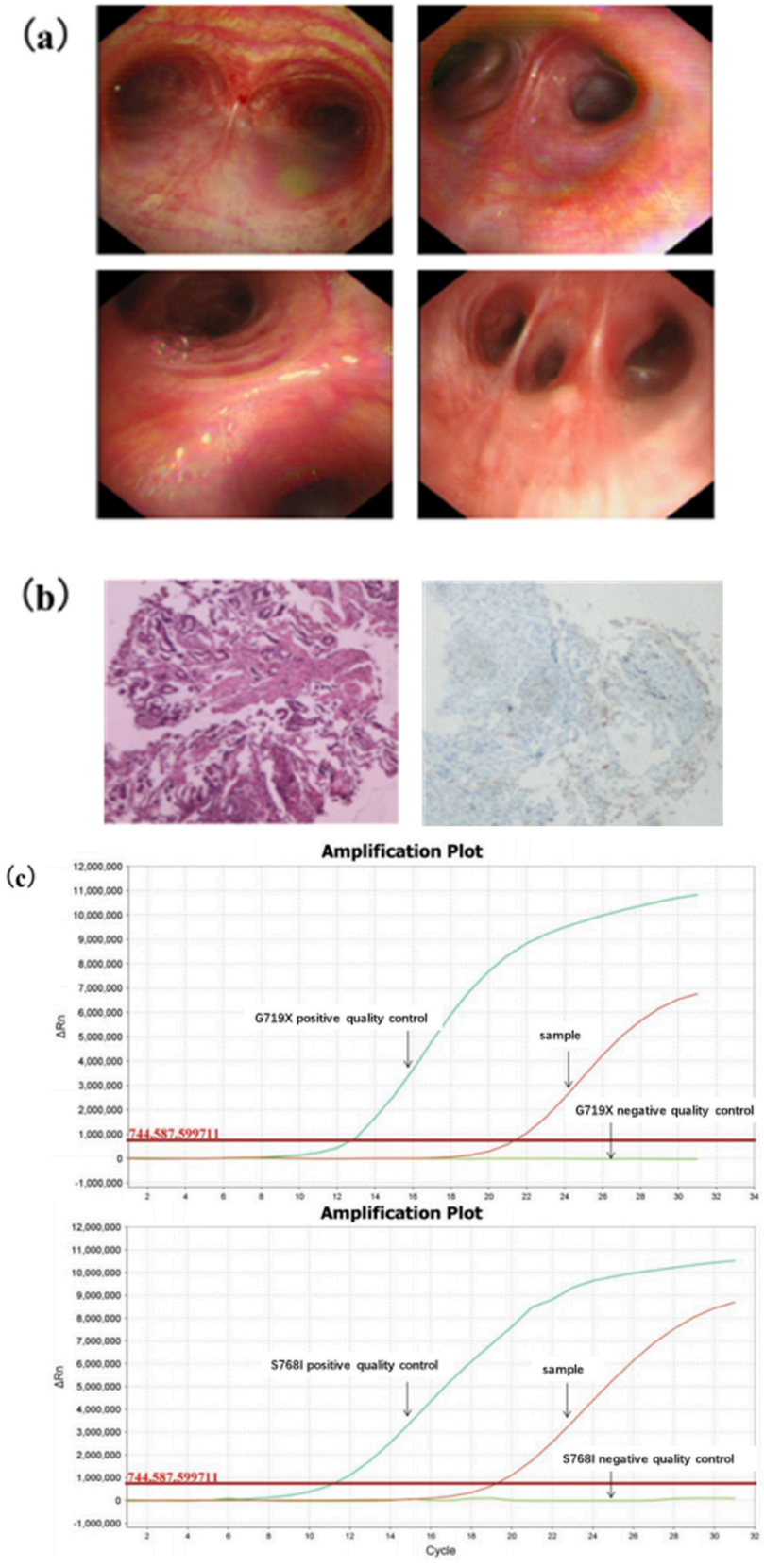

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Fig. 2. Bronchoscopic findings and pathological and genetic results. a) Bronchoscopic bronchial lumen; b) HE staining (× 100 times) and PD-L1 immunohistochemical staining (× 100 times); c) Genetic test results.

September 2021, the patient developed significant chest distress, and an ECG was suggestive of paroxysmal atrial flutter. Therefore, Cordarone (200 mg tid) and Digoxin (0.125 mg qd) was orally administered to the patient to control the ventricular rate. Angiographic ultrasonography suggested an intramuscular vein thrombosis in the left calf. Symptomatic supportive therapy was initiated owing to a

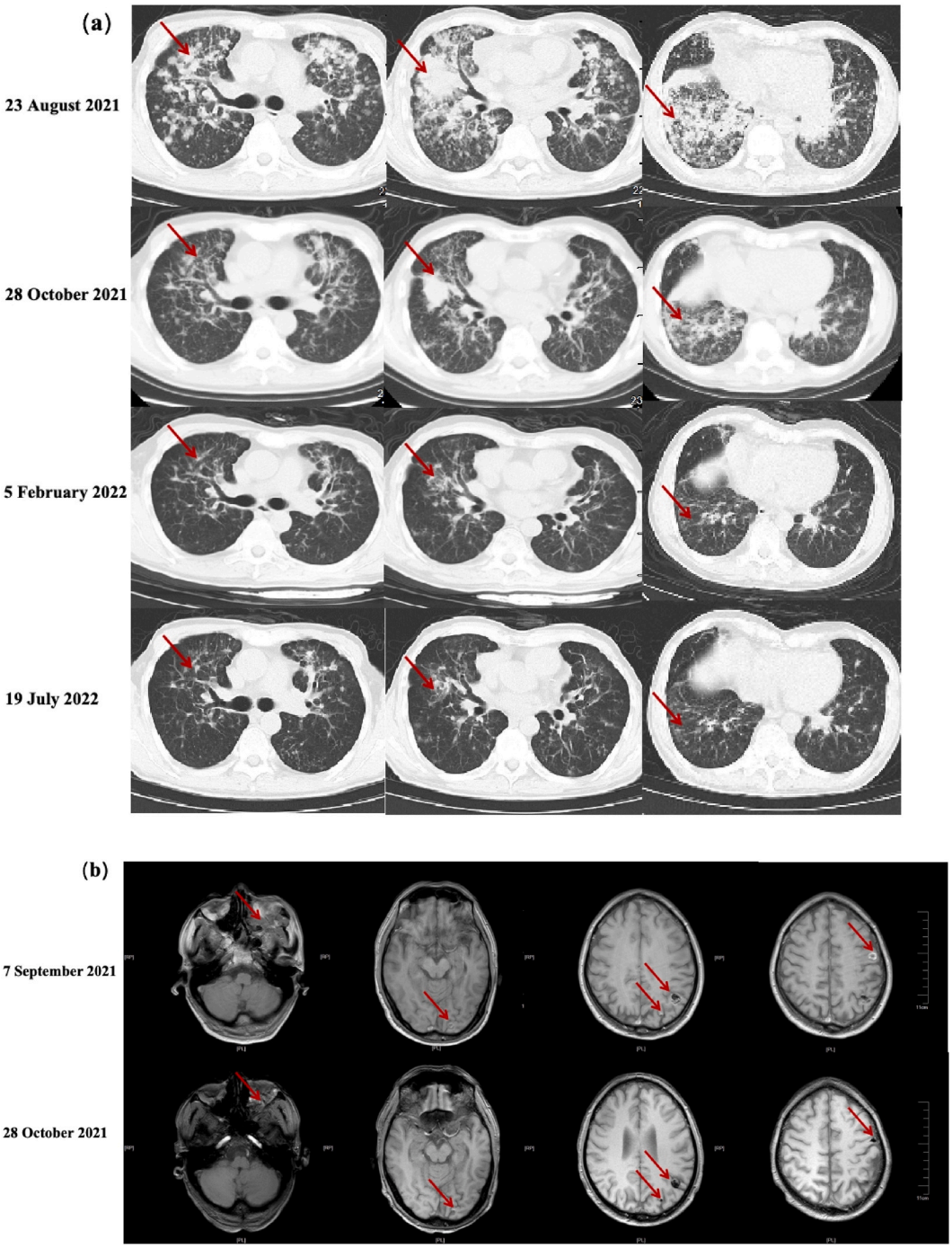

Fig. 3. Dynamic changes of chest CT (a) and cranial MRI (b) images of patients before and after treatment. Chest CT suggested partial remission (multiple nodules, plaques, and masses in both lungs were smaller than before). Cranial MRI (left septal sinus invasion extent, left parieto-occipital lobe, and left frontal lobe metastases were smaller than before).

decline in the patient's physical status (PS) score to 4, rendering him unable to tolerate d8 albumin paclitaxel chemotherapy. The patient received oral furmonertinib (80 mg, qd) from 20 September 2021.

The patient's blood tumour indicators were monitored dynamically, and the specific values obtained on 29 October 2021 were as follows: CEA: 37.9 ng/mL (0–5 ng/mL); CYFRA211: 3.0 ng/mL (0–3.3 ng/mL); NSE: 17.9 ng/mL (0–17 ng/mL); and CA125: 40.1 U/mL (0–35 U/mL). After 38 days of furmonertinib treatment, the patient showed significant regression of the diffuse lesions in both lungs and smaller cranial metastases than those pre-treatment. Chest CT (Fig. 3a) and cranial MRI at the time of re-examination suggested partial remission (the extent of left septal sinus invasion, left parieto-occipital lobe, and left frontal lobe metastases were smaller than those pre-treatment) (Fig. 3b). Furthermore, the chest distress, cough, and sputum symptoms were significantly relieved, and the physical status score increased to 1. The patient was satisfied with the outcome, as being diagnosed with lung cancer led him to anticipate a shorter life expectancy. After 4.5 months of furmonertinib treatment, the chest CT on 5 February 2022 (Fig. 3a) suggested continued shrinkage of the lung lesions compared to the previous assessment on 28 October 2021. After 10 months of furmonertinib treatment, the chest CT on 19 July 2022 (Fig. 3a) indicated stable lung lesions compared to those on 5 February 2022. After 14 months of furmonertinib treatment, the patient discontinued the drug for personal reasons, and no further review of the chest CT and tumour markers was conducted. In addition, the patient did not experience any drug-related adverse events such as rash, diarrhoea, or liver function impairment during the follow-up period, leading to a significant improvement in his quality of life. Currently, the patient is still undergoing follow-up via telephone. The treatment history of the patient is summarised in Fig. 4.

Written informed consents for treatment and the publication of this case report were obtained from the patient. Patient details have been de-identified.

3. Discussion

Advances in biomolecular diagnostic techniques and genetic analyses have revealed that abnormalities in certain genes can drive the onset and progression of lung cancer, with *EGFR* being the most commonly mutated gene in NSCLC. *EGFR*-TKIs have been repeatedly discussed as promising antitumour agents in *EGFR* mutation-positive NSCLC patients; therefore, the introduction of this targeted therapy has changed the treatment strategy for NSCLC [5]. However, most current studies have targeted classical *EGFR* mutations, and limited studies have been conducted on rare *EGFR* mutations. Because compound mutations involving two rare mutations are infrequent, clinical data on the use of *EGFR*-TKIs in compound mutation cases are scarce. In 2018, FDA (Food and Drug Administration) approved the second-generation *EGFR*-TKI afatinib for treating the three rare *EGFR* point mutations (S768I, L861Q, and G719X) based on the data from clinical trials of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 [6]. However, the side effects of afatinib treatment remain a challenge. Intolerable grade 3-4 adverse events, such as rash, mucositis, and diarrhoea, often interrupt treatment procedures [7,8]. Two studies have reported that the third-generation *EGFR*-TKI osimertinib is partially effective in rare *EGFR* mutation-positive NSCLC patients [9,10]. However, the enrolment in these studies was low, and larger real-world cohort studies are warranted.

In this case, histopathological examination suggested lung adenocarcinoma, and genetic testing indicated *EGFR*-related mutations of G719X and S768I However, no mutations were detected in ALK, ROS1, RET, KRAS, NRAS, BRAF, PIK3CA, HER-2, and MET. At an early stage of the diagnostic process, we performed PD-L1 immunohistochemical testing which yielded negative results. After considering the patient's financial situation and communicating with him, we administered first-line chemotherapy with albumin-paclitaxel in combination with cisplatin. The patient developed malignant arrhythmia during chemotherapy and left calf intramuscular venous thrombosis. As the patient's PS score dropped to 4, he could not tolerate systemic chemotherapy; hence, the treatment regimen was adjusted to oral furmonertinib (80 mg once daily). Afatinib and Osimertinib have been demonstrated encouraging efficacy in uncommon *EGFR* mutations, excluding exon 20 insertion mutations. Considering the patient's financial constraints and the reported adverse effects of Afatinib, the patient opted for furmonertinib. Furmonertinib is a new third-generation *EGFR*-TKI drug for treating advanced lung cancer and is a national class I innovative drug designed in China which was approved in March 2021 [11]. The

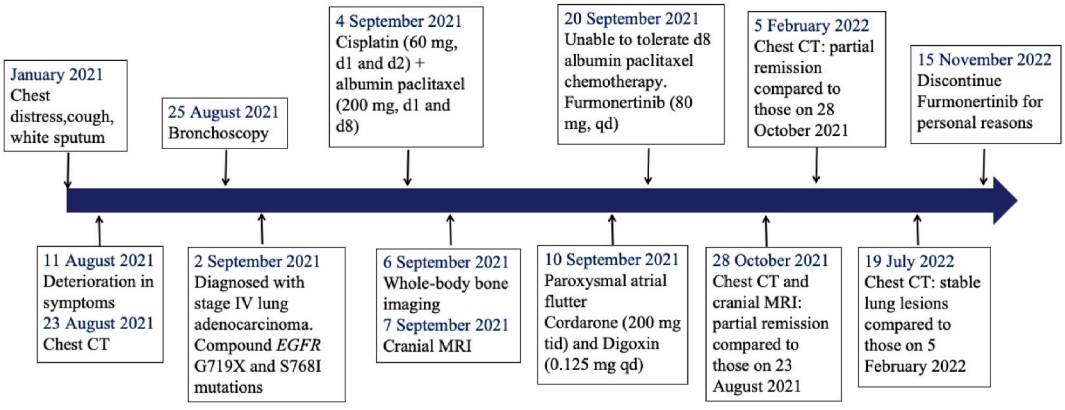

Fig. 4. Diagram of the course of disease management.

results of a phase IIb clinical study (NCT03452592) of furmonertinib showed an objective remission rate of 74%, a disease control rate of 94%, and a median progression-free survival of 9.6 months in 48% of patients who developed brain metastases at baseline. The relevant findings from the aforementioned study were published in *The Lancet* [12]. Furthermore, a clinical trial showed that furmonertinib showed superior efficacy compared to gefitinib as first-line therapy in Chinese patients with *EGFR* mutation-positive NSCLC, along with an acceptable safety profile without new signal [13]. After treatment, the patient's cranial and pulmonary lesions shrank significantly, and the PS score returned to 1. The expanding body of research on furmonertinib indicates that single-agent furmonertinib at 160 mg, either alone or in combination with an anti-angiogenic agent, is an optional salvage therapy for advanced NSCLC patients experiencing brain metastases/leptomeningeal metastasis progression after prior *EGFR*-TKI treatment. The therapy has demonstrated promising efficacy and maintains an acceptable safety profile, warranting further exploration [14]. Another study revealed that furmonertinib functions as a modulator of both ABCB1 and ABCG2 transporters and can sensitise multidrug-resistant cancer cells that overexpress ABCB1 and ABCG2 to cytotoxic anticancer drugs by attenuating their drug efflux function [15].

Genetic testing of the patient suggested a rare compound mutation in G719X and S768I. After 38 days of furmonertinib treatment, the patient showed significant regression of the diffuse lesions in both lungs and a smaller cranial metastasis than that pre-treatment. After 14 months of furmonertinib treatment, the patient discontinued the drug for personal reasons. As of 5 November 2023, the patient remains alive, and no other antitumour drugs have been administered. However, the patient, guided by personal beliefs, has chosen not to receive further treatment, and his current PS score indicates a relatively poor health condition.

This case study had several limitations. The patient failed to continue dynamic follow-up with chest CT and tumour markers during the course of the disease. Additionally, the patient discontinued taking the drug for personal reasons. Moreover, we were unable to employ NGS to evaluate other concomitant gene mutations or amplifications owing to financial reasons. Nevertheless, these clinical data will offer valuable insights for healthcare professionals administering furmonertinib to patients with G719X and S768I compound mutations.

4. Conclusion

Furmonertinib, a third-generation *EGFR*-TKI, may be effective in controlling the *EGFR* G719X and S768I compound mutations. However, further research is required to provide more robust evidence to determine the effectiveness of furmonertinib in addition to dosage and toxicity management strategies.

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Additional information

No additional information is available for this paper.

Ethics statement

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University (approval reference number: JD-HG-2022-01, Date of approval: January 6, 2022). Written informed consent was obtained from the patient for the publication of his clinical details.

Data availability statement

Data included in article.

CRediT authorship contribution statement

Xue Pan: Writing – original draft. **Minhua Shi:** Writing – review & editing, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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