Case Report

Prominent response to savolitinib monotherapy in high-grade fetal adenocarcinoma with *MET* amplification and concurrent brain metastasis: a case report

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Background: Mesenchymal-epithelial transition (*MET*) represents a potential therapeutic target in various cancers, with amplification of the *MET* gene identified in a subset of patients with pulmonary adenocarcinomas. However, *MET* gene amplification is rarely observed in high-grade fetal adenocarcinoma (H-FLAC).

Case Description: Here we present a novel case of a patient diagnosed with stage IV H-FLAC harboring *MET* amplifications and treated with savolitinib. The 69-year-old male patient, who presented with a primary complaint of cough and white sputum, had a history of hypertension for over 10 years and a 45-year smoking history. The patient received savolitinib monotherapy treatment due to brain metastases. Despite the omission of radiotherapy for asymptomatic brain metastases, a notable response to savolitinib therapy was observed, with a partial response (PR) achieved after 4 weeks and a reduction in the brain tumor. At the time of the submission of this report, the patient received over 24 weeks of savolitinib treatment, and was maintained PR. The patient was still undergoing treatment. This highlights the potential clinical benefits of targeted therapy against *MET* amplification in H-FLAC.

Conclusions: H-FLAC harboring *MET* amplification and brain metastasis is rare. Treatment with savolitinib monotherapy resulted in a PR, providing preliminary insights to the efficacy of savolitinib for H-FLAC with *MET* amplification.

Keywords: Case report; mesenchymal-epithelial transition (*MET*); high-grade fetal adenocarcinoma (H-FLAC); savolitinib

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Introduction

High-grade fetal adenocarcinoma (H-FLAC) is one form of fetal adenocarcinoma that constitutes only 0.1–0.5% of all pulmonary neoplasms (1,2). It commonly presents in elderly men with a heavy history of smoking and is often diagnosed at advanced stages (3). Previous research has revealed that beta-catenin expression in H-FLAC is typically membranous, and these tumors often exhibit overexpression of p53, resembling conventional lung adenocarcinoma (4). At present, therapeutic interventions, including chemotherapy and immunotherapy, exhibit limited efficacy in the management of fetal-type lung adenocarcinoma. Furthermore, the genetic profile of fetal-type lung adenocarcinoma remains poorly elucidated. Unlike conventional lung adenocarcinomas, key gene

mutations such as epidermal growth factor receptor (*EGFR*) and Kirsten rat sarcoma viral oncogene homolog (*KRAS*) are rarely observed in fetal-type lung adenocarcinoma (4,5). Consequently, the specific target antigens for this subtype of cancer have yet to be identified.

Recently, mesenchymal-epithelial transition (*MET*) exon 14 skipping mutations and *MET* amplification have emerged as novel and actionable oncogenic alterations in non-small cell lung cancer (NSCLC), demonstrating sensitivity to MET inhibitors (6,7). MET is a receptor tyrosine kinase that becomes activated upon binding to its ligand, hepatocyte growth factor (8). Savolitinib, a potent and highly selective oral MET tyrosine kinase inhibitor (TKI), has demonstrated promising activity in various NSCLC subtypes and has received conditional approval in China. In this report, we present a case of H-FLAC with brain metastasis harboring *MET* amplification that has shown benefit from savolitinib.

Rationale and knowledge gap

MET amplification has emerged as a novel and actionable oncogenic alteration in NSCLC, showing sensitivity to MET inhibitors like savolitinib. However, the response of H-FLAC with *MET* amplification to MET inhibitors remains unknown. We present this case in accordance with the CARE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-124/rc).

Highlight box

Key findings

- This report presents a patient with high-grade fetal adenocarcinoma (H-FLAC) harboring mesenchymal-epithelial transition (*MET*) amplification and brain metastasis who received monotherapy of savolitinib and achieved partial response after 4 weeks of therapy.

What is known and what is new?

- Savolitinib, a potent oral MET tyrosine kinase inhibitor, shows promising efficacy across non-small cell lung cancer (NSCLC) subtypes with *MET* exon 14 skipping mutation or *EGFR* mutation with concomitant *MET* amplification after failure to isolated tyrosine kinase inhibitor.
- Savolitinib demonstrated efficacy in H-FLAC patients with brain metastasis and *MET* amplification, providing a therapeutic benefit.

What is the implication, and what should change now?

- Despite the current lack of evidence for H-FLAC with *MET* amplification, our case treatment suggests potential broad-spectrum benefits from targeting this genetic alteration. However, validation demands further case accumulation and extensive research.

Case presentation

A 69-year-old male was admitted to the Shanghai Chest Hospital in March 2022 with the primary complaint of cough and white sputum (*Figure 1A*). Additionally, a lung mass was discovered during a physical examination three months before admission. He had a 45-year smoking history with exposure of 20 pack-years. Additionally, he had a history of hypertension for over 10 years, which is currently well-controlled. The enhanced chest computed tomography (CT) scan report revealed a 4.3 cm mass in the right upper lobe, along with multiple nodules in both lungs. There was significant enlargement of lymph nodes in the right pulmonary hilum and mediastinum. Findings also included pulmonary emphysema, bullae, fibrous lesions in both lungs, and interstitial changes in the right lung. The enhanced CT scan of the head showed no evidence of metastasis at the initial diagnosis. The Karnofsky performance status score was 90 points and the pain number rating scale score was 0 point.

The right upper lobe of the lung biopsy was performed for immunohistochemical (IHC) staining (*Figure 1B,1C*), and the results showed a positive expression in SALL4, P53, Glypican-3, and membrane expression of beta-catenin, but negative expression in thyroid transcription factor-1 (TTF-1), Napsin A, smooth muscle actin (SMA), S-100, Syn, CgA. The Ki-67 score was 20%. The tumor proportion score for programmed death-ligand 1 (PD-L1) was <1%. The hybrid-capture next-generation sequencing (NGS; Illumina, San Diego, CA, USA) report revealed a *MET* amplification of 28.04-fold, *CDK4* amplification of 5.41-fold, and *TP53* mutation at 68.71%. Fluorescence in situ hybridization (FISH) was also performed to verify the *MET* amplification (*Figure 1D*). Following an integrated analysis of clinical and pathological findings, the patient was diagnosed with a stage IV (c-T2bN2M1a) H-FLAC.

Following admission, the patient underwent comprehensive ancillary examinations and received the etoposide plus carboplatin (EC) regimen [etoposide (100 mg/m^2, 0.18 g days 1–3)] and carboplatin [area under the curve (AUC) =5, 550 mg day 1] for chemotherapy. The chemotherapy was administered for a total of six cycles, concluding on August 24, 2022. The chest computed tomography (CT) scan revealed a partial response (PR) which was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. He experienced grade 2

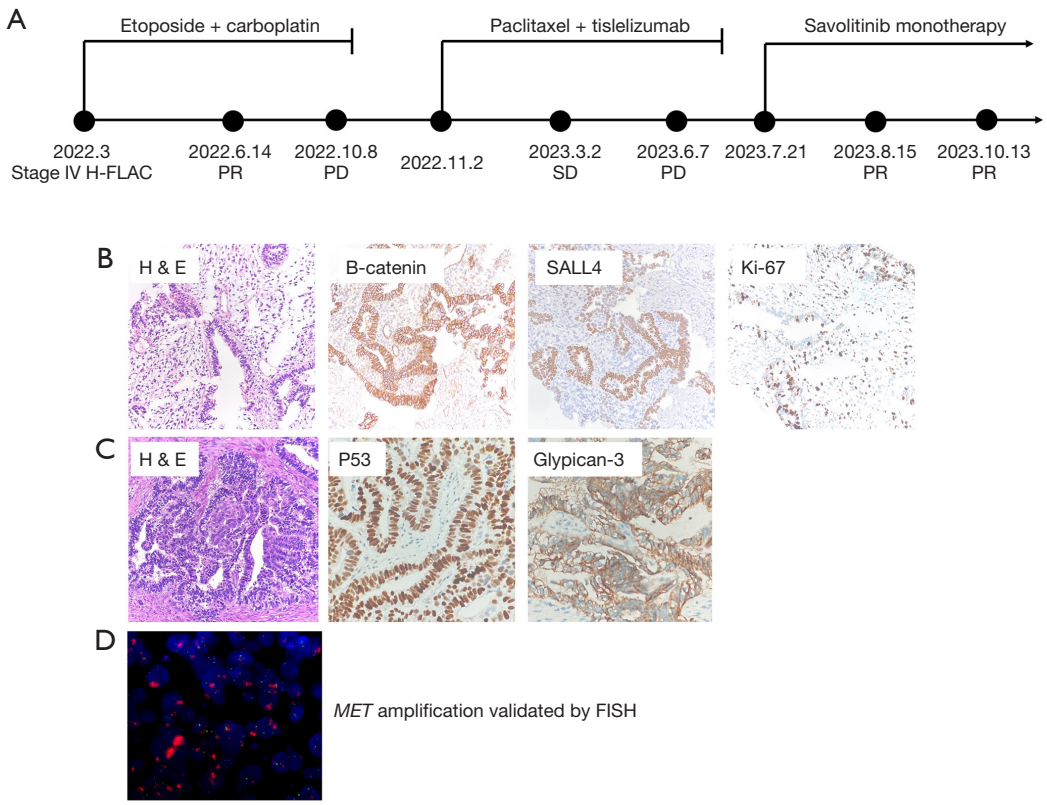

Figure 1 The treatment history and pathological diagnosis of the patients. (A) The timeline of treatment. (B) Pathological examination of the biopsy at diagnosis. Hematoxylin-eosin staining (×40) showed glandular and tubular structures in myxoid stroma that was lined with columnar cells. IHC testing (×40) showed positive expression of membrane β-catenin, SALL4, and Ki-67. (C) Hematoxylin-eosin staining (×40) showed complex papillotubular structures composing of pseudostratified columnar cells and morule formation. IHC testing (×40) showed positive expression of P53 and Glypican-3. (D) FISH (×400) validated *MET* amplification. H-FLAC, high-grade fetal adenocarcinoma; PR, partial response; PD, progressive disease; SD, stable disease; H&E, hematoxylin and eosin; IHC, immunohistochemical; *MET*, mesenchymal-epithelial transition; FISH, fluorescence in situ hybridization.

neutropenia, grade 1 thrombocytopenia, anaemia, vomiting, and anorexia during the treatment.

On October 8, 2022, a follow-up chest CT scan revealed disease progression by an enlargement of the right lung mass and pulmonary nodules. On November 2, 2022, the patient underwent second-line treatment consisting of paclitaxel 240 mg in combination with tislelizumab 200 mg for a total of six cycles, concluding in May 2023. The best response was stable disease (SD). He experienced grade 1 neutropenia during the treatment.

On June 7, 2023, a chest CT scan showed an enlargement of mass in the right lung, along with obstructive pneumonia and an increased extent of lesions with multiple nodules in both lungs (*Figure 2A*). Enlargement of mediastinal and right hilar lymph nodes was noted. On July 20, 2023, the patient experienced aggravated shortness of breath, with a performance status (PS) score of 2. A brain magnetic resonance imaging (MRI) showed a metastatic lesion in the left parietal lobe (*Figure 2A*). Serum analysis showed an alpha-fetoprotein (AFP) of 1,443.90 ng/mL. Radiotherapy was not performed for brain metastases since the patient had asymptomatic brain metastases. Considering the brain metastasis and *MET* amplification, the patient was treated with savolitinib monotherapy as a third-line treatment on July 21, 2023, administered orally at 400 mg once daily. After 4 weeks (as of August 15, 2023), a chest CT scan showed PR (*Figure 2B*). The brain MRI report indicates a reduction in the size of the metastatic tumor in the left occipital lobe and decreased enhancement compared to the previous examination (*Figure 2B*). His serum AFP level

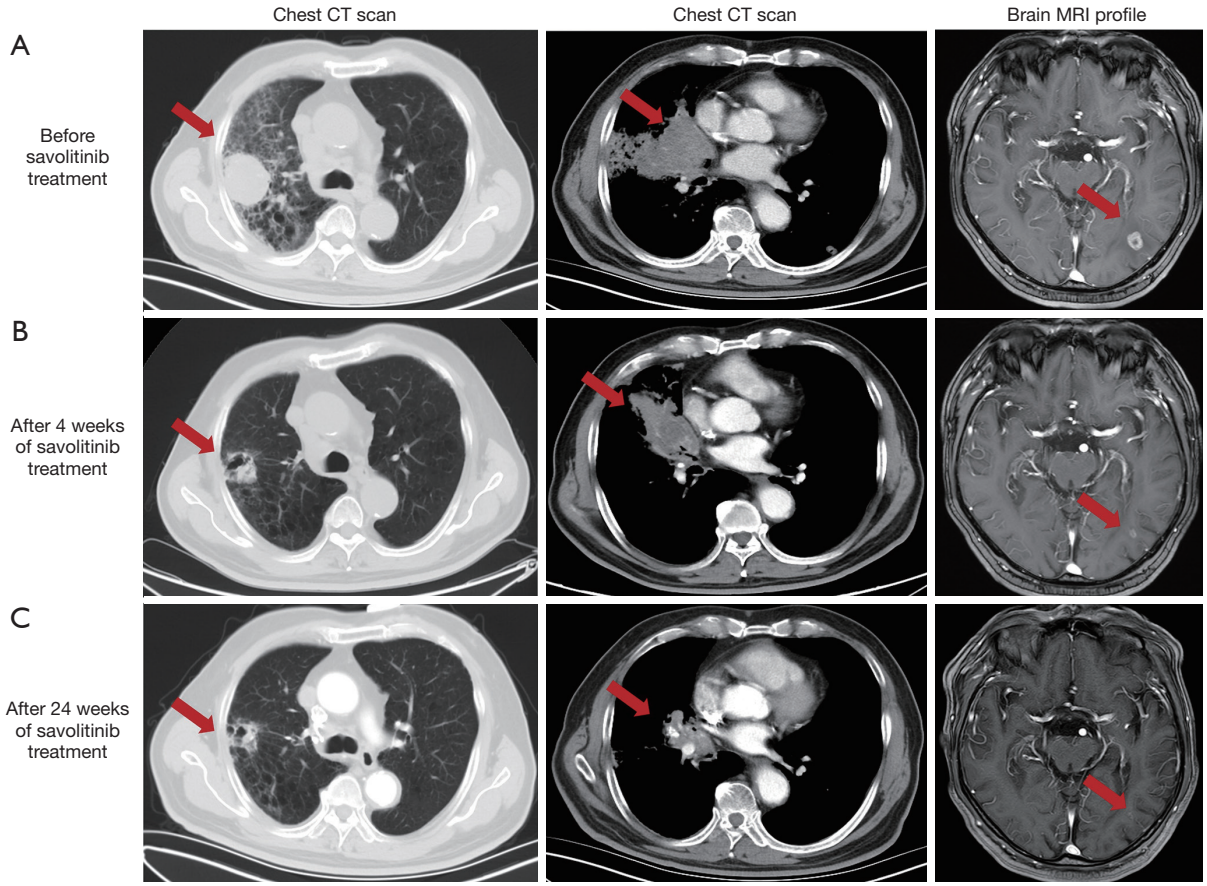

Figure 2 Response evaluation by chest CT scan and brain MRI. The tumor assessment was performed according to the RECIST version 1.1. The red arrow indicates the location of the lesion. (A) Chest CT scan of lung lesions and brain MRI before savolitinib treatment. (B) Chest CT scan of lung lesions and brain MRI after 4 weeks of savolitinib treatment revealed a partial response. (C) Chest CT scan of lung lesions and brain MRI after 24 weeks of savolitinib treatment revealed a partial response. CT, computed tomography; MRI, magnetic resonance imaging.

decreased gradually during the treatment period from 1,443.90 to 349.04 ng/mL. Adverse events include grade 2 increased alanine aminotransferase, and elevated aspartate aminotransferase. At the time of the report, the patient received over 24 weeks of savolitinib treatment, and was still effective. The chest CT scan and brain MRI report showed PR (*Figure 2C*). The patient was still undergoing treatment.

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 2013). Written informed consent was obtained from the patient for 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.

Discussion

Patients with H-FLAC were commonly present in elderly males with a heavy smoking history (93% smoking rate) and are often diagnosed at advanced stages (stage III–IV) (9). The typical morphologic and IHC features of H-FLAC include expression of beta-catenin, p53, SALL-4, and glypican-3 (10). In this case, it presents adescription of H-FLAC with *MET* amplification and brain metastasis in a smoking patient, demonstrating a notable response to savolitinib.

MET is a potential therapeutic target in various cancers, and regulatory approval has been granted for several TKIs in the treatment of patients with these tumors. Amplification and overexpression of the *MET* gene have been identified in a subset of patients diagnosed with pulmonary

adenocarcinomas lacking *EGFR* gene mutations (11). *MET* amplifications are detected in less than 1–5% of NSCLCs and are associated with a poor prognosis (12). Moreover, the literature indicates that in comparison to low-level *MET* amplifications, higher-level *MET* amplifications are more likely to signify oncogenic dependence on *MET* (13).

Interestingly, we discovered that this patient had *MET* amplification without *MET* exon 14 skipping. Previous studies examining *MET* amplification in the absence of *MET* exon 14 alteration indicate that higher levels of *MET* amplification are associated with increased objective responses to MET TKIs (14). In the study led by Wolf *et al.*, assessing the efficacy of capmatinib (a MET TKI) in NSCLC patients with *MET* amplification (gene copy number over 10), an overall response was observed in 29% of previously treated individuals and 40% of treatment-naïve subjects (15). These findings suggest that patients exhibiting high *MET* amplification may derive benefit from targeted MET therapy. Savolitinib, an inhibitor of the MET receptor, exhibited comparable tumor responses irrespective of pathological subtype or prior lines of treatment [objective response rate (ORR) of 40.5% in later lines *vs.* 46.4% in treatment-naïve patients] (16). A post hoc analysis further revealed that savolitinib achieved effective control of brain metastases (16). In our case, the patient presented with a *MET* amplification featuring a gene copy number of 28 folds at the time of diagnosis, and he achieved a PR under the savolitinib monotherapy after only 4 weeks of treatment.

Clinical trials of systemic treatments often exclude patients with brain metastases. However, in a phase II study of savolitinib, 15 patients with brain metastases demonstrated stable or decreased brain lesions after treatment [ORR: 46.7%; median progression-free survival (mPFS): 6.7 months] (16). Some clinical trials have included *MET* ex14 skipping positive patients with brain metastases. For instance, in the VISION study, among the 11 patients with brain metastases, the ORR was 55%, and mPFS was 10.9 months (17). A recent study reported a patient with concomitant *EGFR L861Q* mutation and *MET* amplification at the initial diagnosis. This patient achieved a PR with afatinib and crizotinib, maintaining a PFS of 2.5 months. Subsequently, the treatment was switched to osimertinib plus crizotinib due to the development of brain metastases, and the patient sustained SD for 6 months (18). In our case, the patient was switched to savolitinib due to brain metastases, and despite the omission of radiotherapy for asymptomatic brain metastases, a noteworthy response to savolitinib therapy was observed, with a PR achieved after 4 weeks and a reduction in the brain tumor. The maintenance of this PR persisted until the submission of this report.

While there is currently a lack of clinical study evidence or case reports regarding H-FLAC carrying *MET* amplification, our case treatment provides preliminary evidence within the current clinical landscape. This implies that targeted therapy against this genetic alteration might confer clinical benefits across a broad spectrum of cancers without restricting to specific subtypes. However, additional case accumulation and further clinical research are necessary for validation.

Our present study has certain limitations. It is based solely on a single-patient case report, and the sensitivity of H-FLAC with *MET* amplification to savolitinib remains unclear. Additionally, the follow-up time is relatively short, as the patient is still undergoing treatment at the time of this report.

Conclusions

We present the case of a patient with H-FLAC harboring *MET* amplification and brain metastasis who received monotherapy of savolitinib. This report highlights the successful use of savolitinib monotherapy in the H-FLAC patient with *MET* amplification, achieving PR after 4 weeks of therapy. These results offer preliminary insights into the efficacy of MET-targeted therapy for H-FLAC.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-124/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-124/coif). The authors

have no conflicts of interest to declare.

Ethical Statement: 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 2013). Written informed consent was obtained from the patient for 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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