Advanced lung adenocarcinoma patient with *EGFR* exon 20 insertion benefits from high-dose furmonertinib for nine months after progression from mobocertinib: a case report

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Background: The treatment landscape of non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (*EGFR*) mutation has significantly changed in the past decade. However, *EGFR* exon 20 insertion (20ins), which accounts for at least 9% of all *EGFR* mutated cases, has been generally associated with resistance to common *EGFR* tyrosine kinase inhibitors (TKIs). In recent years, major progress has been made in the precision treatment of NSCLC harboring *EGFR* exon 20ins, thanks to the development of TKIs and mAb-based agents specifically targeting *EGFR* 20ins. However, the efficacy of these novel agents, such as mobocertinib and amivantamab, is not quite satisfactory. Therefore, there is an urgent need to identify other effective targeted drugs.

Case Description: Herein, we describe a case with *EGFR* 20ins diagnosed by amplification refractory mutation system polymerase chain reaction (ARMS-PCR) who benefited from high-dose (160 mg/d comparing with Phase II recommended dose 80 mg/d) furmonertinib, a novel third-generation *EGFR* TKI, after progression from mobocertinib. A 58-year-old male was referred to our clinic with multiple lung lesions detected in computed tomography (CT) scanning. The patient participated in a phase I/II trial (NCT02716116) receiving TAK-788 and was confirmed with partial response at follow-up. Intriguingly, after progression from 9 months of TAK-788 treatment, the patient still showed response to furmonertinib. The progression free survival was 10 months with no complications or adverse events observed. The overall survival was 34 months till last follow-up in March, 2022. The patient is still in follow-up.

Conclusions: Supported by this case and data from other studies, the potency of furmonertinib warrants further evaluation in patients with *EGFR* 20ins, especially those pretreated with TKIs.

Keywords: Lung adenocarcinoma; *EGFR* exon 20 deletion; mobocertinib; furmonertinib; case report

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Introduction

In the past decade, the treatment of epidermal growth factor receptor (*EGFR*) gene mutated non-small cell lung cancer (NSCLC) has undergone a revolution due to the development of generations of *EGFR* tyrosine kinase inhibitors (TKIs) (1,2). However, *EGFR* exon 20 insertion (*EGFR* 20ins), which accounts for approximately 10% of all *EGFR*-mutated NSCLC cases, is less likely benefit from these approved *EGFR*-TKIs (3). Fortunately, major progress has been made against *EGFR* 20ins NSCLC (4). In 2020, two novel agents, mobocertinib and amivantamab, have been approved for this particular indication. However, the efficacy of these agents has been rather moderate in comparison with *EGFR*-TKIs targeting canonical *EGFR* mutations, and other more potent anti-cancer drugs are needed in this setting. Herein, we present a case of advanced adenocarcinoma patient with *EGFR* 20ins which had previously failed from mobocertinib who gained benefit from high-dose treatment of furmonertinib, a third generation *EGFR*-TKI. This case might provide an alternative approach in the treatment of NSCLC patients with *EGFR* 20ins. We present the following article in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1167/rc).

Case presentation

Patient information

This patient was a never smoker, 58-year-old male who admitted to Shanghai Pulmonary Hospital in May, 2019 due to fever. 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.

Clinical findings

Computed tomography (CT) scanning showed alveolar consolidation and mass lesions diffused in bilateral lobes, mainly distributed in the right lower lobe. No extra-thoracic metastasis was found.

Timeline

Treatment timeline is displayed in *Figure 1*.

Diagnostic assessment

A CT-guided core biopsy revealed pulmonary adenocarcinoma. A 10-gene panel testing based on amplification refractory mutation system polymerase chain reaction (ARMS-PCR) showed *EGFR* 20ins (5-7). The staging was cT4NxM1a-IVa.

Therapeutic intervention and outcomes

The patient received first-line treatment of carboplatin plus pemetrexed chemotherapy and experienced disease progression. Then, he participated in a phase I/II trial (NCT02716116) and received TAK-788 160 mg orally once per day. From July, 2019 to March, 2020, the patient showed benefit from TAK-788 treatment judged by self-reported alleviated shortness of breath and reduced density of most lesions in follow-up CTs in the initial 5 months of treatment (*Figure 2A*,*2B*). However, CT scanning in March, 2020 displayed disease progression due to multiple newly emerged lesions in bilateral lobes and the total duration of TAK-788 treatment was 9 months (*Figure 2C*). The re-biopsy showed that the pathological type was still adenocarcinoma harboring *EGFR* 20ins without other known resistance mechanisms.

From April, 2020 to February, 2021 the patient received the combination therapy of nab-paclitaxel, pembrolizumab, and bevacizumab in his local hospital with a partial response. Subsequently, he participated in a phase I study of JS108 (recombinant humanized anti-Trop2 mAb-Tub196 conjugate) in patients with advanced solid tumors (NCT04601285) in March, 2021 but was quickly withdrawn from the trial due to disease progression. Considering that re-biopsy molecular testing revealed *EGFR* 20ins, this patient received high-dose (160 mg/d) furmonertinib from June 2021. In September 2021, we observed a partial response (*Figure 3A-3C*). This patient remains in benefit from furmonertinib till the last revise of this paper (March 2022). The overall PFS was 9 months with no complications nor adverse events.

Discussion

Herein, we have firstly reported a case of advanced

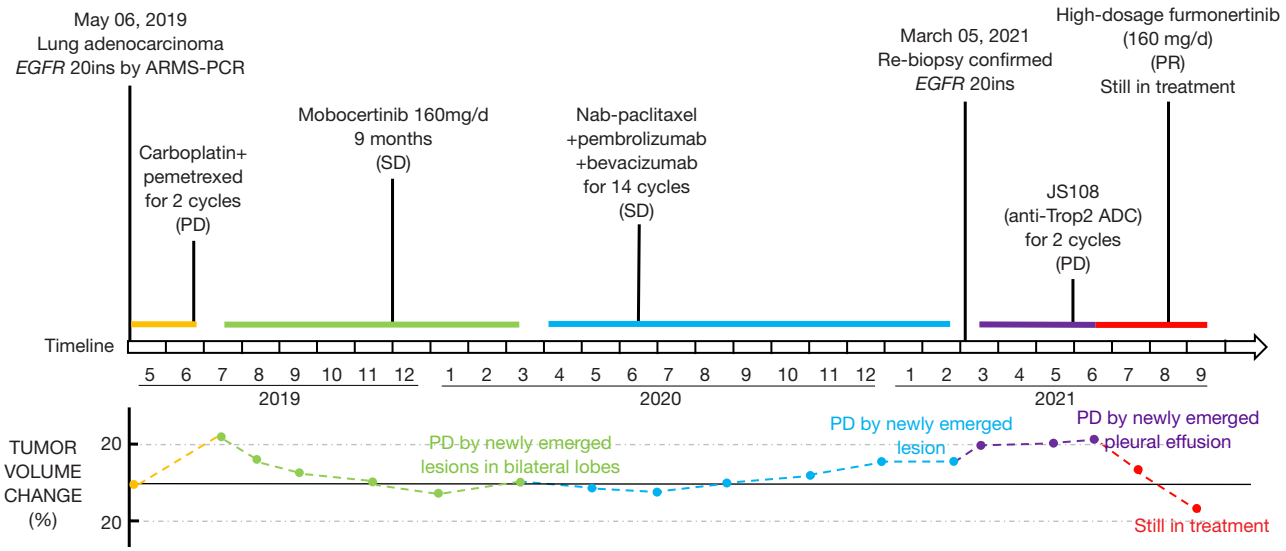

Figure 1 Timeline of case treatment course. Notice the patient is still in benefit from furmonertinib in March, 2022. *EGFR*, epidermal growth factor receptor; ADC, antibody-drug conjugate; SD, stable disease; PD, progressive disease; PR, partial response.

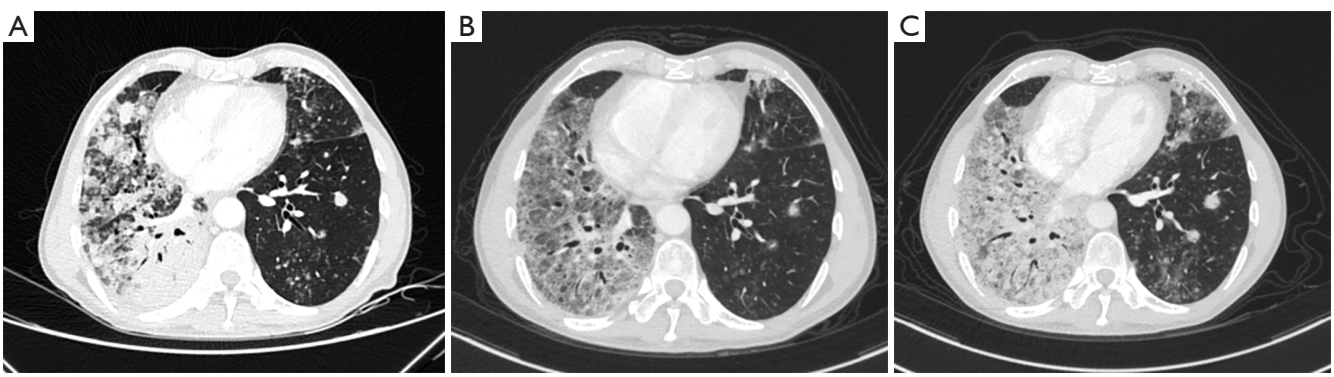

Figure 2 Follow-up CT scanning in mobocertinib treatment. (A) Baseline scan at 24 July, 2019. (B) Best response to mobocertinib at 18 November, 2019. (C) Disease progression at 10 March, 2020. CT, computed tomography.

pulmonary adenocarcinoma with *EGFR* 20ins benefit from the subsequent treatment of mobocertinib and high-dosage furmonertinib and who achieved an overall survival of more than 34 months. This patient had a partial response from mobocertinib with a progression-free survival (PFS) of 9 months in a second-line setting. After that, high-dose furmonertinib still demonstrated encouraging efficacy against his disease with 10 months PFS with no complications nor adverse events observed and still in follow-up. Currently the patient remains on furmonertinib treatment.

The *EGFR* 20ins insertion comprises approximately 10% of all *EGFR*-mutated NSCLC cases. Like most *EGFR* activated mutations, *EGFR* 20ins maintains *EGFR* molecules in an active conformation in the absence of ligand binding, via altering the position of C-helix. However, unlike canonical *EGFR* mutations, *EGFR* 20ins does not diminish the affinity to adenosine triphosphate (ATP) or early-generation TKIs, hence is not likely benefit from these agents (3). Until recently, the standard-of-care therapy was chemotherapy. Several TKIs and mAb-based agents targeting *EGFR* 20ins have been developed. Other than the 2 approved drugs, mobocertinib and amivantamab, preliminary results from ongoing trails of DZD9008, ABT806, and CLN-081 have also demonstrated moderate efficacy against *EGFR* 20ins NSCLC (8,9). The responses

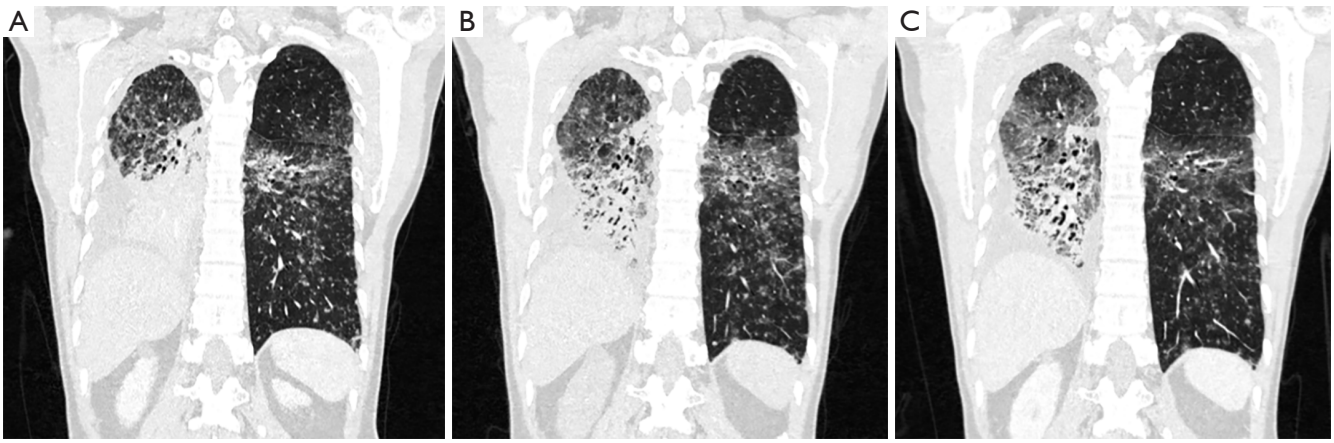

Figure 3 Follow-up CT scanning in high-dosage furmonertinib treatment. (A) Scan before treatment at 16 June, 2021. (B) First month follow-up at 19 July, 2019 showing minor disease regression. (C) Partial response reached at 6 September, 2021. CT, computed tomography.

have ranged from 23% to 45% and the median PFS has been from 5.3 to 7.3 months, which are inferior compared with *EGFR*-TKIs targeting canonical *EGFR* mutations (8-11). Thus, a new challenge lies ahead for clinicians to identify more potent therapies.

Furmonertinib (also known as Alflutinib/AST2818) is another newly developed third-generation *EGFR*-TKI. Similar to other third-generation *EGFR*-TKIs, it irreversibly binds both *EGFR* sensitizing and T790M resistance mutants. It was also approved by the National Medical Products Administration (NMPA) for treatment of *EGFR* T790M mutation-positive NSCLC patients who had been treated with at least 1 prior *EGFR*-TKI. Preclinical data has also demonstrated that furmonertinib has an antitumor effect in *EGFR* 20ins BaF3 cell line and patient derived *EGFR* 20ins xenograft models (12).

In this case, after failure from chemotherapy, mobocertinib, and chemoimmunotherapy, a high dose of furmonertinib was administrated as salvage therapy since re-biopsy confirmed the existence of *EGFR* 20ins without bypass activation. As far as we know, this is the first report of response to third-generation *EGFR*-TKI furmonertinib in a patient previously treated with mobocertinib. Consistently, it was reported that 2 patients pretreated with mobocertinib or poziotinib gained partial response from CLN-081 in a phase I/IIa trail (NCT04036682) (8), suggesting that furmonertinib and CLN-081 are not in cross-resistance to mobocertinib and might overcome the resistance of other targeting-*EGFR* 20ins agent in patients who were on-target resistant. These clinical findings indicate that sequent application of other TKIs target *EGFR* 20ins is a possible approach. Moreover, they also highlight the different resistant mechanisms of these agents. Future biomarker analyses are needed to clarify the underlying mechanisms.

The limitation about this case is obvious. First, data from the combined therapy of nab-paclitaxel, pembrolizumab, and bevacizumab was poorly supplied. And the lack of biopsies cannot support further biomarker analyses.

In conclusion, this is the first report of a case of advanced NSCLC harboring exon 20 insertion and response to furmonertinib who previously failed from mobocertinib. A large cohort study is needed to further validate the efficacy of furmonertinib in this setting.

Acknowledgments

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Footnote

Reporting Checklist: The authors have completed the CARE

reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-1167/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-1167/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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