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CASE REPORT

De Novo MET-amplified NSCLC treated with savolitinib achieved remarkable tumor regression: a case report and review of literature

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Abstract

Primary *MET* amplification is an infrequent tumorigenic driver gene alteration identified in pulmonary neoplasms. Data on the effectiveness of MET-tyrosine kinase inhibitor (TKI) therapy in *de novo MET* amplification are relatively scarce, and there remains a dearth of empirical evidence supporting the use of precision therapy as first-line treatment for advanced non-small cell lung cancer (NSCLC) with primary *MET* amplification. We present a case of advanced lung adenocarcinoma in an elderly patient with primary *MET* amplification. The patient had an initial ECOG Performance Status (PS) 2. DNA-NGS analysis of tissue samples revealed a *MET* gene copy number (GCN) of 8, indicating *MET* amplification, without other oncogenic mutations associated with available drugs being detected. This finding was validated by *MET* fluorescence in situ hybridization (FISH), which showed cluster amplification. Initial treatment with savolitinib resulted in a sustained partial response lasting more than sixteen months. Our results suggest that savolitinib is effective and safe for the treatment of elderly patients with *de novo* amplified *MET* metastatic NSCLC and may therefore be considered a potential treatment option worthy of prospective study confirmation.

Keywords Non-small cell lung cancer · Senior patients · Primary *MET* amplification · Targeted therapy · Case report · Review

Introduction

Receptor tyrosine kinase MET and its ligand hepatocyte growth factor (HGF), which act as oncogenic drivers in various human malignancies, often indicating aggressive disease and are associated with poor prognosis. (Cappuzzo et al. 2009; Di Renzo et al. 1995; Nakajima et al. 1999) Oncogenic alterations in the *MET* comprise *MET* exon 14 skipping mutations (*METex14*), elevated *MET* GCN, *MET* amplification, MET protein overexpression, *MET*-fusion and *MET* mutations.(Recondo et al. 2020; Vansteenkiste et al. 2019) The incidence of *de novo MET* amplification in non-small cell lung cancer (NSCLC) ranges from 1 to 5%. *METex14* usually do not occur simultaneously with *EGFR*, *ROS1*, *BRAF*, *and ALK* variants.(Awad et al. 2016) Meanwhile, *MET* amplification was infrequent among NSCLC patients in China who lacked *EGFR* mutation, presenting a prevalence of approximately 1%.(Song et al. 2017) However, *MET* amplification has been identified as a secondary mechanism of resistance in NSCLC patients with *EGFR* mutations who acquire resistance to EGFR-tyrosine kinase inhibitors (TKIs). (Sequist et al. 2020)

Despite the low incidence of primary *MET* amplification in lung cancer, its oncogenic potential highlights the need for targeted treatments instead of resorting to options for driver gene negative lung cancer. Currently, FDA approved TKIs that target *METex14* include capmatinib, (Dagogo-Jack et al. 2021; Wolf et al. 2020a, b) and tepotinib. (Paik et al. 2020; Wu et al. 2020) The efficacy of these TKIs in primary *MET*-amplified NSCLC was less favorable, with median PFS of 4.2–6.7 months and ORR of 40-41.7% in *de novo* high-level *MET* amplification identified by *MET*-fluorescence in situ

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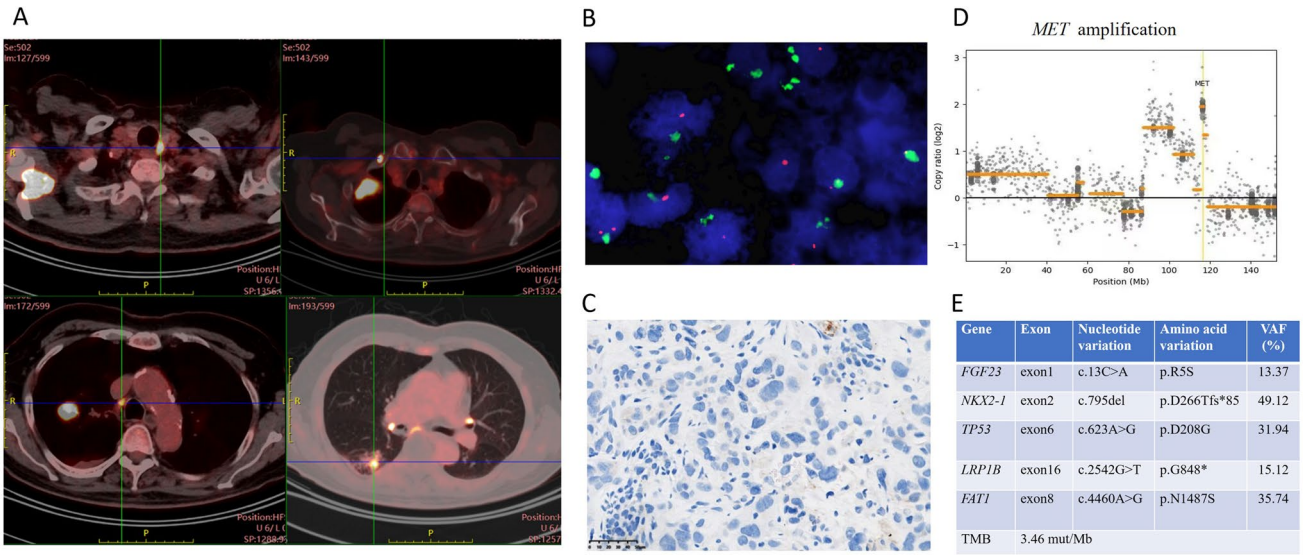
hybridization (FISH) or next-generation sequencing (NGS) in post-hoc analysis. Besides, the definition of high *MET* amplification levels is shifting and may vary depending on the test. For NGS-based results, copy numbers greater than 10 are consistent with high levels of *MET* amplification. (Ettinger et al. 2023).

Savolitinib (Orpathys®, developed by HUTCHMED in collaboration with AstraZeneca) is a potent and highly specific TKI that effectively targets MET protein. It has demonstrated encouraging efficacy and safety profiles in patients with NSCLC harboring *MET*ex14 mutations. (Lu et al. 2021) Moreover, the combination of savolitinib and osimertinib shows great promise as a therapy for patients with advanced NSCLC who have *MET* amplification/overexpression and *EGFR* mutations, whose disease has progressed after prior EGFR-TKI treatment.(Hartmaier et al. 2023; Sequist et al. 2020) Savolitinib has been approved in China for the treatment of NSCLC patients with *MET* exon 14 skipping mutations. However, as of the knowledge cutoff date in 2024, it has not yet received approval from the U.S. Food and Drug Administration (FDA). However, data on the efficacy of savolitinib in primary *MET*-amplified lung cancer require further investigation to reach a definitive conclusion. Additional research is also required to determine the correlation between *MET* amplification and savolitinib effectiveness, utilizing FISH and NGS assays.

Detailed case description

An 86-year-old Chinese man with no smoking history was referred to our hospital in June 2022. He reported experiencing pain in his right shoulder for the past two months without any identifiable triggers. On the right shoulder, he showed limited range of motion and tenderness. Positron emission tomography (PET)/computed tomography (CT) scans revealed a mass in the right upper lung and metastases in the right hilar lymph node, lower right lung, and right scapula. The maximum diameter of the primary focus in the right upper lung was 4.9 cm and the SUV max was 16.33 (Fig. 1A). This suggested a clinical diagnosis of stage IVB lung cancer. Figure 1B shows that the pulmonary biopsy revealed well differentiated pulmonary adenocarcinoma. PD-L1 Tumor Proportion Score (TPS) was negative (TPS < 1%) by VENTANA PD-L1 (SP263) Assay (Fig. 1C). Subsequent targeted NGS with tumor DNA based on Illumina NextSeq 500 platform (Illumina, San Diego, USA) identified *MET* amplification, with GCN as 8 (Fig. 1D). Amplification test by FISH revealed a cluster *MET* amplification (MET/CEP7 ratio ≥ 2.0 and MET CN ≥ 5). *METex14* mutations have been tested and excluded. Tumor mutation burden (TMB) was 3.46 mut/Mb, and concomitant genomic alterations and variant allelic frequency (VAF) identified by NGS were presented in Fig. 1E. However, targeted therapeutic agents have not yet been developed for these five



Gene	Exon	Nucleotide variation	Amino acid variation	VAF (%)
FGF23	exon1	c.13C>A	p.R5S	13.37
NKX2-1	exon2	c.795del	p.D266Tfs*85	49.12
TP53	exon6	c.623A>G	p.D208G	31.94
LRP1B	exon16	c.2542G>T	p.G848*	15.12
FAT1	exon8	c.4460A>G	p.N1487S	35.74
TMB	3.46 mut/Mb			

Fig. 1 Baseline PET-CT imaging, histopathological, and molecular pathological information. (**A**) High uptake of fluorodeoxyglucose (FDG) in the mass of the right lobe and metastases in the right hilar lymph node, lower lobe, and shoulder. (**B**) FISH assay targeting MET on lung biopsy specimens. The presence of *MET* amplification, showing clusters of MET signals, is demonstrated with ZytoLight SPEC MET/CEN7 Dual Color Probe. Green represents the MET probe, while red indicates the centromeric probe. (**C**) The VENTANA PD-L1 SP263 immunohistochemistry assay for PD-L1 expression revealed that TPS was negative. Scale bar = 50 μm. (**D**) Integrative Genomics Viewer (IGV) screenshot showing *MET* amplification at Chromosome 7. The histograms above each sample readout show the depth of sequencing at that location. (**E**) Gene mutational profile of tissue specimens analyzed by NGS. The indicated genomic alterations and VAF were identified by NGS with tissue samples. CT, computed tomography. FISH, Fluorescent in situ hybridization. NGS, Next Generation Sequencing. PET, Positron emission tomography. VAF, variant allelic frequency. TMB, tumor mutation burden. TPS, tumor proportion score

co-mutated genes (*FGF23*, *NKX2-1*, *TP53*, *LRP1B*, and *FAT1*). Baseline serum tumor marker glycated antigen 125 (CA125) was significantly elevated to 710.8 U/mL (Range: 0–35 U/mL), accompanied by a mild Cytokeratin 19 fragment (Cyfra21-1) elevation to 4.31 µg/L (0–3.1 µg/L) and normal CEA levels.

Nevertheless, the patient's PS and advanced age rendered him ineligible for palliative chemotherapy. No benefit from immunotherapy was anticipated as the patient's tumor tissue exhibited negative PD-L1 TPS, along with low TMB. Following thorough communication, the patient commenced first-line treatment with savolitinib 400 mg daily starting July 12, 2022. Notably, there was a remarkable improvement in his clinical symptoms one week later, resulting in the postponement of the scheduled bone metastasis radiotherapy. The patient was given 120 mg of denosumab subcutaneous injection every 4 weeks to simultaneously manage bone metastases. One month later, the CT scan showed a significant reduction in disease compared to the previous evaluation, which was sustained for more than 16 months with good tolerance (Fig. 2A). Peripheral serum tumor markers CA125 and Cyfra21-1 gradually decrease to normal levels during treatment (Fig. 2B and C). Although there were repeated occurrences of grade 3 edema in the lower limbs according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0), effective management was achieved through progressive dose modification and symptomatic therapy. Savolitinib has been decreased to 300 mg once daily since October 12th, 2022 and remains ongoing. Subsequently, the adverse event (AE) of lower limb edema persisted at grade 1 according to CTCAE. During the course of treatment until October 29, 2023, regular medical imaging tests indicated partial remission. However, the patient later developed respiratory failure as a secondary complication due to community-acquired pneumonia, and eventually died on January 25, 2024.

Discussion

Primary *MET* amplification is an infrequent oncogenic driver gene variant in lung cancers. Here we report a rare case of advanced lung adenocarcinoma with primary *MET* amplification in an elderly patient. The individual initially had an ECOG PS 2. NGS analysis of tissue samples demonstrated *MET* GCN of 8, indicating *MET* amplification. This finding was confirmed by MET-FISH, which showed cluster amplification. No other oncogenic mutations were detected. PD-L1 TPS was negative. Initial treatment with savolitinib at a dose of 400 mg once daily resulted in a partial response that persisted for more than 16 months. Our report demonstrated the effectiveness and safety of savolitinib as the

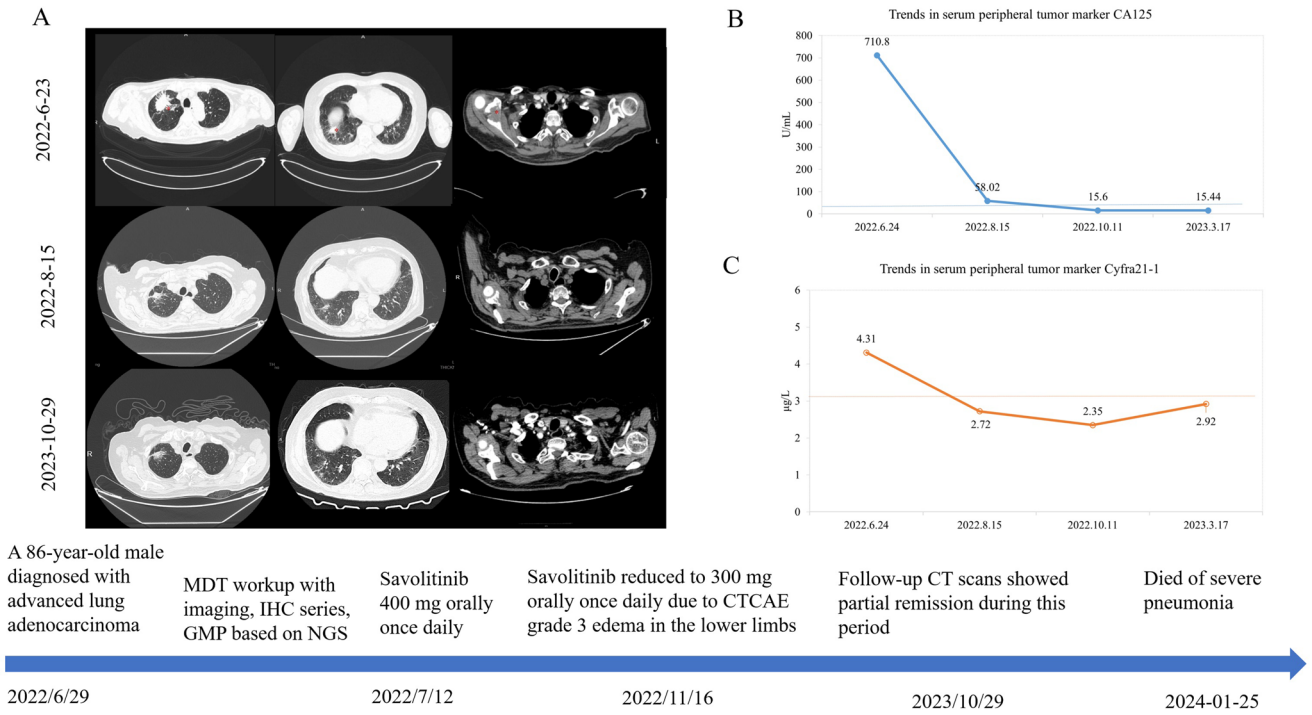


Fig. 2 The patient's clinical course schedule. (**A**) Computed tomography scans of lesions at baseline (upper line) and after treatment (middle line and lower line) with savolitinib. (**B**) Trends in serum peripheral tumor marker CA125 and Cyfra21-1. Serum peripheral tumor marker Cyfra21-1trends Peripheral serum tumor markers CA125 and Cyfra21-1 gradually decrease to normal levels during treatment. (**C**) Timeline of patient's diagnosis and treatment. NGS, Next Generation Sequencing. CA125, glycated antigen 125. Cyfra21-1, Cytokeratin 19 fragment. GMP, gene mutational profile

Table 1 Representative clinical trials of MET inhibitors in NSCLC with primary *MET* amplification

MET inhibitors	Crizotinib	Crizotinib	Tepotinib	Capmatinib
Study	AcSé Trial (Moro-Sibilot et al. 2019)	NCT00585195 (Camidge et al. 2021)	VISION (Paik et al. 2020; Xiuning Le et al.)	GEOMETRY mono-1 (Wolf et al.2020)
Inclusion criteria	MET-to-CEP7 ratio ≥6	NSCLC Patients With *MET*-Amplified (MET-to-CEP7 ratio≥1.8 by local FISH)	Patients with advanced NSCLC without *MET* exon14 mutation or EGFR/ALK mutations	Patients with advanced *MET*-amplified NSCLC
Numer of patients (n)	25	38	24 (1 L=7;2 L=11,3 L=6)	1 L (cohort 5a), *n*=15 2 L+ (cohort 1a), *n*=69
Criteria for high *MET* amplification	MET/CEP7≥6	MET/CEP7≥4	GCN≥2.5	GCN≥10
ORR (%)	32%	38.1%	Overall: 41.7% 1 L:71.4% 2 L:27.3% 3 L:33.3%	1 L: 40% 2 L°29%
mDOR months(95%CI)	3.5 (10–30.6)	5.2 (3.3–25.8)	Overall: 14.3 (2.8-NE) 1 L: 14.3 (2.8-NE)	1 L: 7.5 (2.6–14.3) 2 L: 8.3 (4.2–15.4)
mPFS months(95%CI)	3.2 (1.9–3.7)	6.7 (3.4–9.2)	Overall:4.2(1.4–15.6) 1 L: 15.6 (1.4-Ne)	1 L: 4.2(1.4–6.9) 2 L: 4.1(2.9–4.8)
mOS months(95%CI)	7.7 (4.6–15.7)	11.4 (7.2–19.3)	Overall:7.5(4.0-15.6) 1 L: 14.3 (4.0-Ne)	NA

first-line treatment for advanced NSCLC with primary *MET* amplification.

MET is known to stimulate cancer cell motility, survival and angiogenesis. (Trusolino et al. 2010) These collectively function as a potent instigator for neoplastic invasion and the development of secondary metastases. Furthermore, it has been observed that certain primary tumors may harbor gain-of-function genetic alterations in the *MET* gene, which contribute to maintain the transformed phenotype of these tumors.(Trusolino et al. 2010) Increased *MET* GCN may be caused by focal amplification or polyploidy. (Recondo et al. 2020; Kumaki et al. 2023) Focal amplification refers to an increase in the copy number of a specific gene without simultaneously increasing the copy number of an entire chromosome or a neighboring gene. Polyploidy, on the other hand, is characterized by an increase in copy numbers of an entire chromosome or multiple chromosomes. In the case of *MET*, polyploidy is typically triggered by a copy number gain on chromosome 7, producing a simultaneous copy number increase in *MET* and its neighboring genes (e.g., *CDK6* and *BRAF*). (Kumaki et al. 2021)

Presently, numerous TKIs directed towards MET protein have advanced into the clinical setting. Representative clinical trials of MET inhibitors in NSCLC with primary *MET* amplification are listed in Table 1. It is noteworthy that there are inconsistencies in the inclusion of specific studies and no unanimously agreed upon standards for the identification, classification, and threshold of *MET* amplification. In studies of crizotinib monotherapy for primary *MET*-amplified NSCLC, ORR was14.3-38.1% and median PFS was 1.8–6.7 months. Even in the high lever *MET*-amplification (MET/CEP7≥4), patients exhibited an ORR of 38.1% and a PFS of merely 6.7 months.(Awad et al. 2016) In another study evaluating the efficacy of crizotinib in patients diagnosed with NSCLC with amplified *MET*, 15 (78.9%) of the 19 patients analyzed had *MET* copies of 6 or more based on NGS results. Of these 15 patients, an objective response to crizotinib at a dose of 250 mg orally twice daily was observed in 6 (40%), two of whom also had concomitant *MET* mutations.(Camidge et al. 2021) Higher levels of *MET* amplification may correlate with higher rates of tumor response, but this correlation did not lead to a significant improvement in progression-free survival (PFS). Even in the primary treatment population with highly amplified *MET* (NGS GCN≥10), capmatinib achieved an ORR of 40% and a median PFS of 4.2 months.(Wolf et al. 2020a, b) In addition, tepotinib monotherapy for primary *MET*-amplified NSCLC showed ORR of 41.7% and median PFS of only 4.2 months.(Xiuning Le et al. 2022a, b).

Savolitinib has recently emerged as a potent MET inhibitor, which has significant in vitro inhibitory activity on MET.(Gu et al. 2019) Based on the results of a pivotal trial in patients with NSCLC/pulmonary sarcomatoid carcinoma, savolitinib was recently granted approval in China for the treatment of metastatic NSCLC with *MET exon 14*-skipping mutations in patients who have progressed after or

who are unable to tolerate platinum-based chemotherapy. (Lu et al. 2021) Although savolitinib in combination with osimertinib has demonstrated inspiring effectiveness in patients with *MET* amplification following the development of resistance to EGFR-TKI (Hartmaier et al. 2023), data on the efficacy of savolitinib in primary *MET*-amplified lung cancer are inconclusive. In a retrospective study conducted in China, 34 cases of NSCLC with *MET* alterations were analyzed. Seventeen patients exhibited *MET* amplification and six patients were treated with savolitinib. Savolitinib contributed a median PFS of 7.1 months, which was significantly better than the median PFS of 1.4 months observed in patients treated with crizotinib ($p=0.05$). (Miao et al. 2023) It is noteworthy that participants in the study with *MET* amplification had co-existing *EGFR*-sensitive mutations, and no patients with primary *MET* amplification were included.

Currently, there is no universal standard or threshold for the detection of *MET* amplification.(Kumaki et al. 2023) This could potentially result in variable results in different studies. Besides, it should be noted that while *MET* GCN values can be continuously evaluated and quantified, the specific criteria for positivity may differ. While there was agreement between the MET-to-CEP7 ratio determined by FISH and *MET* GCN as identified through NGS, this concurrence was not definitive.(Camidge et al. 2021; Peng et al. 2021) Based on the research involving biomarker analysis, MET GCN≥5 determined through NGS was unable to predict a favorable response to MET-TKI therapy.(Peng et al. 2021) In this context, it is critical to consider the possible co-occurrence of oncogenic mutations with the induction of another oncogenic driver pathway. When acquired *MET* amplification coincides with the activation of driver genes such as *EGFR* mutations, a single MET-TKI approach is unlikely to provide effective disease control, while combination strategies may be necessary.(Sequist et al. 2020) In this particular case, the individual was elderly and presented with a weakened baseline physical condition alongside advanced lung adenocarcinoma with numerous metastases. *MET* amplification was detected along with five non-druggable co-mutated alterations (*FGF23*, *NKX2-1*, *TP53*, *LRP1B*, and *FAT1*). However, no corresponding targeted therapeutic drugs have been developed for these five co-mutated genes, and these co-mutations may reduce MET-TKI's effectiveness. Despite these challenging circumstances, the patient experienced an unexpected partial remission that persisted for more than sixteen months following first-line treatment with savolitinib. On the one hand, this can be attributed to the successful suppression of MET activity. Meanwhile, detection of *MET* amplification via NGS and orthogonal *MET*-FISH, coupled with the absence of other oncogenic driver genes as indicated by comprehensive genomic profiling (CGP) data, provides further validation for savolitinib's efficacy as a stand-alone treatment option. The optimal strategy for identifying patients with a higher probability of responding to MET-TKIs may involve the use of integrated *MET* diagnostic methods and other onco-driver genes detection.

Conclusions

Savolitinib shows promising anti-tumor efficacy in this lung adenocarcinoma patient exhibiting primary *MET* amplification, while its adverse event is typically manageable and well-tolerated. Experience with this case highlights the need for further research on savolitinib in advanced lung adenocarcinoma with *de novo MET* amplification, as well as continued investigation of the association between *MET* amplification level and clinical efficacy of Savolitinib.

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Data availability All relevant information is presented in the case report. Any additional data may be made available on reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate This study was approved by the Medical Ethical Committee of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University and the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. In this case, all patient data and images were published with their written informed consent.

Consent for publication The included patient gave his oral and written informed consent.

Competing interests The authors declare no competing interests.

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