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CASE REPORT

Acquired BRAF-AGK Fusion Following Osimertinib Plus Savolitinib in EGFR-Mutated MET-Amplified Non-Small-Cell Lung Cancer: Durable Response to Gefitinib and Trametinib in a Case Report

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Background: Osimertinib is one of the standard first-line treatments for advanced epidermal growth factor receptor (EGFR)-mutated non-small-cell lung cancer (NSCLC). Approximately 25% of patients acquire MET amplification upon disease progression on osimertinib and may respond to combined EGFR–MET inhibition (e.g, osimertinib plus savolitinib). However, whether secondary targetable alterations emerge after dual EGFR/MET inhibition, and whether existing targeted agents retain therapeutic relevance in this setting, remain insufficiently characterized.

Case Presentation: We report a 59-year-old female non-smoker with stage IV EGFR Leu858Arg-mutated lung adenocarcinoma who sequentially received first-line osimertinib (~9 months), second-line osimertinib plus savolitinib for MET amplification (~20 months), third-line platinum-based chemotherapy with local ablative therapy for oligo-progression, and fourth-line docetaxel. Comprehensive genomic profiling (CGP) of an archival cervical lymph node specimen (resected June 2019) subsequently identified an acquired BRAF-AGK fusion alongside the original EGFR Leu858Arg mutation; MET amplification was no longer detected in this specimen. Fifth-line gefitinib plus trametinib (initiated July 2020) was administered for approximately 19 months. Serial thoracic computed tomography, reassessed by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, showed a best overall response of stable disease, with the dominant target thoracic lesion decreasing from 16.8 mm at baseline to a nadir of 13.8 mm (17.9% maximum reduction). The course was complicated by central nervous system (CNS) progression managed with brain tumor resection and whole-brain radiotherapy, by transient thoracic re-progression during a 48-day treatment interruption that resolved on retreatment, and by trametinib dose reductions for grade 2 toxicities.

Conclusion: This case illustrates that an acquired BRAF fusion may emerge as a potentially targetable bypass alteration in EGFR-mutated MET-amplified NSCLC after progression on combined EGFR–MET inhibition and that the combination of a first-generation EGFR-TKI and a MEK inhibitor can be associated with prolonged systemic disease control. The findings are hypothesis-generating and support the value of CGP at sequential progression points to guide mechanism-based therapy in oncogene-driven NSCLC.

Keywords: lung adenocarcinoma, acquired resistance, osimertinib, savolitinib, BRAF-fusion

Introduction

Treatment options and outcomes have rapidly evolved for patients with advanced non-small-cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR)-sensitizing mutations in recent years.[1] First-line treatment with osimertinib, a third-generation oral irreversible EGFR tyrosine kinase inhibitor (TKI) that selectively inhibits both EGFR-TKI-sensitizing and EGFR Thr790Met resistance mutations was found to be associated with longer progression-free survival and overall survival compared with treatment with first-generation EGFR-TKIs in this population, subsequently emerging as a standard of care.[2]

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Resistance to oncogene-targeted therapy in EGFR-mutated NSCLC is increasingly recognized as a temporally dynamic process: distinct resistance mechanisms can emerge sequentially under successive lines of therapeutic pressure, with one bypass alteration giving rise to another over time.[1,3,4] Upon assessing acquired resistance to osimertinib, up to 25% of the patients had MET amplification, and approximately 2.3% harbored a BRAF rearrangement.[5] Other reported resistance mechanisms include HER2 (ERBB2) amplification, KRAS or PIK3CA mutations, oncogenic fusions involving RET, ALK or NTRK, and small-cell histologic transformation.[5] In an early-phase trial, the combination of osimertinib and savolitinib (a potent MET inhibitor) demonstrated promising anti-tumor effects in patients with EGFR-mutated, MET-amplified NSCLC following osimertinib progression.[6] The confirmatory SAVANNAH trial (NCT03778229) demonstrated the efficacy of MET inhibition in patients harboring MET amplification-mediated resistance.[7] Moreover, BRAF rearrangement was shown to be inhibited by the combination of EGFR-TKI and MEK inhibitors.[8,9]

Importantly, BRAF mutations and BRAF fusions differ substantially in biology and therapeutic implications. BRAF Val600Glu (V600E) point mutations activate the MAPK/ERK pathway as monomers and are sensitive to combined BRAF and MEK inhibition (eg, dabrafenib plus trametinib), whereas BRAF fusions typically retain the intact kinase domain at the 3′-end while losing the N-terminal autoinhibitory domain, leading to RAS-independent dimerization and downstream MAPK activation. This dimerization-dependent signaling renders BRAF fusions largely insensitive to first- and second-generation BRAF inhibitors—and potentially subject to paradoxical ERK activation—but susceptible to MEK inhibition (eg, trametinib) or pan-RAF inhibition.[9,10]

However, in patients with EGFR-mutated and MET-amplified NSCLC who develop acquired resistance to combined EGFR-TKI and MET inhibitor therapy, the emergence of subsequent targetable genetic alterations and the potential efficacy of existing targeted agents remain insufficiently characterized;[11] whether secondary targetable alterations emerge after dual EGFR/MET inhibition remains unclear. In the present case report, we describe a patient with EGFR-mutated and MET-amplified lung adenocarcinoma in whom acquired resistance to osimertinib and savolitinib was associated with a BRAF-AGK fusion as a putative resistance driver, and who subsequently derived a durable clinical benefit from combination therapy with gefitinib and trametinib.

Case Presentation

A 59-year-old female non-smoker was diagnosed with EGFR-mutated (Leu858Arg) stage IV (cT4N3M1a; American Joint Committee on Cancer, 9th edition) lung adenocarcinoma, having presented with cough and dyspnea for weeks. Her diagnosis was confirmed via pleural biopsy. The patient received first-line treatment as part of the FLAURA trial[2] since December 2015, and the left lower main tumor progressed after 9 months of osimertinib therapy (80 mg once daily). Following tumor re-biopsy confirming MET amplification, the patient was enrolled in the TATTON trial[6] and second-line therapy with osimertinib plus savolitinib was initiated in October 2016.

After 20 months of therapy, thoracic computed tomography (CT) in June 2018 demonstrated disease progression. Subsequently, the patient received third-line platinum-doublet chemotherapy, followed by single-agent maintenance. During this period, she underwent local ablative interventions, including surgical resection of the oligo-progressive primary tumor in the left lower lung and the left cervical lymph node in February and June 2019, respectively. In January 2020, fourth-line docetaxel was administered due to systemic progression, including a newly developed left lower lobe tumor and right pleural effusion (Figure 1A and B). To identify potential targetable oncogenic drivers following multiple lines of therapy, the patient underwent molecular pre-screening for the STARTRK-2 (NCT02568267) clinical trial.[12] As part of this process, the archival cervical lymph node specimen resected in June 2019 was subjected to comprehensive genomic profiling (CGP) using the FoundationOne CDx assay (Foundation Medicine, Inc., Cambridge, MA, USA). The analysis identified the primary EGFR Leu858Arg mutation alongside an acquired BRAF-AGK fusion, an ARID1A frameshift alteration (M1634fs*14) and CCNE1 amplification, with a tumor mutational burden of 8.83 mutations/Mb and microsatellite-stable status (Table 1 and Supplementary Document 1). Notably, MET amplification, present at the time of osimertinib progression in 2016, was no longer detected in this 2019 specimen. One plausible explanation is clonal replacement of the MET-amplified subclone by alternative resistance pathways under successive therapeutic pressure, although spatial sampling heterogeneity cannot be excluded, given that the 2019 specimen originated from a cervical lymph node rather than the original thoracic primary tumor.

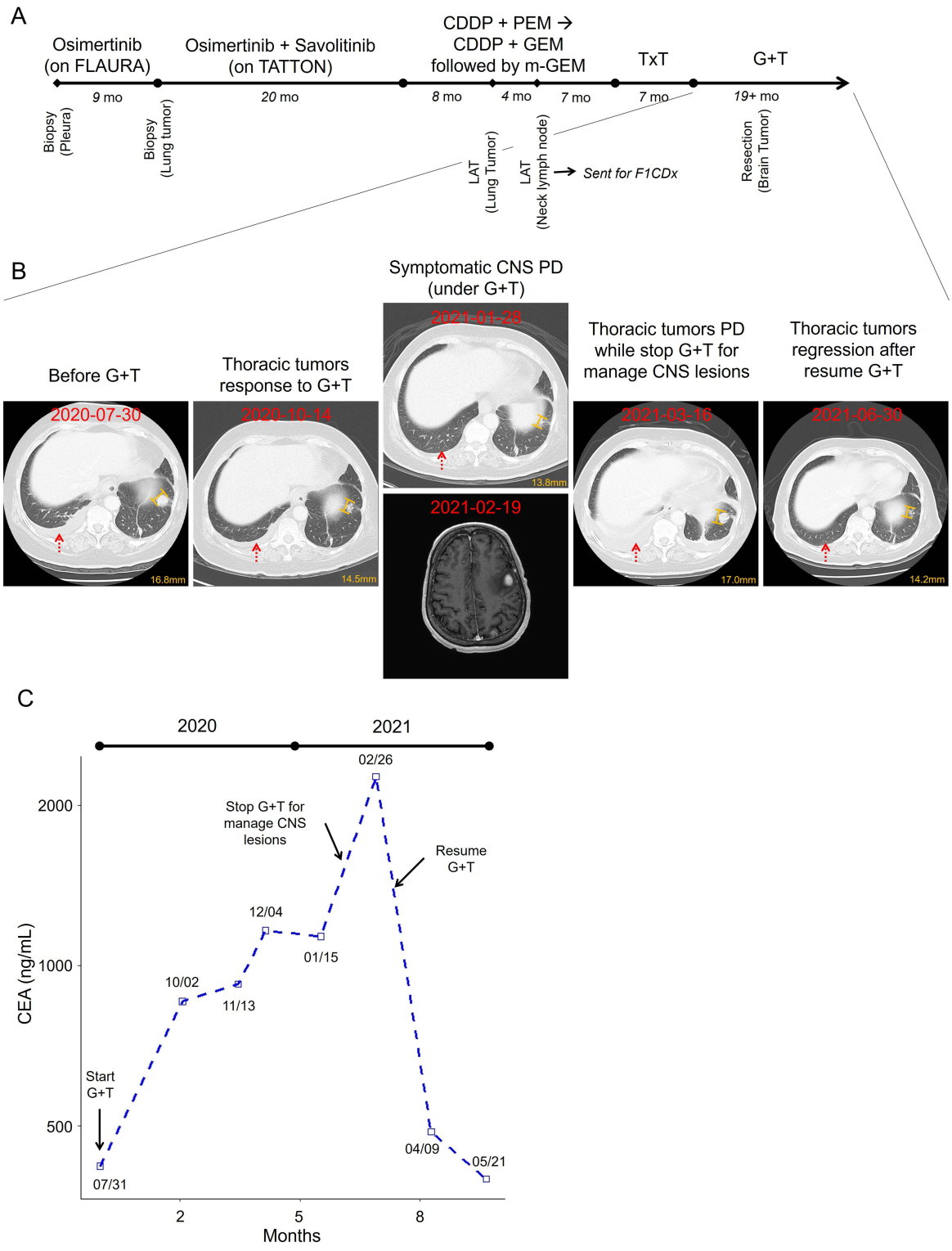

Figure 1 Treatment course, radiologic response and serum carcinoembryonic antigen (CEA) levels for an EGFR-mutated, MET-amplified non-small-cell lung cancer patient with an acquired BRAF-AGK fusion treated with combined gefitinib and trametinib. (**A**) Schematic summary of the clinical treatment course. CDDP, cisplatin; PEM, pemetrexed; GEM, gemcitabine; m-GEM, maintenance gemcitabine; TxT, docetaxel; G+T, gefitinib plus trametinib; LAT, local ablative therapy; F1CDx, FoundationOne CDx assay. (**B**) Serial thoracic computed tomography (CT) and brain magnetic resonance imaging (MRI) during combined gefitinib and trametinib therapy. Yellow caliper marks indicate the longest diameter of the target thoracic lesion; red dashed arrows indicate pleural effusion. (**C**) Serial changes in serum carcinoembryonic antigen (CEA) levels during gefitinib and trametinib treatment (normal value <5 ng/mL). The Y-axis is presented on a $\log_{10}$ scale.

Abbreviations: CDDP, cisplatin; PEM, pemetrexed; GEM, gemcitabine; m-GEM, maintenance gemcitabine; TxT, docetaxel; G+T, gefitinib and trametinib; LAT, local ablative therapy; CNS, central nervous system; PD, progressive disease; mo, months; F1CDx, FoundationOne CDx assay; CT, computed tomography; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer.

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Table 1 Comprehensive Genomic Profiling of the Archival Cervical Lymph Node Specimen (Resected June 2019; FoundationOne CDx Assay)

Gene	Alteration
Genomic alterations identified	
ARID1A	M1634fs*14
BRAF	BRAF-AGK fusion
CCNE1	Amplification
EGFR	L858R
Variants of unknown significance	
ATM	M1131I
ATRX	D980G
ATRX	L647I
BRCA2	G2901D
CALR	K368del
HSD3B1	T328S
IGF1R	E229K
INPP4B	D762V
JAK2	I899T
MLL (KMT2A)	F2437Y
MLL (KMT2A)	G2892A
RAC1	Amplification
Additional biomarkers	
Tumor mutational burden (TMB)	8.83 mutations/Mb (intermediate)
Microsatellite status	MSI-Stable

Previous preclinical studies and case reports demonstrated that acquired BRAF fusion was one of the driver resistance mechanisms to EGFR-TKIs in EGFR-mutated NSCLC and that this genetic alteration could respond to the combination of EGFR-TKIs and MEK inhibitors, such as osimertinib or erlotinib combined with trametinib.[9,13,14] Due to insurance reimbursement restrictions for osimertinib after disease progression and the financial burden of self-payment, gefitinib was selected as the EGFR-TKI backbone, as it was covered by Taiwan National Health Insurance for patients who had progressed after receiving platinum-based chemotherapy. Trametinib was obtained via a compassionate use program.

Fifth-line gefitinib plus trametinib was initiated on July 31, 2020. Serial follow-up thoracic CT was reassessed using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[15] The target thoracic lesion measured 16.8 mm at baseline (July 30, 2020), 14.5 mm on October 14, 2020, and reached a nadir of 13.8 mm on January 28, 2021, representing a maximum reduction of 17.9% relative to baseline (Figure 1B). The accompanying pleural effusion, classified as a non-target lesion under RECIST v1.1, also showed concurrent radiologic improvement. The best overall response was therefore stable disease, with sustained thoracic disease control over the first six months of treatment. Despite radiographic stability of the thoracic disease, however, serum carcinoembryonic antigen (CEA) levels rose progressively over the same period (Figure 1C). This discordance between radiologic stability and rising serum CEA was most consistent with a mixed response, suggesting the possibility of uncontrolled extra-thoracic disease.

In January 2021, symptomatic oligometastatic central nervous system (CNS) lesions were identified, and the patient underwent brain tumor excision in February 2021. To minimize unanticipated peri-operative interactions, gefitinib and trametinib were temporarily discontinued. Symptomatic thoracic progression then ensued in March 2021, with massive pericardial and pleural effusion accompanying re-growth of the target thoracic lesion to 17.0 mm on March 16, 2021 (Figure 1B). After a 48-day discontinuation, gefitinib and trametinib were resumed on the same day, accompanied by palliative thoracentesis and pericardiocentesis. Following stabilization of her general condition, the patient also received palliative whole-brain radiotherapy to optimize CNS disease control. Follow-up thoracic CT on June 30, 2021, demonstrated regression of the target lesion to 14.2 mm (a 16.5% reduction from the pre-resumption measurement), and serum CEA decreased to levels lower than at the start of fifth-line therapy (Figure 1C). The clinical course thus illustrated compartment-specific resistance and the dynamic, temporally heterogeneous behavior of acquired resistance in oncogene-driven NSCLC,[1,11] in which systemic disease control was achieved with combined EGFR-TKI and MEK inhibition while CNS disease progression required local ablative measures.

During gefitinib and trametinib therapy, the patient experienced recurring grade 2 diarrhea, anorexia, rash, mucositis and eyelid swelling, consistent with previous reports of combined EGFR-TKI and MEK inhibitor therapy.[13,14] To maintain tolerability, the dosing schedule of gefitinib (250 mg) was reduced from once daily to every other day, and trametinib (2 mg) was reduced sequentially from once daily, to every other day, to thrice weekly, and finally to twice weekly (mean trametinib dose, ~0.57 mg/day).

However, follow-up imaging in April 2022 revealed ongoing progression in thoracic disease and para-aortic lymphadenopathy. Docetaxel was administered from April to July 2022 as sixth-line systemic therapy. Nevertheless, clinical deterioration ensued, with progressive anorexia, weakness and the emergence of new neurological symptoms. Brain imaging in late August 2022 revealed CNS progression with obstructive hydrocephalus, for which a ventriculoperitoneal shunt was placed. Given the persistent disease progression, declining functional status (Eastern Cooperative Oncology Group performance status 3), and poor tolerance to further systemic therapy, the patient was transitioned to best supportive care.

Discussion

In the literature, two groups used different CGP platforms and analyzed over 10,000 clinical samples at the pan-tumor level;[16,17] these studies consistently showed that BRAF rearrangement was a rare (~0.3%) genetic alteration that was enriched in spitzoid melanoma, pilocytic astrocytoma, pancreatic acinar carcinoma and papillary thyroid cancers. In NSCLC, 4.4% of lung tumors were found to have BRAF genetic alterations, and among them, 2.8% of the tumors were identified to have BRAF fusion.[18] This type of kinase fusion has been more frequently reported as an acquired resistance alteration following EGFR-TKI treatment in EGFR-mutated lung cancer (accounting for ~2.3% of resistance mechanisms).[9]

Acquired BRAF fusions have been previously reported as a resistance mechanism to EGFR-TKIs in EGFR-mutated NSCLC; notably, this resistance genotype exhibits sensitivity to dual EGFR and MEK inhibition.[8,9,13,14] The present case extends this experience to the specific clinical setting of progression after combined EGFR-TKI and MET inhibitor therapy, and adds a longer follow-up data point to the limited literature on combined EGFR-TKI and MEK inhibition in this molecular setting.

Several aspects of this case warrant cautious interpretation. First, attribution of the BRAF-AGK fusion specifically to dual EGFR/MET resistance is inferential. The 2019 lymph node specimen used for genomic profiling was archival material obtained approximately 12 months into third-line platinum-based chemotherapy, following both the period of EGFR/MET inhibitor therapy and a substantial period of cytotoxic chemotherapy; whether the BRAF fusion emerged under EGFR/MET inhibition, under subsequent chemotherapy pressure, or was already present at low frequency before any treatment cannot be determined from the available data, and functional validation that the fusion drove resistance in this patient was not performed. Longitudinal molecular monitoring through serial tissue or liquid biopsies (including circulating tumor DNA) at successive progression points was not available in this real-world clinical setting; the molecular landscape may therefore have continued to evolve during the interval between specimen acquisition and the initiation of fifth-line therapy, and additional resistance alterations not captured by the FoundationOne CDx panel cannot be ruled out. Second, if the loss of the previously detected MET amplification on the 2019 CGP reflects true clonal replacement rather than spatial sampling bias, the implied pattern of sequential clonal substitution—rather than simple

linear accumulation of bypass mechanisms—would be consistent with the temporal heterogeneity increasingly recognized in EGFR-mutated NSCLC.[1,11] Third, the clinical benefit observed during gefitinib and trametinib therapy occurred against a background of multiple confounders, including prior systemic therapies (osimertinib, savolitinib, platinum-based chemotherapy and docetaxel) and local ablative interventions (lung and lymph node resection in 2019, brain tumor excision in 2021, and whole-brain radiotherapy). Local ablative therapy of oligo-progressive disease has been shown to prolong disease control on TKI therapy in oncogene-addicted NSCLC,[19] and likely contributed to the duration of systemic control in this patient.

In terms of the underlying mechanism, the majority of oncogenic BRAF fusions, including the AGK-BRAF rearrangement identified in our patient, occur as a bypass resistance mechanism that reactivates the MAPK/ERK pathway despite upstream EGFR inhibition. A preclinical study showed that these BRAF fusions, typically retaining the intact in-frame BRAF kinase domain at the 3′-end while lacking the N-terminal autoinhibitory domain, lead to constitutive, RAS-independent dimerization of RAF proteins. This structural alteration activates downstream MAP kinase signaling, which is susceptible to inhibition via MEK inhibitors.[20] The efficacy of this approach is supported by Yasui et al[21] and Yu et al,[22] who reported clinical observations in which patients harboring SND1-BRAF or the novel SLC44A1-BRAF fusions achieved rapid partial responses or disease control with the MEK inhibitor trametinib. Further, Vojnic et al[9] and Piotrowska et al[8] demonstrated that the combination of osimertinib and trametinib could inhibit EGFR-mutated and BRAF-fusion NSCLC cell proliferation by blocking both EGFR-mutated and BRAF-fusion-driven signaling activities. Notably, in one Phase I/II clinical trial, Luo et al[14] reported on a patient with EGFR-mutated lung adenocarcinoma harboring an acquired BRAF fusion whose response to erlotinib and trametinib lasted for 5.5 months after progression on osimertinib. The findings of these previous studies are consistent with our observation in this patient. We emphasize, however, that these mechanistic interpretations are derived from the published literature; the present case does not in itself functionally demonstrate that the BRAF-AGK fusion drove resistance in this patient.

Several other clinically meaningful features of this case deserve emphasis. First, our patient, who presented with cerebral and pleural metastases, exhibited the well-documented disease flare phenomenon upon EGFR-TKI discontinuation,[23] with rapid thoracic progression after the 48-day interruption of gefitinib and trametinib and renewed control after rechallenge. Second, the choice of a first-generation EGFR-TKI (gefitinib) rather than osimertinib as the EGFR backbone has clear biological limitations, particularly with respect to CNS penetration. The inferior blood-brain barrier permeability of gefitinib compared with osimertinib likely contributed to the discordant response observed in this case, in which systemic thoracic disease was well controlled while symptomatic CNS progression occurred and required local ablative therapy.[2] This pattern of compartment-specific resistance highlights the need to integrate systemic therapy and CNS-directed local ablative measures when first-generation EGFR-TKIs are used as the backbone of combination regimens.[2,24] Third, given the substantial overlap in the toxicity profiles of EGFR and MEK inhibitors, combinations involving non-EGFR-mutant-specific TKIs such as gefitinib require careful, individualized dose attenuation to maintain tolerability;[13,14] the marked trametinib dose reduction in our patient is consistent with previous reports but limits direct comparison with regimens using full-dose trametinib and may affect reproducibility. Nonetheless, the iterative, tolerability-driven schedule documented here may serve as a practical reference for clinicians managing similar combinations in real-world practice.

Taken together, the clinical course in this patient supports, but does not establish, a model in which acquired BRAF fusion contributes to resistance after combined EGFR-TKI and MET inhibitor therapy in EGFR-mutated MET-amplified NSCLC, and in which combined EGFR-TKI plus MEK inhibition can be associated with prolonged systemic disease control when integrated with local ablative therapy. These observations are hypothesis-generating and need to be tested in larger prospective cohorts that incorporate longitudinal CGP, including circulating tumor DNA at sequential progression time points, before more definitive conclusions can be drawn.

Conclusion

We describe a patient with EGFR-mutated, MET-amplified lung adenocarcinoma in whom an acquired BRAF-AGK fusion was identified following progression on osimertinib and savolitinib. Subsequent therapy with gefitinib plus trametinib, integrated with local ablative therapy for CNS and oligo-progressive disease, was associated with approximately 19 months of systemic disease control. The clinical benefit must be interpreted in light of multiple intervening therapies, the use of

archival rather than fresh tissue for genomic profiling, the absence of longitudinal molecular assessment, and the need for substantial trametinib dose reductions; the findings should therefore be regarded as hypothesis-generating rather than definitive. The case nonetheless illustrates that an acquired BRAF fusion can emerge as a potentially targetable bypass alteration in EGFR-mutated MET-amplified NSCLC after dual EGFR/MET inhibition and that combined EGFR-TKI and MEK inhibition with individualized dose modification may merit further evaluation in this setting. The case underscores the value of CGP at sequential progression points to identify rare but potentially druggable acquired drivers and to expand therapeutic options for patients after standard targeted therapies.

Ethical Statement

Institutional approval to publish this case report, including the de-identified clinical and genomic data presented herein, was required and was obtained from the Institutional Review Board of National Cheng Kung University Hospital, Tainan, Taiwan (approval number A-EC-110-023). Written informed consent for the publication of this case report and any accompanying images was obtained from the patient prior to manuscript preparation.

Consent for Publication

Written informed consent for the publication of this report, including all clinical details, imaging and genomic findings, was obtained from the patient.

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Disclosure

The authors report no conflicts of interest in this work.

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