CASE REPORT

Combined RET and MEK Inhibition as a Treatment for *RET* Fusion-Positive NSCLC With Acquired *BRAF* Fusion: A Case Report

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ABSTRACT

RET fusions are present in 1% to 2% of NSCLCs. Although RET inhibitors like selpercatinib are effective, resistance inevitably develops. We present the case of a 28-year-old female with recurrent NSCLC and a *CCDC6::RET* fusion treated with selpercatinib. Testing at the time of progression revealed a new *SKAP2*::BRAF fusion. She was then treated with a combination of selpercatinib and trametinib, which led to a likely partial response, despite the combination demonstrating side effects. This case report details the first known instance of NSCLC with a *RET* fusion developing resistance by means of a *BRAF* fusion, treated with combined RET and MEK inhibition.

Keywords: Non–small cell lung cancer; Molecular targeted therapy; Antineoplastic drug resistance; Case report; RET fusion; BRAF fusion

Introduction

Roughly two-thirds of all NSCLCs have an identifiable driver mutation, with almost half now considered targetable with small molecule inhibitors. Alterations in the protooncogene, *RET*, which encodes a transmembrane receptor tyrosine kinase, are found in 1% to 2% of patients with NSCLC.[1] Real-world analysis of these patients has shown that the median age of diagnosis is 63 years, and treatment with RET inhibitors such as selpercatinib elicit median overall response rates and progression-free survival rates up to 76% and 16.2 months respectively.[2] Mechanisms of acquired resistance to RET inhibitors are under investigation but have been shown to involve on-target and off-target mutations that affect the MAPK pathway.[3] We present, to the best of our knowledge, the first known case of *RET* fusion-positive NSCLC with an acquired *BRAF* fusion, treated with combined RET inhibition and MEK inhibition.

Case Presentation

Patient Information

A 28-year-old female with a past medical history of ulcerative colitis presented for management of recurrent poorly differentiated adenocarcinoma of the lung. She was initially treated with multiple rounds of platinum-based chemotherapy regimens containing taxanes, pemetrexed, and anti-VEGF therapies (Fig. 1). Four years

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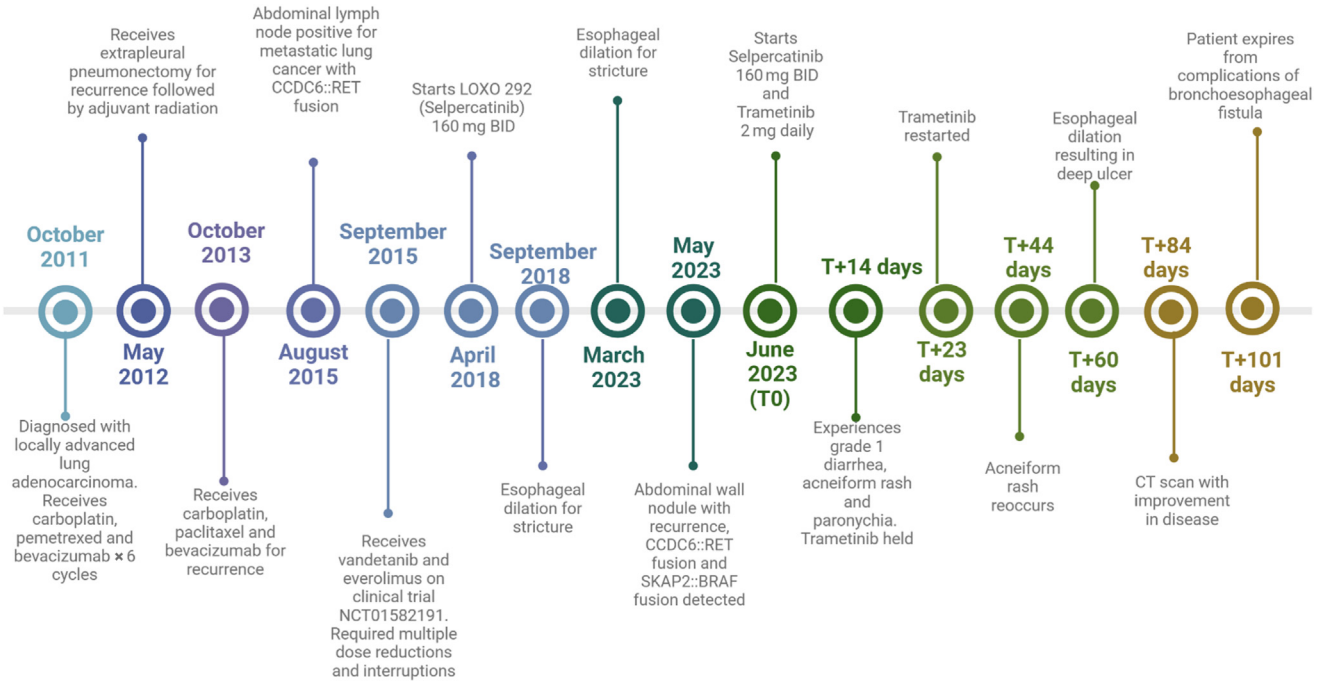

Figure 1. Timeline of clinical course and treatment history. Chronological display of patient's prior treatments and diagnostic tests. Initiation of combined selpercatinib and trametinib is denoted as T0. Subsequent relevant clinical time points are denoted as T + #number of days. Created with BioRender.com. T, day of therapy start; BID, twice daily; CT, computed tomography.

after diagnosis, positron emission tomography (PET) scans revealed avidity in the left upper abdominal quadrant and associated lymphadenopathy. Next-generation sequencing with Foundation Medicine from a biopsy of an abdominal lymph node revealed a *CCDC6::RET* fusion. She was subsequently treated with a combination of vandetinib and everolimus on trial. After three years of treatment, PET scans revealed worsening peritoneal carcinomatosis without clinically relevant activity in other parts of the body. Repeat molecular testing was not performed at this time. The patient started on selpercatinib 160 mg twice daily with excellent response and without significant side effects.

In terms of her ulcerative colitis, the patient underwent multiple esophagogastroduodenoscopies demonstrating esophageal stricture that required dilations in September 2018 and March 2023. A colonoscopy in 2023 did not reveal active ulcerative colitis in the lower gastrointestinal (GI) tract.

Diagnostic Assessment

In the interim, the patient presented to our institution. Three years after the initiation of selpercatinib, a PET scan revealed metabolic activity throughout the abdomen and pelvis including multiple lymph nodes, the peritoneum, and the cervix. No definitive activity was seen in the chest or the liver. Next-generation sequencing from a biopsy of a new subcutaneous abdominal nodule revealed a new *SKAP2::BRAF* fusion, with the persistence of the *CCDC6::RET* fusion. RNA-sequencing was performed with the University of Chicago's RNA Fusion Assay for gene fusion analysis, which is a hybrid capture-based RNA-sequencing assay for detecting known and novel fusions involving any of the 1005 targeted cancer-associated genes, as previously described.[4]

Therapeutic Intervention and Clinical Findings

The patient began treatment with selpercatinib 160 mg twice daily and trametinib (a MEK inhibitor) 2 mg daily. Two weeks after initiation of therapy, trametinib was held owing to grade 1 diarrhea and grade 2 dermatologic toxicities (i.e., acneiform rash and paronychia). The patient self-initiated topical tretinoin for her facial rash which was discontinued when she noticed it was causing worsening xeroderma. Trametinib was restarted after a nine-day dose interruption at 1 mg every other day and was increased to 1 mg daily seven days later. She experienced recrudescence of her dermatologic toxicities after three weeks of therapy requiring topical steroids (Fig. 2*A* and *B*).

Follow-Up and Outcomes

Follow-up imaging roughly three months after treatment initiation revealed near complete resolution of her disease (Fig. 3*A–F*). The patient underwent

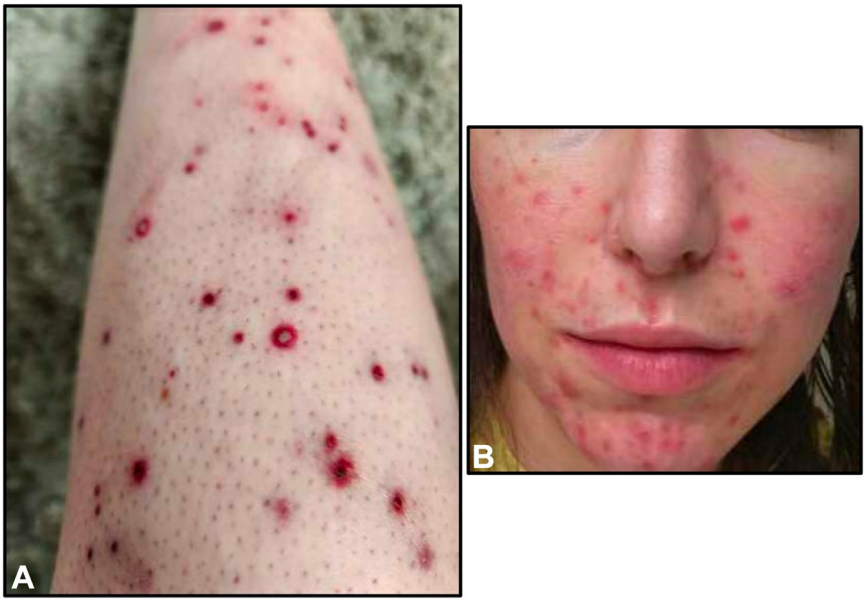

Figure 2. Dermatologic side effect. The patient experienced an acneiform rash on the lower extremity (*A*) and face (*B*), which is a common side effect of small molecules targeting the MAPK pathway. MAPK, mitogen-activated protein kinase.

esophagogastroduodenoscopy in August 2023 due to dysphagia which revealed recurrent esophageal stricture with ulceration, requiring dilation. This was complicated by a deep esophageal tear after dilation. The following month, the patient presented to the emergency room due to hemoptysis with evaluation revealing an esophageal bronchial fistula. Unfortunately, she soon suffered a cardiac arrest resulting in her death.

Discussion

Targeted therapies are an essential component of contemporary treatment for NSCLC. Nevertheless, patients almost invariably develop resistance to these therapies, so identification of mechanisms of resistance remains a critical area of investigation. *BRAF* alterations are drivers in 2% of NSCLC and are increasingly recognized as secondary alterations in patients receiving therapies targeting the MAPK pathway (e.g., EGFR, KRAS, RET).[1,5] The most recognized *BRAF* alterations are class I mutations comprising point mutations in the V600 locus.[6] This class of mutations is typically treated with dual BRAF and MEK inhibition when used as a treatment for de novo disease and an acquired resistance mechanism.

BRAF fusions are class II variants that create BRAF dimers that function independently of RAS activation.[7] BRAF inhibitors are ineffective against the RAF dimerization caused by this class of variants[8]; in fact, the use of BRAF inhibitors in *SKAP2::BRAF* fusion-positive tumors may cause paradoxical hyperproliferation.[9] MEK inhibitors, act downstream of this pathway and remain a viable therapeutic option. A preclinical study revealed the synergy of trametinib with osimertinib in blocking cellular growth in *EGFR*-mutated NSCLC with secondary *BRAF* fusions.[10] A subsequent case report reported the clinical efficacy of this combination.[11] To our knowledge, our case is the first report to reveal the clinical efficacy of combined selpercatinib and trametinib in overcoming *BRAF* fusion acquired as a resistance mechanism to therapy with RET inhibitors.

Our patient experienced primarily dermatologic and GI toxicities with the combined therapy. The clinical timeline of our patient's symptoms suggests that the toxicities were exacerbated by the addition of trametinib. Acneiform rash is a common dermatologic toxicity of trametinib, the frequency of which might be decreased with the addition of BRAF inhibition.[12,13] Because BRAF inhibitors are not expected to provide therapeutic benefits as discussed above, this was omitted from our patient's treatment. Although the patient did have underlying inflammatory bowel disease, a recent colonoscopy did not reveal active disease. Therefore, although this may have been an underlying risk factor, we do not think this was a significant contributor to the GI toxicities she experienced.

Similarly, GI perforation is a rare complication of MEK inhibitors, occurring in less than 1% of cases and occurring primarily in the intestines.[14] As our patient experienced esophageal perforation and fistualization soon after dilation, this was thought not to be related to either drug or combination.

As our patient required multiple dose interruptions or reductions and the need for therapies to overcome resistance persists, investigation of alternative dosing strategies is warranted. In a five-year overall survival

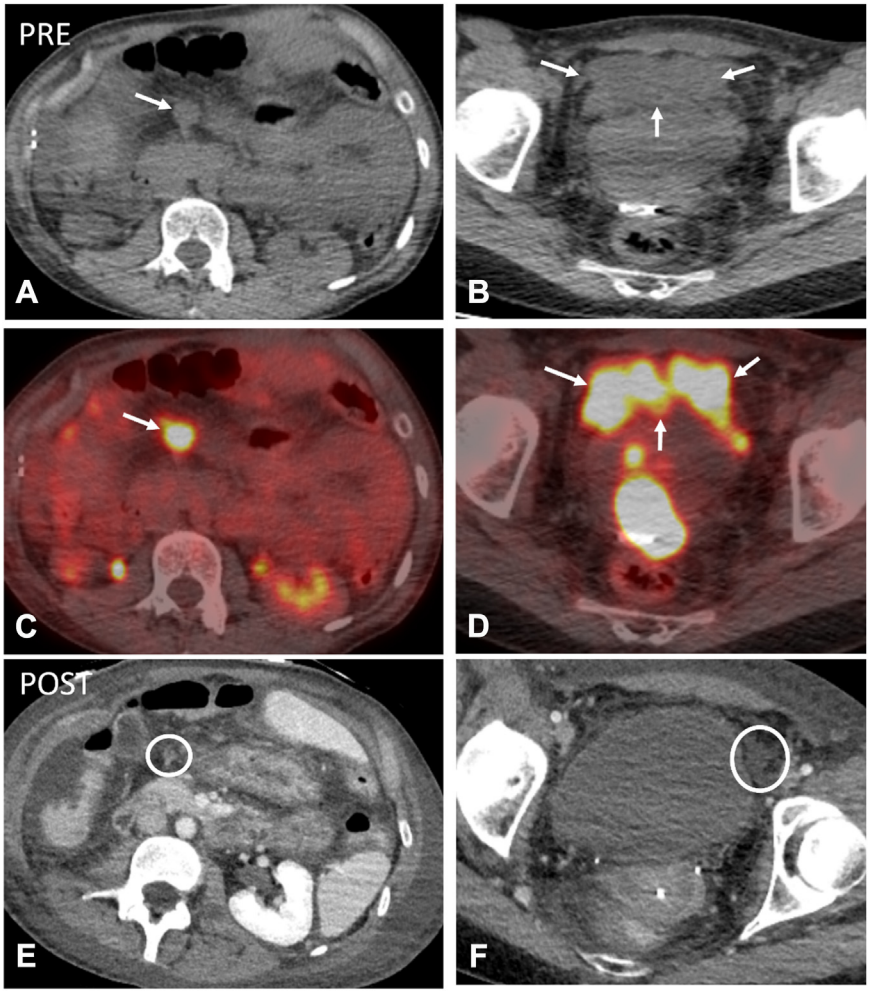

Figure 3. Pre and posttreatment imaging. PET CT images before therapy (*A-D)* including axial localizing CT images in soft tissue window (*A* and *B*) and fused corresponding fused PET CT images (*C* and *D*) showing metabolically active mesenteric soft tissue implants (arrows; A and B) and an infiltrative prevesical soft tissue lesion (arrows, *C* and *D*) compatible with disease involvement. Axial images in soft tissue window from follow-up abdominal CT 4 months after treatment (*E* and *F*) showing substantial treatment response with nearly resolved mesenteric implant (circle, *E*) and resolved prevesical soft tissue infiltration with trace ascites (circle, *F*). CT, computed tomography; PET, positron emission tomography.

analysis of dabrafenib and trametinib, approximately 33% of patients required a dose reduction of MEK inhibitor[15] Although this involves a different combination, it provides useful context regarding the tolerance of trametinib when used with other drugs. Considering the patient's history of ulcerative colitis, the limited literature, and the lack of extensive experience in treating *BRAF* fusions with unique combinations of oral oncolytics, we could have considered starting with a lower dose of trametinib (1 mg daily.) In future similar situations, assessing patient comorbidities to determine if starting at lower doses and increasing as tolerated with follow-up every one to two weeks could be appropriate. Nevertheless, we acknowledge that the lack of pharmacokinetics data for the combination makes it difficult to provide firm recommendations.

Conclusion

In conclusion, our case highlights that *BRAF* fusions are an acquired resistance mechanism to therapy with RET inhibitors which may be overcome by adding a MEK inhibitor. Further studies investigating the optimal treatment strategy to maximize efficacy and minimize toxicity are needed.

CRediT Authorship Contribution Statement

Jacobi B. Hines: Writing - original draft, Writing - review & editing.

Benjamin C. Bowar: Writing - review & editing.

Margaret Colleton: Writing - review & editing.

Lydia Chelala: Writing - review & editing, Resources.

Peng Wang: Writing - review & editing, Resources.

Angad Chadha: Writing – review & editing.
Jeremy Segal: Writing - review & editing
Christine M. Bestvina: Conceptualization, Writing - review & editing, Resources.

Disclosure

Dr. Bestvina reports Consulting: Amgen, AstraZeneca, Bristol-Myers Squibb, Daiichi, EMD Serono, Gilead, Guardant, Mirati, Novocure, Sanofi, Tempus, Turning Point Therapeutics; Research funding to the institution: AstraZeneca, Bristol-Myers Squibb. Dr. Chadha reports being part of the advisory board: Boehringer Ingelheim. The remaining authors declare no conflict of interest.

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