

Response to Dabrafenib Plus Trametinib in a Patient With an Uncommon Activating *BRAF* Mutation: A First in Non–Small Cell Lung Cancer

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ABSTRACT

Mutations in *BRAF* are present in 4% of non–small cell lung cancer (NSCLC), of which half are well-characterized activating variants affecting codon 600 (classified as class I). These mutations, most commonly *BRAF* V600E, have been associated with response to BRAF/MEK-directed small molecule kinase inhibitors. NSCLC with kinase-activating *BRAF* mutations occurring at other codons (class II variants) represent a substantial portion of *BRAF*-mutated NSCLC, but use of targeted therapy in these tumors is still under investigation. Class II mutations have been described in other tumor types and have been associated with response to BRAF/MEK-targeted agents, although optimal treatment strategies for these patients are lacking. This report presents a case of a woman with metastatic NSCLC harboring a class II *BRAF* p.N486_P490del variant who had a sustained clinical response to combination therapy with dabrafenib and trametinib. This first report of the use of BRAF/MEK-targeted therapy for this variant in NSCLC supports consideration of such treatment for tumors with class II *BRAF* variants.

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BRAF is a serine/threonine protein kinase that plays a crucial role in the MAPK pathway, which governs cellular proliferation and survival.¹ Mutations in *BRAF*, specifically V600E, have long been recognized as driving tumorigenesis in various cancer types.² Blocking the aberrant signaling cascade caused by this mutation using targeted therapies has been shown to lead to improved outcomes in several tumor types, including malignant melanoma,³ anaplastic thyroid cancer,⁴ and colorectal cancer.⁵

BRAF mutations occur in 4% of all non–small cell lung cancer (NSCLC) cases; however, 50% are non-V600 mutations.⁶ *BRAF* mutations are categorized into 3 classes depending on their effects on kinase activity, RAS-dependency, and dimerization status.⁷ Class I mutations occur at the V600 codon and strongly stimulate kinase activity via monomeric activation of BRAF in a RAS-independent manner. Class II mutations also strongly activate kinase activity via RAS-independent BRAF dimerization. Many non-V600 mutations, including the mutation to be described in our patient, fall into class II. Class III mutations, also referred to as “kinase-dead” mutations, are defined by their very low kinase activity compared with wild-type *BRAF*. Although the combination of dabrafenib and trametinib—agents targeting BRAF and MEK, respectively—has demonstrated promising activity in metastatic NSCLC harboring class I *BRAF* mutations, specifically V600E,⁸ its role in the treatment of class II and III mutations is unclear.

This report presents a patient with previously treated metastatic lung adenocarcinoma that harbored a *BRAF* p.N486_N490del mutation who received treatment with combination dabrafenib+trametinib and achieved a clinical response. To our knowledge, this is the first reported instance of a patient with NSCLC harboring this mutation to respond to agents targeting the BRAF/MEK pathway.

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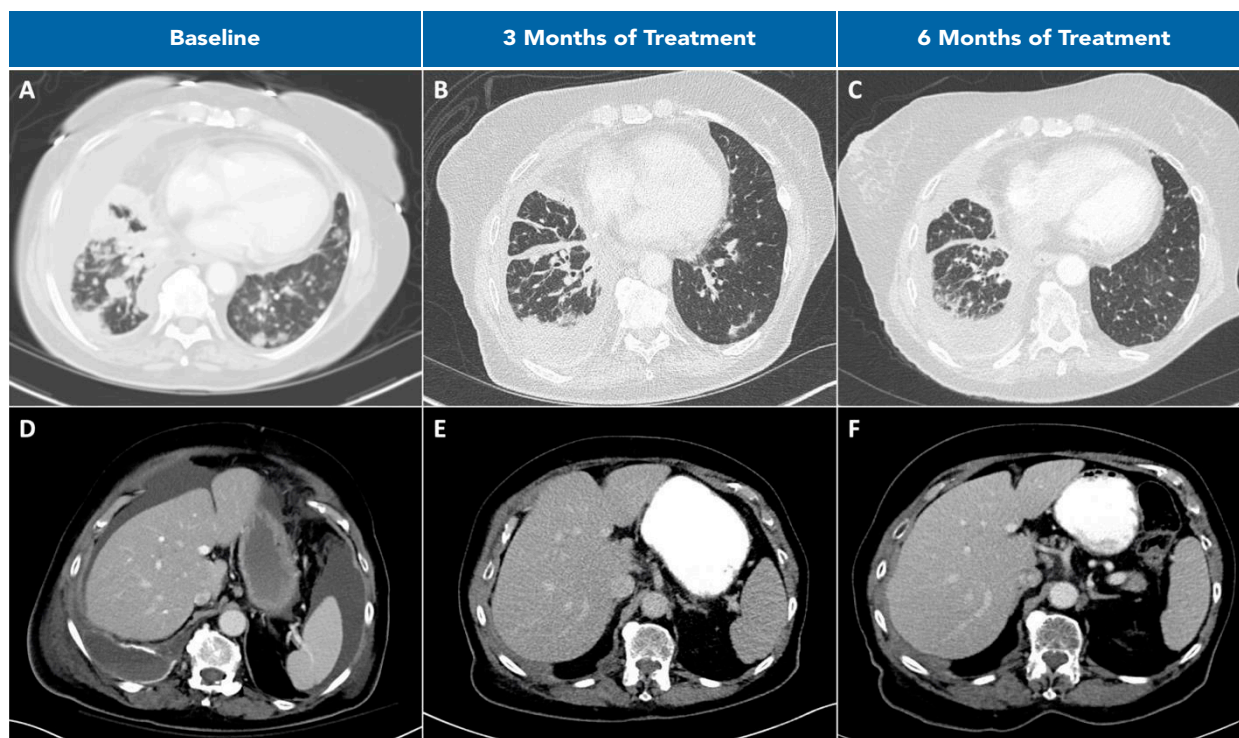


Figure 1. Cross-sectional imaging before and after treatment with BRAF/MEK inhibition. **(A)** Baseline CT chest showing numerous pulmonary masses and a loculated pleural effusion. **(B)** CT chest after 3 months on dabrafenib+trametinib showing decreased size and number of pulmonary masses and improvement in effusion. **(C)** CT chest after 6 months of dabrafenib+trametinib showing complete resolution of pulmonary masses. **(D)** CT abdomen showing numerous peritoneal carcinomatosis and malignant ascites. **(E)** CT abdomen after 3 months on dabrafenib+trametinib showing decreased carcinomatosis and improvement in ascites. **(F)** CT abdomen after 6 months of dabrafenib+trametinib showing resolution of malignant ascites.

Case Presentation

A 79-year-old woman with a history of metastatic adenocarcinoma of the lung developed new malignant ascites while receiving treatment with third-line docetaxel. She had been diagnosed with stage IV NSCLC one year prior after being found to have a malignant pleural effusion. At that time, her tumor cells were noted to have PD-L1 tumor proportion score (TPS) of 90%, with a targeted mutation panel showing no genetic alterations that represented indications for treatment with FDA-approved medications. However, expanded genomic analysis (a 547-gene next-generation sequencing [NGS] panel with full gene coverage) revealed an uncommon *BRAF* p.N486_P490del insertion-deletion mutation predicted to produce a BRAF protein with active kinase (see Figure S1 in the supplementary materials, available online with this article).

She initially received treatment with pembrolizumab monotherapy, which was discontinued due to grade 2 colitis that recurred upon rechallenge with pembrolizumab. She next received carboplatin and pemetrexed followed by maintenance pemetrexed until she developed progression with hepatic metastases and peritoneal carcinomatosis. Of note, left upper and left lower lobe pulmonary emboli were incidentally detected at the time of her

NSCLC diagnosis, and therefore bevacizumab was omitted from her second-line regimen following a risk/benefit discussion, given the increased incidence of venous thromboembolism observed with this therapeutic agent.⁹ She was then switched to docetaxel and received 3 cycles before developing symptomatic malignant ascites requiring repeated paracenteses.

At the time of disease progression, testing of her ascites fluid revealed metastatic lung adenocarcinoma (Supplementary Figure S2), with *BRAF* p.N486_N490del again detected by NGS. Other mutations detected included pathogenic mutations in *IDH1* (p.R132C), *TET2* (p.N71fs), and *TP53* (p.G245S), as well as a variant of uncertain significance in *ATR* (p.I859K). Based on the likely functional impact of the *BRAF* mutation as well as reports describing sensitivity to inhibitors of the BRAF/MEK pathway in other tumor types (Supplementary Table S1), off-label dabrafenib and trametinib therapy was offered to the patient and was obtained through a medication assistance program. Staging CT scans of her chest, abdomen, and pelvis at the time of starting dabrafenib+trametinib revealed numerous pulmonary masses, a loculated right-sided pleural effusion, mediastinal adenopathy, peritoneal nodules, and ascites (Figure 1). A

brain MRI with and without contrast demonstrated no definitive metastatic disease.

She had been requiring monthly paracenteses to manage her malignant ascites. Shortly after beginning dabrafenib+trametinib, her paracentesis requirement completely resolved and she showed no further clinical evidence of ascites. After 3 months on therapy, repeat imaging revealed interval treatment response with decreased size and number of multiple pulmonary masses and improvement of her ascites (Figure 1). Her most recent CT scans after 6 months on therapy demonstrated continued response to dabrafenib+trametinib, which she continues to receive after 9 months on treatment. Notable adverse effects include transient grade 3 neutropenia without fever and not requiring growth factor support, and grade 1 thrombocytopenia without bleeding and not requiring transfusions.

Discussion

We report the first case, to our knowledge, of a patient with NSCLC harboring a *BRAF* p.N486_P490del mutation who sustained a deep and durable response to combination therapy with dabrafenib and trametinib. This case reinforces the need to continue to expand our understanding of non-V600 mutations within *BRAF* and other targetable mutations in patients with NSCLC.

Since their recognition as targetable genetic alterations, testing for the presence of oncogene “driver” mutations and rearrangements in NSCLC has become imperative to devising an optimal management strategy.¹⁰ However, the clinical relevance and therapeutic implications of many mutations and alterations remain undefined, and therefore ongoing efforts are needed to establish which alterations are truly predictive of response to targeted therapies.

The role of targeted therapies for *BRAF*-mutated NSCLC has focused on class I mutations, primarily V600E. The role of treatment with *BRAF* and *MEK* inhibition was established in a nonrandomized, phase II study in which patients with metastatic *BRAF* V600E-mutated NSCLC received dabrafenib and trametinib in combination.⁸ Patients were split into treatment-naïve and previously-treated cohorts. In total, 36 treatment-naïve and 57 previously treated patients were enrolled. In extended follow-up, 23 (63.9%) of the treatment-naïve patients achieved an investigator-assessed objective response compared with 39 (68.4%) of the previously treated patients.¹¹ This ultimately led to the approval of combination dabrafenib+trametinib for metastatic NSCLC harboring the *BRAF* V600E mutation.¹² Ongoing research efforts are also underway in this space investigating the activity of encorafenib+binimetinib in patients with metastatic NSCLC harboring V600 mutations (including V600E, V600K, and V600D).¹³ Although the trial is still ongoing,

data for patients harboring *BRAF* V600E mutations have been recently published.¹⁴ Clinical activity was demonstrated in both treatment-naïve (n=59) and previously treated (n=39) patients. The overall response rate was 75% (95% CI, 62%–85%) among treatment-naïve patients and 46% (95% CI, 30%–63%) in previously treated patients, with median duration of response not estimable (95% CI, 23.1 months–not estimable) and 16.7 months (95% CI, 7.4 months–not estimable), respectively. This combination demonstrates another viable therapeutic option for patients harboring the class I *BRAF* V600E mutation.

Class II mutations, on the other hand, are uncommon and heterogeneous, and their therapeutic implications are incompletely understood. A review of the mechanistic understanding of tumorigenesis and the variable susceptibility to targeted therapies for each of the >25 class II mutations that have been described is beyond the scope of this article.^{7,15–25} However, in the case of the particular class II mutation seen in our patient, *in vitro* studies have demonstrated that it results in constitutive activation of *BRAF* via an alteration in the β 3/ α C-helix loop moiety of the *BRAF* protein, which functionally locks the protein into its α C helix-in active conformation via creation of a Glu501/Lys483 salt bridge.²⁶ This in turn exposes multiple amino acid residues to participate in homodimerization between 2 mutant *BRAF* proteins at Arg506/Asp449 and Arg509/Thr508. The result is activated dimerized *BRAF* proteins that drive cellular growth and proliferation. Interestingly, preclinical studies demonstrate that treatment of cell lines harboring p.N486_P490del mutations with dabrafenib has had mixed results, with one study demonstrating sensitivity to dabrafenib²⁷ and another showing no significant arrest of cell growth.²⁶ In the negative study, however, treatment with trametinib resulted in robust inhibition of cellular proliferation. These observations suggest an antineoplastic pharmacologic effect may occur at the level of the mutant protein or possibly downstream, but a precise understanding remains elusive. Further structural-empirical correlative studies are needed to develop a useful mechanistic model of the therapeutic effect of *BRAF*/*MEK*-targeted therapies in this mutation.

Robust clinical evidence is similarly lacking to guide the treatment of patients with NSCLC with non-V600 class II and III *BRAF* mutations. Unfortunately, patients with NSCLC harboring class II or III *BRAF* mutations have been shown to have inferior progression-free survival and overall survival compared with patients harboring class I mutations when receiving nontargeted therapies.²⁸ These findings emphasize the need for therapies tailored to class II mutations, such as the p.N486_P490del mutation seen in our patient. Although the molecular biology differs between class I and II mutations, they share a pathogenic overactive kinase mechanism of tumorigenesis,

which provides a rationale for targeting BRAF/MEK inhibition. Indeed, this treatment strategy has been associated with clinical response in other tumor types harboring this p.N486_N490del mutation (see Supplementary Table S1). Multiple case reports have been published of patients with metastatic pancreatic adenocarcinoma harboring BRAF p.N486_N490del mutation in which clinical responses were achieved with the use of BRAF and/or MEK inhibitors and sustained for up to 6 months.^{29–31} Similarly, 2 patients with Langerhans cell histiocytosis harboring p.N486_N490del were successfully treated with trametinib, with clinical responses lasting upwards of 1 year.³²

Although limited clinical data are available to guide treatment of patients with non-V600 BRAF mutations, ongoing efforts may soon shed light on optimal strategies. Several prospective clinical trials are evaluating BRAF/MEK-targeted therapies for advanced malignancies harboring non-V600 BRAF mutations (ClinicalTrials.gov identifiers: NCT04439279, NCT04620330, NCT04488003, and NCT03839342). We aim to add to the body of literature surrounding this class II BRAF p.N486_N490del mutation. To our knowledge, this is the first report of a patient with metastatic NSCLC harboring BRAF p.N486_N490del that responded to treatment with BRAF/MEK-directed therapy. This response to targeted therapy is notable because optimal management strategies for patients with non-V600 class II and III BRAF mutations remain unclear.

Conclusions

This report presents a patient with NSCLC harboring an atypical, class II BRAF p.N486_N490del mutation who experienced a sustained clinical response to combination dabrafenib+trametinib, the first such case in the literature

to our knowledge. Although targeted agents exist for NSCLC harboring class I BRAF mutations, roughly half of BRAF mutations in NSCLC are class II or III, and therefore an unmet need for targeted agents remains. This example of a robust response to dabrafenib+trametinib in a patient harboring a BRAF p.N486_N490del mutation suggests that utilization of therapeutic agents targeting V600E mutations may be of benefit in this population, although further prospective studies are required to address this question.

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