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Research Perspective

MEK inhibitors in non-V600 BRAF mutations and fusions

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ABSTRACT

Mutations in BRAF at the 600th codon have proven sensitive to combination BRAF and MEK inhibition. Mutations outside this codon, however, are approximately as common but do not have approved targeted therapy approaches. Herein, we discuss targeting these non-V600 mutation and fusions in BRAF with MEK inhibitors.

INTRODUCTION

Developing active, molecularly targeted agents against mutated *BRAF* has been a major success story of the precision-cancer movement. Mutations affecting the 600th codon may be targeted by several approaches, including mutant-specific BRAF inhibitors, blockers of downstream signal partners MEK1/2, or the combination of both. In particular, the management of *BRAF* V600-mutant melanoma, lung cancer, hairy cell leukemia, and thyroid cancer has been transformed by these agents, which produce high response rates, occasionally resulting in durable responses [1–5].

In contrast to the high-profile success of pharmacologic blockade of mutant *BRAF* V600, approaches to targeting other mutations in *BRAF* outside of the 600th codon have been less active. When taken together, these mutations include over 200 BRAF-mutant alleles corresponding to about 30 distinct BRAF mutations. Non-V600 mutations are approximately as common as V600 mutations, and are found in 1–3% of all cancers, including in many common histology types (lung, colon, prostate, gynecologic malignancies) as well as less common tumor types (primary brain tumors, neuroendocrine tumors, and hematologic malignancies) [6–8]. These mutations all seem to activate mitogen activated protein kinase (MAPK) pathway signaling and may be classified into one of three different types based on their mechanism of action [9–11]. Class 1 mutations, which are exclusively *BRAF* V600 mutation, signal as monomers in constitutively active fashion. Class 2 mutations function as constitutively active dimers. Class 2 mutations include L597 and K601 mutations, which have been subject to several case reports demonstrating activity for MEK inhibition. Class 3 mutations, which include G466, D594, and A581 mutations, induce preferential binding to wild type RAF, and are kinase dead or have impaired kinase activity. These mutations, however, are still associated with enhanced RAS/MAPK activation, potentially due to other mechanisms such as growth factor signaling or concurrent MAPK pathway mutations (e.g., *RAS* or *NF1*) [10].

Several pre-clinical studies and isolated case reports have demonstrated impressive efficacy for MEK inhibitors in patients with non-V600 *BRAF* mutations, as well as *BRAF* fusions [12–16]. These studies, however, were largely conducted in melanoma patients (a histology where MEK inhibitors are approved therapy, and have activity in *BRAF* V600 mutant melanoma), and with class 2 mutations (specifically for L597 and K601 mutations) or fusions. Thus, a larger study to test the concept more generally was planned.

With that backdrop, we studied trametinib, a second-generation allosteric inhibitor of MEK1/2 in patients with solid tumors and lymphomas harboring mutations in *BRAF* outside the V600 codon, as well as BRAF fusions [17]. This subprotocol was a subset of the National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) study, a large platform trial with multiple parallel phase II studies that were designed to evaluate genomically-targeted therapies matched to specific genomic alterations. Per study design, 32 patients with non-V600 *BRAF* alterations (13 class 2 mutations, 19 class 3 mutations, and 1 fusion) were enrolled, and received trametinib 2 mg daily until disease progression (dose reduction permitted for severe toxicity). Patients were heavily pre-treated (69% with 3 or more lines of therapy), and most often had cancers of the lung ($n = 9$),

colon/rectum (n = 7), and prostate (n = 4). Unfortunately, activity was disappointing. Of these, one patient with breast cancer and a *BRAF* G469E mutation (class 2) had a partial response (response rate 3%), one patient with lung adenocarcinoma and a *BRAF* G469A mutation remains on therapy at 20.4 months, and an additional 3 patients had progression-free survival (PFS) of > 6 months. Median PFS and overall survival were 1.8 and 5.7 months, respectively.

Why the lack of activity? We did attempt to identify explanations within the trial data, although no subgroups had exceptionally good outcomes. Trends toward worse outcomes were noted in patients with colorectal cancer, high *BRAF* mutant allele frequency, and class 3 mutations, whereas concurrent mutations (including *RAS* mutations) did not impact outcomes. We speculate that histology does still matter, as many patients in the study had tumors that have historically been resistant to MAPK pathway inhibition (e.g., colon cancer) [18, 19], and only 1 patient had melanoma. It is possible that tumors with class 3 mutations harbored many alternative genetic and epigenetic causes of alternative cellular pathway activation, such that simply blocking MEK1/2 was not sufficient for growth attenuation [10]. Exceedingly low incidence of recurrent BRAF fusions limited enrollment of such patients (1 patient), though at least some prior case reports suggest potential for good response with MEK inhibition [13, 20, 21].

What are the next steps? First, our study does not change available data suggesting that MEK inhibition may be still considered for melanoma patients whose tumors harbor class 2 *BRAF* mutations [22, 23], or perhaps non-small cell lung cancer patients [24]. More recent studies have even suggested that combining BRAF and MEK inhibitors is the most active strategy in these patients [14, 25]. However, this is only a modestly effective solution for a small subset of these patients, and MEK inhibition cannot be recommended for most other patients with non-V600 *BRAF* mutations. Second, one approach might be studying dual blockade of MAPK pathway and other parallel signaling networks (e.g., PI3K pathway). These types of approaches, however, have neither promising activity nor safety in early studies [26–28]. However, histology specific approaches, such as combination of BRAF, MEK, and EGFR inhibition in *BRAF* V600-mutant colon cancer demonstrate, may hold promise as well [29]. Third, more complete extinguishment of MAPK signaling may hold promise. Early studies have shown that blocking the final member of the pathway, ERK, may produce responses in these patients [30]. The tolerability and generalizable response rate is not clear with ERK inhibition; a follow-up study within the NCI-MATCH is currently being conducted with the ERK inhibitor ulixertinib in this same population. Alternative RAF inhibitors could also play a role. So-called "dimer disrupting" or "paradox breaker" RAF inhibitors have also shown preliminary activity; these agents block MAPK signaling by disrupting BRAF-containing dimers, while also blocking monomeric BRAF signaling [31, 32]. This theoretically would facilitate broad targeting of MAPK-driven tumors, including *BRAF* V600, *BRAF* non-V600, and *RAS* mutant tumors. This strategy also prevents paradoxical MAPK upregulation in *BRAF* wild type cells, thus avoiding the cutaneous squamous cell cancers that are promoted by mutant specific BRAF inhibitors [33]. However, further development of this agent (PLX8394) is not clear (NCT02428712).

In conclusion, the activity of MEK inhibition (specifically, trametinib) outside the narrow window of patients with melanoma and class 2 mutations, does not appear robust in cancers harboring non-V600 *BRAF* mutations. Innovative approaches to block parallel signaling networks or more thorough downstream MAPK pathway activation may hold promise for this challenging population.

CONFLICTS OF INTEREST

DBJ serves on advisory boards for Array Biopharma, BMS, Catalyst, Jansen, Iovance, Merck, and Novartis, and receives research funding from BMS and Incyte.

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