Old Habits Die Hard: Addiction of BRAF-Mutant Cancer Cells to MAP Kinase Signaling

Catherine B. Meador¹ and William Pao¹,²

Summary: Dual and triple combination therapies with RAF inhibitors plus other targeted agents have demonstrated promising clinical utility in BRAFV600E/mutant solid tumors. However, despite vertical inhibition at multiple nodes on the MAPK signaling pathway, resistant tumors emerge. Ahronian and colleagues show that in BRAFV600E-mutant colorectal cancer, resistance involves reactivation of RAS/RAF/MEK/ERK signaling and may be overcome by newly emerging ERK inhibitors. Cancer Discov; 5(4): 348–50. © 2015 AACR.

See related article by Ahronian et al., p. 358 (4).
Figure 1. Schematic representation of mechanisms of resistance to BRAF/EGFR or BRAF/MEK inhibitor combinations in BRAF<sup>V600</sup>-mutant colorectal cancer (CRC). **A**, comparison of response of BRAF<sup>V600</sup>-mutant melanoma versus colorectal cancer to single-agent BRAF inhibition. Left, BRAF inhibitors (BRAFi) effectively inhibit MAPK signaling and induce tumor regression in over half of BRAF<sup>V600</sup>-mutant melanomas, when used as monotherapy. Mechanisms of resistance in nonresponsive tumors are not depicted. Right, BRAF inhibitors result in reactivation of EGFR-mediated MAPK signaling in BRAF<sup>V600</sup>-mutant colorectal cancer, contributing to the low overall response rate to single-agent BRAF inhibition. **B**, mechanisms of resistance to various combinations of BRAF/EGFR or BRAF/MEK inhibitors were identified by Ahronian and colleagues via in vitro modeling of acquired resistance or analysis of tumor samples after progression on combination therapy. KRAS<sub>G12D/G13D</sub> mutations and amplification of wild-type KRAS or mutant BRAF were found to confer resistance to dual inhibition of BRAF/EGFR and BRAF/MEK. A MEK<sub>F53L</sub> substitution mutation was found to confer resistance to dual BRAF/MEK inhibition. All models of resistance to combination BRAF/EGFR and BRAF/MEK inhibition retained sensitivity to ERK inhibition.

was switched to the BRAF/EGFR (encorafenib/cetuximab) regimen. This finding further validates the authors’ in vitro result that KRAS-mediated activation of MAPK signaling can confer cross-resistance to both BRAF/MEK and BRAF/EGFR inhibition.

In addition, the authors identified co-occurring acquired missense mutations in MEKI and ARAF in a BRAF<sup>V600</sup>-mutant colorectal cancer sample with acquired resistance to BRAF/MEK inhibition (dabrafenib/trametinib). Follow-up in vitro analysis revealed that the MEKI<sub>F53L</sub> mutation, but not the ARAF<sub>Q489L</sub> mutation...
mutation, was sufficient to confer resistance to dabrafenib/ trametinib in vitro, although the two mutations were not tested for cooperativity within the same cell (Fig. 1B). As the authors point out, this result highlights a separate important principle regarding the significance of findings revealed by comprehensive mutational profiling, i.e., that thorough and efficient biologic validation of novel mutations is critical to distinguish passenger versus driver mutations, especially when two obvious signaling molecules in the same pathway harbor mutations.

Taken together, the translational data from Aharonian and colleagues (4) have multifaceted implications for our ongoing understanding of the underlying biology and clinical treatment of BRAFV600-mutant tumors. Context-dependent differences in sensitivity to single-agent RAF inhibition reveal varying levels of “addiction to mutant BRAF signaling” across histologic subtypes. These differences appear to extend to the setting of combination therapies as well. Although combined BRAF/EGFR and combined BRAF/MEK inhibition thus far demonstrate improved clinical outcomes in BRAF-mutant colorectal cancer compared with BRAF inhibition alone, response rates to combination therapy still range from 12% to 29% only. By comparison, compared with BRAF inhibition alone, response rates to combined BRAF/MEK inhibition thus far demonstrate a response rate of 64% (8). Biologic mechanisms underlying these phenomena are not yet fully understood but could be explained by differences in factors such as cell lineage, epigenetics, and microenvironment of the tumor. The 12% to 29% response rate indicates that it will take more than dual combination therapy to target BRAFV600-mutant colorectal cancer to the same extent as BRAFV600-mutant melanoma; however, it is also evident that even in BRAFV600-mutant melanoma, dual BRAF/MEK inhibition is not curative.

Finally, the authors of this study leave us with the hope that newly developed ERK inhibitors may successfully overcome MAPK-driven resistance to combined BRAF/EGFR or BRAF/MEK inhibition in BRAFV600-mutant colorectal cancer. Recent preclinical studies have also demonstrated that ERK inhibitors may be effective at overcoming acquired resistance to BRAF/MEK inhibition in BRAFV600-mutant melanoma (9). It remains to be seen whether ERK inhibitors will be effective in overcoming all mechanisms of resistance to BRAF/MEK/ EGFR–targeted therapies, as well as whether ERK inhibitors will be useful as first-line therapies across different histologic groups of BRAF-mutant tumors. Factors mediating sensitivity to ERK inhibition will probably vary according to cellular context, as we have seen with BRAF inhibitors. Biomarkers of sensitivity to ERK inhibition will be important as clinicians are faced with questions about how best to administer these therapies to provide maximal benefit to patients.

These studies spark a broader discussion regarding the utility of monotherapy versus combination therapy in personalized cancer medicine. Maximizing combination therapy in the first-line setting makes intuitive sense, with the goal being to limit any residual resistant disease that will ultimately result in tumor progression or recurrence. However, the current reality in metastatic solid tumors is that resistance almost invariably develops for the targeted agents in clinical use. It remains to be seen whether the addition of new “downstream” ERK inhibitors will result in longer time to resistance. It is also unknown whether resistance to such newer therapies will result in more aggressive tumors that are unresponsive to other targeted agents (10).

In the case of BRAFV600-mutant colorectal cancer, for example, the addition of an ERK inhibitor to the BRAF/MEK or BRAF/ EGFR combination could significantly extend progression-free survival. However, if acquired resistance after the addition of an ERK inhibitor occurs within a similar time frame as seen with BRAF/MEK and BRAF/EGFR inhibitor combinations, a patient could potentially benefit from receiving the dual inhibitor combination first, followed by an ERK inhibitor once the tumor has progressed. The question of which strategy will provide the best outcome for patients can only be answered clinically. In the meantime, studies such as those performed by Aharonian and colleagues (4) are critical to pave the road ahead.

Disclosure of Potential Conflicts of Interest

W. Pao is Global Head, Oncology Discovery and Translational Area, at Roche; reports having received commercial research grants from AstraZeneca, Bristol-Myers Squibb, and Symphogen; and has been a consultant/advisory board member for AstraZeneca, Bristol-Myers Squibb, and Exelixis. No potential conflicts of interest were disclosed by the other author.

Grant Support

The authors acknowledge support from the NIH grants R01-CA12120 and P01-CA129243.

Published online April 6, 2015.

REFERENCES

Old Habits Die Hard: Addiction of *BRAF*-Mutant Cancer Cells to MAP Kinase Signaling

Catherine B. Meador and William Pao


**Updated version**

Access the most recent version of this article at:

http://cancerdiscovery.aacrjournals.org/content/5/4/348

**Cited articles**

This article cites 6 articles, 2 of which you can access for free at:

http://cancerdiscovery.aacrjournals.org/content/5/4/348.full#ref-list-1

**Citing articles**

This article has been cited by 1 HighWire-hosted articles. Access the articles at:

http://cancerdiscovery.aacrjournals.org/content/5/4/348.full#related-urls

**E-mail alerts**

Sign up to receive free email-alerts related to this article or journal.

**Reprints and Subscriptions**

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

**Permissions**

To request permission to re-use all or part of this article, use this link http://cancerdiscovery.aacrjournals.org/content/5/4/348.

Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.