In-Review: Two New Melanoma Agents Approved

Utilizing genetic abnormalities, new therapies are carving out new possibilities for melanoma treatment.

BY JONATHAN WOLFE, MD

“The treatment realm for melanoma was given a boost recently, with the FDA approvals of two new therapies: dabrafenib (Tafinlar, GlaxoSmithKline) and trametinib (Mekinist, GlaxoSmithKline). Both are oral agents and together they represent a potentially new threshold in melanoma care. While not directly related to dermatologists, these are the first therapies to utilize genetic abnormalities for treatment-guided purposes. Moreover, they are drastically changing the way melanoma is treated and approached.

UNDERSTANDING BRAF AND MEK
Dabrafenib is the second BRAF inhibitor approved for melanoma, after vemurafenib (Zelboraf, Genentech). It has demonstrated efficacy in patients with BRAF mutant melanoma, but more recently, the BREAK-MB trials have shown evidence of disease activity in patients with metastatic melanoma brain metastases and potential abrogation of BRAF inhibitor resistance.1

There has been some concern regarding toxicity associated with BRAF treatment, particularly from the standpoint of reported rates of cutaneous squamous cell carcinoma (SCC) resulting from treatment.2 While both agents have previously been shown to have similar efficacy, authors of a recent study note that some disparities have arisen regarding SCC toxicity.2 They cite emerging reports of non-cutaneous malignancies propagated by BRAF inhibitors that are of some concern, especially since BRAF inhibitors are thought to be driven by the same process that leads to SCC.2 The true relative prevalence of SCCs with vemurafenib and dabrafenib may inform the relative risk of other non-cutaneous malignancies with these drugs, which should serve to influence clinical management and drug design.

On the other hand, trametinib is an oral Mitogen-activated protein kinase (MEK) inhibitor, which has been found to be an effective agent.3 One recent study assessed the potential of trametinib in combination with gemcitabine for advanced solid tumors and showed good efficacy results.3 The authors noted that while most toxicities were manageable, the addition of trametinib may possibly increase gemcitabine-associated myelosuppression. Thus, they recommended that future studies of this combination will require monitoring to maintain dose and schedule.

A New Zealand study recently compared responses of melanoma cell lines to MEK and BRAF inhibitors and found...
that cell lines sensitive to vemurafenib were also sensitive to trametinib. These findings support the notion that MEK inhibitors might be combined with BRAF inhibitors in the treatment of melanomas with activated BRAF. Moreover, given the high sensitivity to trametinib of some lines with wildtype BRAF status, the study indicates that MEK inhibitors could have a therapeutic effect against some melanomas as individual agents.

While the ability to target the mitogen-activated protein kinase (MAPK) pathway with BRAF or MEK inhibitors can result in rapid clinical benefit, there may be limited durability of response coupled with resistance developing either via re-activation of the MAPK pathway or via bypass signalling pathways; combination approaches have been proposed to increase efficacy and overcome resistance mechanisms. Specifically, the combination of dabrafenib and trametinib has shown promising results clinically and with an improved toxicity profile. Other combination strategies with agents that target the PI3K pathway, angiogenesis, and the immune system are in development or already underway, but it’s worth pointing out again that potential overlapping toxicities require close monitoring.

**DISCUSSION**

The data for both dabrafenib and trametinib are still somewhat limited, particularly regarding toxicities. However, they have each shown encouraging enough efficacy numbers to secure approvals and will continue to be examined under a variety of circumstances. While therapeutic limitations continually define melanoma treatment, the approval of these agents is a signal of hope that researchers and clinicians are gaining newer and deeper understandings of melanoma. Hopefully this will result in the study of new agents and pathways that increase the survival of our patients.

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**Dr. Wolfe has no relevant disclosures.**

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