

MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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Is There a Role for Single-Agent MEK Inhibition in Melanoma?



Douglas Johnson, MD, MSCI
Assistant Professor of Medicine
Clinical Director, Melanoma
Vanderbilt-Ingram Cancer Center
Nashville, Tennessee

H&O Which MEK inhibitors have been approved for use in melanoma?

DJ The US Food and Drug Administration has approved 2 MEK inhibitors for use in advanced *BRAF* V600-mutant melanoma: trametinib (Mekinist, Novartis) and cobimetinib (Cotellic, Genentech). Trametinib is approved for use as a single agent and in combination with the BRAF inhibitor dabrafenib (Tafinlar, Novartis), whereas cobimetinib is approved for use only in combination with the BRAF inhibitor vemurafenib (Zelboraf, Genentech/Daiichi Sankyo).

H&O What makes MEK inhibition a good approach in melanoma?

DJ Researchers have been fascinated by the possibilities of MEK inhibition in melanoma because the mitogen-activated protein kinase (MAPK) signaling pathway is activated in most melanomas. This pathway is activated through a variety of different genetic mechanisms, including mutated *BRAF* V600, other less common *BRAF* mutations, mutated *NRAS*, and mutations in *NFI*. As a result, using MEK inhibitors—either as monotherapy or in combination with other agents—is a very rational treatment strategy in melanoma.

The clinical experience has shown that MEK inhibitors are variably effective in these genetically defined subsets of melanoma, and they remain attractive in these patients—at least as part of combination therapy.

H&O What are the most important studies of MEK inhibition in melanoma?

DJ Regarding monotherapy, the study by Flaherty and colleagues that appeared in the *New England Journal of Medicine* in 2012 is the one that led to the approval of trametinib for use in patients with advanced *BRAF* V600-mutated melanoma. This was a phase 3 study that found that trametinib improved response rates, progression-free survival, and overall survival in these patients compared with conventional cytotoxic chemotherapy. Importantly, this improvement in overall survival occurred even though patients were allowed to cross over from chemotherapy to trametinib.

Several studies also established the use of combination therapy in patients with *BRAF*V600-mutated melanoma. A phase 1 and 2 study by Flaherty and colleagues that appeared in the *New England Journal of Medicine* in 2012 found that trametinib/dabrafenib improved progression-free survival and response rates compared with dabrafenib alone. A phase 3 study by Larkin and colleagues that was published in the same journal in 2014 found that cobimetinib/vemurafenib improved progression-free survival compared with vemurafenib alone. Finally, a study by Long and colleagues that appeared in the *Lancet* in 2015 found that trametinib/dabrafenib improved overall survival compared with dabrafenib alone.

More recently, Dummer and colleagues presented a study at the 2016 annual meeting of the American Society of Clinical Oncology (ASCO) that compared the experimental MEK inhibitor binimetinib vs chemotherapy using dacarbazine in treatment-refractory melanoma. The patients in this study, called NEMO (*NRAS*-Mutant Melanoma), had *NRAS* mutations rather than *BRAF* mutations. This trial is particularly important because *NRAS* mutations occur in approximately 15% to 20% of

melanomas, and at this time we do not have any approved targeted approaches for these patients.

This study found improvements in progression-free survival, overall response rate, and disease control rate with the use of binimetinib, which suggests that MEK inhibitors may have some benefit in patients with *NRAS*-mutated melanoma. The researchers were unable to show an improvement in overall survival, however. It is possible that improved overall survival will occur with longer follow-up; we will need to see the final results of this study before conclusively evaluating the efficacy of binimetinib in this setting.

H&O What are the main side effects of MEK inhibitors?

DJ MEK inhibitors are fairly well tolerated overall. The main side effects that we see are acneiform rash, gastrointestinal symptoms, nausea, and peripheral edema. Rare

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side effects include decreased cardiac ejection fraction and retinal events. Interestingly, BRAF inhibitors also produce many cutaneous events when given as single agents, including squamous cell carcinoma and various types of skin eruptions due to paradoxical MAPK signaling activation. MEK inhibitors, by contrast, cause a hypoproliferative acneiform rash due to MAPK inhibition. When used in combination, these effects cancel each other out and cutaneous toxicities are substantially decreased.

H&O What are the main limitations of their use?

DJ The main limitation of MEK inhibitors is that they are less effective on their own than in combination with BRAF inhibitors. They also have limited activity in most patients with *BRAF*-wild-type melanoma. Another limitation is that the role of MEK inhibitors has diminished now that immunotherapy has become a frequent first-line treatment approach for patients with melanoma. Finally, both BRAF and MEK inhibitors usually are associated with acquired resistance that occurs after a median of 9

to 12 months when given in combination, although it is becoming increasingly clear that a subset of patients experience prolonged benefit with these agents that can persist for years. In a study by Long and colleagues that recently appeared in the *Journal of Clinical Oncology*, approximately 20% of patients had excellent outcomes and were alive and progression-free 3 years after starting therapy.

H&O Given the availability of immunotherapy and the use of BRAF/MEK inhibitor combinations, is there still a role for single-agent MEK inhibition in melanoma?

DJ Going forward, I think the role for single-agent MEK inhibition in melanoma is likely to be in specific genetic subsets. For example, the NEMO study mentioned earlier ultimately may lead to approval of a single-agent MEK inhibitor for use in patients with *NRAS*-mutant melanoma. The use of MEK inhibitors also may prove to be an active approach in patients with atypical *BRAF* mutations. Approximately 5% of melanomas have non-V600 mutations in *BRAF*. A number of case reports have pointed to single-agent MEK inhibition as a highly active treatment approach for those patients. Another group that may benefit from single-agent MEK inhibition is the 1% of patients with melanoma who have activation of the MAPK signaling pathway caused by *BRAF* gene fusions.

H&O Which experimental MEK inhibitors are being studied for use in melanoma?

DJ Binimetinib, the agent that was compared with dacarbazine in *NRAS*-mutant cutaneous melanoma in the NEMO study, is the one that is furthest along. The agent selumetinib also is being studied in uveal melanoma, although a recent study by Carvajal and colleagues found that the agent had a modest effect on progression-free survival and response rate compared with chemotherapy but no improvement in overall survival.

H&O What other emerging combination approaches are being used with MEK inhibitors?

DJ A number of emerging combinations are very interesting, including the combination of MEK inhibition plus inhibition of CDK4/6 with palbociclib (Ibrance, Pfizer) or ribociclib (formerly LEE011). Another interesting combination is MEK inhibition plus immunotherapy. MEK inhibitors seem to enhance the presentation of antigens on the tumor, which has the potential to make immunotherapy more active.

There was a presentation by Bendell at the most recent ASCO annual meeting that was very provocative, in which

cobimetinib plus the programmed death ligand 1 (PD-L1) inhibitor atezolizumab (Tecentriq, Genentech) produced responses in colorectal cancer that were far better than what would be expected with either agent alone—the response rate was 17%.

Finally, we have seen a lot of interest in combining MEK inhibitors with agents that block the phosphoinositide 3-kinase (PI3K) pathway. So far the results of these studies have been disappointing, but it is possible that we simply have not yet found the right combination of MEK inhibitors and PI3K pathway inhibitors.

H&O What would you say is the future of MEK inhibition in melanoma?

DJ Based on the fact that MAPK signaling is present in essentially all melanomas, I think that MEK inhibitors are a very attractive agent for use in combination therapy strategies. Although monotherapy is unlikely to play a major role in melanoma, it will continue to be used in a small subset of melanomas, at least in the near future.

H&O What role might MEK inhibitors play in other types of cancer besides melanoma?

DJ The MAPK signaling pathway is activated in numerous cancers, so a number of studies are looking at the use of MEK inhibitors in patients with *KRAS*-mutated lung or pancreatic cancers. Another important study is the NCI-MATCH trial from the National Cancer Institute (NCI Molecular Analysis for Therapy Choice; NCT02465060), in which researchers perform next-generation sequencing and then match patients' molecular and genetic tumor alterations with the appropriate molecularly targeted therapy.

I am the principal investigator for the arm evaluating trametinib in patients with atypical *BRAF* mutations and fusions. Additional arms are addressing MEK inhibitors in patients with mutations in *NF1*, *GNAQ*, and *GNA11*, and one arm is looking at the use of a MEK inhibitor plus a CDK4/6 inhibitor for patients with *NRAS* mutations.

NCI-MATCH should give us a good sense of whether MEK inhibition can be an effective treatment strategy in patients with these atypical *BRAF* mutations not just in melanoma, but across a variety of tumor types.

Disclosures

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