MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

Section Editor: John M. Kirkwood, MD

Molecular Approaches to Tumor Inhibition in Melanoma

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H&O What molecular agents are currently available for use in melanoma?

MD The US Food Administration (FDA) has approved several molecularly targeted agents for use in patients with metastatic melanoma who have *BRAF* V600 mutations. First came vemurafenib (Zelboraf, Genentech/Daiichi Sankyo), an inhibitor of the mutant BRAF protein, which was approved in 2011. Next came dabrafenib (Tafinlar, Novartis), a second mutant-specific BRAF inhibitor, which was approved in 2013. Then came trametinib (Mekinist, Novartis), an inhibitor of MEK, which is activated by the mutant form of BRAF. It was approved as a single agent in 2013. The combination of dabrafenib and trametinib was approved in 2014, and the combination of the MEK inhibitor cobimetinib (Cotellic, Roche) and vemurafenib was approved in November of this year, in both cases for the treatment of patients with metastatic melanoma and the *BRAF* V600 mutation.

H&O What targeted agents are being used off label in melanoma?

MD KIT inhibitors are FDA-approved for use in certain cancers that are characterized by frequent mutations in the c-*KIT* gene, such as gastrointestinal stromal tumors (GISTs). A number of case reports and recent clinical trials have demonstrated that those same KIT inhibitors can have clinical activity in patients with metastatic melanoma who have c-*KIT* mutations. c-*KIT* mutations occur frequently in patients with mucosal melanomas and acral lentiginous melanomas, and rarely in patients with cutaneous melanomas. Probably the most commonly used KIT inhibitor is imatinib (Gleevec, Novartis).

H&O Does developing new molecular agents for melanoma continue to be an active area of research?

MD Yes, and it remains an important area. Melanoma has a higher rate of mutations than any other cancer, and virtually every patient with melanoma has detectable genetic aberrations. A number of these mutations could be targetable.

Research in the area of molecularly targeted agents for melanoma falls broadly into 2 categories. The first effort is focused on the development of new agents that either will make the FDA-approved BRAF and MEK inhibitors more effective, or will work in patients with *BRAF* 600 mutations after failure of FDA-approved therapies. The second area of research is the identification of therapeutic approaches that are effective for patients who do not have the *BRAF* V600 mutation.

H&O What specific tools have been developed that have aided our understanding of genomic alterations?

MD The use of targeted therapies in melanoma was predicated upon the development of platforms and technologies that allow the detection of mutations in tumors clinically. Whereas molecular testing in most melanoma centers initially was performed by testing 1 gene at a time, now it has evolved so that increasingly

large and broad mutation panels are being evaluated in patients with metastatic melanoma and other cancers. The increasing availability of these panels is leading to a better understanding of the molecular diversity and heterogeneity of melanoma, and the identification of many new potentially targetable mutations in patients with this disease.

H&O What somatic mutations are being found in melanoma that could be potential targets for molecular agents?

MD We certainly have proof of concept—via what we have accomplished with the *BRAF* V600 mutation—that oncogenic mutations that drive tumor growth can be good therapeutic targets in this disease. A number of other mutations appear to drive tumor growth and therefore may be beneficial to target. For example, clinical trials are currently testing the hypothesis that MEK inhibitors are effective in patients with non-V600 mutations in the *BRAF* gene in their tumors. Mutations in cell cycle regulators, including alterations in *CDKN2A, CDK4,* and *CCND1*, also have been implicated as predictors of sensitivity to CDK4 inhibitors in preclinical studies in human melanoma cell lines, as in work published by Young and colleagues in 2014.

Mutations in *NRAS* are relatively common in melanoma and are detected in 20% to 25% of cutaneous melanomas. Preclinical studies have shown that MEK inhibitors can be effective for such tumors, but multiple studies (including work by Kwong and colleagues in *Nature Medicine*) suggest that they will need to be combined with other targeted therapies to achieve clinical efficacy. A number of trials that are testing combinations of targeted therapies are open specifically for patients with *NRAS* mutations. These approaches may also be effective for patients who have tumors with loss-of-function mutations in the *NF1* gene, as NF1 is a negative regulator of RAS.

Mutations in growth factor receptors also occur frequently in melanoma. As noted earlier, the KIT receptor tyrosine kinase is mutated in 15% to 30% of mucosal melanomas and acral lentiginous melanomas, and clinical trials have demonstrated that a subset of patients with these mutations respond to KIT inhibitors. Mutations are also detected frequently in other growth factor receptors for which there are active inhibitors (ie, the epidermal growth factor receptor). However, the translation of this information is complicated by the fact that many of the mutations that are identified in these and other genes in melanoma have never been reported before. Thus, it is often unknown whether those mutations will predict benefit from targeted therapies.

H&O How does metastasis of tumors affect these mutations?

MD This is an area of research that has been inadequately studied to date. There are data to support high concordance between primary tumors and metastases for *BRAF* V600 mutations and for *NRAS* mutations. We have very limited data, however, on the concordance of most other mutations that have been detected in this disease.

H&O What should oncologists do for a patient who has a genetic alteration with a targeted treatment that is indicated for a different type of cancer?

MD That question is becoming more and more clinically important, particularly as molecular testing platforms become more readily available. As we discussed earlier, KIT inhibitors achieve high response rates in patients with GIST who have somatic mutations in c-*KIT*. In contrast, only 10% to 30% of patients with melanoma who have c-*KIT* mutations respond to these agents. This rate is actually much higher than the response rates observed with KIT inhibitors in unselected patients with metastatic melanoma, so it does support the potential benefit of molecular screening. However, more studies are needed to determine the benefit of targeted agents for patients with melanoma who have mutations in actionable genes.

H&O How should genotype-selected trials be designed?

MD Genotype-selected trials for melanoma should take into account specific mutations, not just which genes are mutated. We are still determining the best way to characterize mutations in different genes, and how to predict their likely impact on the function of the proteins that they encode. Only by appropriately stratifying the mutations that we detect in patients' tumors can we design meaningful clinical trials to test the efficacy of inhibiting those targets.

H&O Could you talk about ASCO's TAPUR (Targeted Agent and Profiling Utilization Registry) study?

MD This interesting initiative is taking on the challenge of determining the clinical benefit of detecting mutations that may be targetable, particularly by FDA-approved targeted therapies that are available for use in other diseases. In this protocol, a participant who is found by molecular testing to have such a mutation can be matched up to a corresponding targeted therapy

if one is available. Patients receive the medication free of charge. This type of study can let us know whether various mutations match up with sensitivity to specific therapies across different cancer types.

Identifying mutations that benefit from molecularly targeted therapy is particularly important in melanoma because, as I mentioned, many of the mutations that are detected in this disease are of unknown functional significance. This trial addresses the limitation that many of these mutations are uncommon by making targeted treatment broadly available to patients. In the long run, the trial should provide important information to help us guide the use of appropriate and optimized personalized therapeutic approaches.

H&O What other studies in this area are important?

MD The National Cancer Institute is running a trial of precision medicine called NCI-MATCH (NCI-Molecular Analysis for Therapy Choice). Another important study is the MPACT (Molecular Profiling-Based Assignment of Cancer Therapy) trial, which also is trying to optimize the use of molecular testing to guide patients to effective therapeutic approaches. These are challenging trials for melanoma because of the high mutation rate that we see in this disease, but they provide the opportunity for patients without *BRAF* V600 mutations to be matched up to new therapeutic approaches that may be beneficial.

H&O Is there anything that you would like to add?

MD The increasing availability of molecular profiling provides an important opportunity to improve outcomes in patients with melanoma. Certainly there are many challenges to this, but also many opportunities. One of the emerging areas of research is investigating whether this information can be used not only to guide patients to targeted therapies, but also to optimize the use of immunotherapy in melanoma. Immunotherapy is the other primary therapeutic modality used for patients with metastatic melanoma.

This is an exciting time in melanoma treatment, with many effective therapies becoming available. Addressing the need to personalize and optimize the treatment for each patient is a very active and important ongoing field of research.

Suggested Readings

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