MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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What Is Optimal First-Line Treatment of Unresectable or Advanced *BRAF*-Mutant Melanoma?

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H&O How common are *BRAF* mutations in patients with melanoma?

MA Approximately 50% of patients with melanoma have a V600E or V600K mutation in *BRAF*, each of which has been shown to affect response to treatment. An additional 10% of patients have other mutations in *BRAF* that go undetected by the standard assays but can be seen with the use of next-generation sequencing. We do not know how these other mutations affect response to treatment.

H&O What are the differences in presentation between *BRAF*-mutant melanoma and *BRAF*–wild-type melanoma?

MA *BRAF*-mutant melanomas tend to develop in preexisting moles. They also tend to affect younger patients; 70% to 80% of the patients who are younger than 30 years when melanoma develops have *BRAF*-mutant tumors. Conversely, *BRAF*–wild-type melanomas tend to develop in heavily sun-damaged skin. They tend to affect older patients, especially those aged 70 years and older. Most acral and nearly all mucosal melanomas are *BRAF*–wild-type.

As far as prognosis is concerned, acral melanomas and mucosal melanomas tend to have a worse prognosis than other melanomas, so patients with *BRAF*–wild-type melanoma may have a worse outcome. Among patients with *BRAF*–wild-type melanoma, those with *NRAS*-mutant melanoma have the worst prognosis.

H&O Which agents are approved for the first-line treatment of patients with *BRAF*-mutant melanoma?

MA Dabrafenib (Tafinlar, Novartis) and the MEK inhibitor trametinib (Mekinist, Novartis) are approved for use alone or in combination for patients with *BRAF*-mutant melanoma; oncologists generally use the combination. Vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) can be used alone or in combination with the MEK inhibitor cobimetinib (Cotellic, Genentech) for *BRAF*-mutant melanoma. This combination is used less frequently because it was only recently approved.

The checkpoint inhibitors ipilimumab (Yervoy, Bristol-Myers Squibb), pembrolizumab (Keytruda, Merck), and nivolumab (Opdivo, Bristol-Myers Squibb), as well as a combination of nivolumab and ipilimumab, also are approved for the first-line treatment of patients with advanced melanoma, including those with *BRAF*-mutant tumors. Other approaches that are approved as first-line treatment but rarely used are high-dose interleukin 2 and talimogene laherparepvec (Imlygic, Amgen), which is often called T-VEC.

We also can use chemotherapy agents for melanoma, such as carboplatin, paclitaxel, nab-paclitaxel (Abraxane, Celgene), and dacarbazine, but chemotherapy is rarely used in melanoma now that better options are available.

H&O What is the optimal approach for individualized treatment of patients with *BRAF*-mutant melanoma?

MA I usually make the argument in debates for immunotherapy because it produces durable responses and because it works as well in *BRAF*-mutant melanoma as it does in *BRAF*–wild-type melanoma. In addition, data presented at the 2015 American Society of Clinical Oncology (ASCO) annual meeting by Jedd Wolchok and by Steven Hodi showed that a combination of ipilimumab and nivolumab produces response rates nearly as good as those seen with dabrafenib plus trametinib, and the responses tend to be more durable.

At the same time, there is an argument to be made for prioritizing BRAF inhibitors. First of all, BRAF inhibitors are more reliable because they work in nearly everybody with *BRAF*-mutant melanoma. In addition, they probably begin working faster. As long as patients can swallow, they can take these drugs even if they are very sick, and the BRAF inhibitors seem to be better tolerated overall than immunotherapy. Finally, they appear to have a reasonable duration of benefit when used in combination.

Patients with a normal lactate dehydrogenase (LDH) level tend to have the best prognosis no matter what treatment they receive. Although combination treatment with a BRAF/MEK inhibitor traditionally has been felt to work best in patients with an elevated LDH level, new data on dabrafenib and trametinib from Georgina Long and colleagues, published in the *Journal of Clinical Oncology*, support the idea that patients with a lower LDH level should be the ones to receive a BRAF inhibitor. In this study, approximately 75% of patients with normal LDH levels were alive at 2 years and 62% were alive at 3 years.

As for combination therapy with ipilimumab plus nivolumab, we have data from the CA209-004 trial (Dose-Escalation Study of Combination BMS-936558 and Ipilimumab in Subjects With Unresectable Stage III or Stage IV Malignant Melanoma), published in the *New England Journal of Medicine* in 2013 by Jedd Wolchok and updated at the 2014 ASCO and 2015 Society for Melanoma Research annual meetings by Mario Sznol. These data suggest that patients with a normal LDH level do best with the combination of ipilimumab and nivolumab, which produces a 2-year survival rate of approximately 80%. Those patients with an elevated LDH level also do remarkably well with the combination, which produces a survival rate of approximately 61% at both 1 and 2 years. Based on these data, patients with elevated LDH appear to fare especially well in the long run with immunotherapy rather than with BRAF inhibitor therapy.

These findings have caused some confusion as to which treatment is most appropriate for a particular group of patients. Although previously we would have recommended BRAF inhibitor therapy for patients with more aggressive disease and immunotherapy for those with less aggressive disease, this in fact may not be the best approach.

H&O How should the various agents be sequenced?

MA We do not know the best approach. If a patient receives a BRAF inhibitor first and then symptomatic progression develops, a full course of immunotherapy may not be possible. In addition, data from Ackerman and colleagues, Robert and colleagues, and Weber and colleagues suggest that immunotherapy works better in patients undergoing first-line treatment than in those whose tumors have become resistant to BRAF inhibitors. Those are arguments in favor of using immunotherapy first. In addition, there is a tail on the curve for patients with an elevated LDH level if they receive immunotherapy; this is not seen with BRAF inhibitor approaches, so perhaps these are the patients who should receive immunotherapy first.

On the other hand, because the effects of immunotherapy persist in the body for a long time, toxicity may be accentuated when BRAF inhibitors are given after immunotherapy rather than up front.

In light of this confusing information, we decided to undertake a national clinical trial of patients with *BRAF*-mutant melanoma and LDH levels as high as 10 times the upper limit of normal (Dabrafenib and Trametinib Followed by Ipilimumab and Nivolumab or Ipilimumab and Nivolumab Followed by Dabrafenib and Trametinib in Treating Patients With Stage III-IV BRAFV600 Melanoma; NCT02224781). Patients are being randomly assigned to either the BRAF/MEK inhibitor first and ipilimumab/nivolumab at the time of disease progression, or the converse. We are examining baseline LDH levels and various other clinical characteristics to see how they may correlate with response and long-term survival. The trial is open and accruing patients; it should be a priority for everybody in the melanoma research community to encourage eligible patients to enroll so that we can definitively address these unknowns.

H&O When should single-agent therapy be used rather than combination therapy?

MA Nobody should be using single-agent BRAF inhibitor therapy anymore; these agents should always be combined with a MEK inhibitor in patients who have advanced melanoma. The question of whether combination immunotherapy is better than monotherapy is more complicated. My view, which probably is still the minority view, is that everybody who is able to tolerate the toxicity of combination immunotherapy should receive it. The data that Wolchok and colleagues published in the *New England Journal of Medicine* suggest that combining immunotherapy agents increases the number of

tumor responses, including complete responses, and also improves the amount of tumor shrinkage. The increase in toxicity with combination immunotherapy scares clinicians, but I need to emphasize that this is potentially curative therapy. If patients experience more side effects from treatment but also have more cures—meaning fewer cancer-related complications—that is a worthwhile trade-off. In general, I think we do a better job at treating the toxicities of immunotherapy than we do at managing treatment-resistant melanoma.

H&O What treatment approach should be used for patients who are not eligible for the trial?

MA Every patient who is eligible should be enrolled in the trial. But if patients are not eligible for the trial because they have an autoimmune disease or because their performance status is 3, their only option is targeted therapy. Patients with extensive brain metastases are not eligible for the trial, but they may be able to participate in an alternative immunotherapy trial if they have no more than 3 brain metastases and the lesions are not too large (CA209-204; A Multi-Center Phase 2 Open-Label Study to Evaluate Safety and Efficacy in Subjects With Melanoma Metastatic to the Brain Treated With Nivolumab in Combination With Ipilimumab Followed by Nivolumab Monotherapy; NCT02320058). If they have more widespread central nervous system (CNS) disease, it might make more sense to try to control the CNS disease with stereotactic radiation and/or BRAF inhibitor therapy before immunotherapy is considered.

H&O What other factors play a role in treatment decisions for these patients?

MA Logistics and reimbursement issues affect our decisions. Other factors include toxicity, survival curves, the tumor microenvironment, options for salvage therapy, and quality-of-life issues—all of which are being addressed in the trial. The sooner we complete the trial, the sooner we can answer these questions.

Suggested Readings

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