MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

Section Editor: Sanjiv S. Agarwala, MD

Immunotherapy in the Adjuvant Setting for High-Risk Melanoma

Jeffrey S. Weber, MD, PhD
Laura and Isaac Perlmutter Professor of Oncology
NYU School of Medicine
New York, New York

H&O Which patients with melanoma are at elevated risk for a recurrence after surgical resection?

JW A patient at elevated risk is one whose 5-year risk for recurrence is 33% or higher. That applies to anyone with an ulcerated primary lesion, meaning stage IIC or later, and anyone with more than 1 mm of disease in a sentinel lymph node.

At the most recent annual meeting of the American Association for Cancer Research (AACR), Lex Eggermont presented very convincing data suggesting that patients who have more than 1 mm of tumor in the sentinel lymph node need further therapy. He and his coinvestigators found that the relapse rate in these patients without therapy is approximately 25% at 18 months, which suggests that it will be higher than 33% by 5 years.

H&O Which patients with resected melanoma are eligible for adjuvant therapy?

JW Patients with resected *BRAF*-positive stage III disease are eligible for adjuvant treatment with dabrafenib (Tafinlar, Novartis) and trametinib (Mekinist, Novartis); the US Food and Drug Administration (FDA) approved the combination for this use in April. Patients with resected stage III or IV disease have been eligible for adjuvant treatment with nivolumab (Opdivo, Bristol-Myers Squibb) since December 2017. In other words, we can offer adjuvant treatment to a patient with stage IIIA disease. Ipilimumab (Yervoy, Bristol-Myers Squibb) is also approved as adjuvant therapy in patients with resected stage III disease, but it has fallen out of use in these patients because CheckMate 238 (Efficacy Study of Nivolumab Compared to Ipilimumab in Prevention of Recurrence of Melanoma After Complete Resection of Stage IIIb/c or Stage IV Melanoma) clearly showed that nivolumab is significantly more effective in terms of relapse-free survival—both statistically and clinically—than ipilimumab. It is also less toxic.

Is it worth treating a patient with a stage IIIA tumor and 1 mm or less of disease in the sentinel lymph node? The 10-year melanoma-specific mortality rate for these patients is less than 10%. If we could cut that rate from 10% to 5%, for example, we would be treating 20 patients to benefit one. Does that warrant treatment, when the chance of benefit is less than the chance of some significant toxicity? I do not encourage the use of adjuvant therapy in a patient with early stage IIIA disease unless the patient is very young—younger than 30 years—and has 1 mm or less of disease in the sentinel lymph node. Although I would be willing to give adjuvant therapy to a patient who is vehemently in favor of it, this patient is someone with a good chance of cure without any further therapy.

Our field is crying out for a biomarker with a high negative predictive value—we need to be assured that patients with this biomarker are very unlikely to experience a relapse. As soon as we can pick out whom not to treat, we will be in pretty good shape. Instead of treating 20 patients to benefit one, we want to be treating 2 patients to benefit one. Even in the high-risk population from CheckMate 238, physicians treated 4 patients to benefit one.

H&O Should the number of positive lymph nodes be factored into the decision to provide adjuvant therapy?

JW The number of positive nodes certainly is factored into the decision, as laid out in the current American Joint Committee on Cancer (AJCC) Cancer Staging Manual. Although I would not recommend treatment for a patient with a single positive node and a small disease burden, the risk goes up with 2 or more positive lymph nodes, and a patient with 3 or more positive nodes has a 50% risk for relapse. The more advanced the stage, the greater the risk for relapse and the greater the potential relative benefit.

H&O Should patients with a microscopic lymph node metastasis (N1a) receive adjuvant therapy, given that most patients do not receive completion lymphadenectomy for a positive sentinel node?

JW As Dr Max Madu discussed at the most recent American Society of Clinical Oncology (ASCO) meeting, the burden of tumor in that sentinel lymph node is what determines outcome. If the patient has a stage IIIA tumor, there is no need for a completion lymphadenectomy. If microscopic N1a disease is found in the lymph node, my advice would depend on the tumor burden in the lymph node. If the tumor burden is 1 mm or less, I would not recommend adjuvant therapy. If the tumor burden is more than 1 mm, I would probably vote for adjuvant therapy. I would absolutely recommend adjuvant therapy for patients with stage IIIB disease and for those with resected stage IIIC or IV disease. If a relevant trial is available, I generally recommend a trial. If none is available, I recommend adjuvant therapy, usually nivolumab.

H&O Which patients should receive immunotherapy vs targeted therapy?

JW This was a topic of some discussion at the most recent ASCO meeting. During the melanoma panel discussion, one of my colleagues challenged me to state which I would use first in a patient with *BRAF*-mutated disease now that 2 FDA-approved options are in use—dabrafenib/trametinib and immunotherapy. The trend in the United States is to use immunotherapy. We do not have good data to support one approach over the other, however, and I suspect that the results will prove to be similar with the 2 approaches.

The big trial of dabrafenib/trametinib, of course, is COMBI-AD (A Study of the BRAF Inhibitor Dabrafenib in Combination With the MEK Inhibitor Trametinib in the Adjuvant Treatment of High-risk BRAF V600 Mutation-Positive Melanoma After Surgical Resection). In this phase 3 trial, 870 patients with resected stage III melanoma and a *BRAF* mutation were randomly assigned to daily dabrafenib/trametinib or placebo for 12 months. At a median follow-up of 2.8 years, the estimated 3-year rate of relapse-free survival was 58% with dabrafenib/trametinib vs 39% with placebo. The hazard ratio for recurrence or death was 0.47 (95% CI, 0.39-0.58; $P<.001$). In addition, an early interim analysis suggested that 3-year overall survival was longer with dabrafenib/trametinib vs placebo, although this difference had not reached statistical significance.

The big trial of immunotherapy in these patients is CheckMate 238. Early results of this trial appeared in the *New England Journal of Medicine* to coincide with presentation at the 2017 European Society for Medical Oncology (ESMO) annual meeting, and I presented updated and extended results at the most recent ASCO meeting. CheckMate 238 is a phase 3 study in which 906 patients with resected stage IIIB, IIIC, or IV melanoma were randomly assigned to nivolumab or ipilimumab for up to 1 year, or until disease recurrence or unacceptable toxicity. The most recent data, after 24 months of follow-up, showed that relapse-free survival continued to be longer with nivolumab than with ipilimumab in all patient subgroups, regardless of disease stage, programmed death ligand 1 (PD-L1) expression, or *BRAF* mutation status. Not only was a clear benefit in relapse-free survival noted for nivolumab compared with ipilimumab, but also less toxicity.

The study populations were different in COMBI-AD and CheckMate 238, but if you look only at the patients with stage IIIB or IIIC disease in both studies, the outcomes at 12, 18, and 24 months look pretty similar. When CheckMate 238 has 36 months of follow-up, I predict we will continue to see similar results in the 2 studies.

I think that both of these adjuvant regimens work very well. Physicians tend to favor immunotherapy, however, for several reasons. First, the rate of side effects leading to treatment discontinuation was 26% in COMBI-AD vs just 8% in CheckMate 238. That is a big difference, and it suggests that toxicity is less severe with nivolumab than with dabrafenib/trametinib. Second, immunotherapy is generally believed to have a longer tail on the survival curve, which is probably true when it comes to metastatic disease. Finally, there is an urban legend—it is not backed up by data—that you cannot stop targeted therapy at 1 year the way you can stop immunotherapy without increasing the risk for relapse. So I think that most physicians will choose immunotherapy over dabrafenib/trametinib for these patients, even those with *BRAF* mutations.

H&O What other studies have looked at the use of immunotherapy as adjuvant therapy in melanoma?

JW As I briefly mentioned earlier, Lex Eggermont presented results from KEYNOTE-054 (Study of Pembrolizumab Versus Placebo After Complete Resection of High-Risk Stage III Melanoma) at the 2018 AACR

annual meeting, which were simultaneously published in the *New England Journal of Medicine*. In this phase 3 trial, 1019 patients with resected stage III melanoma who were at high risk for recurrence were randomly assigned to pembrolizumab (Keytruda, Merck) or placebo for 12 months. Patients were considered at high risk for recurrence if they had a sentinel lymph node with a disease burden of more than 1 mm.

After a median follow-up of 15 months, the 1-year rate of recurrence-free survival was significantly longer with pembrolizumab than with placebo: 75.4% vs 61.0%. So there was clearly a benefit for pembrolizumab. These patients were different from those in CheckMate 238; the patients in KEYNOTE-054 had stage IIIA, IIIB, or IIIC disease by the old AJCC criteria (7th edition), whereas the patients in CheckMate 238 had stage IIIB, IIIC, or IV disease. The only way to compare the studies would be to pull out the stage IV patients from CheckMate 238 and the stage IIIA patients from KEYNOTE-054. If you do a quick back-of-the-napkin calculation, you see that the results appear to be the same for nivolumab and pembrolizumab. Each of these trials confirms the data of the other and supports the benefit of programmed death 1 (PD-1) blockade as adjuvant therapy for melanoma.

Another interesting fact about KEYNOTE-054 is that patients in the placebo arm are allowed to receive pembrolizumab if they have a relapse and metastatic disease develops. So this trial will provide information about the timing of pembrolizumab—whether it works as well when given later.

H&O How do physicians select the best checkpoint inhibitor to use for each patient?

JW There is no longer any indication for the use of ipilimumab as frontline adjuvant therapy because CheckMate 238 clearly showed that nivolumab is significantly more effective—both statistically and clinically—than ipilimumab. It is also less toxic.

Nivolumab and pembrolizumab are equally effective drugs, although nivolumab is slightly more convenient because it is administered every 4 weeks rather than every 3 weeks. More importantly, pembrolizumab is not yet approved for use as adjuvant therapy in these patients. So at this point, doctors will always choose nivolumab over pembrolizumab. If pembrolizumab is approved, as expected, some doctors will switch, but I suspect that most will stick with nivolumab out of habit.

H&O When should patients be recommended for clinical trials?

JW I believe that until we are able to cure at least 90% of patients, we should discuss enrollment in a clinical trial with all patients who have metastatic or high-risk resected melanoma. We have so many effective drugs in the melanoma field that virtually all trials today use an existing drug as a backbone. In other words, the chance that a patient would do worse in a trial than with standard therapy is really small. Could there be more side effects? There could be. But I think nearly all patients are candidates for a clinical trial as long as they fit the eligibility criteria. That's the way we should be thinking in every academic center.

H&O What do you think that future studies should address?

JW We certainly have come a long way with metastatic melanoma. Median survival was 7 or 8 months 20 years ago, and now it is 3 or 4 years. Despite this dramatic improvement, we still have a long way to go. First, we need better drugs and drug combinations, which means we need a better understanding of resistance mechanisms. Second, as I mentioned earlier, we need better biomarkers, especially when it comes to adjuvant treatment. This is less exciting than new drugs, but it's just as important to know which patients can be followed expectantly rather than undergo potentially toxic treatment.

The other point I would like to make is that we should be avoiding failed phase 3 trials whenever possible by conducting larger phase 2 studies. This will cost more money up front, but it will save money in the long run. Phase 3 studies should almost always work.

Disclosure

Dr Weber has consulted for, served on advisory boards for, or holds equity in Altor BioScience, AstraZeneca, BioND, Bristol-Myers Squibb, cCAM Biotherapeutics, Celldex Therapeutics, CytomX Therapeutics, EMD Serono, Genentech, GlaxoSmithKline, Incyte, Medivation, Merck, Nektar, and Novartis. His institution has received research support from AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Merck, and Novartis.

Suggested Readings

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