MELANOMA IN FOCUS

Current Developments in Melanoma

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The Role of Triple Therapy in BRAF-Positive Melanoma

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H&O How common is BRAF-positive melanoma?

RS Melanoma is BRAF-positive in approximately 50% of cases that arise on the skin; 10% to 20% of cases that arise on mucosal surfaces, such as those of the mouth, sinuses, genitals, and rectum; 20% to 25% of cases of ocular melanoma affecting the conjunctiva; and no cases of ocular melanoma affecting the choroid.

H&O What is considered standard post-surgical treatment for patients with BRAF-positive stage II or III melanoma?

RS Some patients with stage IIB or IIC disease and most patients with stage III disease are eligible to receive adjuvant treatment, even though a significant number would not experience a recurrence after surgery. In stage IIB or IIC disease, the approved option for adjuvant therapy is the programmed death 1 (PD-1) inhibitor pembrolizumab (Keytruda, Merck). In stage III disease, the approved options are pembrolizumab, nivolumab (Opdivo, Bristol Myers Squibb), and other anti–PD-1 agents, as well as the combination of the BRAF inhibitor dabrafenib (Tafinlar, Novartis) and the MEK inhibitor trametinib (Mekinist, Novartis). We do not have any head-to-head data looking at whether the anti–PD-1 agents or the dabrafenib/trametinib combination is more effective in patients with resected BRAF-mutated stage III melanoma. Cross-trial comparison, however, suggests that the options are similar in efficacy, so drug selection often comes down to a discussion of the toxicities.

H&O What is the standard treatment for patients with BRAF-positive metastatic melanoma?

RS Regarding the metastatic setting, the DREAMseq trial established that virtually all patients with BRAF-positive disease should receive anti–PD-1 therapy plus anti–cytotoxic T-lymphocyte–associated antigen 4 (anti–CTLA-4) therapy. This study found that the 2-year overall survival rate was significantly higher when nivolumab/ipilimumab was given first than when dabrafenib/trametinib was given first—at 72% vs 52%, respectively. The alternative therapy was given at disease progression.

Only those patients with BRAF-positive metastatic disease that is progressing very rapidly, and who have a life expectancy of only days or weeks, should receive BRAF-targeted therapy—specifically BRAF/MEK inhibitor doublets—as frontline therapy.

The US Food and Drug Administration (FDA) also recently approved a fixed-dose combination of nivolumab and the LAG3-blocker relatlimab-rmbw (Opdualag, Bristol Myers Squibb) for use in patients with unresectable or metastatic melanoma. Approval was based on results of the phase 2/3 RELATIVITY-047 trial, which compared the combination vs nivolumab alone.

H&O What should be the second-line treatment?

RS For second-line therapy after immune checkpoint inhibition, the choice is either another immunotherapy or BRAF-targeted therapy. If the patient is not benefiting from immunotherapy, we may offer BRAF-targeted

therapy as a last resort, but it does not lead to durable benefit in most patients.

H&O What toxicities occur with these agents?

RS BRAF-targeted therapy can cause side effects such as nausea, vomiting, and rash. It is associated with higher toxicity rates than anti–PD-1 agents, but the side effects tend to be reversible almost immediately upon cessation of the drug. Most patients experience toxicity during peak exposure to the drug or drugs that resolves shortly after the agent has been discontinued. The side effect profile is very different with anti–PD-1 agents, which can cause autoimmune toxicities affecting the joints, skin, digestive system, and other body systems that may be long-lasting or even permanent. In the absence of data showing clear superiority of one approach over the other, such as in the stage III adjuvant setting, the differences among the side effect profiles are very important. Do patients prefer the idea of being more likely to experience toxicity but less likely to have lingering problems? Or do they prefer being less likely to experience toxicity with a small risk for lingering problems? Most people who receive anti–PD-1 agents feel fine and have an easier year than do those treated for a year with dabrafenib/trametinib. Some patients experience challenging side effects from anti–PD-1 therapy, however. I think that either approach is reasonable in stage III melanoma.

H&O What triple-therapy regimens are in use?

RS The only triple-therapy regimen that has received approval is the programmed death ligand 1 inhibitor atezolizumab (Tecentriq, Genentech) plus vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) and cobimetinib (Cotellic, Genentech). This combination is not commonly used, in part because the regimen requires a lead-in of BRAF-targeted therapy (vemurafenib and cobimetinib) before atezolizumab is started, which is somewhat complicated. In addition, atezolizumab is widely considered to be inferior to anti–PD-1 therapy, although no head-to-head data are available to support this idea. A more commonly used triple-therapy regimen that is used off label is pembrolizumab plus dabrafenib and trametinib, on the basis of results of KEYNOTE-022. This randomized phase 2 trial found that the addition of pembrolizumab to dabrafenib/trametinib improved median progression-free survival, although it increased the risk for adverse events. Another off-label regimen that is in use is encorafenib (Braftovi, Pfizer)/binimetinib (Mektovi, Pfizer) plus either nivolumab or pembrolizumab. The phase 3 STARBOARD trial is currently enrolling patients with advanced or metastatic melanoma to look at the combination of encorafenib, binimetinib, and pembrolizumab (NCT04657991) vs pembrolizumab alone. The design of this study is important because previous studies compared triplet regimens with BRAF/MEK inhibition, which we rarely use now as frontline therapy in melanoma. STARBOARD is far more relevant because it is using frontline treatment with an anti–PD-1 agent as the comparator. In addition, a phase 2 trial is comparing encorafenib, binimetinib and nivolumab vs ipilimumab (Yervoy, Bristol Myers Squibb) plus nivolumab in patients who have BRAF-positive melanoma with brain metastases (NCT04511013).

H&O What are the advantages of using triple-therapy regimens?

RS Some patients will have widespread disease with symptoms that require immediate relief. The beauty of BRAF-targeted therapy is that patients' symptoms usually decrease within 1 to 2 days, sometimes within a matter of hours. One of the nice things about triplet therapy is that we can combine the short-term relief of BRAF inhibitors with the durable control of disease seen with immune checkpoint inhibitors—we can provide both.

H&O What other triple-therapy combinations have been studied?

RS The phase 3 COMBI-i study investigated the addition of the anti–PD-1 antibody spartalizumab to dabrafenib plus trametinib. Although this study showed an improvement in progression-free survival similar to what has been seen with vemurafenib/cobimetinib/atezolizumab and with dabrafenib/trametinib/pembrolizumab, the results of COMBI-i did not reach statistical significance.

H&O Are any other triple-therapy combinations being investigated?

RS Many trials are ongoing. I am the principal investigator of a phase 1/2 trial that is examining the addition of the BCL-2 inhibitor navitoclax to the combination of dabrafenib and trametinib in people with BRAF-positive melanoma (NCT01989585). We expect to have results before the end of the year. In addition, the phase 2 BAMM2 trial from the ECOG-ACRIN Cancer Research Group is looking at the addition of hydroxychloroquine to dabrafenib and trametinib in patients with stage IIIC or IV BRAF-positive melanoma (NCT04527549); preclinical and clinical data suggest a high rate of response with that combination.

Regarding triplet immunotherapies, a trial from the ECOG-ACRIN Cancer Research Group is looking at the addition of the granulocyte-macrophage colony–stimulating factor (GM-CSF) sargramostim (Leukine, Partner Therapeutics) to ipilimumab and nivolumab

in patients with unresectable stage III or IV melanoma (NCT02339571). That study is based on the previous finding in a randomized trial by Hodi and colleagues, in which GM-CSF lowered the toxicity of ipilimumab and improved overall survival.

At the 2021 European Society for Medical Oncology (ESMO) Congress, Dr Jeffrey Weber reported on the use of ipilimumab/nivolumab plus the interleukin 6 (IL-6) receptor blocker tocilizumab (Actemra, Genentech) in 28 patients with untreated, unresectable advanced or metastatic melanoma. The purpose of the tocilizumab was 2-fold. First, some data suggest that higher levels of IL-6 are associated with reduced benefit from ipilimumab/nivolumab and lower survival rates, so it was theorized that using tocilizumab to reduce levels of IL-6 might improve the response to checkpoint inhibition. In addition, tocilizumab is commonly used to reduce the toxicity of systemic therapy, which in turn might make the therapy more tolerable and therefore more efficacious. I was one of the co-investigators for this study, which represents a conflict, but the data showed a 70% overall response rate at 6 months and a favorable toxicity profile; both findings suggested results as good as or better than what we might have predicted, but not clearly. This study is continuing to recruit patients.

H&O What are the disadvantages of triple therapy?

RS We are concerned about toxicity, of course, because triplet regimens tend to cause more toxicity than doublet regimens. The third agent does not always make a big difference, however. The combination of vemurafenib and cobimetinib is already quite toxic, and the addition of atezolizumab does not make a large difference in toxicity. In contrast, the addition of pembrolizumab or spartalizumab to dabrafenib and trametinib seems to cause a significant increase in toxicity. We have become better at treating the toxicities associated with dabrafenib and trametinib, particularly febrile syndrome, but the addition of a PD-1 inhibitor can exacerbate those toxicities. In fact, analyses suggest that the addition of a PD-1 inhibitor can cause reductions in the amount of dabrafenib and trametinib that patients receive.

H&O What questions would you like to see answered?

RS I would be interested to learn whether there is an advantage to triplet therapy vs other regimens as second-line therapy after ipilimumab/nivolumab or nivolumab/relatlimab. Such a study would be relatively simple to conduct because we have many BRAF-positive patients who receive ipilimumab/nivolumab as first-line therapy for brain metastases, and they still have the brain metastases when we are selecting a second-line regimen. Should we use triplet therapy instead of doublet therapy in the second or third line for patients who are sicker?

The place of triplet therapy is uncertain because the data are not strong enough to justify supplanting our other combination immunotherapies in the front line, and we do not yet have enough data to know whether we should be using triplet therapy in the second or third line.

H&O When do you use triplet therapy?

RS I generally use triplet therapy when patients are in trouble up front and I do not anticipate that they will survive more than a few weeks. In that case, starting with ipilimumab/nivolumab means that if the patient does not respond, I have a limited time in which to transition to BRAF/MEK inhibition. In that case, I may choose triplet therapy with vemurafenib, cobimetinib, and atezolizumab.

The other time I consider using triplet therapy is for a patient who has derived some benefit from checkpoint inhibitors in the past and whose disease is now starting to progress, which is an off-label indication. I think that adding BRAF/MEK inhibition to checkpoint inhibition makes particular sense for patients with brain metastases. Again, we do not have the data to say whether we should be doing that, but there is some logic to support the decision.

Disclosures

Dr Sullivan has received research funding from Merck and has done consulting for and/or served on the advisory boards of Bristol Myers Squibb, Merck, Novartis, and Pfizer.

Suggested Readings

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