MELANOMA IN FOCUS

Current Developments in Melanoma

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Adjuvant Therapy in High-Risk, Node-Negative Melanoma

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H&O Which patients with high-risk, node-negative melanoma should receive adjuvant therapy?

MR First, it is important to define what is meant by "high-risk," or what the melanoma community considers to be a high enough predicted risk for relapse and death to justify the use of adjuvant therapy. The "high-risk" node-negative melanoma population includes patients with American Joint Commission on Cancer (AJCC) pathologic stages IIB and IIC disease. These AJCC stages are defined by a primary cutaneous melanoma with a Breslow tumor thickness range of 2 to 4 mm with ulceration (IIB), more than 4 mm without ulceration (also IIB), or more than 4 mm with ulceration (IIC) and a pathologically negative sentinel lymph node (SLN). The melanoma-specific 10-year survival is approximately 82% for stage IIB disease and 75% for stage IIC disease. These patients are considered high-risk because they have less favorable survival outcomes than patients with stage IIIA disease (thin primary nonulcerated tumors and small-volume SLN metastases) and a similar risk for relapse and death as patients with stage IIIB disease.

Based on statistically improved survival results from large, phase 3, randomized placebo-controlled trials, both the US Food and Drug Administration (FDA) and the European Medicines Agency have recently approved adjuvant therapy for pathological stages IIB and IIC disease with single-agent immune checkpoint blockade using pembrolizumab (Keytruda, Merck) after complete surgical resection of disease in these patients. The same adjuvant regimen is used in patients with stage III disease. Standard complete surgical resection includes a wide local skin and soft tissue resection of the primary tumor with appropriate margin width, and SLN biopsy. The goal of adjuvant treatment, which is used after surgery with curative intent, is to eradicate any micrometastatic disease, thereby preventing clinical disease relapse and death. Although adjuvant immunotherapy is now approved for these high-risk node-negative patients, the decision to treat a specific patient is not an easy one. Treatment decisions should be individualized and require a thoughtful shared decision-making process between patient and provider that is often referred to as the risk/benefit ratio discussion. Considerations include the predicted risk for relapse; the risk for severe short- and long-term immune-related toxicity;

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the patient's general performance status and underlying comorbidities; and the predicted treatment benefit, specifically the actual/absolute percentage point reduction in the risk of relapse. The predicted absolute reduction in risk of relapse, on an individualized basis, is a function of 2 critical pieces of information: (1) the established relative reduction in relapse risk, which is derived from the results of randomized trials as the hazard ratio (HR) and (2) the predicted risk for relapse and death.

H&O Could you discuss the research on immunotherapy in high-risk, node-negative melanoma?

MR A good place to start is to summarize the results of trials that have demonstrated improved survival outcomes, including how much actual benefit patients experienced. We have data from two phase 3 randomized trials: KEYNOTE-716 and CheckMate 76K. The KEYNOTE-716 trial, which was published in the *Lancet* in 2022, involved medical centers and hospitals in 16 countries. A total of 976 patients aged 12 years or older with newly diagnosed, completely resected stage IIB or IIC melanoma were randomly assigned to receive adjuvant treatment with the programmed death 1 (PD-1) inhibitor pembrolizumab or a placebo for up to 12 months.

At the first interim analysis, with a median follow-up of 14 months, the risk of disease recurrence or death was 11% in the pembrolizumab group and 17% in the placebo group (HR, 0.65; 95% CI, 0.46-0.92; *P*=.0066). At the second interim analysis, with a median follow-up of 21 months, the risk of disease recurrence or death was 15% in the pembrolizumab group and 24% in the placebo group (HR, 0.61; 95% CI, 0.45-0.82).

These results led the FDA to approve the use of pembrolizumab in these patients. It should be emphasized, however, that the HR of 0.61 represents a reduction from 24% to 15%, meaning that the absolute improvement in relapse-free survival (RFS) with pembrolizumab alone is 9%. Therefore, 91 out of 100 patients treated would be at risk for significant treatment-related adverse events without the potential of treatment benefit.

The CheckMate 76K trial, which was presented at the 2022 Society for Melanoma Research Annual Meeting, also enrolled patients with completely resected stage IIB or IIC melanoma. A total of 790 patients were randomly assigned to adjuvant treatment with the PD-1 inhibitor nivolumab (Opdivo, Bristol Myers Squibb) or a placebo for up to 12 months. At a prespecified interim analysis, the trial met its primary endpoint of RFS, with nivolumab reducing the risk of recurrence or death by 58% vs placebo (HR, 0.42; 95% CI, 0.30-0.59; *P*<.0001). These results were similar to those seen in KEYNOTE-716. The 12-month RFS rate was higher for nivolumab than for placebo, at 89% vs 79%, respectively.

Both of these trials highlight the double-edged sword that applies to treating patients in the adjuvant setting. Efficacy in preventing disease relapse in some patients was clearly demonstrated, but because many of these patients either would have been cured with surgery alone or harbored treatment-resistant disease, the majority of them were subjected to the risk of unnecessary treatment-related toxicities and costs without the possibility of treatment benefit. Both trials reported similar immune-related adverse events in nearly 20% of patients, many of which are autoimmune endocrinopathies requiring lifelong treatment and affecting quality of life. Given this combination of issues, it is not surprising that only around 50% of real-world patients accept the recommendation for treatment. A variety of strategies are being pursued to improve the "risk/benefit" ratio. Despite the high cost of treatment with adjuvant pembrolizumab, studies report that this therapy is cost-effective because of the extremely high costs associated with treating the higher rates of relapse in the placebo arm. A more selective approach to treatment could make this therapy even more cost-effective.

H&O What additional methods are used to determine whether these patients might benefit from adjuvant therapy?

MR A brief discussion about the value of prognostic (risk of relapse and death) and predictive (chance for treatment efficacy) biomarkers is relevant.

The prognosis for patients with pathologically staged AJCC IIB/C melanoma is determined primarily by primary tumor thickness and ulceration. The overall population-based risk of relapse, as determined by large, published databases and the placebo-controlled arms of the 2 randomized trials described above, is approximately 25% to 35%. In other words, 65% to 75% of patients are cured by surgery alone. If all patients receive treatment, at least 65% would be treated unnecessarily—they are unable to benefit from treatment but are still at risk for severe immune-related toxicity. Another group of patients, as predicted by the HR, will relapse despite treatment. Without knowing which patients are going to relapse and which patients have been cured with surgery alone, more discriminating biomarkers are needed to enrich the group of patients treated with those who have the highest risk for relapse, while avoiding the associated toxicity and costs of treatment in those most likely to have achieved a surgical cure. Prognostic modeling and nomograms have been developed using established non-AJCC clinical/pathological factors such as gender, age,

and tumor mitotic rate combined with tumor thickness and ulceration to provide a more personalized calculation of risk. However, these models still need validation. Ongoing clinical research is evaluating a gene expression profile (GEP) obtained from primary tumor tissue to further dichotomize high-risk from very low-risk prognostic groups. Although many of the published findings are promising, clinical utility studies are needed before these can be applied to clinical practice. One example of such an effort is the NivoMela study, which has finished recruiting patients (NCT04309409). This study is examining whether the MelaGenix GEP assay (from NeraCare in Germany) can accurately determine which patients with stage II melanoma are low-risk enough to undergo surveillance only, and which are in the very high-risk group that can benefit from nivolumab treatment. The trial design uses the results of the GEP assay (low-risk vs high-risk) to allocate patients into treatment arms, with the high-risk group randomized to nivolumab vs placebo and the low-risk patients randomized to observation.

Other strategies to improve risk stratification include evaluating the role of detection of circulating tumor cells and circulating tumor DNA in patients' blood before and after surgery. Ongoing longitudinal studies are designed to determine whether the presence or absence of circulating tumor products correlates with poor or favorable survival outcomes, respectively.

In terms of biomarkers that predict treatment benefit from immunotherapy for high-risk stage II melanoma, little valuable information currently exists. Similar to more advanced stages of disease, tumor programmed death ligand 1 (PD-L1) expression does not appear to significantly increase the likelihood of benefit with immune checkpoint blockade in stage II patients. *BRAF* mutational status is valuable and essentially required for making adjuvant treatment decisions for patients with resected stage III disease, given that only patients with *BRAF*-mutated tumors can benefit from FDA-approved combination targeted therapy with adjuvant BRAF/MEK inhibition. Unfortunately, the placebo-controlled, randomized COLUMBUS-AD trial in stage IIB/C patients with *BRAF*-mutated tumors has not completed study accrual (NCT05270044). Therefore, no BRAF/MEK combination treatment is currently available for these patients.

H&O What treatment is preferred as adjuvant therapy in patients with high-risk, node-negative melanoma that is *BRAF*-mutated?

MR As stated above, BRAF/MEK combination targeted therapy is not approved for the high-risk node-negative population, and therefore partially answers this question. It is interesting to note that although patients with either *BRAF* wild-type or mutated tumors can benefit from immune checkpoint blockade, some data suggests that patients with *BRAF*-mutated tumors appear to derive more benefit from immune checkpoint blockade compared with patients with *BRAF* wild-type tumors. It has been suggested that the overall greater mutational tumor burden existing within these tumors is in part responsible for these observations of higher efficacy with immunotherapy. However, there have been no head-to-head trials comparing immune checkpoint blockade vs BRAF/MEK targeted therapy in the adjuvant setting of any stage of melanoma. Given the highly significant results of the randomized, phase 3, placebo-controlled COMBI-AD trial, which studied adjuvant BRAF/MEK combination therapy in stage III patients with *BRAF*-mutated tumors after resection of regional lymph node metastases, it would be surprising for similar efficacy not to be observed in high-risk, node-negative patients.

H&O What other ongoing clinical trials are of special interest?

MR Another strategy to help overcome the challenges posed by the decision to treat in the adjuvant setting is to build upon the success of single-agent checkpoint blockade and offer patients a combination therapy that has higher efficacy (lower HR) without significantly increasing treatment-related toxicities. To this end, 2 exciting regimens are in development.

The first is a combination checkpoint-blocking regimen that combines pembrolizumab with a novel antibody that blocks the immune inhibitory activity of a T-cell immunoreceptor with Ig and ITIM domains (TIGIT) found on a variety of tumor-infiltrating lymphocytes. A phase 3 randomized adjuvant trial called KEYVIBE-010 is currently accruing patients across different stages of melanoma, including those with stages IIB/C disease. This trial aims to compare the combination with the standard control of single-agent pembrolizumab (NCT05665595).

The second strategy is a personalized messenger RNA (mRNA) vaccine that encodes the message to produce relevant neoantigens identified in each patient's tumor. In the phase 2b KEYNOTE-942 trial, the combination of the mRNA-4157 vaccine and pembrolizumab improved RFS compared with pembrolizumab alone in patients with stage III/IV melanoma following complete resection, according to a press release from Moderna and Merck. In collaboration with Moderna, Merck plans to launch a phase 3 randomized registration trial later this year to evaluate this combination vs pembrolizumab in patients with stages IIB to IV resected disease. I expect this to be the fastest-accruing trial we have ever seen in adjuvant therapy for melanoma.

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

MR I am hopeful that prognostic modeling that combines a variety of biomarkers will provide the pathway to greater insight into which patients are most likely to experience a disease recurrence and which are likely to be cured with surgery. The current ongoing and future planned combination immunotherapy trials will lead to the approval of regimens with improved efficacy. Collectively, these advances are likely to accomplish the following: (1) recommendations for treatment of patients in defined homogeneous high-risk groups; (2) de-escalation or even avoidance of treatment for patients in homogeneous low-risk groups, sparing them unnecessary morbidity and cost; (3) improved cost-effectiveness; and (4) higher acceptance of potentially life-saving treatment.

Disclosures

Dr Ross is a member of the global advisory board of Merck, is a paid speaker for Merck and Amgen, and has received a research grant from Amgen.

Suggested Readings

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