MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

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Does Adjuvant Therapy for High-Risk Melanoma With Either Immunotherapy or Targeted Therapy Affect Therapeutic Choices at Relapse?

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H&O What are the main treatments used for adjuvant therapy in melanoma?

MP The drugs that have received approval from the US Food and Drug Administration (FDA) for this use are interferon alfa-2b, ipilimumab (Yervoy, Bristol-Myers Squibb), and now nivolumab (Opdivo, Bristol-Myers Squibb). We hope that the BRAF inhibitor dabrafenib (Tafinlar, Novartis) and the MEK inhibitor trametinib (Mekinist, Novartis), which have good data supporting their use in the adjuvant setting, will receive FDA indications for use as adjuvant therapy in melanoma.

H&O How effective is immunotherapy as adjuvant therapy in melanoma?

MP Adjuvant therapy is demonstrating better efficacy in melanoma than ever before. We first learned that interferon improves recurrence-free survival, but it was not as effective as we wanted it to be. Later we found that dabrafenib and trametinib also improve recurrence-free survival. We have seen that ipilimumab improves recurrence-free survival and overall survival, and most recently we have seen that nivolumab is even more effective than ipilimumab at improving recurrence-free survival with better tolerability.

H&O Are you able to provide specific numbers?

MP I hesitate to give specific numbers because those depend to some extent on the stage of the disease, but both anti–programmed death 1 (PD-1) immunotherapy and dabrafenib/trametinib can cut the risk for recurrence of surgically resected high-risk melanoma by approximately half, which is a huge difference.

For example, in a study by Weber and colleagues that appeared in the *New England Journal of Medicine* in 2017, nivolumab reduced the risk for recurrence by 35% compared with ipilimumab. Had the control group been followed with observation alone rather than treated with ipilimumab, nivolumab presumably would have cut the

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risk by even more than that.

In addition, according to a press release from Merck that came out on January 8, pembrolizumab (Keytruda, Merck) improved recurrence-free survival in patients with resected high-risk melanoma by 43% compared with placebo.

H&O How effective is targeted therapy as adjuvant therapy in melanoma, and how does this compare with the effectiveness of immunotherapy?

MP It is difficult to compare the efficacy of targeted therapy as adjuvant therapy vs the efficacy of immunotherapy as adjuvant therapy because these treatment modalities were tested in separate clinical trials. The use of dabrafenib plus trametinib in patients with a BRAF mutation produces a reduction in risk similar to what we see with immunotherapy. In a study by Long and colleagues that appeared in the *New England Journal of Medicine* in 2017, the hazard ratio for relapse or death was 0.47 with dabrafenib/trametinib vs placebo in patients with stage III *BRAF*-mutated melanoma—a 53% reduction in risk. Again, these are 2 very different studies, but the reduction in risk is approximately 50% with both checkpoint inhibitors and BRAF and MEK inhibitors.

H&O What treatment options are available for patients with melanoma after a relapse?

In the adjuvant setting, the biggest question now is how much more effective immunotherapy is when ipilimumab is added to treatment with pembrolizumab or nivolumab.

MP It depends on what the patient received as adjuvant therapy. The drugs that I mentioned—ipilimumab, pembrolizumab, nivolumab, combinations of ipilimumab and nivolumab, and combinations of BRAF and MEK inhibitors—are all available for use after recurrence. The choice depends to some degree on which, if any, adjuvant therapy was used.

Table. Selected Ongoing Phase 3 Clinical Trials of Adjuvant PD-1 Immunotherapy in Melanoma

Study (Identifier)	Eligible Patients	Arms
CheckMate 915 (NCT03068455)	Resected stage IIIB or higher melanoma	Nivolumab/ipilimumab vs nivolumab alone
EORTC 1325 (NCT02362594)	Resected high-risk stage III melanoma	Pembrolizumab vs placebo
SWOG S1404 (NCT02506153)	Resected stage III or higher high-risk melanoma	Pembrolizumab vs high-dose recombinant interferon alfa-2b or ipilimumab

PD-1, programmed death 1.
Source: ClinicalTrials.gov.

H&O How are the choices affected specifically?

MP Only patients with a *BRAF* mutation are eligible for treatment with BRAF and MEK inhibitors. Immunotherapy can be given to patients regardless of their BRAF status. If a patient requires second-line treatment after adjuvant BRAF and MEK inhibition, the next choice would be a single checkpoint inhibitor or the combination of nivolumab plus ipilimumab. If the patient had immunotherapy as first-line adjuvant therapy, the next treatment would likely be a different immunotherapy approach or BRAF plus MEK inhibitors if the patient had a BRAF mutation. Immunotherapy with a PD-1 inhibitor—pembrolizumab or nivolumab—is always preferred to single-agent ipilimumab, which is a cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor. However, single-agent ipilimumab is a reasonable second-line approach after progression on a PD-1 inhibitor. Some oncologists prefer to use a combination of ipilimumab and a PD-1 agent as first-line treatment, but this is controversial. The combination of ipilimumab and a PD-1 agent is not recommended for adjuvant therapy outside a clinical trial.

H&O What questions are being addressed in clinical trials?

MP In the adjuvant setting, the biggest question now is how much more effective immunotherapy is when ipilimumab is added to treatment with pembrolizumab or

nivolumab and whether adjuvant anti–PD-1 or BRAF plus MEK inhibitors improve overall survival. In the metastatic setting, randomized trials are testing triple combinations of BRAF inhibitors, MEK inhibitors, and PD-1/programmed death ligand 1 (PD-L1) inhibitors. Another big question that still needs to be answered in the metastatic setting is whether immunotherapy is better than targeted therapy.

H&O What studies are addressing these questions?

MP The US Intergroup is conducting a large phase 3 study of dabrafenib plus trametinib vs ipilimumab plus nivolumab as therapy in patients who have advanced, unresectable melanoma with a *BRAF* V600 mutation (NCT02224781). In addition, CheckMate 915 is comparing nivolumab alone vs nivolumab plus ipilimumab as adjuvant therapy in patients who have undergone surgical removal of stage IIIB or higher melanoma (An Investigational Immuno-therapy Study of Nivolumab Combined With Ipilimumab Compared to Nivolumab by Itself After Complete Surgical Removal of Stage IIIb/c/d or Stage IV Melanoma; NCT03068455).

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

MP I hope that with better adjuvant treatments, we will see fewer patients who have metastatic disease. We also need to learn how to determine individual patients' risk profiles better before administering adjuvant therapy, so that we avoid overtreating those patients who can be cured with surgery alone.

Disclosure

Dr Postow has received honoraria from Bristol-Myers Squibb and Merck and has participated in advisory boards for Bristol-Myers Squibb, Merck, Novartis, Array BioPharma, NewLink Genetics, and Incyte.

Suggested Readings

ClinicalTrials.gov. An investigational immuno-therapy study of nivolumab combined with ipilimumab compared to nivolumab by itself after complete surgical removal of stage IIIb/c/d or stage IV melanoma (CheckMate 915). https://clinicaltrials.gov/ct2/show/NCT03068455. Identifier: NCT03068455. Accessed April 4, 2018.

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Merck's KEYTRUDA® (pembrolizumab) significantly improved recurrence-free survival compared to placebo as adjuvant therapy in patients with stage 3 resected high-risk melanoma (EORTC1325/KEYNOTE-054) [press release]. http://investors.merck.com/news/press-release-details/2018/Mercks-KEYTRUDA-pembrolizumab-Significantly-Improved-Recurrence-Free-Survival-Compared-to-Placebo-as-Adjuvant-Therapy-in-Patients-with-Stage-3-Resected-High-Risk-Melanoma-EORTC1325KEYNOTE-054/default.aspx. Posted January 08, 2018.

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