MELANOMA IN FOCUS

Current Developments in Melanoma

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Update on Adjuvant Therapy in Late-Stage Resected Melanoma

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

AT Systemic adjuvant therapy that targets residual micrometastatic disease—which is the source of future melanoma relapse and death—was tested primarily in patients with surgically resected stage III or IV melanoma, who are the main candidates for adjuvant therapy. Among these patients, those with stage IIIA disease are eligible only if they have at least one sentinel lymph node micrometastasis measuring 1 mm or greater in diameter. The current 3 first-line adjuvant therapy agents that have received approval based on recently reported phase 3 studies are nivolumab (Opdivo, Bristol Myers Squibb), pembrolizumab (Keytruda, Merck), and—for patients with *BRAF* V600E/K–mutated melanoma—the BRAF inhibitor dabrafenib (Tafinlar, Novartis) in combination with the MEK inhibitor trametinib (Mekinist, Novartis). Although the CheckMate 238 study that tested nivolumab is the only one that enrolled patients with resected stage IV disease, I believe that the use of any of these agents is justified for patients with resected stage III or IV disease.

H&O What have specific trials shown about each of these agents or regimens?

AT For the current 3 first-line adjuvant therapy regimens, the US Food and Drug Administration approvals were based on 3 phase 3 studies: CheckMate 238, KEYNOTE-054, and COMBI-AD. CheckMate 238 compared adjuvant nivolumab at 3 mg/kg every 2 weeks vs ipilimumab (Yervoy, Bristol Myers Squibb) at 10 mg/kg every 3 weeks for 4 cycles (n=453) and then every 12 weeks (n=453) in patients with resected stage IIIB, IIIC, or IV melanoma for up to 1 year. This study showed a significant improvement in the primary endpoint of relapse-free survival (RFS), with a hazard ratio (HR) of 0.71 with the use of nivolumab. The study did not show a significant difference between nivolumab and ipilimumab in terms of overall survival (OS), however.

Similarly, KEYNOTE-054 compared adjuvant pembrolizumab at 200 mg (n=514) vs placebo (n=505) every 3 weeks for up to 18 cycles in patients with resected stage IIIA (at least one lymph node metastasis >1 mm), IIIB, or IIIC melanoma. At a median follow-up of 42 months, the study demonstrated a significant improvement in RFS, the study's primary endpoint, with pembrolizumab vs placebo, with an HR of 0.59.

In patients with *BRAF* V600E/K–mutated melanoma, COMBI-AD compared a combination of 2 oral medications, dabrafenib at 150 mg twice daily plus trametinib at 2 mg once daily (n=438), with placebo (n=432) in patients with resected stage IIIA (at least one lymph node metastasis >1 mm), IIIB, or IIIC melanoma. This study also found a statistically significant benefit in the investigational group vs the control group in RFS, the primary endpoint, with an HR of 0.51.

Another clinical trial that may have applications in the clinic is the randomized phase 2 IMMUNED study, which compared nivolumab plus ipilimumab (n=55) and nivolumab alone (n=56) with placebo (n=51) in patients who had resected stage IV melanoma. Patients in the nivolumab/ipilimumab group received intravenous

nivolumab at 1 mg/kg every 3 weeks plus intravenous ipilimumab at 3 mg/kg every 3 weeks for 4 cycles, followed by nivolumab at 3 mg/kg every 2 weeks for up to 1 year. Patients in the nivolumab-alone group received intravenous nivolumab at 3 mg/kg every 2 weeks. At a median follow-up of 28.4 months, this study showed significant improvements in RFS with nivolumab/ipilimumab vs placebo, with an HR of 0.23. Nivolumab alone also improved RFS vs placebo, with an HR of 0.56. The study was not powered to find a difference between nivolumab/ipilimumab and nivolumab alone, although we did see a separation between the Kaplan-Meier curves of these 2 groups.

The rate of grade 3/4 treatment-related adverse events in IMMUNED was 71% in the nivolumab/ipilimumab arm and 27% in the nivolumab-alone arm. Because of the toxicity risk, I would avoid the use of adjuvant nivolumab/ipilimumab in favor of single-agent checkpoint inhibition for patients with resected stage IV M1a or M1b disease. Dual-therapy checkpoint inhibition would be most appropriate for patients with resected stage IV melanoma who are at especially high risk for recurrence, such as those with resected brain metastases. Approximately 42% of the patients in IMMUNED had cerebral metastases.

Another interesting relevant study is CheckMate 915. This well-designed, international phase 3 study enrolled 1943 patients with resected stage IIIB, IIIC, IIID, or IV melanoma. Patients were randomly assigned to nivolumab plus ipilimumab or to nivolumab alone for up to 1 year. This trial used a lower dose of ipilimumab than the smaller, phase 2 IMMUNED trial, as well as less-frequent dosing: 1 mg/kg every 6 weeks, rather than 3 mg/kg every 3 weeks for 4 treatments followed by maintenance nivolumab in IMMUNED.

The CheckMate 915 result was negative, and the trial did not meet the co-primary endpoints of RFS and RFS in patients whose tumors did not express programmed death ligand 1 (PD-L1). Of note, the median duration of treatment was shorter in the patients who received the combination than in those in the nivolumab-alone arm: 7.6 vs 11.1 months, respectively. As expected, rates of grade 3/4 adverse events and adverse events leading to discontinuation were higher in the combination arm than in the monotherapy arm. These results support the use of nivolumab monotherapy as the frontline standard adjuvant option in this patient population.

H&O Should OS be an endpoint for adjuvant therapy trials?

AT I would support having OS as a co-primary endpoint, along with RFS, to help us answer the question of whether systemic therapy should be introduced early or late in patients with high-risk operable disease. A lot of debate is ongoing in the field about when to introduce systemic therapy, especially in patients with relatively low-risk resected disease. In a patient with resected stage IIIA, minimally micrometastatic disease, as an example, should we treat with adjuvant therapy now, or save systemic therapy for later use at the time of disease relapse? The fact that we have agents that work very well in the salvage setting in melanoma make this a justified and important question. Does the timing of systemic therapy affect OS?

H&O How do you determine the best adjuvant therapy for a specific patient?

AT The most obvious factors to look at are disease stage and *BRAF* mutation status. Patients whose disease is *BRAF* wild-type are offered adjuvant immunotherapy with an anti–programmed death 1 (anti–PD-1) agent, either pembrolizumab or nivolumab. Patients whose disease has a *BRAF* V600 E/K mutation have the additional option of dabrafenib plus trametinib. This combination has the advantage of being taken in tablet form. Another consideration is the differing side-effect profiles of the 2 treatment approaches. For example, we avoid the use of immunotherapy in patients with active autoimmune disease, who are at elevated risk for immune-related adverse events. On the other hand, immunotherapy is usually a better choice than tyrosine kinase inhibition in patients with conditions such as heart arrhythmias. A final consideration is what to do if the treatment fails to work; some patients elect immunotherapy up front and reserve BRAF/MEK inhibitors as the salvage option in case of disease relapse.

H&O Do you have any concerns regarding using the 4- or 6-week schedule instead of standard dosing for nivolumab and pembrolizumab, respectively?

AT No, I do not have concerns about those dosing schedules. On the basis of the current data, we are able to offer immunotherapy patients the choice of more-frequent or less-frequent visits to the clinic, as long as the patients are monitored relatively closely and communication between the treating team and the patient is good. Physicians and patients generally prefer the convenience of less-frequent dosing. If patients do not have a good support system at home, or if other barriers to adherence are a possibility, however, it may be preferable to see them in the clinic more frequently.

H&O Are there any situations in which you use ipilimumab?

AT We may offer ipilimumab to patients whose disease fails to respond to adjuvant anti–PD-1 therapy and continues to be resectable. The use of adjuvant ipilimumab is supported by the results of the EORTC 18071 and ECOG-ACRIN E1609 phase 3 studies. In E1609, we found that the RFS and OS benefits with the 3-mg/kg dose of ipilimumab were similar to those with the 10-mg/kg dose, but with significantly less toxicity.

A lot of debate is ongoing in the field about when to introduce systemic therapy, especially in patients with relatively low-risk resected disease.

H&O Are there any circumstances in which you might use interferon?

AT No, I do not see a role for adjuvant interferon in the clinic in the current era.

H&O What questions remain to be answered when it comes to adjuvant therapy?

AT One unanswered question is whether adjuvant anti–PD-1 immunotherapy improves OS in all patients with resected high-risk melanoma. This question is complicated by the fact that the trials that compared anti–PD-1 agents with active controls have not shown improvement in OS. For example, CheckMate 238 compared nivolumab with ipilimumab and showed significant improvement in RFS but not in OS. Similarly, the S1404 study compared pembrolizumab with both ipilimumab and interferon alfa and also showed significant improvement in RFS but not in OS.

The anticipated improvement in OS has special implications for decision making when it comes to lower-risk patient populations, such as those with stage IIIA disease. Do we improve OS in these patients, who are already at a lower risk for relapse? We need to try to answer this question in future phase 3 studies by continuing to mandate crossover at the time of relapse, and by looking at OS as a co-primary endpoint if possible.

Another open question regards the use of prognostic biomarkers that may allow us to stratify patients' risks better and decide who requires adjuvant therapy and who can be safely observed. These biomarkers should be integrated into the design of future randomized, controlled studies. In addition, we need to invest more effort in identifying biomarkers that may allow us to predict which patients are more likely to benefit from specific agents, such as immunotherapy and targeted therapy.

Disclosure

Dr Tarhini has done consulting or served on the advisory boards of Merck, Bristol Myers Squibb, Novartis, Genentech-Roche, Partner Therapeutics, Sanofi-Genzyme, Regeneron, Eisai, and Clinigen Group. He has conducted contracted research for OncoSec Medical, Clinigen Group, Genentech-Roche, Bristol Myers Squibb, Nektar Therapeutics, Sanofi-Genzyme, Regeneron, and Navigate BioPharma Services.

Suggested Readings

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