Strides in Melanoma Announced: Maximizing Value Comes Next

By Rabiya S. Tuma

After 30 years of negative phase III trials, melanoma research turned a corner last year when a large randomized phase III trial showed that ipilimumab (Yervoy), an immune system-stimulating antibody, prolonged survival in patients with metastatic melanoma who had failed prior therapy. The U.S. Food and Drug Administration (FDA) approved the drug in March of this year for use in that patient population.

Researchers have now extended that critical advance with two additional phase III trials that
showed better overall survival in newly diagnosed patients with metastatic melanoma, according to work presented at the annual meeting of the American Society of Clinical Oncology (ASCO) in June. One trial demonstrated that ipilimumab also works in this patient group, while the other trial showed that a molecularly targeted drug, vemurafenib (formerly PLX4032), induces rapid responses and longer survival. Field leaders lauded the work during the meeting and then quickly shifted their focus to what questions must be addressed to maximize the power of these active agents.

**Novel Treatments**

A total of 502 patients enrolled in the phase III trial that compared ipilimumab plus dacarbazine (DTIC) with placebo plus DTIC (until recently, the latter was the only FDA-approved chemotherapy for metastatic melanoma). The median duration of response was 19.3 months in the experimental arm and 8.1 months in the control arm, while the median overall survival time was 11.2 months compared with 9.1 months, respectively.

The proportion of patients alive in the experimental arm was higher than in the control arm at 1 year (47.2% vs. 36.3%), 2 years (28.5% vs. 17.9%), and 3 years (20.8% vs. 12.2%).

“This is now the second phase III trial with ipilimumab showing an improvement in overall survival,” said Jedd Wolchok, M.D., Ph.D., a melanoma specialist at Memorial Sloan-Kettering Cancer Center in New York, during his plenary presentation of the study.

More patients in the ipilimumab-DTIC arm experienced grade 3/4 adverse events than did patients in the placebo-DTIC arm (89.5% vs 76.9%). Colitis and diarrhea were common in the ipilimumab-DTIC combination, with any grade affecting 4.5% and 36.4% of patients, respectively, and grade 3/4 affecting 2.0% and 4.0% of patients. In comparison, only 0.4% of patients in the control arm developed low grade colitis, and 24.7% had low-grade diarrhea. Additionally, a greater proportion of patients in the ipilimumab arm had grade 3/4 elevation in liver enzymes, than did patients in the control arm (ALT: 21.9% vs 0.8%; AST: 18.2% vs 1.2%). There was one treatment-related death in the control arm, but none in the experimental arm. Given the toxicities seen with the ipilimumab-DTIC combination, Wolchok said that ipilimumab monotherapy is likely to become the standard regimen, even though this trial did not test it.

Kim Margolin, M.D., a professor of medicine at the University of Washington in Seattle and a melanoma specialist at the Fred Hutchinson Cancer Research Center in Seattle, agreed that ipilimumab by itself is preferable at this point because liver toxicity was common with the ipilimumab-DTIC combination, but has not been common in ipilimumab monotherapy trials. “In view of the increased hepatotoxicity of ipilimumab plus DTIC in combination, and the strong sense that there was no benefit to the addition of the cytotoxic agent, it would not be advisable to include this agent in the standard clinical use of ipilimumab at any dose and schedule,” she said during her plenary discussion.

**BRAF Inhibitors**

Early-phase trials suggested that many patients whose tumors carry a V600E mutation in the BRAF gene will respond to a BRAF inhibitor, and the new phase III data confirmed that hypothesis. Nearly half of the evaluable patients treated with vemurafenib had an objective response, including 0.9% with a complete response and 47.5% with a partial response. By contrast, just 5.5% of the evaluable patients treated with DTIC had a partial response. (Absolute numbers for objective responses and the number of currently evaluable patients were not presented.)

Overall survival also appears to be better in patients treated with the experimental agent than patients treated with the control therapy. The estimated 6-month survival rate was 84% for patients in the vemurafenib arm compared with 64% for patients in the DTIC arm, which was a statistically significant difference. However, the investigators cannot yet estimate the median overall survival in either arm because less than 10% of the 665 patients in the trial had been part of the study for 7 or more months at the time of the analysis. The team was able to calculate the median progression-free survival (5.3 months for vemurafenib vs. 1.6 months for DTIC).

The full benefit of the therapy will be known only with longer follow-up, according to Paul Chapman, M.D., a melanoma oncologist at Sloan-Kettering, who presented the data at ASCO. Even so, he is confident of vemurafenib’s value. “Vemurafenib is a promising new therapy for patients with metastatic BRAF V600E-mutated melanoma, and a foundation upon which to build combination therapy in the future,” Dr. Chapman concluded, during his plenary presentation.

**Combinations**

Although many patients with the BRAF V600E mutation initially respond to vemurafenib, their responses tend to be short-lived. To slow or prevent resistance, researchers combined a new BRAF inhibitor, called GSK2118436 (GSK436), and a MEK inhibitor called GSK1120212 (GSK212) in a phase I/II trial.

Early results, presented by Jeffrey Infante, M.D., director of drug development at the Sarah Cannon Research Institute in Nashville, Tenn., suggest that the combination is very active in patients with metastatic melanoma and that they tolerate it well. Of 71 patients who had no prior BRAF inhibitor therapy and who were evaluable at the time of the current analysis, 5 (7%) had a complete response and 47 (66%) had a partial response. Unfortunately, it is still too early to know whether the combination will prolong the duration of responses beyond what is seen with the BRAF inhibitor alone.

Remarkably, the worst toxic effects associated with each agent alone appeared to be less frequent with the combination therapy. In phase I trials with the MEK inhibitor, an acne-like rash affected approximately three-quarters...
of the patients. In this trial, the rate of any-grade rash was 25%, whereas the rate of grade 3/4 rash was 2%. Similarly, the frequency of cutaneous squamous cell cancers was just 1%, which is substantially lower than what patients taking only the BRAF inhibitor experienced.

**New Future, Many Questions**

With the value of the BRAF inhibitor vemurafenib and the immune modulator ipilimumab now proven, melanoma researchers have many opportunities and questions to confront. One pressing question will be determining the optimal dose and schedule for ipilimumab. The FDA approved the drug at a dose of 3 mg/kg of body weight in previously untreated patients. However, phase II trials suggested that a 10 mg/kg may be more effective, which was the dose that the current trial tested in newly-diagnosed patients.

Researchers and clinicians are also trying to work out how best to use BRAF inhibitors and ipilimumab in patients with BRAF-mutant tumors, who comprise approximately half of all melanoma patients. The progression-free survival curves of the two agents differ markedly: Vemurafenib induces rapid tumor shrinkage and symptom relief but relatively rapid progression, whereas ipilimumab takes weeks or months to start working, but then confers durable benefit. Sequential therapy, or a concurrent combination may work, but which option would be best is not yet clear.

The good news is that the companies that make the two agents – Bristol-Myers Squibb and Roche – recently signed an agreement to run a clinical trial to test the combination. “The trial has been written,” Wolchok said during an interview. “We haven’t seen the final version, but I think we will very shortly.”

Another key issue that Margolin raised during her discussion of the phase III trials is the need to move these agents into patients with earlier-stage disease, when it is likely to be curable. The European Oncology Research Trials Consortium has almost completed accrual for an adjuvant therapy trial comparing ipilimumab with placebo in high-risk stage III melanoma patients to determine whether the drug can reduce the risk of progression after surgery. Meanwhile, an Eastern Cooperative Oncology Group trial is almost ready to start enrolling patients with stage IIIB, IIIC or IV melanoma whose disease has been surgically removed to determine whether ipilimumab is better than interferon for reducing risk of recurrence.

As researchers address these questions, clinical care is already shifting. Infante and others said that they have started genotyping all newly diagnosed patients and assigning them to their first therapy – ipilimumab or vemurafenib or a clinical trial – based on the BRAF mutation status of their tumors. And having options, even a few options, is a novelty in melanoma care. “There is a lot of learning going on quickly, and we have a lot of options,” Infante said during a phone interview. “But I don’t think we’re playing chess quite yet.”

*Dr. Wolchok is a consultant for Bristol-Myers Squibb, which makes ipilimumab.*

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