Promising Data on Ipilimumab and Other Investigational Melanoma Therapies

The annual meeting of the American Society of Clinical Oncology offered some promising findings on potential new treatments for advanced melanoma.

By Jonathan Wolfe, MD

A much-publicized highlight of the 2010 Annual Meeting of the American Society of Clinical Oncology (ASCO) was the presentation of data showing that ipilimumab, a human monoclonal antibody that targets CTLA-4, improved overall survival in patients with previously treated metastatic melanoma. Results come from the first ever phase III randomized, controlled trial in which a therapy has been shown to improve overall survival in patients with stage III or IV melanoma. The full study was also published in the June 5 online edition of *The New England Journal of Medicine*.[1]

Ipilimumab for Melanoma

Cytotoxic T-lymphocyte-associated antigen-4 or CTLA-4 has been recognized to play a role in limiting the body's immune response to cancer by down-regulating T-cell activation. Ipilimumab blocks CTLA-4 to promote tumor-targeted immune response. In phase II studies, ipilimumab was shown to have antitumor activity when used as monotherapy in patients with metastatic melanoma.

The current study compared the effects of ipilimumab alone to those of gp100, a cancer vaccine shown to induce immune response but with limited antitumor activity, and to ipilimumab plus gp100. Subjects included 676 previously treated patients with inoperable, late stage melanoma tumors that had already spread through the body. Patients received ipilimumab 3mg/kg plus gp100 peptide vaccine, ipilimumab plus placebo vaccine, or gp100 vaccine plus placebo antibody administered once every three weeks for four total treatments.

There was no difference in overall survival between the ipilimumab and ipilimumab plus vaccine groups. Among evaluable patients receiving all four treatments, the median overall survival was 10 months in the ipilimumab plus vaccine group, 10.1 months in the ipilimumab alone group, and 6.4 months in the vaccine alone group.

Overall survival rates at 12, 18, and 24 months are shown in Table 1. The effects of treatment were independent of age, sex, serum lactate dehydrogenate levels, metastasis stage, or any previous IL-2 therapy.

Ipilimumab was also shown to affect disease progression. Ipilimumab plus gp100 showed a 19 percent reduction risk of progression compared to gp100 alone; ipilimumab alone showed a 36 percent reduction in risk of progression compared to gp100 alone. Patients in the ipilimumab alone group had the highest percentage of objective response or stable disease.

Treatment presents a risk for notable adverse events. Sixty percent of patients developed immune-related adverse events; grade 3 or 4 immune-related adverse events were reported in 10 to 15 percent of patients receiving ipilimumab. The authors note that prompt medical attention and administration of corticosteroids effectively manage immune-related adverse events.

Table 1. Overall Survival Rates (%) Reported for Ipilimumab

	Ipilimumab	Ipilimumab plus vaccine	Vaccine
Month 12	45.6	43.6	25.3
Month 18	33.2	30.0	16.3
Month 24	23.5	21.6	13.7

Ipilimumab is in development by Bristol-Myers Squibb, which supported the study.

Of note, another publication last month reported the first case of ipilimumab monotherapy resulting in durable complete remission of untreated, progressive brain metastases in a patient with stage IV melanoma.[2] The authors of this report note that there have been numerous anecdotal reports of similar complete or partial remissions associated with ipilimumab therapy.

Additional Promising Reports

• Also presented at the ASCO meeting were positive data on the first 40 subjects enrolled in a phase 2 clinical trial of PV-10 for metastatic melanoma. According to the data, subsequently reported by Provectus, 61 percent of subjects had an objective response to treatment with PV-10, a proprietary, injectable formulation of Rose bengal for chemoablation of cancer cells.

PV-10 has been shown to selectively target lysosomes within cancer cells, leading to necrosis of treated tumors. Rose bengal has been used in ophthalmology, as a histologic stain, and as an intravenous diagnostic to detect ailments of the liver. It is a small molecule agent with an established safety history, a short half-life in the bloodstream, and is excreted via the liver and kidneys.

In the recently reported study, Complete Response was seen in 33 percent of subjects and locoregional disease control was seen in 79 percent of subjects. Untreated bystander lesions in 43 percent of subjects had an objective response to treatment.

Mean progression free survival for all subjects was 8.5 months. Adverse experiences during the study interval were generally mild to moderate, locoregional and transient, with no deaths or life-threatening experiences attributable to use of PV-10.

• Interim Phase 2 results from 24 patients treated with interleukin 21 (IL-21) show that 29 percent had a partial response, and 33 percent of had stable disease, according to a statement issued by ZymoGenetics. Two schedules testing 50mcg/kg were evaluated in a total of 10 patients; they were poorly tolerated due to adverse events including neutropenia and skin rash. The trial will be completed with a full cohort of 30 patients treated at a dose of 30mcg/kg dose. The most common adverse events reported in the interim data were mild or moderate fatigue and rash.

• Multipeptide vaccine preparations (12 MHC class I-restricted melanoma peptides (12MP)) were shown to stimulate CD4+ and CD8+ T-cell responses in patients with advanced melanoma, and were associated with objective clinical regressions in five of patients, according to data presented at ASCO (Abstract 8508). Addition of 6MHP melanoma peptides provided no clinical or immunologic benefit over use of either peptide mixture alone.

• Percutaneous hepatic perfusion (PHP-mel) improved progression free survival in patients with hepatic metastases from primary melanoma versus best available care (Abstract LBA8512). Median hepatic progression-free survival (H-PFS) was 245 days for PHP-mel vs. 49 days for BAC ($p < 0.001$). Overall response rate was 34.1 percent for PHP (15/44) vs. two percent (1/49) for BAC. ■

Dr. Wolfe has no relevant disclosures.

1. Hodi SF, O'Day S, McDermott DF, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. NEJM e-pub June 5, 2010.

2. Schartz NE, Farges C, Madelaine I, Bruzzoni H, Calvo F, Hoos A, Lebbé C. Complete regression of a previously untreated melanoma brain metastasis with ipilimumab. Melanoma Res. 2010 Jun;20(3):247-50.

3. ASCO abstracts available on-line at http://abstract.asco.org/index20100505.html.