Combination Immunotherapy Superior to Monotherapy in Patients with Melanoma

By Chase Doyle

Combination treatment with the 2 immunotherapies nivolumab and ipilimumab led to a doubling in progression-free survival (PFS) compared with ipilimumab alone in patients with advanced melanoma, investigators from the CheckMate 067 trial reported at ASCO 2015.

The study also suggested promise for PD-ligand 1 (PD-L1) as a biomarker of response that could help determine whether patients would benefit most from 1 or from 2 forms of immunotherapy, said Jedd D. Wolchok, MD, PhD, Chief of the Melanoma and Immunotherapeutics Service at Memorial Sloan Kettering Cancer Center, NY.

"Based upon the available evidence, the combination represents a means to improve outcomes, versus nivolumab alone, particularly for patients whose tumors have <5% PD-L1 expression," Dr Wolchok said.

Patients who expressed PD-L1 derived essentially as much benefit from single-agent nivolumab as from the combination of nivolumab and ipilimumab, he said.

The important findings were presented at a plenary session at ASCO 2015. Results of the phase 2 clinical trial were presented earlier this year.

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"Nivolumab alone and nivolumab plus ipilimumab significantly improved progression-free survival and objective response rates versus ipilimumab alone in patients with previously untreated melanoma."

—Jedd D. Wolchok, MD, PhD

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—Michael B. Atkins, MD

The CheckMate 067 Phase 3 Trial

CheckMate 067 was the first phase 3 clinical trial to evaluate the combination of an anti–PD-1 and an anti–CTLA-4 agent. The trial randomized 945 treatment-naïve patients with advanced or metastatic melanoma in a 1:1:1 fashion to 1 of 3 arms—(1) nivolumab 1 mg/kg every 2 weeks plus ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks; (2) nivolumab 3 mg/kg every 2 weeks plus placebo; or (3) ipilimumab 3 mg/kg every 3 weeks for 4 doses plus placebo, until disease progression or unacceptable toxicity.

The study's coprimary end points were (1) PFS with nivolumab alone and (2) PFS with nivolumab plus ipilimumab versus ipilimumab alone.

"Nivolumab alone and nivolumab plus ipilimumab significantly improved progression-free survival and objective response rates versus ipilimumab alone in patients with previously untreated melanoma," Dr Wolchok said.

In the overall population, the median PFS was 11.5 months with the combination (hazard ratio [HR], 0.42 vs ipilimumab; P <.001), 6.9 months with nivolumab alone (HR, 0.57 vs ipilimumab; P <.001), and 2.9 months with ipilimumab alone.

The combination also produced a higher response rate of 57.6% versus 43.7% with nivolumab alone and 19.0% for ipilimumab alone; both nivolumab-containing arms were statistically significant versus the ipilimumab monotherapy arm (P <.001).

The duration of response in all 3 arms was not yet reached at a minimum follow-up of 9 months. The median change in tumor burden was –51.9% with the combination, –34.5% with nivolumab alone, and +5.9% with ipilimumab alone.

The Importance of PD-L1 Expression

PD-L1 expression defined a group of patients with melanoma whose outcomes were different from the overall study population. In patients whose tumors had at least 5% PD-L1 expression, nivolumab alone and nivolumab plus ipilimumab resulted in a similar prolongation in PFS, 14 months in each arm, versus 3.9 months with ipilimumab alone, Dr Wolchok reported.

Steven O'Day, MD, a melanoma expert, commented, "Right now, in PD-L1–positive patients, we can be fairly reassured that their progression-free survival will be very similar," whether they receive a single-agent anti–PD-1 therapy or 2 immunotherapies together.

The dual immunotherapy regimen proved to be relatively well-tolerated, although 55% of patients had grade 3 or 4 adverse events compared with 16.3% of patients receiving nivolumab and 27.3% receiving ipilimumab, Dr Wolchok reported. These side effects were consistent with previous reports.

"We had no drug-related deaths in the combination arm. This is a very important point, because the trial was conducted in 137 sites globally. Safety guidelines were put into place so that physicians in a variety of venues were able to handle the side effects," Dr Wolchok said.

Superior Combination

Michael B. Atkins, MD, Deputy Director, Lombardi Comprehensive Cancer Center of Georgetown University, Washington, DC, discussed CheckMate 067 at the plenary session, commenting, "Nivolumab and nivolumab plus ipilimumab are superior to ipilimumab. These treatments (along with pembrolizumab [Keytruda]) are a new standard for advanced melanoma therapy."

However, Dr Atkins objected to the concept of PD-L1 as a biomarker, at least at this point. "PD-L1 must be viewed as a weak biomarker," he maintained.

For a number of reasons, he said, PD-L1 and its assays need to be validated before PD-L1 can be used for clinical decision-making.

Dr Atkins added that based on available data on the 2 PD-1 inhibitors, nivolumab and pembrolizumab have no "clear-cut distinction of therapeutic index."

In the absence of a clinical trial, he believes physicians will choose them based on factors such as dosing schedule, clinical experience, marketing, predictability of biomarkers, and cost. ■

Nivolumab First Immunotherapy to... *Continued from page 30*

during or after chemotherapy with a platinum-based regimen. Patients were randomized to nivolumab (N = 135) 3 mg/kg intravenously every 2 weeks or to docetaxel (N = 137) 75 mg/m^2 intravenously every 3 weeks. The major efficacy outcome was overall survival (OS).

The OS was 9.2 months with nivolumab compared with 7.3 months with docetaxel, a significant improvement (P = .002).

Additional efficacy support was provided from a single-arm, multinational, multicenter trial in 117 patients with metastatic squamous NSCLC whose disease progressed after platinum-based chemotherapy and ≥1 additional systemic regimens. Objective response rate, the major efficacy outcome, was 15%. At the time of analysis, the response duration was ≥6 months in 59% of the responding patients.

Adverse events were similar to previous trials with nivolumab. Immune-mediated adverse reactions included pneumonitis, colitis, hepatitis, nephritis/renal dysfunction, hypothyroidism, and hyperthyroidism. (**March 4, 2015**) ■