MedicalXpress

Immunotherapy combo increases progression-free survival in advanced melanoma patients

May 31 2015

Treating advanced melanoma patients with either a combination of the immunotherapy drugs nivolumab (Opdivo) and ipilimumab (Yervoy) or nivolumab alone significantly increases progression-free survival (PFS) over using ipilimumab alone, according to new findings from researchers at Memorial Sloan Kettering Cancer Center (MSK) simultaneously presented today at the American Society of Clinical Oncology (ASCO) annual meeting and published online in the *New England Journal of Medicine* (*NEJM*). Examining specific characteristics of each patient's tumor has also given researchers clearer understanding of which patients should receive the combination.

These initial findings from the phase III clinical trial confirm the results of the phase II trial, presented just weeks ago at the American Association of Cancer Research annual meeting in Philadelphia and published by MSK researchers online in *NEJM*.

Jedd Wolchok, Chief of MSK's Melanoma and Immunotherapeutics Service, designed and led the phase III randomized, double-blind trial, in which 945 patients with untreated advanced melanoma were randomized to receive ipilimumab alone, nivolumab alone, or a combination of the two.

While this study was not designed for a formal statistical comparison between the nivolumab group and the combination group, exploratory analyses revealed more frequent responses and longer PFS in the combination group when compared with nivolumab alone. Patients

receiving the combination experienced a median PFS of 11.5 months, while median PFS for patients receiving nivolumab alone was 6.9 months and ipilimumab alone was 2.9 months.

Of the 314 patients receiving the combination, 57.6 percent had an objective response, measured as a significant reduction in tumor size, versus 43.7 percent of the 316 receiving nivolumab alone and 19 percent of the 315 receiving ipilimumab alone.

"All the early preclinical and clinical work supported the idea that combining these two immunotherapy drugs could result in better outcomes for patients," said Dr. Wolchok. "We're encouraged by the progression-free survival data we're currently reporting. It is a testament to how drastically immunotherapy has altered the prognostic landscape for some advanced melanoma patients. Just five years ago, many of these patients would have been expected to live for only seven months following diagnosis—but it's important to remember that overall survival data for this group is not yet available."

Adverse side effects such as diarrhea and increased lipase occurred in 55 percent of patients receiving the combination—leading about one-third of these patients to stop the regimen. About 16 percent of patients receiving nivolumab alone and 27 percent of patients receiving ipilimumab alone experienced side effects, with nearly 8 percent and 15 percent of patients discontinuing, respectively.

Ipilimumab and nivolumab are part of a class of drugs called immune checkpoint inhibitors, which unleash patients' immune system to attack their cancer. The immune system has several checkpoints in place to avoid an overreaction. Ipilimumab works by blocking the CTLA-4 checkpoint, a molecular brake that stops T cells from becoming fully and persistently activated. Similarly, nivolumab prevents the molecule PD-L1, expressed by tumors, from binding to T cells and deactivating them.

Notably in this trial, patients whose tumors expressed PD-L1 experienced a median PFS of 14 months regardless of whether they received the combination or nivolumab alone, but for patients whose tumors did not express PD-L1, the median PFS was longer on the combination (11.2 months) than on nivolumab alone (5.3 months).

"One of the biggest questions in the field of immunotherapy has been how to determine which patients will respond to immune-modulating drugs. Now we have another piece of data," said Dr. Wolchok. "A simple pathology test can identify patients whose tumors express PD-L1, and this information will help the patient and physician decide whether to use the combination or nivolumab alone, knowing the toxicity risks and the difference in PFS. However, if a patient's tumor does not express PD-L1, the data suggests it makes more sense to offer the combination. This understanding gets us closer to 'precision immunotherapy.'"

Dr. Wolchok, who is also the Associate Director of the Ludwig Center for Cancer Immunotherapy at MSK, designed this clinical trial on a napkin at the 2012 ASCO annual meeting ¬before the data from the phase I trial were even presented.

"Even then, we knew the potential that immunotherapy could have for the lives of patients diagnosed with advanced melanoma and other cancers," he said. "As we present this exciting and hopeful data to the international oncology community, we pause and thank the patients who enrolled in this—and all—clinical trials. These individuals are blazing the trails of cancer research, and we are indebted to them for helping to better the care of patients for generations to come."

Provided by Memorial Sloan Kettering Cancer Center