FIVE-YEAR SURVIVAL QUADRUPLED IN RESPONDERS TO NIVOLUMAB FOR NON–SMALL CELL LUNG CANCER

By Alice Goodman
May 10, 2017

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At 5 years, the overall survival rate was 16% in patients with advanced non–small cell lung cancer (NSCLC) treated with single-agent nivolumab (Opdivo), according to follow-up of a phase Ib dose-ranging study (CA209-003), presented at the American Association for Cancer Research (AACR) Annual Meeting.[1] This represents the longest follow-up data on single-agent anti–programmed cell death protein 1/ programmed cell death ligand 1 (PD-1/PD-L1) in NSCLC and a quadrupling of 5-year survival reported with standard chemotherapy.

"This is the first report of long-term survival rate in patients with metastatic NSCLC treated with an immune checkpoint inhibitor. Our study results show that for a small subset of patients, immunotherapy can work for a very long time," stated lead author **Julie R. Brahmer, MD**, Director of the Thoracic Oncology Program and Associate Professor of Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore.

"The 5-year rate of overall survival in this study is much higher than what is reported for this patient population treated with standard-of-care chemotherapy. Most patients with advanced disease die within 1 year from the time of diagnosis, and the 5-year survival rate for metastatic NSCLC is about 4%," she said.

"The majority of survivors had no evidence of disease progression at the time of their last follow-up. These findings offer important new insights into the long-term clinical profile of nivolumab in this patient population," said senior author **Scott N. Gettinger, MD**, Associate Professor of Medicine at Yale Cancer Center, New Haven, Connecticut.

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Nivolumab is approved by the U.S. Food and Drug Administration for second-line treatment of patients with advanced NSCLC.

Study Details

CA209-003 was a phase Ib, open-label, multicenter, dose-escalation study of nivolumab in 129 patients with advanced or recurrent NSCLC.

Patients had been previously treated with 1 to 5 systemic therapies and received nivolumab in 3 dosing cohorts (1, 3, and 10 mg/kg given intravenously every 2 weeks for < 96 weeks). Patients were enrolled regardless of PD-L1 expression levels in the tumor. The data presented at the AACR meeting represent pooled data for all three dosing cohorts for NSCLC patients enrolled in the trial.

The estimated 5-year overall survival rate was 16%. Median overall survival was 9.9 months at a minimum of 58 months of follow-up. Five-year survival rates were consistent across histologies (squamous = 16%, nonsquamous = 15%).

Long-Term Immunotherapy for NSCLC

- Sixteen percent of patients with advanced NSCLC treated with nivolumab were alive 5 years after treatment; this compares with only about 4% of patients alive at 5 years with conventional chemotherapy.
- The study failed to identify biomarkers that could predict survival. The search continues to determine which patients might best respond to immunotherapy and reap a survival benefit.

In 68 of 129 patients with evaluable PD-L1 expression (53% of patients), 5-year survival rates increased in a linear fashion with increasing levels of PD-L1 expression. Five-year survival rates were 20% in patients with PD-L1 < 1%, 23% in those with PD-L1 ≥ 1%, and 43% in those with PD-L1 ≥ 50%. “The survival curve seems to flatten out after 3 years,” Dr. Brahmer noted.

PD-L1 status was not evaluable in 47% of patients. Among patients with unknown PD-L1 expression levels, the estimated 5-year overall survival rate was 10%.

Additional Data

Of 16 patients who survived for at least 5 years, 9 were male and 12 were current smokers at trial enrollment. Twelve patients had a partial response, 2 had stable disease, and 2 had progressive disease as best response to treatment.

Eight patients completed 2 years of treatment with no side effects, and 4 stopped treatment early due to side effects. None of these 12 patients required further cancer treatment, and all of them had no evidence of disease progression at their last follow-up visit.

The investigators were not able to detect a consistent pattern for clinical and tumor characteristics that could predict survival. Although baseline tumor biopsy was a study requirement, not all patients had adequate samples for determining PD-L1 status.

“PD-L1 status was not clearly associated with long-term survival in this small group of patients,” she said.

Dr. Brahmer and colleagues plan to perform further studies of these survivors to determine why they had such a good outcome. “We also want to better understand which patients can stop treatment at 2 years and which of them need to continue treatment beyond 2 years,” she said.

Implications of Findings

Press conference moderator **Suzanne L. Topalian, MD**, Professor of Surgery and Oncology, John Hopkins Medicine; Associate Director of the Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins; and Melanoma Program Director at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, noted that these are long-term results from the very first trial of any anti–programmed cell death protein 1 (PD-1) immune checkpoint inhibitor in cancer.

“These results represent a landmark in the history of immunotherapy in cancer. Results showed immunotherapy could be used to treat common cancers and brought it out of the realm of specialized treatment into the broader realm of oncology. This is the longest follow-up to date of an immune checkpoint inhibitor. Five-year overall survival quadrupled in NSCLC compared with what we would expect from chemotherapy,” she said.

“The study shows the durability of response with checkpoint inhibitors. On this trial, patients received a maximum of 2 years of therapy. Currently, many patients are getting this therapy indefinitely,” she added. “When the drug was stopped early, 75% of patients maintained their responses. This brings up the issue of how long these drugs should be given.”

At the press briefing, Dr. Brahmer replied that when the phase III trials were designed, the optimal duration of therapy was unknown. “Based on these data, I think we can shorten the amount of time patients are treated. But we need to identify those patients who develop immune memory [on immune checkpoint inhibitors] to combat their cancer long term. Ongoing trials are being

amended. CheckMate 153 is comparing continuous dosing until progression vs 2 years of nivolumab," Dr. Brahmer said.

"We can safely say not all NSCLC patients need indefinite treatment. We want to personalize therapy. We are continuing to look for biomarkers for response and long-term control," she noted. "In this trial, no clinical characteristic stands out to identify long-term survivors." ■

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Disclosure: Dr. Brahmer has received research support and been an advisor for Bristol-Myers Squibb, Merck, and AstraZeneca. Dr. Topalian has been a consultant for, received research support from, or owned stock in AbbVie, Bristol-Myers Squibb, Five Prime Therapeutics, Amgen, Compugen, Jounce Therapeutics, MedImmune, Merck, Pfizer, Potenza Therapeutics, Sanofi, and Tizona.

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