Expansion of circulating tumor-specific T cells after treatment suggested systemic antitumor immunity

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The anti-PD1 immunotherapy nivolumab (Opdivo) given prior to surgical resection of stage 1-3 non-small cell lung cancer (NSCLC) was safe and resulted in major pathological responses in 45 percent of the patients, according to data from a clinical trial presented at the AACR Annual Meeting 2018, April 14-18.

A major pathologic response is defined as 10 percent or fewer viable cancer cells detectable in the resected tumor following neoadjuvant treatment.

This study is being simultaneously published in the *New England Journal of Medicine*.

"The rationale for neoadjuvant anti-PD1 treatment of resectable NSCLC was essentially to use the primary tumor as a "vaccine" to induce T cells against the tumor antigens that would then circulate through the body systemically and seek out any distant sites of micrometastases," said senior author of the study Drew Pardoll, MD, Ph.D., director of Bloomberg~Kimmel Institute for Cancer Immunotherapy and director of Cancer Immunology at Johns Hopkins School of Medicine. "Micrometastases are the primary source of relapse after surgery."

Conventional neoadjuvant therapy, chiefly comprising chemotherapy or chemoradiotherapy, is given to lung cancer patients to shrink a large, non-

metastasized tumor located near an important organ or a blood vessel. The tumor is temporarily shrunk prior to surgery to improve surgical outcomes, Pardoll explained.

"The most stunning finding was that nine of the 20 patients who had surgery after neoadjuvant anti-PD1 had a major pathologic response," Pardoll noted. "Two patients had no evidence of viable cells in the resected specimen. This is particularly striking given that surgery was done, in most cases, just four weeks after the first dose of anti-PD1 treatment."

He added, "Our result of a 45 percent major pathologic response rate is very encouraging, considering prior studies showing that a major pathologic response after neoadjuvant chemotherapy in lung cancer is associated with long-term survival."

Pardoll and colleagues enrolled 21 patients with stage 1-3A NSCLC in this trial between August 2015 and October 2016; 62 percent had adenocarcinoma. All patients received at least one dose of nivolumab. The median time from second dose of nivolumab to surgery was 18 days, and 20 of 21 eligible patients underwent complete tumor resection. "The anti-PD1 treatment was tolerated well and there were no surgical delays related to neoadjuvant treatment," Pardoll noted.

Major pathologic responses were observed in the patients' tumors irrespective of PD-L1 expression by tumor cells. Tumor mutation burden closely predicted the degree of pathologic response. After a median follow-up of 12 months, 16 of 20 patients who underwent surgical resection were alive and recurrence-free. Recurrence-free survival at 18 months was 73 percent, and the median recurrence-free survival had not been reached at the time of data analysis.

To test their hypothesis that checkpoint blockade induces the expansion

of tumor-specific T cells in the circulation, the researchers analyzed T-cell responses in the blood on the day of nivolumab treatment and 44 days after surgery. "There was a big burst of tumor-specific T cells in the blood within, in most cases, four weeks after initiation of anti-PD1 treatment suggesting that neoadjuvant treatment may have enhanced antitumor immunity systemically," Pardoll said.

"While it is still too early to tell whether our findings will translate into lower relapse rate and improved survival, pending confirmation in a larger study, we are very optimistic that this approach will eventually be practice-changing and may augment or even replace chemotherapy prior to surgical resection," Pardoll said.

"We have to be careful not to compare these outcomes with historical outcomes given the small size of this single-arm study; however these initial results are highly encouraging and, allied to the translational science, will spur interest in further neoadjuvant clinical trials across tumor types," concluded study leader and co-principal investigator of the trial, Patrick Forde, MBBCh, assistant professor of oncology at Bloomberg~Kimmel Institute for Cancer Immunotherapy.

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