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Combining cytokine-based immunotherapy AM0010 with Pembrolizumab

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A combination of the immunotherapies AM0010 and the immune checkpoint inhibitor pembrolizumab was well tolerated and resulted in durable objective tumor responses in some patients with renal cell carcinoma (RCC) and non-small cell lung cancer (NSCLC), according to data from a phase Ib clinical trial presented at the Second CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference: Translating Science into Survival, held Sept. 25–28.

"Immunotherapy has improved the prospects for many cancer patients by providing long-term benefit, but not all patients respond to the currently available immuno-oncology drugs," said Aung Naing, MD, an associate professor in the department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center in Houston. "Rational combinations of immune therapies are likely to expand the tumor-specific immune activation and lead to more durable tumor responses."

Naing and colleagues are investigating a novel immunotherapy, AM0010, which is a PEGylated form of the recombinant human cytokine IL-10. This therapy has specific immune-stimulating effects that induce the activation, proliferation, and survival of cytotoxic CD8-positive (CD8+) T cells present within the tumors of patients, Naing explained.

The targets of AM0010 and pembrolizumab, IL-10 receptor and PD-1, respectively, are both present on CD8+ T cells. AM0010 enhances the

survival and tumor cell-killing activity of CD8+ T cells and complements the activity of pembrolizumab that blocks the immune-suppressive PD-1/PD-L1 pathway, thus providing a rationale for this combination, Naing said.

"In this clinical trial, we found that the two immunotherapies were well tolerated, without overlapping toxicity or severe autoimmunity, while providing strong antitumor responses," Naing said. "In addition, we detected new, expanding T-cell clones in the blood of all patients who received AM0010. Many of those T-cell clones were not detectable before treatment. This is reminiscent of tumor-specific vaccination."

In this multi-cohort phase I clinical trial, the investigators enrolled 19 patients with advanced melanoma, RCC, or NSCLC to a cohort in which patients received one of the two doses of AM0010 daily and 2 mg/kg body weight pembrolizumab every three weeks.

After 10 to 15 months of observation, two of the eight patients with renal cell carcinoma had a complete reduction of their tumor burden (complete responses) and two had a 77 and 92 percent reduction (partial responses (PR)), respectively. Of the six melanoma patients, two had PR, and two others had an initial increase in tumor volume followed by a decrease (known as pseudoprogression).

The most common side effects associated with AM0010 were anemia, thrombocytopenia, and fatigue, which were all manageable. Importantly, AM0010 did not lead to autoimmune side effects.

The weapons used by CD8+ T cells in killing cancer cells are the cytotoxic molecules —granzymes, FasL and lymphotoxin beta. With AM0010 treatment, the levels of these cytotoxic molecules were elevated in the serum of the patients, which provides further evidence of the systemic activation of the cytotoxic arm of the immune system,

according to Naing.

Effects such as the elevation of cytotoxic molecules and the expansion of T-cell clones in the blood were also observed in patients from other cohorts in this clinical trial in which AM0010 was tested as monotherapy or in combination with chemotherapies.

The main limitation is that this is a study with a small number of patients with RCC and NSCLC; however, the immunological profiles and early results support the interpretation, Naing said.

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