Modified Personalized Cancer Vaccine Generates Powerful Immune Response

Dana-Farber researchers designed a novel formulation and delivery approach for the NeoVax personalized cancer vaccine and observed strong vaccine-specific immune responses in patients with melanoma.

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Results of a Dana-Farber Cancer Institute-initiated phase 1 clinical trial for patients with melanoma show that an updated formula and delivery of the NeoVax personalized cancer vaccine called NeoVax^{MI} is safe, feasible, and improves the vaccine-specific immune response compared to previous trials of the platform. The findings are published in Cell.

“We believe that the immunogenicity of current personalized cancer vaccines, considered critical for their effectiveness, can be improved substantially,” says senior-author Patrick Ott, MD, PhD, clinical director of the Melanoma Disease Center at Dana-Farber. “This study provides evidence showing that changes in formulation and administration improve the power of the vaccines.”

Ott initiated the trial enrolling patients with previously untreated advanced or high-risk melanoma with the goal to fully vaccinate all patients with NeoVax^{MI} and perform in depth analysis of their immune responses. No formal clinical outcome assessments beyond the safety and feasibility of the vaccine were planned for the trial.

NeoVax^{MI} is a personalized neoantigen-targeted vaccine based on the NeoVax platform originally developed at Dana-Farber by Ott and Catherine Wu, MD, chief of the Division of Stem Cell Transplantation and Cellular Therapies, who is also a senior author on the paper. NeoVax includes personalized neoantigens, which are protein fragments that appear on an individual patient’s cancer cells and not on normal cells, plus an immunostimulant called poly-ICLC. NeoVax^{MI} adds another immune-boosting compound called Montadine to the mix.

Administration ofNeoVax^{MI} in the trial also changed to include two additional immunotherapies. Patients received systemic nivolumab [Opdivo] prior to, during, and after the vaccine series. Systemic nivolumab reduces immune suppression and is standard of care therapy for patients with resected or advanced melanoma. They also received ipilimumab [Yervoy] locally at the vaccination site during the vaccine series. The addition of sub-cutaneous delivery of ipilimumab was predicted

to enhance the activation of immune cells called T cells to respond to the antigens introduced by the vaccine.

Nine patients were fully vaccinated. To assess the magnitude of T cell responses induced by NeoVax[MI], the team isolated T cells from patient blood samples after vaccination and assessed their ability to recognize and respond to vaccine-specific neoantigens in a dish. They observed T cell responses to neoantigens in all nine patients and cytotoxic responses by special T cells called CD-8+ T cells in six of nine patients.

“These observations of ex vivo CD-8+ T cell responses are what we want to see in a vaccine, and we were excited to see this important aspect of a cancer vaccine-induced immune response on the current trial,” says Ott.

The investigators also examined skin biopsies taken from the vaccine and ipilimumab injection sites using leading edge single cell sequencing approaches. In these samples, they saw an increase in immune cells called macrophages after vaccination, suggesting that NeoVax[MI] primed the area to initiate immune activation in response to the vaccine.

“The right environment at the injection site to trigger the immune cells to begin an immune activation cascade is critical.” says Ott.

The team also demonstrated that different sets of receptors expressed on the T cells emerged after vaccination compared to the standard treatment nivolumab. The number of types of distinct vaccine-specific T cells activated after vaccination exceeded the number produced after treatment with nivolumab, suggesting a potent vaccine-induced immune response.

Based on tumor samples from four patients and using new technologies enabling definitive interrogation of individual (single) T cells, the team confirmed that the vaccine-induced T cells infiltrated tumors.

“These are exciting observations showing that this new formulation and delivery strategy improves the power of the vaccination,” says Ott. “The methods we used to measure the immune responses are rigorous and unique in the field in the setting of a clinical trial. Studies like this are important if we want to continue to improve personalized cancer vaccines.”

NeoVax[MI] was well tolerated and did not introduce new safety concerns. The study is limited by its small size and by the introduction of three new agents together, which makes it difficult to attribute observed improvements to specific changes to the vaccine.

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