Personalized mRNA Vaccine Delays Melanoma Relapse for Three Years

A customized neoantigen vaccine plus Keytruda significantly reduced the risk of cancer recurrence or metastasis.

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People with advanced melanoma who received a customized messenger RNA (mRNA) cancer vaccine from Moderna and Merck along with checkpoint inhibitor immunotherapy remain less likely to experience recurrence or metastasis at three years, according to study results presented this week at the American Society of Clinical Oncology Annual Meeting (ASCO 2024).

In this planned follow-up analysis from a Phase IIb trial, patients who received the vaccine, dubbed mRNA-4157 (V940), plus Merck's checkpoint inhibitor Keytruda (pembrolizumab) had a 49% lower risk of cancer recurrence or death. These findings, which build on two-year data presented at last year's ASCO meeting, indicate that vaccination appears to be a durable strategy for keeping melanoma under control.

Cancer vaccines are designed to train the immune system to recognize and attack malignant cells. Early studies were disappointing, but now, a better understanding of how cancer develops and how the immune system responds, along with better immunotherapy partners, have renewed hope that therapeutic vaccines could halt disease progression, prevent relapse and perhaps even offer a cure.

The experimental mRNA-4157 (V940) vaccine is based on the same mRNA technology as the Moderna and Pfizer/BioNTech COVID-19 vaccines, which use lipid nanoparticles to deliver genetic instructions for proteins that trigger an immune response. Personalized cancer vaccines contain blueprints for neoantigens—abnormal proteins expressed by cancer cells—selected by sequencing a patient's tumor; mRNA-4157 (V940) contains up to 34 neoantigens.

Some tumors can suppress natural immune responses meant to keep them in check. Combining a neoantigen vaccine with a PD-1 checkpoint inhibitor like Keytruda—a monoclonal antibody that restores T-cell activity—could have the effect of releasing the brakes and stepping on the accelerator at the same time.

Jeffrey Weber, MD, PhD, of Perlmutter Cancer Center at NYU Langone Health, presented the latest findings from the KEYNOTE-942 trial (NCT03897881), which is testing mRNA-4157 (V940) in 157

people with Stage III or IV cutaneous melanoma. Their tumors were completely removed but the cancer had spread to lymph nodes, so they were considered at high risk for recurrence or metastasis.

The study participants were randomly assigned to receive either mRNA-4157 (V940) plus Keytruda or Keytruda alone. Those in the first group had a custom vaccine made using neoantigens from a tumor biopsy sample. They received injections of the vaccine every three weeks for up to nine doses. Patients in both groups received Keytruda by IV infusion every three weeks for approximately one year.

In the primary analysis after a median two years of follow-up, published in The Lancet, people who received the vaccine had longer recurrence-free survival. At 18 months, 79% or patients in the vaccine plus Keytruda group and 62% in the Keytruda monotherapy group were still alive without relapsing—a 44% reduction in the risk of recurrence or death.

With an additional year follow-up, there were few new relapses. The 2.5-year recurrence-free survival rates were 75% in vaccine plus Keytruda group versus 56% in the Keytruda monotherapy group, so the risk reduction reached 49%. What's more, the risk of distant metastasis or death was 62% lower in the vaccine group. These results were consistent regardless of tumor mutation burden, PD-L1 status or individual immune system genetic variations (HLA alleles). Overall survival data are not yet mature, but so far they appear to favor the vaccine group (96% versus 90%).

Treatment was generally safe and well tolerated, and side effects were consistent with those observed in previous studies of Keytruda. Adding the vaccine did not substantially increase severe adverse events or raise the risk of immune-related adverse events. The most common side effects attributed to mRNA-4157 (V940) in combination with Keytruda were fatigue (61%), injection site pain (57%) and chills (49%).

Researchers at several other companies are also working on vaccines for various types of cancer. BioNTech—Moderna's COVID vaccine rival—and Genentech are developing an mRNA vaccine for pancreatic cancer dubbed autogene cevumeran. Half of the patients in a small Phase I study who received the vaccine plus the checkpoint inhibitor Tecentriq (atezolizumab) after surgery developed strong T-cell responses against tumor neoantigens. The latest data, presented at the recent American Association for Cancer Research annual meeting, show that patients with good responses were less likely to experience recurrence over three years of follow-up.

Moderna and Merck are ahead of the pack with their Phase II melanoma data. As longer follow-up continues in that study, larger Phase III trials of mRNA-4157 (V940) for high-risk advanced melanoma and non-small cell lung cancer are currently enrolling. Trials for cutaneous squamous cell carcinoma, kidney cancer and bladder cancer are in Phase II, according to a Moderna and Merck news release.

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