

Experimental mRNA Vaccine Plus Keytruda Delays Melanoma Recurrence

Moderna and Merck's personalized neoantigen vaccine plus checkpoint inhibitor lowered the risk of disease progression after surgery by 44%.

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A personalized messenger RNA (mRNA) cancer vaccine plus the checkpoint inhibitor Keytruda (pembrolizumab) reduced the risk of recurrence or death in people with high-risk advanced melanoma, according to research presented Sunday at the [AACR Annual Meeting 2023](#).

The vaccine, dubbed mRNA-4157 (V940), being jointly developed by Moderna and Merck, uses the same [mRNA technology](#) as the Moderna and Pfizer-BioNTech COVID-19 vaccines. Several companies are working on [vaccines to help the immune system fight cancer](#). mRNA vaccines use lipid nanoparticles (fat bubbles) deliver bits of genetic material that carry instructions for specific proteins. When injected into a muscle, human cells produce the proteins, which trigger an immune response. The COVID vaccines deliver blueprints for the SARS-CoV-2 spike protein. Personalized cancer vaccines contain DNA for neoantigens—abnormal proteins expressed by an individual's tumor cells—selected by sequencing a tumor biopsy sample; mRNA-4157 contains instructions for some three dozen neoantigens.

“Vaccine strategies over the last 25 years attempted to induce immune responses against tumor-associated antigens that are not absolutely specific to the tumor,” presenting investigator Jeffrey Weber, MD, PhD, of NYU Langone Perlmutter Cancer Center, said in an [AACR news release](#). “More recent cancer vaccine approaches have focused on targeting neoantigens originated from individual tumor mutations, which are unique to cancer cells.”

Some tumors can suppress natural immune responses meant to keep them in check. Combining a vaccine that helps immune cells recognize cancer with a PD-1 checkpoint inhibitor such as Keytruda—a monoclonal antibody that restores T-cell activity—could have the effect of letting up on the brakes and stepping on the accelerator at the same time. In a [small Phase I trial](#), mRNA-4157 plus Keytruda shrank tumors in 50% of people with head and neck cancer, though no responses were seen in patients with colorectal cancer.

Given promising early results, a version of the vaccine called mRNA4157 (V940) was evaluated in the Phase IIb KEYNOTE-942 trial ([NCT03897881](#)) as a treatment for advanced melanoma. The study included 157 participants with Stage III or IV cutaneous melanoma that had been completely

removed within the prior 13 weeks, but it had spread to a lymph node, so they were considered at high risk for recurrence. They were randomly assigned to receive Keytruda for up to a year either alone (50 patients) or with the vaccine administered every three weeks for up to nine doses (107 patients).

Over two years of follow-up, the vaccine combination demonstrated “statistically significant and clinically meaningful improvement” over Keytruda alone, Weber reported. Recurrence-free survival rates at one year were 83.4% in the vaccine group versus 77.1% in the Keytruda monotherapy group. At 18 months, the corresponding rates were 78.6% versus 62.2%—a 44% reduction in the risk of recurrence or death.

Another analysis showed that people with a high tumor mutation burden (which could mean they have more neoantigens to target), a high tumor inflammation score (suggesting stronger immune responses) or a high tumor PD-L1 level (a marker for favorable response to PD-1 checkpoint inhibitors) had somewhat better outcomes, but the researchers calculated that the vaccine plus Keytruda combination “is similarly effective in all patient subsets.”

“The novel mechanism of action of mRNA-4157 may both deepen the activity of pembrolizumab and broaden the population of patients that can benefit from immune therapy,” Ryan Sullivan, MD, of Mass General Cancer Center, and colleagues concluded.

Treatment was generally safe, but adverse events were common. Side effects were consistent with those observed in previous studies of Keytruda, and adding the vaccine did not substantially increase severe adverse events (25% in the vaccine group versus 18% in the Keytruda monotherapy group). Just over half of vaccine recipients reported mild or moderate injection site pain.

“For the first time in a randomized study with a control arm, the addition of an mRNA neoantigen vaccine appeared to augment the benefit of PD-1 blockade, without adding significant high-grade toxicity,” Weber said. “This study is extraordinarily important, because it gives hope that this novel strategy will provide clinical benefit.”

Weber noted that a larger Phase III randomized trial to confirm these findings will start soon. Moderna and Merck also plan to expand studies to include other tumor types, such as lung cancer. In addition, Moderna is exploring [other cancer vaccine candidates](#), including mRNA-5671, which targets tumors with KRAS mutations.

Editor’s note: this report has been updated to indicate that mRNA-4157 (V940) is being jointly developed by Moderna and Merck.

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