Personalized mRNA Vaccine Reduces Melanoma Relapse at 5 Years

A customized neoantigen vaccine plus checkpoint inhibitor immunotherapy lowered the risk of recurrence or death by 49% in a mid-stage trial.

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People with advanced melanoma who received a customized messenger RNA (mRNA) vaccine along with the immune checkpoint inhibitor Keytruda (pembrolizumab) continue to show "sustained and clinically meaningful" improvement in recurrence-free survival at five years, Merck and Moderna announced this week.

The vaccine—now dubbed intismeran autogene (previously mRNA-4157 or V940)—plus Keytruda was associated with a 49% reduction in the risk of disease recurrence or death. The news release did not provide further details, but the companies said more information would be presented at an upcoming medical meeting.

Cancer vaccines are designed to train the immune system to recognize and attack malignant cells. They appear to be particularly good at keeping cancer under control and preventing recurrence after surgery to remove tumors.

Intismeran autogene is based on the same mRNA technology as the Moderna COVID-19 vaccine. While that vaccine contains genetic instructions for the SARS-CoV-2 coronavirus spike protein, the melanoma vaccine contains blueprints for up to 34 neoantigens—mutated proteins on cancer cells—selected by sequencing a patient's tumor. PD-1 checkpoint inhibitors like Keytruda restore T-cell activity against cancer. Thus, combining a neoantigen vaccine with a checkpoint inhibitor could have the effect of releasing the immune system's brakes and stepping on the accelerator at the same time.

The Phase IIb KEYNOTE-942 trial (NCT03897881) is evaluating intismeran autogene for people with Stage III or IV cutaneous melanoma. The study enrolled 157 patients who had their tumors completely removed, but their cancer had spread to a lymph node, and they were considered at high risk for recurrence.

The participants were randomly assigned to receive intismeran autogene plus Keytruda or Keytruda alone. Those in the first group had a custom vaccine made using neoantigens from a tumor biopsy sample. They received vaccine injections every three weeks for up to nine doses.

Patients in both groups received Keytruda by IV infusion every three weeks for approximately one year.

Findings from the primary analysis, presented at the 2023 American Association for Cancer Research annual meeting and published in The Lancet, showed that people who received intismeran autogene had longer recurrence-free survival. After 18 months of follow-up, 79% of patients in the vaccine plus Keytruda group and 62% in the Keytruda monotherapy group were still alive and had not relapsed—a 44% reduction in the risk of recurrence or death. Treatment was generally safe and well tolerated, with no severe adverse effects attributed to the vaccine.

With an additional year follow-up, there were few new relapses, investigators reported at the 2024 American Society of Clinical Oncology annual meeting. Recurrence-free survival rates at approximately three years were 75% in the vaccine plus Keytruda group versus 56% in the Keytruda monotherapy group—a 49% risk reduction. What's more, the risk of distant metastasis or death was 62% lower in the vaccine group. Overall survival data were not yet mature but appeared to favor vaccine recipients.

Five-year follow-up data are now available, showing that the reduction in the risk of disease recurrence or death in the vaccine group still holds at 49%, according to this week's news release. The safety profile of intismeran autogene "remains consistent with that previously reported," the companies noted.

"Now with five years of follow-up data, today's results highlight the potential of a prolonged benefit of the intismeran autogene and Keytruda combination in patients with resected high-risk melanoma," said Moderna senior vice president Kyle Holen, MD. "We continue to invest in our platform in oncology because of encouraging outcomes like these, which illustrate mRNA's potential in cancer care."

Larger Phase III trials of the vaccine plus Keytruda are now ongoing for patients with high-risk advanced melanoma (INTerpath-001) and non-small-cell lung cancer (INTerpath-002). Speaking at the recent J.P. Morgan Healthcare Conference, Moderna CEO Stéphane Bancel suggested interim results from the melanoma trial could be available later this year.

In addition, Phase II studies are underway for other malignancies, including kidney cancer (INTerpath-004), bladder cancer (INTerpath-005) and cutaneous squamous cell carcinoma (INTerpath-007). Intismeran autogene is also being tested in combination with Bacillus Calmette-Guerin (BCG)—a different type of immunotherapy—for people with high-risk non-muscle invasive bladder cancer (INTerpath-011).

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