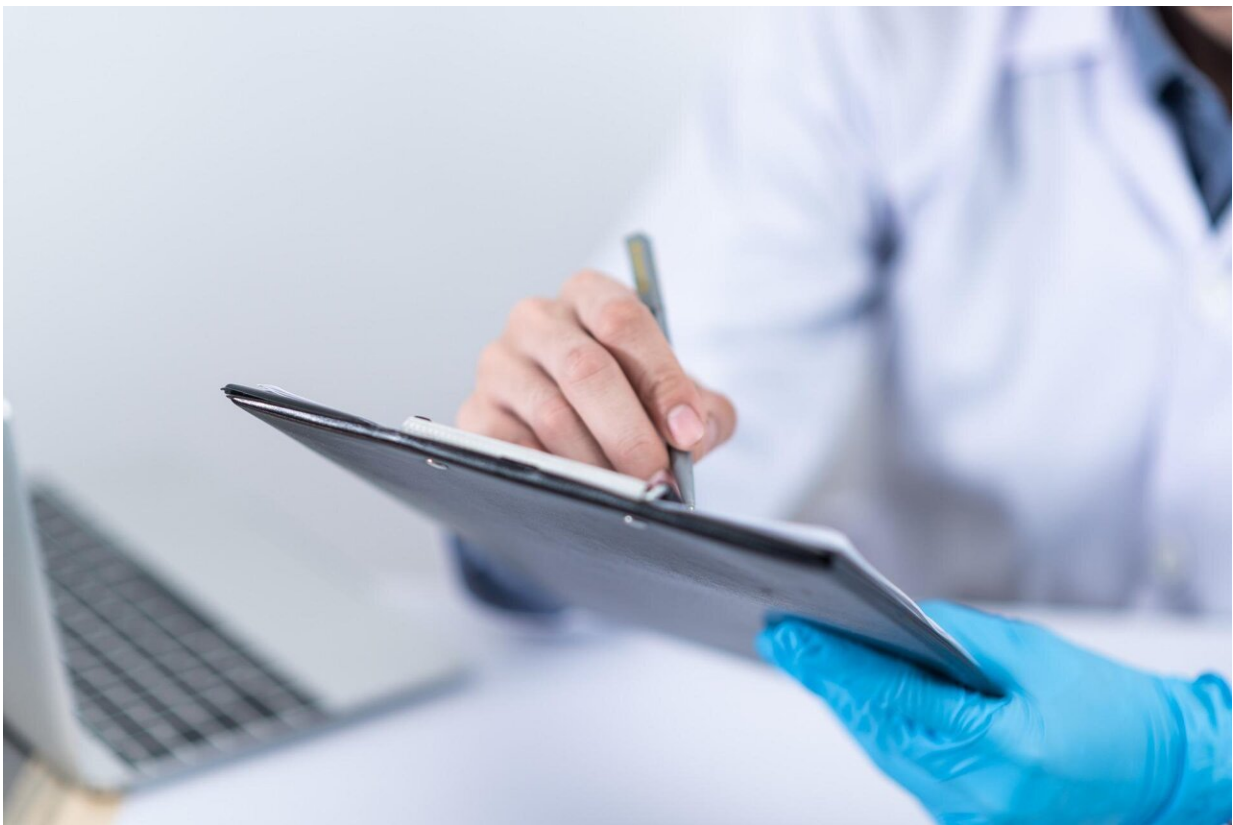


Individualized cancer therapy demonstrates safety and sustained immune responses in Phase I trial

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For decades, researchers have worked to develop therapies that can prime the immune system to recognize and attack proteins on the surface

of tumor cells. However, success has been limited due to the technological challenge of engineering therapies that provide specific enough "training" to the immune system to identify a given patient's neoantigens.

Now, investigators from Massachusetts General Hospital (MGH), a founding member of the Mass General Brigham health care system, have evaluated an investigational, individualized neoantigen therapy (INT), containing patient-specific mRNA-encoded instructions that the immune system can use to target cancer-causing cells.

Their results highlight the safety, feasibility, and therapeutic promise of the approach, which has been designated breakthrough status by the U.S. Food and Drug Administration (FDA) to accelerate further clinical research.

The study, "T Cell Responses to Individualized Neoantigen Therapy mRNA-4157 (V940) Alone or in Combination With Pembrolizumab in the Phase 1 KEYNOTE-603 Study," was published in [Cancer Discovery](#).

"We are entering an era in which we have the tools to make cancer therapies more precise and more personalized," said corresponding author Justin Gainor, MD, program director of the Center for Thoracic Cancers at MGH.

"While it may sound like science fiction, we've shown that we can develop an individualized [neoantigen](#) therapy by leveraging the specific characteristics of a given patient's tumor and cell-type. This therapy was both safe and immunogenic, meaning that we were able to amplify existing responses and induce brand new, long-lasting immune responses."

The Phase I study (NCT03313778) evaluated a novel INT called

mRNA-4157 (V940). The trial included 16 patients, four with resected non-small cell lung cancer and 12 with resected cutaneous melanoma.

The researchers performed comprehensive genomic sequencing of each patient's tumor to determine their top neoantigens, up to 34 of which were then encoded in each mRNA therapy.

Therapies and vaccines that use mRNA can produce robust immune responses and are optimal for individualized cancer therapies because the mRNA corresponding to the patient's neoantigens can easily be inserted into the therapy's delivery system.

Ultimately, 12 patients completed the study: two patients were lost to follow-up, one discontinued due to an adverse event not associated with mRNA-4157 (V940) treatment, and one died of unspecified causes over a year after completing treatment.

Treatment with mRNA-4157 (V940) was not associated with dose-limiting toxicity, study discontinuation, or high-grade adverse events in any patients. The most common side effects included low-grade fatigue, fever and tenderness around the injection site.

In this study, patients with melanoma were treated with both mRNA-4157 (V940) and pembrolizumab, an immune checkpoint inhibitor that boosts anti-cancer activity. Such immunotherapies have become increasingly important in treating cancer and may be used alongside INTs to further increase the immune system's ability to stage a long-lasting response to [cancer](#).

The low toxicity profile of mRNA-4157 (V940) is especially important as it could help simplify combining INTs and other immunotherapies.

The researchers' analysis of patients with blood testing both pre- and

post-treatment showed that mRNA-4157 (V940) induced multiple forms of T cell proliferation, both alone and in conjunction with pembrolizumab.

Importantly, the T cell response to neoantigens was sustained 30 weeks after treatment, testifying to the potential long-term impact of the therapy.

The FDA granted a breakthrough [therapy](#) designation to the study of mRNA-4157 (V940) with pembrolizumab for melanoma treatment, which can help expedite the development and review of the treatment. The researchers are also seeking to further advance the study of the INT in [non-small cell lung cancer](#), renal cell carcinoma, urothelial carcinoma, and cutaneous squamous cell carcinoma.

"The excitement around immune therapies, including this one, is their potential for durability," Gainor said.

"We showed that this INT was able to generate new immune responses against neoantigens, and it appeared that those immune responses were maintained at later time points. The potential for a precise, durable immune response is one of the most exciting aspects of therapies like this one. This may enable a new treatment paradigm for oncology care, particularly in the adjuvant setting."

More information: Gainor, JF et al. T Cell Responses to Individualized Neoantigen Therapy mRNA-4157 (V940) Alone or in Combination With Pembrolizumab in the Phase 1 KEYNOTE-603 Study, *Cancer Discovery* (2024). [DOI: 10.1158/2159-8290.CD-24-0158](https://doi.org/10.1158/2159-8290.CD-24-0158)

Provided by Mass General Brigham

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