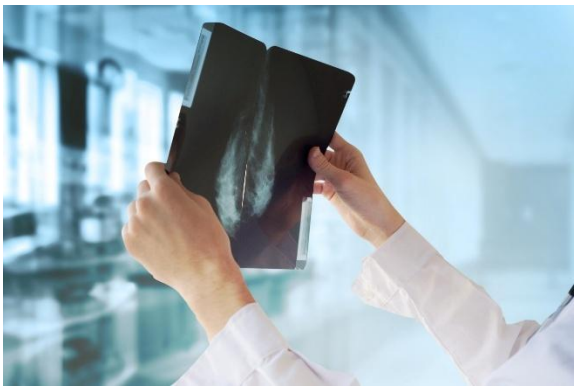
## For Improving TNBC Relapse Risk Precision mRNA Vaccine Strategy Shows Early Promise

Researchers evaluated the feasibility, safety, immunogenicity, and long-term clinical outcomes of an individualized neoantigen messenger ribonucleic acid (mRNA) vaccine in patients with early-stage triple-negative breast cancer (TNBC).



### Study

Immune responses were assessed using interferon gamma enzyme-linked immunospot (ELISpot) assays. Additional immunologic analyses included human leukocyte antigen multimer staining, intracellular cytokine profiling, bulk and single-cell T cell receptor sequencing, and transcriptomic phenotyping. Long-term follow-up was conducted to monitor relapse-free survival and to investigate potential immune-escape mechanisms in patients who experienced recurrence.

All 14 evaluable patients generated vaccine-induced or amplified T cell responses against at least one personalized neoantigen. Most individuals mounted responses against multiple mutations, and nine patients developed T cell responses targeting five or more neoantigens, indicating broad immune activation.

High-magnitude immune responses were detected in 86% of patients via ex vivo interferon gamma ELISpot assays, with several individuals demonstrating 2,000 to 4,000 interferon gamma-producing cells per million peripheral blood mononuclear cells. Among the evaluated neoantigens, 82.9% elicited measurable immune responses that were not detectable before vaccination. Immunogenic targets arose from insertions, deletions, and single-nucleotide variants.

In patients with sufficient samples for in vitro stimulation assays, 51.8% of tested mutations elicited T cell responses. Among these, 64% were mediated exclusively by cluster of differentiation 4 (CD4) positive T cells, 20% by cluster of differentiation 8 (CD8) positive cytotoxic T lymphocytes, and 16% by both CD4 and CD8 T cells. This distribution reflects engagement of helper and cytotoxic T cell compartments, although the trial was not designed to establish a direct causal link between immune responses and clinical outcomes.

Multimer staining confirmed rapid expansion of mutation-specific CD8 positive T cells during vaccination. In certain patients, neoantigen-specific cells constituted up to 17.5% of circulating CD8

positive T cells and persisted for years. In one case, 10.3% of circulating CD8 positive T cells recognized a single mutation at treatment completion, with more than 3% remaining detectable two years later without booster vaccination.

## Findings

Phenotypic analysis demonstrated that many vaccine-induced T cells differentiated into late-stage cytotoxic effector memory CD45RA-expressing cells capable of rapid tumor cell killing. Concurrently, a subset developed into stem cell-like memory T cells expressing T cell factor 1 and interleukin 7 receptor alpha, markers associated with long-term immune regeneration and potential responsiveness to immune checkpoint blockade.

These findings suggest durable immunologic memory capable of sustained tumor surveillance based on mechanistic observations, though not definitively linked to clinical relapse prevention.

After a median follow-up of 62 months (range, 15 to 80 months), 10 of 14 patients remained relapse-free. One additional patient remained relapse-free until death from unrelated causes. Three patients experienced recurrence.

Among these cases, one patient exhibited the weakest vaccine-induced immune response but subsequently achieved a complete response lasting 15 months following anti-programmed cell death protein 1 (PD-1) therapy combined with sequential chemotherapy. Another recurrence arose from a genetically distinct primary tumor not represented in the vaccine design. The third case demonstrated tumor immune escape associated with downregulation and loss of MHC class I expression, impairing antigen presentation but not fully neutralizing circulating T cell responses.

## Conclusion

This study demonstrates that personalized mRNA neoantigen vaccines are feasible, safe, and highly immunogenic in patients with early-stage TNBC. Vaccination induced long-lasting and functional T cell responses that persisted for years without booster doses. The generation of cytotoxic effector and stem-like memory T cells supports the biological plausibility of sustained immune surveillance.

Although most participants remained relapse-free during extended follow-up, the small sample size and absence of a randomized control group limit definitive conclusions regarding clinical efficacy. Observed immune escape mechanisms highlight the complexity of tumor-immune interactions and underscore the need for combination strategies or refined antigen selection.

Overall, these findings position individualized mRNA neoantigen vaccination as a promising adjuvant strategy in high-risk TNBC. Larger, controlled clinical trials are required to determine its impact on long-term relapse-free survival and overall survival in broader breast cancer populations.

## Source:

https://www.news-medical.net/news/20260219/Precision-mRNA-vaccine-strategy-shows-early-promise-for-improving-TNBC-relapse-risk.aspx