KRAS-Targeted Peptide Vaccine Generates Durable Responses, Shows Promise in High-Risk Pancreatic Cancer

Key Takeaways

- mKRAS-VAX targets prevalent KRAS variants across multiple HLA alleles, supporting an off-the-shelf, potentially HLA-agnostic interception approach rather than individualized neoantigen manufacturing.
- Immune responses were most pronounced for KRAS G12A, G12V, and G12R, and half of participants generated significant responses to all six vaccine antigens.
- Durability was evidenced by persistent mutant KRAS-specific T-cell clonotypes up to two years, with most long-term followed patients retaining at least one antigen-specific response.
- Exploratory imaging showed complete or partial pancreatic cyst regression in 37.5% of vaccinated patients versus 6.8% of a post hoc unvaccinated cohort, limited by nonrandomized design.
- Safety was favorable with transient flu-like symptoms, fatigue, and chills; no grade ≥3 vaccine-related toxicities were observed, enabling planned tissue-based infiltration studies pre-resection.

An investigational KRAS-targeted peptide vaccine generated durable immune responses and demonstrated early potential to intercept pancreatic cancer development in high-risk patients.

An investigational peptide vaccine targeting mutant *KRAS* generated durable, mutation-specific T-cell responses and demonstrated encouraging preliminary biologic activity in individuals at hereditary risk for pancreatic ductal adenocarcinoma (PDAC), according to findings from a first-in-human phase 1 study published in *Cancer Discovery*. The study represents the first clinical evidence supporting an oncogene-targeted vaccine designed to intercept pancreatic cancer before invasive disease develops, offering a potential new prevention strategy for individuals with inherited susceptibility.[1]

Among 20 participants with hereditary or familial PDAC risk and radiographic evidence of pancreatic precursor lesions, vaccination with mKRAS-VAX elicited *KRAS*-specific T-cell responses in 90% of patients and produced a median 18.2-fold increase in mutant *KRAS*-specific immune activity. During a median follow-up of 16.5 months, no participant developed pancreatic cancer, and investigators reported no grade 3 or higher vaccine-related adverse events (AEs).[1]

Why Pancreatic Cancer Prevention Matters

PDAC remains one of the deadliest malignancies, largely because most patients are diagnosed after metastatic spread, when curative treatment is rarely possible. Approximately 10% of PDAC cases occur in individuals with hereditary cancer predisposition syndromes, and current surveillance strategies are primarily limited to imaging and clinical monitoring rather than active prevention.[3,4]

Unlike many cancers, PDAC typically develops over years through precursor lesions such as pancreatic intraepithelial neoplasias (PanINs) and intraductal papillary mucinous neoplasms (IPMNs). Because progression from these lesions to invasive cancer may take more than a decade, investigators believe this prolonged premalignant phase provides an opportunity to intervene before malignancy develops.[1]

Mutant *KRAS* represents an ideal interception target because it is the initiating oncogenic driver in more than 90% of PDAC tumors and is present in many precursor lesions. Investigators also noted that premalignant pancreatic tissue is less immunosuppressive than established pancreatic cancer, potentially making vaccination more effective before tumors become immunologically "cold."[1]

mKRAS-VAX Produces Robust Immune Responses

The investigational vaccine, mKRAS-VAX, is a synthetic long-peptide vaccine targeting the 6 most common *KRAS* mutations identified in pancreatic cancer. Participants received 5 subcutaneous vaccinations followed by serial immune monitoring through 17 weeks, with optional annual follow-up extending to 2 years.[1]

Vaccination induced significant immune activation across multiple human leukocyte antigen (HLA) alleles, suggesting the vaccine could function as an off-the-shelf, HLA-agnostic immunotherapy rather than requiring individualized

manufacturing. The strongest responses occurred against KRAS G12A, G12V, and G12R mutations, although half of participants mounted significant immune responses against all 6 vaccine antigens.[1]

Investigators also demonstrated persistence of vaccine-induced mutant *KRAS*-specific T-cell clonotypes for as long as 2 years following vaccination. Among patients with extended follow-up, 3 maintained significant pooled *KRAS*-specific immune responses, while 8 retained responses against at least 1 vaccine antigen, suggesting durable immune memory after the initial vaccination series.[1]

Exploratory MRI Findings Suggest Potential Clinical Activity

Although the trial was designed to evaluate safety and immunogenicity rather than clinical efficacy, exploratory MRI analyses suggested the vaccine may influence pancreatic precursor lesions.[1]

Among 16 patients with evaluable imaging, pancreatic cysts completely resolved in 3 patients and partially regressed in another 3, while the remaining lesions remained radiographically stable. In a post hoc comparison, cyst regression or resolution occurred in 37.5% of vaccinated patients compared with 6.8% of a similar unvaccinated cohort. Investigators cautioned that these findings should be interpreted carefully because the comparison was exploratory and the study lacked a randomized control arm.[1]

Favorable Safety Profile Supports Continued Development

The vaccine was generally well tolerated throughout the study. The most frequently reported treatment-related AEs included fatigue, chills, and influenza-like symptoms, all of which were transient and self-limiting. No participants experienced grade 3 or higher vaccine-related toxicities.[1]

According to senior author Neeha Zaidi, MD, the next phase of research will evaluate whether vaccine-induced immune cells successfully infiltrate pancreatic precursor lesions. Investigators are vaccinating patients before surgical resection of high-risk pancreatic cysts so immune responses can be evaluated directly within pancreatic tissue rather than only in peripheral blood.[2]

Implications for Pharmacy Practice

Although mKRAS-VAX remains investigational, the findings highlight growing interest in preventive cancer immunotherapy for individuals with inherited cancer risk. If future studies demonstrate clinical efficacy, pharmacists may play important roles in identifying appropriate candidates through hereditary cancer programs, counseling patients on expected vaccine-related AEs, supporting adherence to surveillance programs, and coordinating multidisciplinary care.

Larger randomized studies with longer follow-up will be necessary to determine whether mKRAS-targeted vaccination can reduce pancreatic cancer incidence and establish the role of booster vaccination in maintaining long-term immunity.[1]

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