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Combination Immunotherapies

897-B A *DNAJB1-PRKACA* FUSION PEPTIDE VACCINE COMBINED WITH IPILIMUMAB AND NIVOLUMAB ELICITS POLYCLONAL FUSION-SPECIFIC T CELL RESPONSES IN FIBROLAMELLAR CARCINOMA

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Background Fibrolamellar carcinoma (FLC) is a rare liver tumor primarily affecting children and young adults without cirrhosis. The presumed driver of FLC is a recurrent gene fusion between *DNAJB1* and *PRKACA*, which may serve as an ideal shared neoantigen for targeted immunotherapy. We are conducting a phase 1 clinical trial of a peptide vaccine targeting *DNAJB1-PRKACA* in combination with immune checkpoint blockade (ICB) in which neoantigen-specific immunity and clinical responses were observed in a subset of patients. Here we define the fusion-specific T cell responses in an FLC patient who achieved a near-complete response with therapy.

Methods Peripheral blood T cell response to *DNAJB1-PRKACA* fusion neoepitopes was monitored by ELISpot at baseline and throughout treatment. T cells from the peak ELISpot timepoint were expanded as described by Cimen Bozkus et al.[1] and assessed for fusion reactivity via activation induced marker (AIM) and intracellular cytokine staining assays. Single-cell gene expression and T cell receptor (TCR) sequencing were used to obtain activation-associated TCR sequences, which were reconstructed and expressed in T cells to validate specificity and functionality.

Results A young male with histologically confirmed FLC was treated with a 24mer *DNAJB1-PRKACA* synthetic long peptide vaccine with poly-ICLC in combination with ipilimumab and nivolumab on our clinical trial, NCT04248569. The patient experienced an exceptional near-complete response to therapy and was selected for in-depth analysis. Peripheral IFN-γ ELISpot assay demonstrated no reactivity against the vaccinated 24mer peptide at baseline and a brisk IFN-γ ELISpot response against both the long peptide and multiple overlapping 9mer peptides peaking at 6 months after treatment initiation. A population of expanded T cells from the patient obtained at this 6-month timepoint produced cytokines and expressed activation markers in response to stimulation with fusion peptides. These activated cells comprised multiple expanded TCR clonotypes with a polyfunctional CD4 phenotype and shared *TRBV* gene segment usage. These TCR sequences were specific for HLA class II-restricted *DNAJB1-PRKACA* fusion neoepitopes and mediated functional responses to these epitopes.

Conclusions These results demonstrate that combination vaccine and ICB therapy can elicit polyclonal, fusion-specific class II-resricted T cell responses to the *DNAJB1-PRKACA* fusion. Our studies provide a framework to identify these responses in peripheral blood samples from treated patients and thereby determine correlates of response to therapy. Additionally, the defined fusion-specific TCRs show potential for translation to cellular therapies for FLC, highlighting multiple immunotherapeutic strategies that could benefit FLC patients.

Trial Registration ClinicalTrials.gov Identifier NCT04248569

REFERENCE

1. Cimen Bozkus C, Blazquez AB, Enokida T, Bhardwaj N. A T-cell-based immunogenicity protocol for evaluating human antigen-specific responses. *STAR Protoc*. 2021;**2**:100758.

Ethics Approval This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board (IRB), IRB approval number 00222681; and the St. Jude Children's Research Hospital Institutional Review Board, IRB approval number 21-0790.

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