Background Fibrolamellar carcinoma (FLC) is a form of liver cancer primarily affecting children and young adults. The signature genomic event is a chimeric transcript between DNAJB1 and PRKACA. Direct targeting of the fusion has been unsuccessful due to unacceptable on-target toxicities. The DNAJB1-PRKACA fusion breakpoint occurs in an intron, creating a shared neoantigen for patients with FLC. We investigated the safety and immunogenicity of a vaccine targeting the chimera (FLC-Vac) in combination with ipilimumab (IPI) plus nivolumab (NIVO) in FLC patients.

Methods An open-label, single arm phase 1 clinical trial of FLC-Vac plus IPI and NIVO in children or adults with advanced FLC (NCT03299946). The primary objectives are safety and T cell response, defined as 2.5-fold increase of IFN-γ producing DNAJB1-PRKACA chimera-specific T cells in the peripheral blood at week 10 by ELISPOT assay. The study is planned with 12 evaluable patients. FLC-Vac, consisting of a 24 amino acid peptide targeting the DNAJB1-PRKACA chimera with adjuvant poly-ICLC, is administered on weeks 0, 1, 2, 3, 6, 9 during the priming phase of the study and NIVO, 3 mg/kg, are administered every 3 weeks for 4 doses. After completion of the priming phase, FLC-Vac and NIVO are continued in maintenance (figure 1). Key exclusion criteria include age <12 years and prior immune checkpoint inhibitors.

Results At the time of data cutoff (1/1/2023), 16 patients were enrolled, of whom 12 were evaluable for efficacy and immunogenicity endpoints. The median age was 23.5 years (range 12–47), 3/16 were female. Grade 3 treatment-related adverse events were reported by six patients (37.5%) including elevated AST/ALT in three patients (19%), eosinophilia, diabetic ketoacidosis, hypophysitis and pain in one (6%) patient each. No grade 4–5 adverse events observed. The most common vaccine-related adverse events were injection site reactions (100%), headaches (50%) and fatigue (44%), all grade 1–2. In the subset of evaluable patients, 3/12 (25%) had partial responses by RECIST 1.1, and 9/12 (75%) had disease control (figure 2). Peripheral blood T cell responses were noted in 5/12 evaluable patients at week 10 as assessed by IFN-γ ELISPOT. Three additional patients converted to positive responses at later time points, including in patients achieving radiological responses (figure 3).

Conclusions This first-in human study provides initial evidence of safety and clinical efficacy of a vaccine targeting the DNAJB1-PRKACA fusion plus immune checkpoint inhibitor therapy for FLC. T cell responses are consistent with neoantigen-specific immunity against the DNAJB1-PRKACA chimera.

Acknowledgements We thank the patients and their families who participated in this research and the clinical and laboratory research teams. We also acknowledge support from the Fibrolamellar Cancer Foundation and Bristol Myers Squibb.

Trial Registration ClinicalTrials.gov Identifier: NCT04248569

Ethics Approval The protocol was approved by the Institutional Review Board (IRB) at Johns Hopkins University, IRB00222681.
Abstract 641 Figure 2  Efficacy by best overall response by RECIST 1.1

Abstract 641 Figure 3  On-target immunity against the chimera in most patients

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0641