Abstract #C005

A phase 1b/2 trial of pepinemab and avelumab as second line immunotherapy for patients with chemotherapy-refractory metastatic pancreatic adenocarcinoma

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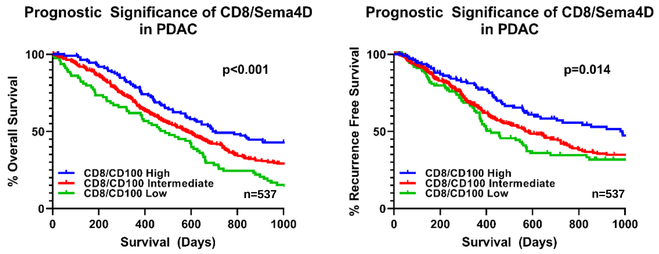
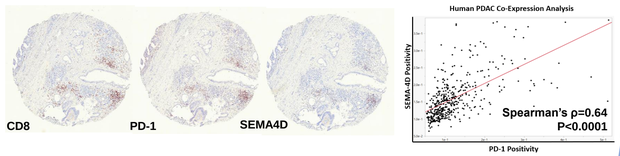
Background

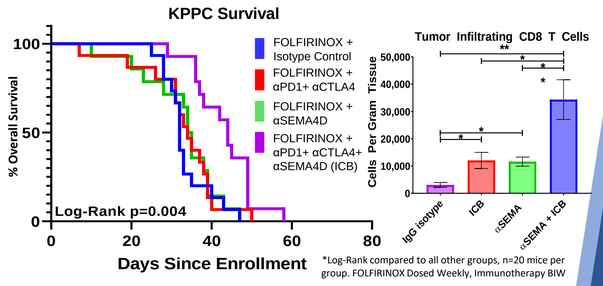
Pancreatic adenocarcinoma (PDAC) is one of the leading causes of cancer-related mortality and with poor prognosis despite maximal therapy. Additionally, PDAC has proven unresponsive to immune checkpoint blockade (ICB) alone. It is hypothesized this failure is driven in part by the uniquely desmoplastic and immune-suppressed tumor microenvironment. Thus, novel strategies to overcome this immune-suppressed environment and facilitate adaptive immune responses are greatly needed.



Semaphorin 4D (CD100) and CD8 positivity are prognostic in patients who underwent resection, identifying Sema4D as a novel therapeutic target.



SEMA4D is expressed primarily on lymphocytes within the PDAC TME (left) and correlates with activated CD8+ T-cells (right).

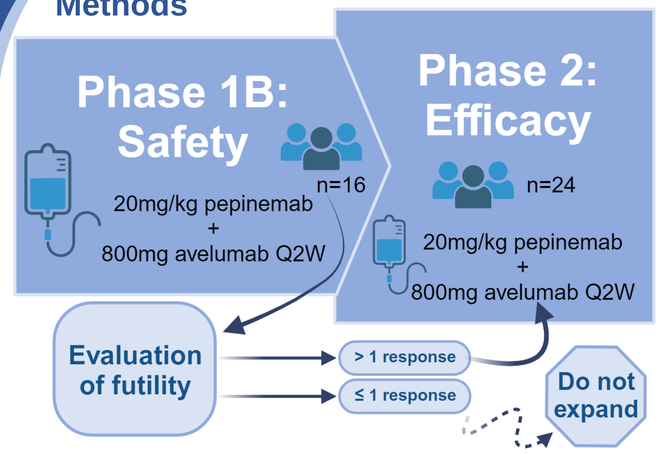


*Log-Rank compared to all other groups, n=20 mice per group. FOLFIRINOX Dosed Weekly, Immunotherapy BIW

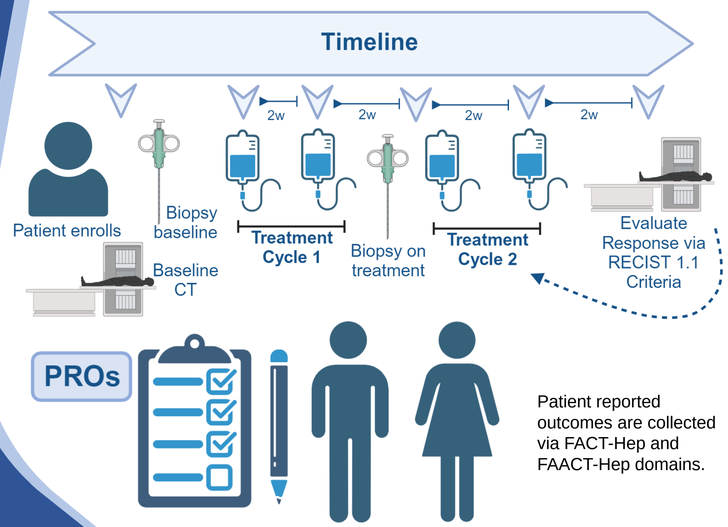
Preclinical murine modeling demonstrates enhanced efficacy of immune checkpoint blockade following treatment with anti-Sema4D therapy in a spontaneous KPPC* model of PDAC (left). Flow cytometric analysis of tumors demonstrates increased penetrance of CD8+ Effector T-cells with anti-Sema4D therapy (right).

*KPPC KrasG12D/+; Trp53R172H/R172H; P48-Cre

Methods



Study utilizes a dose de-escalation schema and patients enroll via Bayesian Optimal Interval Design (BOIN) targeting a dose-limiting toxicity rate of 30% or less. After 16 subjects receive a given combination dose, a Simon's two stage assessment of futility will be undertaken with expansion to phase 2 if 2 or more subjects demonstrate response. The trial is designed to evaluate a total of 40 subjects and powered to detect a response rate of 23% or greater, with alpha set at 0.1% and 80% power.



Patient reported outcomes are collected via FACT-Hep and FAACT-Hep domains.

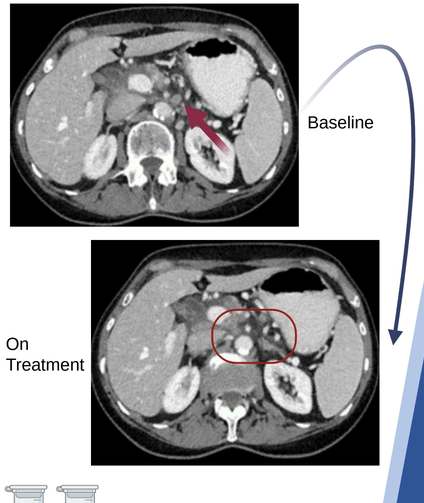
Preliminary Results

Seven patients enrolled to date

No treatment-related toxicities encountered

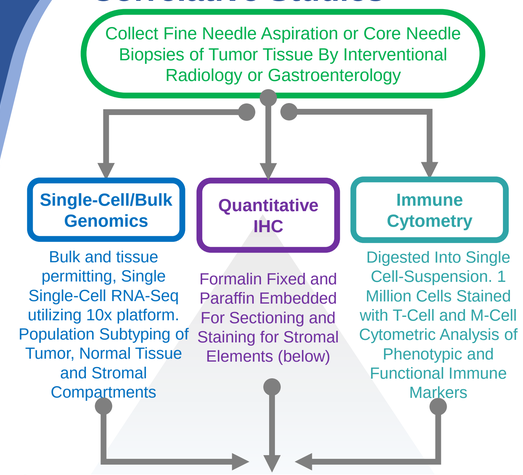
Four patients terminated due to disease progression though 1 demonstrated mixed response with some lesions showing radiologic partial and even complete response.*

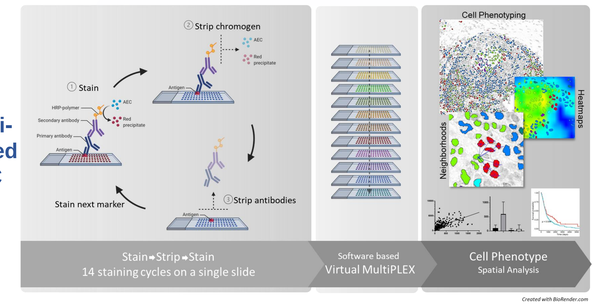
Mixed Response*



Four of four paired (baseline and on-treatment) biopsies collected.

Correlative Studies





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- Avelumab is being provided by the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945), previously as part of an alliance between the healthcare business of Merck KGaA, Darmstadt, Germany."