Phase 1b/2 trial of pepinemab plus avelumab as second line combination immunotherapy for patients with metastatic pancreatic adenocarcinoma

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Study Population Patients with metastatic pancreatic adenocarcinoma, refractory to first line chemotherapy**

NCT05102721

PHASE 1b Safety Run-in
20 mg/kg pepinemab + 800 mg avelumab Q2W
intervienious injections
n=16*

PHASE 2 Efficacy
20 mg/kg pepinemab + 800 mg avelumab Q2W
intervienious injections
n=24

*Accrual for the Phase 1b portion follows a **Bayesian Optimal Interval Design** (BOIN), targeting a dose limiting toxicity rate of 30%. Phase 2 begins after 16 subjects are enrolled at an MTD dose, permitting a **Simon's two stage assessment of futility**.

Primary Objectives
- Determine MTD of pepinemab and avelumab
- Efficacy of combination, overall response based on RECIST1.1

Exploratory Objectives
- Assess immunophenotypic and stromal changes to the TME after treatment
- Correlate TME changes with clinical response

**Patients must have received 5FU or gemcitabine-based first line therapy with evidence of intolerance or treatment failure, including progression both during or after completing first-line treatment.

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Proof-of-concept study goals
- Evaluate safety
- Efficacy
- TME biomarker changes of treatment

Combination of pepinemab plus avelumab for second line treatment of patients with metastatic PDAC

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

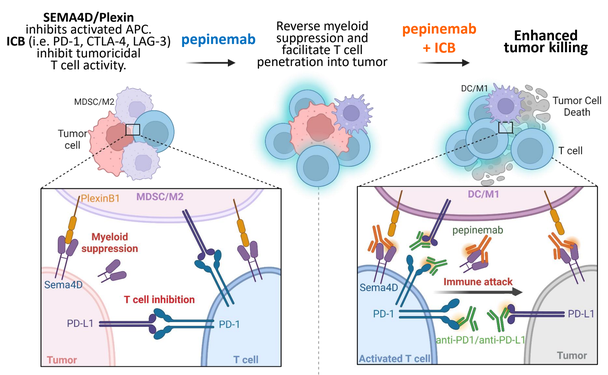
SCAN ME

Background / Mechanism of Action

Monotherapy with immune checkpoint inhibitors (ICB) is not effective in metastatic pancreatic ductal adenocarcinoma (PDAC), likely due to the unique immunosuppressive tumor microenvironment (TME) of PDAC, thus safe and novel strategies to overcome resistance and facilitate adaptive immune responses are a major unmet need.

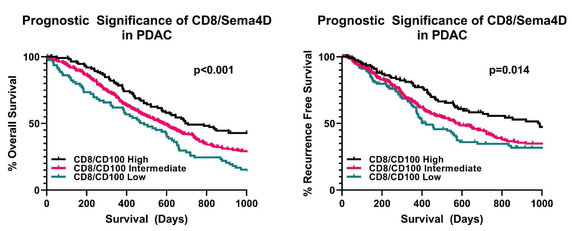
Preclinical and clinical studies demonstrated that antibody blockade of semaphorin 4D (SEMA4D) promotes tumoral infiltration, organization, and activation of dendritic cells (DCs) and CD8+ T cells and reverses immunosuppression, including attenuation of MDSC recruitment and function, leading to enhanced efficacy of ICBs. Notably, pepinemab does not increase toxicity of companion ICB.

1. Proposed MOA [1, 2]



2. SEMA4D is an activation marker on T cells

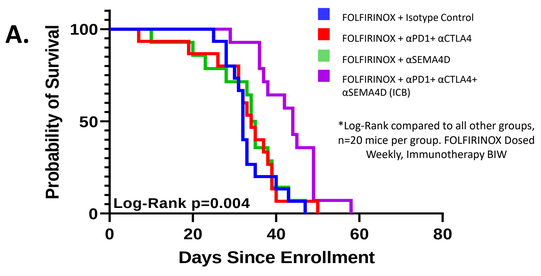
Human pancreatic cancer tissue analysis demonstrates **Sema4D (CD100) and CD8 positivity is prognostic** in resected patients for both recurrence free and overall survival, identifying Sema4D as a novel therapeutic target. [3]

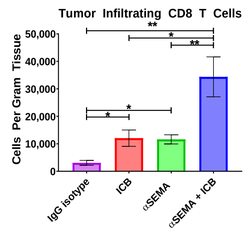


3. Preclinical Data

Preclinical murine KPPC* model of spontaneous PDAC demonstrates **enhanced efficacy of immune checkpoint blockade** (ICB) combined with monoclonal anti-Sema4D therapy (A). Flow cytometric analysis demonstrates increased penetrance of CD8+ effector T-cells following combination treatment of anti-Sema4D monoclonal therapy with ICB (B). [3]

*KPPC: LSL-Kras^G12D/+; Trp53^(flox/flox); p48-Cre



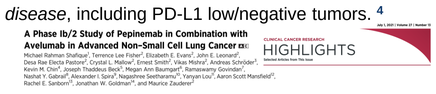


4. Clinical Proof of Concept / Lessons from other studies

- **Well tolerated.** Pepinemab does *not* appear to increase toxicities of partner drug.

NSCLC	Melanoma	HNSCC
Combo with avelumab NCT03268057	Combo with nivolumab and/or ipilimumab NCT03769155	Combo with nivolumab or ipilimumab NCT04815720

- **Unmet need:** Pepinemab in combination with avelumab → antitumor activity observed in *immune checkpoint resistant/refractory disease*, including PD-L1 low/negative tumors. [4]

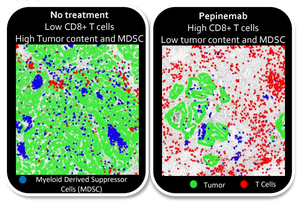


Combination of pepinemab with avelumab **ORR ~ 25-33%**

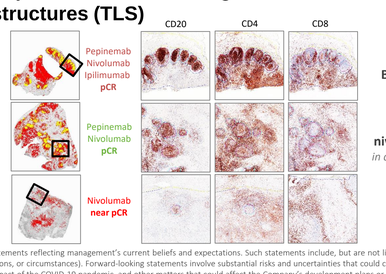
Reported single agent anti-PD-1/L1: **ORR~10-15%**

- **Pepinemab improves T cell infiltration and reverses myeloid suppression**

Biopsies from patients with metastatic MSS Colorectal Cancer, Neoadjuvant treatment with pepinemab
Human metastatic colorectal tumor, in collaboration with Winship Cancer Institute, Emory University integrated biomarker study (NCT03373188) [5]

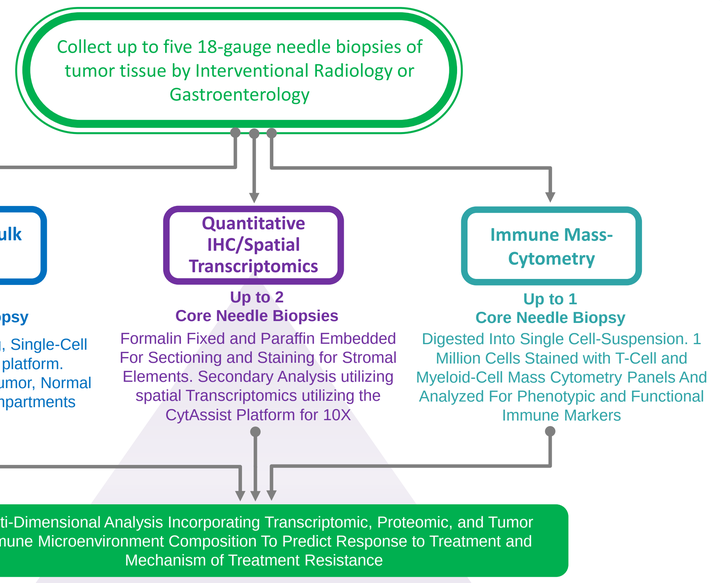


- **Pepinemab increases organization of tertiary lymphoid structures (TLS)**

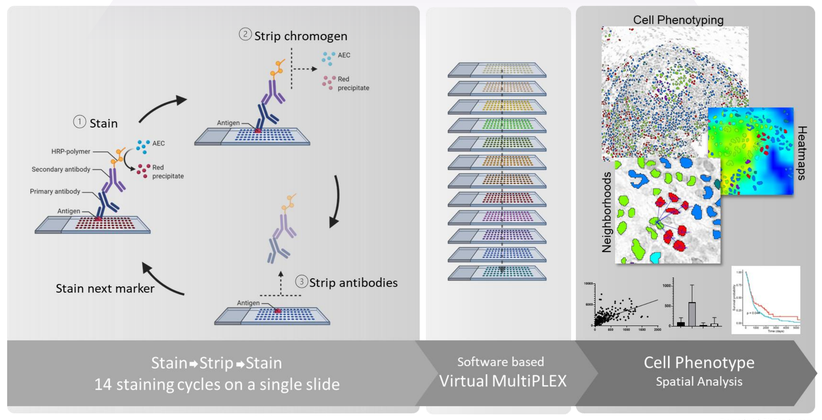


Biopsies from patients with metastatic melanoma Neoadjuvant treatment with pepinemab and nivolumab and/or ipilimumab
in collaboration with Winship Cancer Institute, Emory University integrated biomarker study (NCT03690986) [6]

Correlative Studies
Baseline & On-Tx Biopsies



Multiplexed IHC



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Complex staining panels for phenotyping

Lymphocyte Panel	APC Panel	Myeloid Panel
Hematoxylin	Hematoxylin	Hematoxylin
Sema4D	Sema4D	CD33
PD-1	CD163	CD15
CD69	CD11c	CD14
CD8	HLA-DR	Arg1
CD4	CD68	HLA-DR
FoxP3	CD141	Sema4D
CD26	CD206	S100A9
CD20	Arg1	CD16
CD39	PanCK	PanCK
CD45	PD-L1	PD-L1
TCF1		
PanCK		
Ki67		

SEMA4D represents a novel immunotherapeutic target to reverse suppressive TME in pancreatic cancer

A Phase 1b/2 clinical trial incorporating anti-SEMA4D and ICB is actively enrolling patients at URMC with three subjects enrolled to date (NCT05102721)

Methods in Clinical Cancer Research

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

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