

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

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Abstract ID:
TPS4195

Poster #: 504a

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

NCT05102721



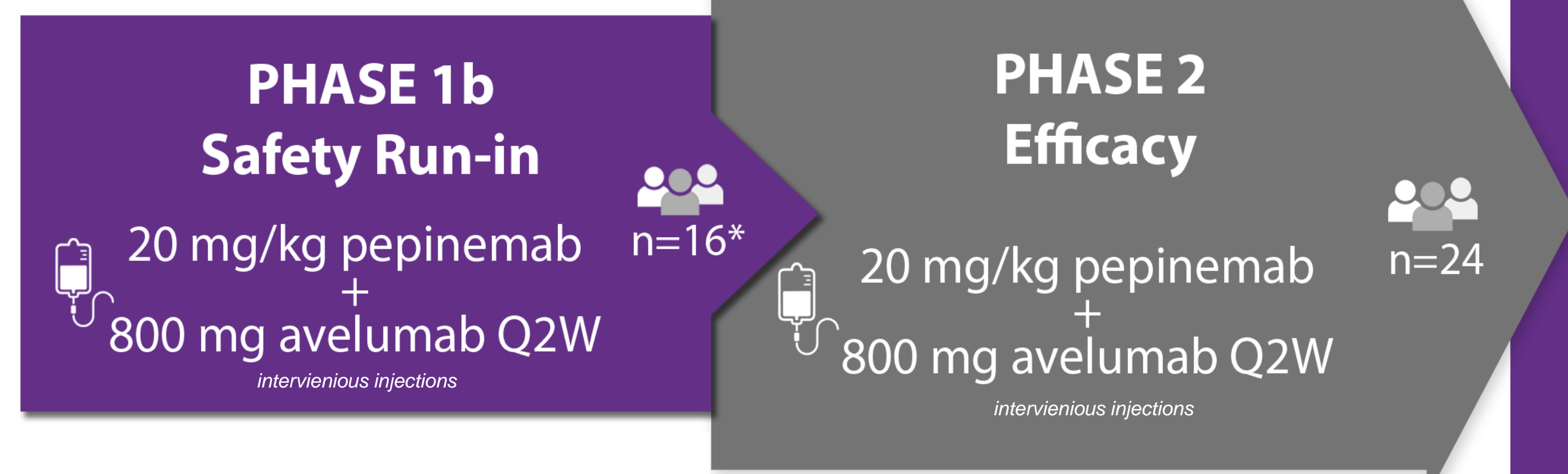
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Proof-of-concept study goals

- 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.



*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

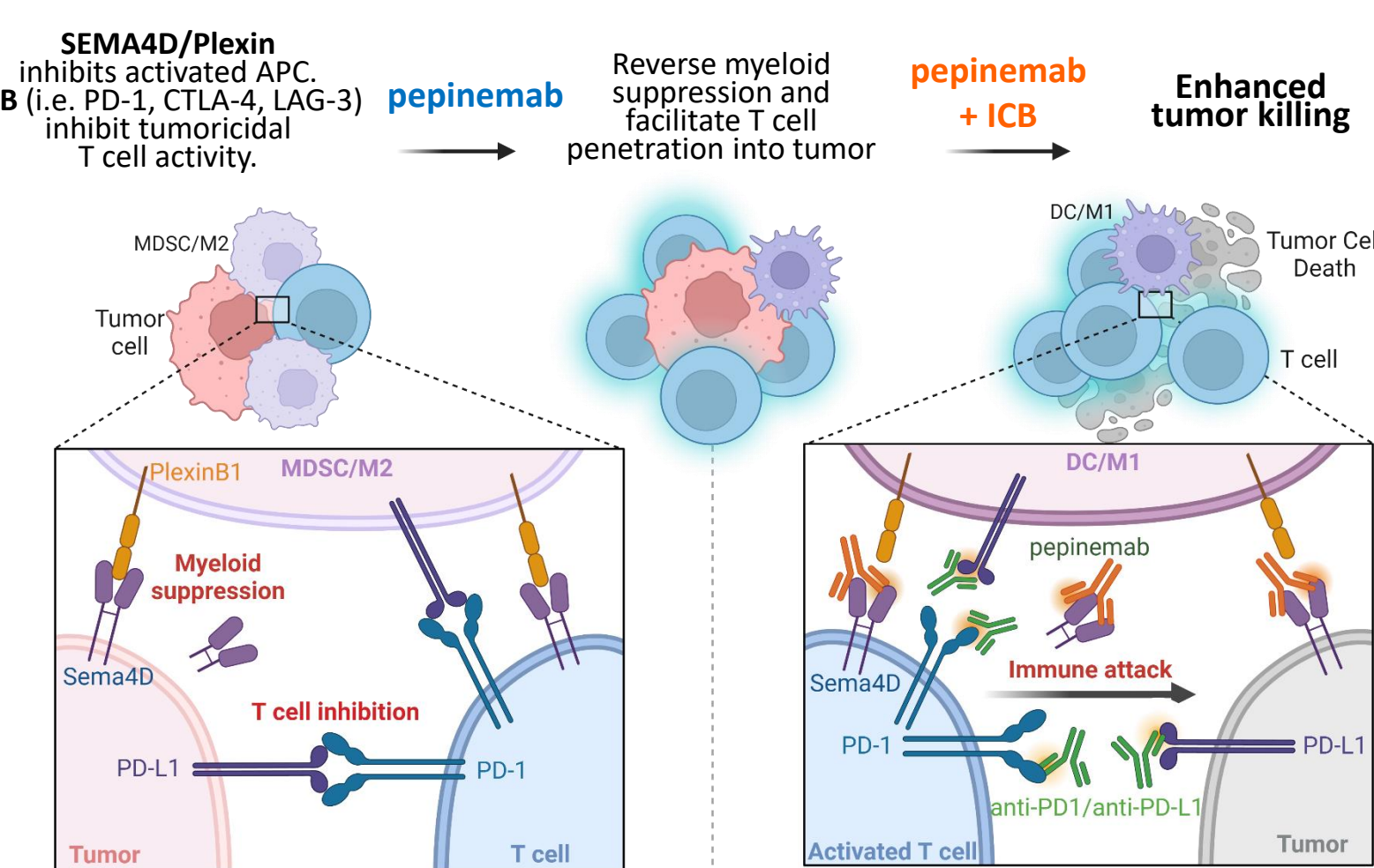
**Patients must have received 5FU or gemcitabine-based first line therapy with evidence of intolerance or treatment failure, including progression both during or after completing first-line treatment.

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.

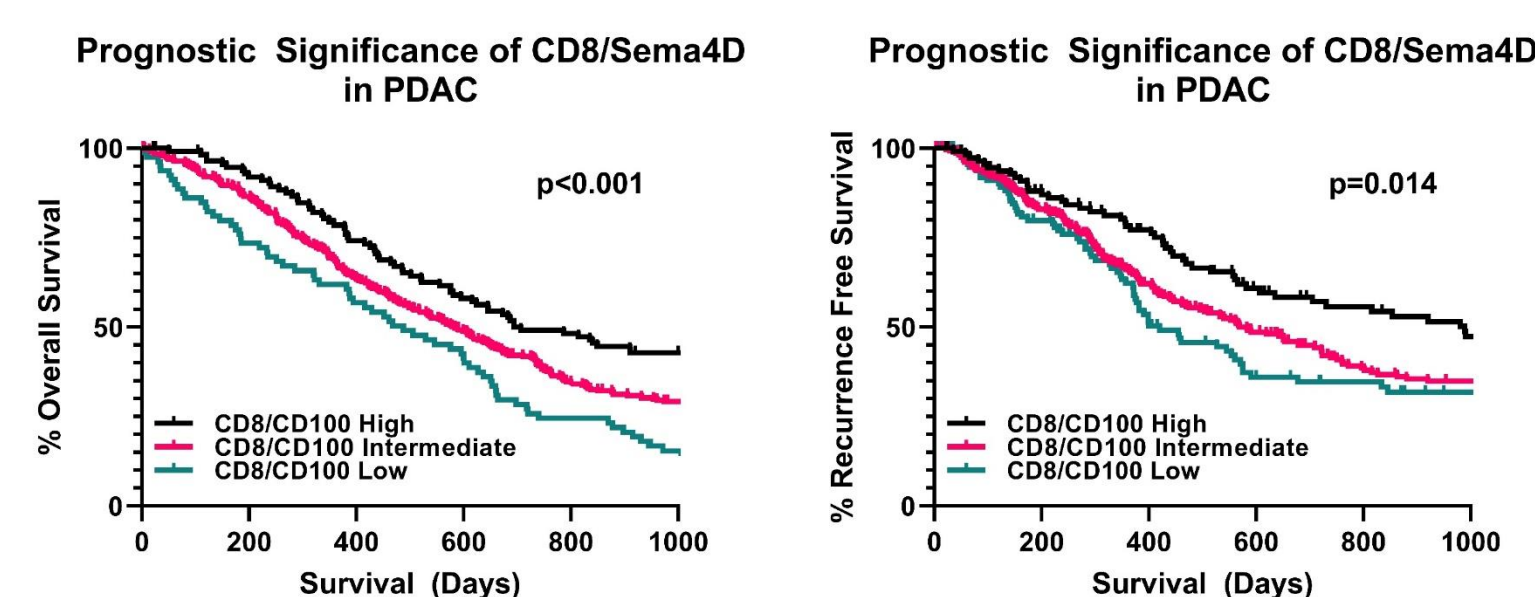
Preclinical and clinical studies demonstrated that antibody blockade of semaphorin 4D (SEMA4D) promotes tumoral infiltration, and activation of dendritic cells (DCs) and CD8+ T cells and reverses immunosuppression, including attenuation of MDSC recruitment and function, leading to enhanced efficacy of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

1. Proposed MOA 1, 2



2. SEMA4D is an activation marker on T cells

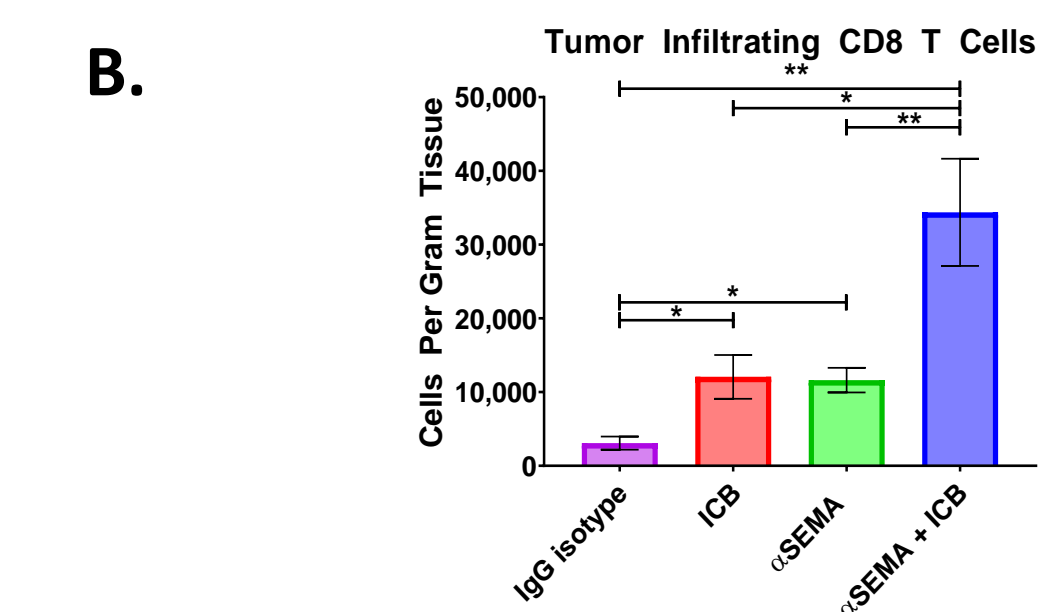
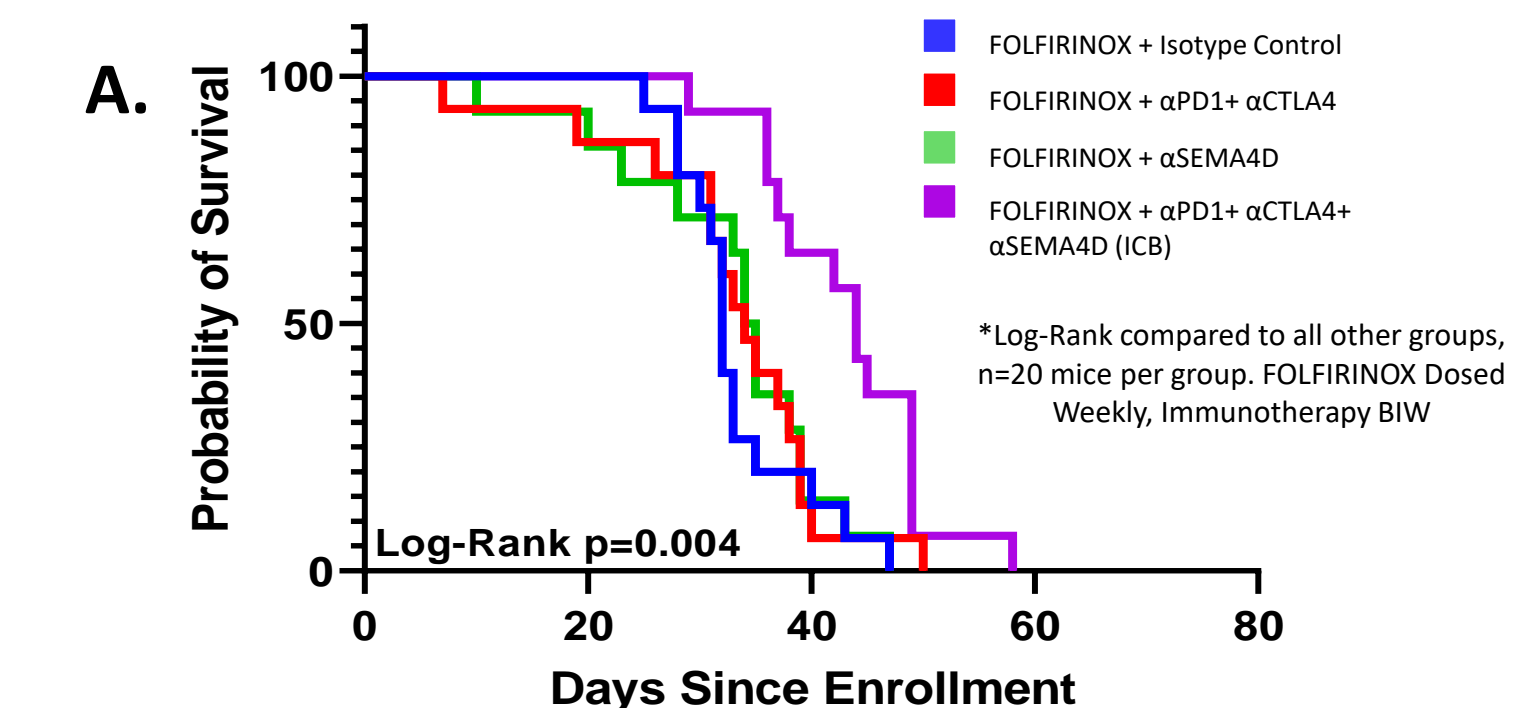
Human pancreatic cancer tissue analysis demonstrates **Sema4D (CD100) and CD8 positivity is prognostic** in resected patients for both recurrence free and overall survival, identifying Sema4D as a novel therapeutic target. ³



3. Preclinical Data

Preclinical murine KPCC* 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

*KPCC: LSL-Kras^{G12D/+}; Trp53^{fl/lox}; p48-Cre



4. Clinical Proof of Concept / Lessons from other studies

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

- NSCLC: Combo with nivolumab NCT0268057
- Melanoma: Combo with nivolumab and/or ipilimumab NCT03769155
- HNSCC: Combo with nivolumab and/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

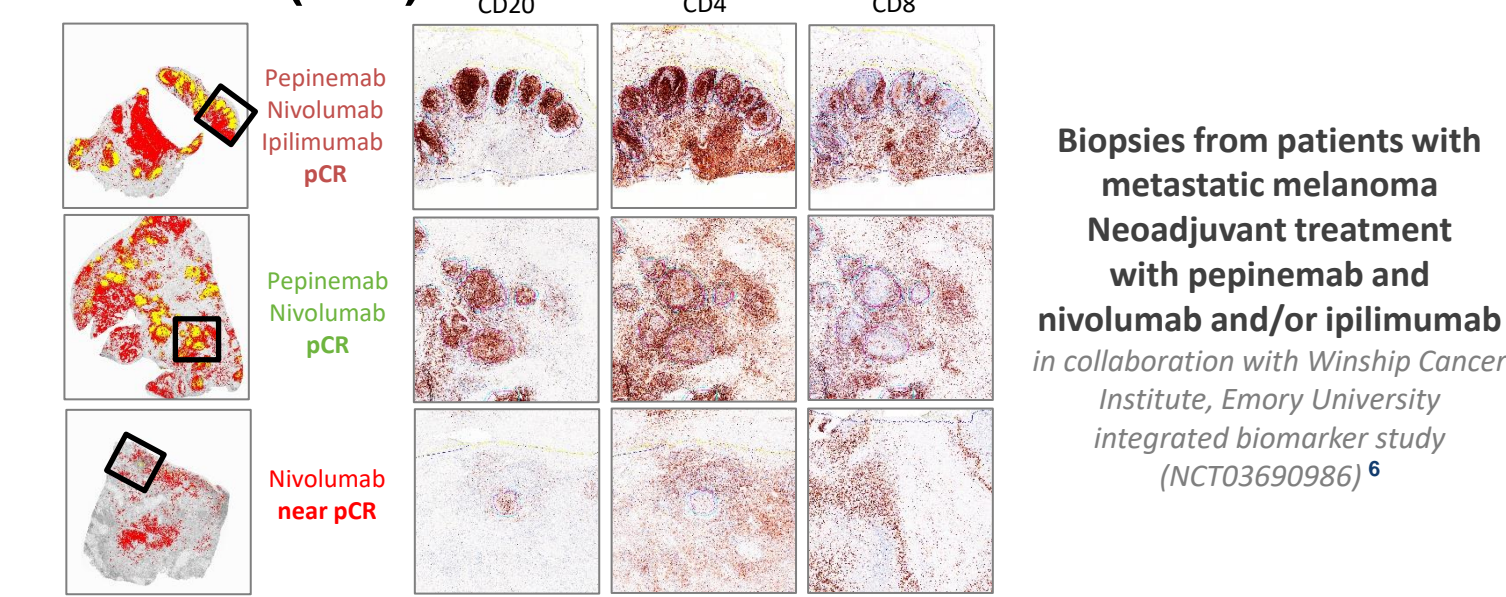
A Phase 1b/2 Study of Pepinemab in Combination with Avelumab in Advanced Non-Small Cell Lung Cancer: **HIGHLIGHTS**

- 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**

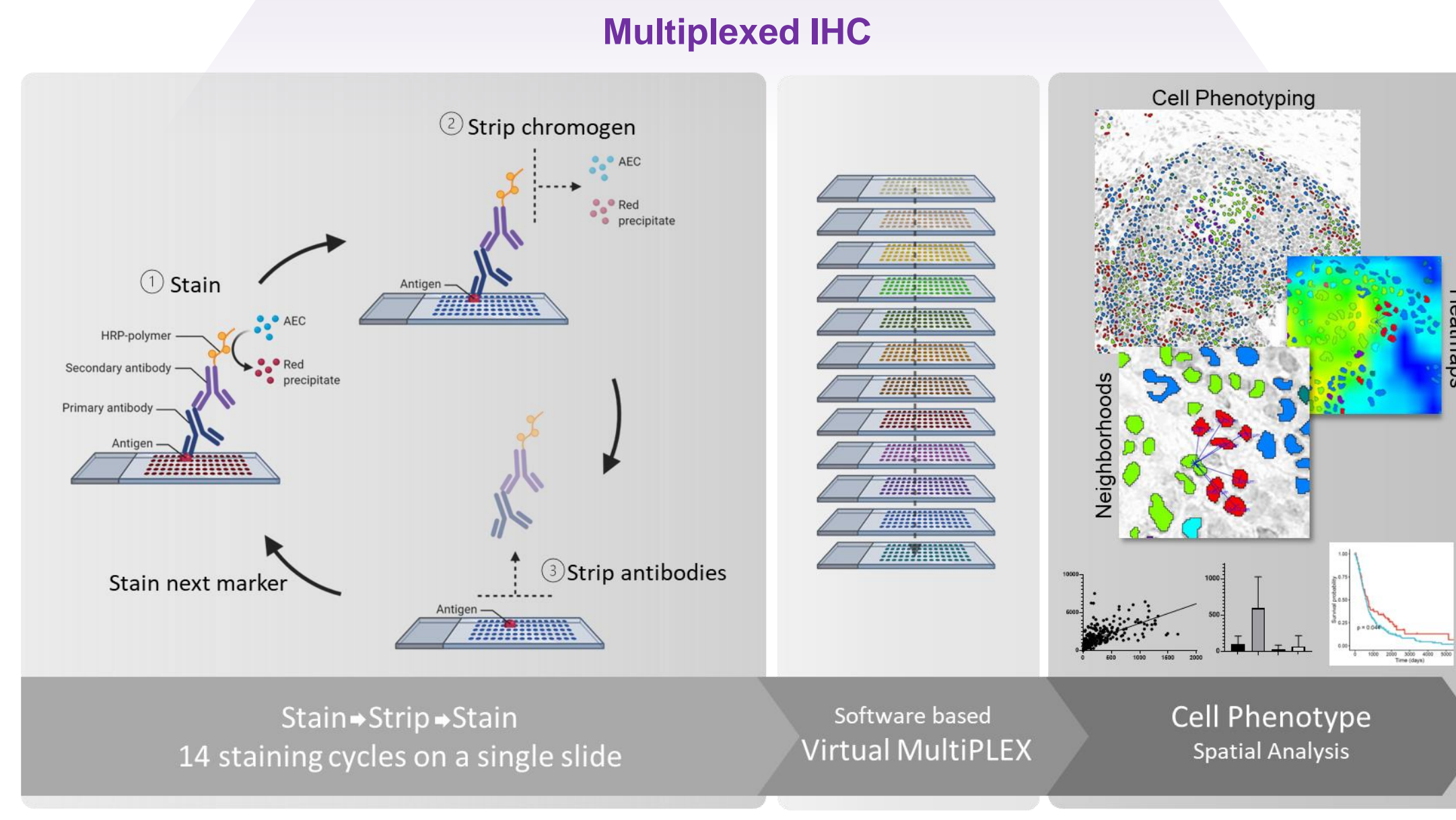
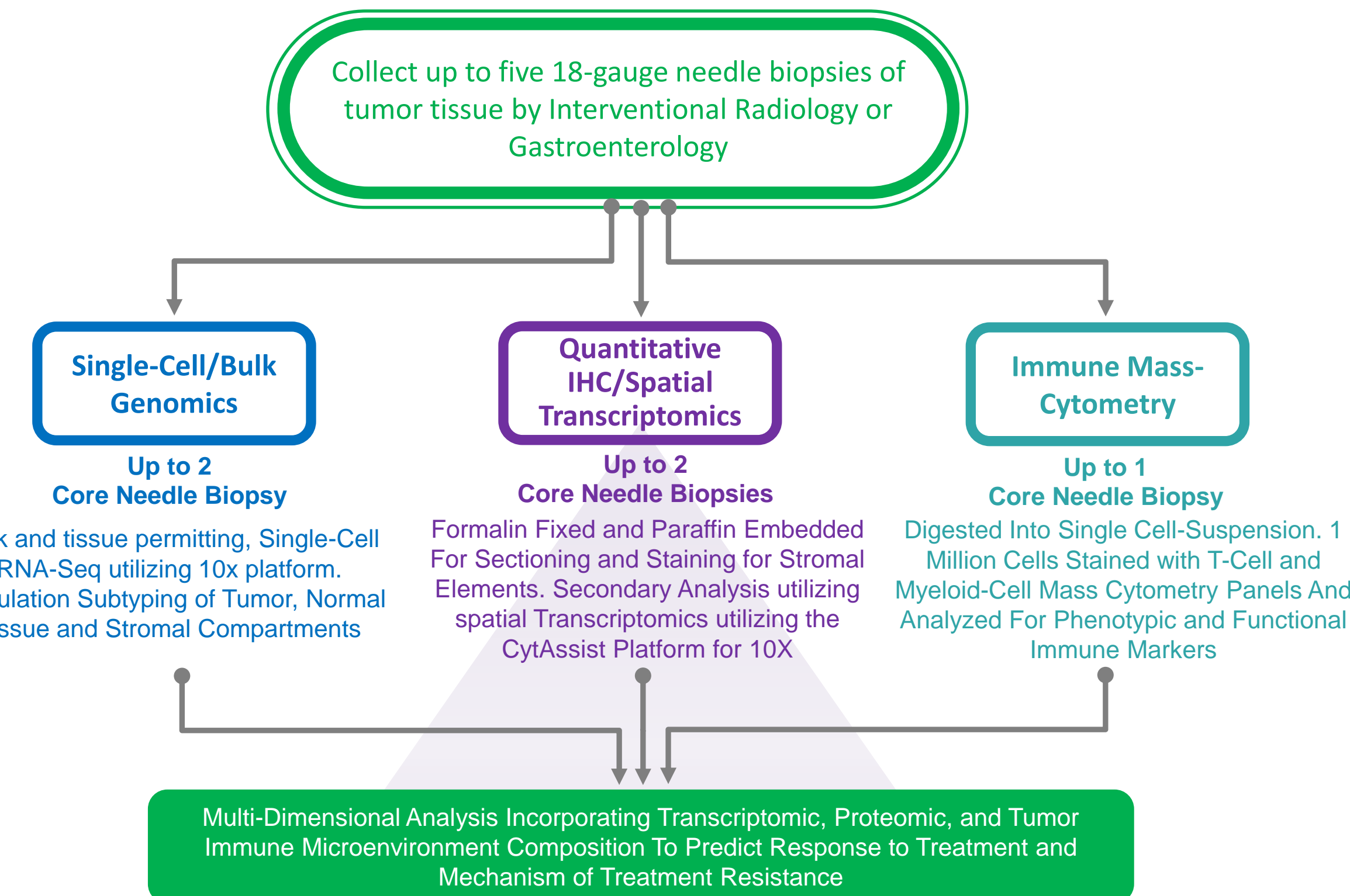
Biopsies from patients with metastatic MSS Colorectal Cancer, Neoadjuvant treatment with pepinemab with avelumab. Human metastatic colorectal tumor, in collaboration with Winship Cancer Institute, Emory University integrated biomarker study (NCT03373188) ⁵

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



Correlative Studies

Baseline & On-Tx Biopsies



| 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 | CD8 | 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 URM with three subjects enrolled to date (NCT05102721)



Methods in Clinical Cancer Research



Funding: NIH R01-CA168863, NIH Score P50-CA196510
 • Gateway Discovery Award (Conquer Cancer Foundation / ASCO) DG-20-100
 • ACS Resident Research Scholarship 2019-2021
 • 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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