Antibody Blockade of Semaphorin 4D Sensitizes Pancreatic Cancer to Immune Checkpoint Blockade

Luis I. Ruffolo, Nicholas A Ullman, Benjamin Dale, Katherine M Jackson, Paul Burchard, Mary Georger, Rachel Jewell, Brian A. Belt, Eva Galka, Luke O. Schoeniger, Crystal L. Mallow, Elizabeth E. Evans, Terrence Lee Fisher, Maurice Zauderer, David C. Linehan

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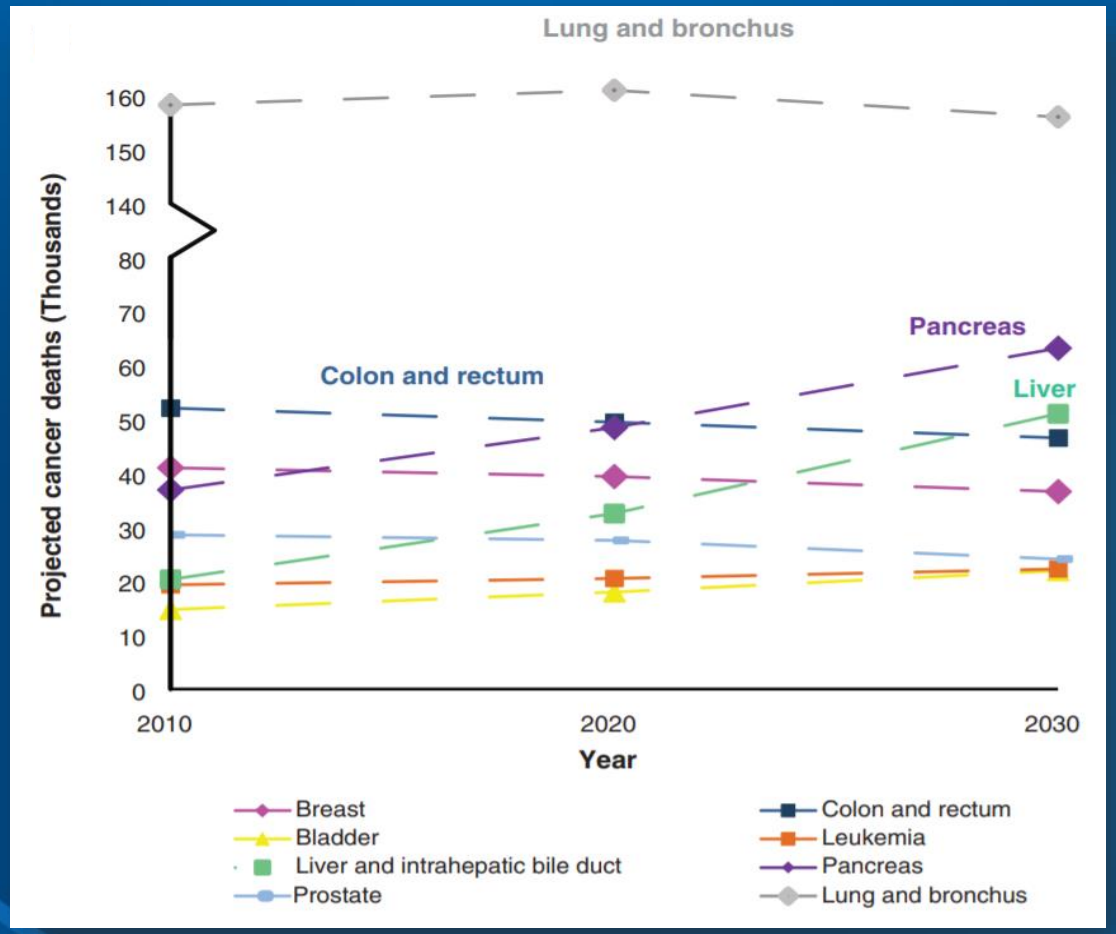
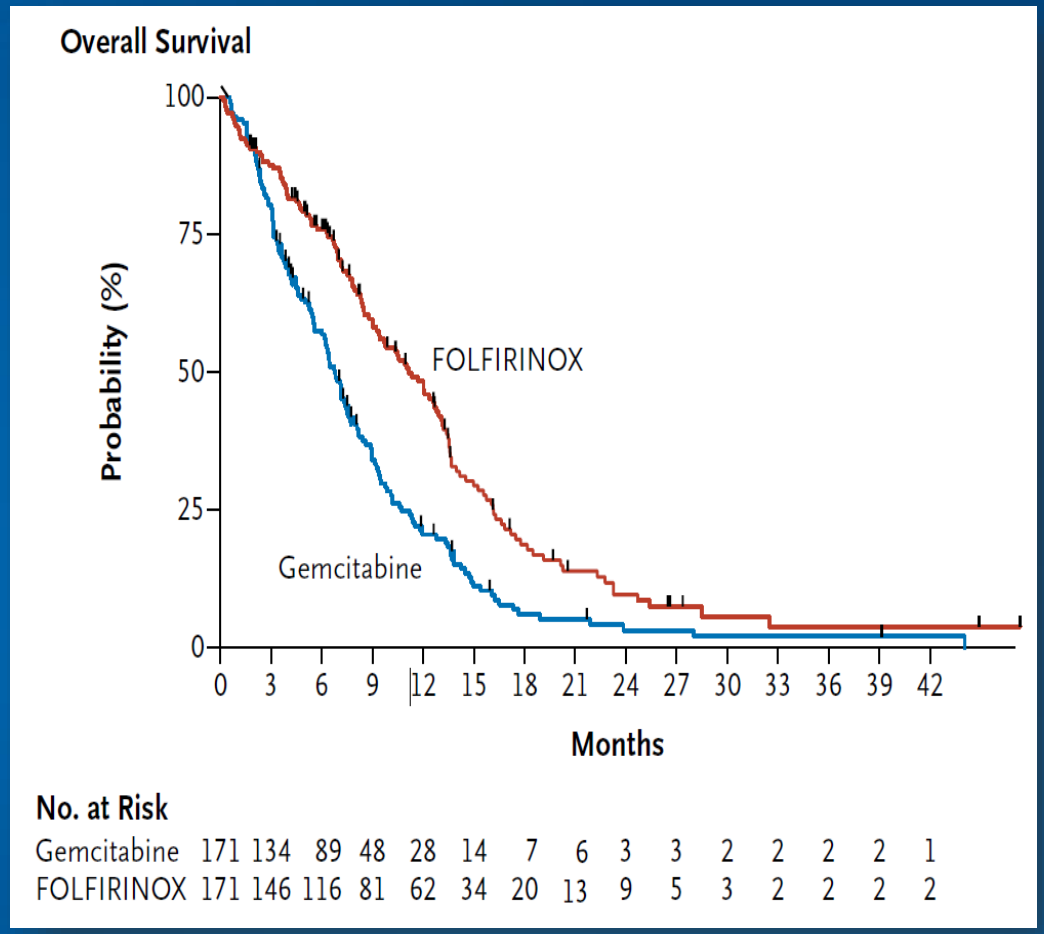
Disclosures

- I have no conflicts of interest to disclose

Rising Burden of Pancreatic Cancer



Rahib et al. Cancer Research 2014



Conroy et al. NEJM 2011

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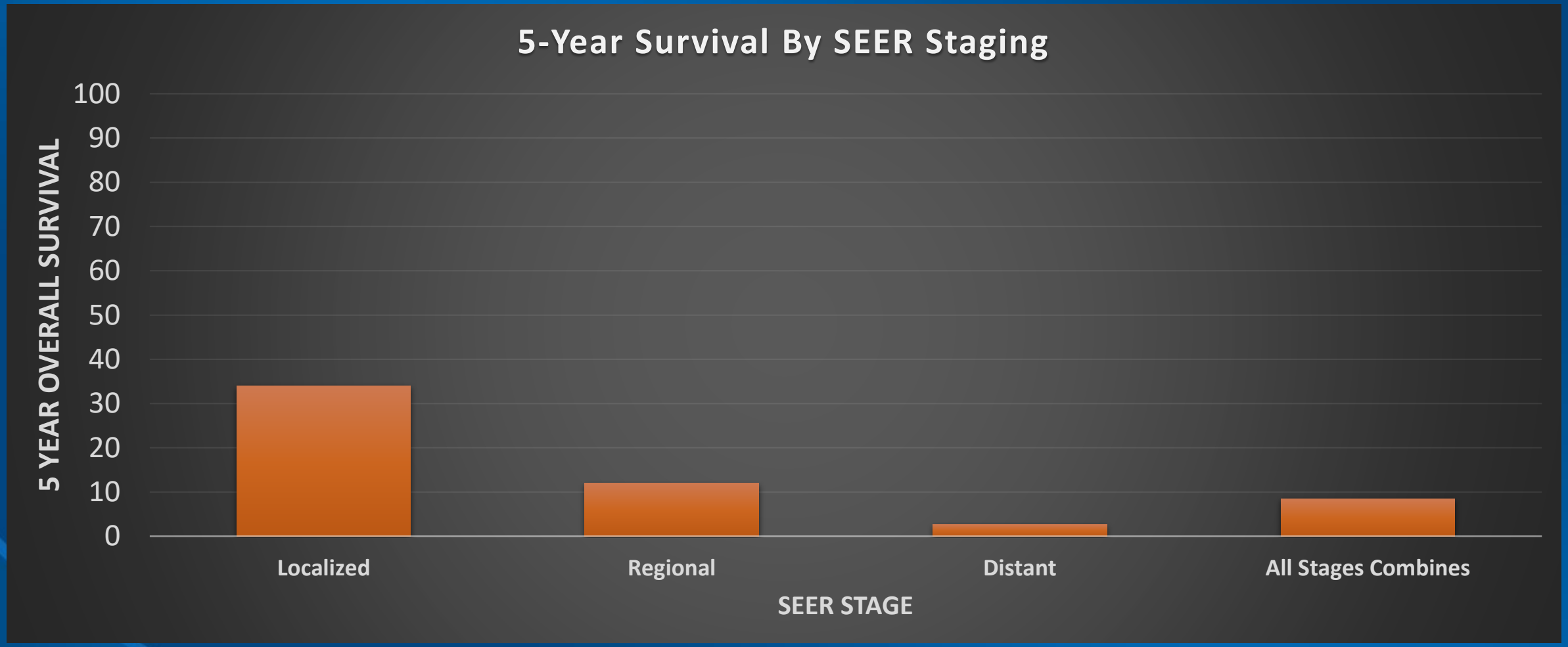
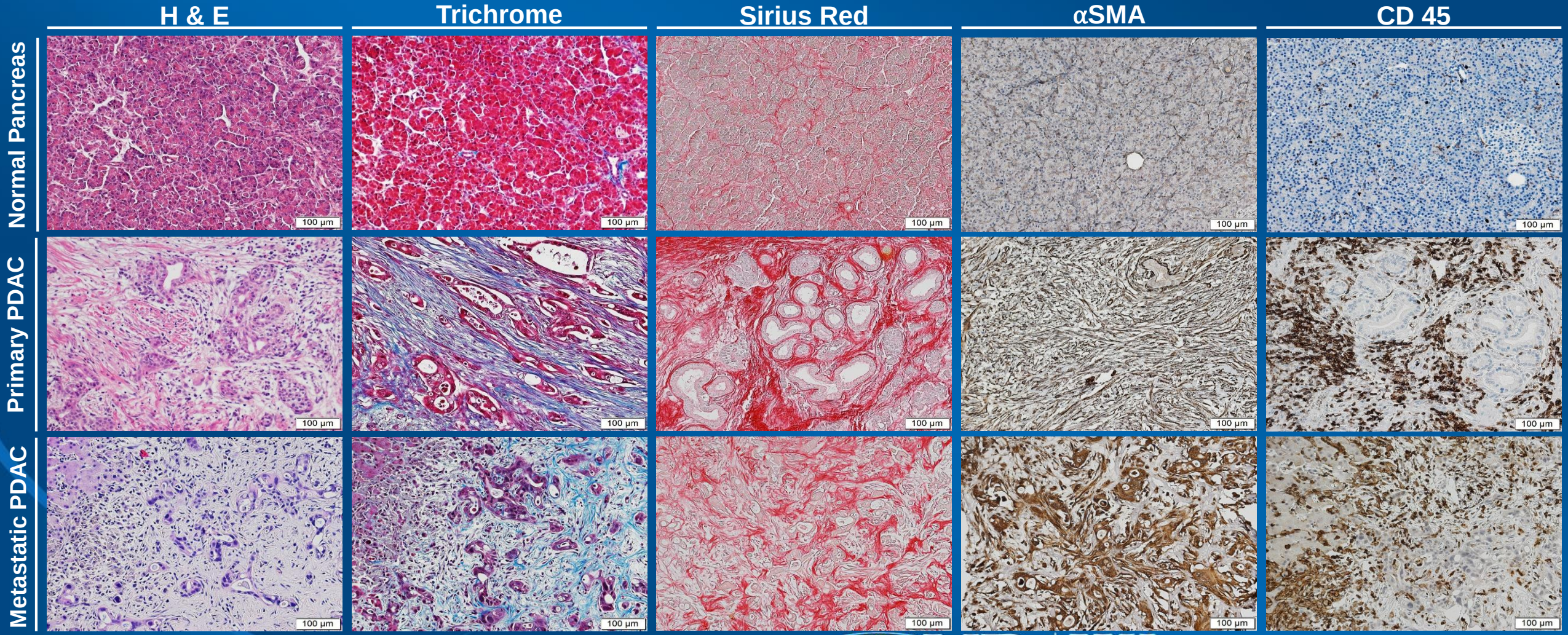
Rising Burden of Pancreatic Cancer



Source: SEER Cancer Statistics

PDAC Tumor Microenvironment Thwarts Adaptive T-Cell Response



PDAC Tumors Are Immunologically Cold and Unresponsive to Immune Checkpoint Blockade

Safety and activity of anti-PD-L1 antibody in patients with advanced cancer.

Brahmer JR[1], Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthy S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM.

Author information

1 Johns Hopkins University School of Medicine and the Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD 21231, USA.

0% ORR in patients with PDAC

Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma.

Royal RE[1], Levy C, Turner K, Mathur A, Hughes M, Kammula US, Sherry RM, Topalian SL, Yang JC, Lowy I, Rosenberg SA.

Author information

1 Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. rroyal@mdanderson.org

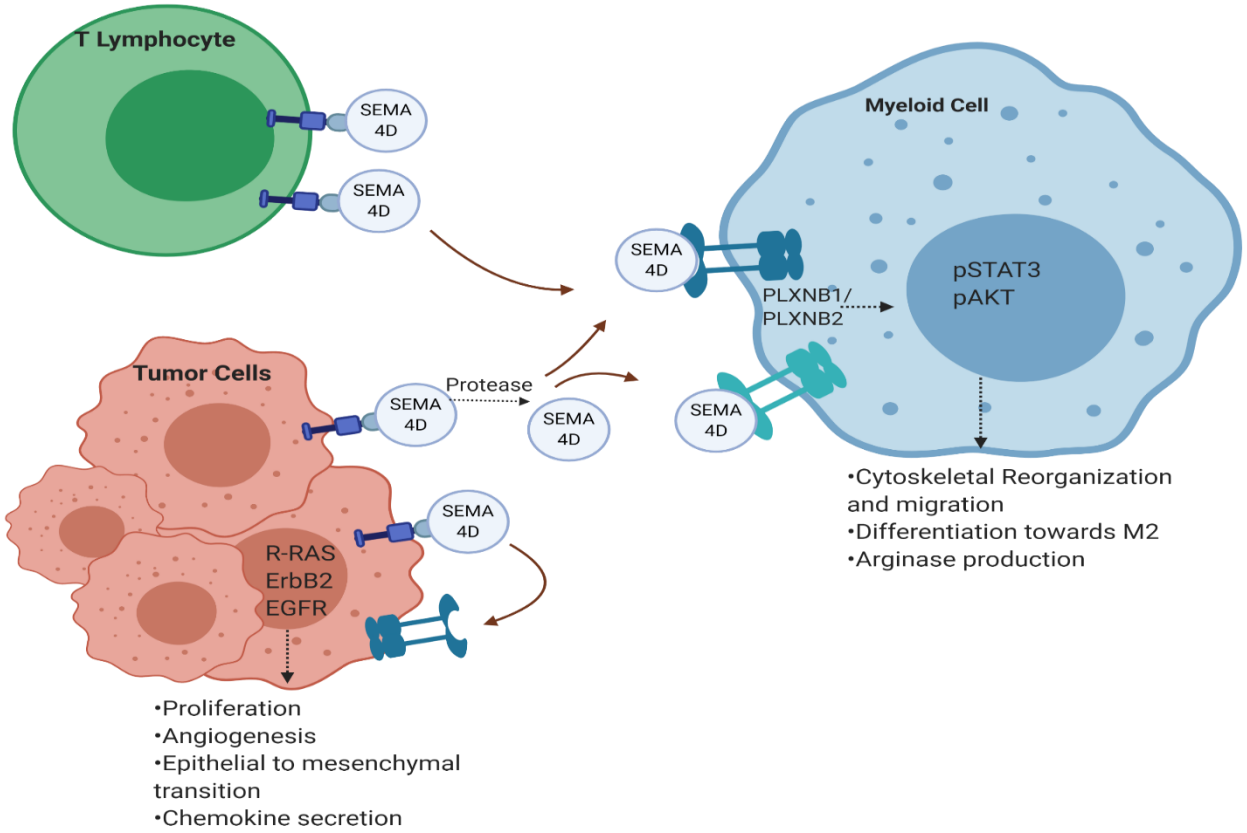
0% ORR

Durvalumab With or Without Tremelimumab for Patients With Metastatic Pancreatic Ductal Adenocarcinoma: A Phase 2 Randomized Clinical Trial.

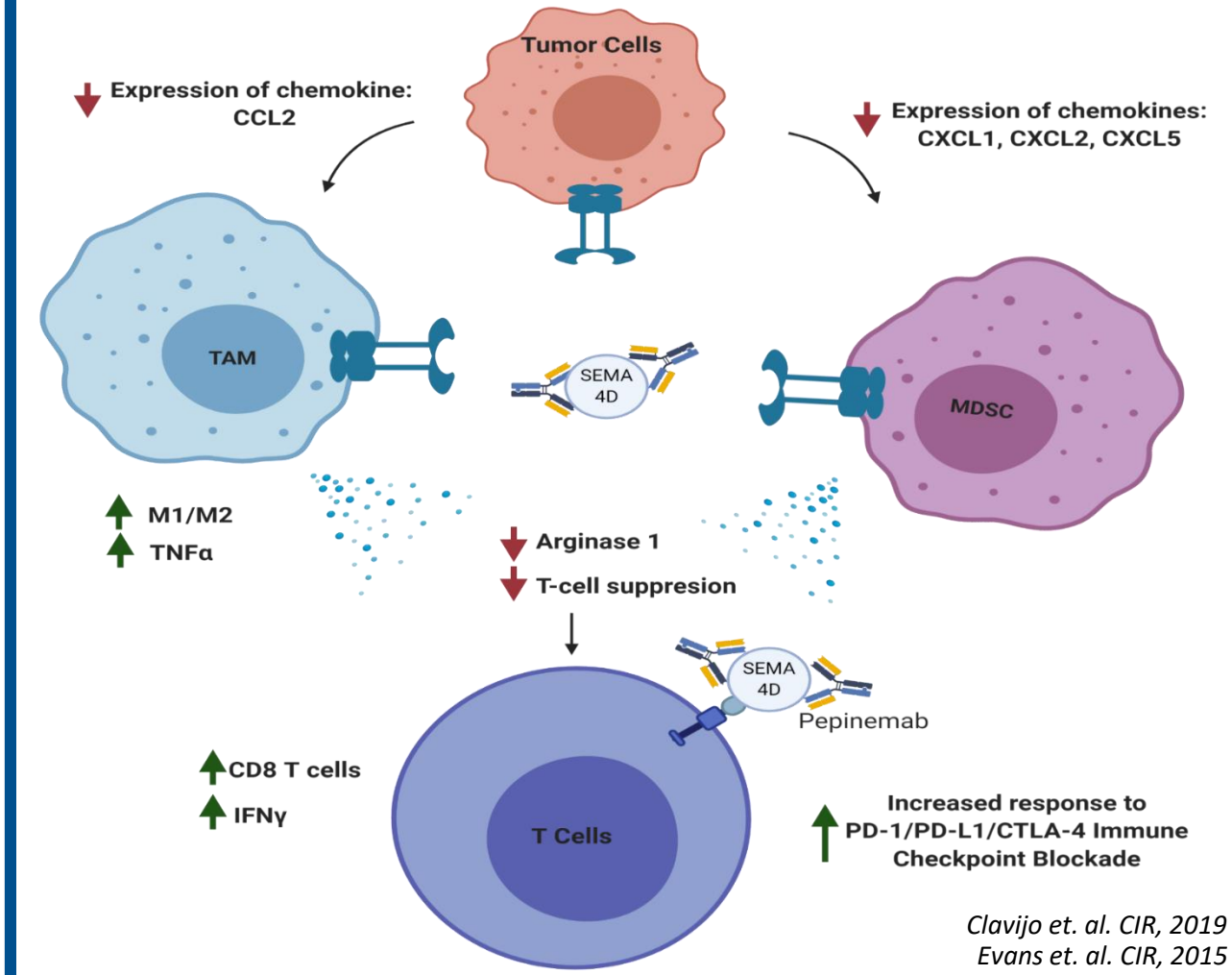
O'Reilly EM[1], Oh DY[2], Dhani N[3], Renouf DJ[4], Lee MA[5], Sun W[6], Fisher G[7], Hezel A[8], Chang SC[9], Vlahovic G[9], Takahashi O[9], Yang Y[9], Fitts D[10], Philip PA[11].

3% ORR

Semaphorin-Plexin Signaling Drives Suppression of T-Cell Response in Murine Models of Solid Tumors

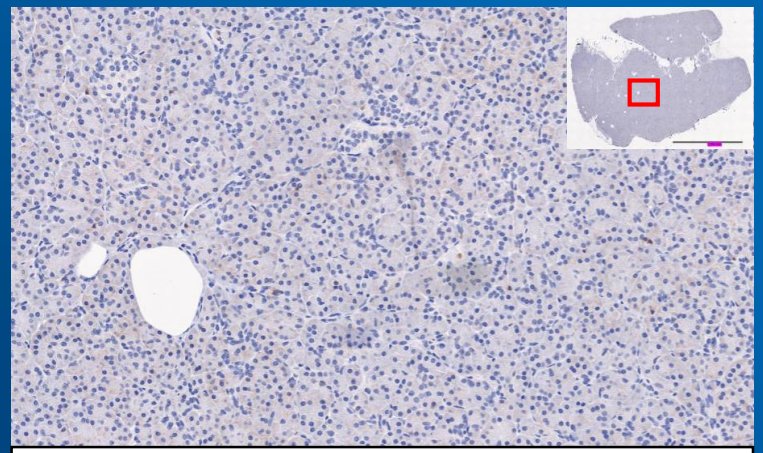


Swiercz et. al. J. Cell Biol., 2004
Peacock et. al. EMBO Mol Med., 2018

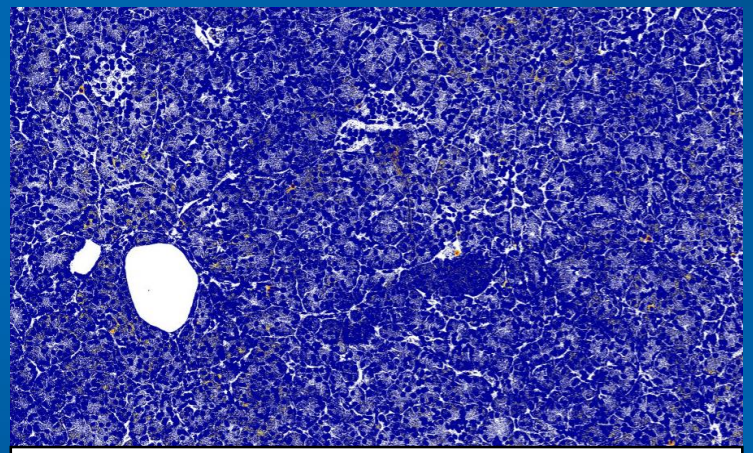


Clavijo et. al. CIR, 2019
Evans et. al. CIR, 2015

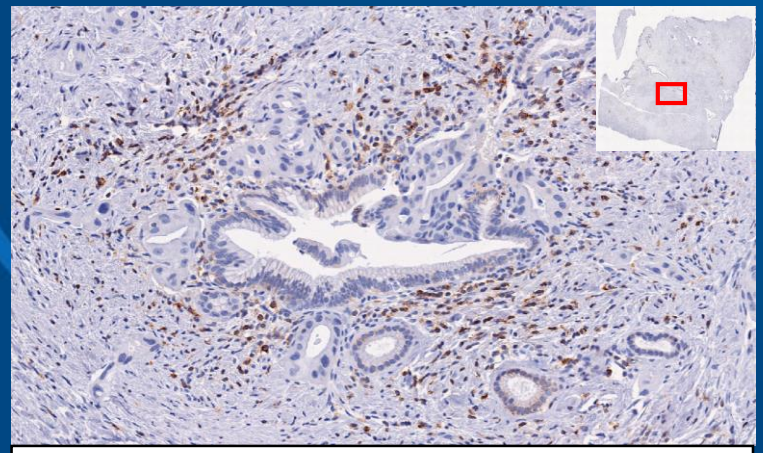
Semaphorin 4D is Overexpressed in the TME of Human PDAC



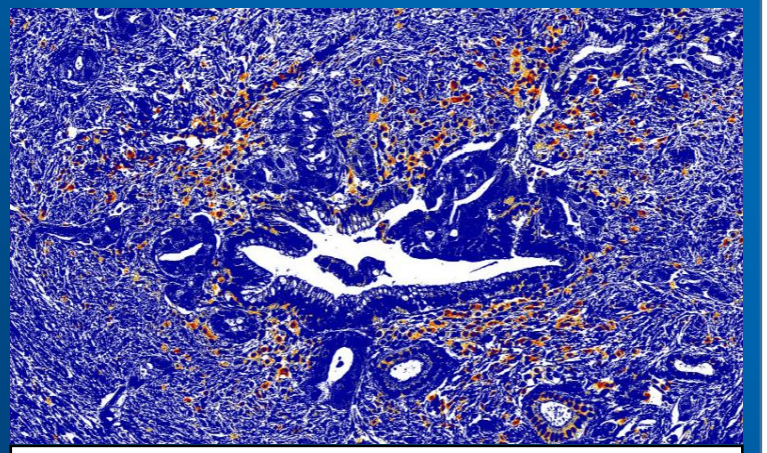
Normal Pancreas Sema 4D IHC, 5X



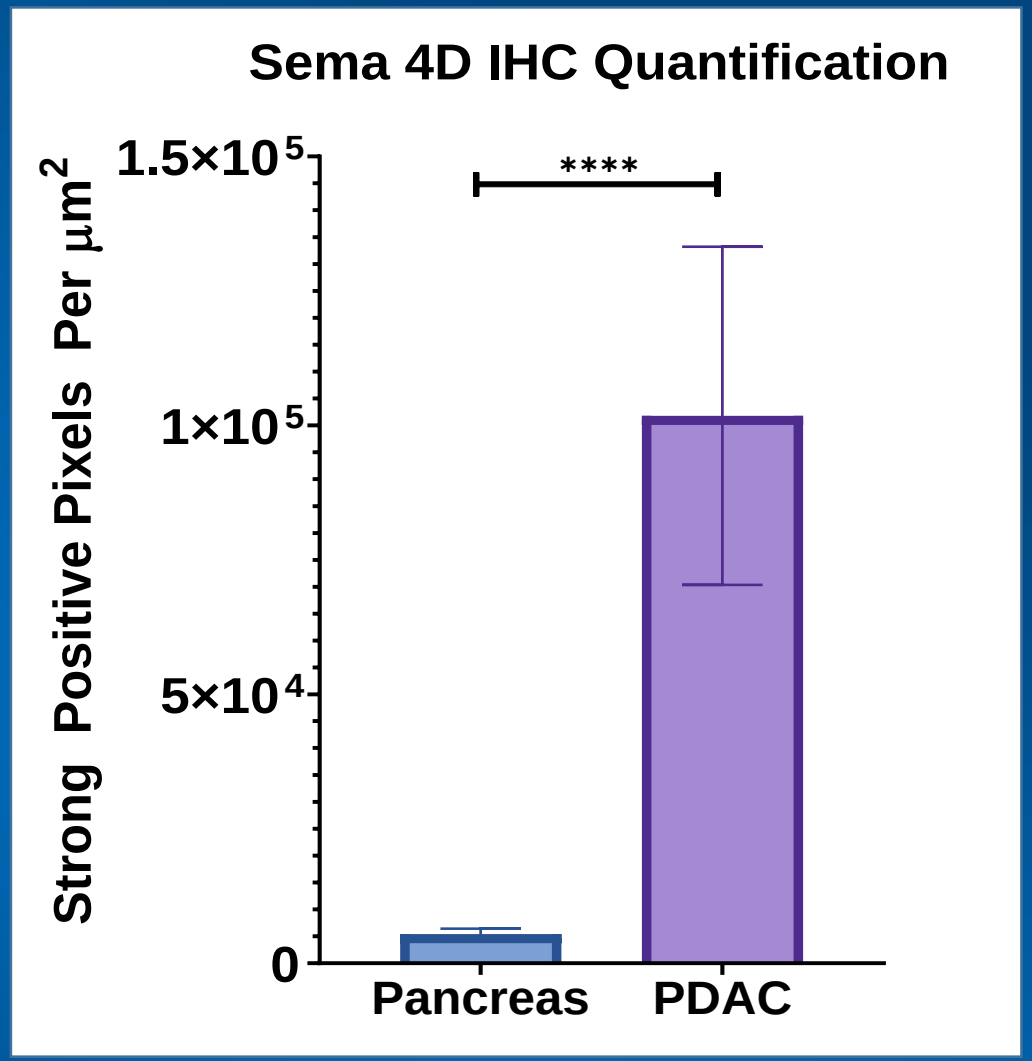
IHC Positive Pixel Count



PDAC Sema 4D IHC, 5X



IHC Positive Pixel Count



n=11 per group, p<0.001

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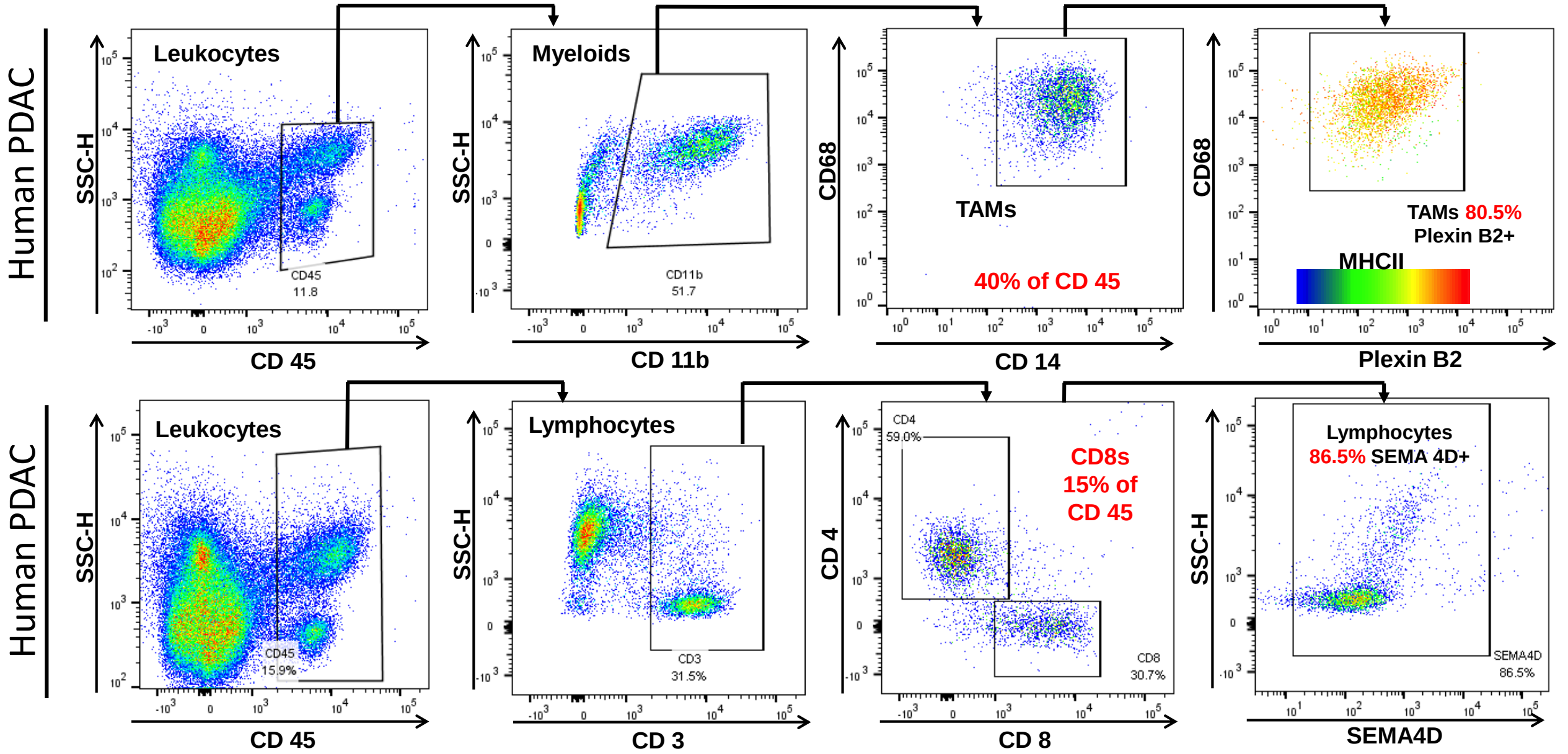
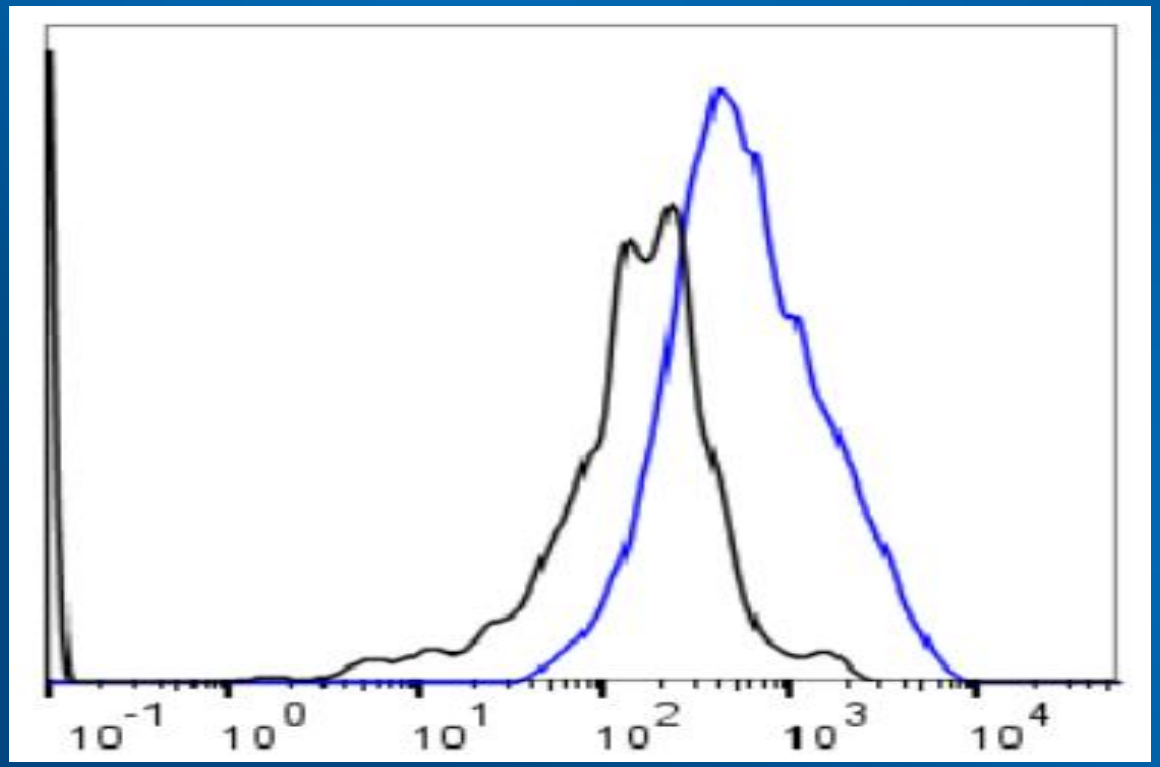
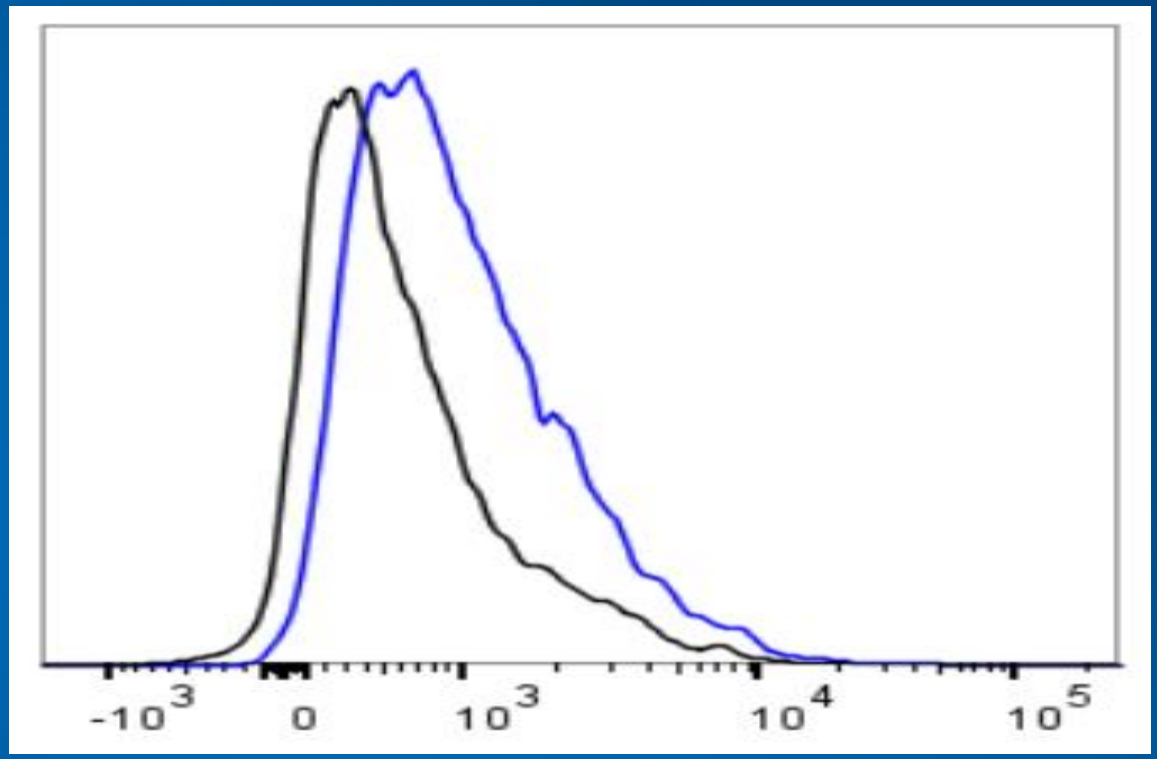

Human PDAC
Leukocytes
SSC-H
CD45
11.8
CD 45
Myeloids
SSC-H
CD11b
51.7
CD 11b
CD68
TAMs
40% of CD 45
CD 14
CD68
TAMs 80.5%
Plexin B2+
MHCII
Plexin B2
Human PDAC
Leukocytes
SSC-H
CD45
15.9%
CD 45
Lymphocytes
SSC-H
CD3
31.5%
CD 3
CD 4
CD4
59.0%
CD8s
15% of
CD 45
CD8
30.7%
CD 8
Lymphocytes
86.5% SEMA 4D+
SSC-H
SEMA4D
86.5%
SEMA4D

SEMA4D and Its Receptor Plexin B2 Are Co-expressed by TAMS



Plexin B2



SEMA 4D

Tumor Associated Macrophages

Fluorescence Minus One Control

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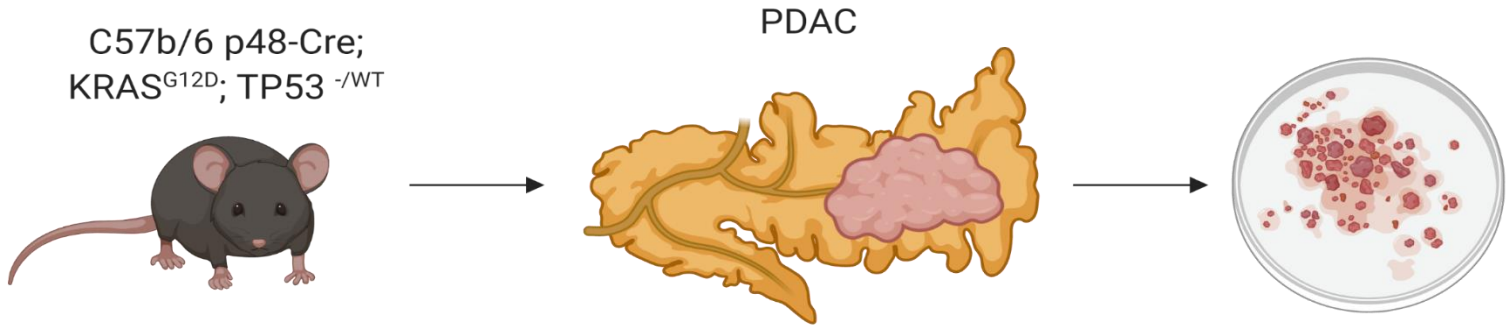
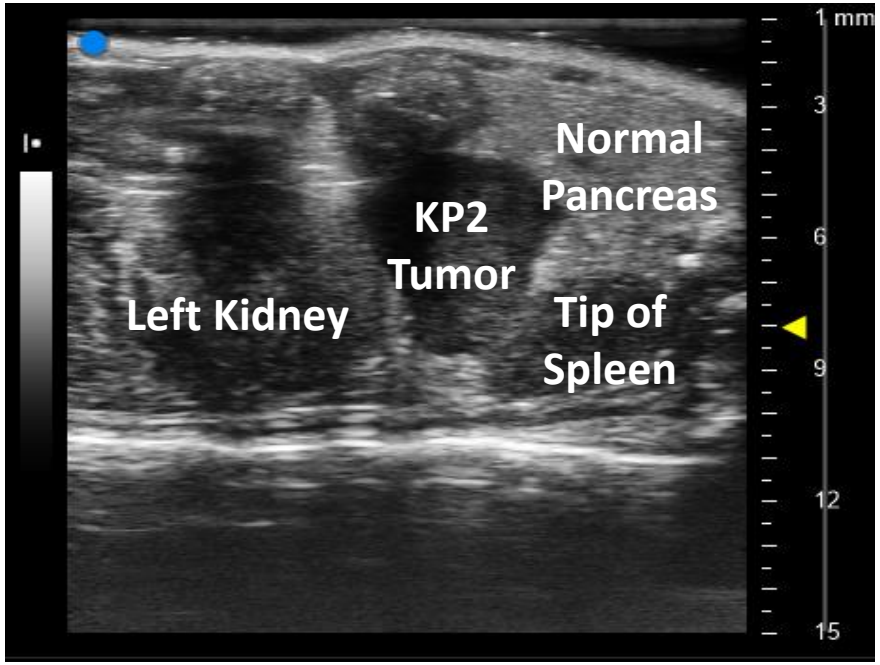
Orthotopic Murine Model of PDAC Closely Recapitulates Human PDAC

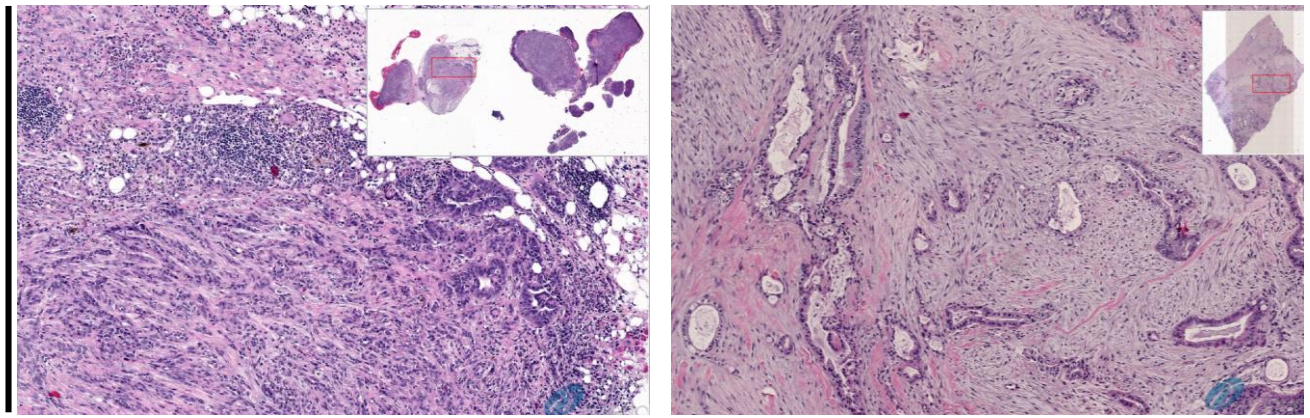


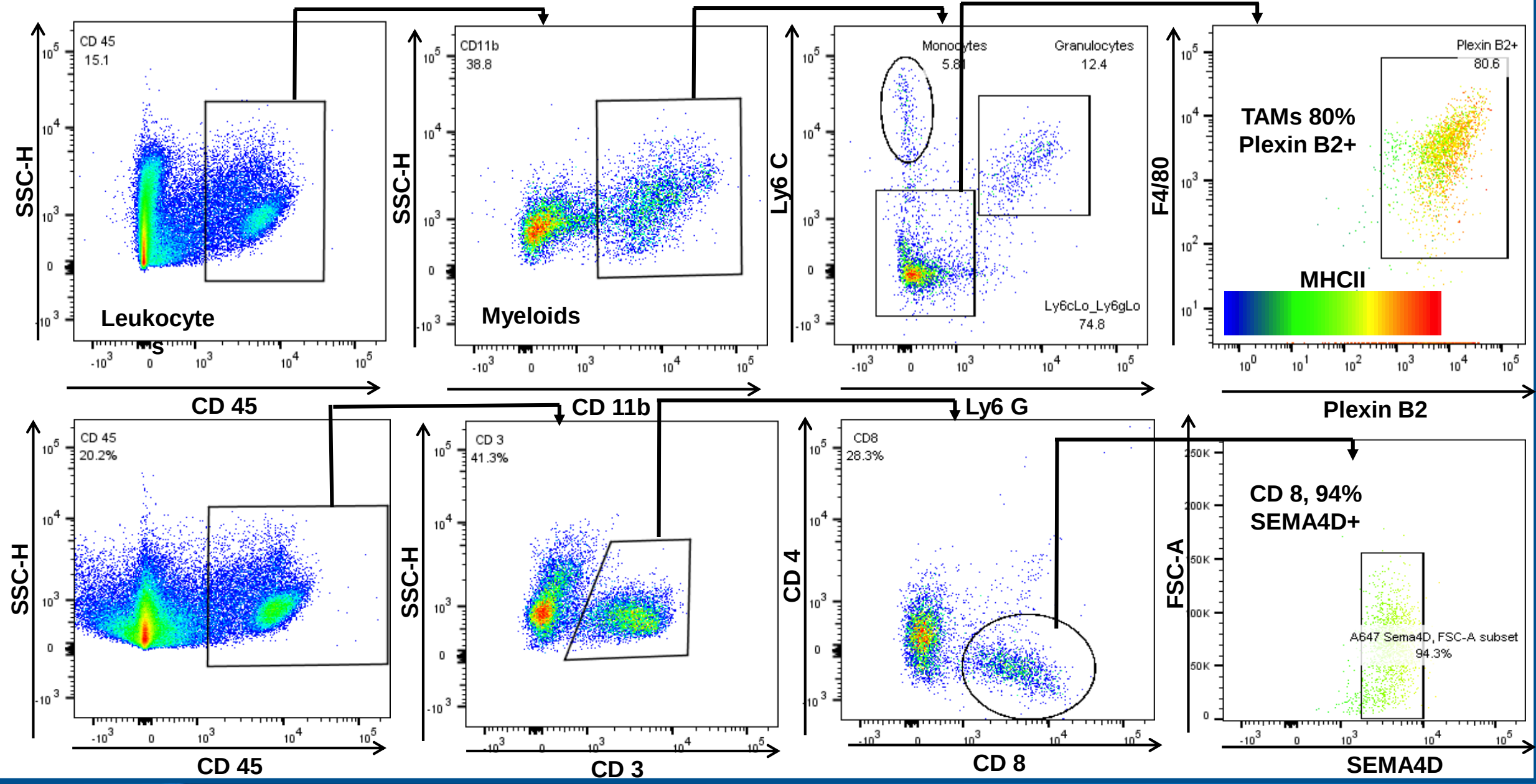
High Frequency Ultrasonography



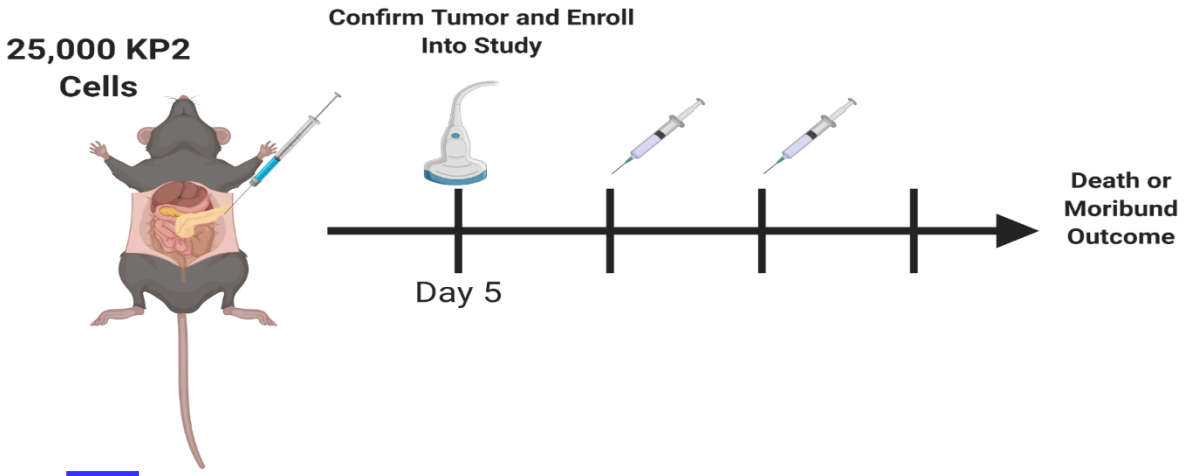
Orthotopic KP2 PDAC | **Human PDAC**

H & E

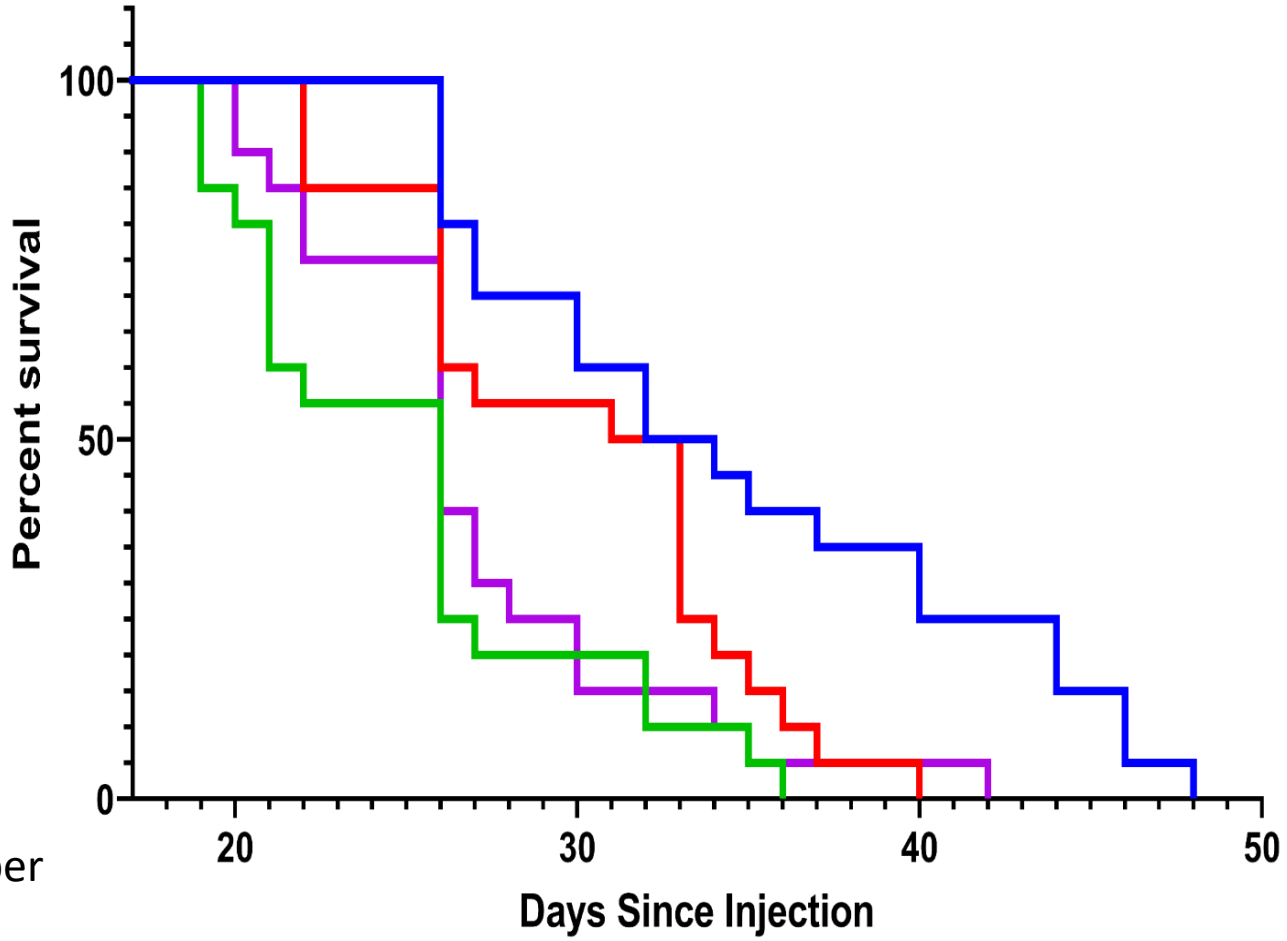



CD 45
15.1
SSC-H
Leukocyte
CD 45
CD11b
38.8
SSC-H
Myeloids
CD 11b
Monocytes
5.8
Granulocytes
12.4
Ly6 C
Ly6cLo_Ly6gLo
74.8
Ly6 G
Plexin B2+
80.6
TAMs 80%
Plexin B2+
MHCII
F4/80
Plexin B2
CD 45
20.2%
SSC-H
CD 45
CD 3
41.3%
SSC-H
CD 3
CD8
28.3%
CD 4
CD 8
CD 8, 94%
SEMA4D+
A647 Sema4D, FSC-A subset
94.3%
FSC-A
SEMA4D

SEMA4D Blockade Augments Dual Checkpoint Therapy in The Context of FOLFIRINOX

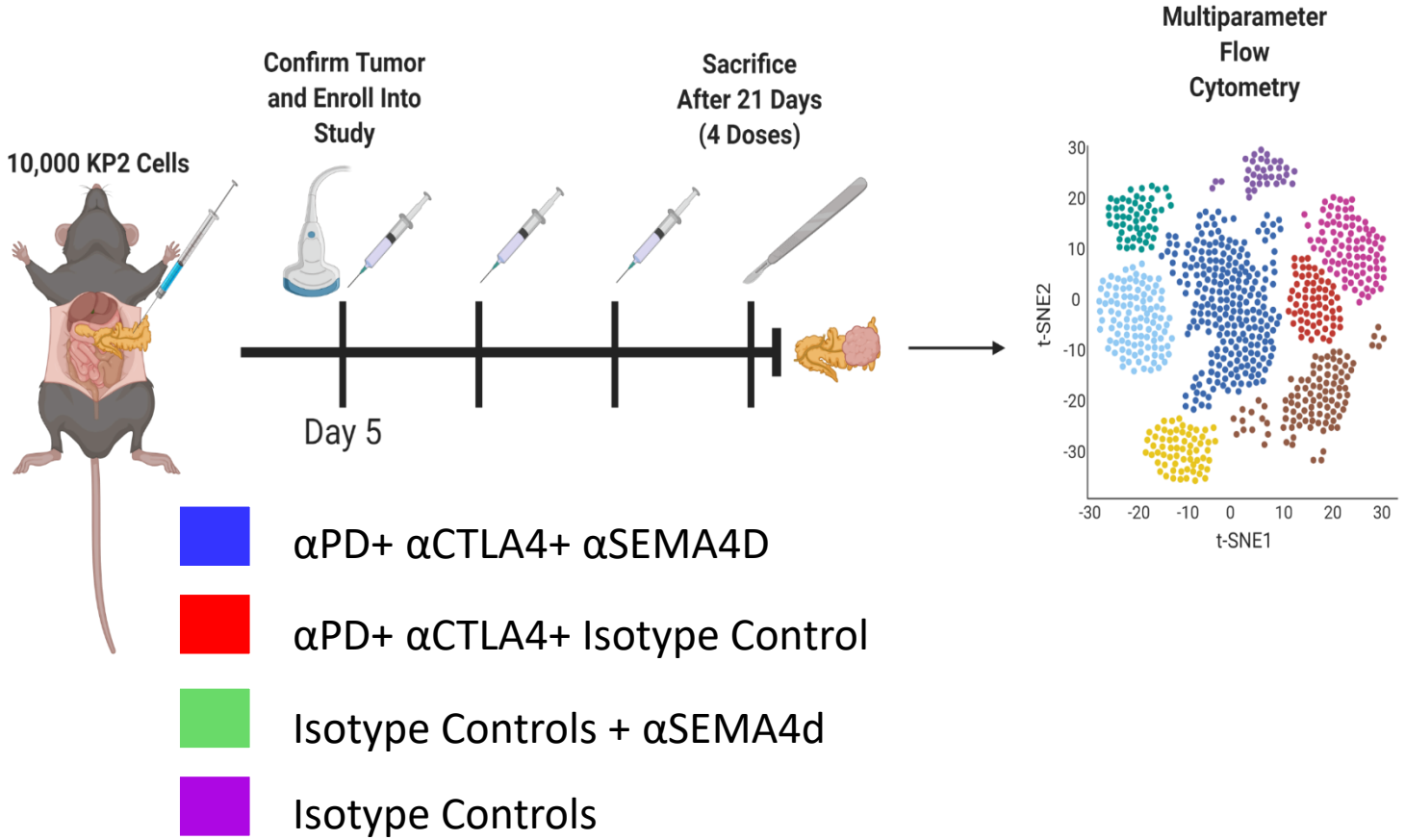


- FOLFIRINOX + αPD+ αCTLA4+ αSEMA4D ✱
- FOLFIRINOX + αPD+ αCTLA4+ Isotype Control
- FOLFIRINOX + Isotype Control+ αSEMA4d
- FOLFIRINOX + Isotype Control

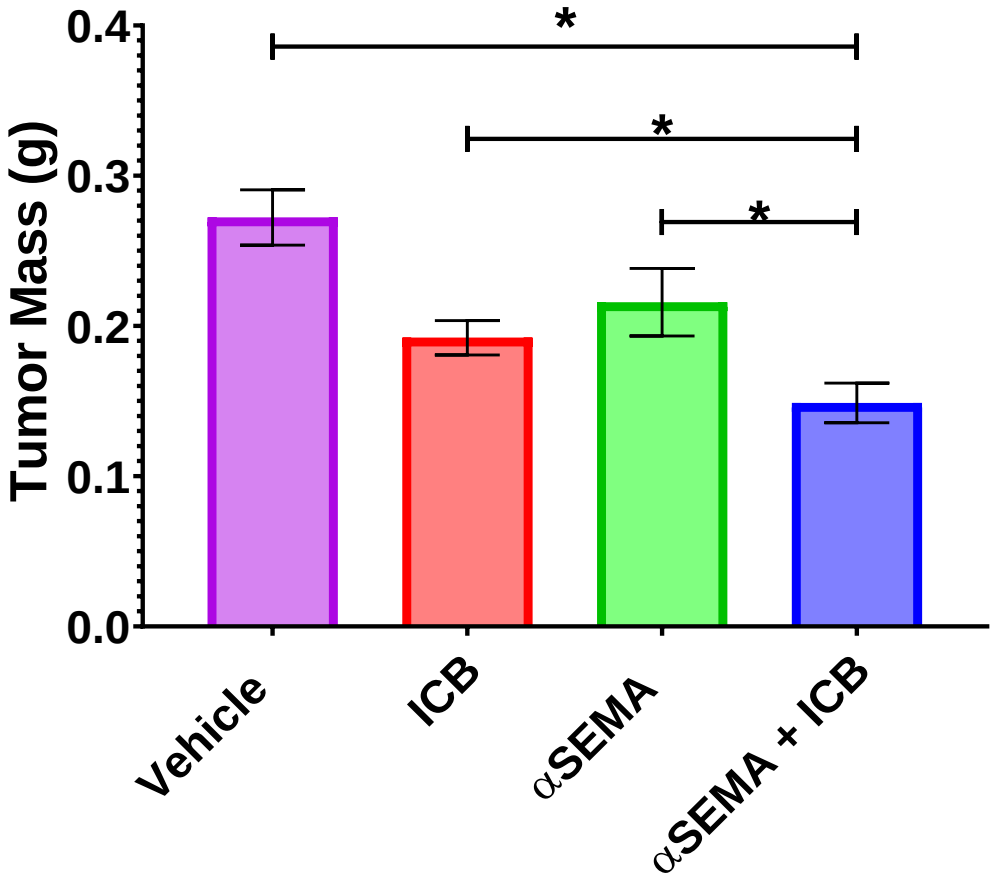


✱ Log-Rank < 0.05 compared to all other groups, n=20 mice per group. FOLFIRINOX Dosed Weekly, Immunotherapy BIW

SEMA4D Blockade Reduces PDAC Tumor Burden

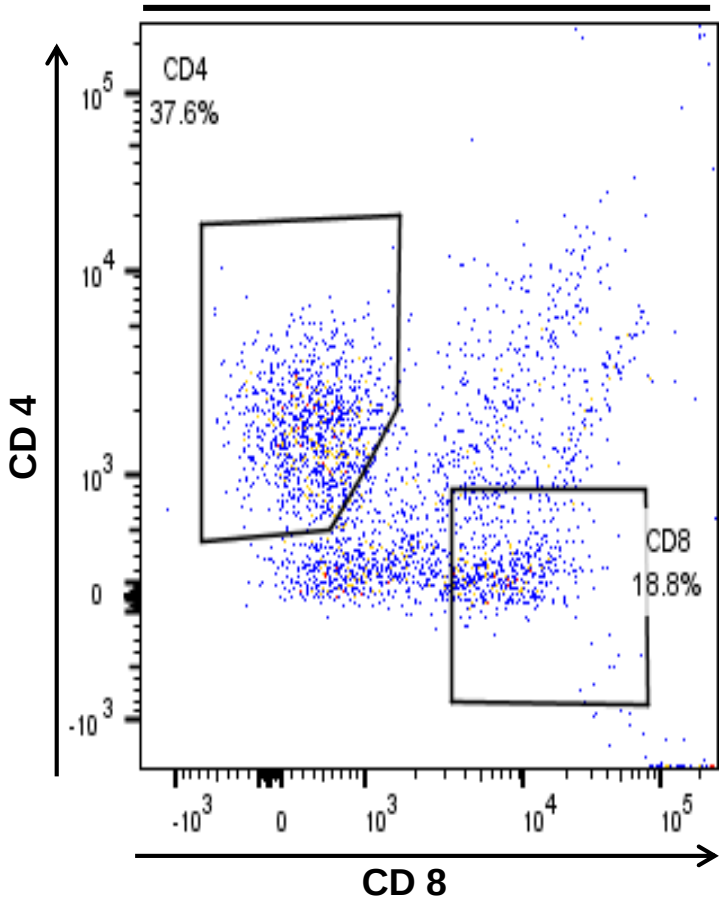


Tumor Weights At Sacrifice

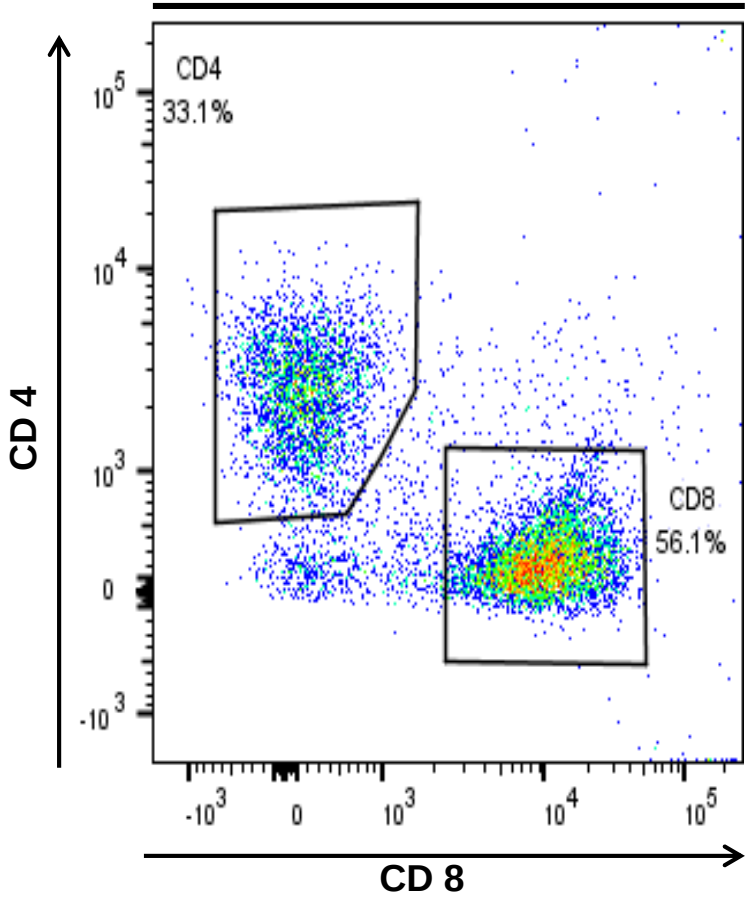


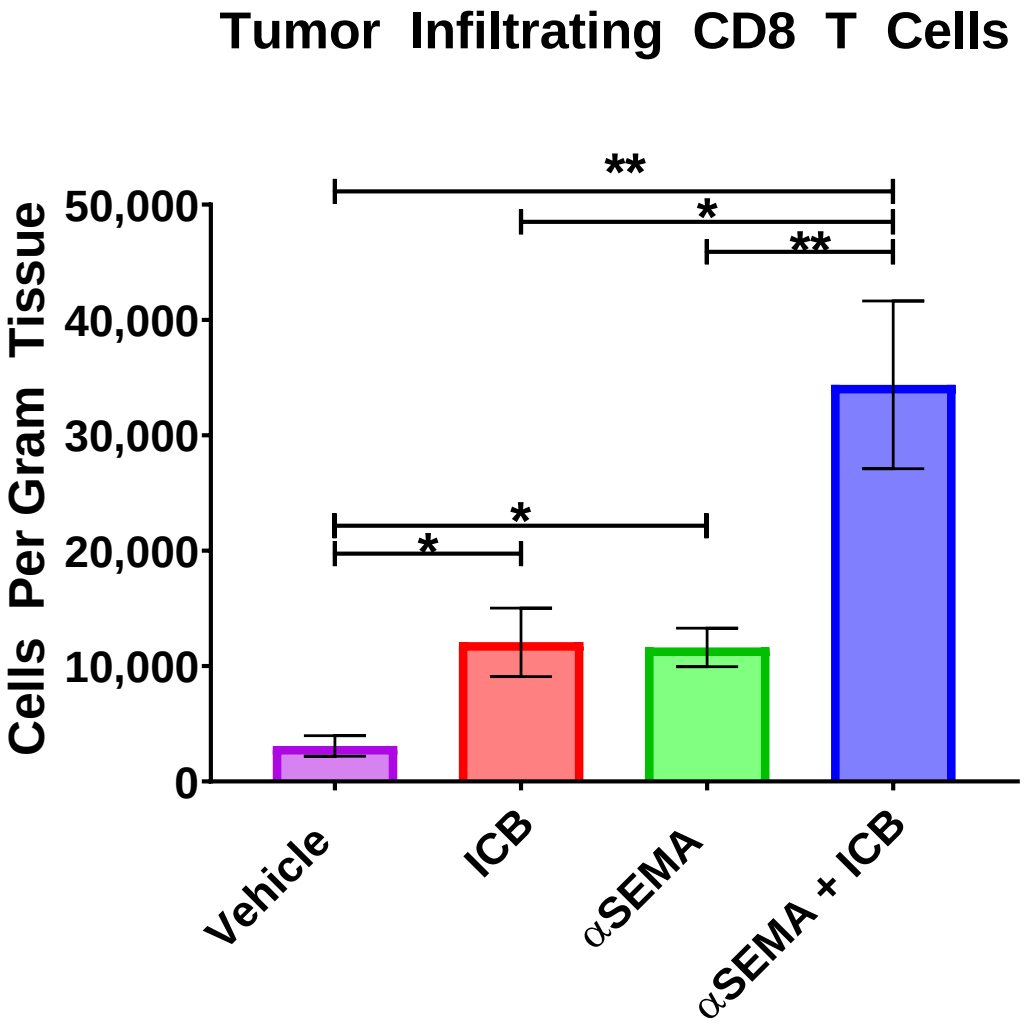
SEMA4D Blockade Increases Tumor Penetration of CD8 T-Cells

ICB + Isotype

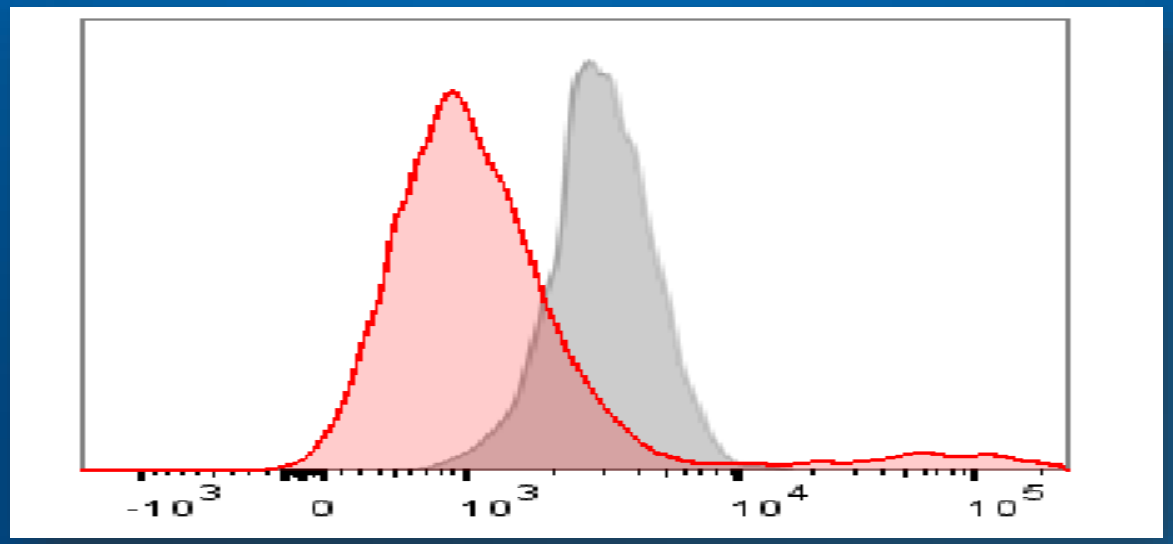


αSEMA4D + ICB



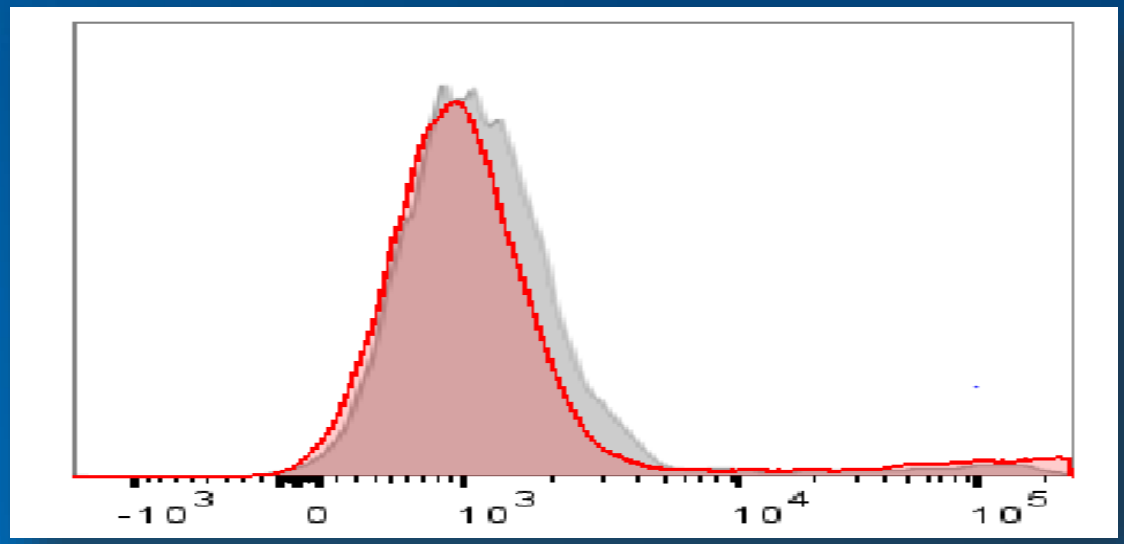


SEMA 4D Blockade Abrogated SEMA4D Signal Within TME



Untreated CD3+, SEMA4D

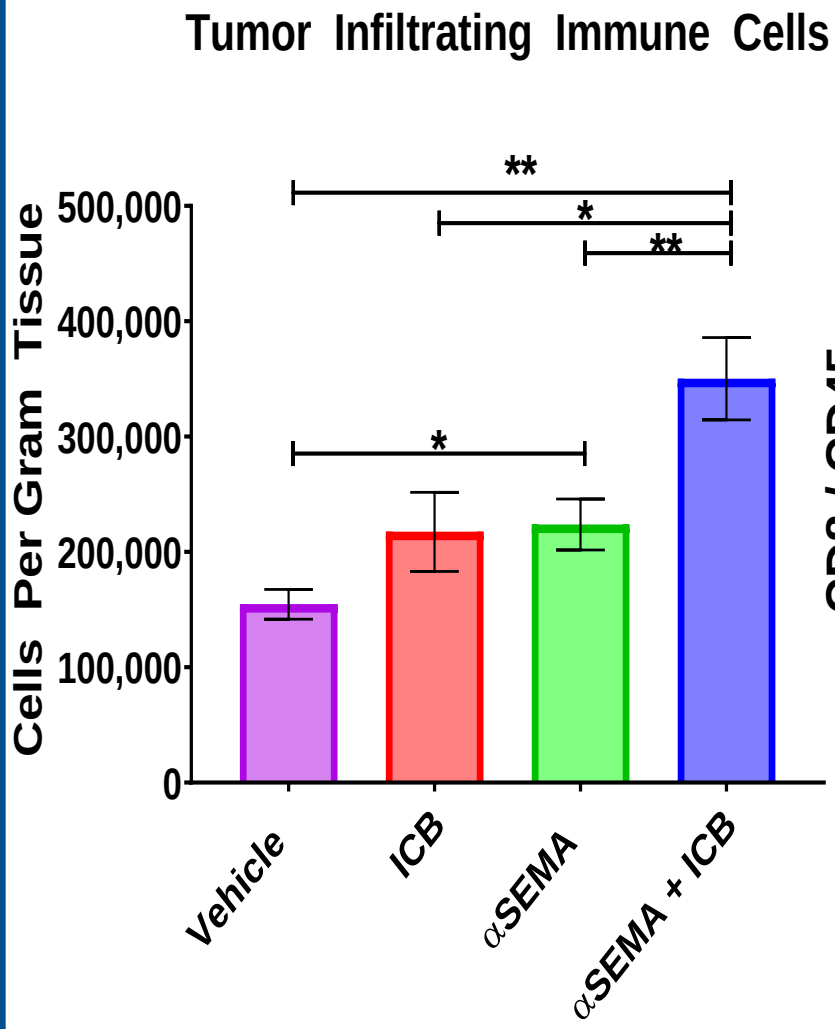
Treated CD3+, SEMA4D

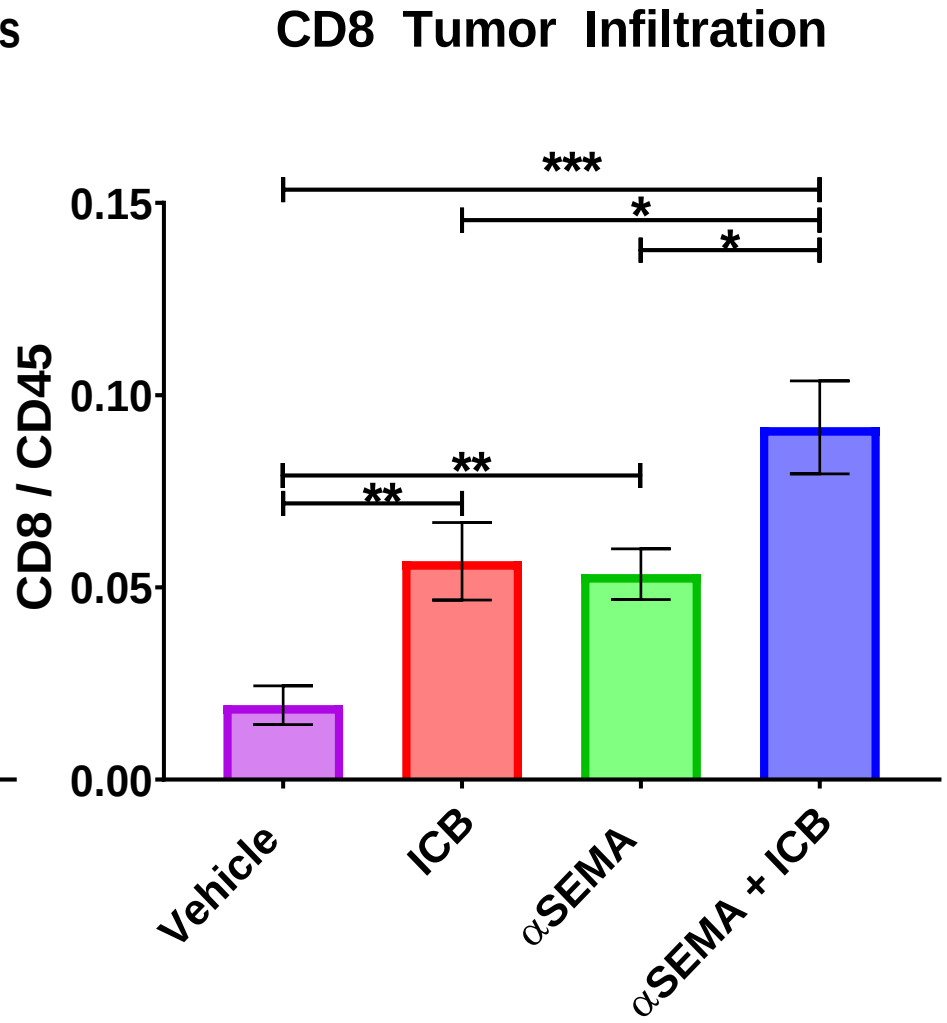


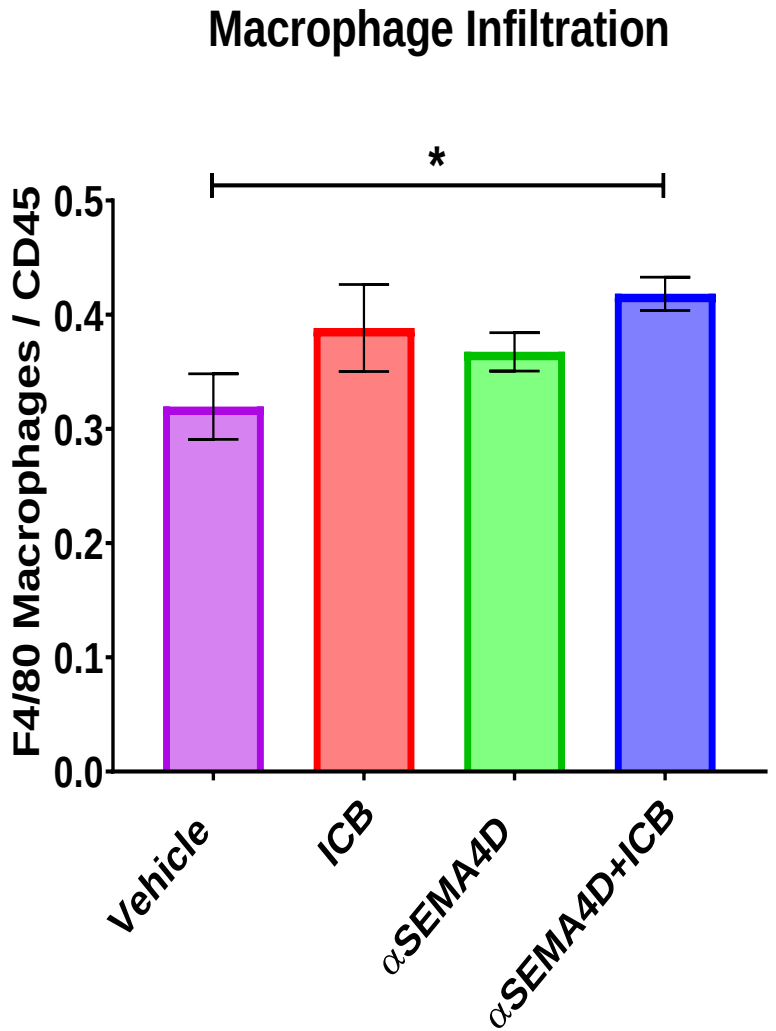
SEMA 4D FMO

Treated CD3+, SEMA4D

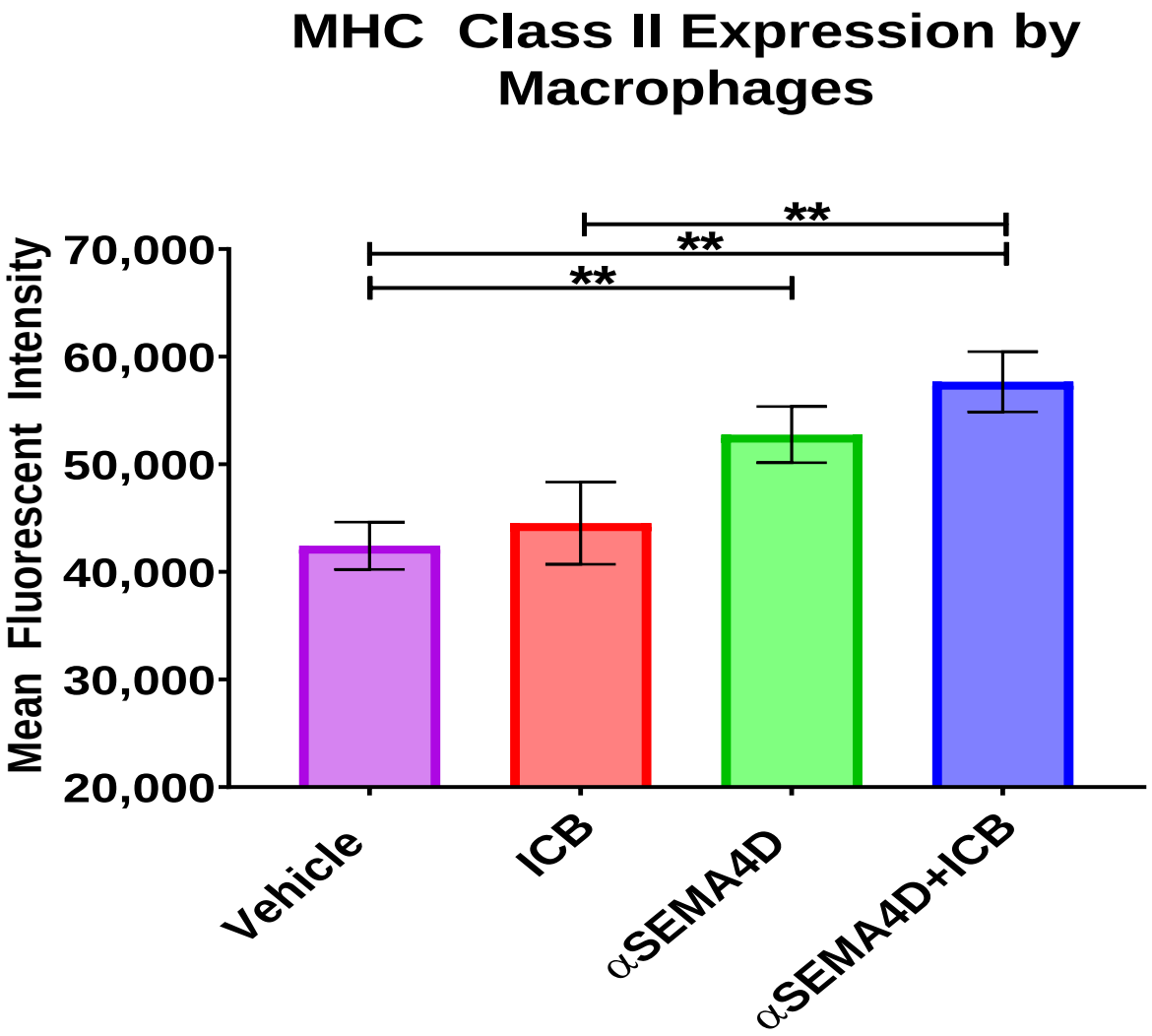
SEMA4D Blockade Turns Immune "Cold" Tumors "Hot"

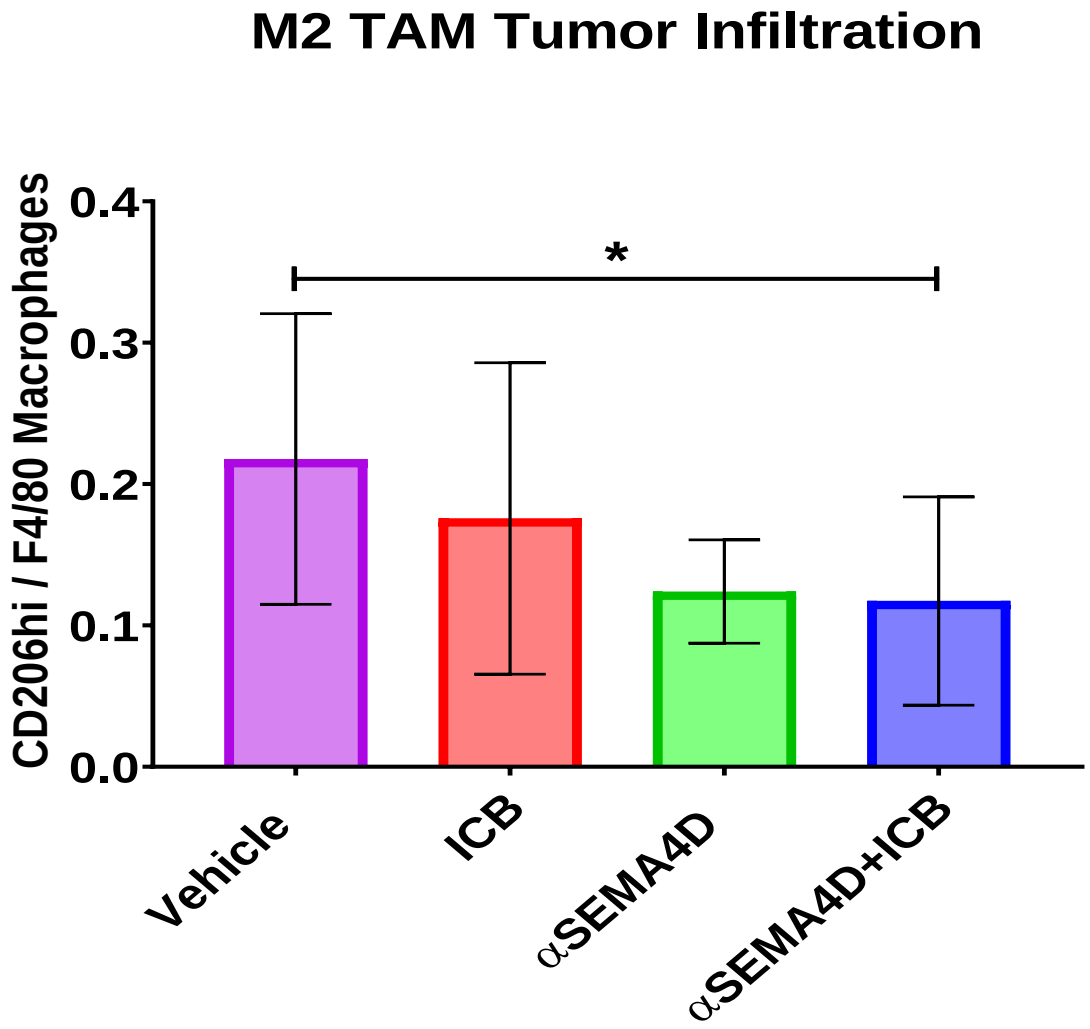






SEMA4D Blockade Shifts Innate Immunity Towards Antigen Presentation





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AACR American Association for Cancer Research®

Phase 1b

BOIN Enrollment Rules

(18-66 patients)

Dose de-escalation

Folfirinox + anti-PD1/PD-L1 + VX15/2503

Phase 2

Expansion Cohort

Simon's Two Stage Design Interim Assessment

(18-46 patients)

MTD Dose of Folfirinox + anti-PD1/PD-L1 + VX15/2503

Recruitment by Medical Oncology

Assessment of eligibility

Consent

Baseline physical exam, Baseline biopsy, Peripheral blood draw.

Enroll into Protocol

After 2nd cycle, Obtain on-treatment biopsy, Peripheral blood Draw

After completion of 12th cycle, continue on immunotherapy at discretion of treating physician

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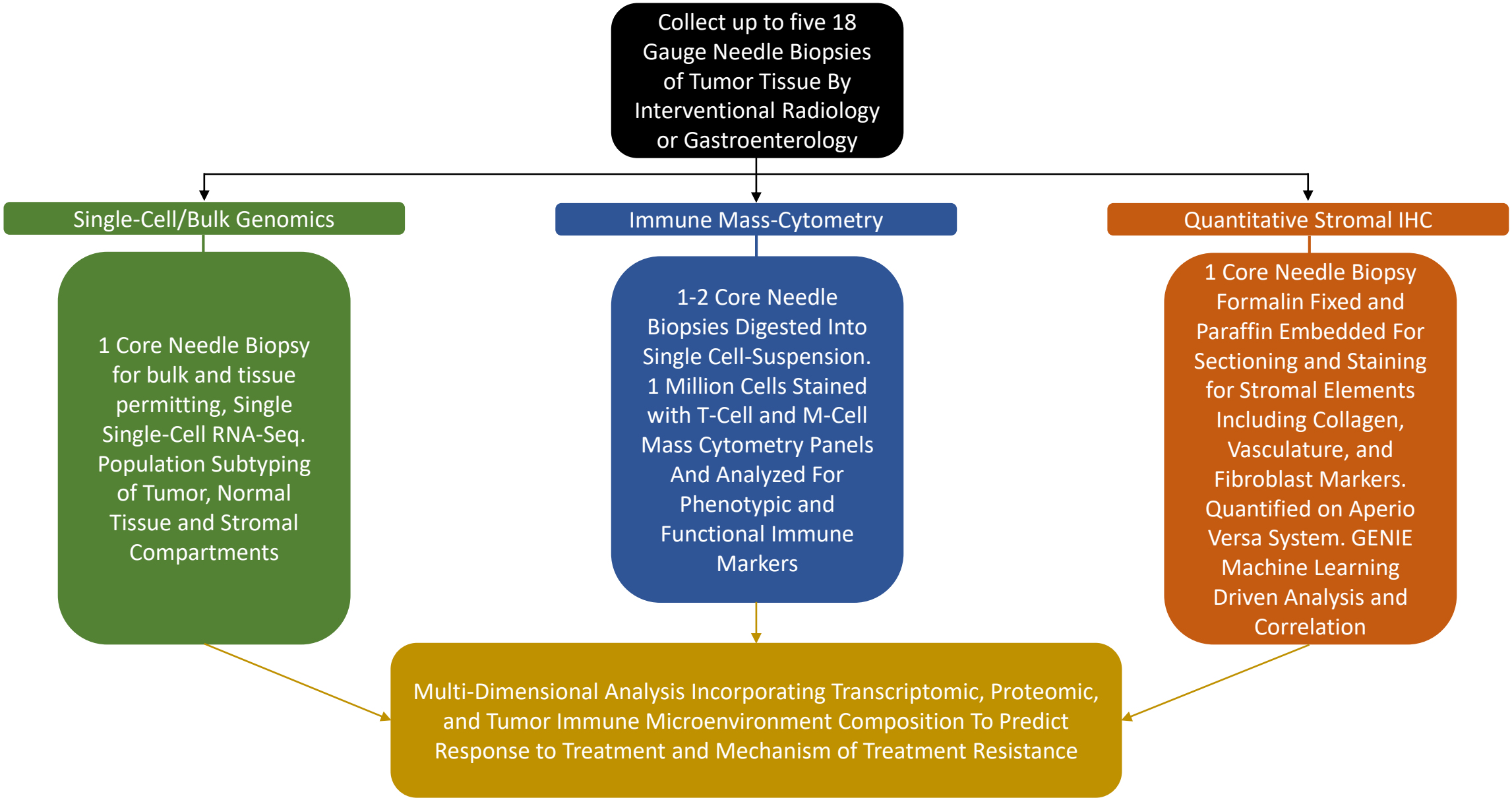
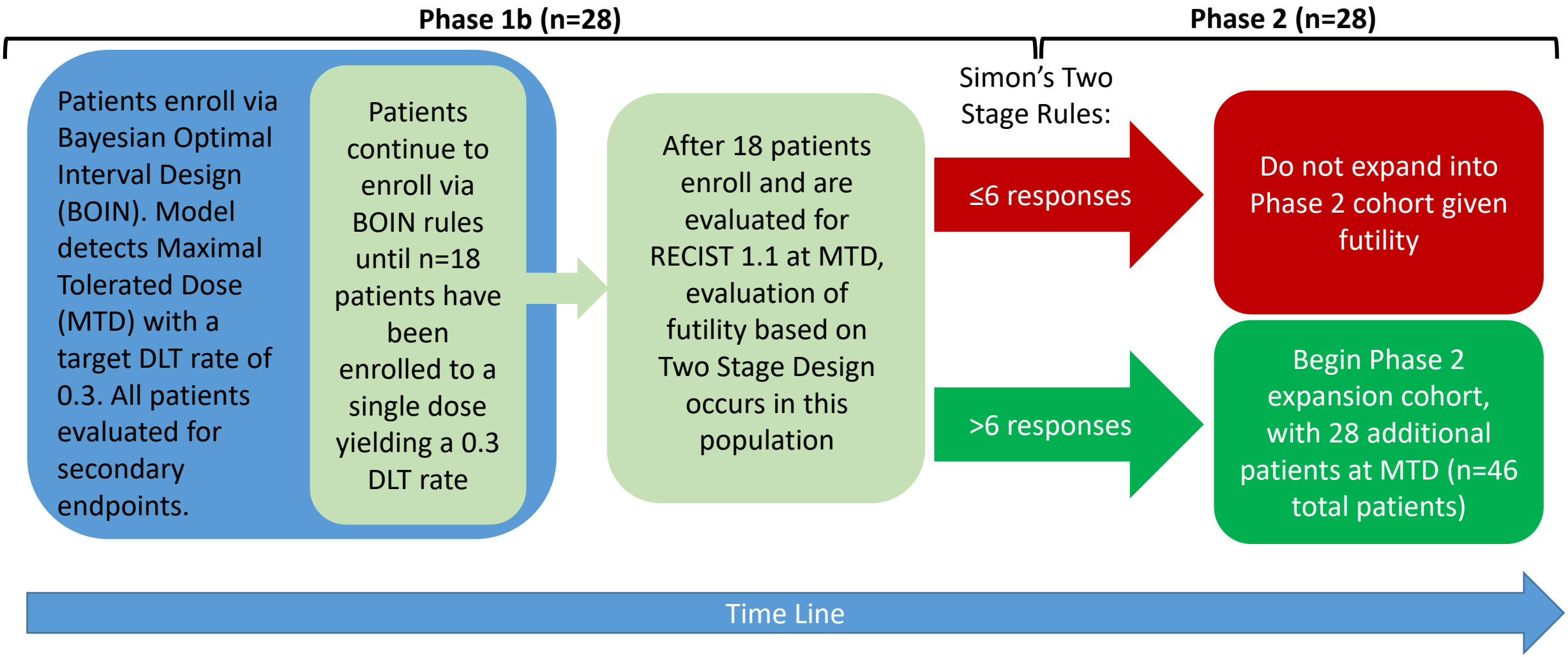

Collect up to five 18 Gauge Needle Biopsies of Tumor Tissue By Interventional Radiology or Gastroenterology
Single-Cell/Bulk Genomics
Immune Mass-Cytometry
Quantitative Stromal IHC
1 Core Needle Biopsy for bulk and tissue permitting, Single Single-Cell RNA-Seq. Population Subtyping of Tumor, Normal Tissue and Stromal Compartments
1-2 Core Needle Biopsies Digested Into Single Cell-Suspension. 1 Million Cells Stained with T-Cell and M-Cell Mass Cytometry Panels And Analyzed For Phenotypic and Functional Immune Markers
1 Core Needle Biopsy Formalin Fixed and Paraffin Embedded For Sectioning and Staining for Stromal Elements Including Collagen, Vasculature, and Fibroblast Markers. Quantified on Aperio Versa System. GENIE Machine Learning Driven Analysis and Correlation
Multi-Dimensional Analysis Incorporating Transcriptomic, Proteomic, and Tumor Immune Microenvironment Composition To Predict Response to Treatment and Mechanism of Treatment Resistance

Phase 1b/2 Design Integrating Evaluation of Safety and Efficacy



Phase 1b: Enrollment begins at dose 0, and proceeds by BION rules dependent on observed rates of DLT, target DLT rate 0.3.

Phase 2: Accrual continues in Phase 1b until the 18th patient is evaluated for RECIST 1.1. Phase 2 Enrollment begins once 18th evaluation passes Simon's Two Stage Rule. Total number of patients between Phase1b/2; n= 18-94, but expected to be 56.

Thank you

Linehan Laboratory

Rachel Jewell
Mary Georger
Brian Belt
Nicholas Ullman
Katherine Jackson
Ben Dale
Paul Burchard

Wilmot Cancer Institute

Aram Hezel
Richard Dunne
Tina Bowdish
Eva Galka
Luke Schoeniger
Vivek Kaul
Truptesh Kothari
Asad Ullah
Shivangi Kothari
Krystle Bittner

Vaccinex, Inc.

Elizabeth Evans
Terry Fisher
Crystal Mallow
Desa Rae Pastore
Maurice Zauderer
Elaine Gersz

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