

Targeting CXCR4 with combination chemotherapy and immunotherapy in Pancreas Ductal Adenocarcinoma

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Disclosures

Research Funding

- Genentech/Roche
- Merck
- BioLineRx
- Regeneron
- Plexxikon

Advisory Role

- Genentech/Roche
- BioLineRx
- Ipsen

Immune Checkpoint Blockade (ICB) and Pancreas Cancer

PDL1 and TIL

Retrospective – Resected PDA (N=51)

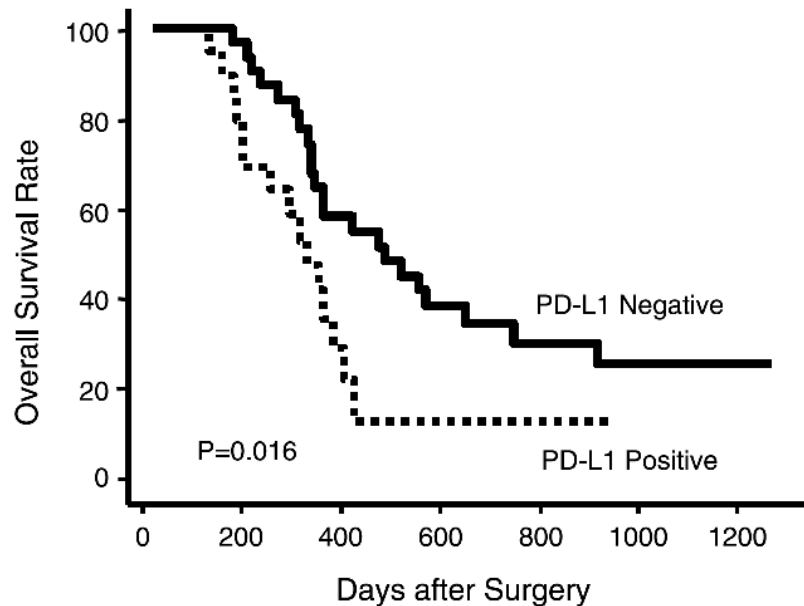
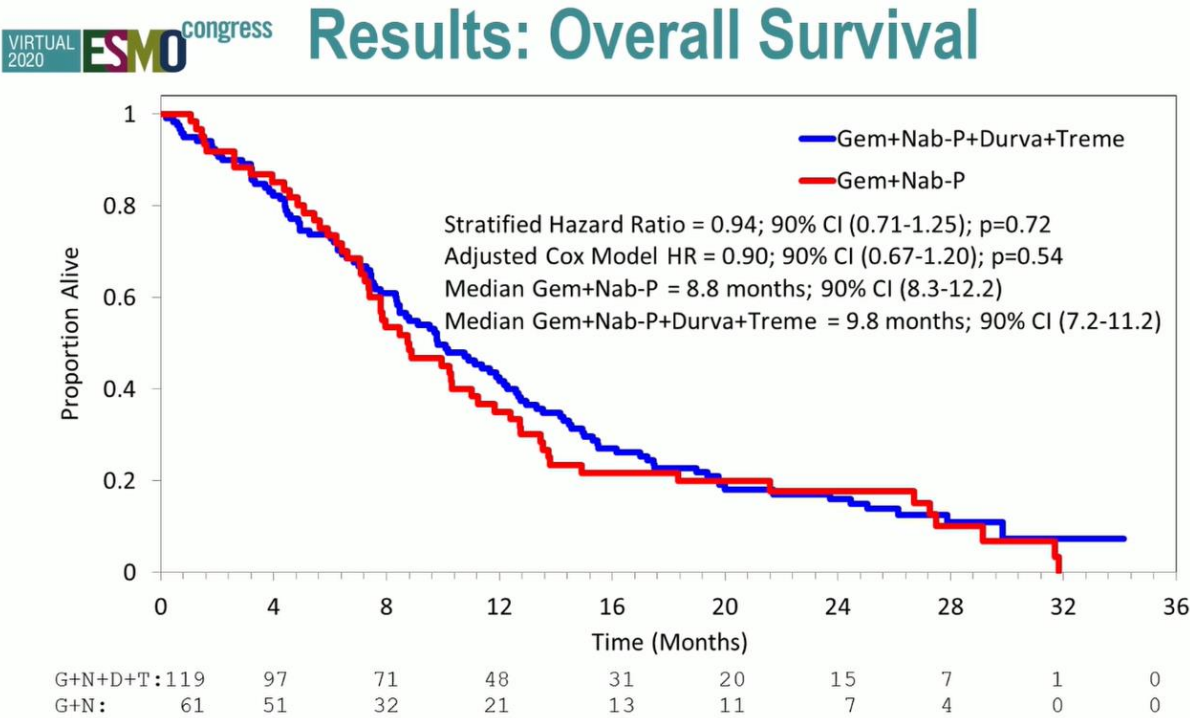


Table 2. Inverse correlation between tumor PD-L1 status and TILs

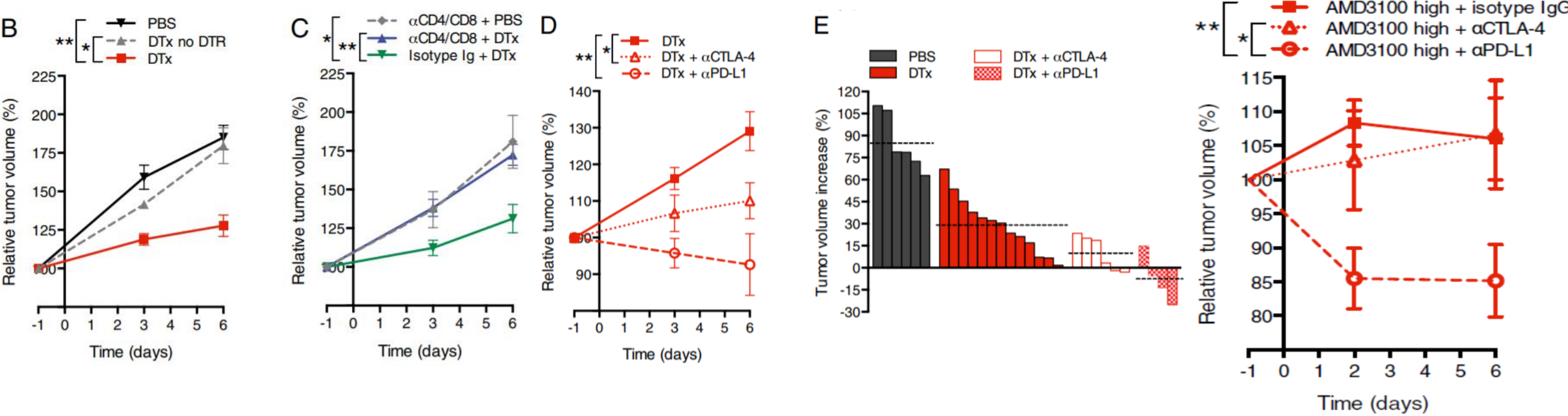
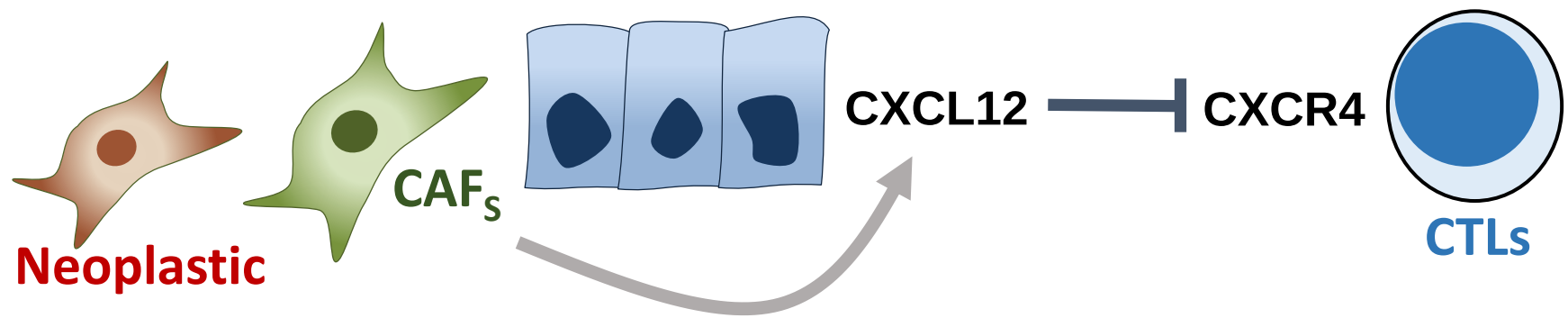
PD-L1	CD4		CD8	
	Positive	Negative	Positive	Negative
Positive	9	11	5	15
Negative	24	7	25	6

Nomi, T. CCR. 2007; 13:251-7



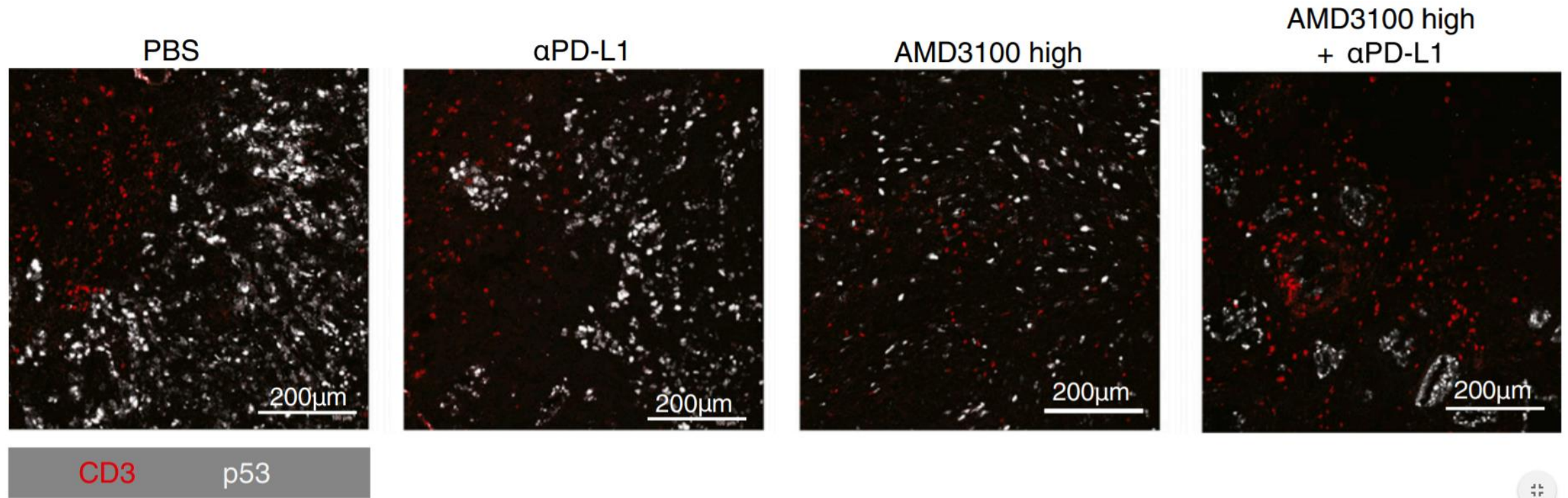
Dr. Daniel Renouf, BC Cancer, University of British Columbia, Vancouver, Canada
Renouf D, Knox J, Kavan P, Jonker D, Welch S, Couture F, Lemay F, Tehfe M, Harb M, Aucoin N, Ko Y, Tang P, Ramjeesingh R, Meyers B, Kim C, Schaeffer D, Loree J, Graham B, Tu D, O'Callaghan C
Canadian Cancer Trials Group
Groupe canadien des essais sur le cancer
40 YEARS

CXCR4 inhibition Leads to Tumor Stabilization - Preclinical



Feig C, et al. PNAS. 2013. 110:20212-7

CXCR4 inhibition (CXCR4i) Leads to T-cell Infiltration



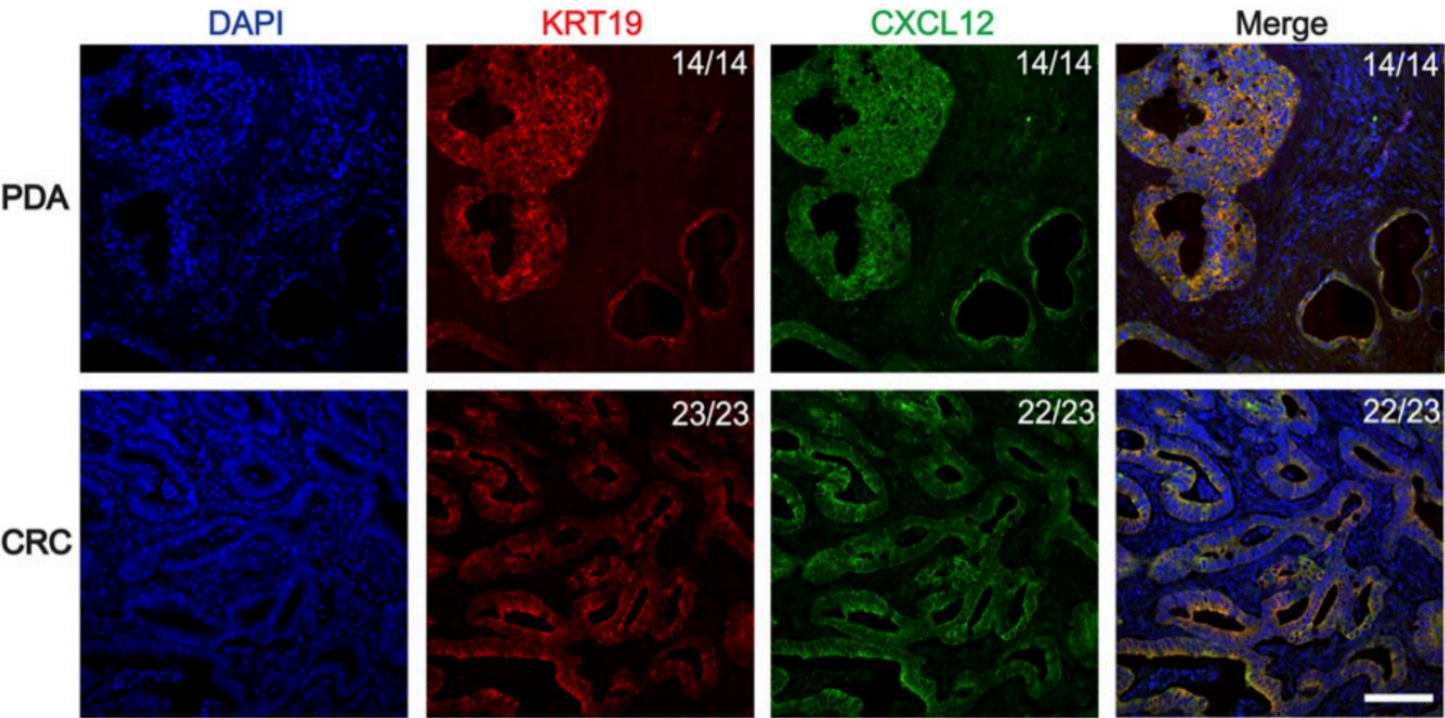
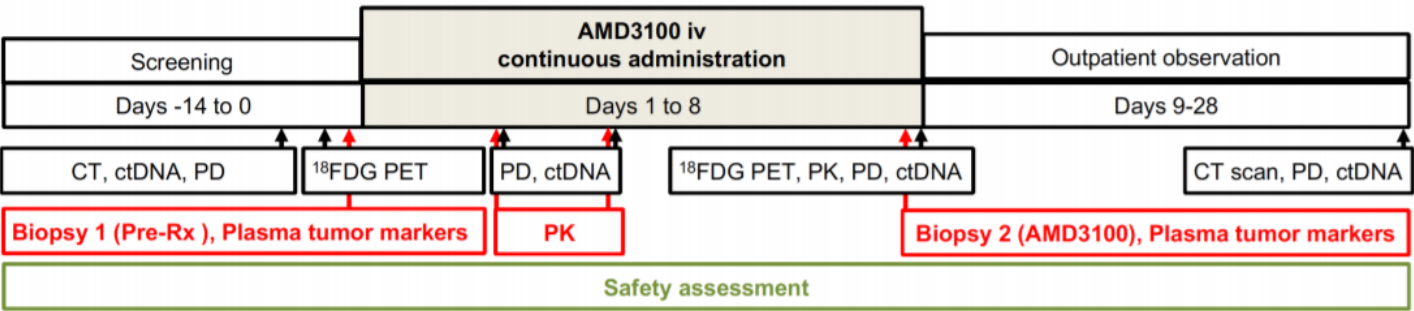
Feig C, et al. PNAS. 2013. 110:20212-7

CXCL12 Colocalizes with Tumor Cells in Pancreatic Cancer

NCT03277209 –

Dose escalation of continuous IV administration of **AMD3100**

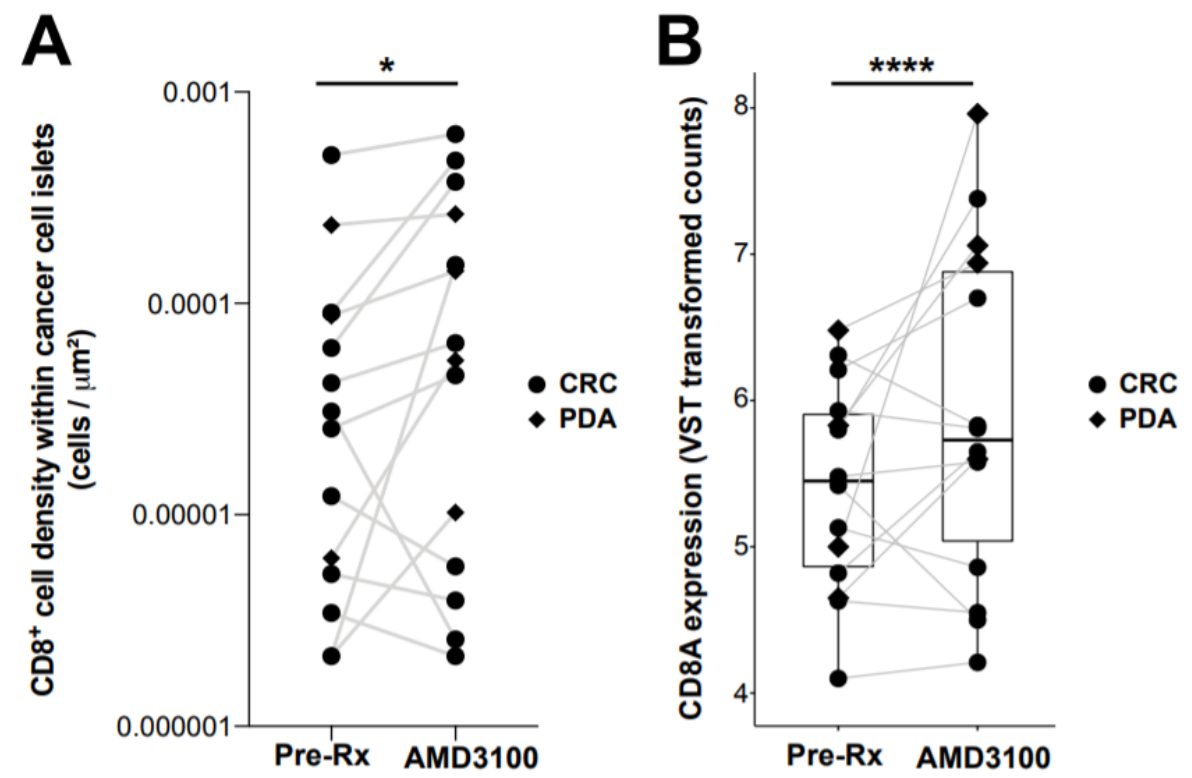
Treatment resistant MSS CRC and PDAC



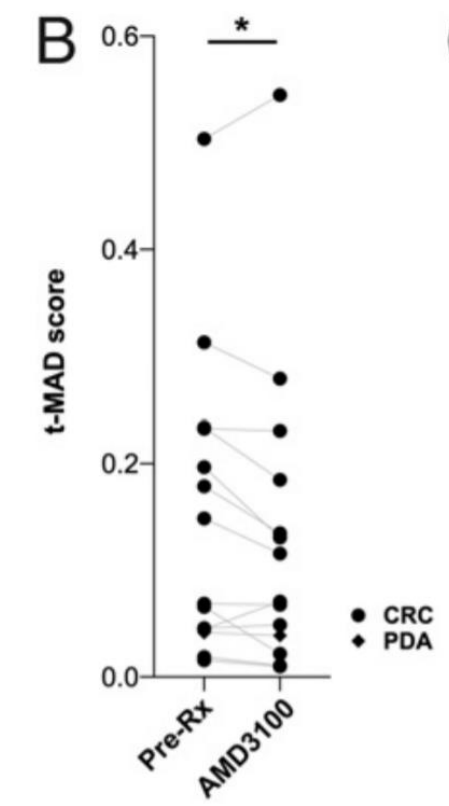
Biasci D, et al. Proc Natl Acad Sci U S A. 2020 Nov 17;117(46):28960-28970.

CXCR4i Increases CD8 T-cell Infiltration

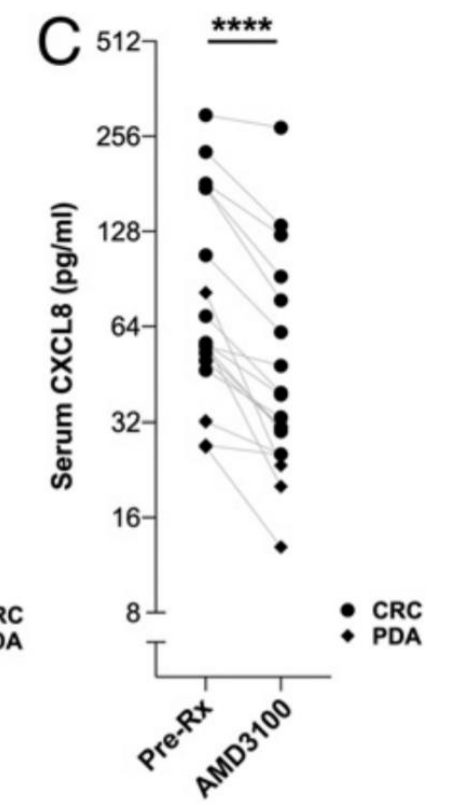
Paired Biopsy CD8⁺ T cells



Plasma ctDNA

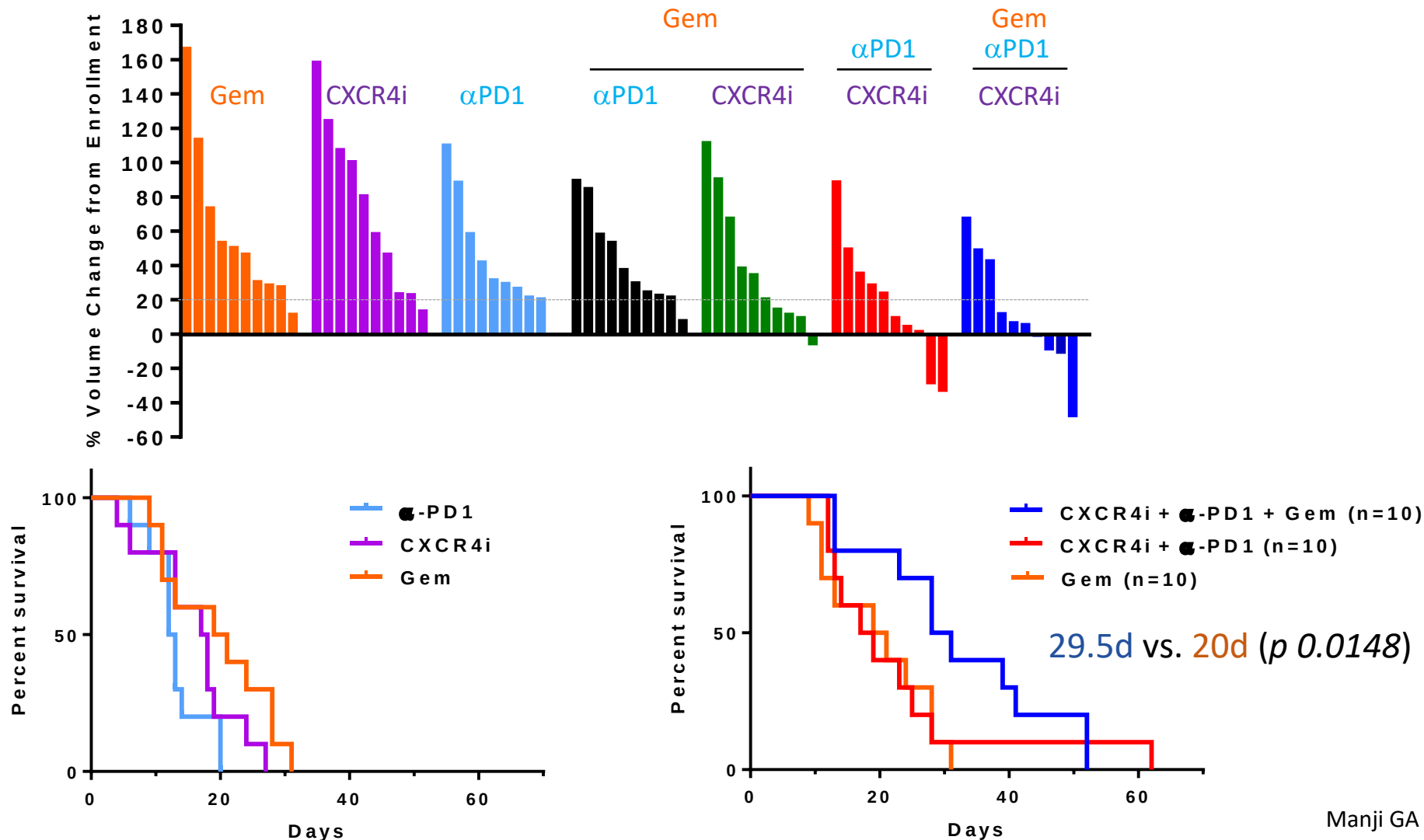


Plasma CXCL8



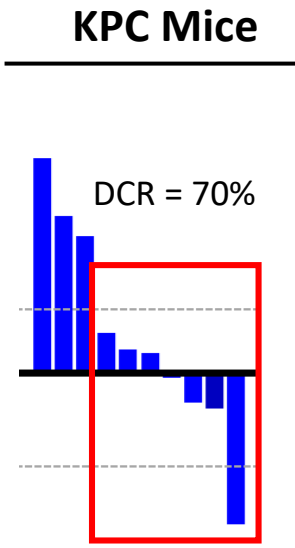
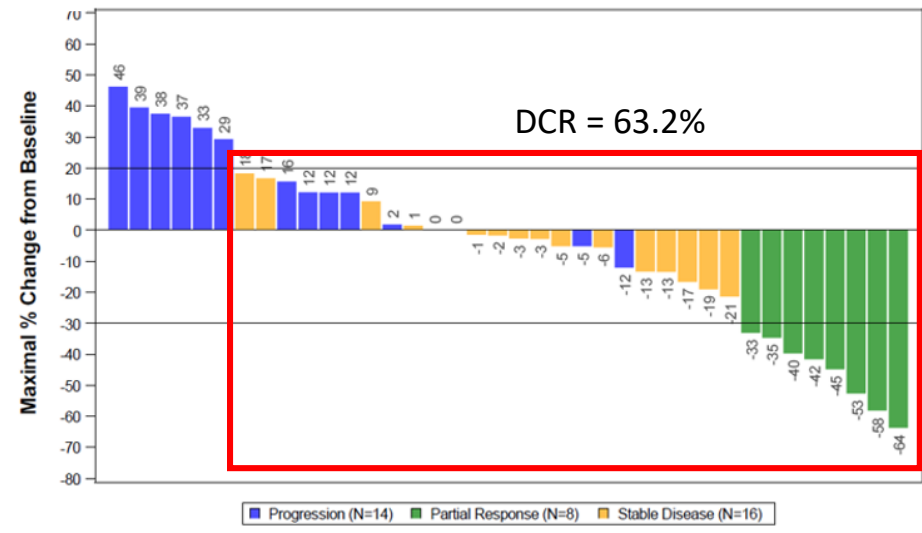
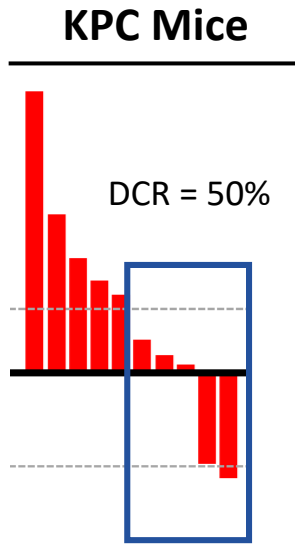
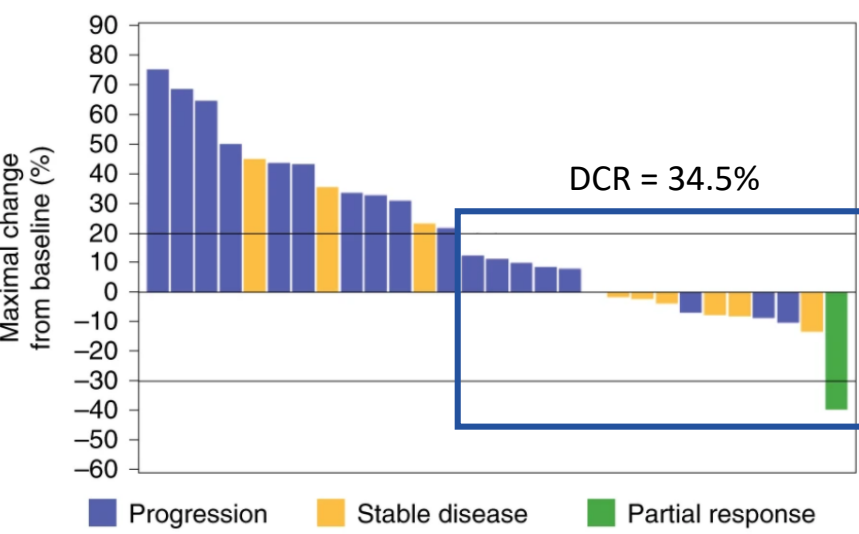
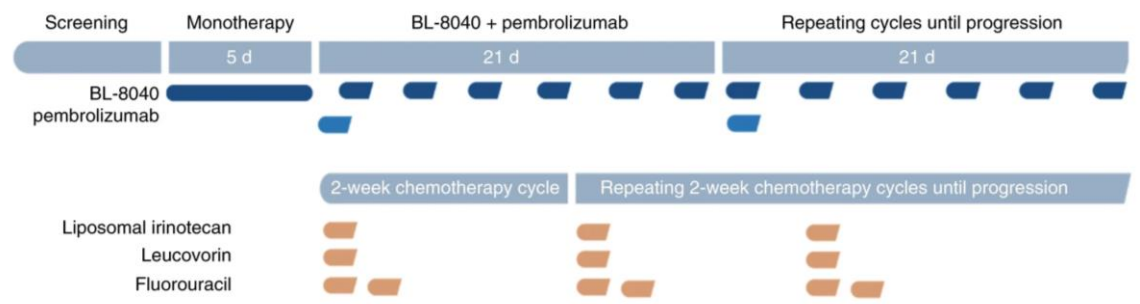
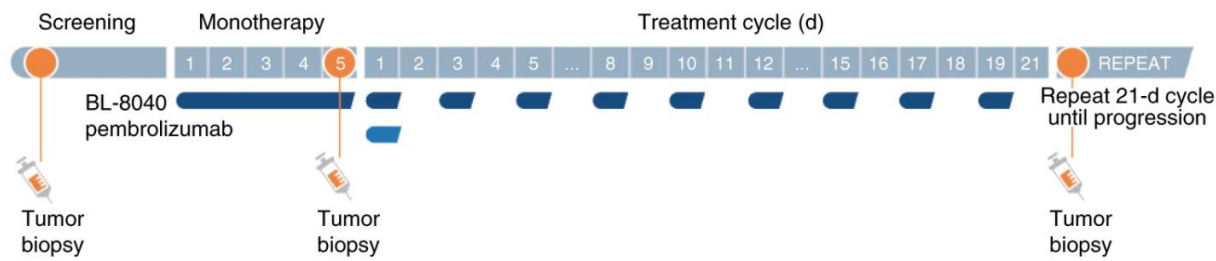
Biasci D, et al. Proc Natl Acad Sci U S A. 2020 Nov 17;117(46):28960-28970.

CXCR4i, ICB, & Gemcitabine Improve Survival - Preclinical



Manji GA and K Olive, Unpublished

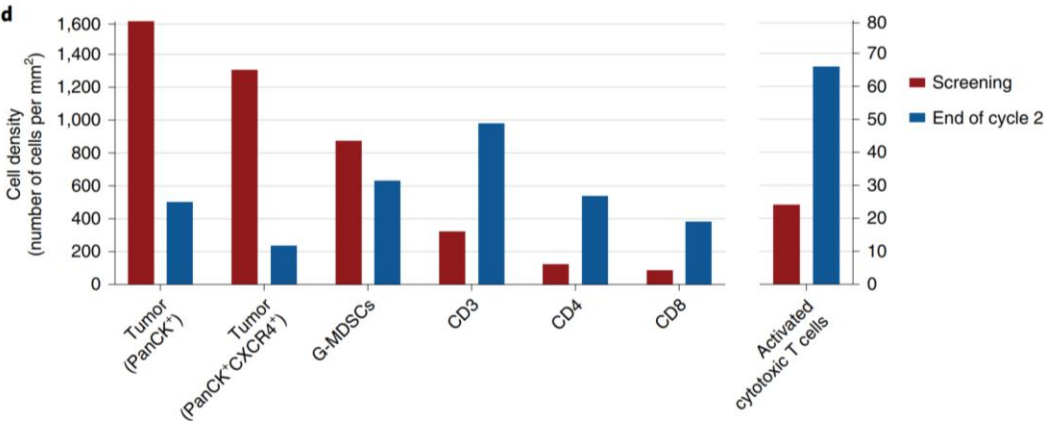
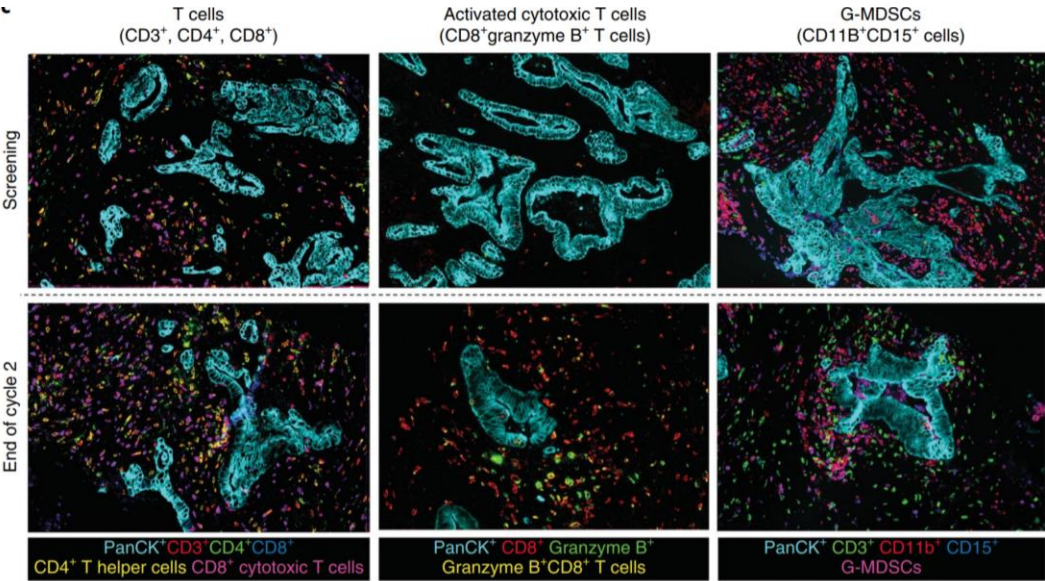
Chemotherapy Enhances Efficacy of CXCR4i and ICB



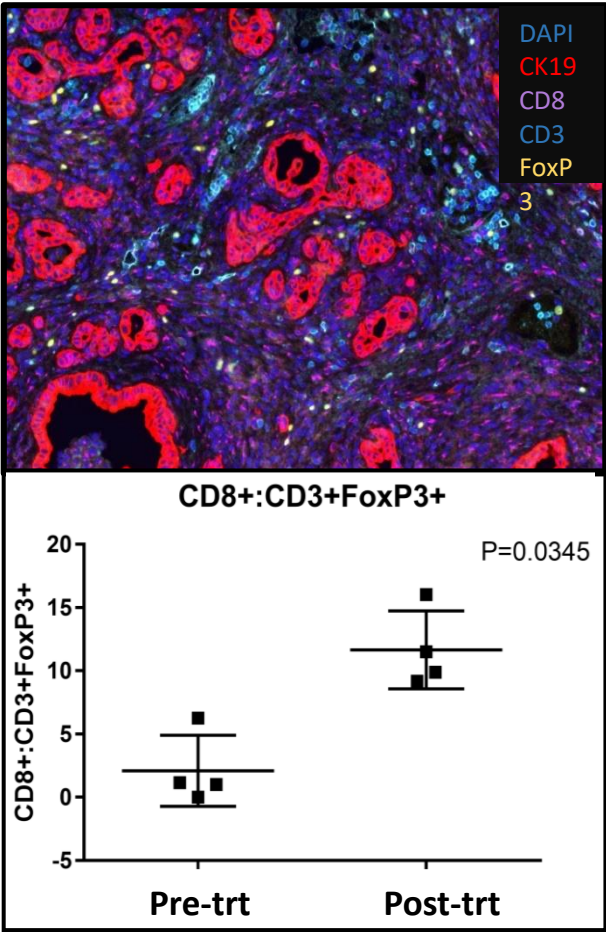
Manji GA and K Olive, Unpublished
Bockorny B et al. *Nature Medicine*. 26, pages878–885(2020)

CXCR4i Improves Tumor Immune Profile

Human – COMBAT Study-dual combination

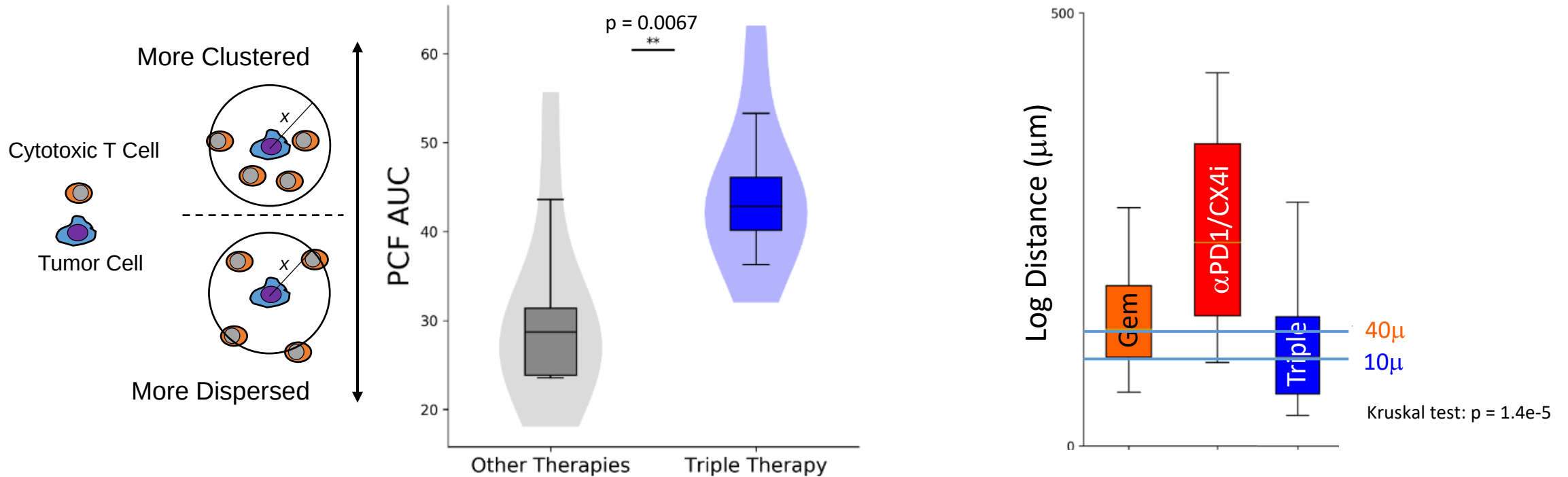


KPC Mice Triple Therapy



Manji GA and K Olive, Unpublished
Bockorny B et al. *Nature Medicine*. 26, pages878–885(2020)

Chemotherapy, CXCR4i and ICB results in T cell clustering



Manji GA and Rabadan R, Unpublished

Summary

- Inhibition of CXCR4 in combination with chemotherapy and ICB in KPC mice –
 - Increases CD 8+ T cell/FoxP3+
 - Improves proximity of CD8+ T cells to neoplastic cells
 - Improves survival
- Inhibition of CXCR4 in patients with pancreas cancer –
 - Increases CD8+ T cells (AM3100 and Motixafortide with ICB)
 - Decreases MDSCs (Motixafortide with ICB)
 - Encouraging efficacy in preliminary study with combination with 5-FU, liposomal irinotecan and ICB