

CD40 agonists in cancer immunotherapy

Robert H. Vonderheide, MD, DPhil

Abramson Cancer Center
Abramson Family Cancer Research Institute
Perelman School of Medicine
University of Pennsylvania

Disclosures

- **Investigational use of CP-870,893**
- **Dr. Vonderheide reports receiving research funding from Pfizer and Roche**

PD-1

+

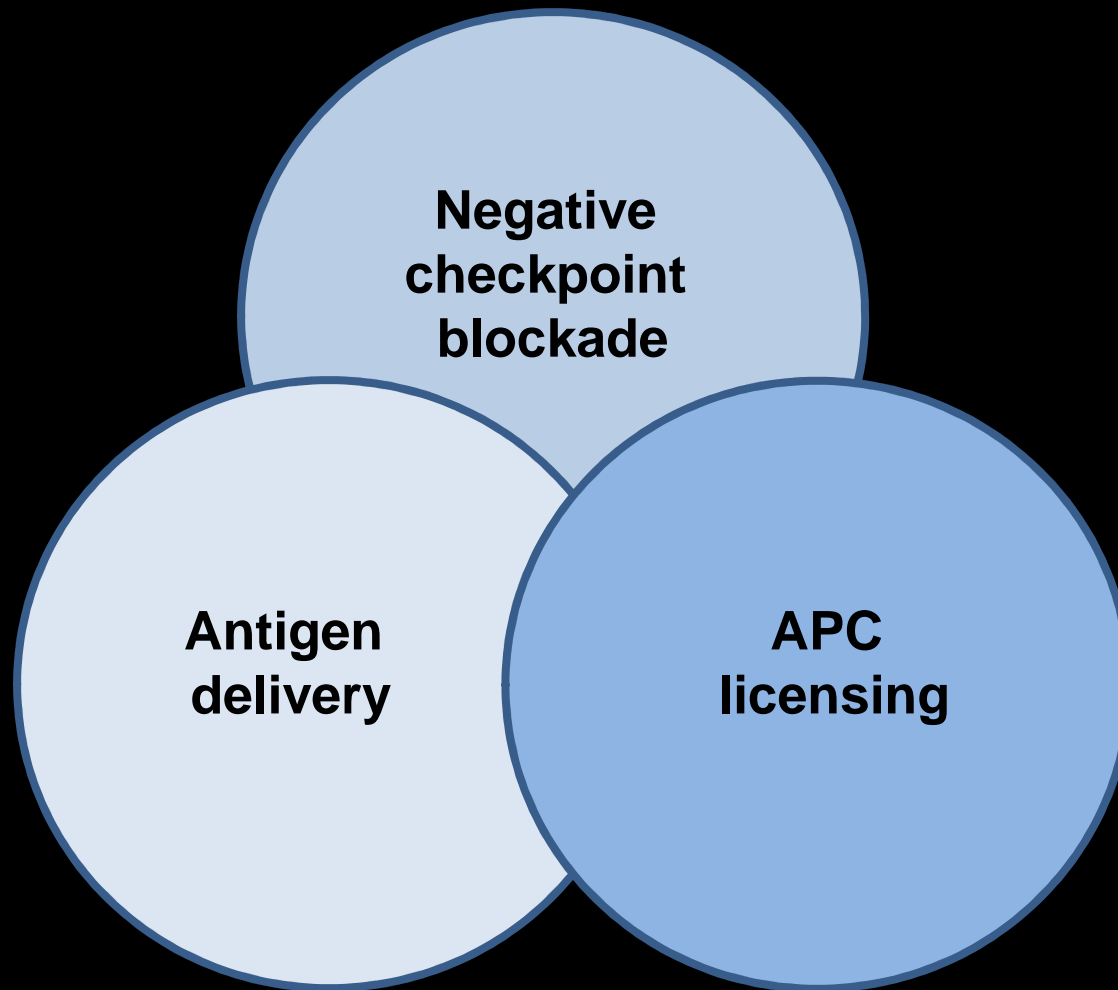
Your Pipeline
Here

?

=

Future
of Cancer
Immunotherapy

Platform for cancer immunotherapy



CD40 by the numbers

Rank on CITN list of investigational agents: 1

CD40 by the numbers

Rank on CITN list of investigational agents: **1**

Number of actively enrolling agonist CD40
mAb cancer clinical trials: **0**

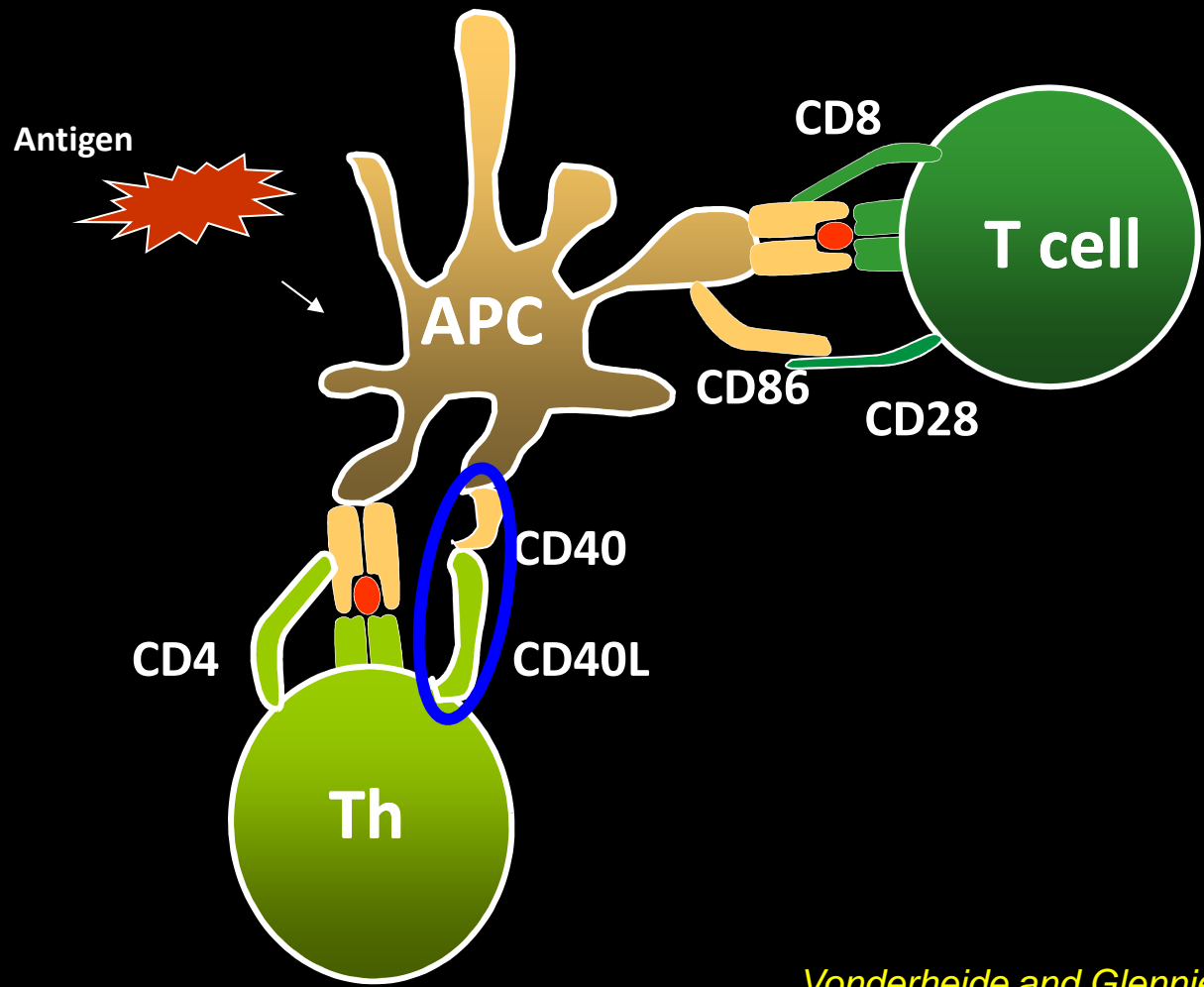
CD40 by the numbers

Rank on CITN list of investigational agents: **1**

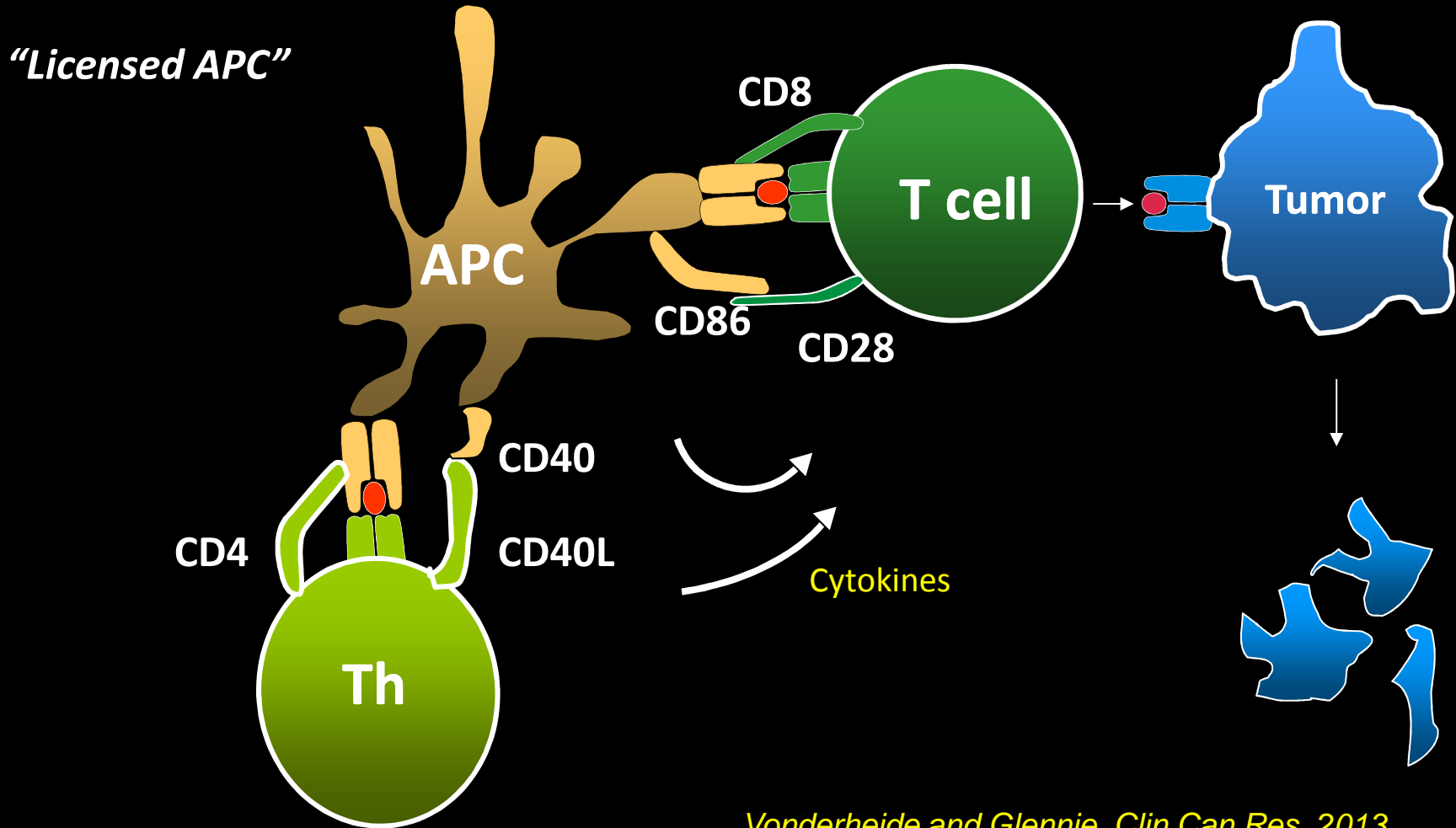
Number of actively enrolling agonist CD40
mAb cancer clinical trials: **0**

Number of years since a patient with
pancreatic cancer was treated with CD40: **4**

CD40 and the T cell hypothesis of tumor immunity



CD40 and the T cell hypothesis of tumor immunity



Agonist CD40 monoclonal antibodies in clinical trials

	mAb		
	CP-870,893	Dacetuzumab	Chi Lob 7/4
Company/institution	Pfizer/VLST	Seattle Genetics	Univ. of Southampton
Formulation	Fully human	Humanized	Chimeric
Isotype	IgG2	IgG1	IgG1
Maximum dose	0.2 mg/kg	Up to 12 mg/kg	Up to 160 mg total
Route of administration	i.v.	i.v.	i.v.
Dosing interval	Every 3–4 wks	Weekly	Weekly × 4
Toxicity	Mild-to-moderate cytokine release syndrome	Mild-to-moderate cytokine release syndrome Noninfectious inflammatory eye disorders	Study to address is underway
Diseases targeted	Melanoma Pancreatic carcinoma Mesothelioma	Hematologic malignancies, especially NHL	Advanced solid tumors and lymphoma
Clinical efficacy	Objective tumor responses reported in melanoma and pancreatic carcinoma (about 20%)	Objective tumor responses (in refractory and relapsed NHL, 12% as single agent; 47% with rituximab and gemcitabine)	Study to address is underway
Combinations explored	Chemotherapy Melanoma vaccine Tremelimumab	Chemotherapy Rituximab	None yet

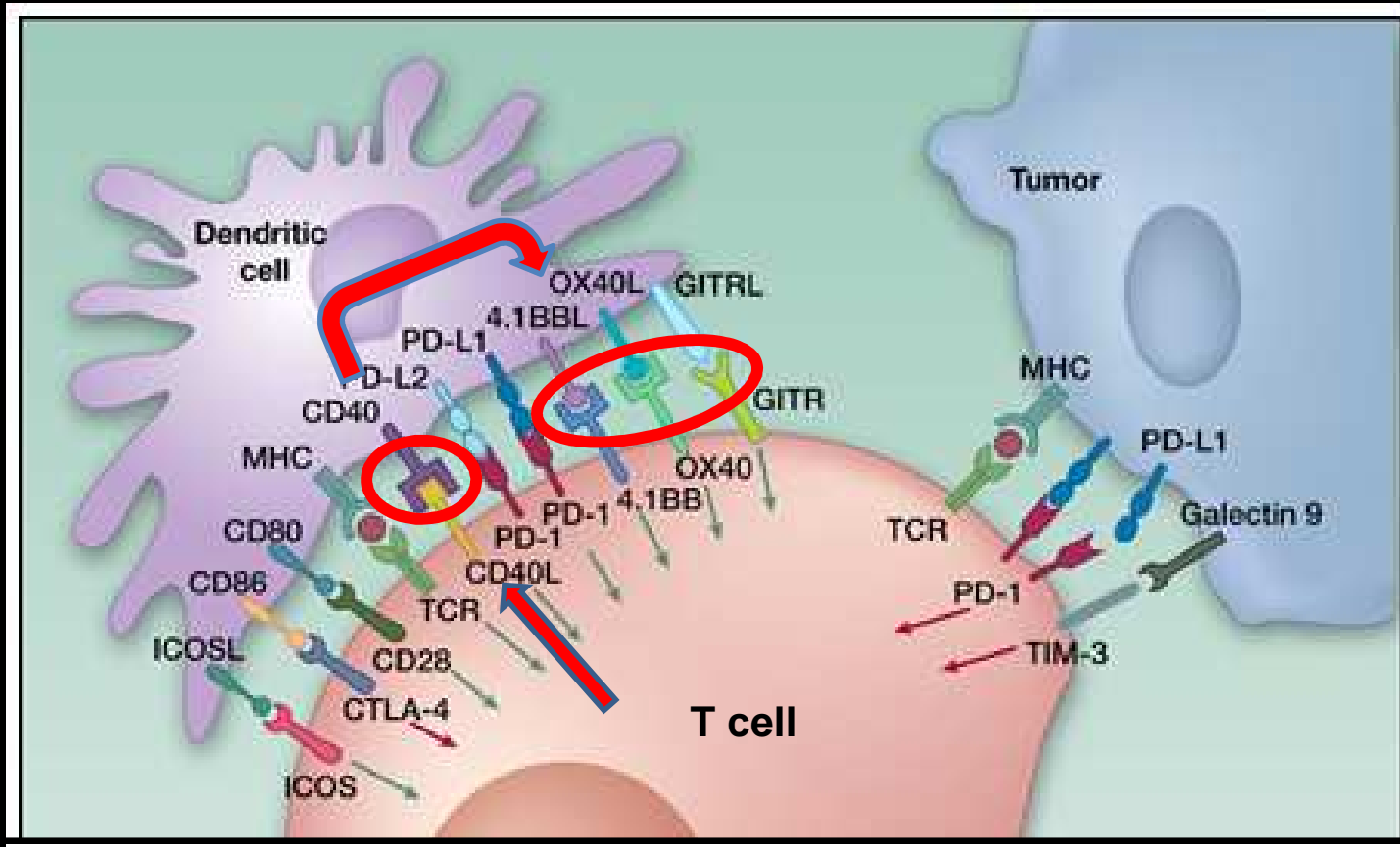
NOTE: Only reagents showing agonistic activity are included and thus lucatumumab (Novartis) has not been discussed.
Abbreviation: NHL, non-Hodgkin lymphoma.

Clinical trials with the agonist CD40 mAb CP-870,893

- **First-in-human, dose-escalation single infusion for pts with refractory tumors**
 - N=29 patients (*Vonderheide et al, JCO, 2007*)
- **Repeated 'single' infusions (q8weeks) in patients with clinical benefit**
 - N=7 patients (*Vonderheide et al, JCO, 2007*)
- **Weekly infusion for patients with solid tumors**
 - N=27 patients (*Ruter et al, Cancer Biol Therapy, 2010*)
- **CP-870,893 with carboplatin and paclitaxel for pts with solid tumors**
 - N=32 patients (*Vonderheide, Oncoimmunology, 2013*)
- **CP-870,893 with gemcitabine for chemo-naïve advanced pancreas cancer**
 - N=21 patients (*Beatty et al, Science, 2011; Beatty et al, Clin Can Res, 2013*)
- **CP-870,893 with tremelimumab (anti-CTLA4) for pts with metastatic melanoma**
 - N=24 patients (sponsor/PI, Vonderheide; Penn)

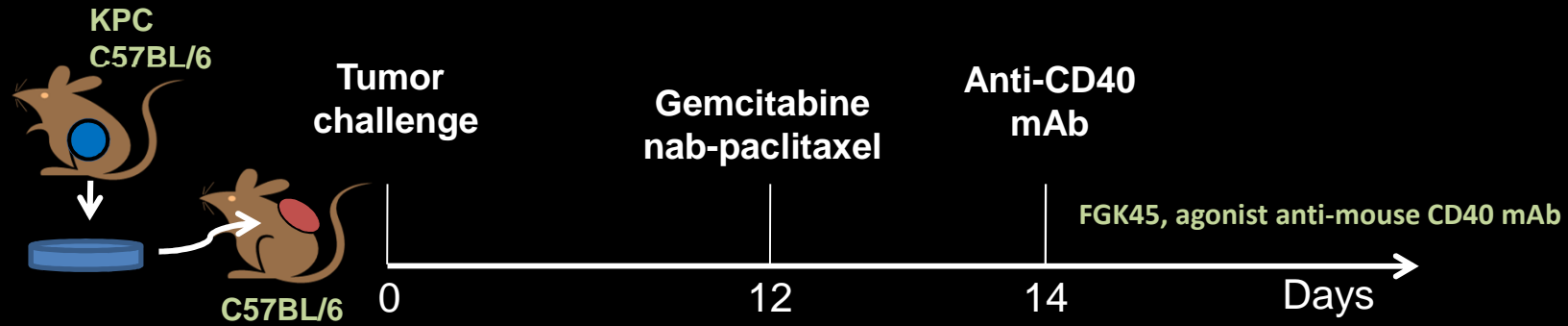
Overall tumor response rate is 20%-25% across studies (more than 130 patients)

CD40 is a 'proximal' TNFR agonist



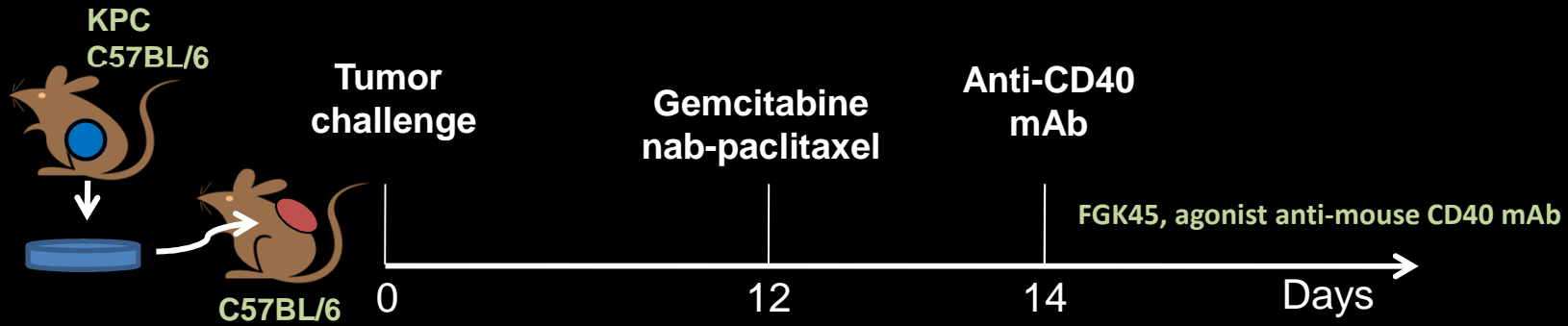
Ott et al, Clin Can Res, 2013

Chemotherapy/CD40 mAb as a vaccine in pancreas ca

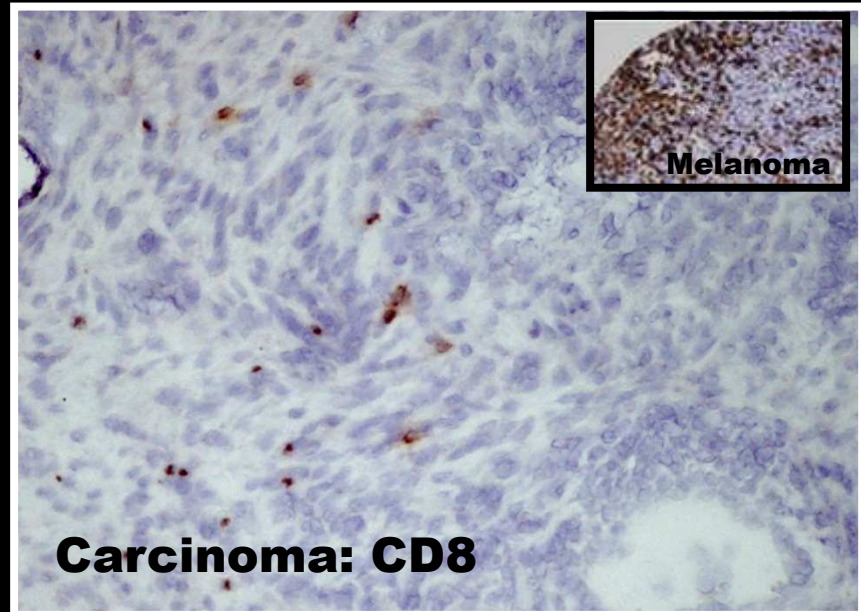
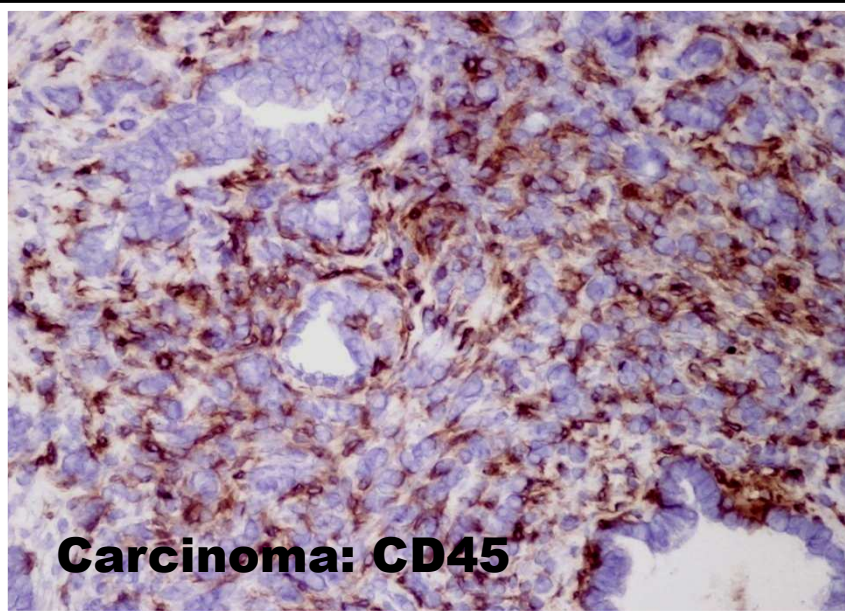


KPC = Kras^{G12D/+} Trp53^{R172H/+} Pdx-1 Cre

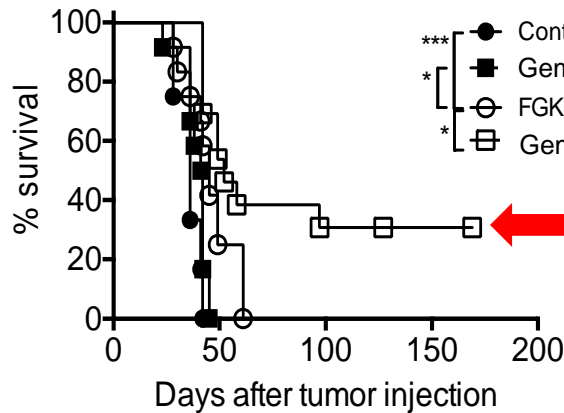
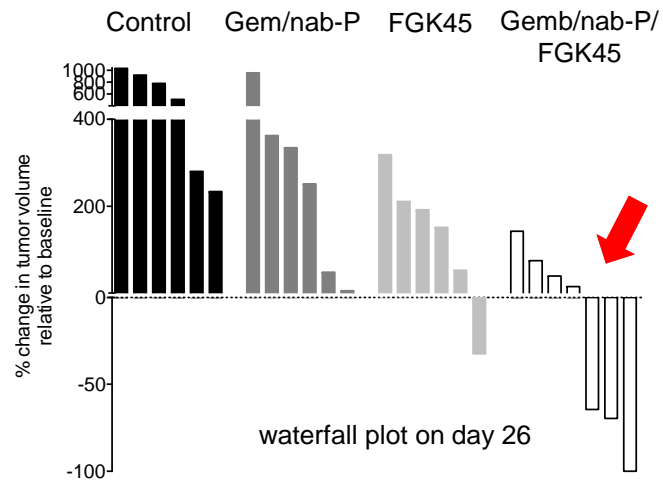
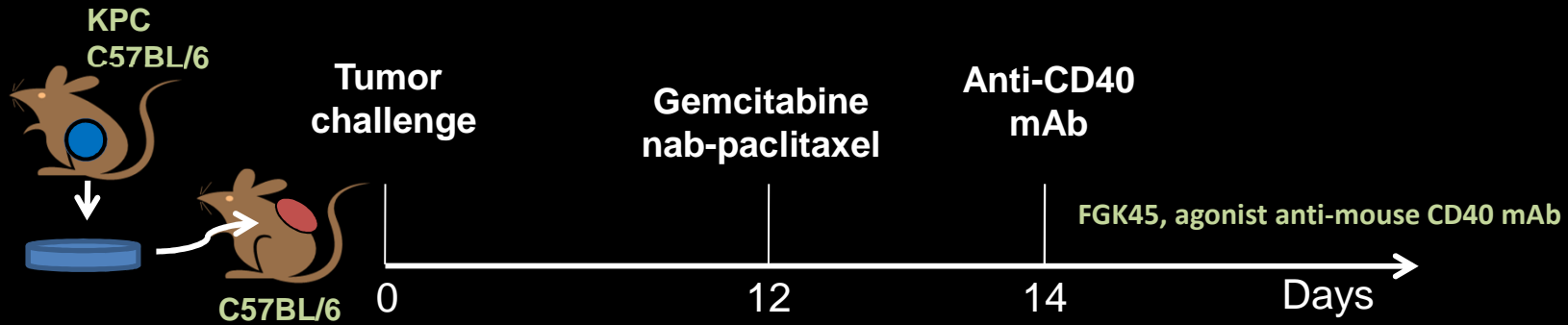
Chemotherapy/CD40 mAb as a vaccine in pancreas ca



KPC = Kras^{G12D/+} Trp53^{R172H/+} Pdx-1 Cre

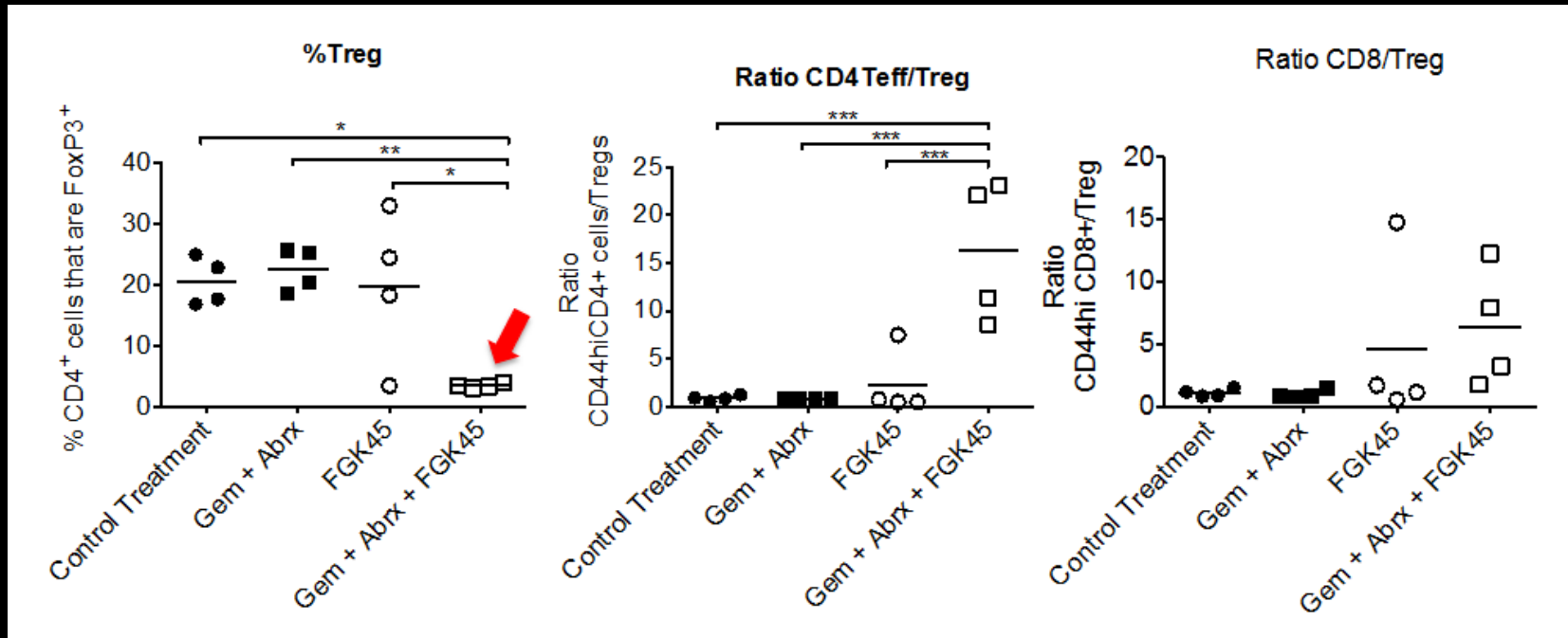


Chemotherapy/CD40 mAb as a vaccine in pancreas ca



If mice are first depleted of T cells, there are no regressions in Gem/nab-P/FGK45 mice (not shown)

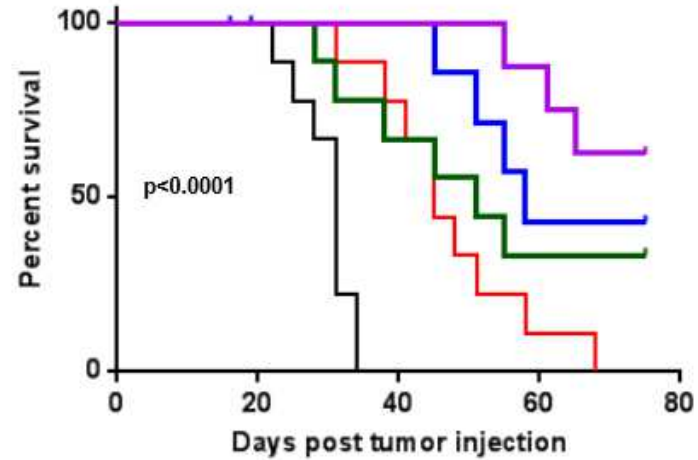
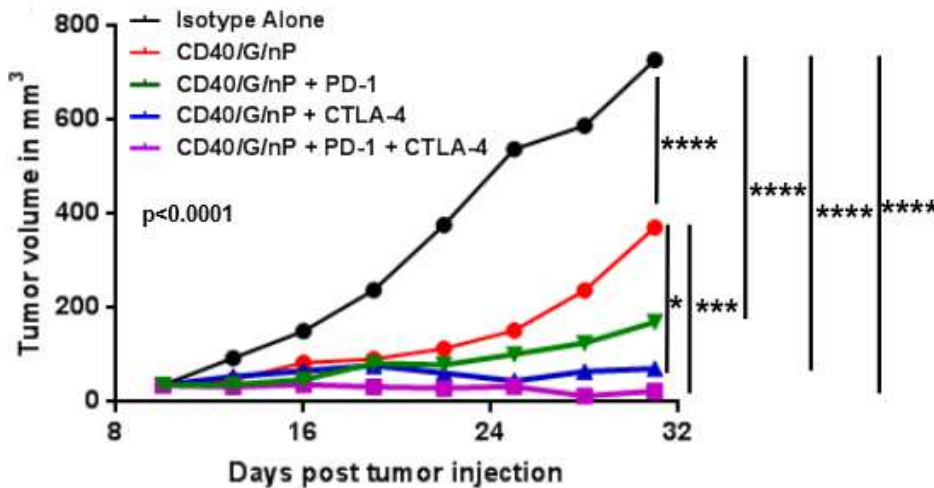
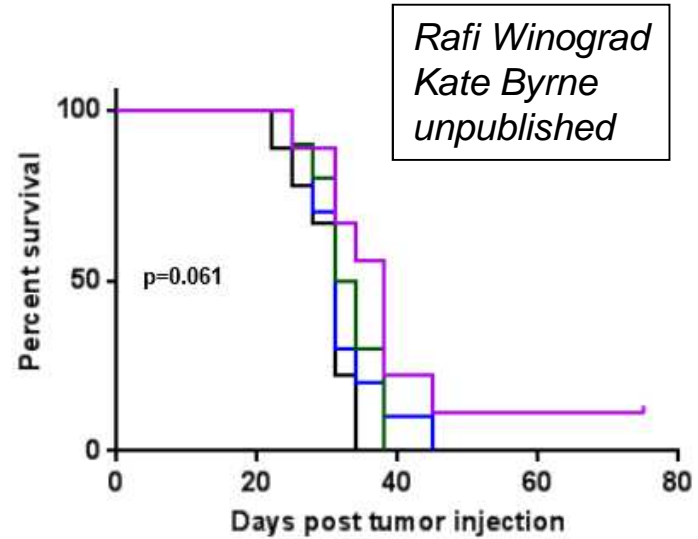
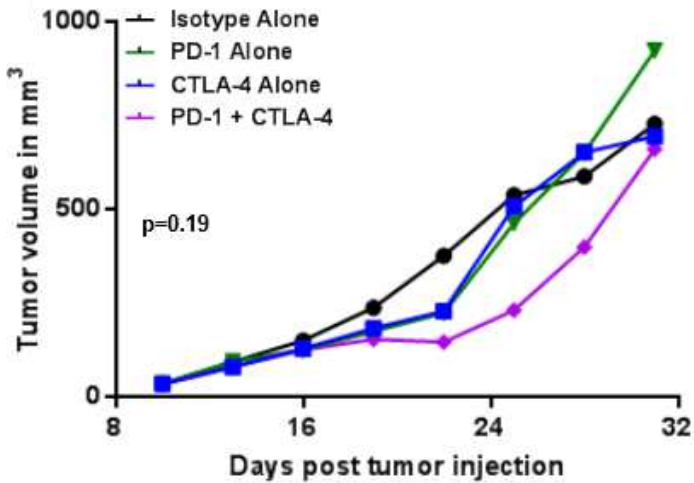
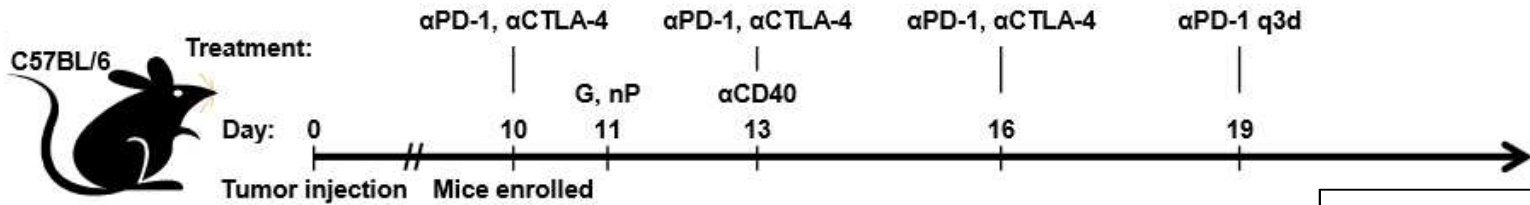
Tumor infiltrating T cells after chemotherapy/CD40



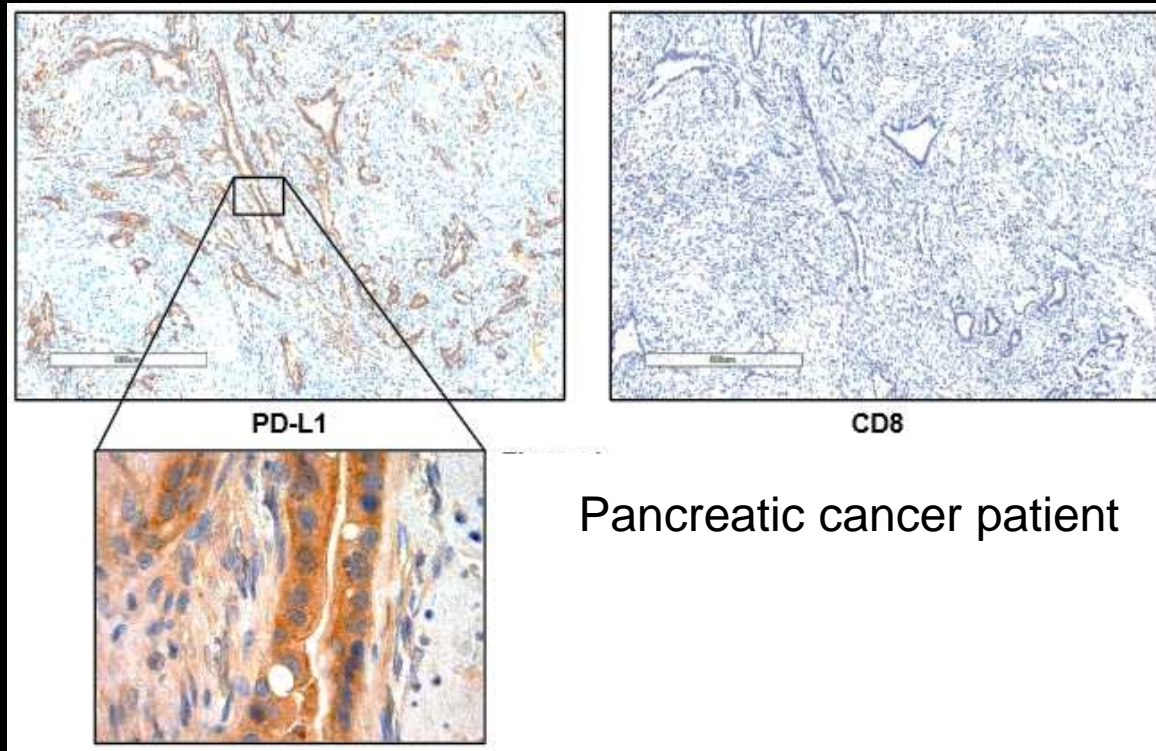
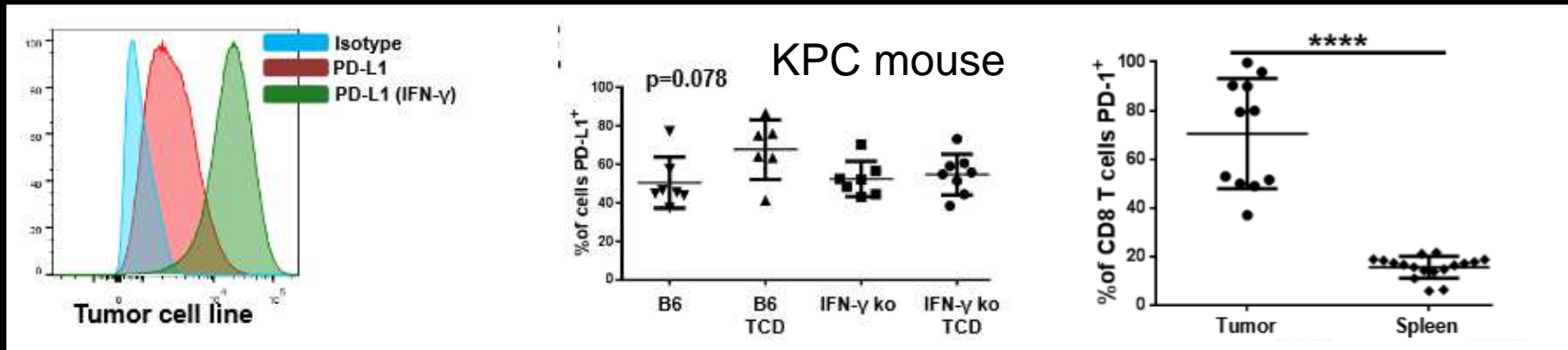
Abrx = abraxane = nab-P

Byrne and Vonderheide,
UPenn; unpublished

CD40/chemo plus checkpoint blockade

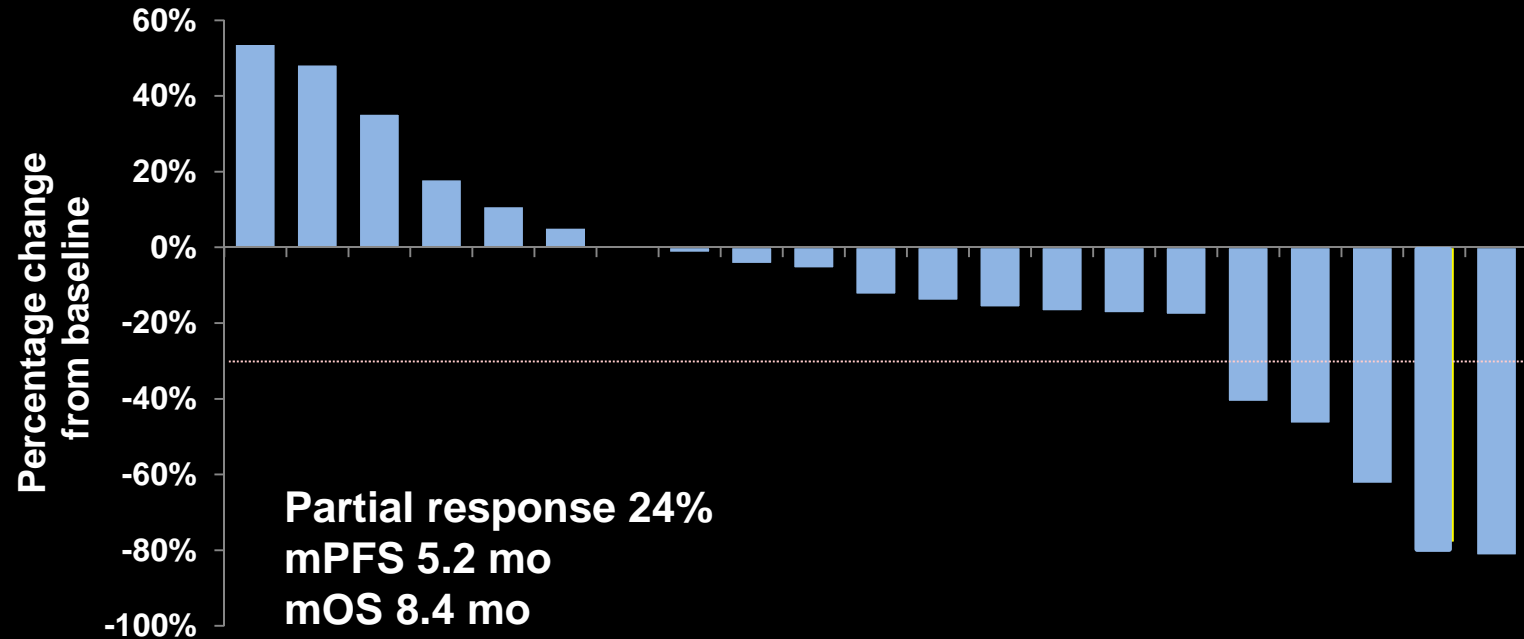


PD-L1 expression is independent of IFN-gamma and T cells



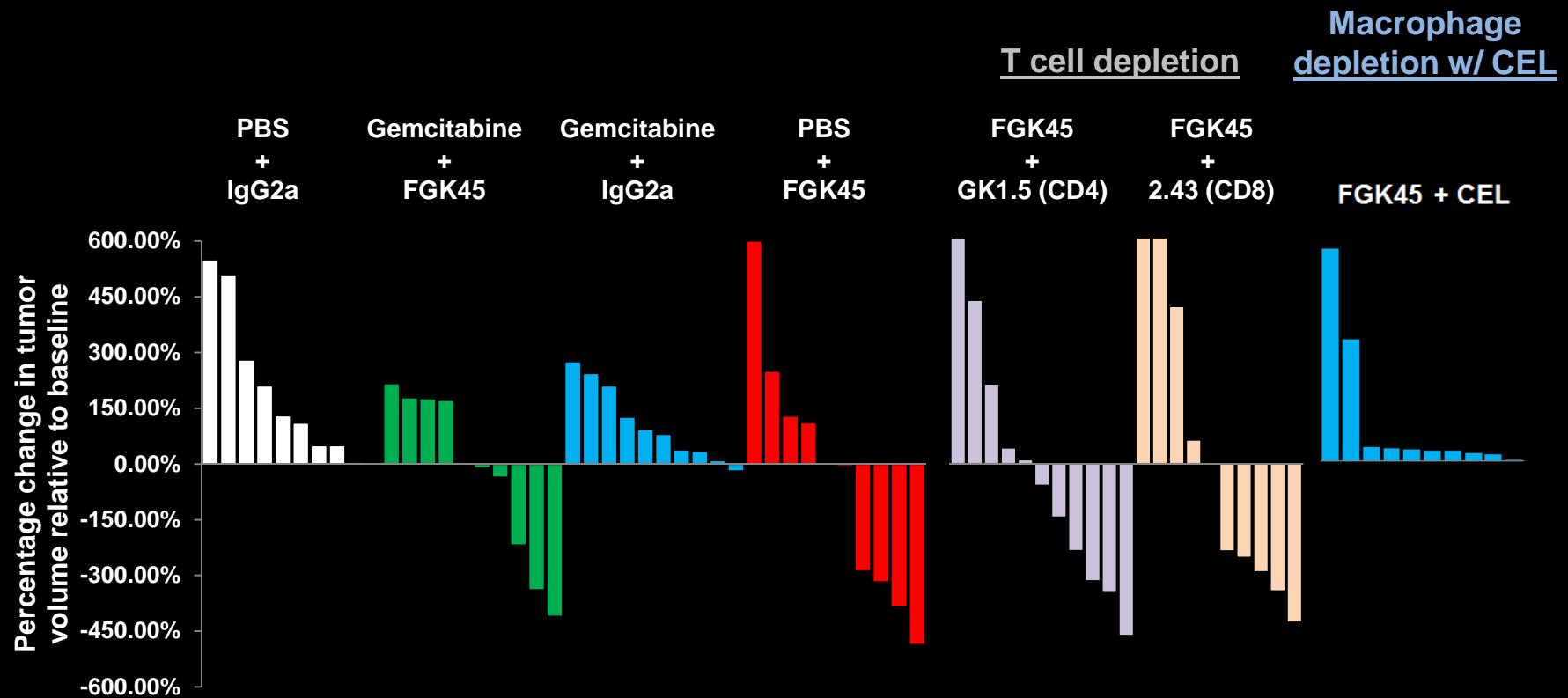
Rafi Winograd
unpublished

Gemcitabine and agonist CD40 mAb CP-870,893 in chemo-naïve metastatic pancreatic carcinoma

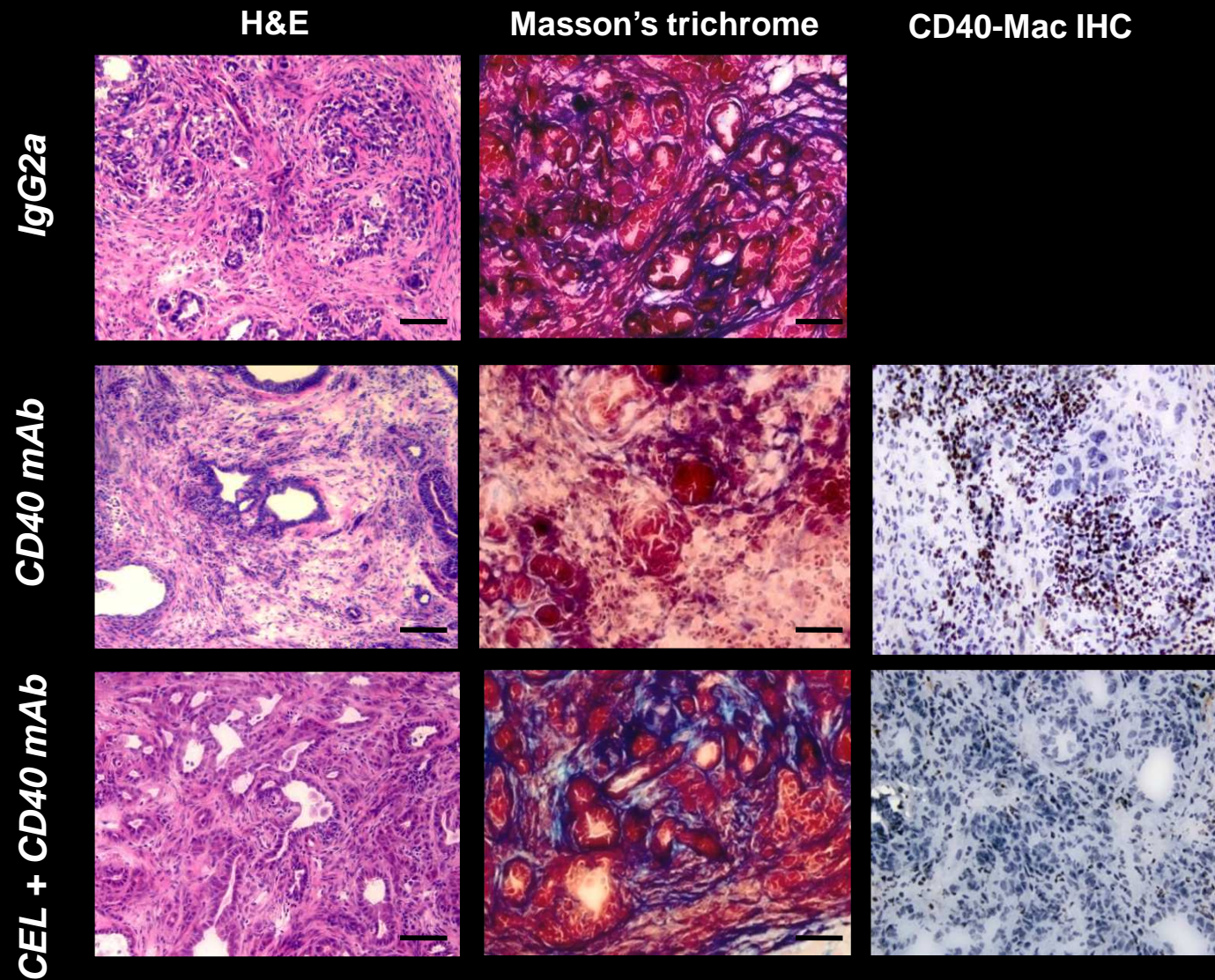


Beatty et al, Science, 2011
Beatty et al, Clin Can Res, 2013

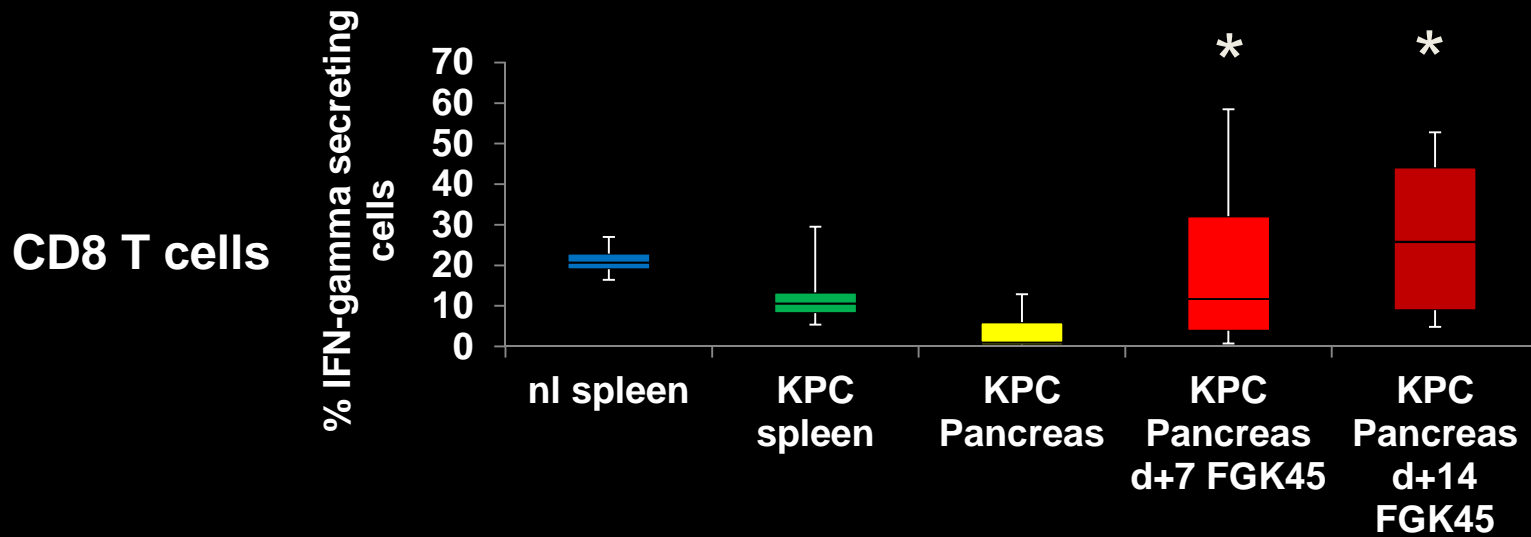
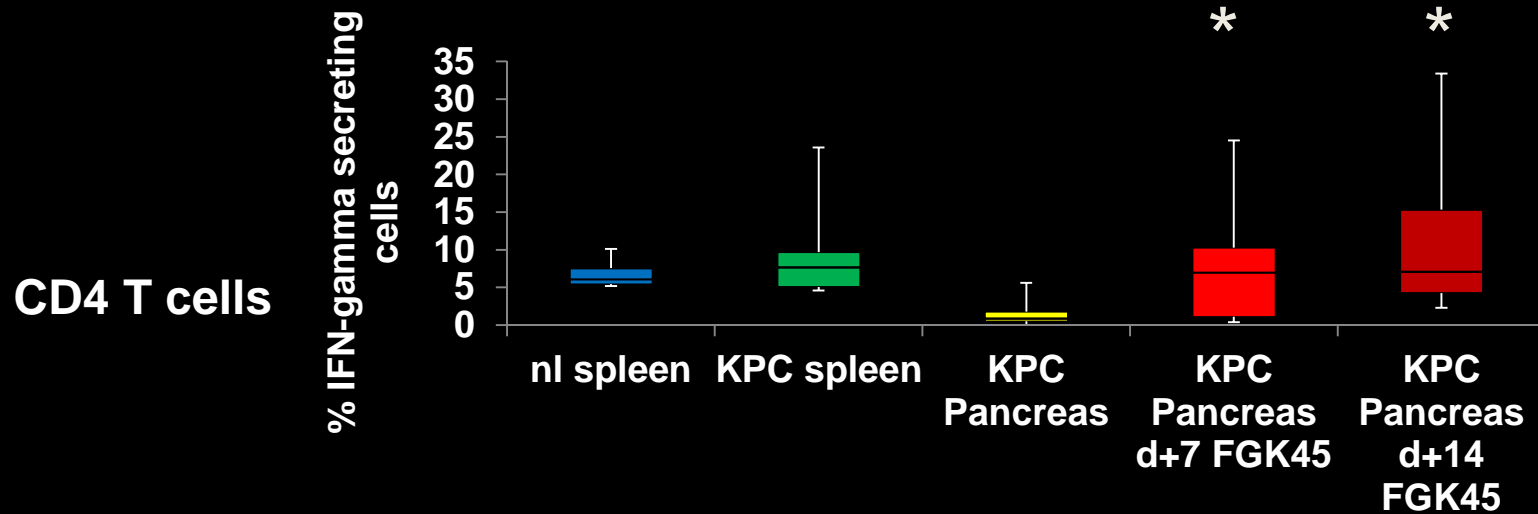
CD40 mAb-mediated tumor regression in KPC mice is T cell-independent & macrophage-dependent



Macrophage-dependent stromal involution with CD40 mAb

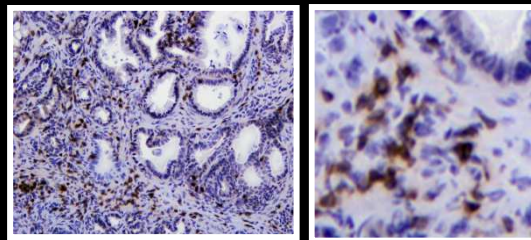


Treatment with CD40 mAb enhances T cell function



Inducing a T cell response with Gem/CD40/CEL

	Rates of regression in KPC mice (%)	T cells in KPC tumor	Regression after T cell depltn (%)
Control	0	No	
Gem	0	No	
Gem/CD40	30	No	
CD40	30	No	30
CEL	0	No	
CD40/CEL	0	No	
Gem/CD40/CEL	67	Yes	0

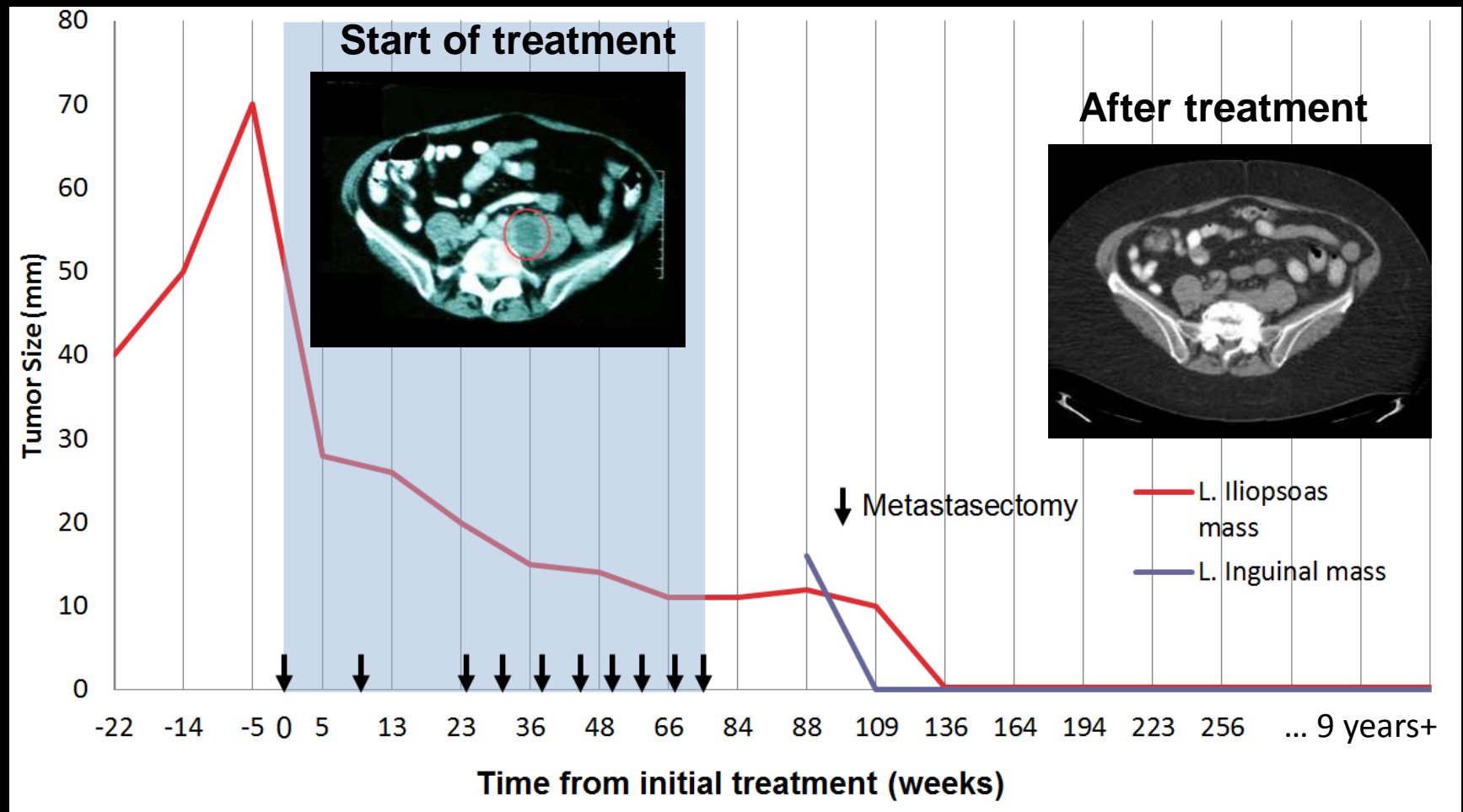


CD3, day 14

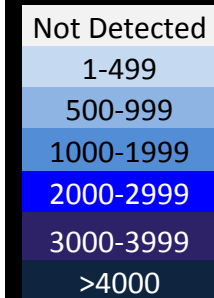
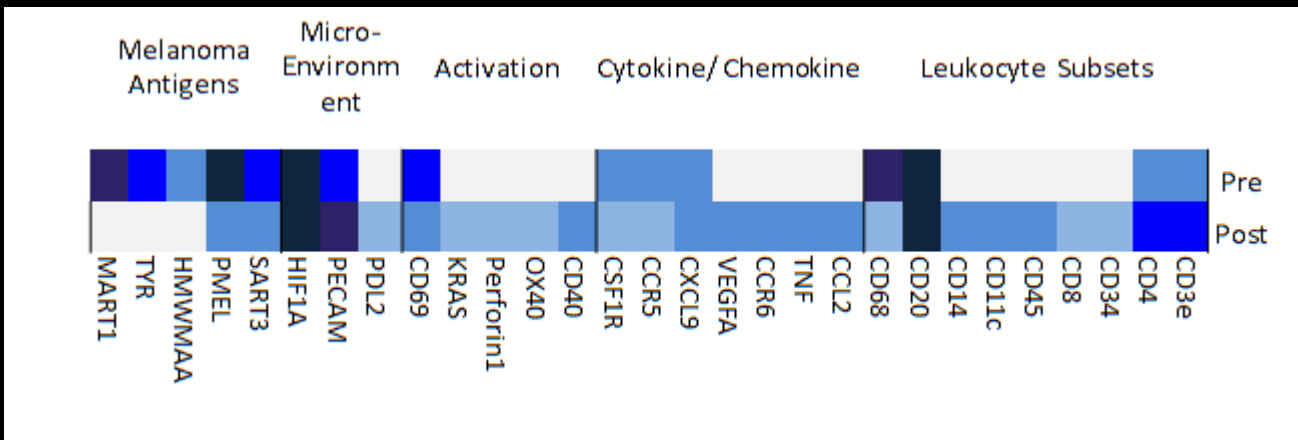
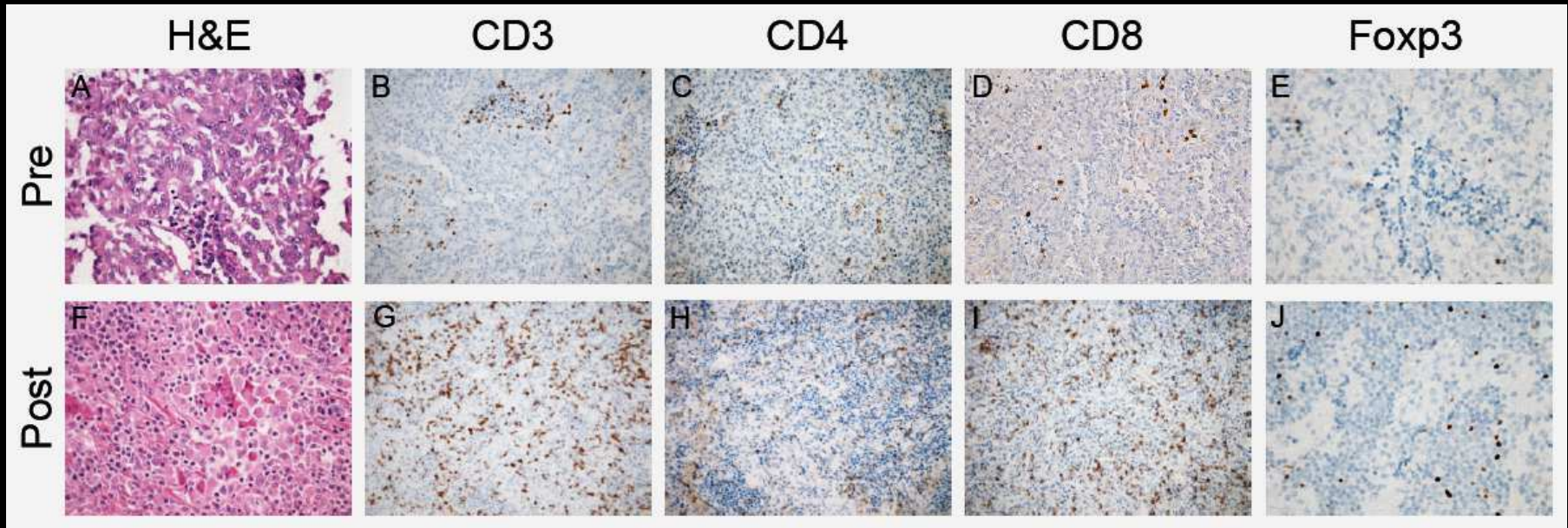
*Beatty and Vonderheide,
UPenn; submitted*

Long-term remission of melanoma from CP-870,893

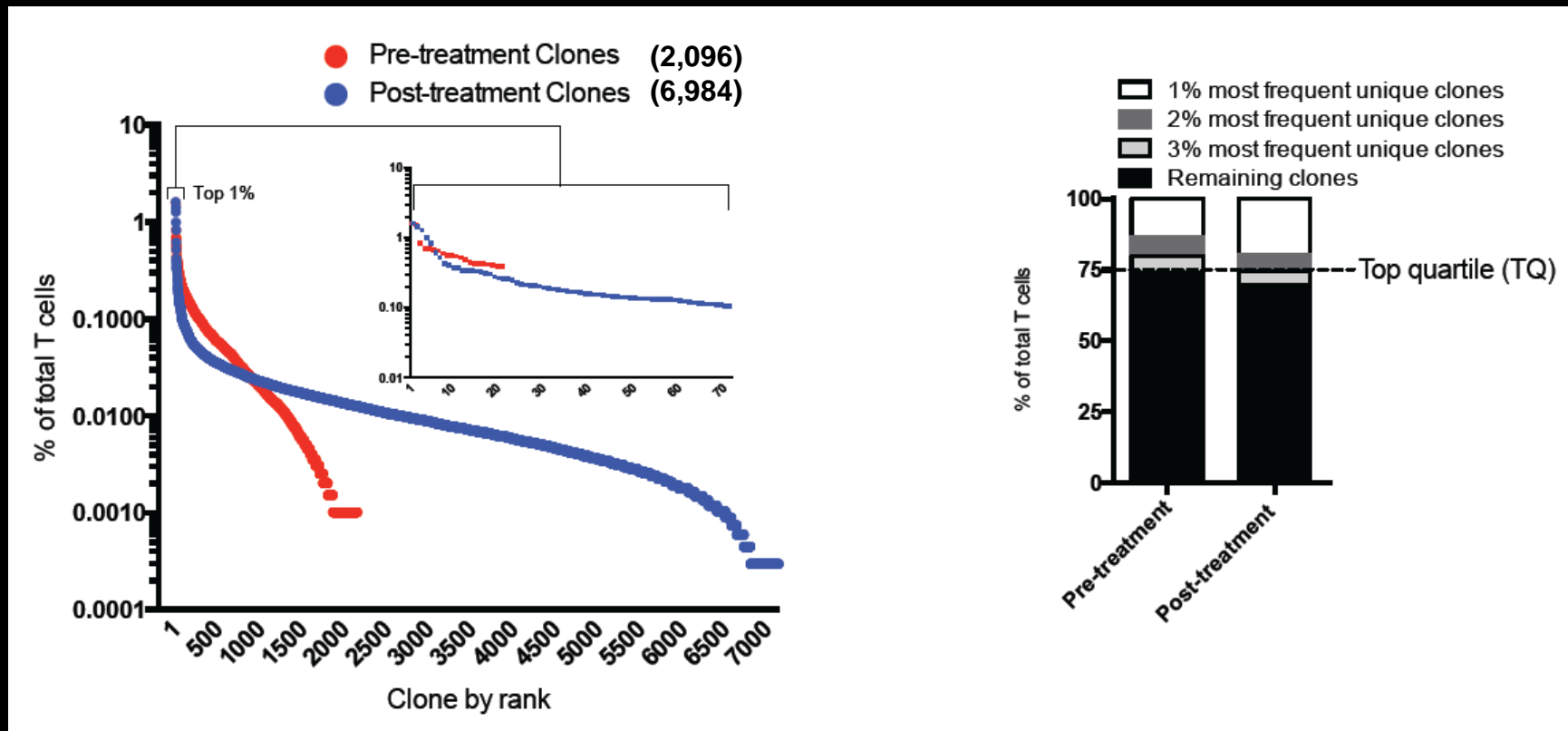
55 yr old woman with metastatic melanoma (Braf V600E), progressive despite chemotherapy and exp therapies, enrolled on first-in-human trial in 2005, received 10 doses of CP-870,893



Change in melanoma microenvironment after CP-870,893

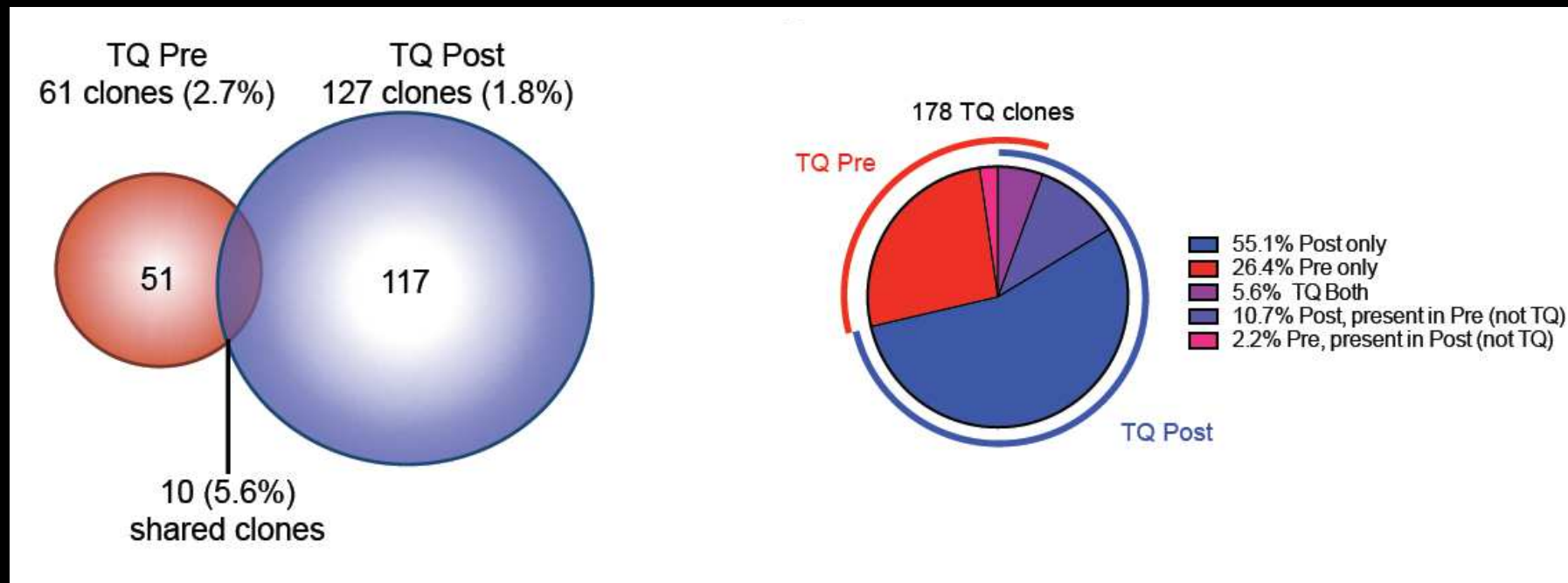


TCR-beta deep sequencing of tumor infiltrating T cells



Bajor et al, Can Immunol Res, 2014

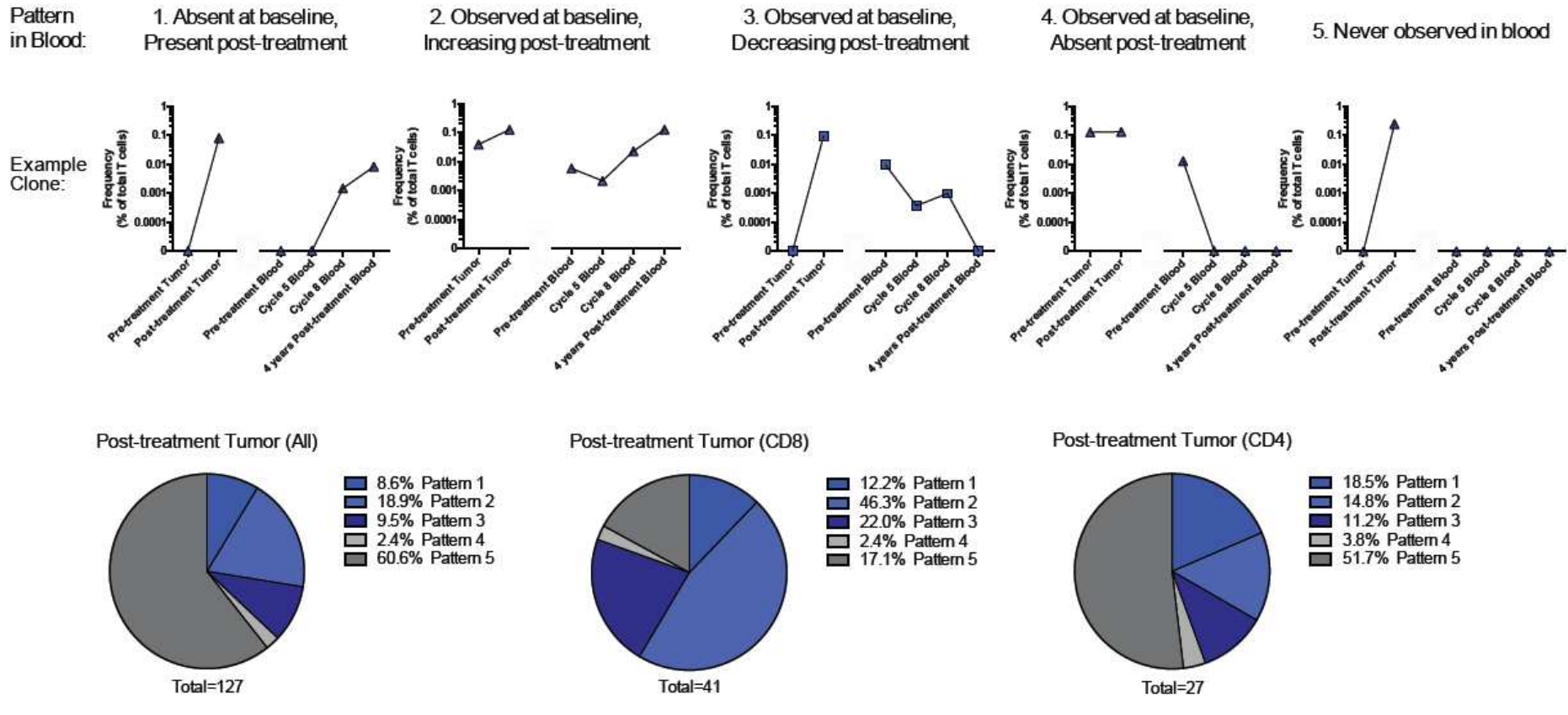
Emergence of a new T cell repertoire in the tumor after treatment with CD40 mAb



TQ= top quartile

Bajor et al, Can Immunol Res, 2014

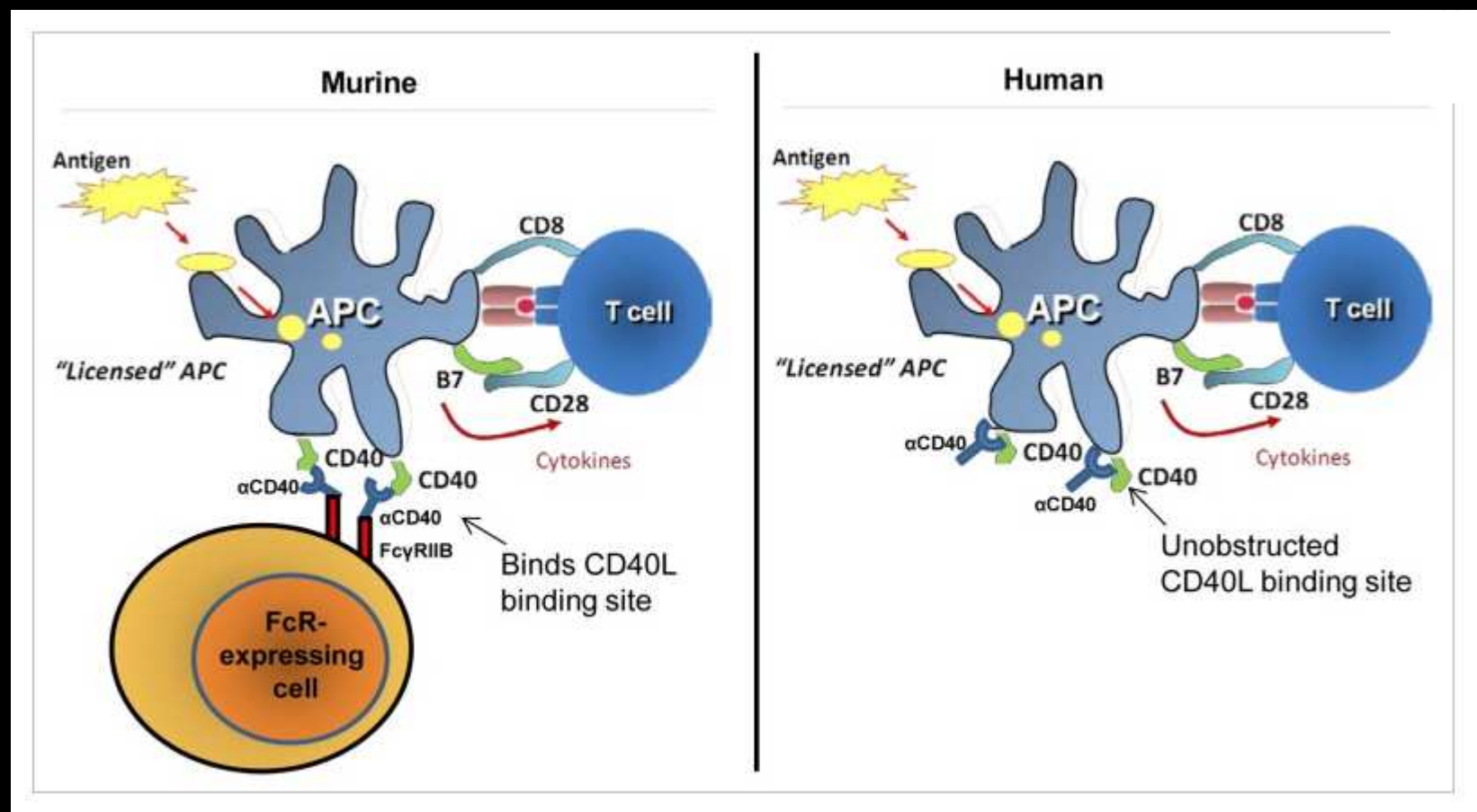
TCR-beta deep sequencing reveals systemic T cell response years after resolution of disease



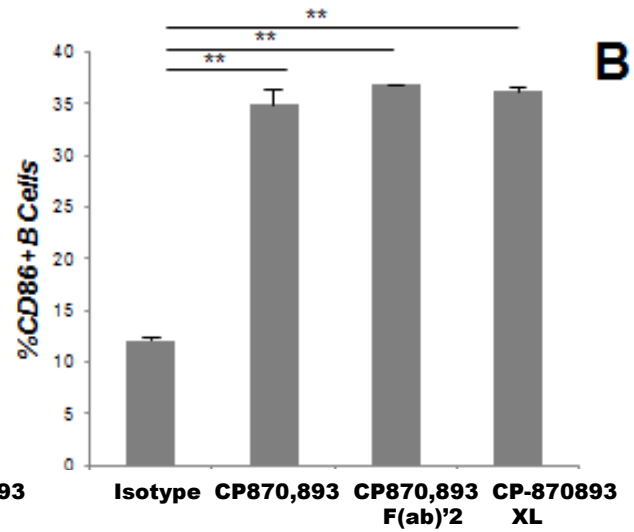
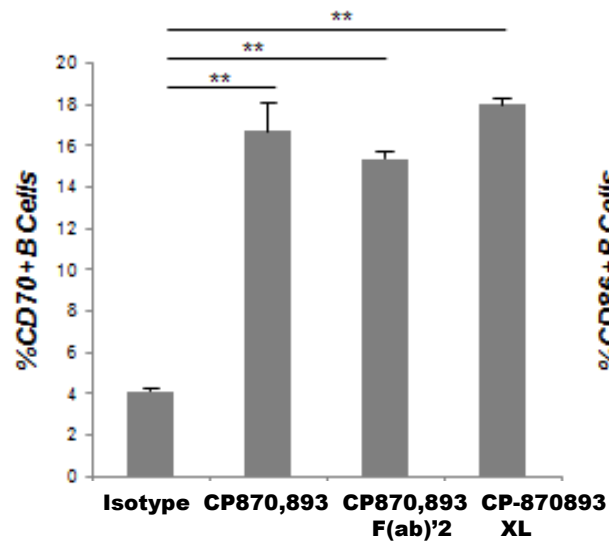
Issues for CD40 mAb clinical development

- **Toxicity**
- **Formulation**
- **Dose and schedule**
- **Route of administration**
- **Optimal combination partners**
- **Drug availability**

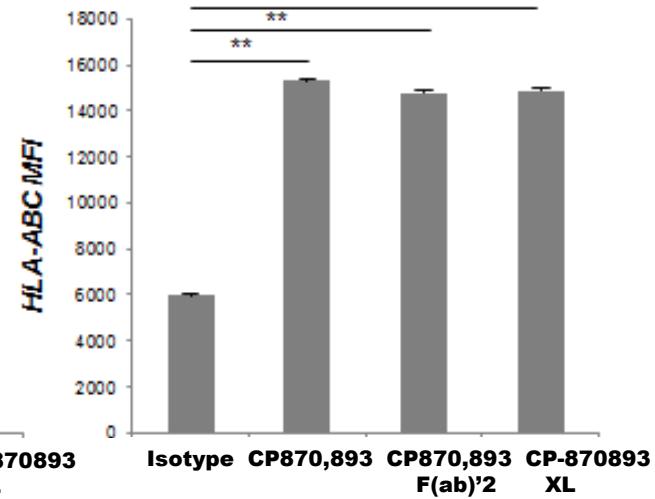
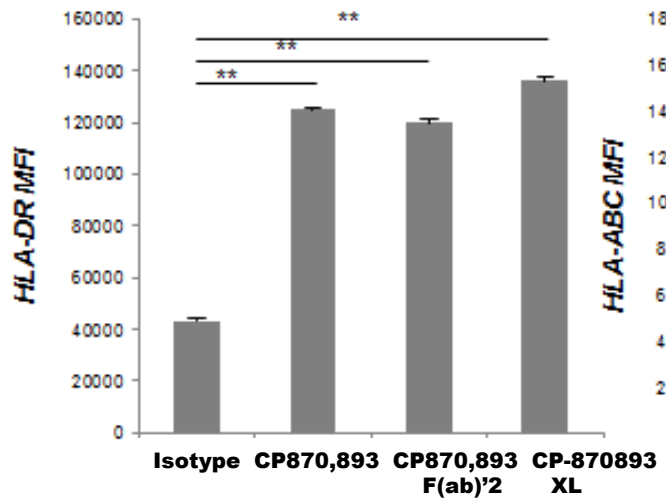
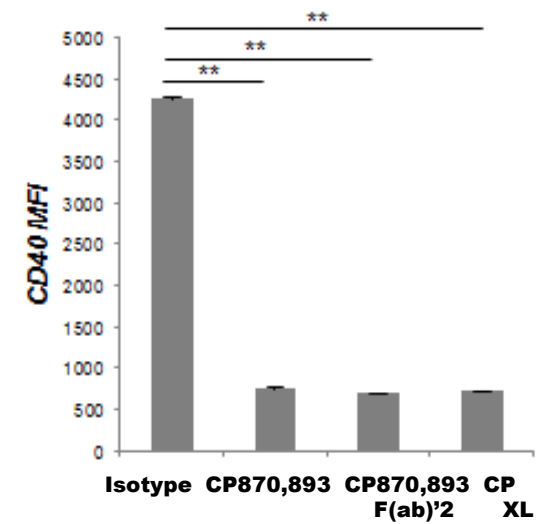
Does CD40 mAb need to be crosslinked?



Richman and Vonderheide, Oncolmunology, 2014



B



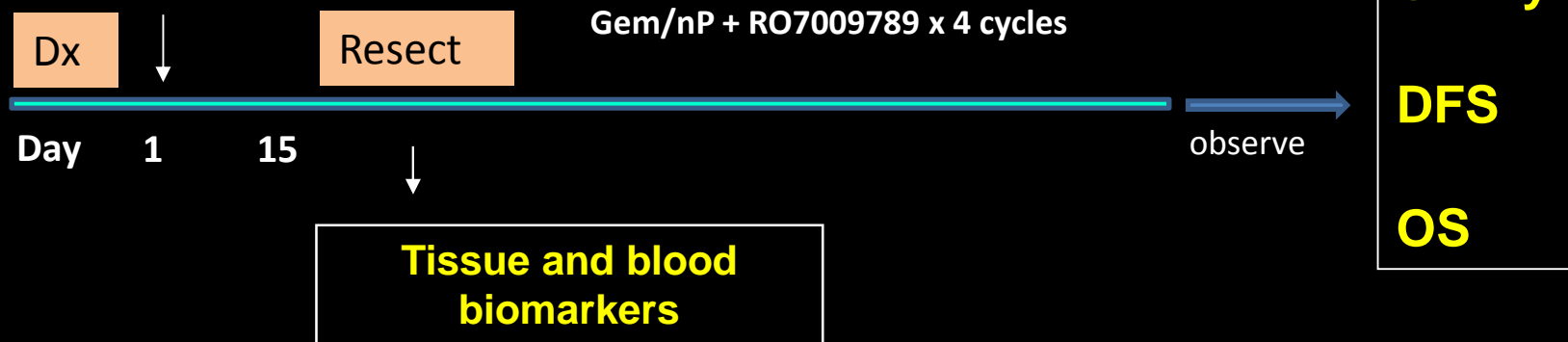
Richman and Vonderheide, Can Immunol Res, 2014

CD40 as neoadjuvant therapy in pancreatic cancer

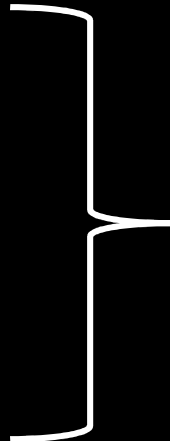
Phase I study of preoperative RO7009789 +/- chemo for patients with newly diagnosed resectable pancreatic carcinoma or stage III melanoma

Arm A: RO7009789

Arm B: Gem/nP then RO7009789



CITN working group view on priority trials

- **As a adjuvant to T cell 'vaccine'**
 - With chemo (current trial)
 - With radiation
 - With anti-tumor mAb (trastuzumab, TDM-1)
 - With an tumor vaccine with defined antigens
 - **Get mechanistic for CITN trials**
 - Window trial design (neoadjuvant pancreas, breast, bladder)
 - Metastatic with pre and post biopsies
- 
- All +/- PD-1

Vaccine

^

PD-1

+

Your Pipeline
Here

?
=

Future
of Cancer
Immunotherapy

It's OK to say the 'V' word

Vaccine



Summary: CD40 mAb for cancer therapy

- **Activates both innate and adaptive immunity**
 - Licenses APC, triggers T cells
 - May be a critically important component for vaccination
- **Established safety profile and reproducible clinical activity**
 - Combination partner: chemotherapy, radiation, CTLA4, PD-1

Acknowledgements

Vonderheide Lab

David Bajor

Kate Byrne

Rafi Winograd

Andrew Rech

Lee Richman

Rebecca Evans

Ran Reshef

Tim Chao

Nate Leissenring

Nune Markosyan

Mouse hospital

Cynthia Clendenin

Scientific collaborators

Andy Minn

John Wherry

Christina Twyman

Michael Kalos

Gregory Beatty

Clinical collaborators

Amit Maity

Steve Hahn

Lynn Schuchter

Tara Gangadhar

Rosemarie Mick

George Xu

Cindy Desmarais (Adaptive)

Current funding

R01 CA 169520

R01 CA158186

R01 CA111377

P30 CA016520

Breast Cancer Res Fnd

SU2C

PanCan Action Network