

**Pancreas Cancer, Immunogenicity,  
and Checkpoint Resistance**

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Abramson Cancer Center  
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University of Pennsylvania**

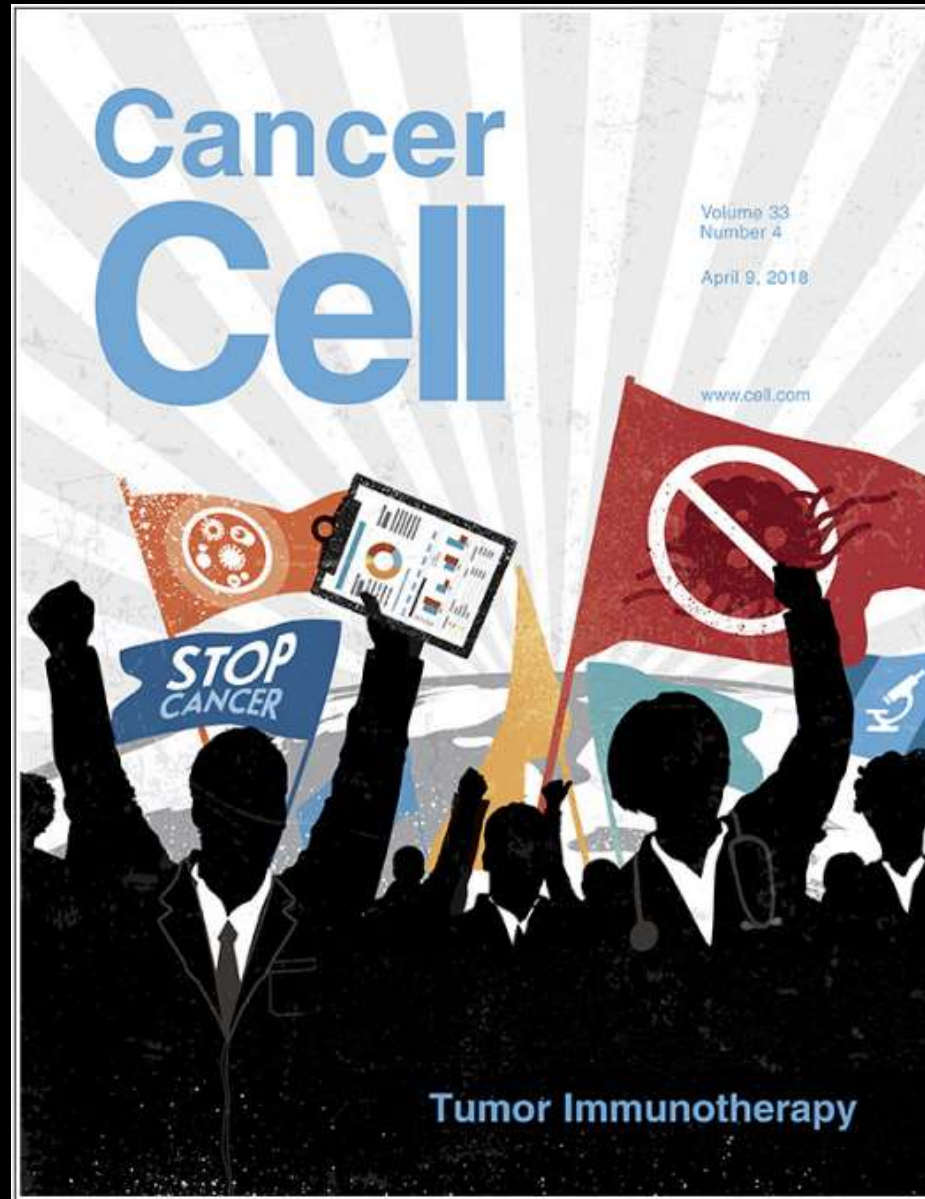
**July 13, 2018**

# Disclosures

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- **Dr. Vonderheide reports research funding from Lilly and Janssen**
- **Will discuss investigational use of RO7009789, APX005M, and nivolumab**

# Cancer Immune Revolution



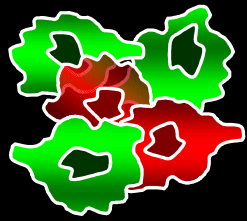
# CAR T cell FDA-approval Flash Mob



August 30, 2017

# T cell immune surveillance of cancer

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Tumor

T cell  
response

Elimination

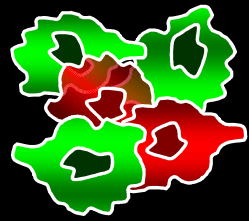
Immunoediting

Escape

Resistance to  
immune therapy



# T cell immune surveillance of cancer



Tumor

T cell  
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Elimination

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Resistance to  
immune therapy

T cell  
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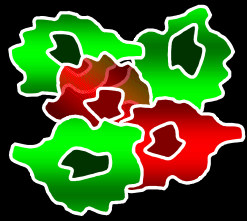
Host/tumor  
immune  
suppression

Peripheral  
tolerance

Escape

Overcome with  
CTLA4 or PD-1  
mAb, or both

# T cell immune surveillance of cancer



Tumor

T cell  
response

Elimination

Immunoediting

Escape

Resistance to  
immune therapy

**HOT**

T cell  
response

Host/tumor  
immune  
suppression

Peripheral  
tolerance

Escape

Overcome with  
CTLA4 or PD-1  
mAb, or both

**COLD**

Host/tumor  
immune  
suppression

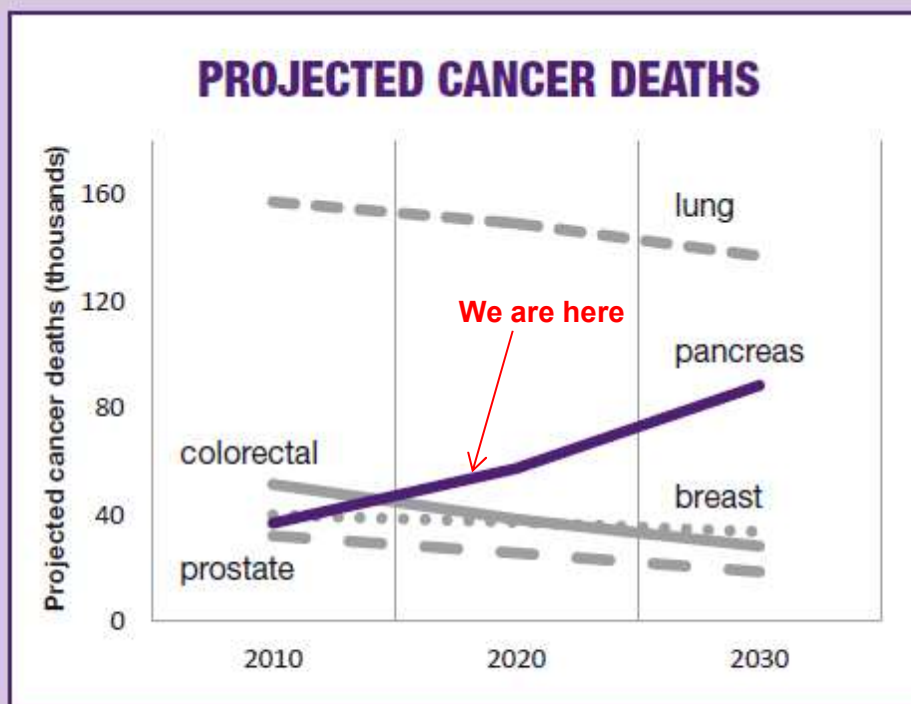
No T cell  
response  
in tumor

Immune  
privilege

No  
Escape

Overcome by  
vaccination  
AND block immune  
suppression  
(either alone  
will not work)

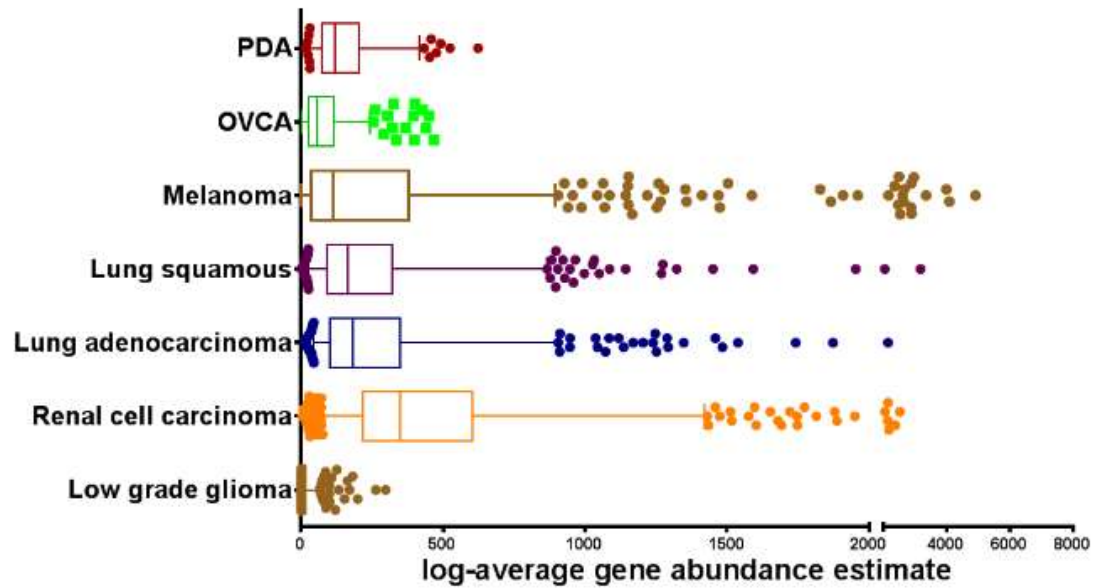
# Pancreatic ductal adenocarcinoma (PDA)



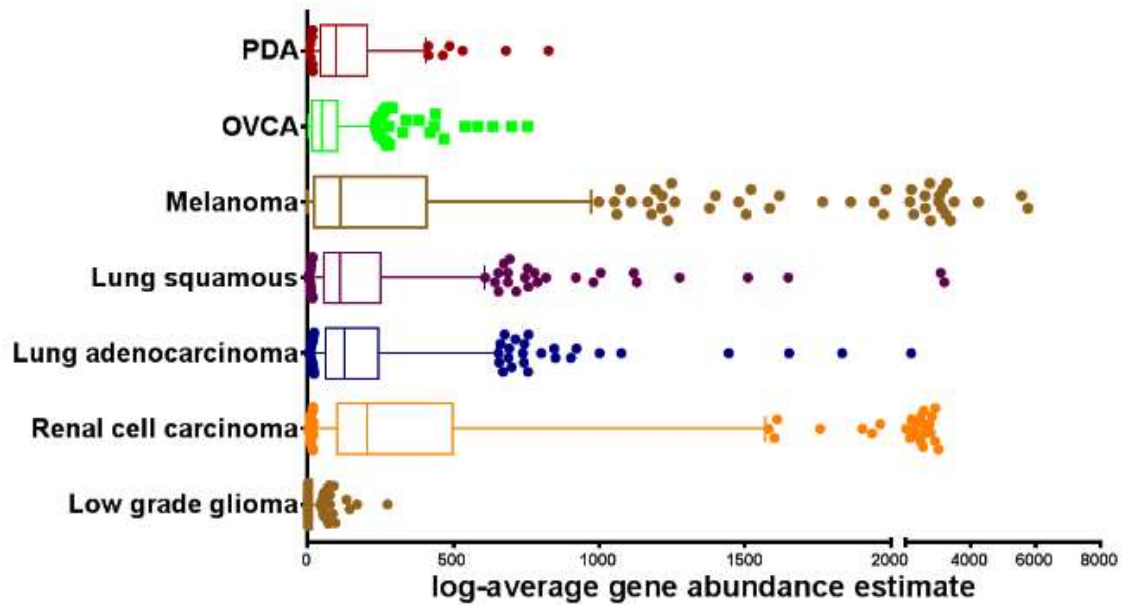
**Projected cancer deaths for the leading cancer killers.** Projections of the number of deaths from the current top five cancer killers indicate that pancreatic cancer will become the second leading cause of cancer deaths as early as 2015. The estimated

*Rahib et al, Cancer Res, 2014*

### Cytolytic Signature

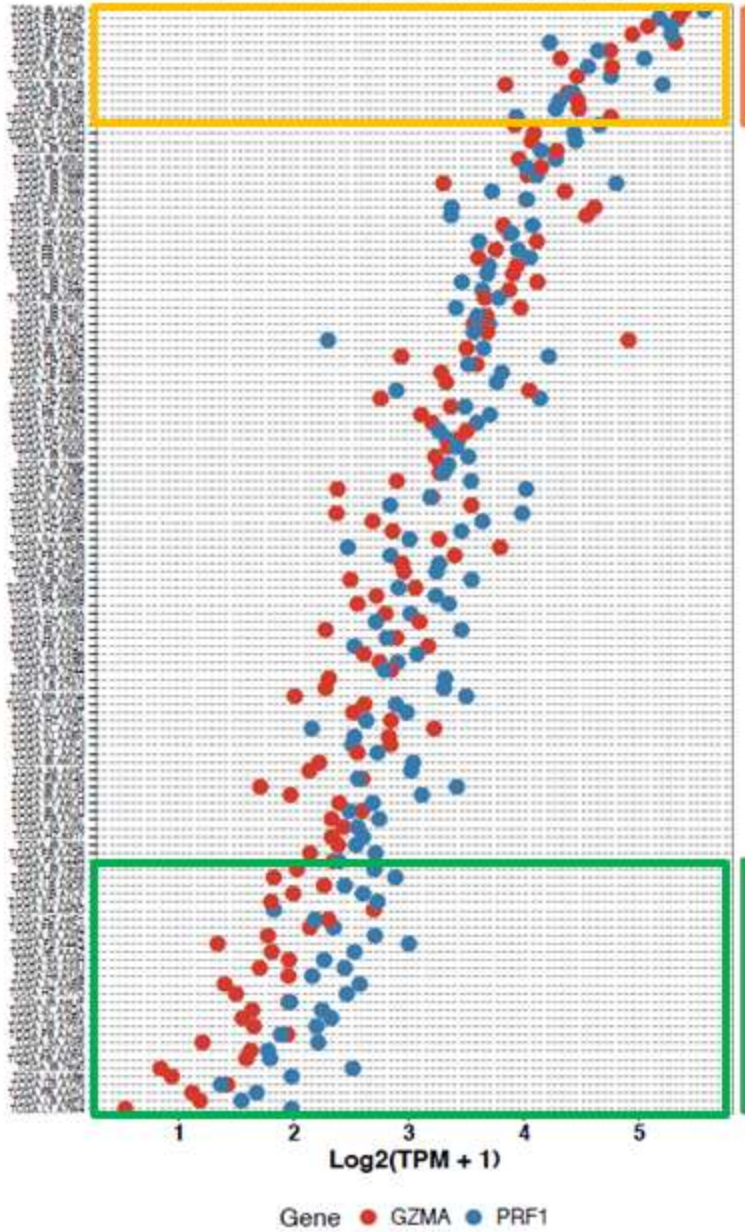


### CD8 Signature



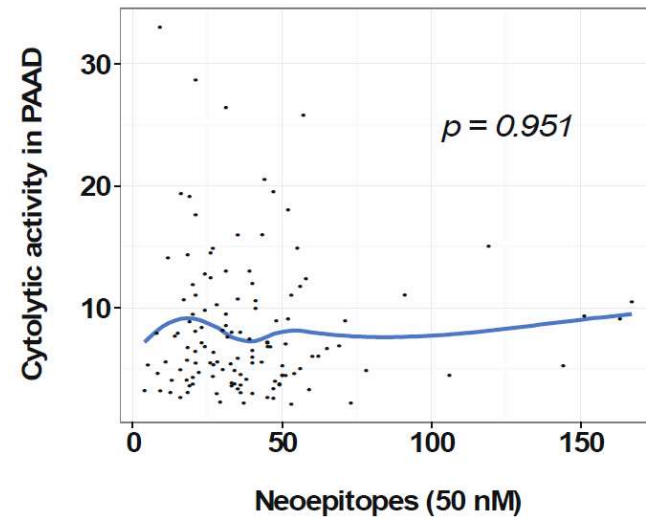
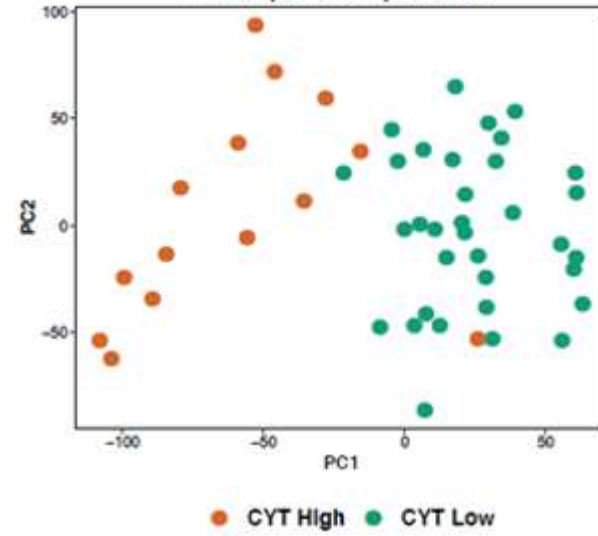
Tim Chao

### Expression of GZMA and PRF1 in Pancreatic Adenocarcinoma



All primary tumors, untreated n=134

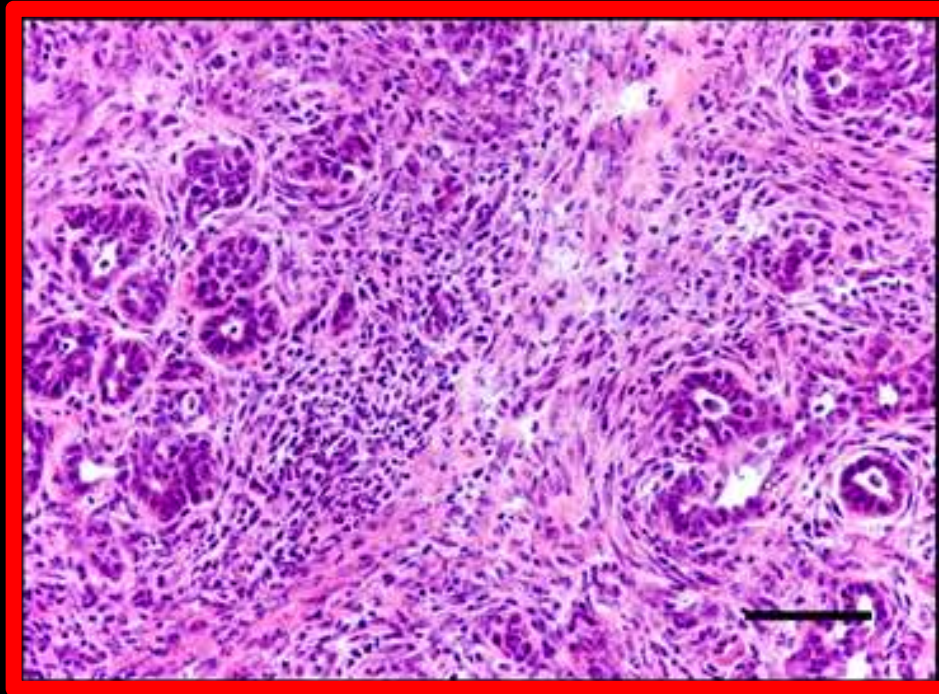
### Principal Components



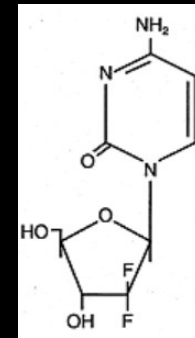
*Balli et al, Clin Can Res, 2017*

# Immunobiology of pancreatic carcinoma

*Mutant Kras*  
*Loss of TS*

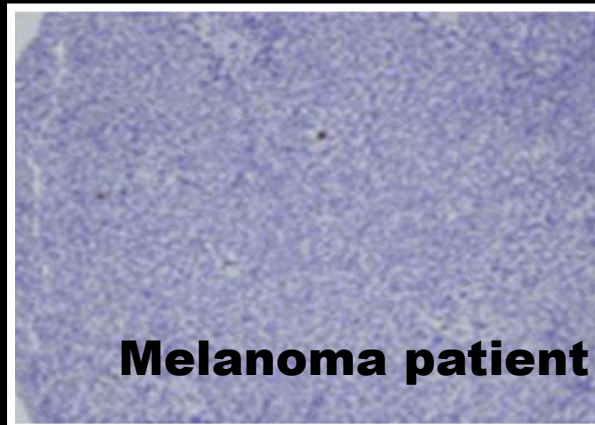
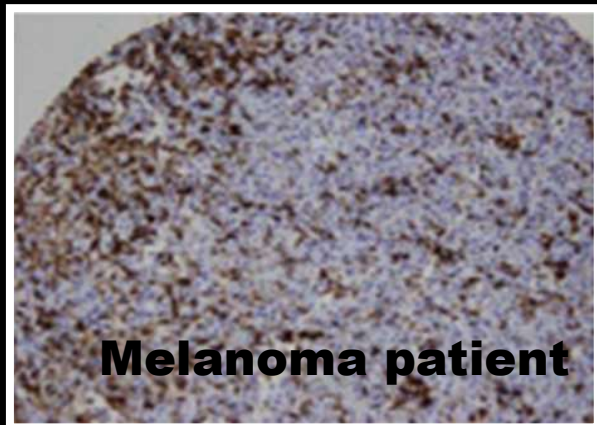
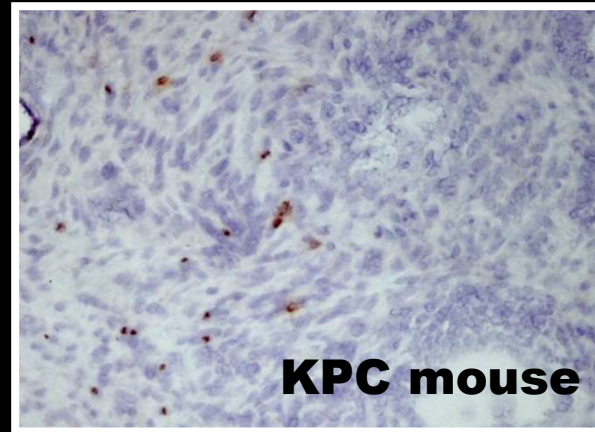
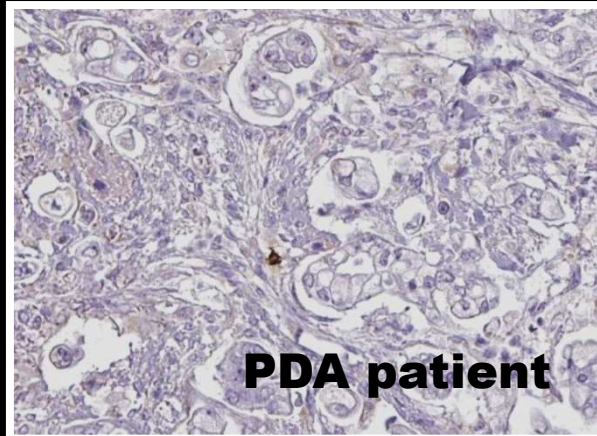


*Desmoplastic stroma*



*Gemcitabine*

# CD3+ T cell infiltration in pancreatic cancer



*Clark et al, Cancer Res, 2007*

*Erdag et al, Cancer Res, 2012*

## **Hypothesis:**

It's not the *physical* barrier of the stroma but rather an acquired network of oncogene-driven immunosuppression that excludes effector T cells

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## **Implications:**

- Immune surveillance in pancreatic carcinoma is more akin to “immune privilege” than “immunoediting”

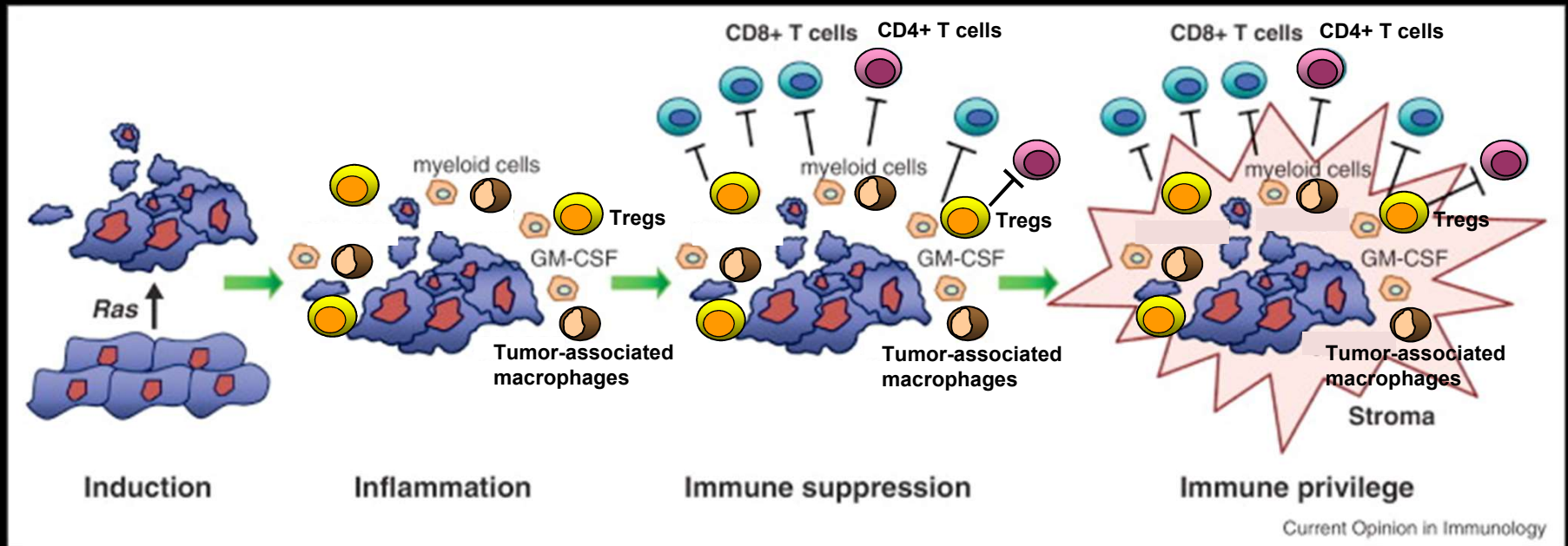
## **Hypothesis:**

It's not the *physical* barrier of the stroma but rather an acquired network of oncogene-driven immunosuppression that excludes effector T cells

## **Implications:**

- Immune surveillance in pancreatic carcinoma is more akin to “immune privilege” than “immunoediting”
- Without Darwinian-like pressure from T cells, the underlying pancreatic tumor cells remain highly susceptible to T cells.... if these can be provoked

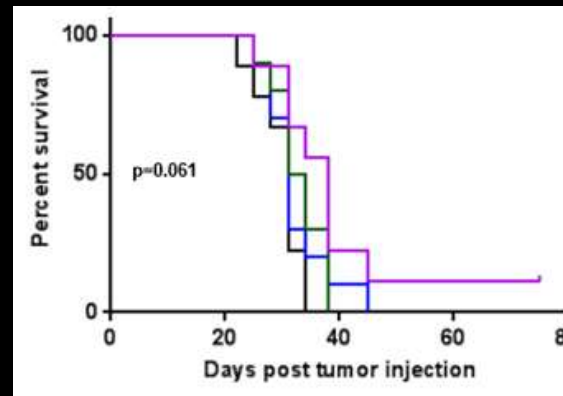
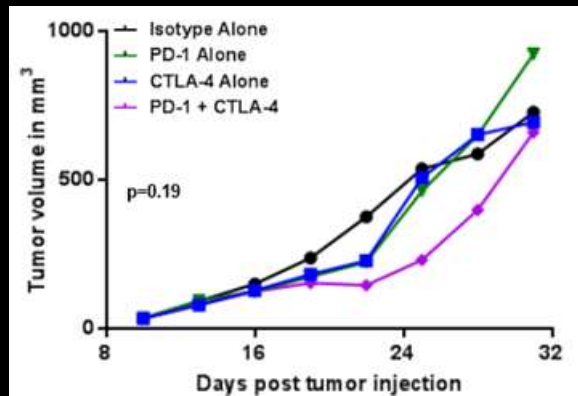
# Acquired immune privilege as a means of evasion



*Vonderheide and Bayne, Curr Opin Immunol, 2013*

# Can we cut and paste single-agent CTLA-4 and PD-1 mAb from melanoma to PDA?

Mouse studies say 'no' (*Winograd et al, Can Immunol Res, 2015*)

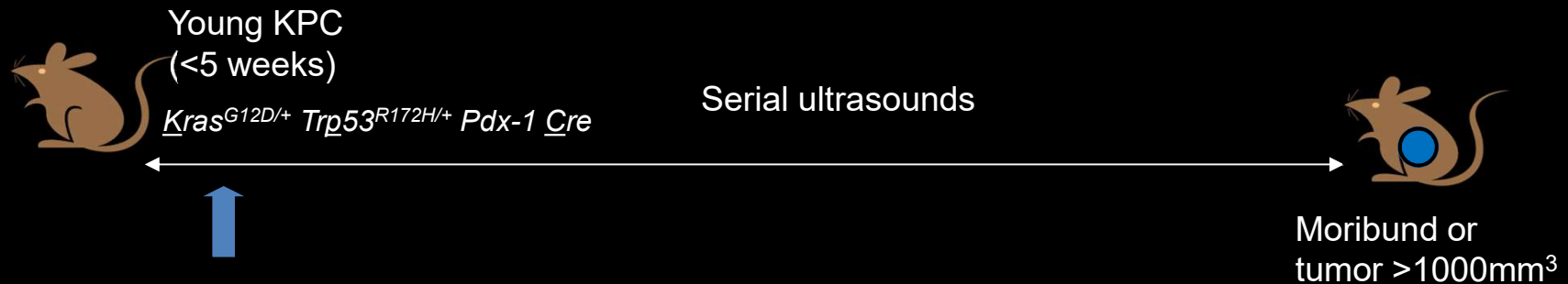


*KPC mouse cell line s.c.*

Clinical results to date say 'no'

- Single agent ipilimumab
  - no responses (*Royal et al, Clin Can Res, 2010*)
- Single agent PD-L1 mAb
  - no responses (*Brahmer et al, NEJM, 2012; Herbst et al, Nature, 2014*)
  - Exception MSI-high (*Le et al, Science, 2017*)

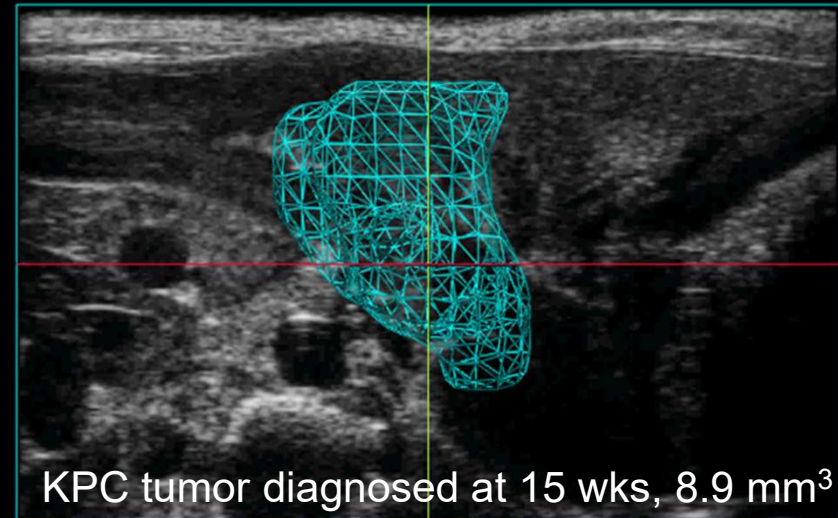
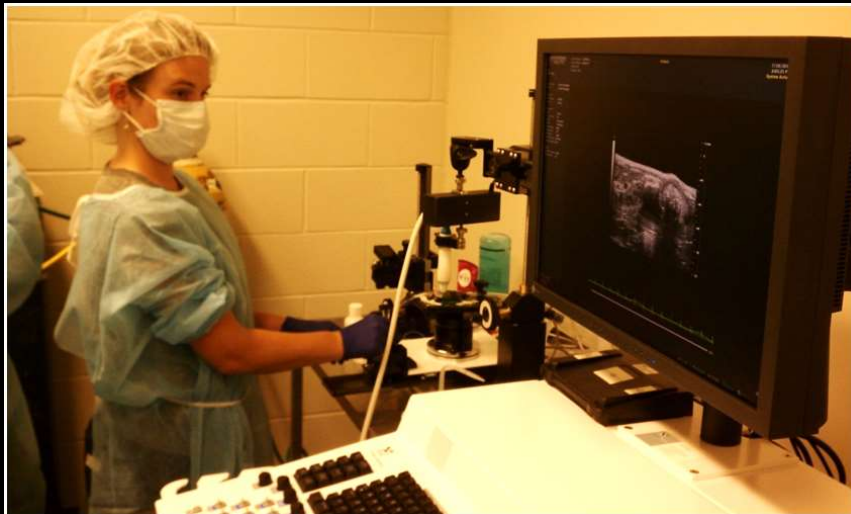
# T cell immunosurveillance in pancreatic cancer?



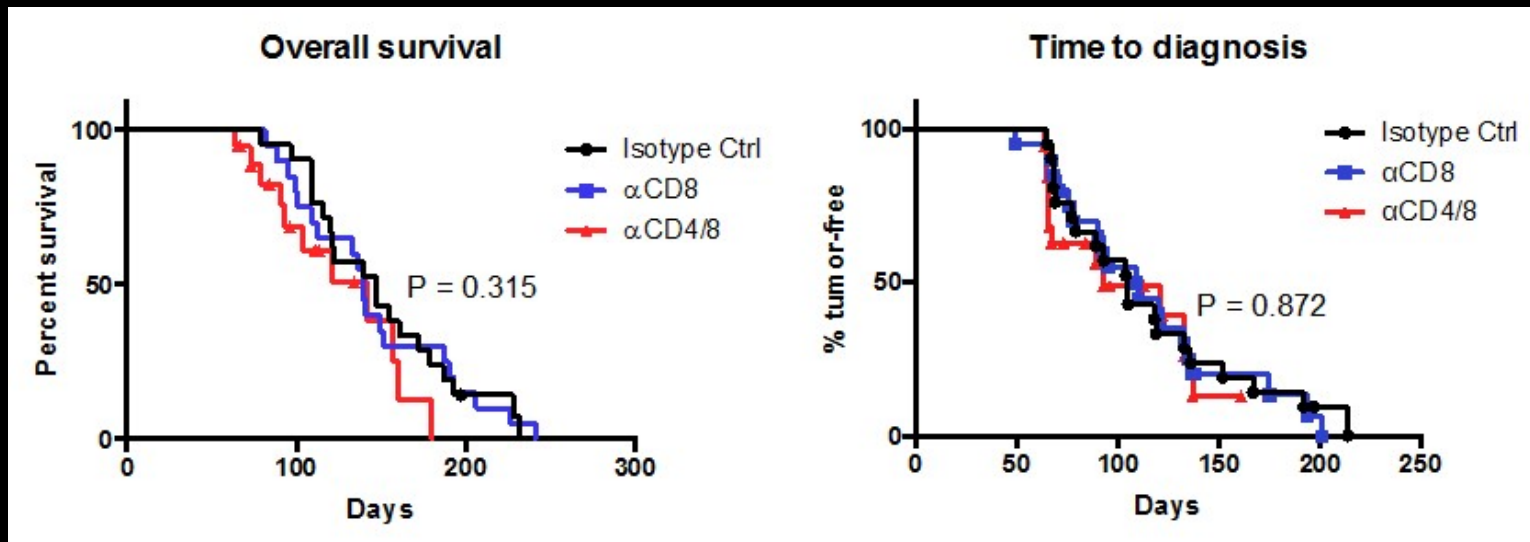
- CD8 (2.43) ± CD4 (GK1.5)
- IgG2b isotype control (LTF-2)

## Endpoints:

- Tumor burden (serial U/S)
- Survival: age at sac



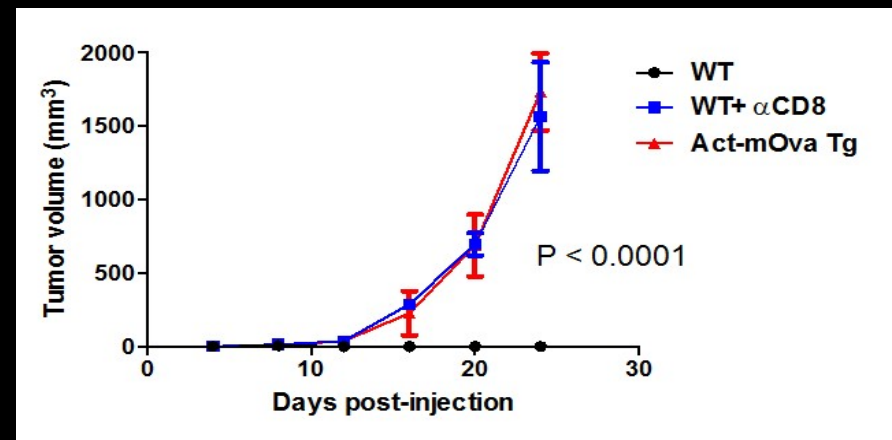
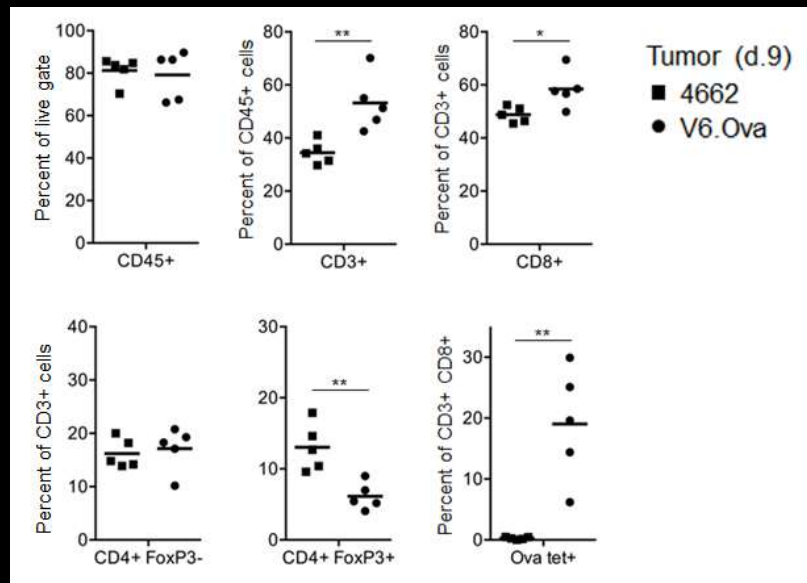
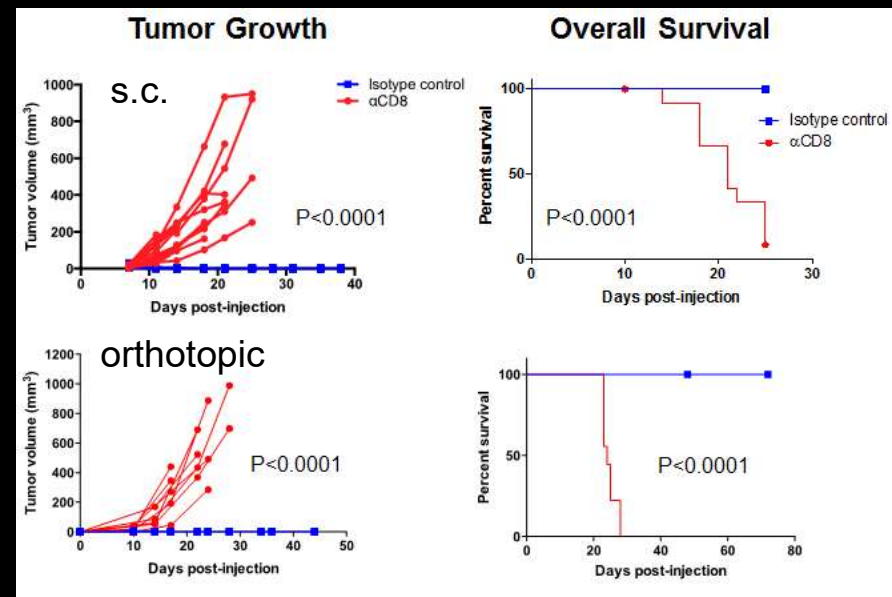
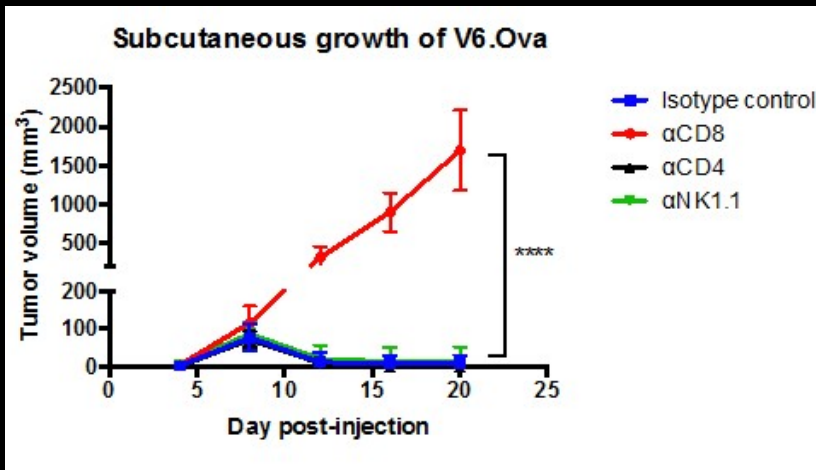
# No T cell immunosurveillance in pancreatic KPC model



- No difference in survival or time to diagnosis in T cell replete vs depleted mice
- KPC tumor cell lines from T cell replete or depleted mice grow same in T cell replete or depleted hosts (never rejected)

*These observations are inconsistent with immunoediting*

# Role of antigenic strength in KPC-OVA tumors



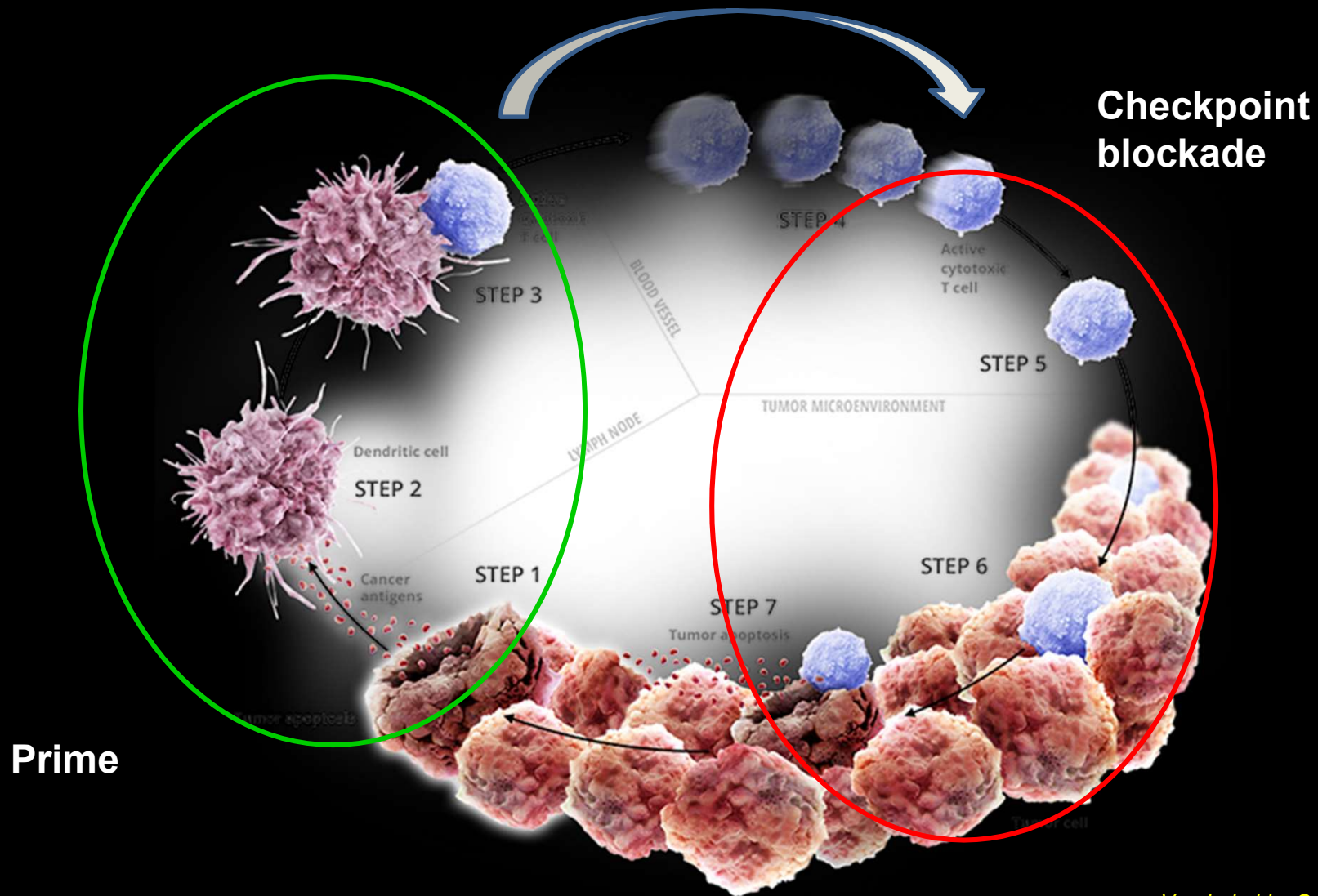
Evans et al, JCI Insight, 2016

# Burden of neo-epitopes in human cancer

Disease	Sample number	NSMs	Neoepitopes (class I)	Neoepitopes (class II)
Colon (COAD)	38	315	291	1014
Melanomam (SKCMm)	282	291	321	316
Stomach (STAD)	271	179	183	361
Melanomap (SKCMp)	60	178	170	314
Lung squamous (LUSC)	175	175	182	240
Lung adeno. (LUAD)	485	155	166	247
Bladder (BLCA)	358	146	141	197
DLBC (DLBC)	48	136	127	212
Head & neck (HNSC)	502	91	86	128
Esophageal (ESCA)	182	81	86	126
Adrenocortical (ACC)	77	73	72	141
Kidney renal CC (KIRC)	45	72	75	184
Liver (LIHC)	363	60	59	120
Uterine (UCS)	57	60	50	120
Cervical (CESC)	47	46	41	123
Testicular (TGCT)	133	42	36	81
Pancreatic (PAAD)	128	41	40	61
Glioblastoma (GBM)	126	32	34	67
Glioma (LGG)	509	31	28	39
Kidney renal pap. (KIRP)	281	31	30	60
Breast TN (TNBC)	203	26	24	31
Sarcoma (SARC)	247	24	22	44
Breast non-TN (BRCA)	495	20	19	27
Prostate (PRAD)	331	18	16	30
Melanoma (uveal) (UVM)	80	11	11	13
Pheochromo. (PCPG)	178	8	8	10
Thyroid (THCA)	391	8	8	13

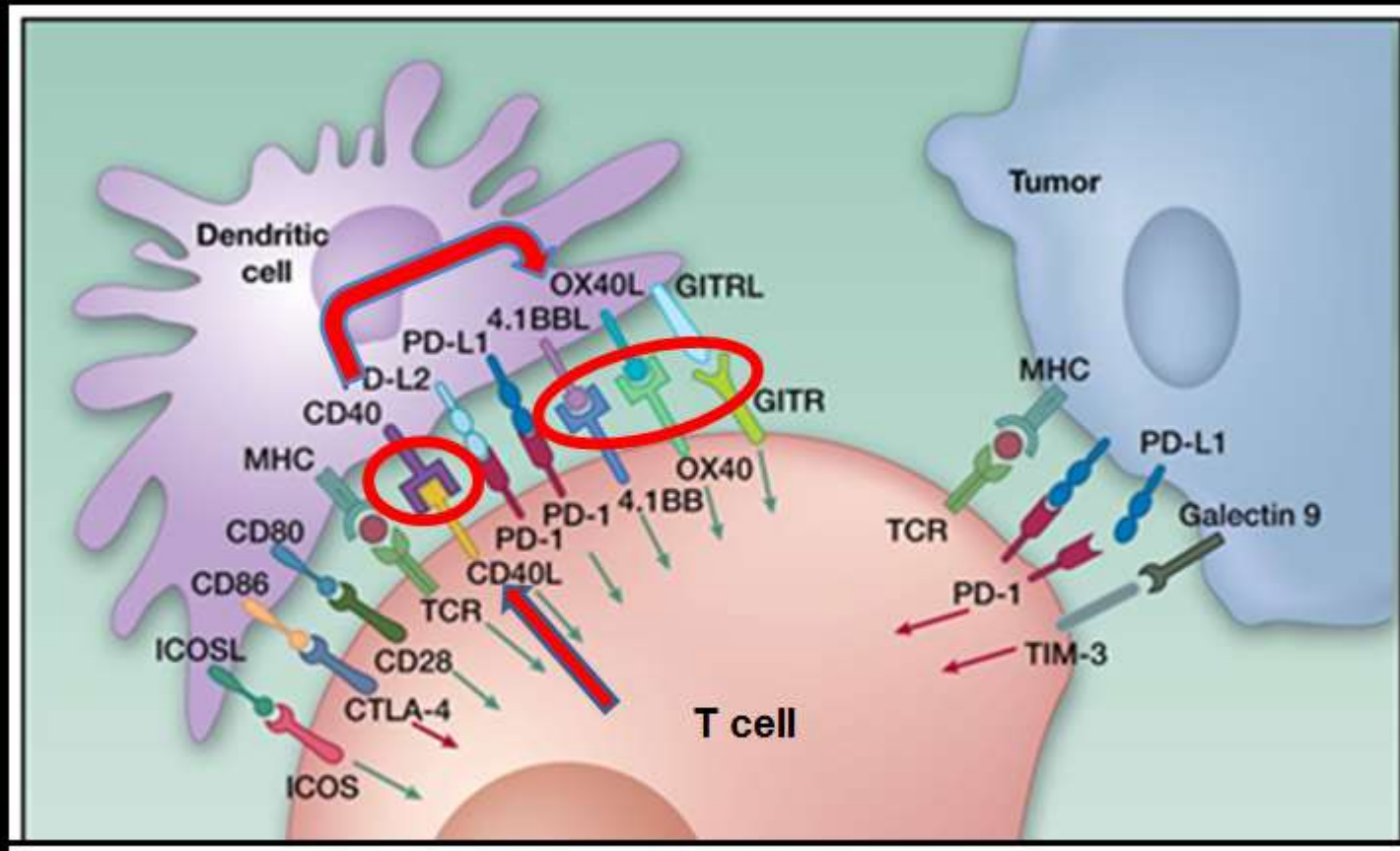


# A case for priming, not checkpoint



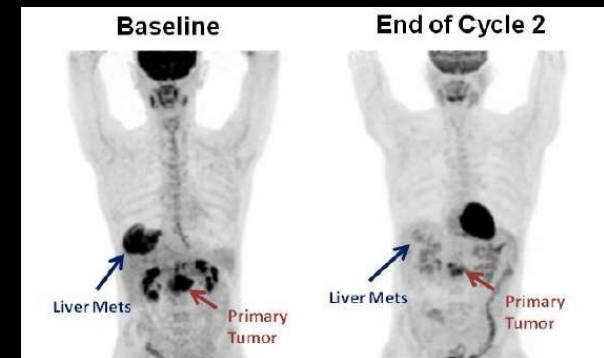
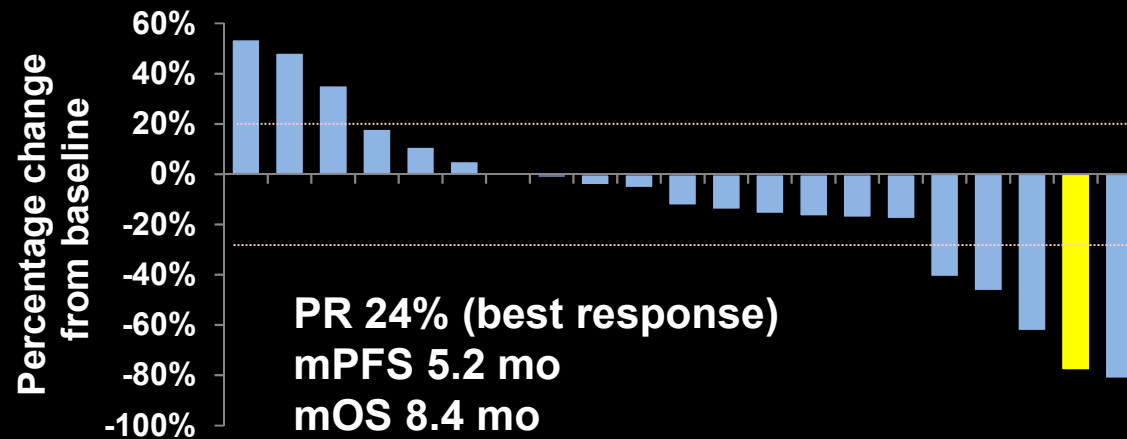
Vonderheide, *Cancer Cell*, 2018  
Figure adapted from Chen and Mellman. *Immunity*, 2013.

# CD40: Role in tumor immunity

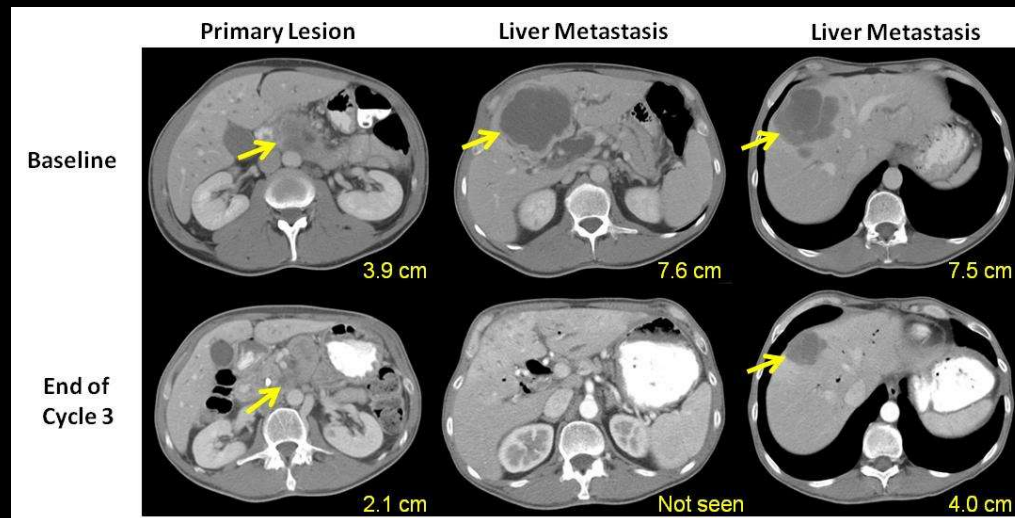


Ott et al, Clin Can Res, 2013

# Gemcitabine and agonist anti-CD40 mAb in chemo-naïve metastatic pancreatic carcinoma

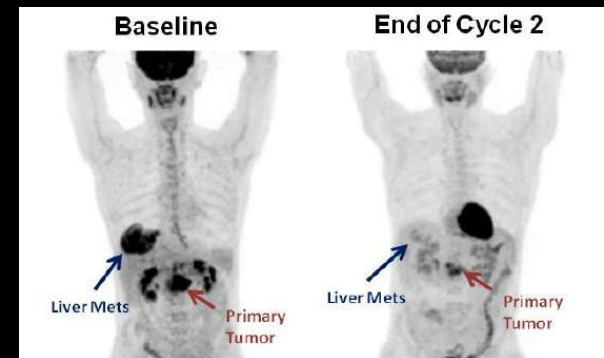
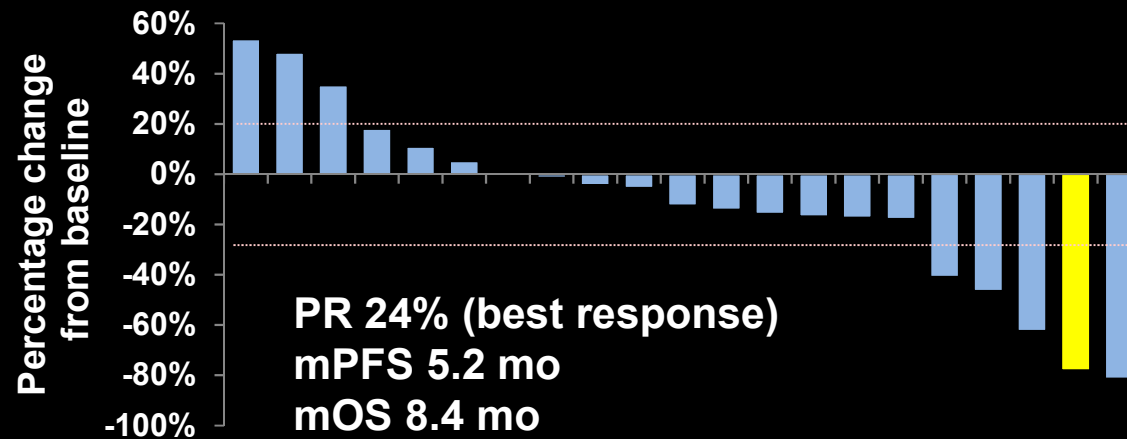


FDG-PET response: 88%

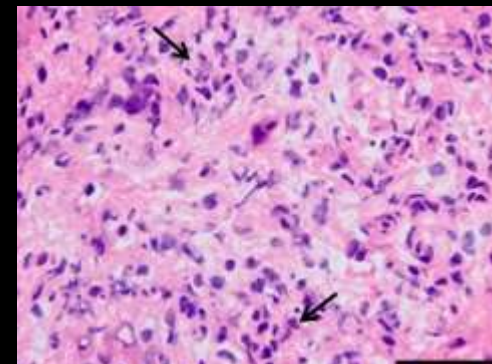
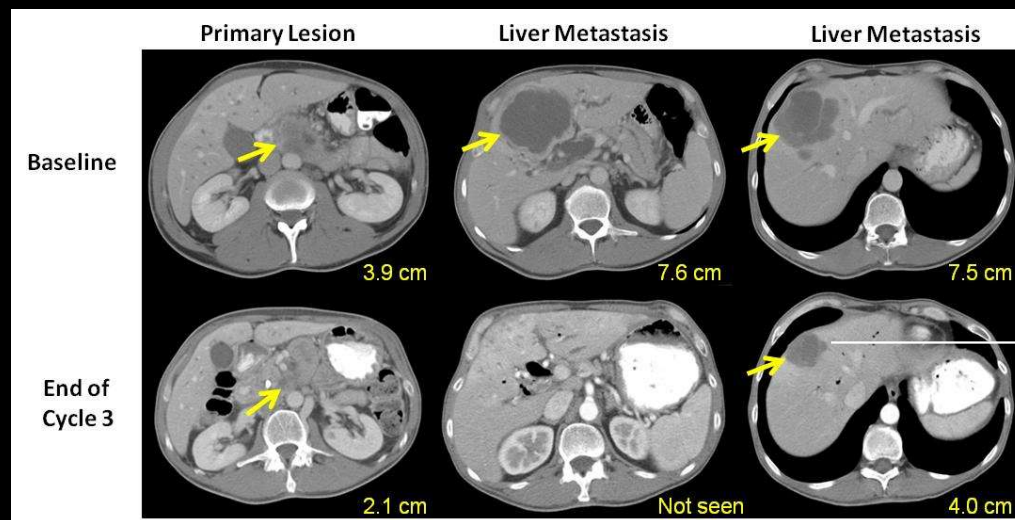


Beatty et al, Science, 2011  
Beatty et al, Clin Can Res, 2013

# Gemcitabine and agonist anti-CD40 mAb in chemo-naïve metastatic pancreatic carcinoma

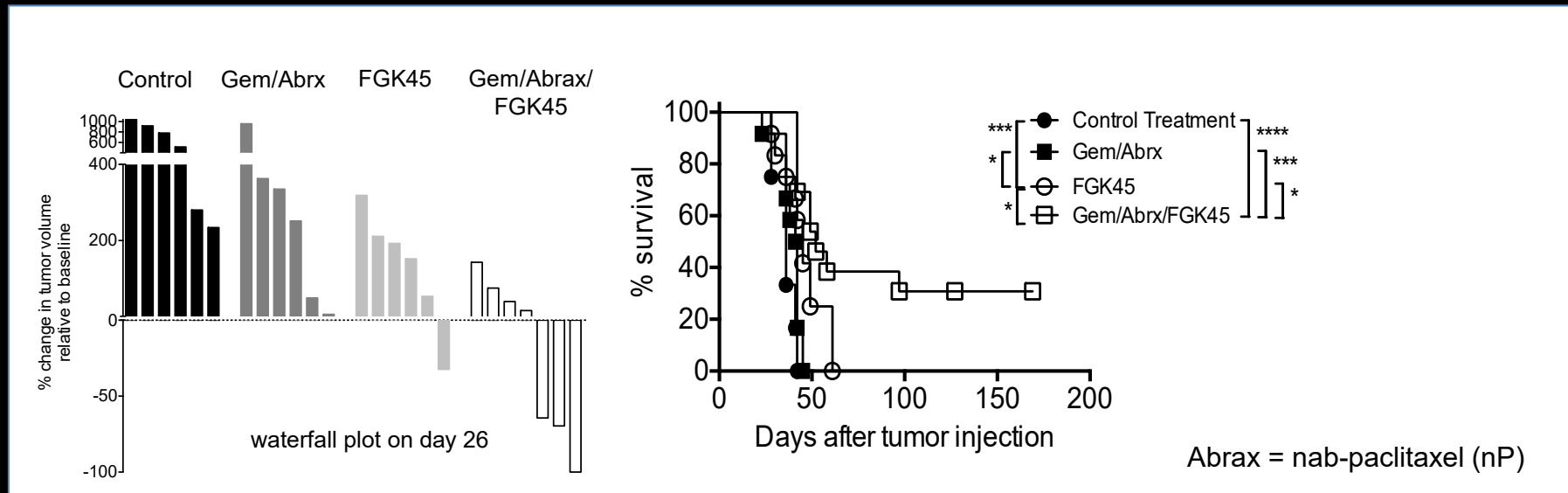


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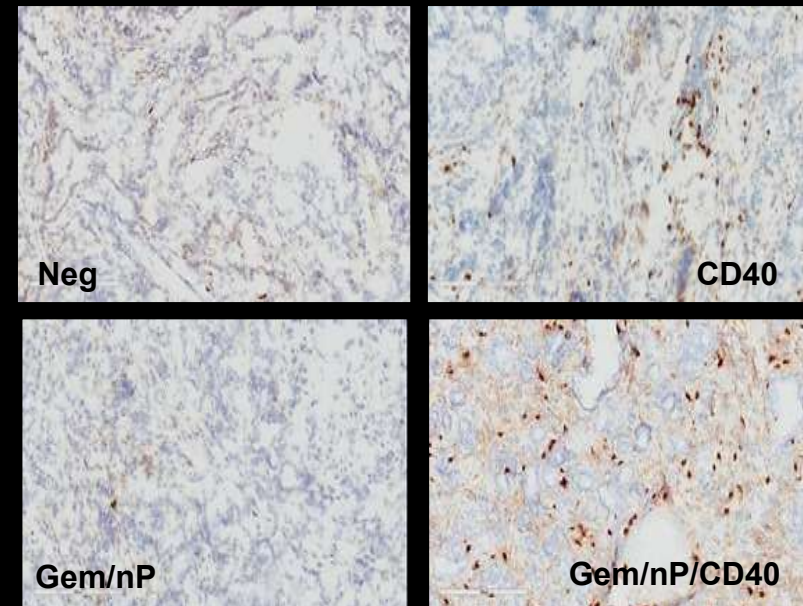
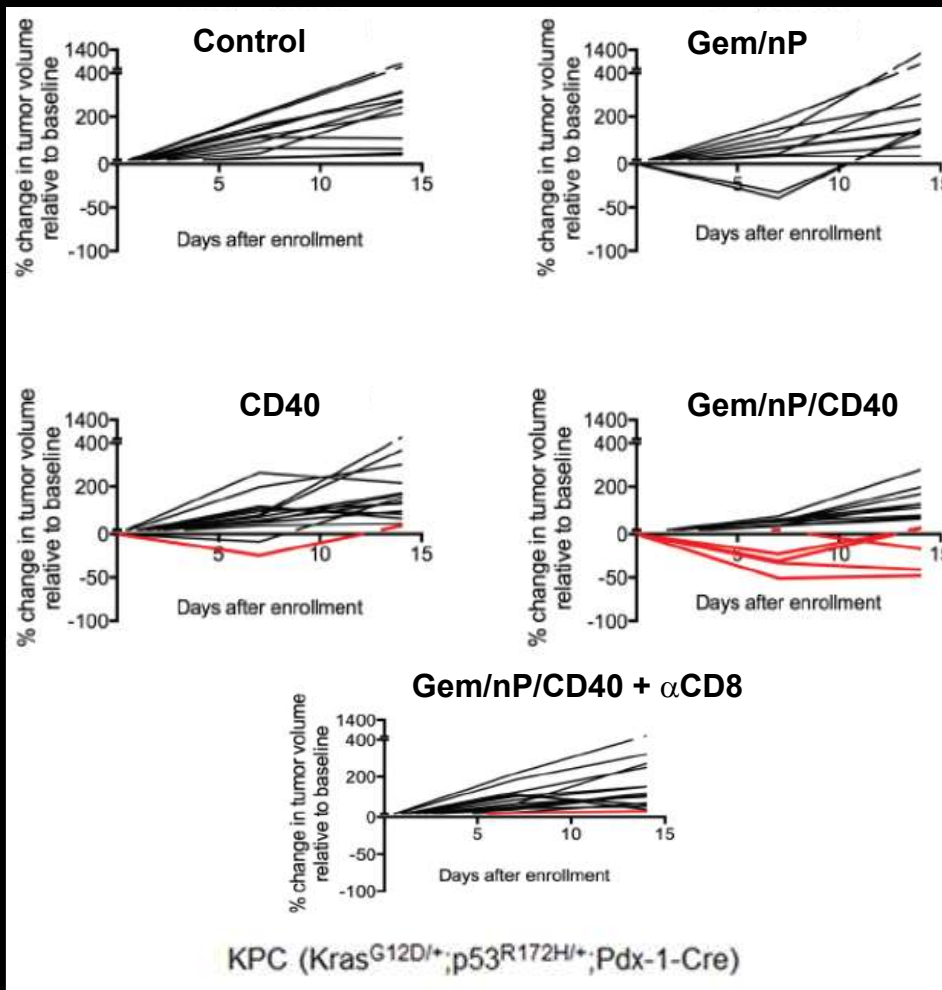
Beatty et al, Science, 2011  
Beatty et al, Clin Can Res, 2013

# CD40/chemo in subcutaneous KPC model (no OVA)



- **No regressions in T cell-depleted mice or IFN $\gamma$  KO mice**
- **In the TME, marked change in T cell infiltration**
  - Skewing toward IFN $\gamma$  and TNF $\alpha$  secreting T cells and activated dendritic cells
  - Increased clonality of infiltrating T cells in tumor by TCR seq
  - Many tertiary lymphoid structures in TME in CD40/chemo mice
- **Dependent on both nP and CD40 for maximal effect**
  - Addition of nP to Gem/CD40 converts mechanism to T cell-dependent, macrophage-independent

# CD40 with chemotherapy in spontaneous mouse model of pancreatic ductal adenocarcinoma



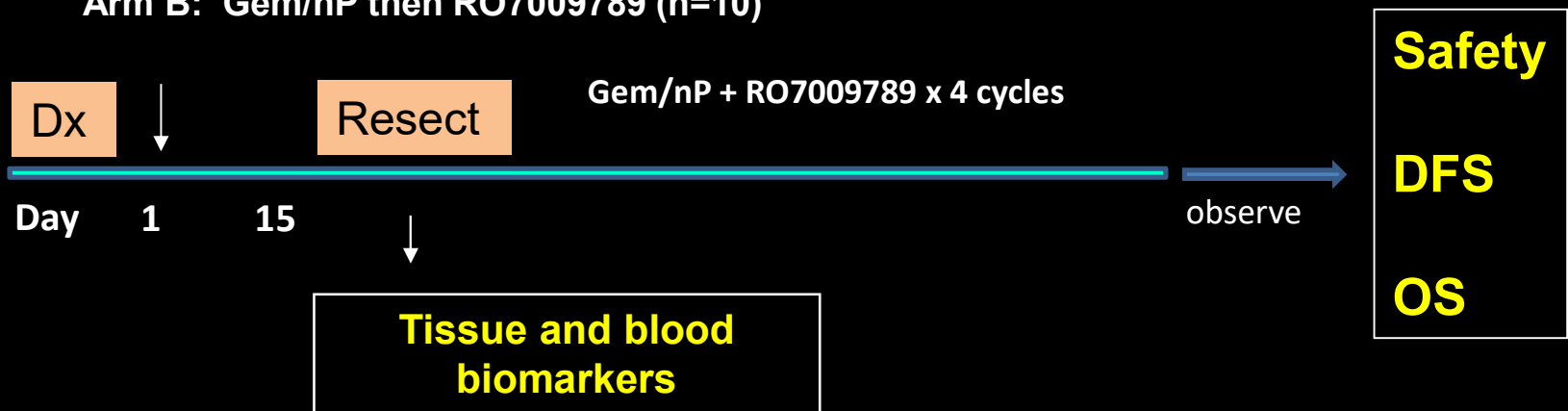
**Gem** – gemcitabine  
**nP** – nab-paclitaxel (Abraxane)

*Byrne et al, Cell Rep, 2016*

# CD40 as neoadjuvant therapy in pancreatic cancer

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

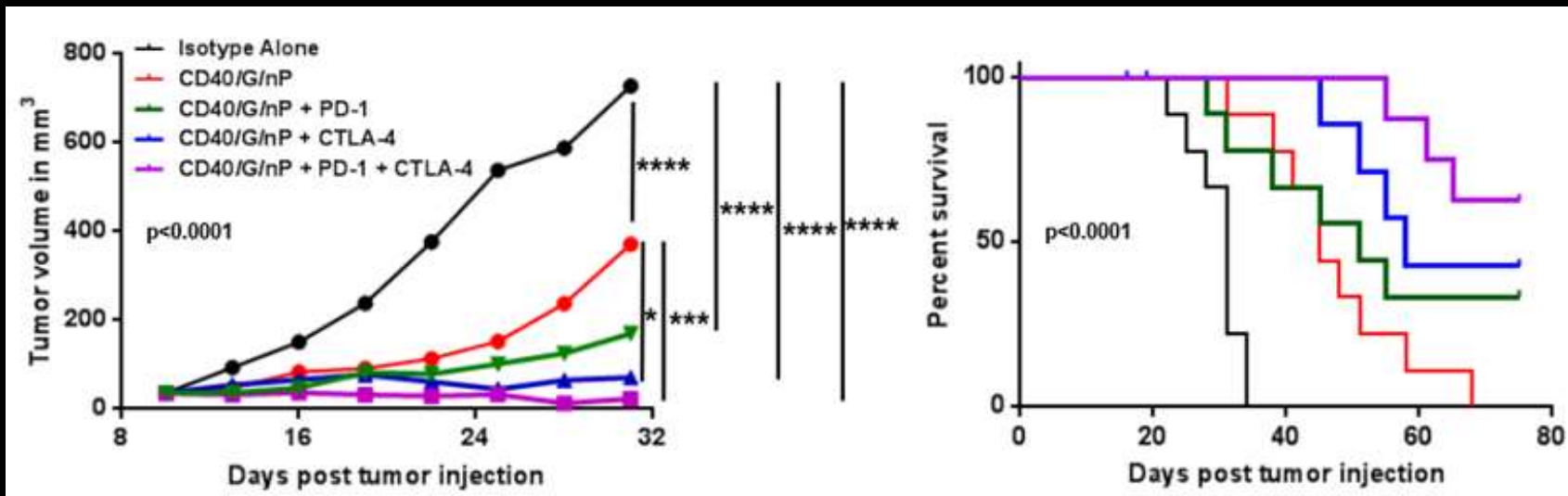
Arm A: RO7009789 (CD40) (n=10)  
Arm B: Gem/nP then RO7009789 (n=10)



IND sponsor, Robert Vonderheide  
Sites: Penn, Hopkins, Case, U Wash, Wisconsin

Collaboration of PanCan, NCI's CITN, SU2C

# CD40/chemo plus checkpoint blockade in PDA



**Gem** – gemcitabine  
**nP** – nab-paclitaxel (Abraxane)

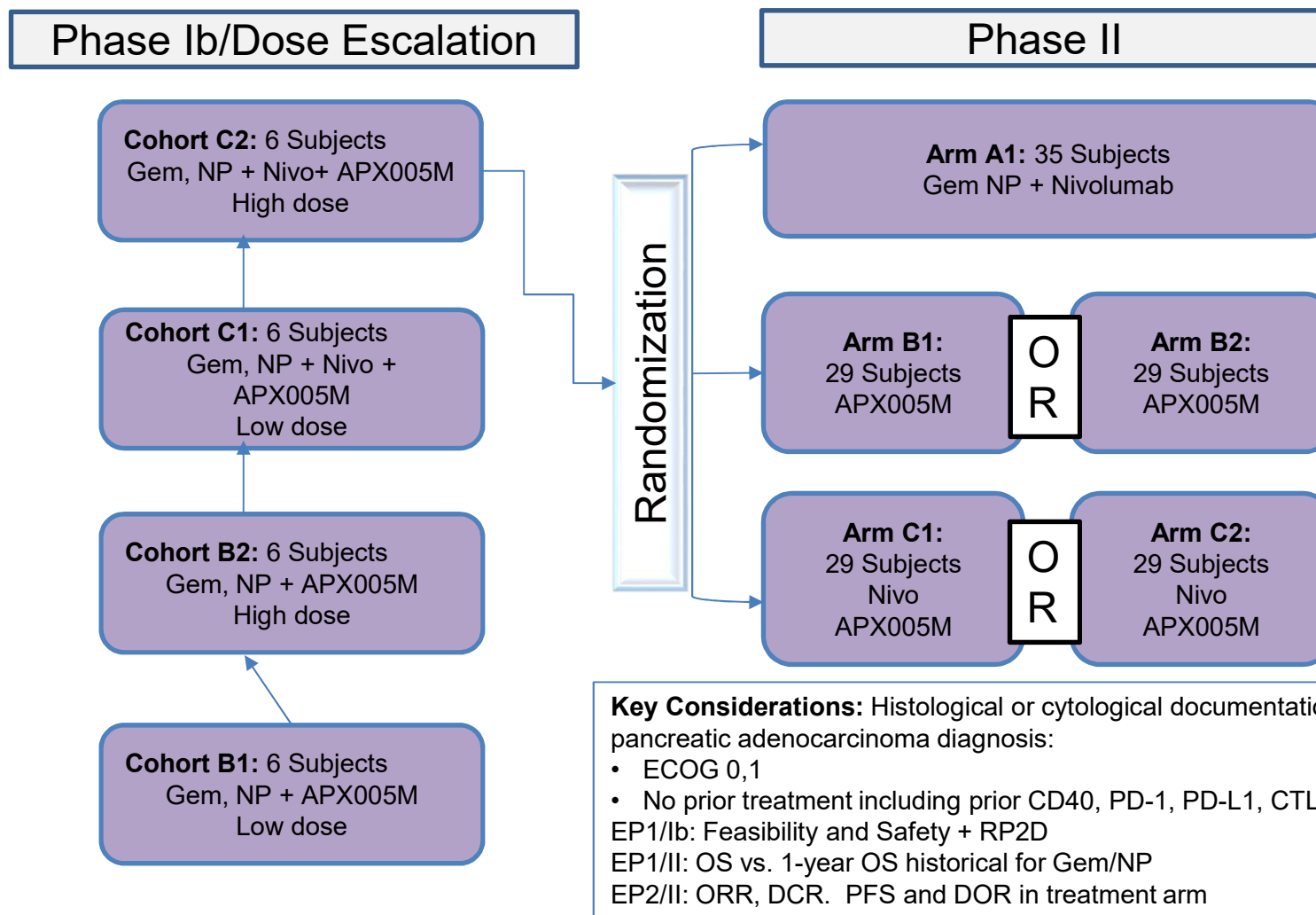
*Winograd et al, Can Immunol Res, 2015*

# PICI0002 Study Design

IND Sponsor: Parker Institute  
Overall PI: Robert Vonderheide  
Penn, MSKCC, MDACC, UCLA,  
UCSF, Stanford

**NCT03214250**

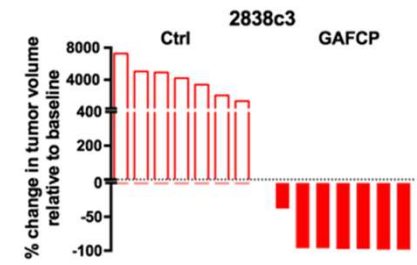
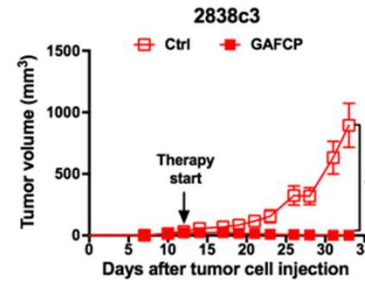
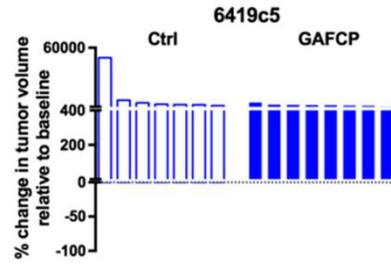
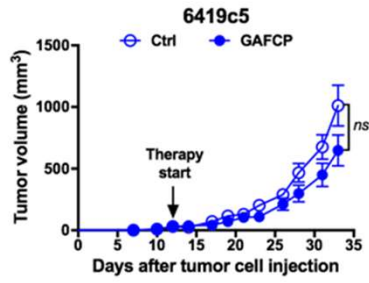
**Gem/NP +/- CD40 +/- PD-1 for patients with first-line metastatic pancreatic carcinoma**



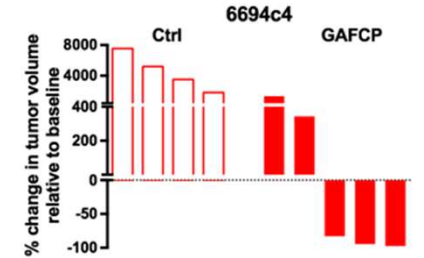
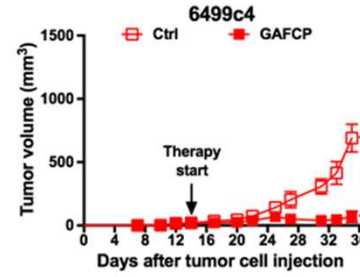
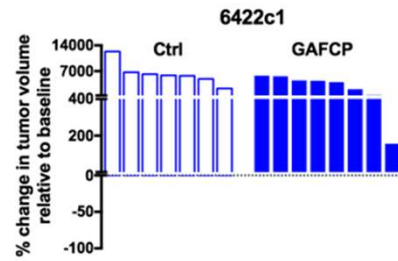
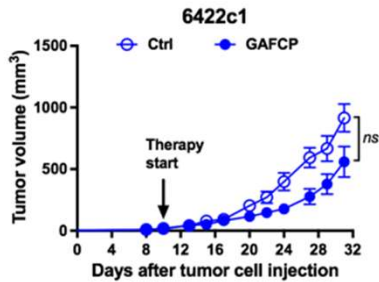
## T cell low

## T cell high

subcutaneous

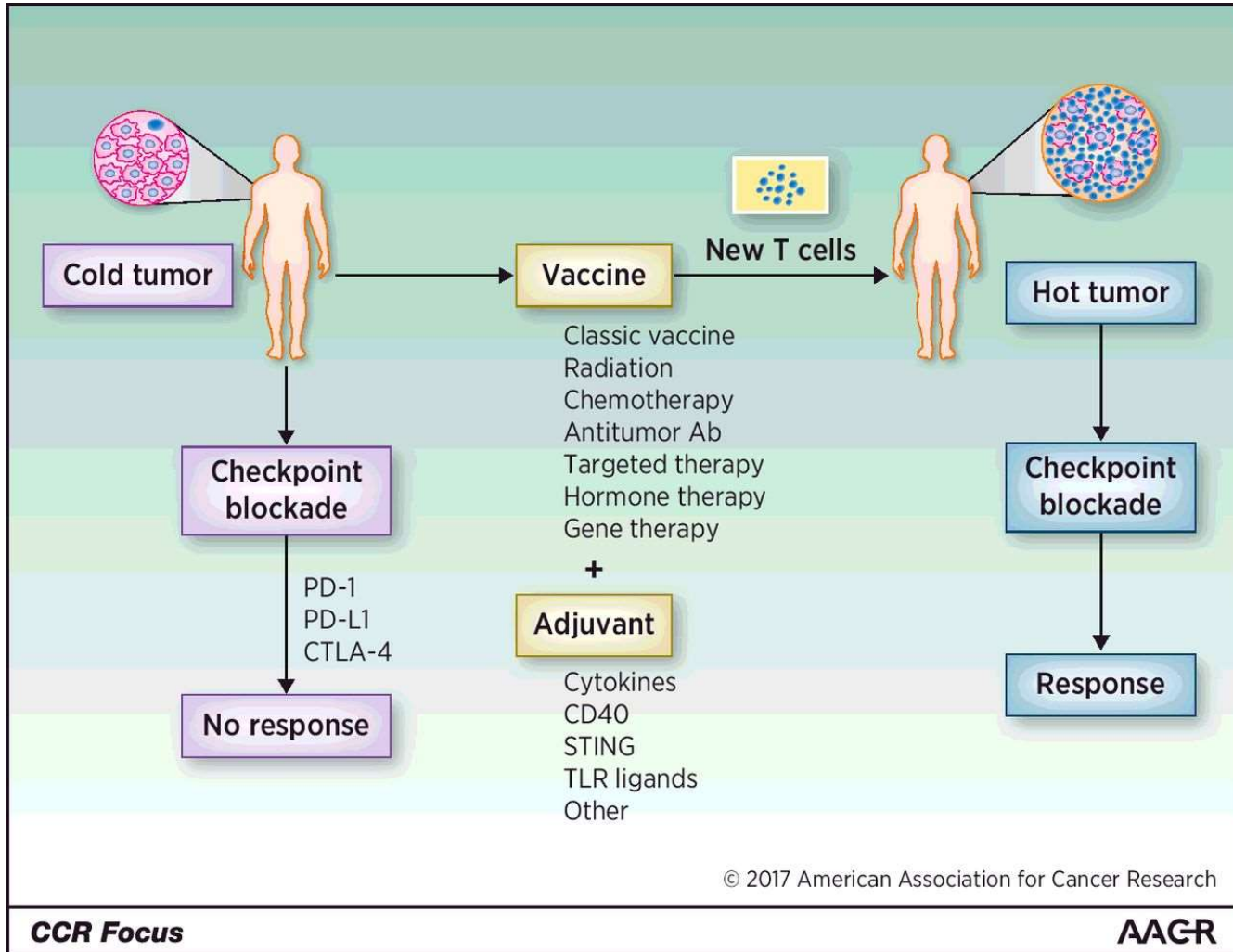


orthotopic



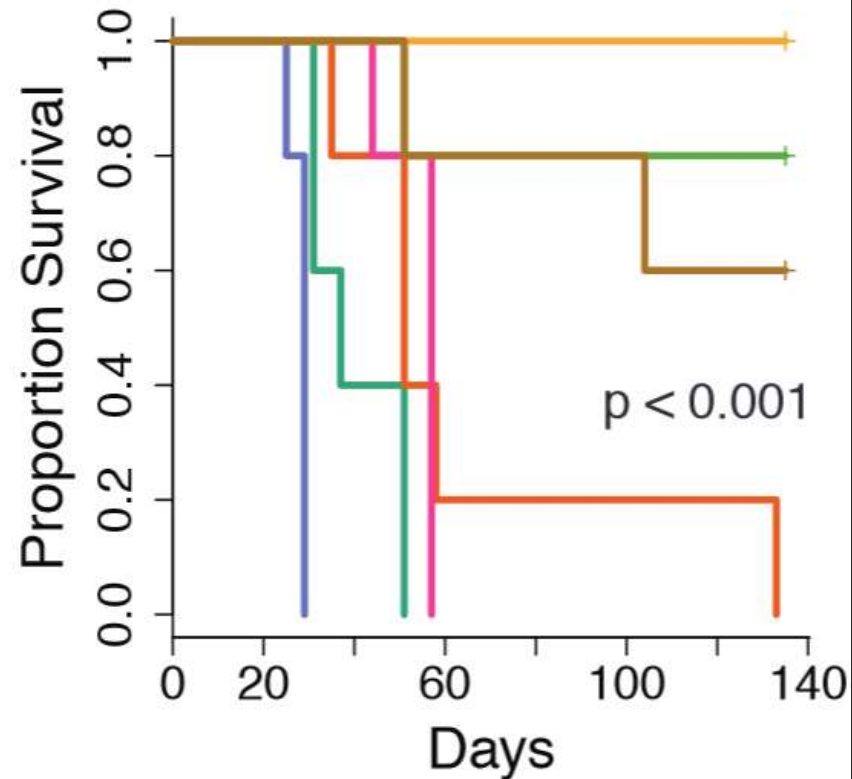
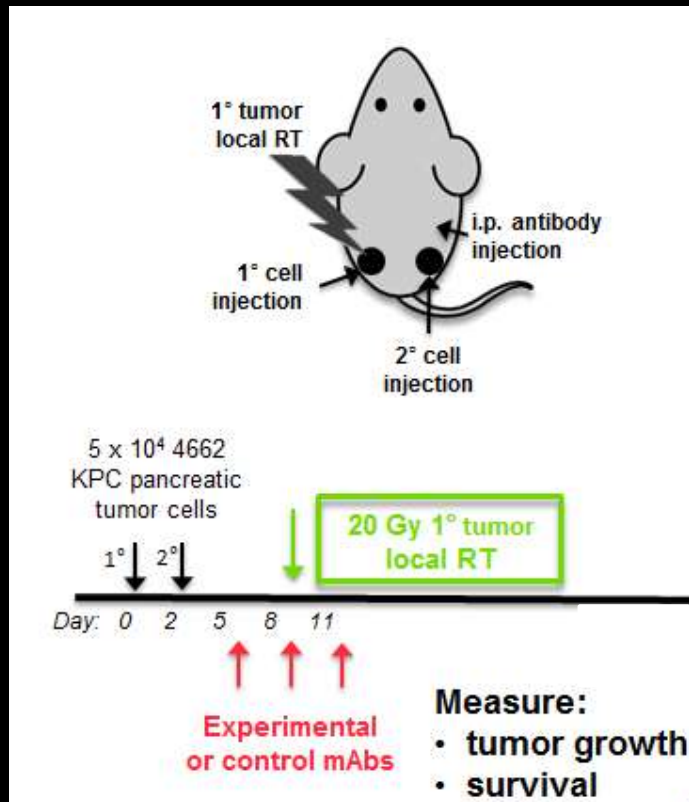
Li et al, Immunity, 2018

# Opportunities beyond checkpoint



Vonderheide et al. Clin Cancer Res 2017;23:2640-2646

# Radiation plus checkpoint blockade in pancreatic cancer



*Twyman-Saint Victor et al, Nature, 2015*

## Summary

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- **There's no immunoediting if there's no immune response**
  - Checkpoint blockade and 'stacking' combinations will be more likely to fail than succeed against tumors if the dominant biology is T cell exclusion, privilege, or ignorance
- **Lack or deficient T cell priming represents a fundamental lesion in cancer immunity, but this can be fixed**
  - CD40 activation of dendritic cells is one (among many) tractable ways to therapeutically repair deficient priming and trigger T cell immunity
  - Return of vaccines in all shapes and sizes
  - Once T cells primed, checkpoint blockade may enable – or even be necessary – for clinically significant T cell immunity

# Acknowledgements

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## Vonderheide Lab

Kate Byrne

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## Clinical collaborators

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Kim Reiss Binder

Ursina Teitelbaum

## Scientific Collaborators

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John Wherry

Andy Minn

Kate Nathanson

Cynthia Clendenin

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R01 CA169520

P30 CA016520

P50 CA174523

P01 CA210944

Parker Institute

Basser Center for BRCA

Breast Cancer Res Found

SU2C-Lustgarten

Pershing Square

Melanoma Res Alliance