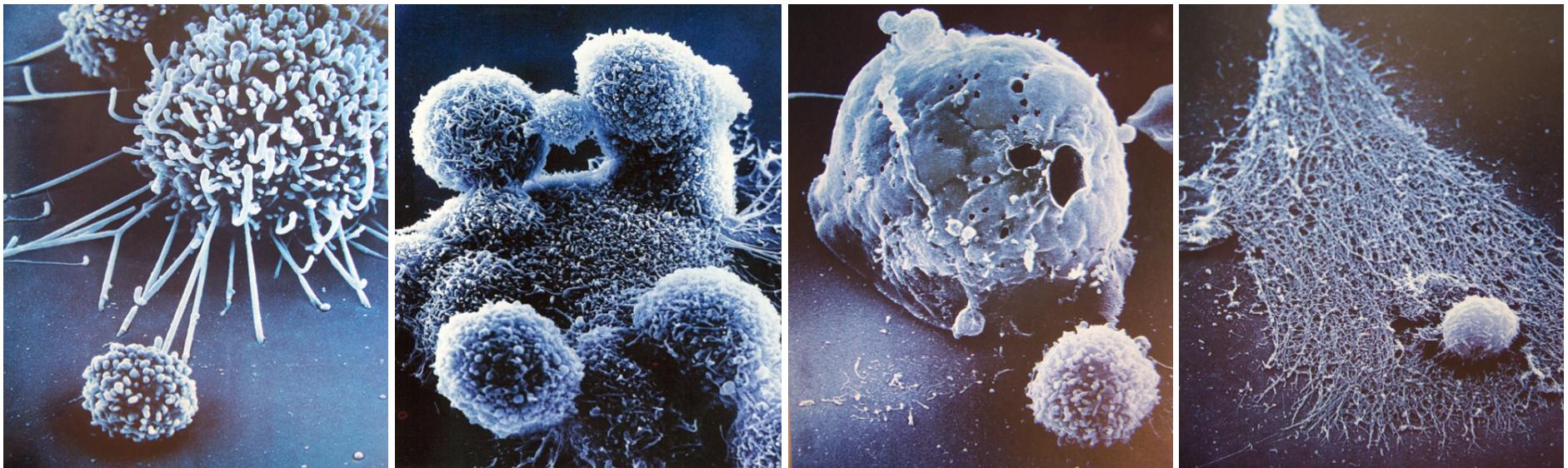


Cancer Immunotherapy and Radiotherapy Immune Modulation

Magical Effects of the healing beam?



Arta M. Monjazeb, M.D., Ph.D.

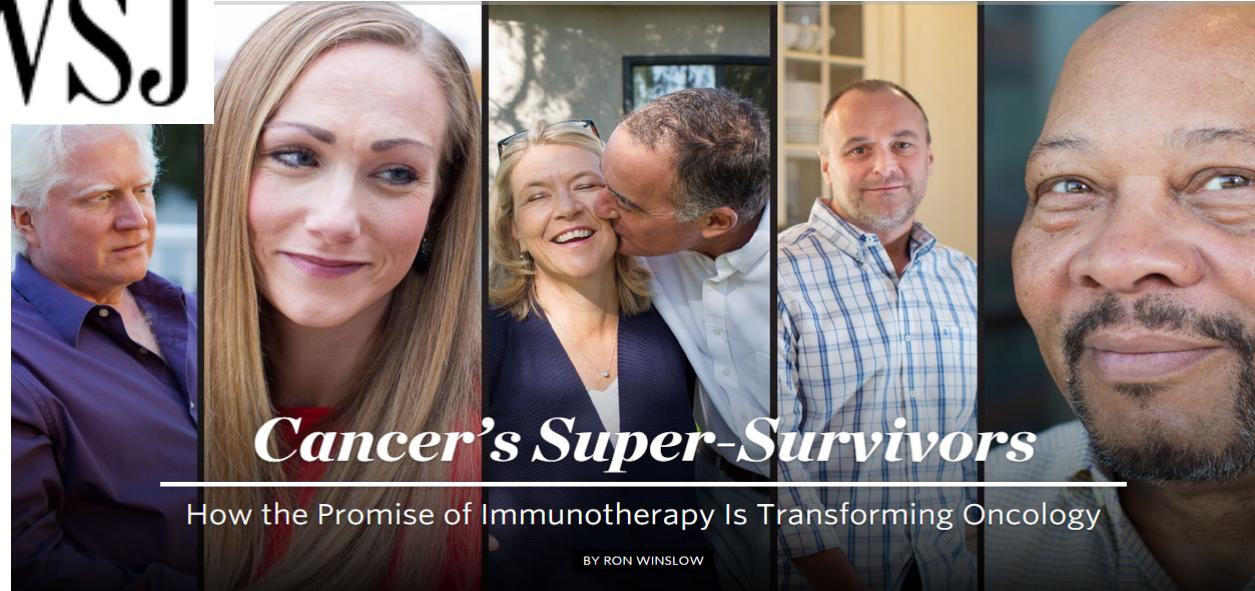
Associate Professor of Radiation Oncology
Laboratory of Cancer Immunology
CCSG Staff Investigator for Immunotherapy
UC Davis Comprehensive Cancer Center

Disclosures

- Clinical Trial & Research Funding
 - Genentech
 - Astra-Zeneca
 - Transgene
 - Incyte
 - Merck
 - Dynavax
 - BMS

Immunotherapy: A Revolution in Cancer Therapy

WSJ



Cancer's Super-Survivors

How the Promise of Immunotherapy Is Transforming Oncology

BY RON WINSLOW

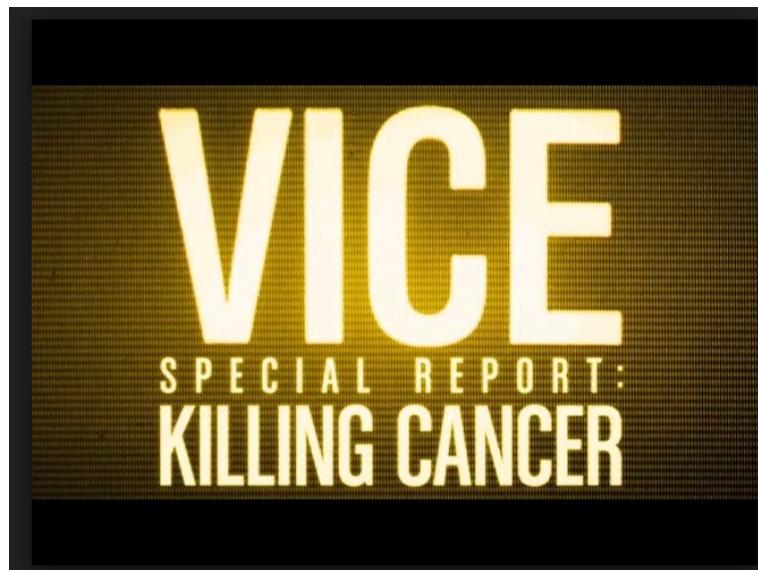
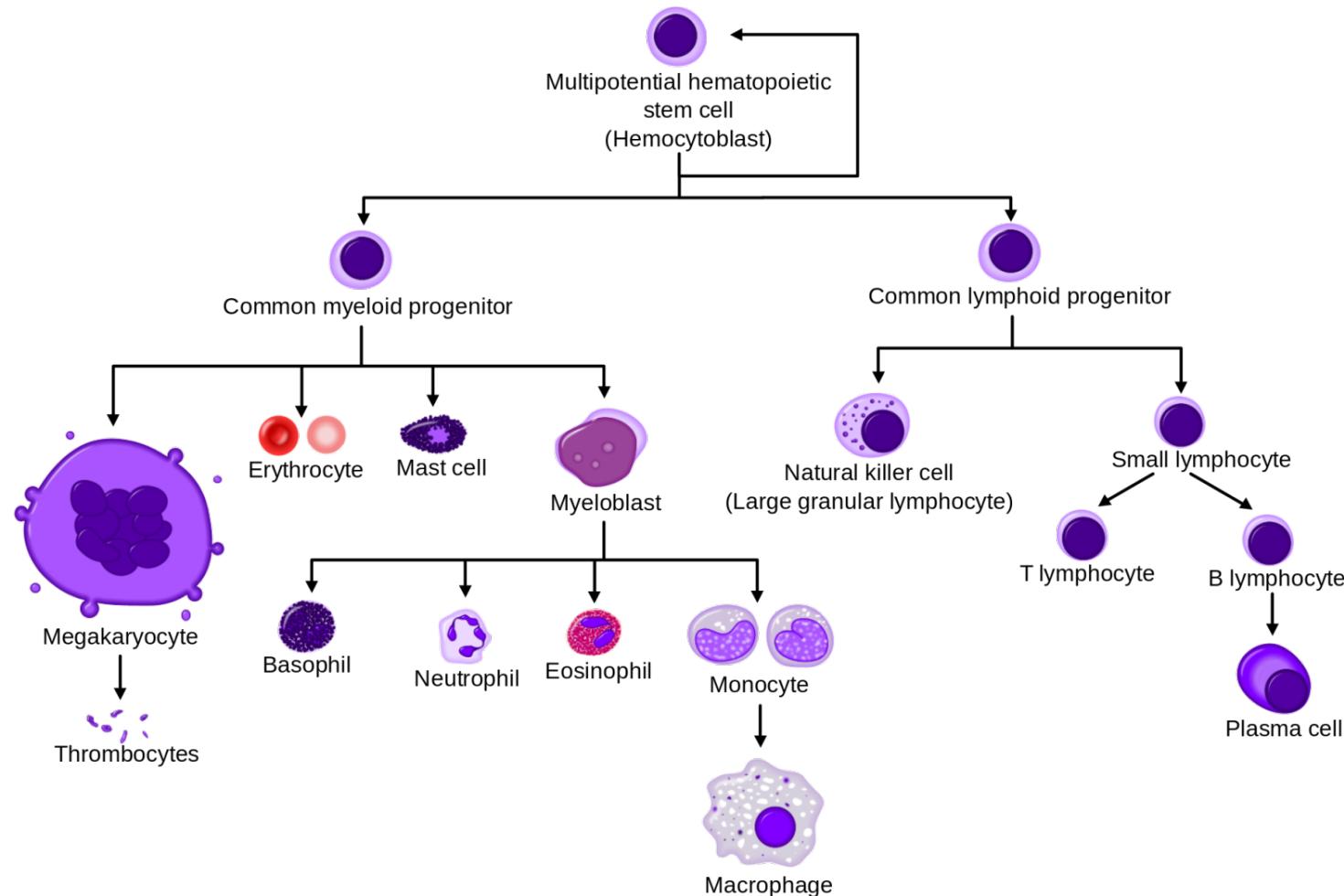


Photo credit: V. ALTOUMANIAN/SCIENCE

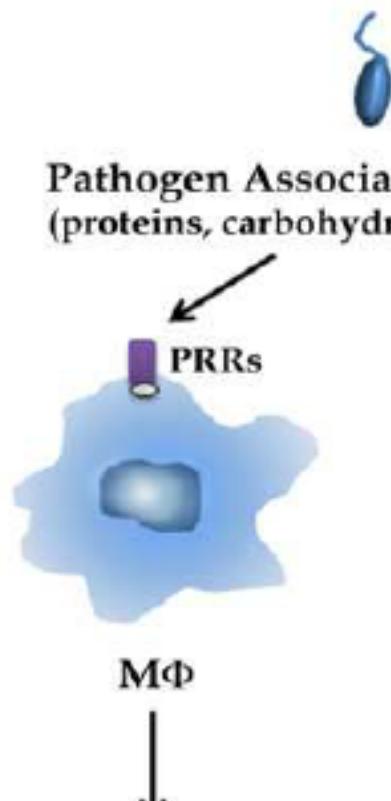
What Is the Immune System

- Main function: recognition of “self” from “non-self” and eliminate “non-self”



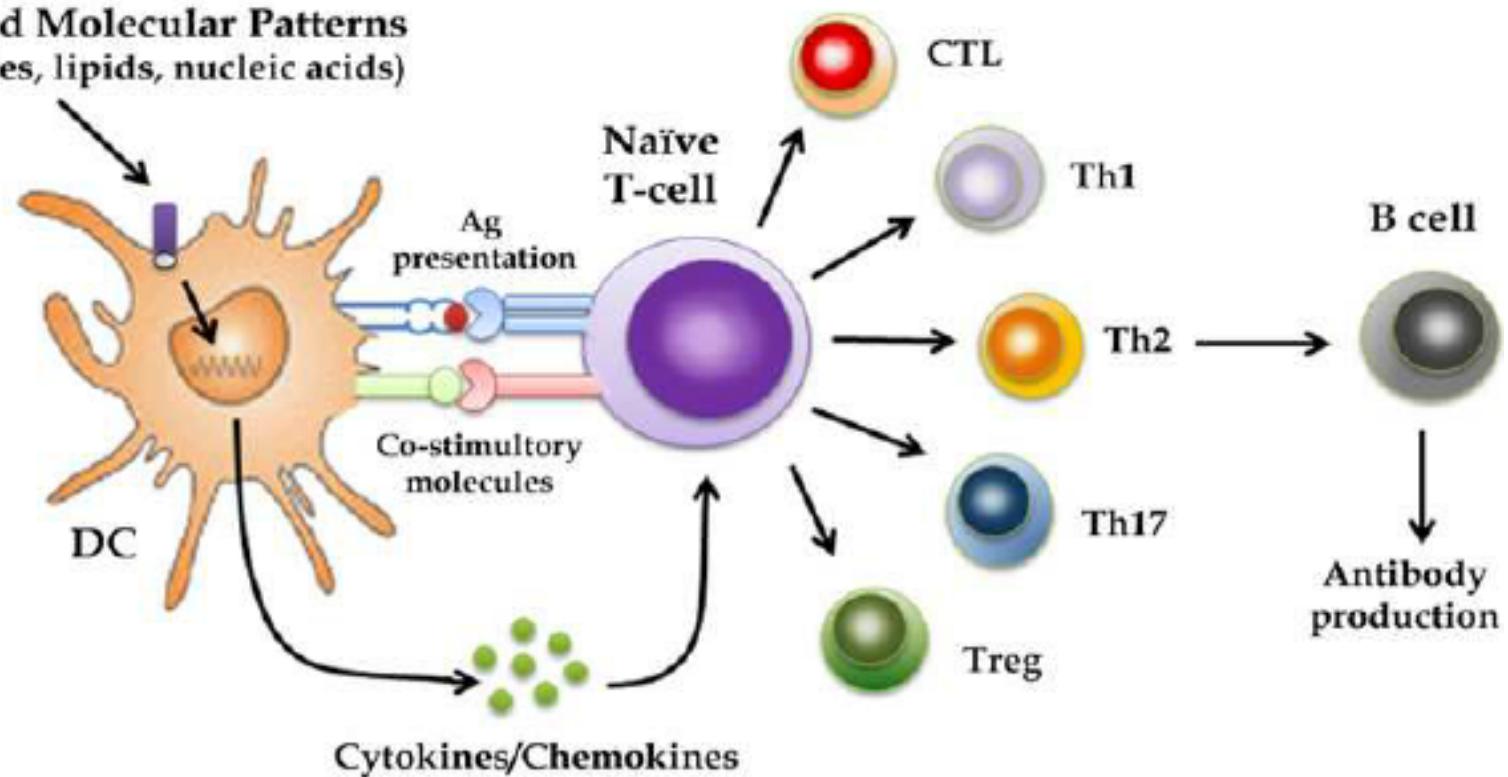
How Immune System recognizes non self

Innate Immunity

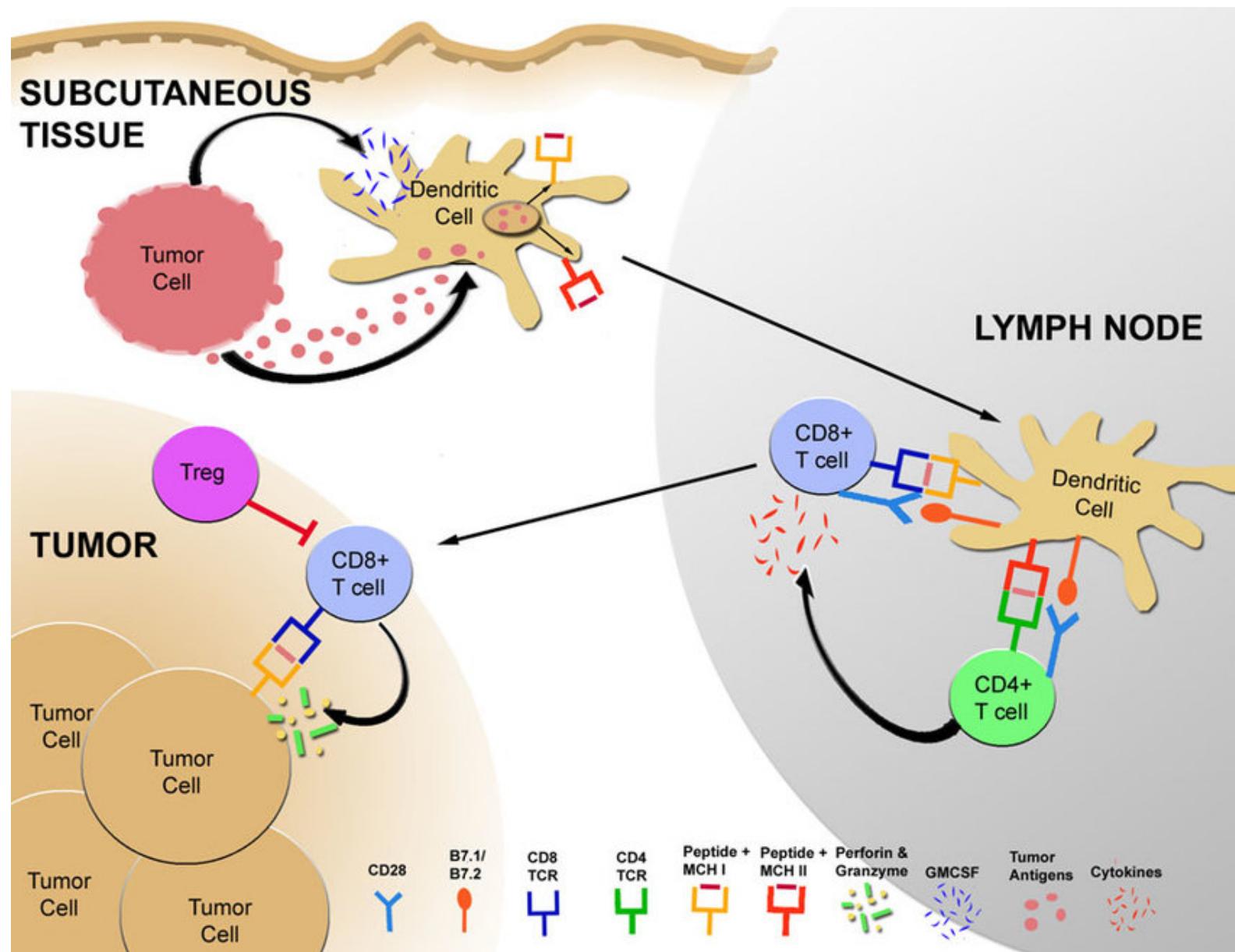


Pathogen Associated Molecular Patterns
(proteins, carbohydrates, lipids, nucleic acids)

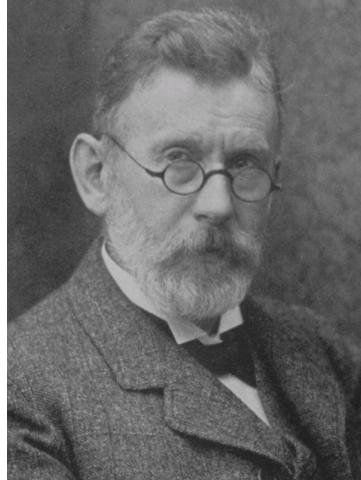
Adaptive Immunity



Pathogen phagocytosis
and elimination

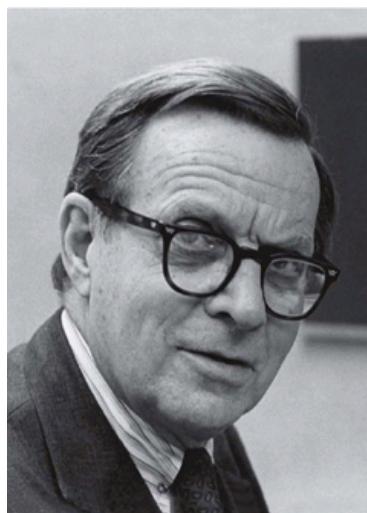


Historical Perspective



1909: Paul Ehrlich proposes concept of immunosurveillance

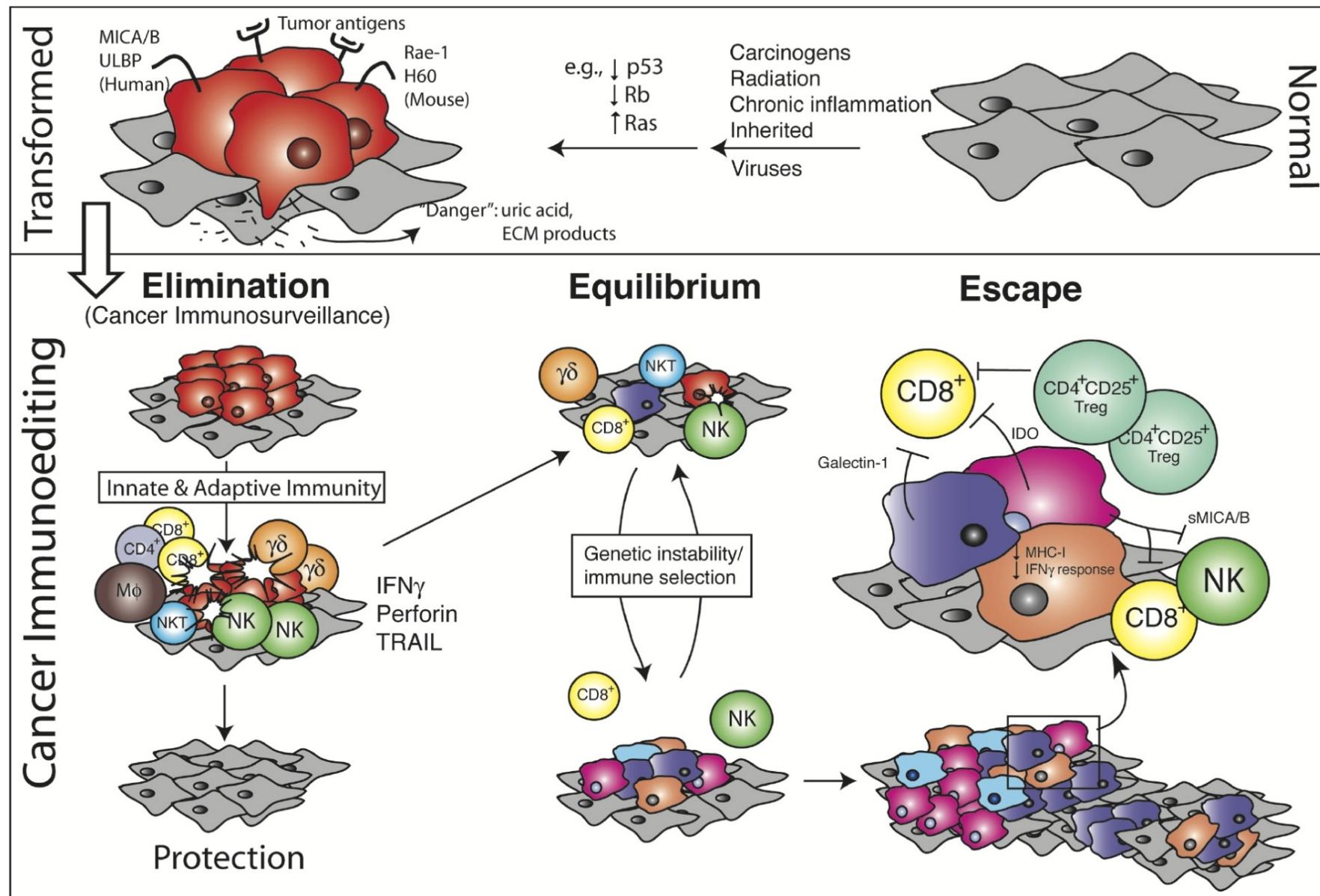
Ehrlich P. Ueber den jetzigen stand der karzinomforschung. Ned Tijdschr Geneeskd 1909; 5:273-290.



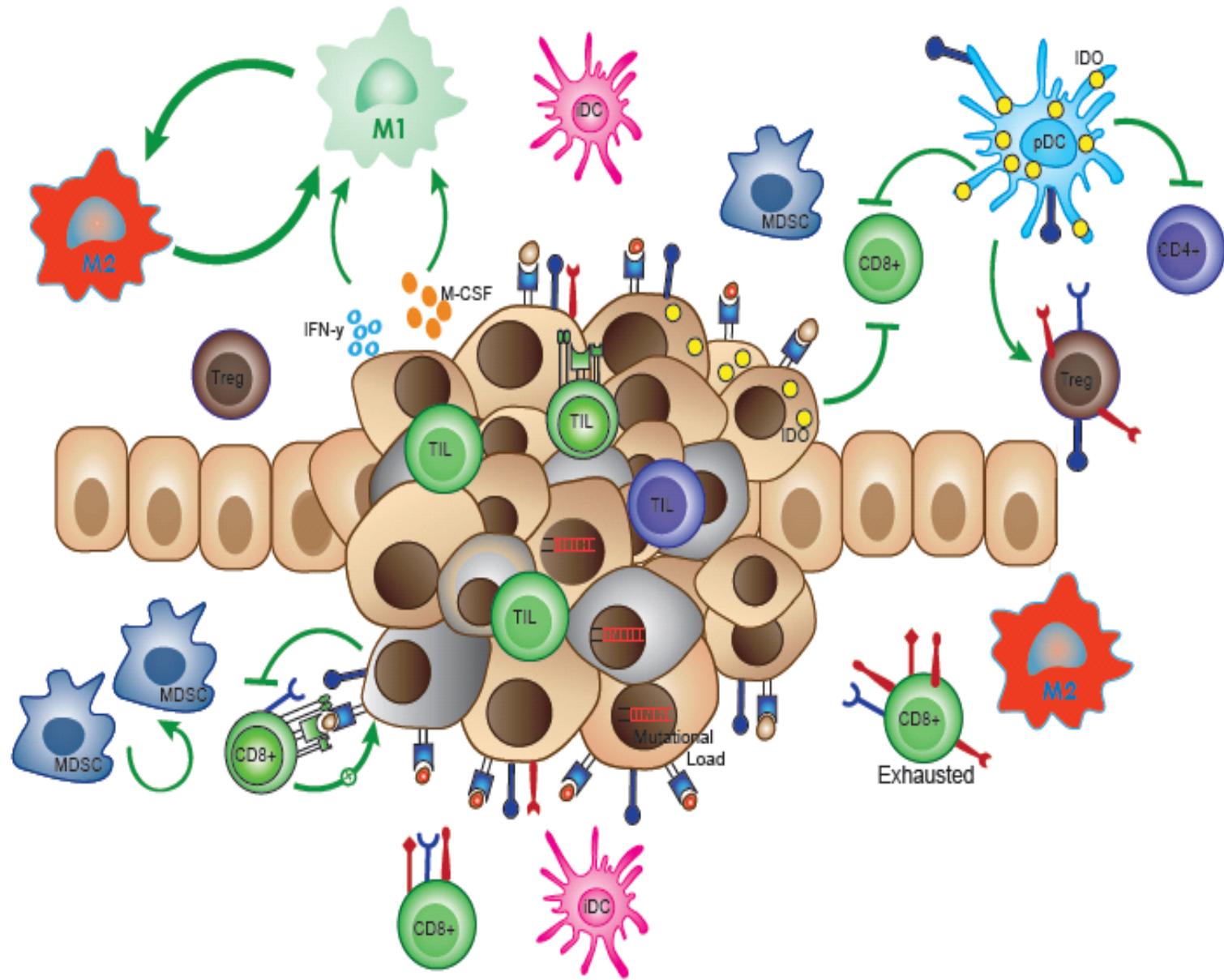
1950's-1980's: Lewis Thomas proposes that the transplant rejection is actually a manifestation of immunosurveillance.

Thomas L. On immunosurveillance in human cancer. Yale J. Biol. Med. 1982; 55:329-333

Immunoediting



- Dunn et al. *Immunity* 2004 (21) 137-148



Timeline of the Development of Immunotherapy

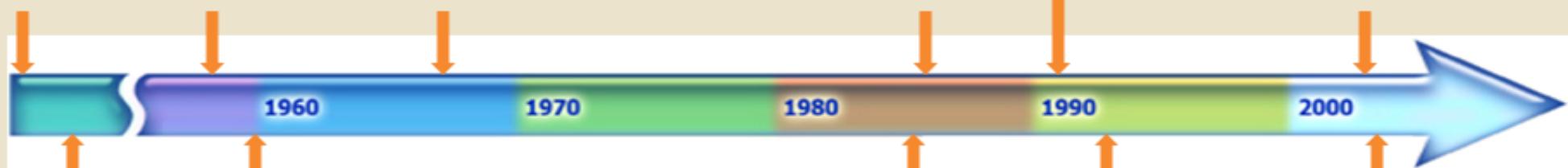
1891
First cancer "vaccine" demonstrated (Coley bacterial toxin)

1960s
Adjuvants (eg, BCG) shown to eradicate some tumors

1986
IFN α approved as cancer immunotherapy

1990
BCG approved for bladder cancer

2010
Sipuleucel-T approved as first autologous cellular immunotherapy



1909
Cancer occurs spontaneously; immune system recognizes and protects (Elrich)

Late 1950s
Immunosurveillance theory introduced (Thomas, Burnet)

1985
Adoptive immunotherapy for patients with cancer

1992
IL-2 approved as cancer immunotherapy

2011
Ipilimumab approved for metastatic melanoma

BCG = Bacille Calmette-Guérin

IFN = interferon

IL = interleukin

TIL = tumor-infiltrating lymphocyte

Coley WB. Ann Surg. 1891;14:199–220.

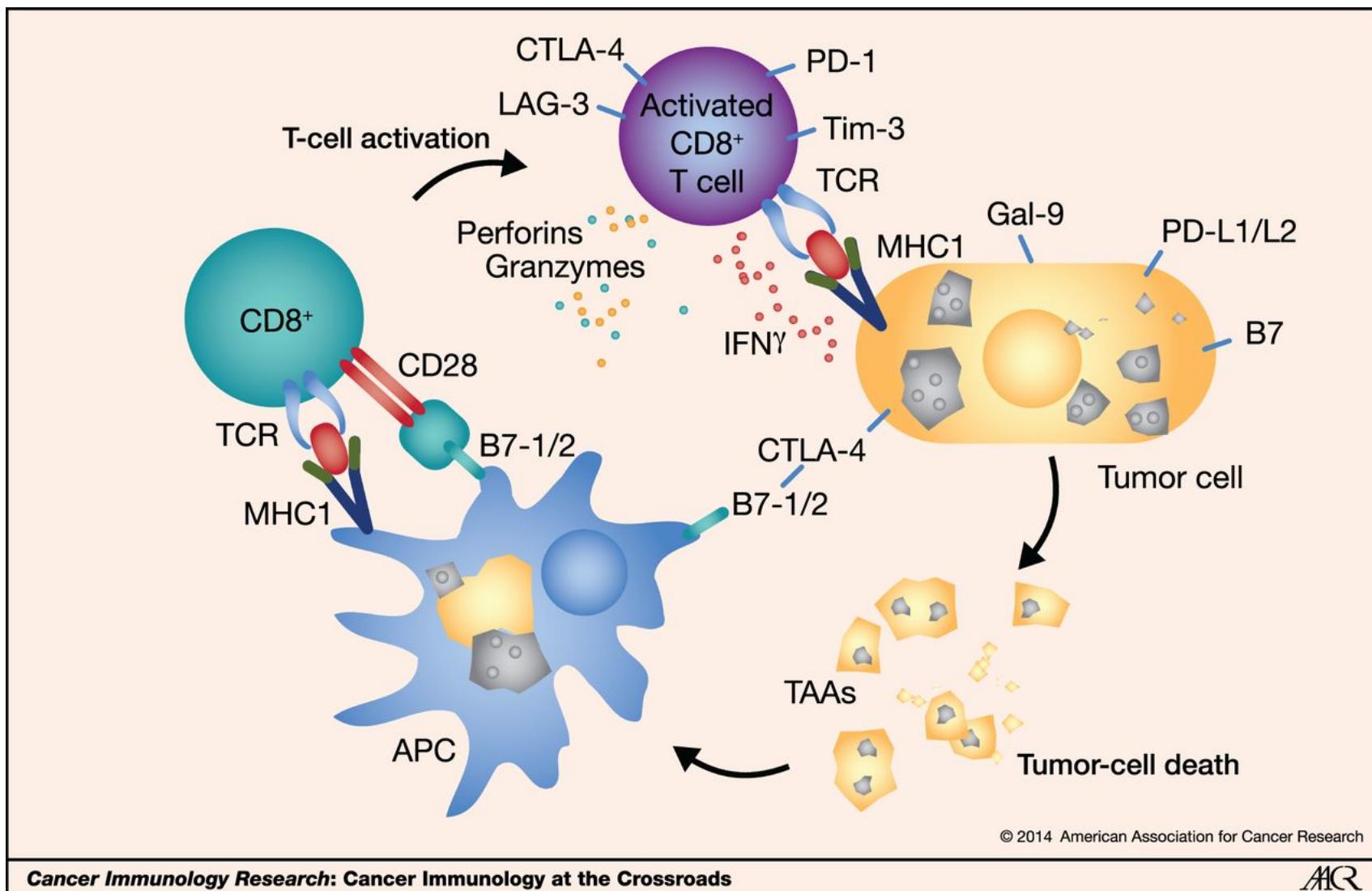
Kim CJ et al. *Cancer Control*. 2002;9:22-30.

Dudley ME et al. *Science*. 2002;298:850-854.

Nature Milestones Cancer 2006; S7-S23.

Cancer: Principles and Practice of Oncology. 9th ed. 2011.

Complex interplay between the host immune cells and the tumor and its microenvironment.



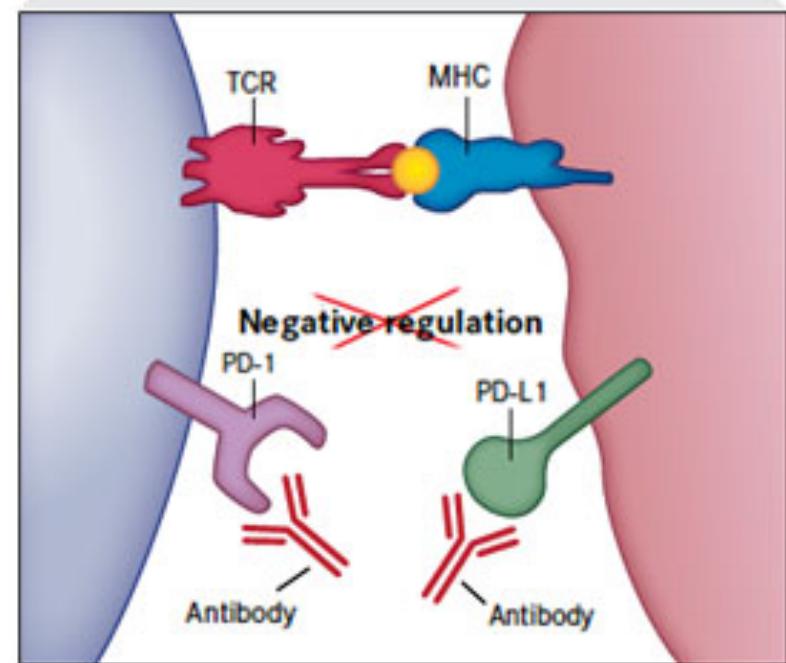
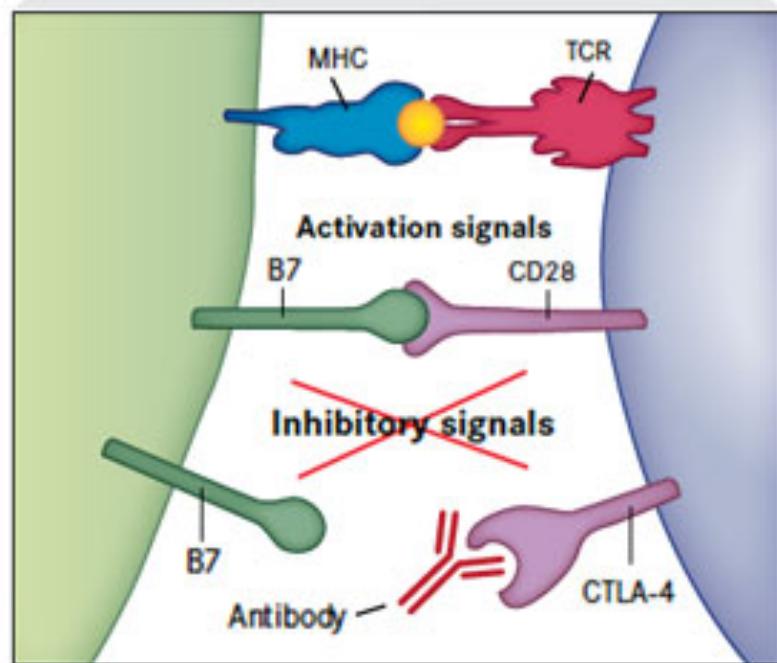
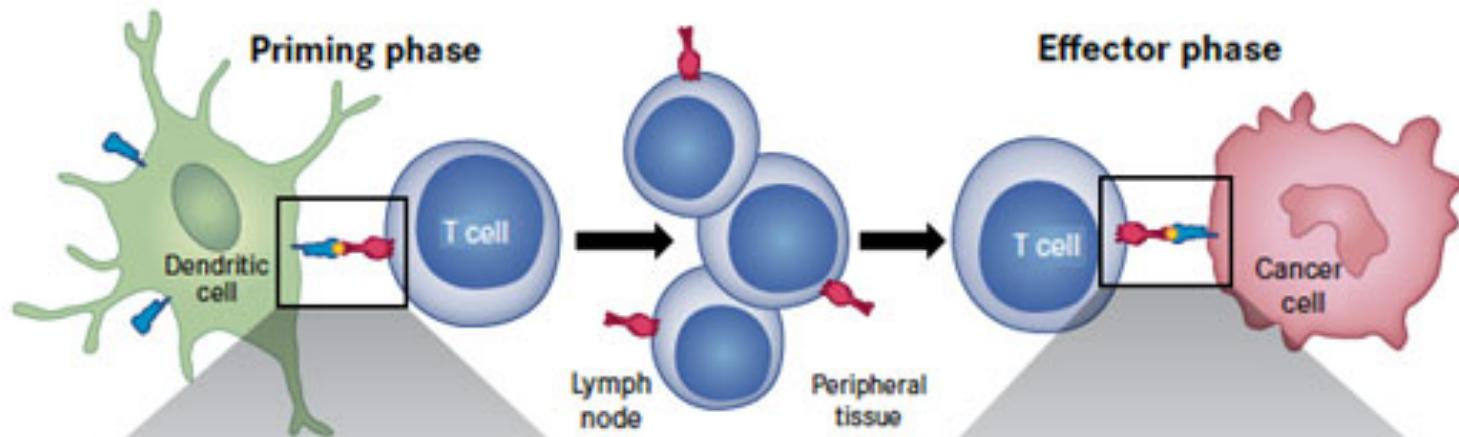
Cancer Immunology Research: Cancer Immunology at the Crossroads

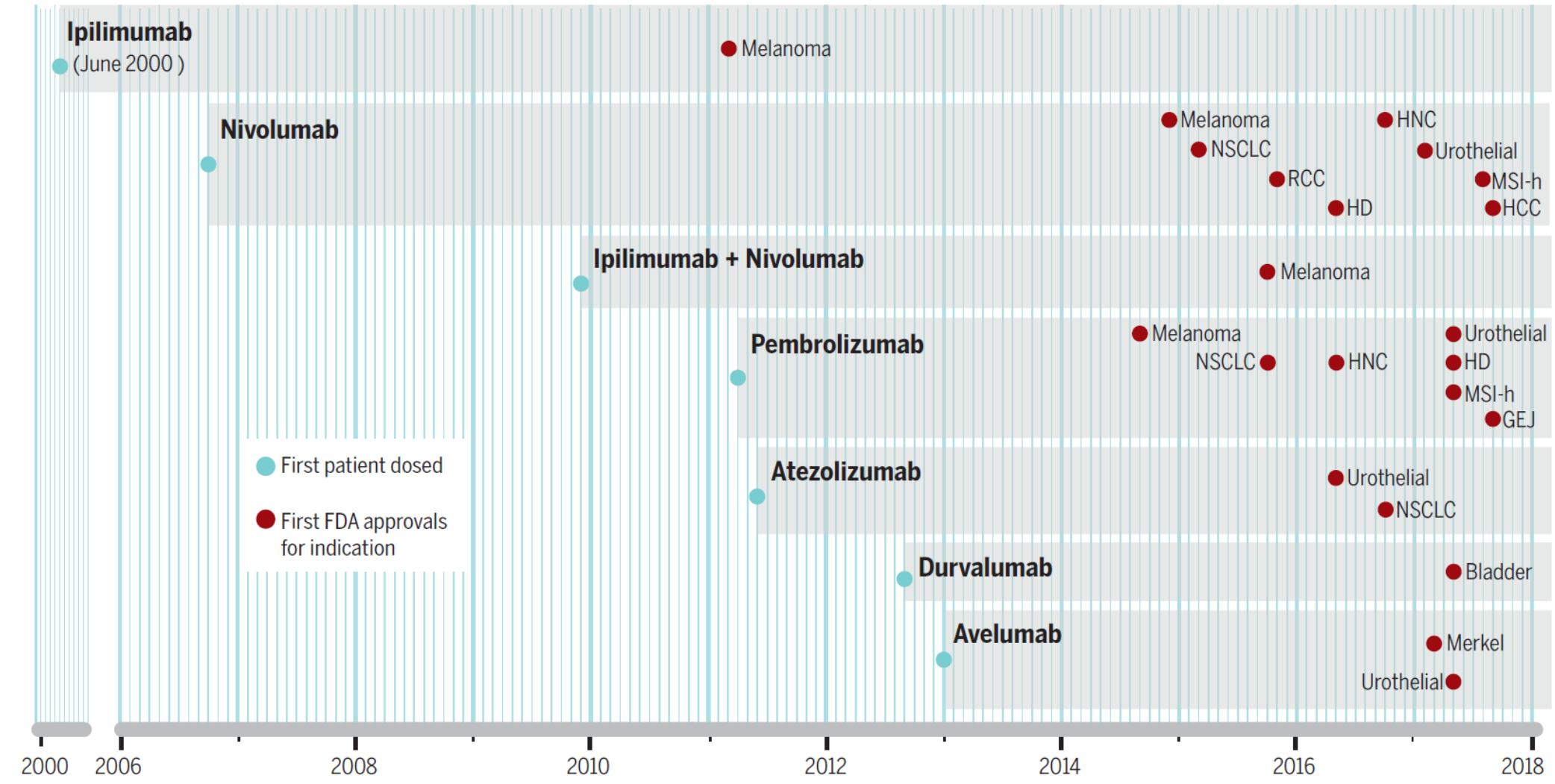


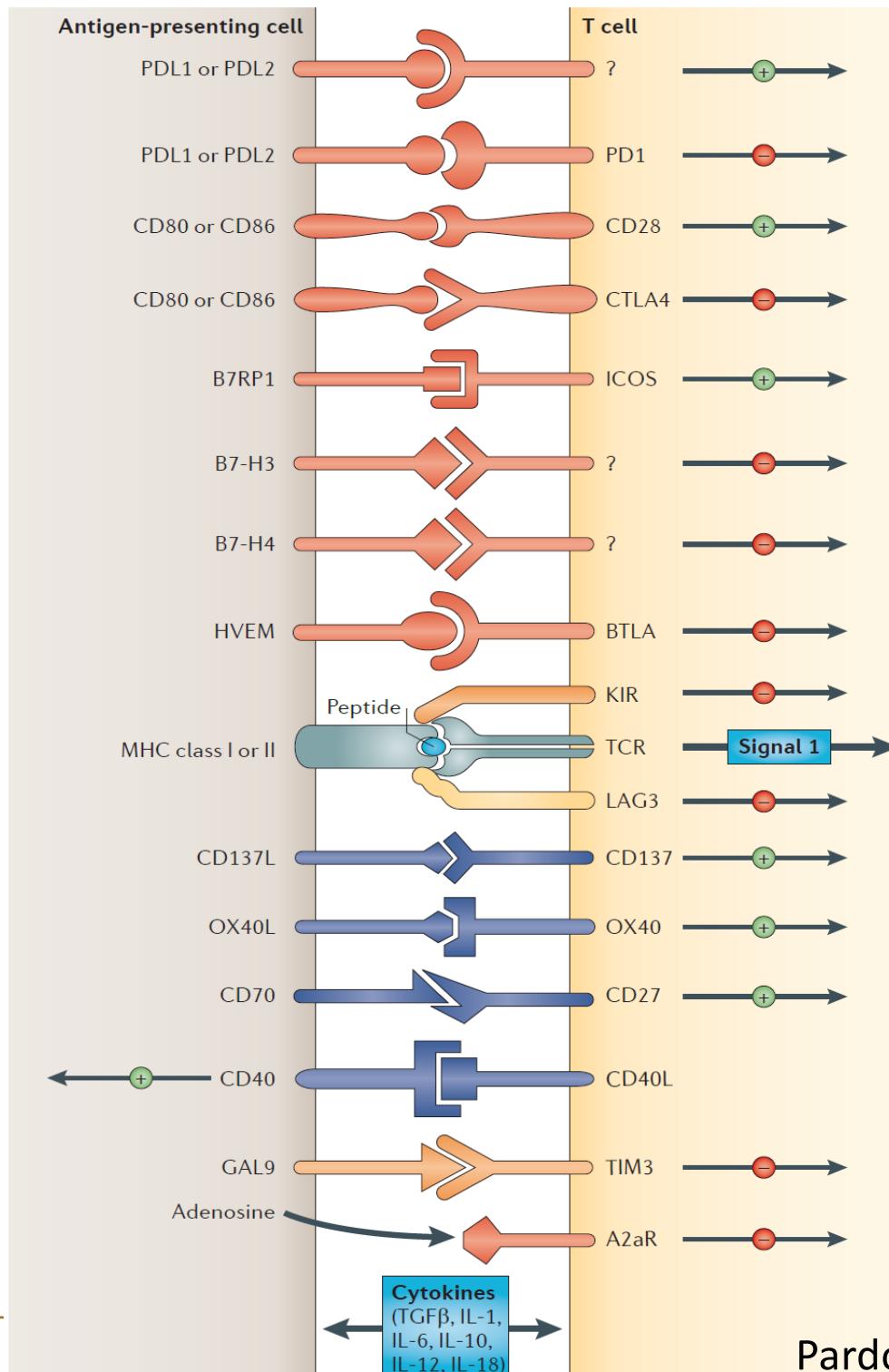
Lauren C. Harshman et al. Cancer Immunol Res
2014;2:1132-1141

Cancer
Immunology Research

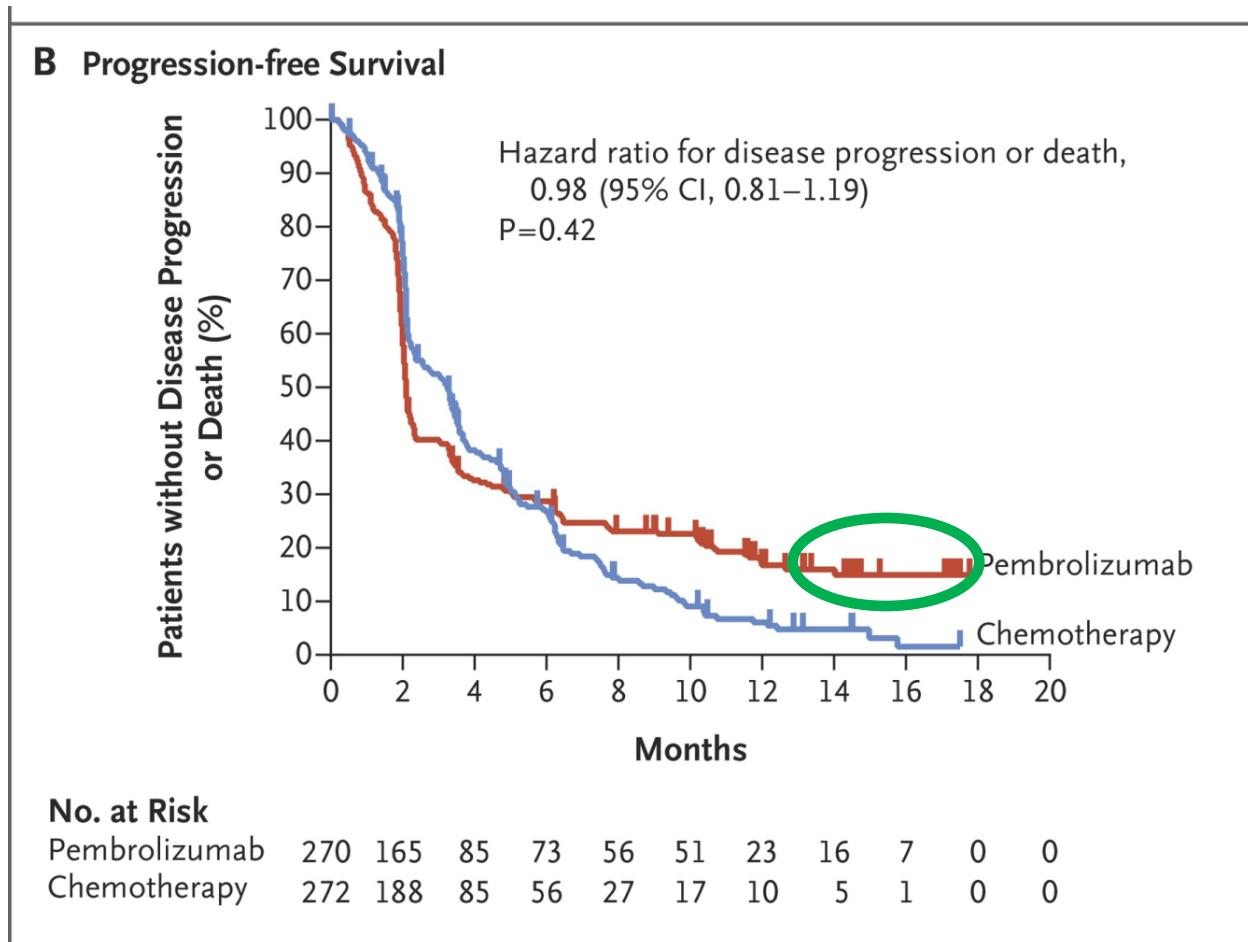
AACR American Association
for Cancer Research



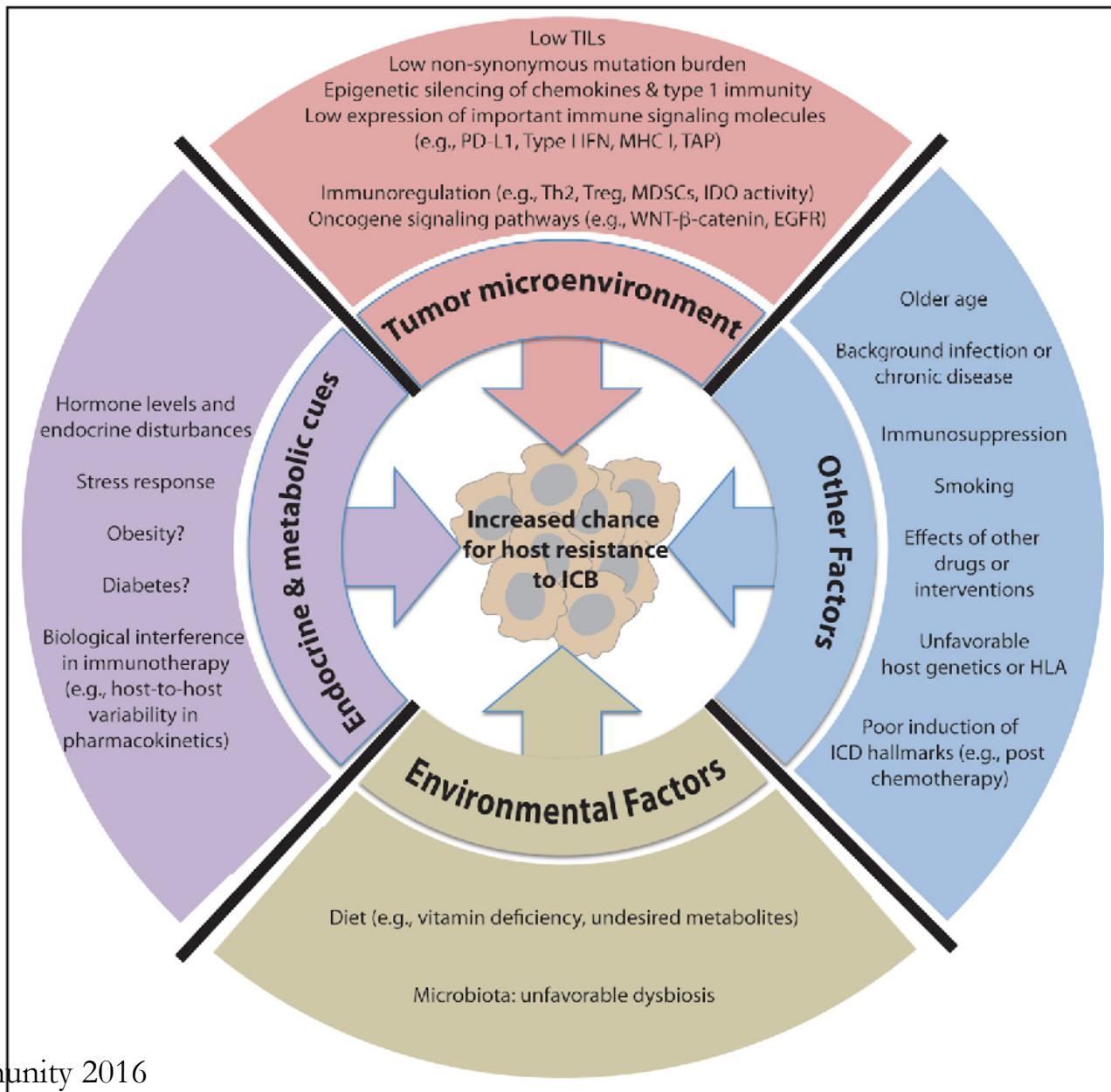




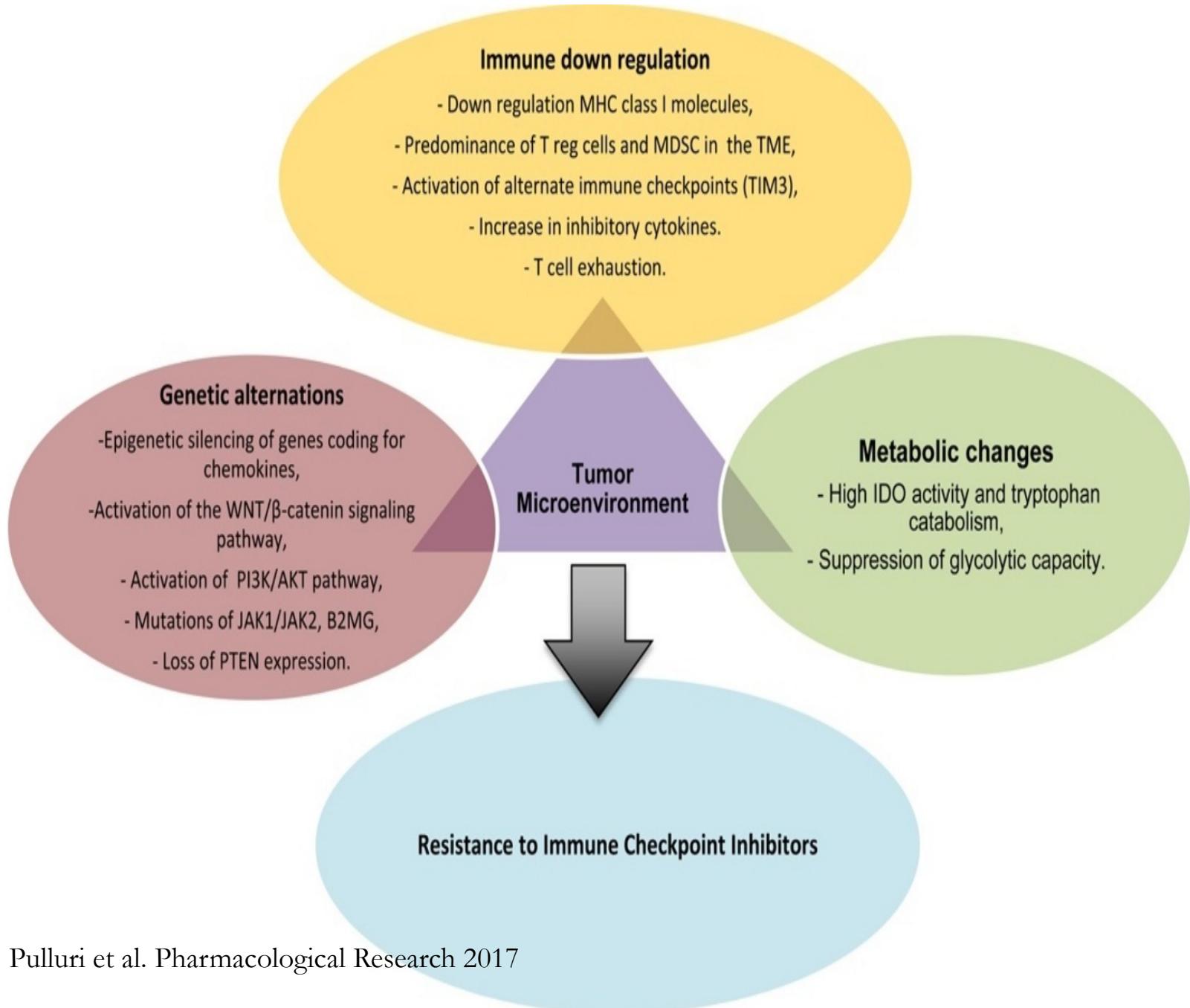
ONLY A MINORITY OF PATIENTS RESPOND TO TREATMENT



WE CAN CURE CANCERS PREVIOUSLY THOUGHT TO BE INCURABLE

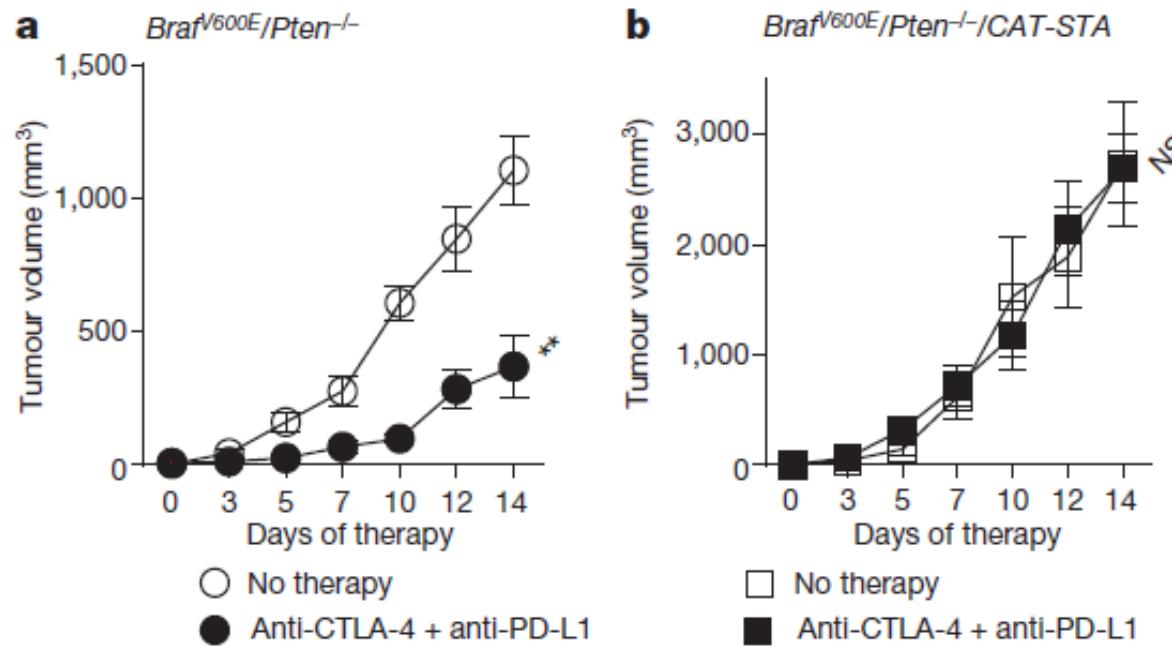
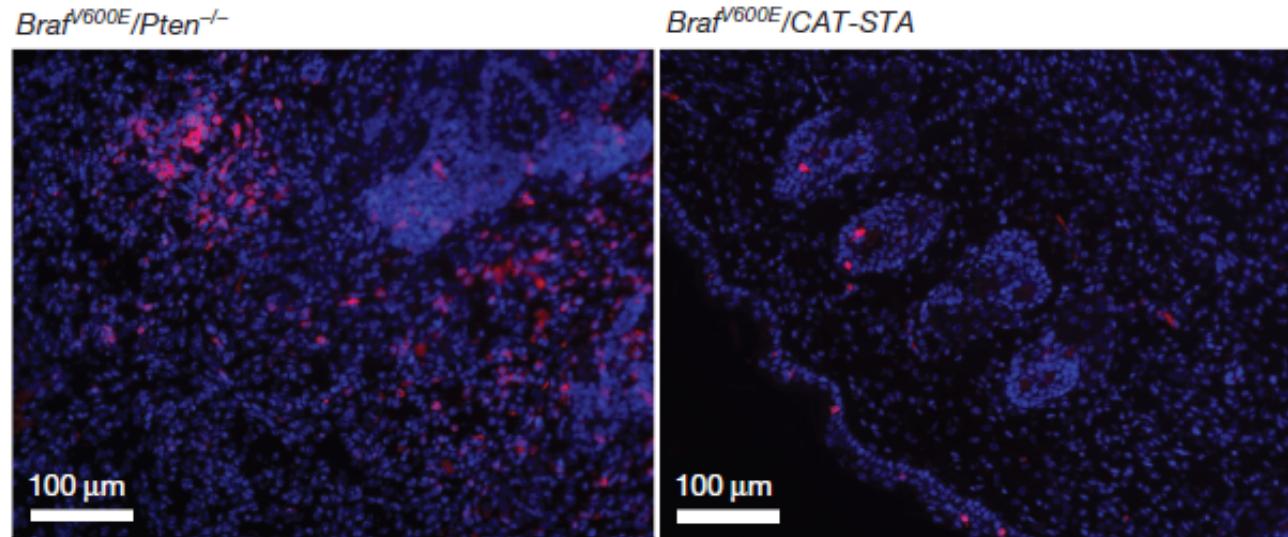


- Pitt et al. *Immunity* 2016

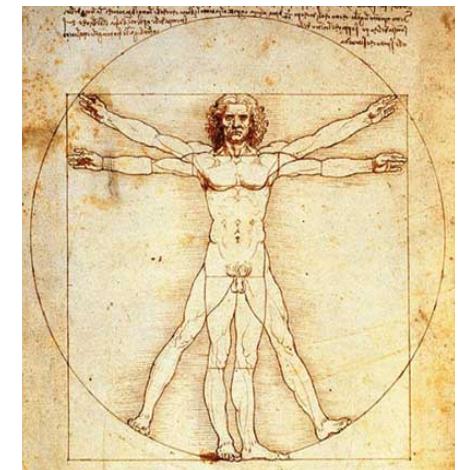
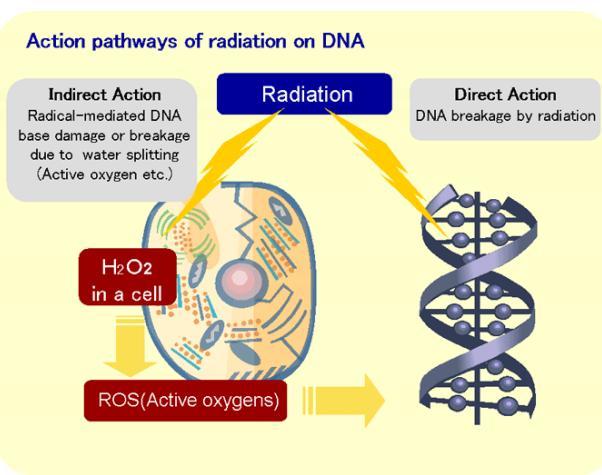
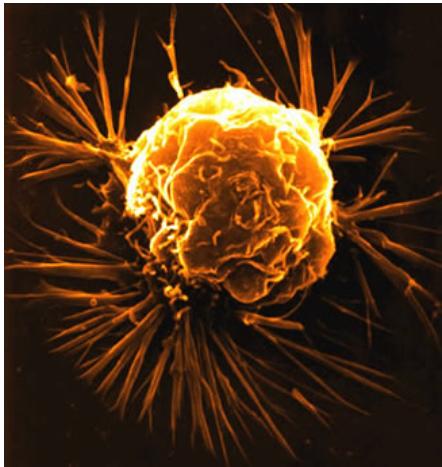


- Pulluri et al. Pharmacological Research 2017

Exclusion of Tumor Infiltrating T-cells is a mechanism of resistance to checkpoint blockade



Radiation: beyond cytotoxicity



Not convinced?

.... Two Case Reports of accidental irradiation, circa 1962

- Dayton, Ohio



- Forest Hills, New York



Immunomodulatory Effects of Radiotherapy

Tumor debulking and releasing tumor antigens

Not systemically immunosuppressive

Up regulation of immunogenic cell surface markers

- ICAM-1
- MHC-1
- Fas

Chakraborty et al. *J Immunol.* 2003; 170: 6338

Formenti et al. *Lancet Oncology.* 2009; 10: 718

Chakraborty et al. *J Immunol.* 2003; 170: 6338

Secretion of danger signals & cytokines

- IFN - g
- TNFa
- IL-1b

Lugade et al. *J Immunol.* 2008 180: 3132

Formenti et al. *Lancet Oncology.* 2009; 10: 718

Formenti et al. *Lancet Oncology.* 2009; 10: 718

Induction of Immunogenic cell death

- Calreticulin
- HMGB-1

Obeid et al. *CDD.* 2007; 18: 1848

Apetoh et al. *Nature Medicine.* 2007; 13(9): 1050

Increased homing of immune cells to tumors

- Normalization of tumor vasculature
- Secretion of chemo-attractants (cxcl16)
- Endothelial expression of VCAM-1
- Improved T-cell homing to tumors

Ganss et al. *Ca Research.* 2002; 62: 1462

Matsumura et al. *J Immunol.* 2008; 181: 3099

Lugade et al. *J Immunol.* 2008 180: 3132

Klug et al. *Cancer Cell.* 2013;24:589-602

Improved antigen presentation by APC's

- Irradiated tumors prime dendritic cells
- Improved antigen presentation via TLR-4

Strome et al. *Ca Research.* 2002; 62: 1884

Apetoh et al. *Nature Medicine.* 2007; 13(9): 1050

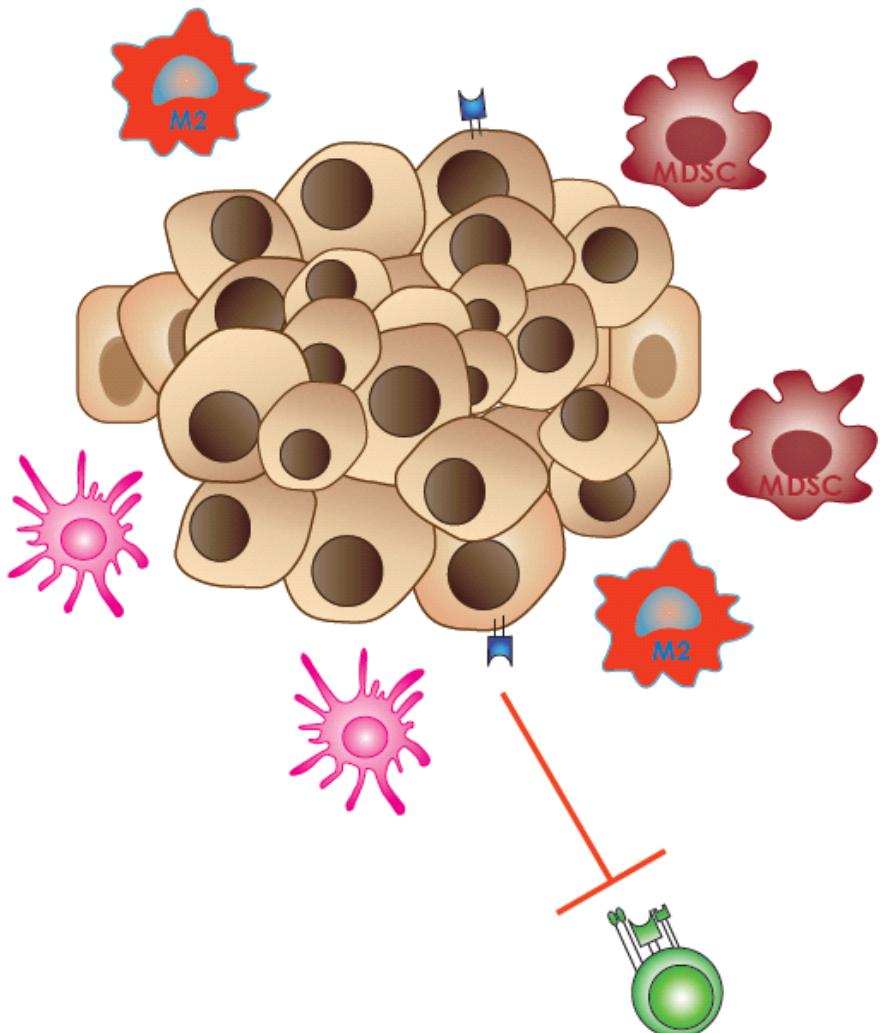
Depletion of immunosuppressive cells

Wu et al. *Clin Cancer Res.* 2014;20:644-57

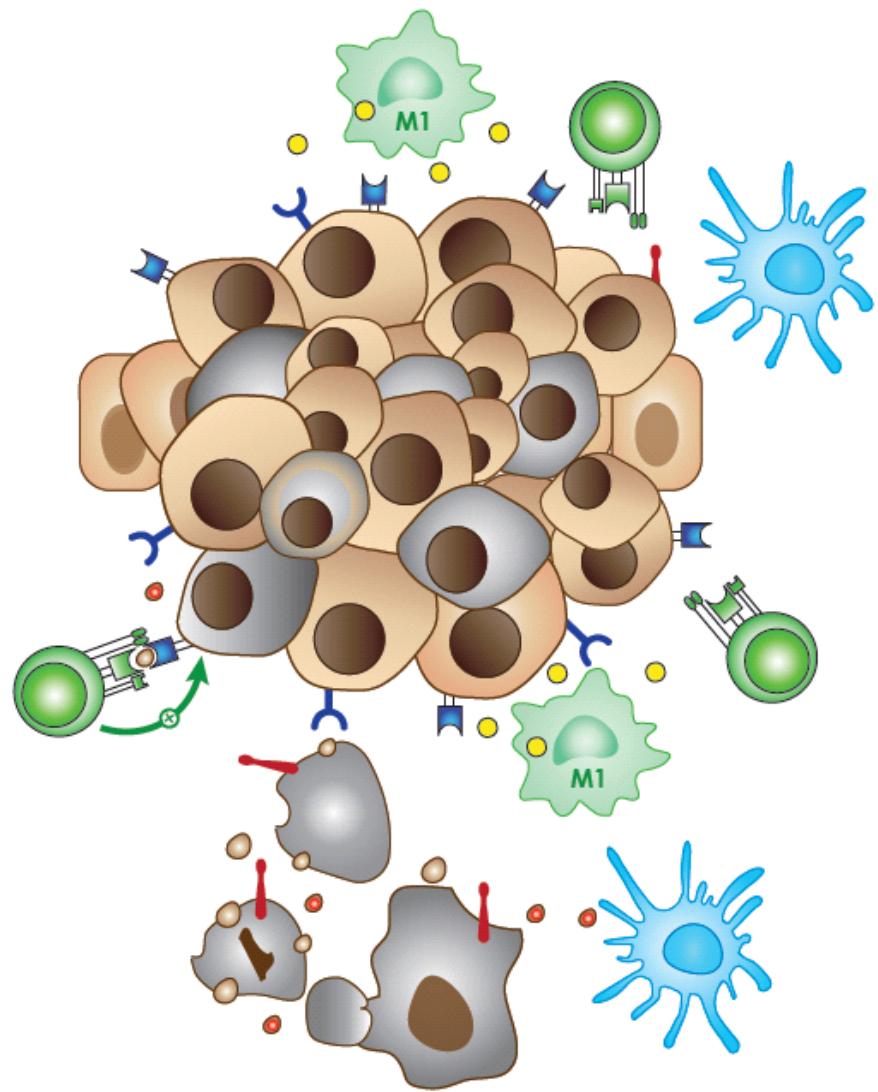
Shifting TAM polarization to M1

Klug et al. *Cancer Cell.* 2013;24:589-602

pre-radiotherapy



post-radiotherapy



tumor cell



dead tumor cell



immature
dendritic cell



dendritic cell



M2
macrophage



M1
macrophage



myeloid derived
suppressor cell



Cytotoxic
T lymphocyte



PD-L1



HMGB1



MHC I

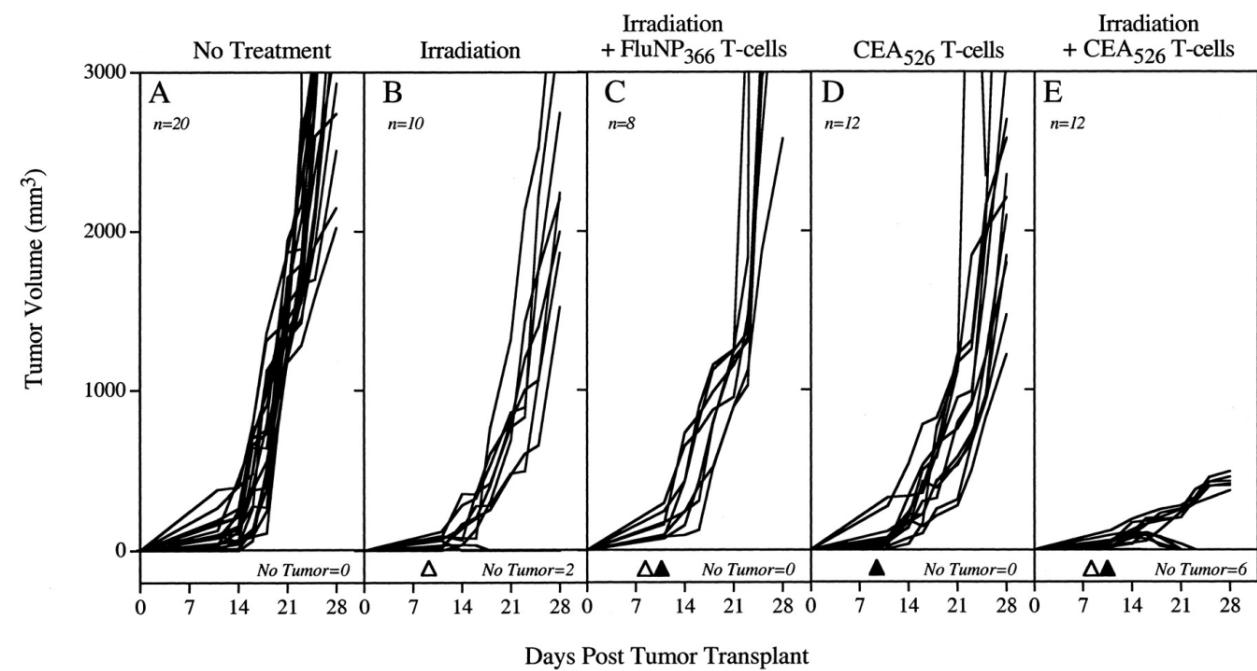
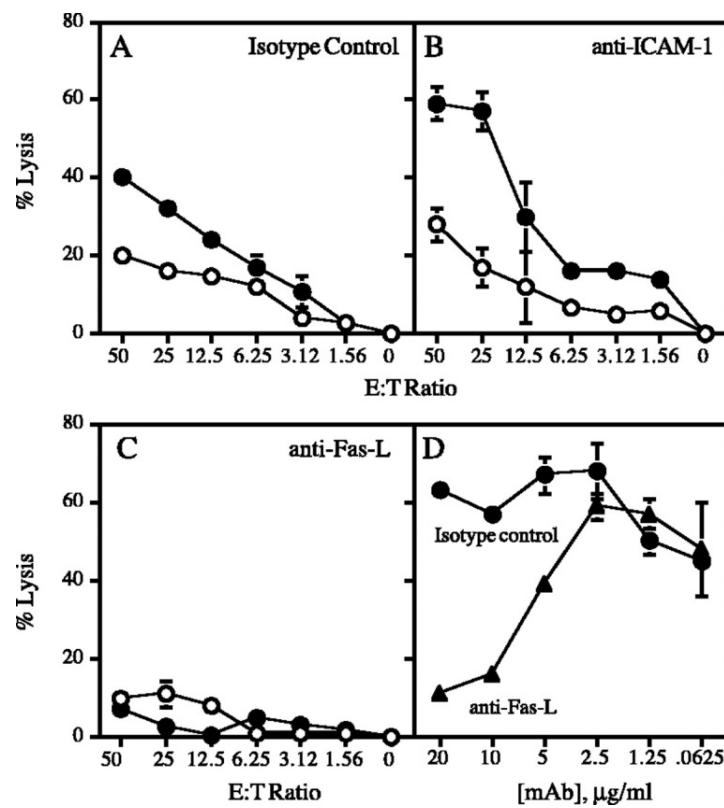
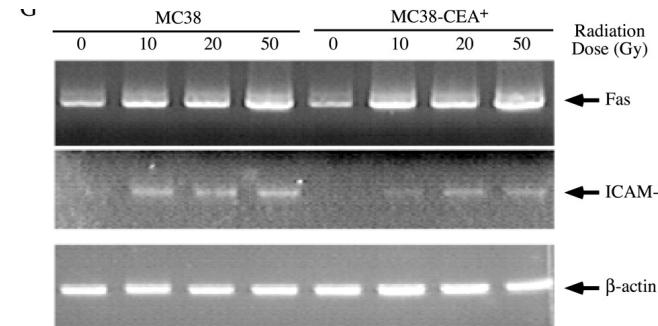
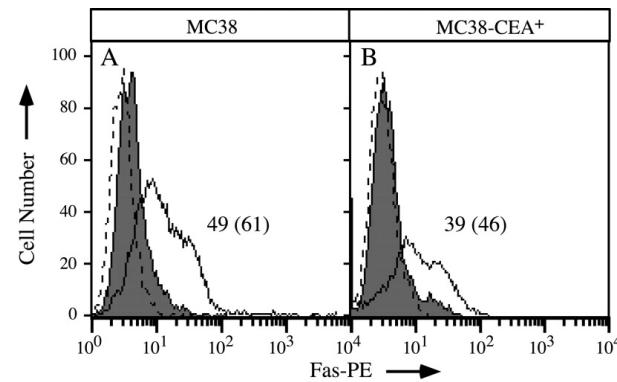


calreticulin

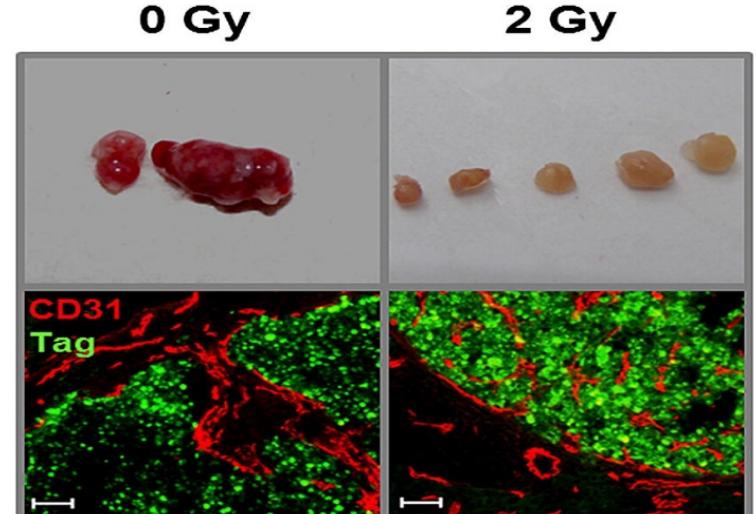
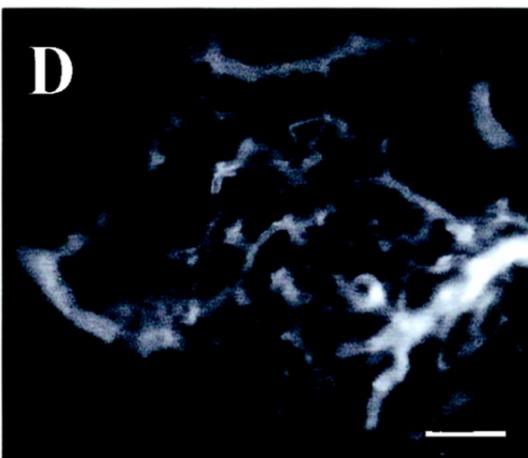
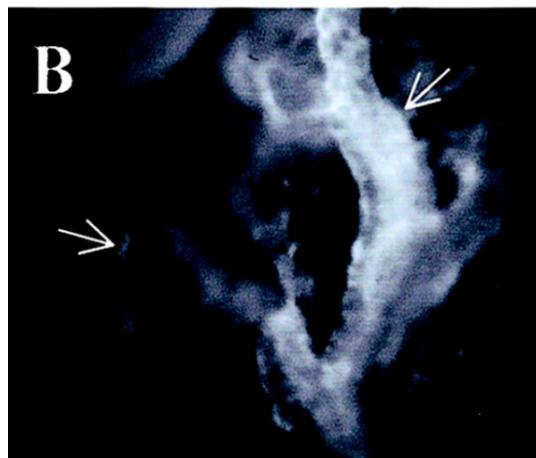


TNF alpha

Upregulation of Immunogenic Cell Surface Markers



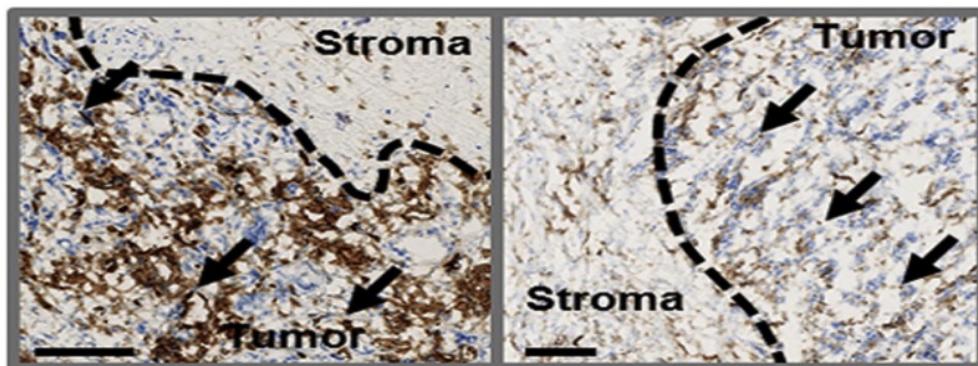
Normalization of Tumor Vasculature



C Vessel phenotype

non-irradiated

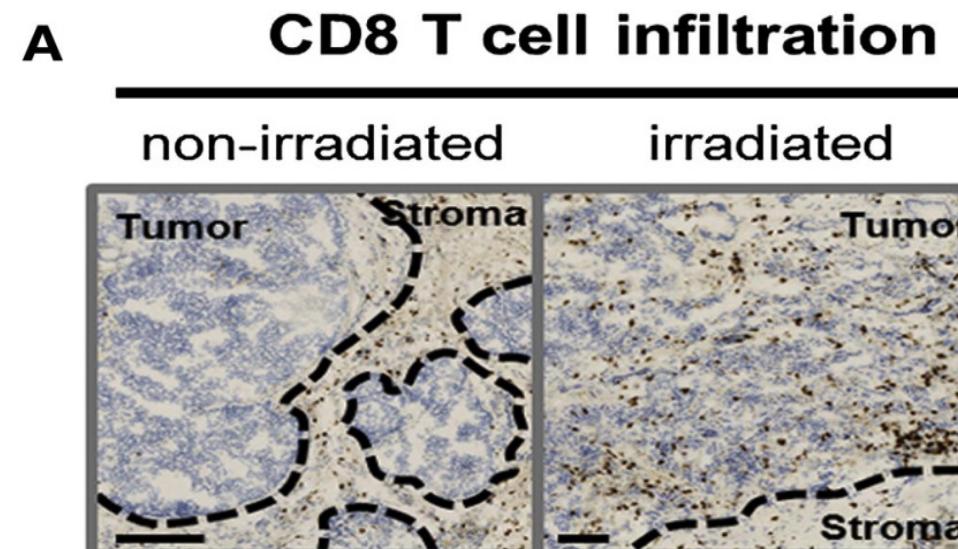
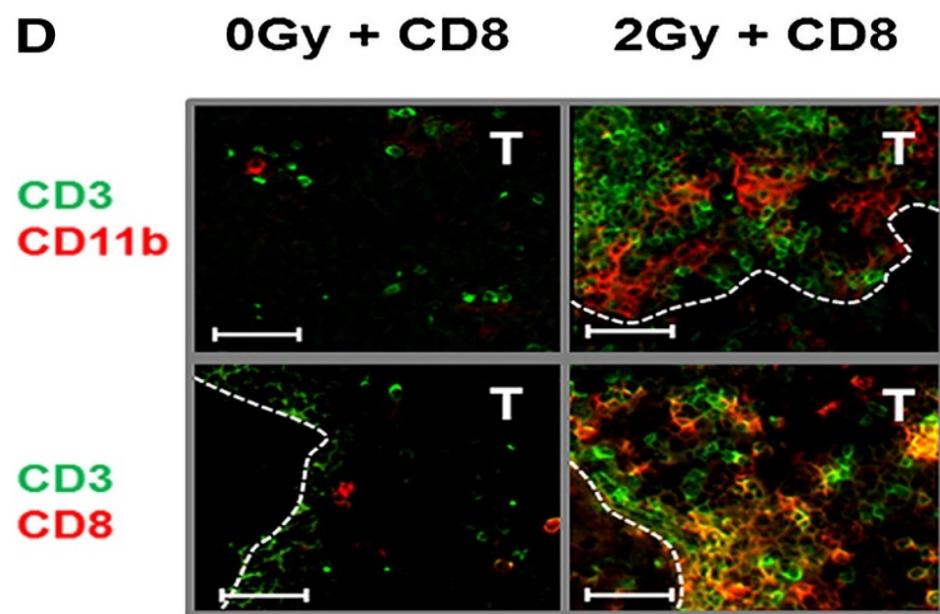
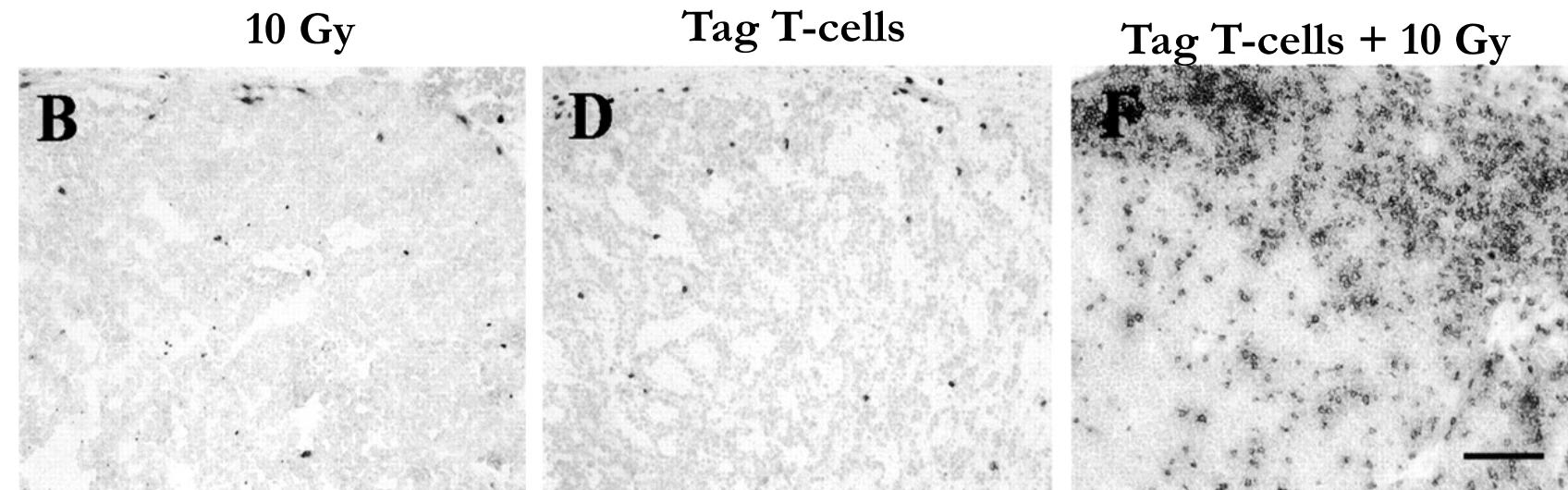
irradiated



Ganss et al. *Ca Research.* 2002; 62: 1462

Klug et al. *Cancer Cell.* 2013;24:589-602

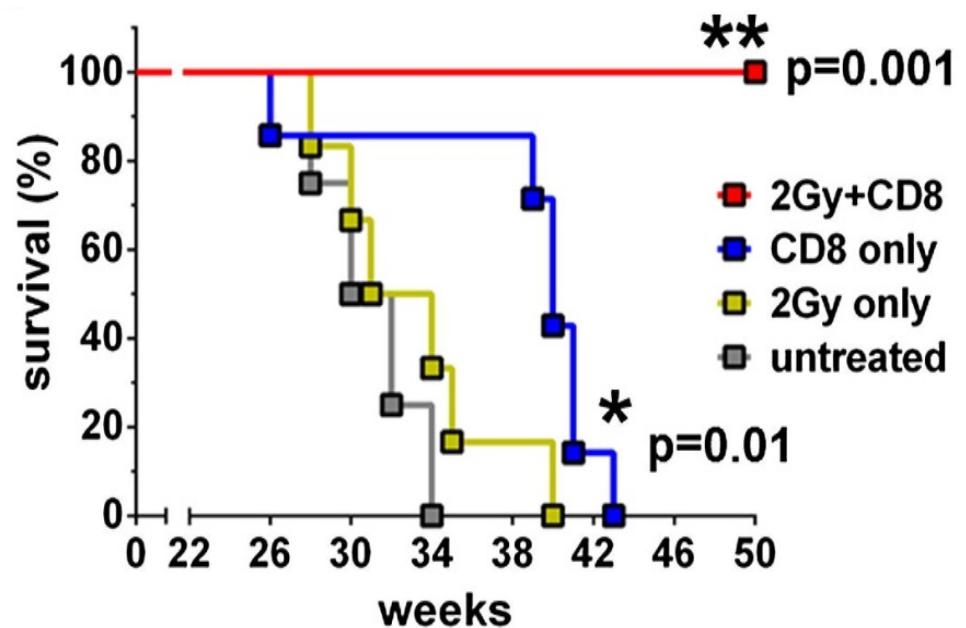
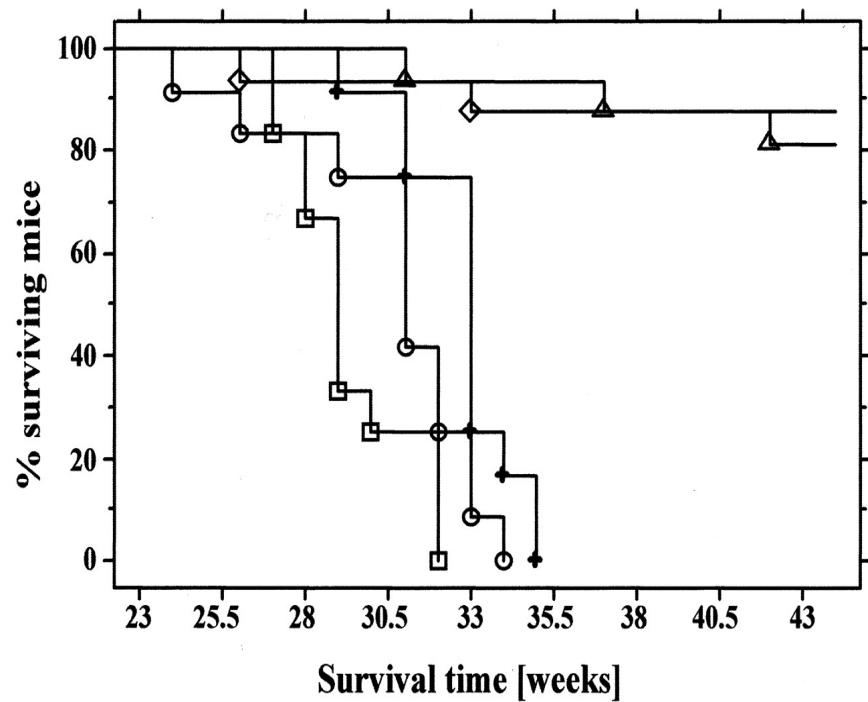
Increased T-cell Infiltration



Ganss et al. *Ca Research.* 2002; 62: 1462

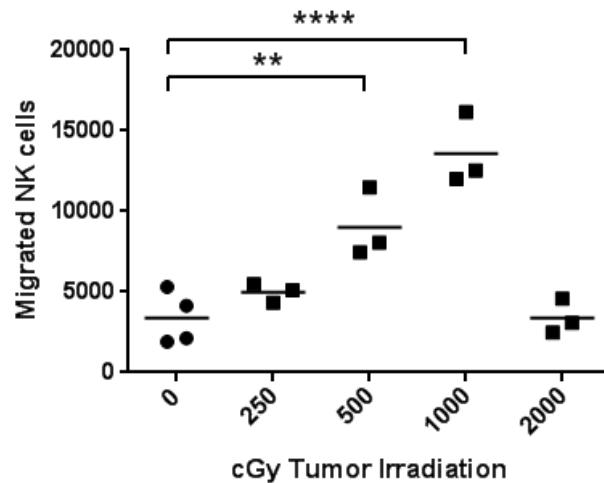
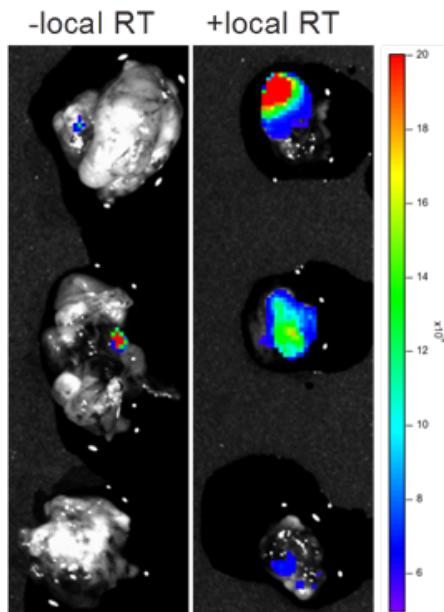
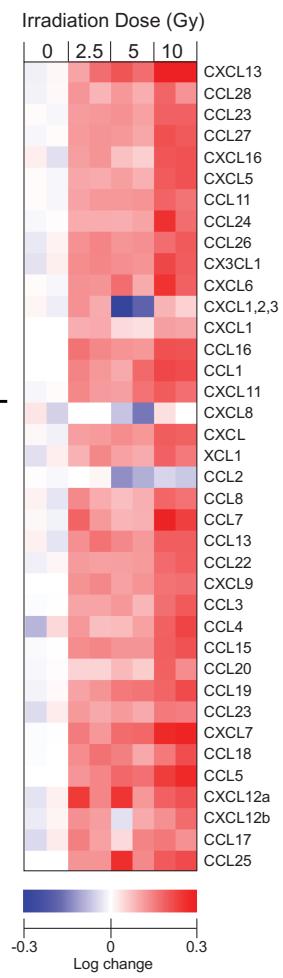
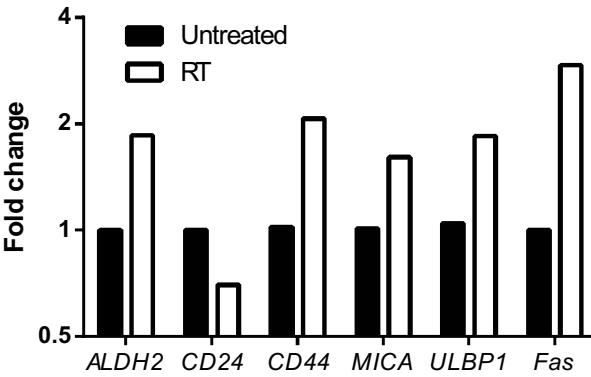
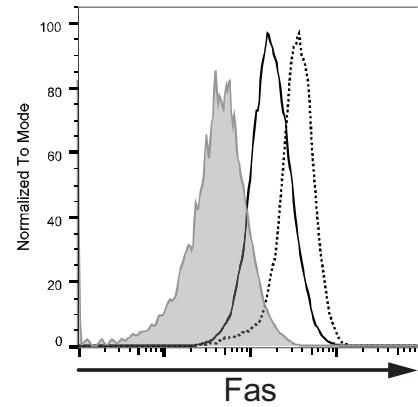
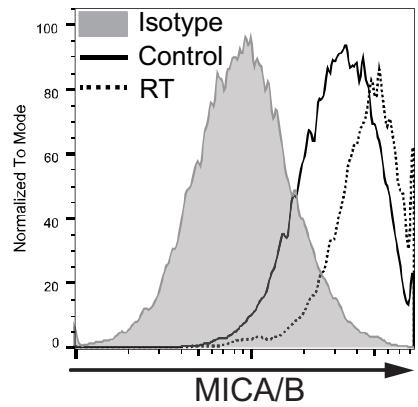
Klug et al. *Cancer Cell.* 2013;24:589-602

Improved Survival

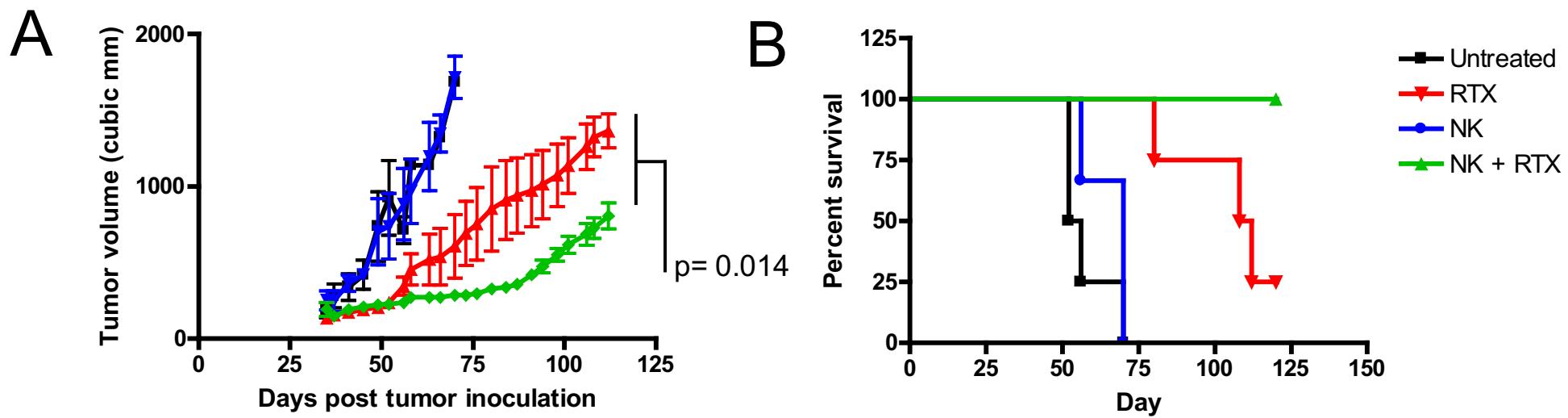


Ganss et al. *Ca Research.* 2002; 62: 1462

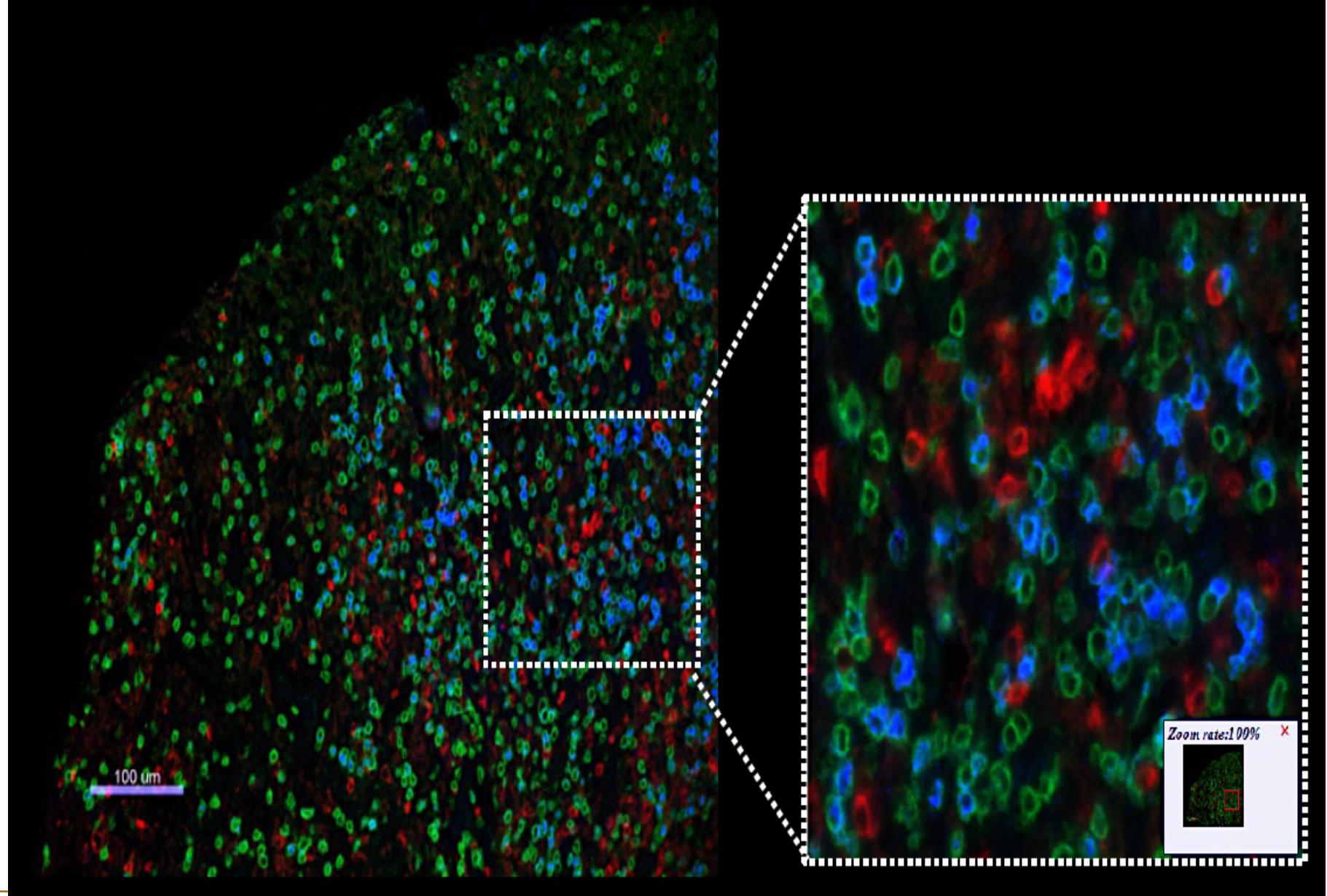
Klug et al. *Cancer Cell.* 2013;24:589-602

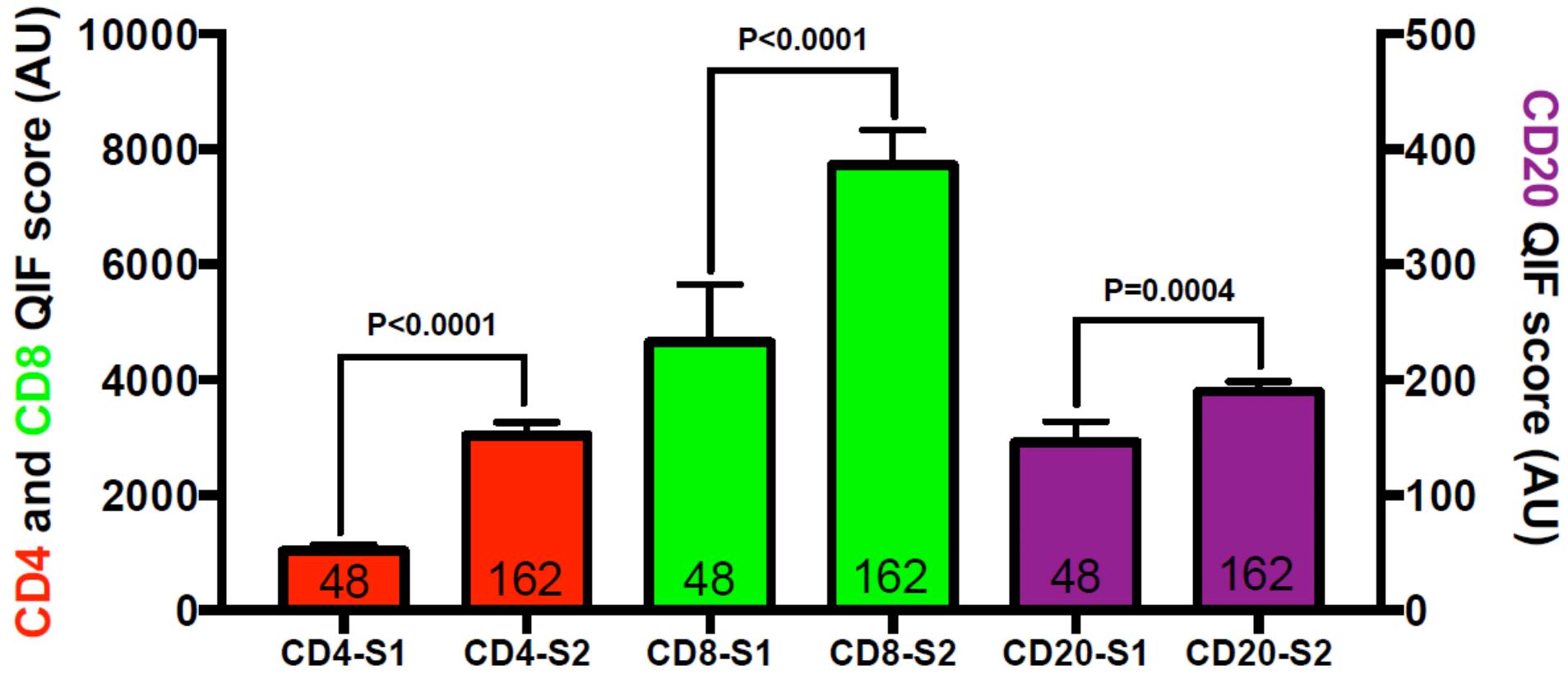


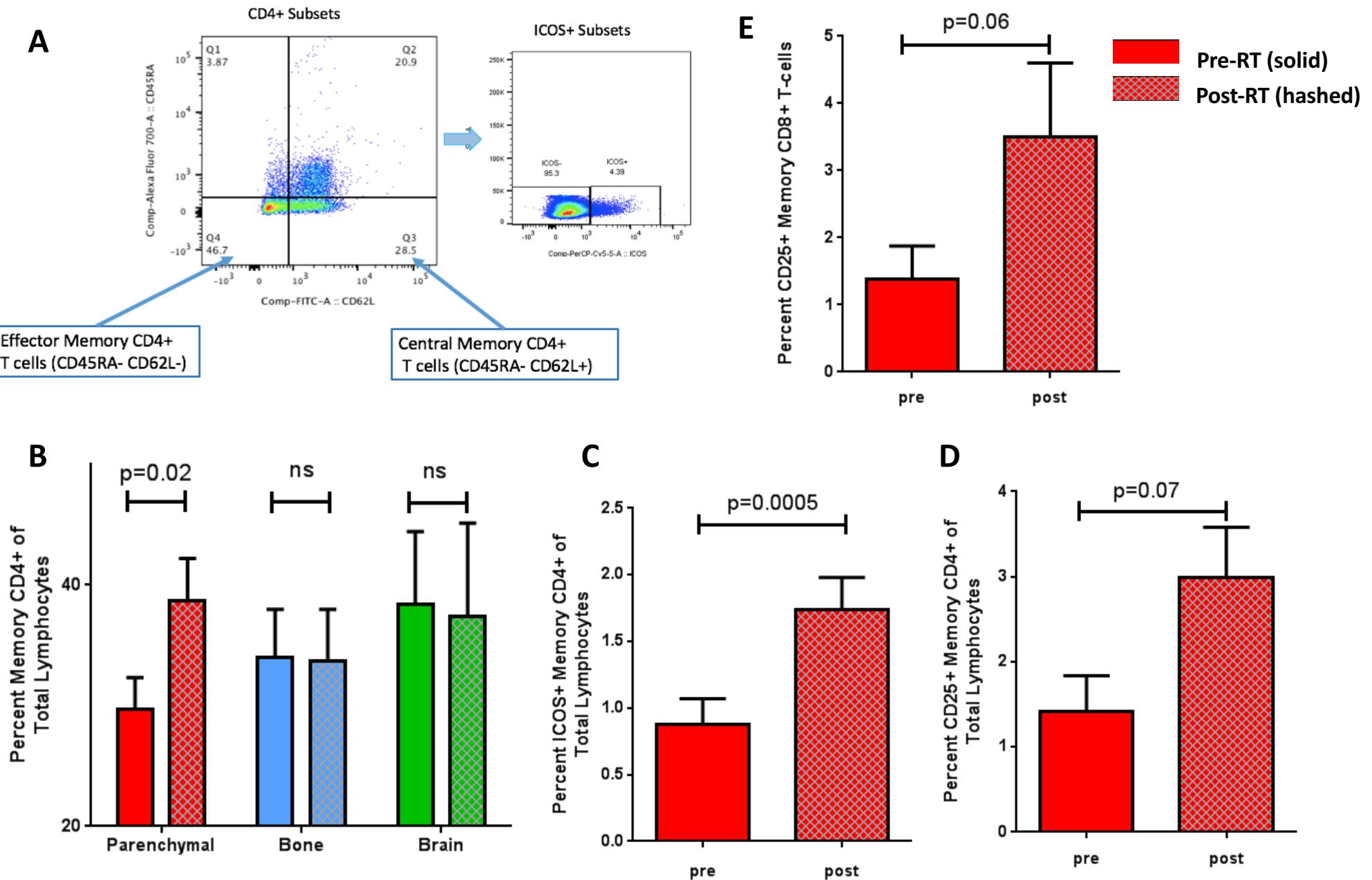
Pancreatic Tumor Progression Treated with NK cells and Local Radiation



CD4/CD8/CD20







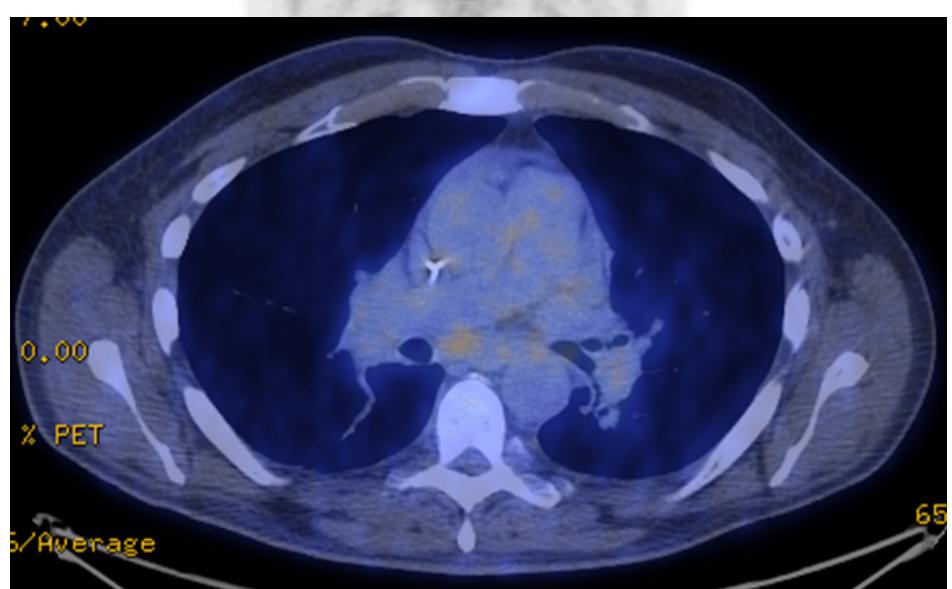
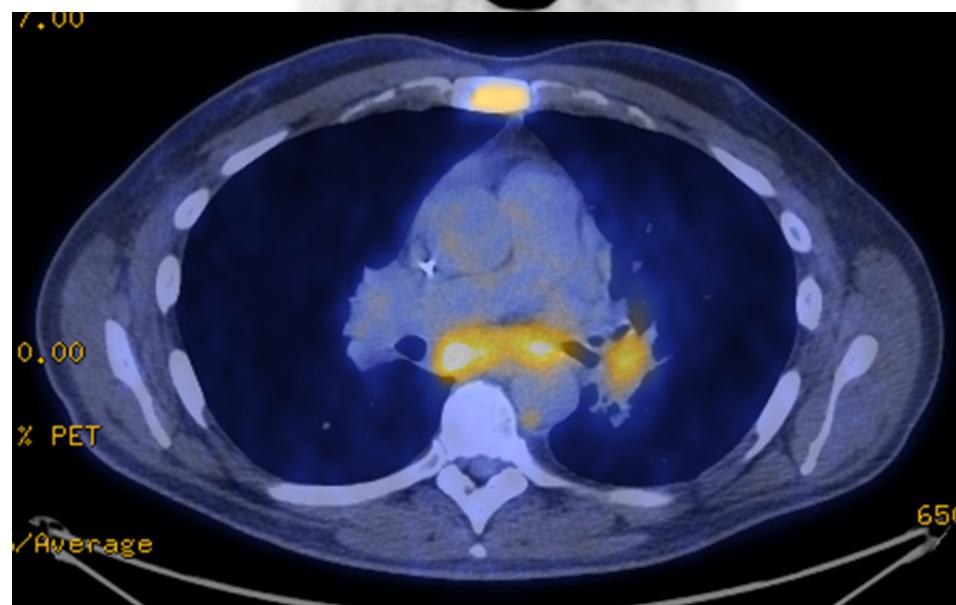
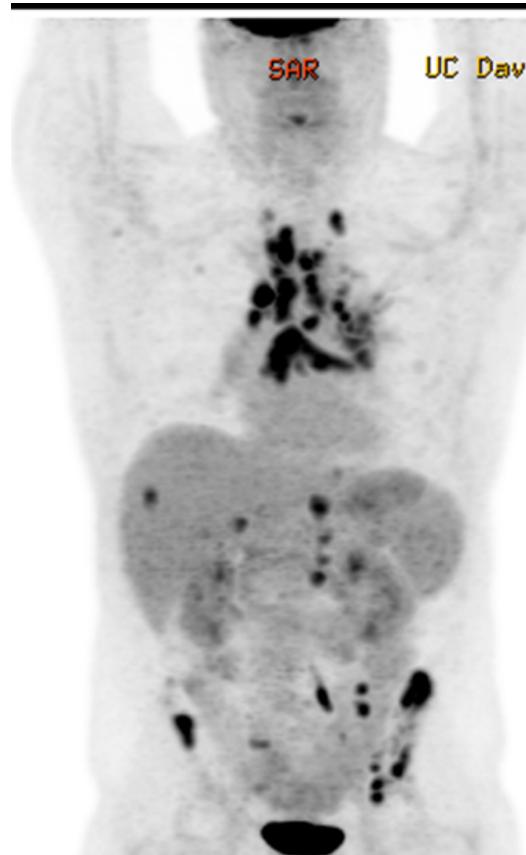
Preclinical evidence for synergy between radiation and PD-1 pathway inhibitors

Study	Model	Radiation Dose	Timing	Benefit
Deng et al. JCI 2014	TUBO (breast) MC38 (colon)	12 Gy x 1 20 Gy x 1	4 doses starting with radiation	- Tumor growth - Rechallenge - Contralateral tumor growth
Dovedi et al. Can Res 2014	4T1 (breast) CT26 (colon) 4434 (melanoma)	2 Gy x 5 or 4 Gy x 5	3qw for 3 weeks starting day 1 or day 5	- Tumor growth - Survival - Rechallenge
Sherabi et al. CIR 2014	B16 (melanoma) 4T1 (breast)	12 Gy x 1	3 injections every 3 days starting 1 day before RT	- Tumor growth - Rechallenge
Tywman-Saint Victor et al. Nature 2015	B16 (melanoma) TSA (breast) PDA (pancreatic)	20 Gy x1 8 Gy x3 20 Gy x1	3 injections every 3 days starting 3 days before or 1 day after RT	- Tumor growth - Survival - Contralateral tumor growth
Zeng et al. IJROBP 2013	GL261 (glioma)	10 Gy x 1	3 injections 2 days apart starting with RT	- Tumor growth - Survival - Rechallenge

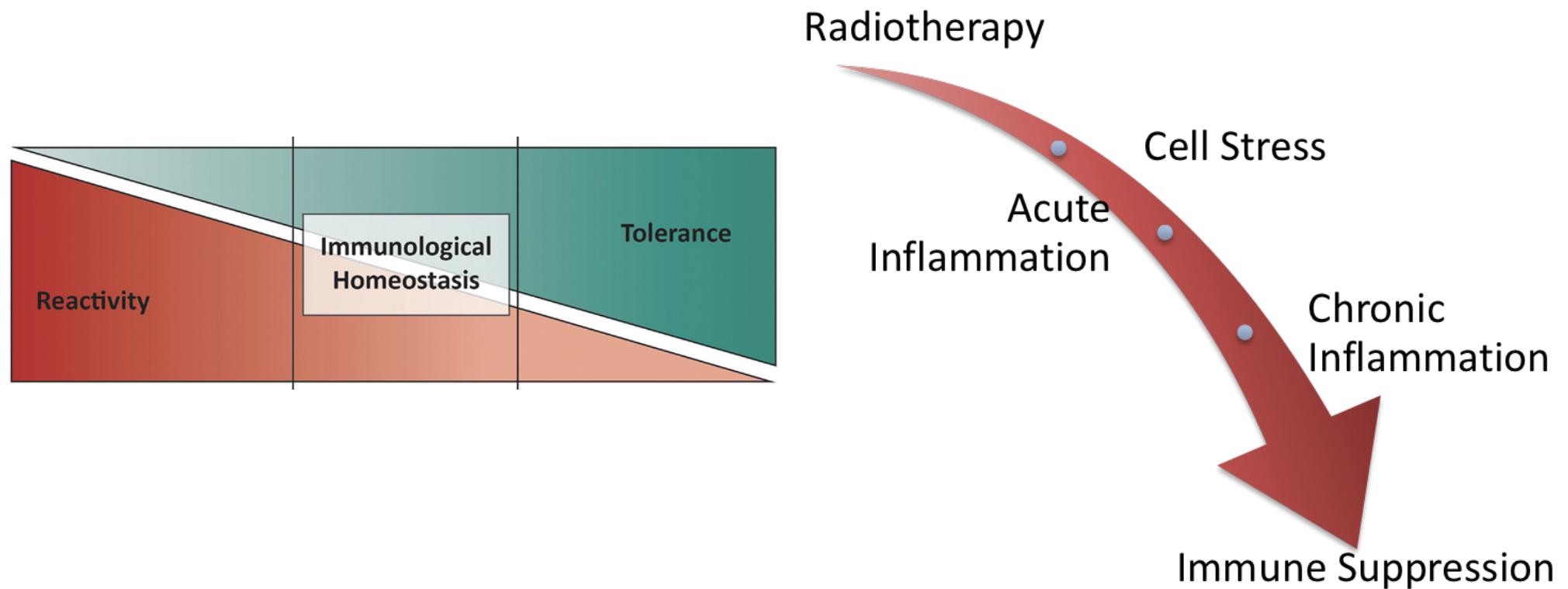
Selected trials testing PD-1 pathway inhibitors and radiation therapy

<u>Histology</u>	<u>Stage</u>	<u>Agent</u>	<u>Type of RT</u>
NSCLC	Metastatic	Pembrolizumab	SBRT or Conformal
SCLC	Limited or extensive	Pembrolizumab+ Carboplatin+Etoposide	Conformal
H&N, RCC, NSCLC Skin, Melanoma	Metastatic	Pembrolizumab	Conformal, multiple regimens
Glioma	Recurrent	Pembrolizumab+ Bevacizumab	SRT
Colorectal	Metastatic	Pembrolizumab	Unspecified
NSCLC	Metastatic	Pembrolizumab	SBRT
H&N	Localized	Pembrolizumab	Fractionated
Pancreatic cancer, Melanoma, NSCLC, breast	Metastatic	Pembrolizumab	Unspecified
Melanoma, NSCLC	Metastatic	Pembrolizumab	SBRT

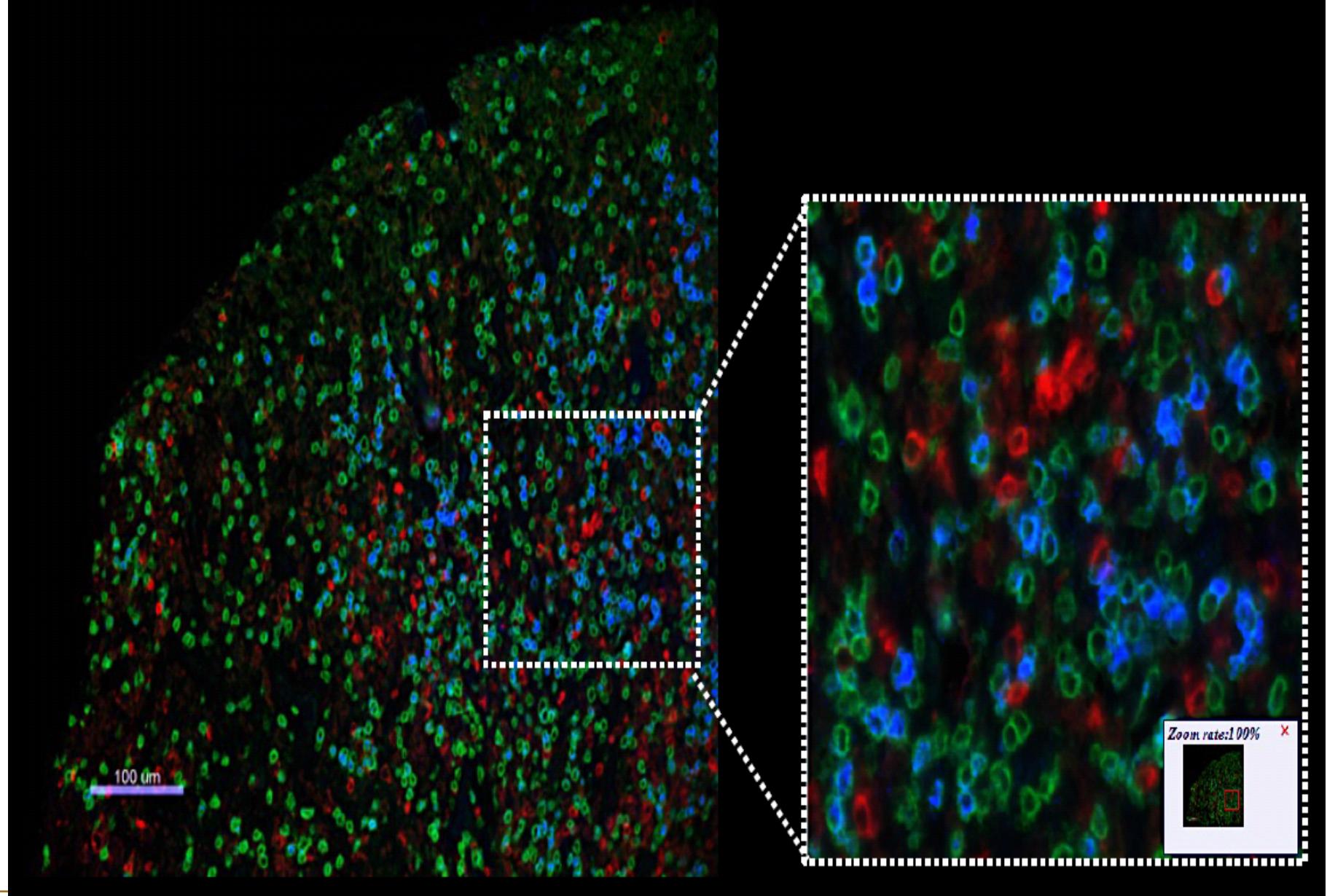
<u>Histology</u>	<u>Stage</u>	<u>Agent</u>	<u>Type of RT</u>
Pancreatic cancer	Locally advanced	Pembrolizumab+ Capecitabine	Fractionated
Breast	Oligometastatic	Pembrolizumab	SBRT
H&N	Locally recurrent	Pembrolizumab	Fractionated
Pancreatic cancer	Unresectable	Durvalumab	SBRT
GBM	Upfront	Durvalumab	Fractionated
NSCLC	IIIA/IIIB	Nivolumab	Fractionated
Multiple histologies	Metastatic	REGN2810	SBRT
NSCLC	Metastatic	MPDL3280	SBRT
NSCLC	Metastatic	MPDL3280	SBRT
Colon	Metastatic	AMP224	Unspecified



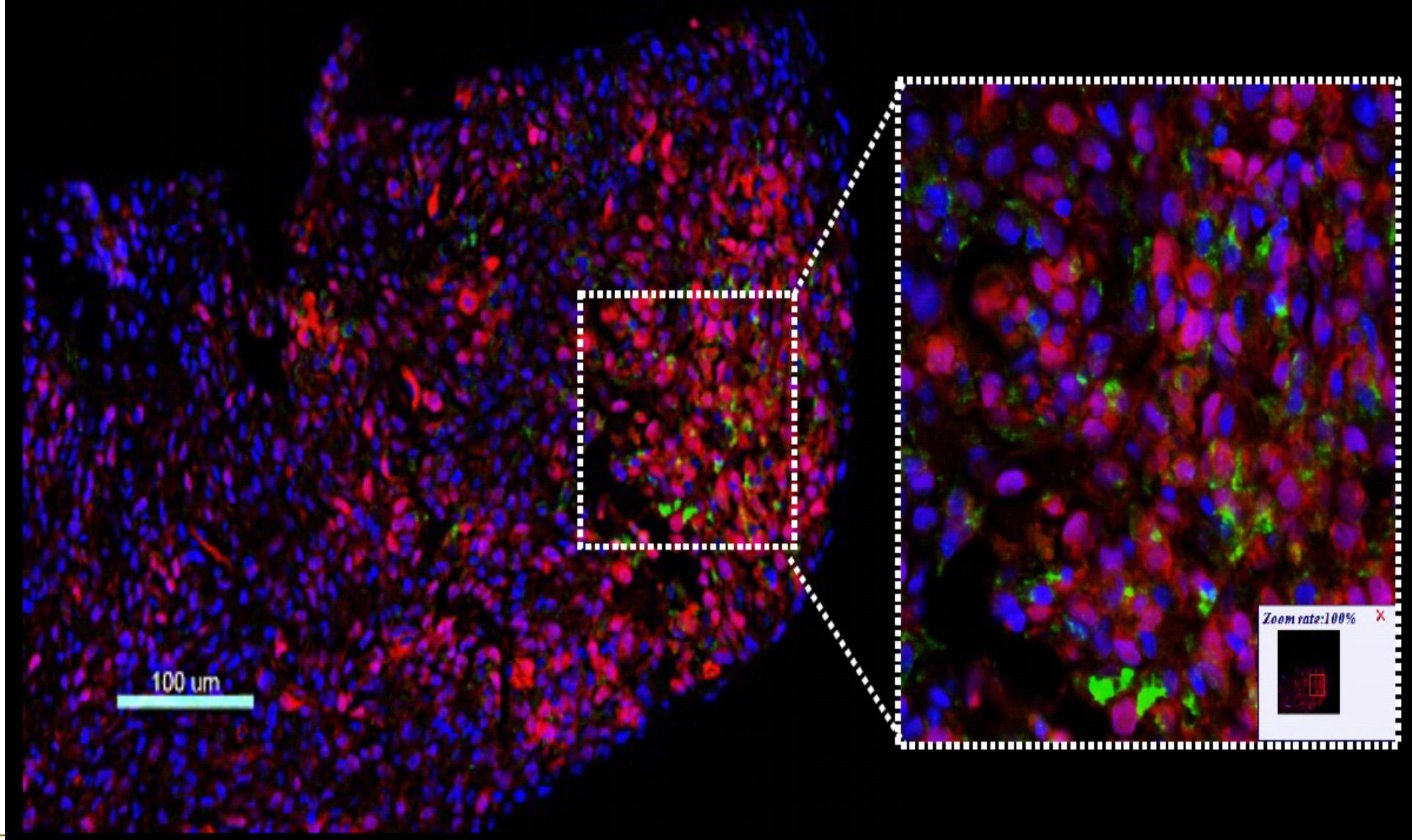
Rebound Immune Suppression



CD4/CD8/CD20

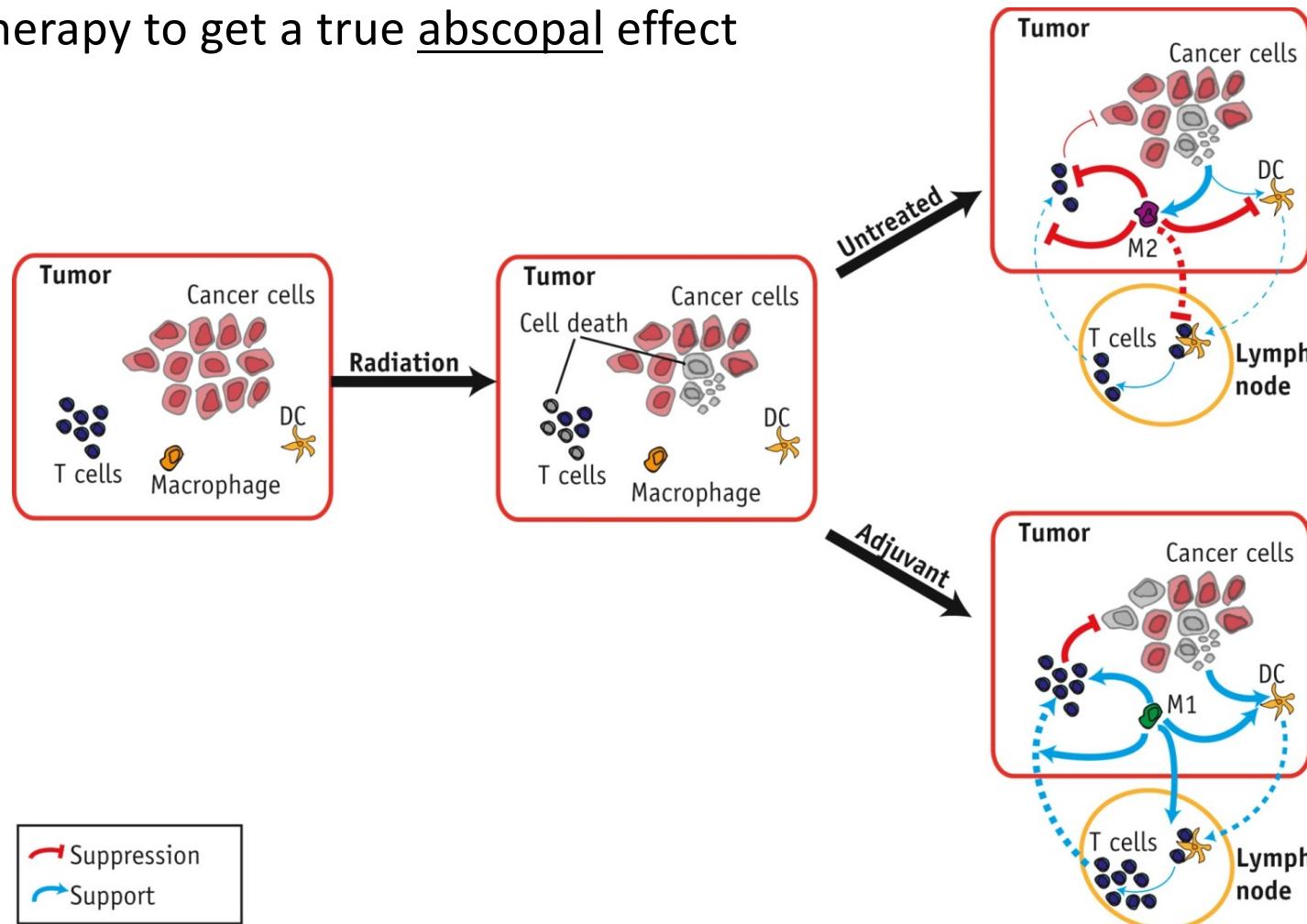


IDO1/PD-L1/DAPI



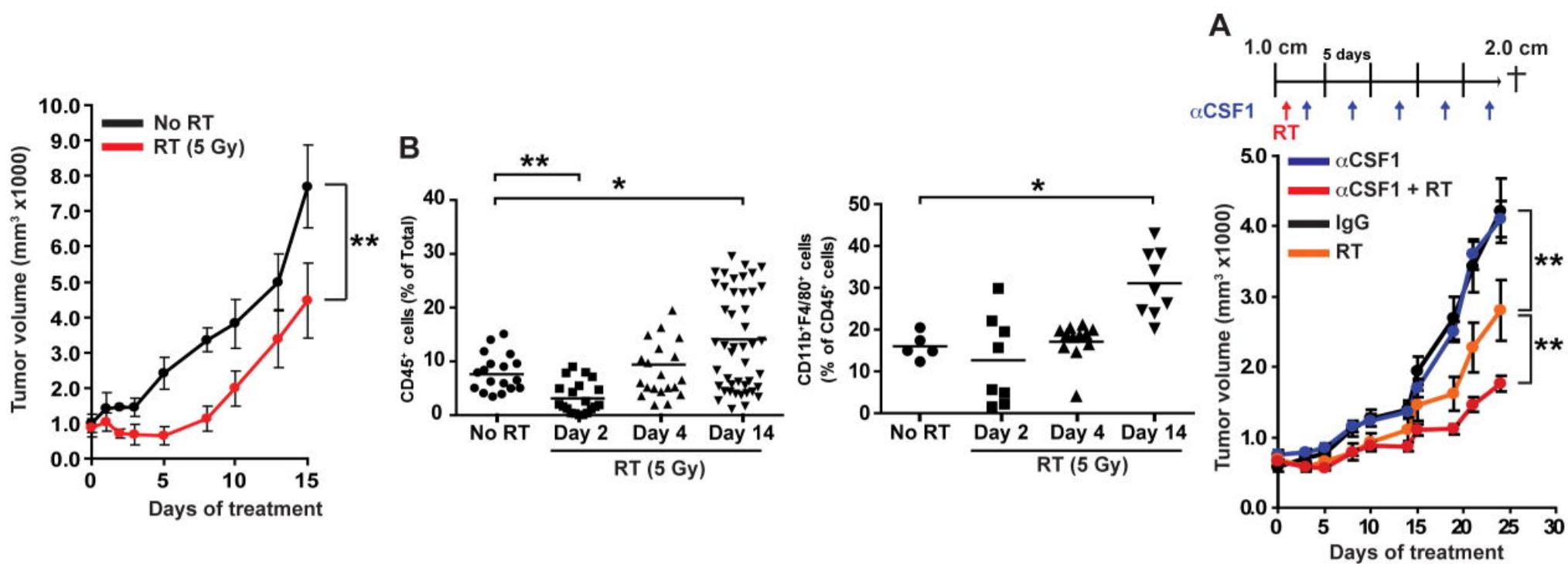
Zoom rate: 100%

RT alone rarely induces a ‘systemic’ anti-tumor response but needs to be combined with immunotherapy to get a true abscopal effect



[Baird et al. Int J Radiat Oncol Biol Phys. 2017 Oct 1;99\(2\):362-373](#)

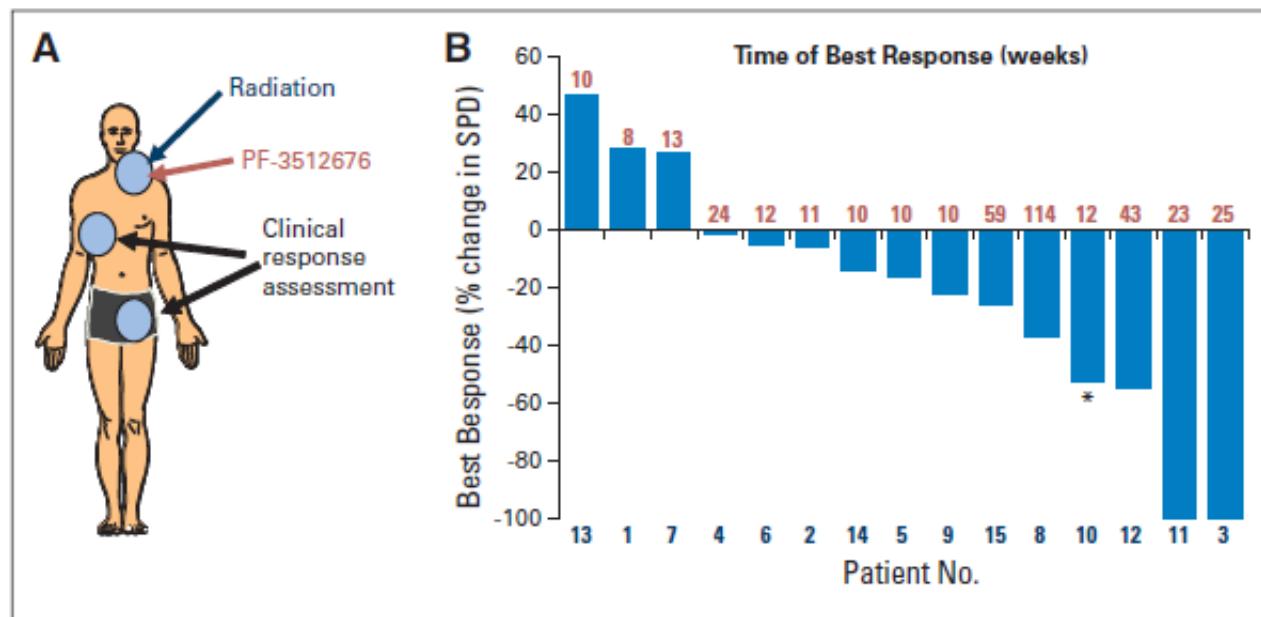
Radiotherapy modulation of TAMs



Shiao et al. Cancer Immunol Res. 2015 May; 3(5): 518–525.

In Situ Vaccination With a TLR9 Agonist Induces Systemic Lymphoma Regression: A Phase I/II Study

Joshua D. Brody, Weiyun Z. Ai, Debra K. Czerwinski, James A. Torchia, Mia Levy, Ranjana H. Advani, Youn H. Kim, Richard T. Hoppe, Susan J. Knox, Lewis K. Shin, Irene Wapnir, Robert J. Tibshirani, and Ronald Levy



IDO expression is up-regulated by inflammatory therapies

A

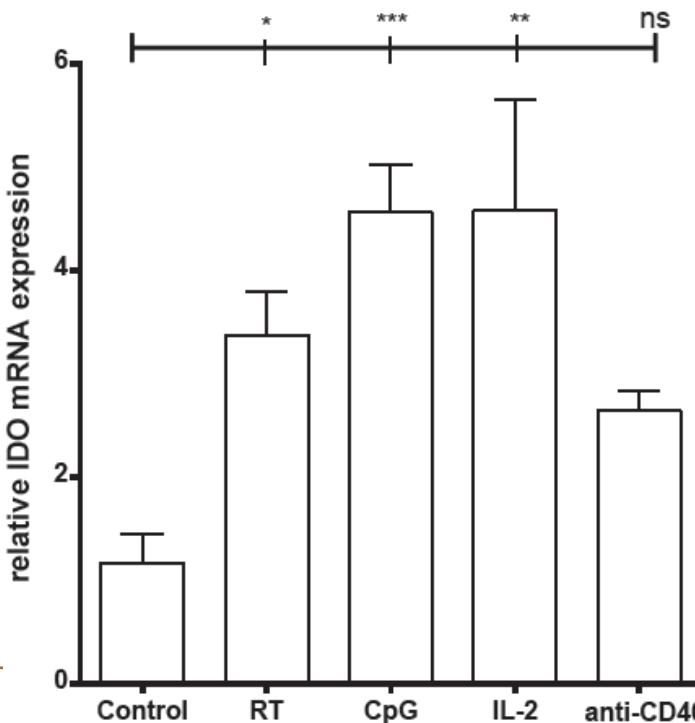
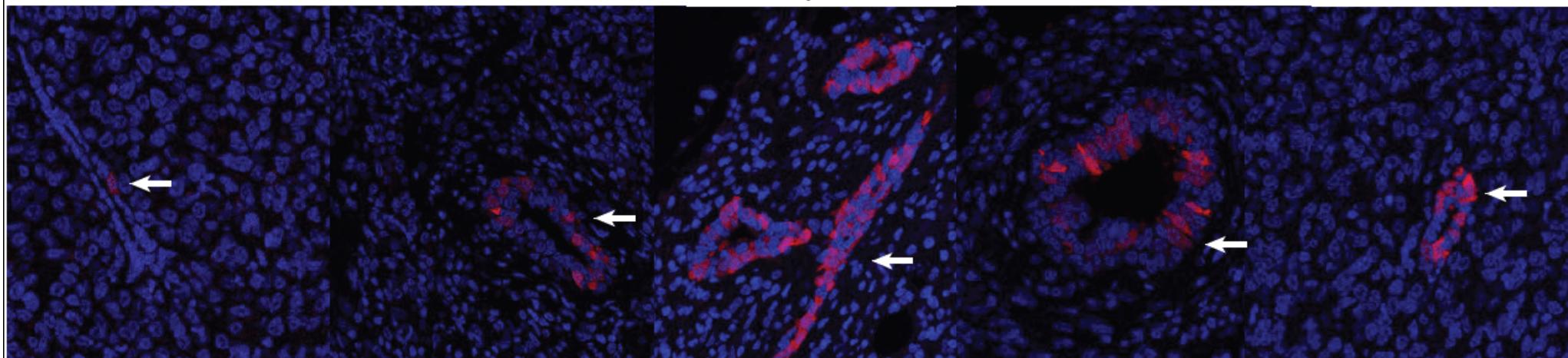
Control

RT

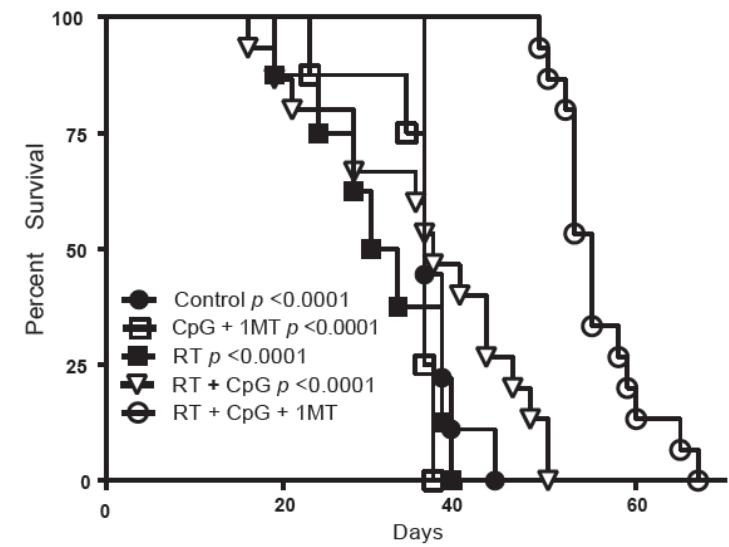
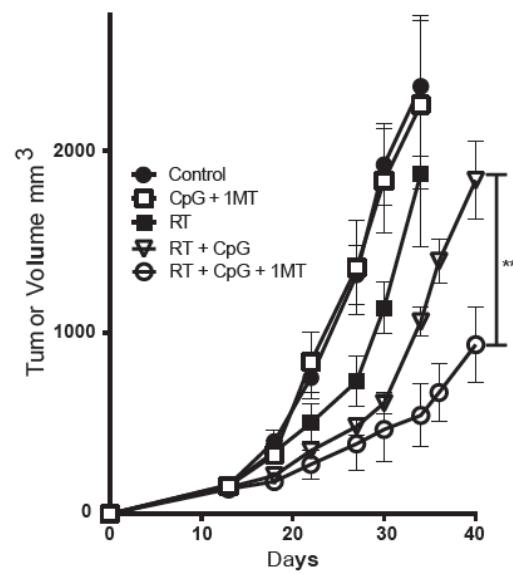
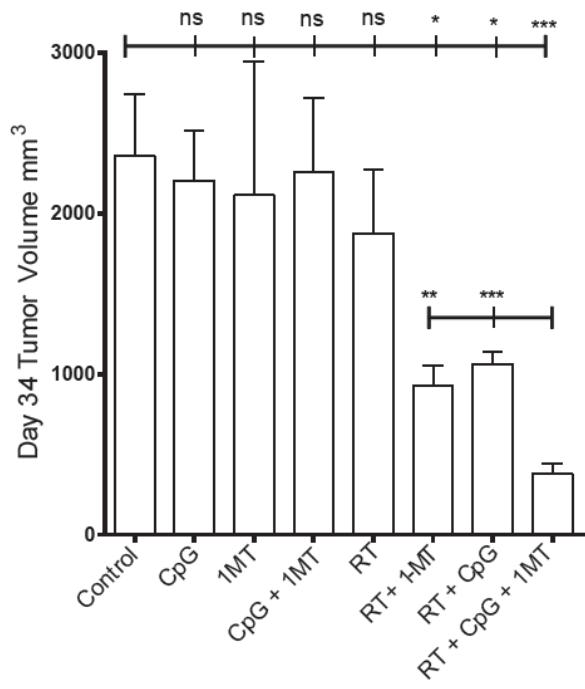
CpG

IL-2

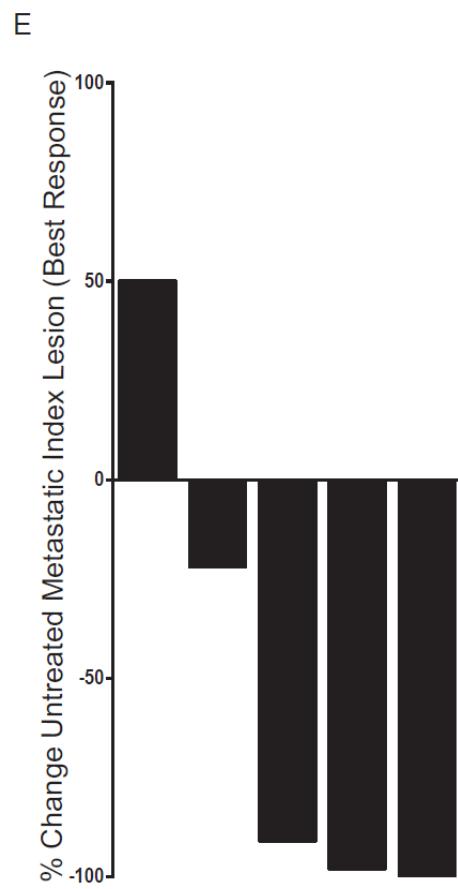
anti-CD40



IDO blockade improves anti-tumor effects of RT + CpG



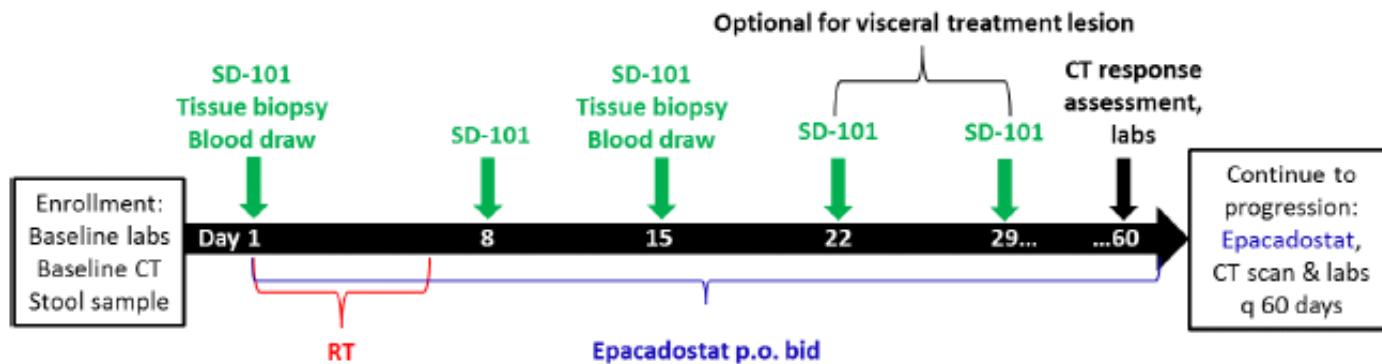
Canine trial: abscopal response



SCHEMA

General Enrollment Criteria

- Advanced refractory solid tumors or lymphoma
- Age ≥ 18
- 14 day treatment washout period
- At least one candidate treatment lesion (subcutaneous, nodal, or visceral)
 - Accessible for RT
 - Accessible and safe for repeat intralesional injections
- At least one candidate target lesion, outside of the RT field evaluable for response per irRECIST
- Adequate hematologic and end organ function
- No active autoimmune disease
- Patients with previous checkpoint blockade therapy are eligible



Concurrent RT (Days 1-5)

- Cohort 1 (solid tumors): (8 Gy x 3) or (4 Gy x 5)
- Cohort 2 (lymphoma): (8 Gy x 3) or (4 Gy x 5) or (2 Gy x 2)

Intralesional SD-101 (Day 1, 8, 15, 22, 29)

4 mg injection into RT treatment lesion

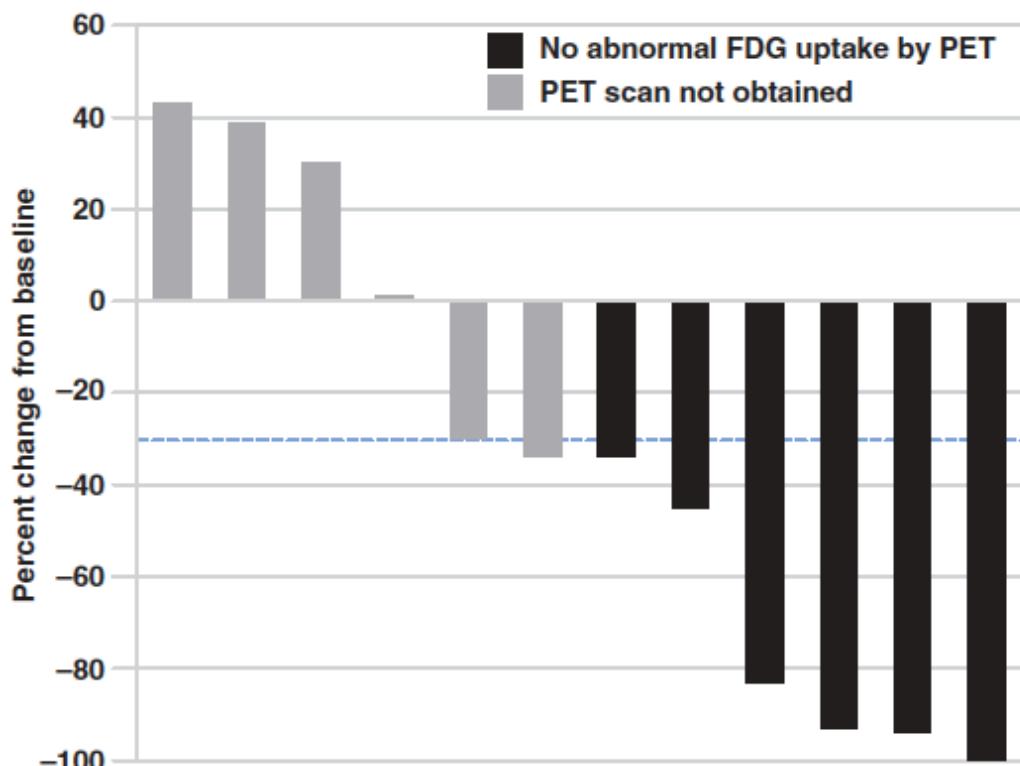
Epacadostat

100-300 mg PO bid

Selected Cancer Immunotherapy Targets/Strategies

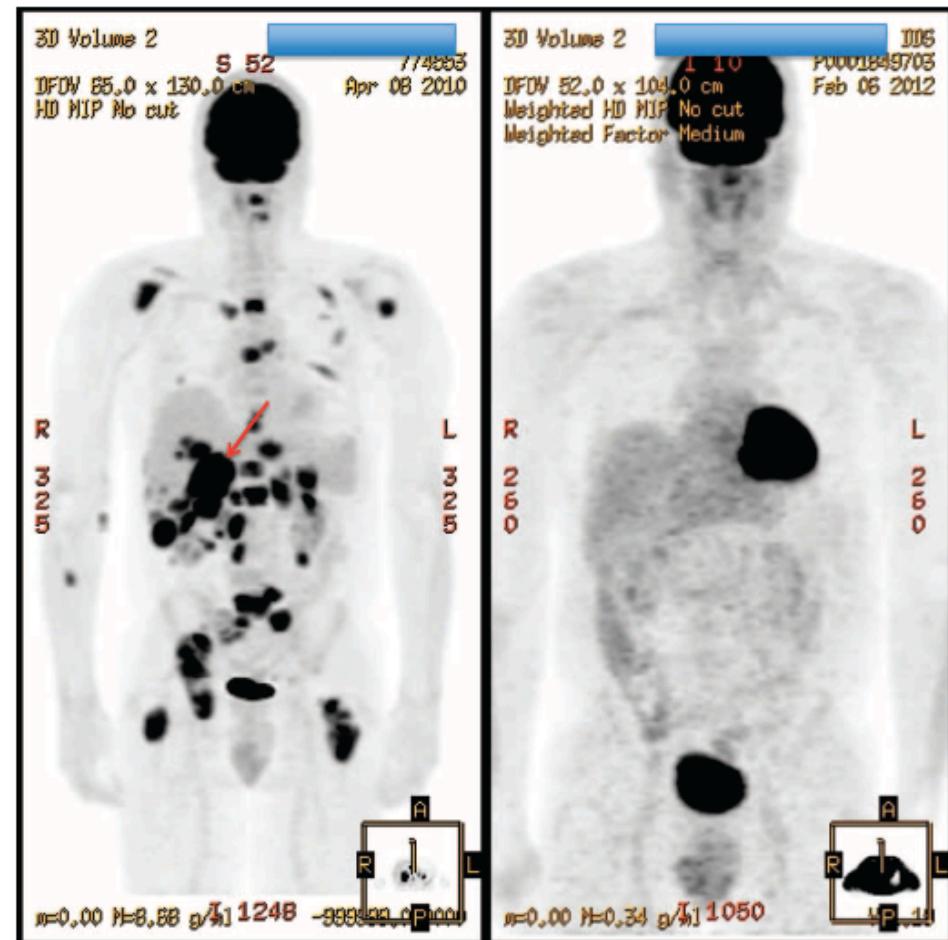
- Inhibitory Signals
 - CTLA-4, PD-1/PD-L1, LAG-3, TIM-3, VISTA, BTLA
- Stimulatory Signals
 - ICOS, CD40, OX40, 41BB
- Cytokines
 - IL-2, IL-12, IL-15, TGF-beta blockade
- CARs
- Adoptive Cell Transfer
- Vaccines
 - PANVAC, Provenge
- Oncolytic Virus
- TLR agonists
- Inhibitory Enzymes
 - IDO, Arginase

RT + HD systemic IL-2

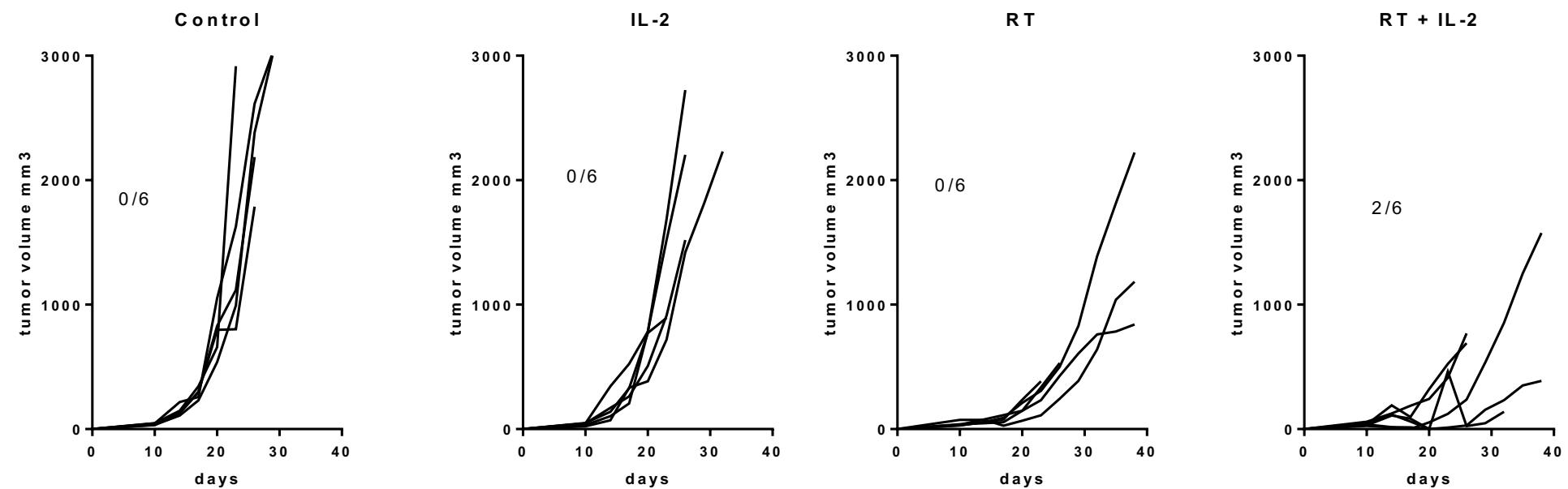


ORR: 66%

Historical response rate: 10-15%



preclinical data: RT + intraleisonal IL-2

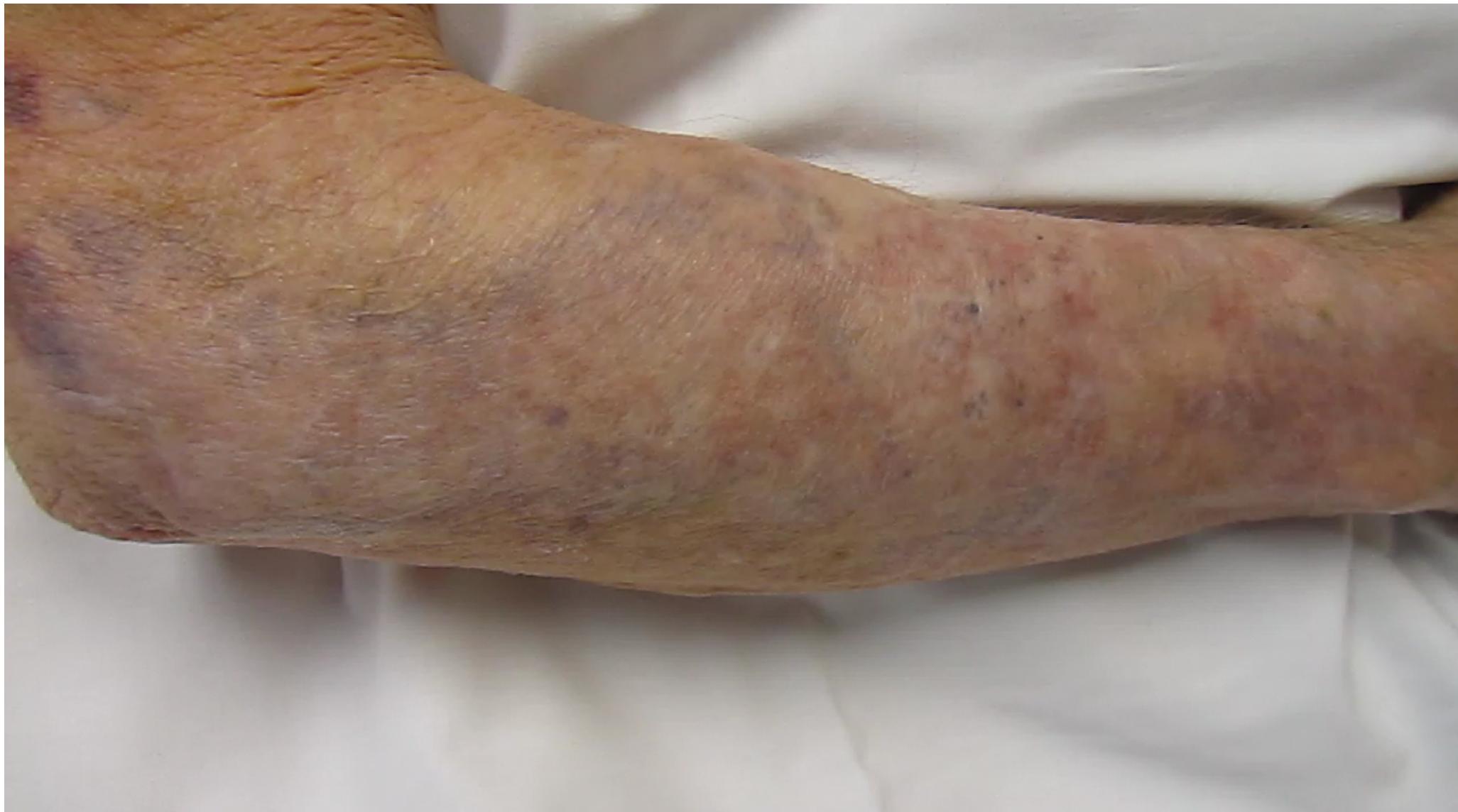




Recurrent Melanoma



2 Years Later



Key Points

- Radiotherapy has diverse immune modulatory effects
- Clinically significant anti-tumor responses from radiotherapy alone are rare
- There is a Potent synergy potential of RT + IT
- It is a complex system – best combinatorial strategies are likely to also be complex (not the simple addition of adding a short course of IT)
- Best strategy may depend on stage, histology, immunotherapy, patient factors, and desired effect

Questions

- Which / how many lesions to treat for an abscopal effect?
- Sequencing / timing ?
- Dose / fractionation?
(eg. Conventional vs SBRT?)

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