NASDC
NCI Awardee Skills Development Consortium

Integrating Radiation Oncology Into Immuno-Oncology

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Disclosures

MSKCC has received funding to support clinical trials from:

- Elekta, Amgen, Merck, AlphaTau Medical, EMD Serono, Regeneron

I have received funding for providing scientific advice to:

- Regeneron

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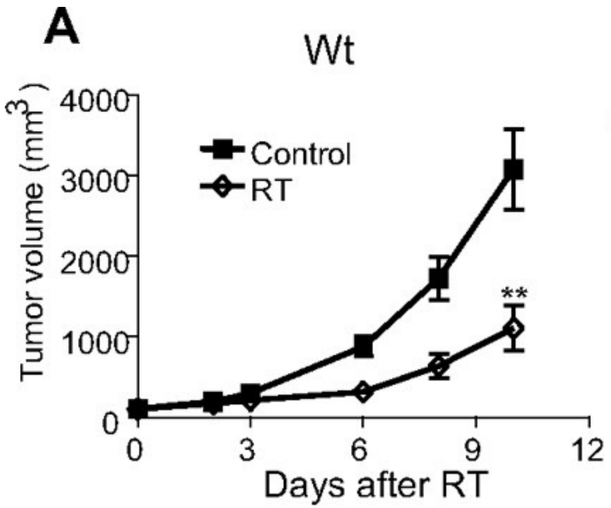
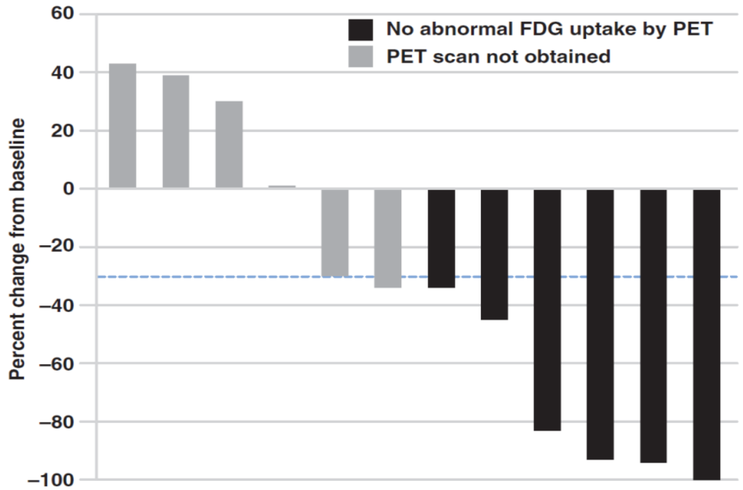
Intersections of radiation and immune system

Historic

Preclinical



Clinical



Contentious history of radiation and immuno-oncology at MSK

William Coley (1862-1936)

Staff Surgeon, New York Hospital/MSK (1893-1933)

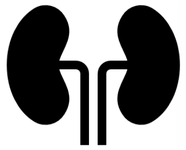
Grandfather of cancer immunotherapy

James Ewing (1866-1943)

Staff Pathologist, New York Hospital/MSK (1899-1939)

Proponent of radiation therapy for cancer

Radiotherapy facilitated “the original immunotherapies”



The New England
Journal of Medicine

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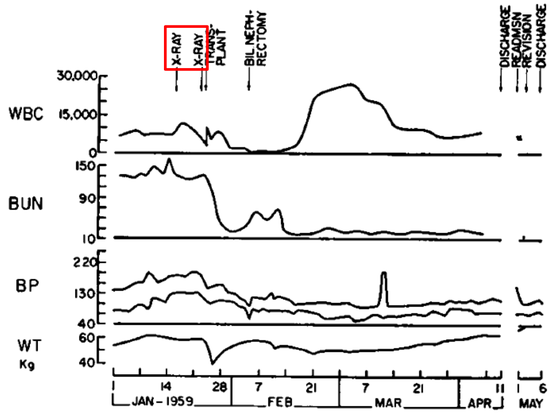
Volume 262 JUNE 23, 1960 Number 25

SUCCESSFUL HOMOTRANSPLANTATION OF THE KIDNEY BETWEEN NONIDENTICAL TWINS*

JOHN P. MERRILL, M.D.,† JOSEPH E. MURRAY, M.D.,‡ J. HARTWELL HARRISON, M.D.,§
ELI A. FRIEDMAN, M.D.,¶ JAMES B. DEALY, JR., M.D.,‖ AND GUSTAVE J. DAMMIN, M.D.**

BOSTON



Merrill et al, NEJM 1960; Buckner et al, Blood 1970

BLOOD *The Journal of Hematology*

JUNE, 1970 VOL. XXXV, NO. 6

Allogeneic Marrow Engraftment Following Whole Body Irradiation in a Patient with Leukemia

By C. DEAN BUCKNER, ROBERT B. EPSTEIN, ROBERT H. RUDOLPH, REGINALD A. CLIFT, RAINER STORB AND E. DONNALL THOMAS

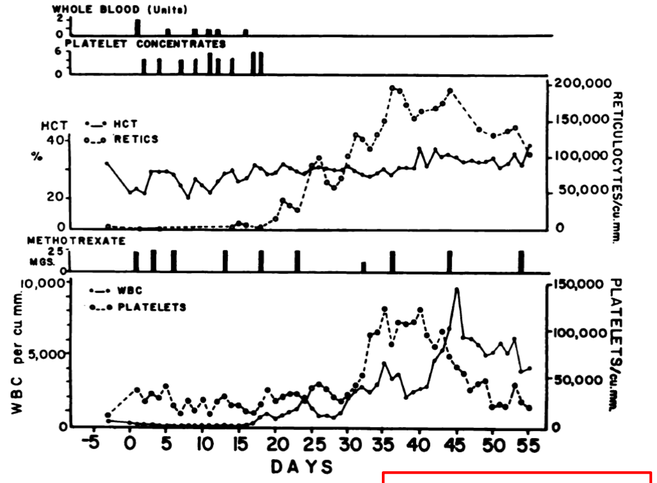
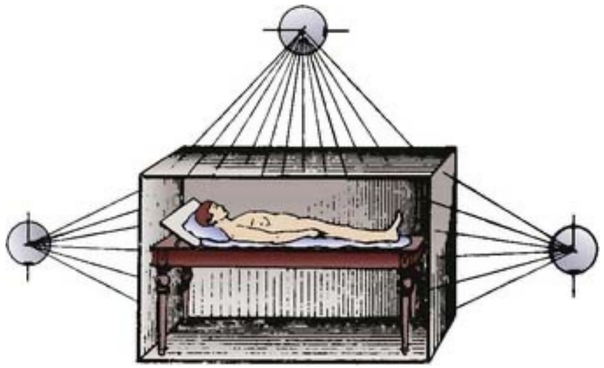
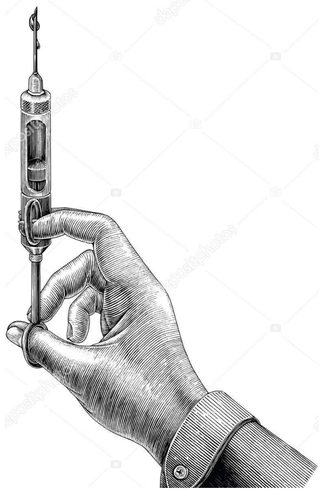


Fig. 1.—Hematological events in patient given 950 rads whole-body irradiation and allogeneic bone marrow.

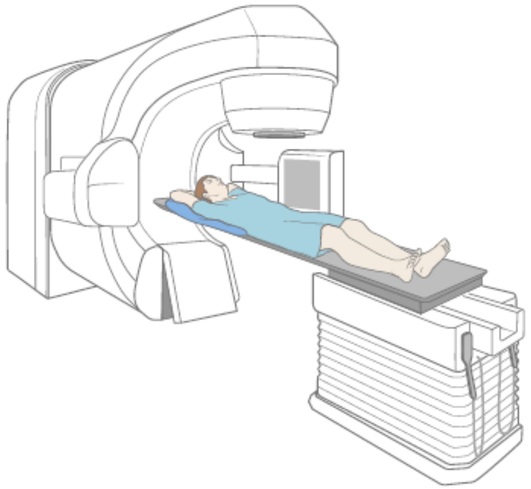
Radiotherapy is a spatially oriented treatment

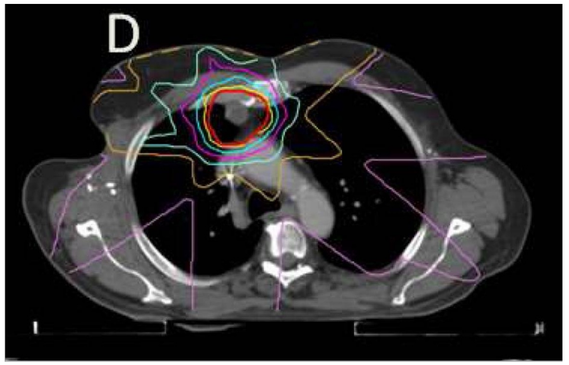
Total body irradiation (TBI) or radionuclide therapy uniformly exposes the entire body or tissue compartments





Tumor radiotherapy (teletherapy, brachytherapy, IMRT, 3DCRT, SBRT) irradiates a tumor or focal area suspected to harbor cancer

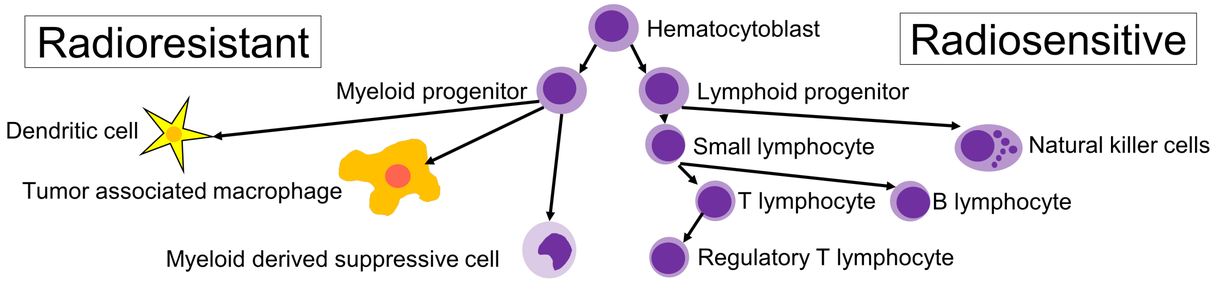




Dessauer FJ Medizinischen Klinic 1905; Barker CA and Postow MA IJROBP 2015

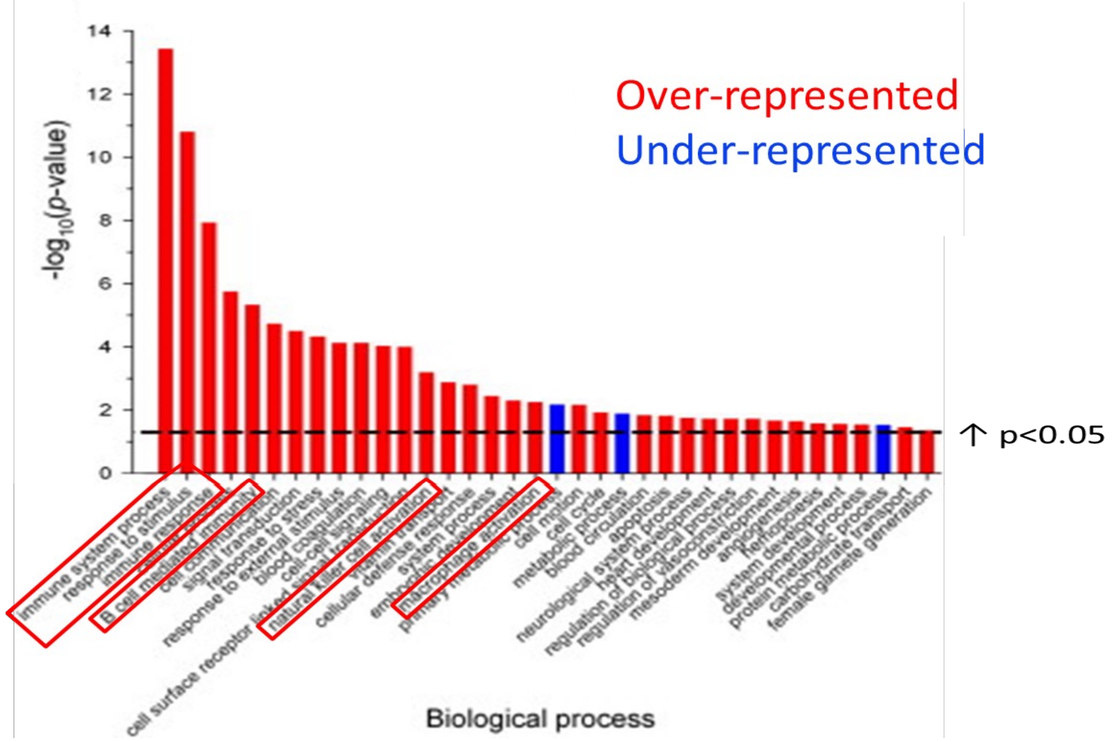
Total body irradiation effects on the immune system

Immune cells are variably sensitive to ionizing radiation

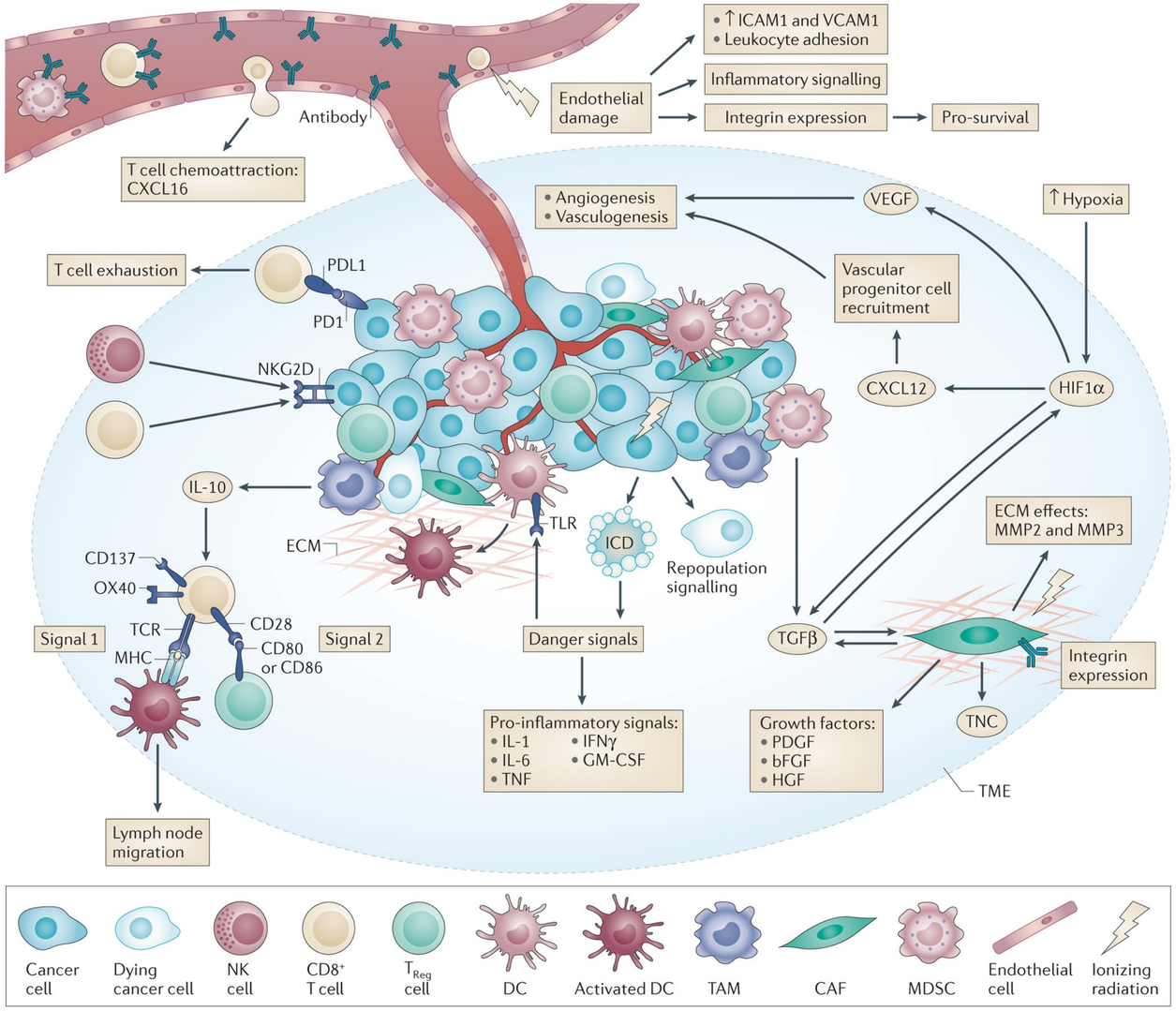


Templin et al, IJROBP 2011

Radiation may alter immune cell function, rather than just killing them

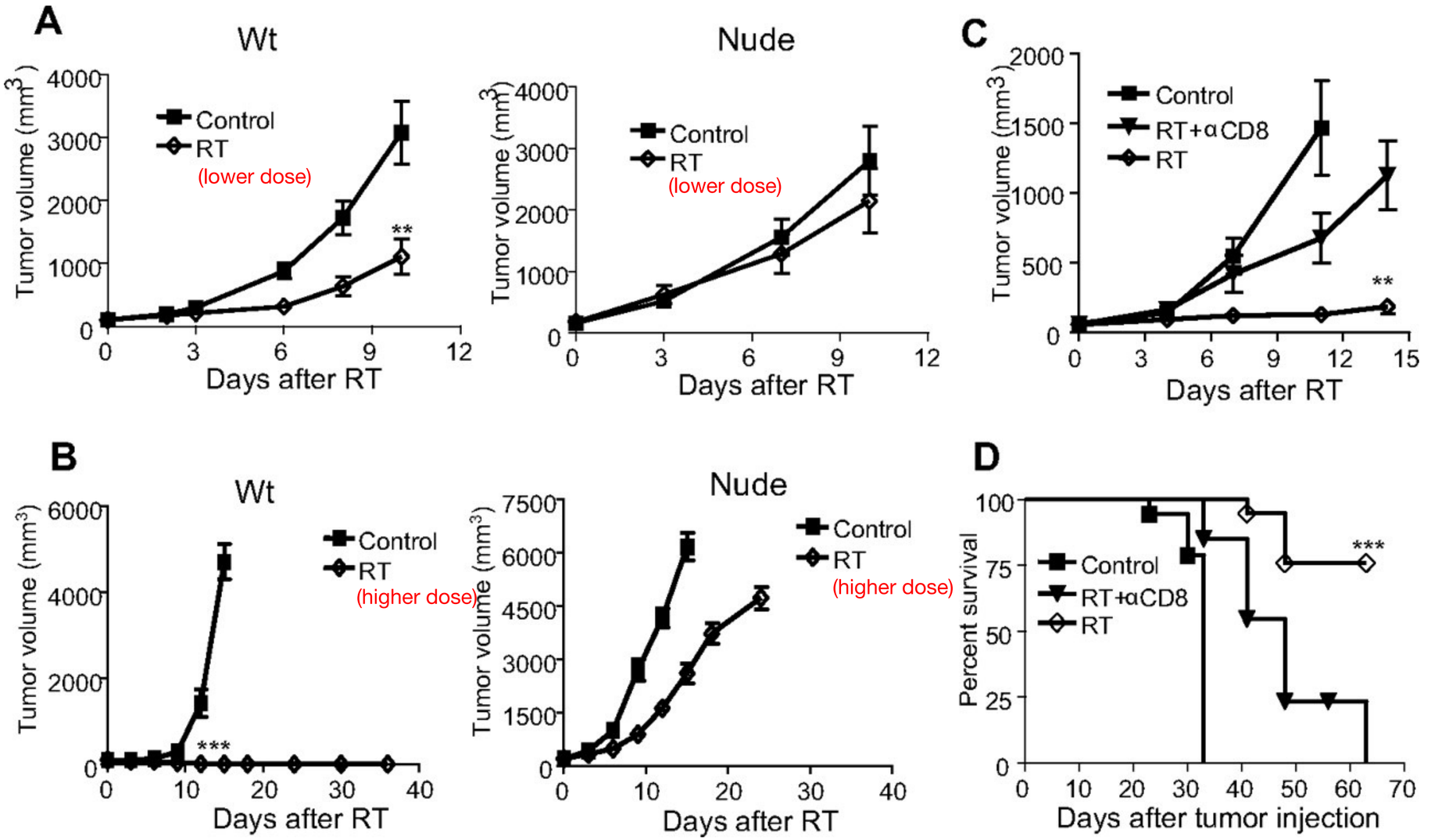


Tumor radiotherapy effects on the microenvironment



Barker et al, Nature Reviews Cancer 2015

Tumor radiotherapy effect is governed (in part) by the immune system



Lee et al, Blood 2009

Is combining radiotherapy and immunotherapy beneficial?

Well-designed, rationale clinical trials may provide the answers…

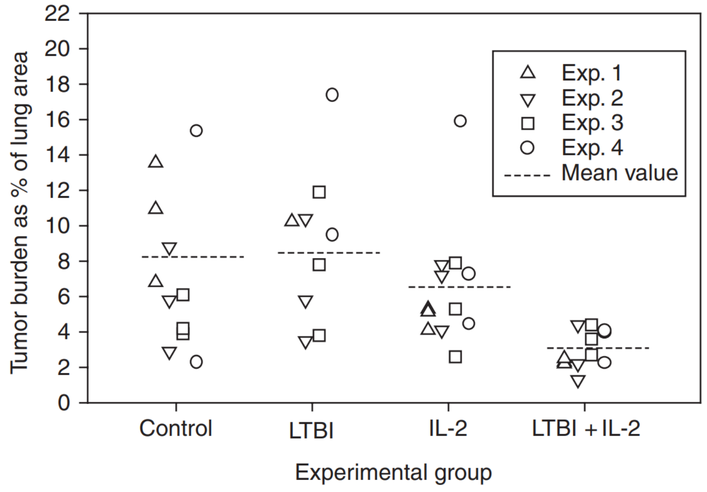
Trials of radiation and:

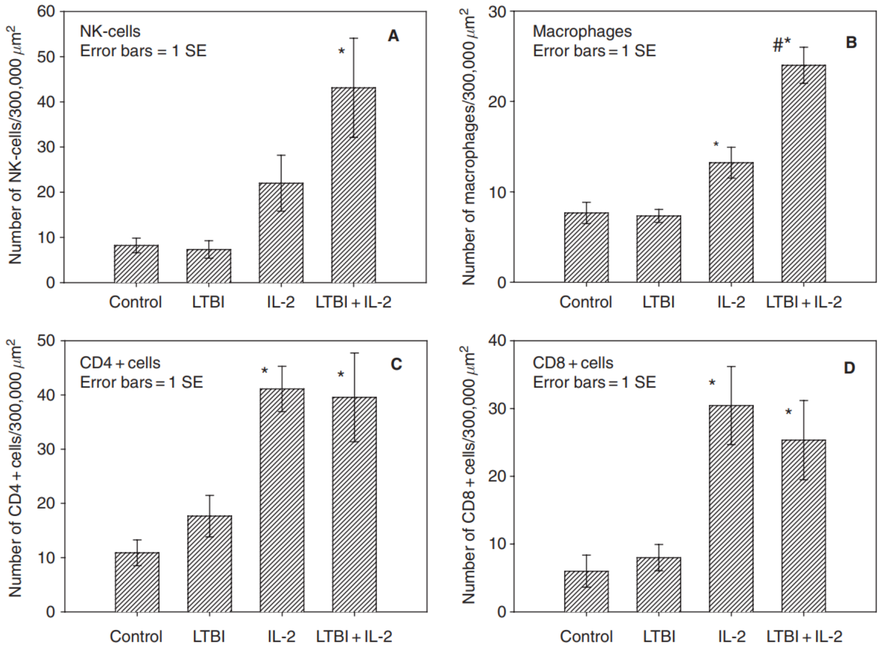
- Cytokine therapy
- Cellular therapy
- Oncolytic therapy
- Immune checkpoint blockade

Cytokine and radiotherapy: Effect of dosing and/or target?

Murine melanoma +/- low dose total body irradiation (LTBI, 0.75 Gy) +/- IL2 (5 days)

Greater tumor reduction, tumor immune infiltrate and peripheral blood NK cells





Experiment group (number)	%CD19$^+$ (SD)	%CD3$^+$ (SD)	%CD4$^+$ (SD)	%CD8$^+$ (SD)	CD4$^+$CD25$^+$ (% of CD4$^+$) (SD)	CD25$^+$ (IL-2Rα) (SD)	CD122$^+$ (IL-2Rβ) (SD)	NK/2B4 (SD)
Lymphocytes from peripheral blood								
Control (8)	42 (11.0)	26 (4.8)	17 (4.4)	12 (1.1)	1.5 (0.4)	1 (0.3)	4 (1.8)	8 (1.7)
LTBI (8)	40 (3.1)	30 (4.7)	18 (2.1)	11 (2.1)	1.3 (0.6)	1 (0.5)	4 (1.9)	12 (4.7)
IL-2 (8)	48 (9.5)	29 (1.1)	13 (1.8)	14 (2.4)	3.0 (2.2)	3 (2.1)	7 (2.5)	10 (1.1)
LTBI + IL-2 (8)	37*$^{\#\#}$ (7.0)	28 (6.0)	15 (1.6)	15 (2.2)	2.4 (1.2)	3 (2.0)	13*$^{\#\#}$ (3.5)	16*$^{\#\#}$ (3.0)
Splenic lymphocytes								
Control (8)	49 (4.0)	31 (4.8)	16 (3.4)	13 (3.2)	4.6 (4.0)	3 (0.9)	3 (1.0)	9 (2.2)
LTBI (8)	44 (5.2)	35 (7.6)	18 (2.4)	12 (3.5)	2.3 (1.0)	4 (1.3)	4 (0.8)	10 (5.1)
IL-2 (8)	47 (3.1)	34 (15.2)	17 (2.3)	14 (9.0)	6.2 (6.0)	3 (1.0)	7* (2.6)	13 (6.0)
LTBI + IL-2 (8)	28*$^{\#\#}$ (13.1)	35 (10.6)	19 (3.9)	15 (5.1)	11.2 (5.3)	10 (8.3)	7* (2.8)	23* (9.5)

The data were obtained using flow cytometry and pooled from two mice per experimental group in four different experiments.
*Significantly different from control.
$^{\#\#}$Significantly different from interleukin-2 (IL-2) alone.

Safwat et al, JETM 2003

Cytokine and radiotherapy: Effect of dosing and/or target?

Metastatic melanoma patients treated with LTBI 0.1 Gy + IL2 (5 days) weekly

Response rate no different than historic experience with IL2 alone

Table 2
Patient characteristics ($n=45$)

	No. of patients	%
Sites of metastatic disease		
Skin/subcutaneous	20	44
Lymph nodes	29	64
Lung	22	49
Liver	18	40
Bone	5	11
Other visceral organs	14	31
No. of metastatic (organ) sites involved		
1	10	22
2	15	33
≥ 3	20	44

Table 2
Patient characteristics ($n=45$)

	No. of patients	%
Performance status		
0	25	56
1	14	31
2	6	13
Previous treatment for metastatic disease		
None	42	93
Regional hyperthermic perfusion	3	7
AJCC stage IV*		
M1a	4	9
M1b	6	13
M1c	35	78

Response evaluation

	Study group ($n=45$)	
	Number	%
Patients	45	100
CR	0	
PR	2	4.4
NC	13	29
PD	30	67
Overall response rate	2	4.4

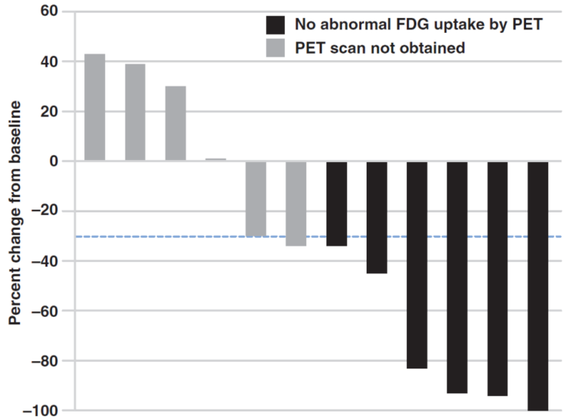
CR, complete response; PR, partial response; NC, no change;

Safwat et al, Rad Onc 2005

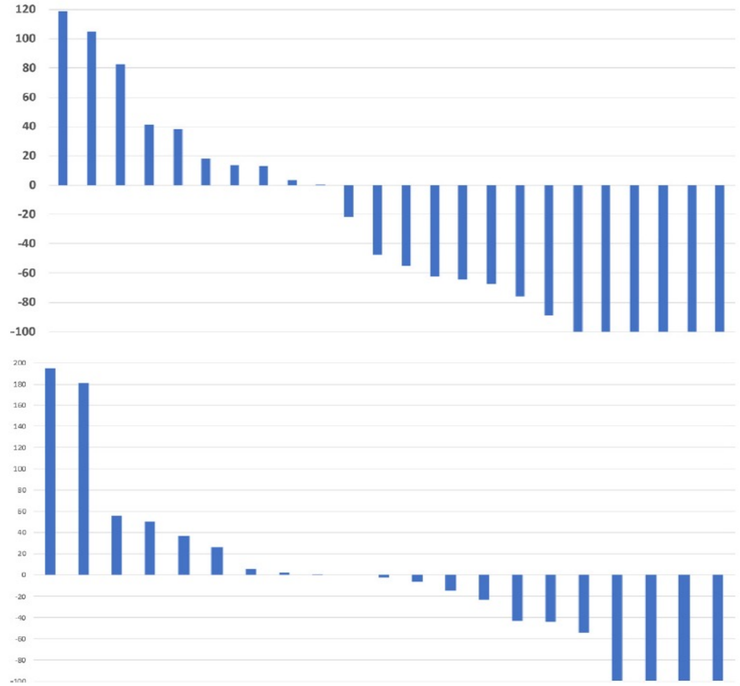
Cytokine and radiotherapy: Effect of dosing and/or target?

Phase I clinical trial of IL2 and stereotactic body radiotherapy (SBRT) for metastases demonstrated high response rates

	CT (%)	PET (%)
Complete response (CR)	1 (8.4)	6 (50)
Partial response (PR)	7 (58.3)	2 (16.7)
Stable disease	1 (8.4)	1 (8.4)
Progressive disease	3 (25)	3 (25)
Overall response (CR + PR)	8 (66.7)	8 (66.7)
Response by disease		
Melanoma (n = 7)	CR 1 (14.3)	CR 5 (71.4)
	PR 4 (57.1)	PR (0)
Renal cancer (n = 5)	CR 0 (0)	CR 1 (20)
	PR 3 (60)	PR 2 (40)



Randomized phase II clinical trial demonstrated adding SBRT to IL2 increased response rate



IL2+SBRT

54% response rate

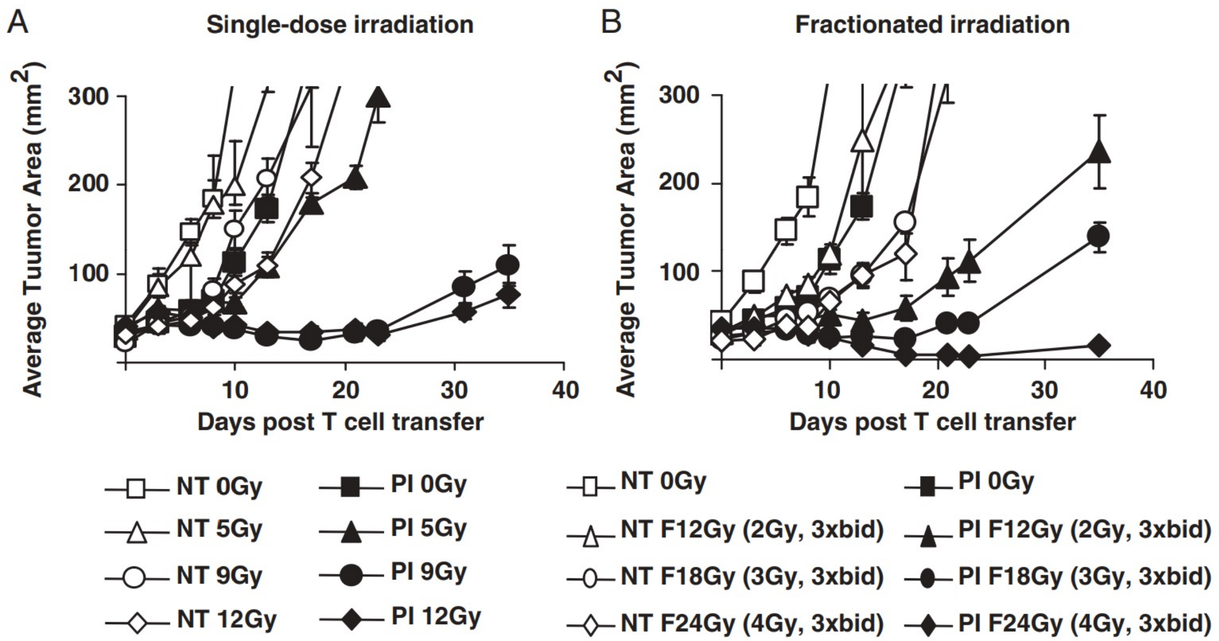
IL2 alone

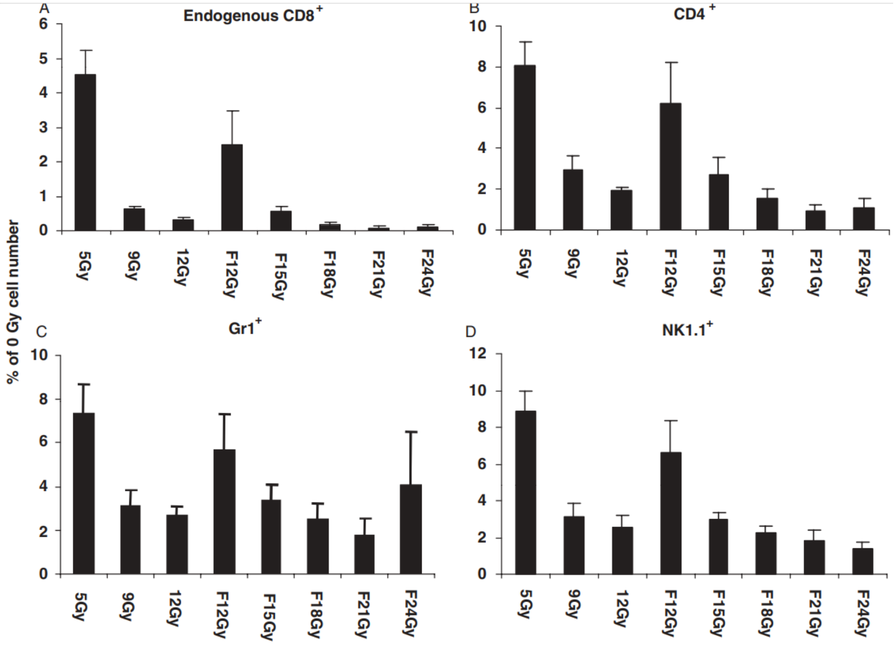
35% response rate

Seung et al, Science Trans Med 2012; Curti et al, JITC 2020

Cytokine and cellular therapy: Augmented with TBI?

Preclinical studies cytokine and cellular therapy and total body irradiation contribute to tumor control in dose dependent manner

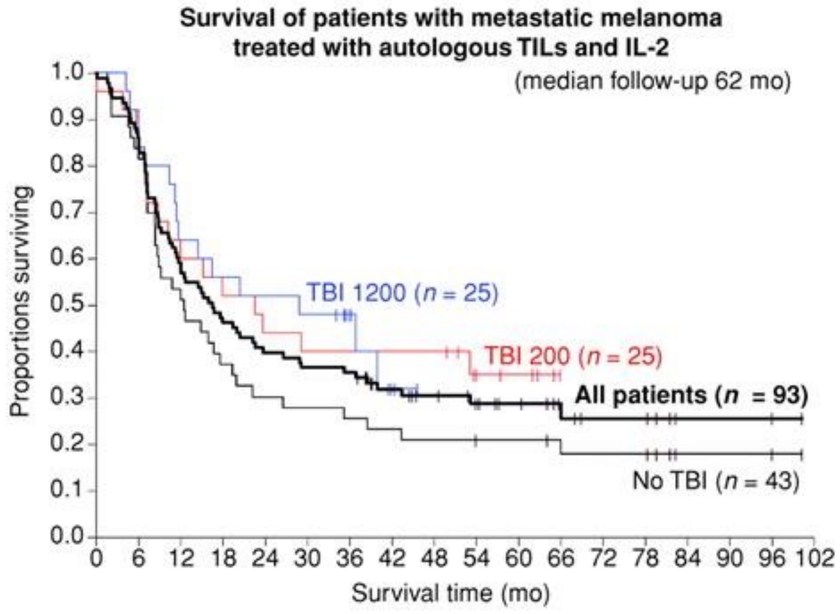




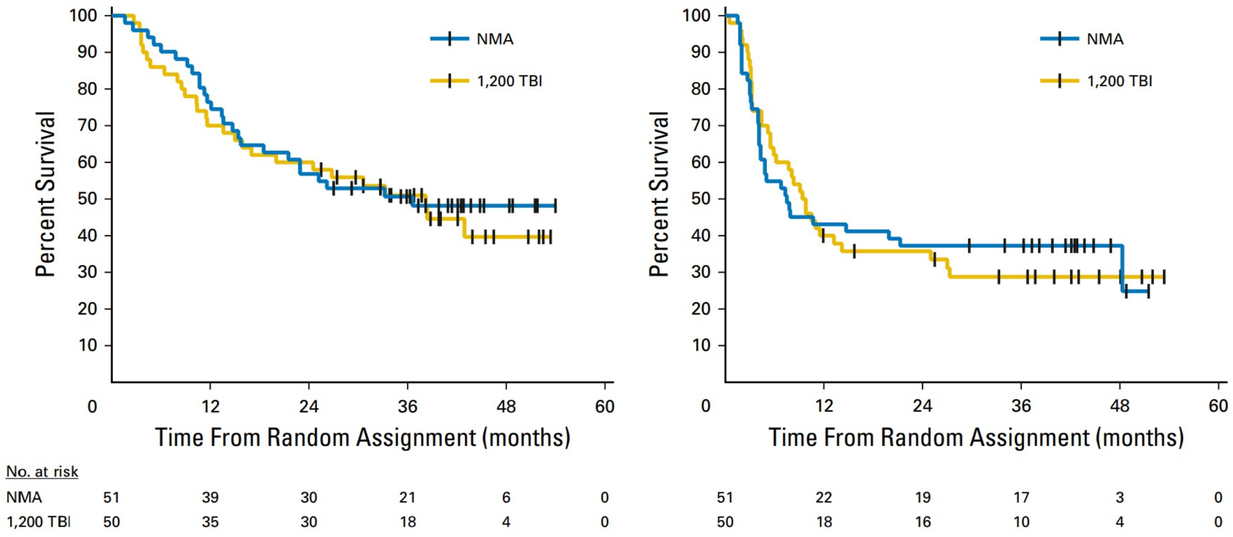
Wrzesinski et al, J Immunotherapy 2010

Cytokine and cellular therapy: Augmented with TBI?

Phase II trials suggest benefit of TBI with cytokine and cellular therapy



Randomized trial demonstrated no difference in overall or progression free survival with or without TBI



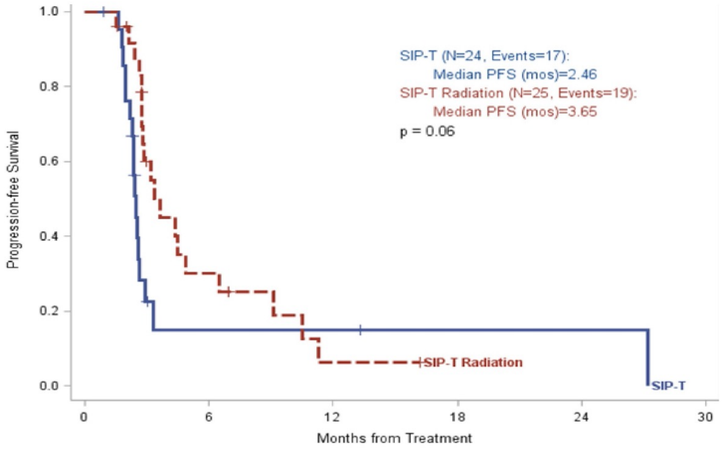
OS **PFS**

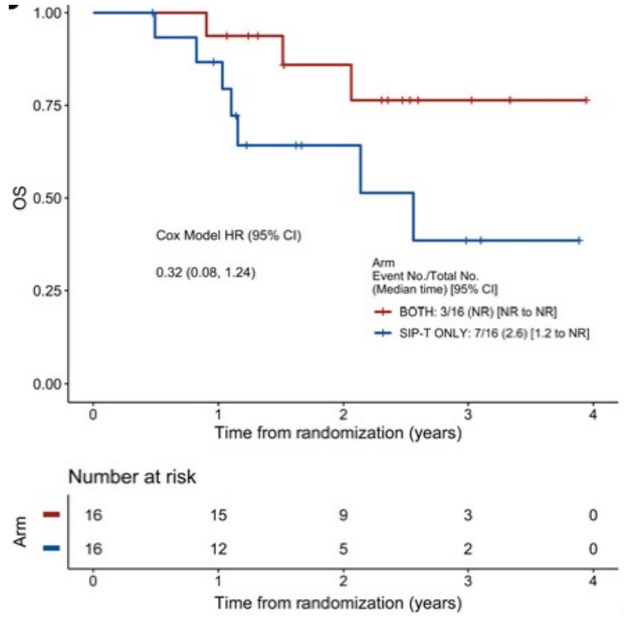
Rosenberg et al, Clin Canc Res 2011; Goff et al, JCO 2016

Cellular therapy +/- radiotherapy: External beam or radioisotope?

Two randomized trials: Prostate cancer

	Population	Control	Experimental
City of Hope 12367	Stage IV castrate-resistant prostate cancer patients previously treated with bone metastases	Sipuleucel-T	Sipuleucel-T and external beam tumor radiotherapy (30 Gy/10 fractions)
Hopkins 00056435	Stage IV castrate-resistant prostate cancer with bone metastases	Sipuleucel-T	Sipuleucel-T and Ra223 (50 kBq q4 weeks for 6 weeks)

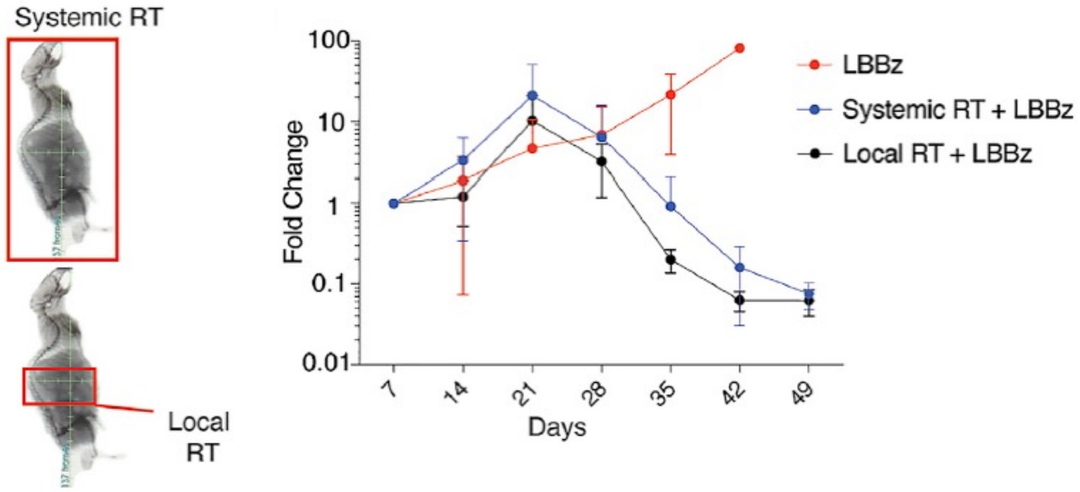




Twardowsi et al, Cancer Treat Res Comm 2019; Marshall et al, Clin Cancer Res 2021

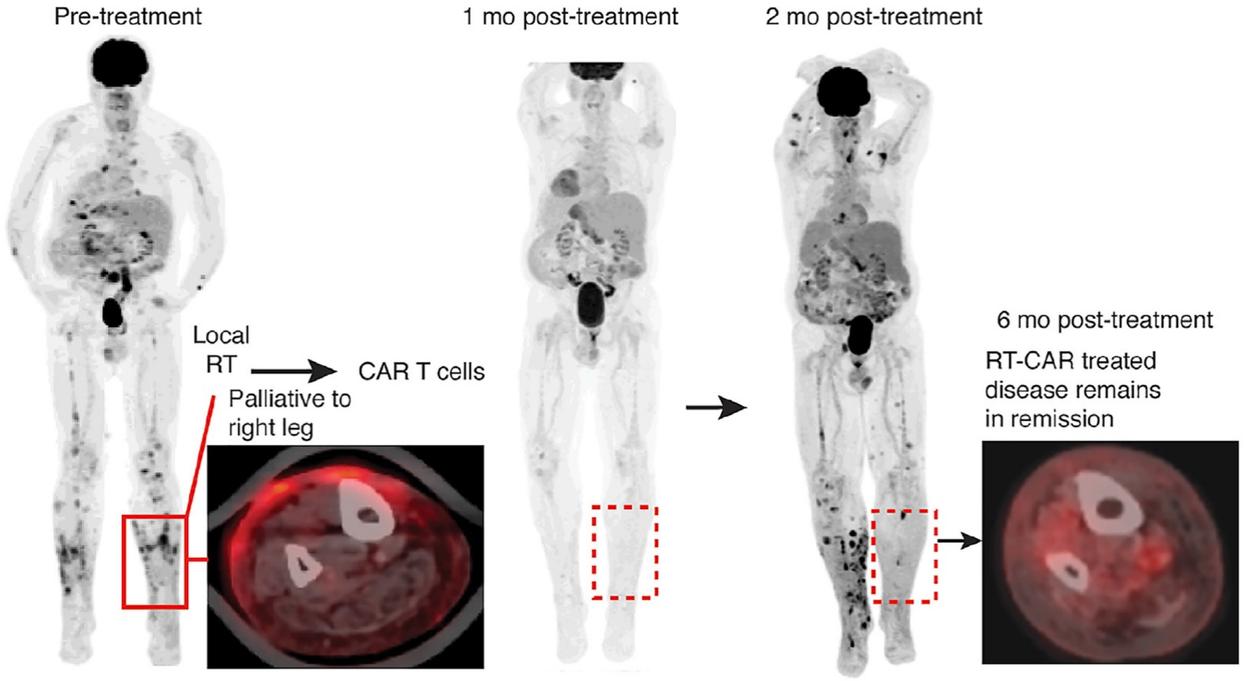
Chimeric antigen receptor (CAR) T cell therapy and radiation

Preclinical studies greater reduction of tumor burden with CAR T cell therapy followed by low dose total body or tumor directed radiotherapy

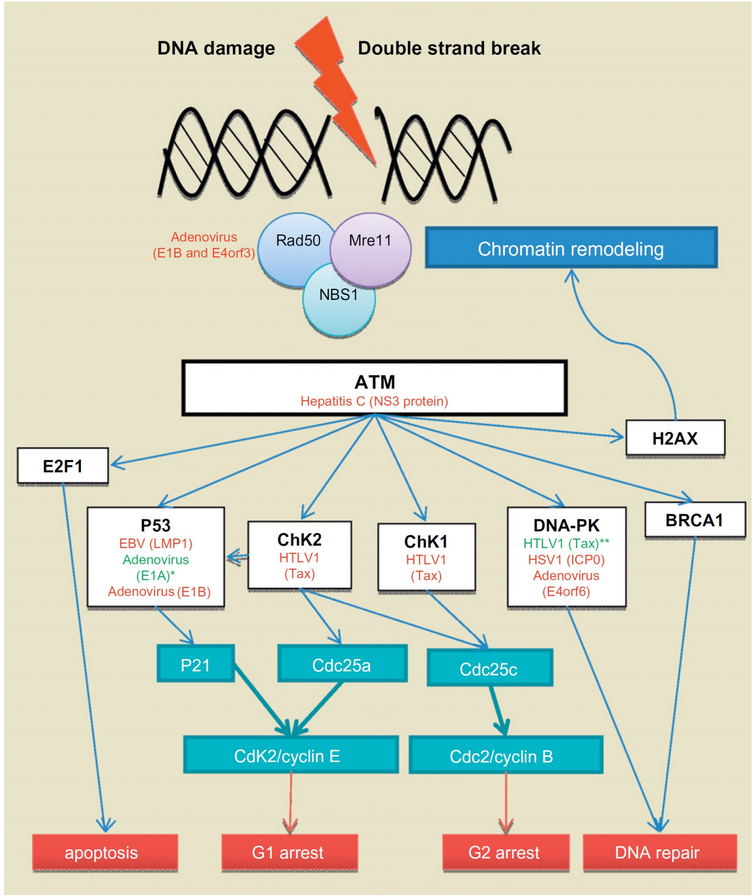


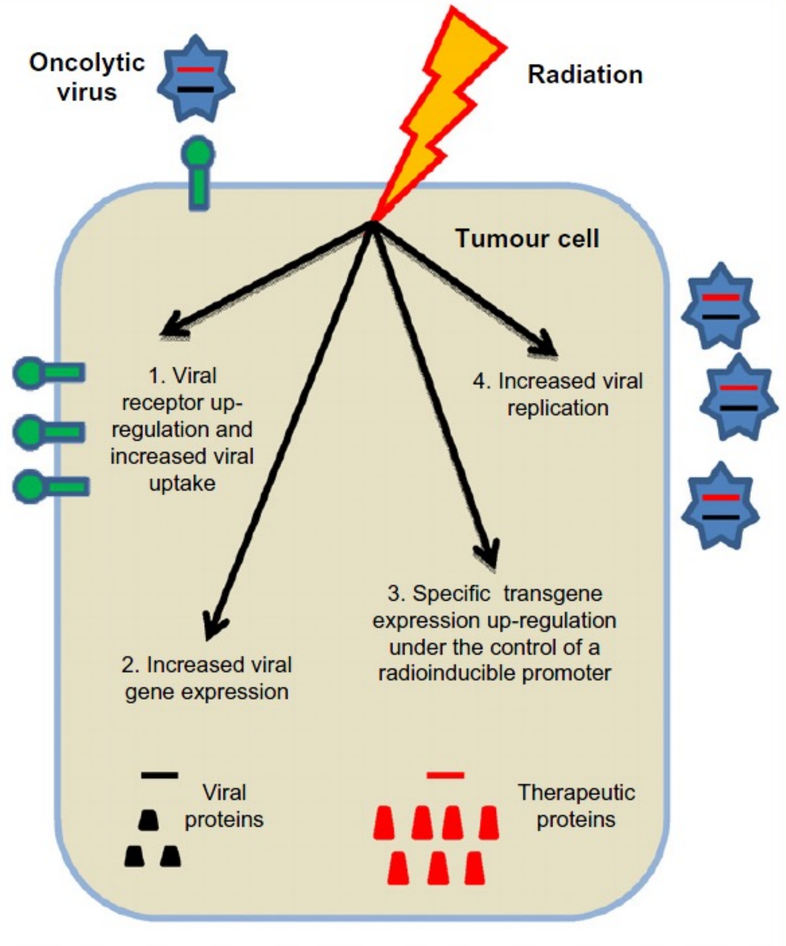
Deselm et al, Molecular Ther 2018

Clinical anecdotes suggest radiotherapy may enhance antitumor effect of CAR T cell therapy



Oncolytic immunotherapy and radiotherapy





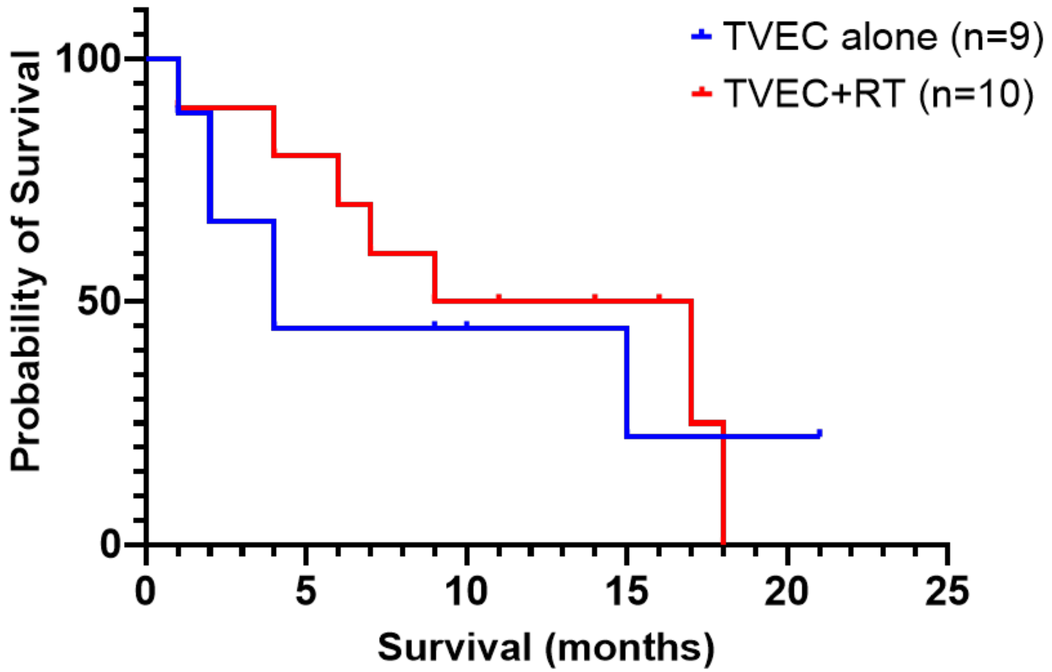
Memorial Sloan Kettering Cancer Center

Touchefeu et al, Rad Oncol, 99 (2011) 262-270

Oncolytic immunotherapy with or without radiotherapy

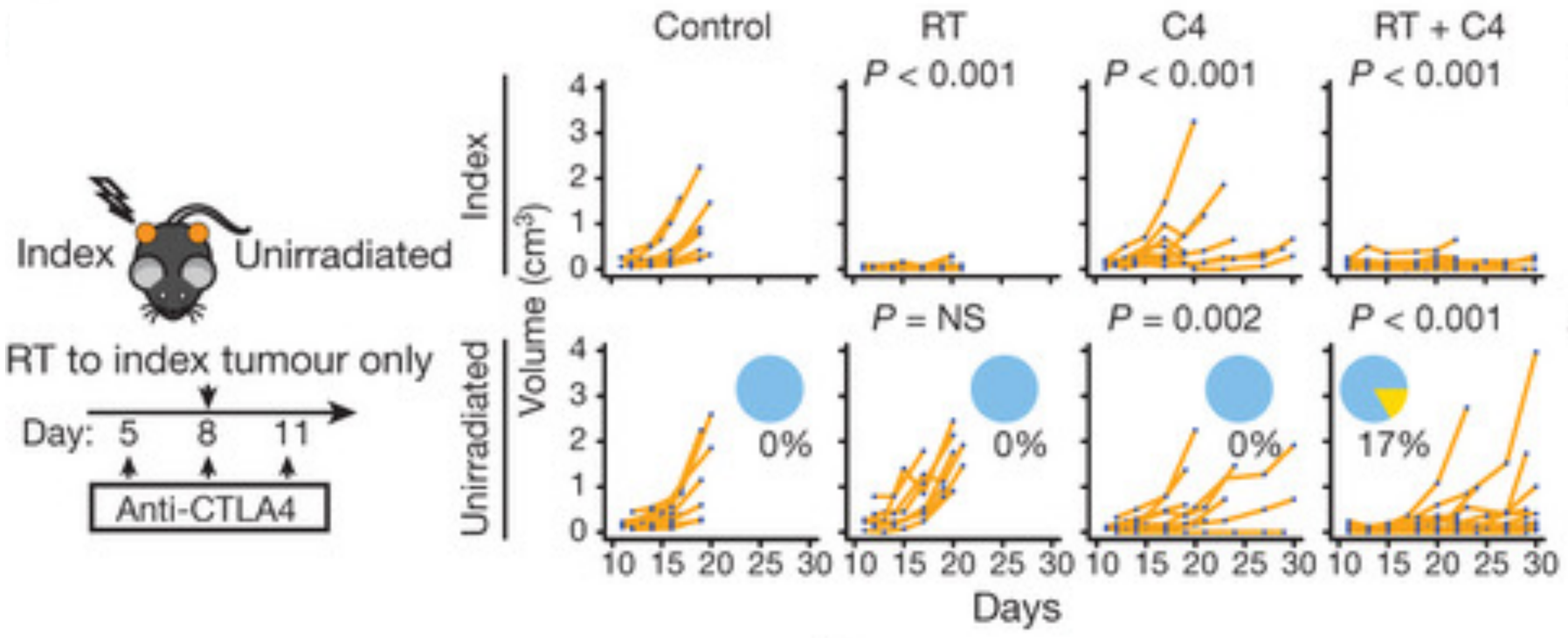
One randomized trial: Various solid tumors with cutaneous metastases

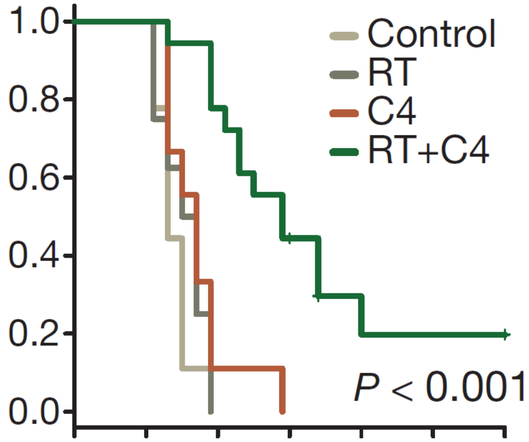
	Population	Control	Experimental
MSKCC 16224	Metastatic cancer patients with cutaneous metastases	Talimogene laherparepvec (TVEC)	TVEC and external beam radiotherapy (27 Gy/3 fractions)



Barker (unpublished)

Immune checkpoint blockade (CTLA4) blockade and radiotherapy (RT) improves durable response and survival

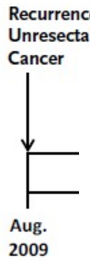




Twyman-Saint Victor et al, Nature, 520 (2015), 373-377

Tumor radiotherapy enables response to checkpoint blockade

A patient with progressing metastatic melanoma despite immune checkpoint blockade exhibited response outside irradiated tumor (so called “abscopal effect”) along with measurable changes in immune system



August 2009

Postow et al, NEJM 2012

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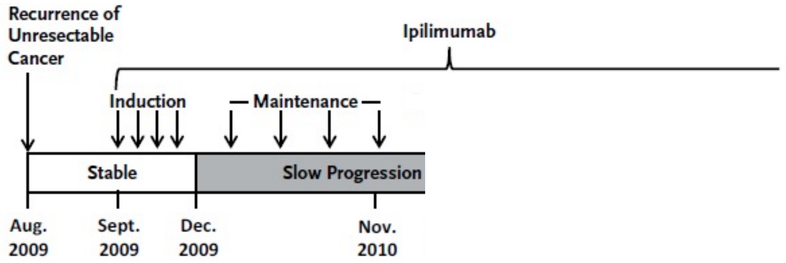
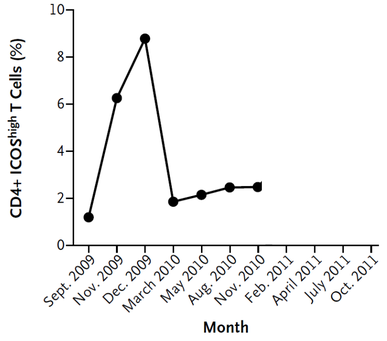
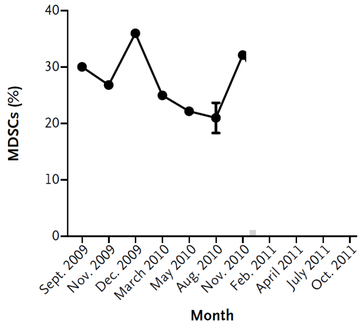
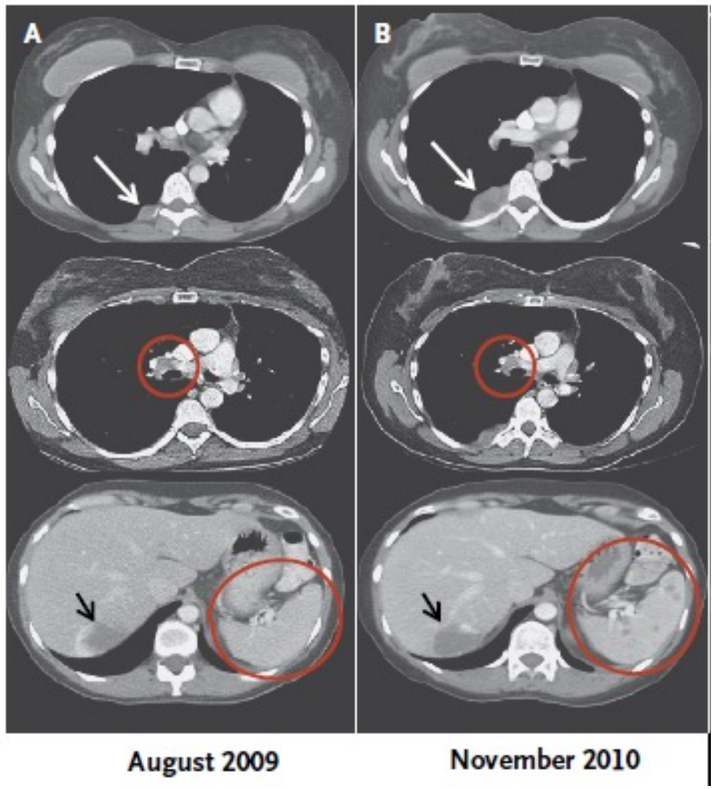






Postow et al, NEJM 2012



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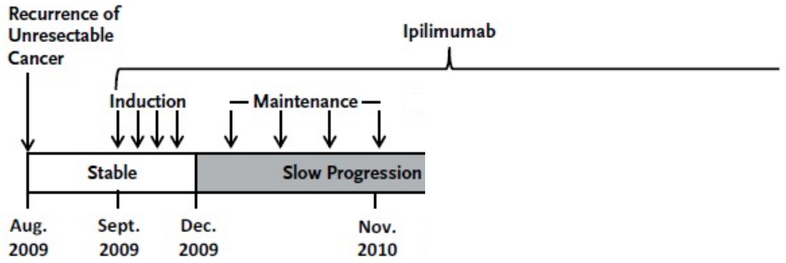
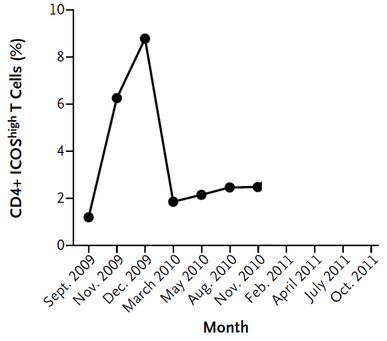
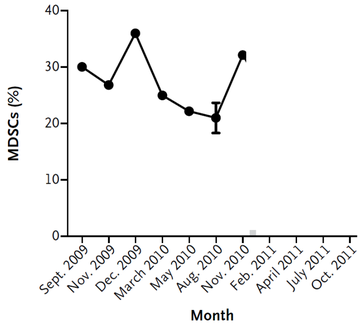
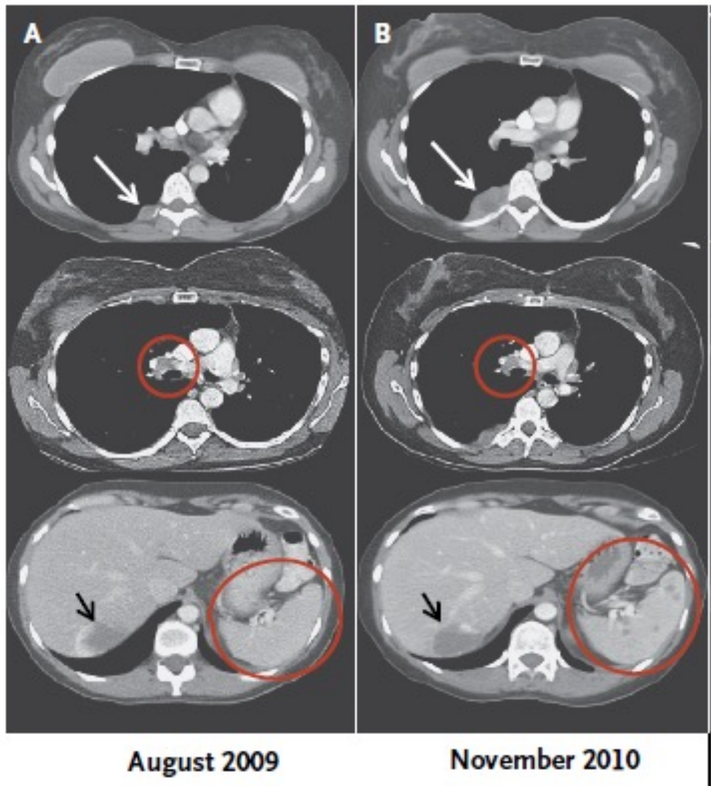
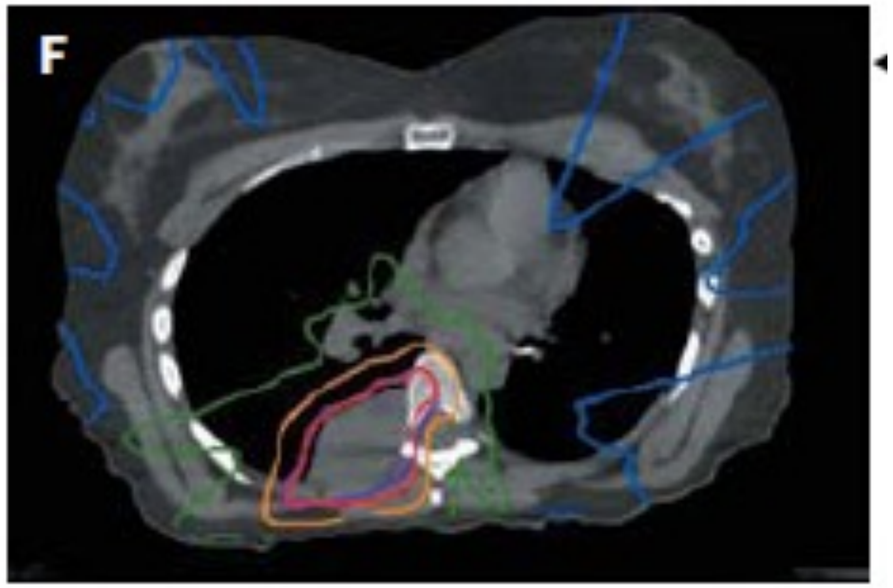






Postow et al, NEJM 2012





December 2010

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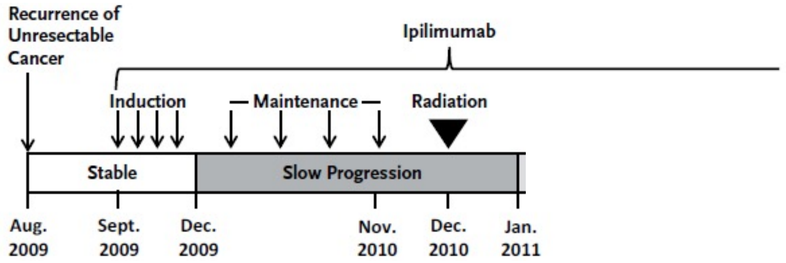
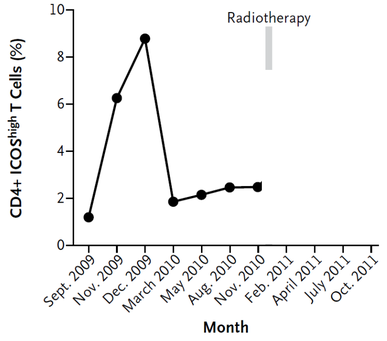
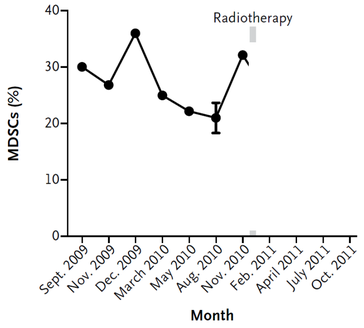
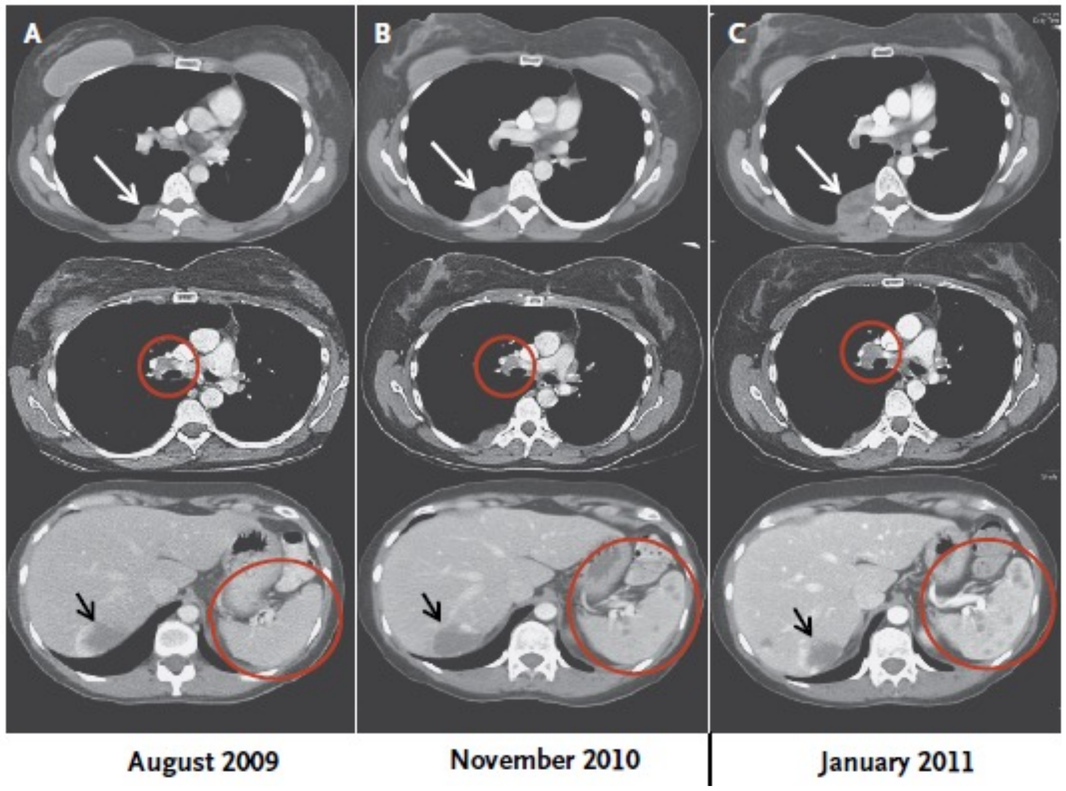






Postow et al, NEJM 2012



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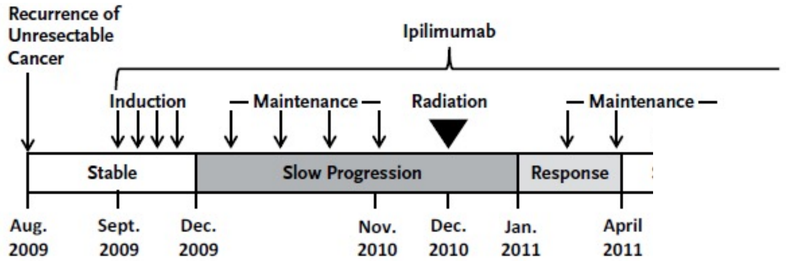

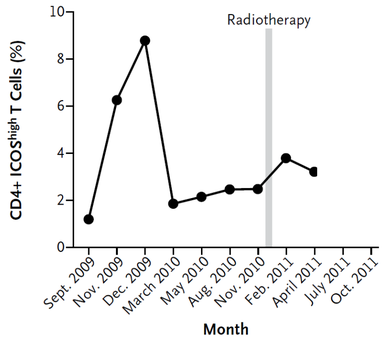

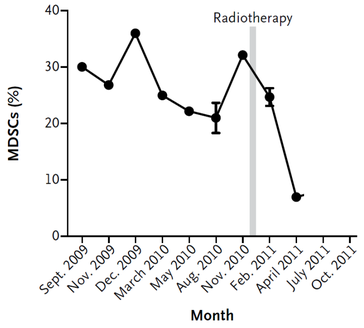

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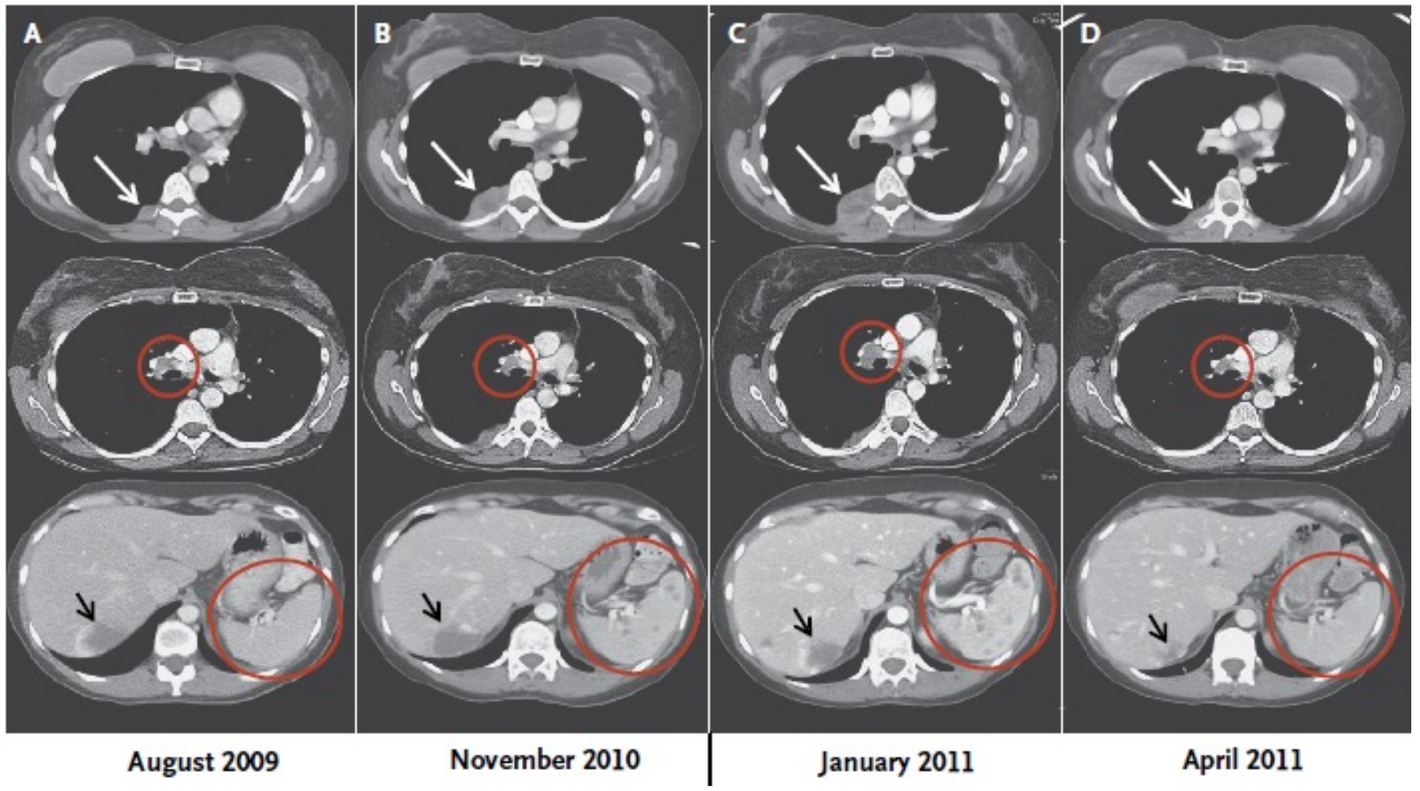

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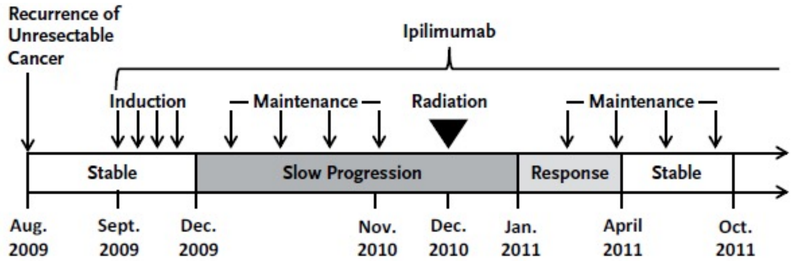

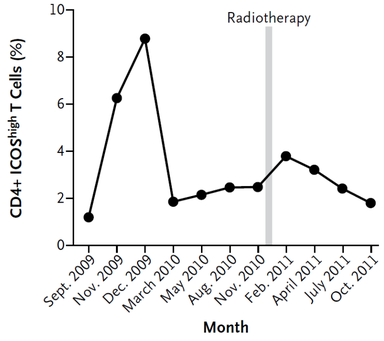

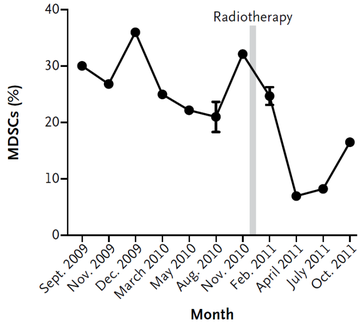

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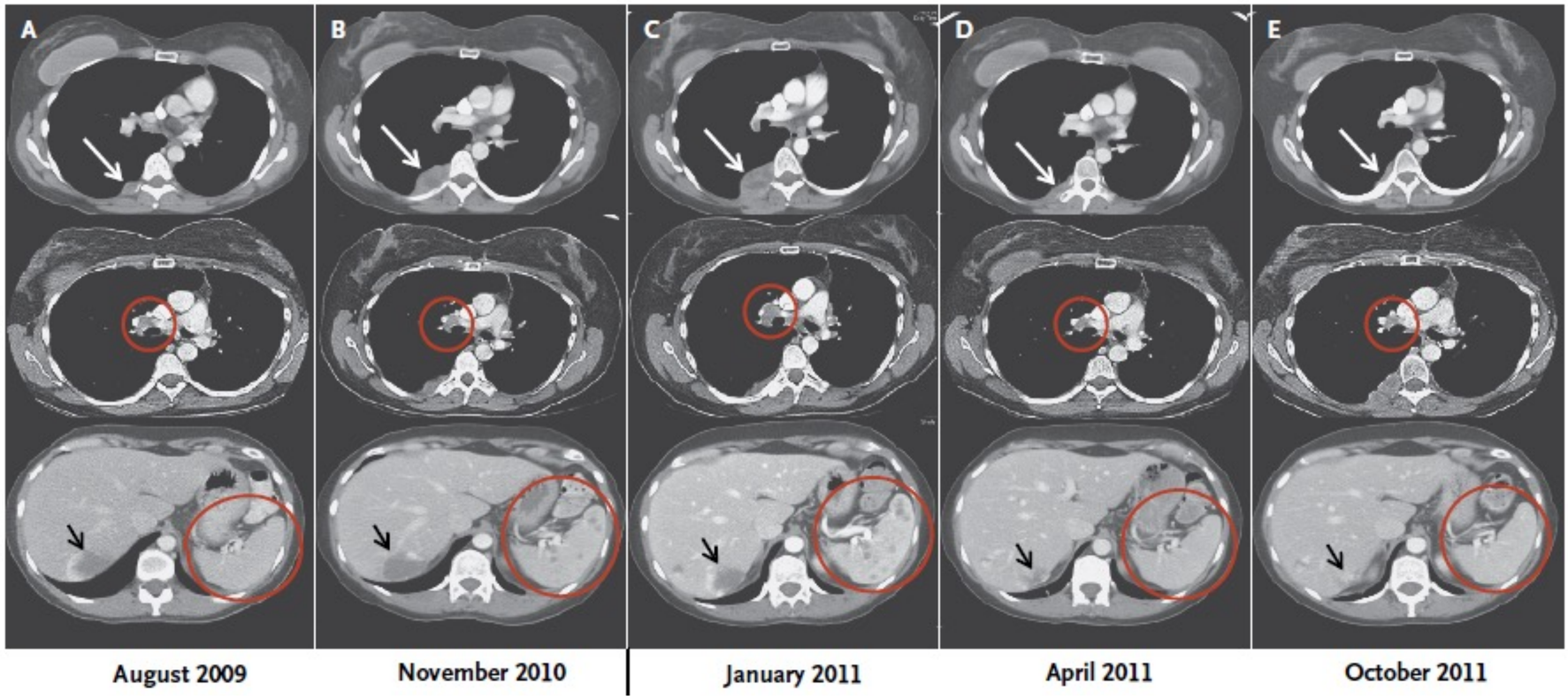


Many preclinical studies suggest favorable interactions of immune checkpoint blockade (ICB) and radiotherapy (RT)

This has led to many clinical trials testing several variables with this combination:

- Radiotherapy (RT) with or without ICB
- Chemoradiotherapy (CRT) with or without ICB
- ICB with or without RT
- RT with ICB or chemotherapy (C)
- RT with single ICB vs dual ICB
- Different RT doses

Radiotherapy with or without immune checkpoint blockade: 1 randomized (phase III) trial

	Population	Control	Experimental	Outcome
CA184-043	Metastatic castrate-resistant prostate cancer patients previously treated with docetaxel treated with radiotherapy	Placebo	Anti-CTLA4 <u>after</u> RT	Longer OS with immunotherapy

Fizazi et al, Eur Urol 2020

Chemoradiotherapy (CRT) with or without immune checkpoint blockade: 6 randomized (n=4 phase III, n=2 phase II) trials

	Population	Control	Experimental	Outcome
PACIFIC (III)	Locally advanced non-small cell lung cancer treated with CRT	Placebo	Anti-PDL1 after CRT	Longer PFS and OS with immunotherapy
Checkmate 548 (III)	Glioblastoma, MGMT methylated treated with surgery then CRT	Placebo	Anti-PD1 during CRT	No difference in PFS or OS
Javelin Head Neck 100 (III)	Locally advanced squamous cell carcinoma of head and neck treated with CRT	Placebo	Anti-PDL1 during CRT	No difference in PFS or OS
STIMULI (II)	Limited stage small cell lung cancer treated with CRT	Observation	Anti-PD1/CTLA4 after CRT	No difference in PFS or OS
Checkmate 577 (III)	Locally advanced gastroesophageal cancer treated with CRT then surgery	Placebo	Anti-PD1 after surgery	Longer PFS with immunotherapy
NRG GI002 (II)	Locally advanced rectal cancer treated with CRT then surgery	Nothing	Anti-PD1 during CRT	No difference in pathologic response

Antonia et al, NEJM 2017; Weller et al, Neuro Onc 2002; Lee et al, Lancet Onc 2021; Peters et al, Ann Onc 2022; Kelly et al, NEJM 2021; Rahma et al, JAMA Onc 2021

Immune checkpoint blockade with or without radiotherapy: 7 phase II randomized trials

	Population	Control	Experimental	Outcome
PEMBRO-RT	Metastatic non-small cell lung cancer treated with anti-PD1	No SBRT	SBRT before ICB	No difference in response rate or PFS
MDACC	Metastatic non-small cell lung cancer treated with anti-PD1	No SBRT	SBRT during ICB	No difference in response rate or PFS
Emory	Extensive stage small cell lung cancer treated with anti-PD1/CTLA4	No SBRT	SBRT before RT	No difference in response rate or PFS
Moffitt	Metastatic Merkel cell carcinoma treated with anti-PDL1/CTLA4	No SBRT	SBRT during ICB	No difference in response rate or PFS
MSKCC	Metastatic head and neck cancer treated with anti-PD1	No SBRT	SBRT during ICB	No difference in response rate or PFS
DFCI	Metastatic adenoid cystic carcinoma treated with anti-PD1	No SBRT	SBRT during ICB	No difference in response rate or PFS
Cornell	Non-metastatic non-small cell lung cancer treated with anti-PD1 then surgery	No SBRT	SBRT during ICB	Higher rate of pathologic response with RT

Theelan et al, JCO 2019; Welsh et al, J Immunother Cancer 2020; Pakkala et al, J Immunother Cancer 2020; Kim et al, Lancet 2022; McBride et al, JCO 2021; Mahmood et al, IJROBP 2020; Altorki et al, Lancet Onc 2021

Radiotherapy with immune checkpoint blockade vs chemotherapy: 2 randomized (1 phase III, 1 phase II) trials

	Population	Control	Experimental	Outcome
Checkmate 498 (III)	MGMT unmethylated glioblastoma	Chemo during RT	Anti-PD1 during RT	No difference in PFS or OS
Changhai (II)	Recurrent pancreas cancer	Chemo after RT	Anti-PD1 after RT	Longer PFS and OS with ICB

Omuro et al, Neuro-Onc 2022; Xhu et al, Lancet Onc 2021

Immune checkpoint blockade with different doses of radiotherapy: 3 (2 phase II randomized, 1 phase I) trials

	Population	Control	Experimental	Outcome
ETCTN (II)	Metastatic colorectal cancer treated with liver metastasis radiotherapy	2 Gy/4 fractions during ICB	24 Gy/3 fractions during ICB	No difference in response rate or PFS
ETCTN (II)	Metastatic non-small cell lung cancer treated with or without radiotherapy	2 Gy/4 fractions during ICB	24 Gy/3 fractions during ICB	No difference in response rate or PFS with or without RT or between doses of RT
MSKCC (I)	Metastatic melanoma treated with anti-PD1/CTLA4	30 Gy/10 fractions during ICB	27 Gy/3 fractions during ICB	No difference in response rate or PFS

Monjazeb et al, Clin Cancer Res 2021; Schoenfeld et al, Lancet Onc 2022; Postow et al, Clin Cancer Res 2020

Historical intersection of radiation and immuno-oncology predict for future integration

Further study needed to better understand how radiation affects

- Immune system
- Tumor microenvironment
- Preclinical models that better predict clinical outcomes

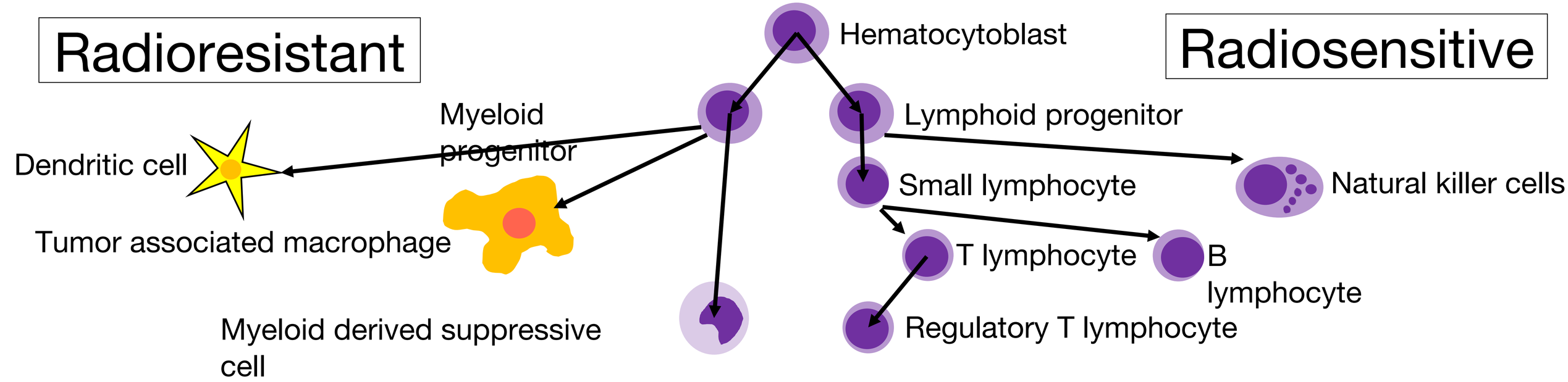
Further study needed to better understand how the immune system affects

- Tumor response to radiation
- Tumor response to radiation-immunotherapy combinations

NASDC
NCI Awardee Skills Development Consortium

Integrating Radiation Oncology Into Immuno-Oncology

Questions


Radioresistant
Radiosensitive
Hematocytoblast
Myeloid progenitor
Lymphoid progenitor
Dendritic cell
Small lymphocyte
Natural killer cells
Tumor associated macrophage
T lymphocyte
B lymphocyte
Myeloid derived suppressive cell
Regulatory T lymphocyte