



Integrating Radiation Oncology Into Immuno-Oncology

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Memorial Sloan Kettering
Cancer Center

Disclosures

MSKCC has received funding to support clinical trials I am leading from:

» Elekta, Amgen, Merck, AlphaTau Medical, EMD Serono

I have received funding for providing scientific advice to:

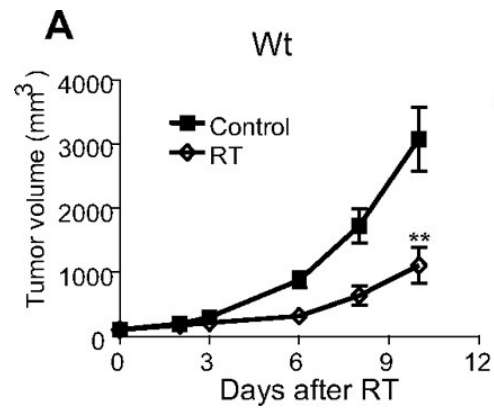
» Regeneron

Intersections of radiation and immune system

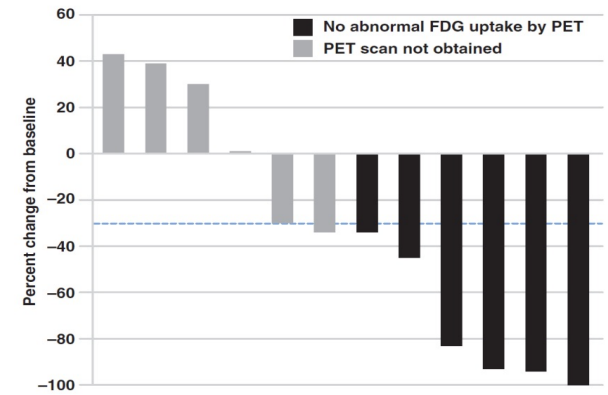
Historic



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

Copyright, 1960, by the Massachusetts Medical Society

Volume 262

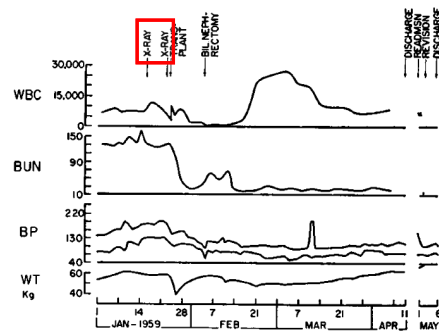
JUNE 23, 1960

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

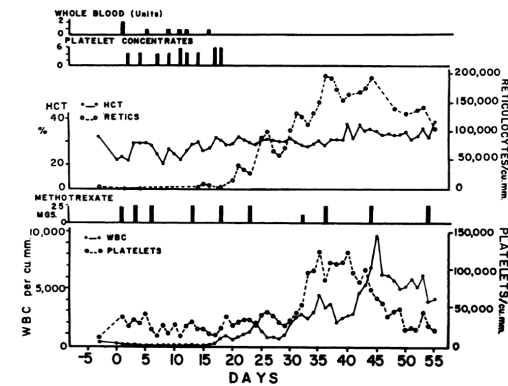
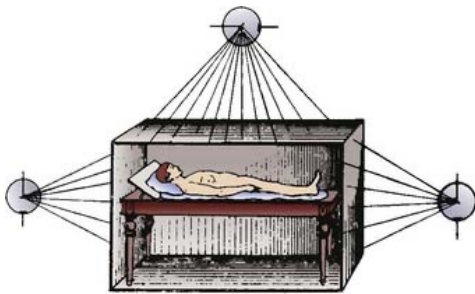


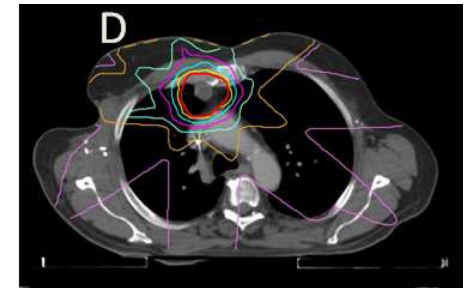
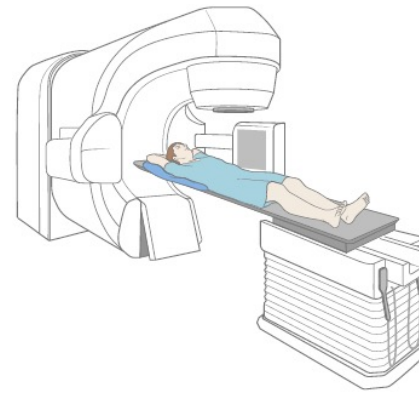
Fig. 1.—Hematological events in patient given 950 rads whole-body irradiation and allogeneic bone marrow.

Radiotherapy can be given in different ways for cancer

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

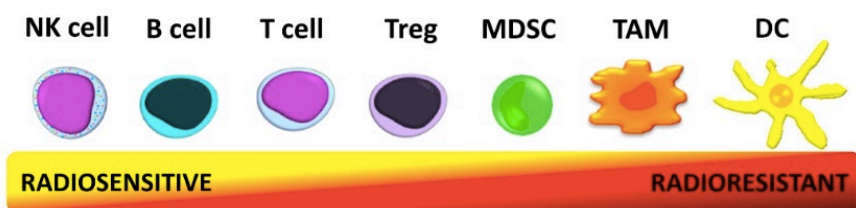


Tumor radiotherapy irradiates a tumor or focal area suspected to harbor cancer

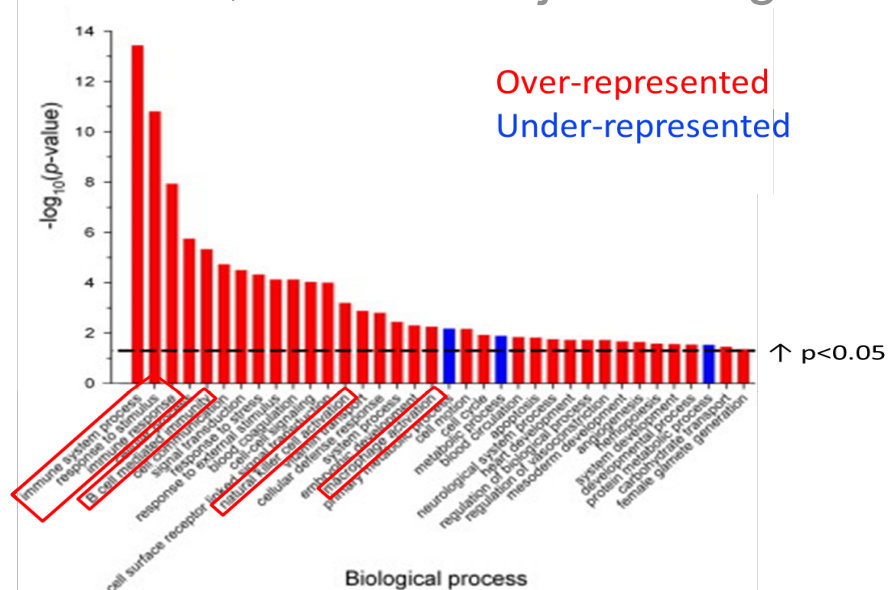


What does total body irradiation do to the immune system?

Immune cells are variably sensitive to effects of radiation



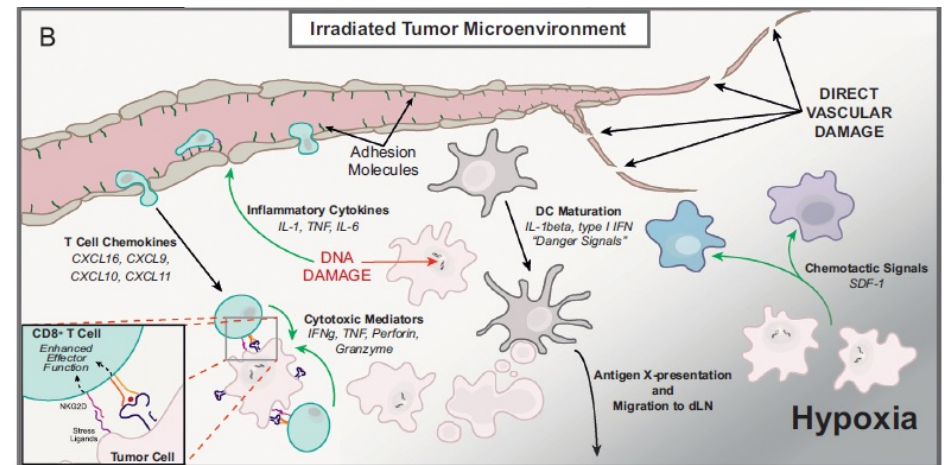
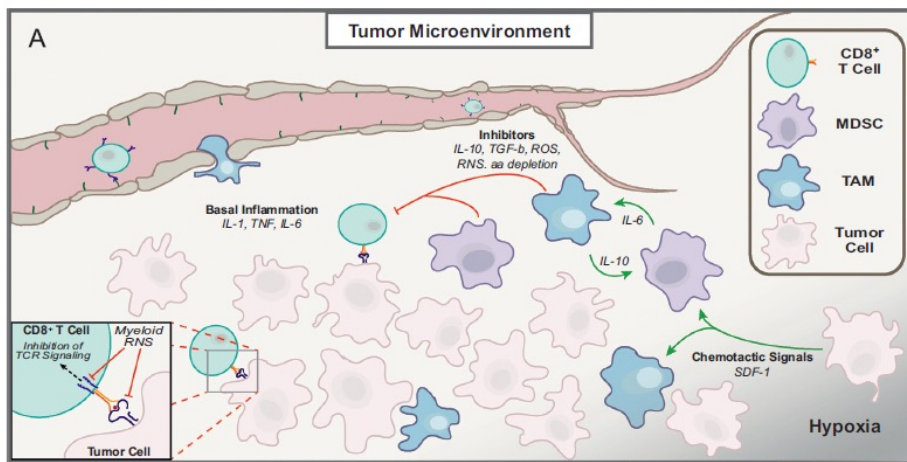
Radiation may alter immune cell function, rather than just killing them



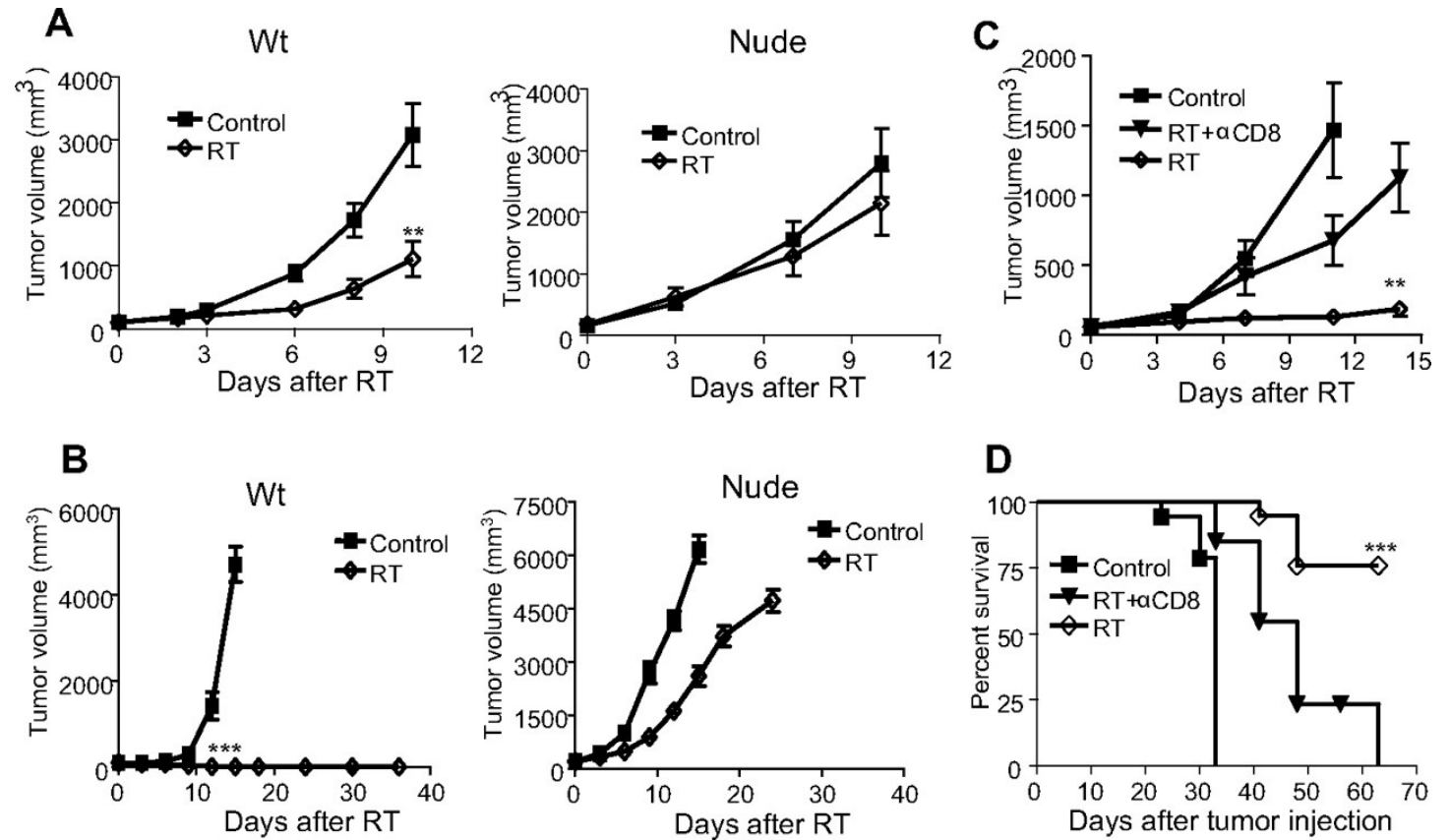
The effect of tumor radiotherapy on tumor microenvironment

Tumor microenvironment is rich with immune system components

Tumor radiotherapy alters the microenvironment producing immune effects



Effect of tumor radiotherapy is governed (in part) by the immune system



Is combining radiotherapy and immunotherapy beneficial?

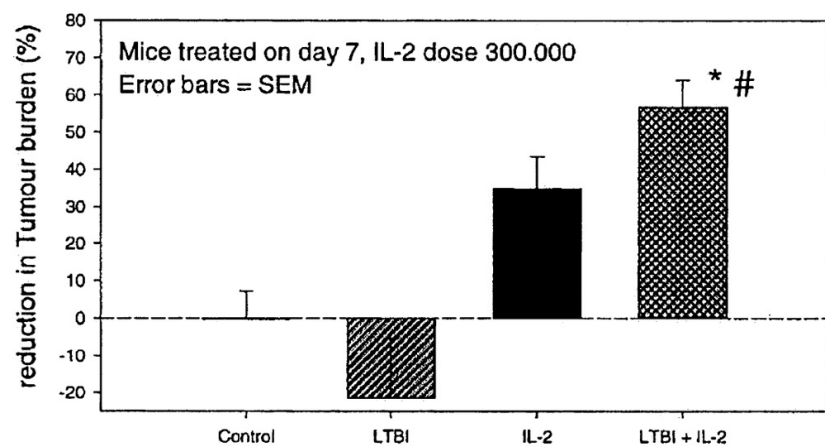
Well-designed, rationale clinical trials may provide the answers...

Trials of radiation and:

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

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

Preclinical data suggested greater reduction in tumor burden with IL2 and low dose total body irradiation (TBI)



Phase II clinical trial of IL2 and TBI was negative (<5% response rate)

Response evaluation

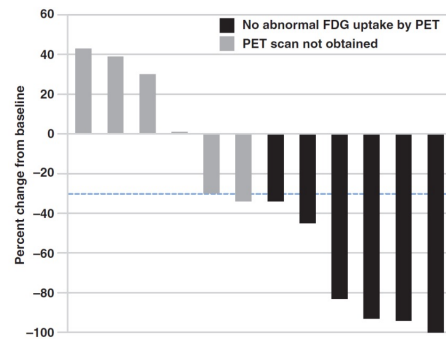
	Study group (n=45)	
	Number	%
Patients	45	100
CR	0	
PR	2	4.4
NC	13	29
PD	30	67
Overall response rate	2	4.4

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

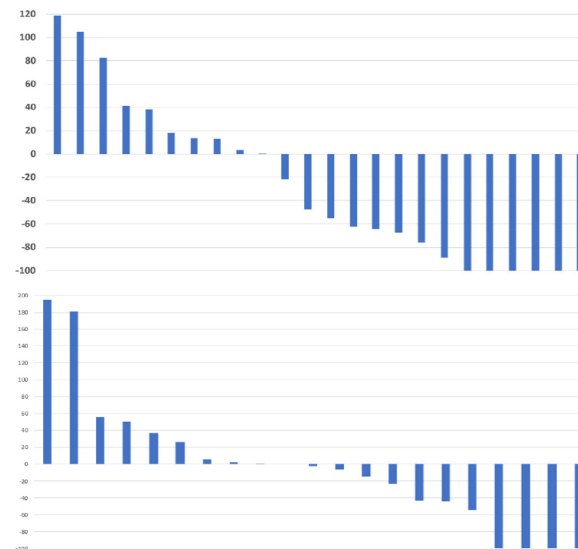
Cytokine and radiotherapy: Effect of dose and/or target?

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) PR 4 (57.1)	CR 5 (71.4) PR 0
Renal cancer (n = 5)	CR 0 (0) PR 3 (60)	CR 1 (20) PR 2 (40)



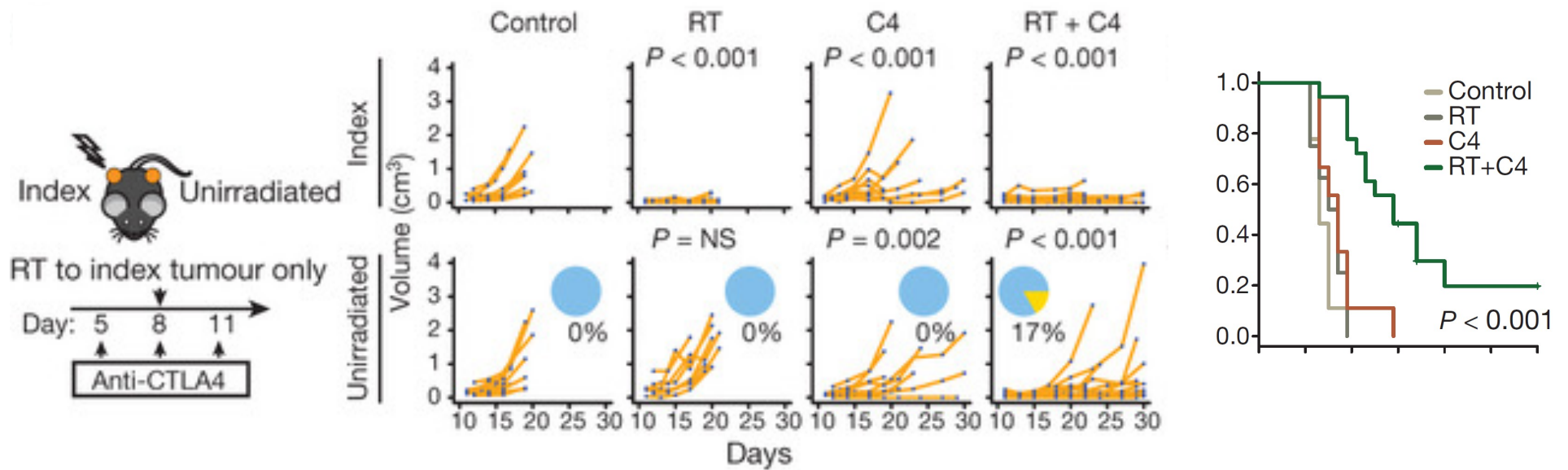
Randomized phase II clinical trial demonstrated adding SBRT to IL2 increased response rate



IL2+SBRT
54% response rate

IL2 alone
35% response rate

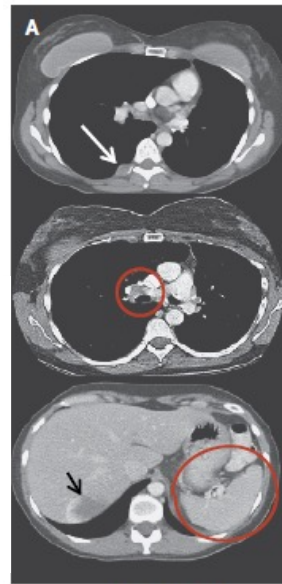
CTLA4 (C4) blockade and radiotherapy (RT) improves durable response and survival



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

Recurrence of
Unresectable
Cancer
↓
Aug.
2009

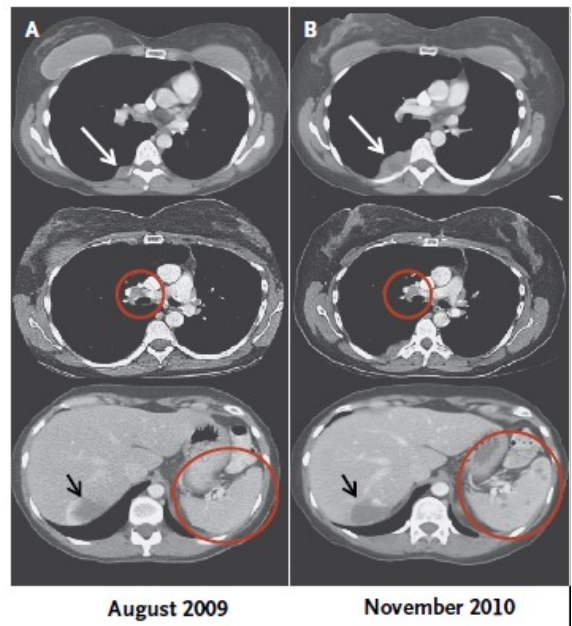
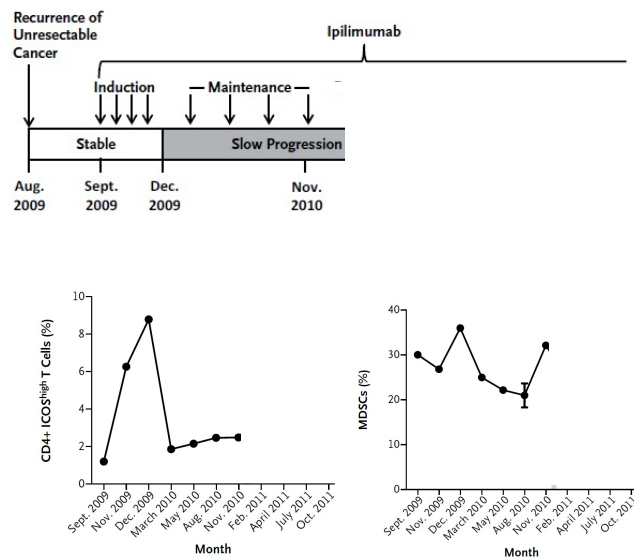


August 2009

Postow et al, NEJM 2012

Tumor radiotherapy enables response to checkpoint blockade

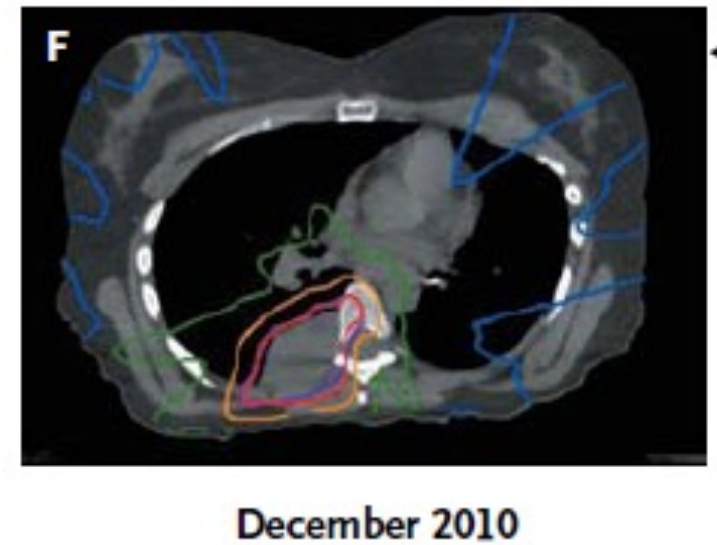
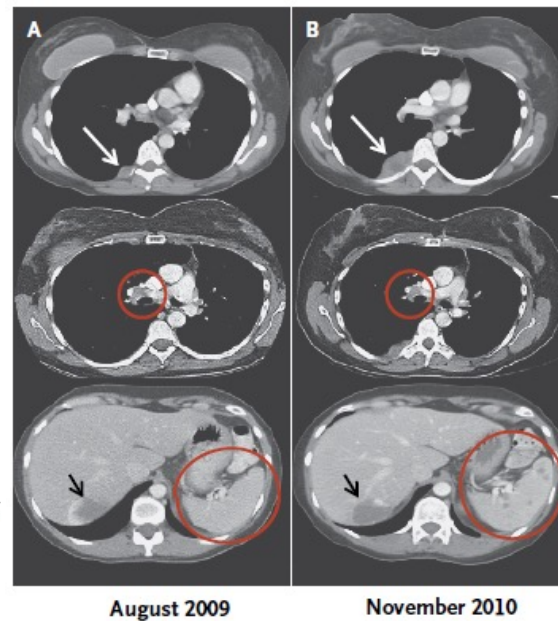
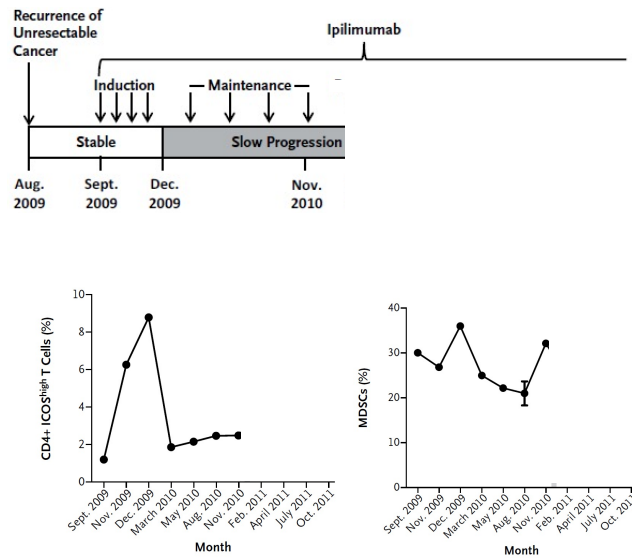
A patient with progressing metastatic melanoma despite immune checkpoint blockade exhibited response outside irradiated tumor (so called “abscopal effect”) along with measurable changes in immune system



Postow et al, NEJM 2012

Tumor radiotherapy enables response to checkpoint blockade

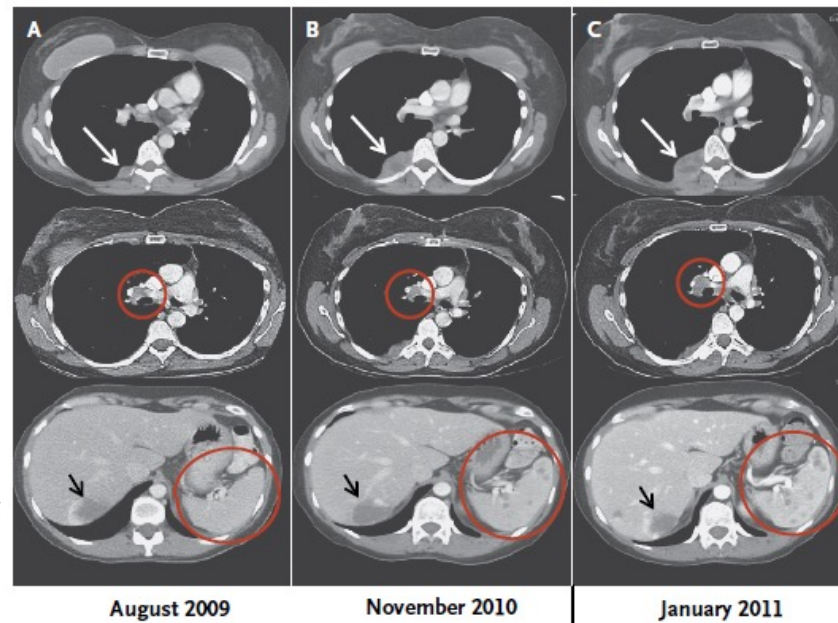
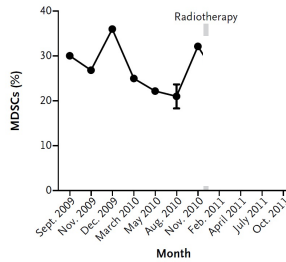
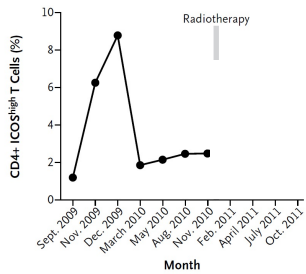
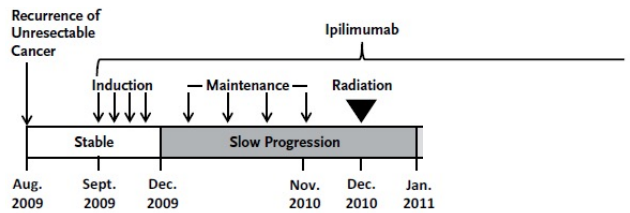
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Postow et al, NEJM 2012

Tumor radiotherapy enables response to checkpoint blockade

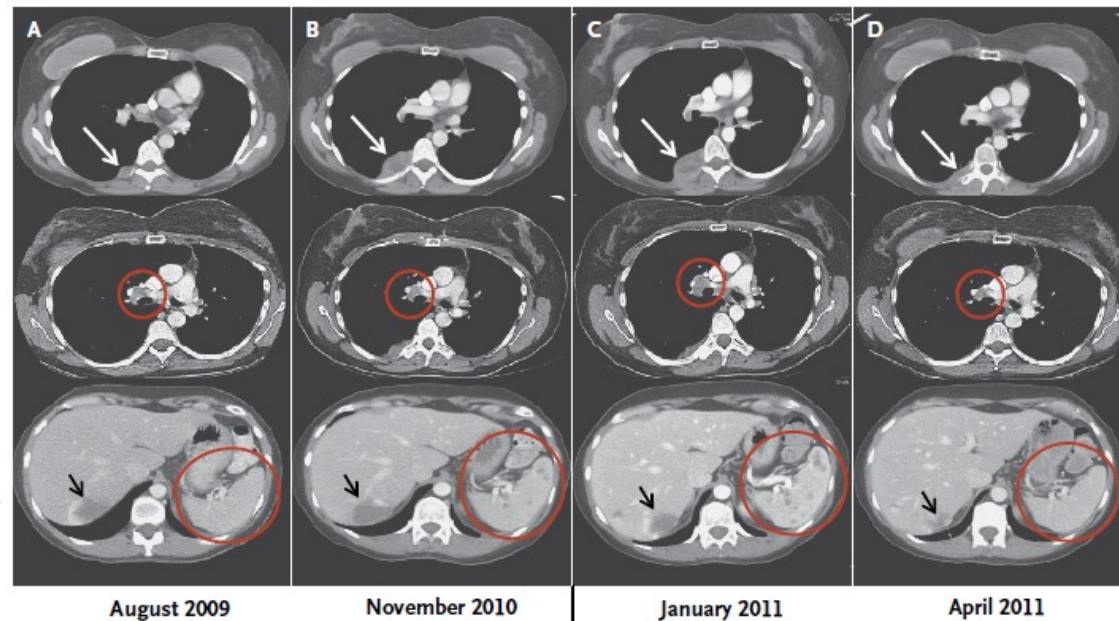
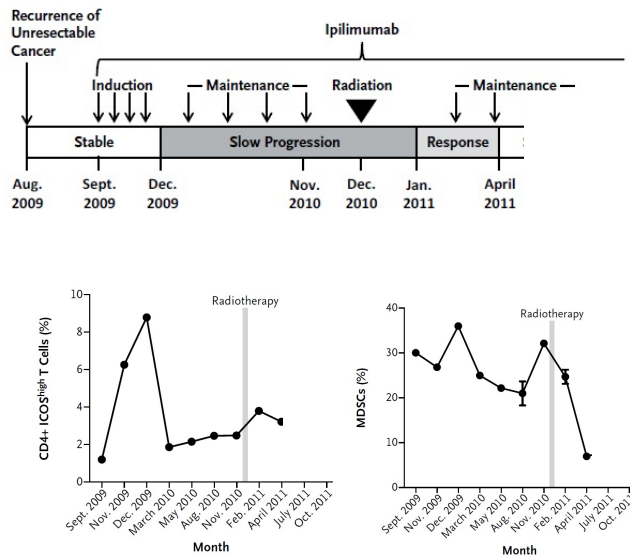
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Postow et al, NEJM 2012

Tumor radiotherapy enables response to checkpoint blockade

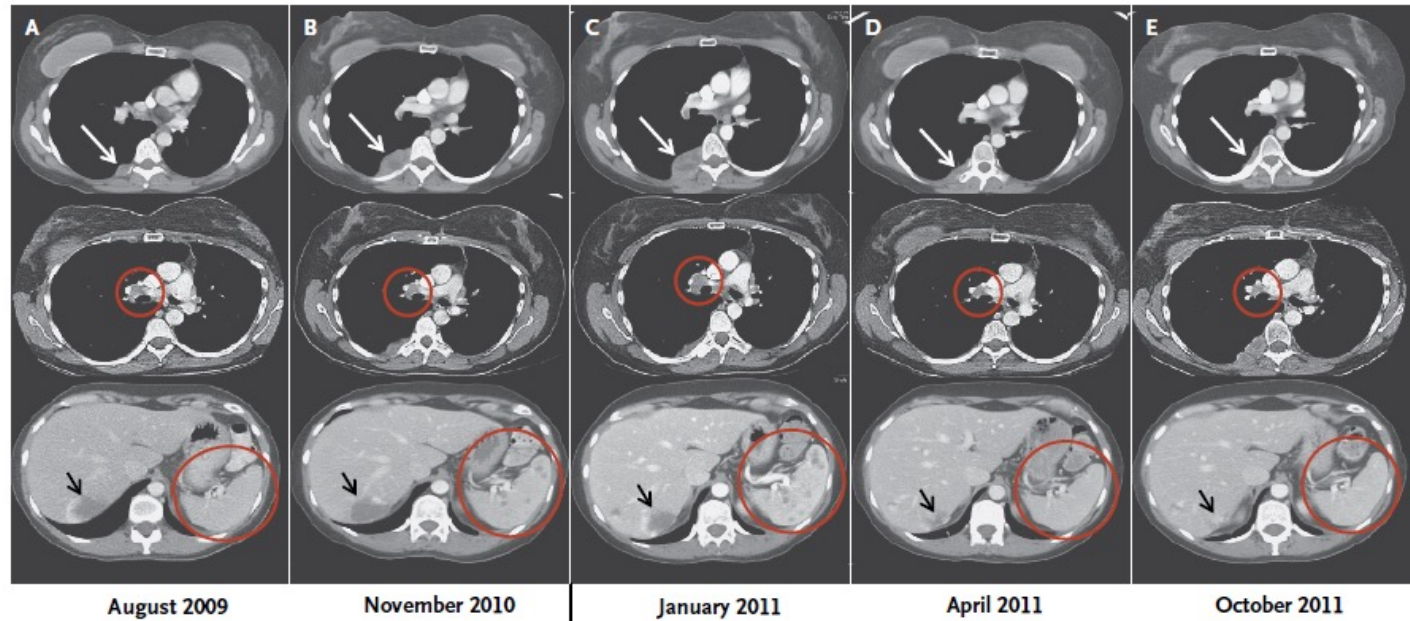
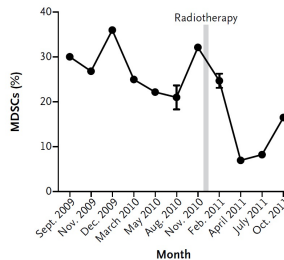
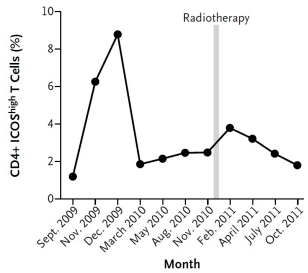
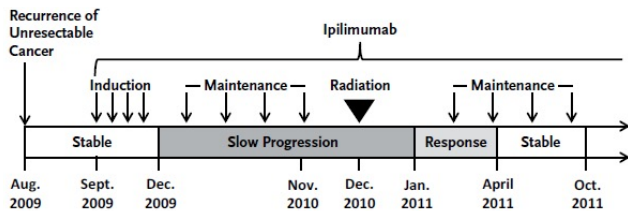
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Postow et al, NEJM 2012

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



Postow et al, NEJM 2012

Radiotherapy with or without immune checkpoint blockade

Two randomized trials: Prostate and lung cancer

	Population	Control	Experimental
CA184-043	Stage IV castrate-resistant prostate cancer patients previously treated with docetaxel treated with bone metastasis directed radiotherapy (8 Gy/1 fraction)	Placebo	Ipilimumab (anti-CTLA4 immunotherapy)
PACIFIC	Stage III non-small cell lung cancer patients treated with definitive chemoradiotherapy (54-66 Gy fractionated)	Placebo	Durvalumab (anti-PD1 immunotherapy)

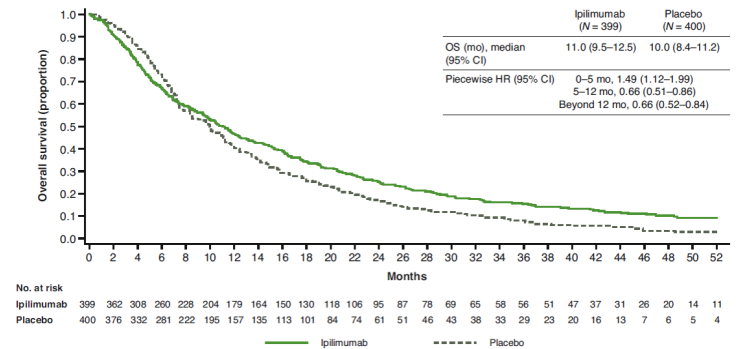
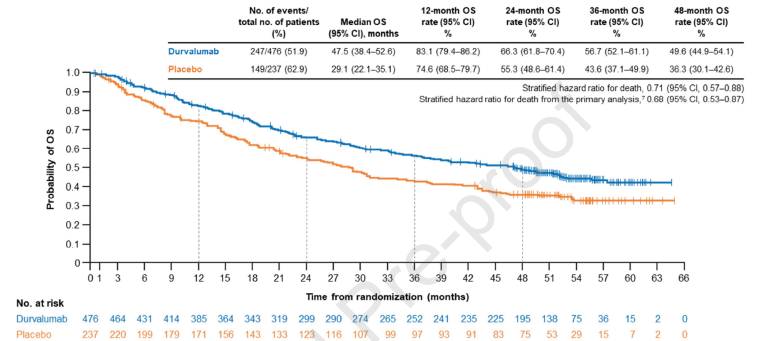


Fig. 1 – Overall survival. CI = confidence interval; HR = hazard ratio; OS = overall survival.

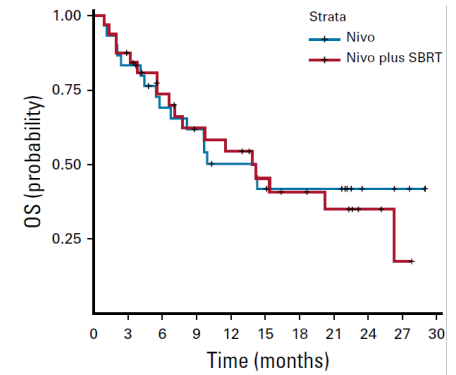


Fizazi et al, Eur Urol 2020; Faivre-Finn et al, JTO 2020

Immune checkpoint blockade with or without radiotherapy

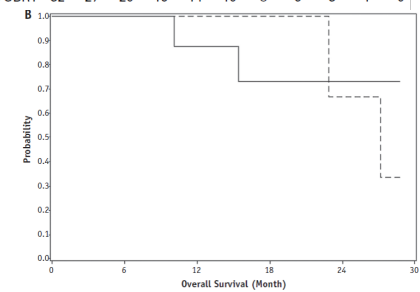
Two randomized trials: Head & neck cancer

	Population	Control	Experimental
MSKCC 15-253	Stage IV mucosal squamous cell carcinoma of the head and neck	Nivolumab (anti-PD1) Immunotherapy	Nivolumab and metastasis-directed SBRT (27 Gy/3 fractions)
DFCI 16-609	Recurrent or metastatic adenoid cystic carcinoma	<u>Pembrolizumab (anti-PD1) Immunotherapy</u>	<u>Pembrolizumab and SBRT (30 Gy/5 fractions)</u>



No. at risk:

	30	25	19	16	12	10	9	9	4	3	0
Nivo	30	25	19	16	12	10	9	9	4	3	0
Nivo plus SBRT	32	27	20	16	14	10	8	6	3	1	0



Arm	TOTAL	DEATH	ALIVE	MEDIAN
Pembro + RT	10	2	8	27.2
Pembro alone	10	2	8	27.2

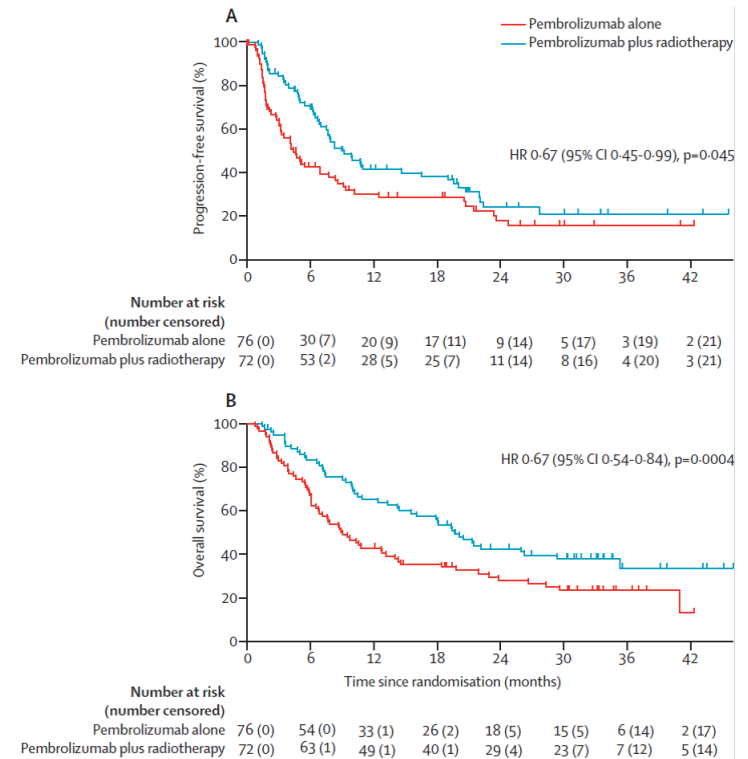
McBride et al, JCO 2020; Schoenfeld et al, IJROBP 2021

Immune checkpoint blockade with or without radiotherapy

Pooled analysis of 2 randomized trials: Lung cancer

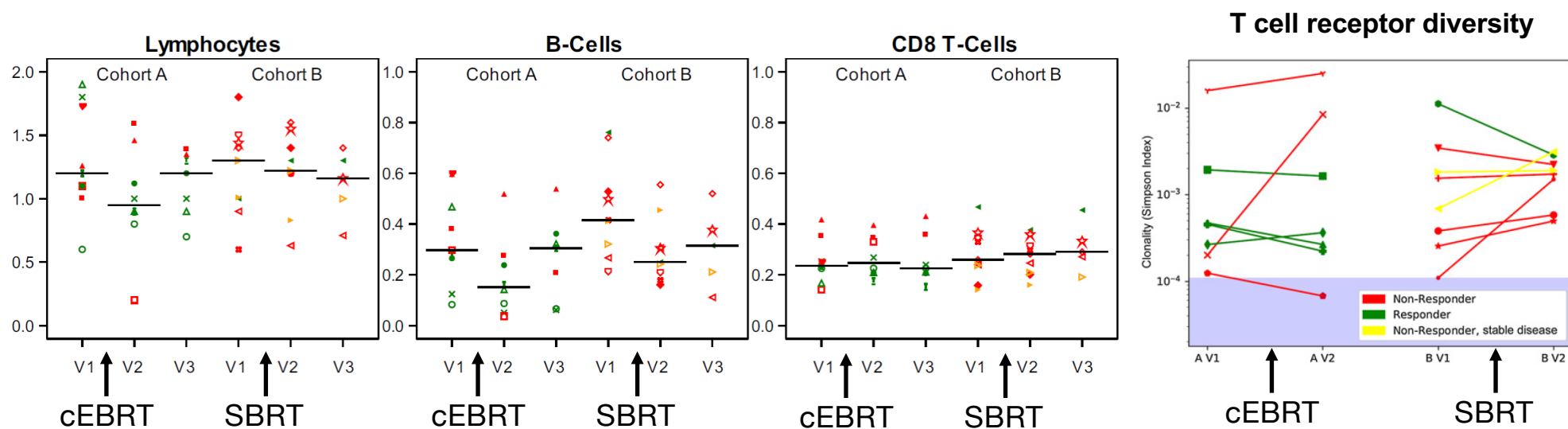
	Population	Control	Experimental
PEMBRO-RT	Stage IV non-small cell lung cancer patients that progressed after at least one prior chemotherapy regimen	Pembrolizumab (anti-PD1) Immunotherapy	Pembrolizumab and metastasis directed SBRT (24 Gy/3 fractions)
MDACC 2014-1020	Stage IV non-small cell lung cancer patients	Pembrolizumab (anti-PD1) Immunotherapy	Pembrolizumab and metastasis directed traditional radiotherapy (45 Gy/15 fractions) or SBRT (50 Gy/4 fractions)

Theelan et al, JAMA Onc 2019; Welsh et al, JITC 2020; Theelan et al, Lancet Resp 2020

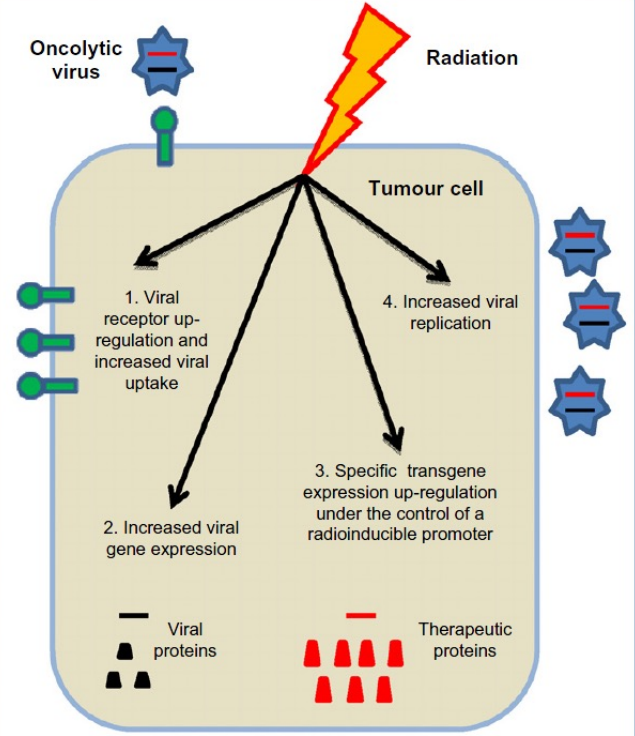
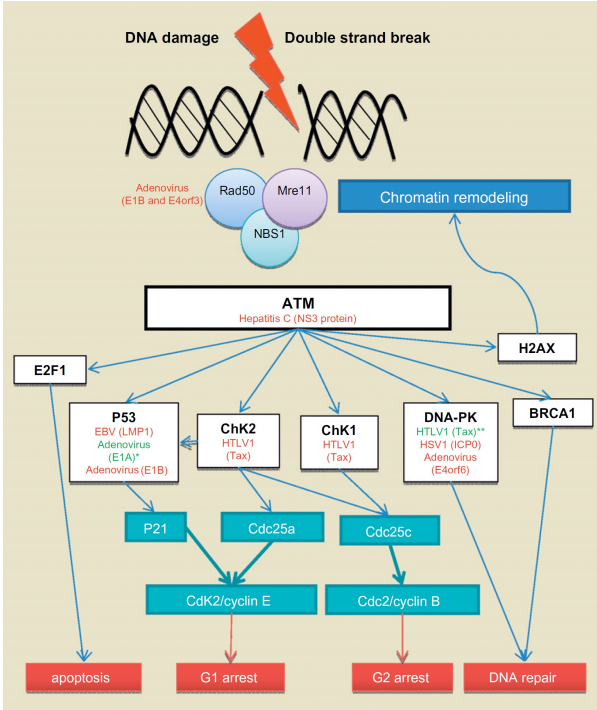


What happens after RT during immune checkpoint blockade?

Metastatic melanoma patients treated with dual immune checkpoint blockade (anti-PD1 and anti-CTLA4) with fractionated traditional RT (Cohort A, 30 Gy/10 fractions) or SBRT (Cohort B, 27 Gy/3 fractions)



Beyond checkpoint blockade and radiotherapy: Oncolytic immunotherapy and radiotherapy

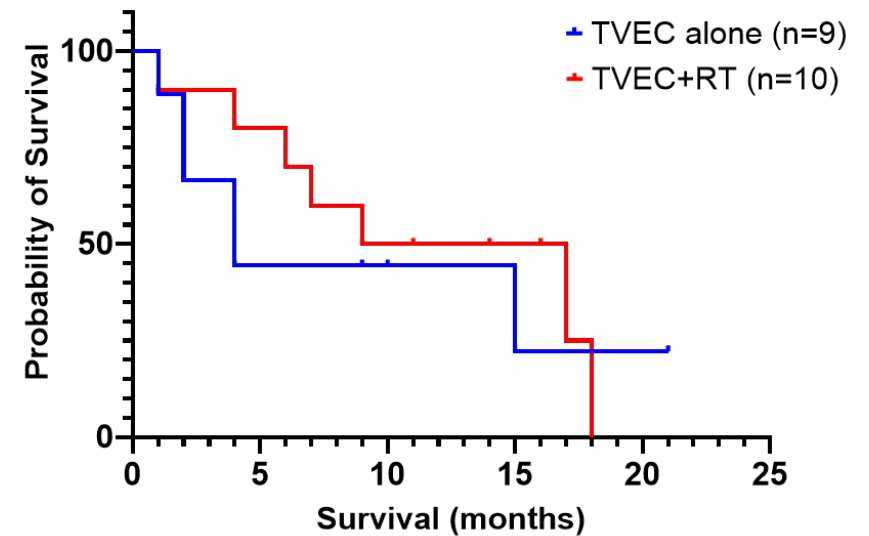


Touchefeu et al, Rad Oncol, 99 (2011) 262-270

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)

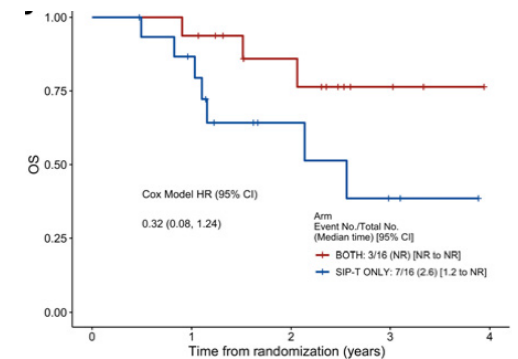
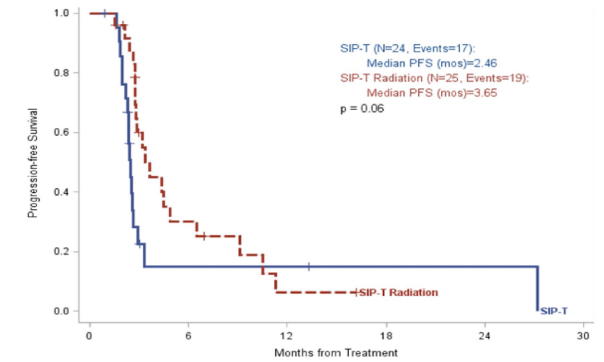


Barker (unpublished)

Autologous cellular therapy with or without radiotherapy

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 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)



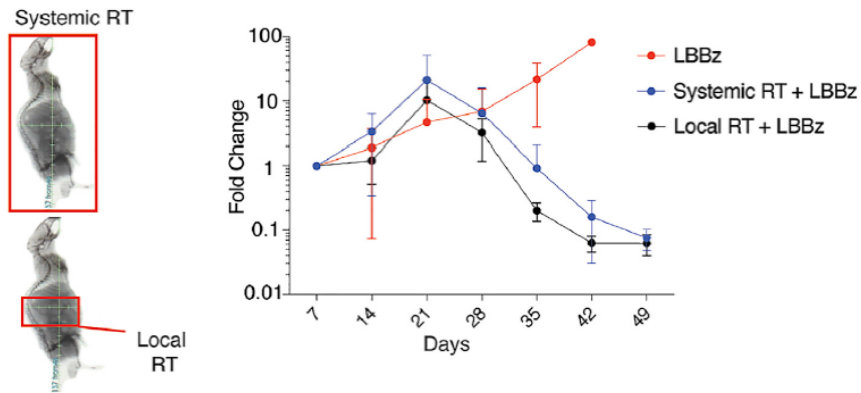
Number at risk

Arm	0	1	2	3	4
BOTH	16	15	9	3	0
SIP-T ONLY	16	12	5	2	0

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

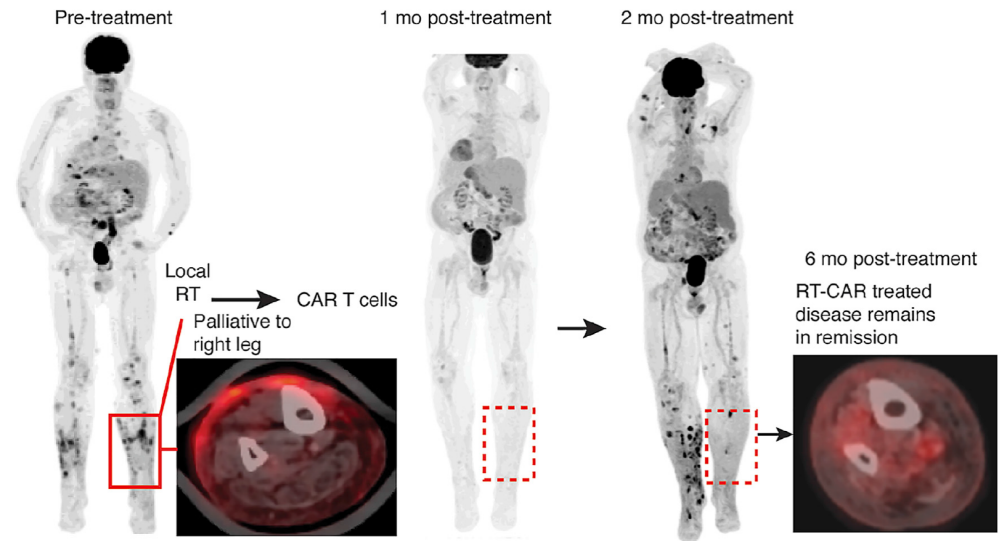
Chimeric antigen receptor (CAR) T cell therapy and radiation

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



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

Further study needed to better understand how radiation affects

- » Immune system
- » Tumor microenvironment

Further study needed to better understand how the immune system affects

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





Integrating Radiation Oncology Into Immuno-Oncology Questions