IS THERE A ROLE FOR RADIATION THERAPY AND IMMUNOTHERAPY?

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DISCLOSURE

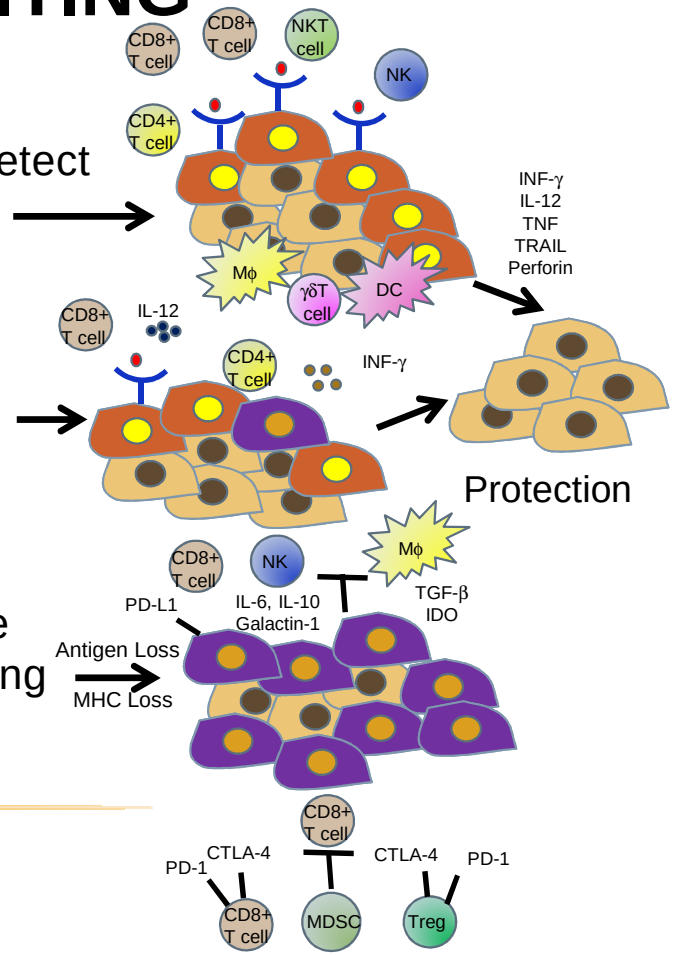
Abney Clinical Scholar

OBJECTIVES

- Review mechanisms of immune escape by cancer cells
- Review radiation effects on the immune system
- Review current strategies to combine RT and immunotherapy
  - IL-2
  - Dendritic cell production
  - Tumor antigen vaccine
  - CTLA-4 antibody/PD-1antibody
  - TLR agonist
  - TGF-β antibody

CANCER IMMUNOEDITING

- Three phases:
  - Elimination – Innate and adaptive immune systems detect and destroy developing tumor before it is clinically apparent.
  - Equilibrium – The immune system maintains residual tumor cells in a functional state of dormancy.
  - Escape – Tumor cells that aquire the ability to escape immune recognition and destruction emerge as growing tumors.



Science. 2011;331:1565-70

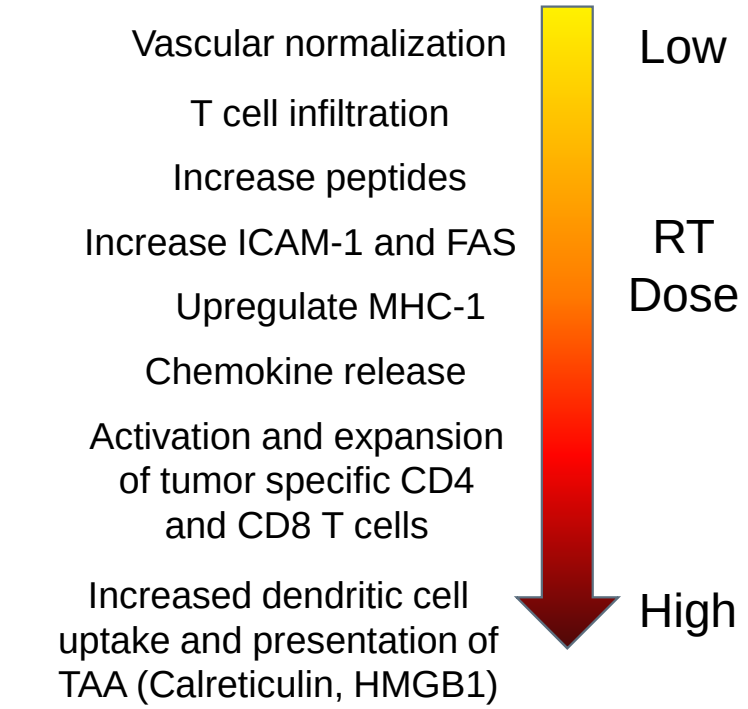
MECHANISMS OF ESCAPE

- Loss of tumor antigen expression
  1. Tumor cells that do not express strong rejection antigens.
  2. Loss of MHC class 1 proteins that present these antigens
  3. Loss of antigen processing function
- Immunosuppresive state in the tumor microenvironment
  1. Production of immunosuppresive cytokines (VGEF, TGF-β, galectin, IDO)
  2. Recruitment of immunosuppressive cells (Treg, MDSCs, TAMs)

Science. 2011;331:1565-70

RADIATION EFFECTS ON THE IMMUNE SYSTEM

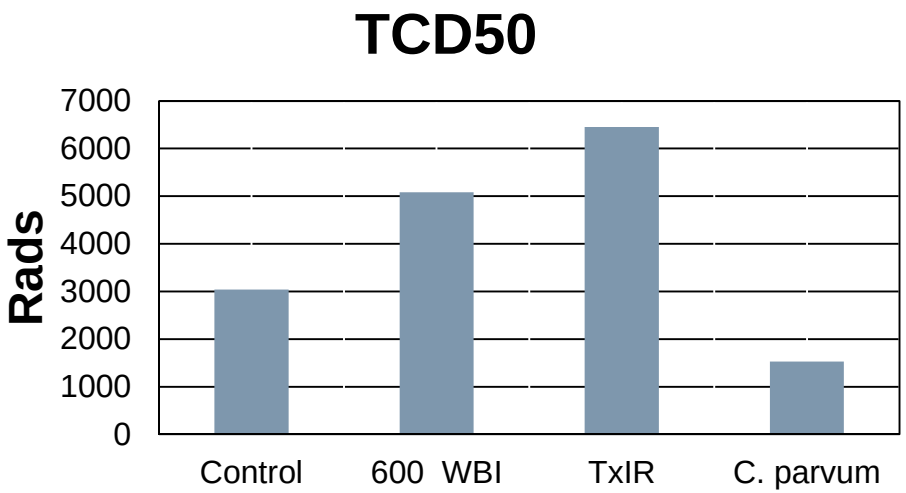
- Upregulation of HLA, presentation of TAAs, FAS expression
  - May restore immune effector recognition and immune-mediated cell death
- Skewing of cytokines to inflammatory repertoire; upregulation of co-stimulatory molecules
- Upregulation of chemokines, adhesion molecules (VCAM-1, E-selectin, ICAM-1)
  - Restoration of regulated APC trafficking
- Upregulation of co-stimulatory molecules
- Suppressive - Increase Tregs and activate TGF-β



PNAS. 1989;86:10104-7 J Immunol. 2003;170:6338-47 Cancer Res. 2004:64:7985-94 J Immunol. 2008;180:3132-9
Nat Med. 2007;13:1050-9 Front Oncol. 2012;2:90 J Clin Invest. 1994;93:892-9

EARLY EVIDENCE

- 3-methylcholanthrene-induced fibrosarcoma (FSa)
  - TCD50 – Radiation dose to control 50% of tumors
- Normal syngeneic C3Hf/Bu mice
- Mice with 600 rad whole body irradiation (WBI)
- Mice permanently immunosuppressed with thymectomy and 900 rads WBI followed by syngeneic bone marrow (TxIR) reconstitution.
- Mice treated with Corynebacterium parvum

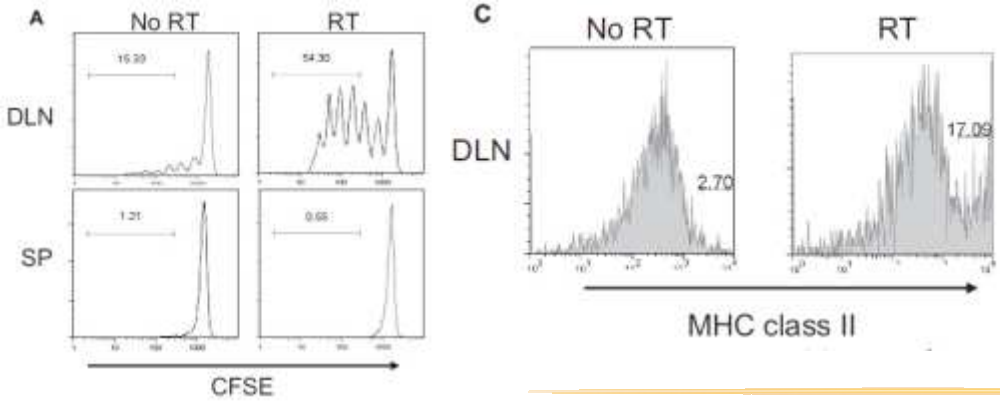


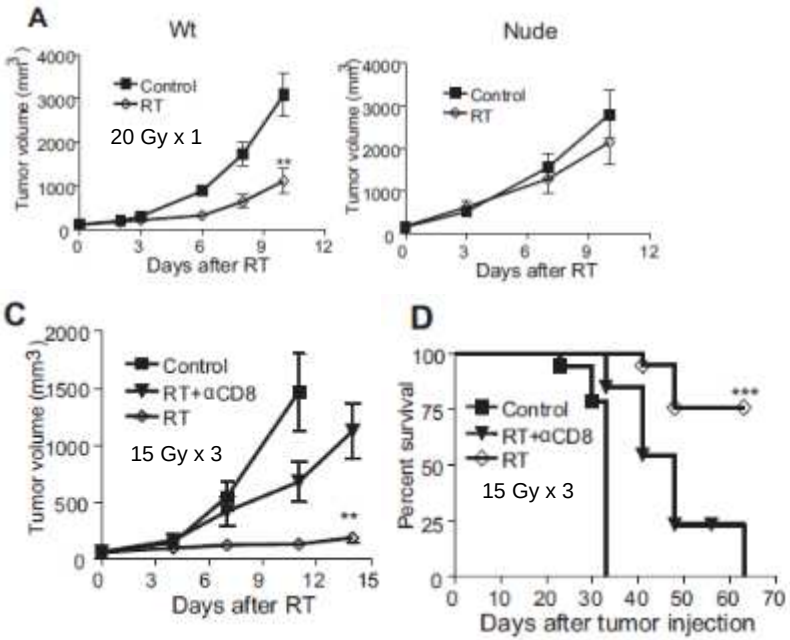
J Natl Cancer Inst. 1979;63:1229-35

RT DOSE AND FRACTIONATION

RT DOSE & FX AND IMMUNE RESPONSE

- WT or nude mice injected with B16 melanoma cells
  - Increasing immunogenicity of B16 cells did not influence RT mediated regression.
  - $CD8^+$ 2C transgenic cells CFSE labeled and transferred into mice.

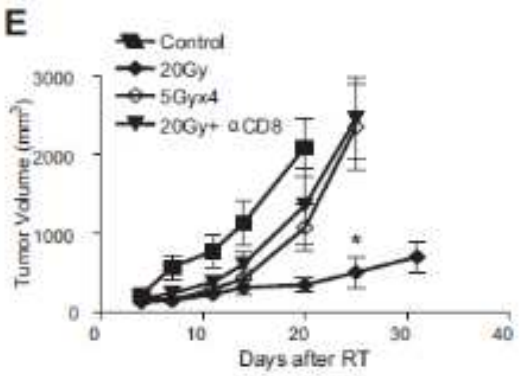


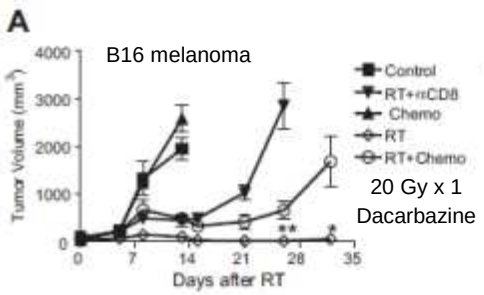


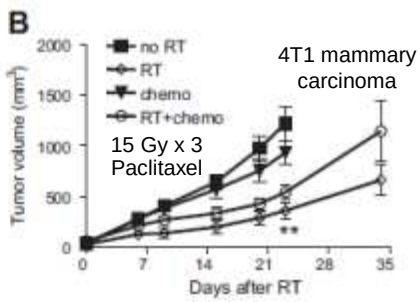
Blood. 2009;114:589-95

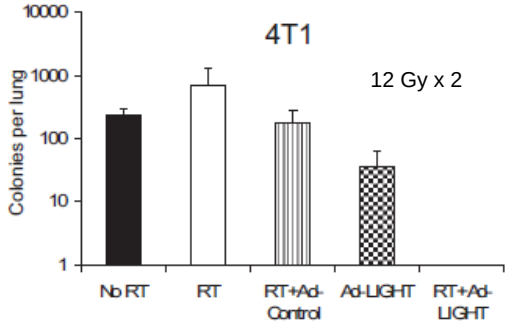
RT DOSE & FX AND IMMUNE RESPONSE

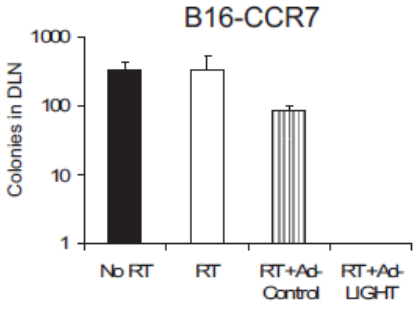
- Chemotherapy and fractionated RT diminish the effect of RT ablation and $CD8^+$ priming.
- RT + Ad-LIGHT immunotherapy reduces lung metastases









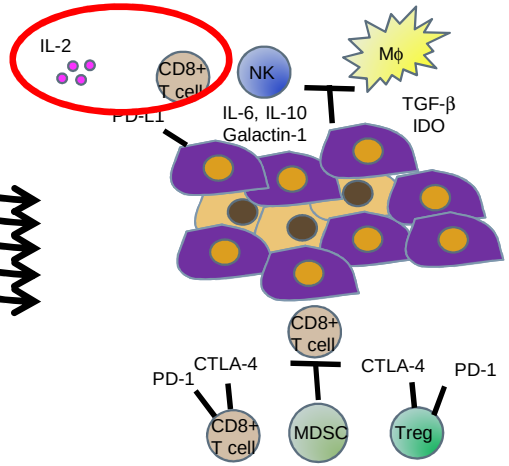


Blood. 2009;114:589-95

PRE-CLINICAL AND CLINICAL EVIDENCE

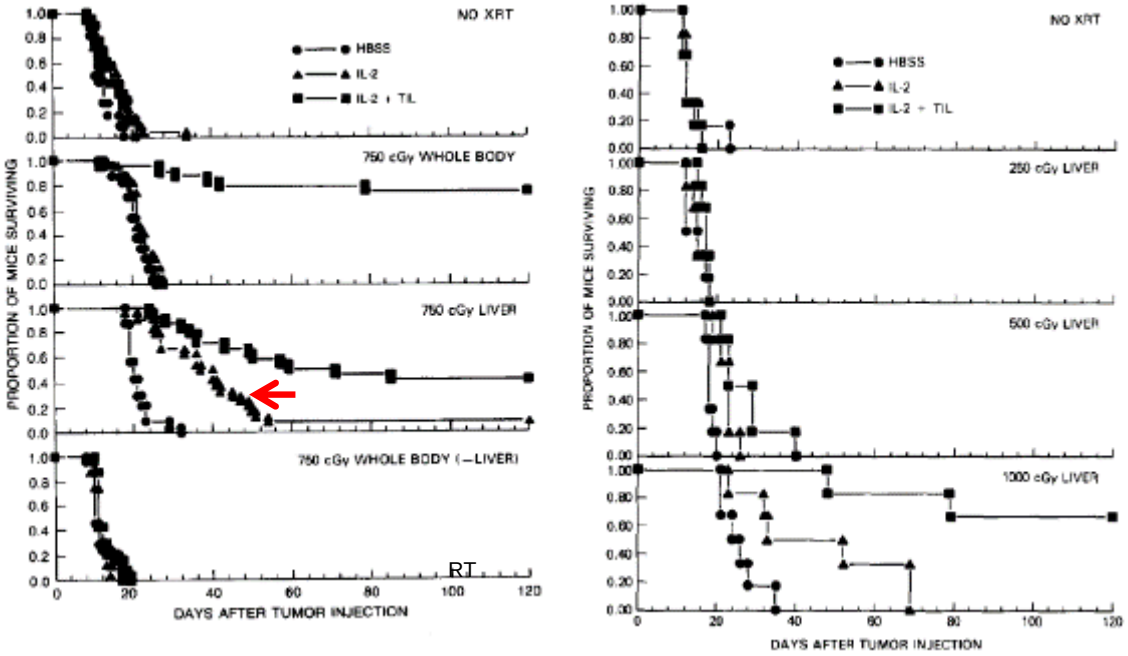
IL-2 and TIL

RT



IL-2, TIL, +RT

- MC-38 adenocarcinoma liver metastases
  - RT effect thought to be to direct anti-tumor activity.
  - IL-2 alone activity with local RT.
  - Dose dependent effect of local RT
  - Treating ½ liver showed no anti-tumor activity with IL-2 and RT



J Exp Med. 1990;171:249-63

PILOT STUDY OF RT AND IL2

- Metastatic cancer with at least two sites of measurable disease.

↓

Surgery for obtaining tumor for TIL preparation

↓

5 Gy bid x 2-4 fx to one site

↓

IL-2 at 720,000 IU/kg q8 hr x 15 planned doses +/- TILs to start 2-24 hrs after RT

↓

IL-2 cycle 2 after 7-10 day break

	n=28
Median Age (range), yrs	48.5 (26-66)
Sex	
Male	21 (75%)
Female	7 (25%)
Histology	
Melanoma	14 (50%)
RCC	12 (43%)
Bladder	1 (3.5%)
Sarcoma	1 (3.5%)
RT Site	
Lung parenchyma	7 (25%)
Lung hilum/mediastinum	5 (18%)
Adrenal	3 (11%)
Bone	4 (14%)
Soft tissue	5 (18%)
Abdominal mass	3 (11%)
Liver	1 (4%)

J Immunother. 1991;12:265-71

PILOT STUDY OF RT AND IL2

- 5 patients received TIL – one PR in field.

- Why no benefit?
  - RT dose too low?
  - RT field to large?

	RT field (%)	Outside RT field (%)
Complete Response	1 (4)	0 (0)
Partial Response	3 (11)	2 (7)
Stable Disease	13 (46)	5 (18)
Progressive Disease	8 (29)	20 (71)
Inevaluable	3 (11)	1 (4)
Overall Response (CR+PR)	4 (14)	2 (7)

J Immunother. 1991;12:265-71

PHASE I STUDY OF SBRT AND IL2

- Metastatic melanoma or RCC with at least one lesion amenable to SBRT in the lung, mediastinum, or liver and at least one other site not treated with SBRT.

↓

20 Gy x 1 fx to one site (2 fx in cohort 2 and 3 fx in cohort 3)

↓

IL-2 at 600,000 IU/kg q8 hr x 14 planned doses to start 3 days after SBRT

↓

IL-2 cycle 2 after 16 day break

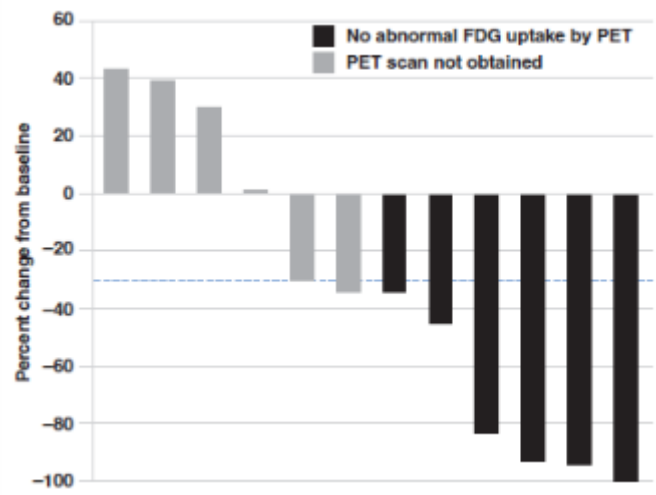
↓

Re-image and repeat IL-2 course if regression

2009-2010	n=12
Median Age (range), yrs	61 (51-65)
Sex	
Male	10 (83%)
Female	2 (17%)
Histology	
Melanoma	7 (58%)
RCC	5 (42%)
SBRT Site	
Peripheral lung	5 (42%)
Central lung	2 (17%)
Mediastinum	1 (8%)
Liver	4 (33%)
SBRT site max diameter (range), cm	1.8 (0.5-6.1)

Sci Transl Med. 2012;137:137ra74

PHASE I STUDY OF SBRT AND IL2

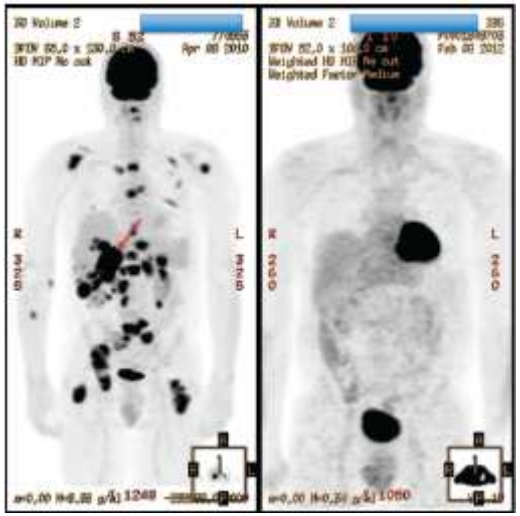


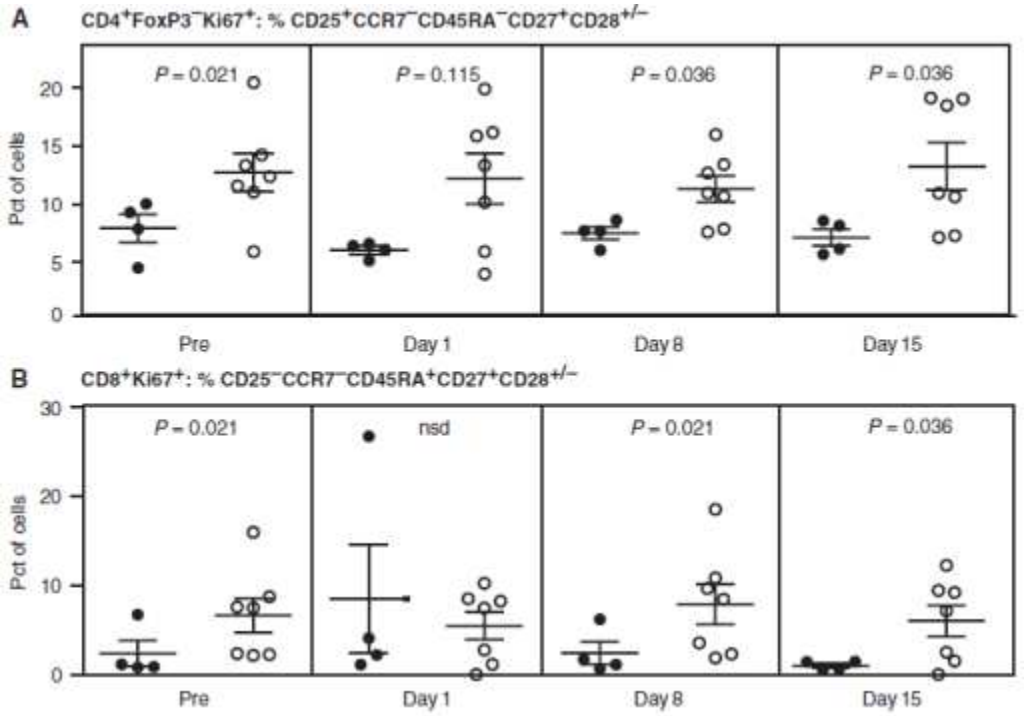
	CT (%)	PET (%)
Complete Response	1 (8.4)	6 (50)
Partial Response	7 (58.3)	2 (16.7)
Stable Disease	1 (8.4)	1 (8.4)
Progressive Disease	3 (25)	3 (25)
Overall Response (CR+PR)	8 (66.7)	8 (66.7)
Melanoma (n=7)		
CR	1 (14.3)	5 (71.4)
PR	4 (57.1)	0
RCC (n=5)		
CR	0 (0)	1 (20)
PR	3 (60)	2 (40)

- ORR for melanoma 71% was > 16% historical for IL-2.
- Of 8 responding patients – 6 maintained response median 480 days.

Sci Transl Med. 2012;137:137ra74

PHASE I STUDY OF SBRT AND IL2





- Responders had a higher frequency of proliferating FOXP3^{-}, Ki67^{+} CD4^{+} TEM phenotype cells as well as CD8^{+} TEM phenotype at baseline and through day 15.

Sci Transl Med. 2012;137:137ra74

RT AND IL2

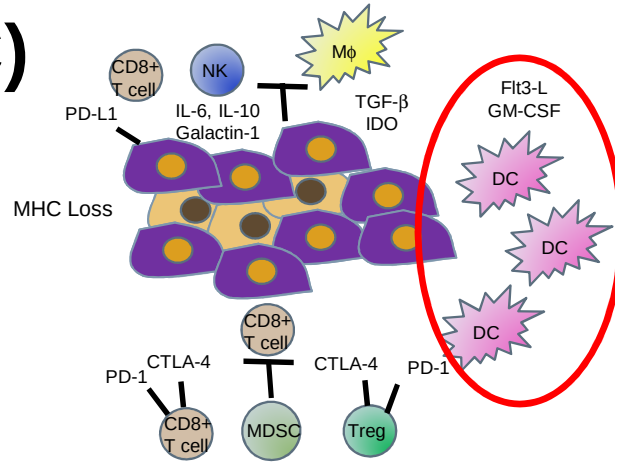
- What will be the role of high dose IL-2 as other immunotherapy strategies evolve and play a more prominent role?

Samples of Ongoing Clinical Trials of IL-2 and RT				
Trial ID	**Accrual Goal**	**Design**	**Histology**	**Primary Endpoint**
NCT01416831 (Phase II)	44	Arm 1: High-Dose IL-2 alone Arm 2: High Dose IL-2 and SBRT (20 Gy x 1 or 20 Gy x 2)	Metastatic Melanoma	ORR
NCT01416831 (Phase II)	84	Arm 1: High-Dose IL-2 alone Arm 2: High Dose IL-2 and SBRT (20 Gy x 2)	Metastatic Melanoma	ORR
NCT01896271 (Phase II)	26	High Dose IL-2 and SBRT (20 Gy x 1-3 fx)	Metastatic Clear Cell RCC	ORR

PRE-CLINICAL AND CLINICAL EVIDENCE

DENDRITIC CELL (DC) PRODUCTION

RT

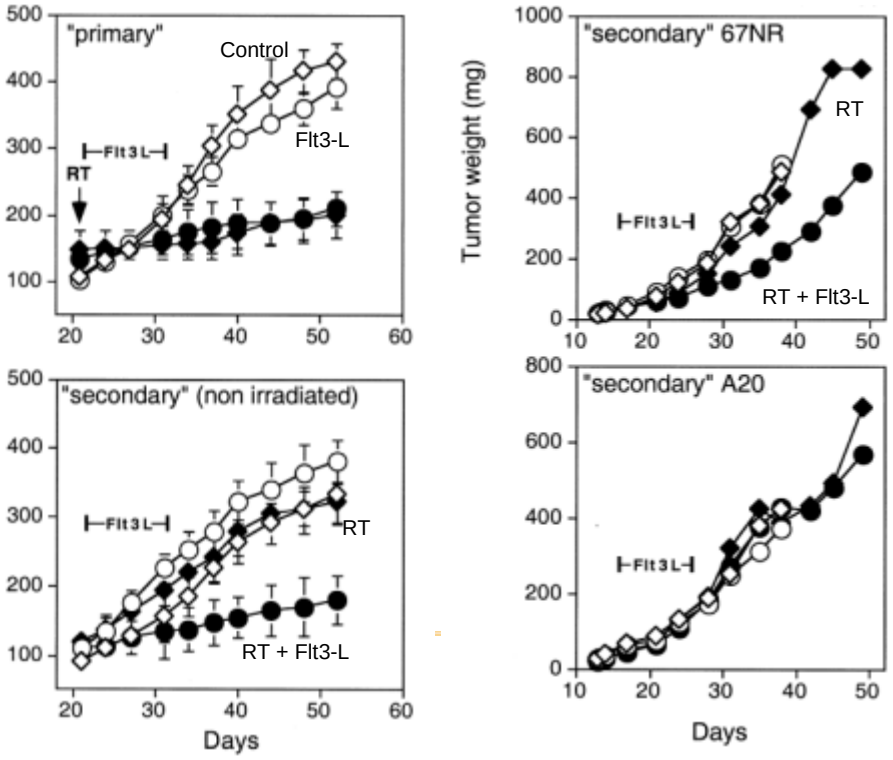


RT ABSCOPAL EFFECT IMMUNE MEDIATED

- Metastatic mouse mammary carcinoma 67NR or A20 lymphoma -> injected s.c. into syngeneic mice in 2 sites -> treatment when primary tumor 100-150 mg

1. Control
2. DC growth factor Flt3-L
3. RT (2 Gy x 1 or 6 Gy x 1) to 1º
4. RT to 1º + Flt3-L

In nude mice -> no secondary tumor growth delay with Flt3-L + RT



Int J Radiation Oncology Biol Phys. 2004;58:862-70

RT + GM-CSF – PROOF OF PRICIPLE TRIAL

- Stable or progressing metastatic solid tumors with at least 3 distinct sites of measurable disease. Maintained on single agent chemotherapy or hormonal therapy.

↓

35 Gy in 10 fx to one metastasis

↓

GM-CSF 125 μg/m^2 daily for 2 weeks starting week two of RT

↓

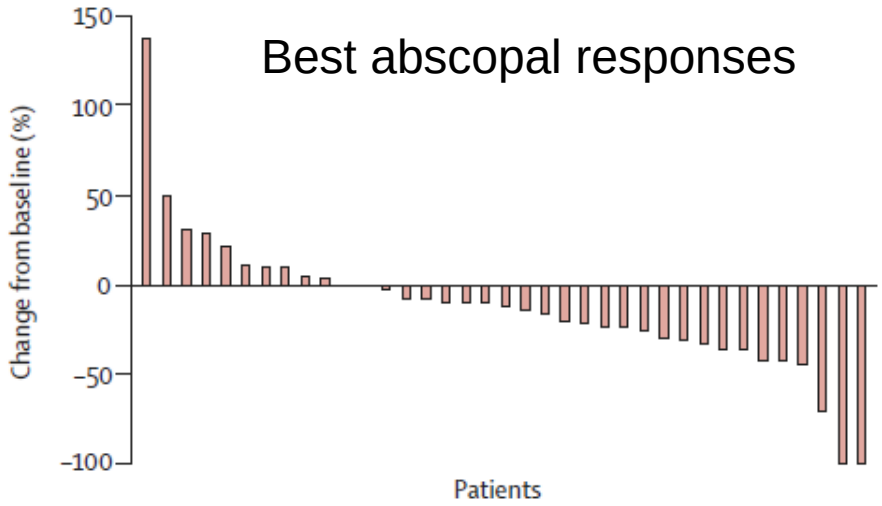
Course repeated to 2nd lesion starting d22

2003-2012	n=41
Median Age (range), yrs	62 (54.5-69.5)
Sex	
Male	8 (20%)
Female	33 (80%)
Number of previous therapies	
RT	1 (0-3)
Chemotherapy	3 (2-4)
Number of measurable lesions	
Chest	2 (1-3)
Abdomen	0 (0-0.5)
Pelvis	0 (0-0)
Any site	3 (2-4)
Number of patients with lesions	
3 lesions	21 (51%)
4-6 lesions	15 (37%)
> 6 lesions	5 (12%)

Lancet Oncol. 2015;16:795-803

RT + GM-CSF – PROOF OF PRICIPLE TRIAL

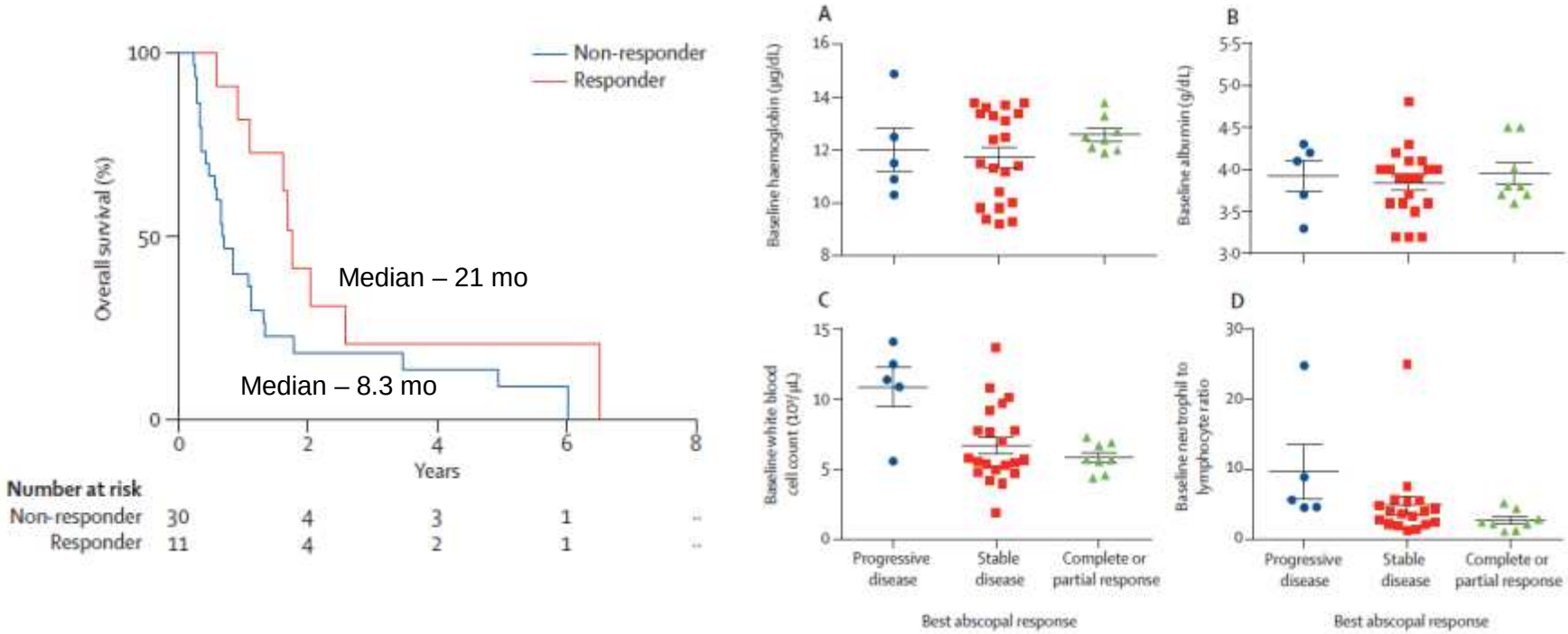
- Simon's optimal two-stage design: Patients could only be enrolled in stage 2 if at least one among the first 10 had an abscopal response.



	Patients	Not assessable for best abscopal response	Assessable for best abscopal response	
			PD/SD	PR/CR
NSCLC	18 (44%)	2 (5%)	12	4
Breast cancer	14 (34%)	1 (2%)	8	5
Thymic cancer	2 (5%)			2
Urothelial cancer	2 (5%)		2	
Ovarian cancer	1 (2%)	1 (2%)	1	
Eccrine cancer	1 (2%)		1	
Cervical cancer	1 (2%)		1	
SCLC	1 (2%)		1	
Total	41 (100%)	4 (10%)	26 (63%)	11 (27%)

Lancet Oncol. 2015;16:795-803

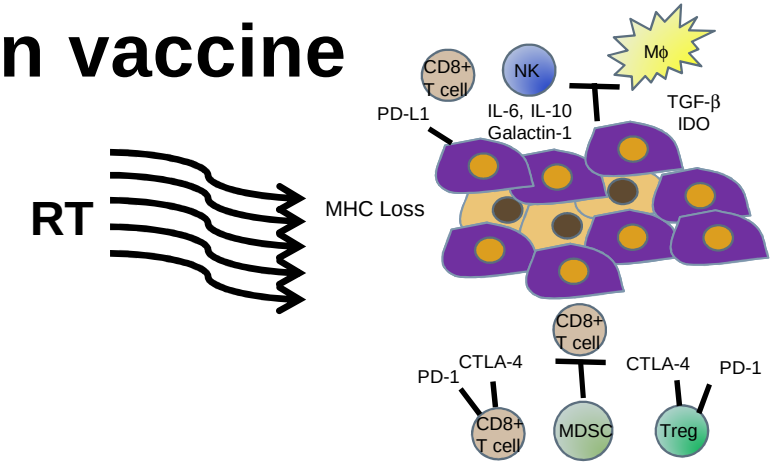
RT + GM-CSF – PROOF OF PRICIPLE TRIAL



Lancet Oncol. 2015;16:795-803

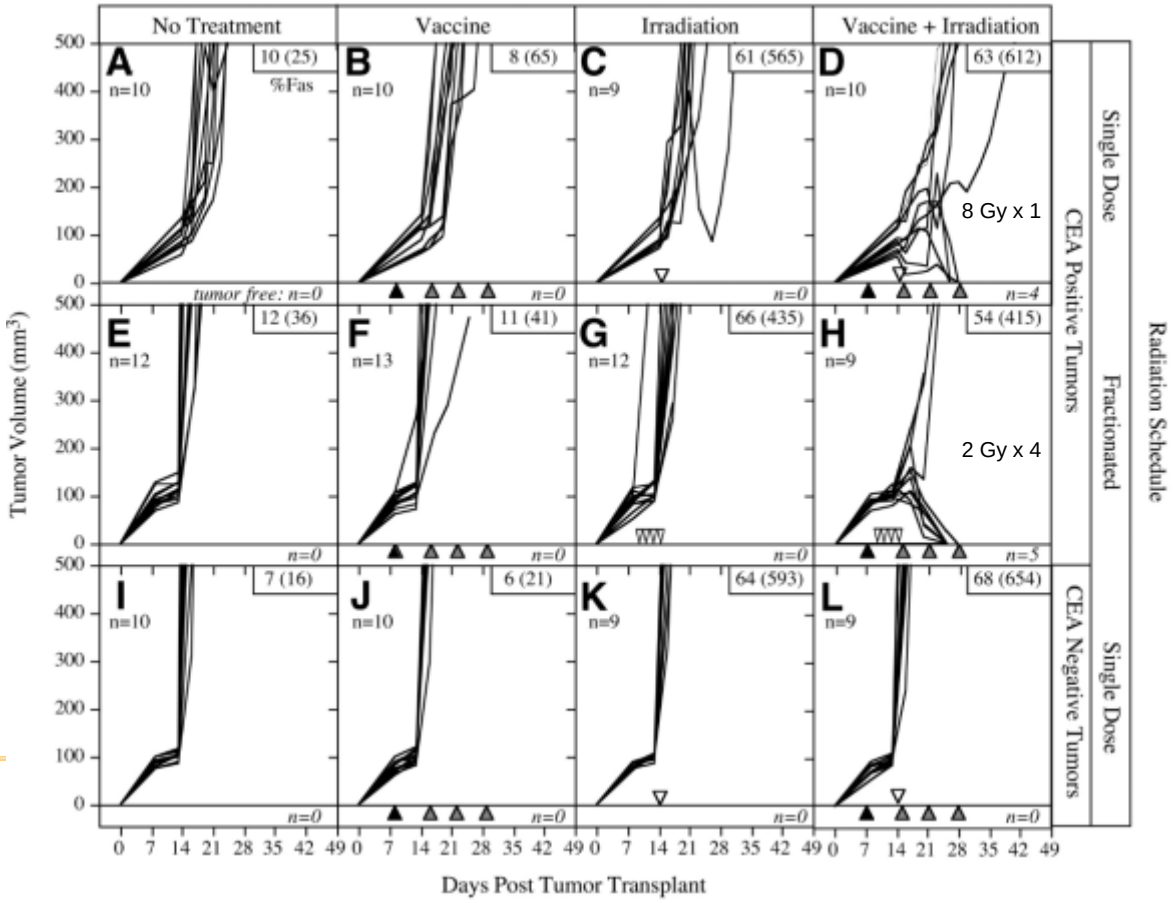
PRE-CLINICAL AND CLINICAL EVIDENCE

Tumor antigen vaccine



EBRT + VACCINE TO CEA COLON ADENO

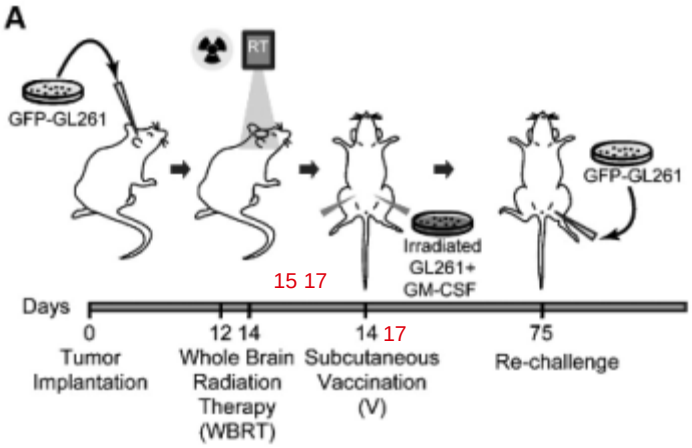
- Murine colon adenocarcinoma MC38
  - Vaccine (expressing CEA and costimulatory molecules)
  - RT (8 Gy – 1 or 4 fx)
  - Combination curative in 55% and imparted protection from subsequent tumor re-challenge
  - Responders demonstrated antigen cascade: T cell responses specific to antigens not included in the vaccine (gp70)

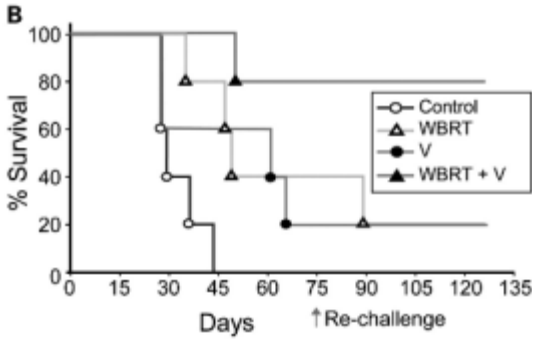


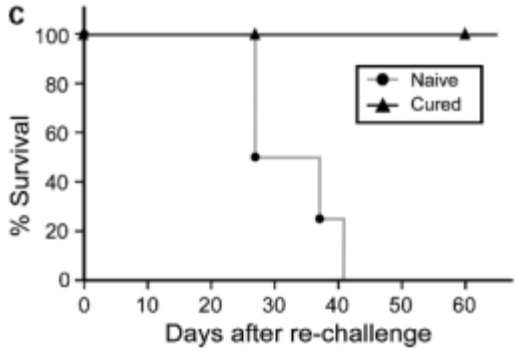
Cancer Res. 2004;64:4328-37

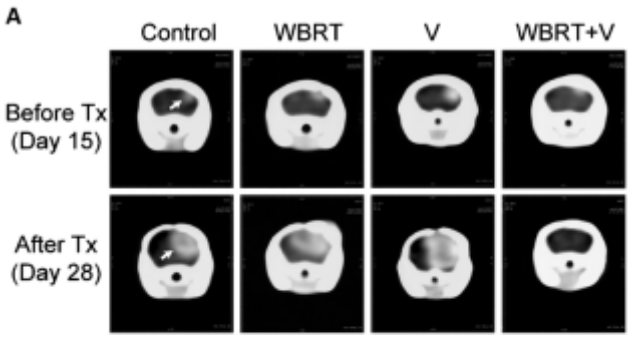
EBRT + VACCINE GLIOMA

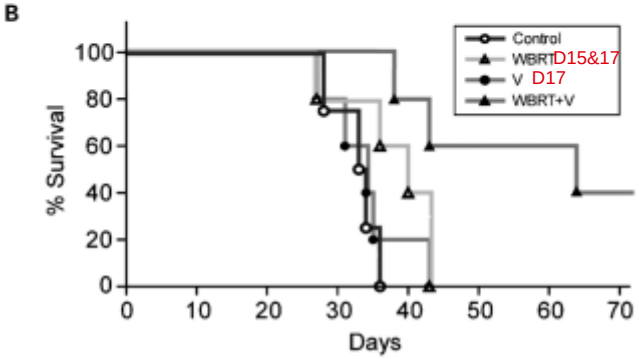
- Murine glioma GL261
  - GL261 vaccine
  - RT (4 Gy x 2 WBRT)











Clin Cancer Res. 2006;12:4730-7

EBRT + PSA VACCINE PHASE II

- Prostate adenocarcinoma candidates for definitive RT.
  - Vaccine q28 days x 7
    - rV-PSA and rVB7.1 vectors for 1st on d2
    - Rfowlpox-PSA for boosts on d2
    - GM-CSF 100 μg/d s.c. on d1-4
    - IL-2 4 MIU/m^2 s.c. on d8-12
  - RT: ≥ 70 Gy at 1.8-2 Gy/fx btn 4th and 6th vaccinations

	RT + VC (n=19)	RT (n=11)
Median Age (range), yrs	59 (50-77)	70 (56-80)
Race		
White	16 (84%)	8 (73%)
Black	2 (10.5%)	2 (18%)
Other	2 (10.5%)	1 (9%)
Risk Group		
Low	2 (10.5%)	2 (18%)
Intermediate	6 (31.5%)	2 (18%)
High	11 (58%)	7 (64%)
PSA (ng/ml), median (range)	14.2 (3.8-206)	8 (4.5-23)
ADT		
Given	15 (79%)	9 (82%)
Not Given	4 (21%)	2 (18%)

Clin Cancer Res. 2005;11:3353-62 Clin Cancer Res. 2010;16:4046-56

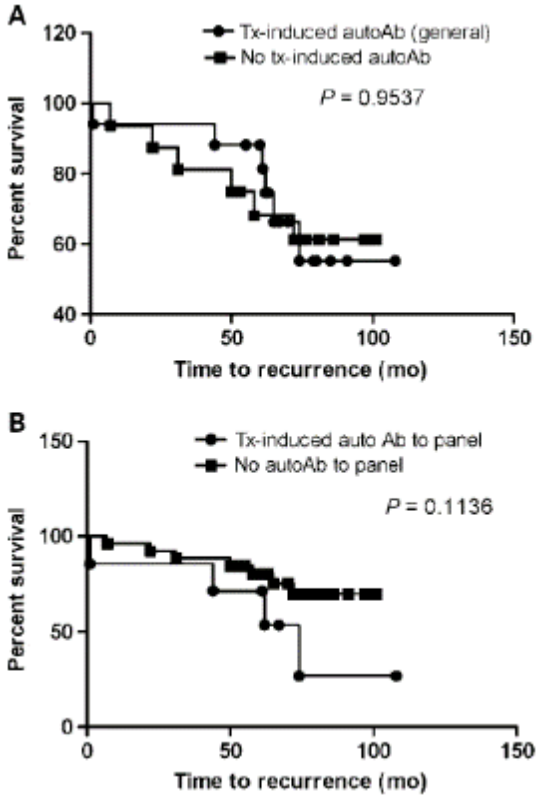
EBRT + PSA VACCINE PHASE II

- 13 of 17 patients in combination arm had 3-fold increase in PSA-specific T cells vs none in RT only arm ($p < 0.0005$).
  - 2/17 had biochemical failure vs 2/9 in RT only at 20-25 month follow-up.

Table 2. Frequency of treatment-induced autoantibody responses observed by Western blot, antigen array, or both

	Vaccine +EBRT (n = 33)	EBRT (no vaccine; n = 8)	ADT+EBRT (n = 15)	WW (n = 9)	Cancer-free controls (n = 15)
Western blot	15 (45.5%)	1 (12.5%)	3* (20.0%)	1 (11.1%)	0 (0%)
Antigen array	7 (21.2%)	0 (0%)	2* (13.3%)	1 (11.1%)	0 (0%)
Overall	17 (51.5%)	1 (12.5%)	3 (20.0%)	1 (11.1%)	0 (0%)

*The treatment-induced responses observed in the ADT + EBRT patients by Western blot and antigen array confirms our previously published results (Nesslinger et al. 2007).



Clin Cancer Res. 2005;11:3353-62 Clin Cancer Res. 2010;16:4046-56

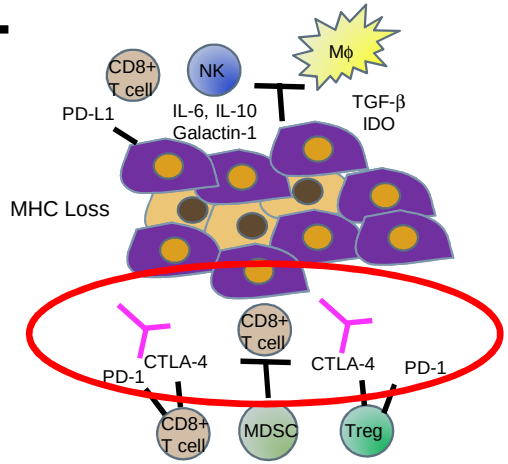
RT AND TUMOR ANTIGEN VACCINE

Samples of Ongoing Clinical Trials of Vaccine and RT				
Trial ID	**Accrual Goal**	**Design**	**Histology**	**Primary Endpoint**
NCT01436968 (Phase III)	711	Arm 1: Placebo + valacyclovir + radiation +/- short term ADT Arm 2: ProstAtak (AdV-tk) + valacyclovir + radiation +/- short term ADT	Prostate cancer	DFS
NCT01807065 (Phase II)	50	Arm 1: Sipuleucel-T Arm 2: Sipuleucel-T and radiation	Hormone refractory metastatic prostate cancer	Complete treatment
NCT01595321 (Phase I)	19	GVAX, low dose cyclophosphamide, fractionated SBRT (6.6 Gy x 5), and FOLFIRINOX	Resected pancreatic adenocarcinoma	Safety
NCT02405585 (Phase II)	48	mFOLFIRINOX -> Algenpantucel-L (HAPa) -> RT (50.4 Gy in 28fx) and gemcitabine	Borderline resectable pancreatic adenocarcinoma	PFS
NCT00589875 (Phase IIa)	52	Resection-> AdV-tk -> RT and temodar	Glioblastoma	Safety

PRE-CLINICAL AND CLINICAL EVIDENCE

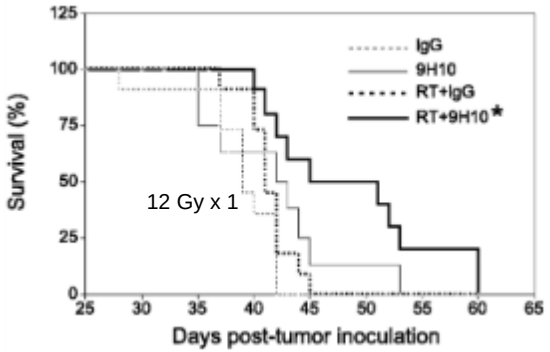
IMMUNE CHECKPOINT INHIBITORS

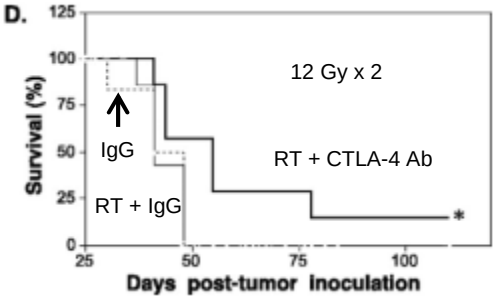
RT

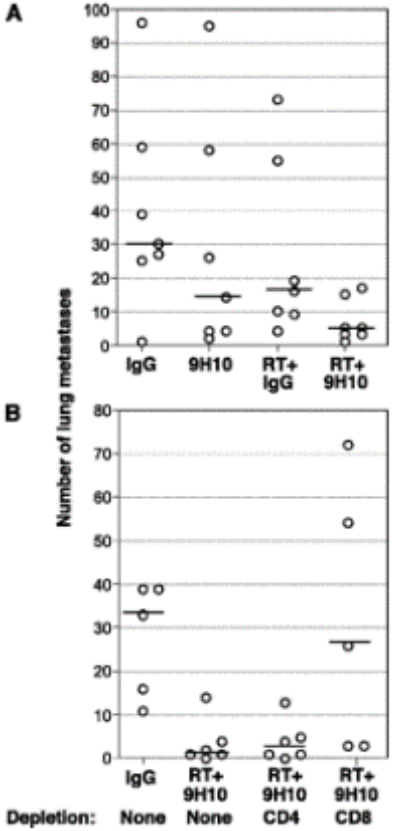


RT AND CTLA-4 BLOCKADE

- Metastatic mouse mammary carcinoma 4T1 -> injected s.c -> treatment started 13 days later with average primary tumor 5 mm
  1. Control IgG
  2. RT (12 Gy x 1 or x 2) + IgG
  3. CTLA-4 antibody
  4. RT + CTLA-4 antibody



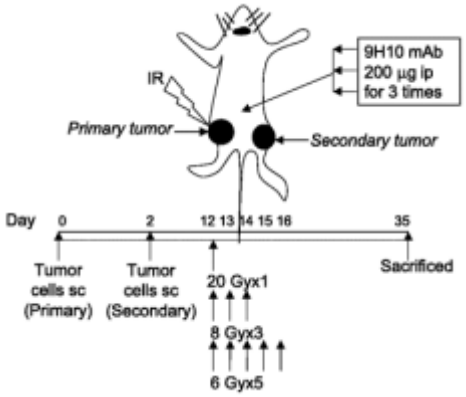


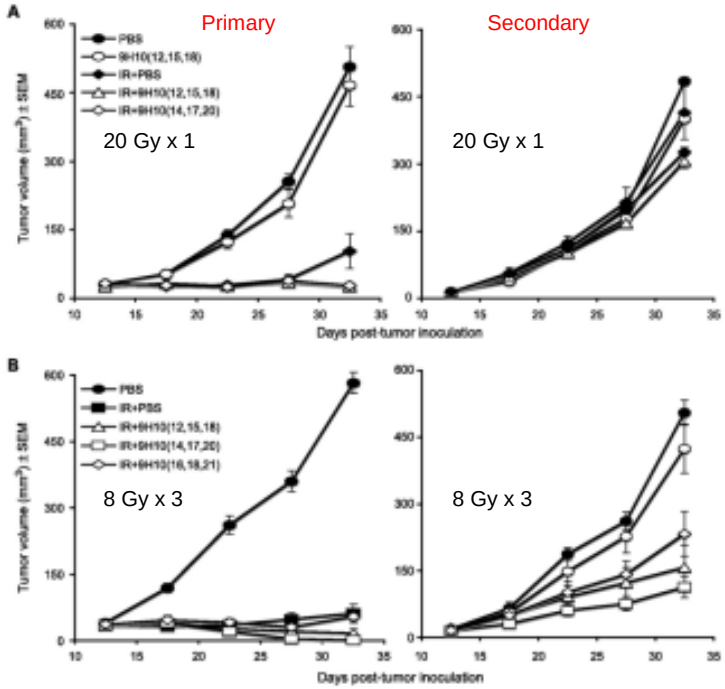


Clin Cancer Res. 2005;11:728-34

RT AND CTLA-4 BLOCKADE

- TSA mouse breast carcinoma cells (some with MCA38 mouse colon carcioma) -> injected s.c. into syngeneic mice in 2 sites -> treatment started when both sites palpable
  1. O Gy, 20 Gy x 1, 8 Gy x 3, 6 Gy x 5
  2. PBS or CTLA-4 ab (4 diff admin schedules)





Clin Cancer Res. 2009;15:5379-88

RT AND CTLA-4 BLOCKADE

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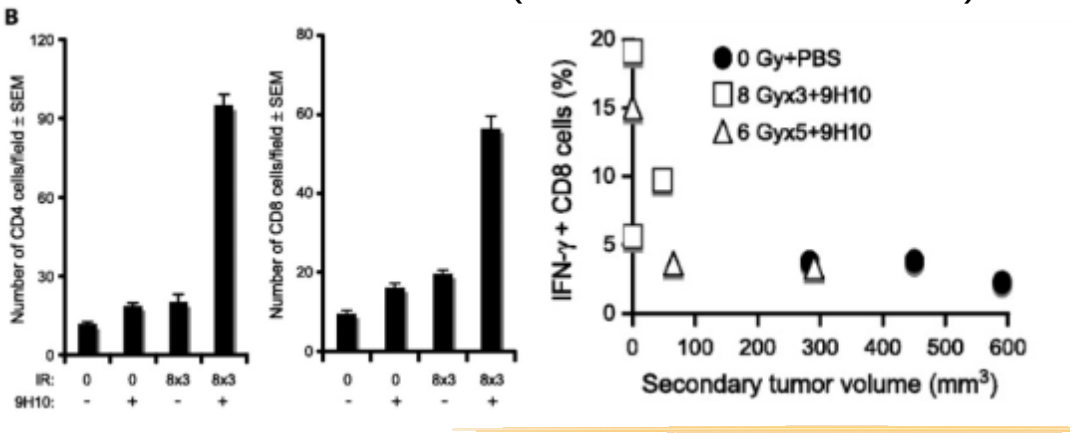
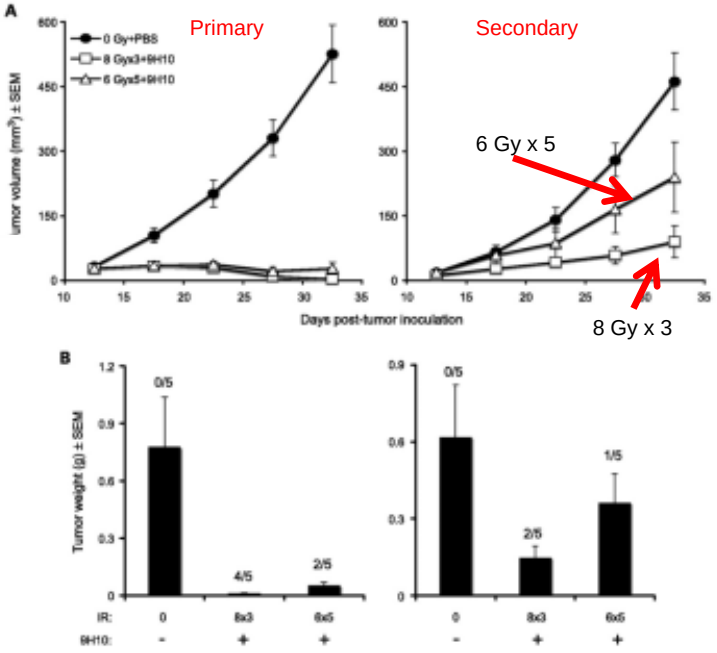
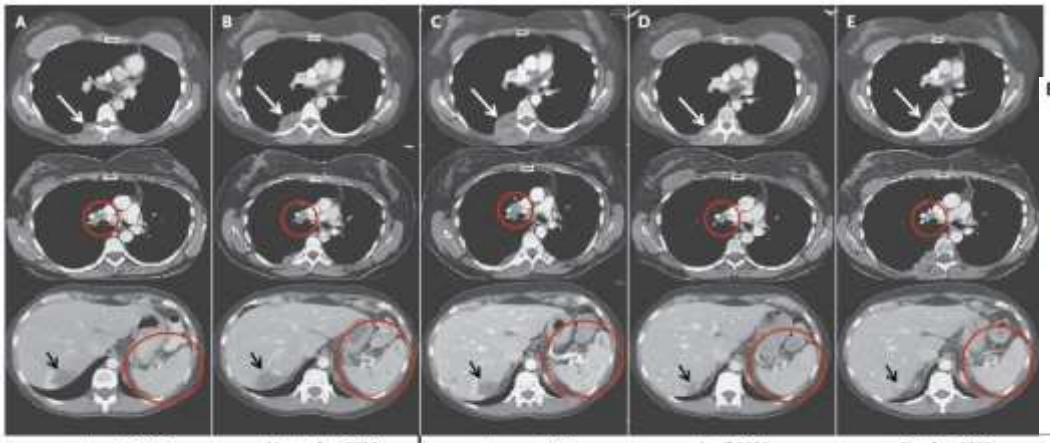
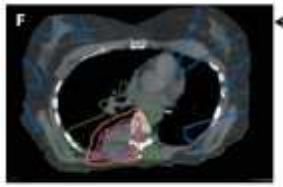




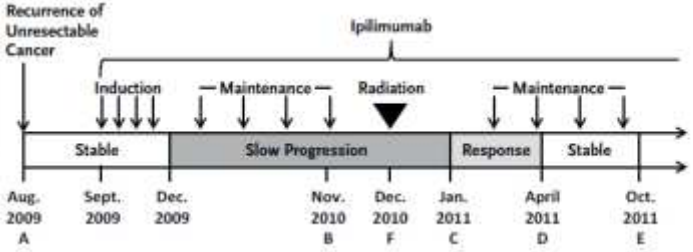
Clin Cancer Res. 2009;15:5379-88

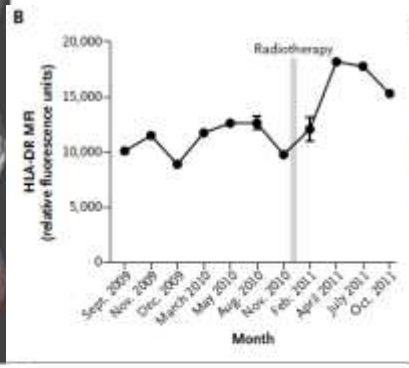
NEJM 2012 CASE REPORT

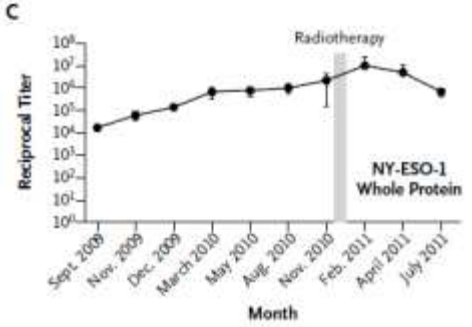


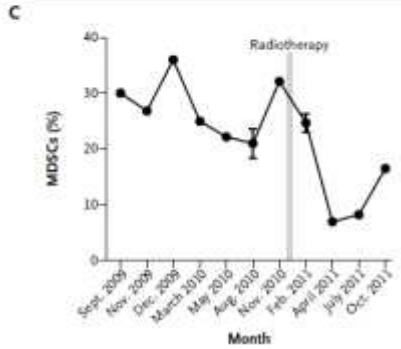


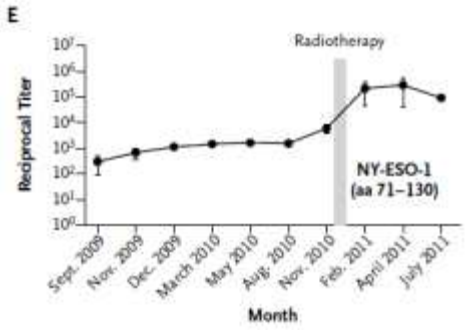
9.5 Gy x 3











N Engl J Med. 2012;366:925-31

IPI + RT NSCLC PHASE II

- Chemorefractory patients with metastatic NSCLC

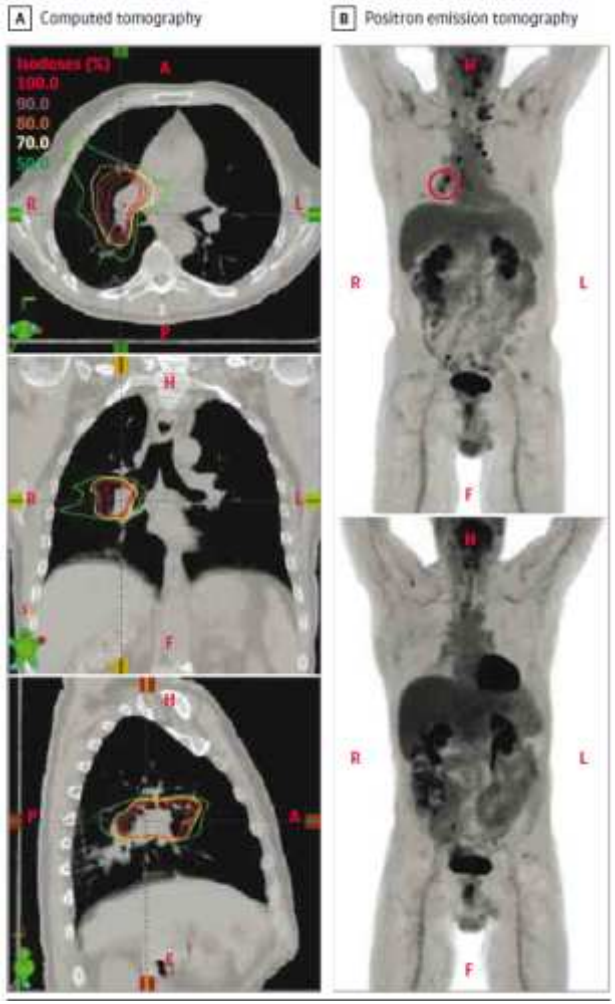
↓

RT to 6 Gy x 5

↓

Ipilimumab 3 mg/kg q3 wk x 4 within 24 hours of starting RT

- Tumor response (n=8)
  - CR – 2
  - PR – 2
  - SD – 2
  - ORR – 4 (50%)



JAMA Oncol. 2015;Epub

IPI + RT MELANOMA PHASE I

- Ipilimumab naive metastatic melanoma

↓

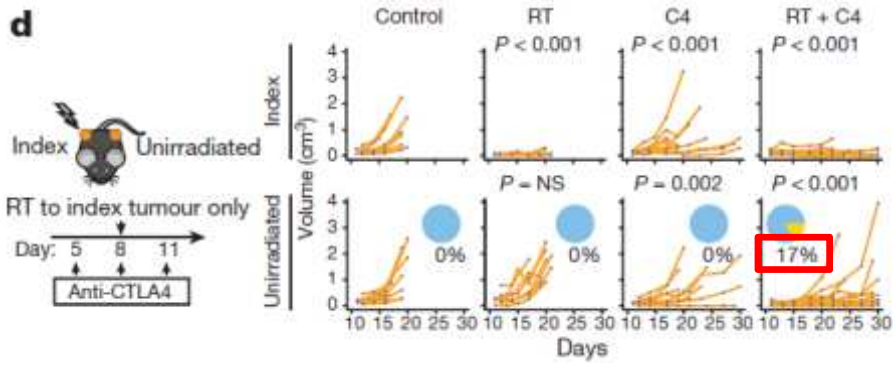
Phase I Dose escalation
Lung/Bone: 8 Gy x 2, 8 Gy x3
Liver or S.C: 6 Gy x 2, 6 Gy x 3

↓

Ipilimumab 3 mg/kg q3 wk x 4

RT: Fractions given day 1, day 3-9, and day 9-13

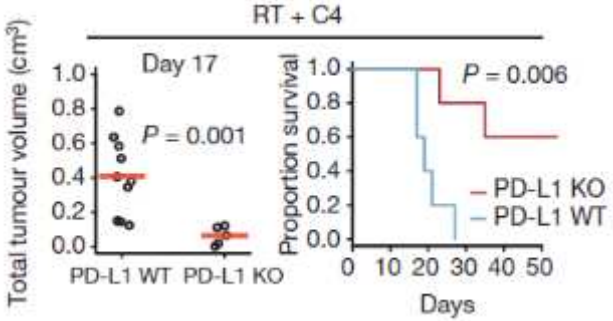
- Unirradiated tumor response:
  - PR – 18%, SD – 18%, PD – 64%
- Mouse model to study mechanisms of response and resistance:
  - B16 melanoma mouse model -> b/l flank tumors



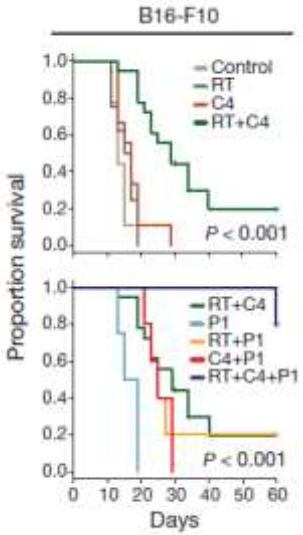
Nature. 2015;520:373-7

IPI +/- RT MELANOMA MOUSE

- Top predictor of resistance was CD8/Treg ratio
- PD-L1 among top 0.2% of upregulated genes for RT + anti-CTLA4 signature

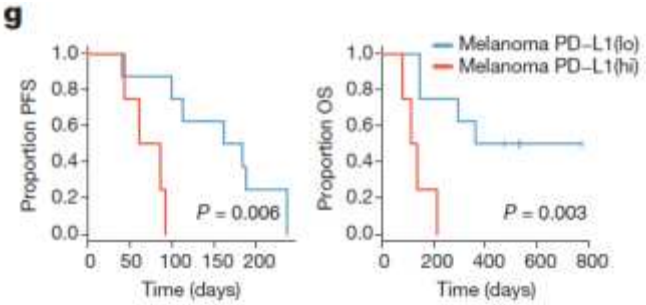


Mice B16 model



Mice B16 model

RECIST	Melanoma PD-L1(lo)	Melanoma PD-L1(hi)
PR	2	0
SD	1	0
PD	5	4



Phase I patients

Nature. 2015;520:373-7

IPI +/- RT MCRPC PHASE I/II

- Hormone refractory prostate cancer with no more than 1 prior chemotherapy.

↓

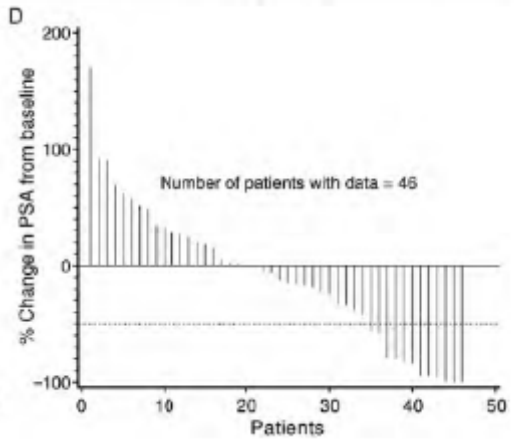
Phase I Dose escalation: Ipilimumab 3, 5, or 10 mg/kg q3 weeks x 4 doses then ipilimumab 3 or 10 mg/kg + RT

↓

Phase II: Ipilimumab 10 mg/kg +/- RT

RT: 8 Gy/1fx up to 3 lesions per patient 24-48 hours prior to RT

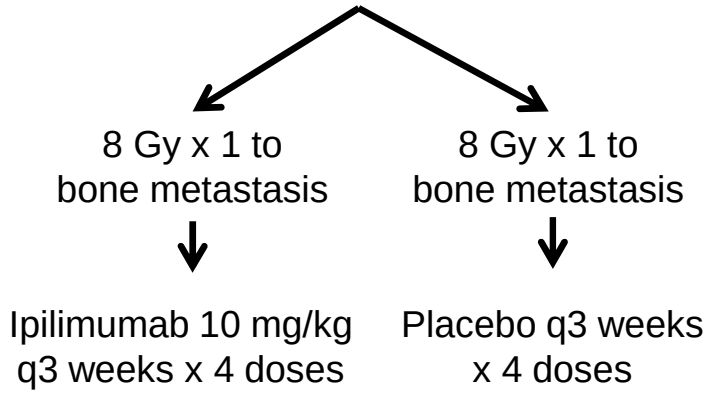
	Ipilimumab dose				
	3 mg/kg		5 mg/kg	10 mg/kg	
	-RT (n=8)	+RT (n=7)	- RT (n=6)	-RT (n=16)	+RT (n=34)
Median Age, yrs	69	68	57	65	66
Median bone lesions	4	6	5	2.5	8
Median PSA	91	47	38	132	120
PSA decline (D85)	1	0	1	3 (19%)	4 (12%)
PSA decline (any)	2	2	1	4 (25%)	4 (12%)



Ann Oncol. 2013;24:1813-21

CA184-043 TRIAL

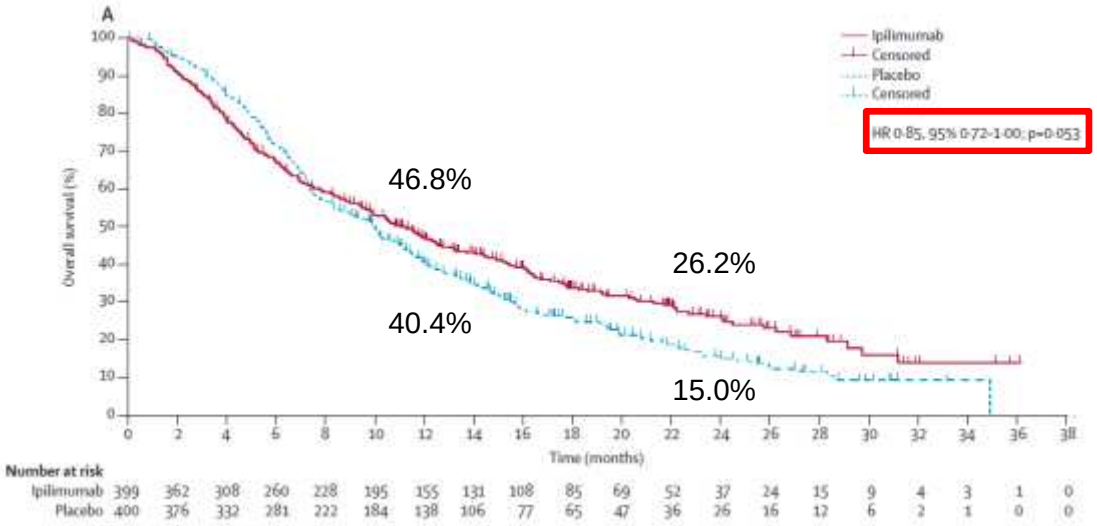
- Hormone refractory prostate cancer with bone metastases and progression within 6 months of docetaxel.



	Ipilimumab (n=399)	Placebo (n=400)
Median Age (range), yrs	69 (47-86)	67.5 (45-86)
Gleason score ≤ 7 > 7	 174 (44%) 192 (48%)	 190 (48%) 187 (47%)
Number of bone metastases ≤ 5 >5	 276 (69%) 103 (26%)	 253 (63%) 111 (28%)
Average daily worst bone pain < 4 ≥ 4	 152 (38%) 197 (49%)	 150 (38%) 186 (47%)
Visceral metastases	113 (28%)	114 (29%)
No pretreatment steroid use	331 (83%)	338 (84%)
Median PSA (range) µg/L	138.5 (0-457)	176.5 (0-13,768)

Lancet Oncol. 2014;15:700-12

CA184-043 TRIAL

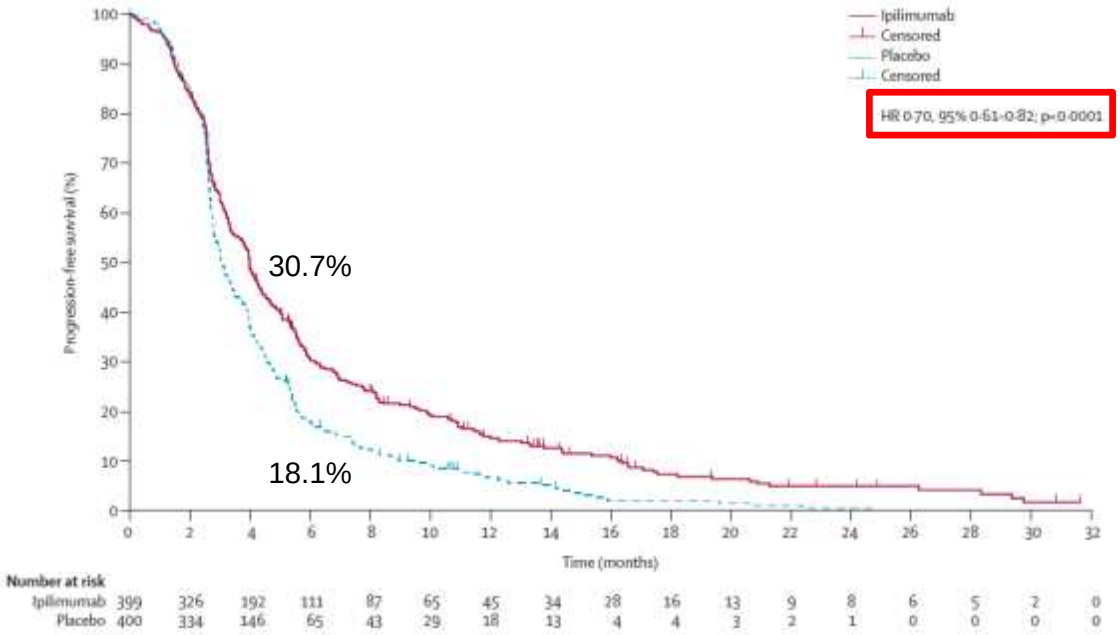


Grade 3-4 Toxicity	Ipilimumab (n=393)	Placebo (n=396)
Fatigue	40 (10%)	35 (9%)
Anemia	40 (10%)	43 (11%)
Diarrhea	59 (15%)	3 (1%)
Colitis	18 (5%)	0
Pruritis	1 (< 1%)	0
Rash	2 (1%)	0

- Post-hoc subgroup analysis found OS 22.7 mo vs 15.8 mo (p=0.0038) in those with favorable prognostic features:
  - Alk Phos < 1.5 x ULN, Hg > 11, & no visceral metastases

Lancet Oncol. 2014;15:700-12

CA184-043 TRIAL



50% PSA reduction

- 13.1% ipilimumab
- 5.2% placebo

Problems:

- Preclinical model did not test CTLA-4 Ab and RT
- Previous cases of CTLA-4 Ab and abscopal effect gave RT after CTLA-4 Ab
- Dose is low to generate immune response
- RT to bone may not be as immunogenic

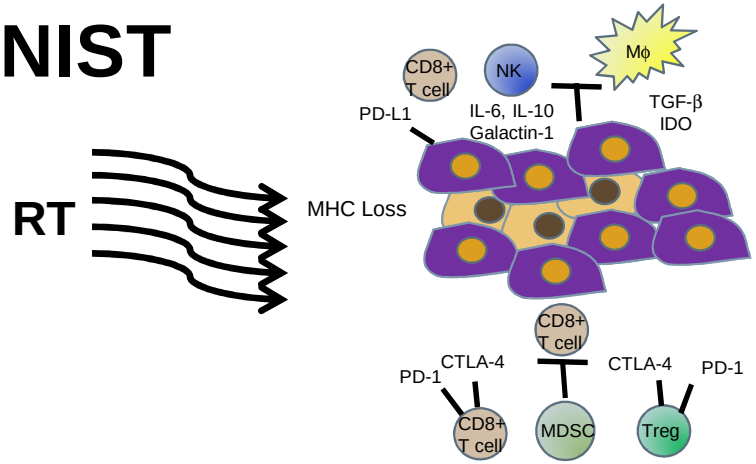
Lancet Oncol. 2014;15:700-12

RT AND IMMUNE CHECKPOINT INHIBITION

Samples of Ongoing Clinical Trials of Immune Checkpoint Inhibition and RT				
Trial ID	**Accrual Goal**	**Design**	**Histology**	**Primary Endpoint**
NCT02221739 (Phase II)	20	RT (6 Gy x 5) + ipilimumab 3 mg/m^2	Chemorefractory NSCLC	ORR
NCT02097732 (Phase II)	40	Arm 1: SRS -> ipilimumab x 4 starting 2-3 weeks later Arm 2: Ipilimumab x 2 -> SRS -> ipillimumab x 2	Melanoma brain metastasas	Local control
NCT01497808 (Phase I/II)	40	Ipilimumab and SBRT	Metastatic melanoma	PFS
NCT02400814 (Phase I)	45	SBRT and MPDL3280A (PD-L1 Ab) -> 3 cohorts (concurrent, induction, sequential)	Metastatic NSCLC	Safety
NCT01711515 (Phase I)	28	RT + cisplatin + ipilimumab	Locally advanced cervical cancer	Safety

PRE-CLINICAL AND CLINICAL EVIDENCE

TLR AGONIST

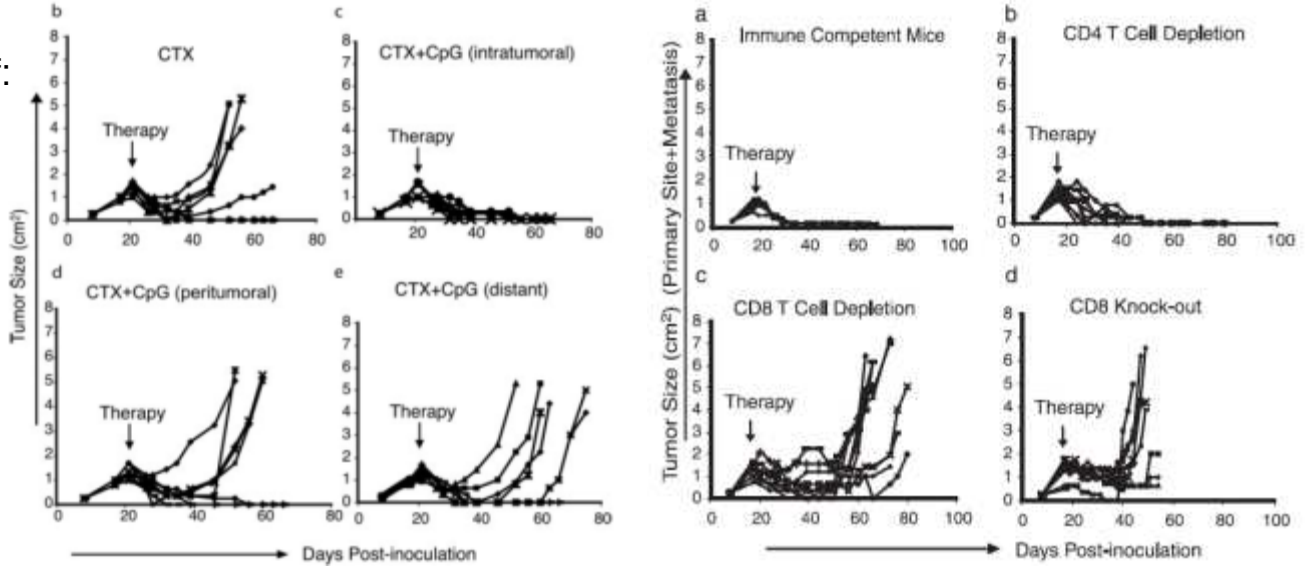


TLR9 AGONIST

- Mouse A20 lymphoma cells-> injected s.c -> treatment started when tumors reached 1.5 cm^2 (~ 20 days) -> Cytoxan and CpG

CpG + chemotherapy effective if:

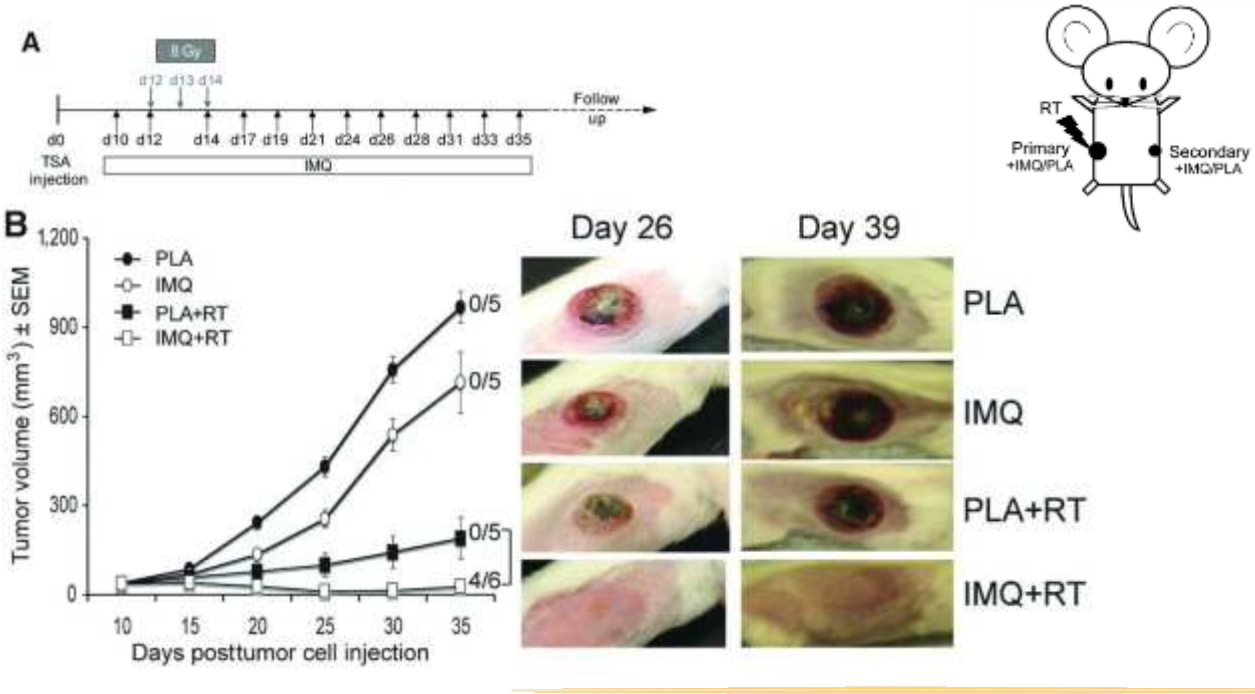
1. Intratumoral CpG injection
2. CD8 T cell immune response
3. TLR9 in tumor or host

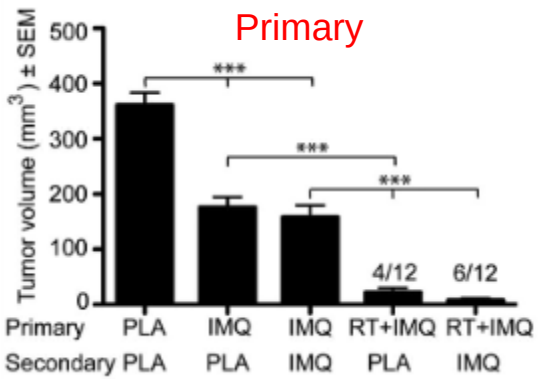


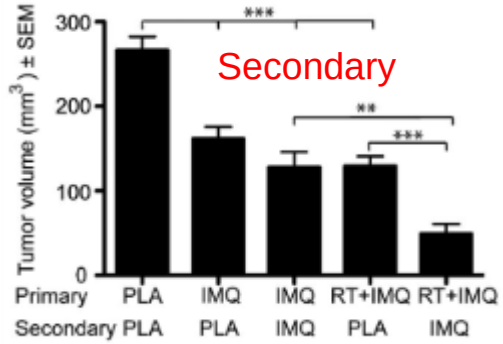
J Immunol. 2007;179:2493-500

TLR7 AGONIST

- Mouse TSA breast cancer cells-> injected s.c







Clin Cancer Res. 2012;18:6668-78

TLR9 AGONIST AND RT PHASE I/II LYMPHOMA

- Low grade B cell lymphoma relapsed after at least one standard therapy with at least 3 sites of disease

↓

4 Gy in 2 fx to one site

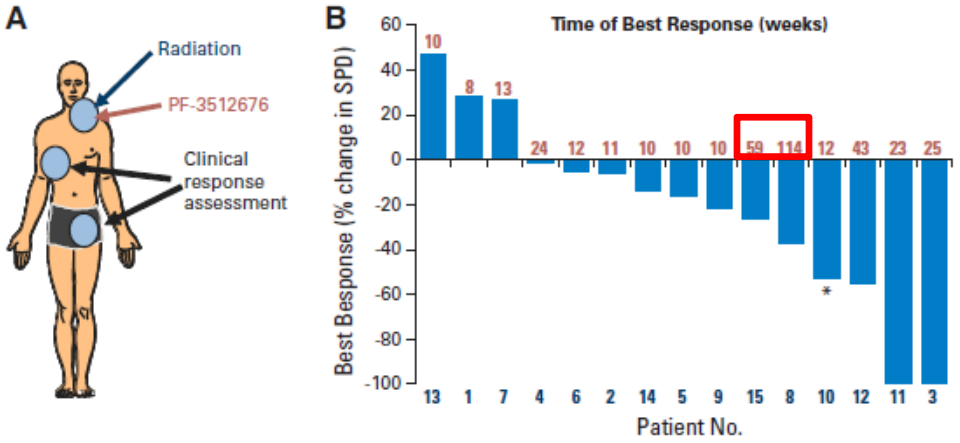
↓

CpG-enriched oligodeoxynucleotide TLR9 agonist 6 mg intratumoral injection immediately prior to 1st RT fraction, after the 2nd fraction, and weekly for 8 weeks

	n=41
Median Age (range), yrs	62 (54.5-69.5)
Sex	
Male	8 (20%)
Female	33 (80%)
Number of previous therapies	
RT	1 (0-3)
Chemotherapy	3 (2-4)
Number of measurable lesions	
Chest	2 (1-3)
Abdomen	0 (0-0.5)
Pelvis	0 (0-0)
Any site	3 (2-4)
Number of patients with lesions	
3 lesions	21 (51%)
4-6 lesions	15 (37%)
> 6 lesions	5 (12%)

J Clin Oncol. 2010;28:4324-32

TLR9 AGONIST AND RT PHASE I/II LYMPHOMA



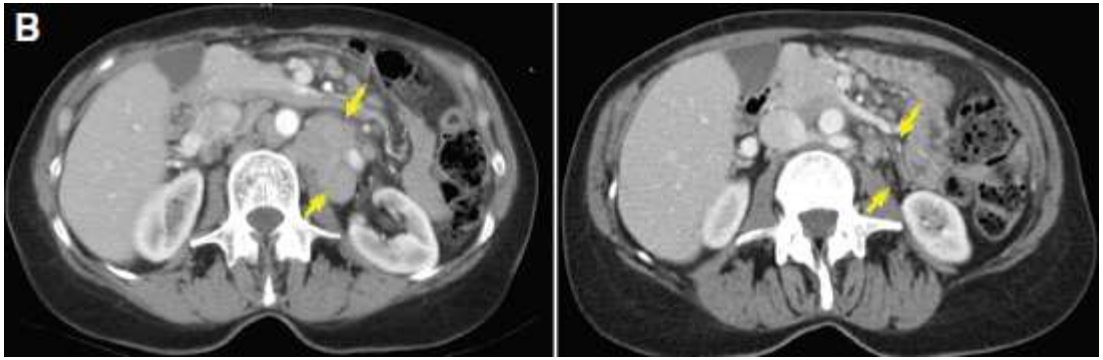
	n=15
Treated Site	
CR	7 (47%)
PR	6 (40%)
SD	2 (13%)
Non-treated Sites	
CR	1 (7%)
PR	3 (20%)
SD	8 (53%)
PD	
Grade 1-2 toxocity	
Systemic Flu-Like reaction	5 (33%)
Injection Site reaction	1 (7%)

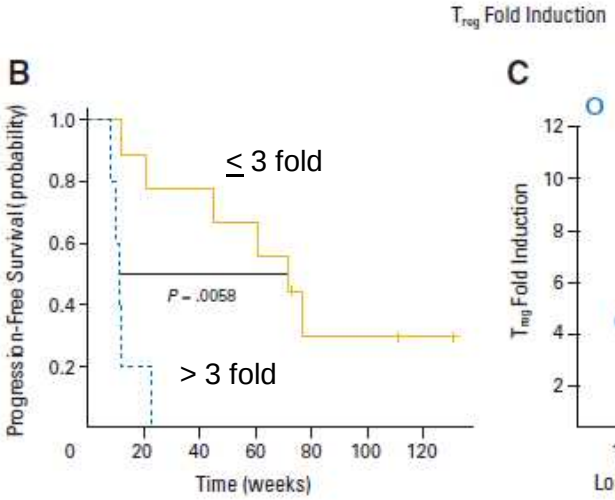
- Greater magnitude of response correlated to:
  - Fewer prior therapies
  - Treatment induced flu-like symptoms

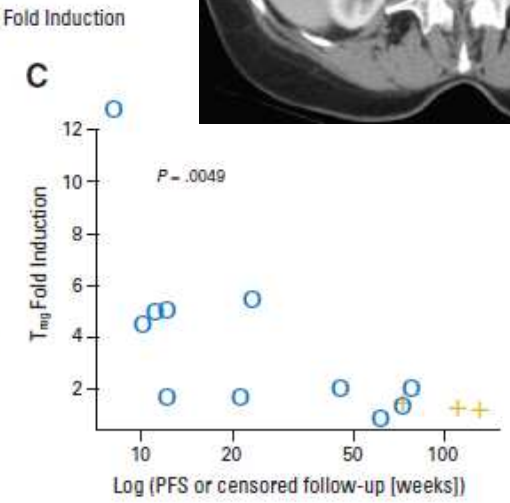
J Clin Oncol. 2010;28:4324-32

TLR9 AGONIST AND RT PHASE I/II LYMPHOMA

- Treated site – left inguinal
- Response - retroperitoneal







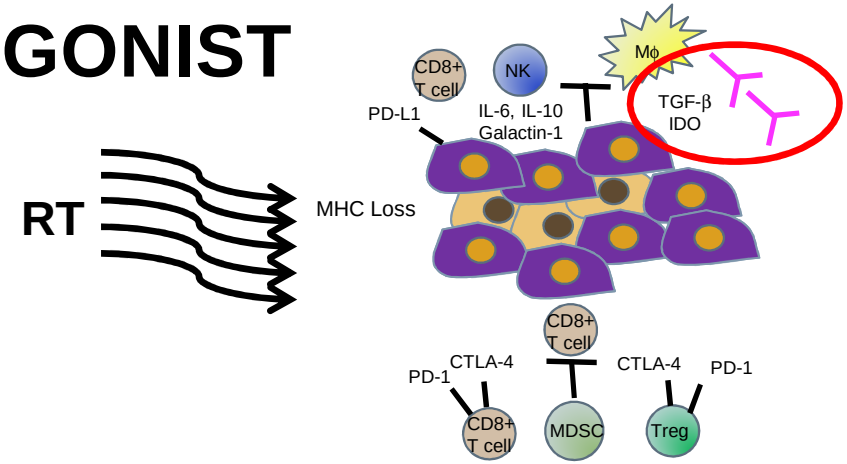
J Clin Oncol. 2010;28:4324-32

RT AND TLR AGONISTS

Samples of Ongoing Clinical Trials of TLR agonists and RT				
Trial ID	**Accrual Goal**	**Design**	**Histology**	**Primary Endpoint**
NCT01421017 (Phase I/II)	55	RT (6 Gy x 5) + imiquimod + cyclophosphamide 200 mg/m^2 x 1	Metastatic breast cancer with skin metastases	ORR
NCT01976585 (Phase I/II)	30	RT (2 Gy x 2) + intratumoral Flt3-L and TLR agonist Poly-ICLC	Recurrent low grade lymphoma	ORR
NCT02254772 (Phase I/II)	27	TLR9 agonist SD-101, RT (2 Gy x 2), and ipilimumab	Recurrent low grade lymphoma	DLT ORR
NCT02180698 (Phase I)	18	TLR4 agonist GLA-SE and RT (5-6 fractions)	Metastatic sarcoma	DLT

PRE-CLINICAL EVIDENCE

TGF-β ANTAGONIST

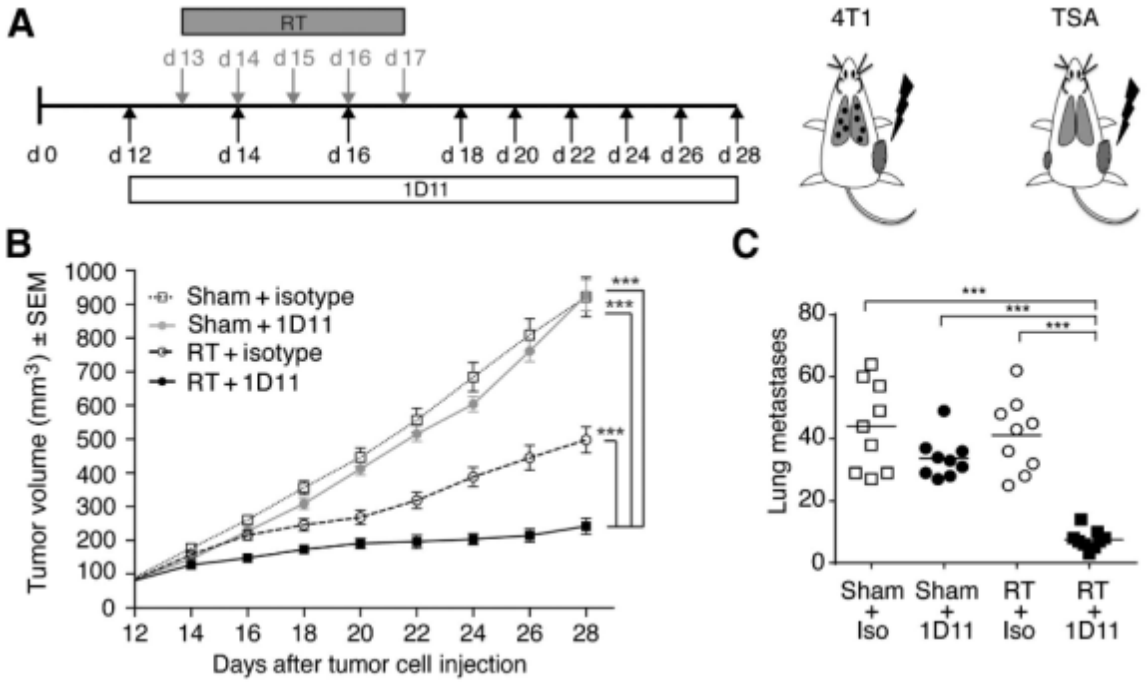


TGF-β ANTAGONIST

- Mouse 4T1 breast carcinoma cells-> injected s.c

TGF-β and RT 1 improved response and decreased lung metastases.

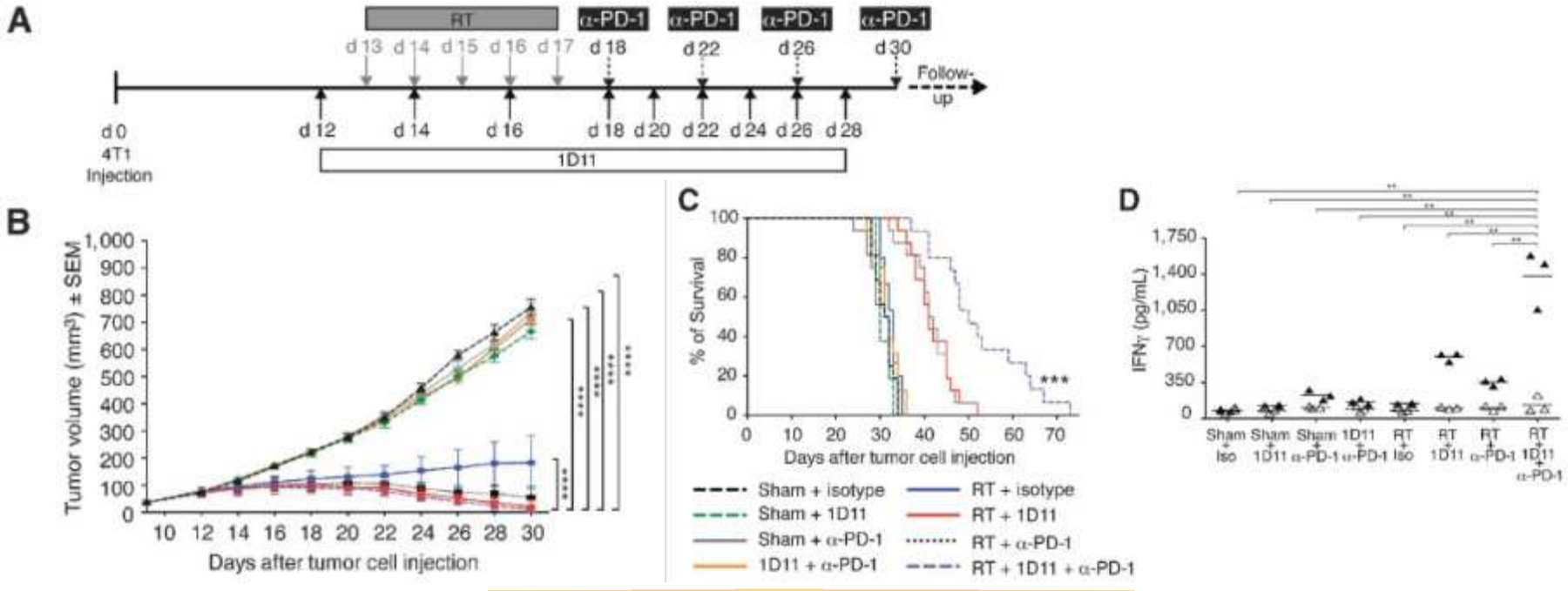
RT was 6 Gy x 5



Clin Cancer Res. 2015;75:2232-42

TGF-β ANTAGONIST

- Mouse 4T1 breast carcinoma cells-> injected s.c



Clin Cancer Res. 2015;75:2232-42

RT AND TGF-β ANTAGONISTS

Samples of Ongoing Clinical Trials of TGF-b Antagonists and RT				
Trial ID	**Accrual Goal**	**Design**	**Histology**	**Primary Endpoint**
NCT01401062 (Phase I)	28	RT (7.5 Gy x) + fresolimumab (1 mg/g and 10 mg/kg)	Metastatic breast cancer	Safety

FUTURE DIRECTIONS

- Can RT + immunotherapy improve overall survival in patient's with metastatic disease?
- Is there an ideal RT dose and fractionation to produce an abscopal response?
- What is the best immunotherapy strategy to give with RT to produce an abscopal response?
- Does body site treated with RT impact the ability to obtain an abscopal response?
- Does tumor histology impact the ability to obtain an abscopal response?
- Do other clinical factors predict the ability to obtain an abscopal response?

QUESTIONS?