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Radiation and Immunotherapy

Encouse Golden M.D., Ph.D.
Department of Radiation Oncology
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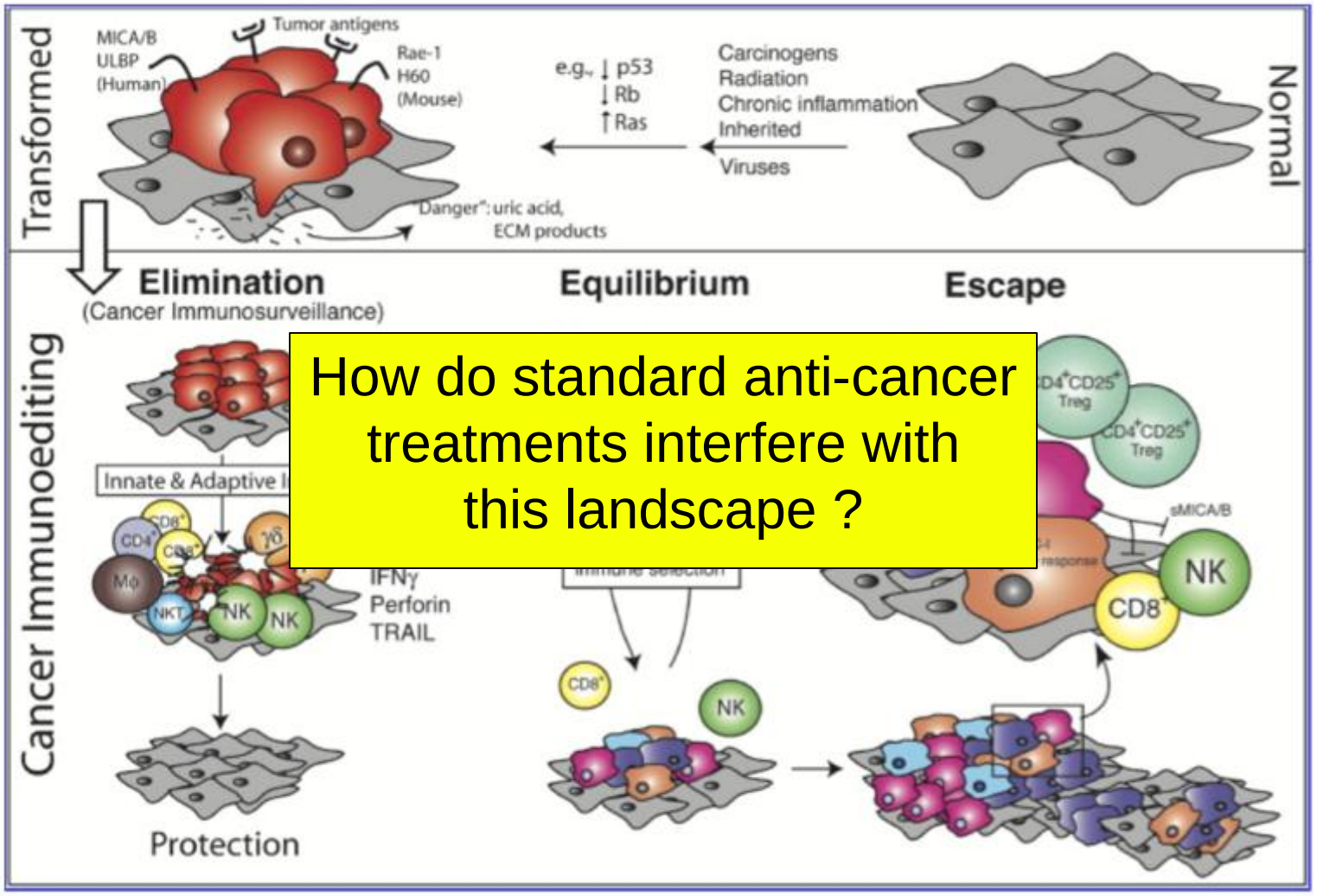

Dunn et al, Nature Immunology 2002
Koebel et al, Nature 2007

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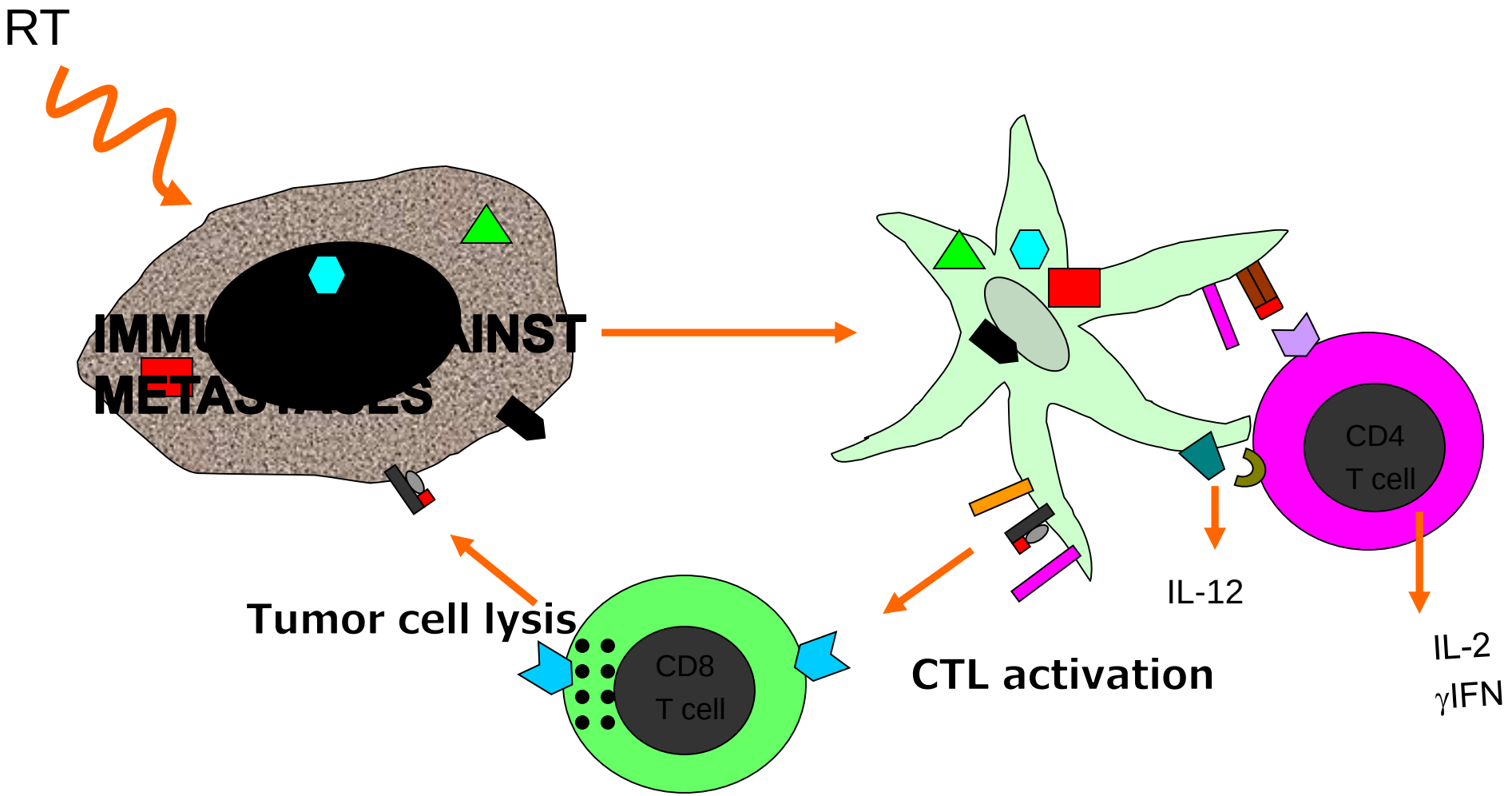
IN SITU VACCINATION HYPOTHESIS



COMBINING RADIOTHERAPY AND IMMUNOTHERAPY: A REVIVED PARTNERSHIP IJROBP, 2005

Radiation Therapy to Convert the Tumor Into an In Situ Vaccine IJROBP, 2012

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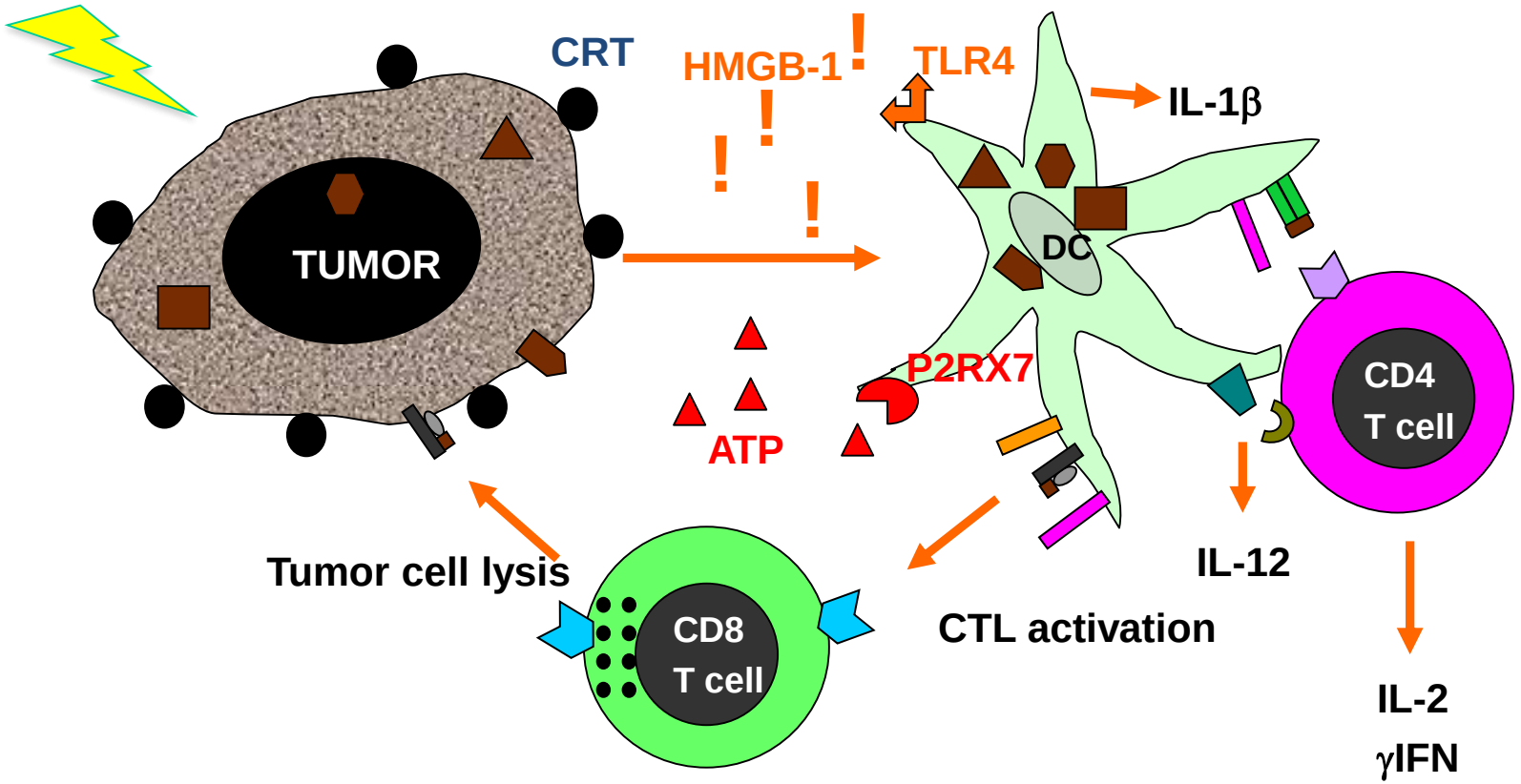
Cross-priming of anti-tumor T cells: immunogenic cell death

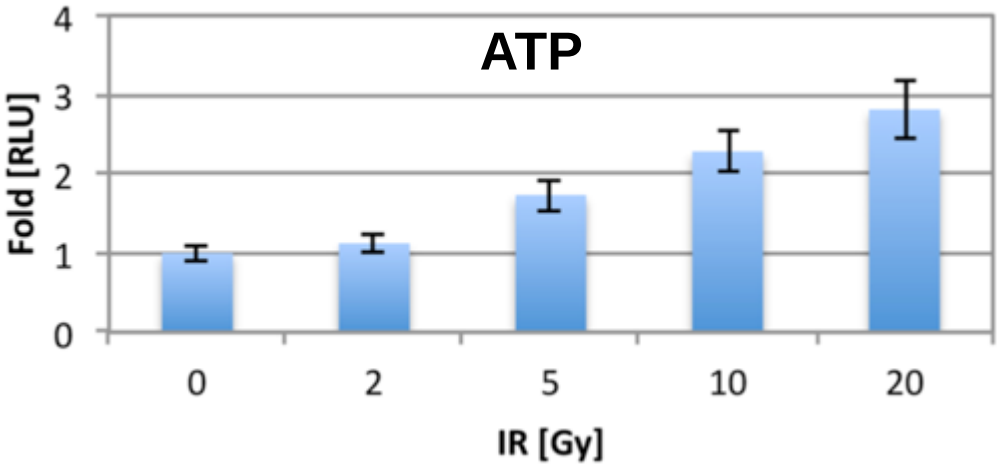


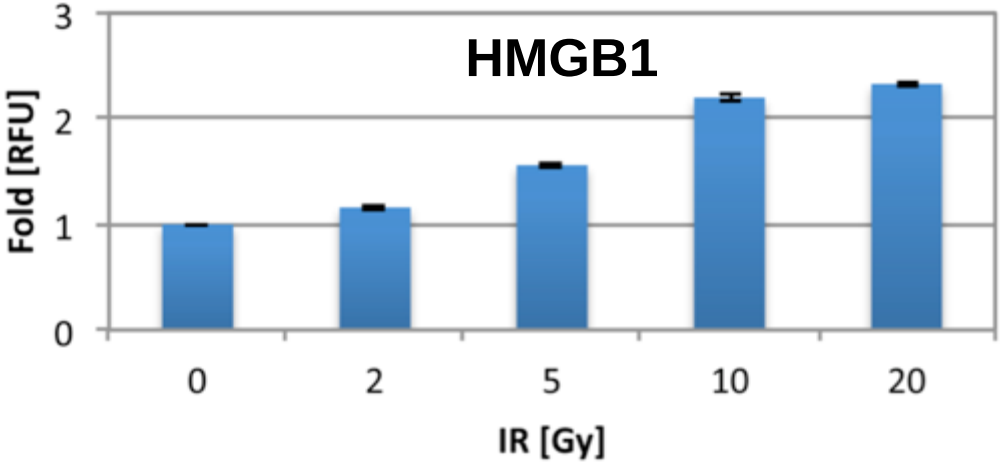
CRT, "eat me" signal, translocates to cell surface (Obeid et al., Nat Med 2007, 13:54-61)

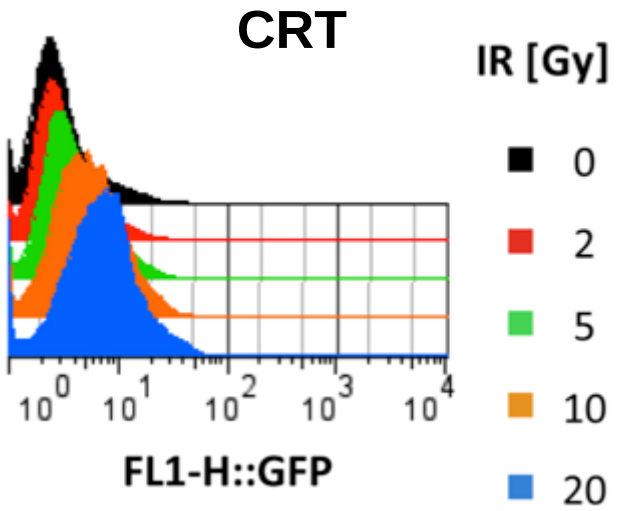
HMGB-1, a damage associated molecular pattern (DAMP) binds to TLR4 to promote cross-presentation of tumor-derived antigens (Apetoh et al., Nat Med 2007, 13:1050)

ATP released by dying cells binds to P2RX7 purinergic receptor leading to inflammasome activation and IL-1β production (Ghiringhelli et al., Nat Med 2009, 15:1170)

Radiation induces Immunogenic cell death







Golden et al, OncoImmunology 3:4, e28518; January 1, 2014.

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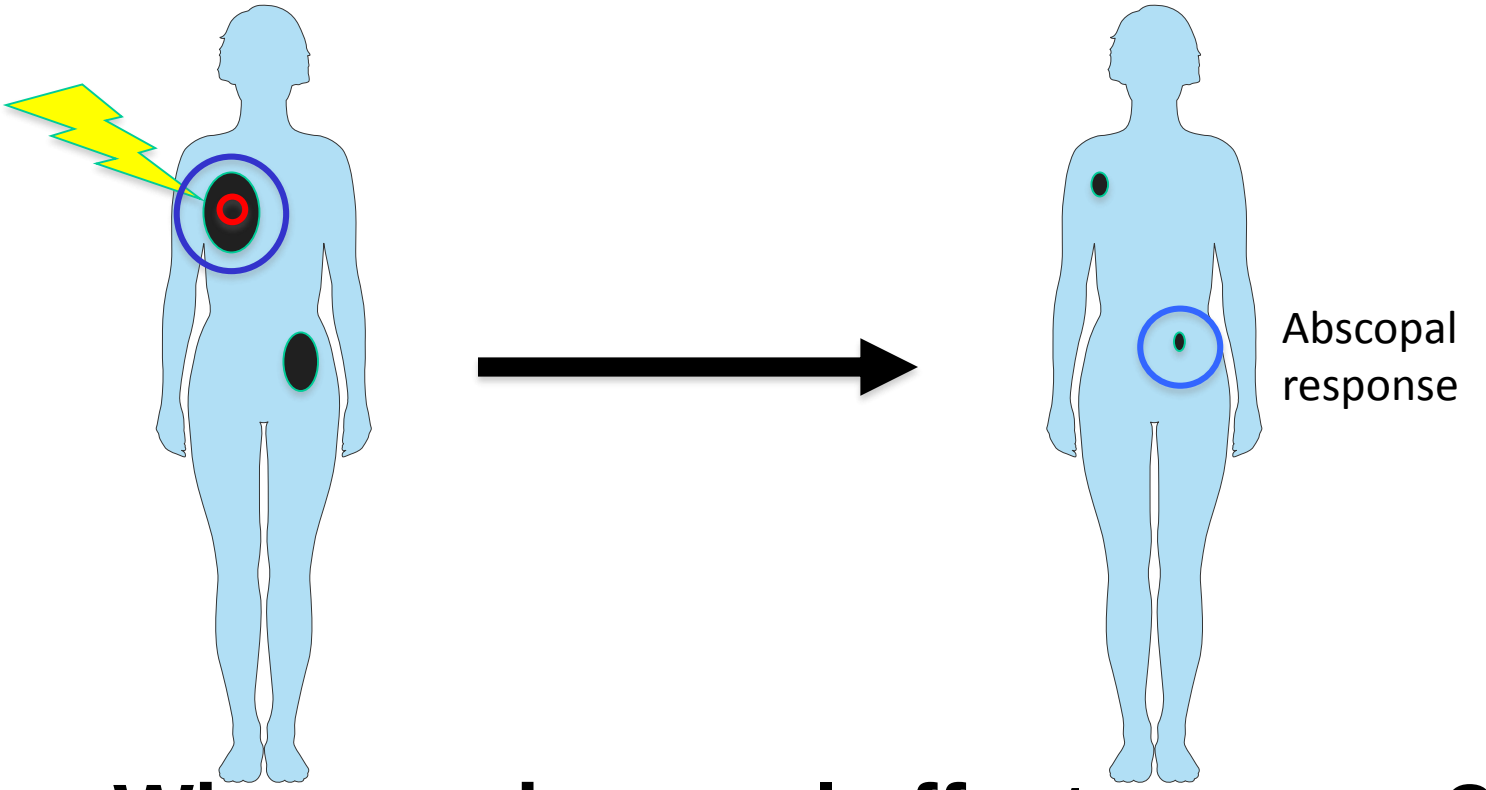
Abscopal Effect

Effect of ionizing radiation on cancer

outside the radiation field

Latin *ab* (position away from) and *scopus* (mark or target)



Why are abscopal effects so rare?

Formenti & Demaria, IJROBP 2004; Lancet Oncology 2009

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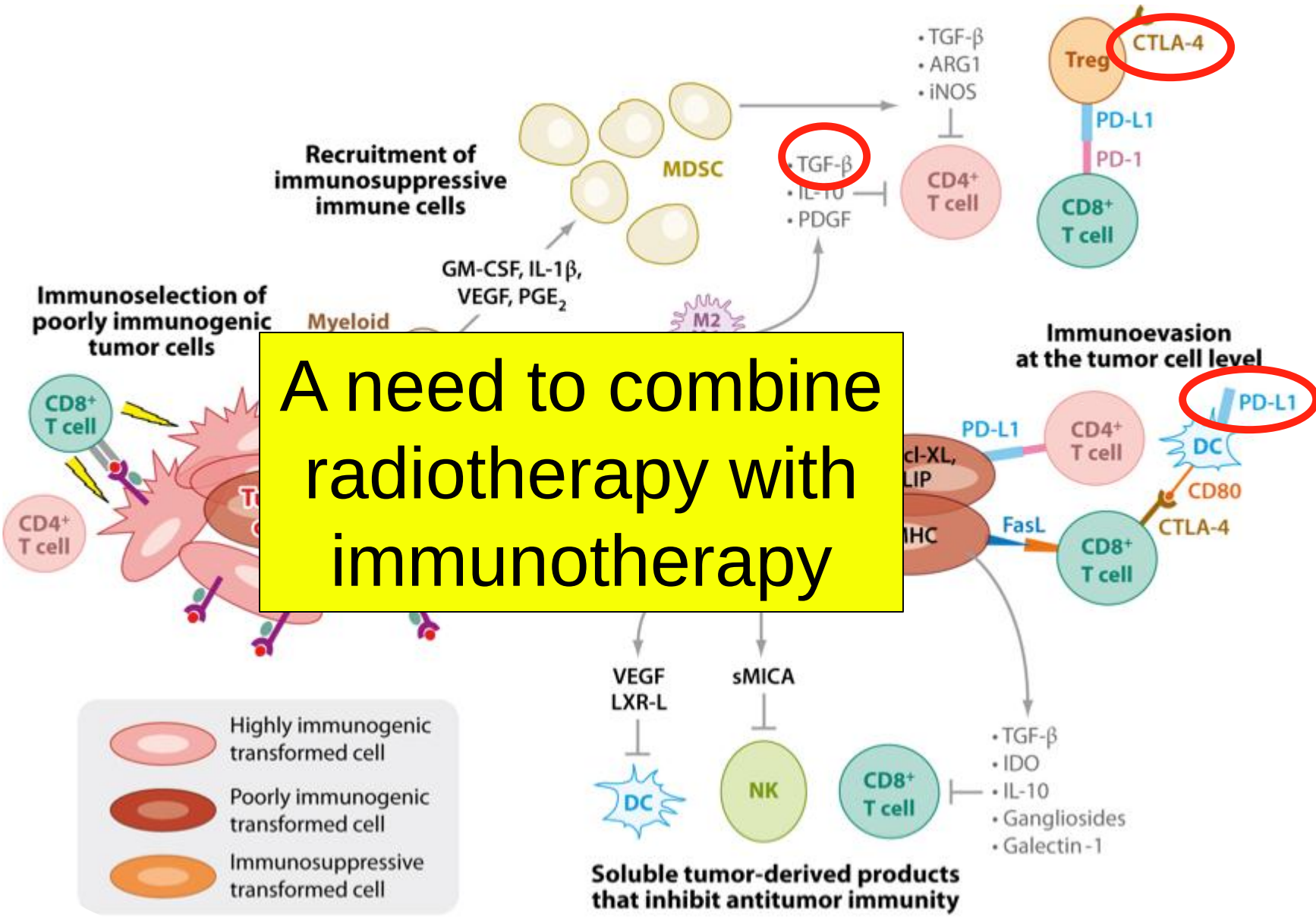
IMMUNOSUPPRESSION DOMINATES IN ESTABLISHED TUMORS



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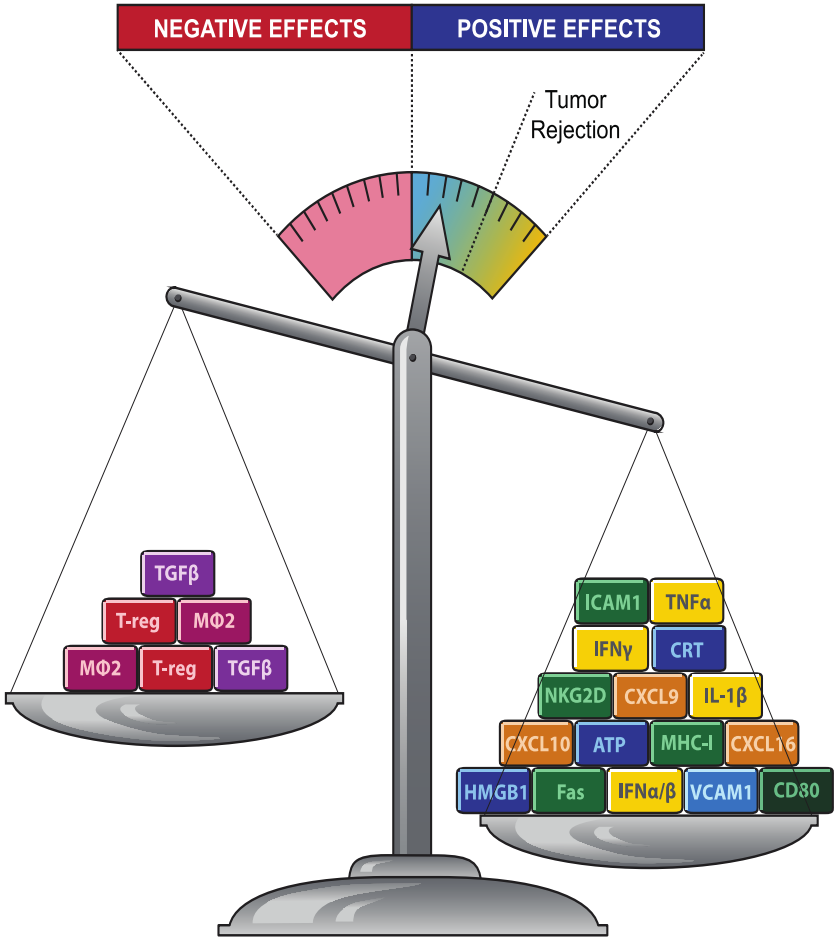
Why are abscopal effects of radiation rarely observed in the clinic?



NYU experience in combining immunotherapy strategies with radiation

Priming phase :

- FLT-3L/GM-CSF
- TLR agonists

Effector phase:

- Anti-CTLA4
- Anti-PD-1
- Anti-TGFβ

Hypothesis:

Ionizing radiation can stimulate anti-tumor immunity –by generating an *in situ* vaccine - and combination with immunotherapy may uncover this effect

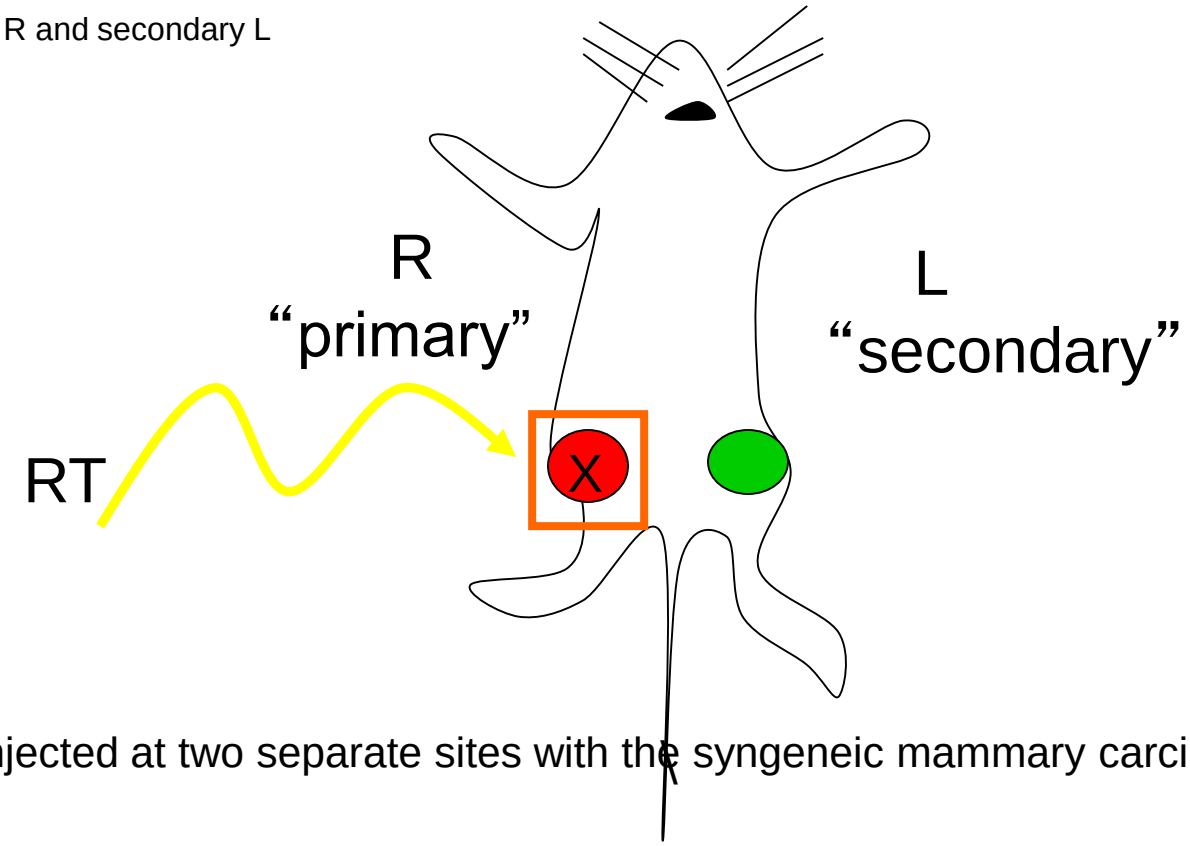
Day: 0 — 20 — 21 — 31

67NR
$5x10^4$ or 10^5
each sides,

primary R and secondary L

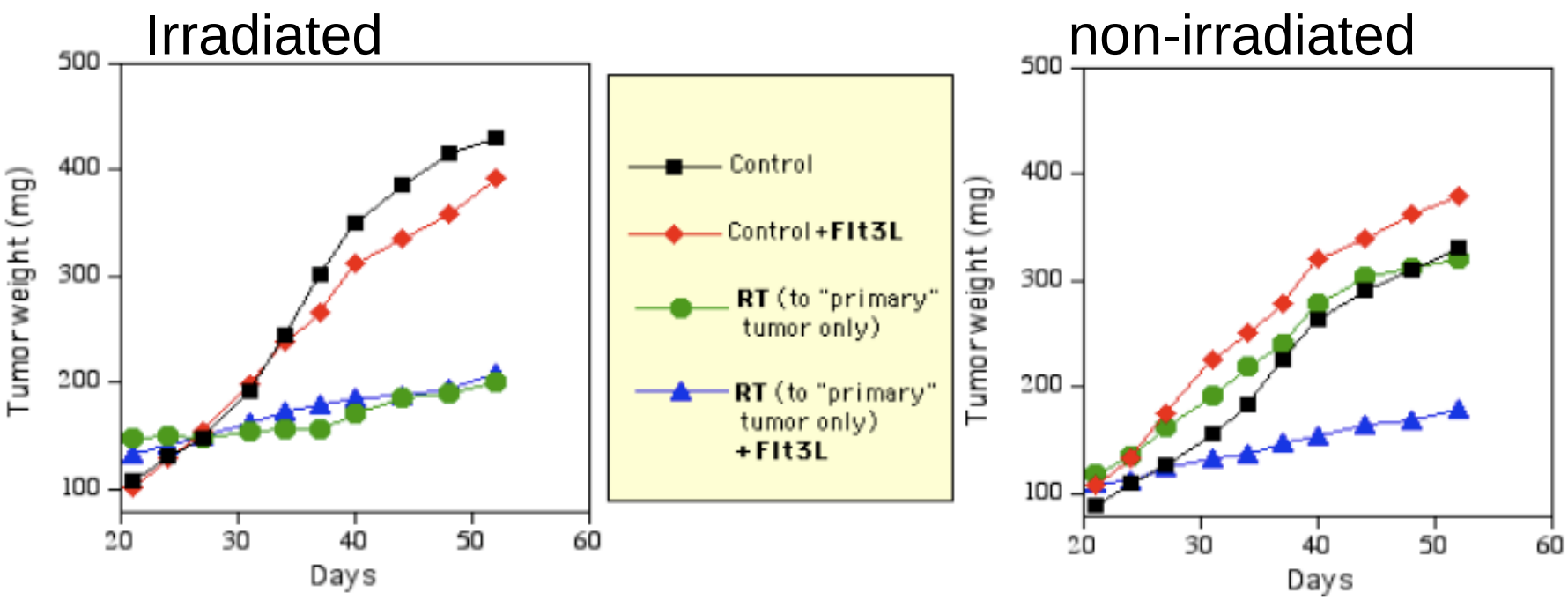
RT
2 Gy

Flt3-L (0.5mg/kg)



BALB/C mice injected at two separate sites with the syngeneic mammary carcinoma 67NR cell line

RT+Flt3-L : systemic anti-cancer effects



Int J Radiation Oncology Biol Phys 2004

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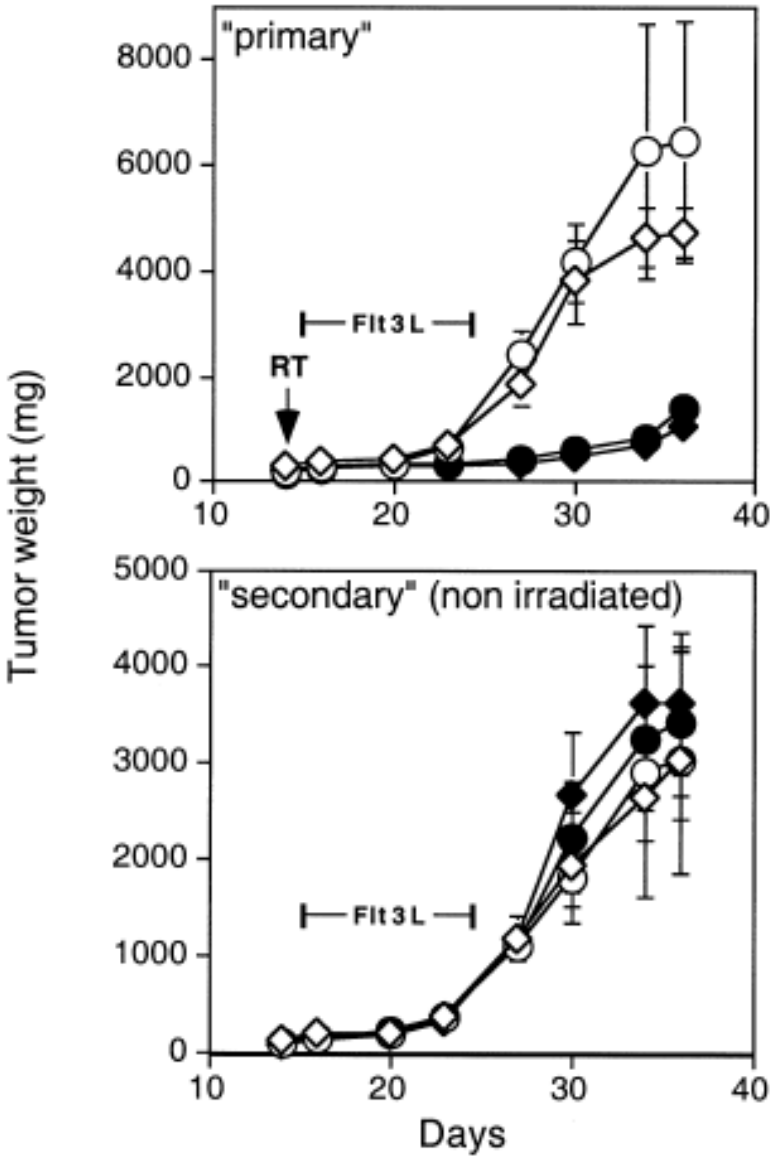
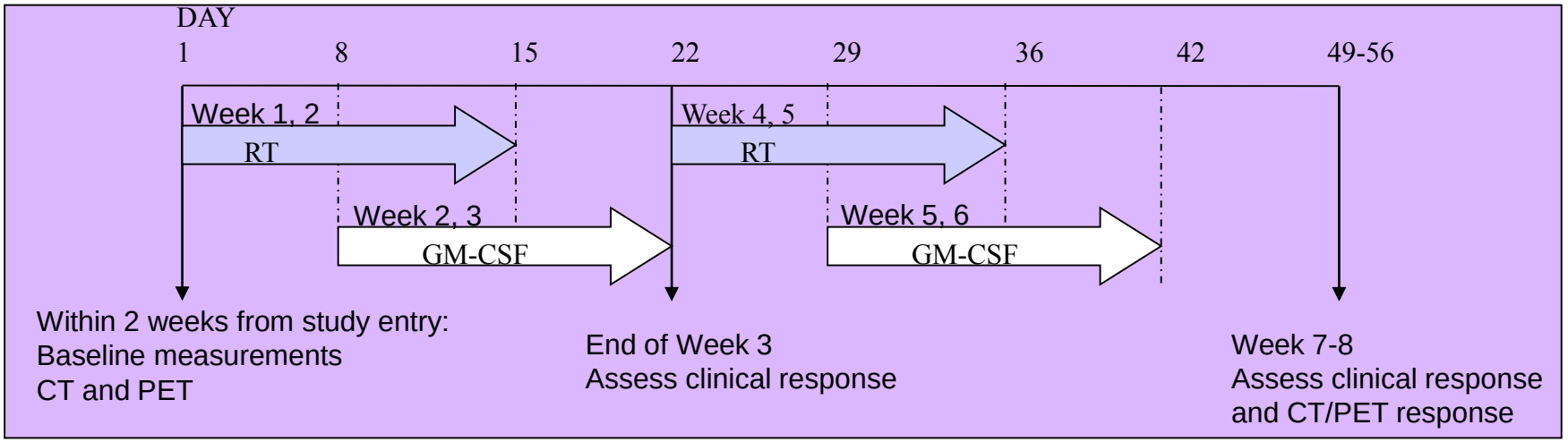
Abscopal Effect is abrogated in nude mice



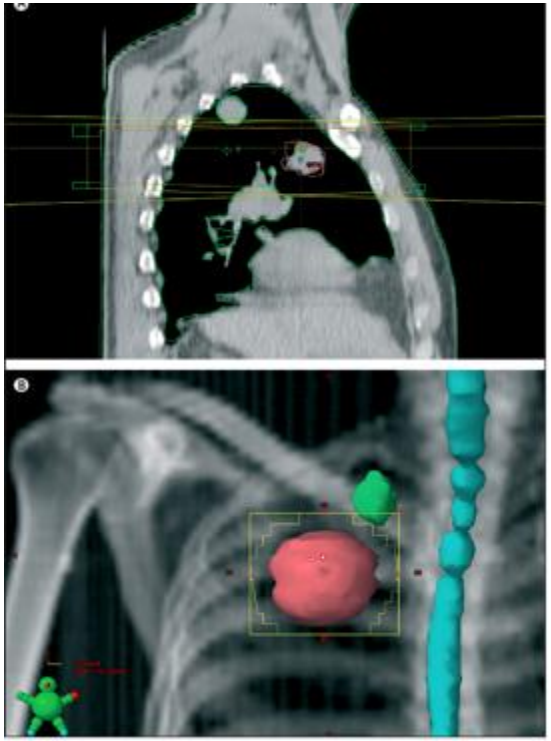
Int J Radiation Oncology Biol Phys 2004

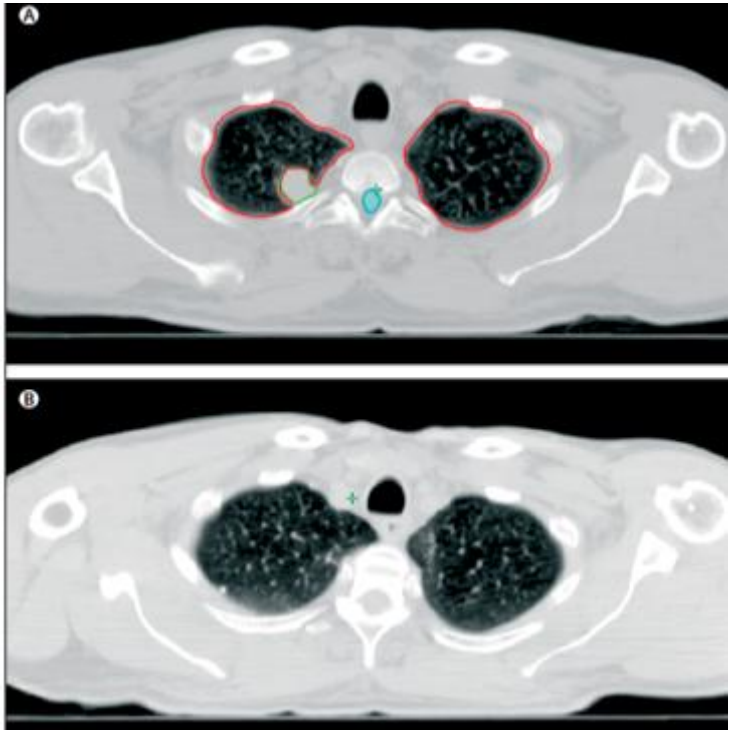
NYU 0258
Abscopal trial RT+GM-CSF in metastatic solid tumors



RT
3.5GyX10

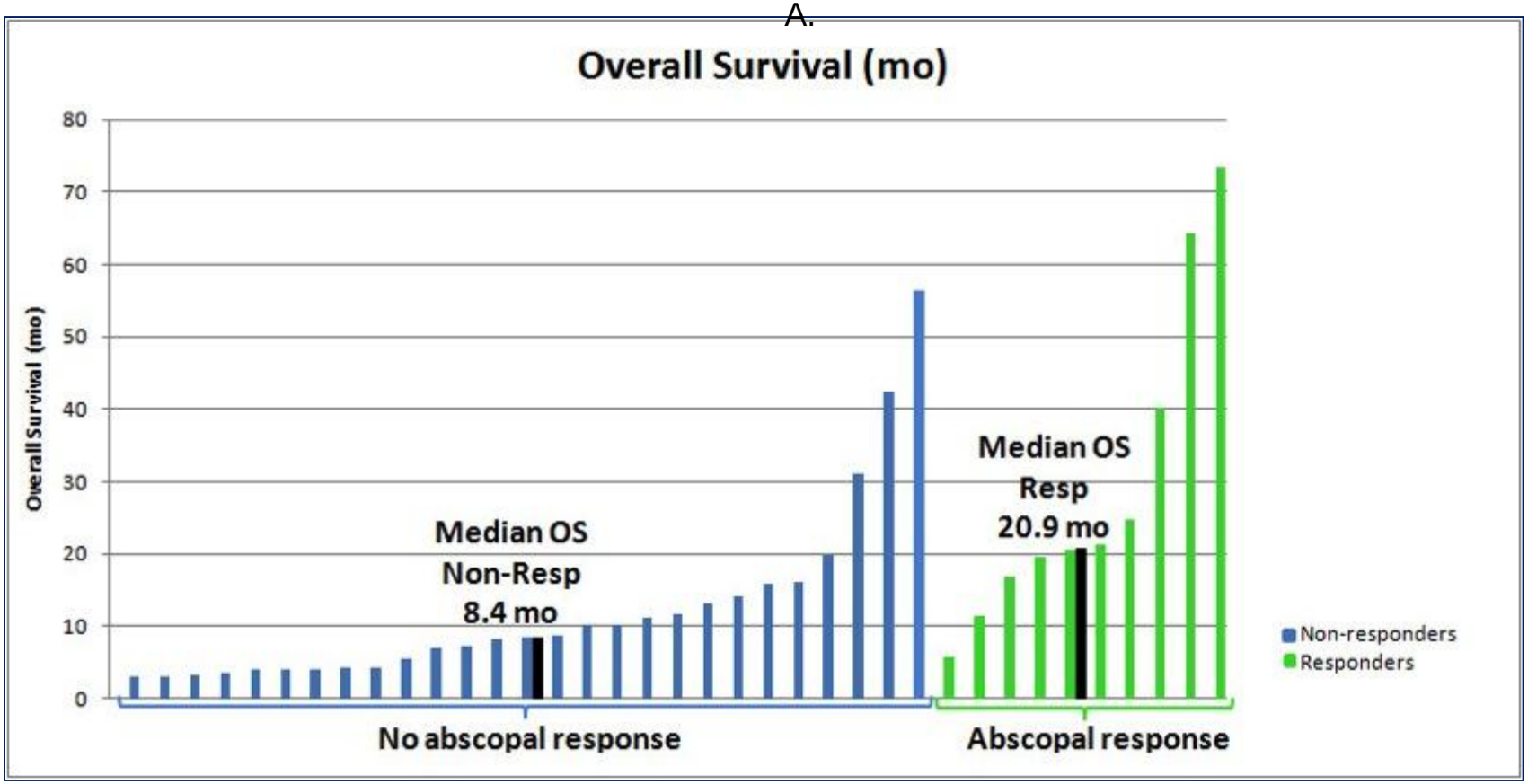
GM-CSF
125 μg/m^2





Abscopal effect 10/37 (27%)
Abscopal effect and survival, 37 patients (NYU 02-58)

A.



Abscopal responders likely to be patients already more immunocompetent

ASTRO 2012

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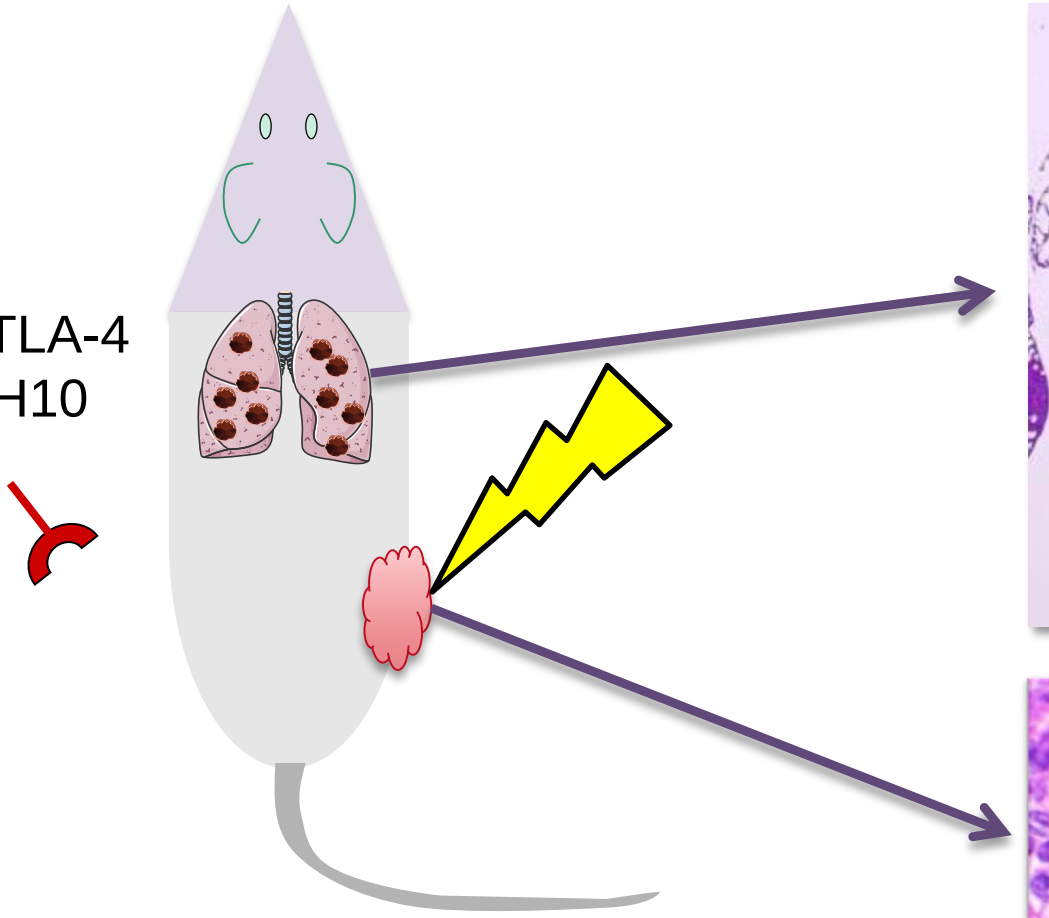
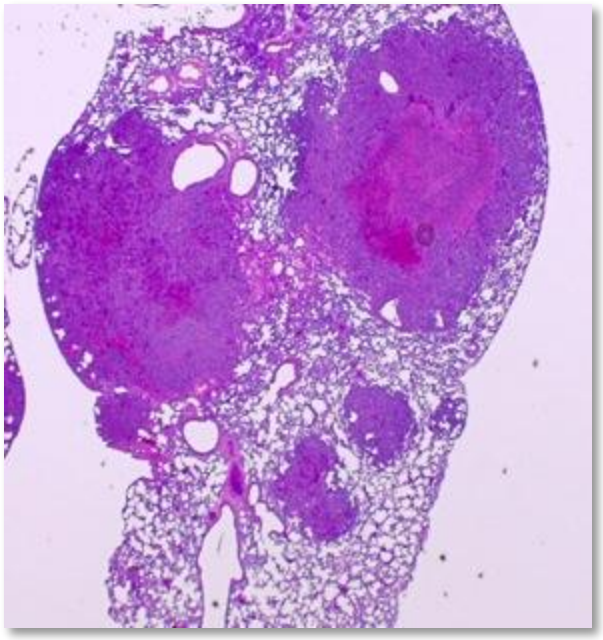
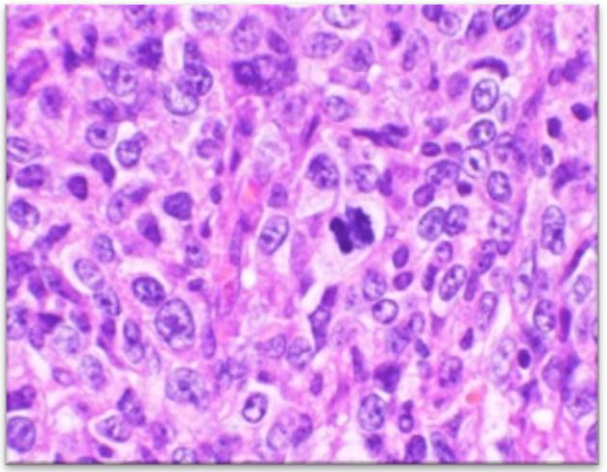
4T1 mouse model of metastatic breast cancer

Anti-CTLA-4
mAb 9H10



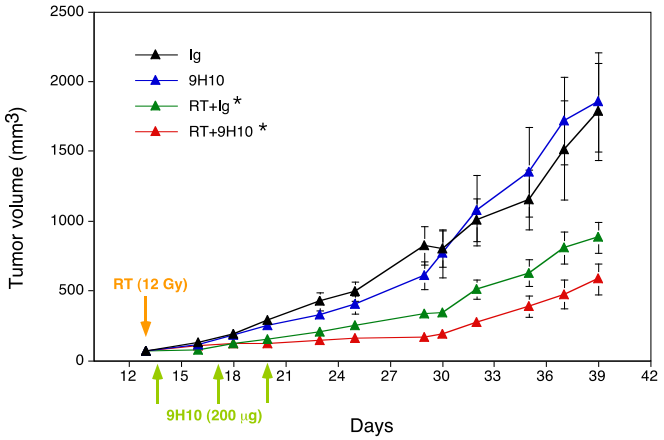


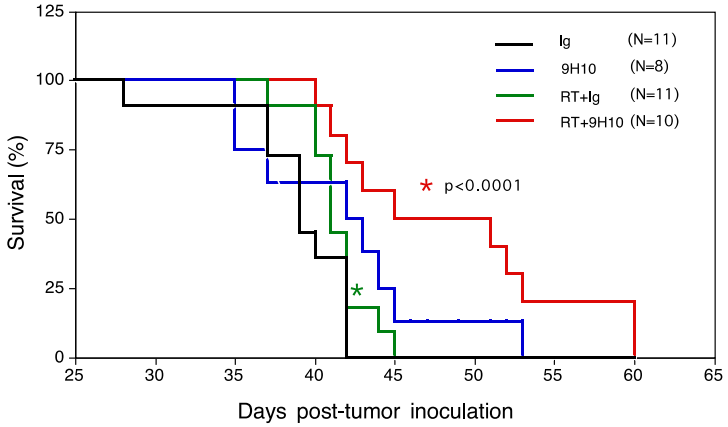


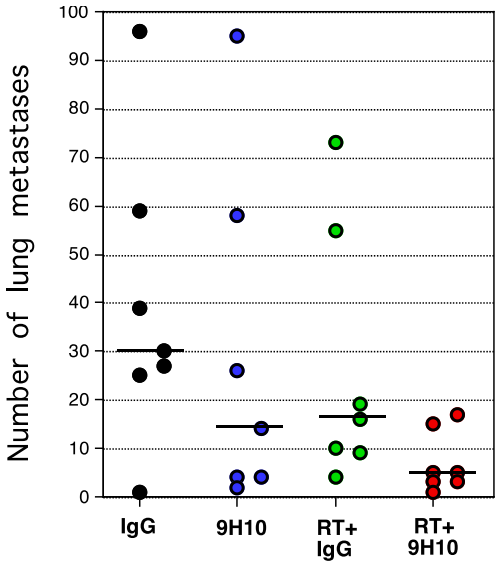
Experimental Endpoints:

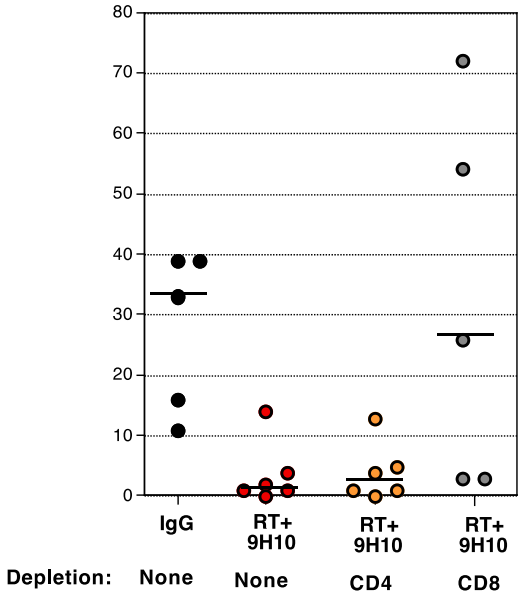
- Primary Tumor growth
- Lung metastasis
- Immune response evaluation

Immune-Mediated Inhibition of Metastases after Treatment with Local Radiation and CTLA-4 Blockade in a Mouse Model of Breast Cancer









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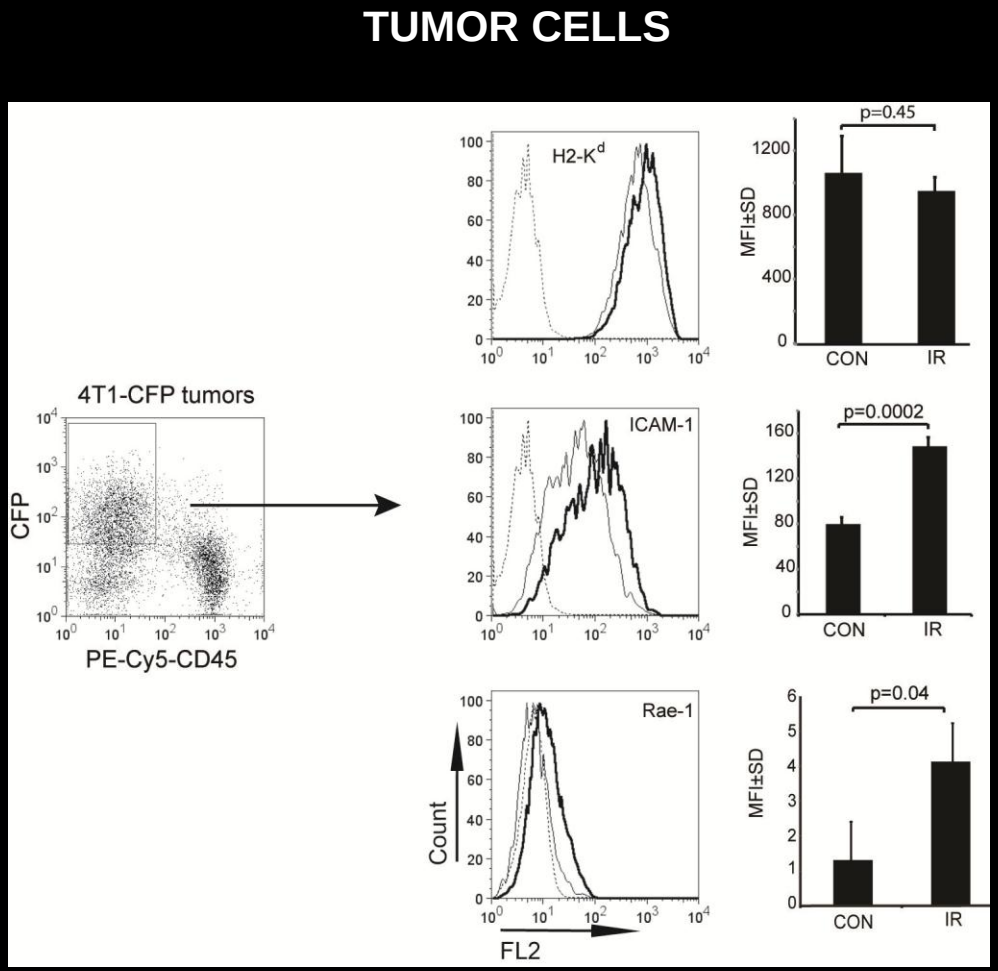
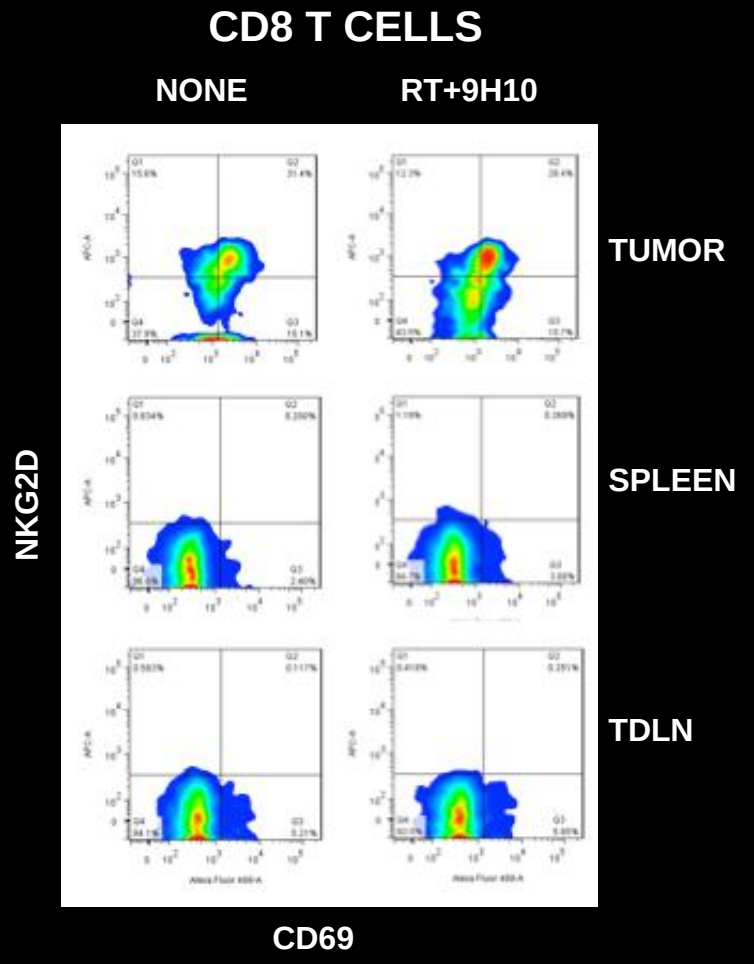
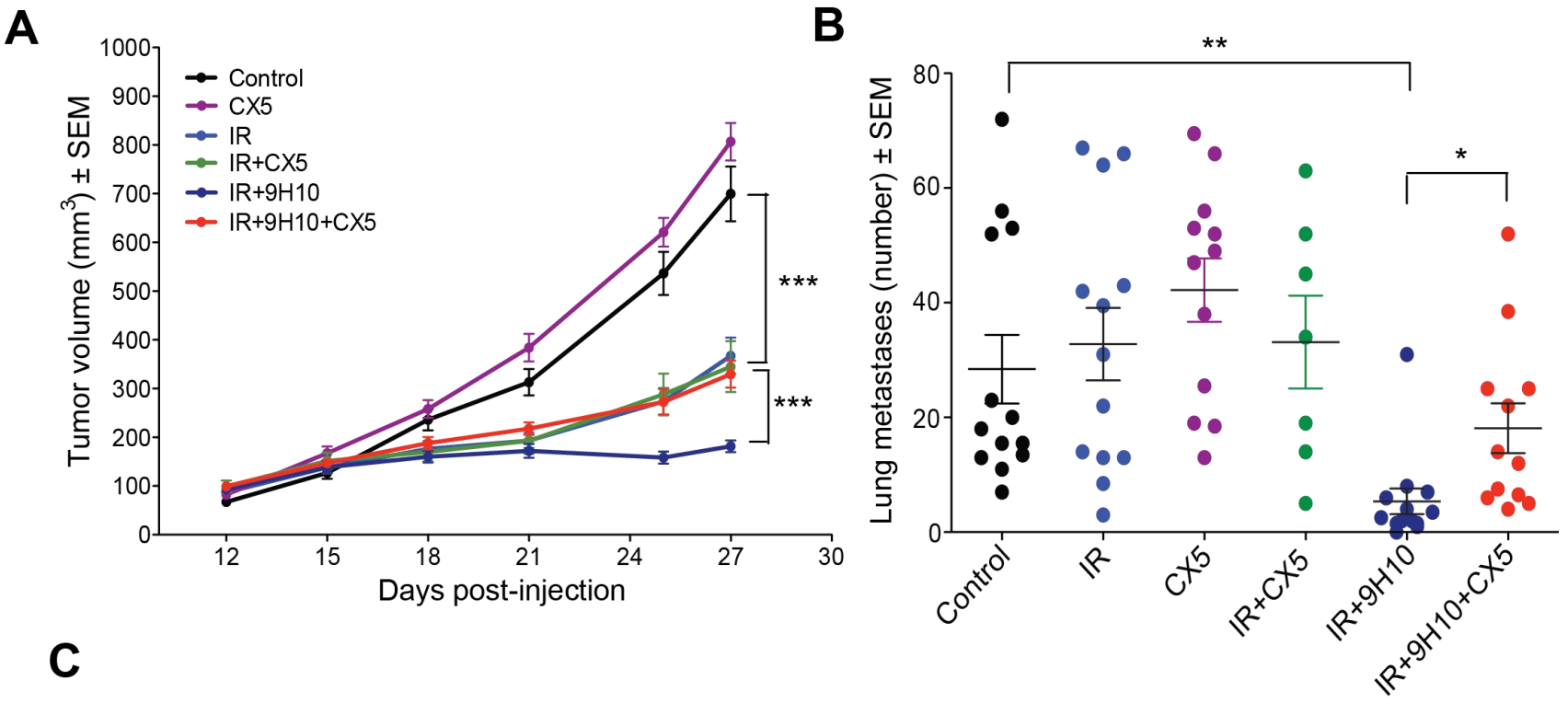
Radiation up-regulates ICAM-1 and Rae1 on 4T1 cancer cells *in vivo*

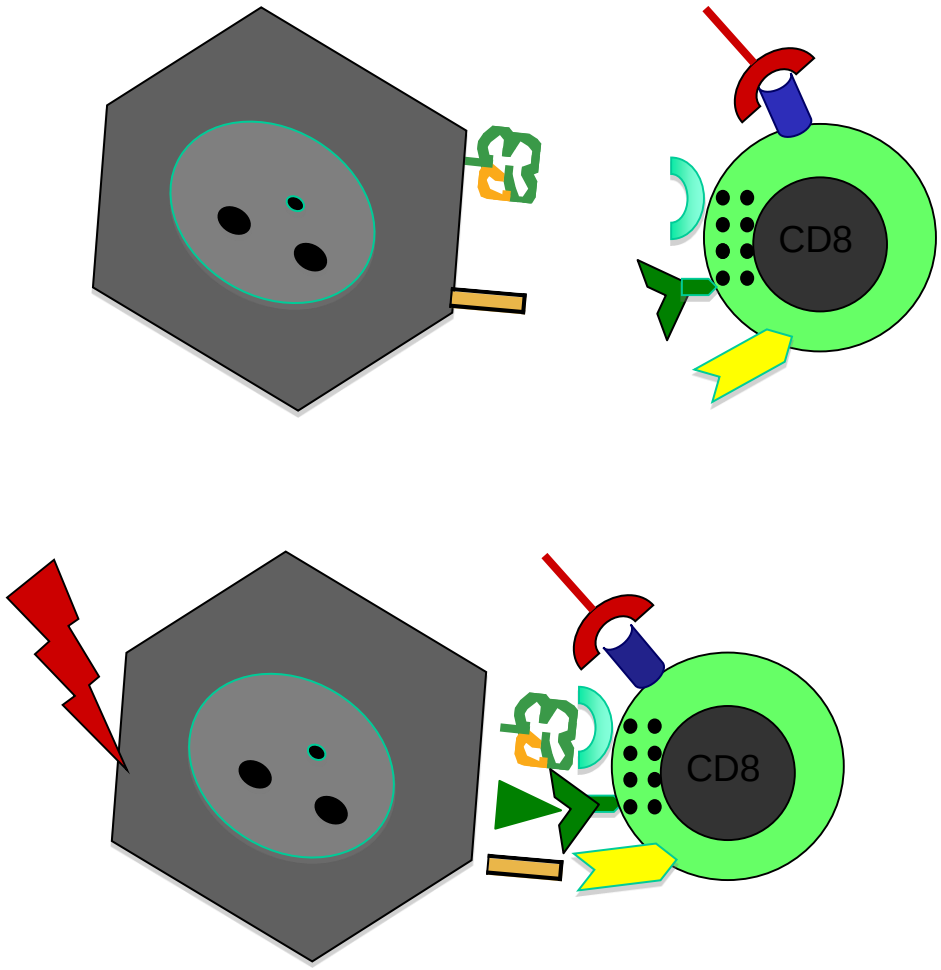




Blocking NKG2D abolishes immune-mediated tumor inhibition by combination of RT+anti-CTLA-4



Radiation-induced Rae-1/NKG2D interaction is required for stable immunological synapse of tumor and T cells



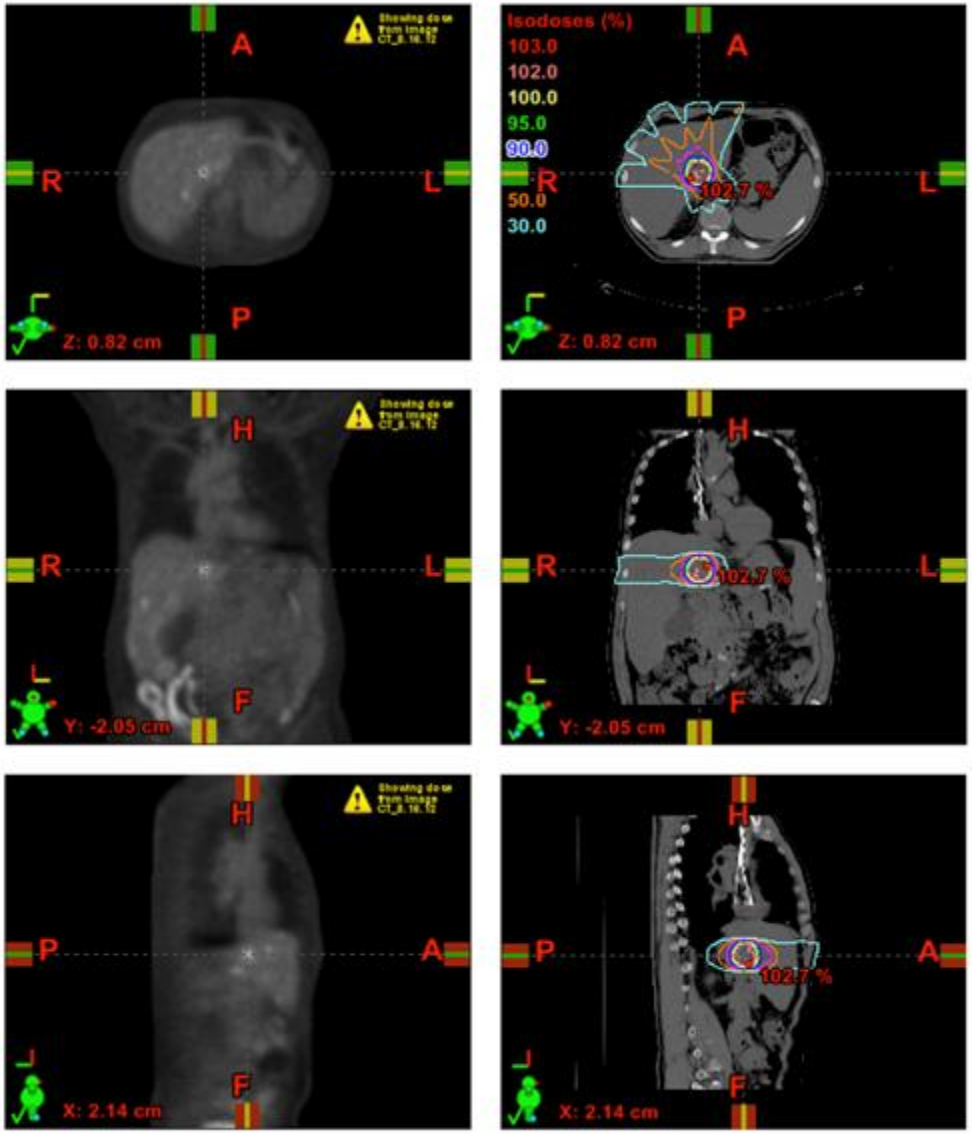
Clinical translation:
NKG2D and its ligand MHC class I chain-related protein A (MICA)

Ruocco et al., J Clin Iinvest 2012

Does this translate to the clinic?

Patient with Metastatic NSCLC

Progressing after 3 lines of chemo and chest RT: Multiple lung, bone and liver metastasis



RT to one liver met6 Gy X 5 (TD 30 GY)
Ipilimumab, 3 mg/Kg, after first RT
q3 weeks, X 4 cycles

Golden et al Cancer Immunology Research, 2014

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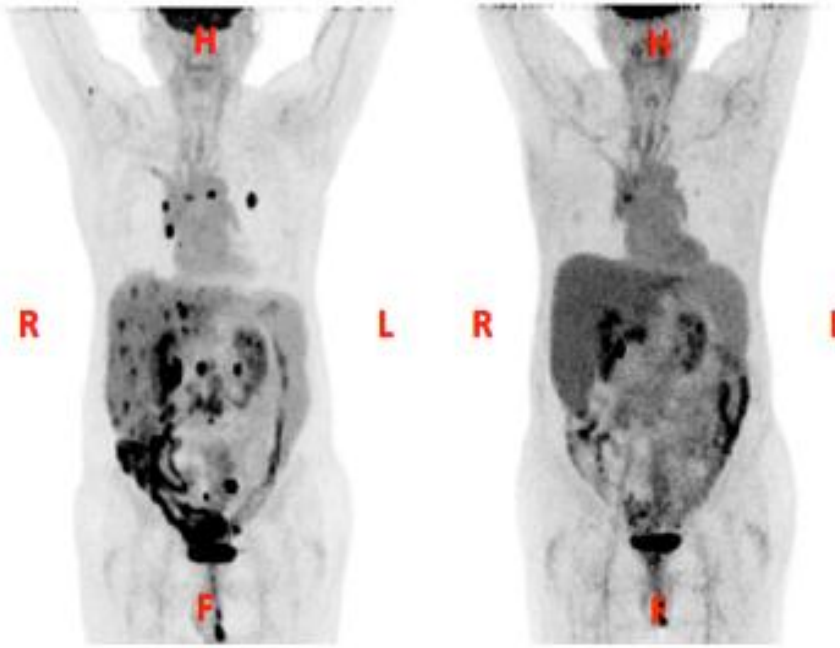
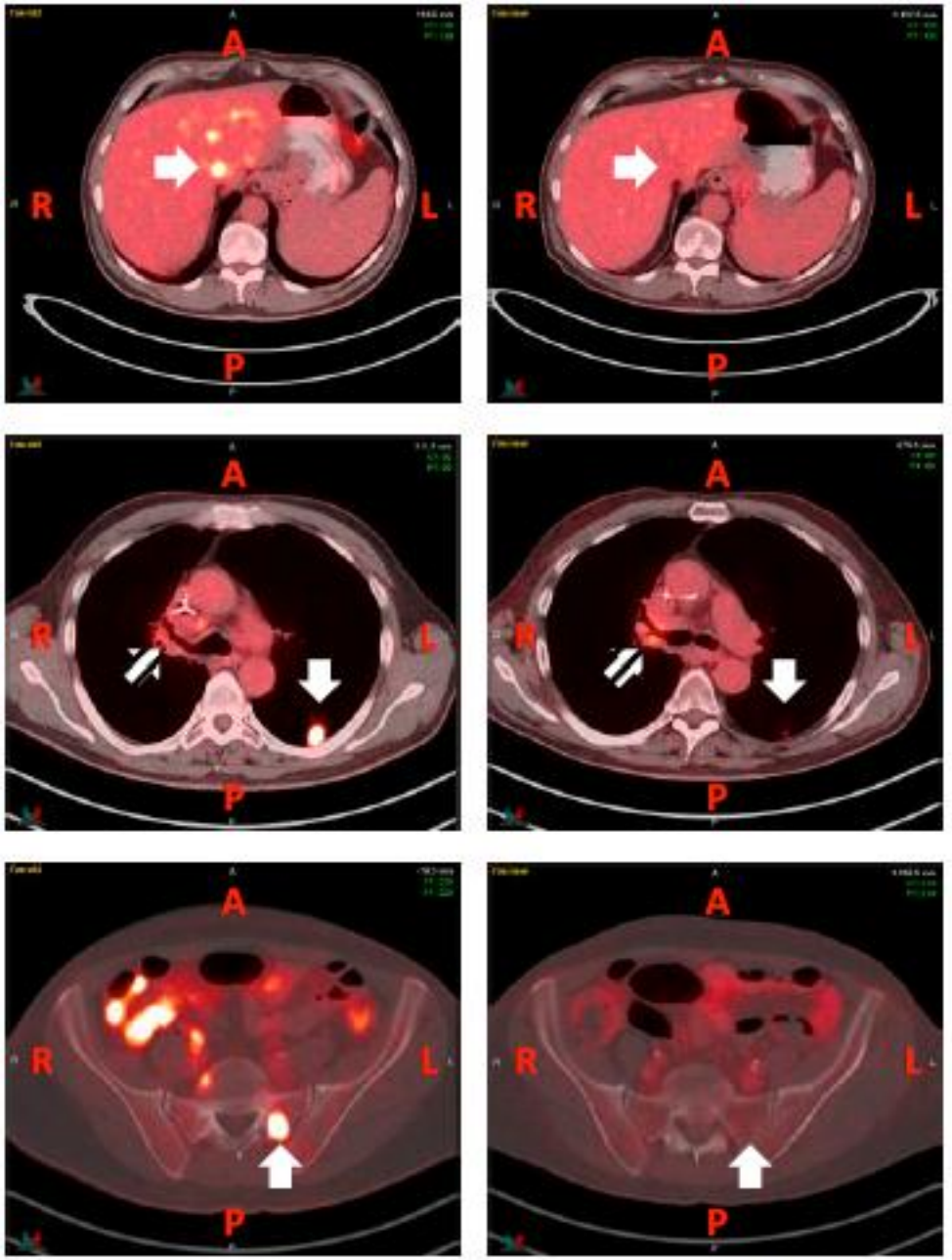
Metastatic NSCLC: Response to RT+ipilimumab



August 2012 PET/CT January 2013 PET/CT



August 2012 PET/CT January 2013 PET/CT

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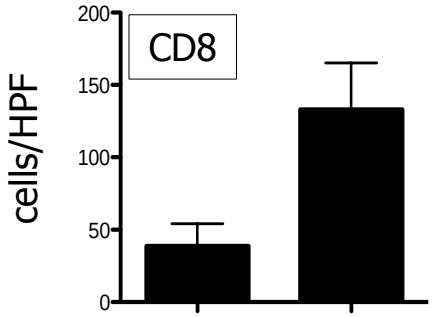
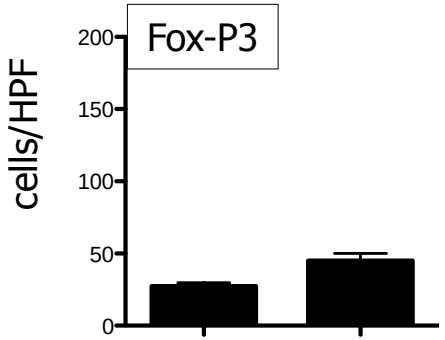
2010 2013

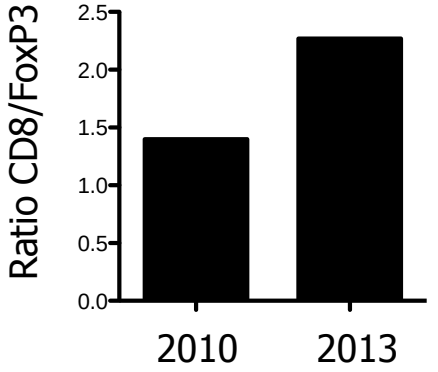
H&E

CD8

TIA-1

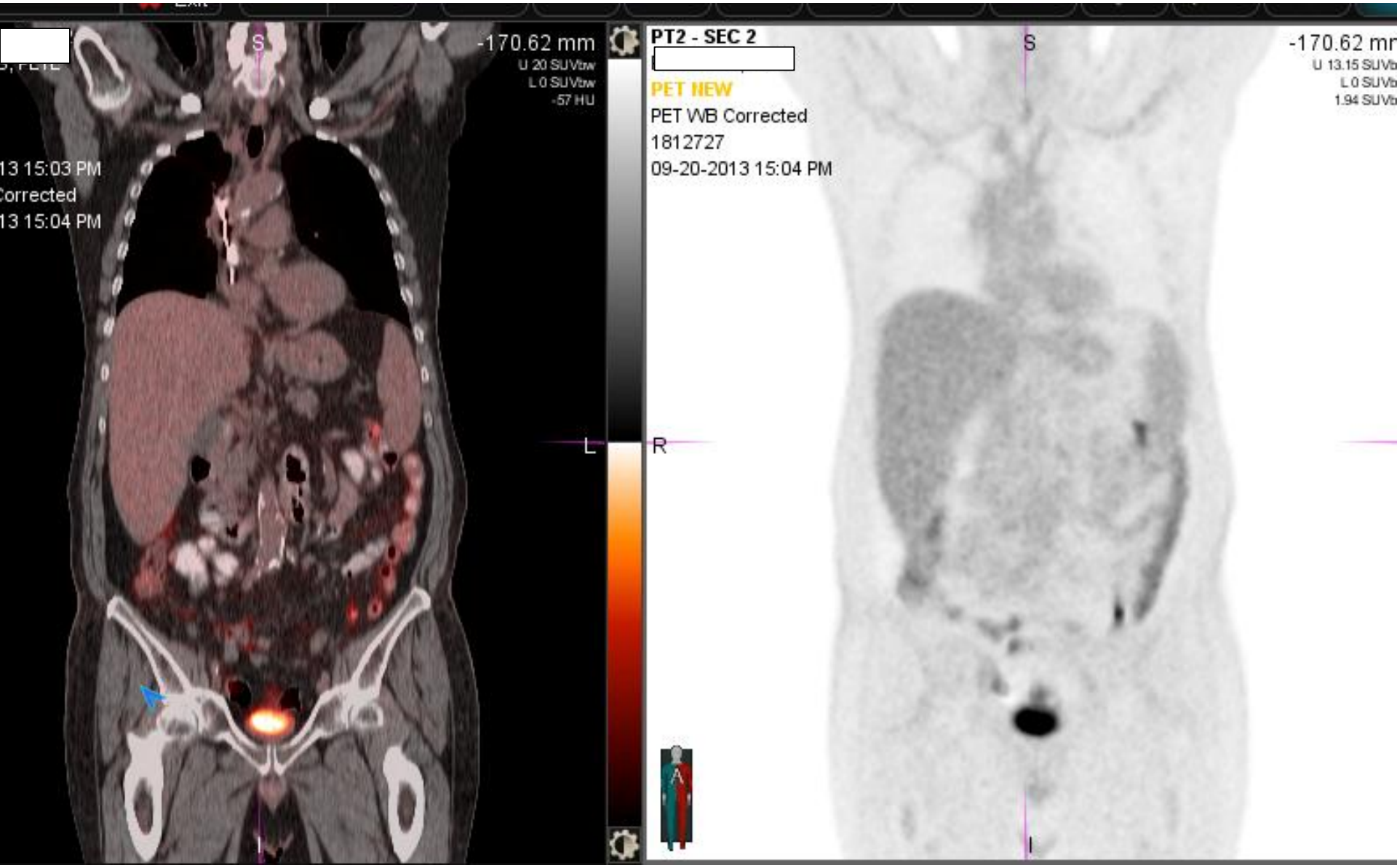






Cancer Imm. Research, 2014

Clinical and radiological CR at one year: currently NED at 25 m



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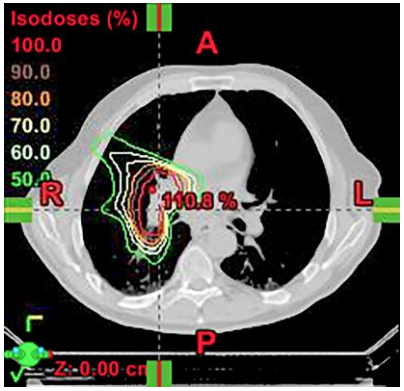
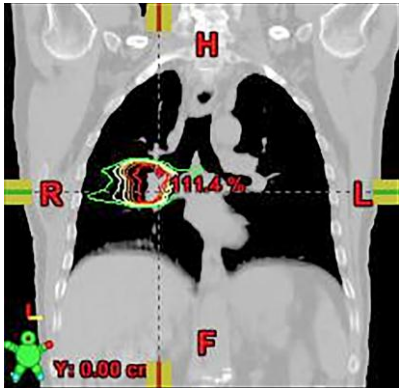
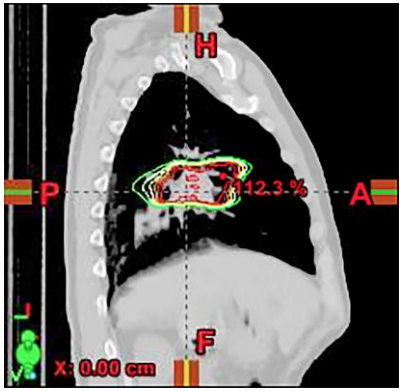
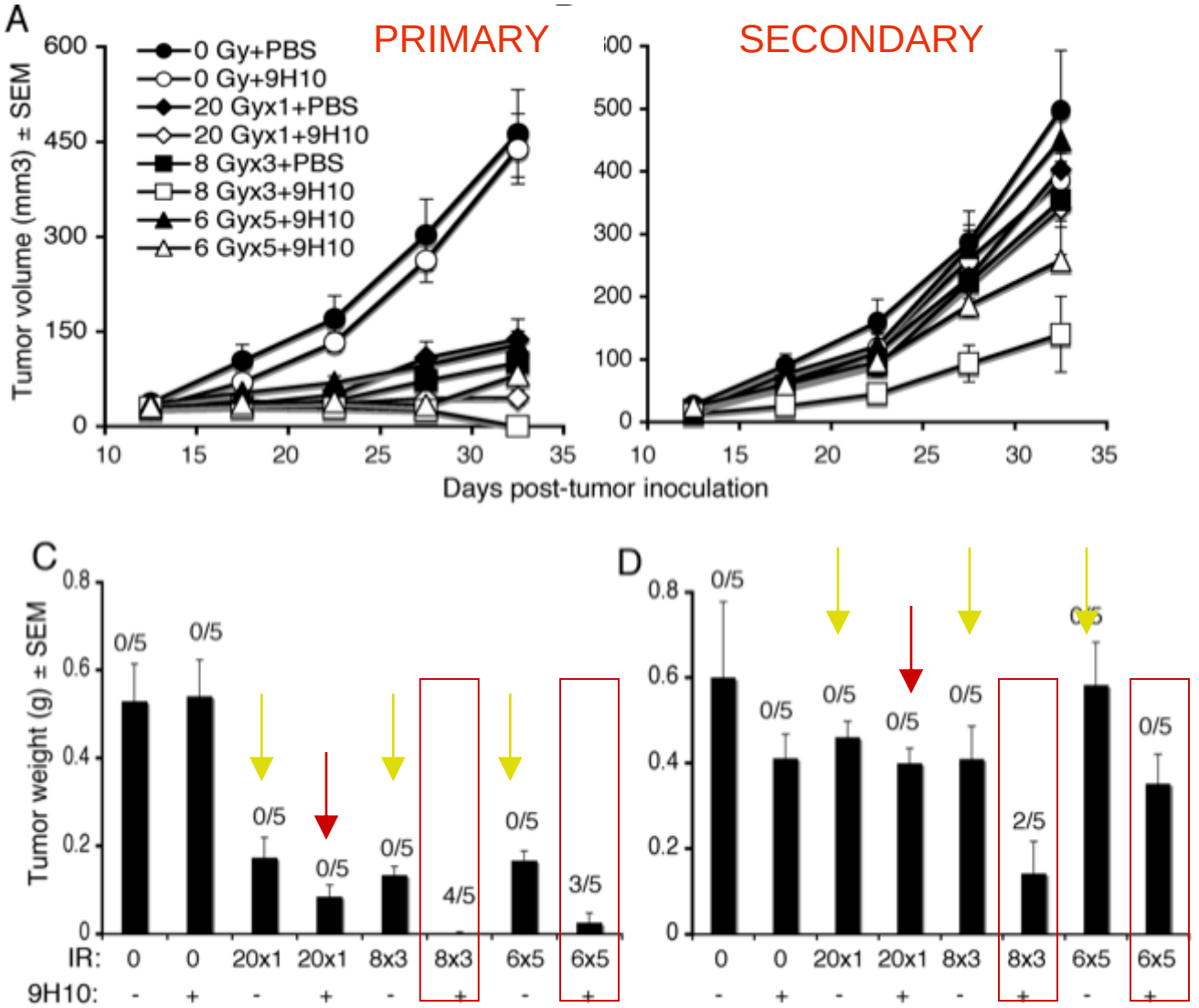
NYU S14-00208 Ipilimumab + RT for NSCLC







Induction of the abscopal effect by fractionated RT and anti-CTLA-4 mAb

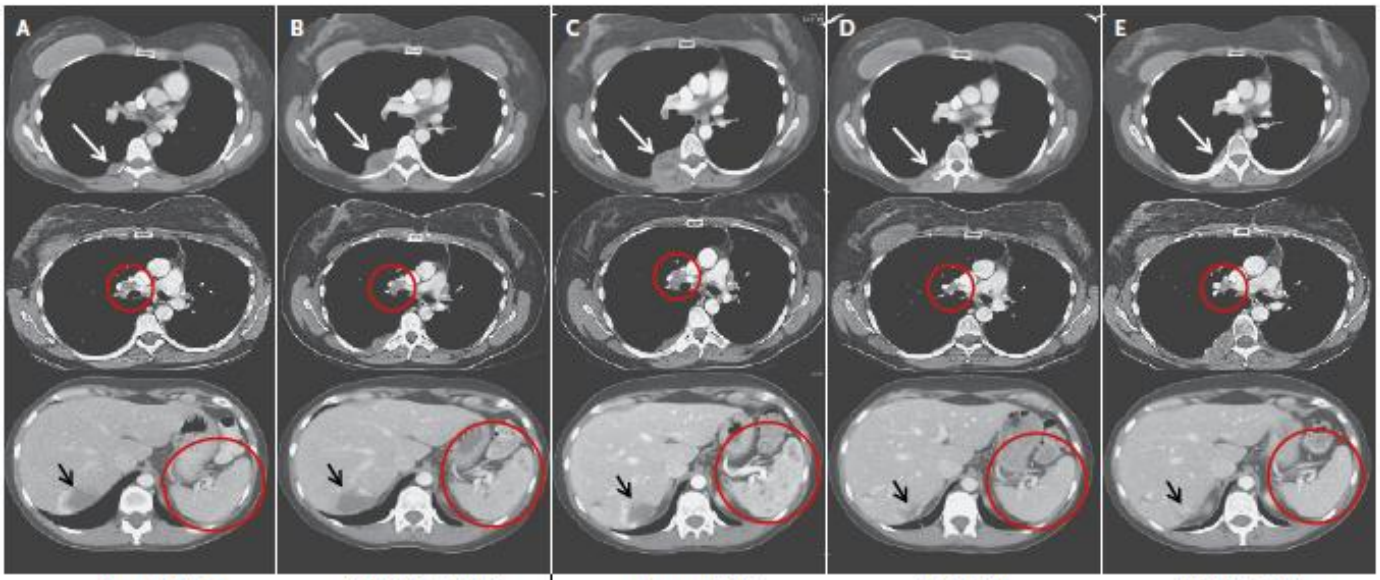


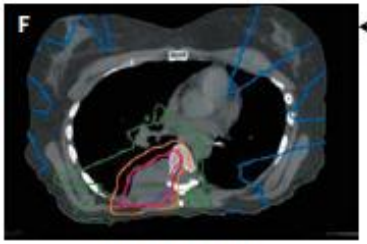
Dewan et al., Clin. Cancer Res. 15:5379-88, 2009

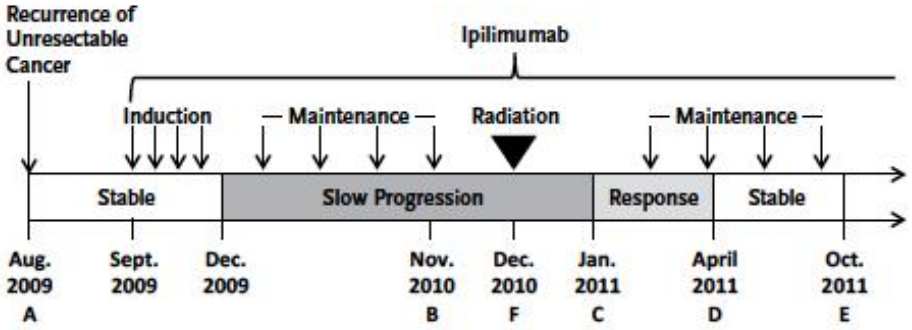
The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma







>20 ongoing trials testing testing combinations of RT and Ipilimumab:

At NYU: NCT01689974

2012

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Clinical translation

RT combination with:	Trial/ tumor site	accrual
Flt3L *(Demaria et al., Int J Radiat Oncol Biol Phys, 2004)*	Proof of principle abscopal trial (met disease all sites) NYU 02-58	37/37
anti-CTLA-4 *(Demaria et al., Clin Cancer Res 2005; Matsumura et al., J Immunol 2008; Pilones et al., Clin Cancer Res 2009; Dewan et al., Clin Cancer Res 2009; Ruocco et al., J Clin Invest 2012)*	Met melanoma R trial NCT01689974	12/48
	Met NSCLC trial NCT02221739	20/29
TLR7-agonist *(Dewan et al. Clin Cancer Res 2012)*	Metastatic breast cancer NCT01421017	14/29
anti-TGFβ *(Bouquet et al Clin Cancer Res 2012)*	Metastatic breast cancer R trial NCT01421017	24/29

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Take Home Message

Preclinical and clinical evidence suggests that local radiotherapy can contribute to the efficacy of cancer immunotherapy, by rendering the irradiated tumor more immunogenic

Radiotherapy can be harnessed as an adjuvant to immunotherapy as it may convert non-responding patients to responders to the same immunotherapy

Dose/fractionation and sequencing of radiotherapy need to be explored in combination with each immunotherapeutic strategy, in prospective PHASE I-II clinical trials

Non-invasive response monitoring tools are warranted: current imaging may be misleading

ELSEVIER

Seminars in RADIATION ONCOLOGY

Volume 25 / Number 1 / January 2015

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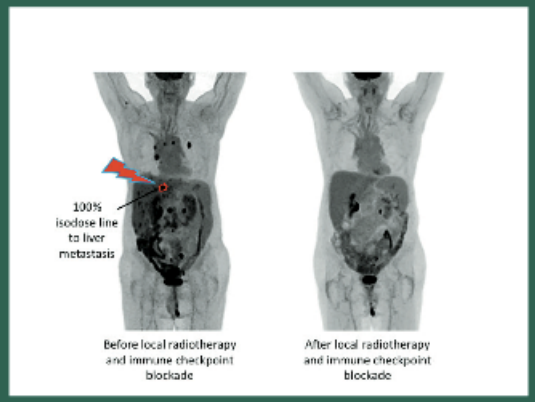
Radiation and the Immune Response

Guest Editor
Silvia C. Formenti, MD



CELEBRATING 25 YEARS

SEMINARS IN RADIATION ONCOLOGY
Radiation and the Immune Response
25(1), January 2015, pp 1–64

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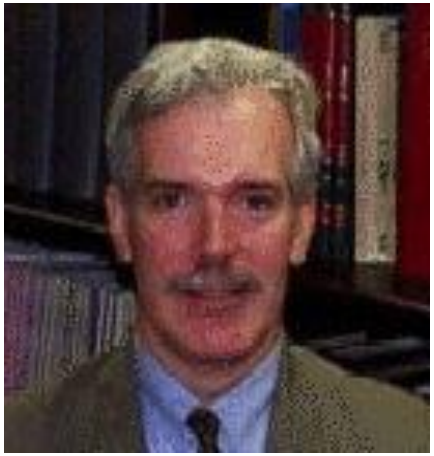

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Our patients