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***Radiotherapy as an adjuvant to immunotherapy:
clinical translation***

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DISCLOSURES

Consultant/Speaker:

Bristol Myers Squibb

Varian

GlaxoSmithKline

Regeneron

Recipient of research support

Janssen

Regeneron

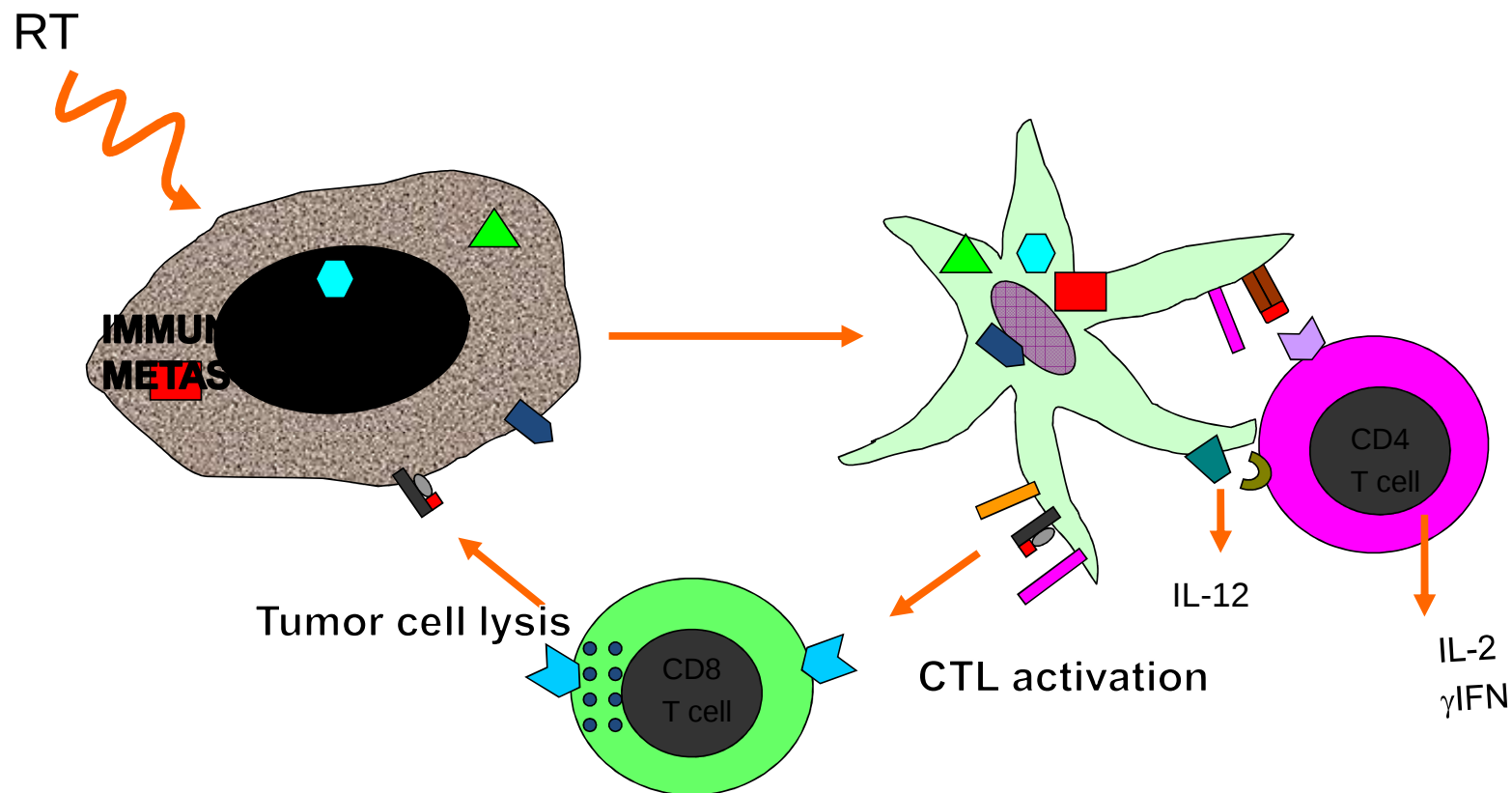
Bristol Myers Squibb



- RT induces immunogenic cell death
- In combination with different forms of immunotherapy RT converts the tumor into an *in situ* vaccine

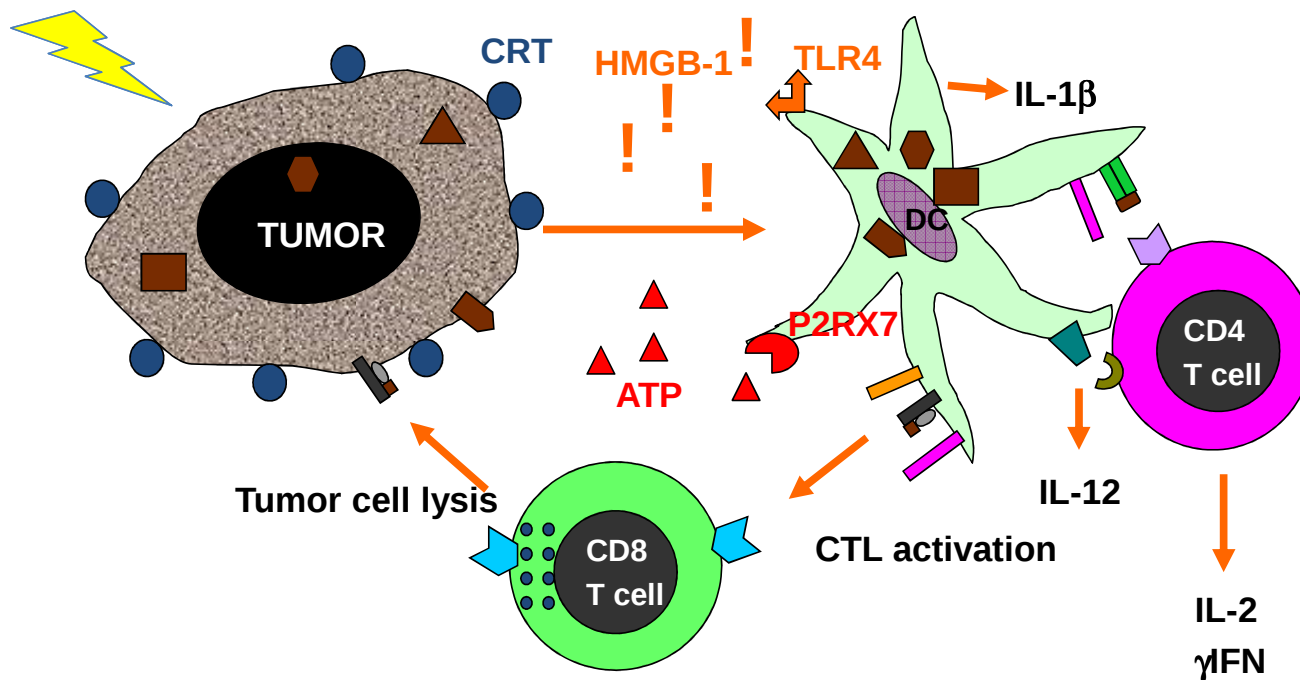


IN SITU VACCINATION HYPOTHESIS





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



CRT, “eat me” signal, translocation to membrane (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-1 β production (Ghiringhelli et al., Nat Med 2009, 15:1170)

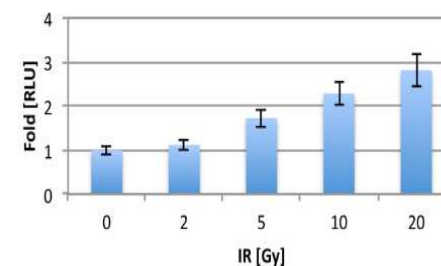
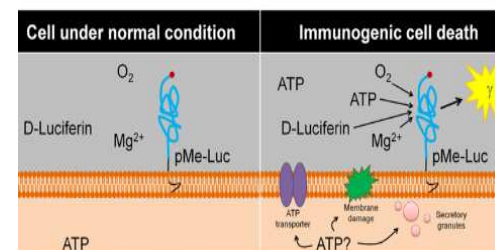
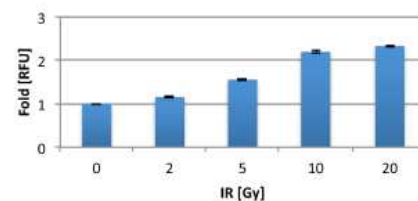
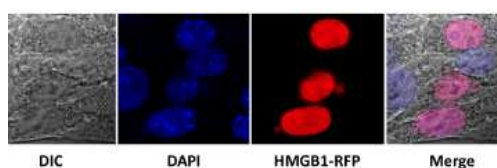
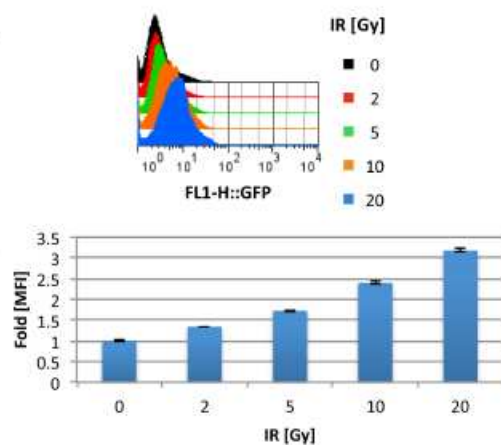
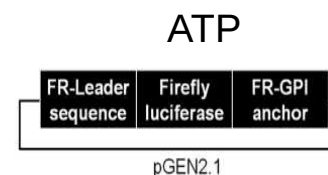
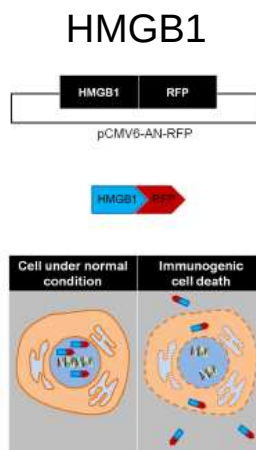
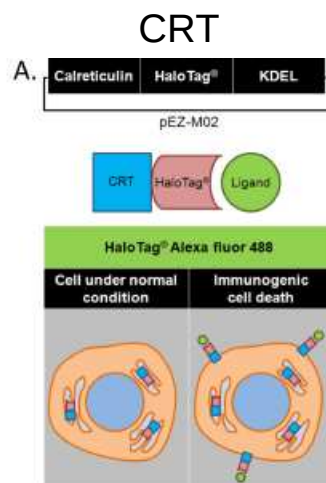


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In vitro assay for RT-induced ICD



Encouse Golden



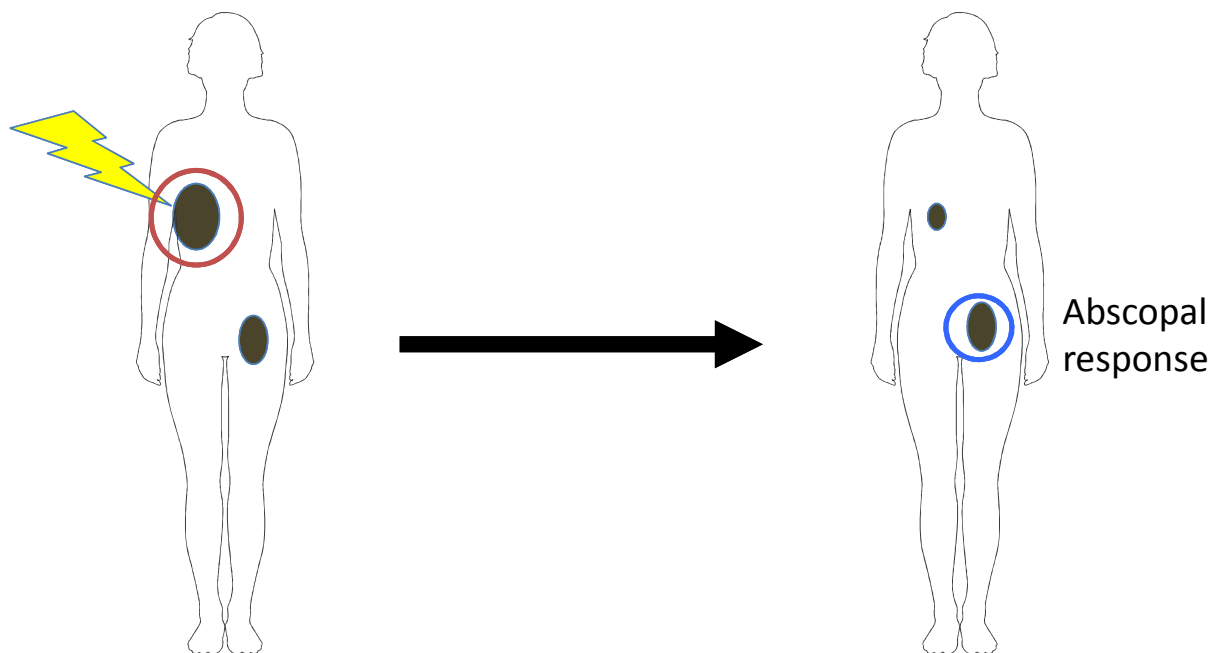
Oncoimmunology, 2014



Clinical study design to test for abscopal responses

Effect of ionizing radiation on cancer outside the radiation field

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

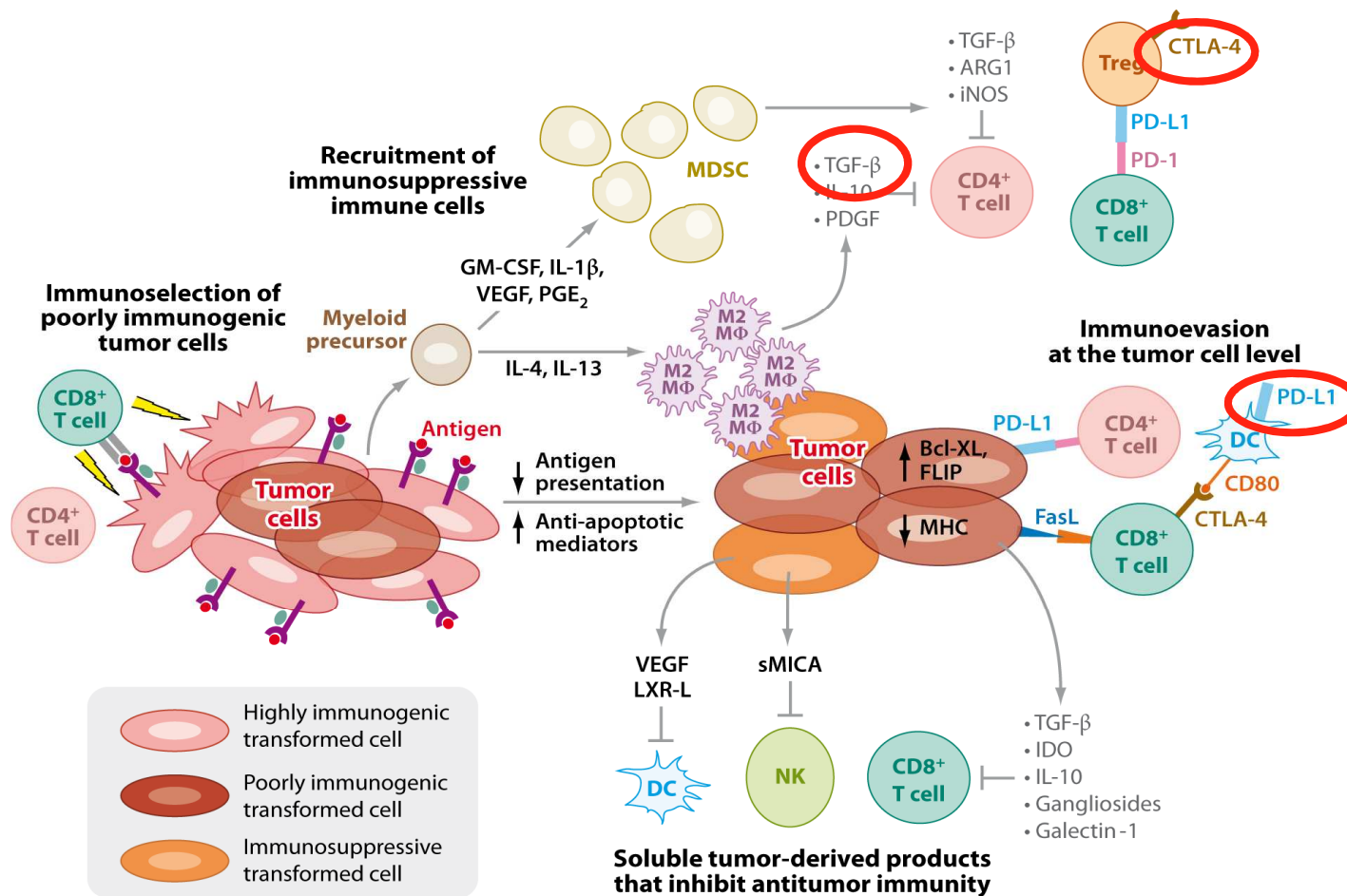


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Abscopal effects are rare



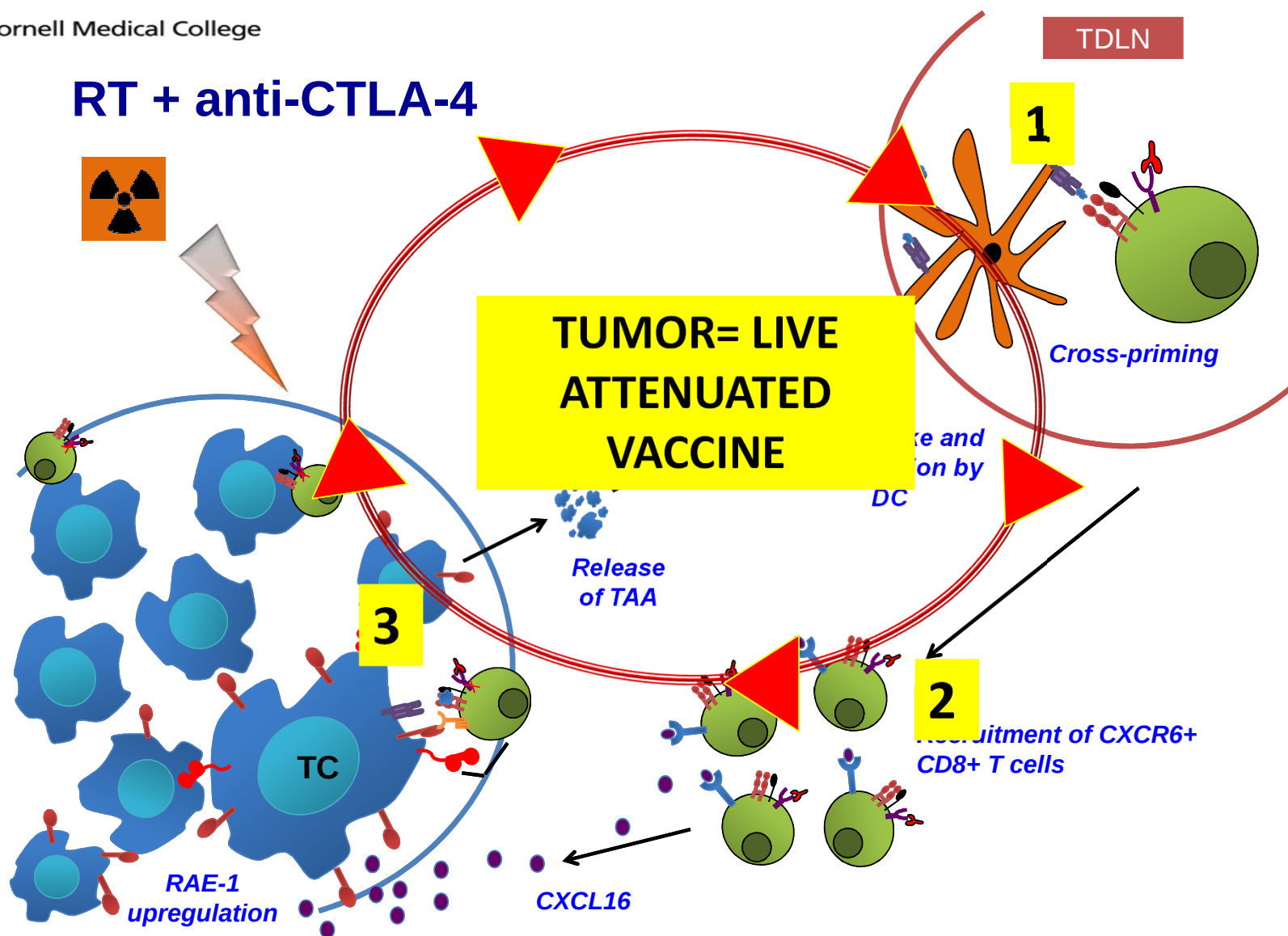
IMMUNOSUPPRESSION DOMINATES IN ESTABLISHED TUMORS





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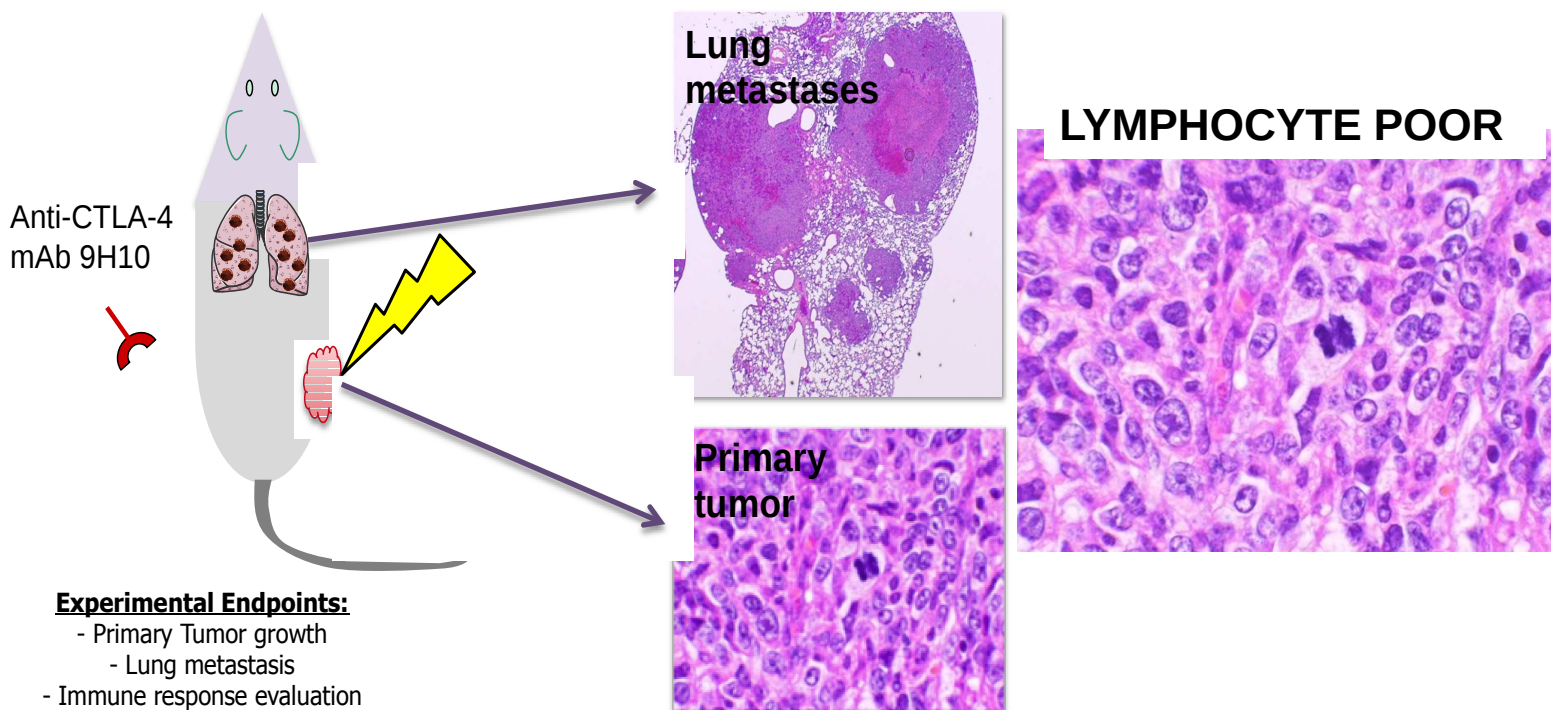
RT + anti-CTLA-4





Mouse model of immunotherapy-refractory tumor

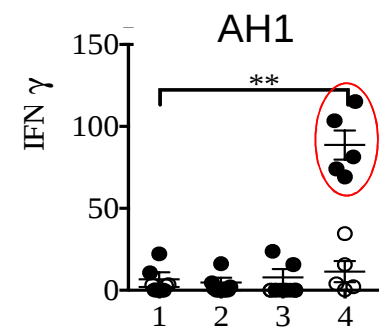
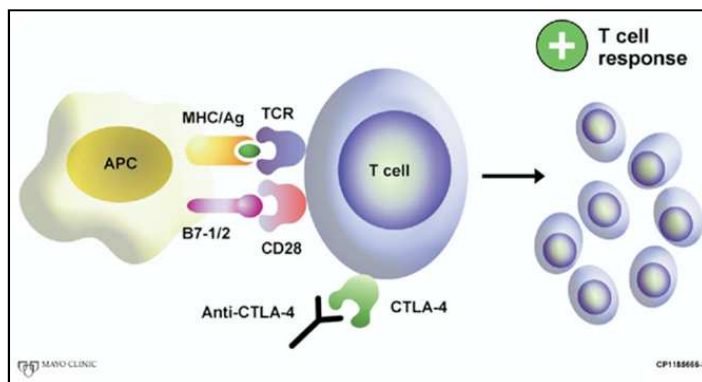
4T1 mouse model of metastatic breast cancer



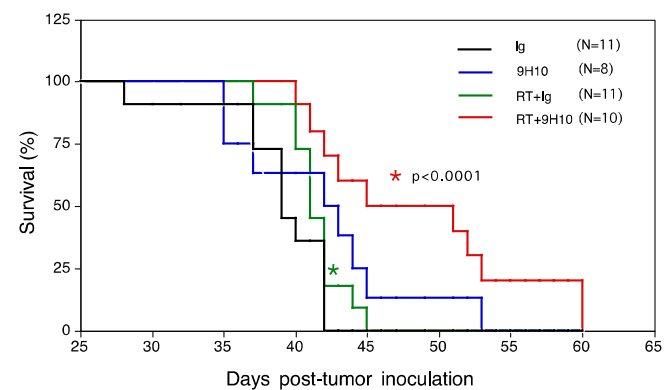
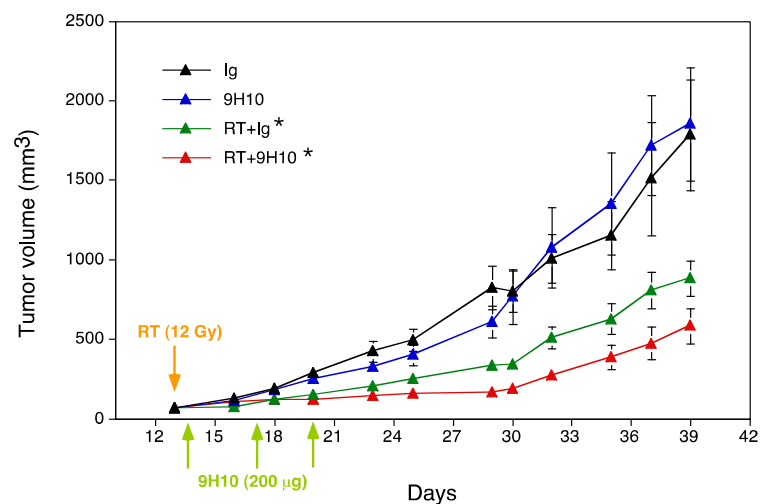


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Generation of anti-tumor T cell responses requires tumor irradiation + CTLA-4 blockade



α -CTLA4	-	+	-	+
RT	-	-	+	+

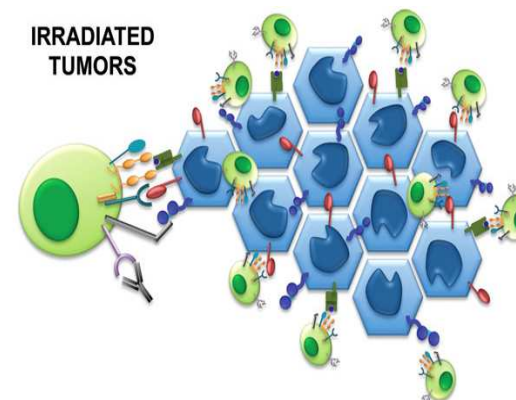
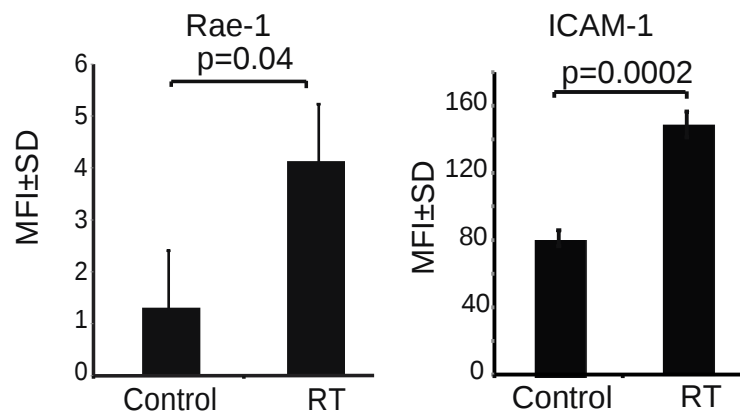
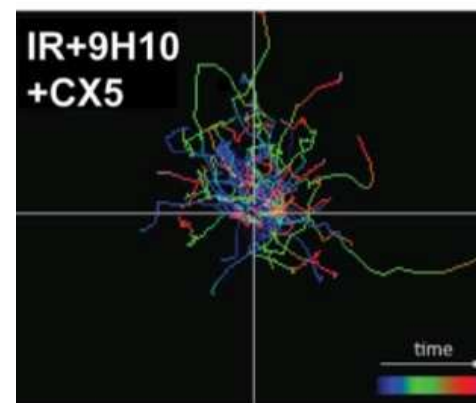
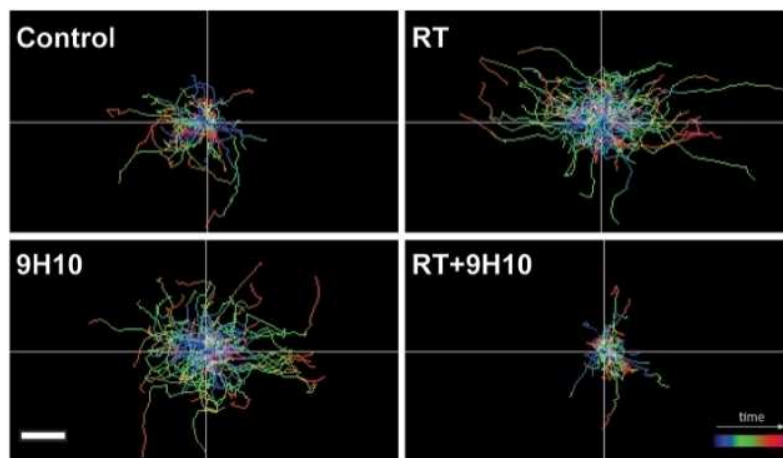


Demaria et al., Clin Cancer Res 2005



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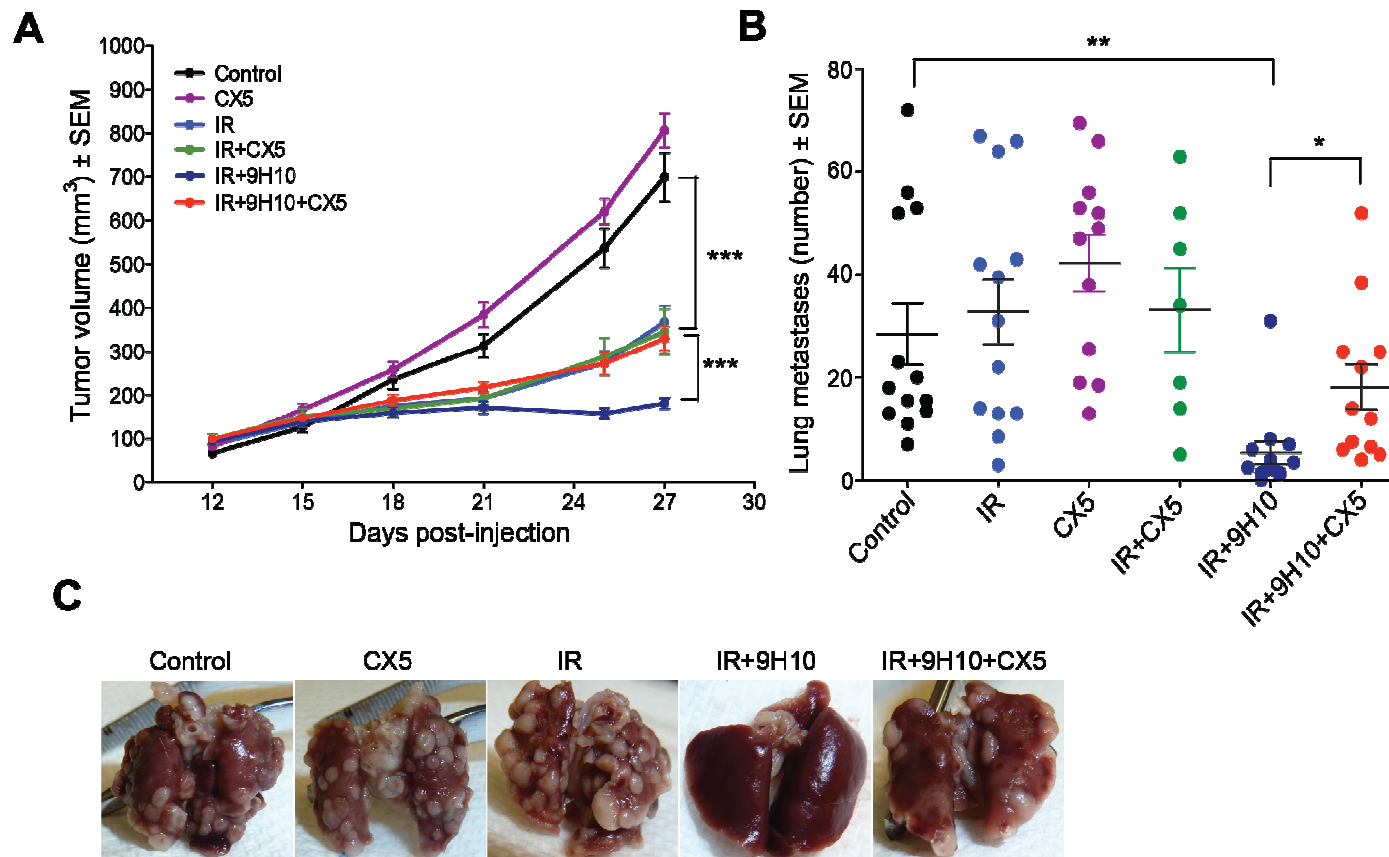
RT-induced Rae-1: NKG2D engagement and stabilization of immune synapse between CD8 T and tumor cells



Ruocco et al., *J Clin Invest* 2012



Blocking NKG2D abrogates effect of RT+CTLA-4 blockade

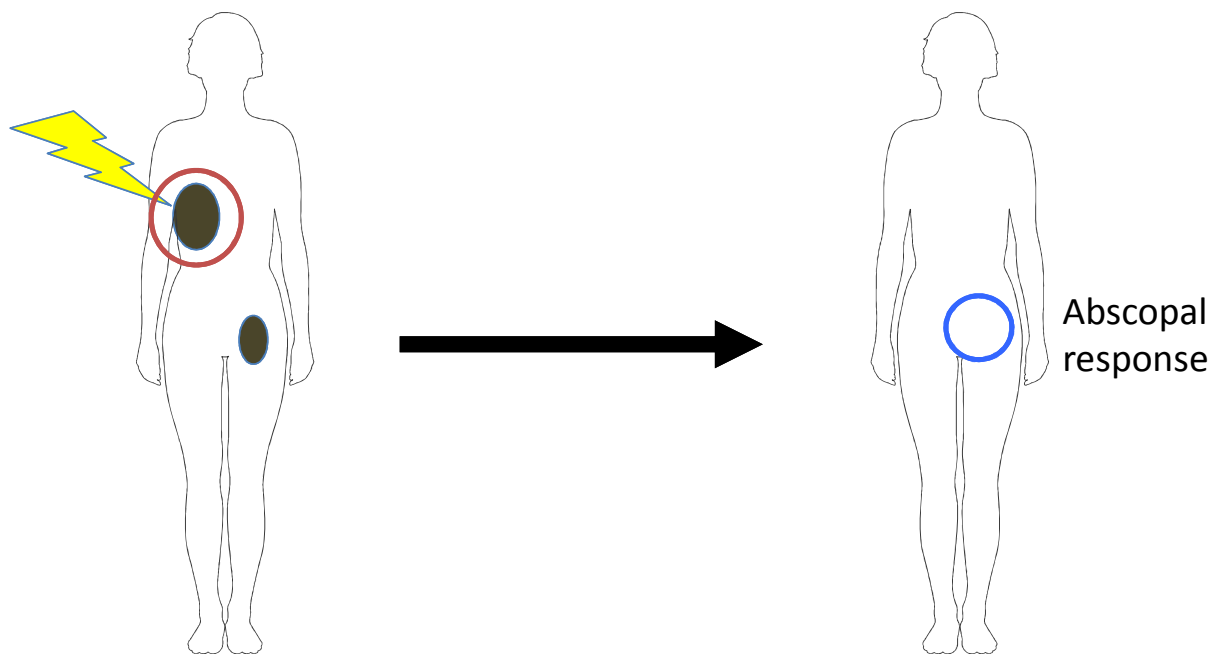




Clinical study design to test for abscopal responses

Effect of ionizing radiation on cancer outside the radiation field

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



- Either a prospective randomized trial (IT+ RT versus IT)
- Or a trial of radiation with an immunotherapy proven ineffective when used alone



Limited objective response rate to CTLA-4 Blockade (without and with chemo) in NSCLC

Reference	Stage	Study Design	# PTS	OR
Zatloukal et al ASCO 2009	LOCALLY ADV/MET S	-TREMELIMUMAB (15 mg/kg) VERSUS BSC	87	4.5% (2 PRs)
Lynch et al JCO 2012	Stage III/IV	Carbo/Taxol vs Carbo/T with Ipi (10mg/kg) Carbo/T and Ipi sequential (10mg/kg)	204	NS PFS

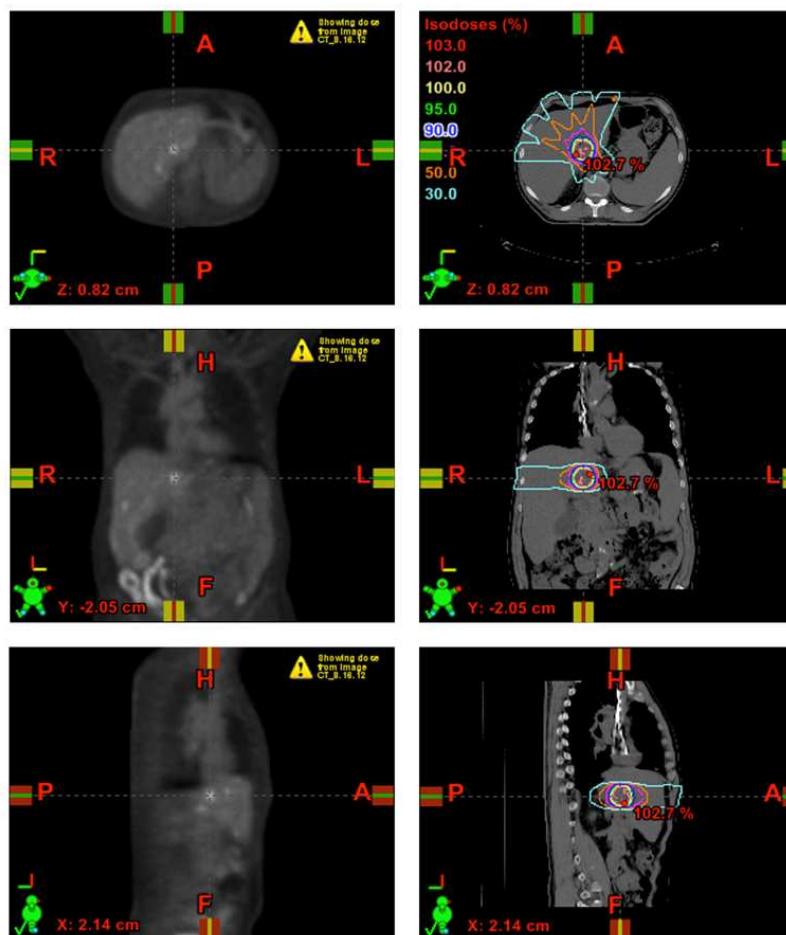
No CRs in either studies



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Patient with Refractory Metastatic NSCLC

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



RT to one liver met 6 Gy X 5 (TD 30 Gy)

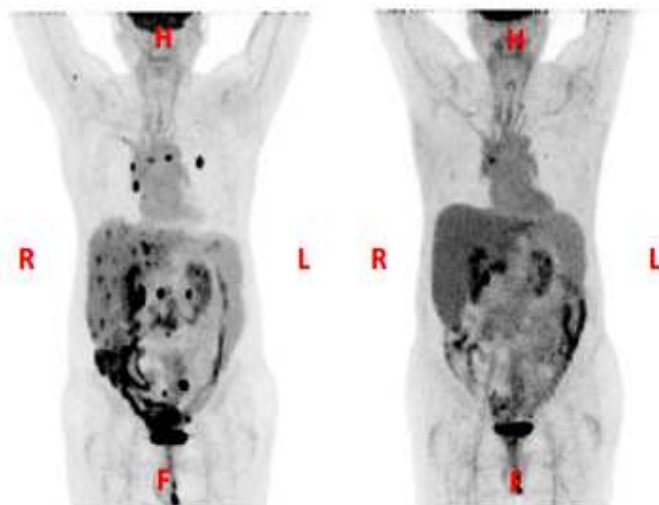
Ipilimumab, 3 mg/Kg, after first RT q3 weeks, X 4 cycles

Golden et al Cancer Immunology Research, 2014



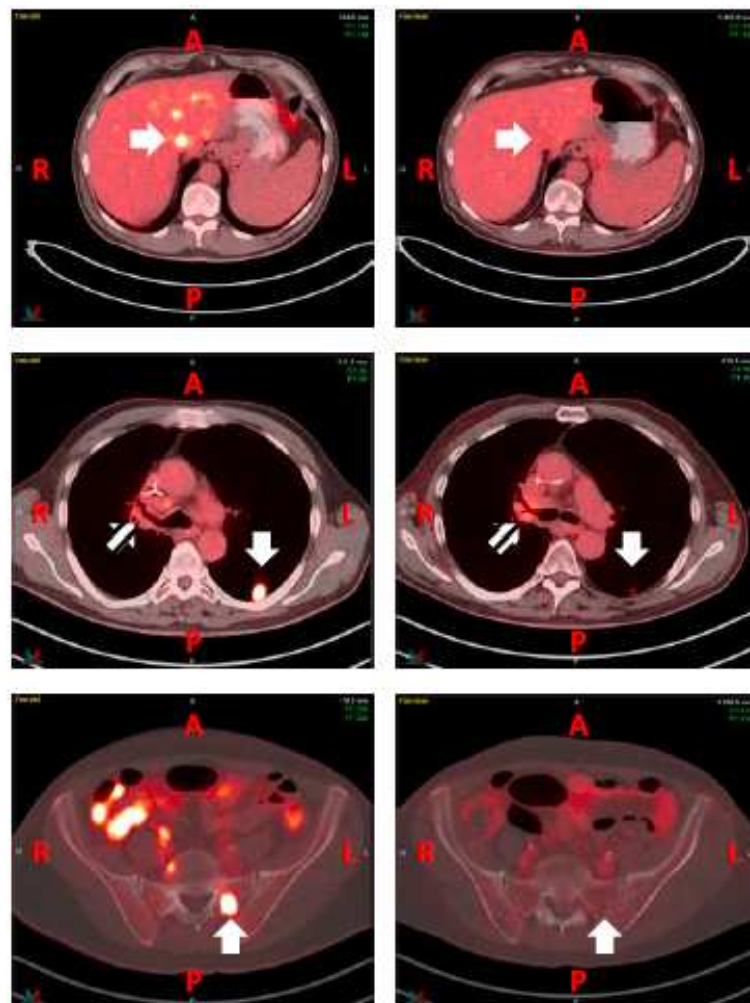
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Same patient,
response to RT+ ipilimumab



August 2012 PET/CT

January 2013 PET/CT



August 2012 PET/CT

January 2013 PET/CT



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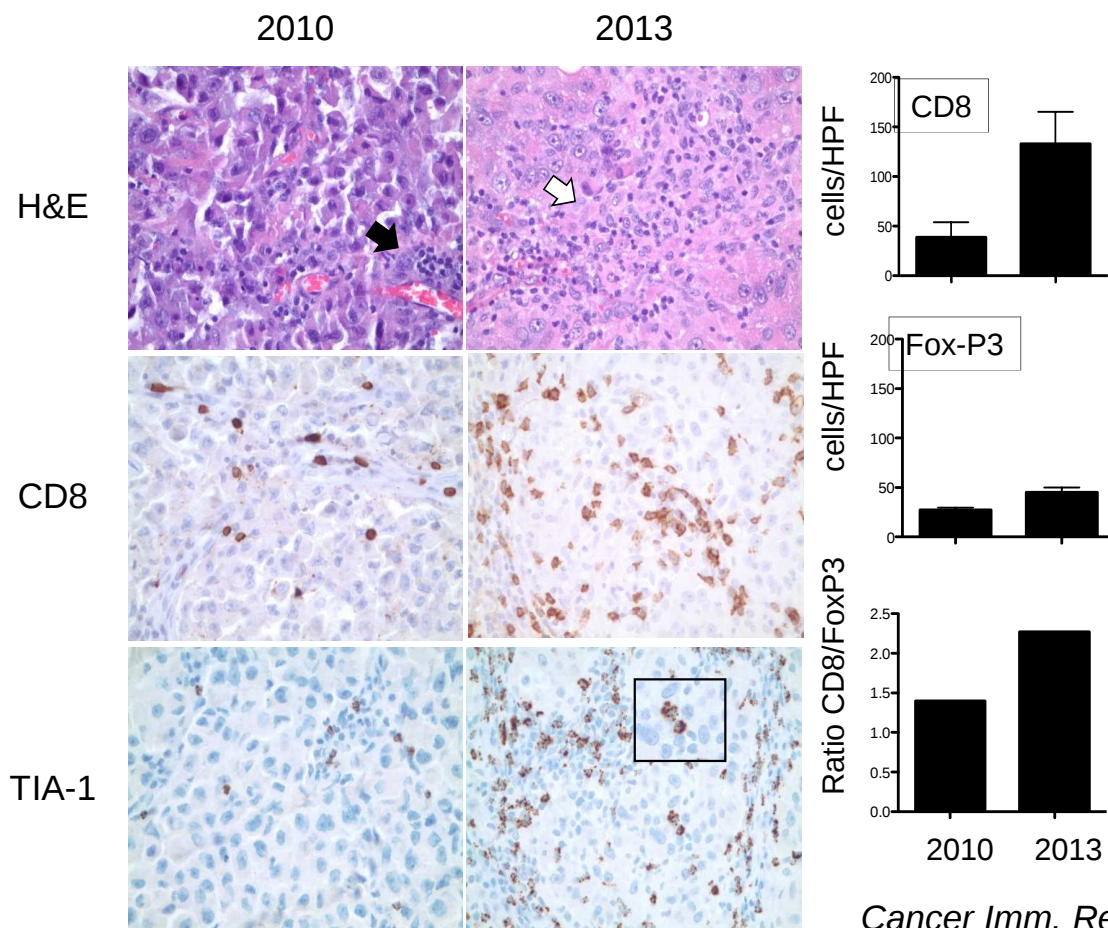
Clinical and radiological CR at one year:
currently NED at 36 m





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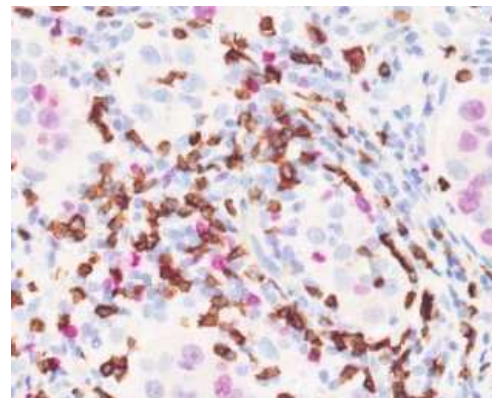
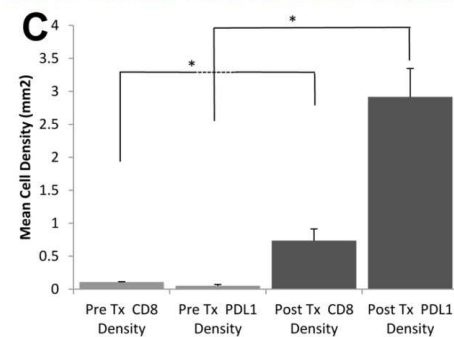
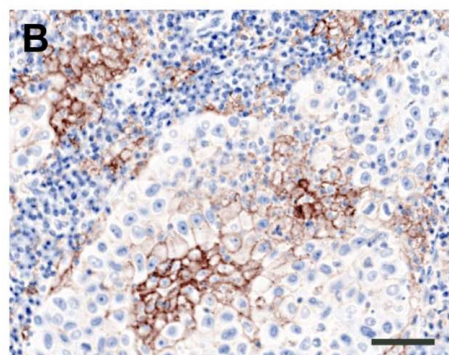
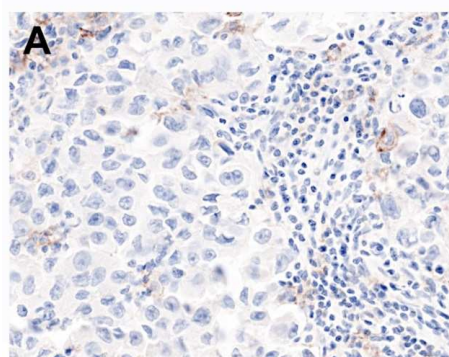
Comparison of SCV node biopsy at diagnosis and after IPI/RT



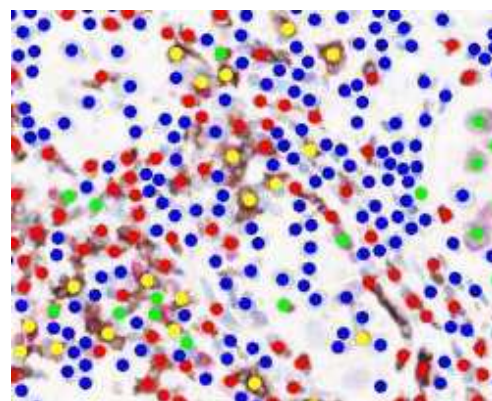
Cancer Imm. Research, 2014



Same patient: PDL-1 up-regulation as a marker for the induction of an effective anti-tumor T cell response



CD8 (brown)
Ki67 (red)



● Other
● CD8+
● CD8+ Ki67+
● Ki67+

12.1% of CD8 T cells are Ki67+

Demaria and Stack, (PerkinElmer)



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NYU S14-00208

**Ipilimumab and localized RT in chemo-refractory
metastatic NSCLC**

Eligibility

- Metastatic NSCLC
- Chemo-refractory
- Measurable disease in at least 2 sites
- Controlled brain metastases
- ECOG PS 0-2



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NYU S14-00208
**Ipilimumab and localized RT in chemo-refractory
metastatic NSCLC**

Study Design

- Phase II, optimal two-stage Simon design
- If ≥ 1 abscopal responses in stage 1, the trial to proceed to enroll an additional 19 patients
- Primary endpoint : response per RECIST v1.1 (baseline and post treatment PET/CT)
- Secondary endpoint = best abscopal response, immunologic biomarkers



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NYU S14-00208

Ipilimumab and localized RT in chemo-refractory metastatic NSCLC

Responses (RECIST v1.1)

- CR = 2
- PR = 5
- SD = 5
- PD = 9

- Total = 39

Non Eval = 18 (<4 Ipi cycles)

Response rates (CR + PR)

Intent to treat = 18 %

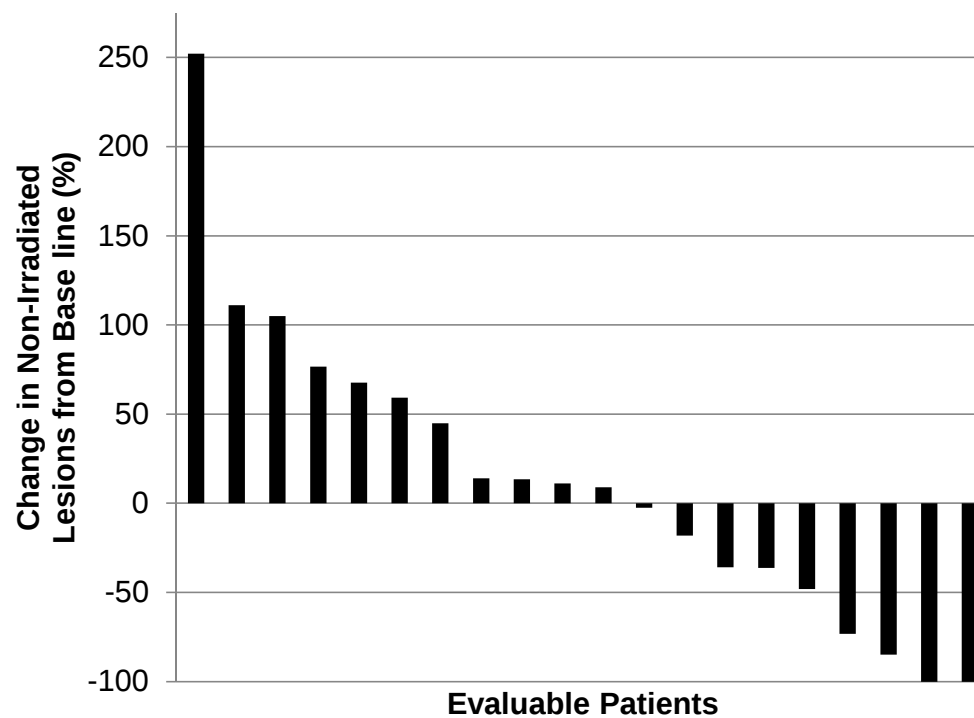
Pts completing 4 Ipi = 33%



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Ipilimumab and localized RT in chemo-refractory metastatic NSCLC

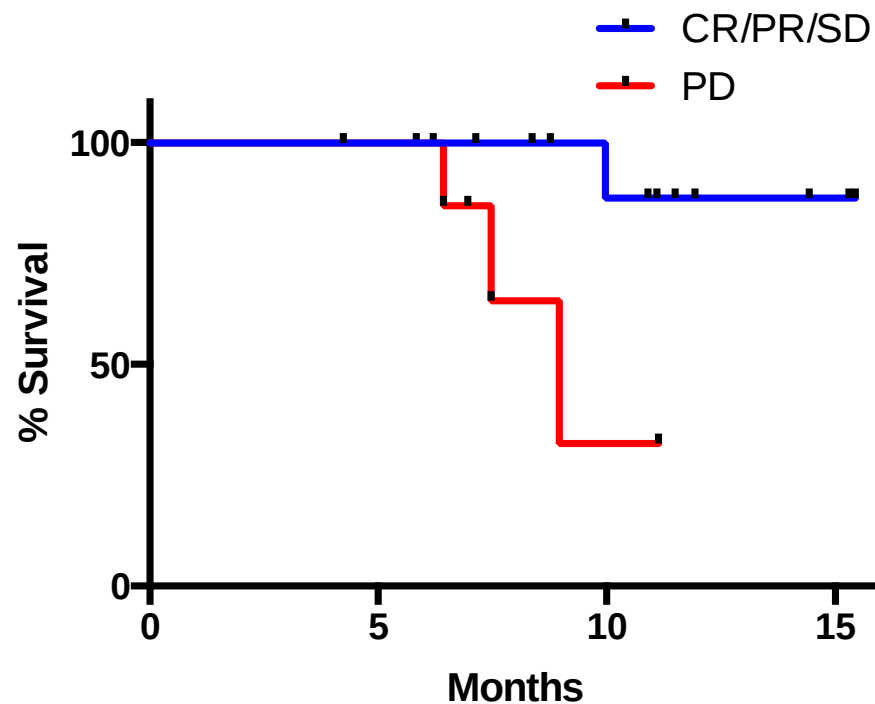




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Ipilimumab and localized RT in chemo-refractory metastatic NSCLC



Median follow-up: 10.9 months

Log-rank test: $p = 0.0161$

HR = 9.174

Median survival: CR/PR/SD = not reached

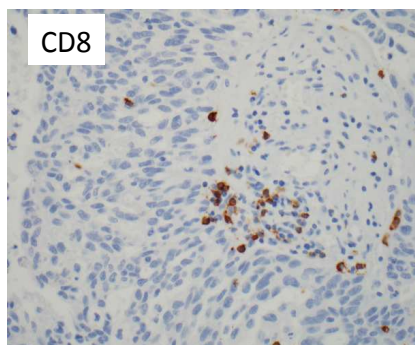
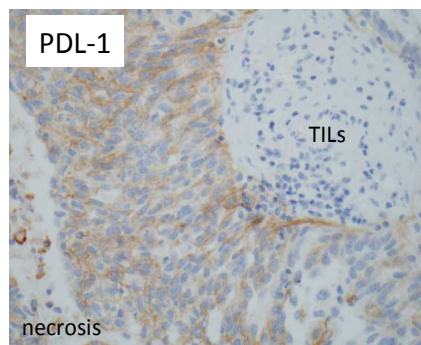
PD = 9 months



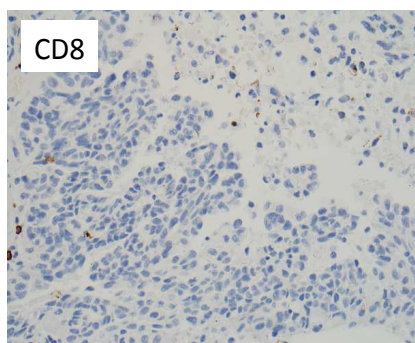
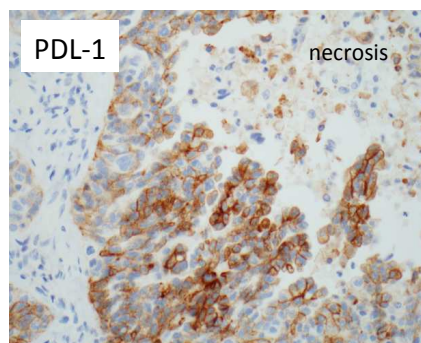
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Patient #4

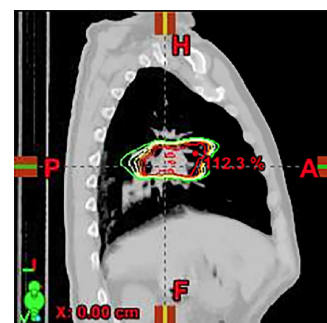
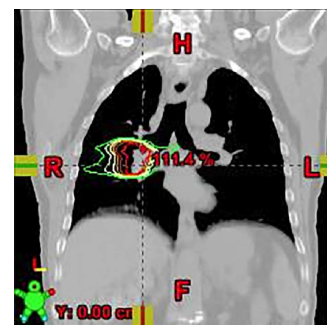
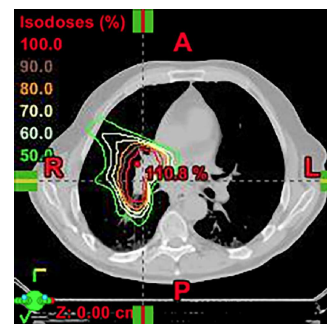
Frontal lobe metastasis



Cerebellum metastasis



April 2014



July 2014



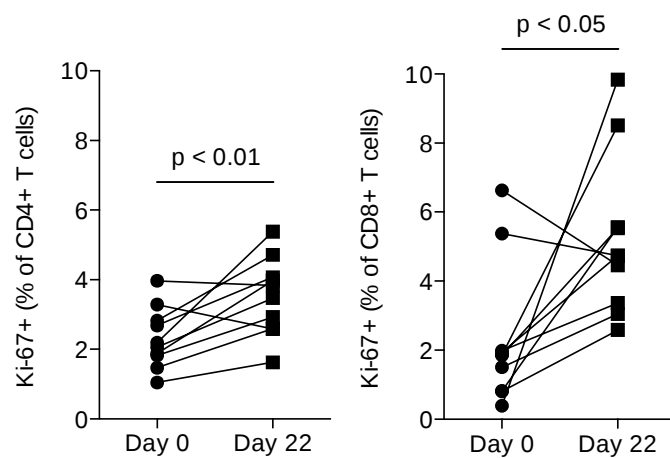
October 2014



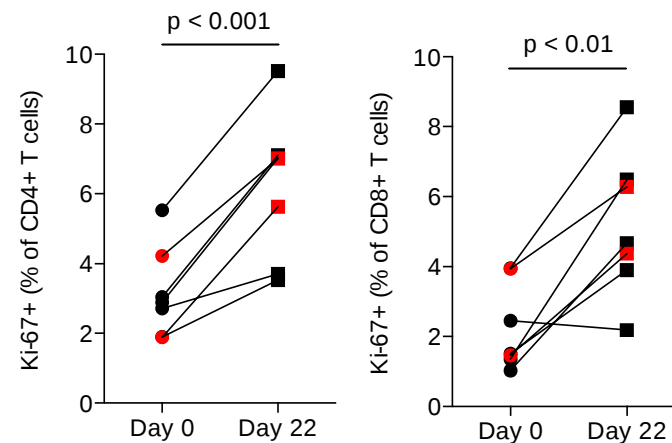


Increased Ki67⁺ CD4 and CD8 T cells (baseline versus day 22)

PD

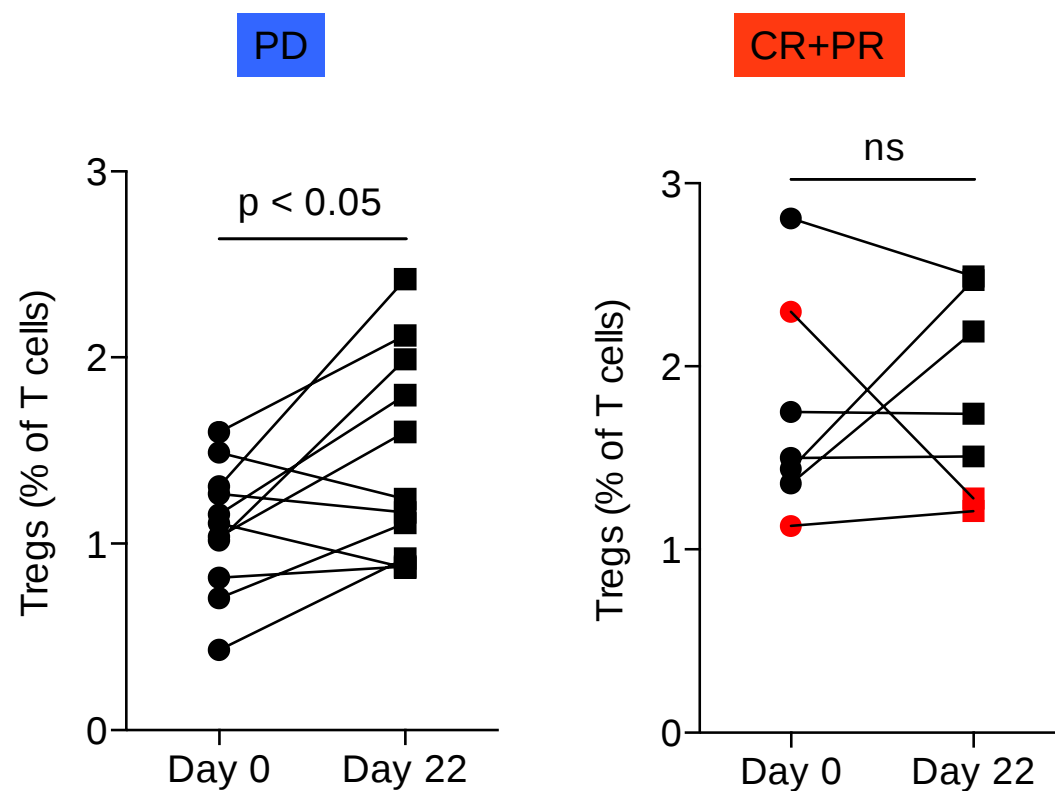


CR+PR



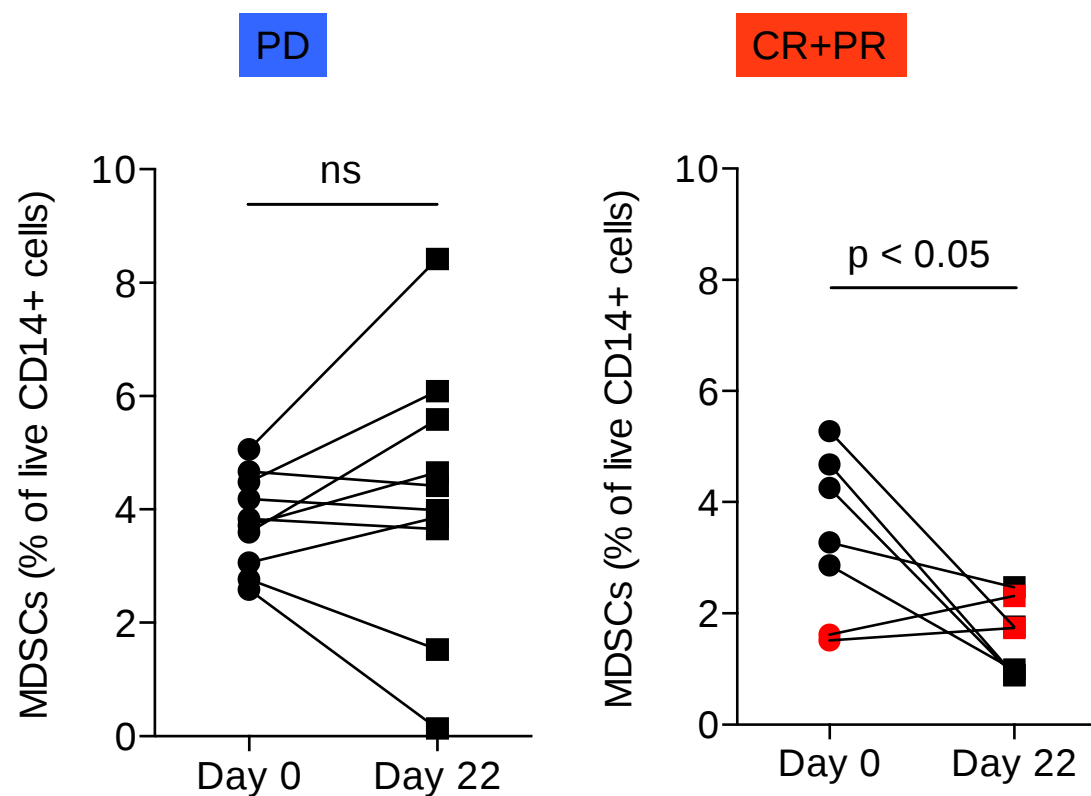


Regulatory T cells significantly increase in non-responders (baseline versus day 22)



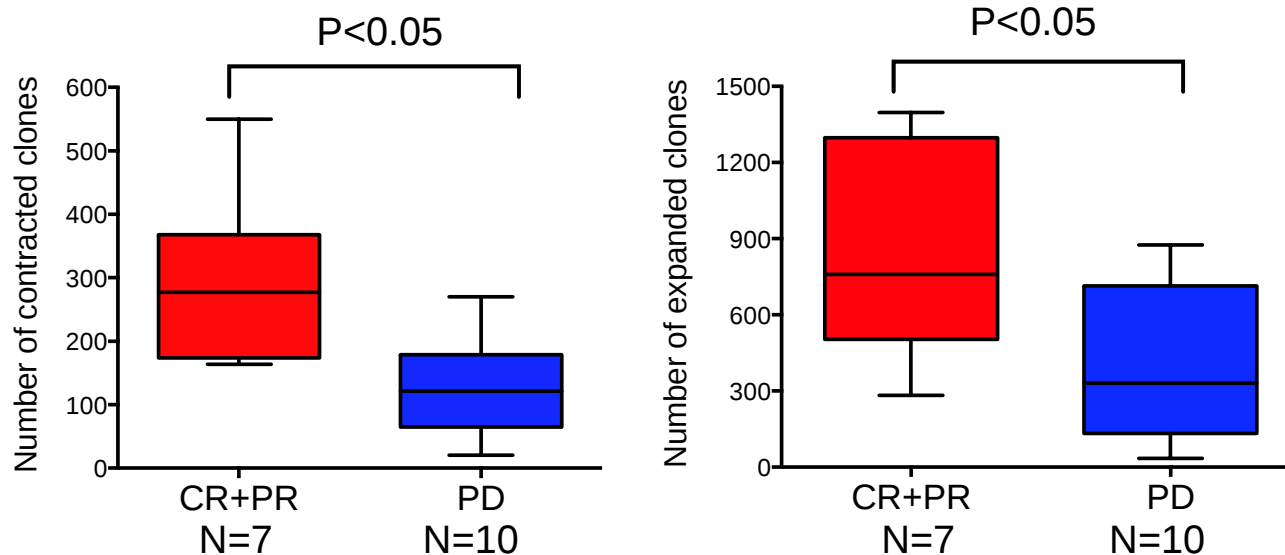


MDSC significantly decrease in responders (baseline versus day 22)





TCR repertoire changes in PBMC of NSCLC patients treated with RT+Ipi (baseline versus day 22)



Adaptive Biotechnologies ImmunoSEQ platform



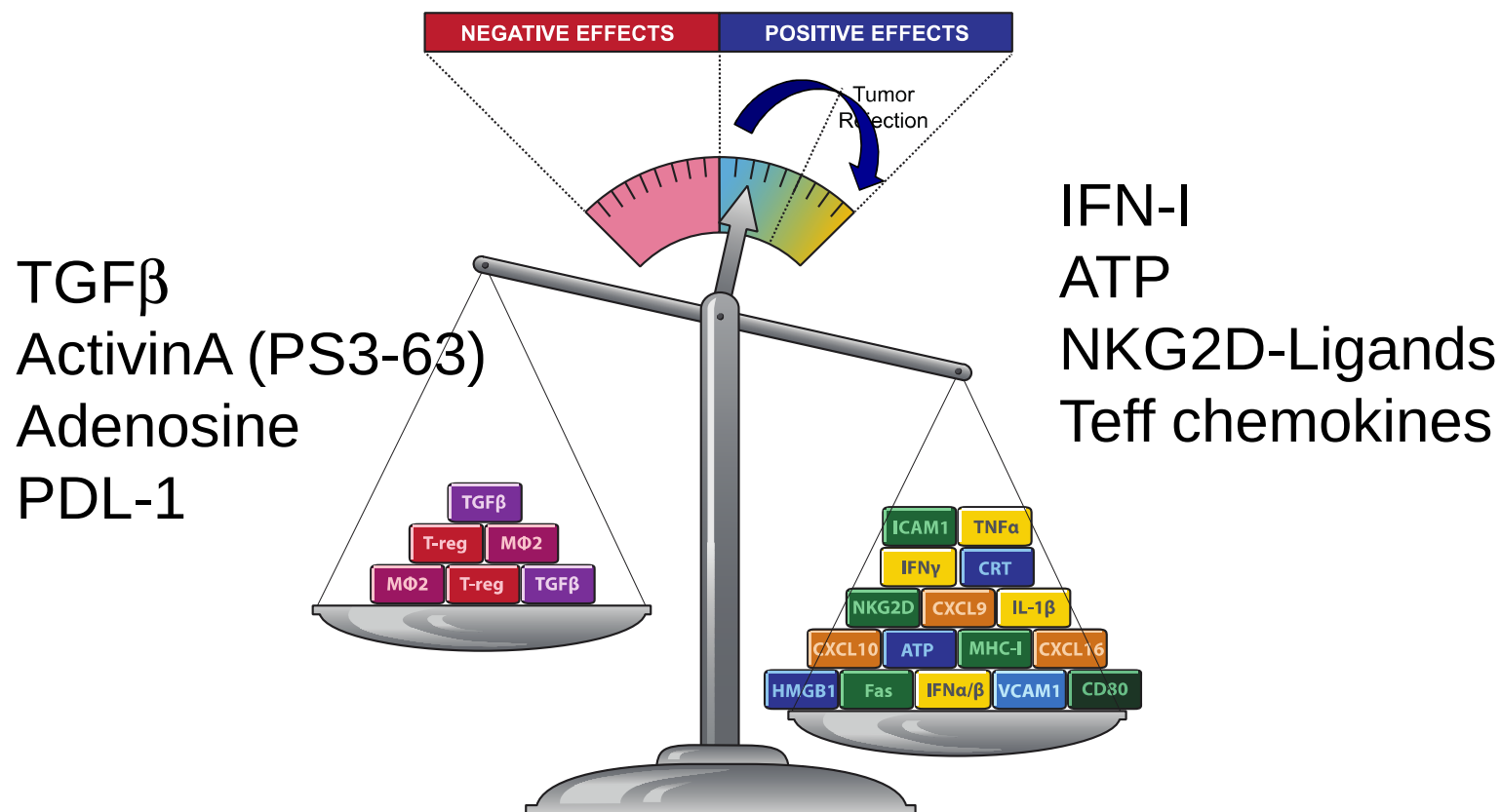
Conclusions

- Radiation and Flt-3L / GM-CSF resulted in preclinical and clinical abscopal effects/objective responses (OR=27%)
- Radiation and CTLA-4 blockade resulted in preclinical and clinical abscopal effects/ objective responses (OR=33%)
- Radiation is a valuable and accessible adjuvant to immunotherapy



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Radiotherapy and immune-mediated rejection: a balancing act



Formenti & Demaria, J Natl Cancer Inst 2013



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Radiation and Immunity research



Sandra Demaria M.D.



Mary Helen Barcellos-Hoff Ph.D.

Our patients



C. Vanpouille-Box, Ph.D.



Erik Wannerberg Ph.D.



K. Pilones, Ph.D.



S.Chandrasekhar, MS



Maria Fenton-Kerimian, NP