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Radiation therapy to ignite an anti-cancer immune response

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DISCLOSURES

Consultant/Speaker:
Bristol Myers Squibb, Varian, Elekta, Janssen, Regeneron, GlaxoSmithKline, Eisai, Dynavax, Astra Zeneca

Principal Investigator:

NCI R01CA161891-01
Immunomodulation of breast cancer via TLR7 agonist IMQ and RT

DOD BC100481 / W81XWH-11-1-0530
Multi-Team Award (MTA)
Radiation-Induced Vaccination to Breast Cancer

13-A0-00-001870-01
Breast Cancer Research Foundation
Targeting key inhibitory pathways to improve radiation-induced vaccination in breast cancer

NIH 1 S10 RR027619-01 Preclinical Research Irradiator

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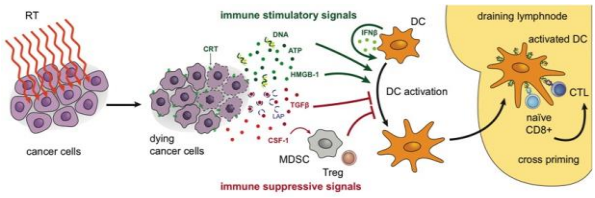

Why are abscopal effects of radiation so rare?

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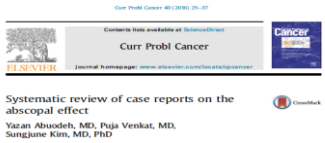

- 1969-2014: 46 abscopal cases
- Median dose 31 Gy; median follow up 17.5 months
- Only one case single dose SBRT (2.1%): all others fractionated RT (wide range of dose and fractions)
- ~ 13% were VMAT/SBRT
- NON ABLATIVE DOSES

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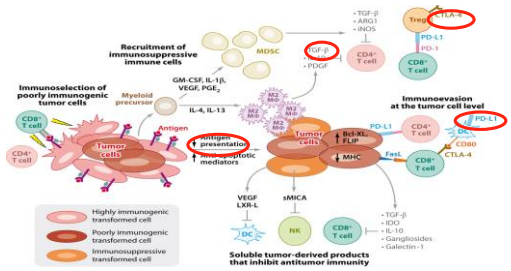
IMMUNOSUPPRESSION DOMINATES IN ESTABLISHED TUMORS



Vesely MD, 2011, Annu.Rev.Immunol 29:235-71

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How to enable the pro-immunogenic effects of radiation:

Overcoming immunosuppressive microenvironment of established tumors	Overcoming RT immunosuppressive effects
- enhancing cross priming - blocking immune checkpoints	- overcoming RT-induced immunosuppression (adenosine,TGFβ) - mitigating RT-induced lymphopenia

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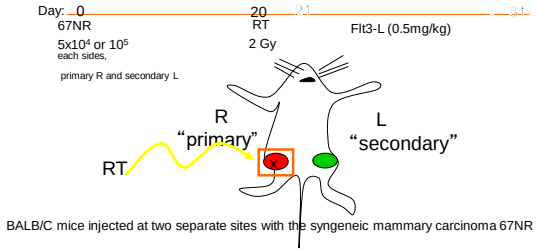
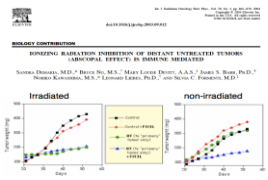
Ionizing radiation stimulates anti-tumor immunity by generating an *in situ* vaccine: combination with immunotherapy uncovers the abscopal effect

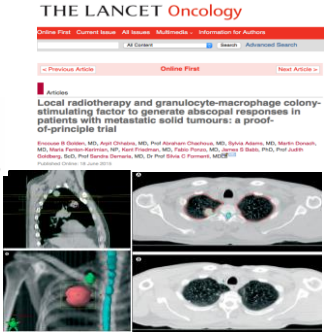


BALB/C mice injected at two separate sites with the syngeneic mammary carcinoma 67NR cell line



RT: 3.5 GyX10
GM-CSF: 125 μg/m²
Daily X 14 days

27% ABSCOPAL ORR



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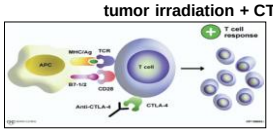
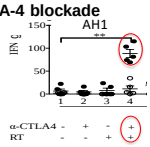
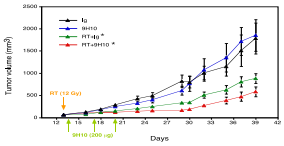
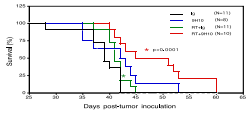
Generation of anti-tumor T cell responses requires tumor irradiation + CTLA-4 blockade

Jim Allison





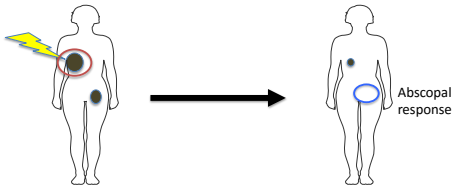




Demaria et al., Clin Cancer Res 2005

Clinical study design to test for abscopal responses

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



IJROBP 2004; Lancet Oncology 2009

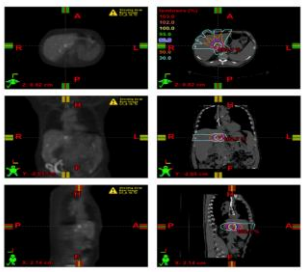
Limited objective response rate to CTLA-4 Blockade (without and with chemo) in NSCLC

Reference	Stage	Study Design	# PTS	OR
Zatloukal et al ASCO 2009	LOCALLY ADV/METS	-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

Patient with Refractory Metastatic NSCLC

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



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

Golden et al Cancer Immunology Research, 2014

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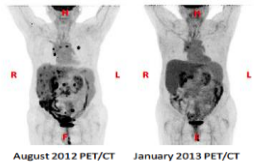
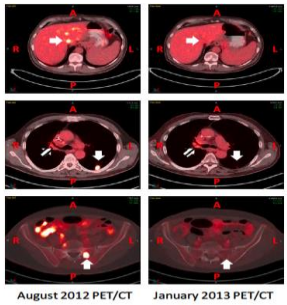
Same patient,
response to RT+ ipilimumab





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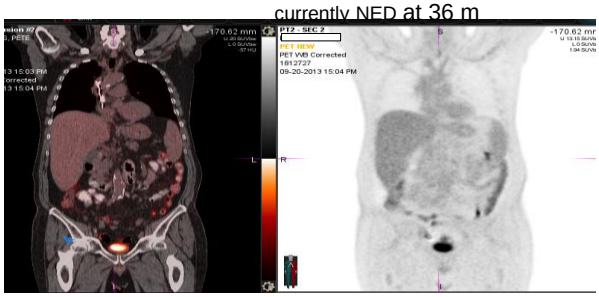
Clinical and radiological CR at one year:
currently NED at 36 m



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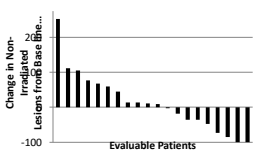
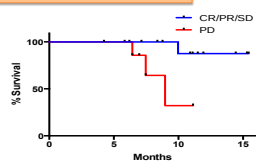
NYU S14-00208

Ipilimumab and localized RT in chemo-refractory metastatic NSCLC

39 patients, Response rates (CR + PR):
Intent to treat = 18 %
Pts completing 4 Ipi = 33%





Median follow-up: 12 months
Median survival: CR/PR/SD = not reached

Log-rank test: p = 0.0161
PD = 9 months

HR = 9.174

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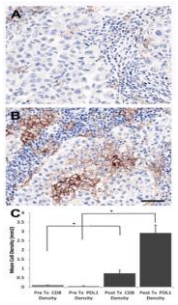
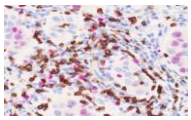
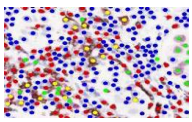
Same patient: PDL-1 up-regulation as a marker for the induction of an effective anti-tumor T cell response





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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How to enable the pro-immunogenic effects of radiation:

Overcoming immunosuppressive effects of RT

- overcoming RT-induced immunosuppression (adenosine,TGFβ)

- mitigating RT-induced lymphopenia

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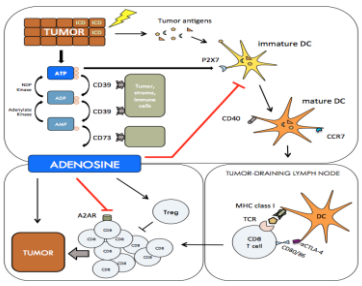
RT-induced adenosine



Erik Wennerberg

AACR 2016, 4033

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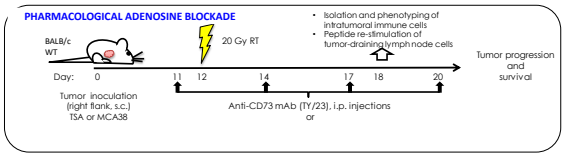

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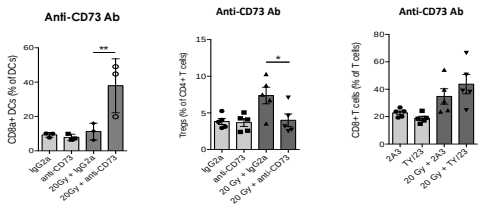
Adenosine-blockade promotes intratumoral infiltration of CD8α+ activated DCs, reduces Treg infiltration while promoting CD8+ T cell infiltration



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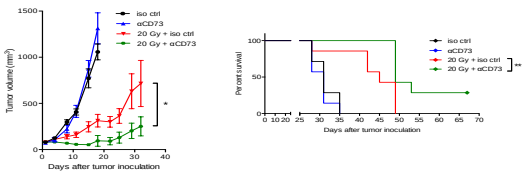
Combined RT and anti-CD73 treatment delays tumor progression and prolongs survival



Modulation of adenosine generation and/or uptake in the TME may facilitate the immunogenic effect of radiation

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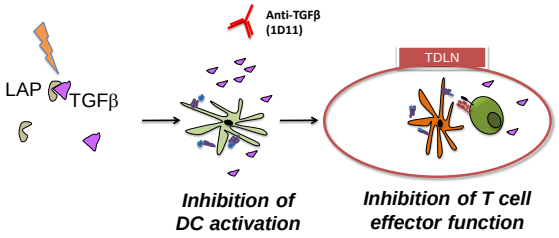
TGFβ activation by radiation-induced ROS hinders priming of anti-tumor T cells



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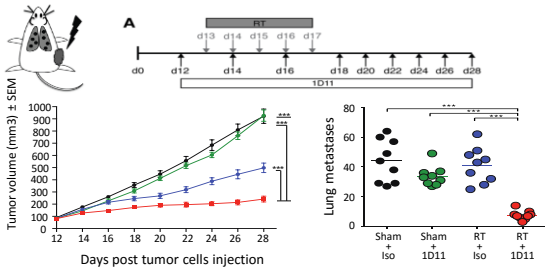
Therapeutic synergy of radiation and TGFβ blockade



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RESULTS

Anti-TGFbeta + RT:
22 patients, <10% ORR

59 F with metastatic Triple Negative Breast Cancer

4th line therapy 18 months after diagnosis: RT+ Fresolimumab

11/18 First Fresolimumab+RT to liver | 2/8/12 Second Freso+RT to breast skin | Response: iSD, 28% reduction, no new lesions

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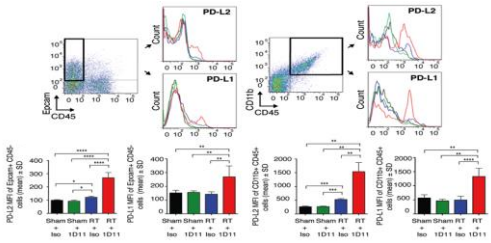
Increased PDL-1 and PDL-2 expression on tumor and myeloid cells by RT and TGFβ blockade



Vanpouille –Box, Cancer Research 2015

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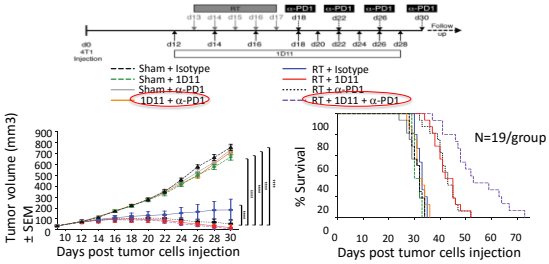
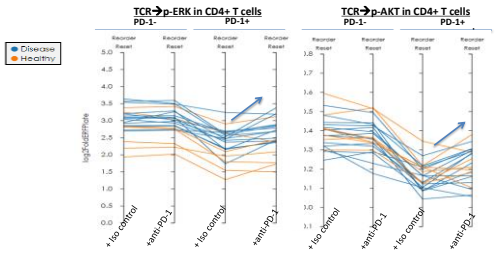
PD-1 blockade extends survival in mice treated with radiation and TGFβ blockade



In vitro anti-PD-1 (pembrolizumab) partially restores TCR→p-ERK /p-AKT



- Basis for in vitro PD-1 patient selection marker for combination therapies

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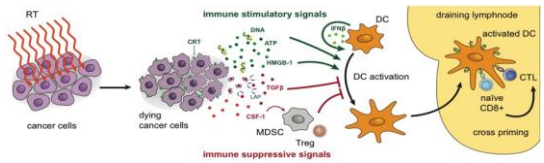
The delicate balance of cross-presentation



Need for sufficient naïve T cells

Cancer Invest. 2013 February ; 31(2): 140–144. doi:10.3109/07357907.2012.762780

The Etiology of Treatment-related Lymphopenia in Patients with Malignant Gliomas: Modeling Radiation Dose to Circulating Lymphocytes Explains Clinical Observations and Suggests Methods of Modifying the Impact of Radiation on Immune Cells

Sasamnah Yovino[1], Lawrence Kleinberg[1], Stuart A. Grossman[2], Manisha Narayanan[2], and Eric Ford[1]
[1]Department of Radiation Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

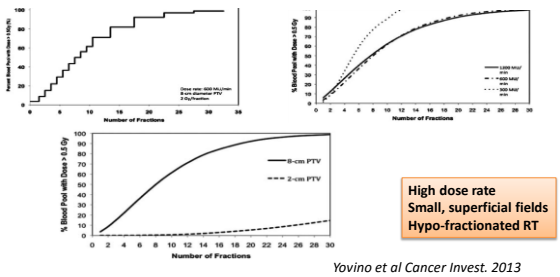
8-cm tumor, 60 Gy/30 fractions modeled with Pinnacle™ radiation planning system
Radiation doses to circulating cells (DCC) analyzed using MatLab™

Circulating lymphocytes : D10 = 3 Gy
D50 = ~2 Gy
D90 = ~.5 Gy

A single radiation fraction delivered 0.5 Gy to 5% of circulating cells, after 30 fractions 99% of circulating blood had received ≥0.5 Gy

Naïve T cells are the most radiosensitive

Impact of Number of fractions, Dose rate, Target Size



High dose rate
Small, superficial fields
Hypo-fractionated RT

Yovino et al Cancer Invest. 2013

Conclusions

- RT- induced signaling effects interacts with multiple immunological pathways, including adenosine, TGF-β,PD-1 etc.
- Success of combination of anti-CTLA-4 and radiation in metastatic NSCLC was independent from PD-L1 expression/blockade. Conversely, effectiveness of blocking TGFβ likely depends on overcoming PD-L1 expression
- Hypo-fractionated, short courses of RT to a small target to avoid lymphopenia is likely to be key to the success of RT and immunotherapy

When combined with Immunotherapy what is the best Radiation Source, Dose, Fractionation?

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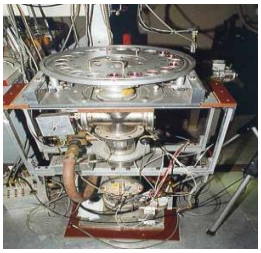
Looking at the ICD of Protons, Deuterons, and Helium

- RARAF Columbia
- Prep Cells for the Track Segment Charged-Particle Accelerator
- Allows for irradiation of particles with Linear Energy Transfer (10-200KeV/mm).



http://raraf.org/tracksegment.html

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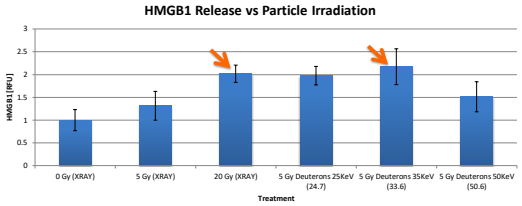
At 35kEV, 5Gy of deuterons ~20 Gy x-rays



(Unpublished data)

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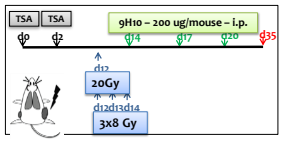
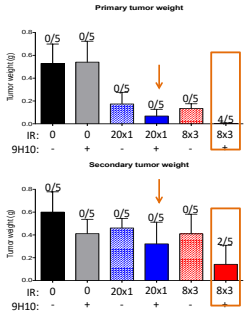
Fractionated but not single dose RT elicits an abscopal response in combination with anti-CTLA-4





Dewan et al. Clin Cancer Res. 2009

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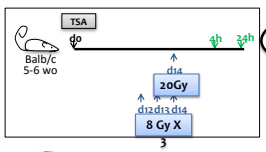
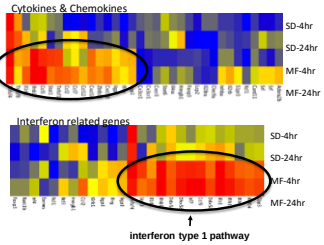


Claire Vanpouille-Box

N. Coleman & M. Aryankalayil
NIH Radiation Oncology Branch



SD – 20 Gy x1
MF – 8 Gy x3

4.0
1.0
0.25

Differentially expressed Immune Response genes in at least one of 4 comparisons(>2-fold, Paired T-test p-value<0.05) are displayed as normalized to 0Gy control within each set of three samples.

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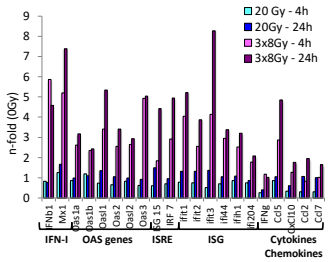
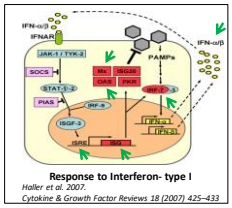
IFN-I pathway activation in Hypo-Fx tumors





Response to Interferon- type I

Haller et al. 2007. Cytokine & Growth Factor Reviews 18 (2007) 425–433

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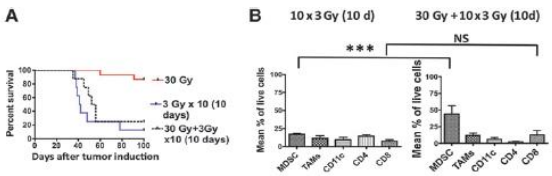
Ablative Tumor Radiation Can Change the Tumor Immune Cell Microenvironment to Induce Durable Complete Remissions



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Ablative Tumor Radiation Can Change the Tumor Immune Cell Microenvironment to Induce Durable Complete Remissions

Mice that developed durable remissions after radiation treatment were resistant to a second challenge with CT26 tumors due to development of systemic immunity that became potent about 1 month after treatment. Second tumors injected at the time of treatment continued to grow while systemic tumor immunity was developing, and the evasive microenvironment of second tumors likely prevented antitumor T-cell infiltration. Second tumor evasion may be overcome by enhancing the rapidity and potency of tumor immunity by combining SBRT with immunotherapy. On

Reject Second Challenge

But concurrent second tumors continue to grow!

No abscopal response demonstrated!

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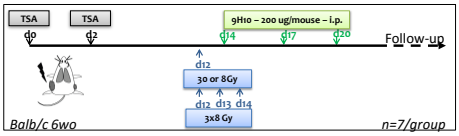
Side-by-side comparison of 30 Gyx1, 8 Gyx1 and 8 Gyx3 with Immune Checkpoint Blockade



	0Gy	30Gy	8Gy	3x8Gy	9H10
Group 1	x				
Group 2	x				x
Group 3		x			
Group 4		x			x
Group 5			x		
Group 6			x		x
Group 7				x	
Group 8				x	x

(Unpublished data)

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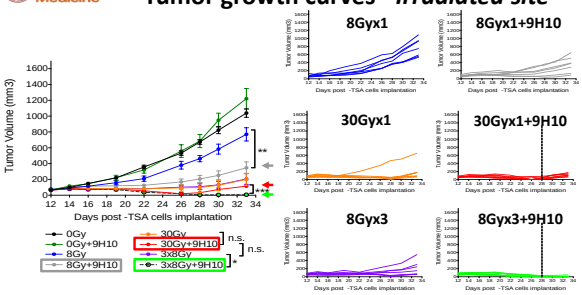
Tumor growth curves - *Irradiated site* -



T-test

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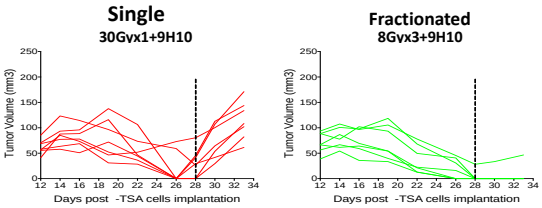

30Gy irradiated tumors regrew faster compared to 8Gy x 3

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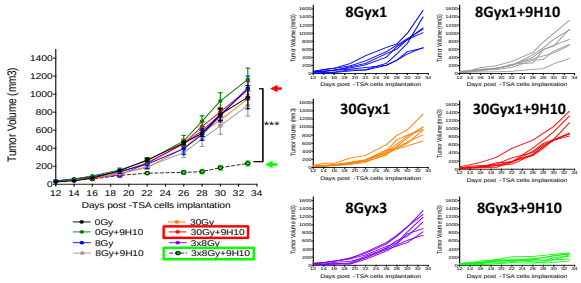
Abscopal site *(non irradiated)*



T-test

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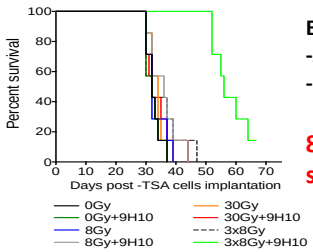
Survival



Endpoints:
-Abscopal response
-Survival

8 Gy X 3 superior to single fraction 8/30 Gy

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Dose and fractionation and RT source

- **When combined with ICB tumor hypo-fractionated regimens are required for abscopal effects**
- **High LET radiation more likely to induce ICD**

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Radiation and Immunity Research Team

Our patients