SITC 2020 Annual Meeting
Session 105: Integrating Radiation and Immunotherapy: New Products, Challenges, and Opportunities for Industry-Academic Collaborations

The Immuno-Radiobiology of Radiation Therapy

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Disclosures

- University of Wisconsin School of Medicine and Public Health - Employer

- Scientific Advisory Board Member
  - Seneca Therapeutics
  - Archeus Technologies Inc.

- Ownership Interest
  - Seneca Therapeutics
  - Archeus Technologies Inc.

- Patents held through the Wisconsin Alumni Research Foundation
  - NM600 for targeted radionuclide delivery and immunomodulation
  - Bacterial membrane nanoparticle to enhance the in situ vaccine effect of radiation
  - Brachytherapy catheter for intratumoral injection

Response to some immunotherapies may be inversely correlated with the burden of metastatic disease

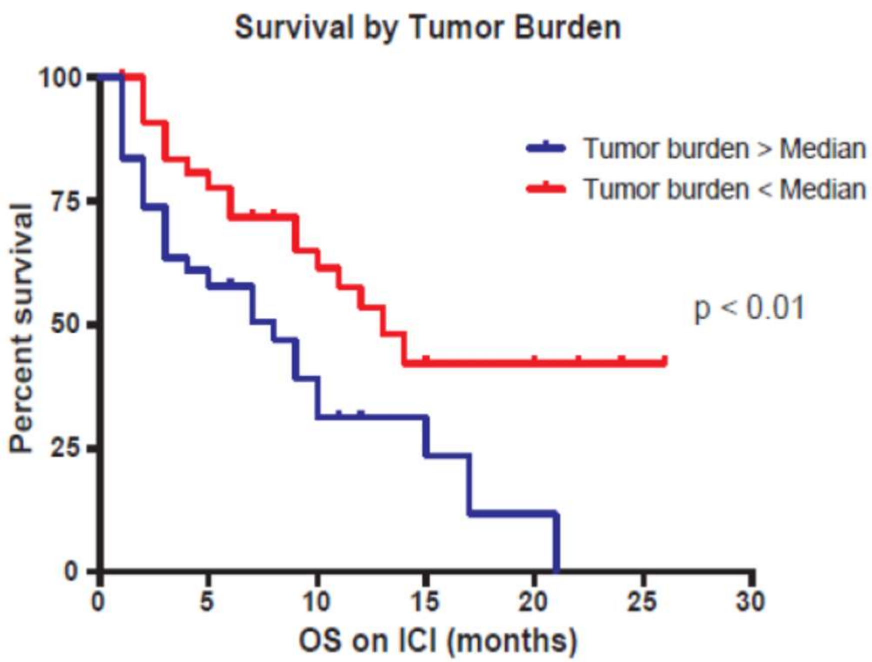


Fig. 3B. Patients whose TB was lower than the median showed improved OS.

Sridharan et al. Oral Oncology 2018.

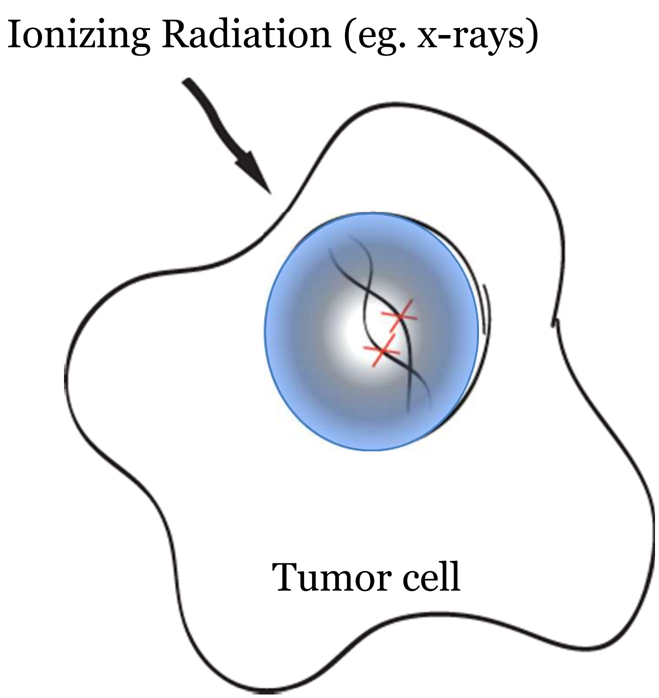
eTable 3. Association Between Baseline Sum of Target Lesion Diameters and 5-Year Survival in All Patients Receiving Nivolumab (N = 270)[a]

Sum of Target Lesion Diameters (mm)	5-Year Survivors	All Other Patients	*P* value
Melanoma	n = 30	n = 77	.0427
Median (IQR)	75 (48-134)	111 (69-189)	
Range	22-374	10-377	
RCC	n = 9	n = 25	.0542
Median (IQR)	98 (89-110)	139 (88-191)	
Range	42-236	43-615	
NSCLC	n = 16	n = 113	.5084
Median (IQR)	83 (62.5-117)	95 (59-147)	
Range	11-291	10-292	
All 3 tumor types	n = 55	n = 215	.0244
Median (IQR)	88 (52-116)	109 (65-165)	
Range	11-374	10-615	

[a] Analysis is based on *t* tests for comparing the 2 subsets of baseline sum of target lesion diameters.
IQR indicates interquartile range.

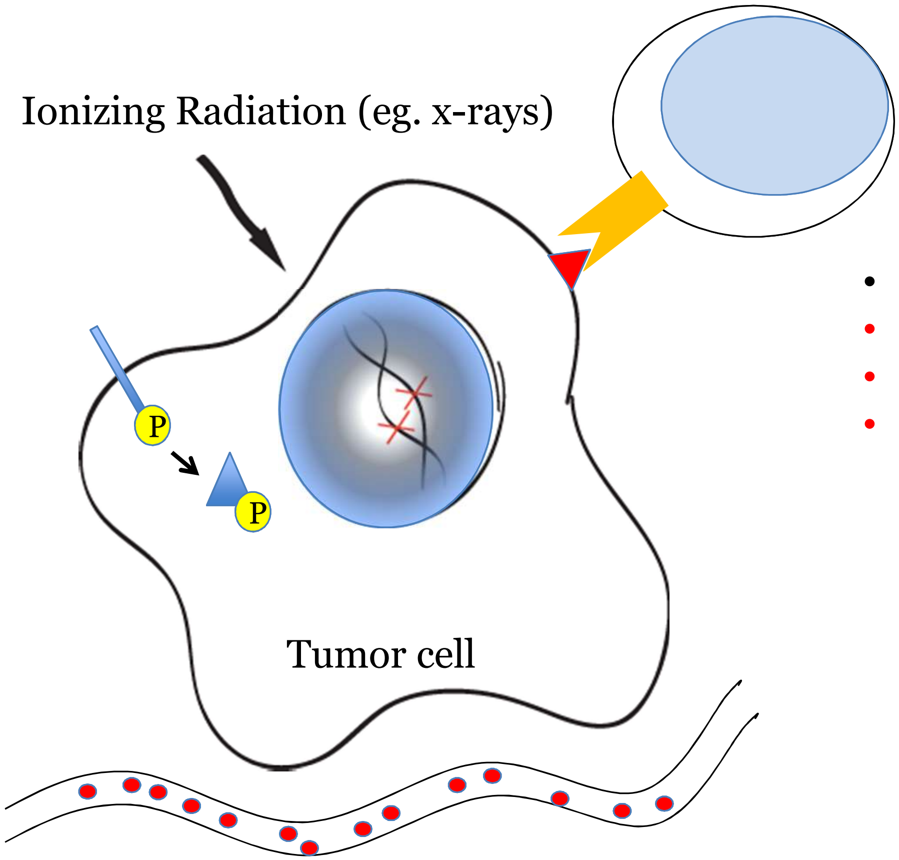
Topalian et al. JAMA Oncol 2019.

Radiation directly kills tumor cells and may reduce the burden of metastatic disease



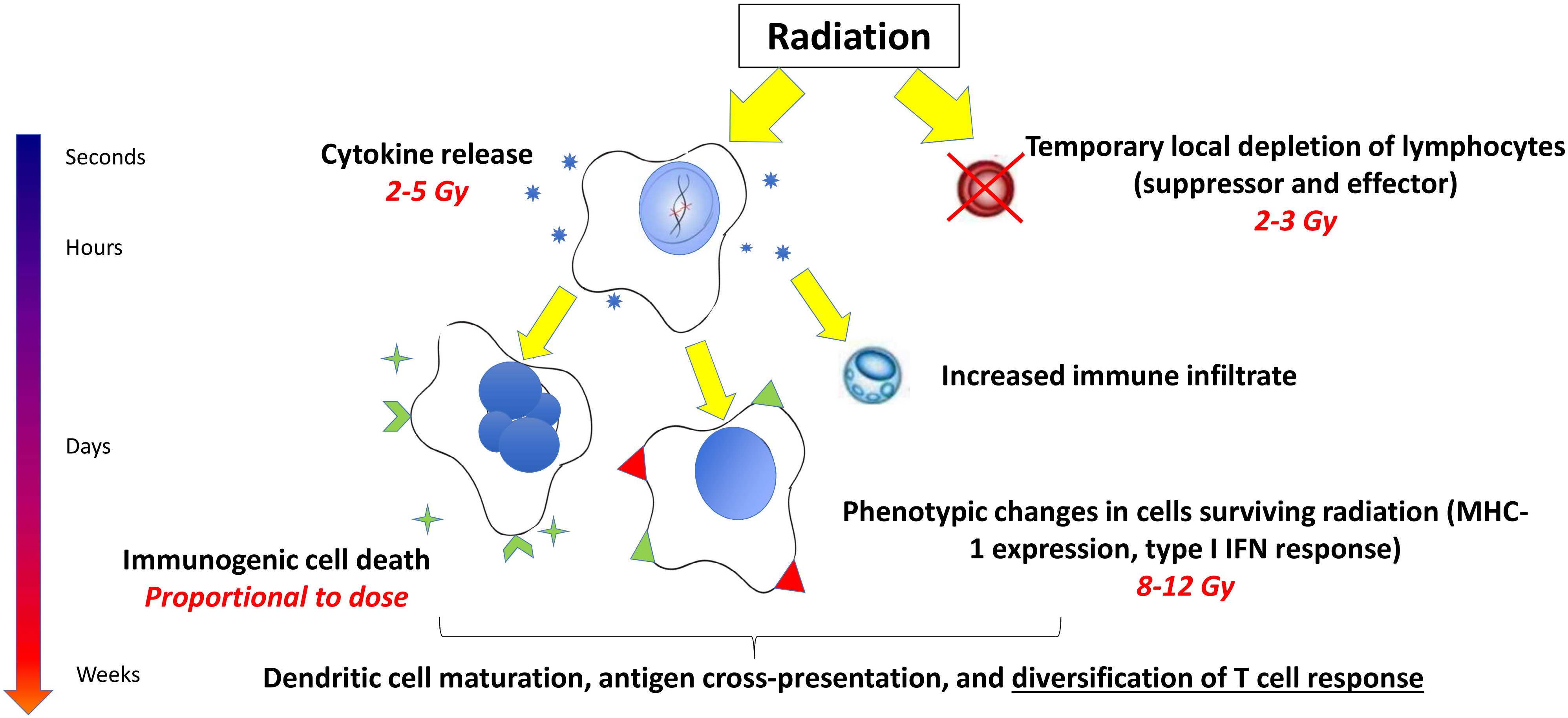
Radiotherapy directly kills tumor cells through induction of DNA damage resulting in death by mitotic catastrophe

Radiation may also favorably modify the tumor-immune interactions



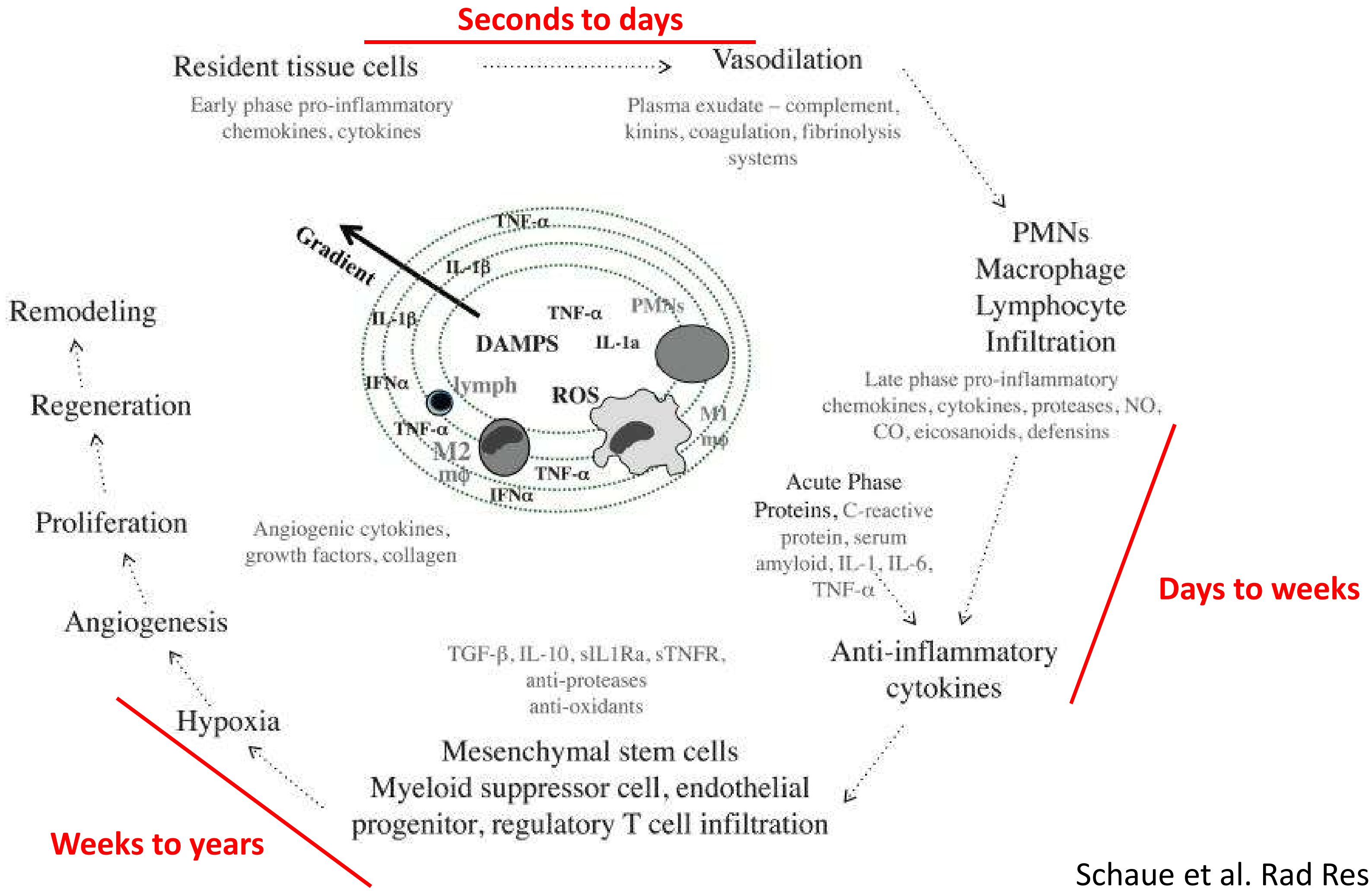
- Cell signaling pathways
- Stroma and vasculature
- Tumor-immune microenvironment
- Tumor cell susceptibility to immune response

Immuno-Radiation Biology of Radiation Therapy



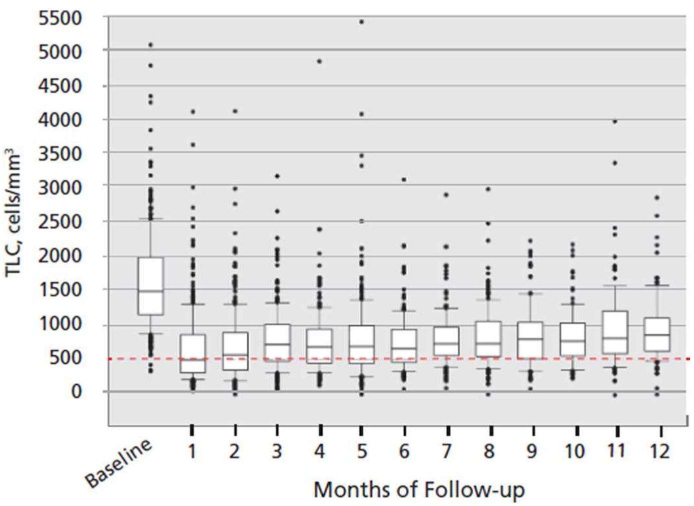
Time, dose, and fractionation may impact these mechanisms in different ways

Cytokine response following radiation therapy

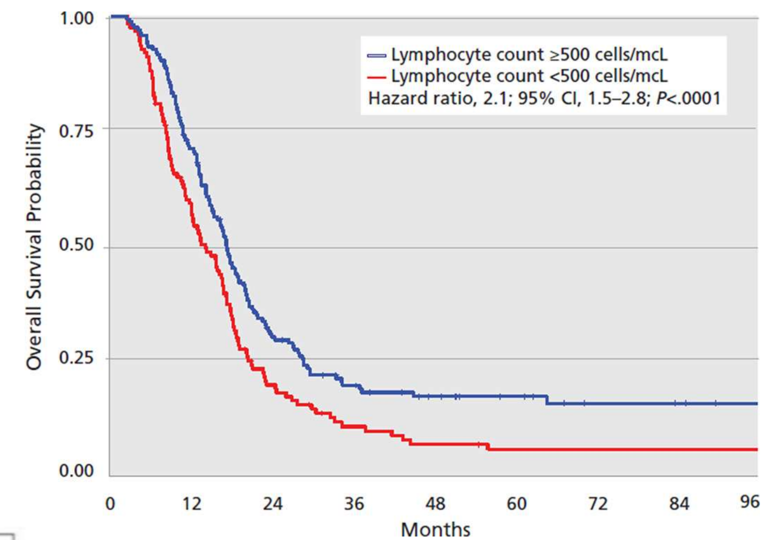


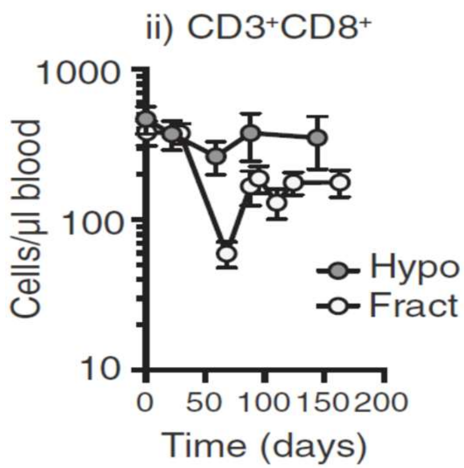
Schaue et al. Rad Res 2012

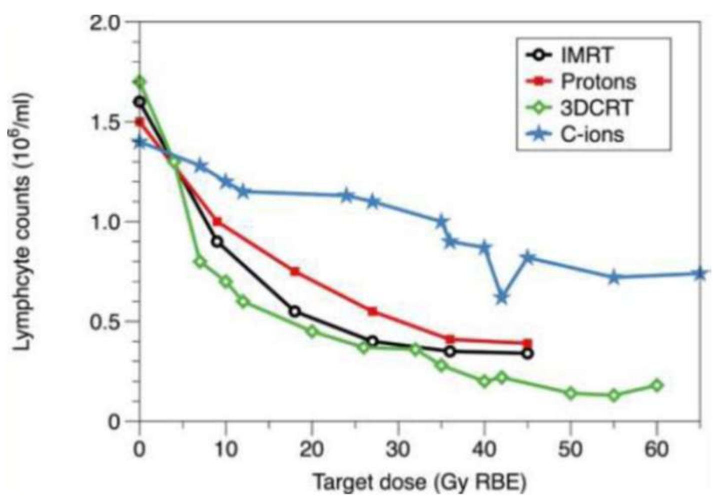
Large field, fractionated radiation therapy may reduce circulating lymphocyte counts



LD50 ~ 2 Gy, LD90 ~ 3 Gy
Apoptotic cell death2



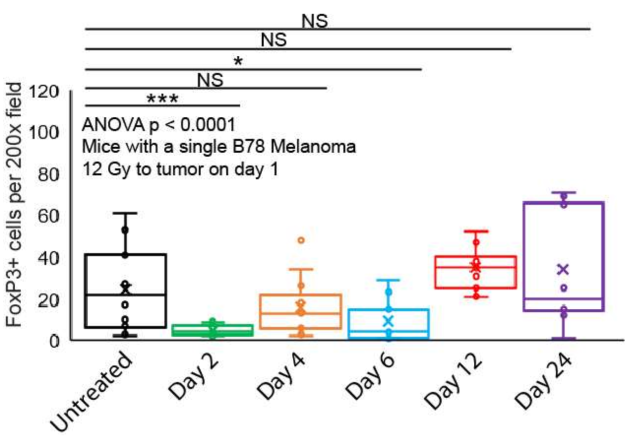




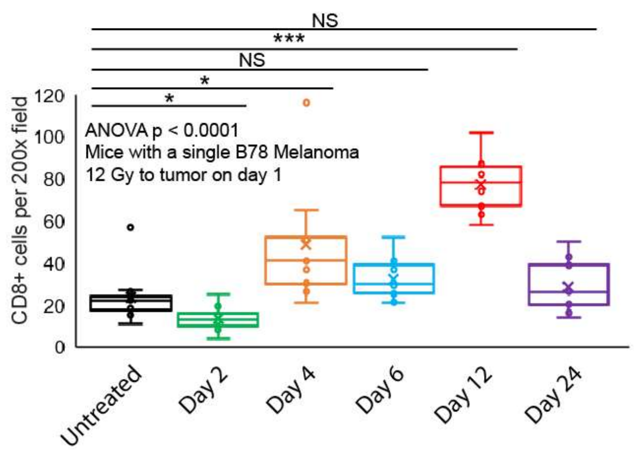
Afghani et al., JCO 2015 – Breast
Jiang et al., IJROBP 2016 - Esophageal
Joo et al., IJROBP 2016 – NSCLC
Rahman et al., IJROBP 2018 - Glioma
Kitayama et al., BMC Cancer 2011 – Rectal
Liu et al., Cancer Res Treat, 2017 – Nasopharynx
Crocenzi *et al.*, JITC, 2016
Grossman *et al.*, JNCCN, 2015
Durante and Formenti, BJR, 2019

Radiation can favorably impact tumor infiltrating T cells and distant non-radiated tumor sites may modify this effect

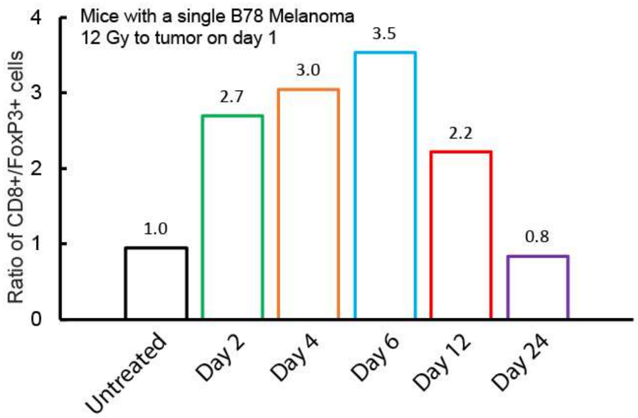
FoxP3+ Tregs



CD8+ T cells



Ratio of CD8+ : FoxP3+ cells



Morris *et al.*, Cancer Imm Res, 2018

5 R's of the effects of radiation on myeloid cells

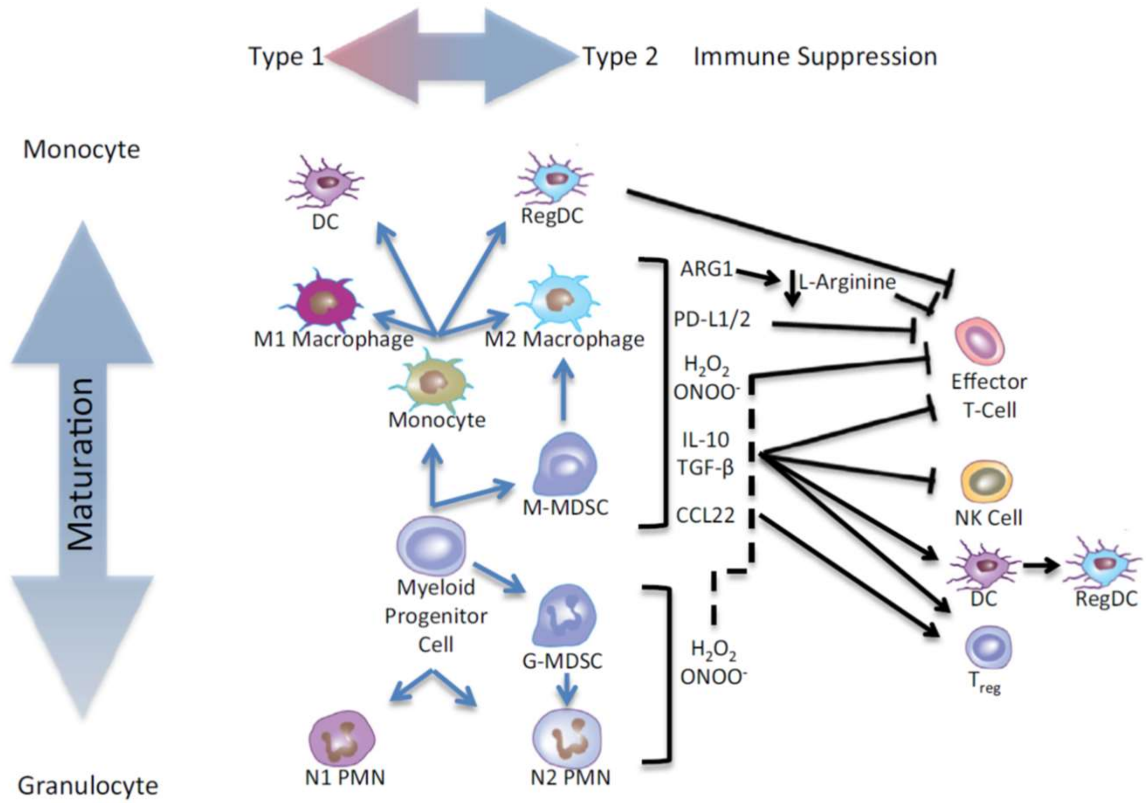
Recruitment
- M2 macrophage increased 7 days – 5 years after RT

Removal
- MDSCs reduced with RT + ImmRx combination, not RT alone

Reorganization
- Increased macrophages in hypoxic and necrotic regions

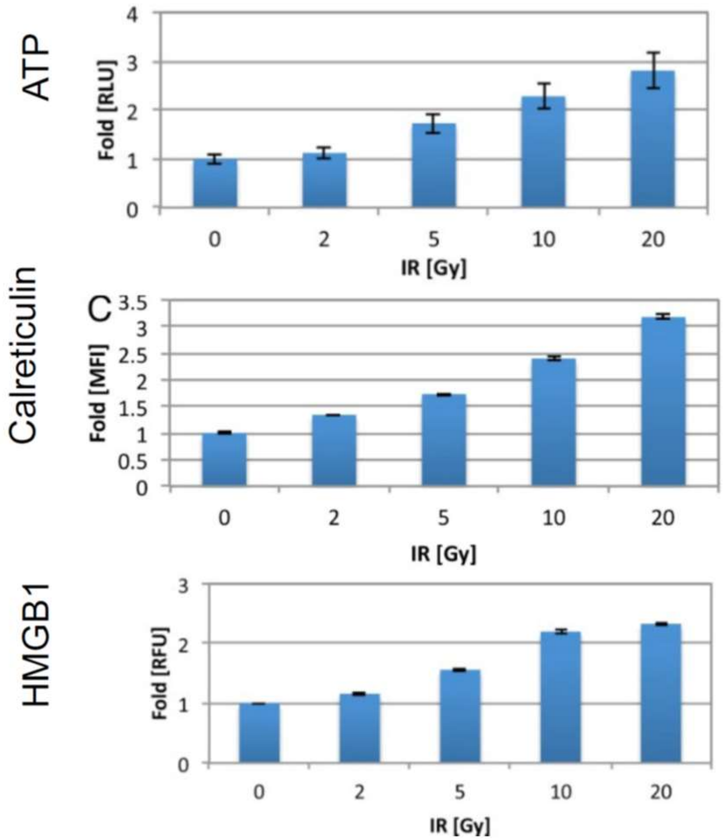
Repolarization
- Increased M2 phenotype

Re-presenation
- Increased dentritic cell antigen cross presentation

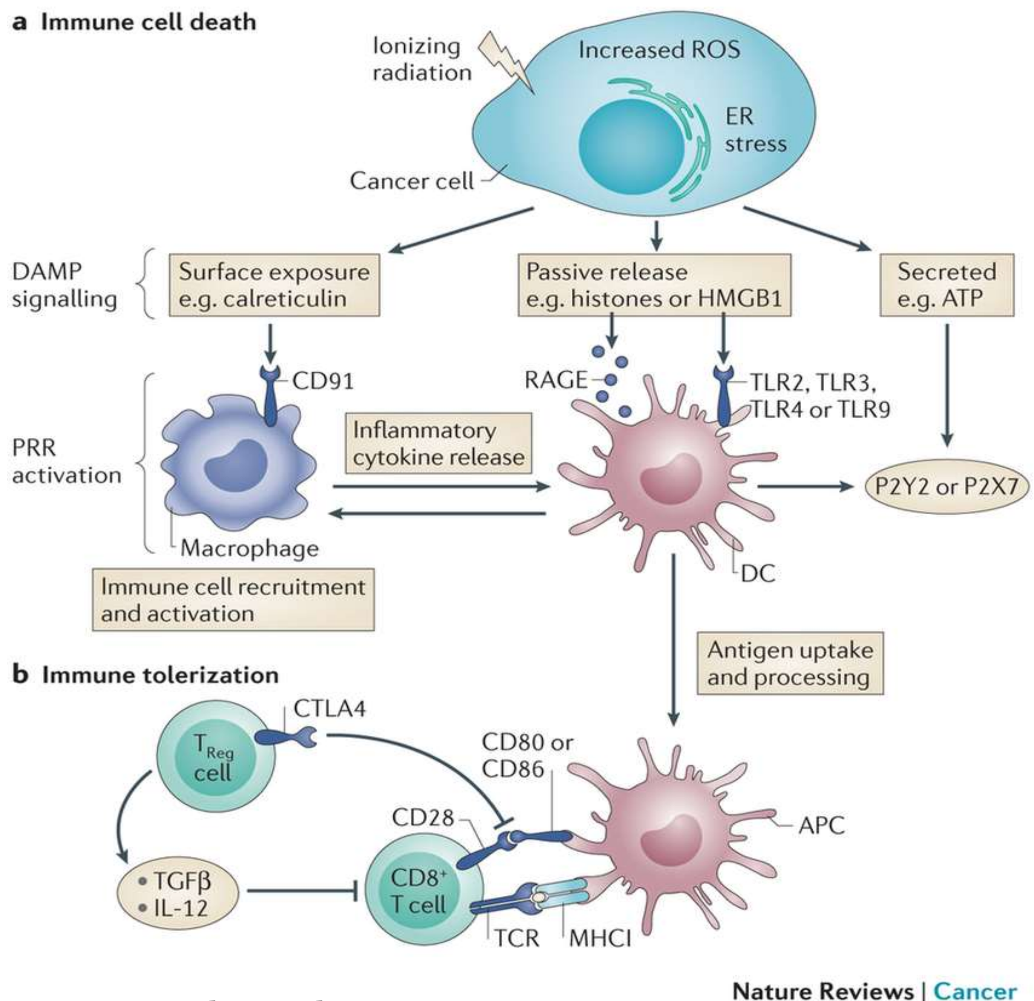


Vatner and Formenti, Sem Radiat Oncol, 2015

Immunogenic tumor cell death following radiation

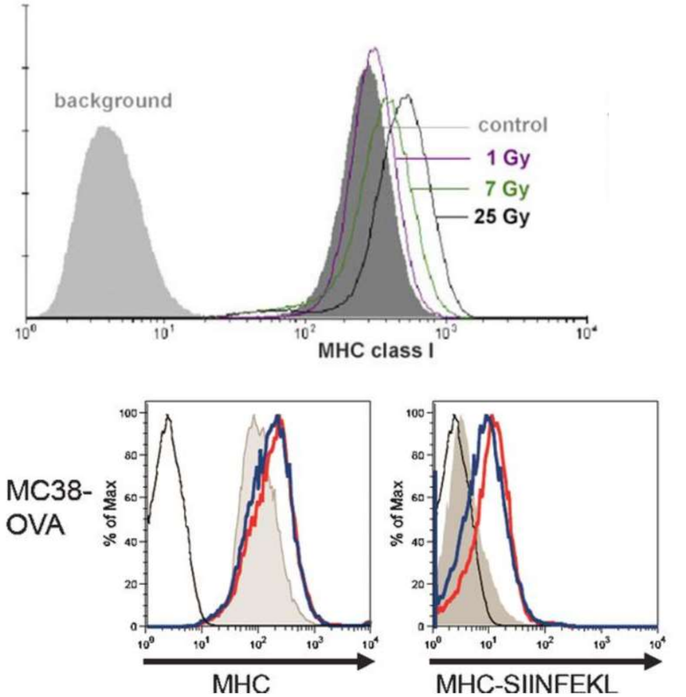


Golden et al., Immunooncology, 2014

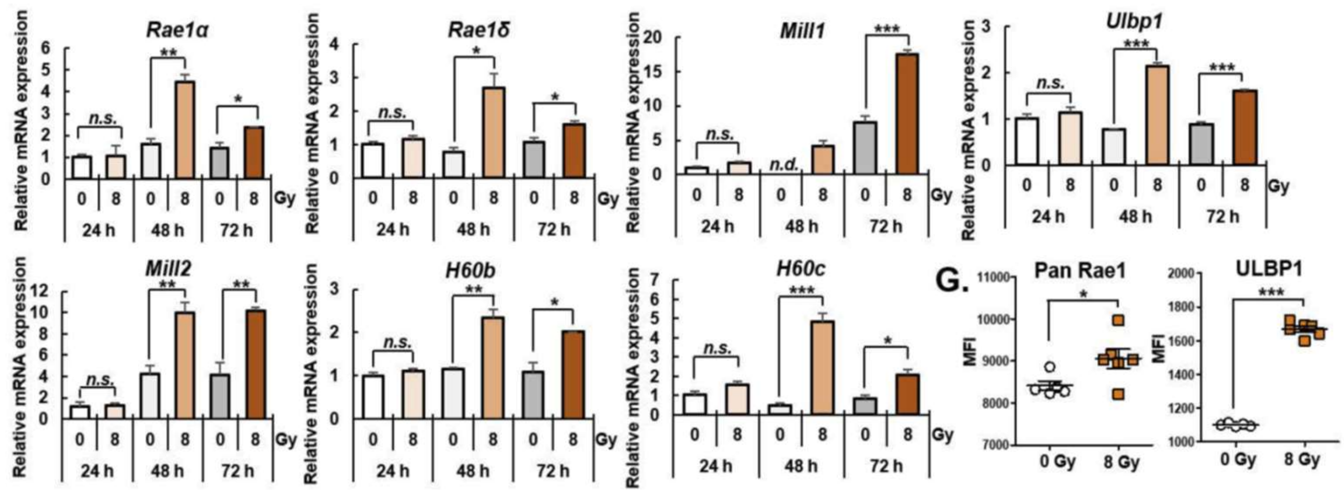


Barker et al., Nat Rev Cancer 2015

Radiation alters expression of genes that modify tumor cell susceptibility to immune response



RT dose leads to increased MHC-I expression on tumor cells

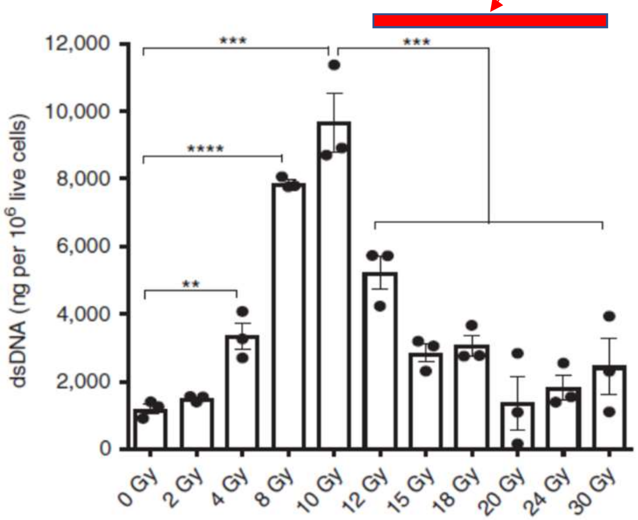


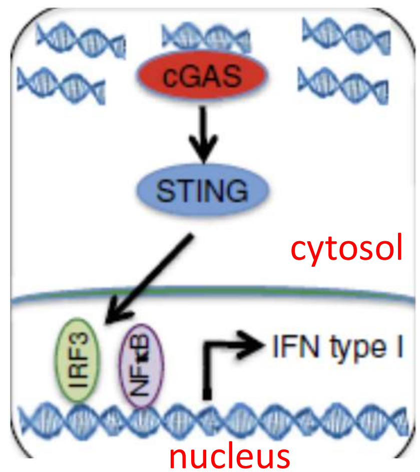
RT leads to increased expression of NKG2D ligands on tumor cells

Reits *et al*, JEM 2006
Sharabi *et al,* CIR 2015
Jin *et al*, Frontiers Immunol, 2020

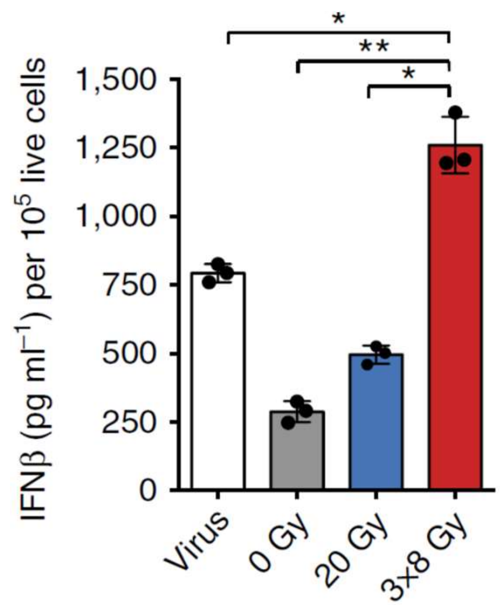
Radiation alters expression of genes that modify tumor cell susceptibility to immune response

Trex1 exonuclease expression ↑ at higher doses decreases dsDNA





Cytoplasmic dsDNA and type I IFN response ↑ with RT dose to 8-12 Gy



Radiation may also lead to activation of cGAS/STING in DCs and tumor stroma, potentially via tumor cell exosomes

Vanpouille-Box *et al.*, Nature Comm, 2017
Diamond *et al.*, Canc Immunol Res, 2018

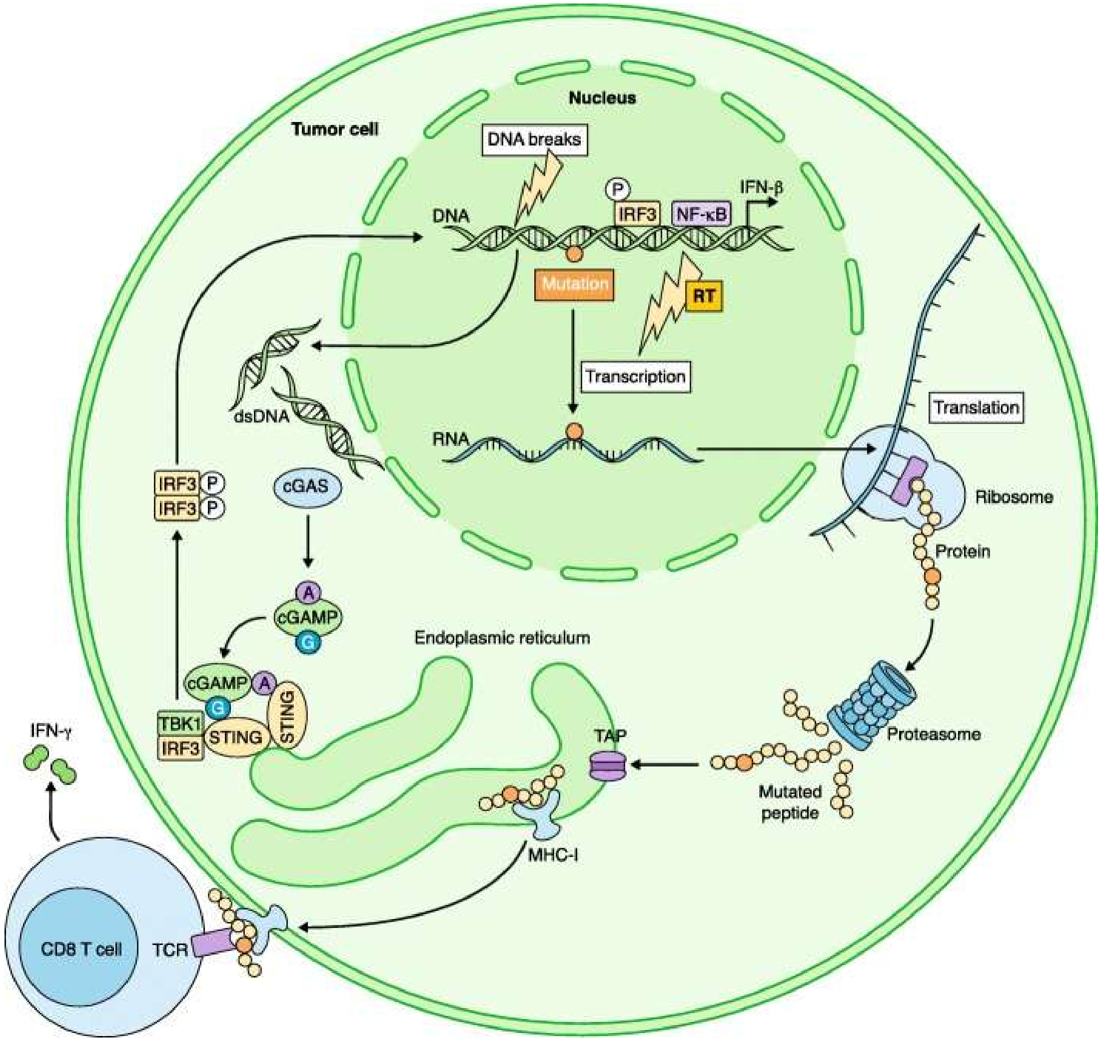
Radiation can have broad impact on the expression of markers of immune susceptibility on tumor cells

Key (Fold Change)
>15.00
14.99
5.00-9.99
3.00-4.99
2.00-2.99
1.5-1.99
<1.5
1.5-1.99
2.00-2.99
3.00-4.99
5.00-9.99
14.99
>15.00

Class		Target	A375 (Human)			B78 (Murine)		
Days After RT Treatment:			2.5	7	14	2.5	7	14
Death Receptors		Fas		*			**	
		DR6						*
		DR5	*	**		***	***	
NK Cell Pathway		Rae-1		**				
T Cell Regulation		ICOS-L						
		CD40		*		***	**	
		OX40-L						
		CD137-L	*	**	*			
		PD-L1		*		*	**	
		MHC I-A		*			*	
DNA Damage		p53						
		MDM2	*	*		**	*	
		Bax	**	***	*	***	*	
Other	ICD	CRT					**	

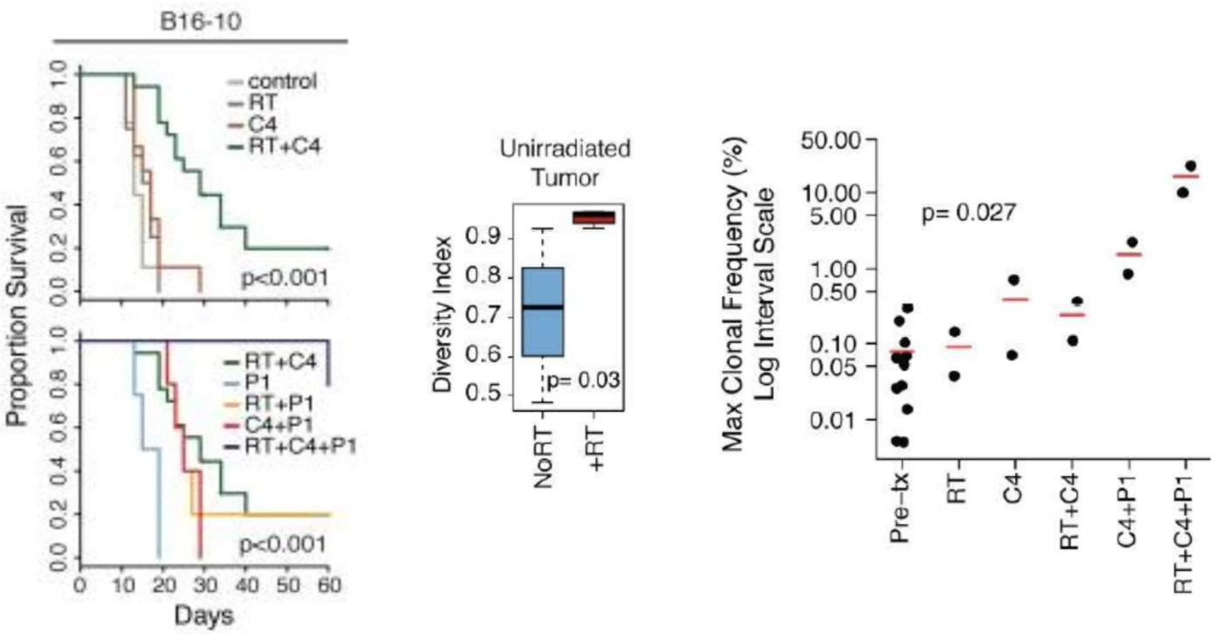
Werner *et al,* Radiother Oncol, 2017

Radiation may modify the expression of pre-existing tumor-associated neoantigens



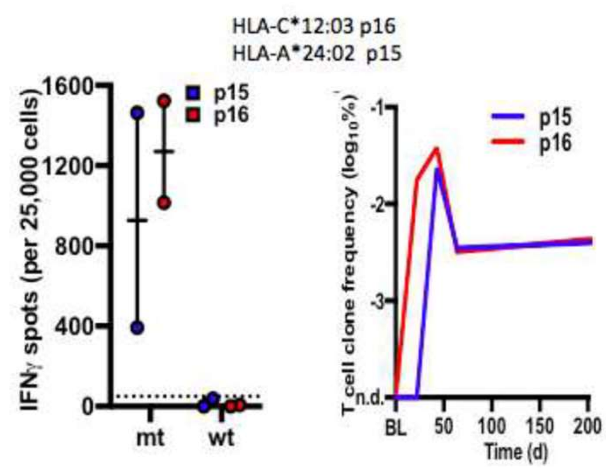
Lhuillier *et al.*, Genome Med, 2019

As a result of these cumulative mechanisms, radiation may elicit an *in situ* vaccine effect and this may prime response to immune checkpoint blockade



Radiation increases T cell receptor diversity among tumor infiltrating lymphocytes.
Checkpoint blockade is needed for clonal expansion of this diversified T cell response.

Preclinical
Twyman-Saint Victor *et al*., Nature, 2015



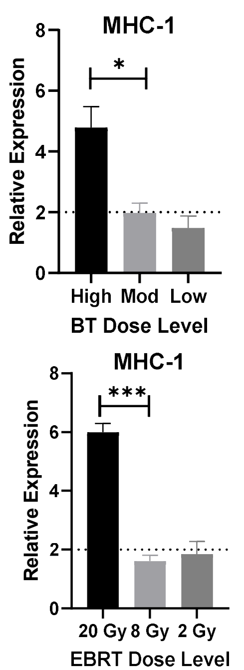
Radiation stimulated recognition of an immunogenic tumor mutation

Clinical
Formenti *et al*., Nature Med, 2018

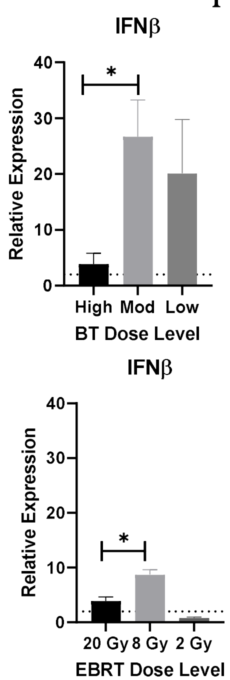
Heterogeneous dose radiation may be more effective for in situ vaccination

B78 melanoma two tumor model

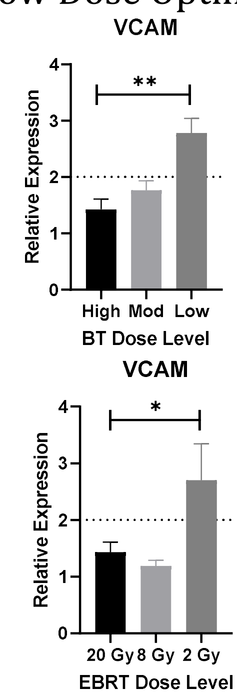
High Dose Optimal

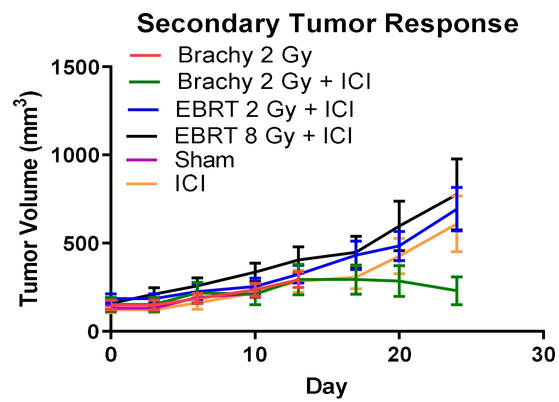


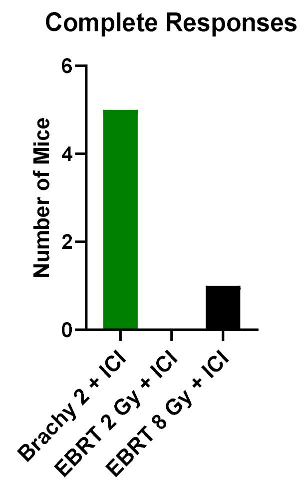
Moderate Dose Optimal

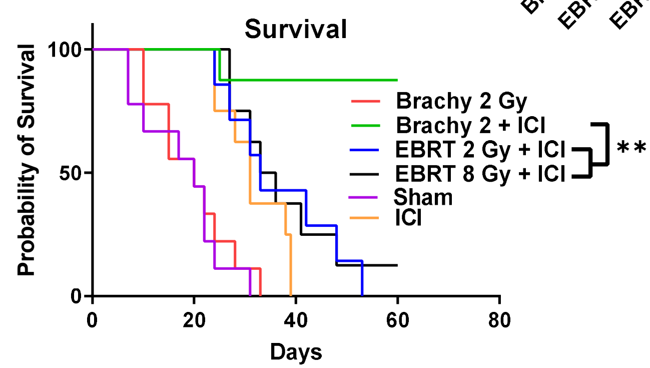


Low Dose Optimal









Justin Jagodinsky, unpublished

Low dose radiation targeting metastatic tumor sites can help propagate anti-tumor immunity and the in situ vaccine effect

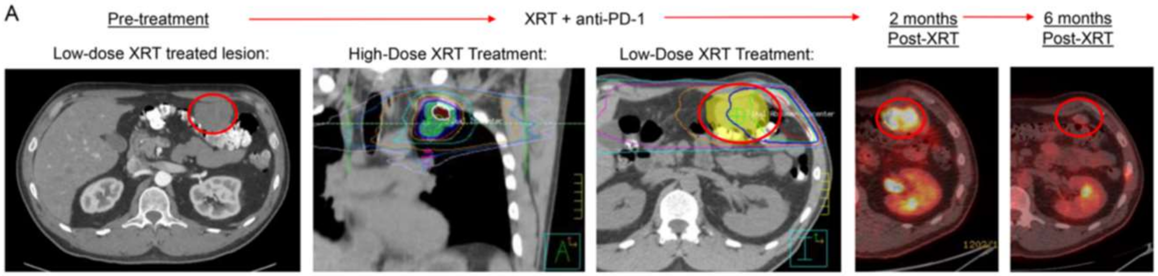
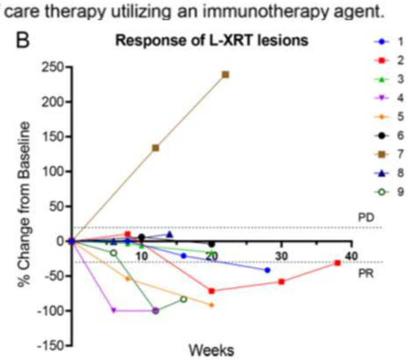


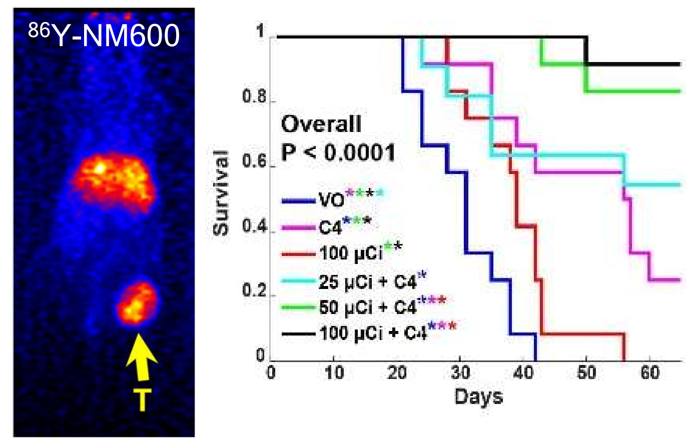
Table 1. Baseline Patient and Disease Characteristics and Treatment Strategies

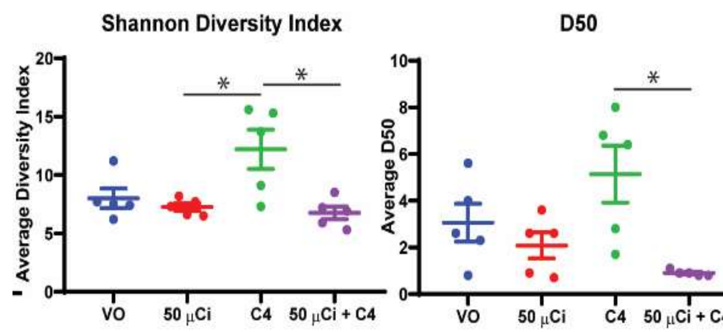
ID #	Age	Sex	Histology	Immunotherapy Agent	Prior receipt of chemotherapy (Y/N)	Prior disease progression on immunotherapy* (Y/N)	High-Dose Radiation Site	High Dose Radiation, (Gy/fx)	Low-Dose Site	Low-Dose Radiation (Gy/fx)	Total # of lesions measured
1	55	M	SCC	Pembrolizumab	Y	Y	Lung	50/4	Abdomen	8/4	6
2	69	M	MCC	Atezolizumab	Y	Y	Adrenal	70/10	Inguinal	6/6	4
3	56	F	Melanoma	Ipilimumab	Y	Y	Spleen	25/5	Liver	7.5/5	6
4	46	M	NPC	Pembrolizumab	Y	Y	Sternum	25/5	Neck	7/5	10
5	74	F	Melanoma	Ipilimumab/Nivolumab	Y	Y	Liver	30/5	Liver	5/5	6
6	30	F	Neuroblastoma	Pembrolizumab	Y	Y	Lung	60/10	Lung	7/5	6
7	62	F	Melanoma	OX40, 4-1BB	Y	Y	Lung	50/4	Lung	7/5	4
8	58	F	SGC	Pembrolizumab	Y	Y	Lung	20/5	Chest	7/5	4
9	73	F	ATC	Atezolizumab	Y	Y	Lung	50/4	Lung	7/5	4

Abbreviations: SCC, squamous cell carcinoma; SGC, salivary gland carcinoma; MCC, Merkel Cell Carcinoma; NPC, nasopharyngeal carcinoma; ATC, anaplastic thyroid carcinoma. *Progressive disease via Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) on prior study or standard of care therapy utilizing an immunotherapy agent.



Barsoumian et al., JITC, 2020





Ravi Patel, unpublished

Questions are welcome during the Q&A to follow!