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SBRT and Immune Activation

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Disclosures

Grant/Research support from: Bristol Myers Squibb, Varian, Eli-Lilly, Janssen, Regeneron, Eisai, Merck, Dynavax

Honoraria from: Bayer, Bristol Myers Squibb, Varian, ViewRay, Elekta, Janssen, Regeneron, GlaxoSmithKline, Eisai, Dynavax, Astra Zeneca, MedImmune, Merck US, EMD Serono/Merck

I will discuss the following off label use and/or investigational use in my presentation:

Ipilimumab (BMS)

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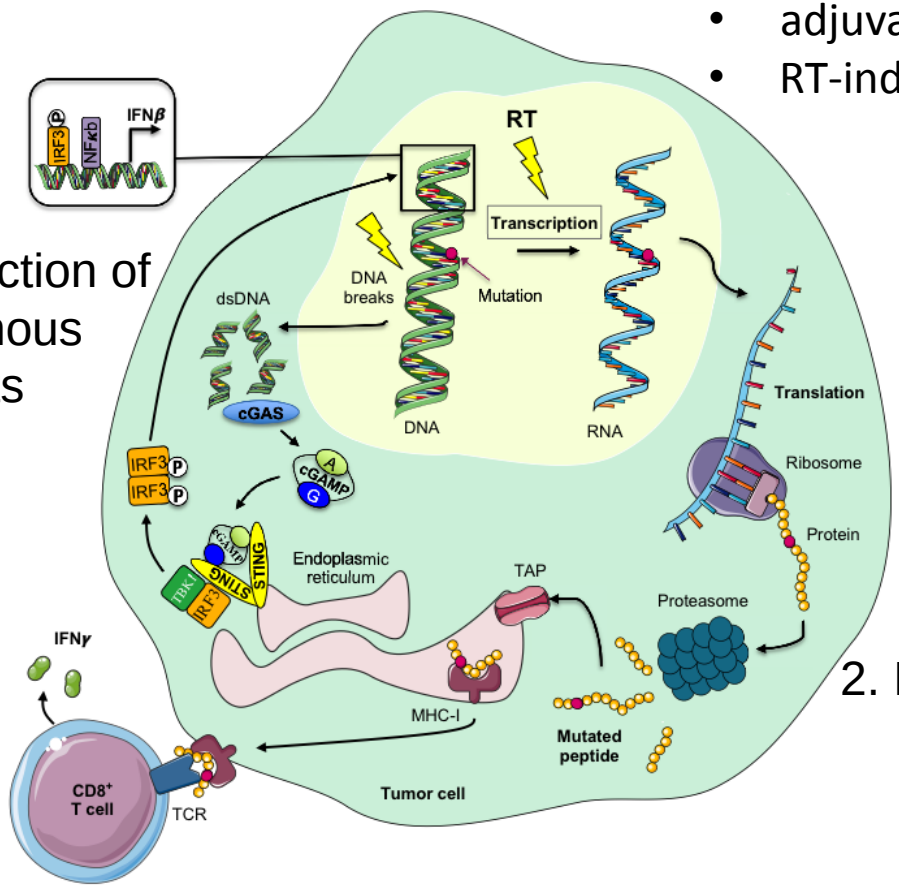
Mechanisms of radiation immunogenicity

- adjuvanticity to immunotherapy
- RT-induced antigenicity

1. Production of endogenous adjuvants



2. Exposure of neoantigens

Formenti et al Nature Medicine 2018

Lhuillier et al, Genome Medicine 2019

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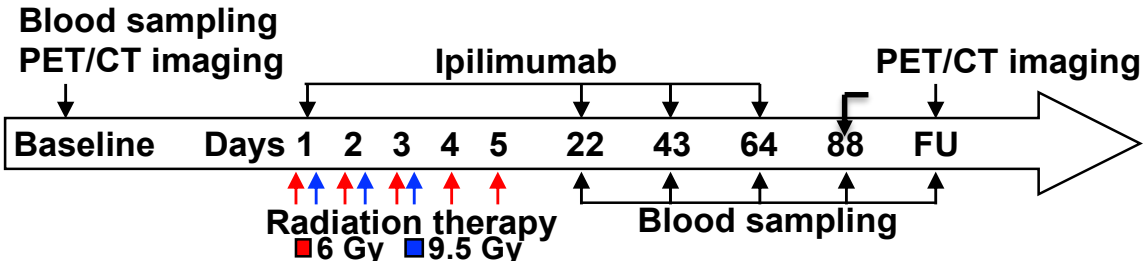
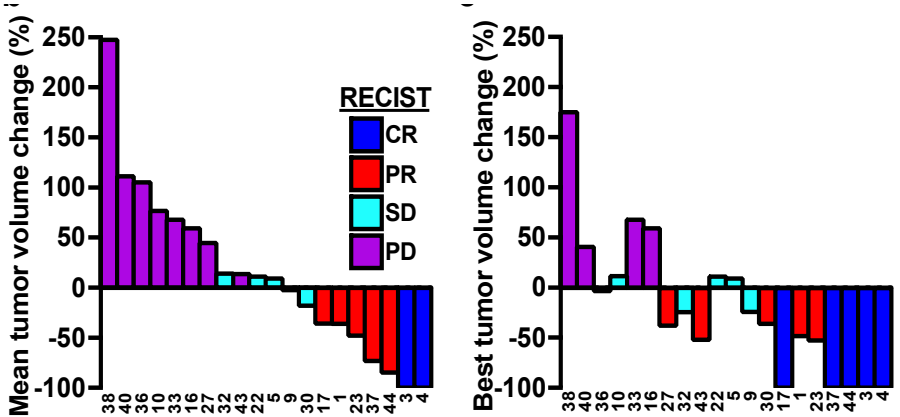
Ipilimumab and localized RT in chemo-refractory metastatic NSCLC (NCT 02221739)





Response : 18%
(RECIST v1.1)

CR = 2
PR = 5
SD = 5
PD = 28

Total pts = 39

Nature Medicine, Nov 2018

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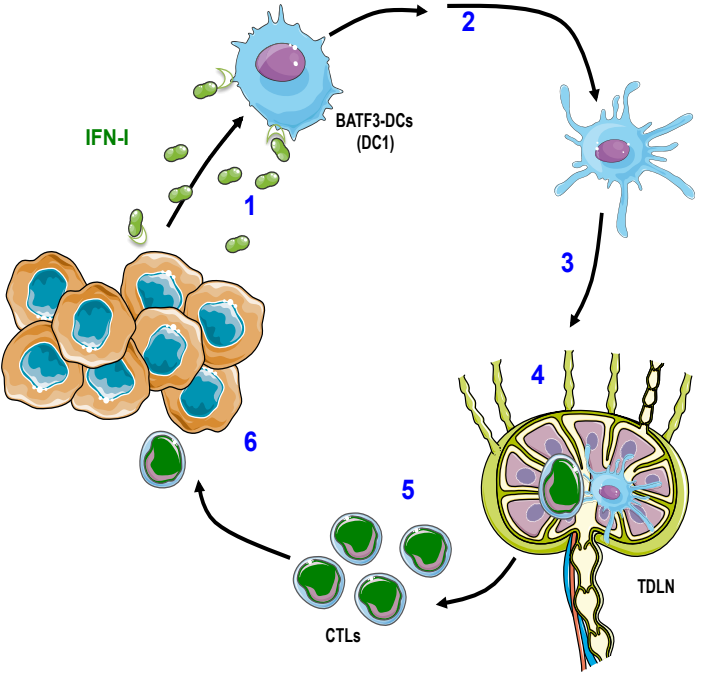
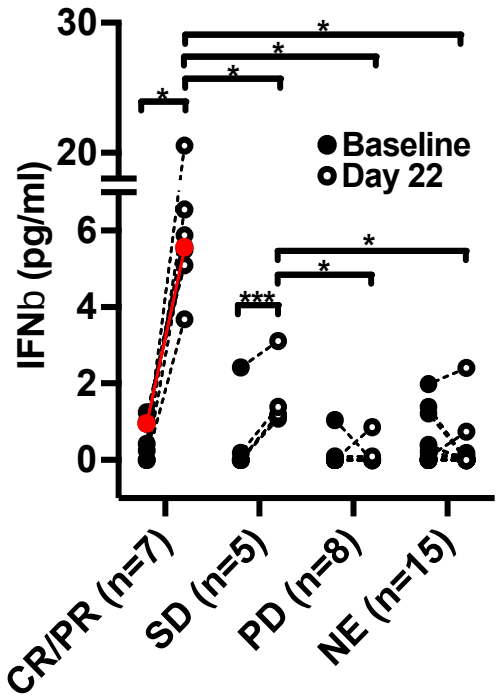
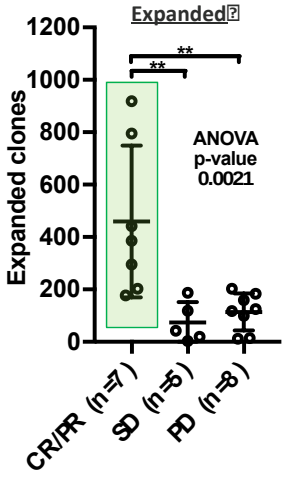
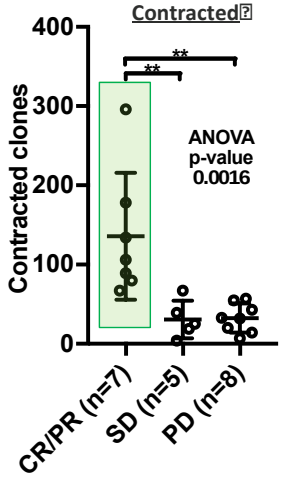
Post-RT increase in IFN-β levels and T cell clonality are associated with response to treatment



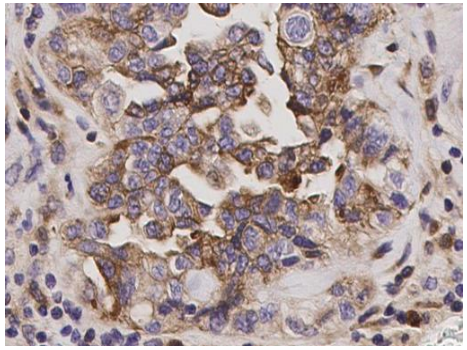






Nature Medicine, Nov 2018

Patient #4 :complete response to Ipi/Rt



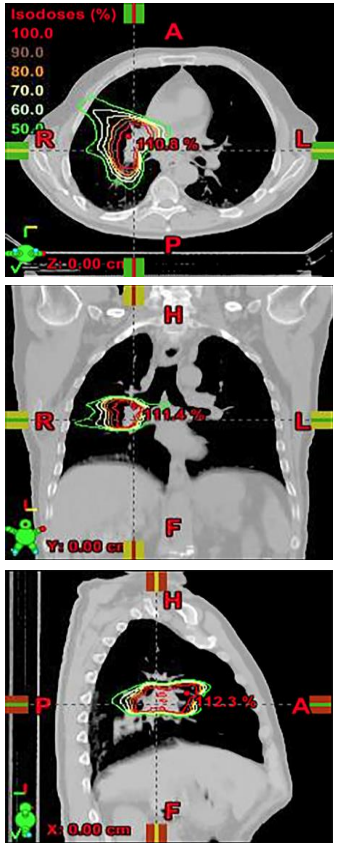
61-year-old man, presented with brain metastases (excised), progressed after first line chemo. At accrual:

right hilum, right lower lobe, multiple mediastinal lymph nodes, and left supraclavicular lymph node

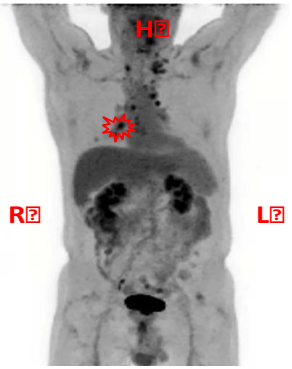
RT (6GyX5) to R hilum + Ipilimumab

Rapid resolution of all disease sites, day 80 from start of treatment

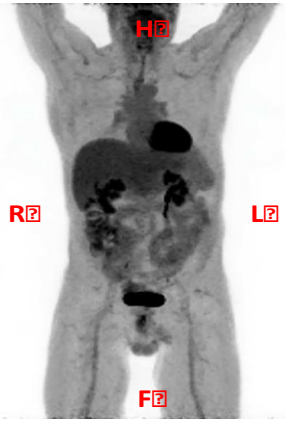
ALIVE, on nivo, 4 years later



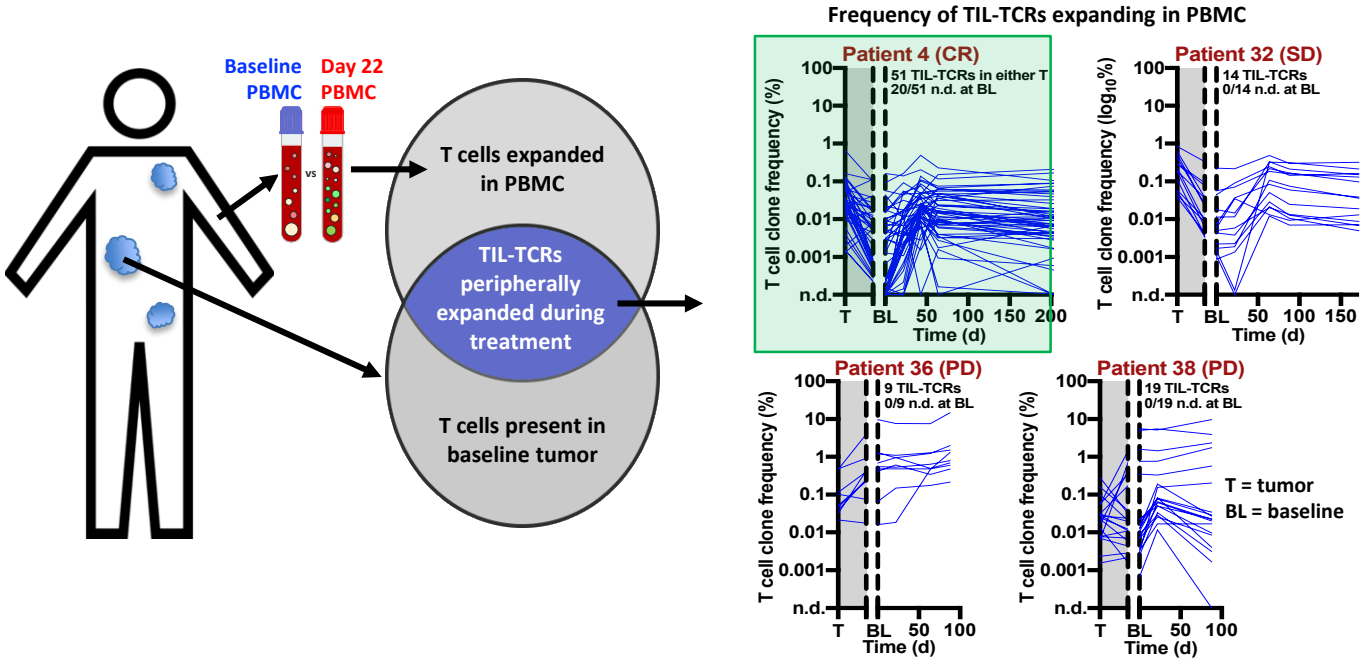
July 2014



October 2014



Expansion of tumor-derived T cell clones in blood of patient 4



Nature Medicine 2018

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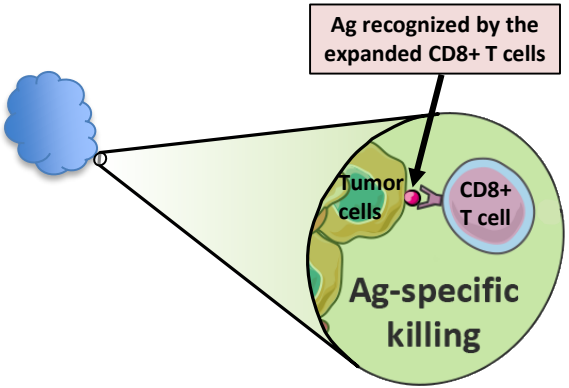
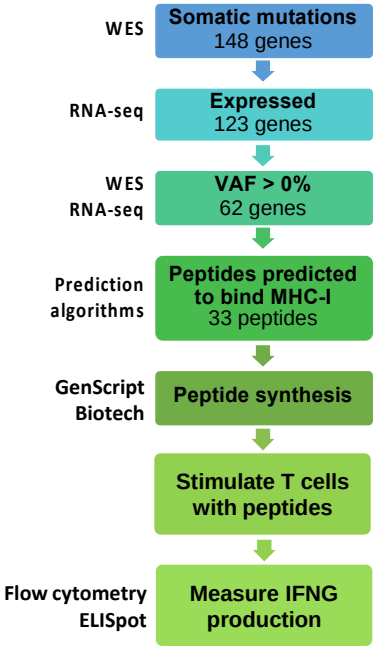
Pipeline for neoantigen prediction and validation

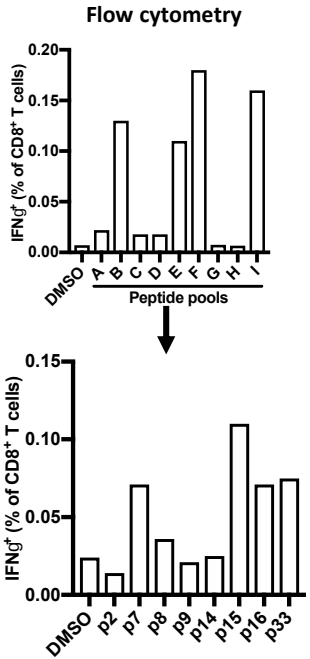



Nils Rudqvist


Claire Lhuillier


Erik Wennerberg





Nature Medicine 2018

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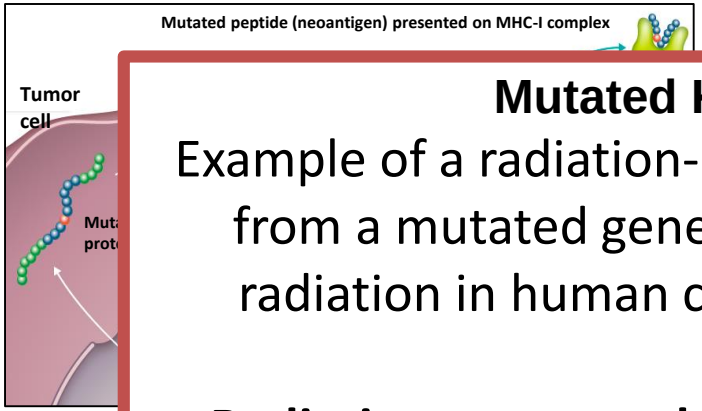
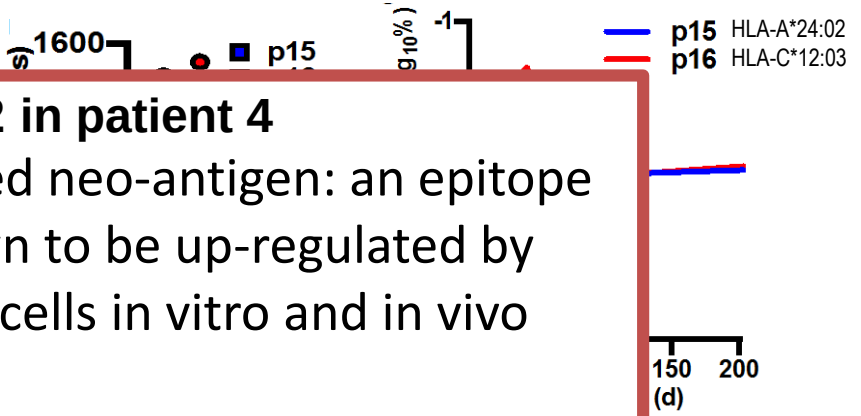
CD8 T cells present in the post-treatment blood of pt #4 recognize an immunogenic mutation in KPNA2 (karyopherin A2)





Mutated KPNA2 in patient 4

Example of a radiation-induced neo-antigen: an epitope from a mutated gene known to be up-regulated by radiation in human cancer cells in vitro and in vivo

=

Radiation converts the tumor into an *in situ* vaccine

p15 *not* detected in pre-tx tumor
p16 detected in pre-tx tumor

Nature Medicine 2018

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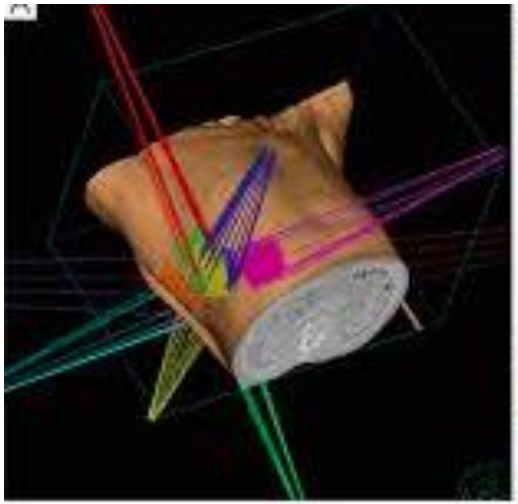
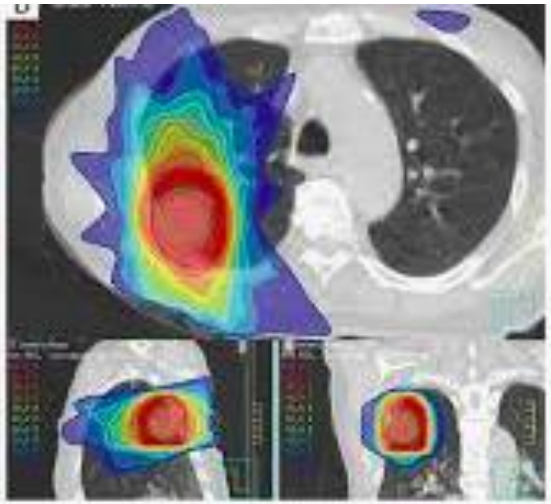
Why SBRT?

Stereotactic Body RadioTherapy





- Optimal immobilization to limit the target movement
- Use of a coordinate-system for exact target localization
- for delivering of dose through multiple non-coplanar arcs
- Enables hypo-fractionation because of with **sharp dose gradients outside the tumor**
  (sparing draining nodes, less circulating blood exposure)

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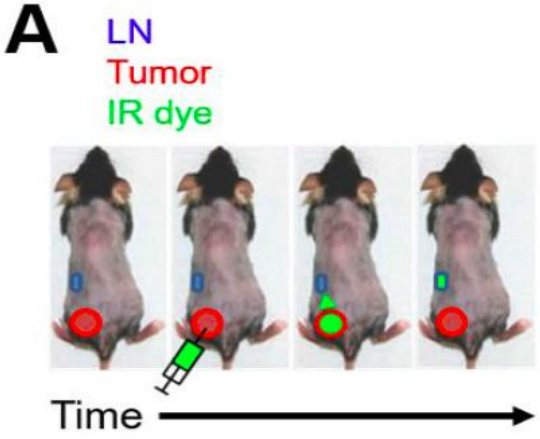
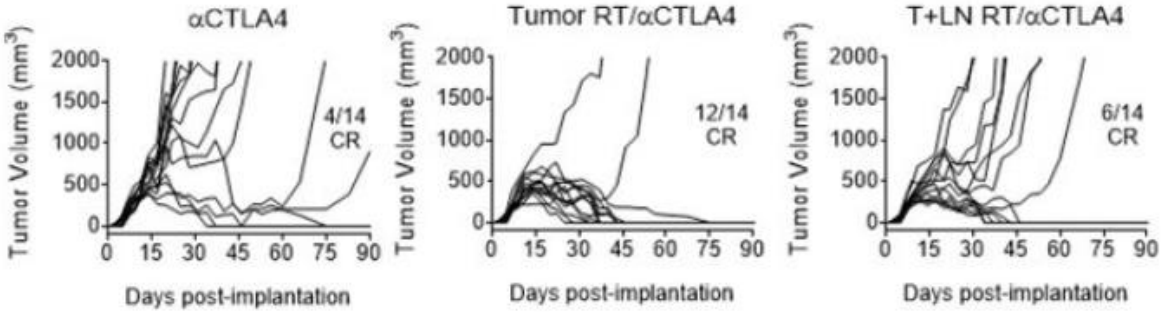
Clinical Cancer Research

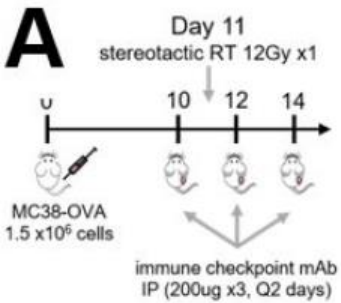
Elective nodal irradiation attenuates the combinatorial efficacy of stereotactic radiation therapy and immunotherapy

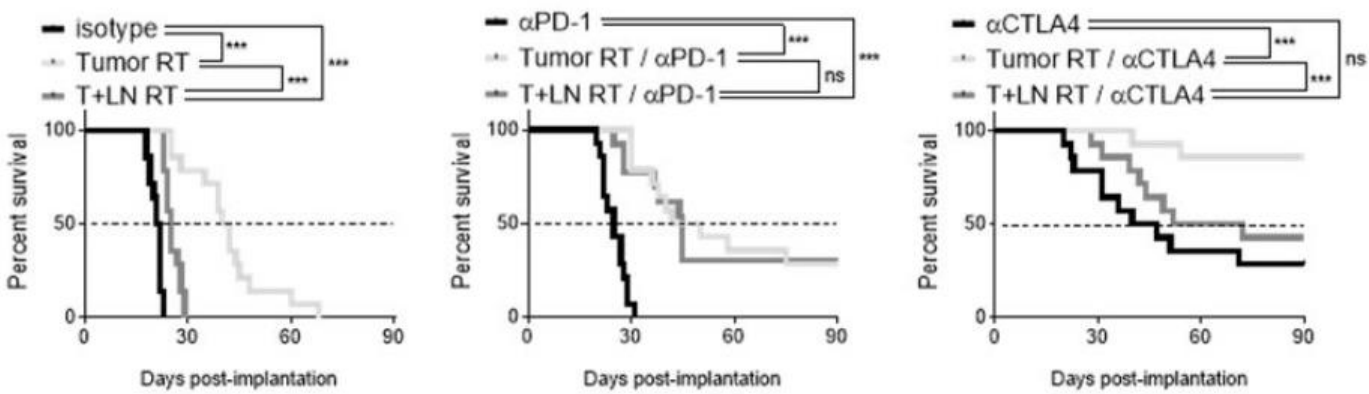
Ariel E. Marciscano, Ali Ghasemzadeh, Thomas R. Nirschl, et al.

Clin Cancer Res Published OnlineFirst June 13, 2018.







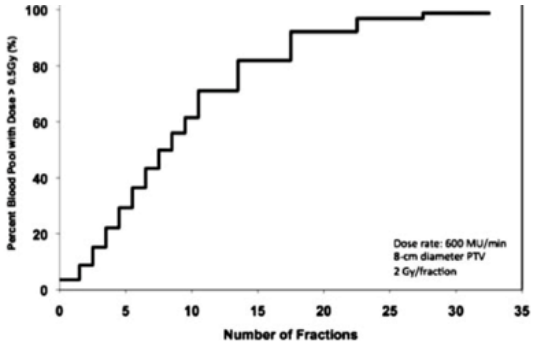


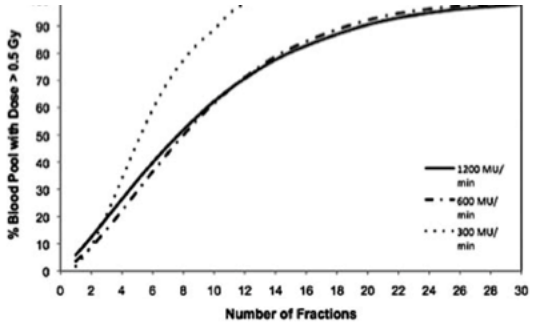
Cancer Invest. 2013 February ; 31(2): 140–144. doi:10.3109/07357907.2012.762780.

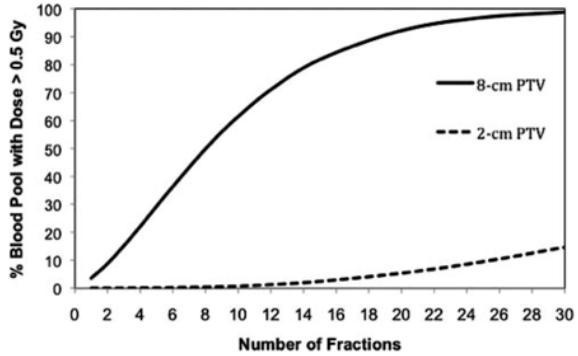
The Etiology of Treatment-related Lymphopenia in Patients with Malignant Gliomas: Modeling Radiation Dose to Circulating Lymphocytes Explains Clinical Observations and Suggests Methods of Modifying the Impact of Radiation on Immune Cells

Susannah Yovino[1], **Lawrence Kleinberg**[1], **Stuart A. Grossman**[2], **Manisha Narayanan**[3], and **Eric Ford**[1]

[1]Department of Radiation Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA



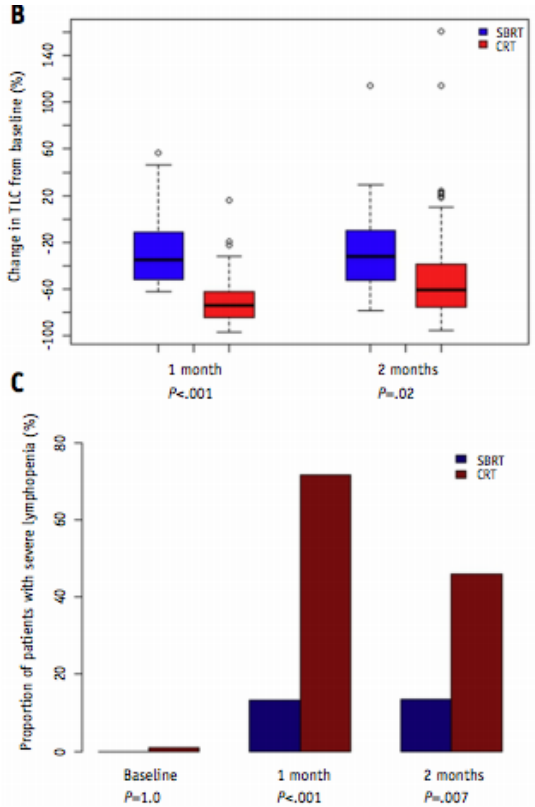


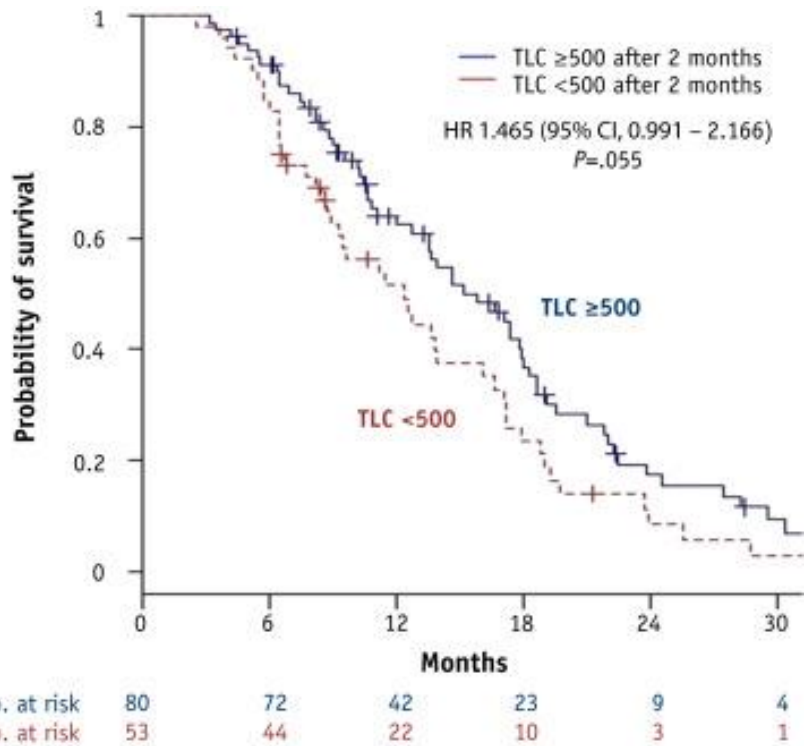


High dose rate
Small PTV
Hypo-fractionated RT

Yovino et al Cancer Invest. 2013

Lymphocyte-Sparing Effect of Stereotactic Body Radiation in Patients With Un-resectable Pancreatic Cancer





Wild et al. IJROBP, Volume 94, Issue 3, 2016, 571–579

Optimal immune activation by RT

- SBRT advantages
- Dose per fraction/total dose
- Single versus multiple doses
- Single versus multiple target
- Ablative versus non ablative
- LET –dependency

sparing of T cells /< high dose to normal tissue/nodes

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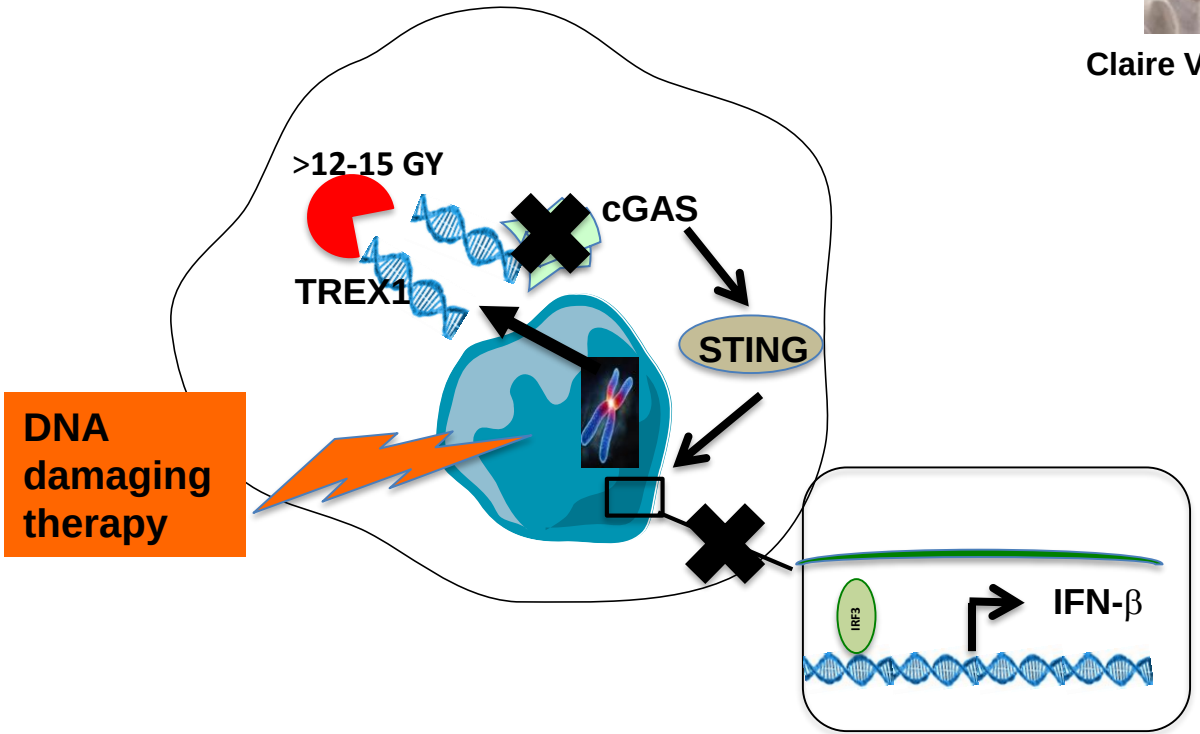
Radiation Fraction Size, IFN-I and TREX1

Claire Vanpouille-Box



Vanpouille-Box et al., Nature Communications, June 2017

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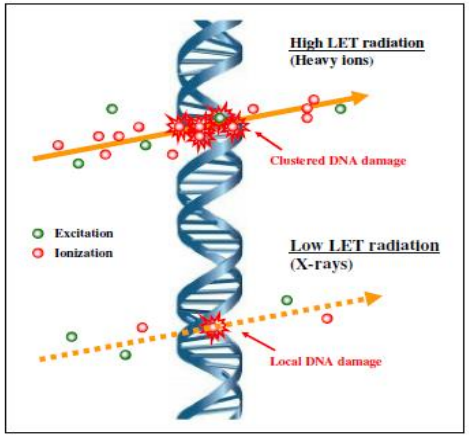
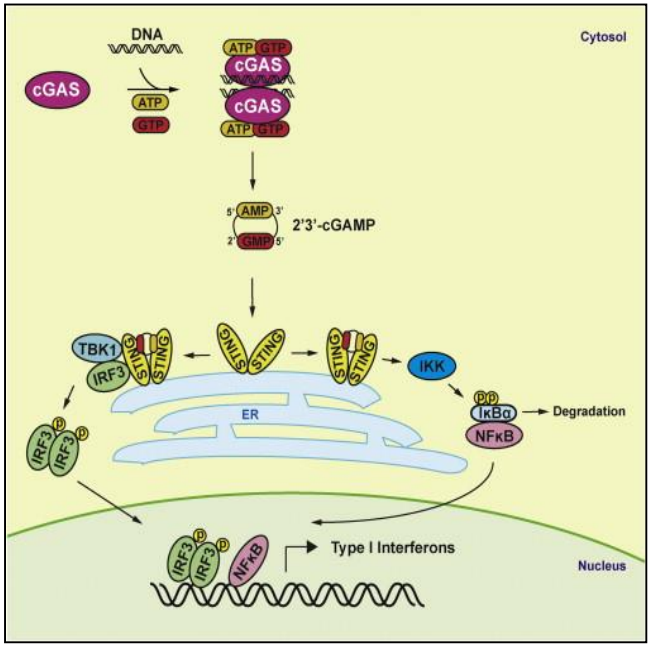
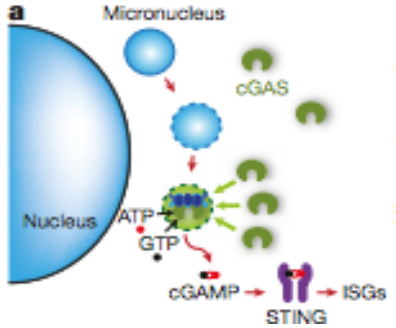
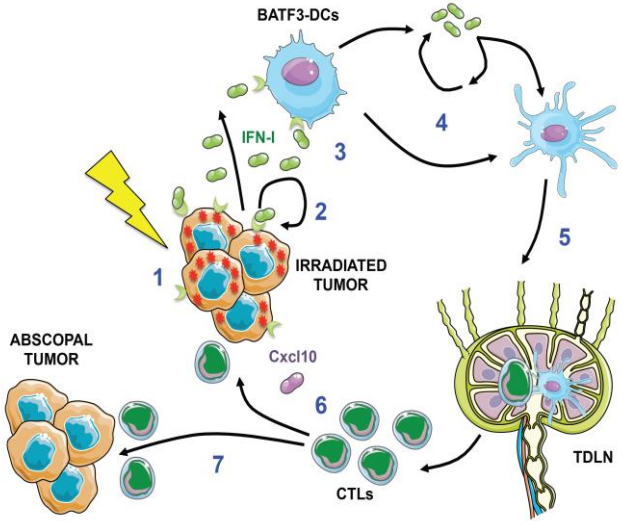
Cytoplasmic dsDNA sensed by cGAS activates IFN-I pathway via STING



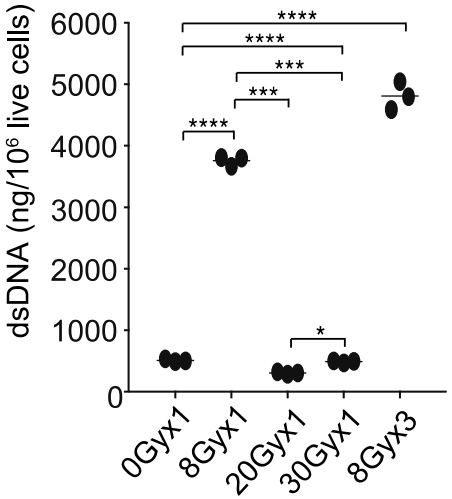


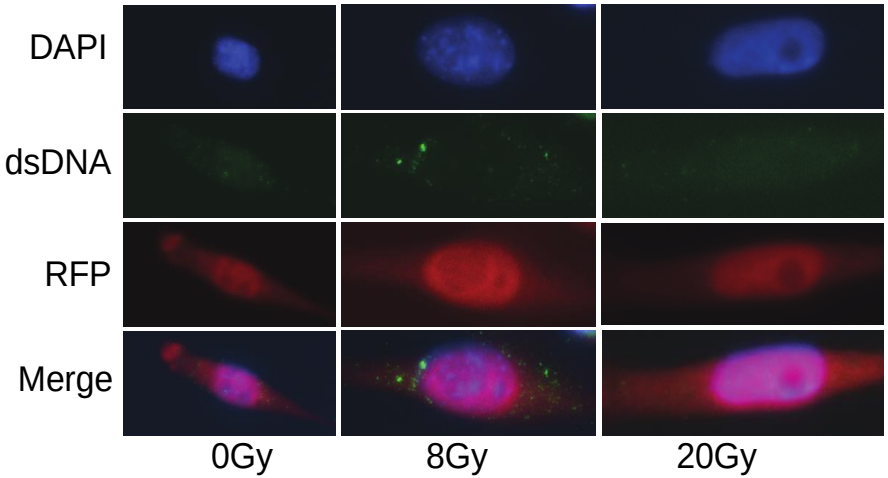


Cai X, et al Molecular Cell. 2014; Deng L, et al Immunity 2014; Mckenzie, et al Nature 2017, Harding, et al Nature 2017



dsDNA accumulation in cytoplasm of cancer cells is dependent on RT dose





Nature Communications, 2017

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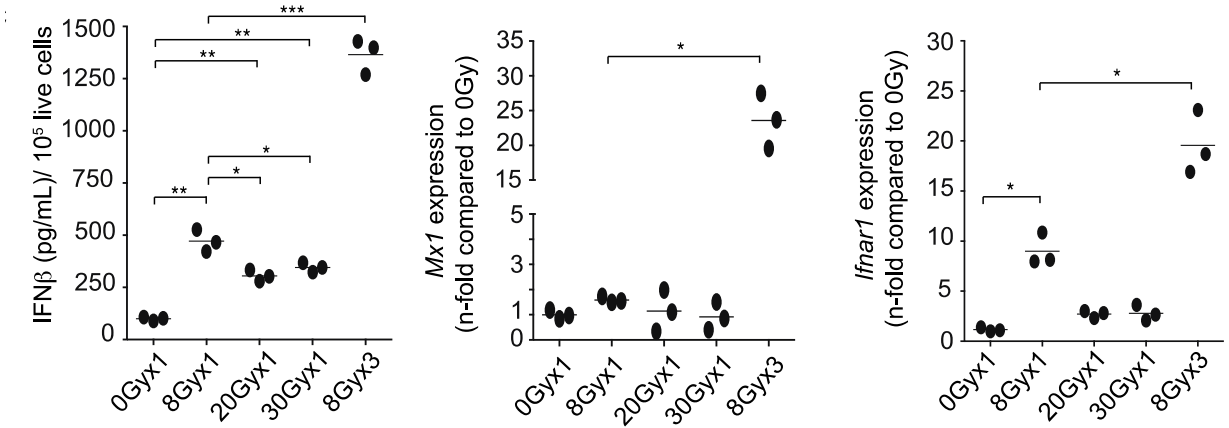
Repeated daily RT is required for amplification of IFN-I pathway in cancer cells



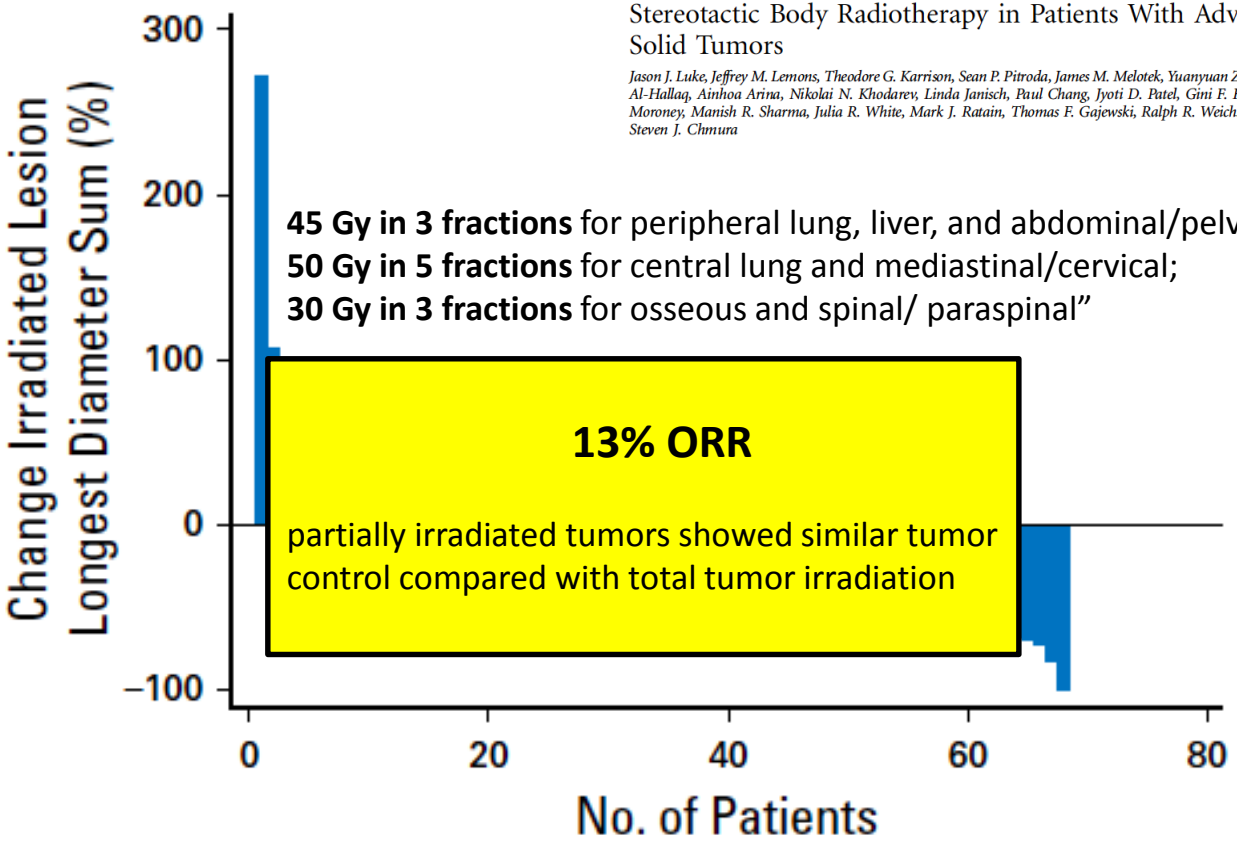
Nature Communications, 2017

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Safety and Clinical Activity of Pembrolizumab and Multisite Stereotactic Body Radiotherapy in Patients With Advanced Solid Tumors

Jason J. Luke, Jeffrey M. Lemons, Theodore G. Karrison, Sean P. Pitroda, James M. Melotek, Yuanyuan Zha, Hania A. Al-Hallaq, Ainhoa Arina, Nikolai N. Khodarev, Linda Janisch, Paul Chang, Jyoti D. Patel, Gini F. Fleming, John Moroney, Manish R. Sharma, Julia R. White, Mark J. Ratain, Thomas F. Gajewski, Ralph R. Weichselbaum, and Steven J. Chmura

45 Gy in 3 fractions for peripheral lung, liver, and abdominal/pelvic;
50 Gy in 5 fractions for central lung and mediastinal/cervical;
30 Gy in 3 fractions for osseous and spinal/ paraspinal"



JAMA Oncology | Original Investigation

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer
Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial

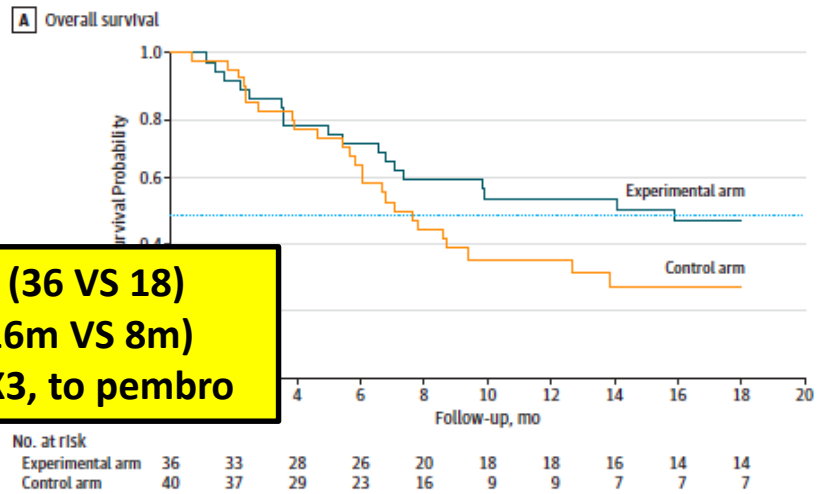
JAMA Oncology 2019

Table. Response to Treatment

Response	Experimental Arm, No./Total No. (%) (n = 36)[a]	Control Arm, No./Total No. (%) (n = 40)[b]
Best overall response, No.		
Complete response	3	1
Partial response	14	8
Stable disease	9	10
Progressive disease	10	21
Objective response rate at 12 wk		
Overall[c]	13/	
PD-L1 TPS, %		
0	4/1	
1-49	3/8	
≥50	6/10 (60)	3/5 (60)
Disease control rate at 12 wk[d]	23/36 (64)	16/40 (40)

Doubling of ORR (36 VS 18)
and median OS (16m VS 8m)
by adding RT, 8 GyX3, to pembro

Figure 3. Overall Survival in the Intent-to-Treat Population



Optimal immune activation by RT

- SBRT advantages — sparing of T cells /< high dose to normal tissue/nodes
- Dose per fraction/total dose — better repeated doses <10 Gy
- Single versus multiple doses — better 3-5 repeated doses
- Single versus multiple target
- Ablative versus non ablative
- LET –dependency

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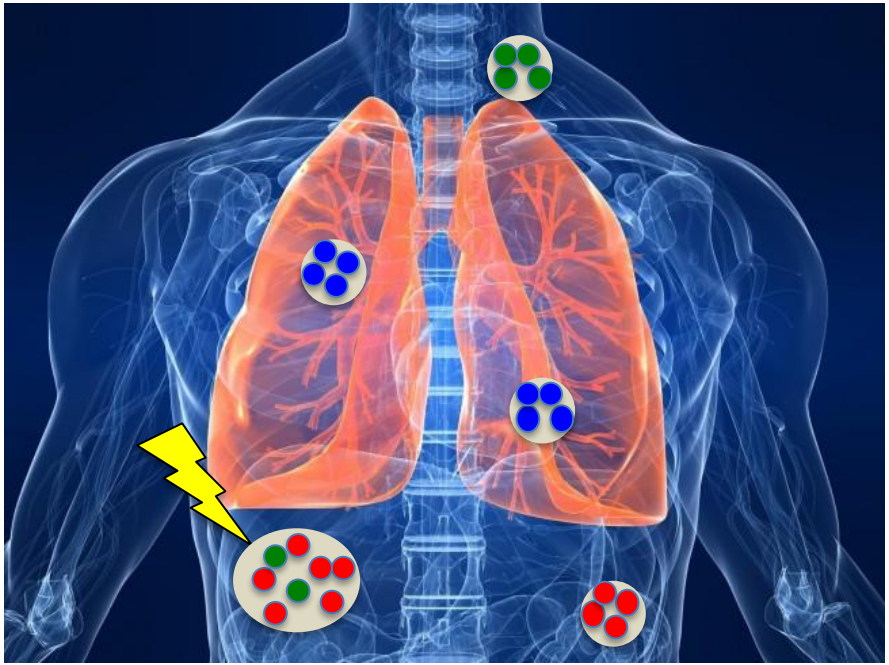
Tumor heterogeneity and resistance to T cells



Antigenic diversity
= multi-site “vaccination”

Downregulation of
cGAS/STING

Loss of MHC/b2m/IFNgR

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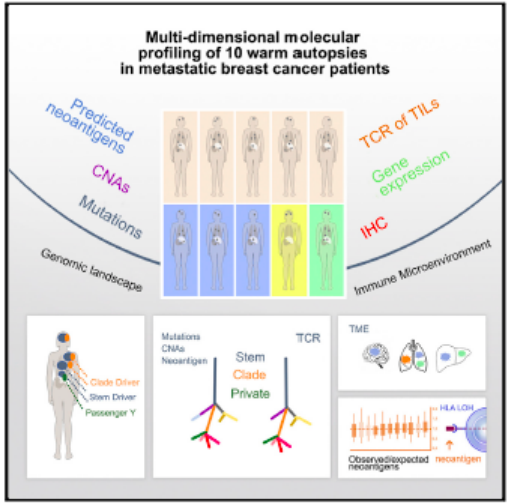
Article

Cell Reports

The Genomic and Immune Landscapes of Lethal Metastatic Breast Cancer

Graphical Abstract



Authors

Leticia De Mattos-Arruda, Stephen-John Sammut, Edith M. Ross, ..., Florian Markowetz, Joan Seoane, Carlos Caldas

Correspondence

jseoane@vhio.net (J.S.), carlos.caldas@cruk.cam.ac.uk (C.C.)

In Brief

De Mattos-Arruda et al. profiled multiple metastases from autopsies of patients with therapy-resistant breast cancer, showing that multi-clonal spreading occurs in a small number of founder events. The analysis characterizes predicted neo-antigen landscapes, tumor microenvironments, and accumulation of HLA LOH. T cell immune responses appear to co-evolve with metastatic cancer genomes.

2019

In summary, metastases keep accumulating mutations, including mutations in known cancer driver genes, but an apparent hierarchy of expression (stem-clade-private) of mutant alleles suggests that, as more mutations accumulate in metastases, these are increasingly passengers (e.g., not expressed).

A fraction of mutations (including drivers) shared across metastases (stem and clade) were not detectable in the available primary tumor tissue blocks, suggesting either their origin from a minor clone in the primary tumor **or their acquisition in metastatic cells that had already left the breast.**

Paper reveals, through analyses of T cell receptor repertoires, that adaptive immune responses appear to co-evolve with the metastatic genomes.

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Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

David A Palma, Robert Olson, Stephen Harrow, Stewart Gaede, Alexander V Louie, Cornelis Haasbeek, Liam Mulroy, Michael Lock, George B Rodrigues, Brian P Yaremko, Devin Schellenberg, Belal Ahmad, Gwendolyn Griffioen, Sashendra Senthi, Anand Swaminath, Neil Kopek, Mitchell Liu, Karen Moore, Suzanne Currie, Glenn S Bauman, Andrew Warner, Suresh Senan

Most common radiation dose fractionations:
35 Gy in five fractions (7GyX5) (for 39 targets),
60 Gy in eight fractions (7.5GyX8) (19 targets),
and 54 Gy in three fractions (18GyX3) (16 targets)

Can survival be further improved by combining SBRT +immunotherapy?

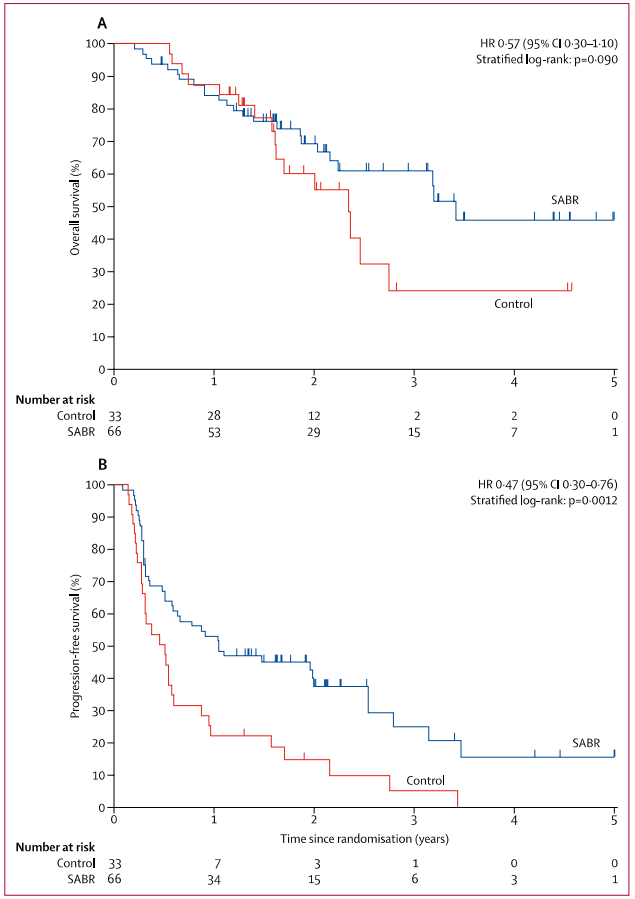
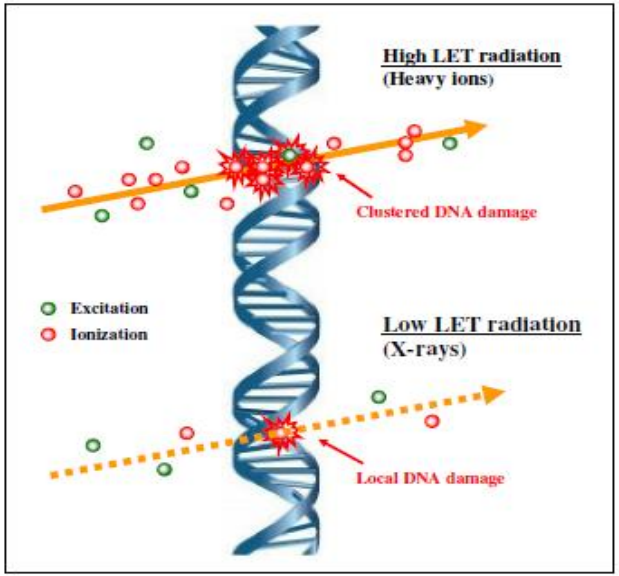


Figure 2: Overall survival (A) and progression-free survival (B)
SABR=stereotactic ablative radiotherapy. HR=hazard ratio.

Palma et al., Lancet 2019

ROLE of LET



$$LET \propto \frac{charge^2}{velocity^2}$$

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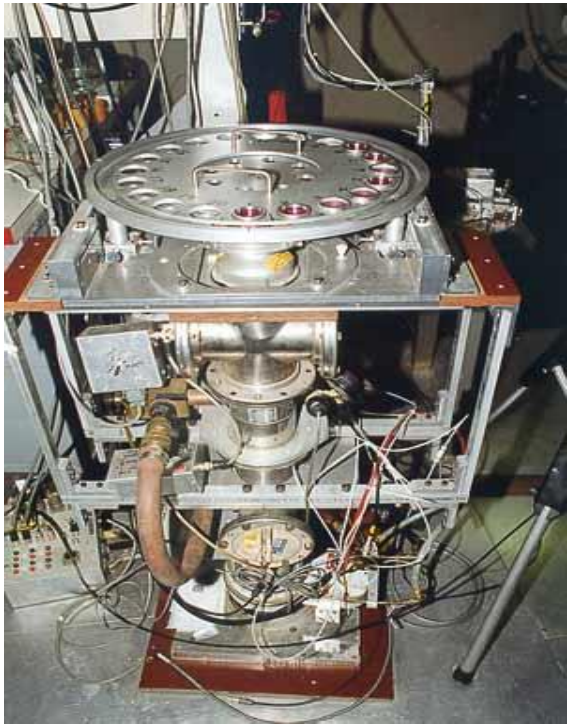
LET for Protons, Deuterons, and Alpha Particles

David J. Brenner

- Radiological Research Accelerator Facility (RARAF) at Columbia University
- Experimental irradiation using the Track Segment Charged-Particle Accelerator
- Allows for irradiation of particles of varying Linear Energy Transfer

Particle	LET Range
Proton	8-60 keV/μm
Deuteron	20-70 keV/μm
Helium-3	50-110 keV/μm
Helium-4	80-200 keV/μm



http://raraf.org/tracksegment.html

Optimal immune activation by RT

- SBRT advantages — sparing of T cells /< high dose to normal tissue/nodes
- Dose per fraction/total dose — better repeated doses <10 Gy
- Single versus multiple doses — better 3-5 repeated doses
- Single versus multiple target — multiple probably better
- Ablative versus non ablative — unknown
- LET –dependency — unknown

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