Weill Cornell Medicine

Combination Immunotherapy and SRS for the Treatment of Brain Metastases

Silvia Formenti, M.D.
Weill Cornell Medical College
New York Presbyterian Hospital
New York, NY

Weill Cornell Medicine

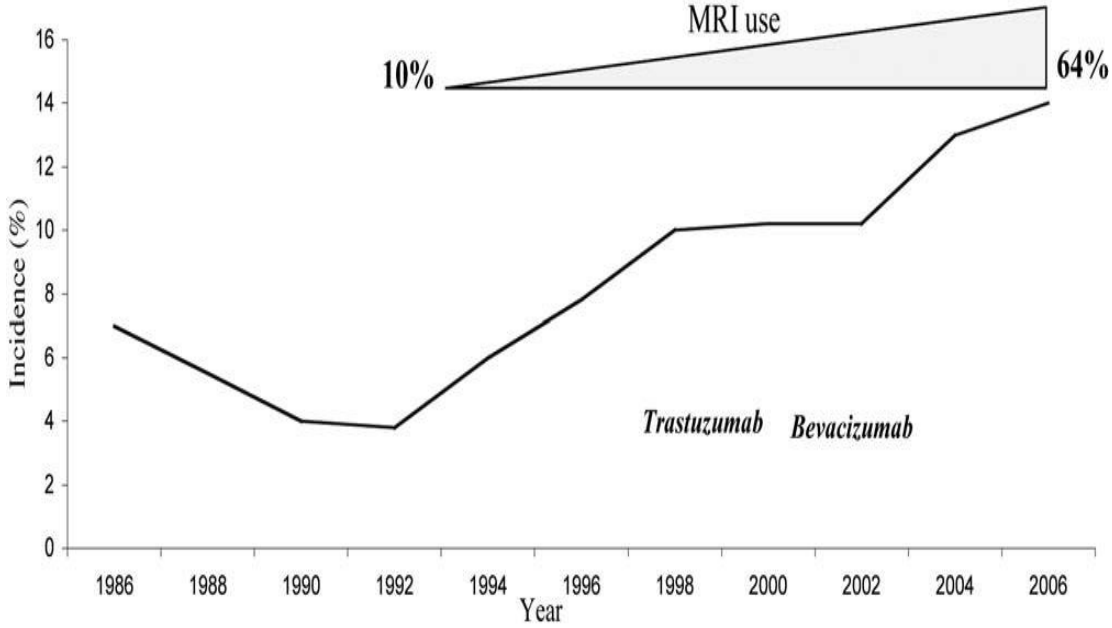
Disclosures

Grant/Research support from: Bristol Myers Squibb, Varian, Janssen, Regeneron, Eisai, Merck

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

Brain Metastases in Cancer

- As therapies and imaging improve, cancer patients both are surviving longer and are more likely to be diagnosed with brain metastases



Cognitive decline: Less radiation is better…

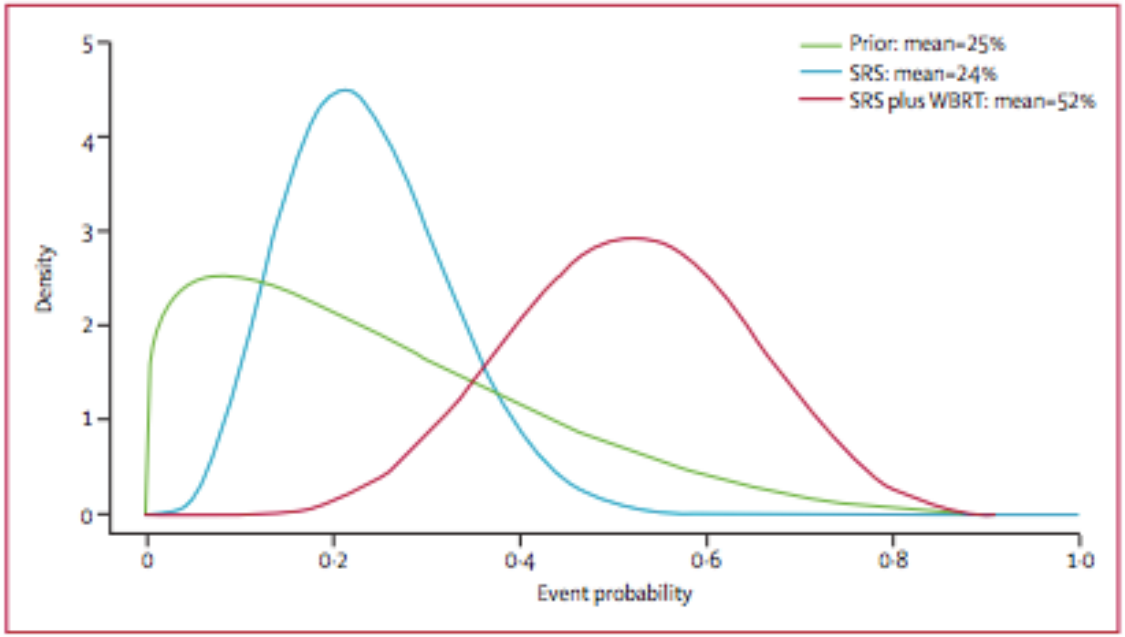


Figure 2: Prior and posterior distributions of probability of cognitive decline (5 points or greater fall from baseline) assessed by HVLT-R (total recall)
SRS=stereotactic radiosurgery. WBRT=whole-brain radiotherapy.

Chang EL et al Lancet Oncol 2009; 10: 1037–44

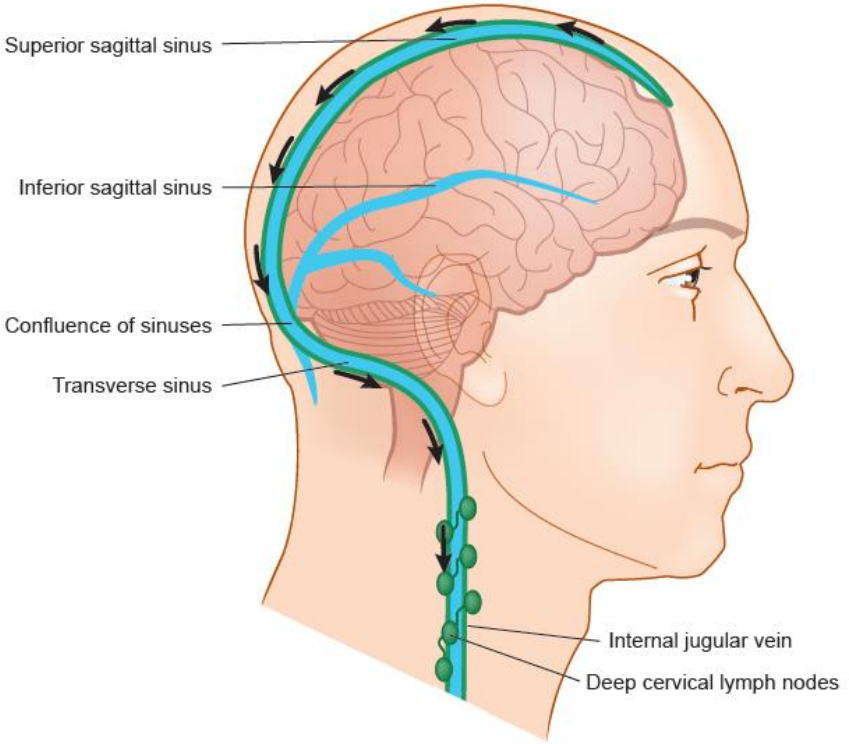
Overarching Hypothesis

Modern immunotherapy can induce an endogenous patient's immune response that successfully eliminates brain metastases, reducing the need for radiotherapy and consequently sparing cognitive decline

- The brain is not an immunological sanctuary
- Immune checkpoint inhibitors (ICB) are effective in melanoma brain metastases
- Radiation synergizes with ICBs, and the effects depends on the dose per fraction
- A protocol to test in brain immunization with SRS and anti-PD1 in metastatic breast cancer
- The future….

Blood Brain Barrier and Lymphatic Channels

- Longstanding dogma maintained that the brain was a sanctuary site with no interface to the adaptive immune system
- Recent studies revealed channels that drain along the sagittal sinuses to secondary cervical lymph nodes
- A preclinical mouse model showed anti-tumor T cells could be primed in cervical lymph nodes and then circulated to infiltrate intracranial melanoma tumors

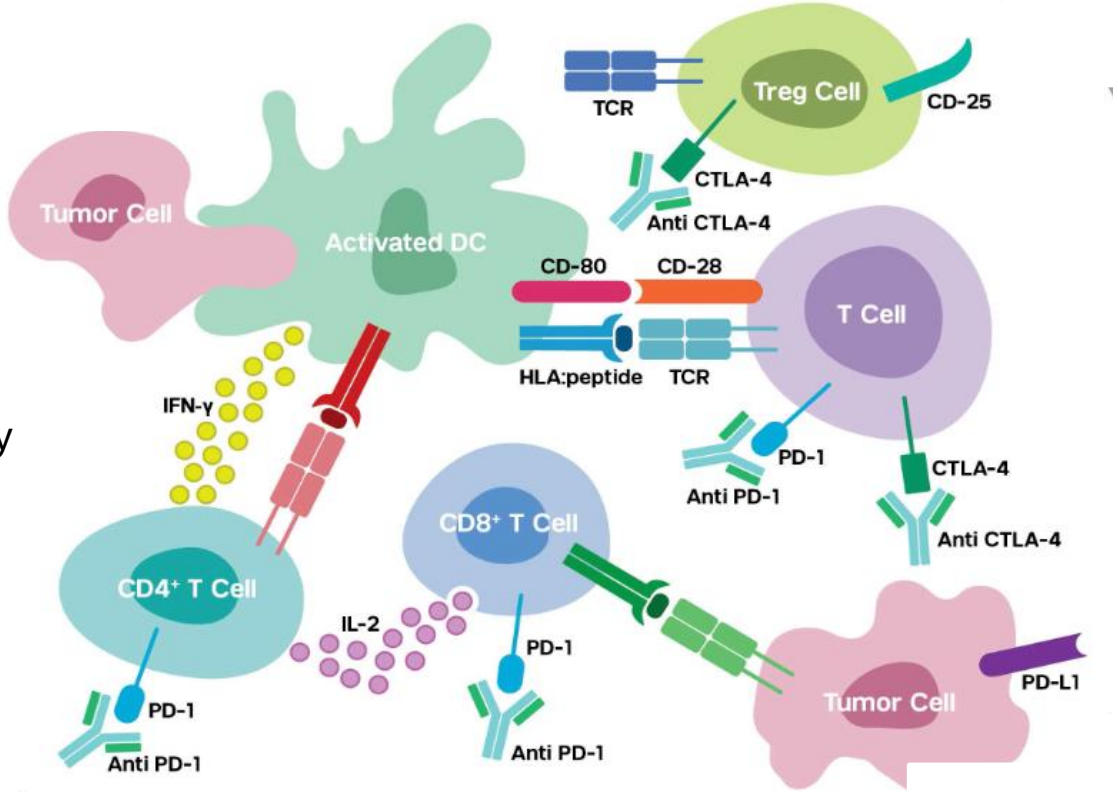


Louveau et al Nature 2015

Immunotherapy: Checkpoint Inhibition

Checkpoint inhibitors “release the brakes” on adaptive immunity by blocking regulatory signals on T cells

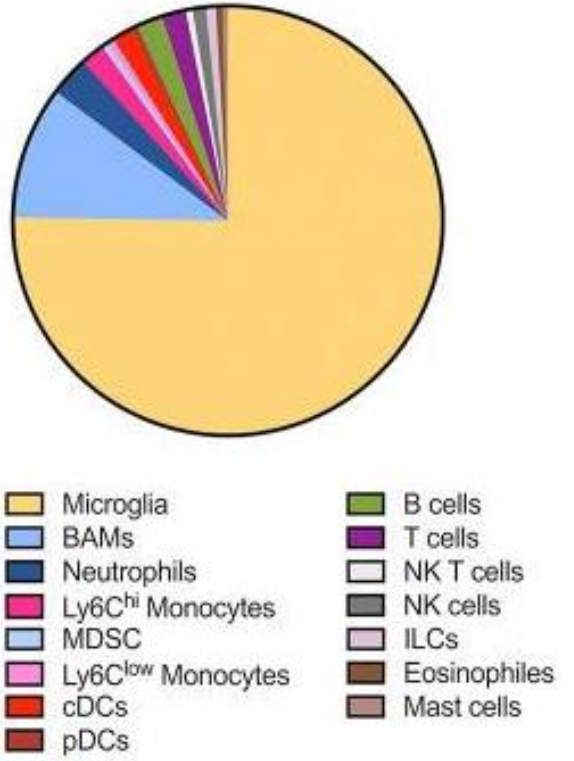
<u>Effects on T cell activity</u>
Reversal of exhaustion
Increased proliferation
Increased cytokine release
Enhanced tumor killing activity



Immunosuppressive Microenvironment of Brain Tumors

- Suppressive Immune Cell Infiltrates
  > myeloid suppressor cells
  > tumor associated macrophages
  > microglia (resident brain macrophages)
- These cell express high levels of PD-L1
- They secrete suppressive cytokines: TGF-b, IL10, IL6
- Low levels of $CD8^+$ T cells are present

Can this microenvironment be re-directed to activate anti-tumor immunity?



Immune Checkpoint Inhibitors for Brain Metastases

- Checkmate 067: phase III clinical trial evaluating monotherapy checkpoint inhibition with ipilimumab or nivolumab versus a combination of ipilimumab and nivolumab in patients with metastatic melanoma.

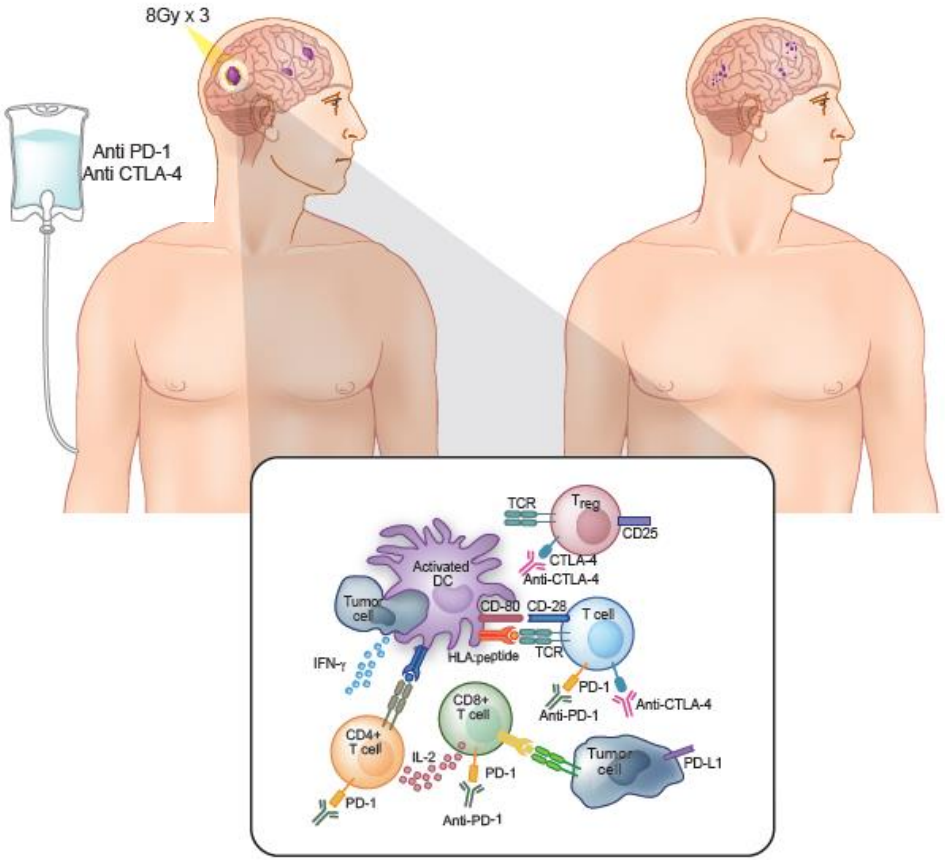
Ipilimumab + Nivolumab Cohort	Global	Intracranial	Extracranial
Best overall response, n (%)			
Complete response	4 (5)	**16 (21)**	5 (7)
Partial response	36 (48)	**25 (33)**	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease[a]	18 (24)	18 (24)	16 (21)
Not evaluable[b]	13 (17)	12 (16)	20 (27)

Ipi + Nivo Intracranial Response Rate = 54%

Tawbi, HA et al. N Engl J Med. 2018 Aug 23;379(8):722-730

Weill Cornell Medicine

Can SRS synergize with ICB to initiate anti-tumor responses in Brain Metastases?



Immune Checkpoint Inhibitors + SRS in melanoma

Ipi + Nivo (without SRS) Intracranial Response Rate = 54%

Memorial Sloan Kettering retrospective database of melanoma

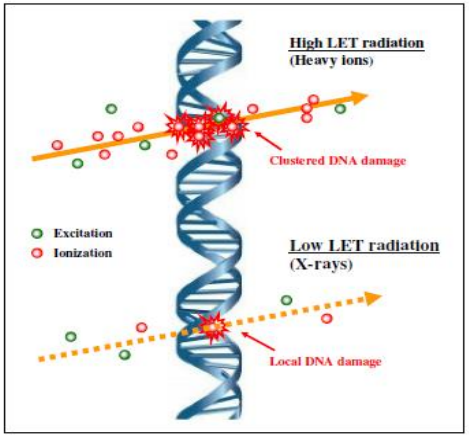
Immunotherapy + SRS	Intracranial response rate
Pembrolizumab + SRS	70%
Ipilimumab + SRS	32%
SRS	22%

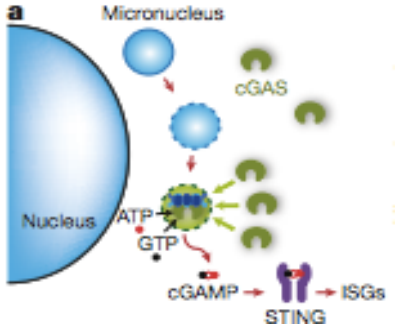
Anderson, ES et al. J Immunother Cancer. 2017; 5: 76

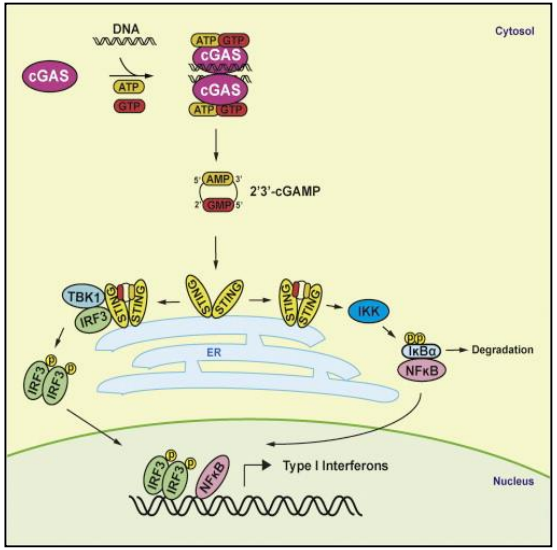
- The brain is not an immunological sanctuary
- Immune checkpoint inhibitors (ICB) are effective in melanoma brain metastases
- Radiation synergizes with ICBs, and the effect depends on the fractionation
- A protocol to test in brain immunization with SRS and anti-PD1 in metastatic breast cancer

Weill Cornell Medicine

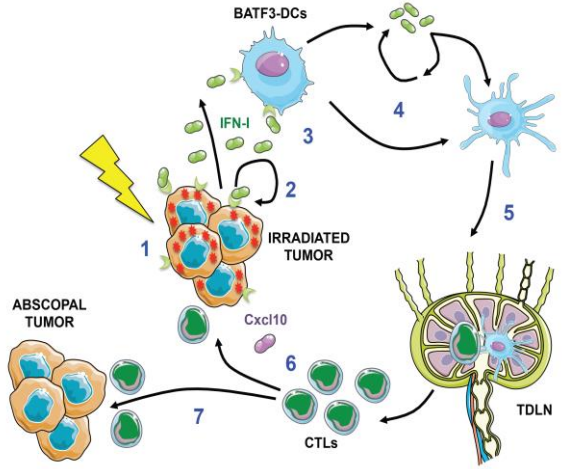
Viral mimicry of radiation: cytoplasmic dsDNA sensed by cGAS activates IFN-I pathway via STING







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

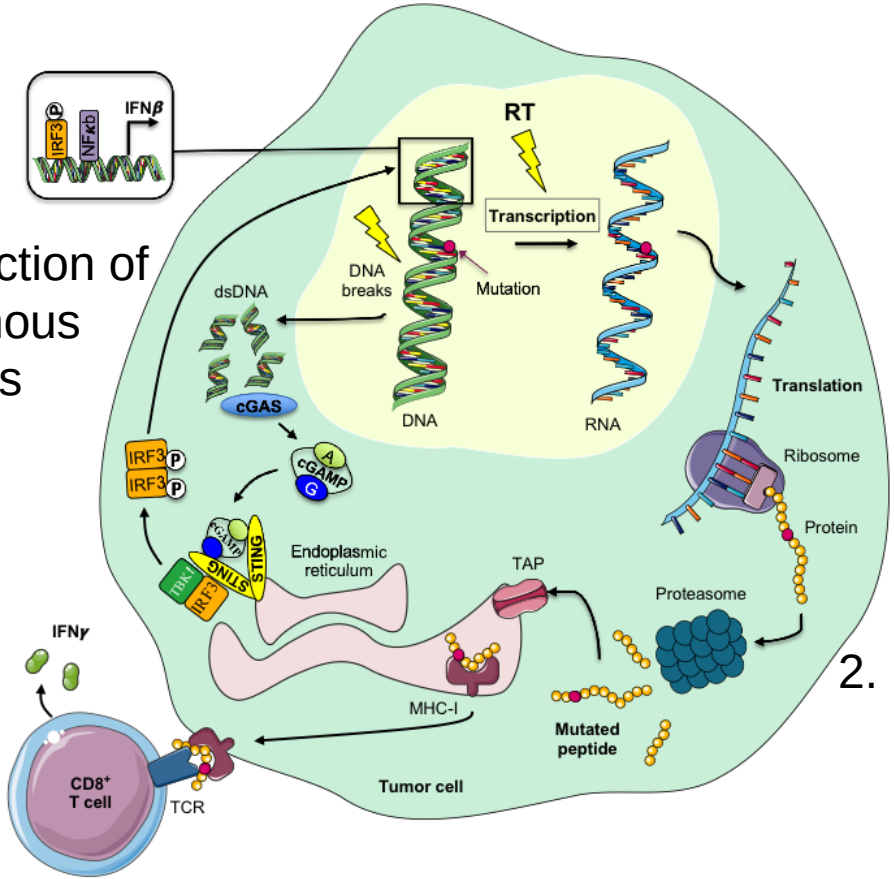


Claire Vanpouille-Box

Weill Cornell Medicine

Viral mimicry of *in situ* vaccination by focal RT

1. Production of endogenous adjuvants



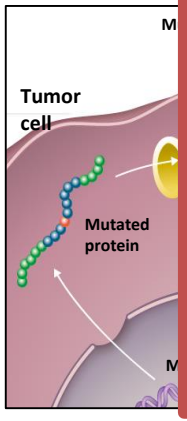
2. Exposure of neoantigens

Formenti et al Nature Medicine 2018

Lhuillier et al, Genome Medicine 2019

Weill Cornell Medicine

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

*24:02
*12:03

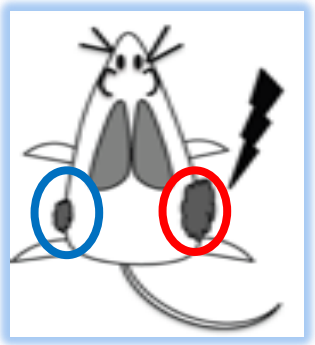
mt wt

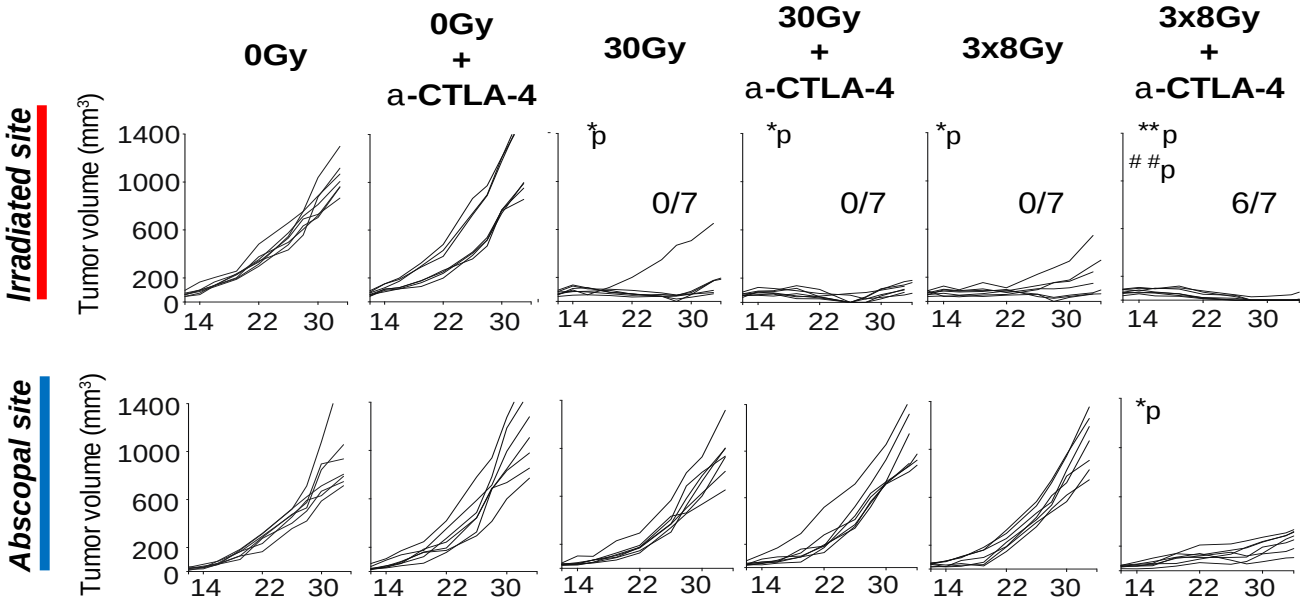
p15 ***not*** detected in pre-tx tumor
p16 detected in pre-tx tumor

Nature Medicine 2018

Weill Cornell Medicine

Dose and fractionation of radiation are consequential for the immune response

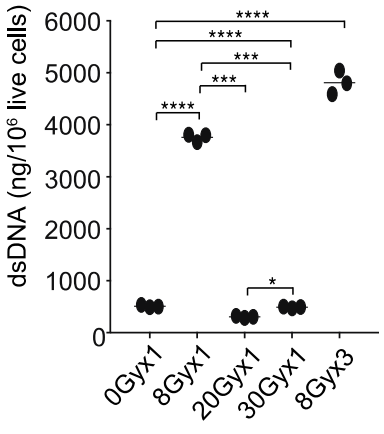


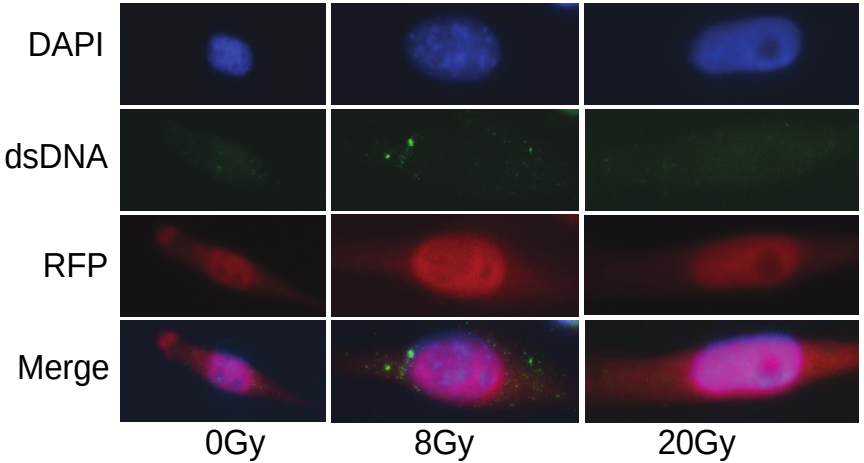


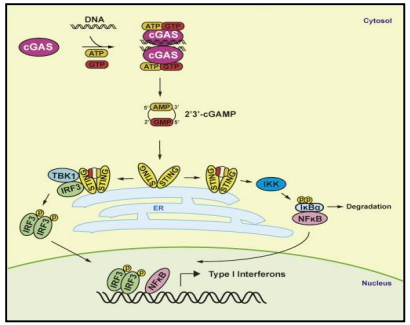
Vanpouille-Box et al., Nature Communications, 2017

Weill Cornell Medicine

Cytoplasmic dsDNA accumulation depends on RT dose per fraction



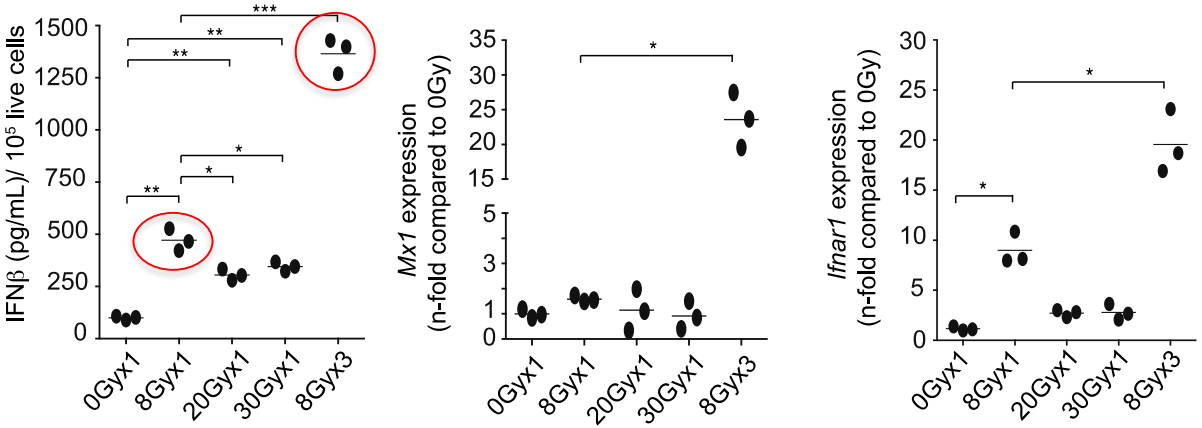




Cai X, ET AL ***Molecular Cell****. 2014;*

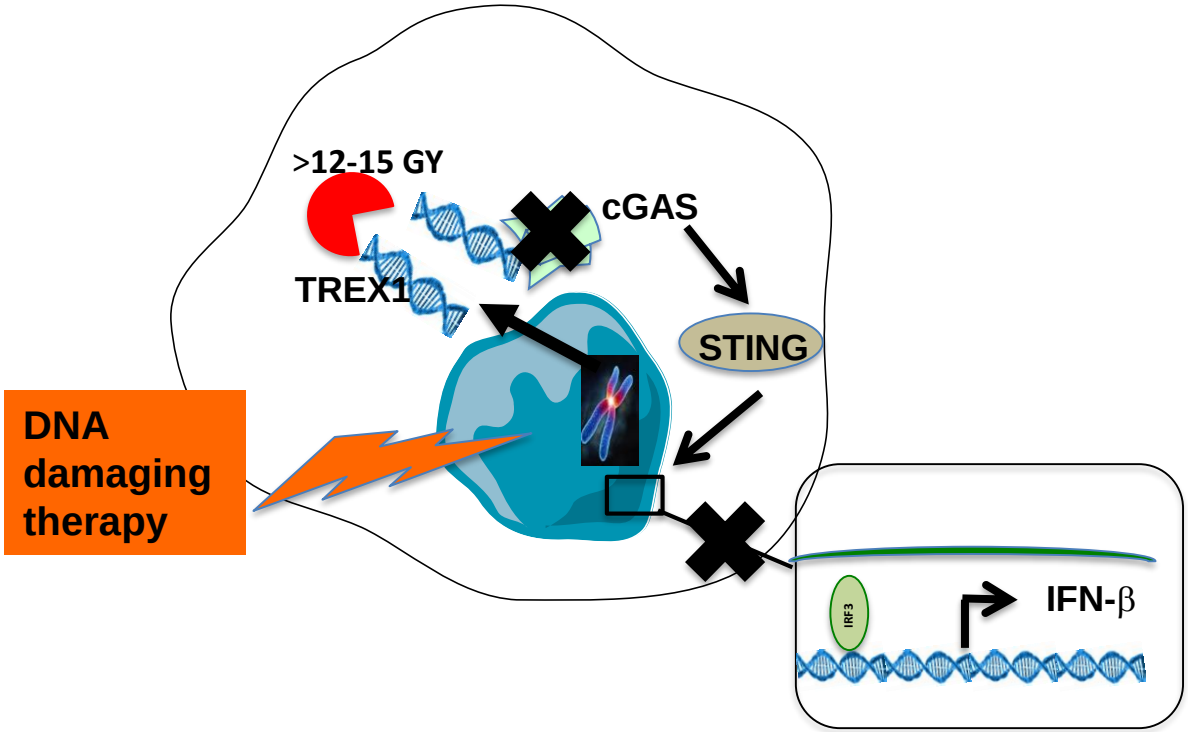
Vanpouille-Box et al., Nature Communications, 2017

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



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

Radiation Fraction Size, IFN-I and TREX1



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

- The brain is not an immunological sanctuary
- Immune checkpoint inhibitors (ICB) are effective in melanoma brain metastases
- Radiation synergizes with ICBs, and the effects depends on the dose per fraction
- A protocol to test in brain immunization with SRS and anti-PD1 in metastatic breast cancer

Weill Cornell Medicine

BREAST CANCER

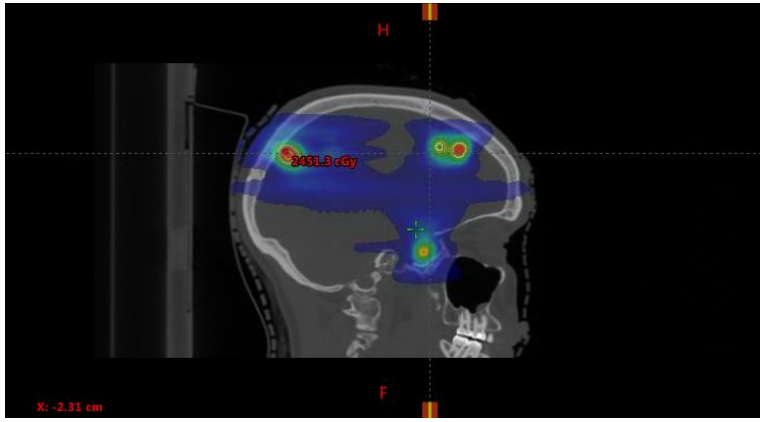
Site of relapse	Brain (%)
Autopsy cases[a]	
Median	21
Range	15–35
All subtypes[b]	12–17
Luminal A	8–15
Luminal B	11
TNBC/basal	25–27
HER2-positive	11–20

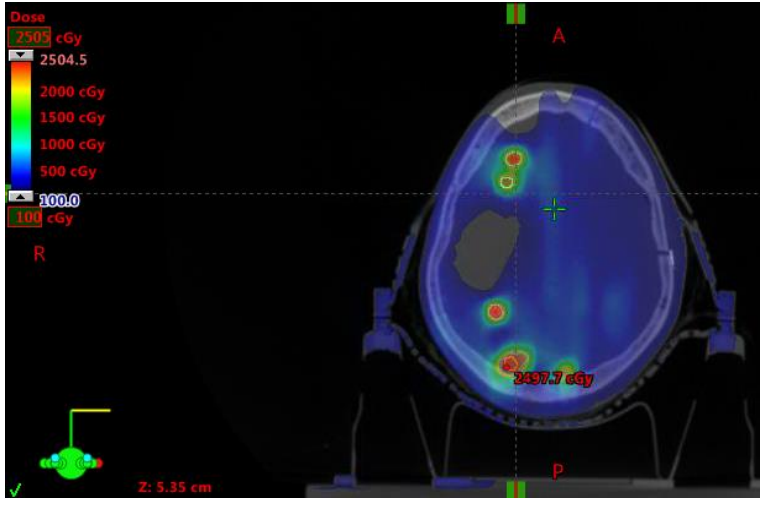
¼ of breast cancer patients, develop brain metastasis Independently from BC subtype

A trial for <u>all</u> BC patients with brain mets

Weill Cornell Medicine

Stereotactic Brain Radiation as an immune adjuvant





Background

- Standard SRS dose is 18-20 Gy

Preclinical data suggests that 8GyX3 is an optimally immunogenic radiation dose

- SRS of multiple metastases (>5) exposes an increased volume of normal brain tissue to a significant dose

If a subset of irradiated lesions could prime an abscopal effect, fewer lesions would need to be treated

More brain tissue could be spared

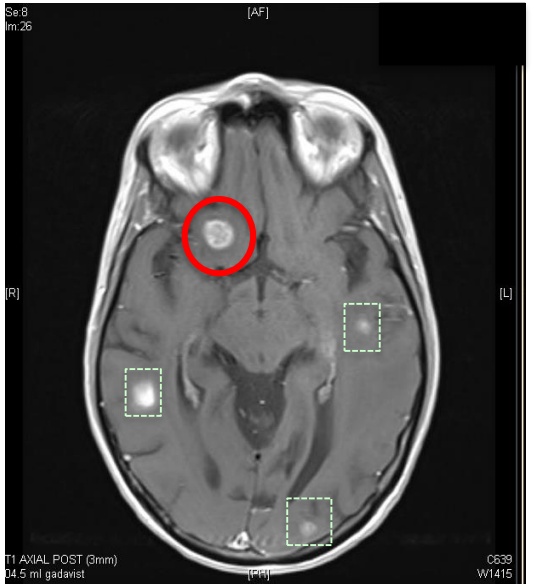
Clinical Trial
NCT03449238

Metastatic breast cancer patients with at least 2 new brain metastases

Day 1 Pembrolizumab 200mg IV
Repeated every 3 weeks until disease progression in the brain or unacceptable toxicity

SRS to target lesions 8Gy x 3, Day 2, 3, 4
Observation of **at least one** untreated lesion (until MRI progression)
Collection of blood specimens

MRI Surveillance every 8 weeks
Endpoints: 1. Response in (a) treated brain lesion (b) untreated brain lesions 2. Time to new brain lesions 3. Systemic disease



The irradiated metastasis = an *in situ* vaccine

NCT03449238

Inclusion criteria

- Men and Pre- or Post-menopausal women
- ECOG performance status of 0-1
- Maximum diameter of treated lesions < 4cm
- Prior SRS is permitted, but the lesions treated on trial must have not been previously treated
- Two week washout from last systemic treatment
- Continuing a concurrent use of hormonal tx allowed
- Sufficient bone marrow reserve and liver function based on laboratory criteria

Exclusion criteria

- Active connective tissue disorders (lupus, scleroderma)
- Current use of chemotherapy or HER2 targeted therapy
- Prior checkpoint inhibitor therapy
- Prior radiation therapy within 2 weeks of start of study Receipt of a live vaccine within 30 days of first dose of Pembrolizumab
- Receipt of an investigational study agent within 30 days of trial therapy
- History of pneumonitis that required steroids

Clinical Case: Patient LM

CC: 47 y.o female with brain metastases secondary to HER2+ breast cancer

9/2010: 40 y.o. diagnosed with a ER negative HER2+ left breast cancer

3/2016: brain metastases (>30), **whole brain radiation therapy (30 Gy in 10 fractions**);

8/2017: MRI progression left thalamus and the right hippocampus mets with surrounding edema. **SRS, 18Gy single fraction**.

10/2017: **MRI: significant progression** increase in size and number of supratentorial and infratentorial brain metastases

11/2017: **Start pembrolizumab** (compassionate use)+ **SRS, 8GyX3** to two progressive lesions left cerebellum and left temporal
11/2017: post –treatment headaches, dizziness requiring steroids
12/2018: Second cycle of pembrolizumab

1/2018: MRI significant OR in post-SRS lesions as well as in several untreated ones

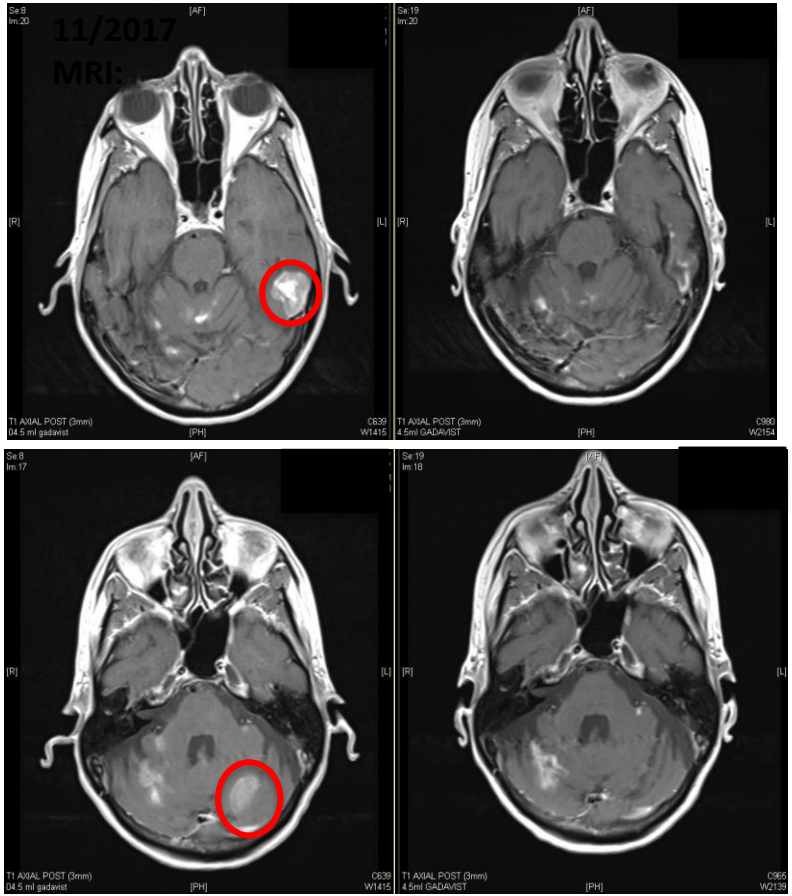
Patient: LM

Pembrolizumab x 2

8Gy x 3
L temporal lesion

8Gy x 3
L cerebellar lesion

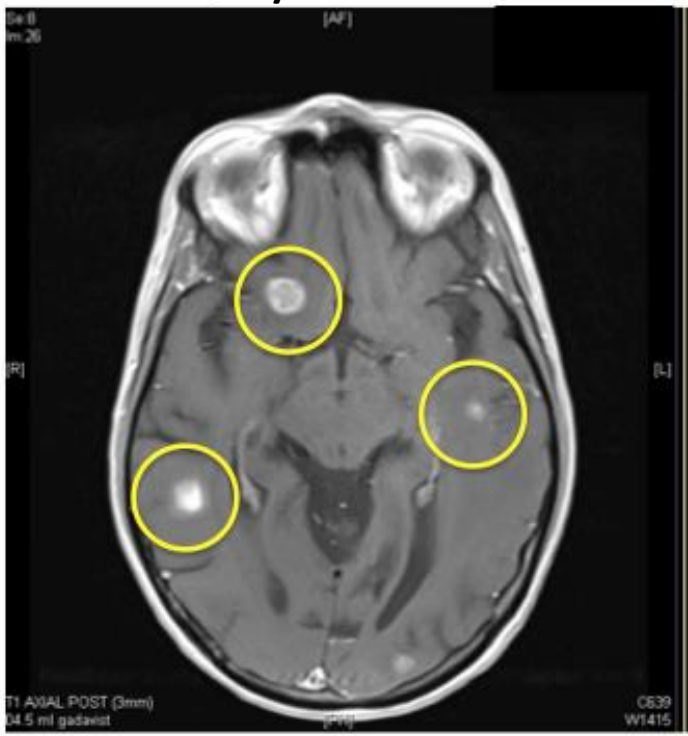
- **11/2017 MRI:**
- **1/2018 MRI:**



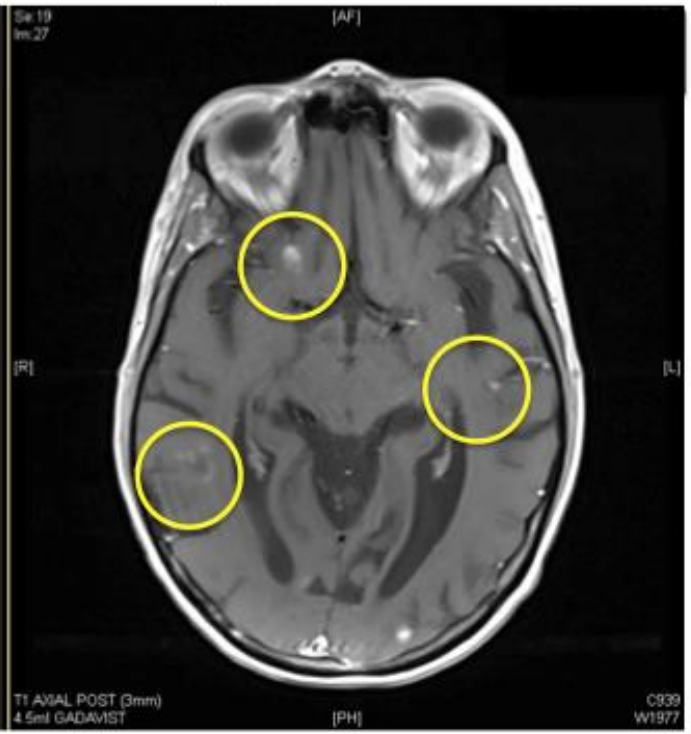
Weill Cornell Medicine

Monitored brain metastases during Pembrolizumab

11/2017 MRI

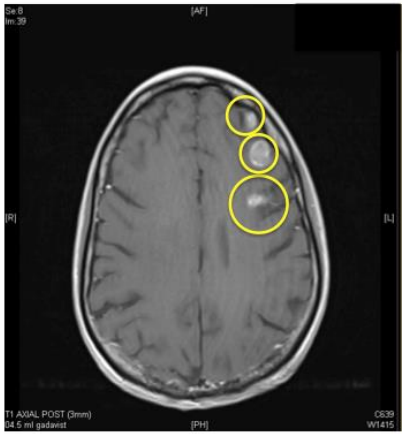


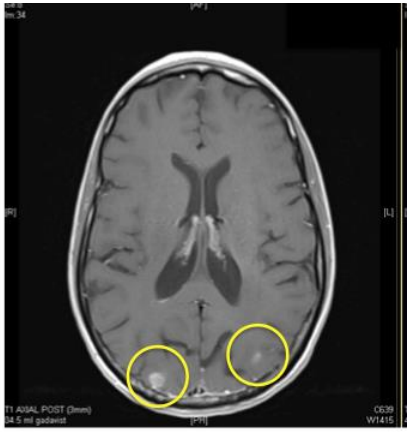
1/2018 MRI



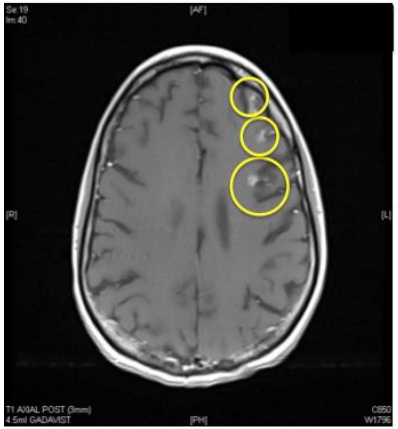
Weill Cornell Medicine

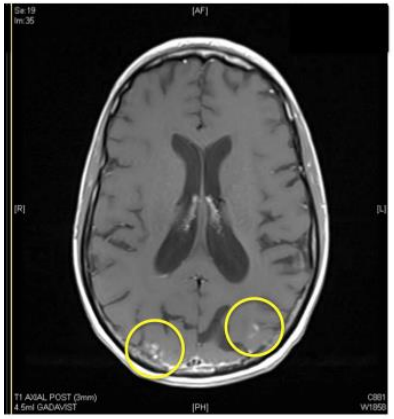
11/2017 MRI





1/2018 MRI





Weill Cornell Medicine

RADIATION & IMMUNITY PROGRAM

Silvia C. Formenti
Encouse Golden
Josephine Kang
Andrew Brandmeier
John Ng
Himanshu Nagar
Eric Ko
J. Keith Dewyngaert

Preclinical Core
Karsten Pilones
Camille Daviaud
Jeffrey Kraynak

Clinical Core
Maria Fenton
Sharanya Chandrasekhar
Pragya Yadav

Sandra Demaria
Claire Vanpouille-Box
Julie Diamond
Erik Wennerberg
Claire Lhuillier
Nils Rudqvist
Sheila Spada
Maud Charpentier
Samantha Van Nest
Yasmeen Sarfraz
Maria Rodriguez-Ruiz

Lorenzo Galluzzi
Takahiro Yamazaki
Aitziber Buque
Ai Sato
Marissa Friedman
Jonathan J.

WCM Biostatistics & Epidemiology
Xi Kathy Zhou

NYU
Abraham Chachoua
Benjamin Cooper
Kent Friedman
Adriana Heguy
Robert Schneider
Beatrix M. Ueberheide
Jessica R. Chapman

Mount Sinai
Sacha Gnjatic
Naoko Imai

NIH, NCI Radiation Branch
Molykutty J. Aryankalayil
Norman Coleman

FUNDING
National Cancer Institute R01 CA201246 & R01 R01CA198533
The Chemotherapy Foundation
BCRF
NYU Vittorio Defendi Fellowship in Pathobiology


THE
FLASH

Weill Cornell Medicine

FLASH History

1959: Oxygen Effect Reduction.

Dewey and Boag noted reduced oxygen effect in bacteria during pulsed e- beams of 100-200 Gy per 2µsec

1971: High Dose Rate RT causes hypoxia.

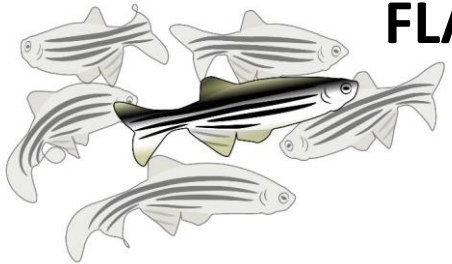
Hornsey and Bewley showed evidence that high dose rate electron beams induces hypoxia (16.7 - 83.3 Gy/s compared with 1 Gy/s)

2014: FLASH is reborn.

Favaudon et al published report on differential response to FLASH (≥40 Gy/s dose rate) between normal and tumor tissue in mice

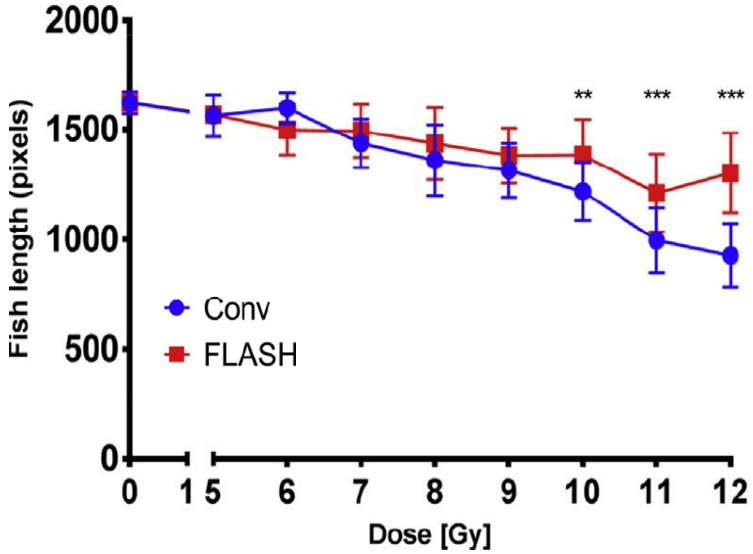
Julianne Pollard-Larkin, "FLASH Photon: One small step for Physics, One huge leap for cancer therapy" AAPM 2019 talk

Weill Cornell Medicine



FLASH effect observed in developing zebrafish embryos

- 4 hours post-fertilization Eggs were given 5-12 Gy delivered with FLASH vs conventional dose rate irradiation.
- RT-induced alteration of zebrafish morphology was assessed 5 days post-fertilization (5dpf) by body length measurement.
- FLASH radiotherapy induced lower morphological alterations than conventional radiotherapy at doses above 10 Gy.



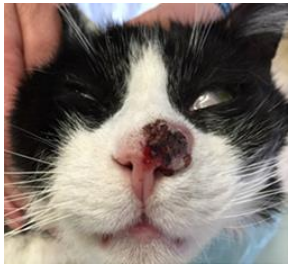
Weill Cornell Medicine

FLASH Dose Escalation Trials in Cats

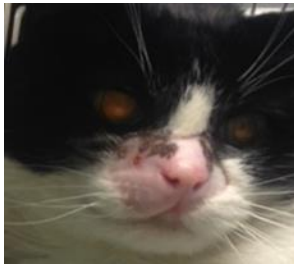
- 6 cats with SCC of nasal planum
  - Four cats -T2
  - Two cats -T3.
- Single doses of irradiation ranging from 25 to 41 Gy

- Maximal tolerated dose (MTD) not reached
- Minimal or mild mucosal and skin reactions
- No major disturbance of food intake and no subsequent late side-effects

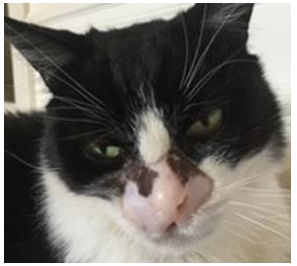
- Tumor control probability = 84% at 1 year.
- Additional studies ongoing at the CHUV



Before RT



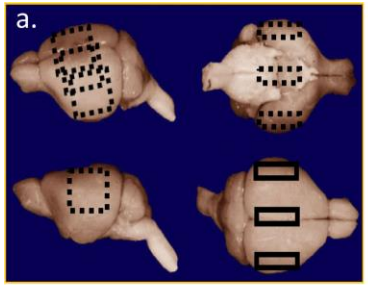
7 month Post FLASH

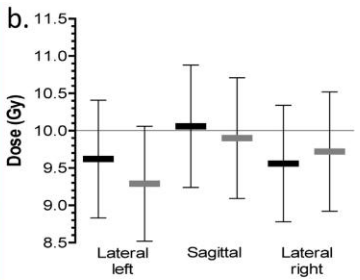


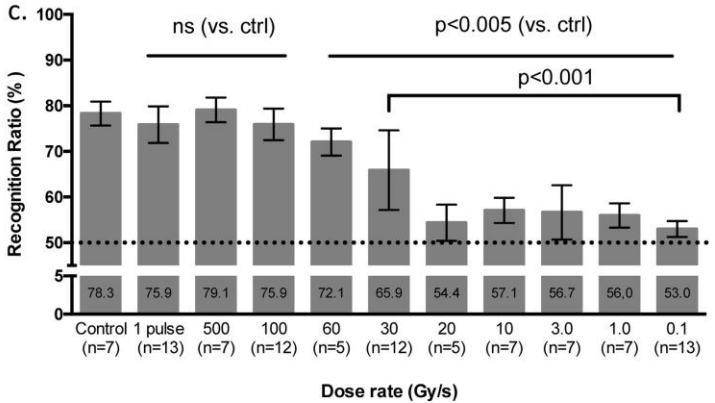
14 months post-FLASH

Weill Cornell Medicine

Sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s







a: TLD chips positions at the center of the brain (sagittal) and at either side of the brain (Lateral left and right);

b: measurement results for a 10 Gy WBI delivery with a single 1.8 µs electron pulse (filled markers) and at a 0.1 Gy/s dose rate (open markers).

c: Evaluation of the Recognition Ratio (RR) two months post irradiation for groups of mice that received sham irradiation (Control) and 10 Gy WBI with a different dose rates 0.1 - 500 Gy/s, and with a single 1.8 ls electron pulse (1 Pulse).

Weill Cornell Medicine

Radiotherapy and Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

An integrated physico-chemical approach for explaining the differential impact of FLASH versus conventional dose rate irradiation on cancer and normal tissue responses

Douglas R. Spitz [a,*], Garry R. Buettner [a], Michael S. Petronek [a], Joël J. St-Aubin [a], Ryan T. Flynn [a], Timothy J. Waldron [a], Charles L. Limoli [b]

[a] Free Radical and Radiation Biology Program, Department of Radiation Oncology, Free Radical Metabolism and Imaging Program, Holden Comprehensive Cancer Center, The University of Iowa, United States; and [b] Department of Radiation Oncology, University of California, Irvine, United States

Spitz et al. suggest that

FLASH may convert all endogenous oxygen into organic hydroperoxides (ROOH) in all tissues, but ROOH are handled preferentially by normal cells through better antioxidant pathways

Clear clinical advantage of FLASH-RT

- Dose delivered in milliseconds shortens treatment time
- Organ or tumor motion-effect is eliminated
- Target margin can be reduced, hence reducing the volume of healthy tissue irradiated
- Potential of fewer treatments (improved tolerance/efficacy)
- Immune effects?

Weill Cornell Medicine

institutCurie

Stanford MEDICINE

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Penn Medicine

CHUV

Weill Cornell Medicine

Columbia University Medical Center

NewYork-Presbyterian

Weill Cornell Medicine

A FLASH device can be built by modifying a conventional LINAC as demonstrated by Stanford and MDAnderson

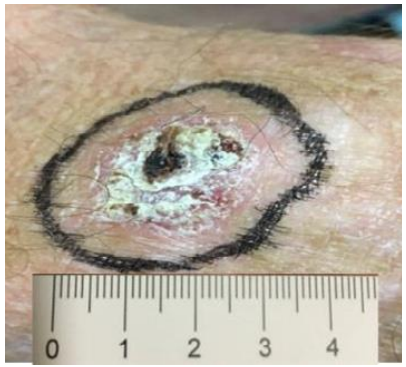
- FLASH dose rate can be achieved on Klystron driven accelerator when operating at photon beam current settings but delivering electrons

- Decommissioned Varian IX (MDA) was modified to deliver 20MeV electrons ≥35 Gy/s at the level of the mirror inside the collimator

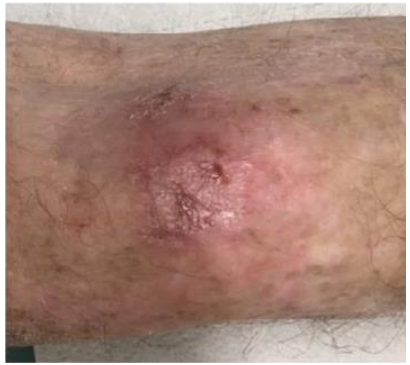
Weill Cornell Medicine

Treatment of a first patient with FLASH-radiotherapy had a favorable outcome both on normal skin and the tumor.

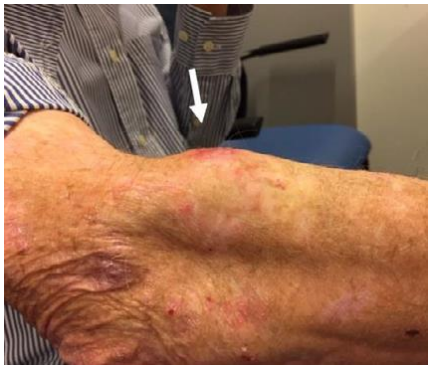
Day 0



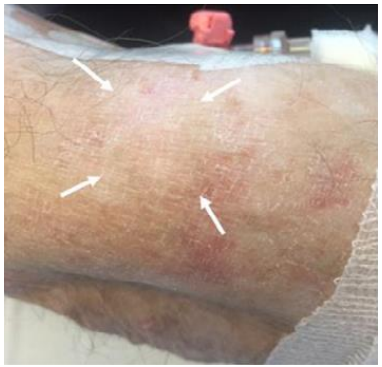
3 weeks



transient edema (max)



5 month



- A 75-year-old patient with a multiresistant CD30+ T-cell cutaneous lymphoma
- Localized skin RT has been previously used over 110 times: KV X-rays, low energy electrons, or MV X-rays, depending on tumor sites and volumes. 20 Gy/10 fxs or 21 Gy/6 fxs, tolerance of the skin was generally poor or very poor.
- **5.6-MeV linac specifically designed for FLASH-RT @ Lausanne University Hospital with prescribed dose to the PTV: 15 Gy, in 90 ms.**
- The tumor started to shrink around 10 days after irradiation, with a complete tumor response at 36 days durable for the subsequent 5 months
- Between days 12 and 24, a grade 1 edema was observed, situated under the skin, surrounding the tumor, unique to the FLASH-RT

J. Bourhis, W. J. Sozzi, P. G. Jorge et al., Treatment of a first patient with FLASH-radiotherapy, Radiotherapy and Oncology

CONCLUSIONS

- The combination of SRS with ICB holds promise, and should be tested at different fractionation (single versus hypo-fractionated)

- FLASH/GRID also hold promise, particularly for their potential to spare late neurocognitive sequelae of brain radiotherapy