Combining Radiation Therapy and Immunotherapy: A Paradigm Shift

Punta Cana, Republica Dominicana

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VI CONGRESO ALATRO

Asociación Ibero Latinoamericana de Terapia Radiante Oncológica

Memorial
Cancer Institute

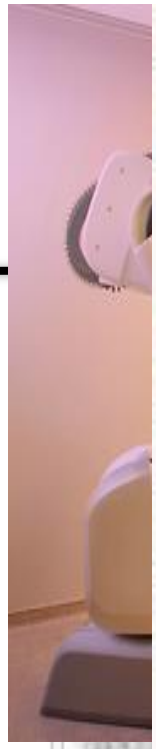
Path Road

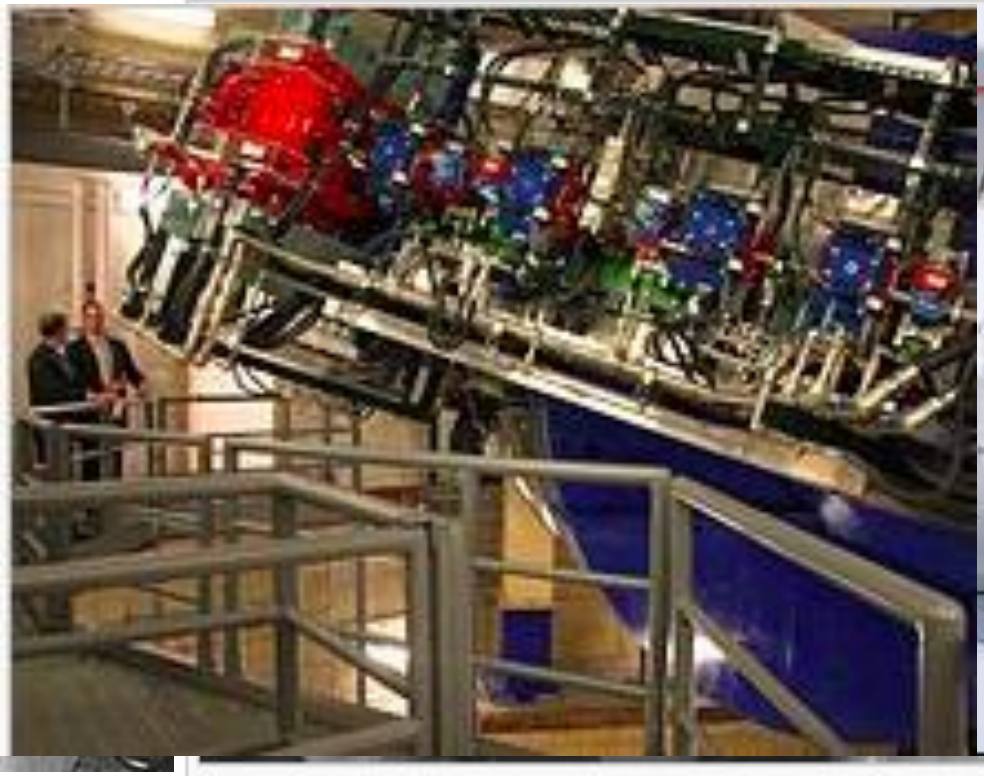
- Summarized Clinical Trials combining Immunotherapy and Radiation (IO+RT)
- To discuss considerations in RT+IO clinical design such as endpoints and response criteria

Impressive Advancements in Radiation Therapy Technology in the Past 100 years

1950's

Cobalt machine





Goal: Increase local control and decrease side effects

Improvements in Radiation Therapy

- More precise target definition
- Correction for heterogeneity
- Better understanding of normal tissue tolerance
- Image-guided radiation therapy that minimizes normal tissue margins and reduces missed target

Ionizing Radiation

Historically, therapeutic application of the IR is based on:

- Its cytocidal power
- Ability to selectively target tumors

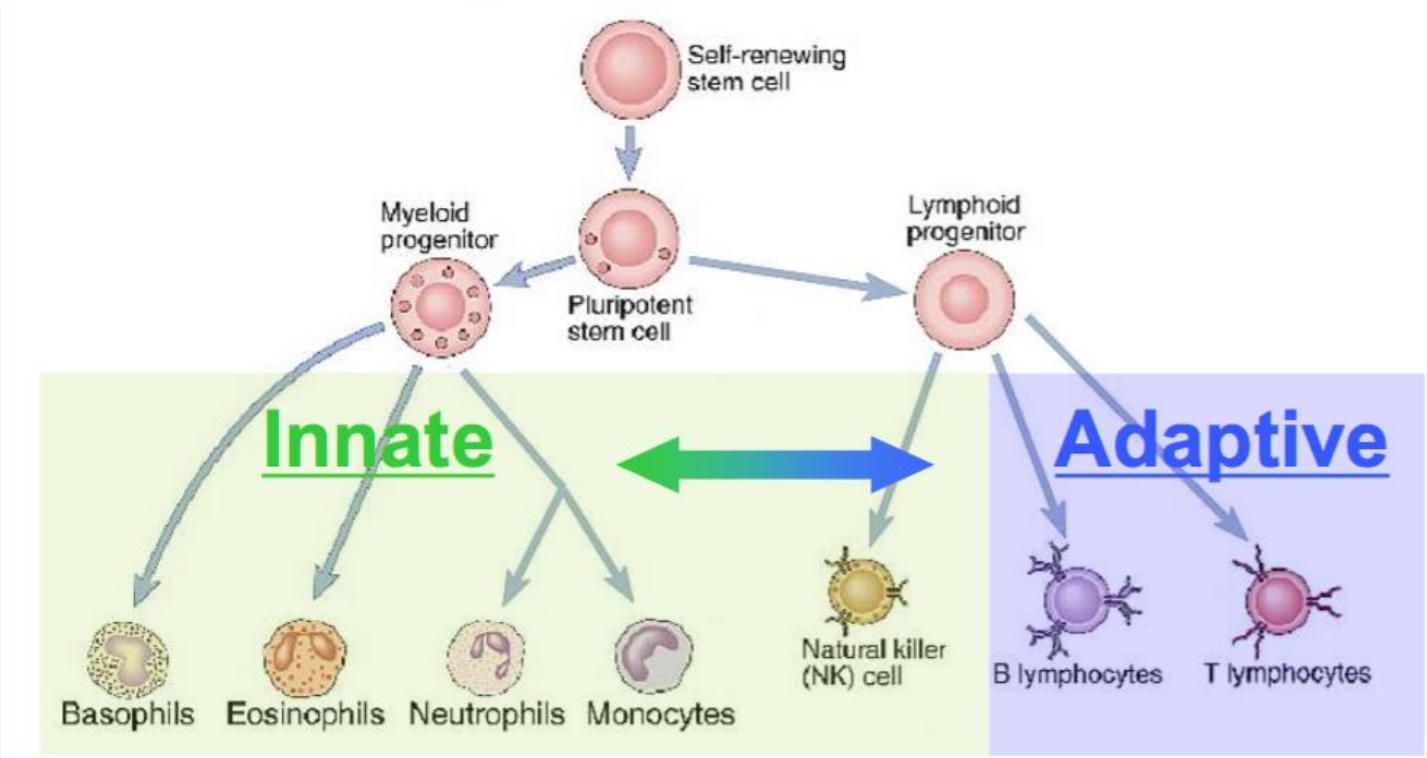
Radiation affects cancer patients survival:

- Improve LC of the tumor
- Decreasing systemic spread

Immunotherapy System

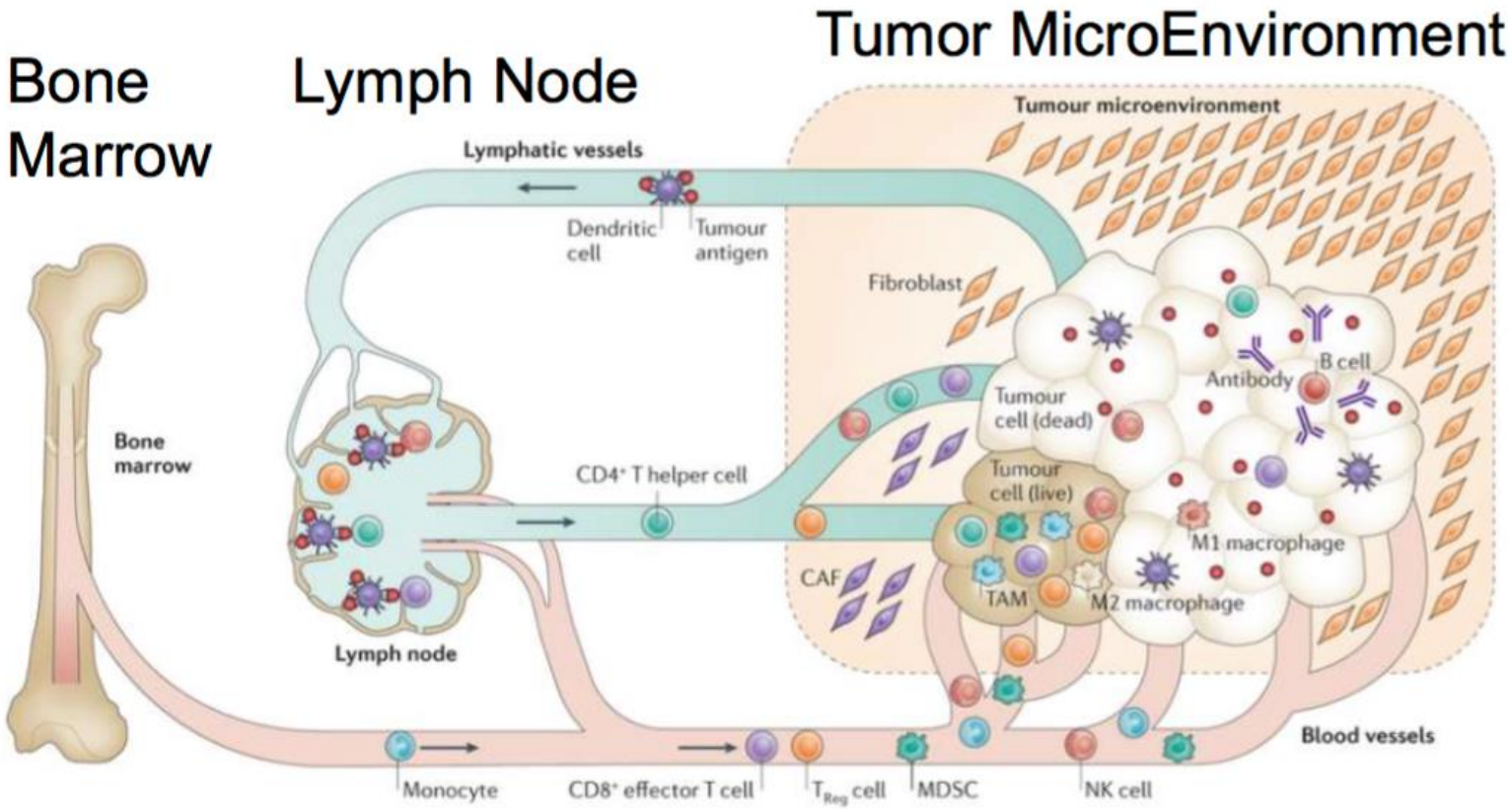
- The immune system plays a key role in controlling and eliminating multiple different types of malignancies (Immuno-surveilance)
- Attempts at directly activating the immune system with positive stimuli have had a limited efficacy
- Checkpoint blockade immunotherapy has revolutionized immunotherapy and oncology
- Radiation may promote key steps in the development of immune responses

Cells of the Immune System

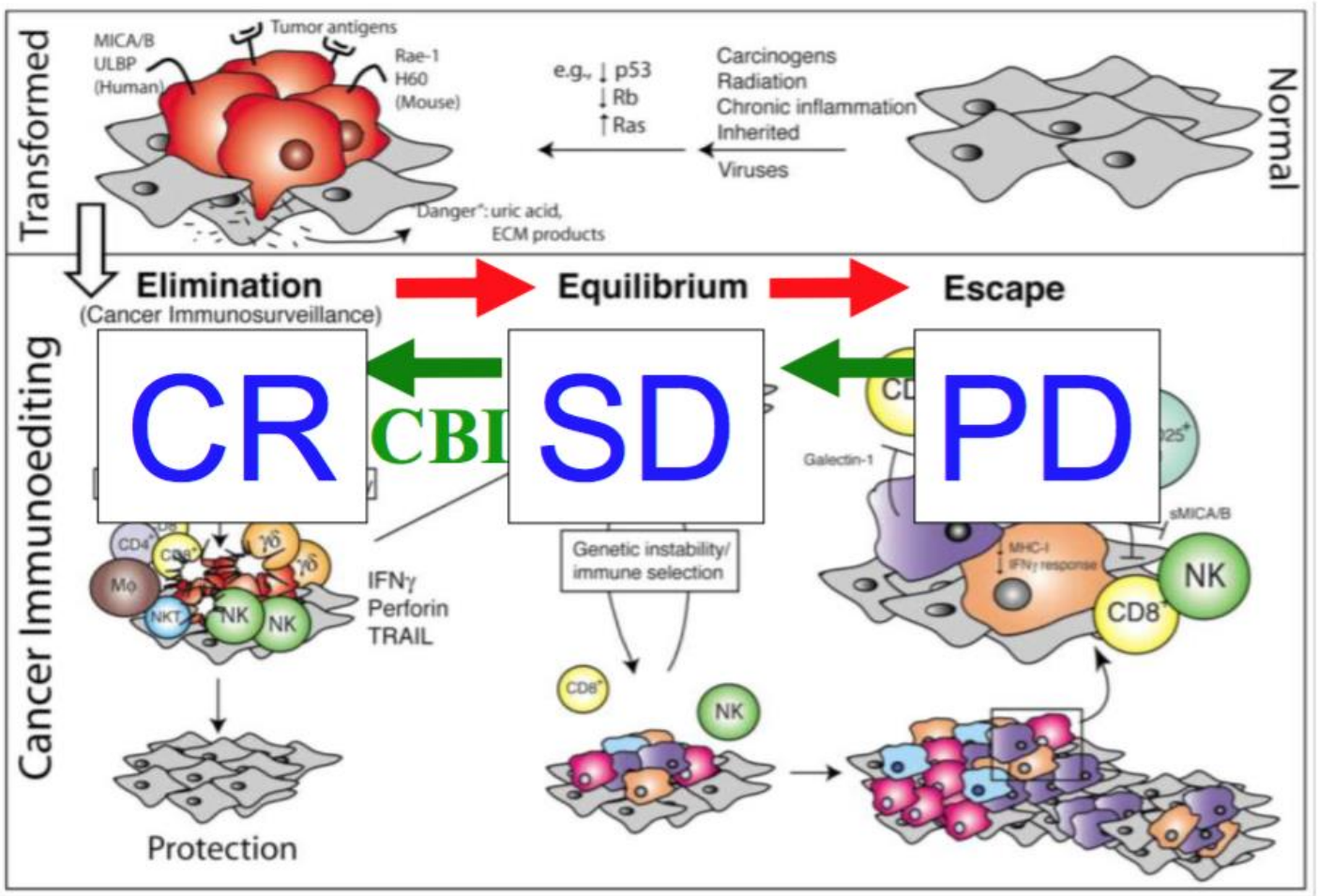


Degranulation Inflammation Chemo-Attraction	Allergies Parasite and Worm Defense	General Attack Bacterial Phagocytosis Tissue Lysis	Antigen Presentation Phagocytosis Cleanup	Tumor Surveillance Antibody Dependent Cytotoxcicity	Antibody Production Antigen Presentation	Immuno Regulation CD4 Helper Responses CD8 mediated cytoxcicity

Flow of the Immune Cells



Cancer Immunoediting



Dunn GP, Old LJ., Schreiber RD. Immunity 2004

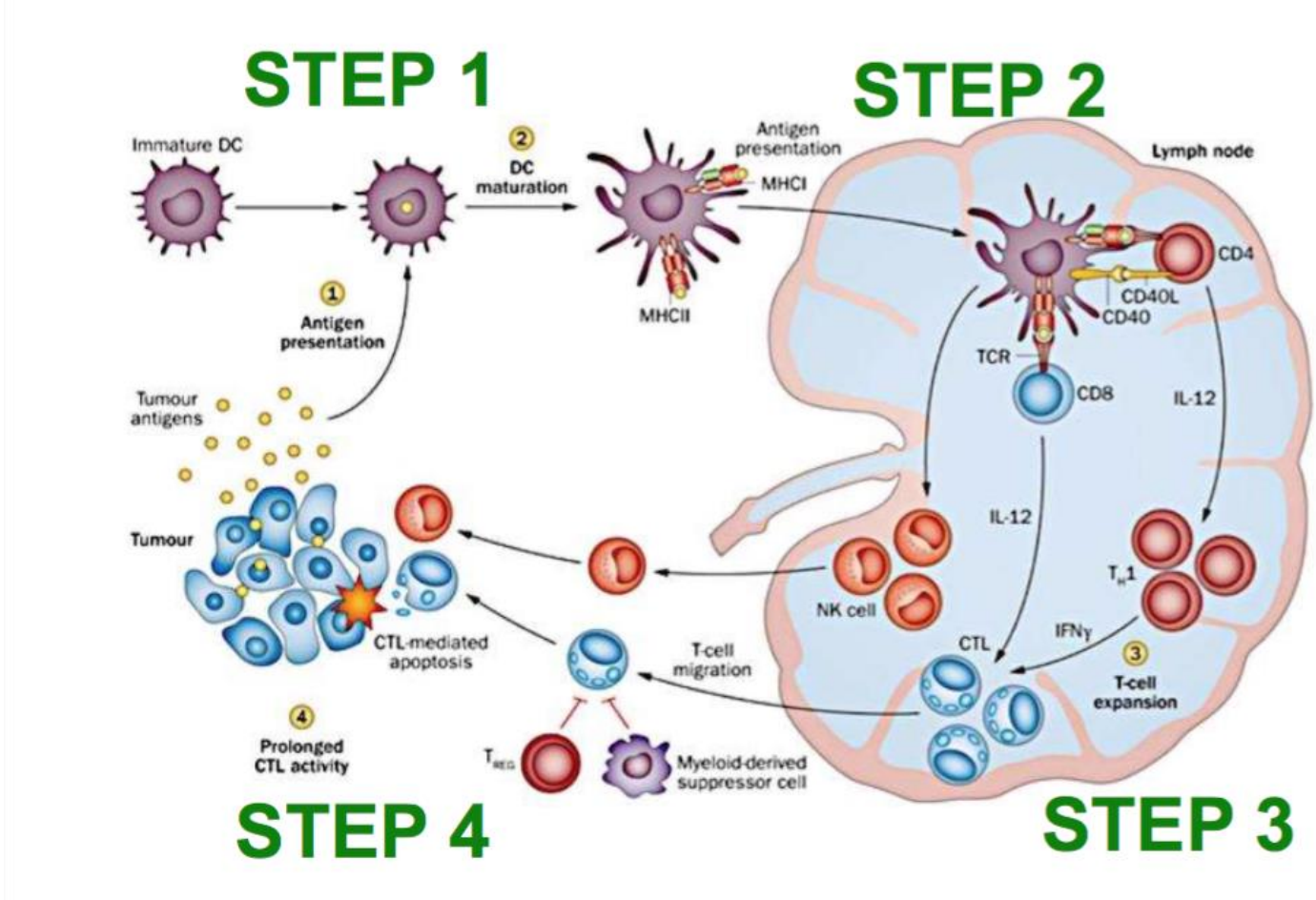
QUESTION

What are the steps required to generate an antigen specific T-cell mediated immune response?

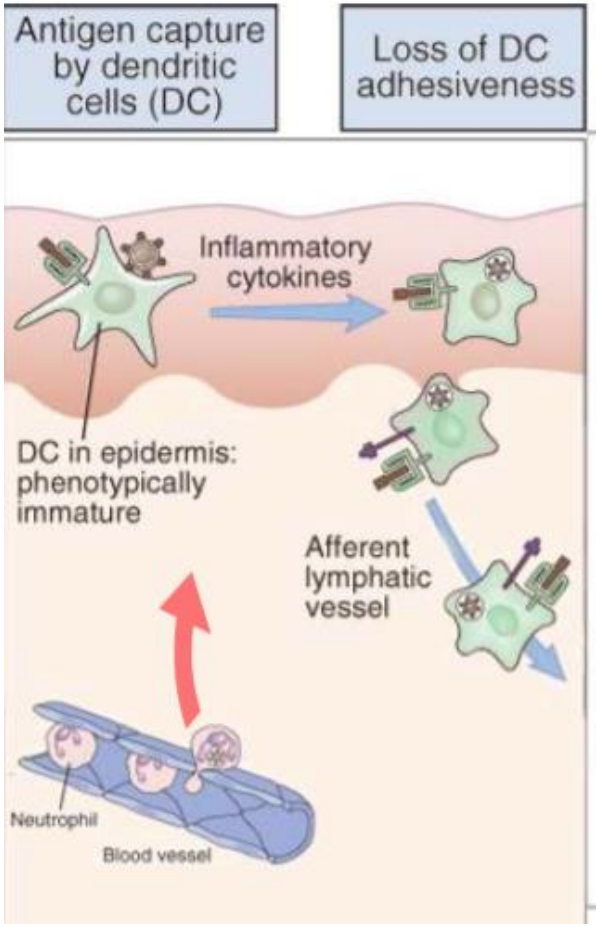
Steps to Generate a Cytotoxic Adaptive Immune Response

- Inflammation, antigen uptake and antigen-presenting cells (APC) maturation
- Migration to the lymph node and antigen processing and presentation
- T-cell priming and clonal expansion
- Cytotoxic effector response, tumor clearance and memory

Sequence of Steps of Cytotoxic Adaptive Immune Response



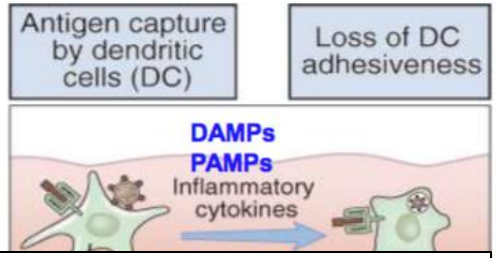
Step 1: Inflammation, Antigen Uptake and APC Maturation



Step 1: Inflammation, Antigen Uptake and APC Maturation

The Professional APC's:

- Dendritic cells!
- **Macrophages:**
  - **Langerhan**
  - **Microglia i**
  - **Kupffer ce**
  - **Alveolar m**
- B cells



Radiation induces immune-mediated cell death and DC maturation

1) F
m
phagocytosis of tumor cells.

2) Radiation induces DAMPs which result in DC maturation

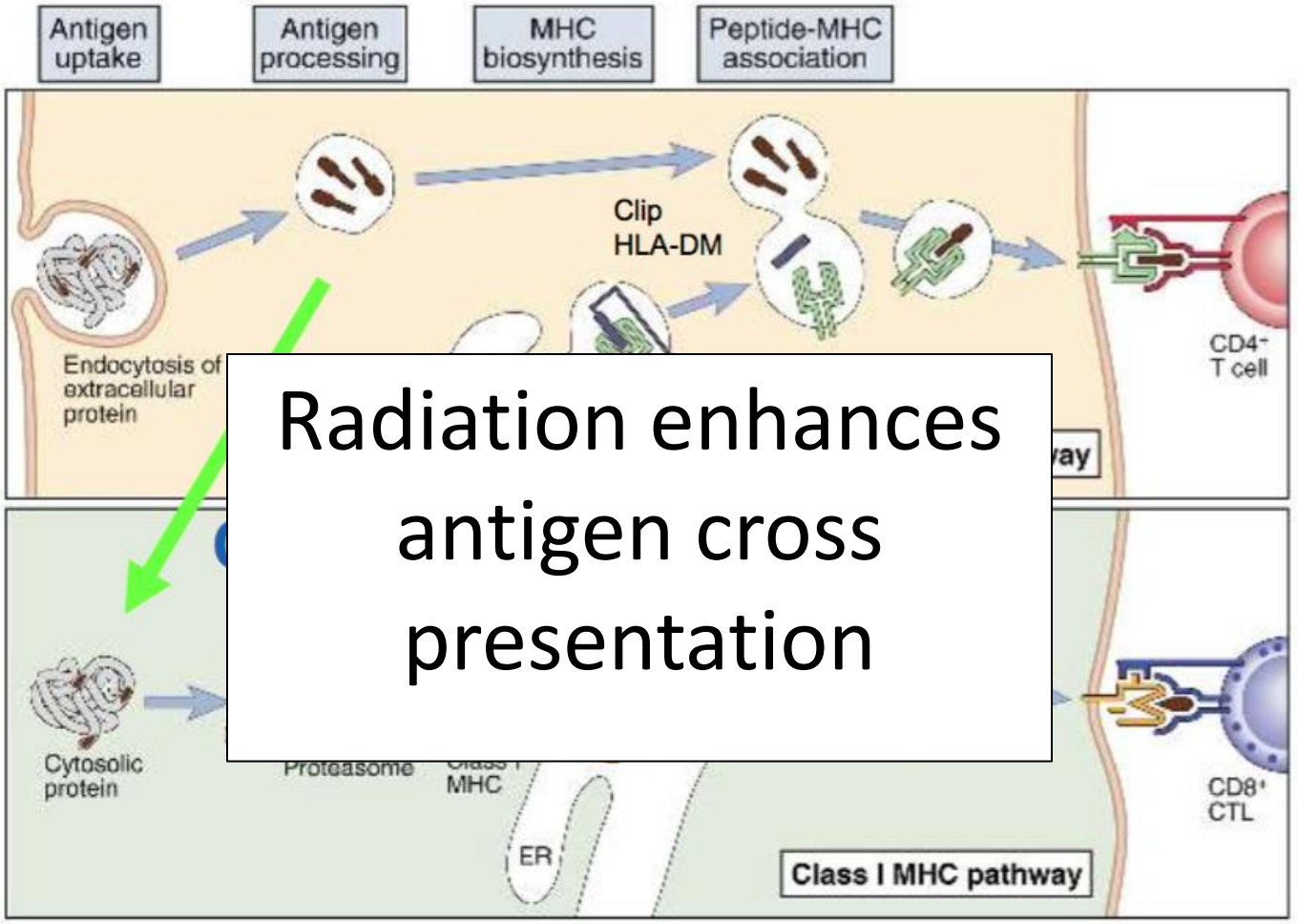
se enhance antigen cross presentation

Radiation Modifies Antitumor Immune Responses

- DNA damage and free oxygen radicals
- Inflammatory tumor cell death
- Activation of the damage-associated molecular patterns (high mobility group box chromosomal protein 1)
- HMGB1 activates antigen-presenting cells

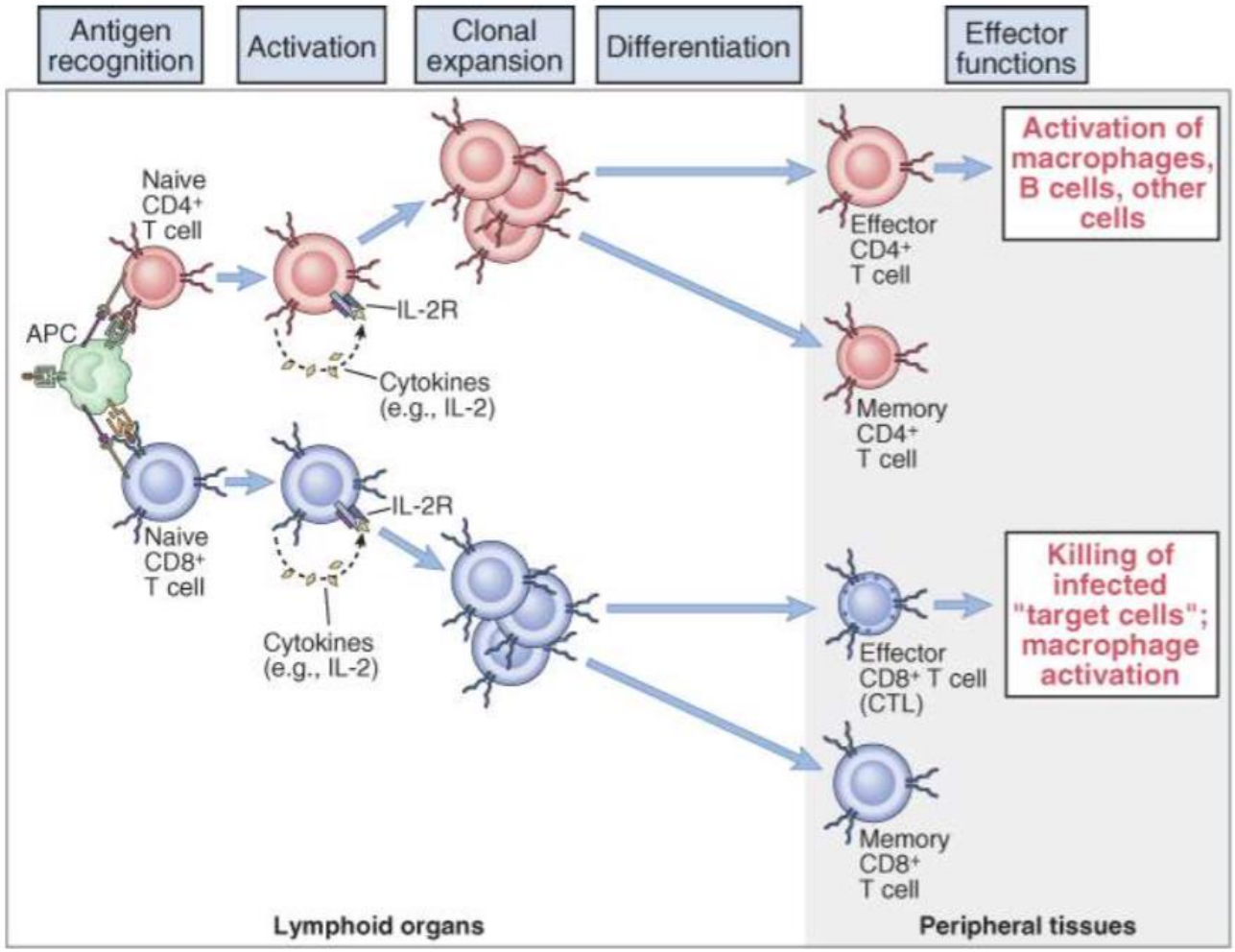
Up regulation of major histocompatibility complexes (MHCs) increasing presentation of antigens on the surface of tumor cells

Step 2: Antigen Processing and Cross Presentation



Radiation enhances antigen cross presentation

Step 3: T-cell Priming and Clonal Expansion



Step 4: CD8 T-cell mediated Cytotoxicity

Two Main Mechanisms of
T-cell mediated cell death:

Radiation induces FAS/FAS-L
and upregulates MHC!

1) FAS/

Radiation induces FAS
and up regulates MHC

2)
Perfo
zyme

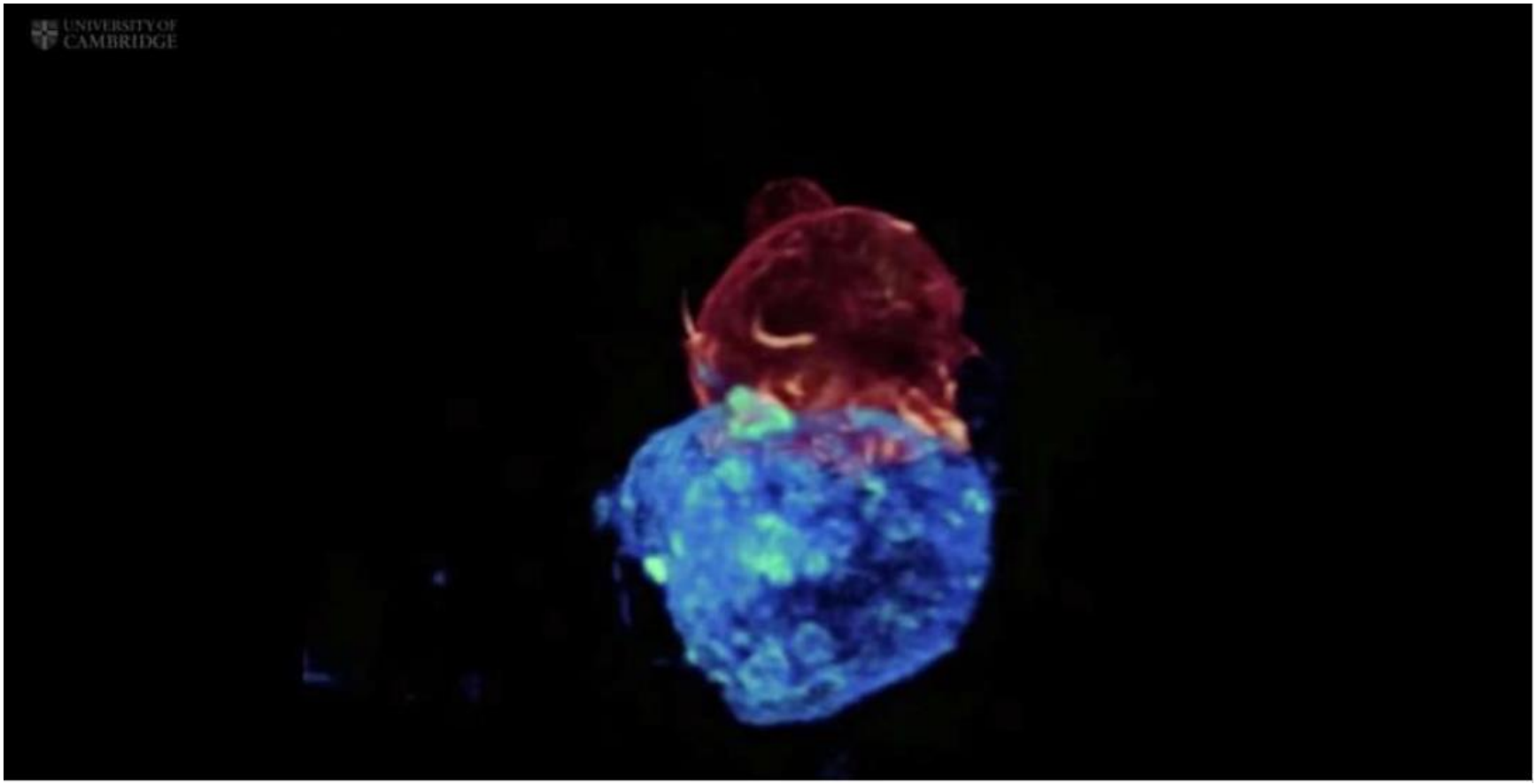
Trapani JA1, Smyth MJ. ***Nature Reviews Immunology*** 2002 Oct;2(10):735-47.

Radiation Modifies Antitumor Immune Responses

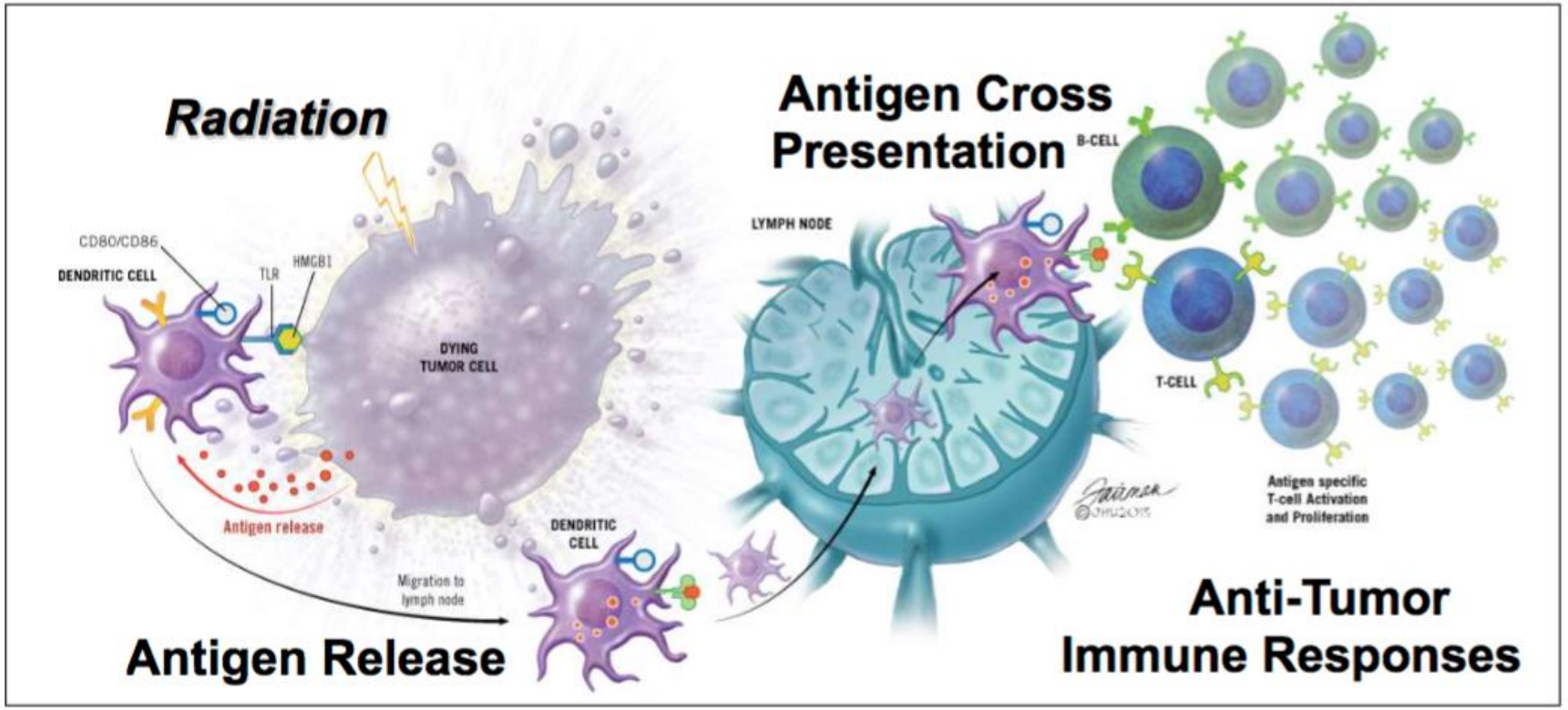
- Interleukin (IL)-1, IL-2, IL-6
- Tumor necrosis factor (TNF)-alpha
- Transforming growth factor (TGF)-beta
- Chemokine (C-X-C motif) ligand 16 (CXCL-16)
- Type I and type II interferon

Radiation modulates the expression of cytokines and chemokines play a critical role immune responses

T-cell mediated Cytotoxicity



Radiation Induced Immune Responses



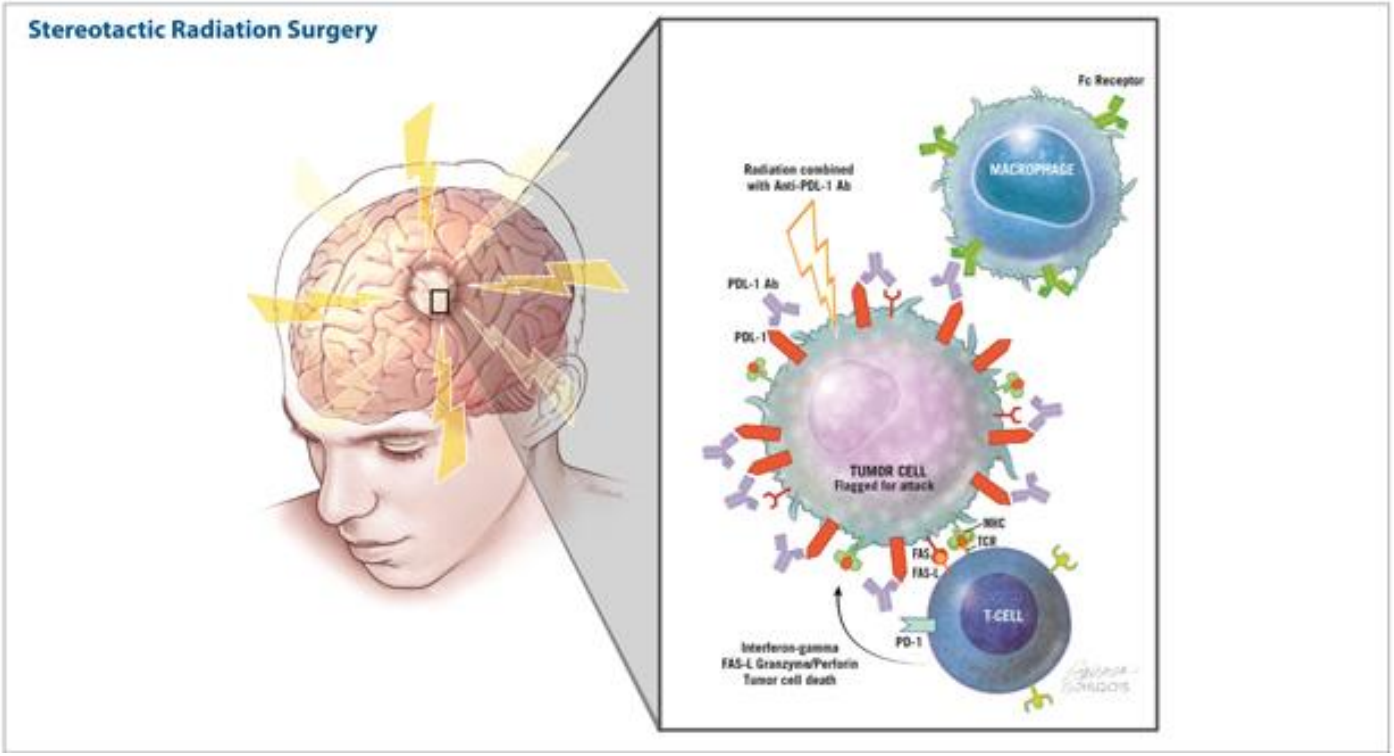
Sharabi et al., Lancet Oncol, 2015 Oct;16(13):e498-509

Myth: “Radiation Is Immunosuppressive”

- Large radiation fields encompassing significant volumes of bone marrow or blood pool have been observed to result in decreases in white blood cell counts
- SRBT significantly limiting the volume of bone marrow, thereby minimizing immunosuppressive effects
- The advance in radiation technology calls for a re-evaluation of the effects of focused radiation on the immune system

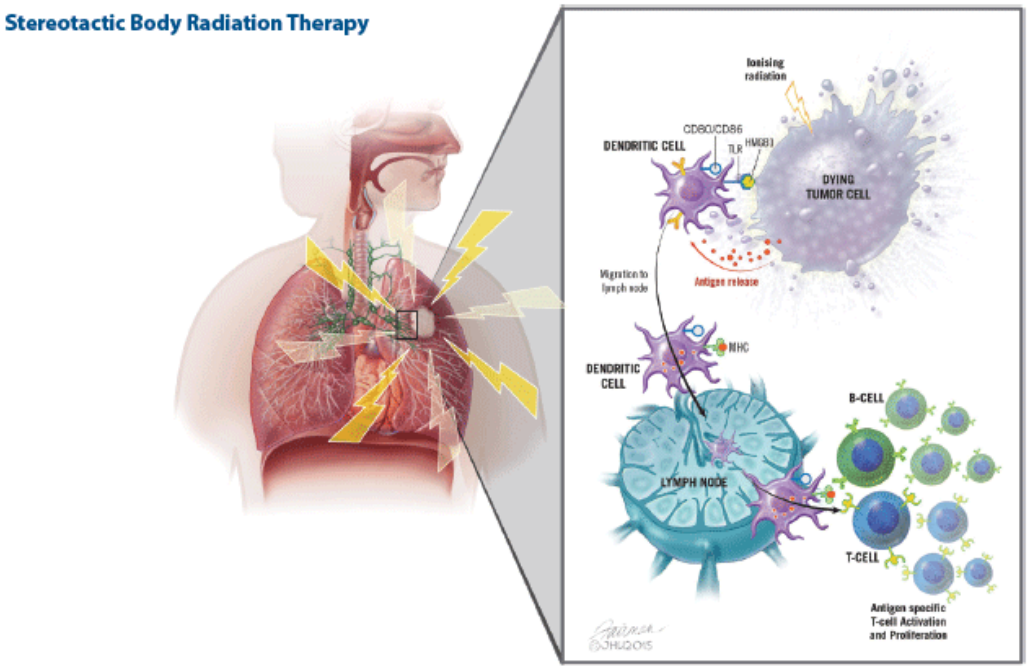
- Experimental data from cancer models have provided sufficient evidence to propose a paradigm shift, whereby the effects of the IR are recognized as contributing to the systemic antitumor immunity
- Traditional palliative role of RT in metastatic disease has evolved into a powerful adjuvant for immunotherapy
- IR has the capacity to convert irradiated tumor in situ, individualized vaccine

Potential Immune-stimulatory Effects of The SRS



- Increases permeability of the blood-brain barrier
- Increases immune cell infiltration

Potential Immune-Stimulatory Effects Of SBRT For Lung Cancer

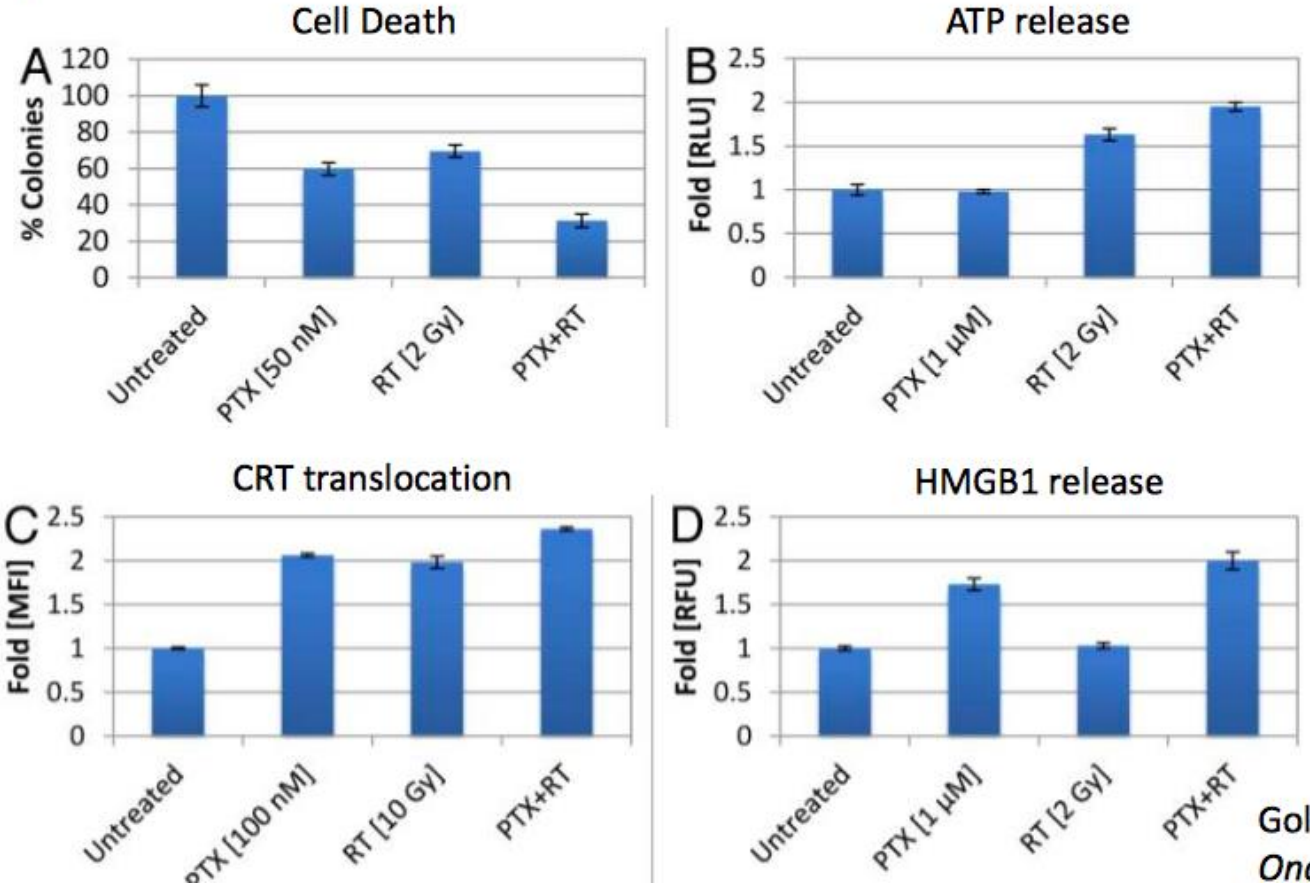


- Activation of antigen-presenting cells
- Enhancement of the tumor antigen cross-presentation in the draining lymph nodes
- Activation and proliferation of tumor-specific cytotoxic T cells

In Vitro Assessment of Immunogenic Death Cell

Implications of Concurrent Chemo-RT

TS/A murine mammary tumor cells



Golden et al.
OncoImmunology

Strong Preclinical Trials

- Immunotherapy enhances the local effects of the radiation
- Radiotherapy potentiates the systemic effects of the immunotherapy:

  Abscopal (Out-field)

  Vaccine-like (In Situ)

Abscopal Effect
Imiquimod and RT

Int. J. Radiation Oncology Biol. Phys., Vol. 58, No. 3, pp. 862–870, 2004

0360-3016/04/$–see front matter

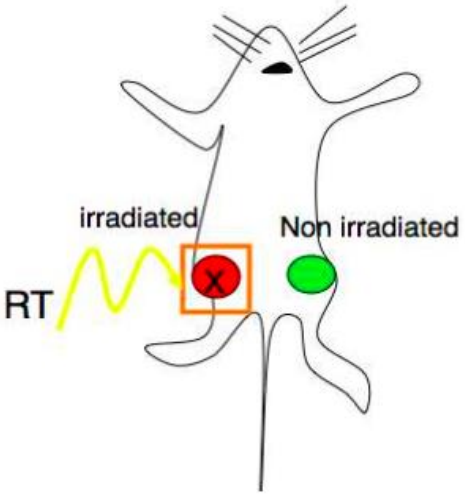
doi:10.1016/j.ijrobp.2003.09.012

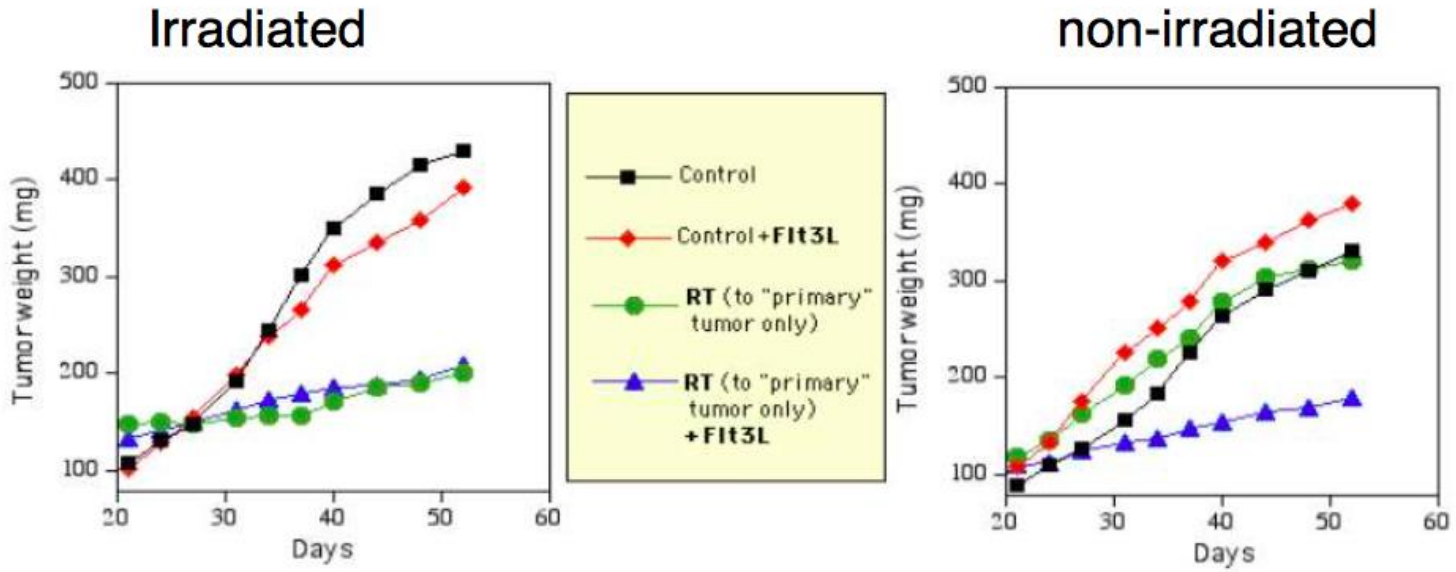
BIOLOGY CONTRIBUTION

IONIZING RADIATION INHIBITION OF DISTANT UNTREATED TUMORS (ABSCOPAL EFFECT) IS IMMUNE MEDIATED

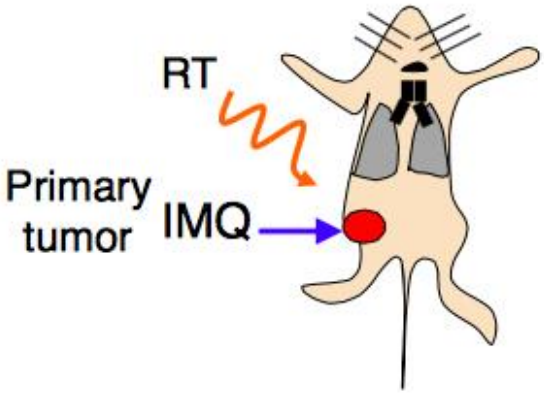
Sandra Demaria, M.D.,* Bruce Ng, M.S.,† Mary Louise Devitt, A.A.S.,‡ James S. Babb, Ph.D.,§ Noriko Kawashima, M.S.,* Leonard Liebes, Ph.D.,† and Silvia C. Formenti, M.D.‡

Departments of *Pathology, †Medicine, ‡Radiation Oncology, and §Radiology, New York University School of Medicine, New York, New York





Abscopal Effect
Imiquimod + RT



Day 0
Inj. of TSA
10^5 cells sc Rt.

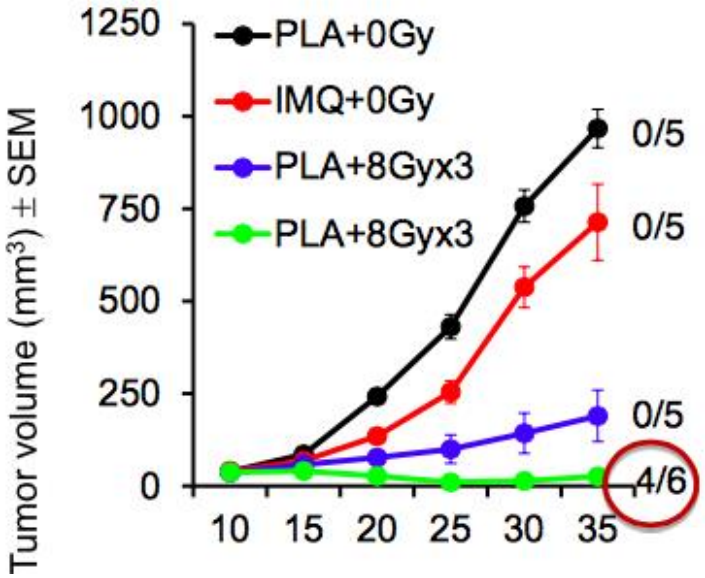
RT (Day12,13,14)

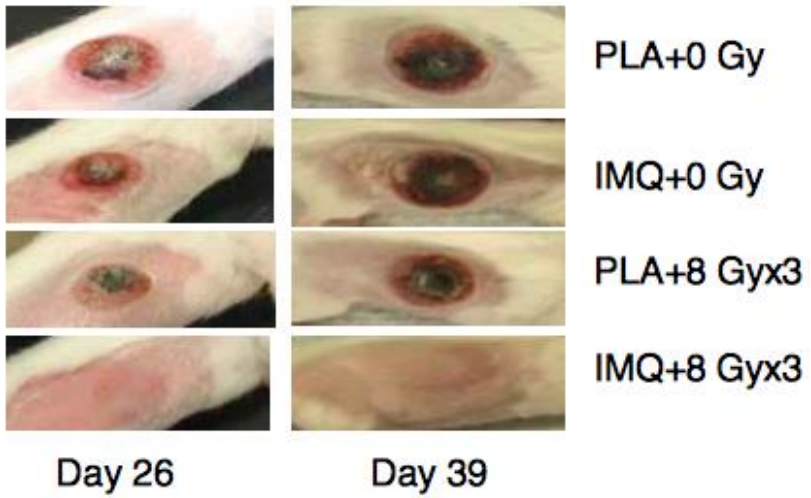
Day 10, 12, 14
Day 17, 19, 21
Day 24

IMQ

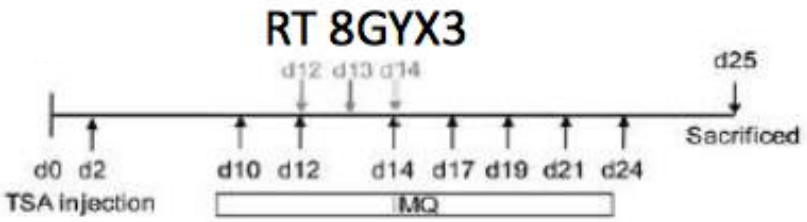
Follow up to Day 40

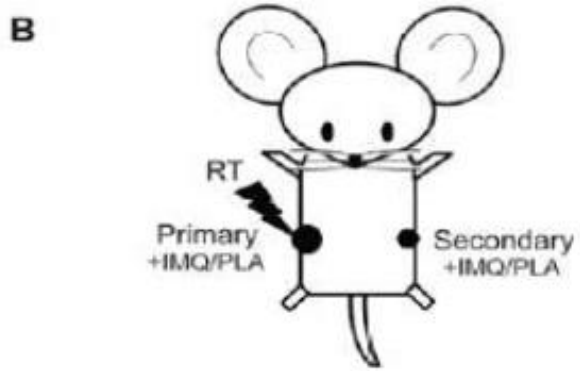
F/U

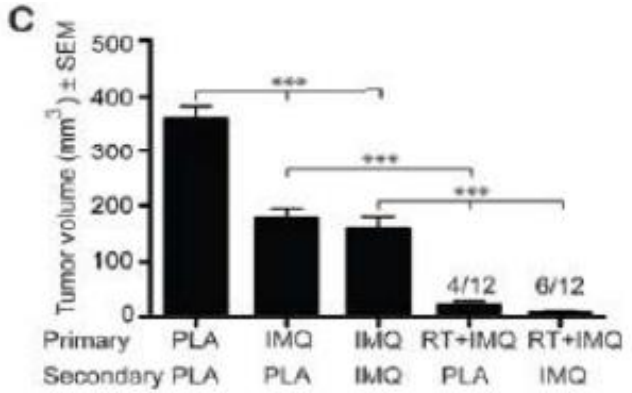


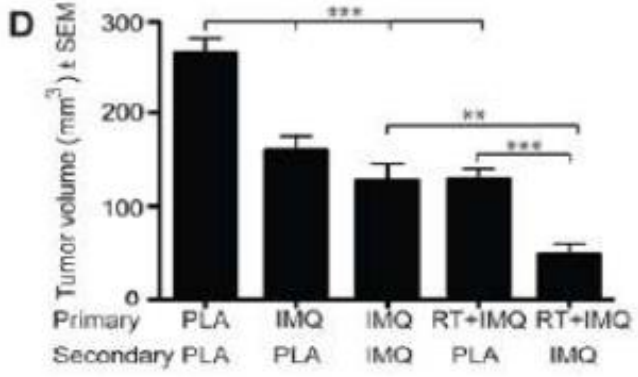


Abscopal Effect









Dewan et al. Clin Cancer Res 2012

Completed Trials: RT + Systemic GM-CSF

Golden et al. Lancet Oncology 2015

- Stable or progressing solid tumors treated with 35 Gy in 10 fractions and systemic GM-CSF

- Endpoint: abscopal responses
  - defined as 30% decrease in non-irradiated lesions

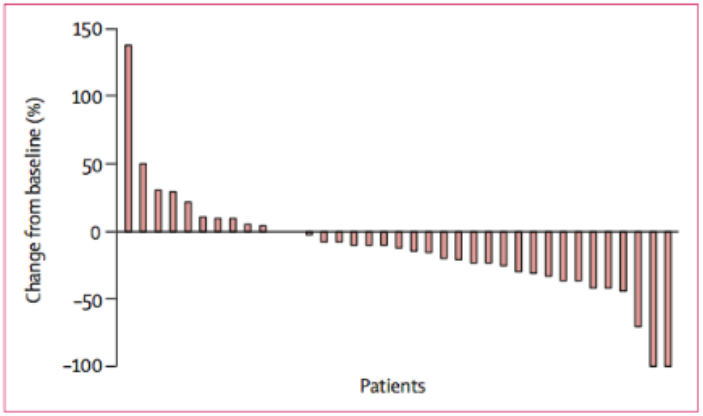
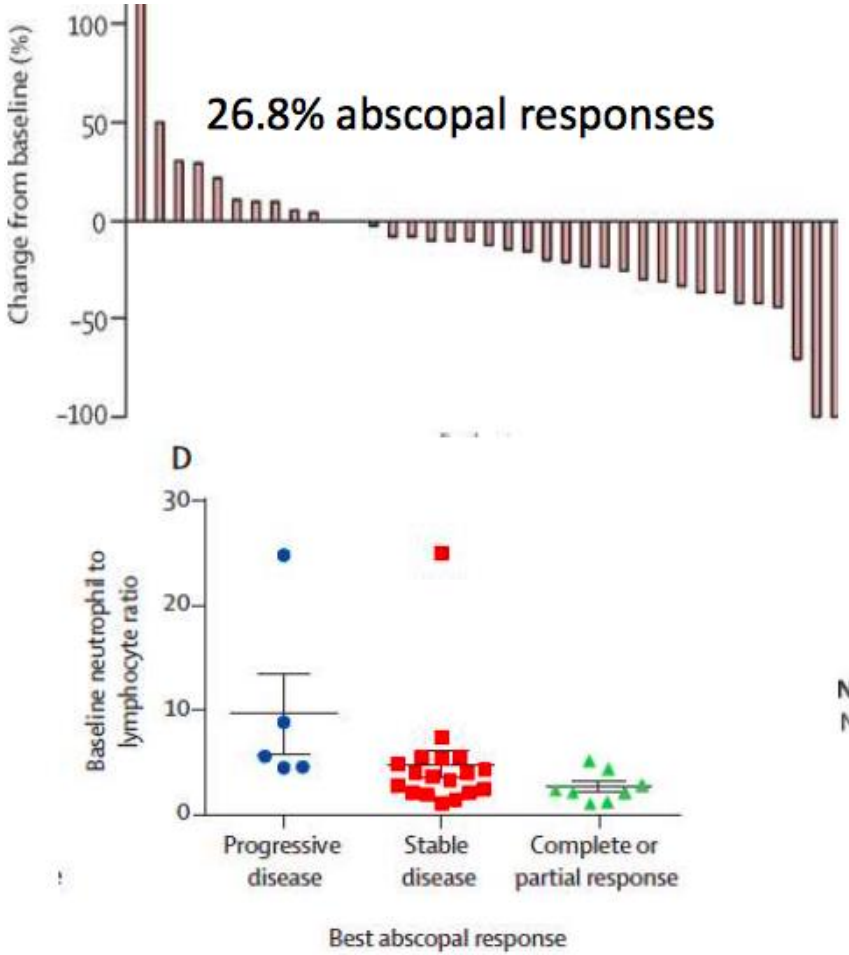


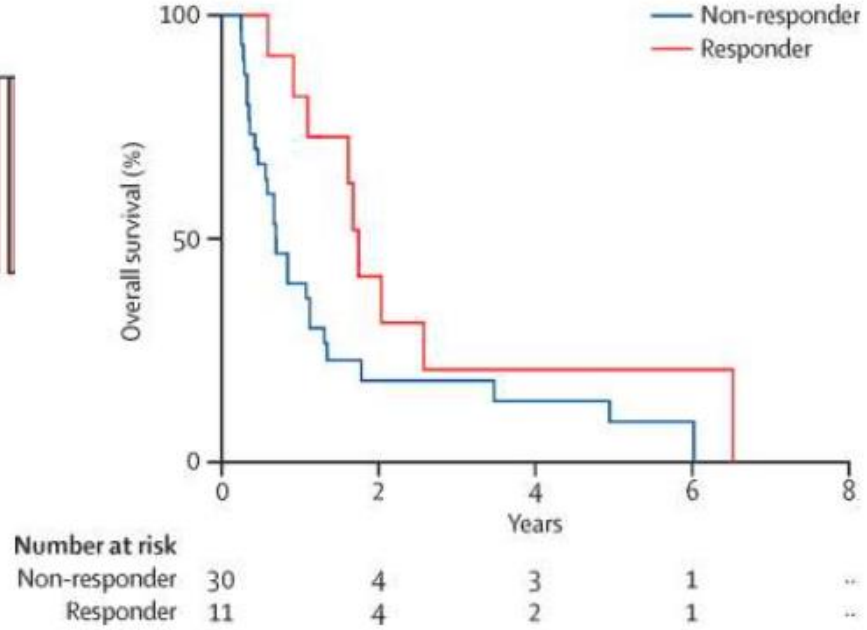
Figure 2: **Waterfall plot of best abscopal responses**
The plot shows the percent change from baseline in the best responding abscopal lesions. Each bar represents the best abscopal response for one patient.

Above: Abscopal responses observed in 11 of 41 patients

Granulocyte Macrophage Colony-Stimulating Factor- Leukine

Abscopal Effect
Increased OS





Median OS: 20.98 versus 8.33 months

Abscopal Effect

In Situ Vaccination with TLR9 Induces Systemic Lymphoma Regression (Phase I/II)

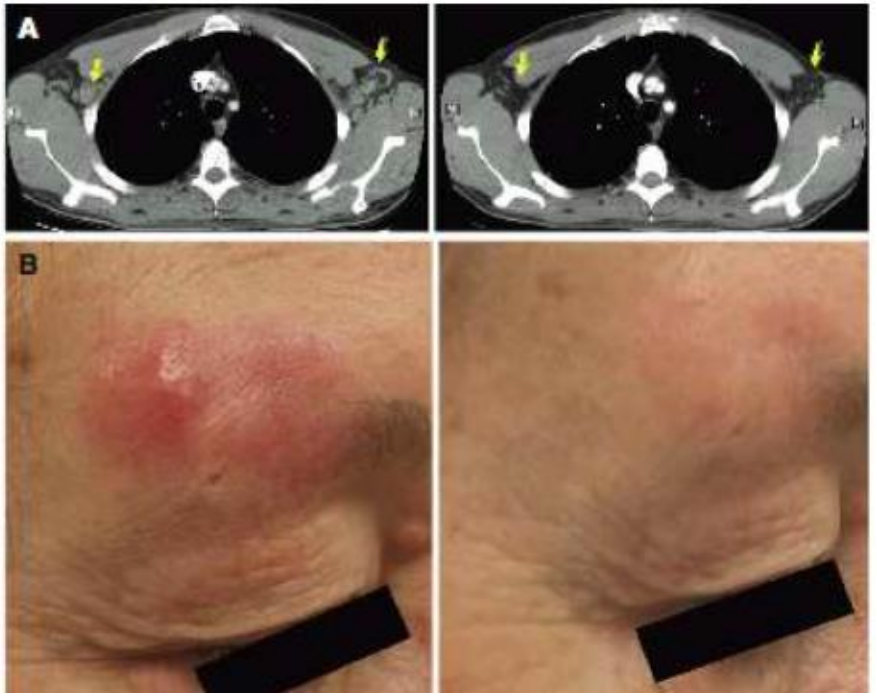
Joshua D. Brody, Weiyun Z. Ai, Debra K. Czerwinski, James A. Torchia, Mia Levy, Ranjana H. Advani, Youn H. Kim, Richard T. Hoppe, Susan J. Knox, Lewis K. Shin, Irene Wapnir, Robert J. Tibshirani, and Ronald Levy

Patient A:

treated at occipital lesion, response in bilateral axilla.

Patient B:

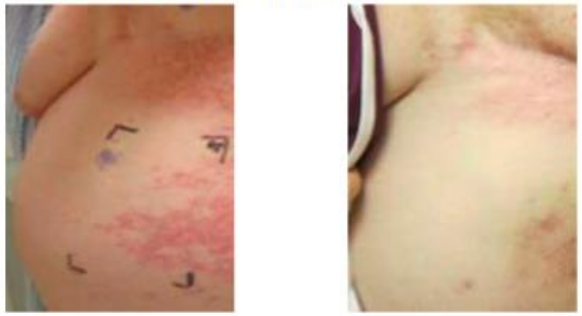
treated at suprasternal cutaneous lesion, response at frontal lesion



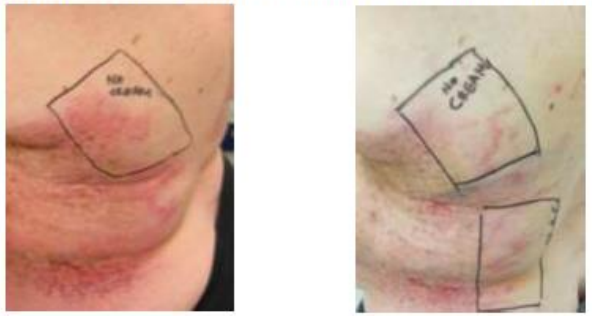
Abscopal Effect

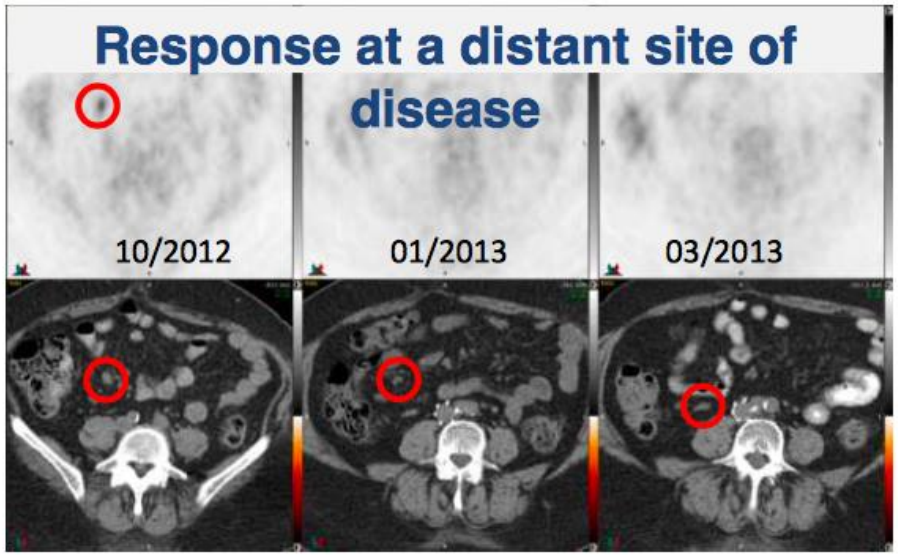
RT +TLR7 agonist Imiquimod: abscopal response

Baseline vs post-tx photo of RT + Imiquimod)



Baseline vs post-tx photo of Control area (No RT or Imiquimod)

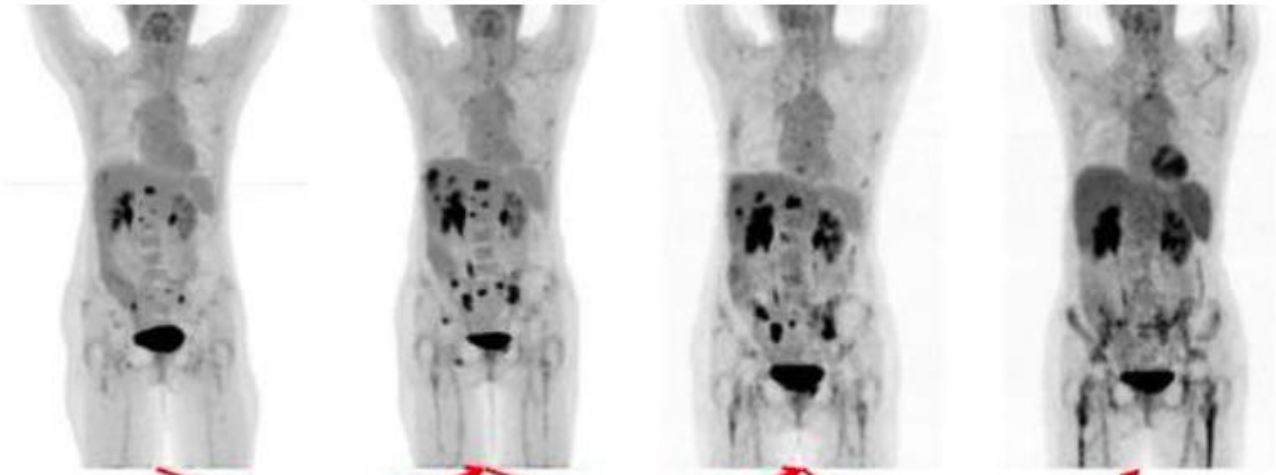




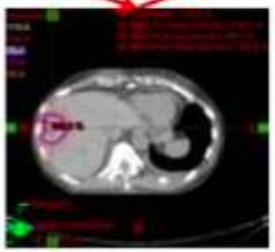
R01 CA161891-01

Abscopal Effect
Abraxane and PDL-1 Blockade

Low dose CTX, IMQ and RT (6 Gy X 5) in metastatic TNBC



- RT
- Imiquimod



- Low dose Cyclophosphamide
- RT
- Imiquimod

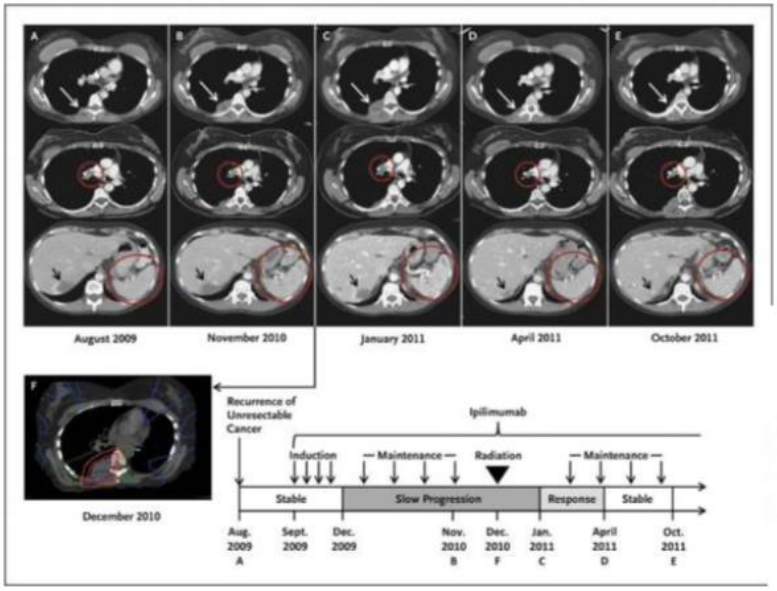
- Abraxane
- PDL-1 blockade

Preclinical trial experiences suggest synergy for radiation and checkpoints

Metastatic melanoma patients

SBRT and Ipilimumab

Abscopal response with immune potentiation in a melanoma patient treated with ipilimumab + RT



Postow MA et al. N Engl J Med 2012;366:925-931.

OncoImmunology 4:11, e1046028; November 2015; © 2015 Taylor & Francis Group, LLC

A systematic evaluation of abscopal responses following radiotherapy in patients with metastatic melanoma treated with ipilimumab

Ravi A Chandra[1,#], Tyler J Wilhite[2,#], Tracy A Balboni[3], Brian M Alexander[3], Alexander Spektor[3], Patrick A Ott[4], Andrea K Ng[3], F Stephen Hodi[4], and Jonathan D Schoenfeld[3,*]

[1]Harvard Radiation Oncology Program; Boston, MA USA; [2]Harvard Medical School; Boston, MA USA; [3]Department of Radiation Oncology; Brigham and Women's Hospital/Dana-Farber Cancer Institute; Boston, MA USA; [4]Medical Oncology and Center for Immuno-Oncology; Dana-Farber Cancer Institute; Boston, MA USA

Annals of Oncology 27: 434–441, 2016
doi:10.1093/annonc/mdv622
Published online 27 December 2015

Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy

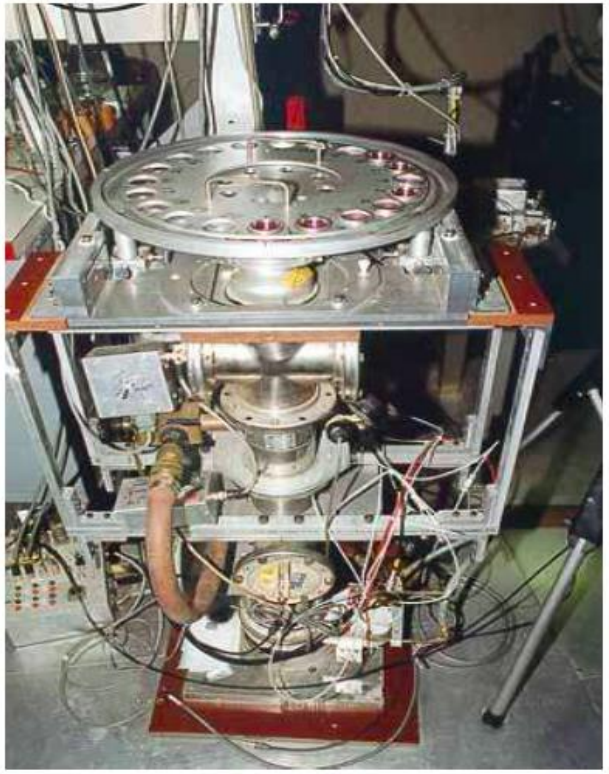
K. A. Ahmed[1], D. G. Stallworth[2], Y. Kim[3], P. A. S. Johnstone[1], L. B. Harrison[1], J. J. Caudell[1], H. H. M. Yu[1], A. B. Etame[4], J. S. Weber[5] & G. T. Gibney[6,7*]

Departments of [1]Radiation Oncology; [2]Radiology; [3]Biostatistics; [4]Neuro-Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa; [5]NYU Langone Medical Center, New York; [6]Department of Oncology, Georgetown-Lombardi Comprehensive Cancer Center, Washington; [7]Department of Medicine, Medstar-Georgetown University Hospital, Washington, USA

Heavy Ions Therapy
Protons, Deutrons and Alpha Particles

- 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

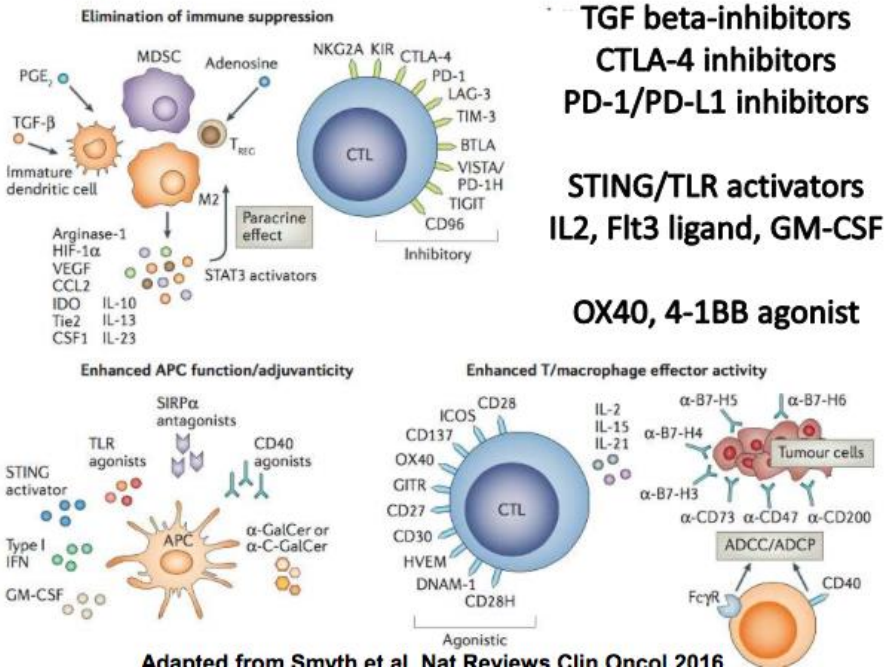


- Radiation is an optimal partner for immunotherapy : strategies to enhance cross-priming enable the abscopal effect
- Hypo-fractionated, short courses of RT to a small target to avoid lymphopenia are preferable.
- IL-15 may enhance RT pro-immunogenic effects.
- Preliminary evidence suggest that heavy ions may induce more ICD and be optimal partners with immunotherapy*

There is a strong preclinical rationale for testing radiation and immunotherapy in clinical trials

- Immunotherapy enhances the local effects of radiation
- Radiotherapy potentiates the SYSTEMIC effects of immunotherapy (abscopal, out-of-field responses, vaccine-like effects)

Synergy observed across IO agents and classes

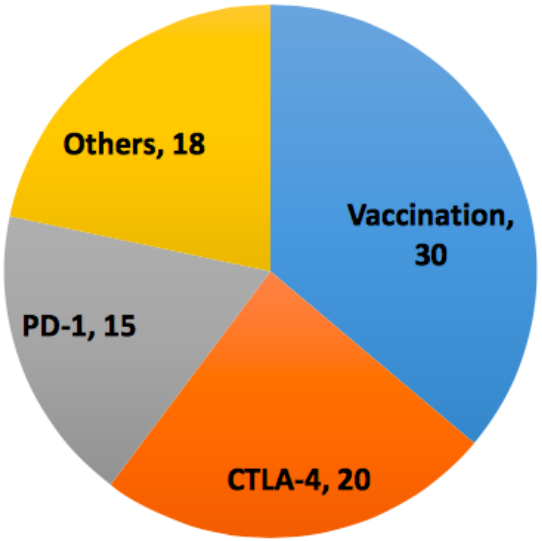


Adapted from Smyth et al. Nat Reviews Clin Oncol 2016

Promising preclinical and anecdotal data has led to the development of numerous RT+IO trials

- Johnson and Jagsi IJROBP 2016:

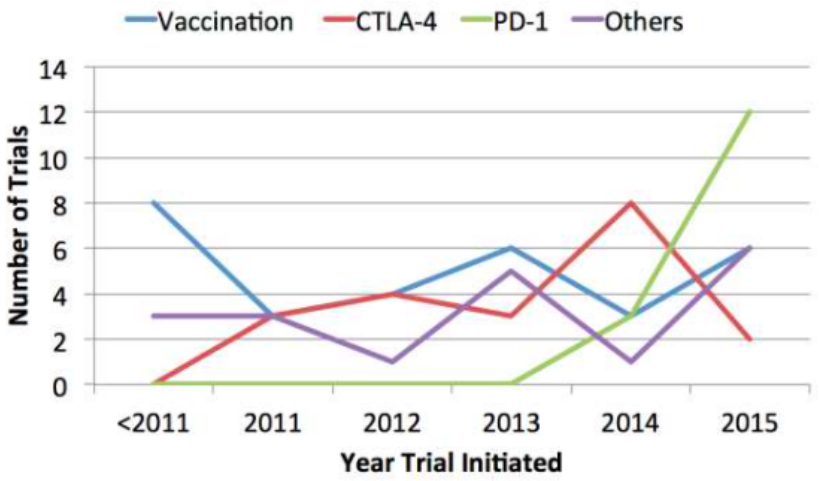
  81 ongoing trials testing radiation-immunotherapy combinations



Adapted from Johnson and Jagsi IJROBP 2016

Promising preclinical and anecdotal data has led to the development of numerous RT+IO trials

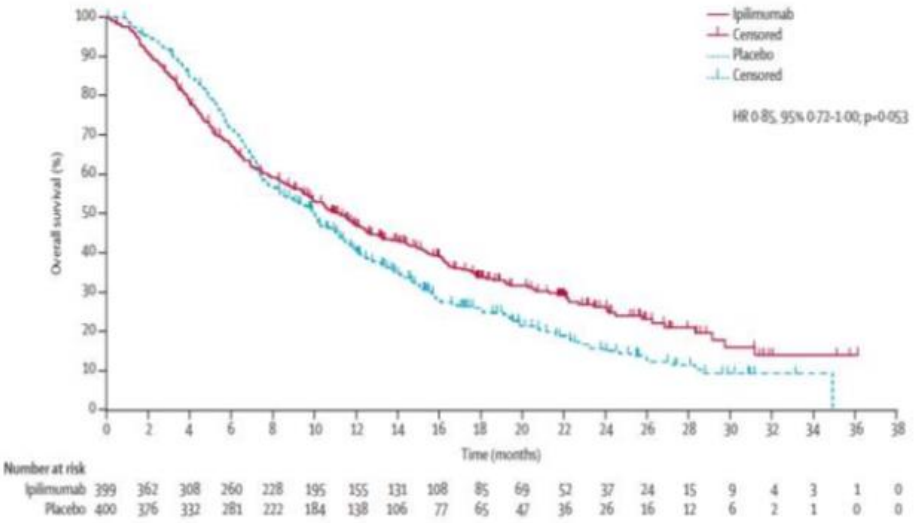
- Johnson and Jagsi IJROBP 2016: 81 ongoing trials testing radiation-immunotherapy combinations
- What can we learn from completed RT+IO trials?
- What are important aspects of trial design unique to IO combinations?



Adapted from Johnson and Jagsi IJROBP 2016

Completed Trials RT + Ipilimumab Trend to increase OS

- Outcome (n=799): negative trial, but trend towards benefit in overall survival
  - median survival 11.2 vs. 10 months, p=0.053
  - several early deaths and then an apparent benefit
- Potentially critical impact of patient selection, RT dose/fractionation/site, ipilimumab dose



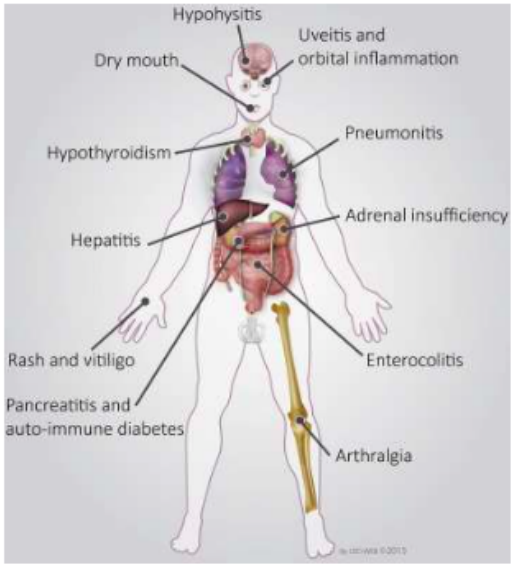
Know et al. Lancet Oncology 2014

End Points for the New Clinical Trials
(Based on lessons from the preclinical trials)

- Abscopal effect
- Response vs. Survival
- Biological effect
- To evaluate a RT/IO isolate component effects: RT timing, total dose/fractionation, site and IO agent
- Safety

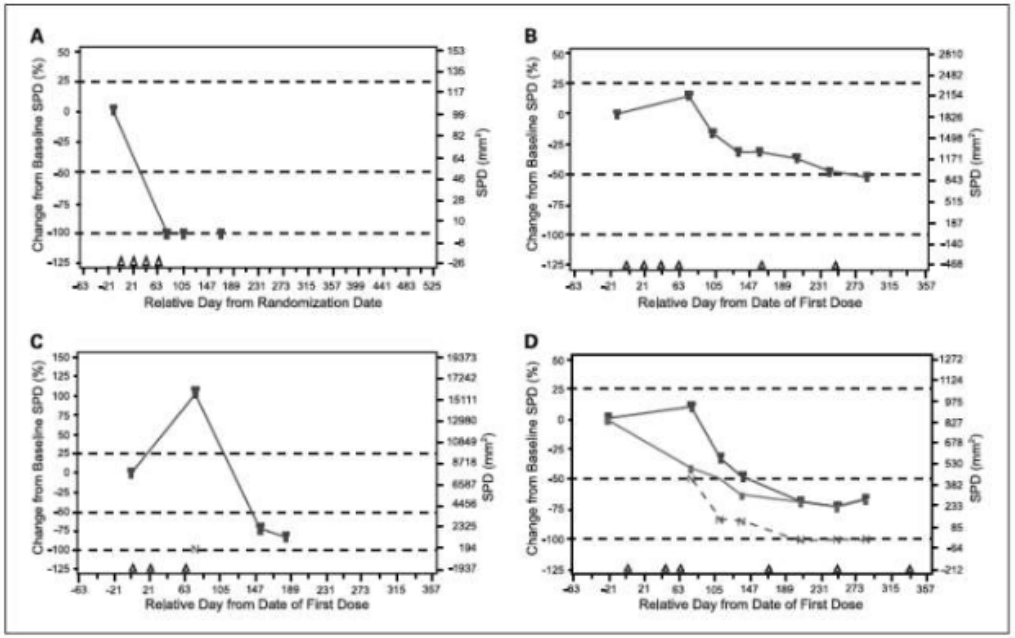
Endpoints in Immunotherapy Trials: Safety Endpoints

- A spectrum of immune-related adverse events has been observed with immune checkpoint inhibition
- Prompt diagnosis and treatment are critical
- Early data suggest that focal RT + immune checkpoint inhibitors are well tolerated (Barker et al. CIR 2013, Wilhite et al. AACR 2016)



Immune related toxicities,
Michot et al. Eur J Cancer 2016

Endpoints in Immunotherapy Trials: Atypical Patterns of Response on CTLA-4 blockade



A: Response after treatment

B: "Stable disease" with slow decrease in tumor volume

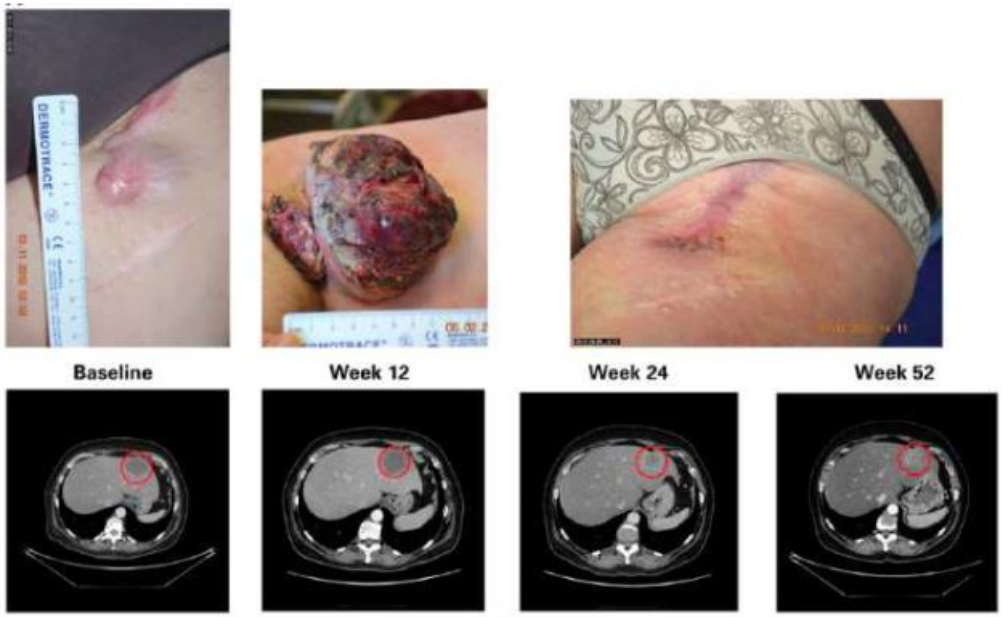
C: Response after initial increase in tumor volume

D: Shrinking target lesions in the setting of new lesions that then regress

* 10% of patients characterized as having PD on initial ipilimumab trials ultimately had evidence of response

Wolchok et al. CCR 2009

Endpoints in Immunotherapy Trials: Atypical Patterns of Response on PD-1 blockade



Hodi et al. JCO 2016

Endpoints in Immunotherapy Trials: Immune Response Criteria (irRC) and Immune RECIST (irRECIST)

Immune-related response criteria (irRC):

- Based on WHO criteria: measuring sum of products of 2 largest perpendicular diameters (SPD) of target lesions
- New lesions are incorporated into tumor burden (not automatic progression) – can be present in cases of partial response
- Progressive disease must be confirmed with scan >4 weeks after first scan

irRECIST:

- Uses unidirectional, longest diameter measurements
- Requires confirmation of progression
- New lesions don't automatically constitute progressive disease
- % changes highly concordant with irRC (Spearman r=0.953-0.965)
- Unidirectional measurements more reproducible

Wolchok et al. CCR 2009 and
Nishino et al. CCR 2013

Endpoints in Immunotherapy Trials: Immune-Related Response Criteria (irRC) Compared with Immune RECIST (irRECIST)

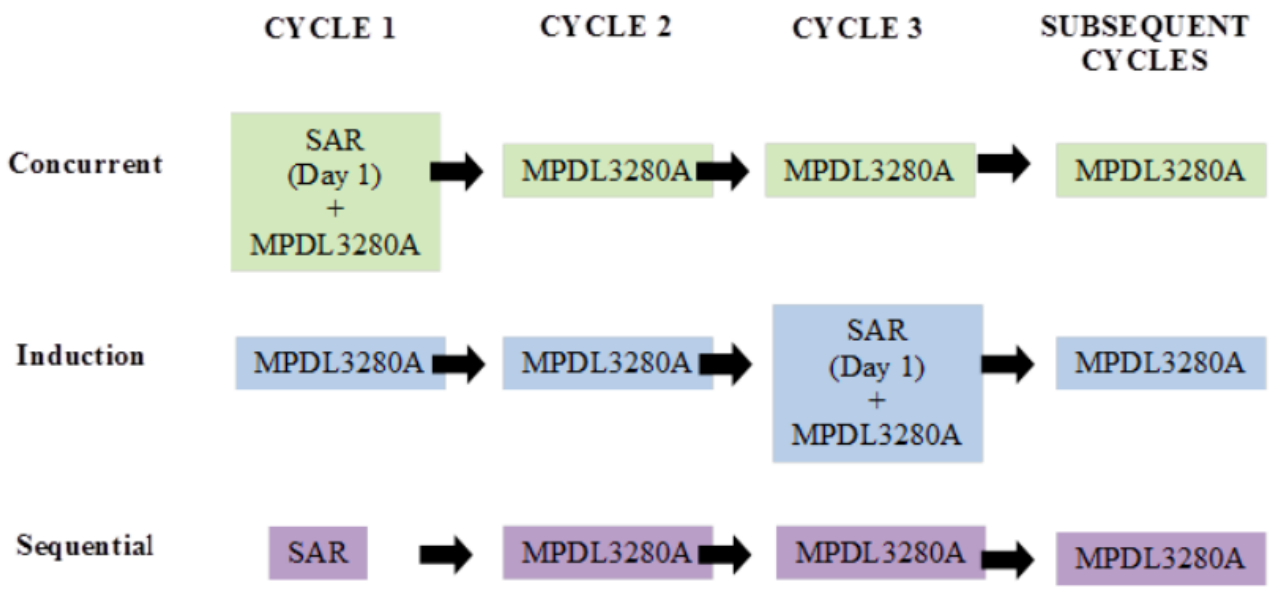
	Bidimensional assessment (the original irRC (7))	Unidimensional assessment
Measurable lesions	$\geq 5 \times 5$ mm^2 by bidimensional measurements	$\geq$10 mm in the longest diameter
Measurement of each lesion	The longest diameter × the longest perpendicular diameter (cm^2)	The longest diameter (cm)
The sum of the measurements	The sum of the bidimensional measurements of all target lesions and new lesions if any	The sum of the longest diameters of all target lesions and new lesions if any
Response assessment	PD: $\geq$25% increase from the nadir PR: $\geq$50% decrease from baseline CR: Disappearance of all lesions	PD: $\geq$20% increase from the nadir PR: $\geq$30% decrease from baseline CR: Disappearance of all lesions
New lesions	The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.	
Confirmation	Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, and PD	

Nishino et al. CCR 20

Radiation/Immunotherapy Trials: Evaluating Treatment Parameters

- Preclinical data suggest:
  - radiation dose / fractionation is important
  - optimal timing of RT may vary in relation to immune agent used
  - improved synergy with certain combinations (e.g., RT+PD-1+CTLA-4)
- These and other treatment parameters should be evaluated in clinical trials
- Correlative studies can help determine the impact of these factors on expected outcomes

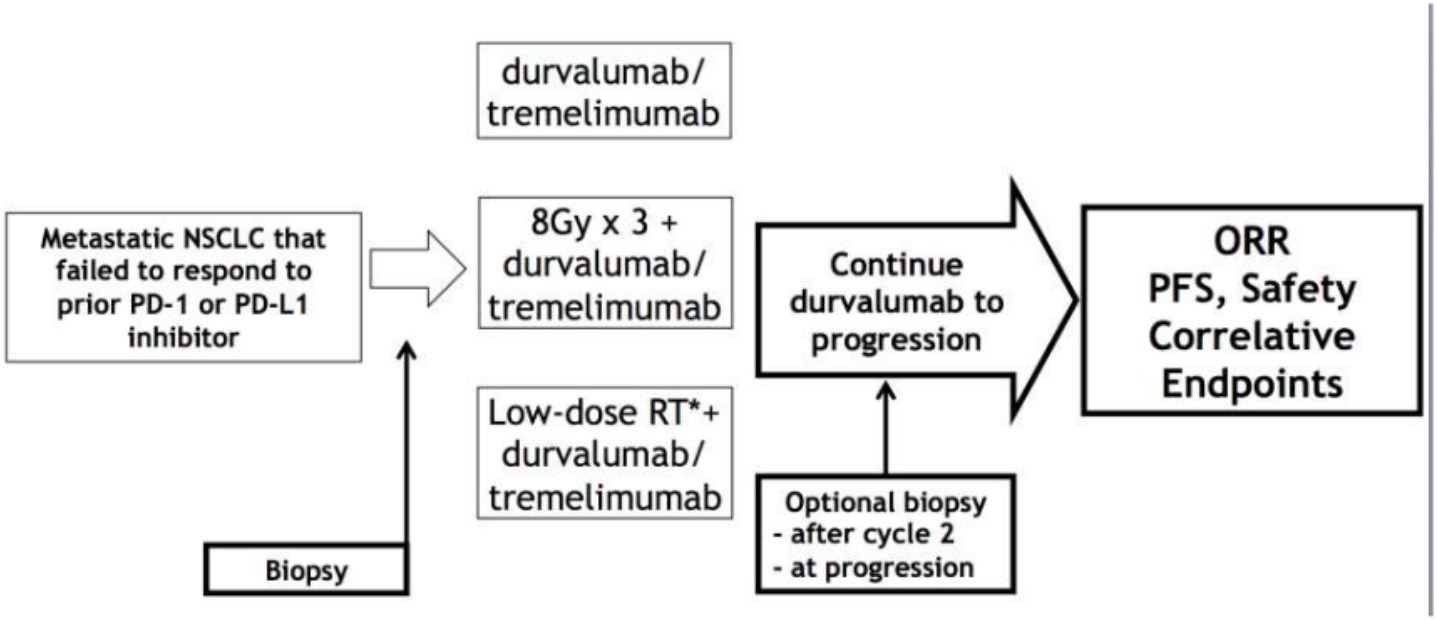
Radiation/Immunotherapy Trials: Evaluating Treatment Parameters + Radiation Timing



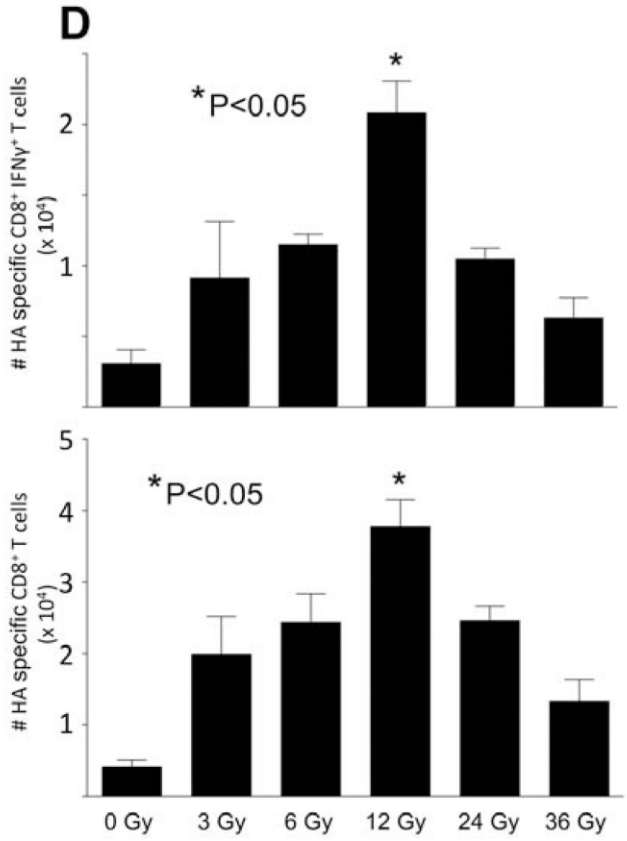
Courtesy of Arta Monjazeb, UC Davis

- Atezolizumab (Tecentriq) humanized monoclonal antibody IgG isotype against PD-L1 for solid tumors.
- FDA aproved 10/2016 for metastatic NSCLC progressing on platinum systemic therapy

Radiation/Immunotherapy Trials: Evaluating Treatment Parameters, Radiation Dose and Mechanisms of Action



SBRT and Immunotherapy
Timing and Dose

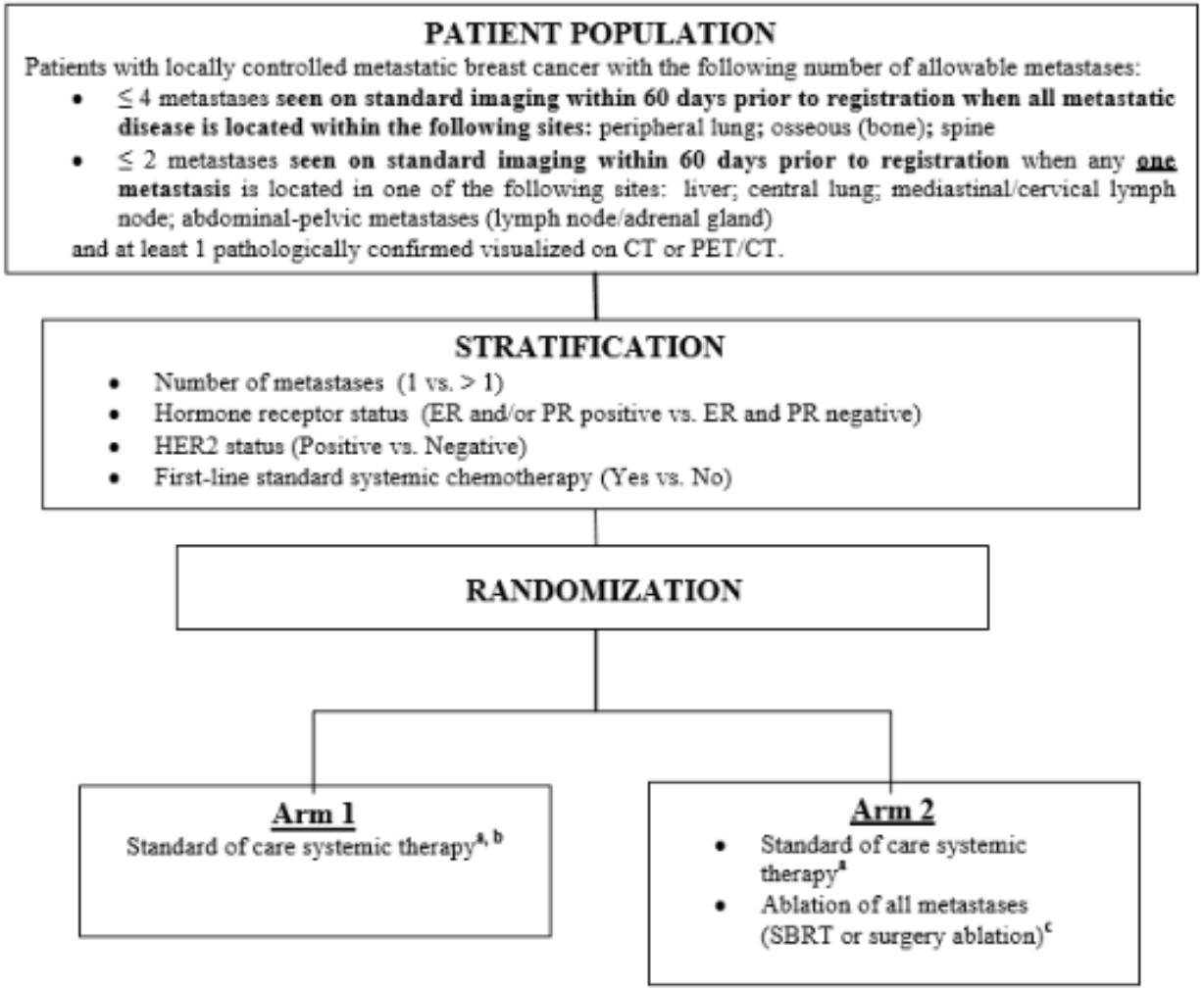


NRG ONCOLOGY

NRG -BR002

A Phase IIR/III Trial of Standard of Care Therapy with or without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Ablation for Newly Oligometastatic Breast Cancer

SCHEMA (9/16/16)



Summary

- Supported by a strong preclinical rationale, an increasing number of prospective clinical trials are testing radiation-immunotherapy combinations
- These studies should be informed by previous studies and data that suggest that unique response criteria are needed in immunotherapy trials
- There is a need for studies that evaluate the biologic and clinical effect of radiation parameters when used in combination with immunotherapy

Gracias por su atencion!