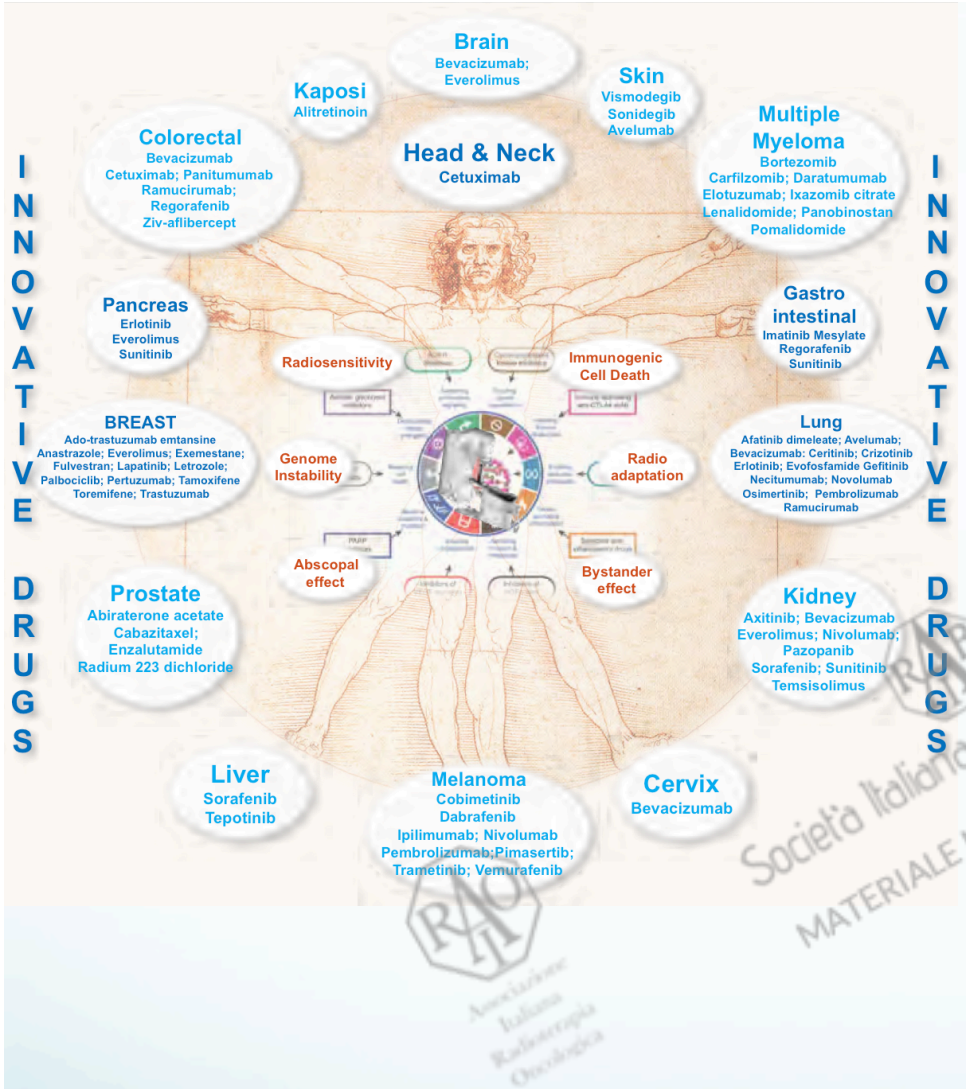
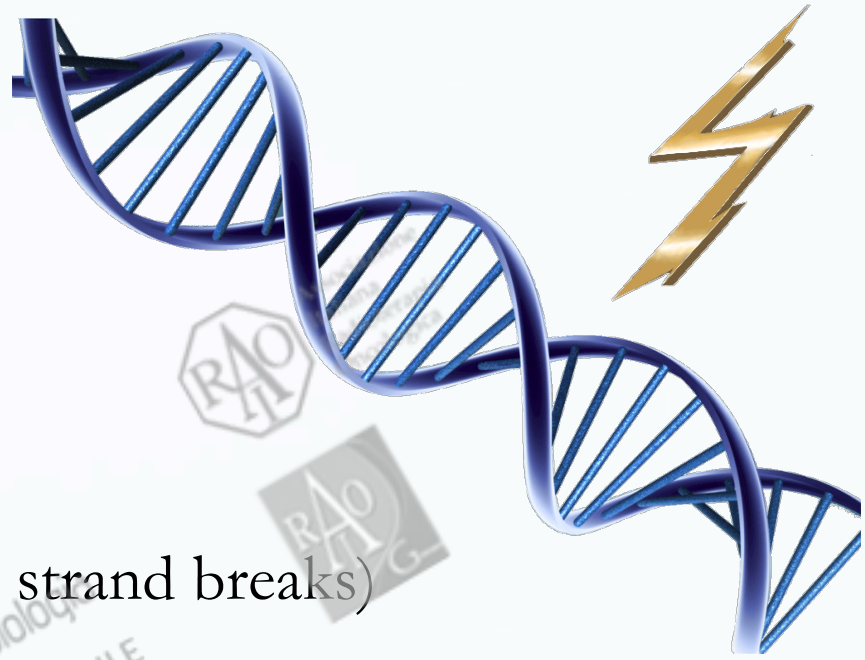


Combinazione tra radioterapia e immunoterapia nel melanoma metastatico: razionale degli studi in corso

Rolando M. D'Angelillo
Radioterapia Oncologica

UNIVERSITA' CAMPUS BIO-MEDICO DI ROMA
www.unicampus.it

COMBINING RADIOTHERAPY AND CANCER IMMUNOTHERAPY: **A PARADIGM SHIFT**



Radiotherapy effects:

- Direct DNA damage (single or double strand breaks)

- Some of the effects of ionizing radiation are recognized as contributing to DEVASCULARIZATION IN TUMORS AND SYSTEMIC ANTITUMOR IMMUNITY

Formenti S, J Natl Cancer Inst;2013;105:256–265

EDITORIAL

A Hypothesis: Indirect Cell Death in the Radiosurgery Era

Paul W. Sperduto, MD, MPP, FASTRO,* Chang W. Song, PhD,†
John P. Kirkpatrick, MD, PhD,‡ and Eli Glatstein, MD, FASTRO§

LQ model and the modified LQ models are based on the assumption that radiation-induced CELL DEATH IN TUMORS IS DUE SOLELY TO DNA STRAND BREAKS.

Both seminal and recent articles, however, strongly suggest that high dose/fraction (>10 Gy) radiation causes DEVASCULARIZATION IN TUMORS, which then induces delayed indirect tumor cell death. (4-9).

hypothesis that indirect tumor cell death from devascularization occurs after high-dose/fraction radiation, and thus it is reasonable to hypothesize that such indirect tumor cell death plays an important role in SRS and SBRT.

EDITORIAL

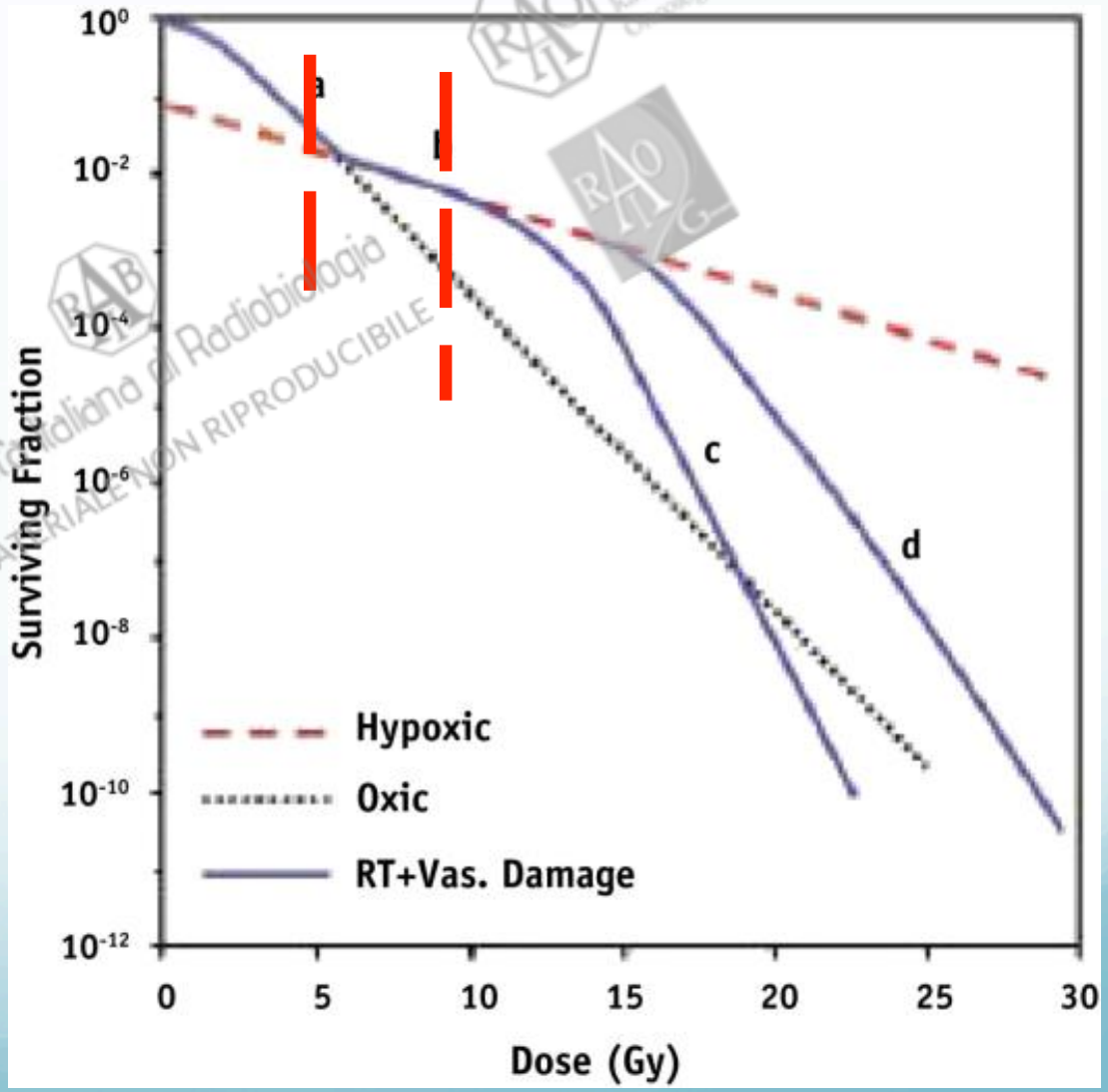
A Hypothesis: Indirect Cell Death in the Radiosurgery Era

Paul W. Sperduto, MD, MPP, FASTRO,* Chang W. Song, PhD,†
John P. Kirkpatrick, MD, PhD,‡ and Eli Glatstein, MD, FASTRO§

0 to 5 Gy / 1 fx:
oxygenated tumors

6-10 Gy / 1 fx:
hypoxic tumors

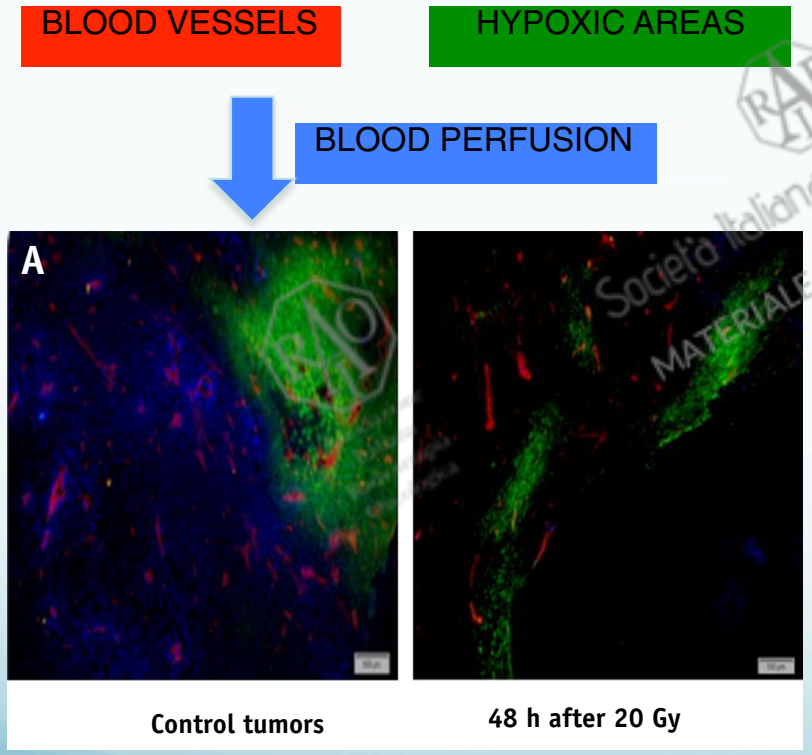
>10 Gy / 1 fx:
devascularization
immune enhancement

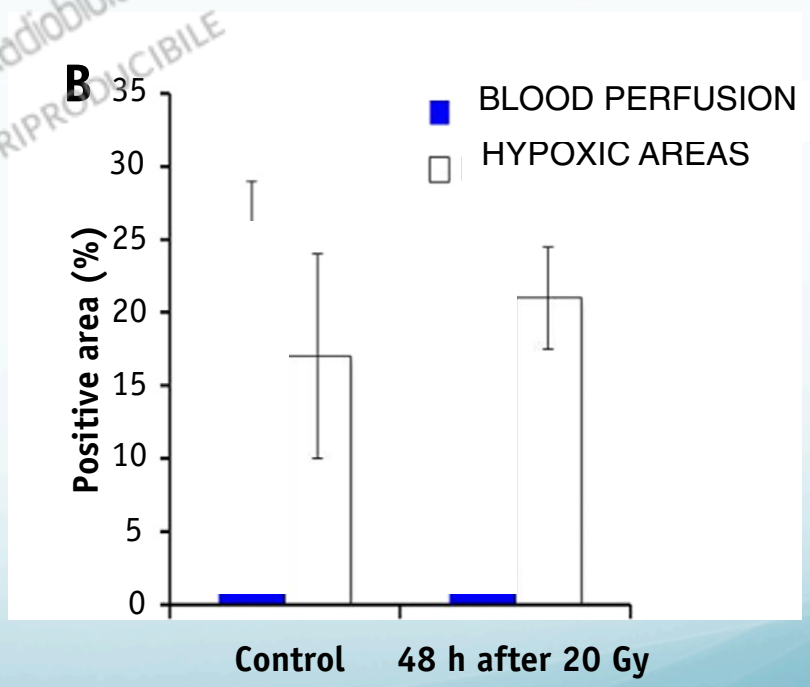


Indirect Tumor Cell Death After High-Dose Hypofractionated Irradiation: Implications for Stereotactic Body Radiation Therapy and Stereotactic Radiation Surgery

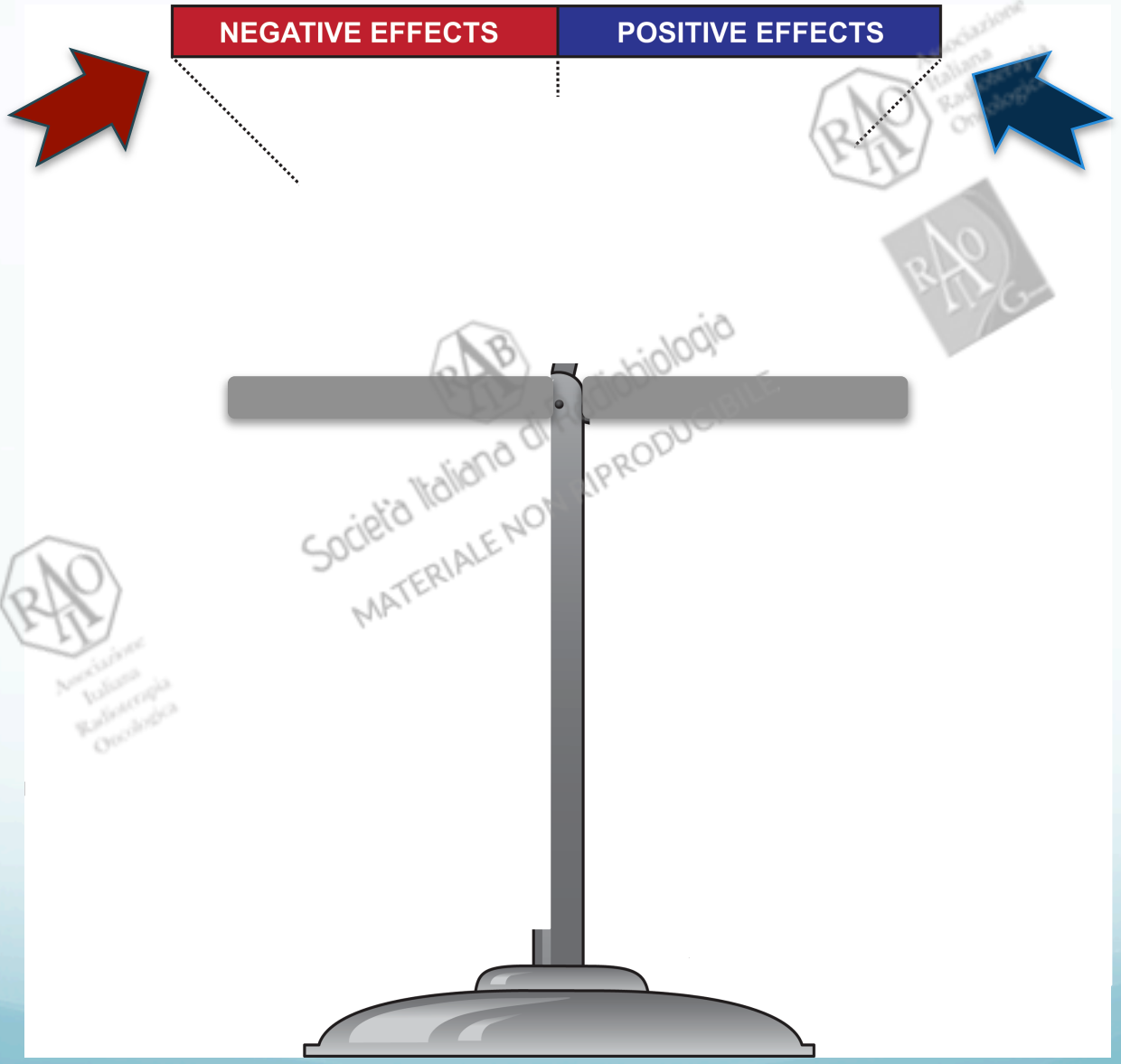
Chang W. Song, PhD,*,† Yoon-Jin Lee, PhD,† Robert J. Griffin, PhD,‡ Inhwan Park, BA,* Nathan A. Koonce, PhD,‡ Susanta Hui, PhD,* Mi-Sook Kim, MD, PhD,† Kathryn E. Dusenbery, MD,* Paul W. Sperduto, MD,§ and L. Chinsoo Cho, MD*

International Journal of Radiation Oncology biology • physics
www.redjournal.org





RADIOTHERAPY
IMMUNOSUPPRESSIVE AND PROIMMUNOGENIC EFFECTS

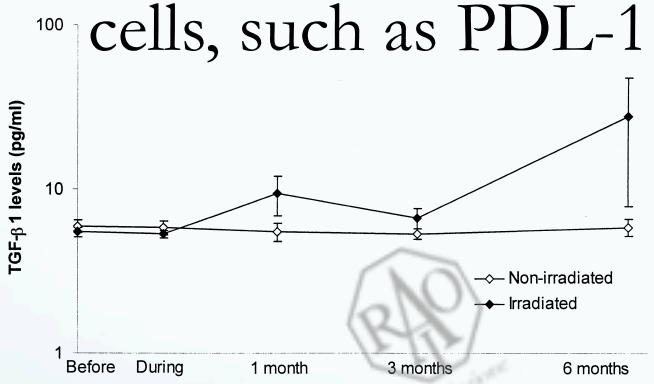


Formenti S, J Natl Cancer Inst;2013;105:256–265

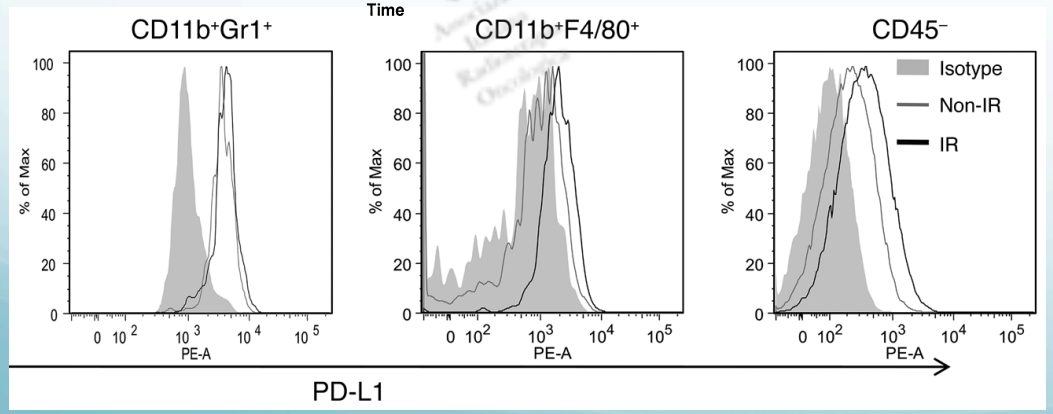
RADIOTHERAPY
IMMUNOSUPPRESSIVE AND PROIMMUNOGENIC EFFECTS

RT enhances:

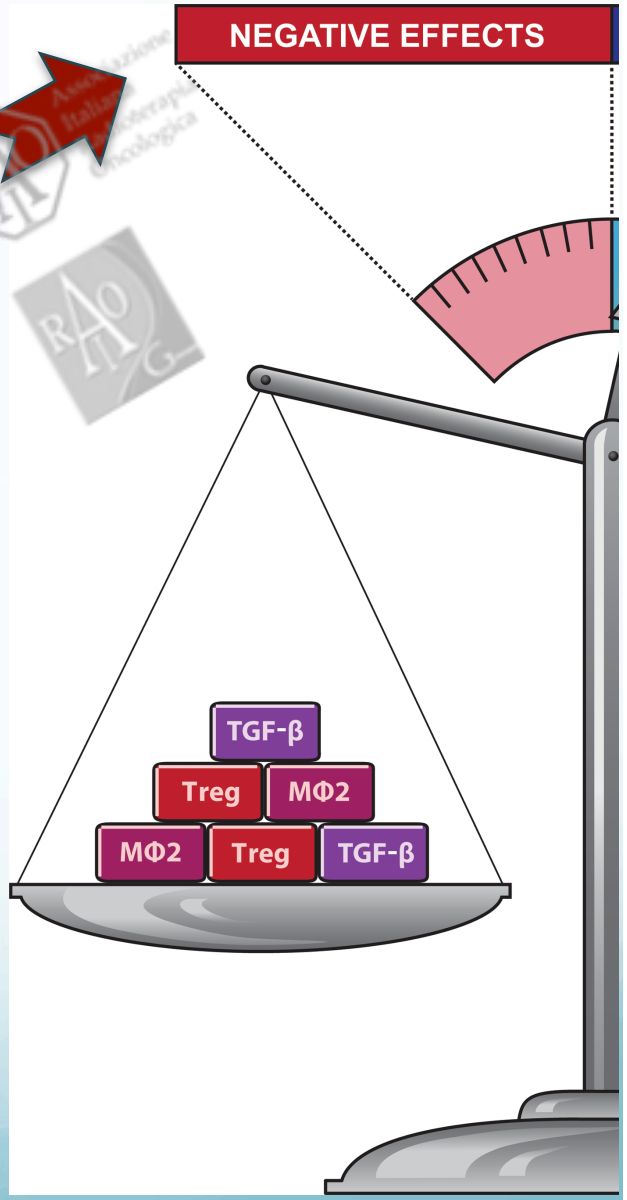
1. Immunosuppressive cytokines, such as TGFβ, and express surface receptors with inhibitory function for T cells, such as PDL-1



Nicole Barthelemy-brichant Int. J. Radiation Oncology Biol. Phys., 58,3: 758–767, 2004



Deng, J Clin Invest. 2014;124(2):687–695

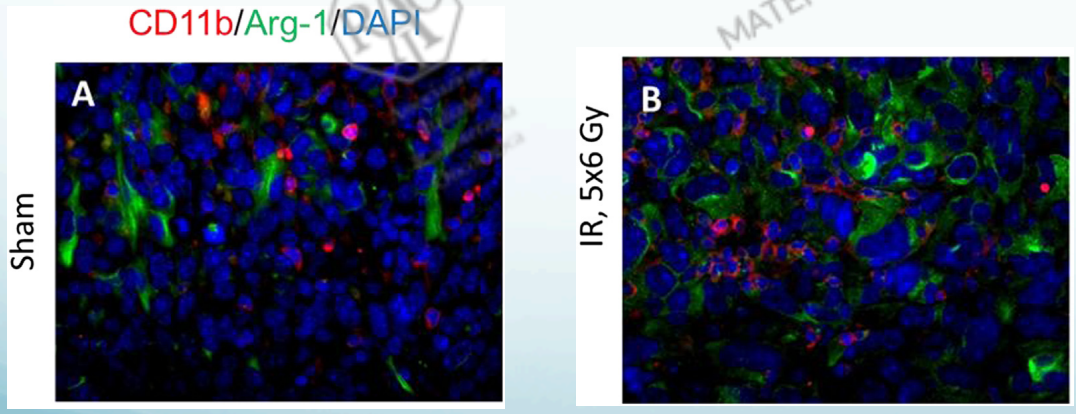


Formenti S, J Natl Cancer Inst;2013;105:256–265

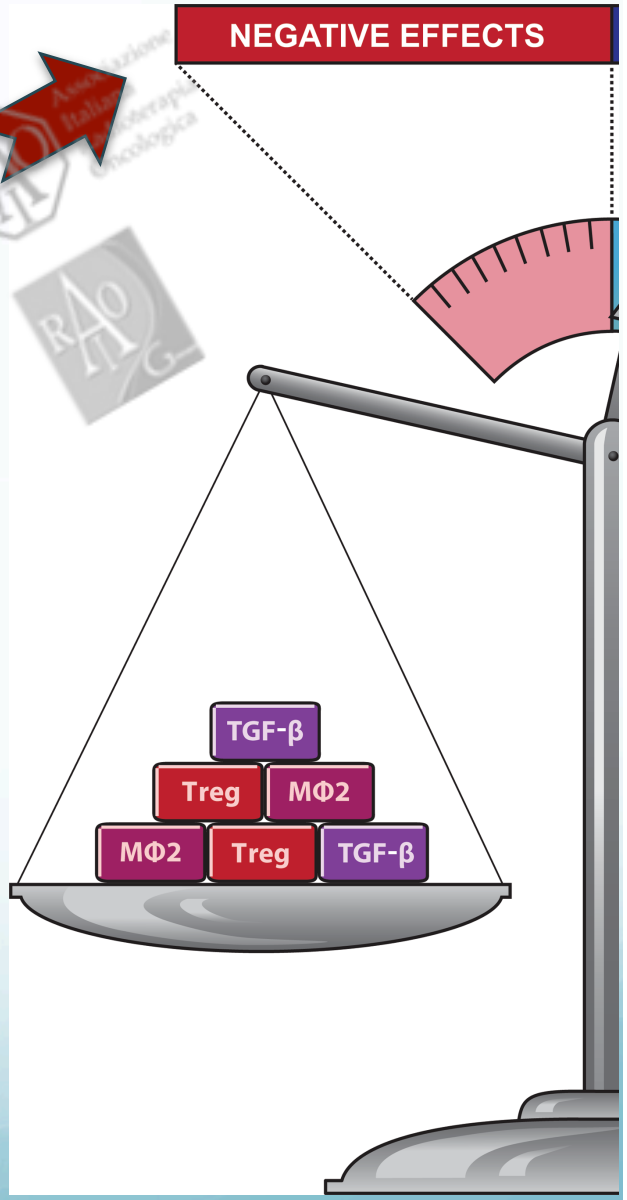
RADIOTHERAPY
IMMUNOSUPPRESSIVE AND PROIMMUNOGENIC EFFECTS

RT enhances:

1. Immunosuppressive cytokines, such as TGFβ, and express surface receptors with inhibitory function for T cells, such as PDL-1
2. M2 macrophages, myeloid-derived suppressor cells



Vatner, Semin Radiat Oncol 25:18-27 C 2015

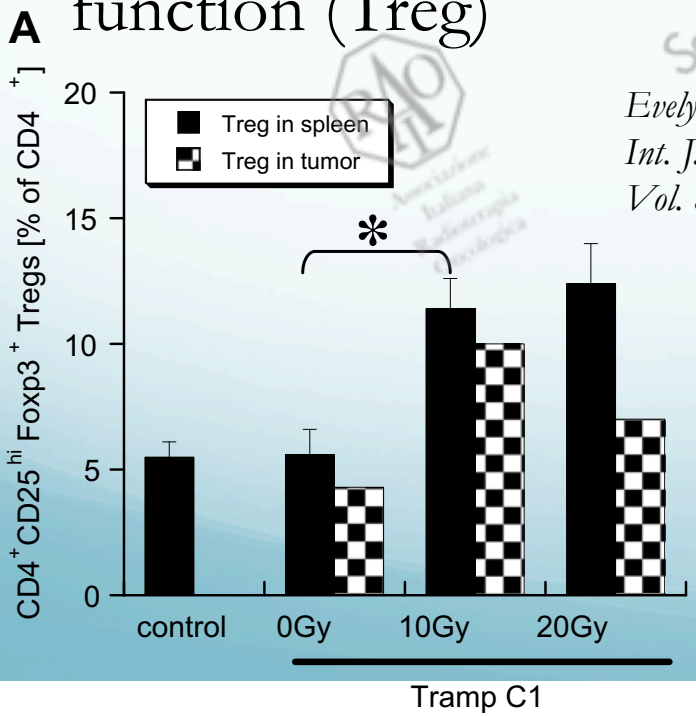


Formenti S, J Natl Cancer Inst;2013;105:256–265

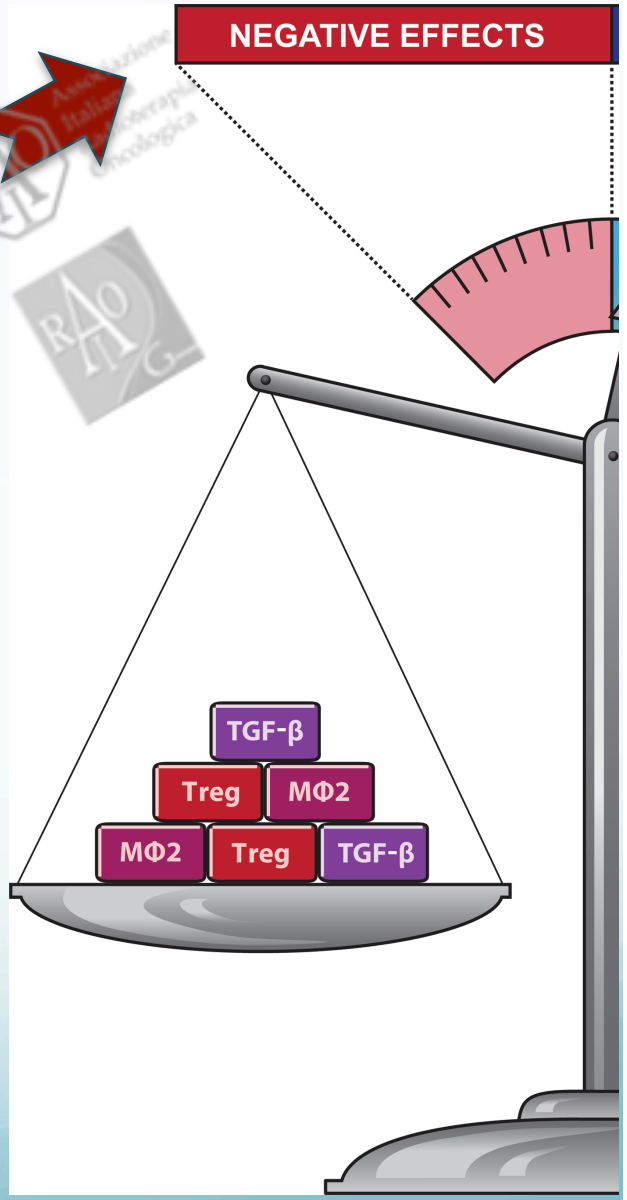
RADIOTHERAPY
IMMUNOSUPPRESSIVE AND PROIMMUNOGENIC EFFECTS

RT enhances:

1. Immunosuppressive cytokines, such as TGFβ, and express surface receptors with inhibitory function for T cells, such as PDL-1
2. M2 macrophages, myeloid-derived suppressor cells
3. CD4 T cells with regulatory function (Treg)

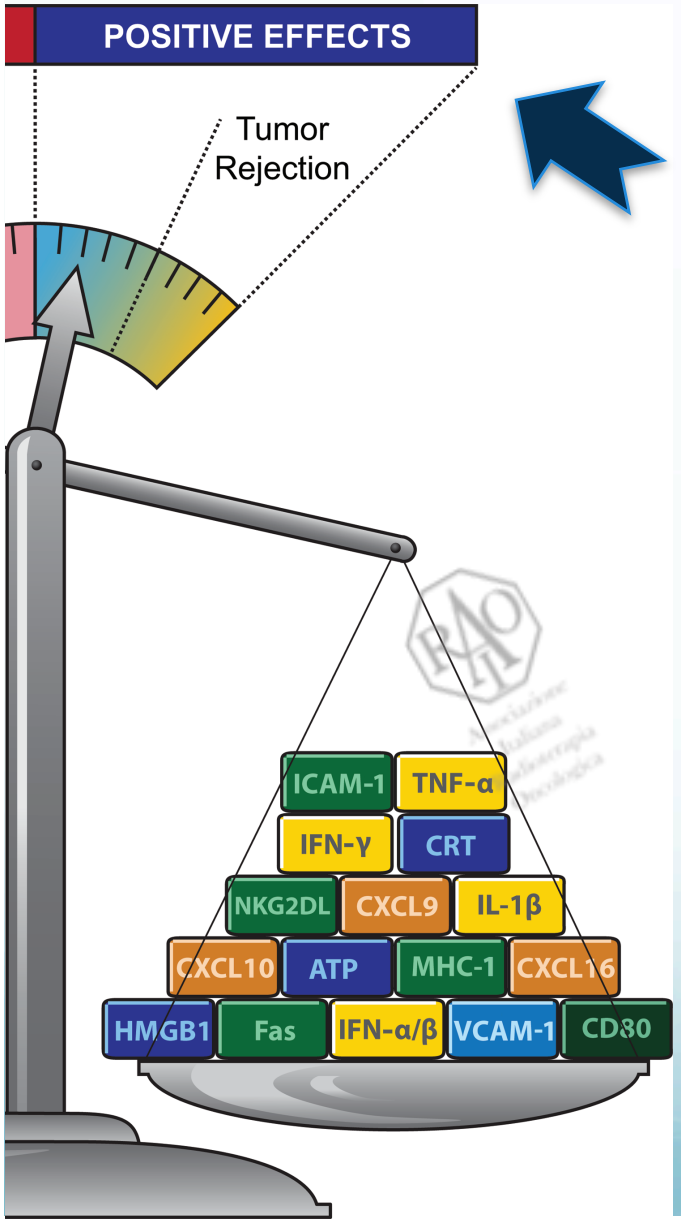


Evelyn L. Kachikwu
Int. J. Radiation Oncology Biol. Phys.,
Vol. 81, No. 4, Pp. 1128–1135, 2011



Formenti S, J Natl Cancer Inst;2013;105:256–265

RADIOTHERAPY
IMMUNOSUPPRESSIVE AND PROIMMUNOGENIC EFFECTS



RT enhances:

1. [redacted] *ANTIGENS EXPOSURE*

Ionizing radiation modifies the tumor cell PHENOTYPE

Formenti S, J Natl Cancer Inst;2013;105:256–265

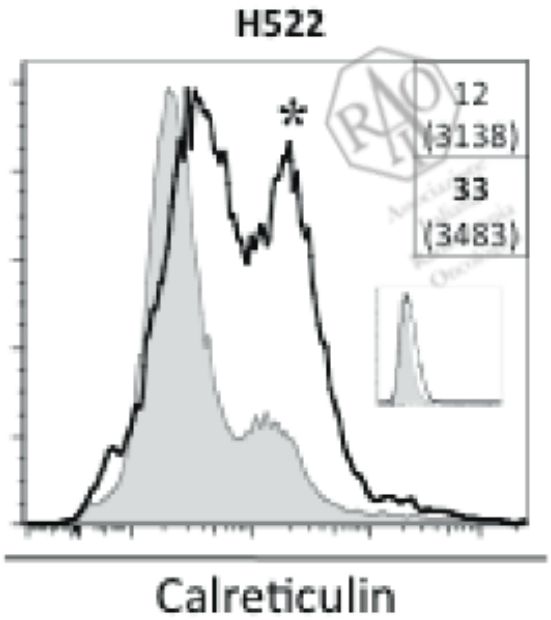
The cardinal signs of **IMMUNOGENIC CELL DEATH** (ICD) are

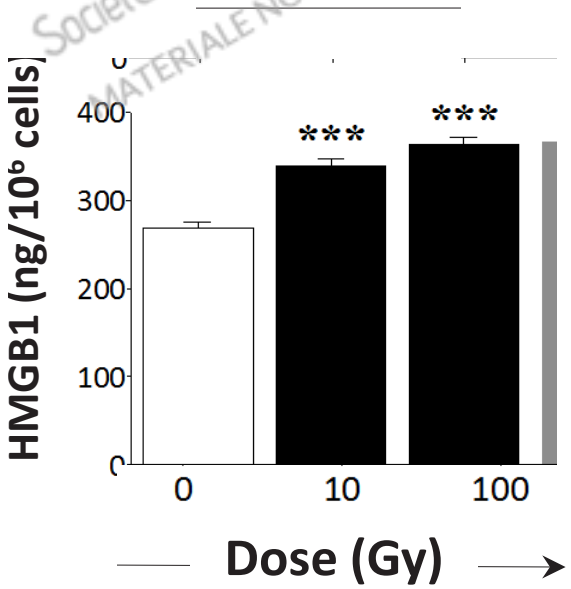
- CALRETICULIN exposure on the surface of dying cells
- Secretion of high-mobility group box 1 (HMGB1) protein
- Release of ATP

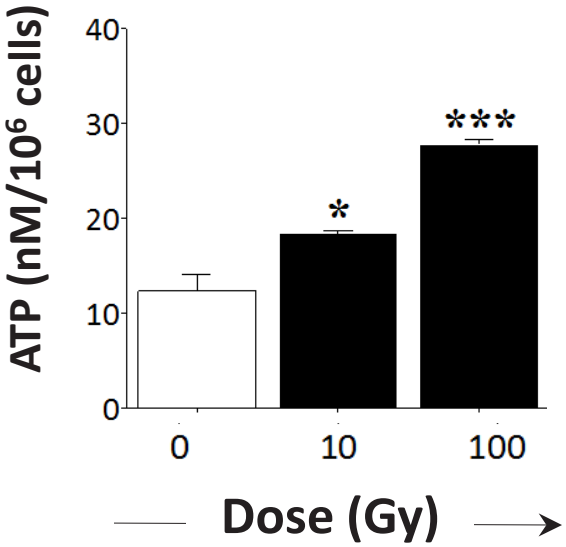
Each of these molecules stimulates dendritic cells (DC) to promote heightened immune responses

RADIOTHERAPY EFFECTS:

death.

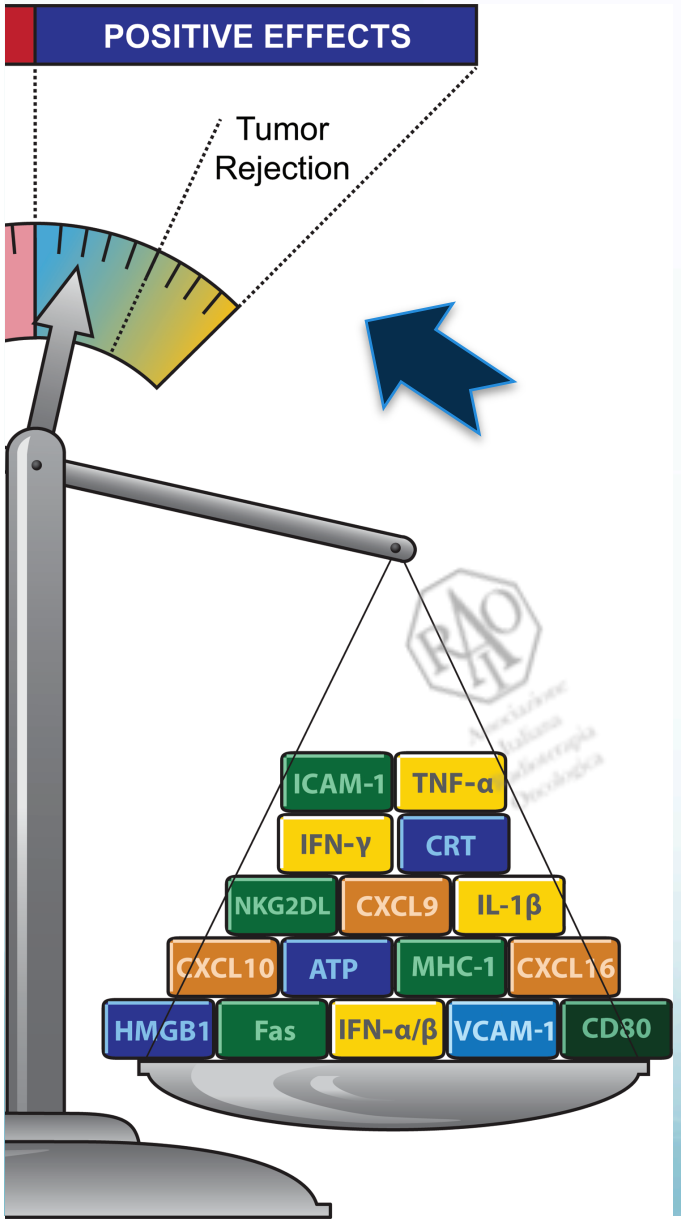






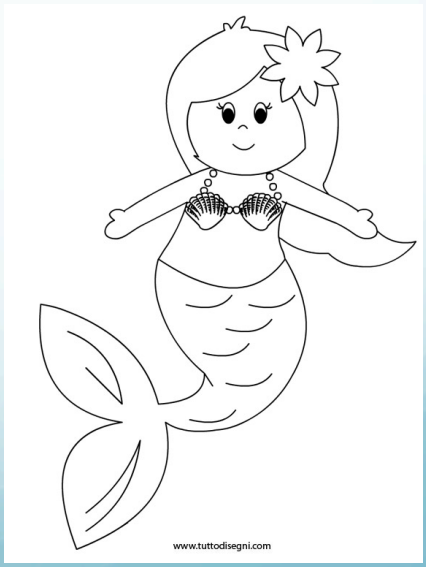
Gameiro SR, Oncotarget 2013

RADIOTHERAPY
IMMUNOSUPPRESSIVE AND PROIMMUNOGENIC EFFECTS



RT enhances:

1. *ANTIGENS EXPOSURE*
2. *ATTRACTION OF ACTIVATED T CELLS*



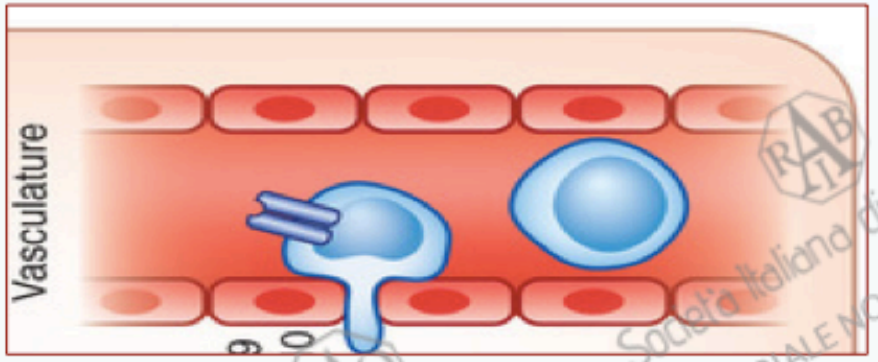
Matsumura, Radiat Res. 2010 April ; 173(4): 418–425.

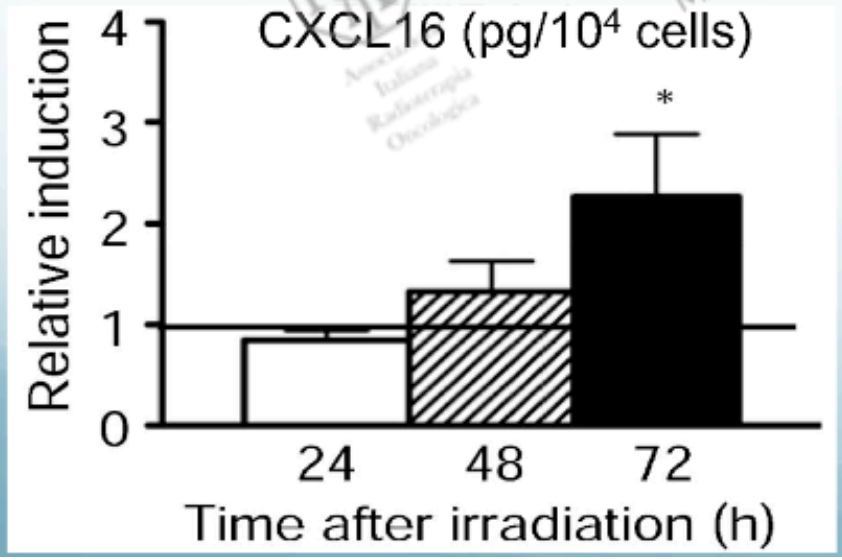
ATTRACTION OF ACTIVATED T CELLS TO THE TUMOR

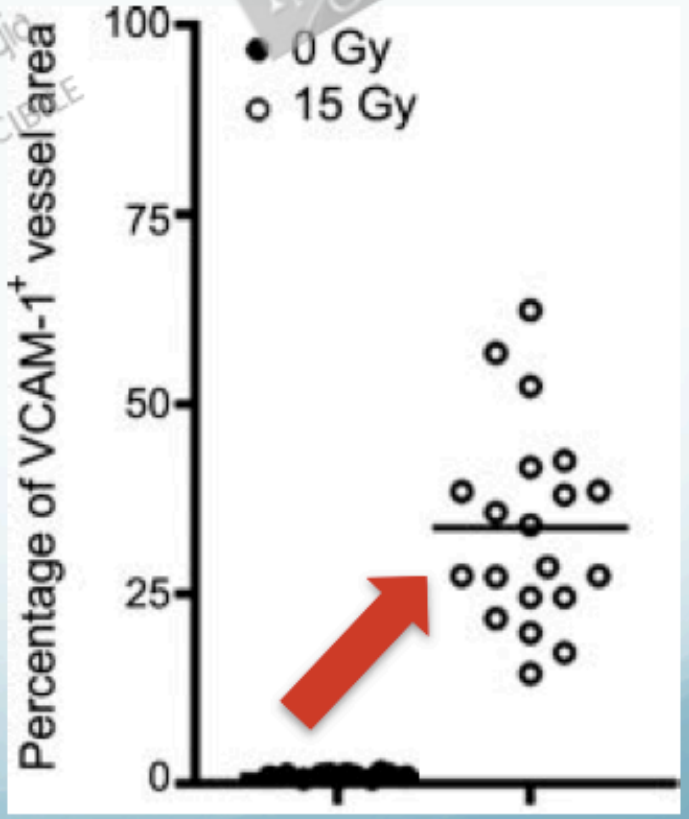
(CXCL9-10-16)

Upregulation of vascular cellular adhesion molecule 1 (VCAM-1) on tumor endothelium facilitates tumor infiltration by T cells.

Tumor infiltration by T cells produces IFN-γ and TNF-α

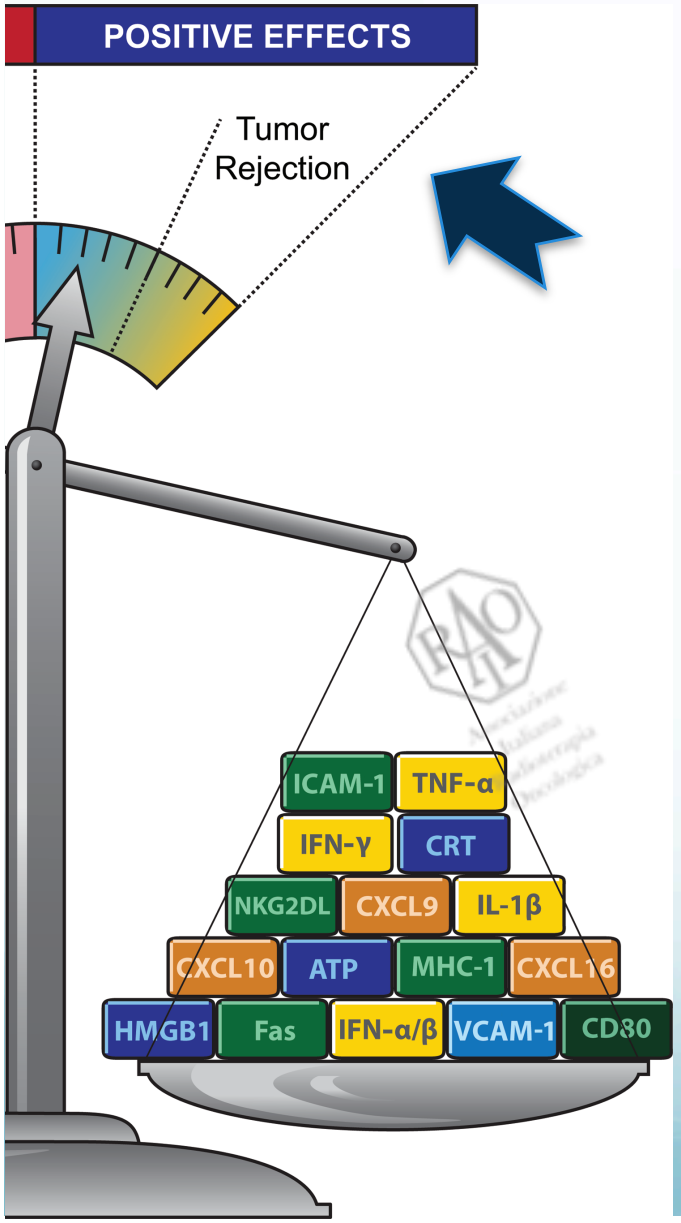






Matsumura, Radiat Res. 2010 April ; 173(4): 418–425.

RADIOTHERAPY
IMMUNOSUPPRESSIVE AND PROIMMUNOGENIC EFFECTS



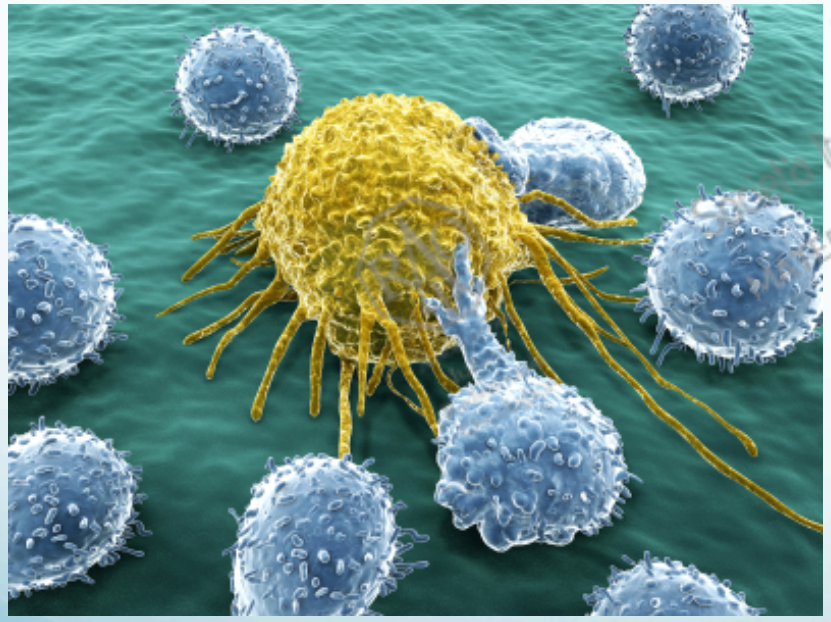
RT enhances:

1. *ANTIGENS EXPOSURE*
2. *ATTRACTION OF ACTIVATED T CELLS*
3. Expression of molecules on *SURVIVING TUMOR CELLS* improves their recognition and killing by T cells

Matsumura, Radiat Res. 2010 April ; 173(4): 418–425.

RADIOTHERAPY
IMMUNOSUPPRESSIVE AND PROIMMUNOGENIC EFFECTS

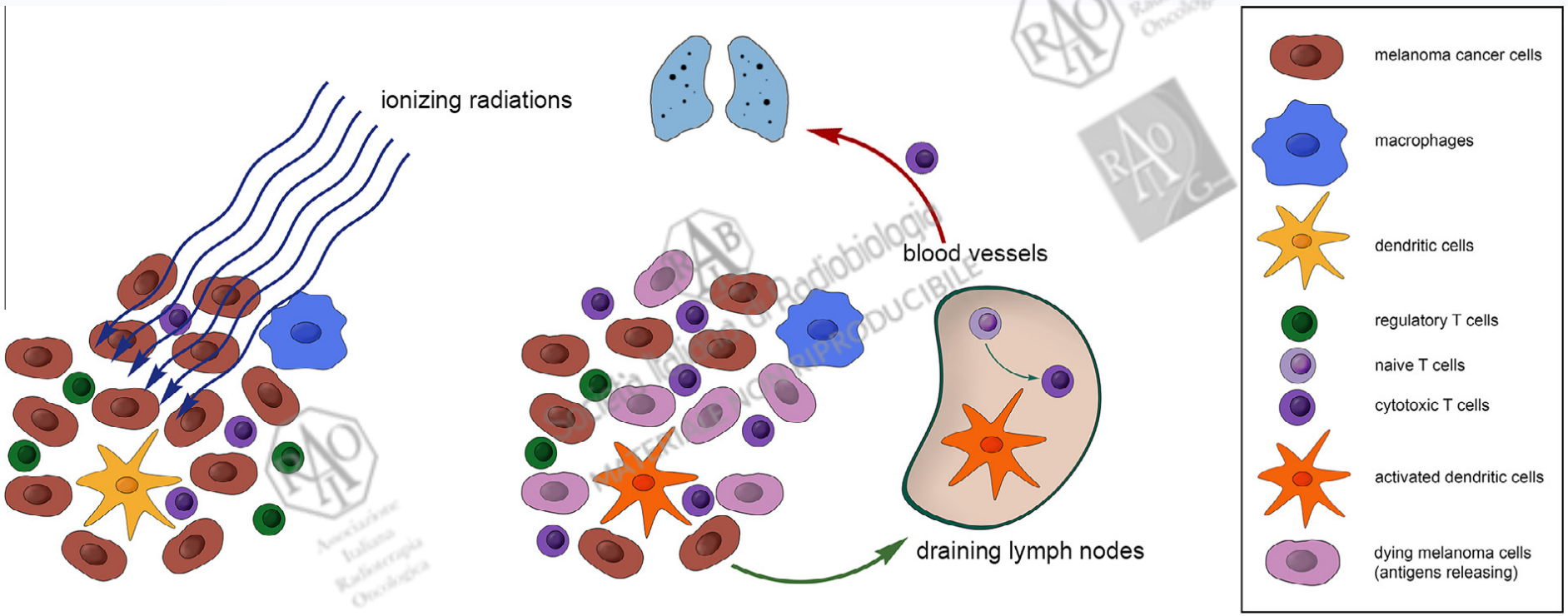
Radiation-induced upregulation of major histocompatibility complex class 1 (MHC-1), NKG2D ligands (NKG2DL), intercellular adhesion molecule 1 (ICAM-1), death receptor Fas, and costimulatory molecule CD80 on surviving tumor cells improves their recognition and killing by T cells.



"Recent discovery suggests that **RT** can be applied as a powerful adjuvant to immunotherapy and, in fact, can contribute to convert the irradiated tumor into an **IN SITU VACCINE**, resulting in specific immunity against metastases"

Formenti S, J Natl Cancer Inst;2013;105:256–265

THE IN SITU VACCINATION CONCEPT

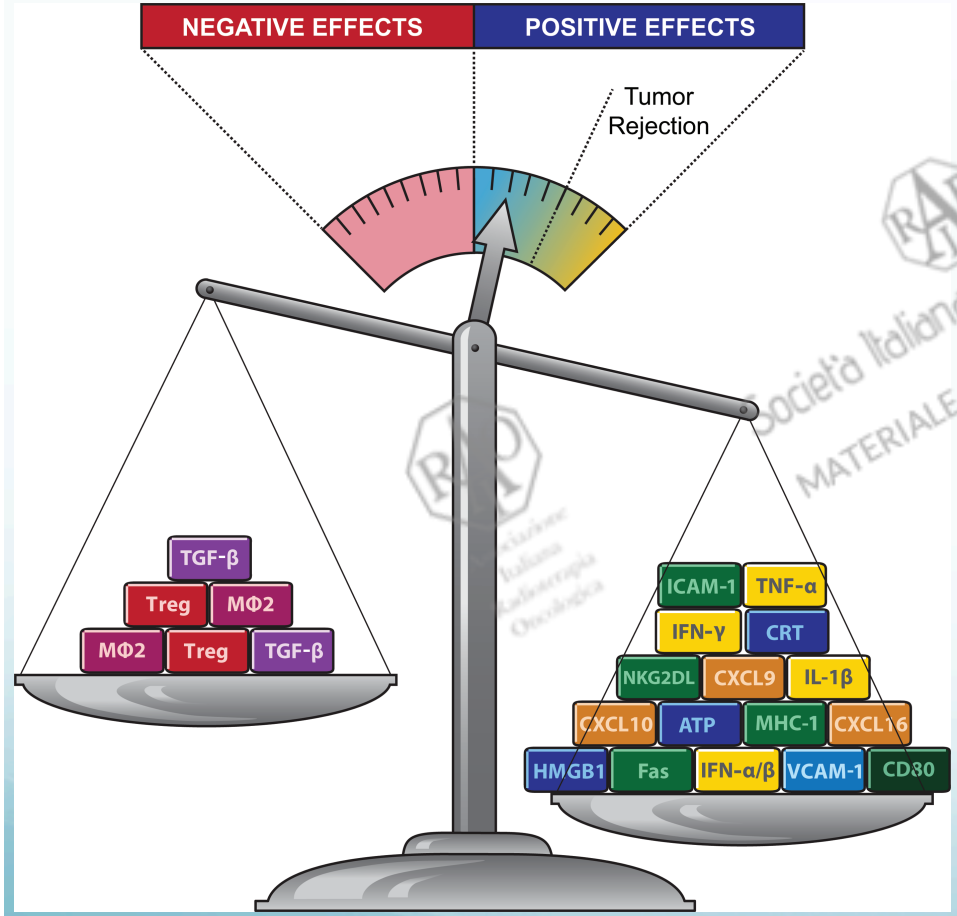


Filippi AR et al, Radiotherapy and Oncology 120 (2016) 1–12

IONIZING RADIATION ACTS AS A MODIFIER OF THE TUMOR MICROENVIRONMENT CONVERTING THE TUMOR INTO AN IN SITU VACCINE.

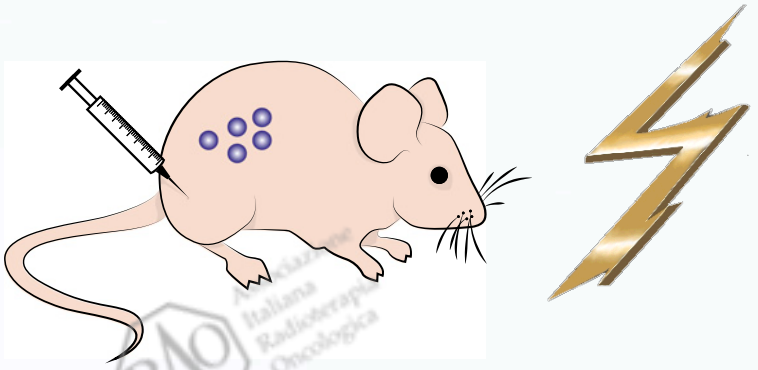
Demaria and Formenti, Frontiers in Oncology 2012

RADIOTHERAPY
IMMUNOSUPPRESSIVE AND PROIMMUNOGENIC EFFECTS



Data suggest that positive effects of radiation often predominate over negative ones but *ARE INSUFFICIENT TO SHIFT THE BALANCE* of the *IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT* to achieve tumor rejection in the absence of targeted immunotherapy.

COMBINING RADIOTHERAPY AND CANCER IMMUNOTHERAPY: **A PARADIGM SHIFT**



Over thirty years ago, Helen Stone and colleagues compared the effects of local tumor irradiation in immunocompetent and T cell deficient mice, providing the first evidence that tumor *RESPONSE TO RADIOTHERAPY IS IMPAIRED IN THE ABSENCE OF A NORMAL T CELL* repertoire.

Stone, H B.; Peters, L J.; and Milas, L, "Effect of host immune capability on radiocurability and subsequent transplantability of a murine fibrosarcoma." (1979). Subject Strain Bibliography 1979. Paper 831.

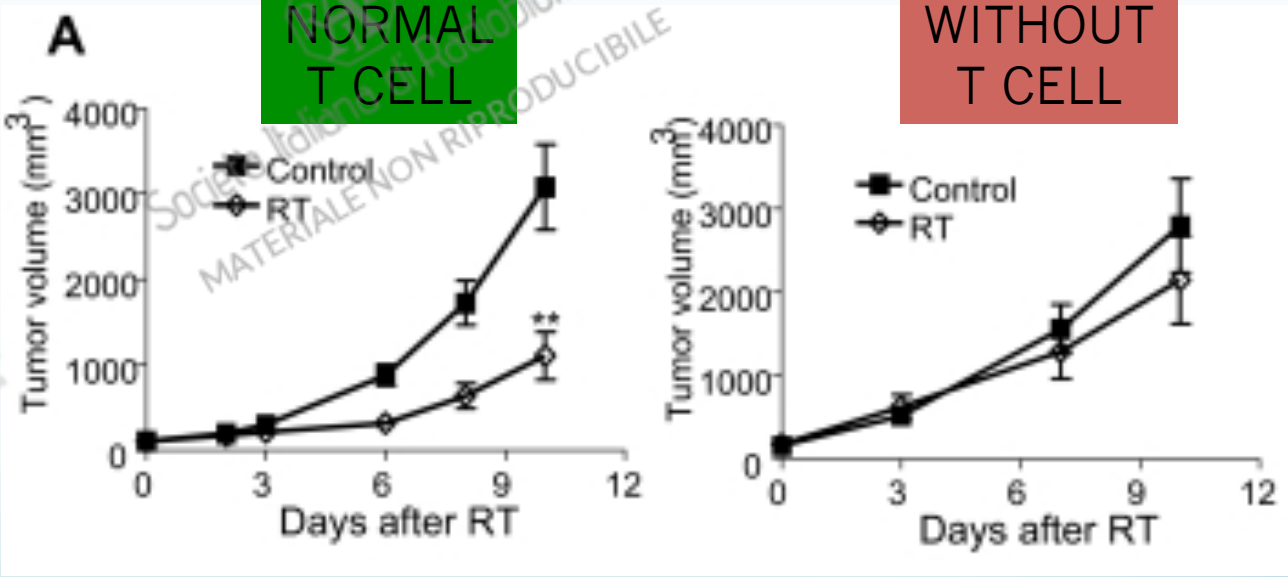
Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment

B16 melanoma is well established to be a highly aggressive, rapidly growing, poorly immunogenic, radio-resistant tumor and also known to resist various treatments

THERAPEUTIC EFFECT OF ABLATIVE RT REQUIRES T CELLS

NORMAL T CELL

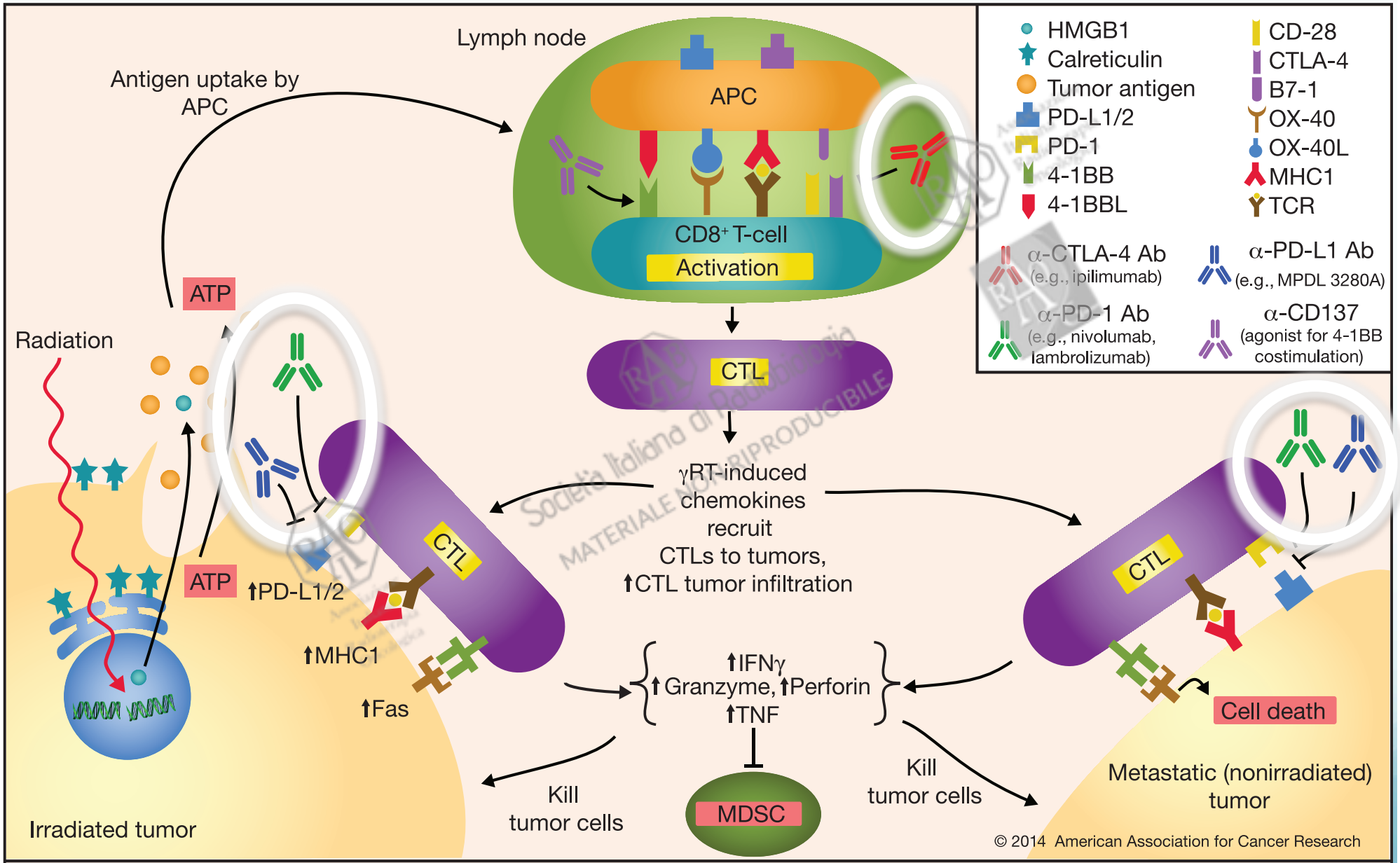
WITHOUT T CELL



after ablative RT (20 Gy × 1), B16 tumors show significant regression in wild-type (WT) mice Impressively, the tumor remained radio-resistant to ablative RT in the absence of T cells

Lee, Blood. 2009 Jul 16; 114(3): 589–595.

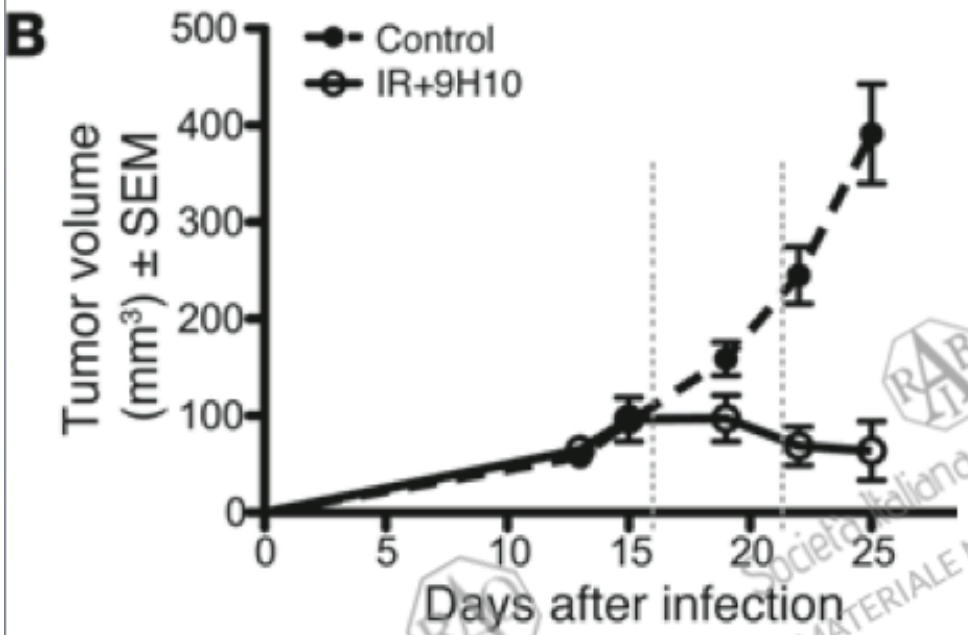
CHECKPOINT INHIBITORS WITH RT-INDUCED IMMUNERESPONSE

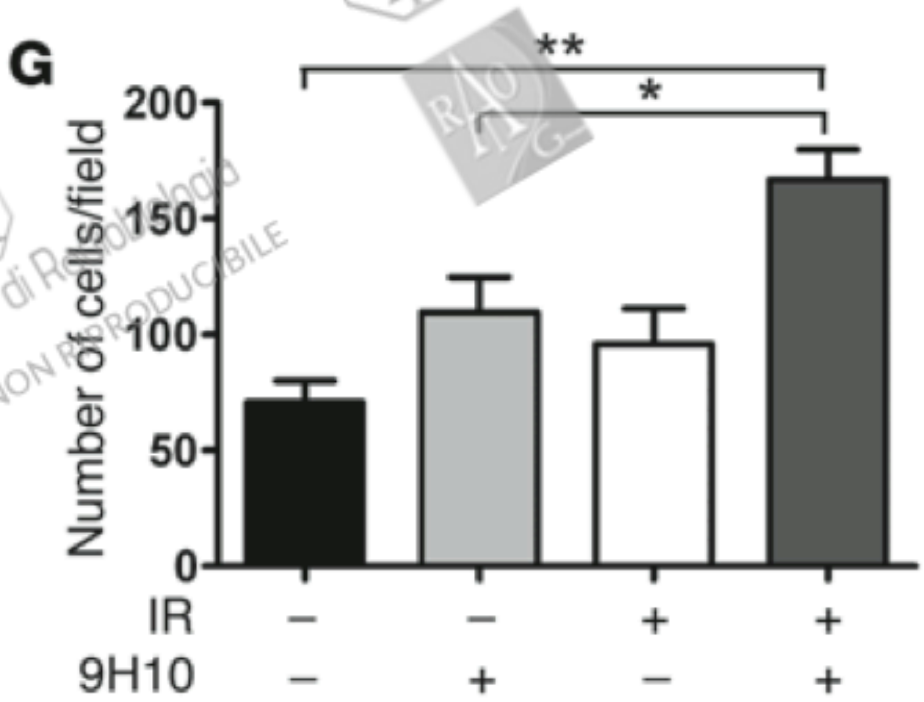


***Cancer Immunology Research*: Cancer Immunology at the Crossroads**

Tand, Cancer Immunol Res 2014; 2(9); 831–8.

COMBINING RADIATION AND ANTI CTLA-4:
TUMOR-INFILTRATING LYMPHOCYTES (TILS) AFTER TREATMENT

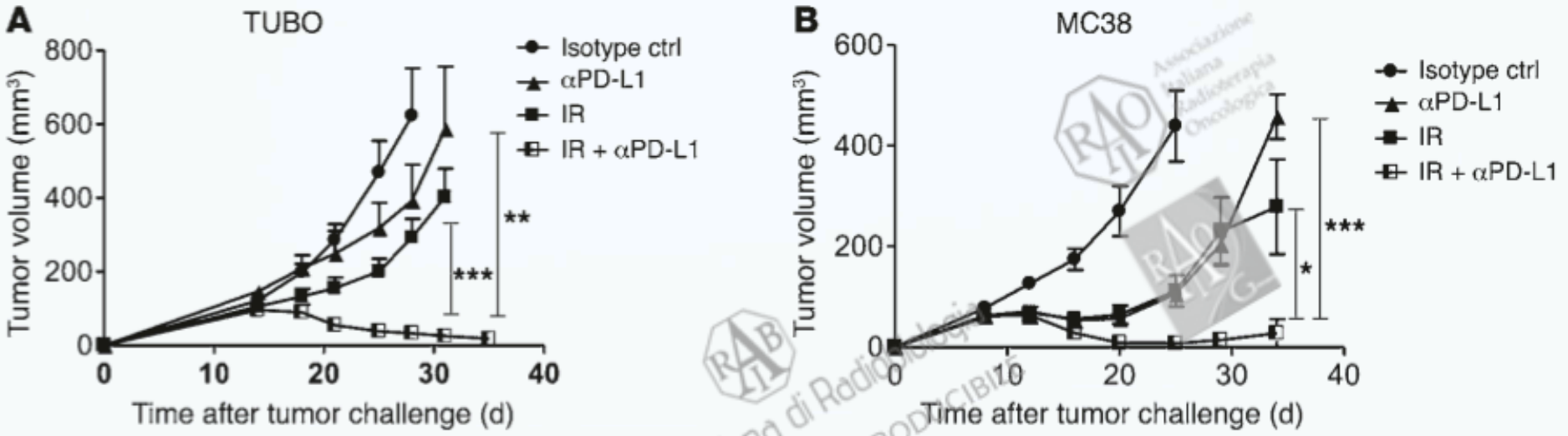


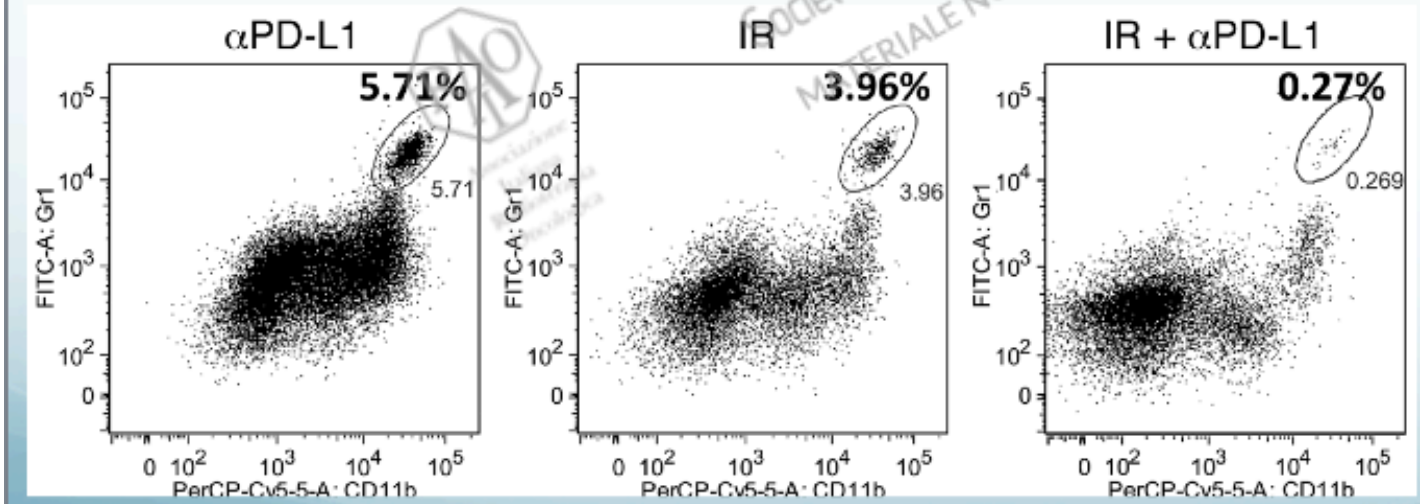


IIR: Radiotherapy
9H10 anti CTLA4 mAB

Ruocco, J Clin Invest. 2012;122(10):3718–3730.

COMBINING RADIATION AND ANTI PD-1/PDL-1





RT REDUCTION OF myeloid-derived suppression cells (MDSCs), which suppress T cell activation and promote tumor outgrowth

Deng, J Clin Invest. 2014;124(2):687–695

COMBINING RADIOTHERAPY AND CANCER IMMUNOTHERAPY: **A PARADIGM SHIFT**

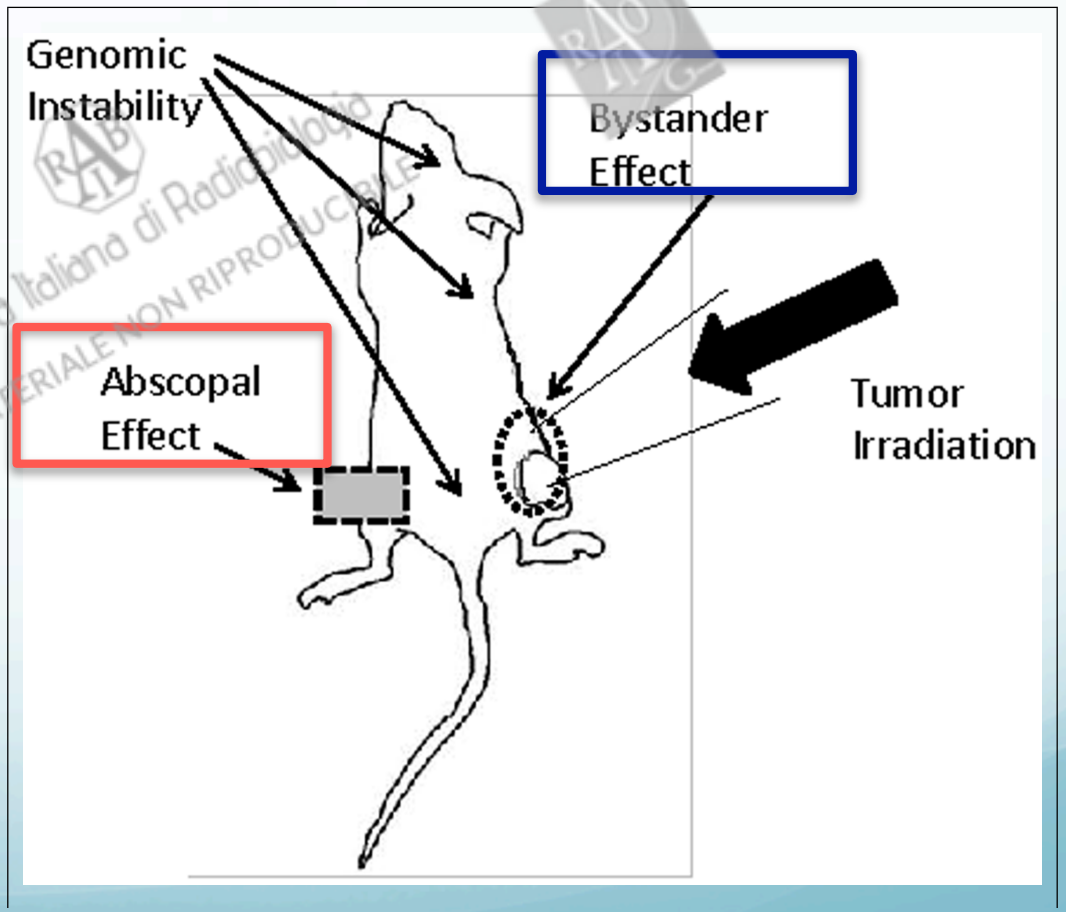
The phenomenon "**ABSCOPAL EFFECT**" or "distant bystander effect" was originally described by Mole (1953) and the term comes from the latin "ab-" (position away from) and "scopus" (mark or target).

Formenti S, J Natl Cancer Inst;2013;105:256–265

COMBINING RADIOTHERAPY AND CANCER IMMUNOTHERAPY: **A PARADIGM SHIFT**

BYSTENDER EFFECT

Radiation-induced bystander effects are defined as biological effects in cells that are in close proximity to cells that have been irradiated (*Hei et al., 2011*).

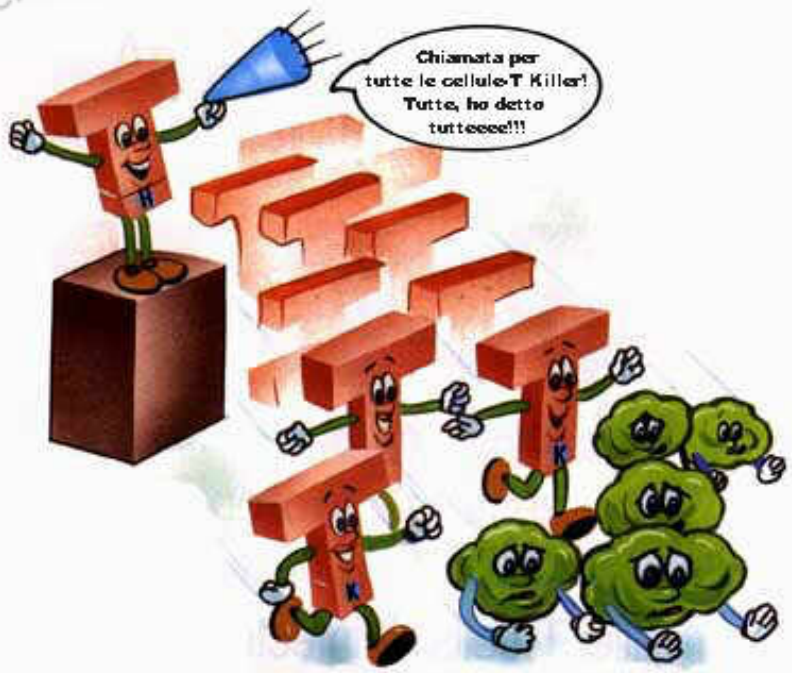


Schmid, Frontiers in Oncol 2012, 2: 67-70

Why are **ABSCOPAL EFFECTS** uncommon?

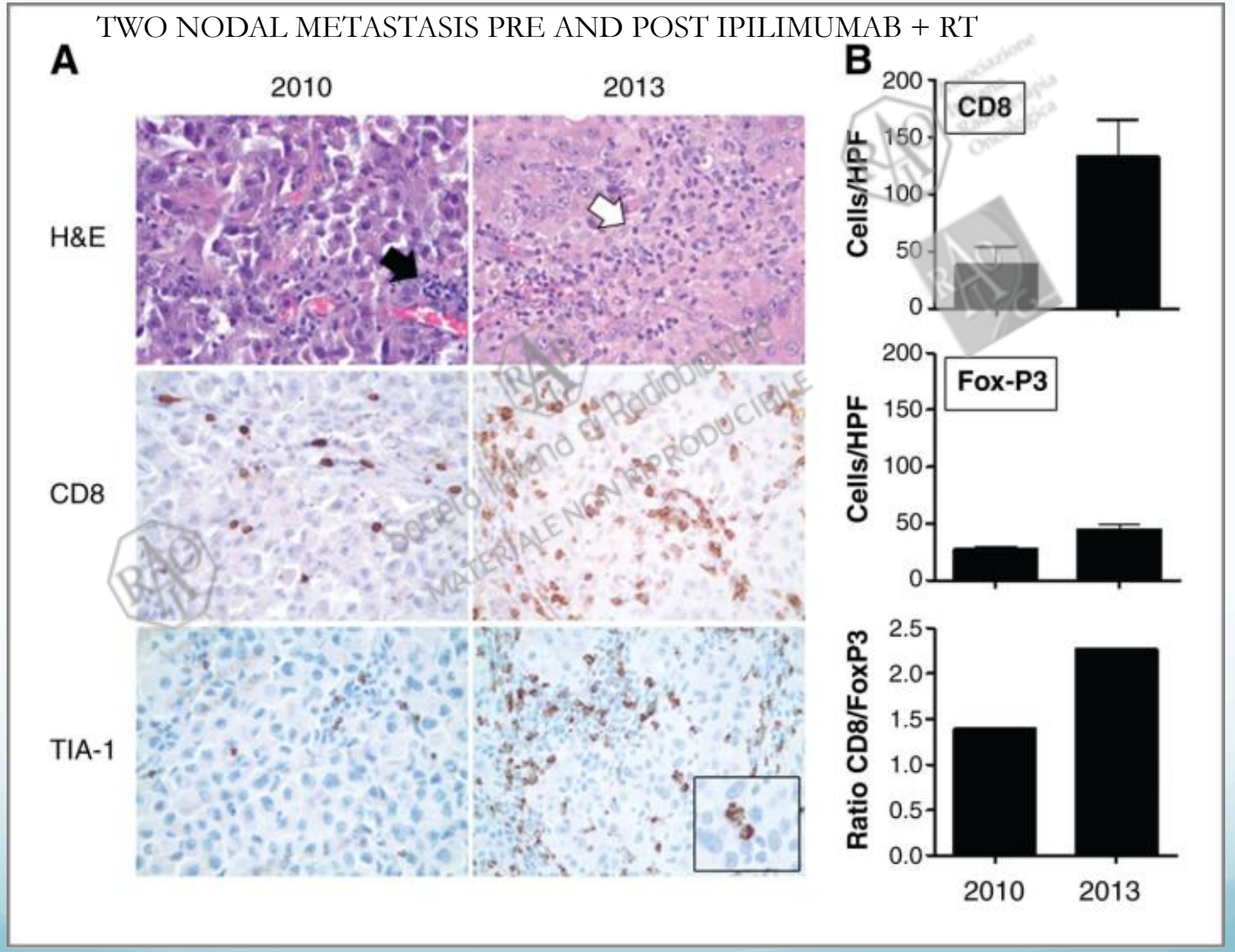
RADIOTHERAPY per se is generally unable to subvert a patient's immune tolerance toward the tumor.

As mentioned before, tumors express a large number of neoantigens, but the antigens that are *STRONGLY IMMUNOGENIC ARE USUALLY ALREADY LOST* at the time of clinical presentation of the disease, "edited" out when tumors escape immune control



CRITICAL CONCENTRATION OF FULLY FUNCTIONAL T CELLS primed against the tumor is required to achieve immune-mediated tumor rejection in experimental tumor models and in the clinic.

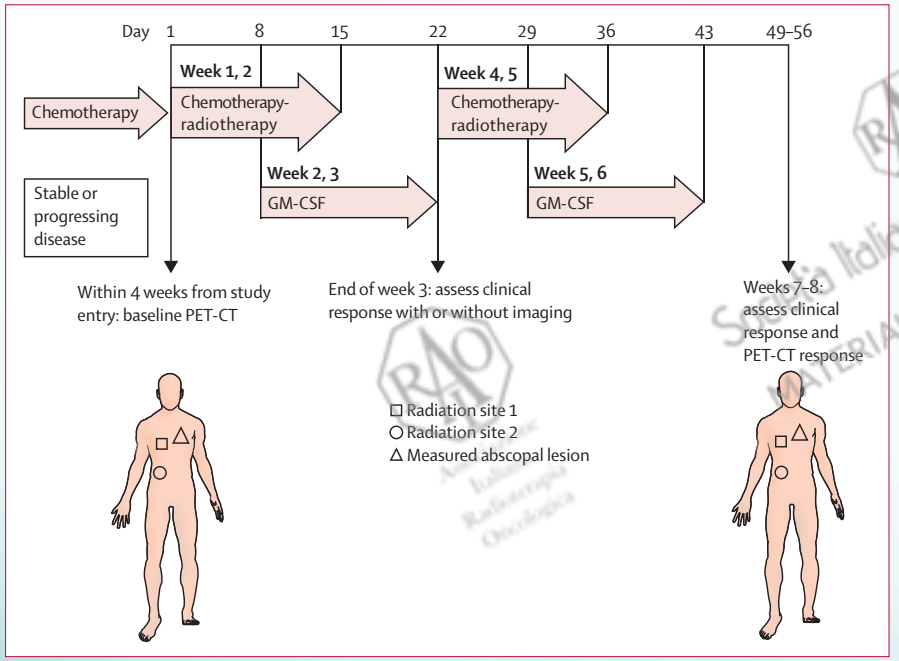
Radiation and Ipilimumab
Enhanced tumor-infiltrating lymphocytes in an abscopal lesion



Encouse B. Golden et al. Cancer Immunol Res 2013;1:365-372

Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial

Encouse B Golden, Arpit Chhabra, Abraham Chachoua, Sylvia Adams, Martin Donach, Maria Fenton-Kerimian, Kent Friedman, Fabio Ponzo, James S Babb, Judith Goldberg, Sandra Demaria, Silvia C Formenti



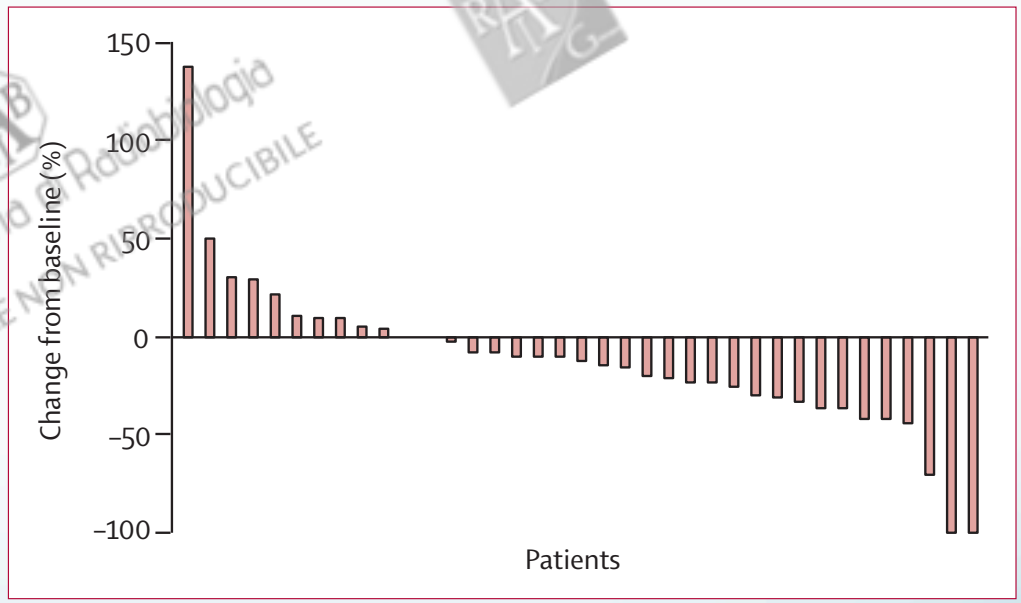


Figure 2: **Waterfall plot of best abscopal responses**

Lancet Oncol 2015; 16: 795–803

Which fractionation?

Which fractionation?

Sinergia tra radioterapia e immunoterapia nella cura dei tumori in stadio avanzato: recenti evidenze di una nuova sfida in oncologia

Renzo Corvò[1,2], Liliana Belgioia[1]

La radioterapia High Tech che eroga alte dosi di radiazioni in pochi minuti di esposizione favorirebbe, per esempio nel *MELANOMA METASTATICO*, amplificati processi biologici di apoptosi, necrosi e autofagia con un'ampia esteriorizzazione di antigeni tumorali; questi antigeni legati alle cellule dendritiche operanti nei linfonodi satelliti alla sede tumorale sarebbero riconosciuti dai linfociti T citossici soprattutto alla presenza d'inibitori del recettore CTLA-4 ad azione immunosopprimente e ora oggetto di ricerca traslazionale.

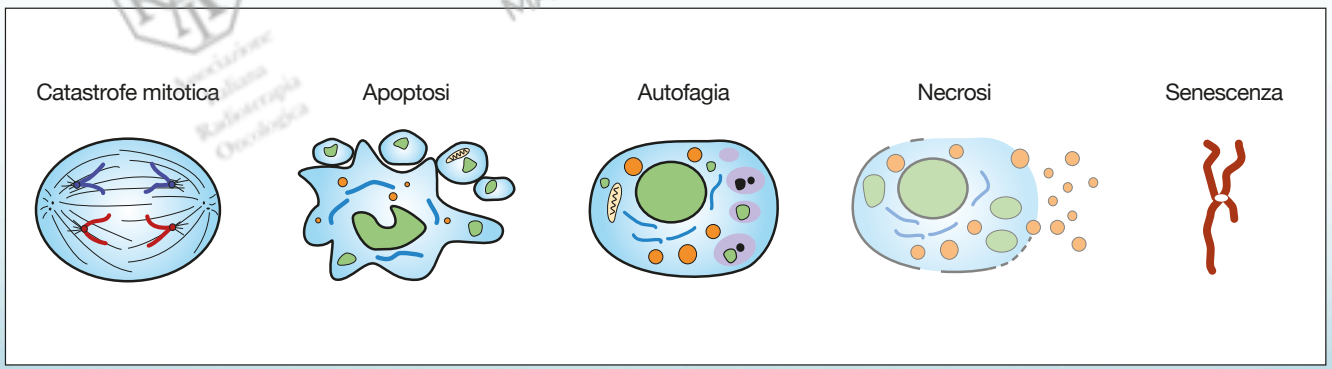


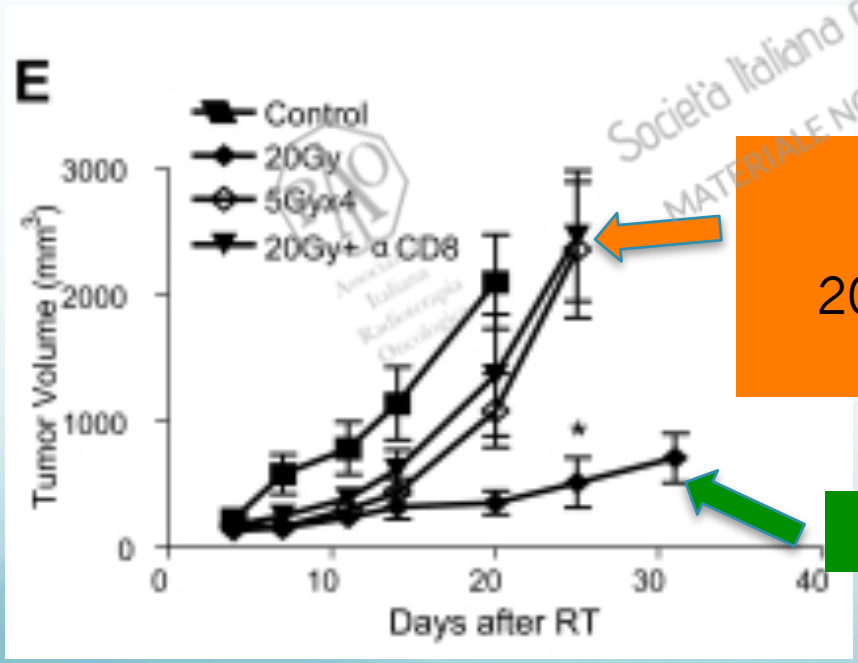
Figura 1. Meccanismi di morte cellulare dopo esposizioni a radiazioni ionizzanti.

Recenti Prog Med 2015; 106: 322-330

Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment

B16 melanoma is well established to be a highly aggressive, rapidly growing, poorly immunogenic, radio-resistant tumor and also known to resist various treatments

FRACTIONATED RT: POTENTIALLY IMMUNOSUPPRESSIVE CONVENTIONAL TREATMENT

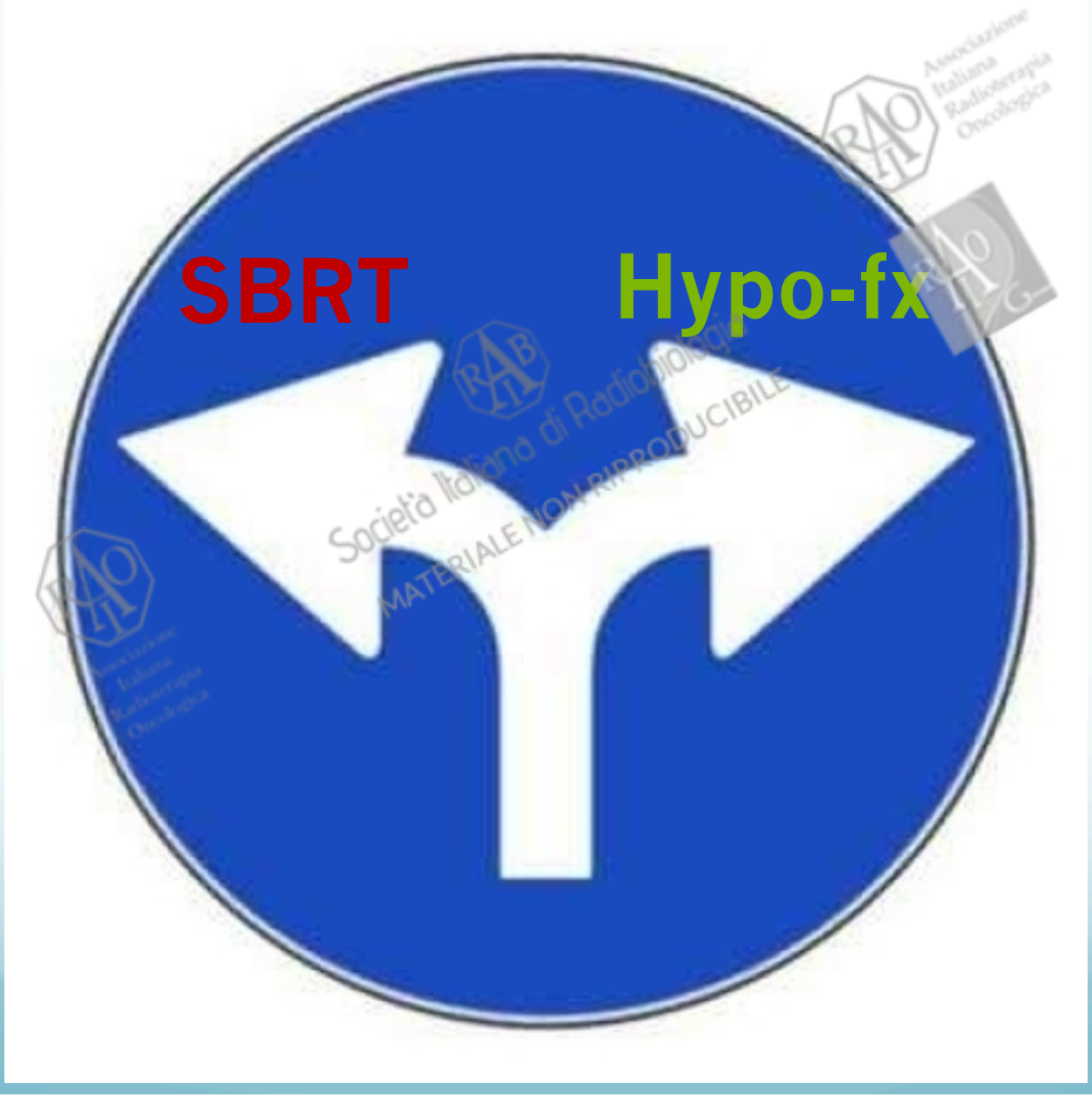


RT 5Gyx4 / 20Gy+ANTI T CELL

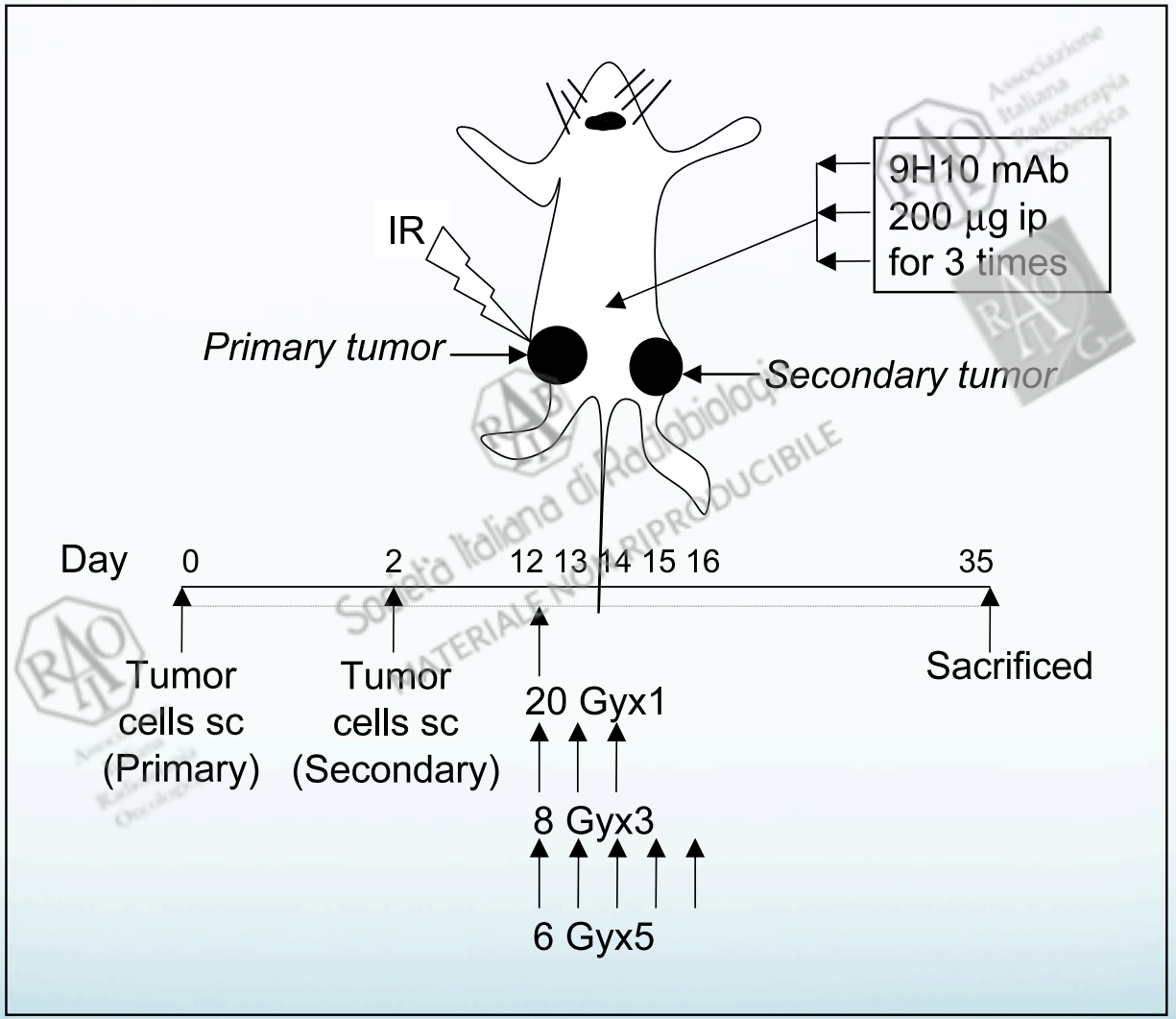
RT 20 Gy

Nonetheless, these findings suggest that the current standard practice of fractionated RT may hinder RT-initiated antitumor immunity

Which fractionation?

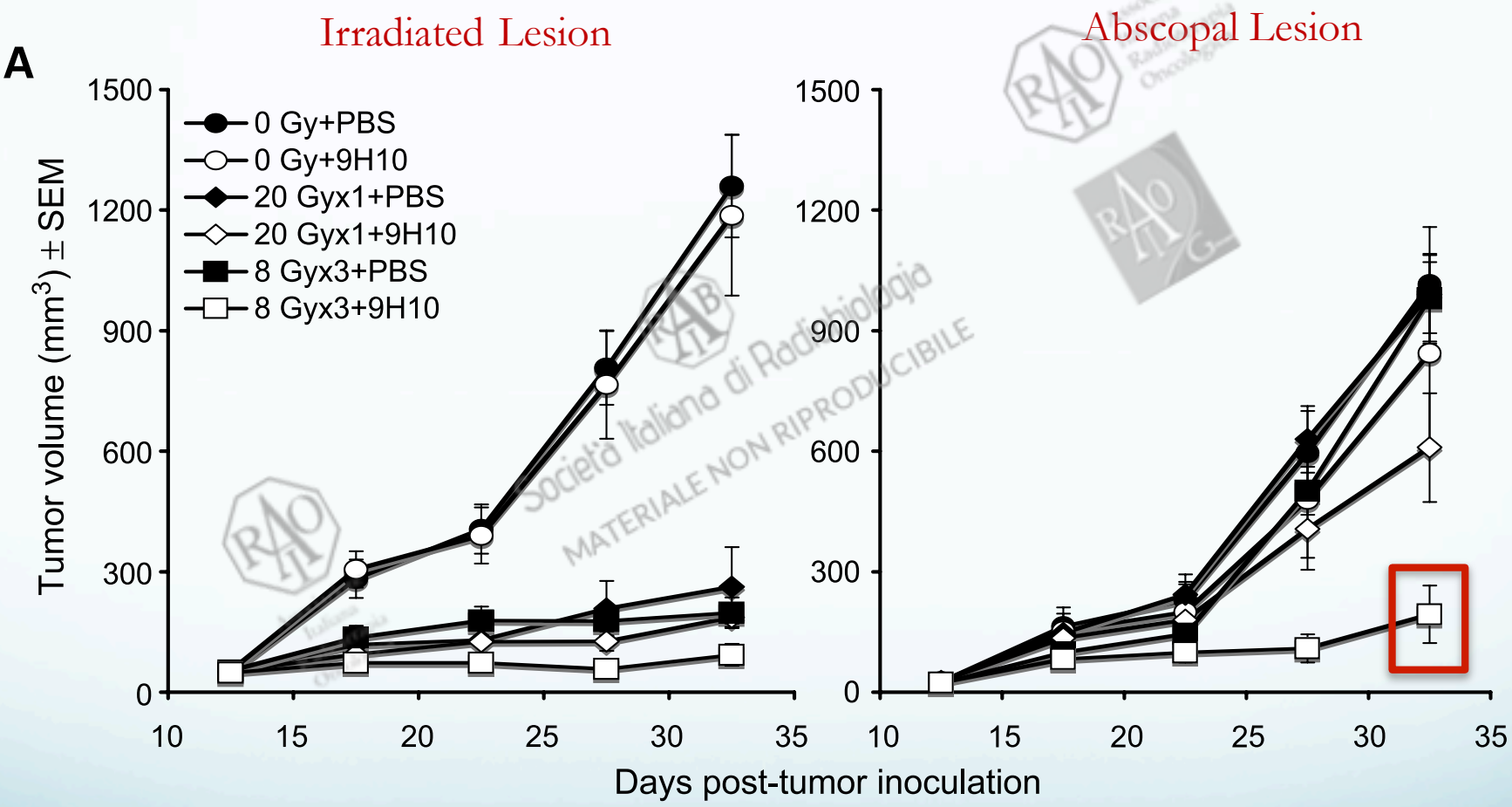


CANCER IMMUNOTHERAPY AND RT



Dewan MZ et al. Clin Cancer Res 2009;15(17):5379–88

CANCER IMMUNOTHERAPY AND RT



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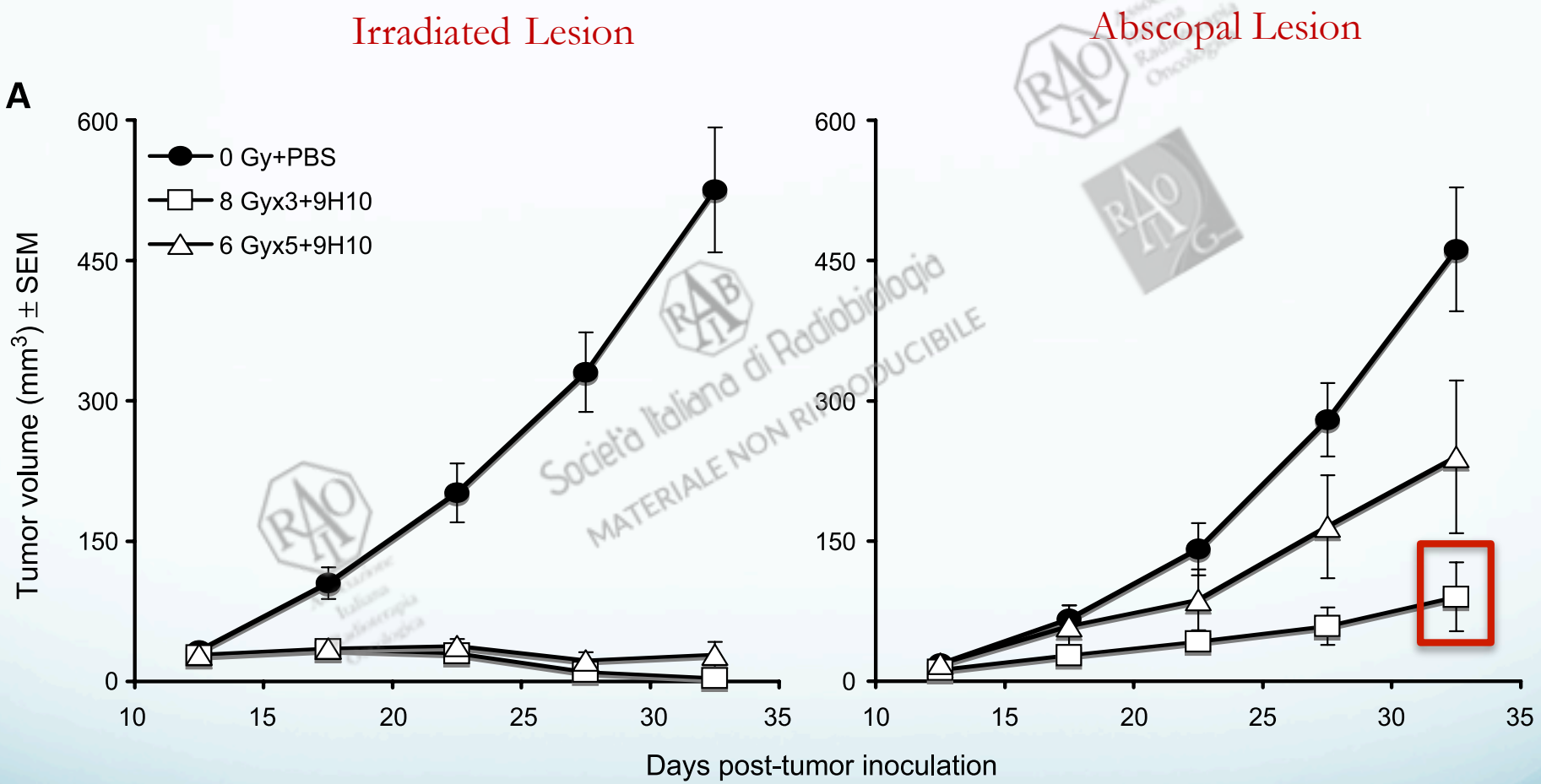

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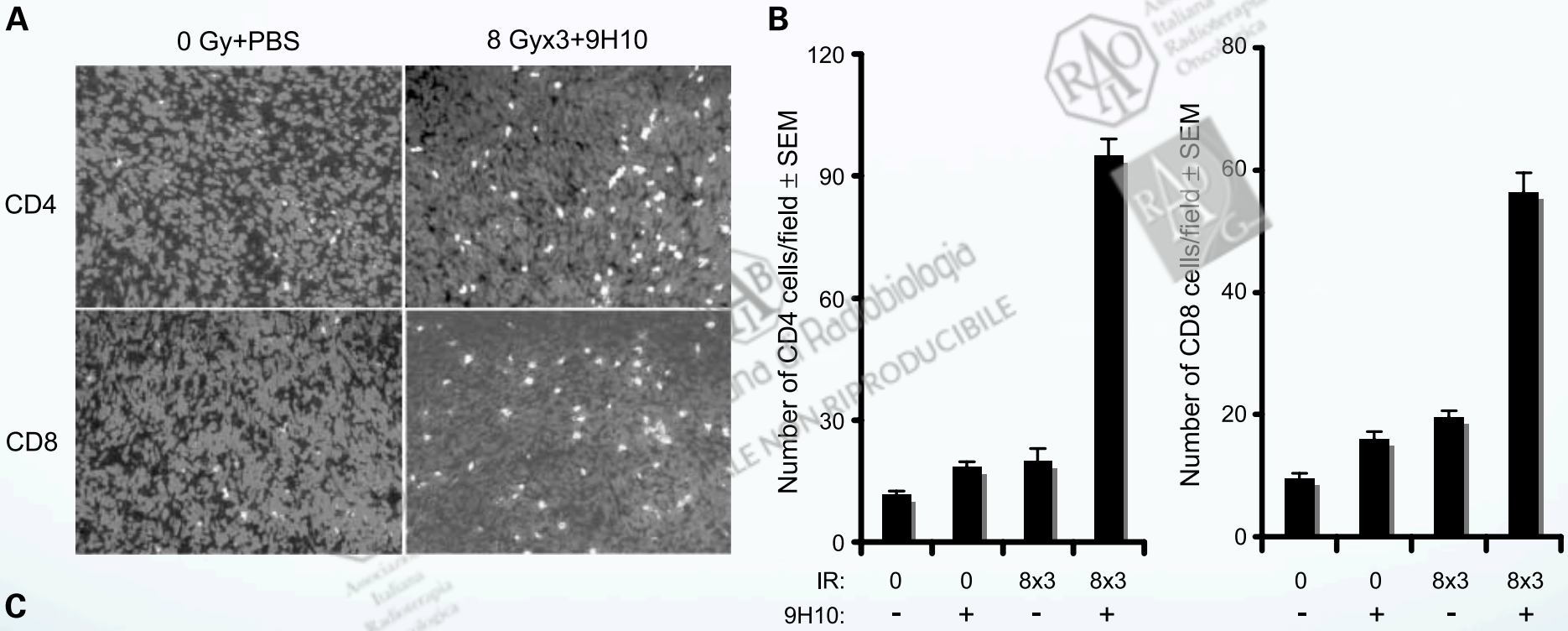

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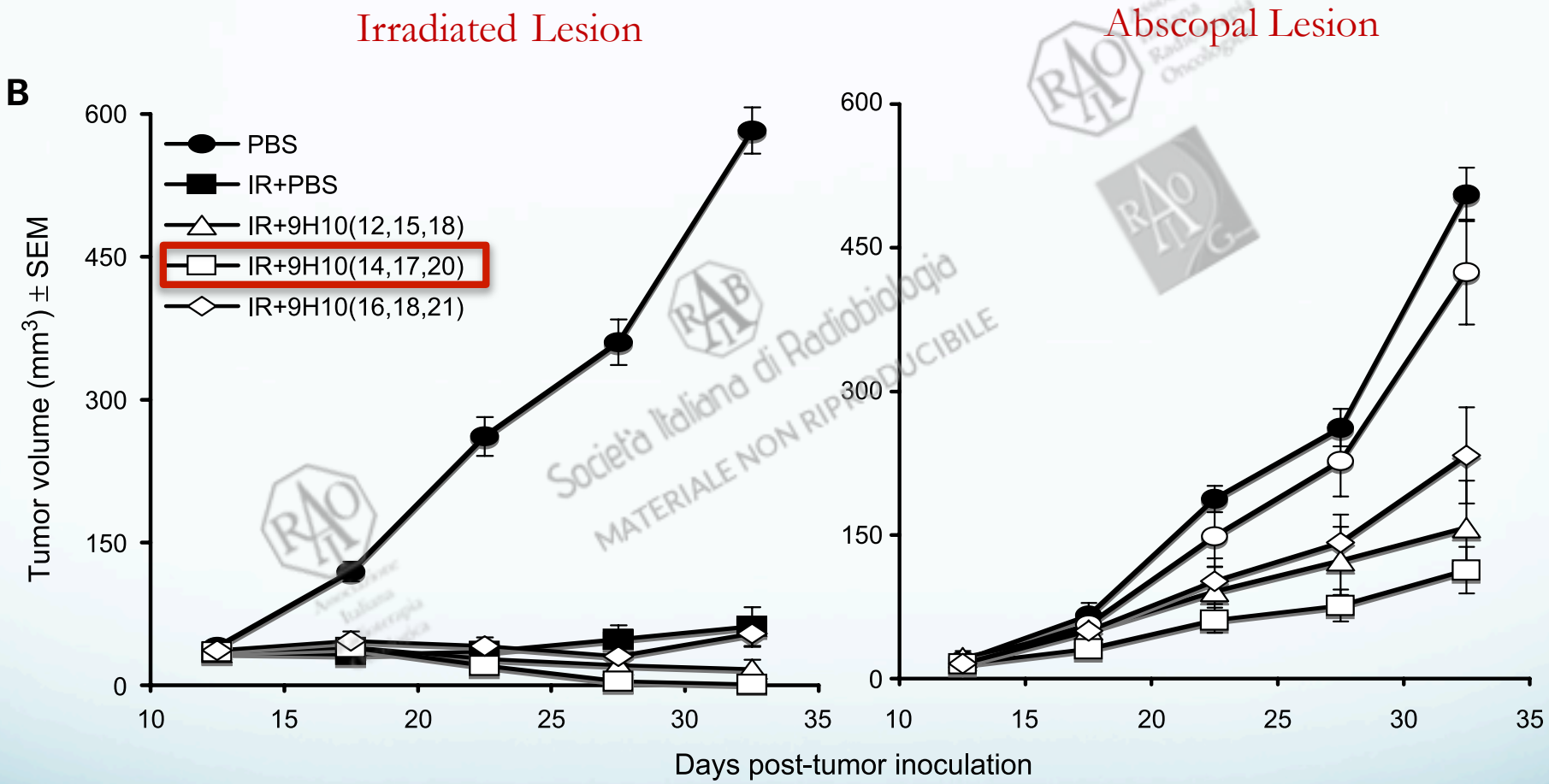
MODULATING CANCER IMMUNOTHERAPY AND SBRT



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JOURNAL OF TRANSLATIONAL MEDICINE

KEYNOTE SPEAKER PRESENTATION Open Access

Combining radiation therapy with immunotherapy: clinical translation

The novel role of radiotherapy as a powerful adjuvant to immunotherapy warrants more research to define the optimal immunotherapy/RT combinations: currently **35 TRIALS OF RT +IMMUNOTHERAPY** are ongoing in USA.

Current Clinical Trials Testing Combinations of Immunotherapy and Radiation

Marka Crittenden, MD, PhD,[*] Holbrook Kohrt, MD,[†] Ronald Levy, MD,[†] Jennifer Jones, MD, PhD,[‡] Kevin Camphausen, MD,[§] Adam Dicker, MD, PhD,[‖] Sandra Demaria, MD,[¶] and Silvia Formenti, MD[#]

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Table 1 Clinical Trials of Immunotherapy and Radiation Currently Open at NYU

Institution/ Study ID	Tumor Site/ Stage (Planned Accrual)	Study Aims	RT Dose/ fraction	Key Inclusion Criteria
NYULMC S11-00533, phase I-II	Breast cancer/ metastatic (28)	Assess the safety and feasibility of combining TGF-β–neutralizing antibody (GC1008, fresolimumab) and local radiotherapy in patients with metastatic breast cancer Determine whether treatment with fresolimumab and localized RT achieves an abscopal tumor regression Examine whether treatment is associated with immunologic changes in patients with metastatic breast cancer	7.5 Gy × 3	At least 2 distinct measurable metastatic sites, with 1 of at least 1 cm or larger in its largest diameter.
NYU S11-00598, phase I-II	Breast cancer/ metastatic (42)	Assess the safety and feasibility of combining a topical toll-like receptor agonist (imiquimod) and local radiotherapy ± low-dose cyclophosphamide in patients with metastatic breast cancer Determine whether treatment with imiquimod and localized RT and ± low-dose cyclophosphamide achieves an abscopal tumor regression Examine whether treatment is associated with immunologic changes in patients with metastatic breast cancer	6 Gy × 5	At least 1 measurable skin metastasis and distant, measurable metastases (outside of skin), or At least 2 distinct measurable metastatic sites, with 1 of at least 1 cm or larger in its largest diameter.
NYU S12-02746, phase II randomized	Melanoma/ metastatic (100)	Evaluate the safety and feasibility of anti–CTLA-4 mAb and concurrent local radiotherapy to a metastatic site Compare systemic response to ipilimumab in patients randomly assigned to radiation to a measurable lesion or not	6 Gy × 5	At least 2 distinct measurable metastatic sites, with 1 of at least 1 cm or larger in its largest diameter and may have additional nonmeasurable but established metastatic lesions (ie, bone metastases).
NYU S14-00208, phase I-II	NSCLC/ metastatic (30)	Evaluate the safety and therapeutic efficacy of anti–CTLA-4 mAb and concurrent local radiotherapy to a metastatic site	6 Gy × 5	At least 2 distinct measurable metastatic sites. Patients may have additional nonmeasurable metastatic lesions (eg, bone metastases).

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Table 2 Clinical Trials of Immunotherapy and Radiation Currently Open at Earle A. Chiles Research Institute (EACRI), Providence Cancer Center

Institution/ Study ID/clinical trials.gov Identifier	Tumor Site/ Stage (Planned Accrual)	Study Aims	RT Dose/fx	Key Inclusion Criteria
PH&S IRB 11-062A NCT01416831/ phase II randomized	Metastatic/ melanoma (44)	Compare response rate of high-dose IL-2 to SBRT and IL-2. Measure the response of SBRT and IL-2 in crossover patients with melanoma who have disease progression after high-dose IL-2 alone. Evaluate markers of tumor lysis, inflammation, and immune activation in the blood of patients receiving combined treatment compared with patients receiving high-dose IL-2 alone	20 Gy × 1 and 20 Gy × 2	At least 2 distinct measurable metastatic sites, with at least 1 metastatic lesion amenable to SBRT in the lung mediastinum or liver.
PH&S IRB 10-088 NCT01303705/ phase Ib	Metastatic/prostate cancer (37)	Determine the maximum tolerated dose of cyclophosphamide administered in combination with radiation and anti-OX40 in men with metastatic castration- and chemotherapy-resistant prostate cancer. Determine the effect of therapy on circulating numbers and phenotypes of CD4 and CD8 T cells. Measure the proliferation and activity of effector and memory T cells following therapy. Perform exploratory studies of cellular and humoral immune responses against prostate cancer cell lines. Estimate the response rate of the regimen that includes the highest dose of CTX determined to be safe.	8 Gy × 1	At least 1 bone metastatic lesion amenable to radiation and measurable or evaluable metastatic adenocarcinoma of the prostate. Patients must have confirmed progression after at least 1 androgen ablation and administration of docetaxel.
PH&S IRB 12-017A NCT01862900/ phase I-II	Metastatic/breast cancer (40)	Determine the maximum tolerated dose and safety profile of radiation administered in combination with anti-OX40 Estimate the response rate of combined modality treatment in both irradiated and nonirradiated tumors Determine the influence of combined treatment on immune parameters.	Cohort 1: 15 Gy × 1 Cohort 2: 20 Gy × 1 Cohort 3: 20 Gy × 2	At least 1 site in the lung or liver that is amenable to SBRT. Evaluable disease that will not receive radiation.
PH&S IRB 10-141B NCT01342224/ phase I	Locally advanced and borderline resectable pancreatic cancer (11)	Evaluate the safety of combination gemcitabine, tadalafil, telomerase vaccine and GM-CSF, and standard fractionated radiation. Determine the response rate of combined therapy. Determine the frequency of telomerase-specific T-cell responses and perform exploratory studies of immune response in the blood and resected tumors.	1.8 Gy × 28	
PH&S IRB 13-026A NCT01903083/ phase I	Locally advanced and borderline resectable pancreatic cancer (10)	Evaluate the safety of combination gemcitabine, tadalafil, and hypofractionated radiation Assess immune infiltrate in resected tumors. Determine the influence of combined therapy on immune parameters.	8-10 Gy × 3	

Current Clinical Trials Testing Combinations of Immunotherapy and Radiation

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Table 3 Clinical Trials of Immunotherapy and Radiation Currently Open at Stanford

Institution/ Study ID	Tumor Site/ Stage (Planned Accrual)	Study Aims	RT Dose/ fx	Key Inclusion Criteria
Stanford, phase I-II	NHL	Evaluate the safety of intratumoral injection of an immunostimulatory CpG, SD101, combined with local radiation for the treatment of recurrent or progressive lymphoma after allogeneic hematopoietic cell transplantation	2 Gy × 2	At least 2 distinct measurable metastatic sites following allogeneic HCT
Stanford, phase I-II	Low-grade NHL	Evaluate the safety of dose escalation and expansion study of intratumoral injections of SD-101 in combination with localized low-dose radiation in patients with untreated low-grade B-cell lymphoma.	2 Gy × 2	At least 2 distinct measurable metastatic sites
Stanford, phase I-II	Melanoma, NHL, and CRC	Evaluate the safety of combining intratumoral anti–CTLA-4 immunotherapy with local radiation therapy with a monotherapy ipilimumab safety lead in	2-10 Gy × 2	At least 2 distinct measurable metastatic sites.

Abbreviations: CRC, colorectal cancer; HCT, hematopoietic cell transplantation.

Table 4 Clinical Trials of Immunotherapy and Radiation Currently Open at National Institutes of Health/National Cancer Institute

Institution/ Study ID	Tumor Site/ Stage (Planned Accrual)	Study Aims	RT Dose/fx	Key Inclusion Criteria
NIH/NCI 11-C-0247 NCT01496131 (phase II)	High- or intermediate-risk prostate cancer (48)	Evaluate the effect of the MUC1-specific vaccine (stimuvax/L-BLP25/tecemotide) on systemic immune responses when given in combination with standard radiation and androgren-deprivation therapy.	Conventional dose and fractionation	Must have no evidence of metastatic disease, based on CT findings, and must have HLA-A2 or HLA-A3 for immune monitoring.
NIH/NCI # pending	Metastatic colorectal cancer (15)	Evaluate the safety of AMP-224—a PD-1 inhibitor—in combination with stereotactic body radiation therapy (SBRT) in patients with metastatic colorectal cancer.	8 Gy × 1 or 8 Gy × 3	Must have at least 1 site of disease in the liver that is amenable to SBRT.

Abbreviation: CT, computed tomography.

Current Clinical Trials Testing Combinations of Immunotherapy and Radiation

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Table 5 Clinical Trial of Immunotherapy and Radiation Currently Open at Thomas Jefferson University

Institution/ Study ID	Tumor Site/ Stage (Planned Accrual)	Study Aims	RT Dose/fx	Key Inclusion Criteria
TJU-NC T01703507	Metastatic melanoma to brain	Determine the maximum tolerated dose (MTD) of ipilimumab when combined with whole-brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) Secondary objectives: Determine local control rate of the brain metastases Determine the rate of developing of new brain metastases Determine the response of extracranial disease Determine the overall survival rate and progression-free survival rate	SRS doses: 24, 21, 18, and 15 Gy. Whole-brain radiation dose: 37.5 Gy	Histologically confirmed patients with melanoma using imaging confirmed brain metastases. Age is 18 years or older. ECOG performance status 0 or 1.

Conclusions

Response to radiotherapy is immune-mediated, and radiotherapy enhances immonogenic response and ICDs

There is a strong biological rationale in exploring f**easibility and efficacy of combining radiotherapy and immunotherapy**

Pre-clinical data support **concurrent immunotherapy and RT** in order to improve results in irradiated tumor

While type of RT (SBRT vs standart fractionation) needs clinical data

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