



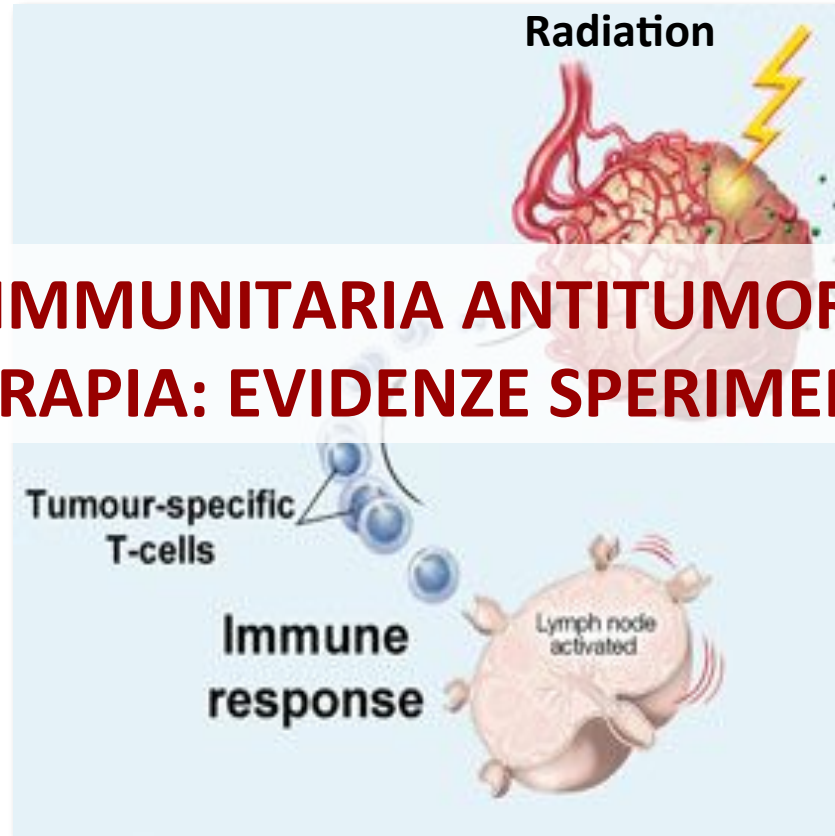
XXIV Congresso Nazionale
dell'Associazione Italiana di Radioterapia Oncologica
Padova, 8-11 novembre 2014

SIMPOSIO AIRO AIRB.

**Microambiente e modulazione della risposta alla radioterapia
10 novembre 2014**



LA RISPOSTA IMMUNITARIA ANTITUMORALE INDOTTA DALLA RADIOTERAPIA: EVIDENZE SPERIMENTALI E CLINICHE



Elena Muraro, PhD
BioImmunoterapie dei Tumori umani
Centro di Riferimento Oncologico di Aviano (PN),
Istituto Nazionale Tumori, IRCCS





Associazione
Italiana
Radioterapia
Oncologica

XXIV CONGRESSO NAZIONALE AIRO 2014

Padova, 8-11 novembre



DICHIARAZIONE

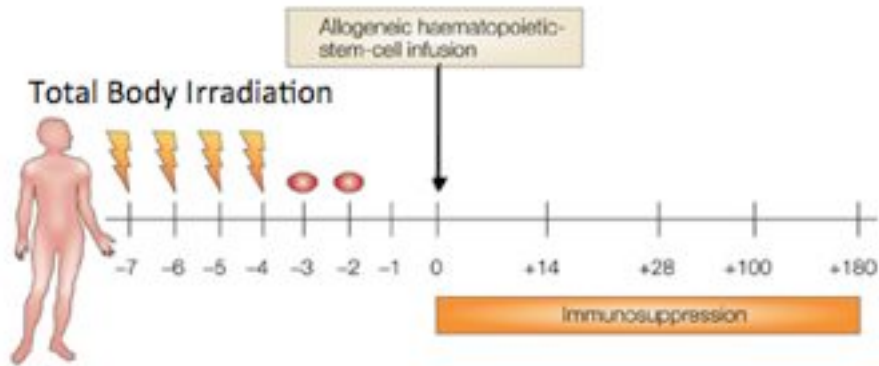
Relatore: Elena Muraro

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

Immune effects of systemic and local RadioTherapy (RT)

Low-doses systemic RT



Bleakley & Riddell, *Nature Rev Canc* 2004

Total Body Irradiation

- Myeloablative
- Immunosuppressive



ICU - Cytophysics 2007

High-doses local RT

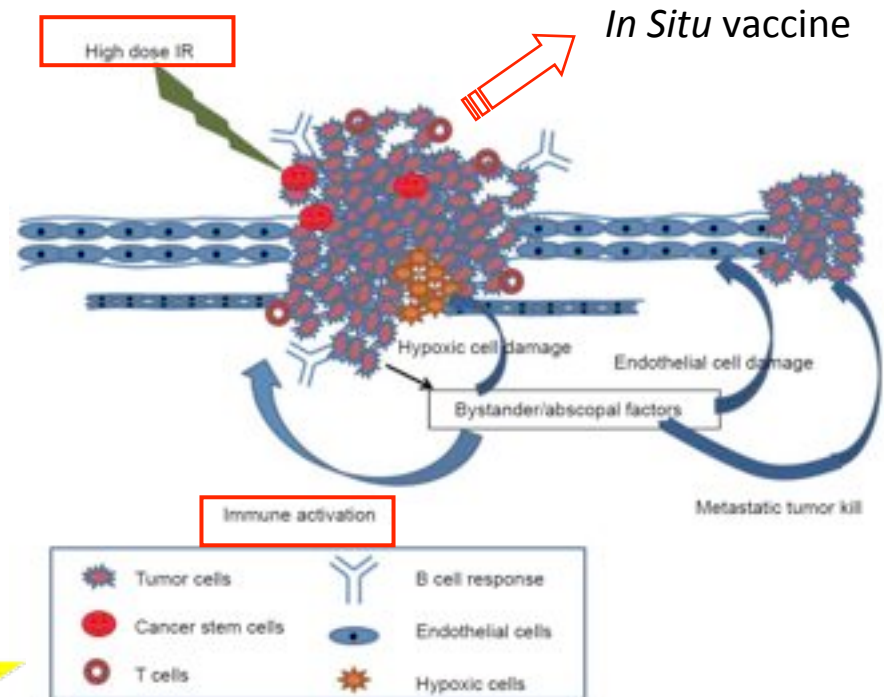
Editorial

Int Journal of Radiat Oncol Biol Phys 2012

Radiation Therapy to Convert the Tumor Into an In Situ Vaccine

Silvia C. Formenti, MD,* and Sandra Demaria, MD†

Departments of *Radiation Oncology, and †Pathology, New York University School of Medicine and NYU Langone Medical Center, New York, New York



Prasanna et al, *Journal of Thoracic Disease* 2014

Hypofractionated high-doses local RT

- may be immunogenic?

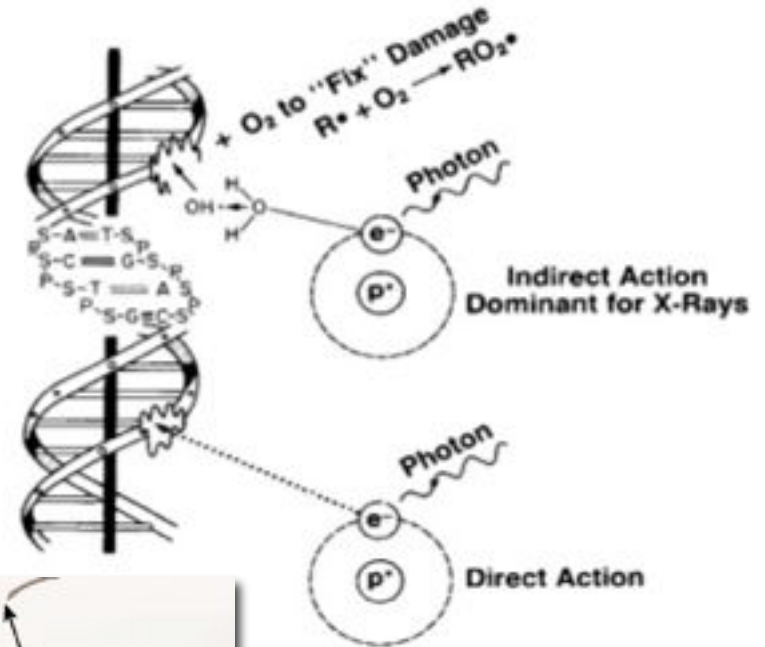
Tumor Rejection by the immune system as the “5th R” of radiobiology

The “4 R’s” of radiobiology

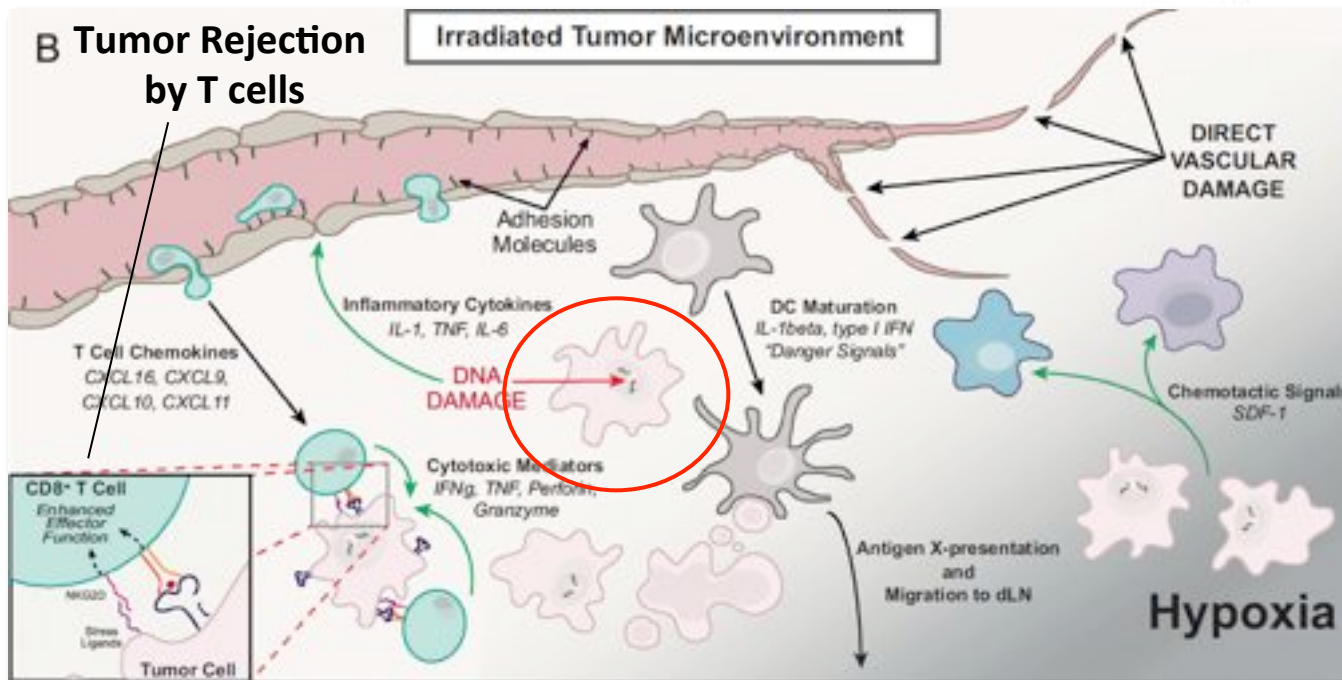
1. Redistribution of cells into radiosensitive phases of the cell cycle (G2/M)
 2. Reoxygenation of hypoxic cells in a tumor core
 3. Repair of sublethal damage
 4. accelerated Repopulation of cells due to proliferation
- + intrinsic Radiosensitivity

Effects caused:

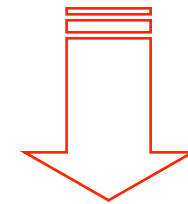
- directly with a damage on DNA of tumor cells
- indirectly after the induction of free radicals



Withers HR, Adv. Radiat. Biol 1975

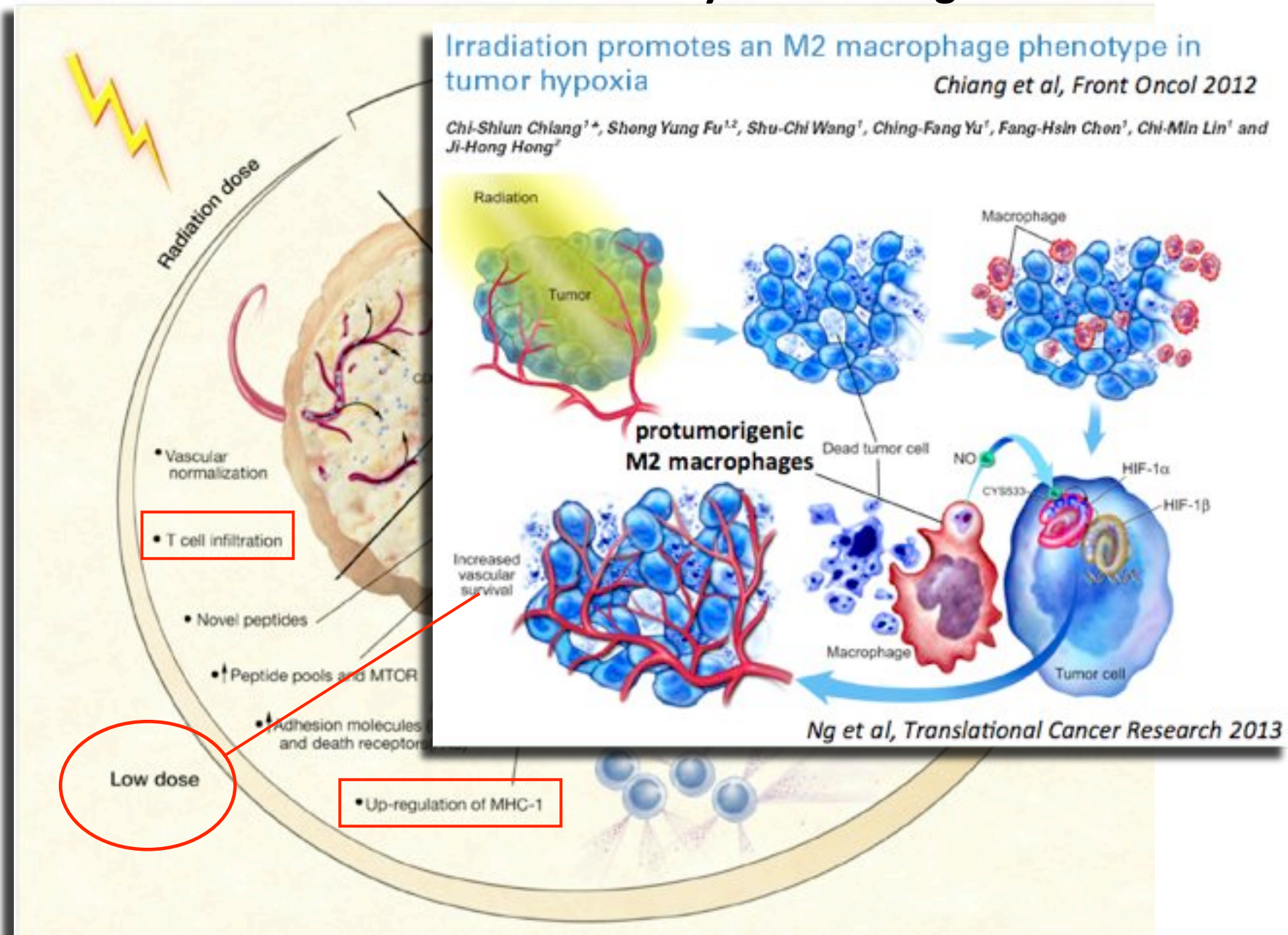


Burnette et al, Semin in Radiat Oncol 2013

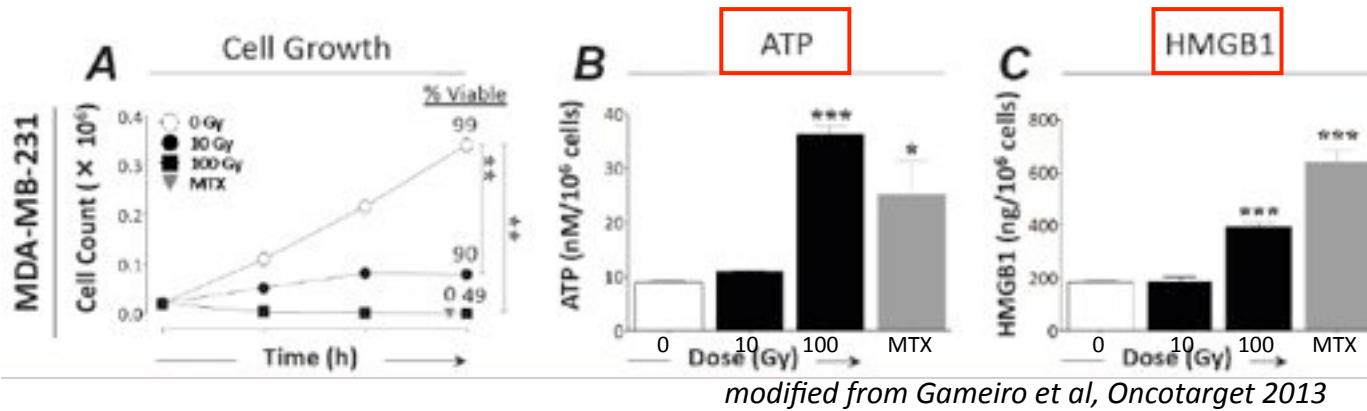


Active crosstalk between tumor microenvironment and immune system

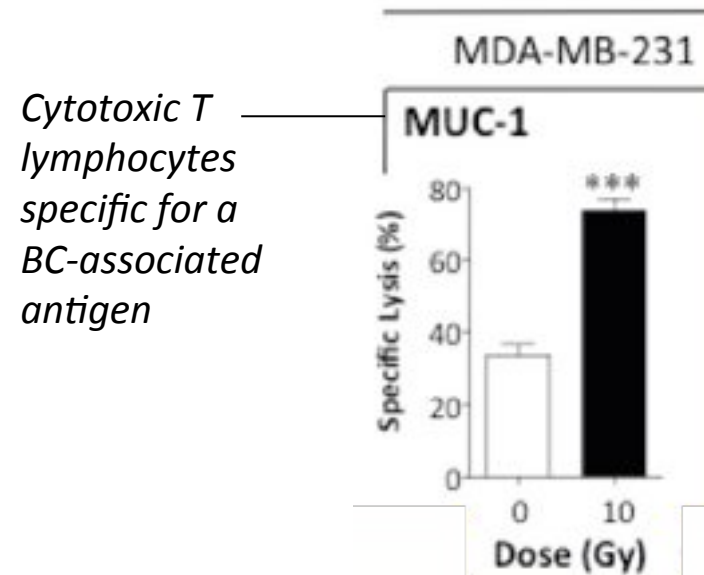
Immune-modulation induced by low and high doses RT



Radiation induces *in vitro* the hallmarks of immunogenic cell death



- radiation-induced immunogenic modulation of tumor enhances antigen-processing and calreticulin exposure, resulting in enhanced T-cell killing

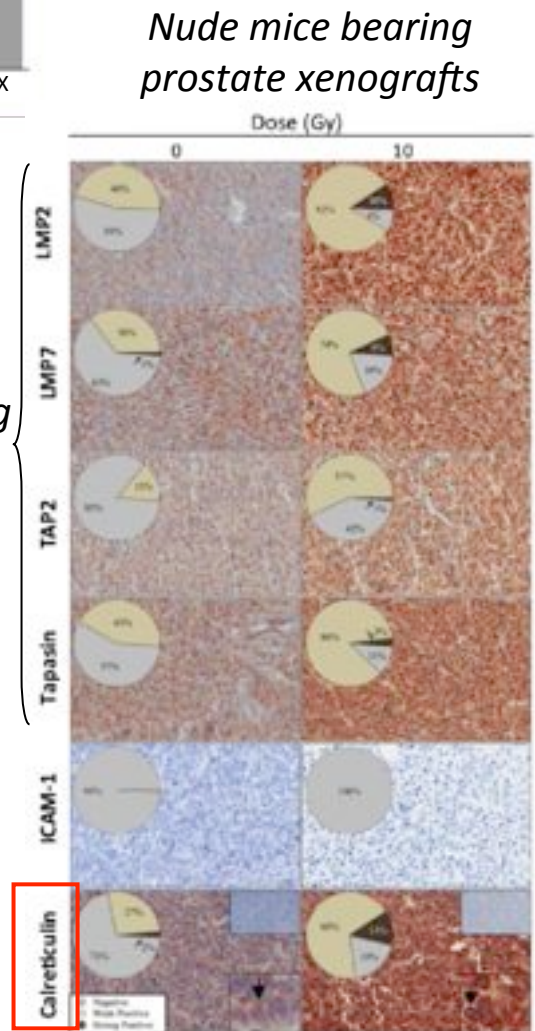


modified from Gameiro et al, Oncotarget 2013

Immunogenic cell death (ICD) features

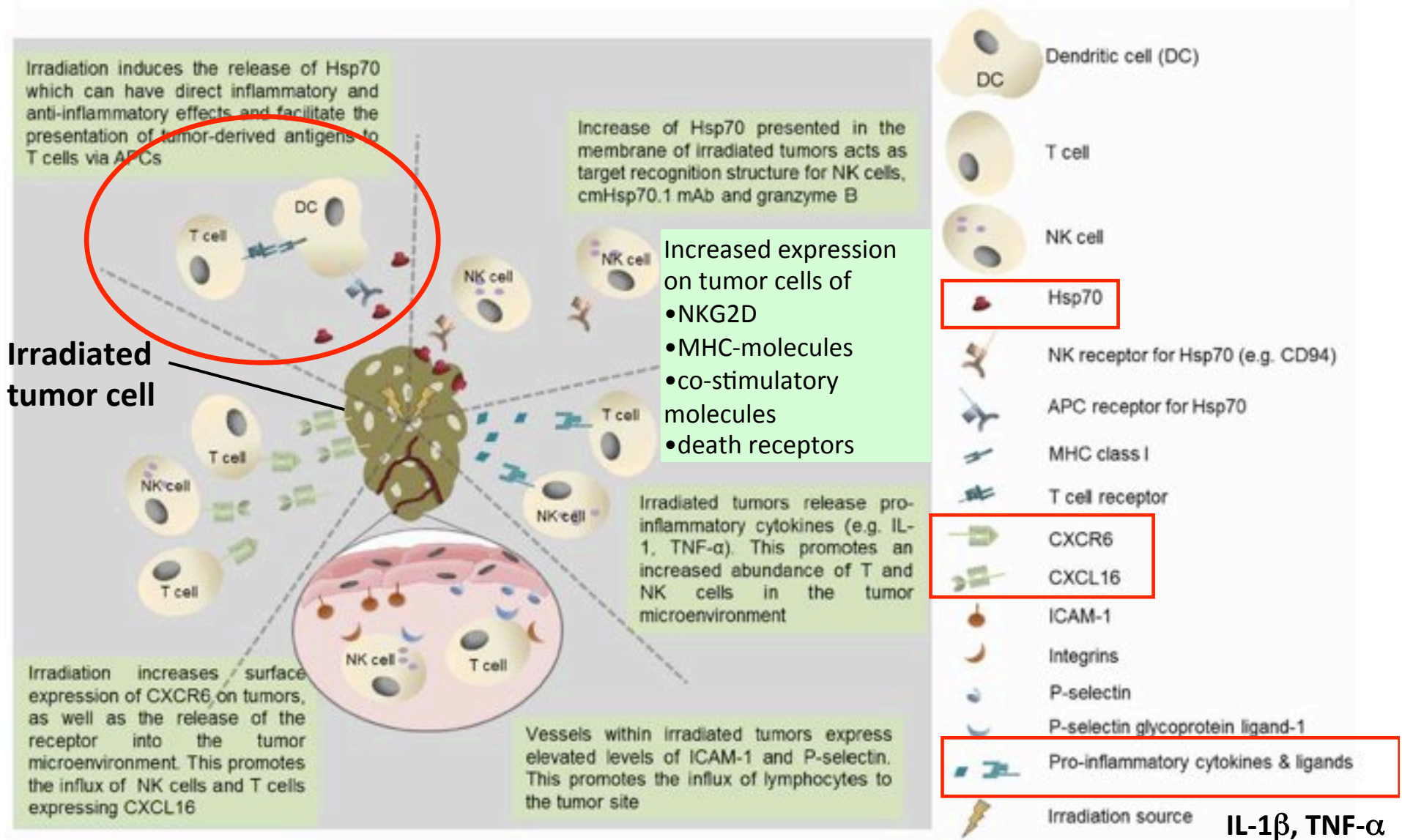
Antigen-processing machinery components

Calreticulin

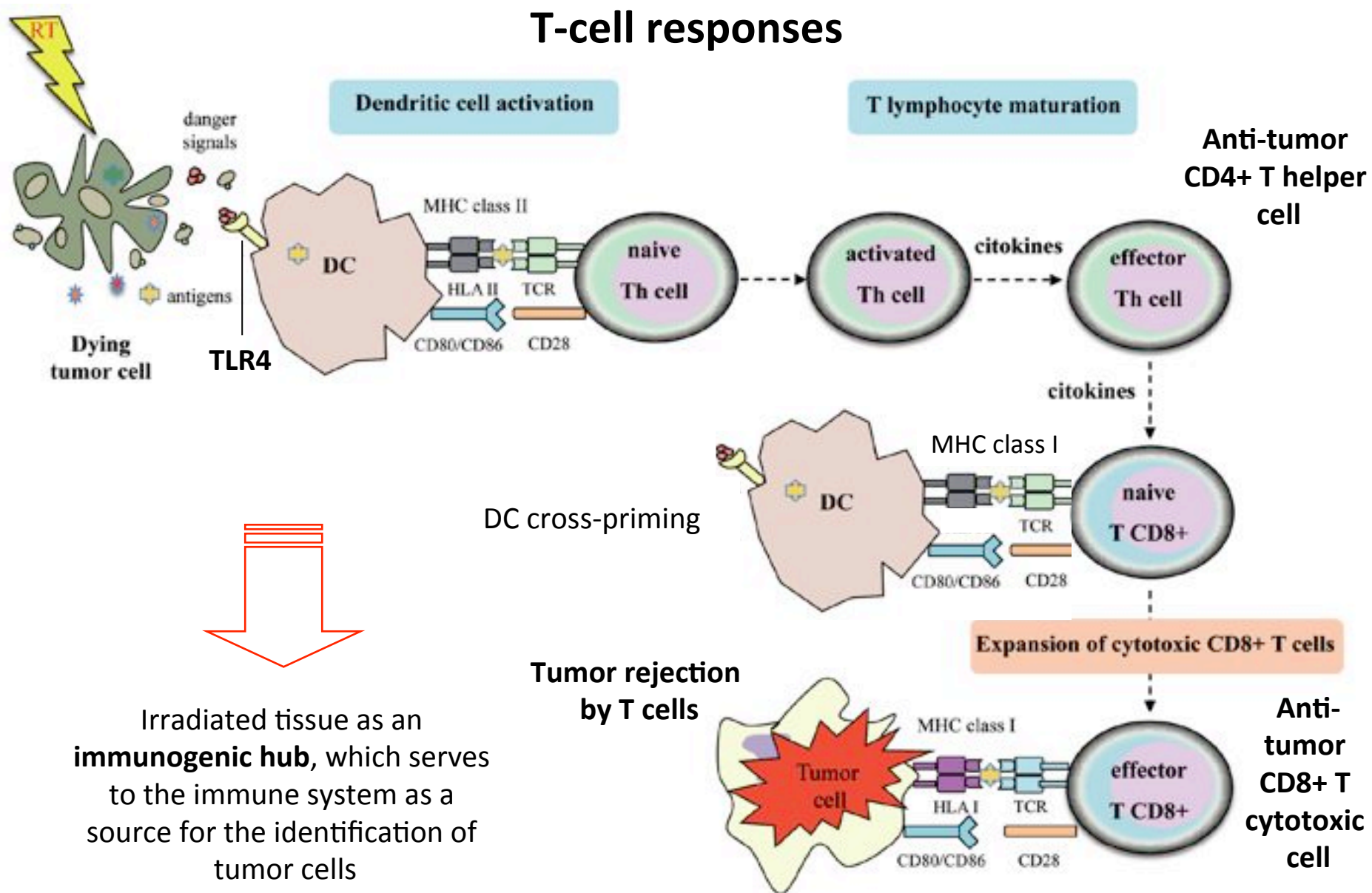


Gameiro et al, Oncotarget 2013

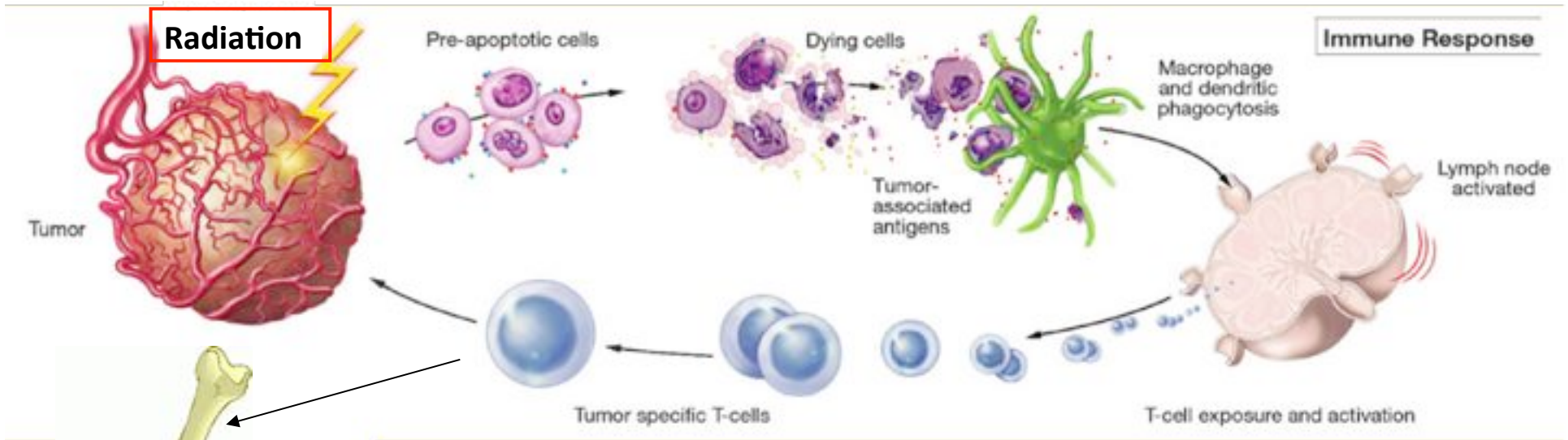
Immunological benefits induced by RT in tumor microenvironment



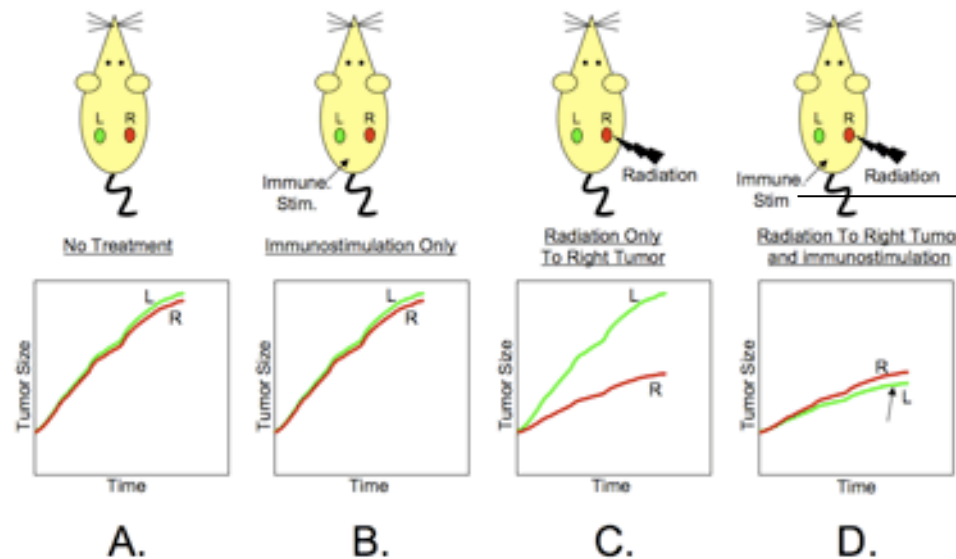
RT immunogenic stimulation reflects in improved anti-tumor T-cell responses



The “vaccine role” of RT may induce the abscopal effect



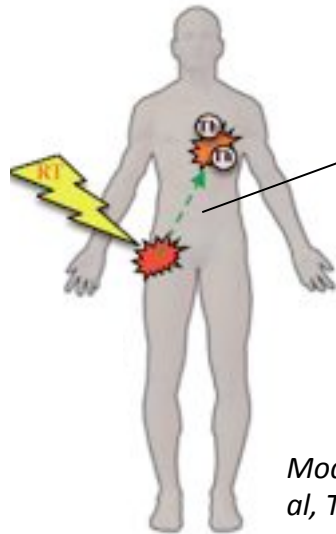
Modified from Kamrava et al, *Molecular BioSystems* 2009



growth factor Flt3-ligand stimulates the production of dendritic cells

Schematized illustration of Demaria et al, *Int J Radiat Oncol Biol Phys* 2004

Potential immune contribution to the abscopal effect

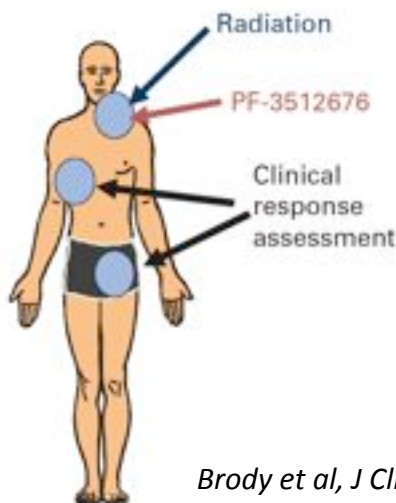


The **delay** of the Abscopal effect may reflect the development of:

- a “systemic cytokine storm” (TNF, IL-4, IL-18, IL-2, GM-CSF)
- anti-tumor humoral immune effects
- anti-tumor immune cell response mediated by T cells

Modified from Sologuren et al, *Trans Canc Res* 2014

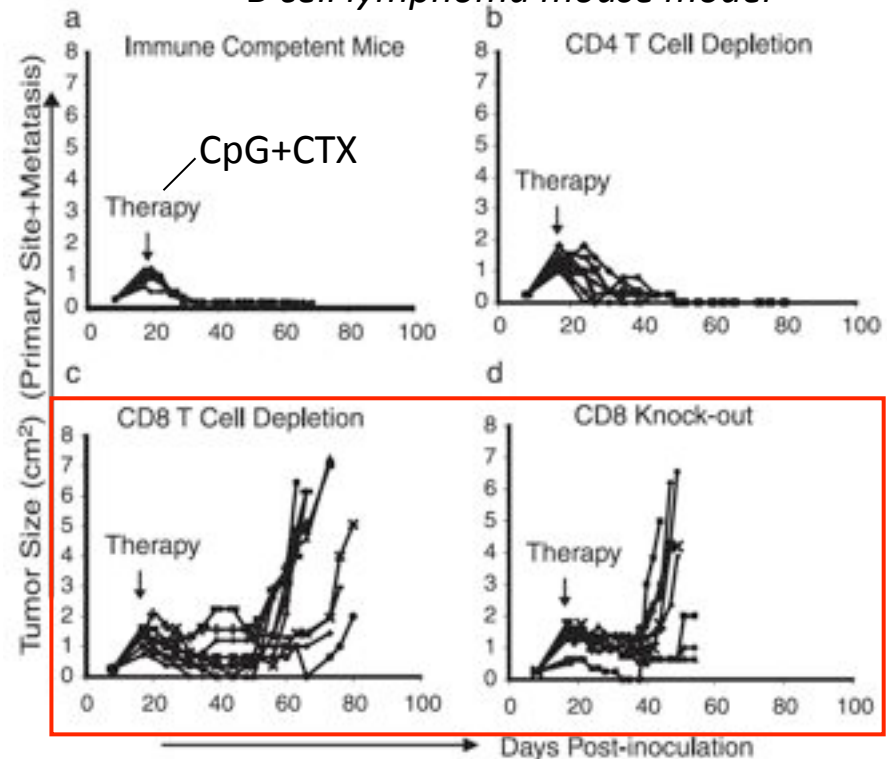
- RT+*in situ* vaccination with a TLR9 agonist induce systemic lymphoma regression exploiting cytotoxic anti-tumor T cell-responses



CpG -
TLR9 agonist

Brody et al, *J Clin Oncol* 2010

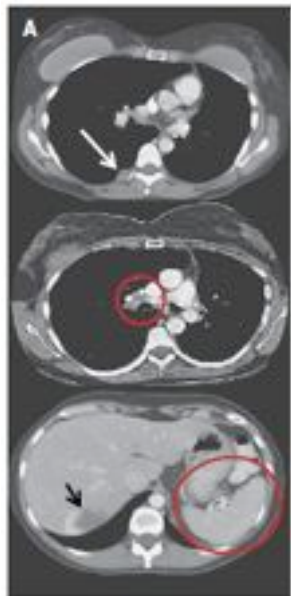
B cell lymphoma mouse model



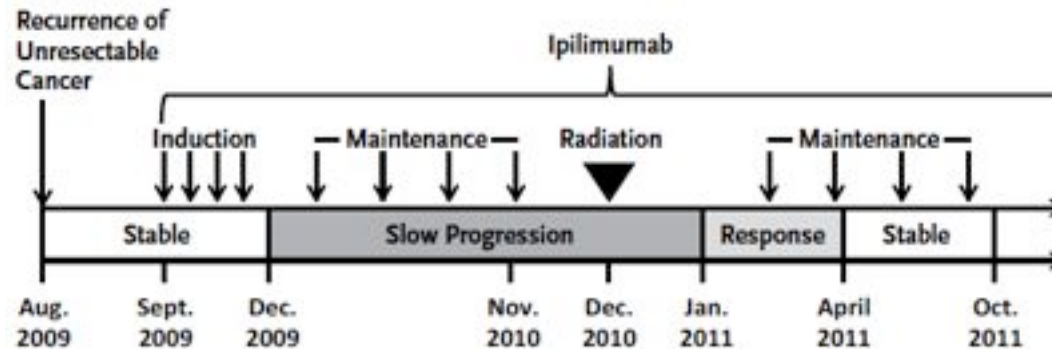
Jiali et al, *J Immunol* 2007

Abscopal effect is associated with increased anti-tumor T-cell responses

- Metastatic melanoma with pleural-based paraspinal mass, hilar lymphadenopathy, and splenic lesions
- Dose RT: 28.5 Gy in 3 fx to pleural-based paraspinal mass



August 2009

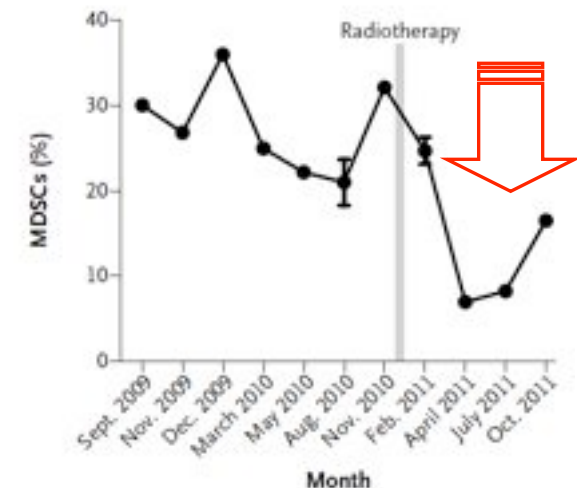
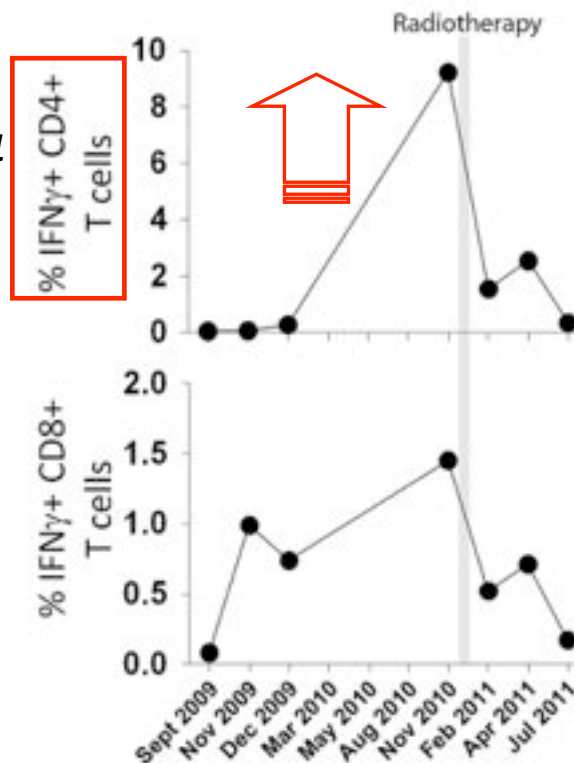


October 2011

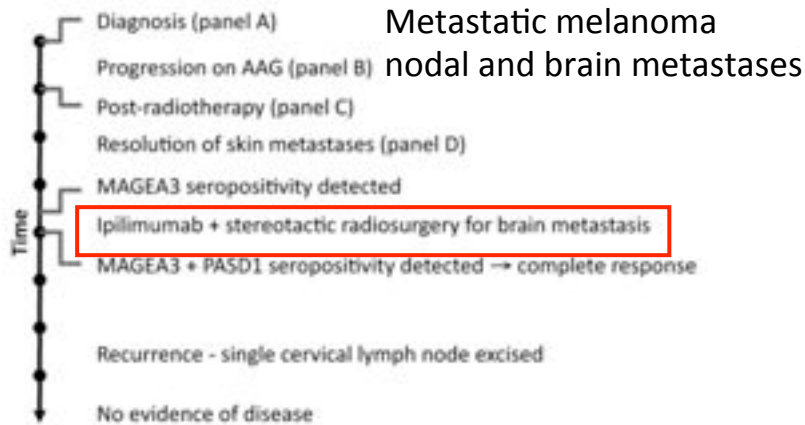
Postow et al, NEJM 2012

Intracellular cytokine analysis after NY-ESO-1 stimulation

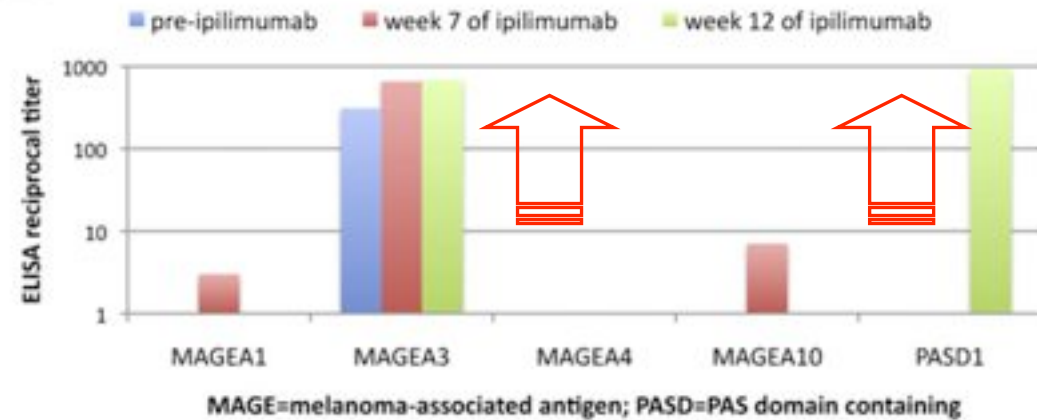
- immunologic correlates:
 - increased NY-ESO-1-specific antibodies
 - increased CD4+ ICOS high
 - increased IFN- γ producing NY-ESO-1 specific CD4+ cells
 - increased HLA-DR-expressing CD14+ monocytes
 - decreased myeloid-derived suppressor cells



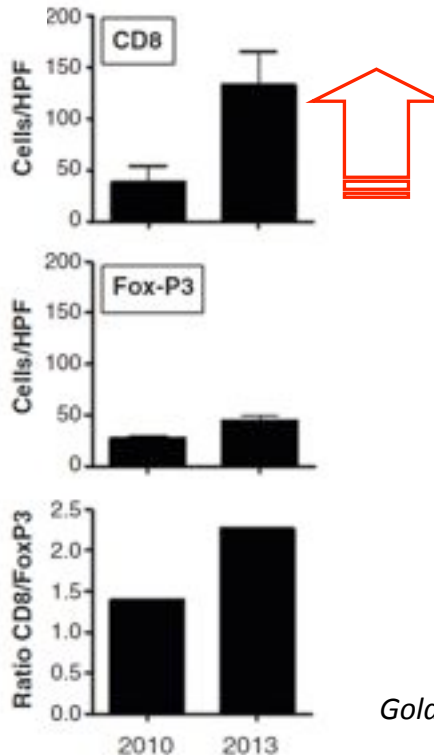
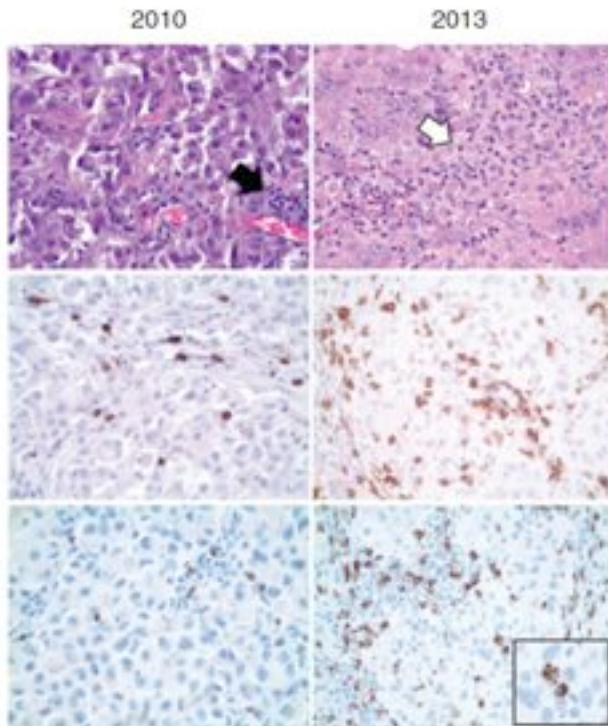
Increased humoral and cellular anti-tumor immunity before the abscopal effect



Seroreactivity To Cancer-Testis Antigens



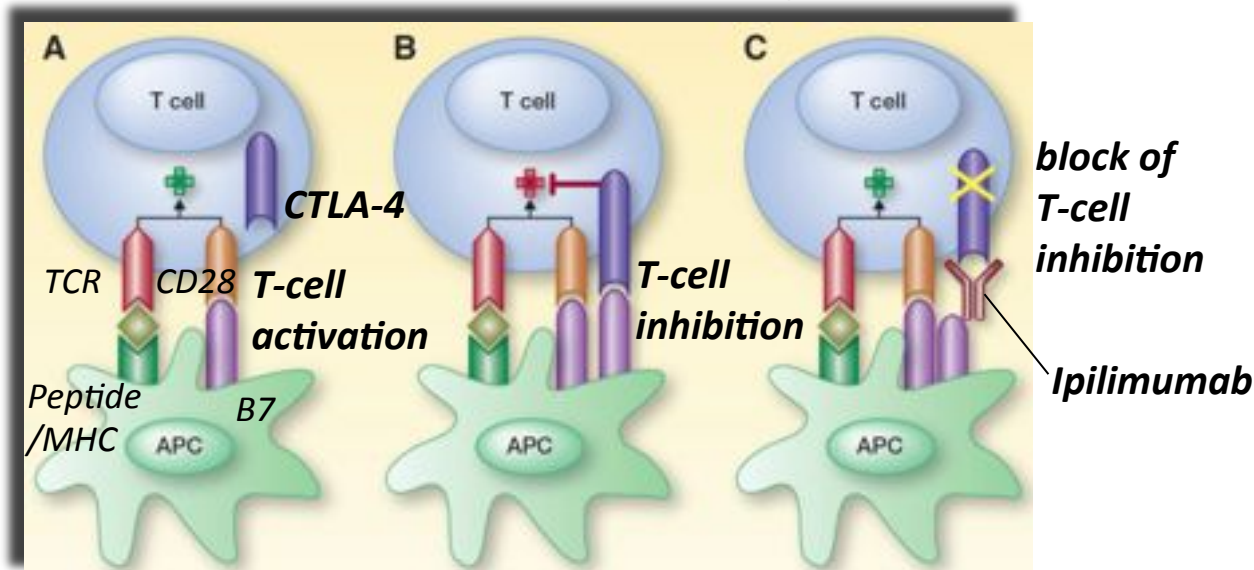
Stamel et al, Int J Radiat Oncol Biol Phys 2013



- Enhanced TILs in a abscopal lesion after RT and **ipilimumab** in NSCLC

Golden et al, Cancer Immunology Research 2013

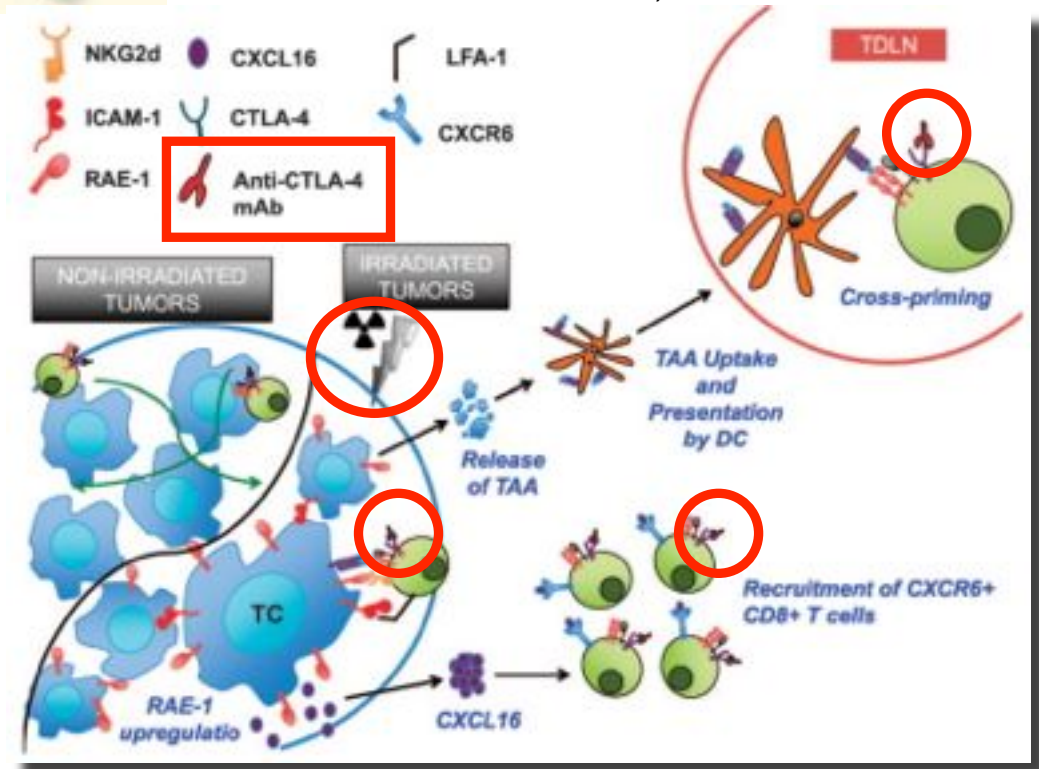
The association RT+Ipilimumab has a synergistic effect



- Ipilimumab blocks cytotoxic T-lymphocytes antigen 4 (CTLA-4) releasing T cells from this immunologic checkpoint to exert their full antitumor effect

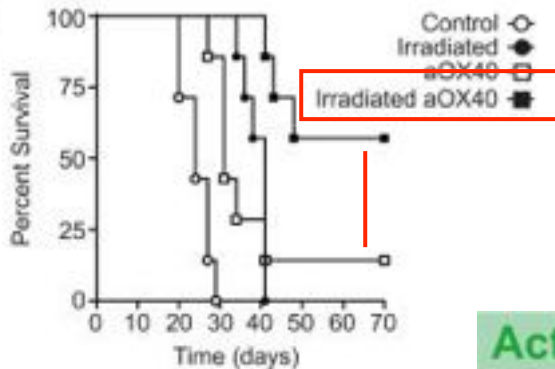
Demaria et al, Radiation Research 2014

Postow et al, Clin Canc Res 2012



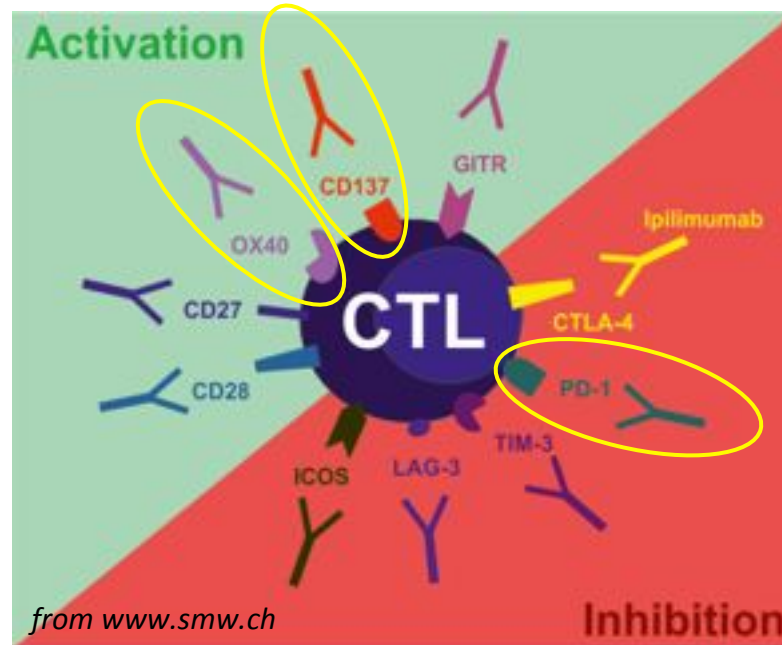
- The association **RT+Ipilimumab** has a synergistic effect:
 1. increased of immune responses against tumor-associated antigens
 2. clinical response

RT+Immunotherapy: improving clinical responses?



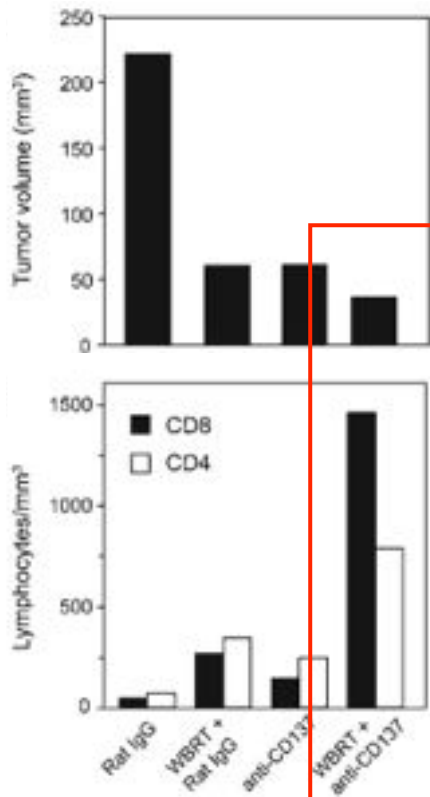
Gough et al, J Immunother 2010

- irradiation and **anti-OX40** treatment synergistically promote infiltrating CD8+ T cells and improve clinical responses in mouse models

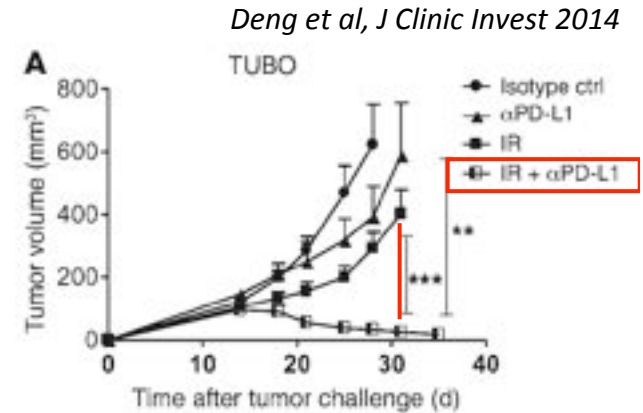


from www.smw.ch

- radiotherapy enhances antitumor effects of **anti-CD137** therapy in a mouse glioma model



Newcomb et al, Radiat Res 2010



- irradiation and **PD-L1 blockade** synergistically reduce tumor infiltration of MDSC promoting anti-tumor immunity in mice

- potential synergistic activity between RT and:
 - cytokines** therapy (GM-CSF, IL-2)
 - infusion of autologous lymphocytes**

Potential predictive role of immune biomarkers in SABR treatment?



Monitoring Anti-Prostate Cancer Immunity Following Stereotactic Body Radiotherapy (SBRT)

This study is currently recruiting participants. (see Contacts and Locations)
 Verified January 2013 by Mayo Clinic

Sponsor:
 Mayo Clinic

Information provided by (Responsible Party):
 Sean S. Park, Mayo Clinic

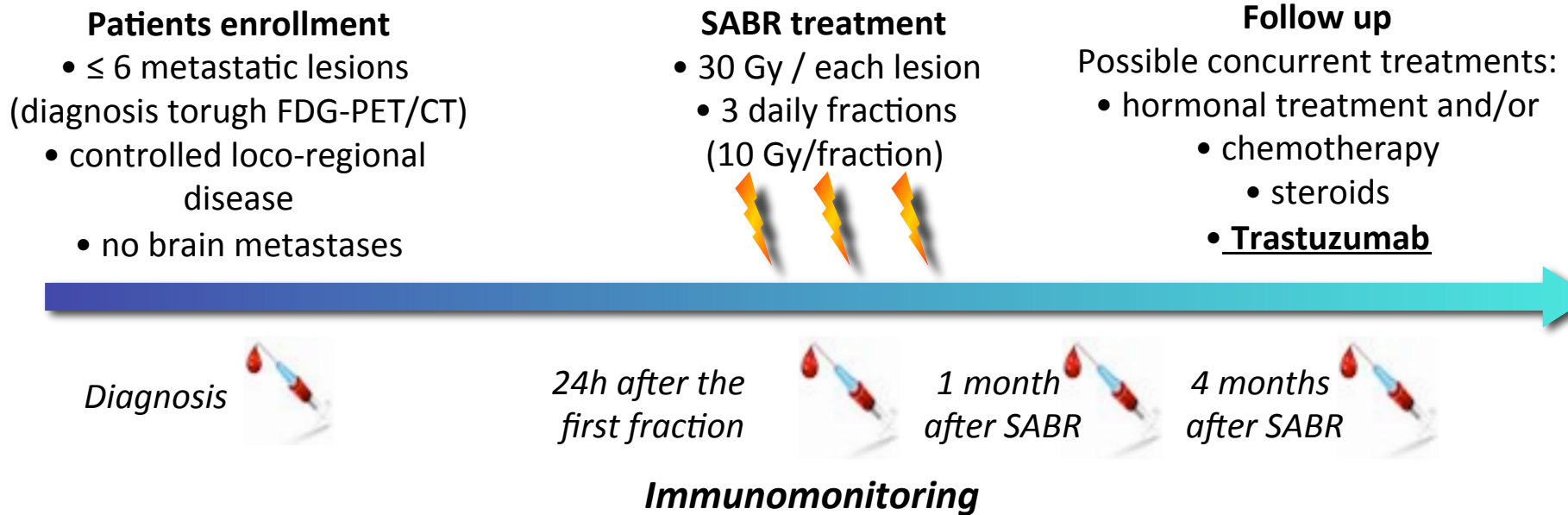
ClinicalTrials.gov Identifier:
 NCT01777802

First received: January 24, 2013
 Last updated: January 28, 2013
 Last verified: January 2013
[History of Changes](#)



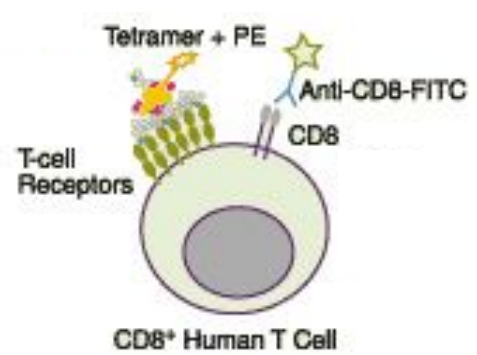
- Phase II clinical trial employing SABR for **oligometastatic breast cancer patients**
- To evaluate SABR effects on anti-tumor immune response

Study design

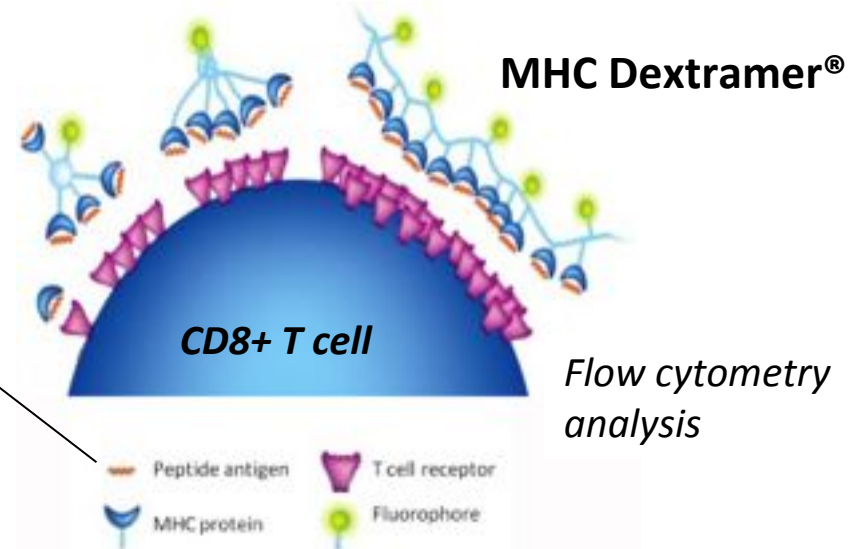
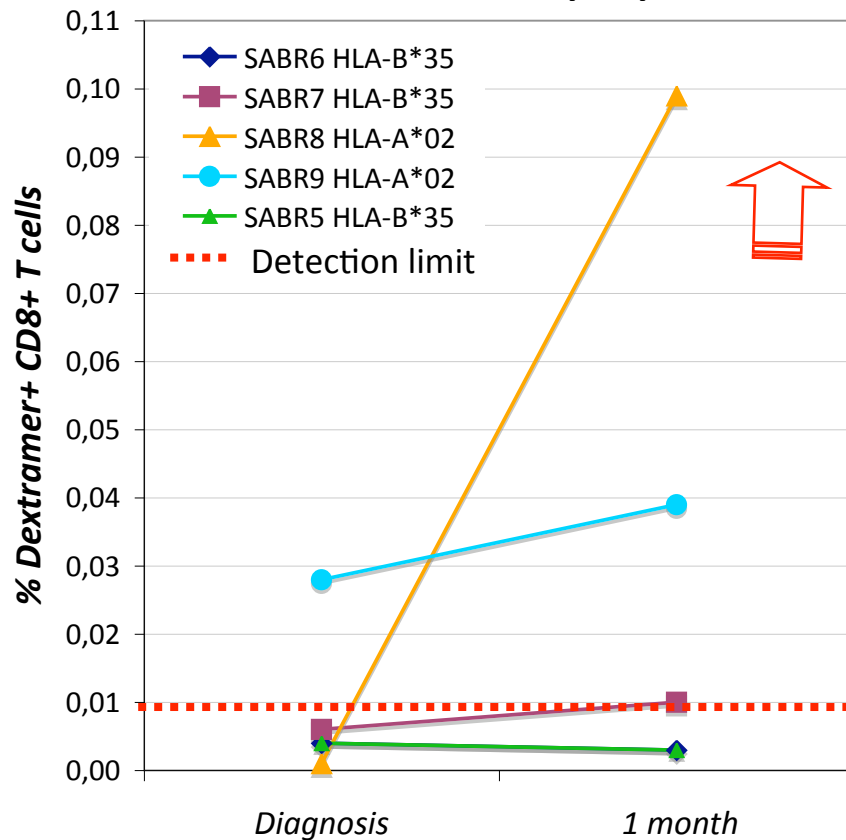


- October 2012-February 2014: 10 evaluable patients with tumor control 6 months after SABR

Enhanced survivin-specific CD8+ T-cell responses 1 month after SABR

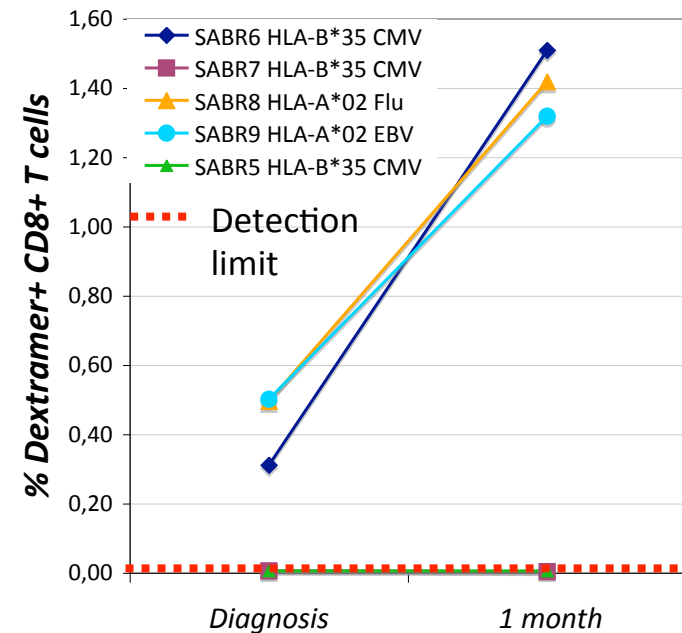


CD8+ T lymphocytes specific for survivin-derived epitopes



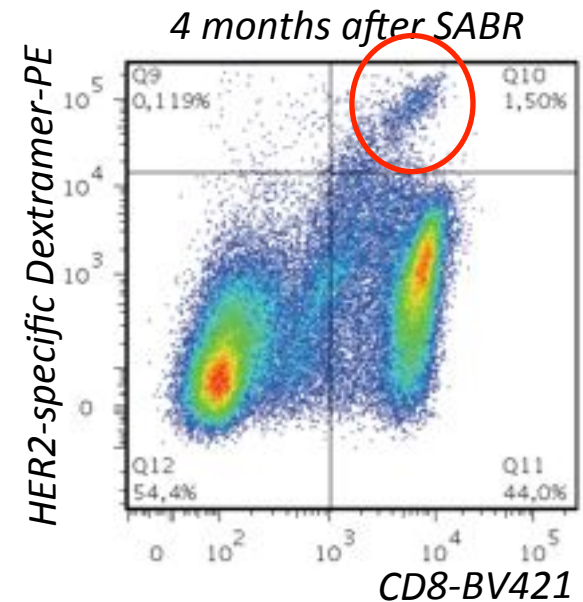
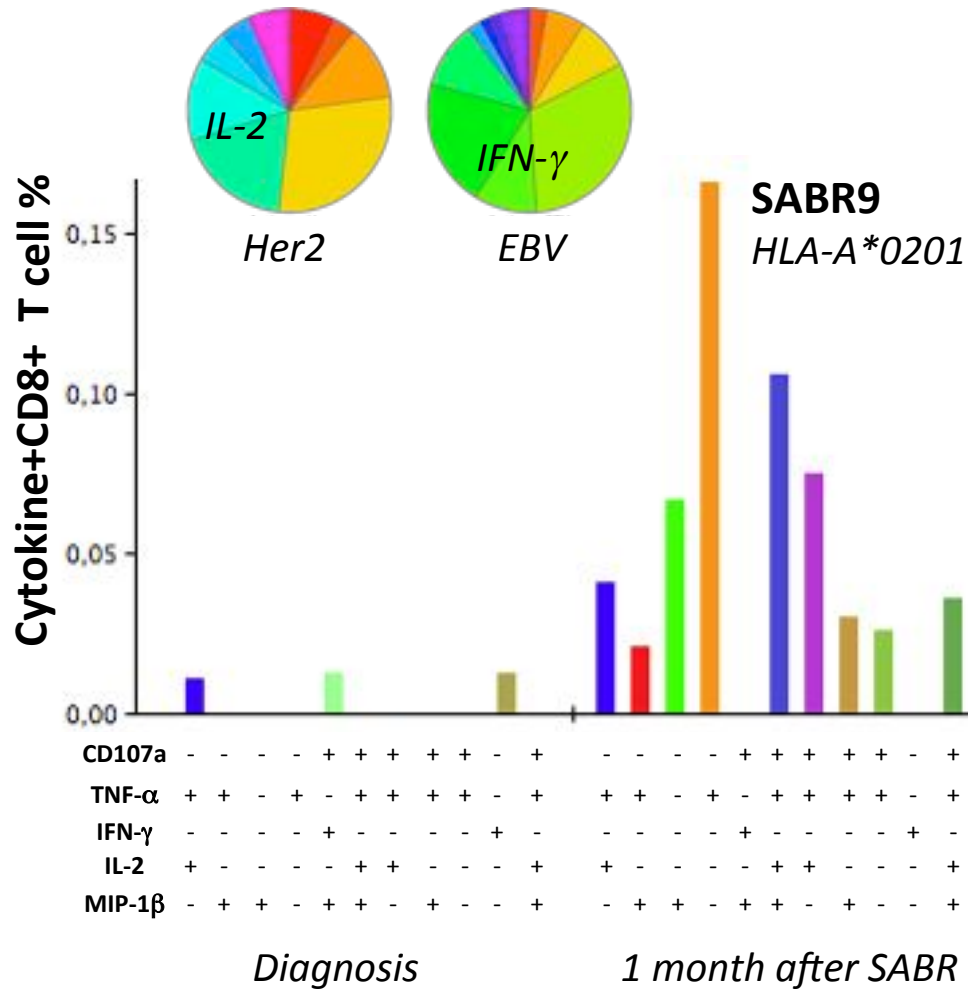
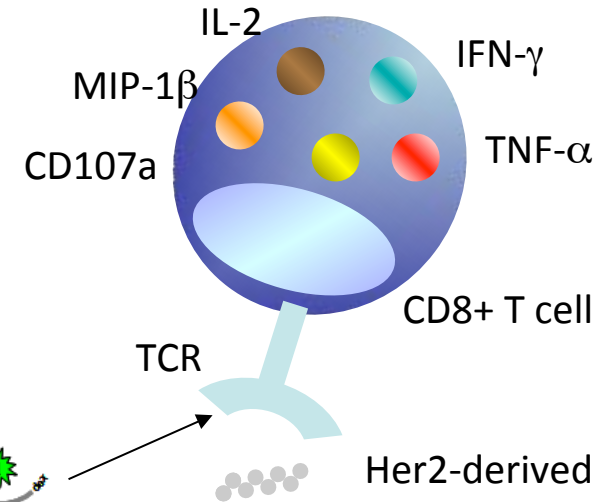
Flow cytometry analysis

CD8+ T lymphocytes specific for viral antigen-derived epitopes

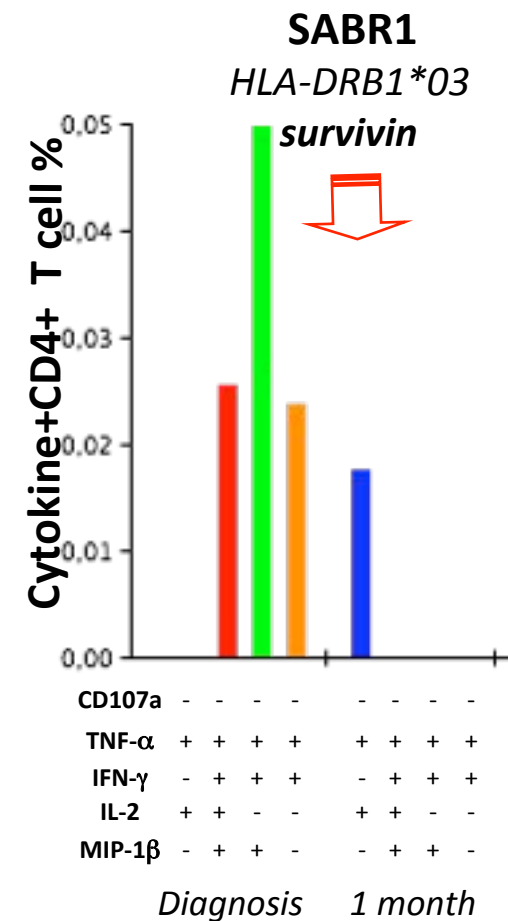
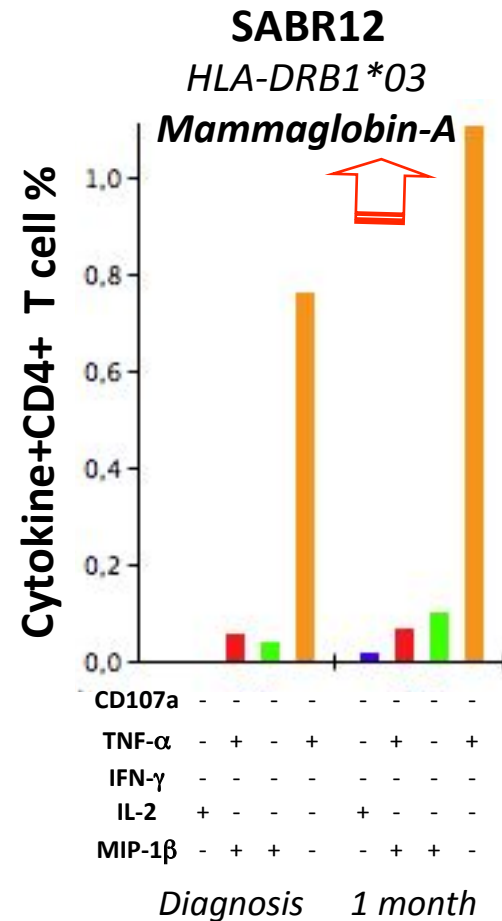
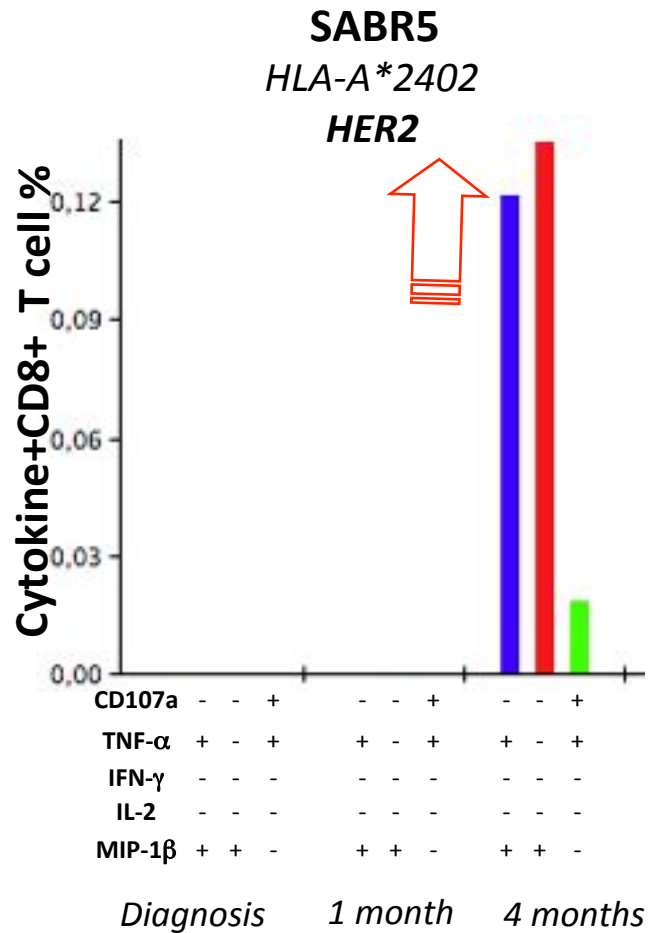


Induction of polyfunctional HER2-specific CD8+ T cell responses after SABR

- In vitro* prestimulation of patients' lymphocytes with HLA-matched epitopes derived from BC-associated antigens (survivin, mammaglobin-A, HER2) for 12 days. Then, flow cytometry characterization of antigen-specific CD8+ T cells



Differential modulation of T-cell responses after SABR



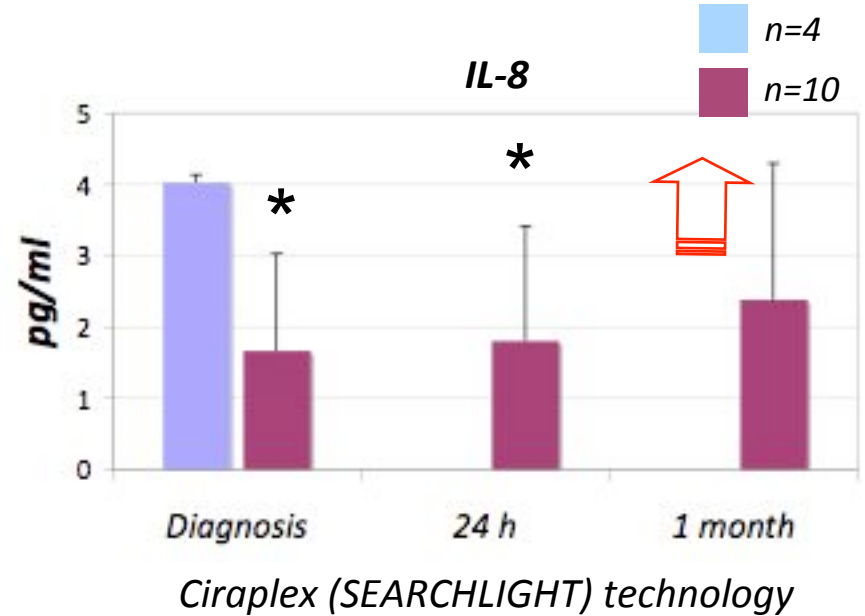
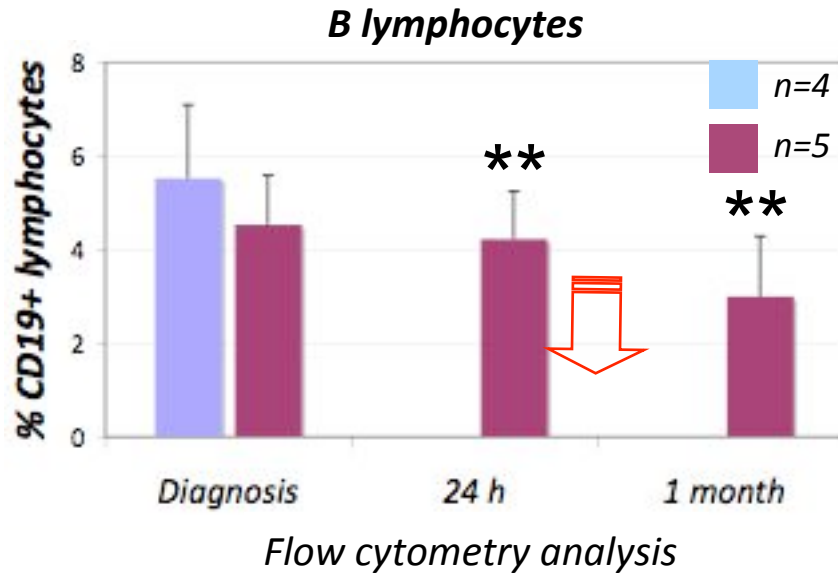
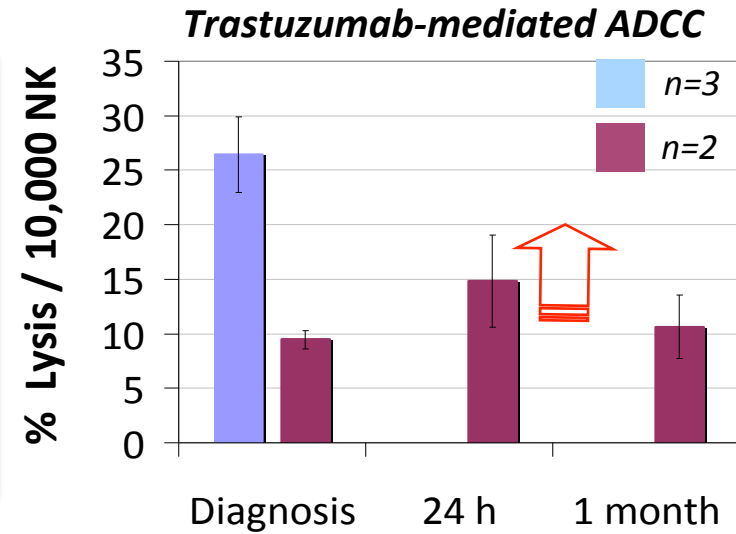
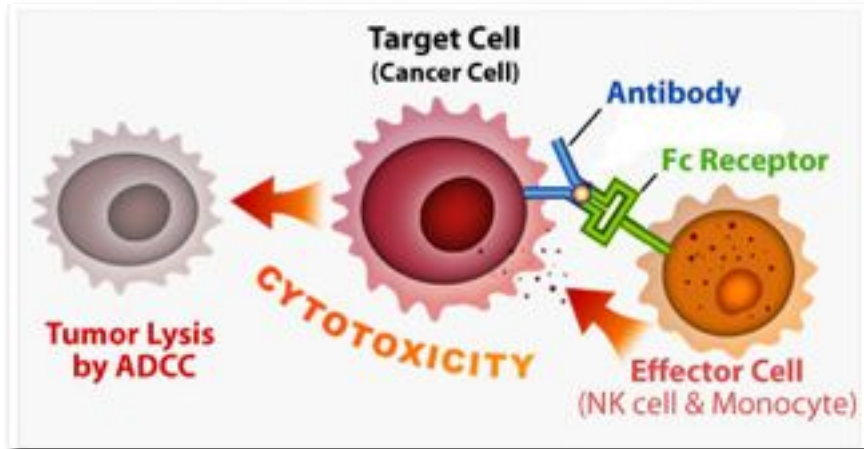
- 5/10 patients showed the enhancement or even the appearance of anti-tumor polyfunctional T cells



Possible correlation with clinical response?

Modulation of other immune parameters after SABR

Healthy women
Patients

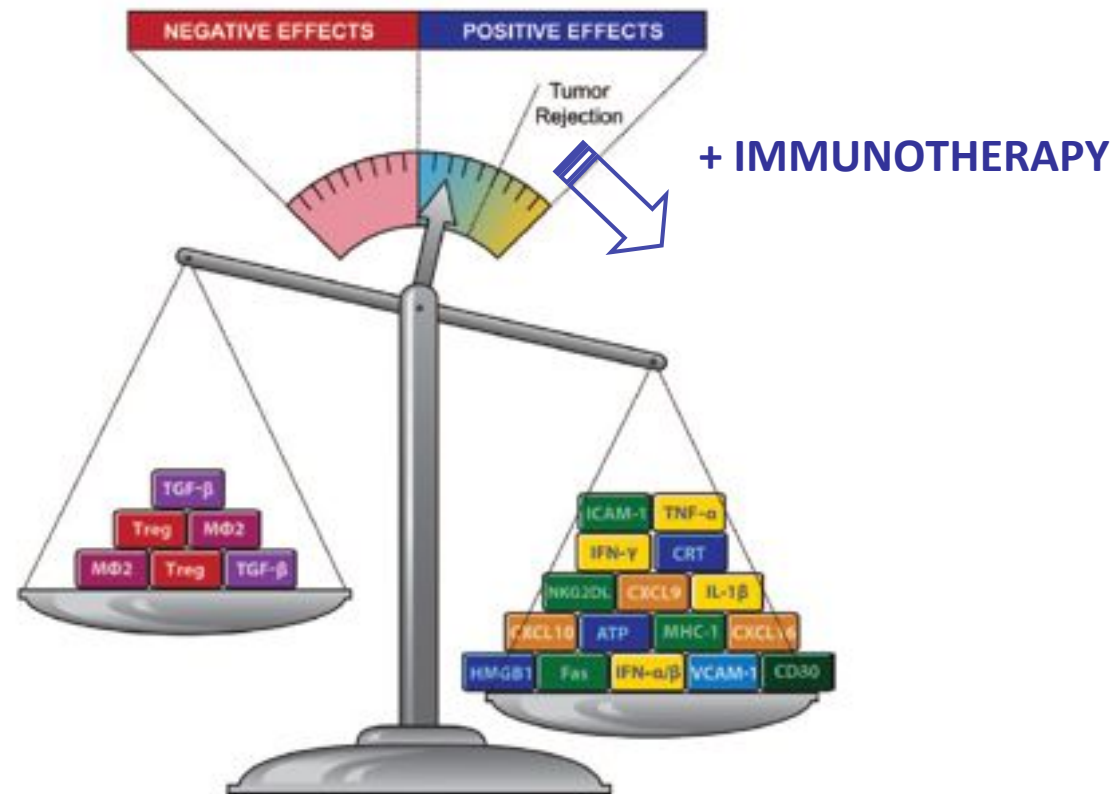


- SABR modulates the anti-tumor immune response in oligometastatic BC patients

Future perspectives

- Study completion
- To evaluate the predictive role of immunological biomarkers
- To propose a combination therapy between RT and immunotherapy

Is it possible to exploit the positive effects of SABR on the anti-tumor immune response?



Formenti et al, JNCI 2012



Ringraziamenti

Marco Trovò
Carlo Furlan

Oncologia Radioterapica
Dip. di Oncologia Radioterapica e
di Diagnostica per Immagini
C.R.O. Aviano



Alessandro Del Conte
Dip. di Oncologia Medica
Azienda Ospedaliera
Santa Maria degli Angeli
Pordenone

Debora Martorelli
Elisa Comaro
Aurora Rizzo
Francesca Colizzi

Katy Mastorci
Damiana Antonia Faè
Jessica Dal Col
Barbara Montico
Elisabetta Fratta
Luca Sigalotti
Stefania Colussi

Riccardo Dolcetti
Bioimmunoterapie
dei Tumori umani
Dip. di Ricerca Traslazionale
C.R.O. Aviano



Massimiliano Berretta
Loredana Militello
Simon Spazzapan
Oncologia Medica C
Dip. di Oncologia Medica
C.R.O. Aviano



**GRAZIE A VOI PER
L'ATTENZIONE!**