Radiation and abscopal effect: lessons from solid tumors

Andrea R. Filippi

Fondazione IRCCS Policlinico S. Matteo, Pavia

1st CUNEO CITY IMMUNOTHERAPY CONFERENCE (CCITC) - IMMUNOTHERAPY IN HEMATOLOGICAL MALIGNANCIES 2018

Cuneo, 17-19 maggio 2018

DICHIARAZIONE

Relatore: Andrea Riccardo FILIPPI

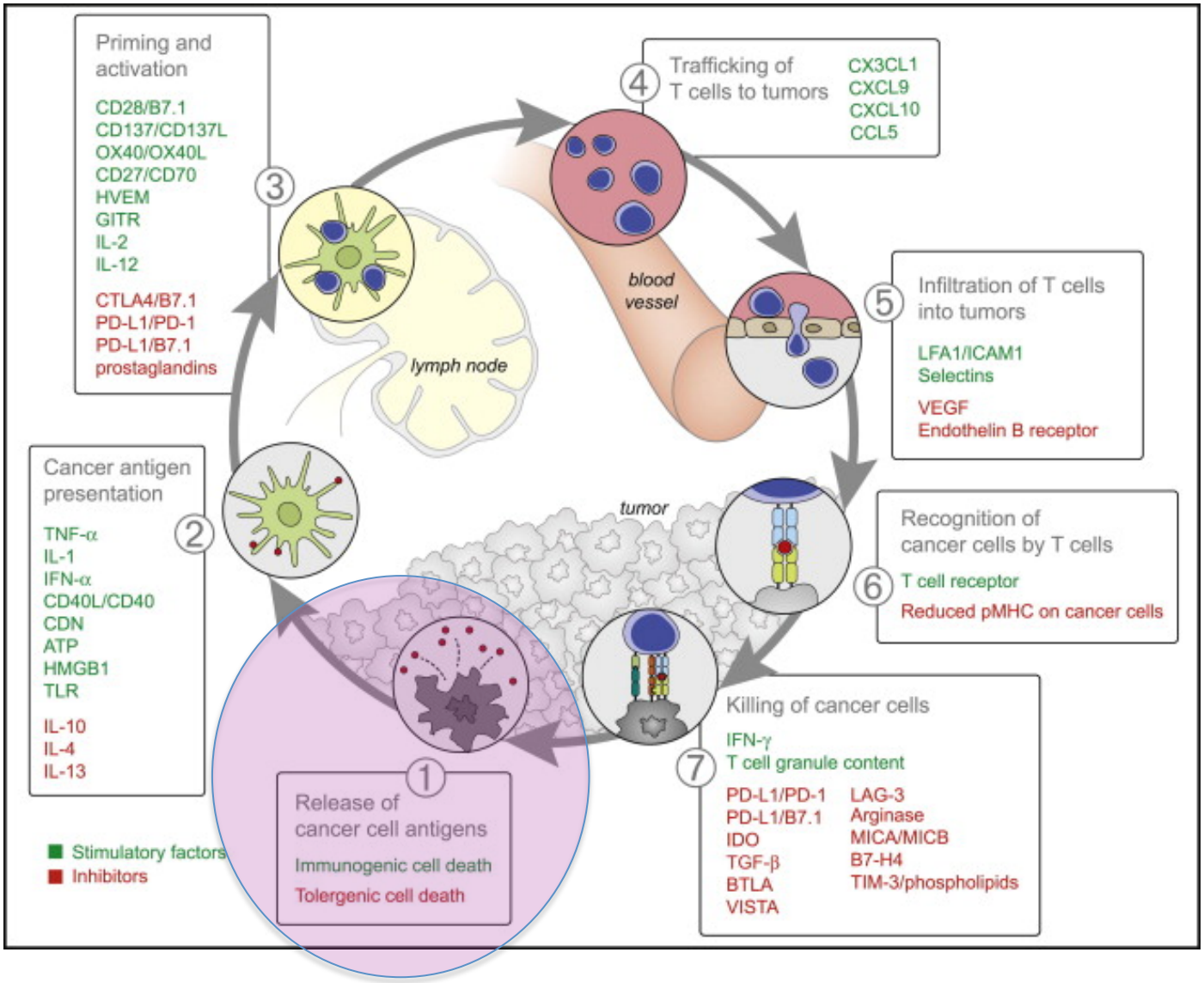
Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- 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 / NOME AZIENDA)**
- Partecipazione ad Advisory Board **(ASTRA ZENECA)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE / NOME AZIENDA)**
- Altro

RT may stimulate the immune system by:

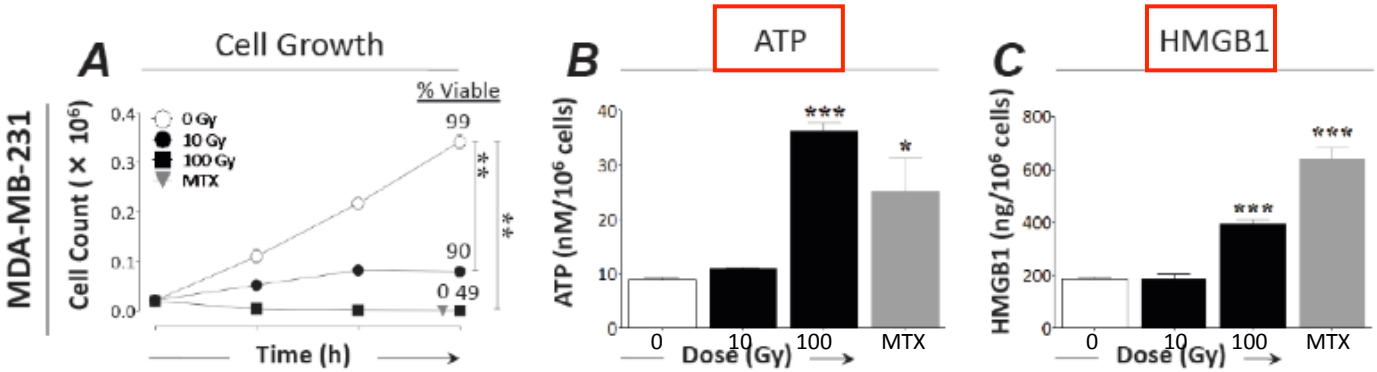
- Broadening up the immune repertoire of T cells (vaccination effect)
- Attracting T-cells to the irradiated site (homing effect)
- Rendering irradiated cells more vulnerable towards T-Cells mediated cell kill (vulnerability effect)

Van Linbergen et al, Brit J Radiol 2017



Chen and Mellman, Cell 2013

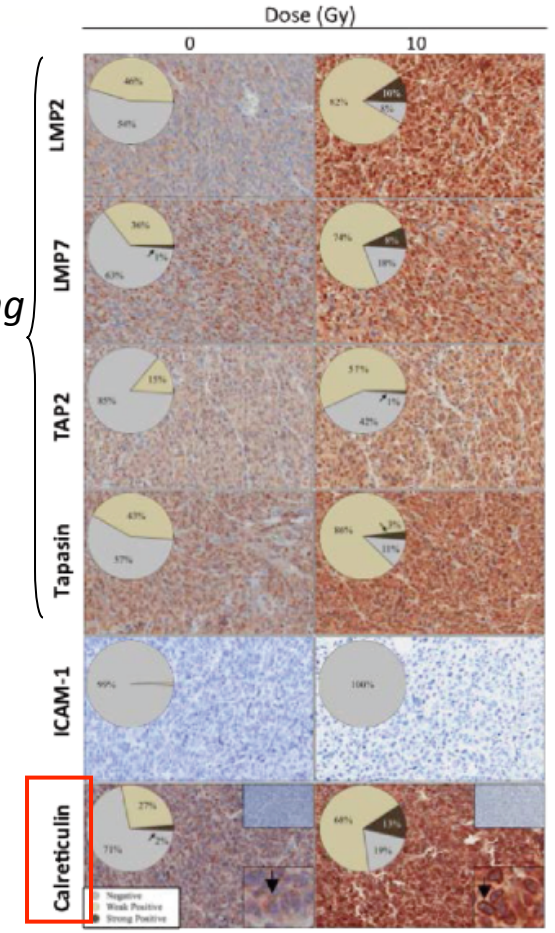
Radiation induces *in vitro* the hallmarks of immunogenic cell death



modified from Gameiro et al, Oncotarget 2013

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

Nude mice bearing prostate xenografts

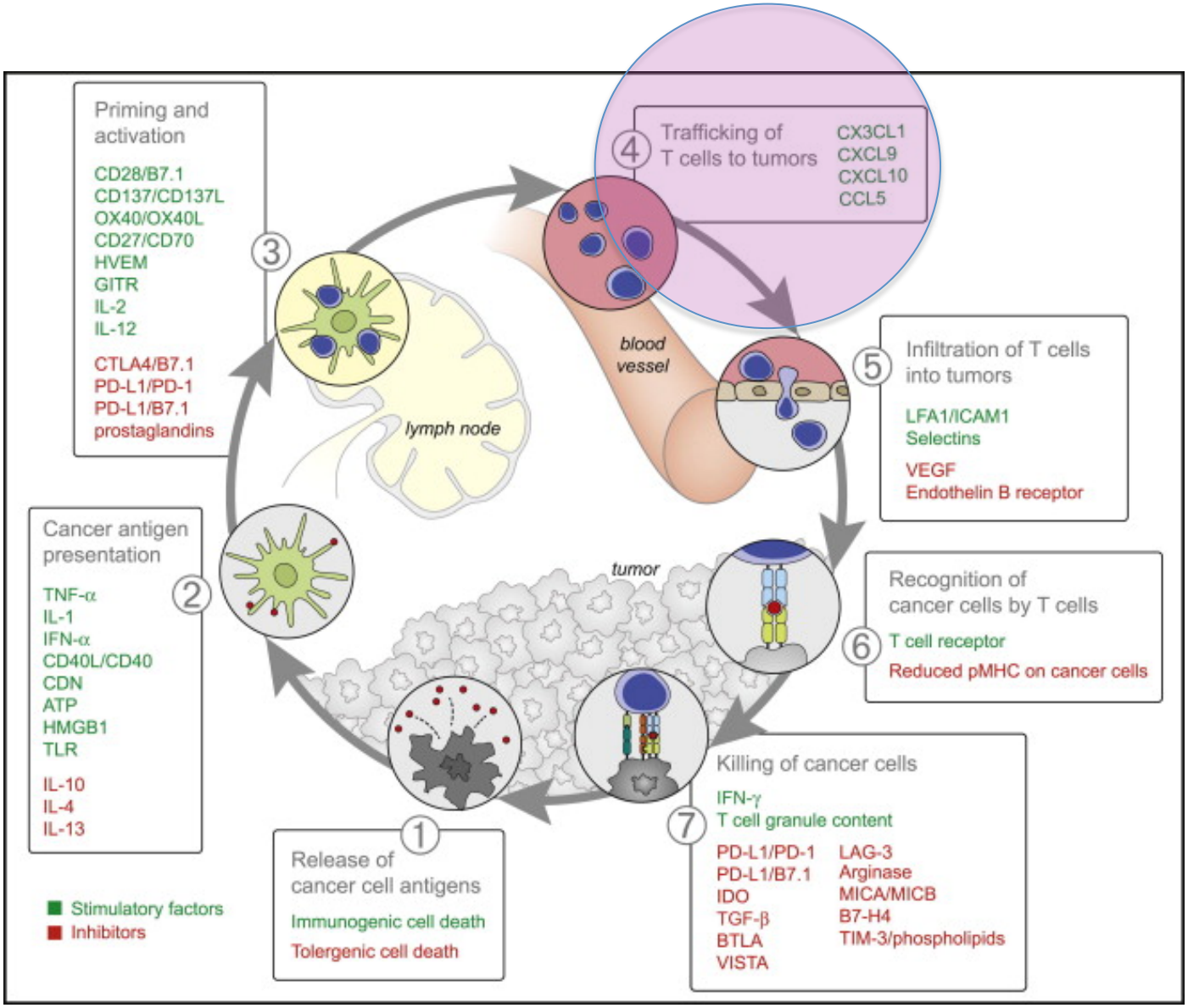


Antigen-processing machinery components

Immunogenic cell death (ICD) features

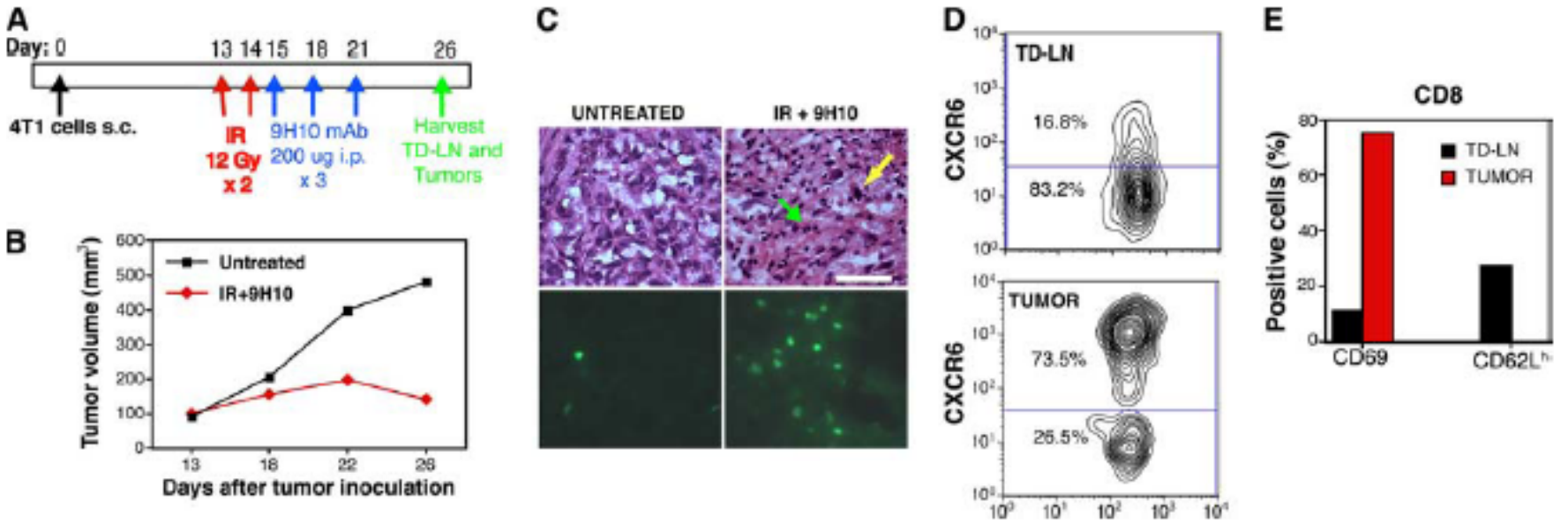
Calreticulin

Gameiro et al, Oncotarget 2013

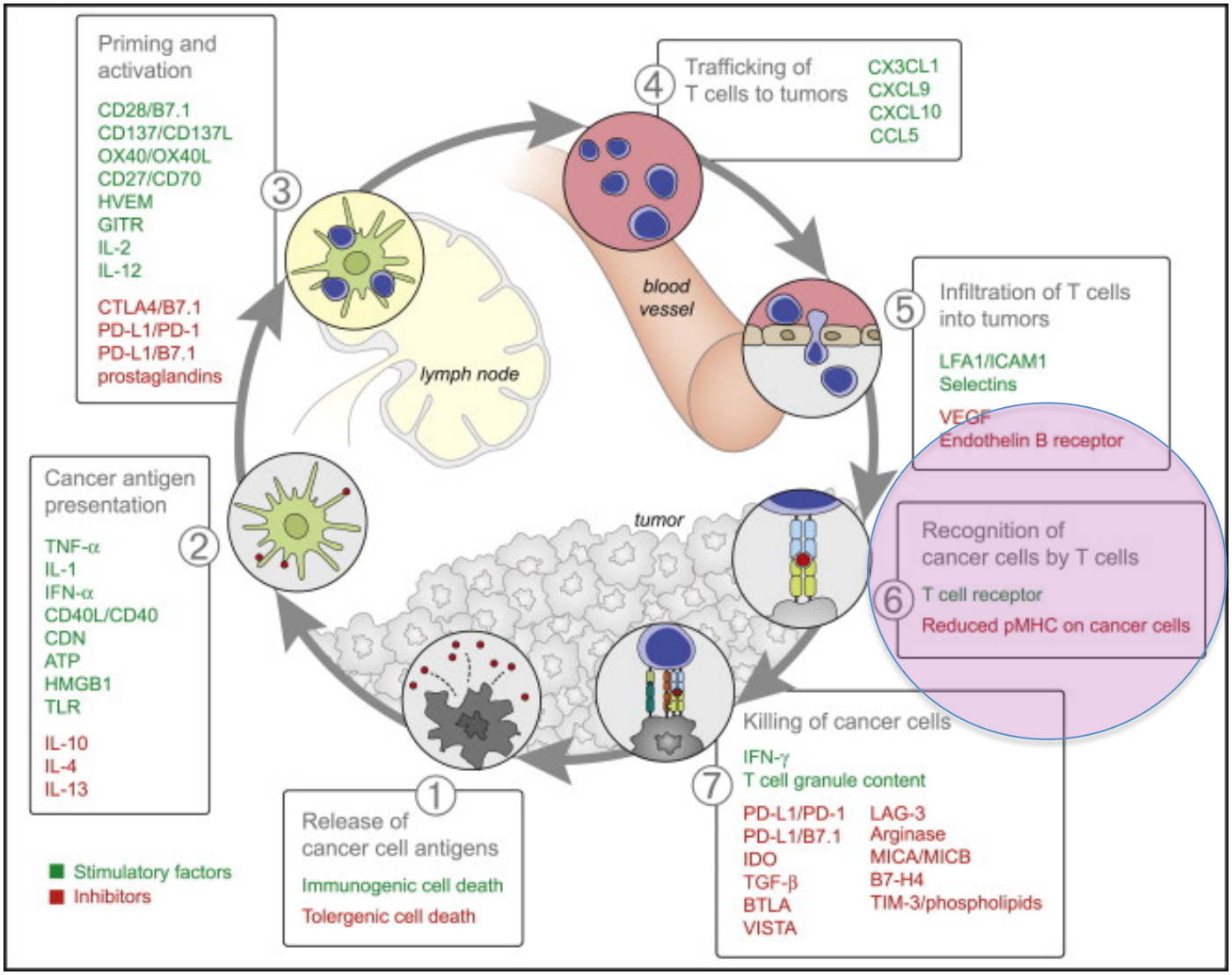


Chen and Mellman, Cell 2013

Migration of T-cells in 4T1 Breast Cancer Mouse Model after RT (2 x 12 Gy)



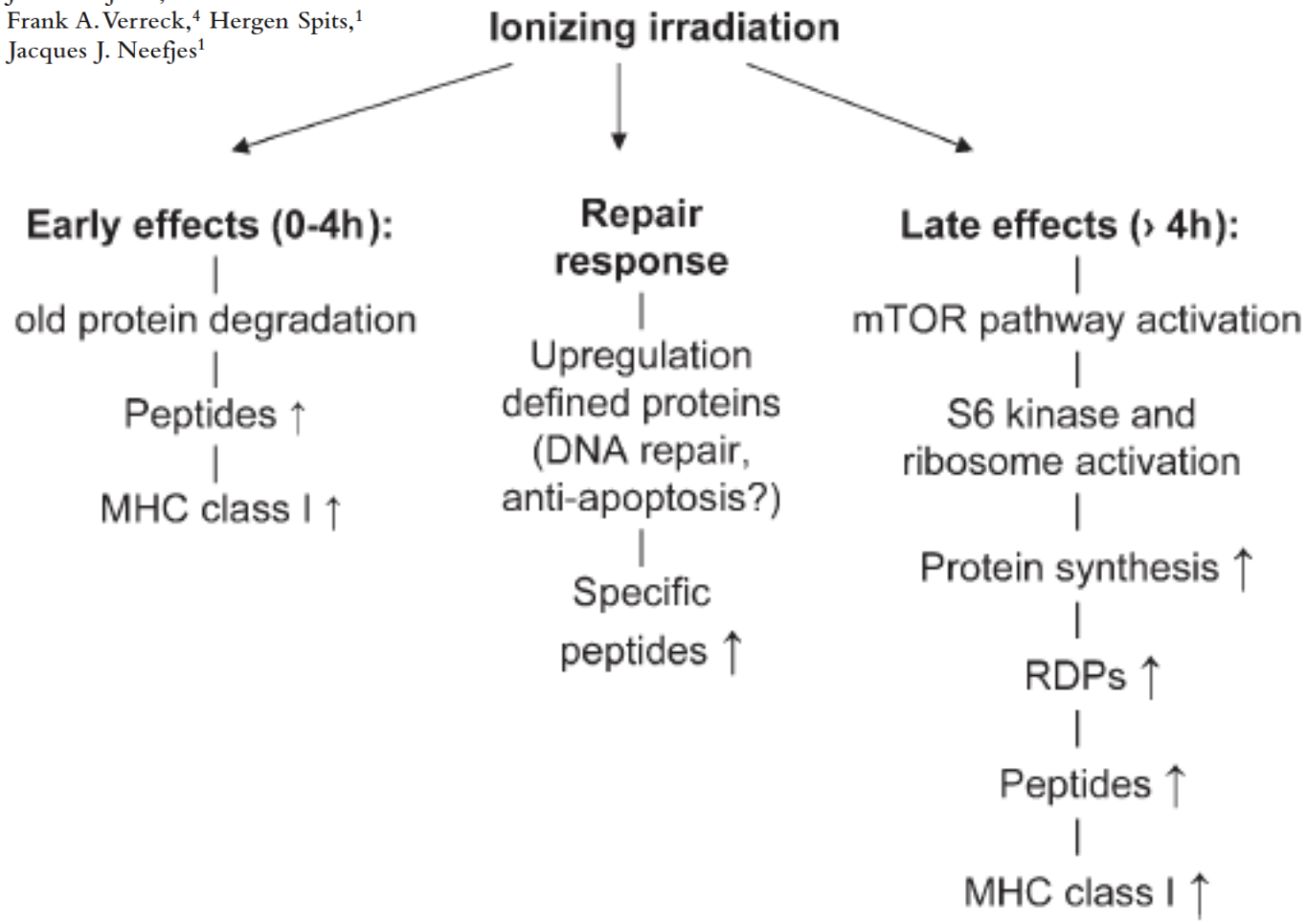
Matsumura/Formenti/Demaria et al., J Imm, 2008
Pilones/Demaria/Formenti et al. Clin Cancer Res, 2009



Chen and Mellman, Cell 2013

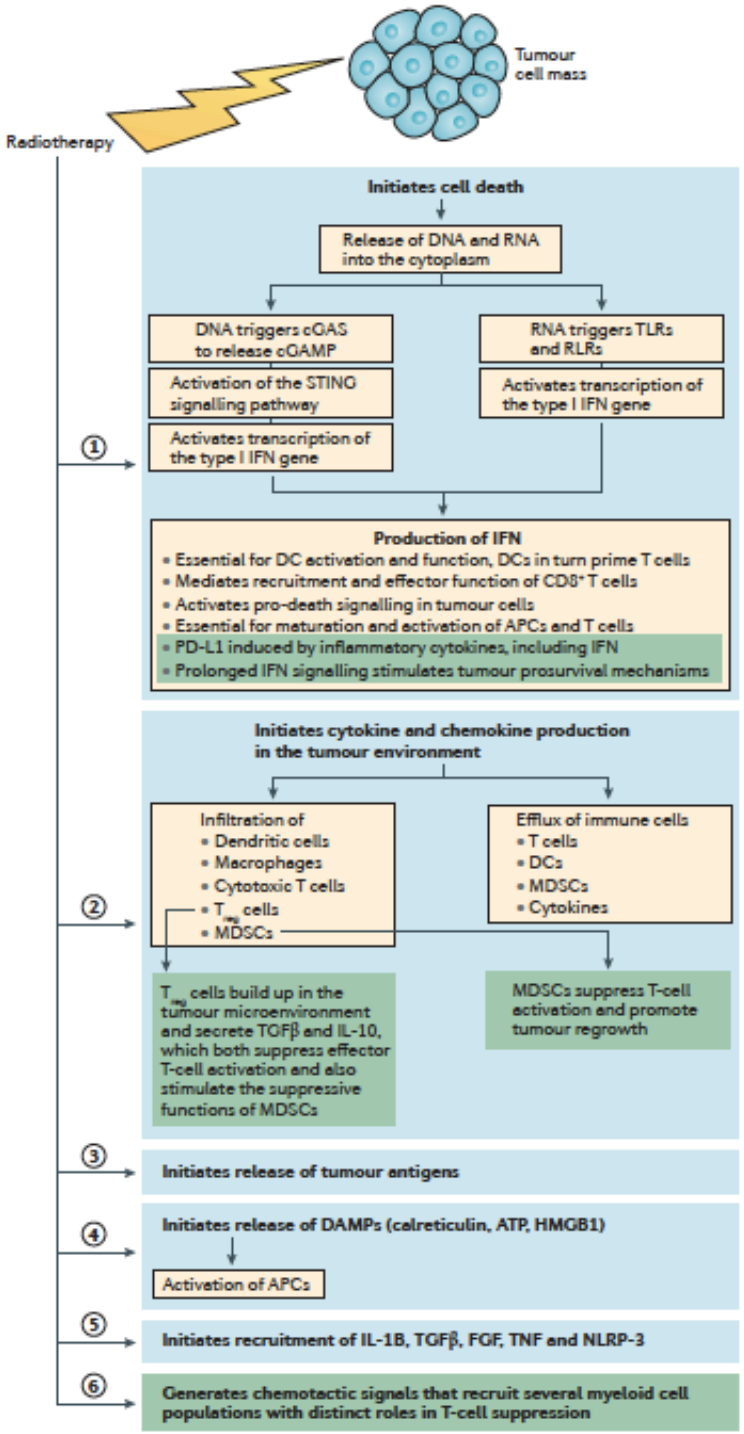
Radiation modulates the peptide repertoire, enhances MHC class I expression, and induces successful antitumor immunotherapy

Eric A. Reits,[1] James W. Hodge,[2] Carla A. Herberts,[1] Tom A. Groothuis,[1] Mala Chakraborty,[2] Elizabeth K. Wansley,[2] Kevin Camphausen,[3] Rosalie M. Luiten,[1] Arnold H. de Ru,[4] Joost Neijssen,[1] Alexander Griekspoor,[1] Elly Mesman,[1] Frank A. Verreck,[4] Hergen Spits,[1] Jeffrey Schlom,[2] Peter van Veelen,[4] and Jacques J. Neefjes[1]



J Exp Med 2006

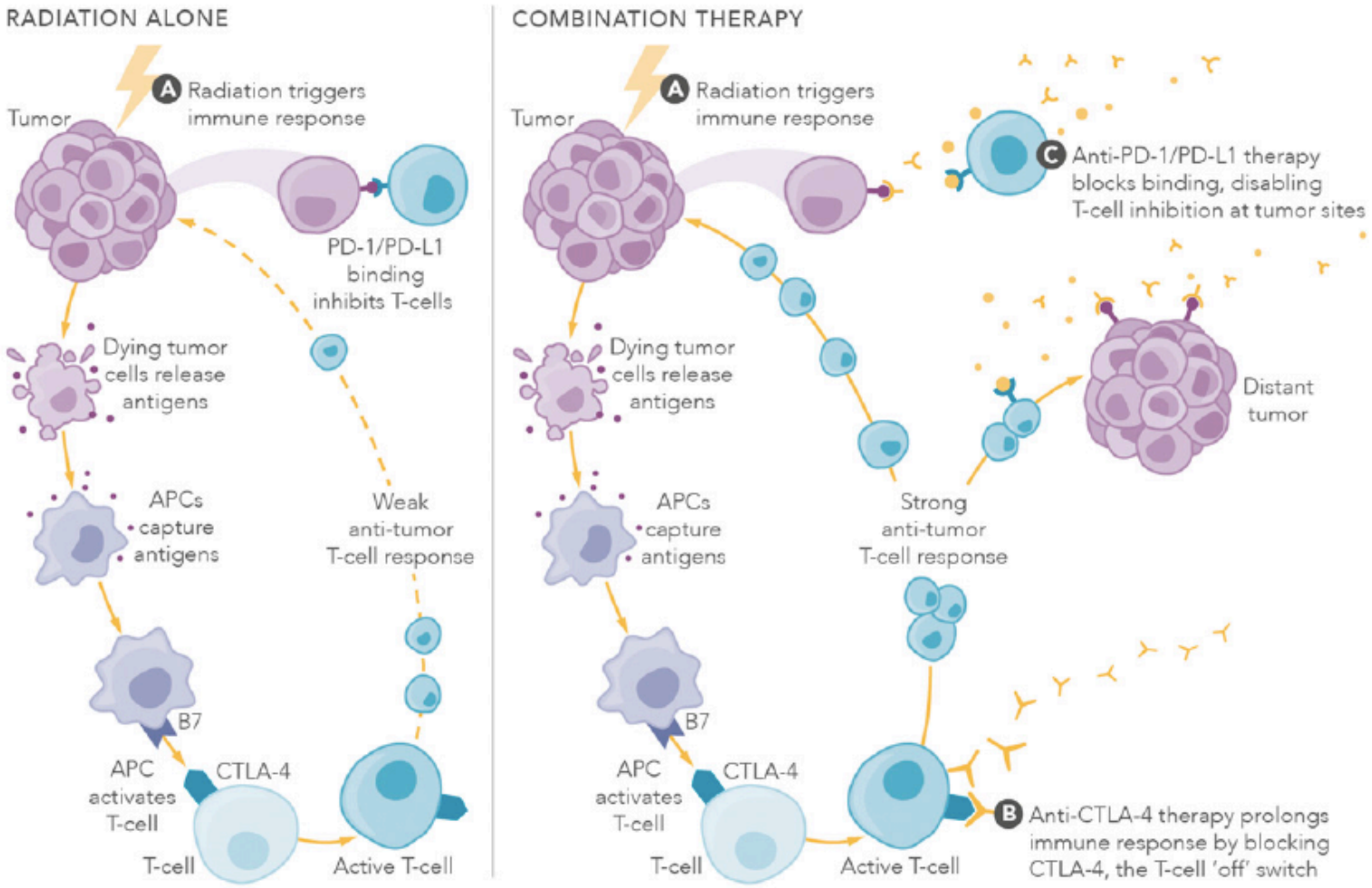
The role of IFN



Wiechselbaum et al, Nat Rev Clin Oncol 2017

Radiation redux

Could traditional radiation treatments work in concert with immunotherapy to mount a more effective assault on cancer?



E. Dolgin PNAS 2017

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

Hypothesis:

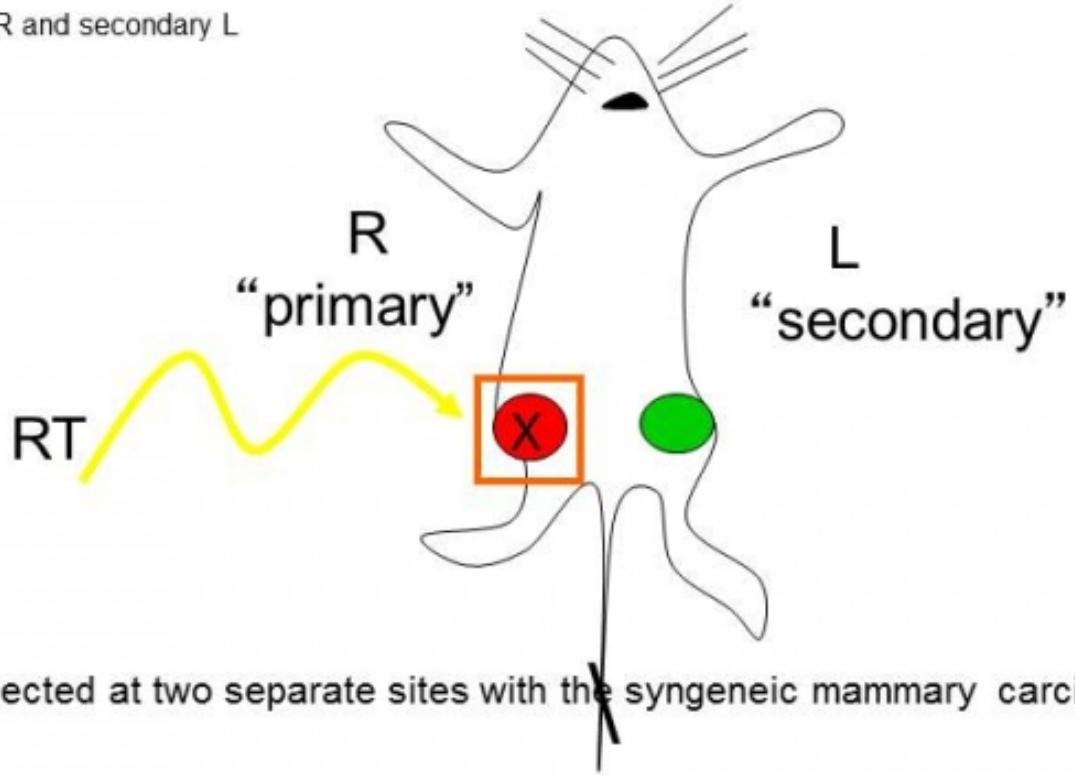
Ionizing radiation can stimulate anti-tumor immunity –by generating an *in situ* vaccine - and combination with immunotherapy may uncover this effect

Day: 0 — 20 — 21 — 31

67NR
$5x10^4$ or 10^5
each sides,
primary R and secondary L

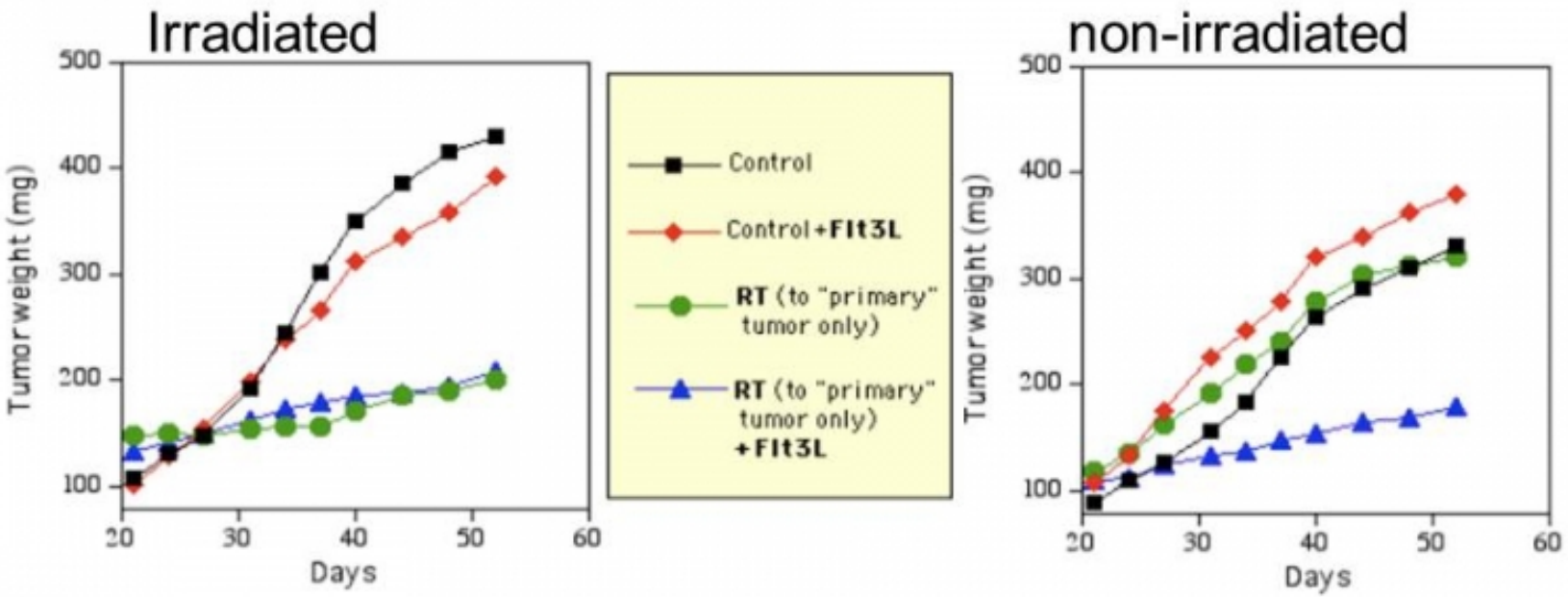
RT
2 Gy

Flt3-L (0.5mg/kg)



BALB/C mice injected at two separate sites with the syngeneic mammary carcinoma 67NR cell line

RT+Flt3-L : systemic anti-cancer effects



Int J Radiation Oncology Biol Phys 2004

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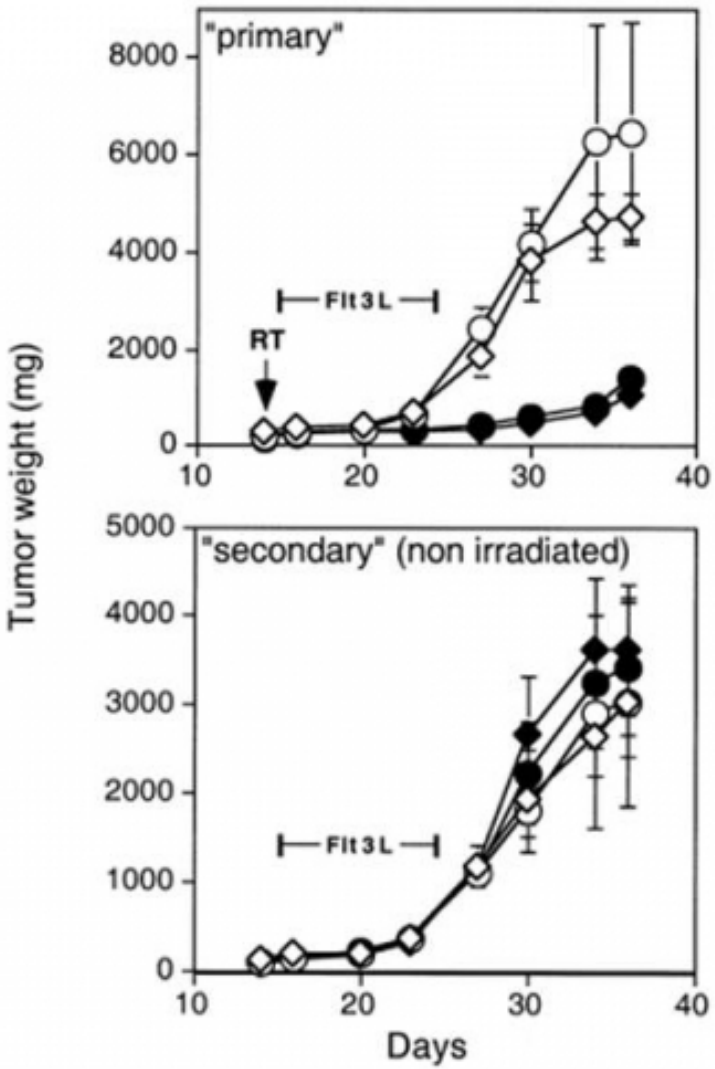
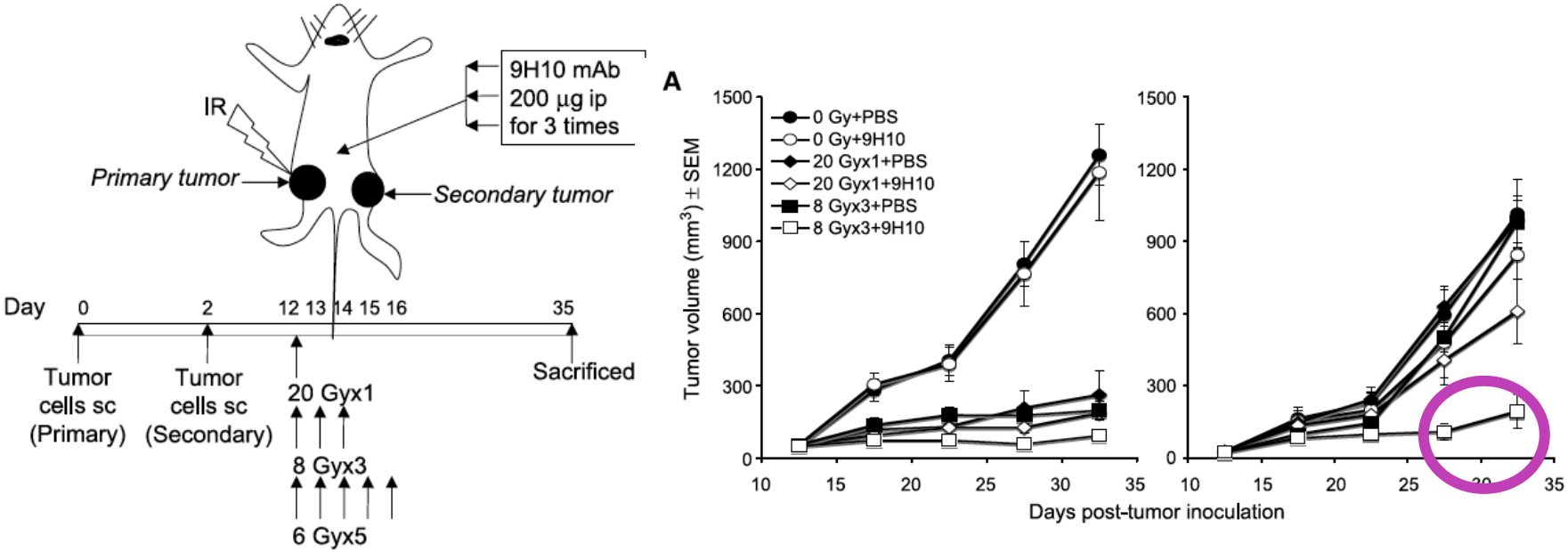
Abscopal Effect is abrogated in nude mice



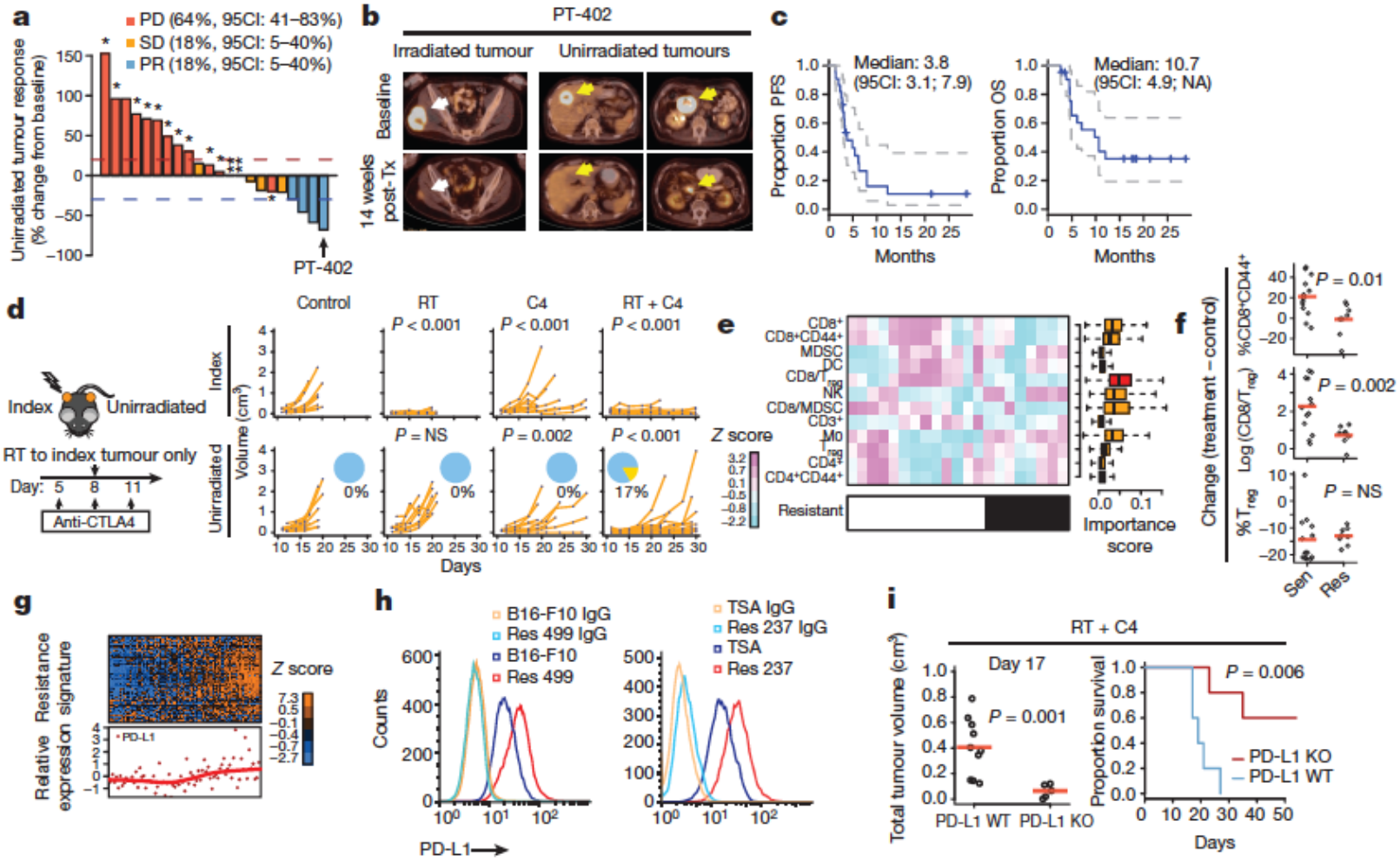
Int J Radiation Oncology Biol Phys 2004

RT + ipilimumab: single fraction vs. fractionated RT



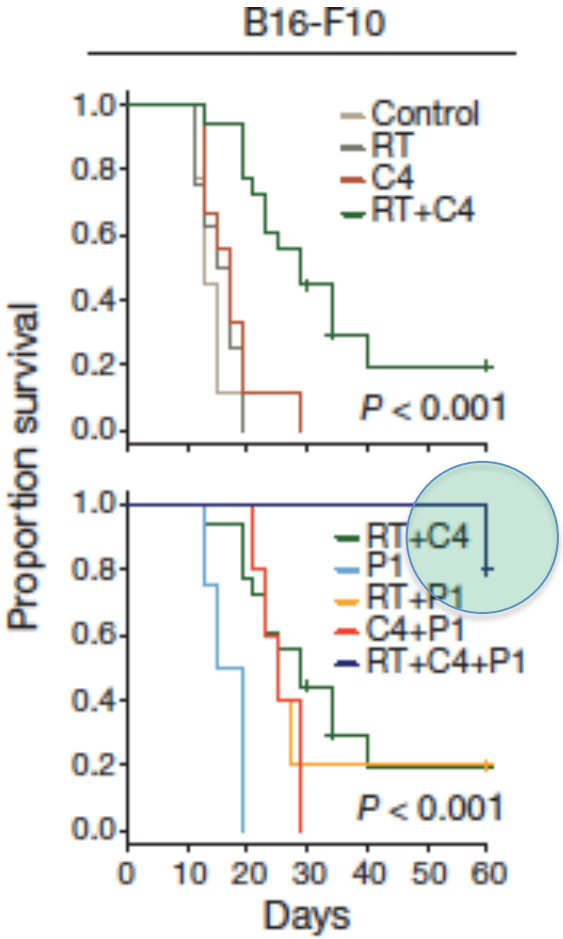
Demaria et al, Clin Canc Res 2009

Radiation and dual checkpoint inhibition activate non-redundant immune mechanisms in cancer



Twyman Saint-Victor et al, Nature 2015

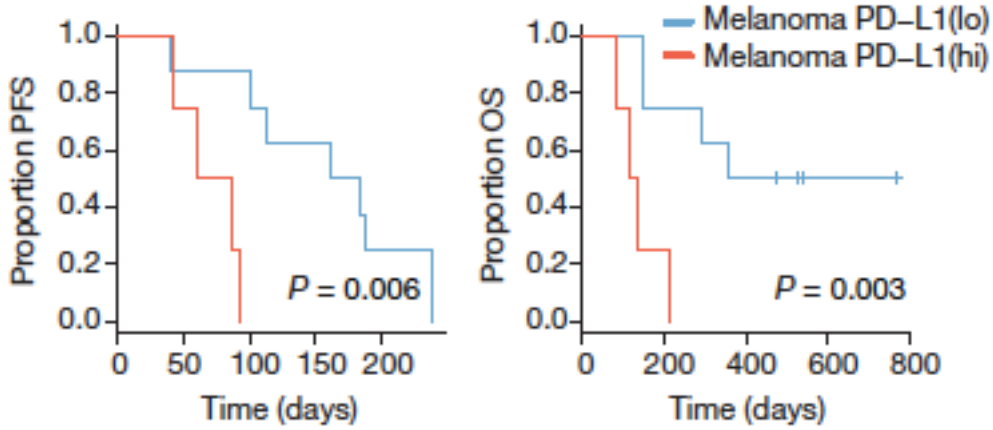
Resistance to anti-CTLA-4 and radiation depends on PD-L1 expression in melanoma patients



f

RECIST	Melanoma PD-L1(lo)	Melanoma PD-L1(hi)
PR	2	0
SD	1	0
PD	5	4

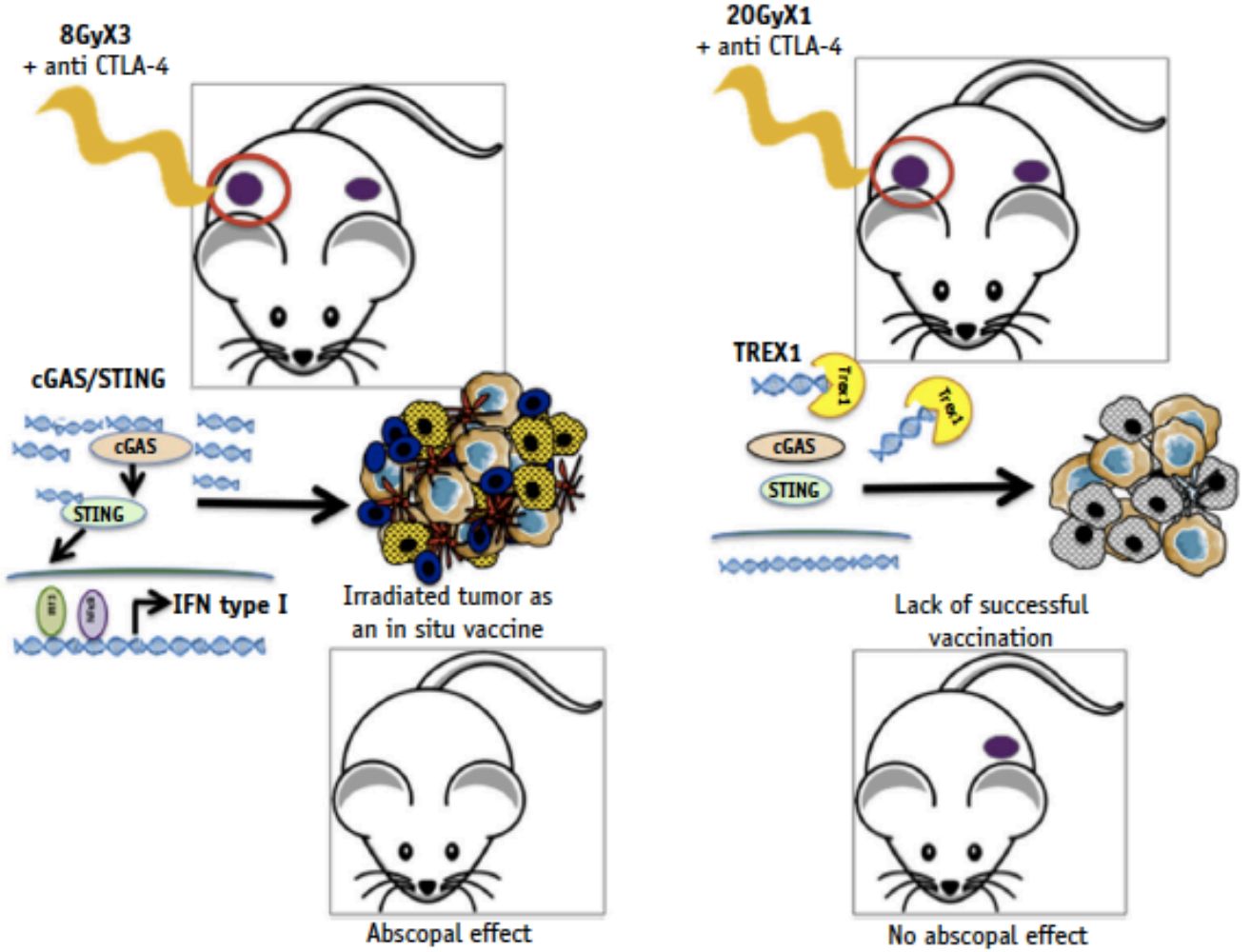
g



Twyman Saint-Victor et al, Nature 2015

DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity

Claire Vanpouille-Box[1], Amandine Alard[2,†], Molykutty J. Aryankalayil[3], Yasmeen Sarfraz[1], Julie M. Diamond[1], Robert J. Schneider[2], Giorgio Inghirami[4], C. Norman Coleman[3], Silvia C. Formenti[1] & Sandra Demaria[1,4]

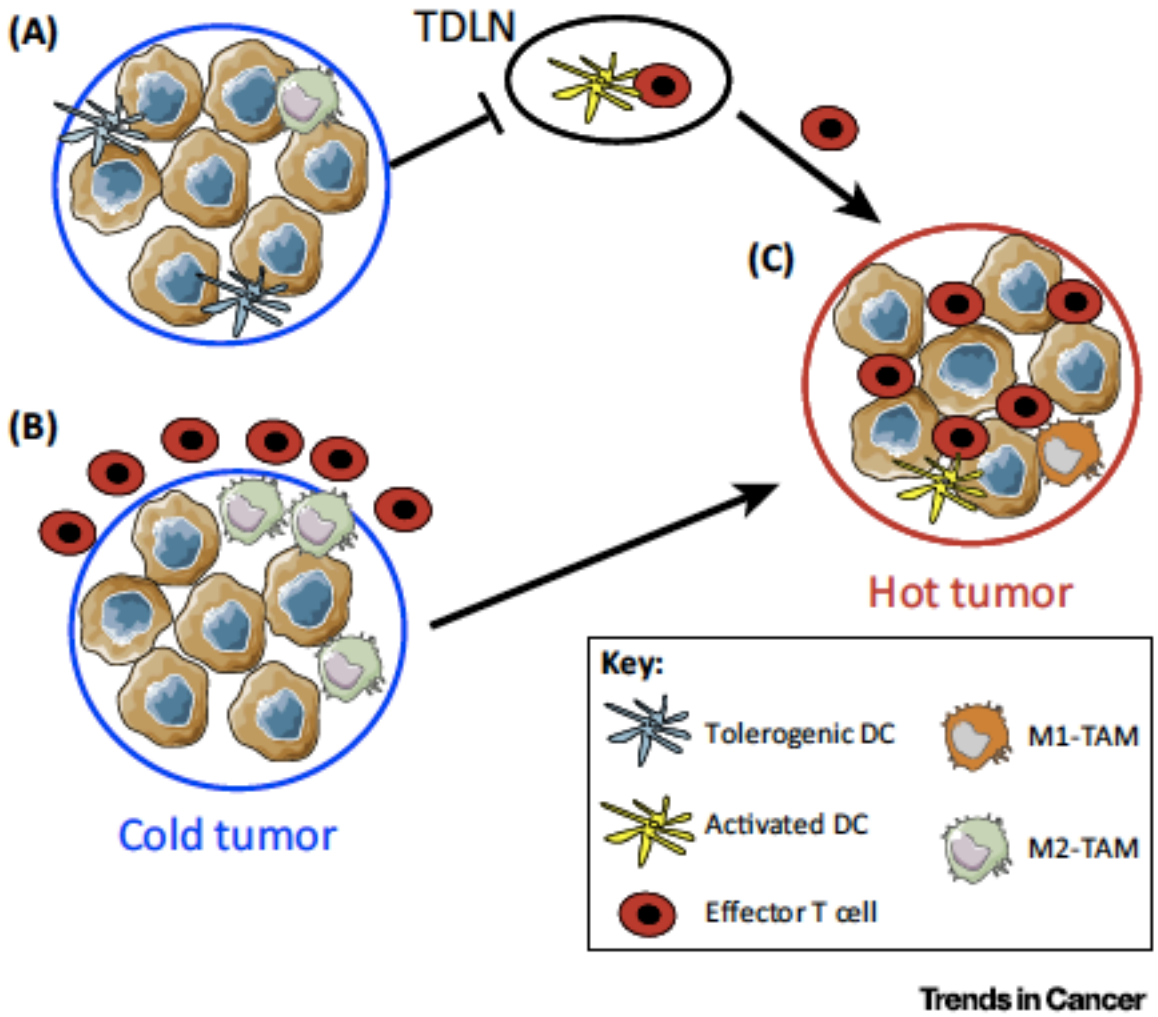


Vanpouille-Box et al, Nat Comm 2017; Formenti et al, IJROBP 2017

Converting 'Cold' Tumors into 'Hot' Ones

High-dose radiation?

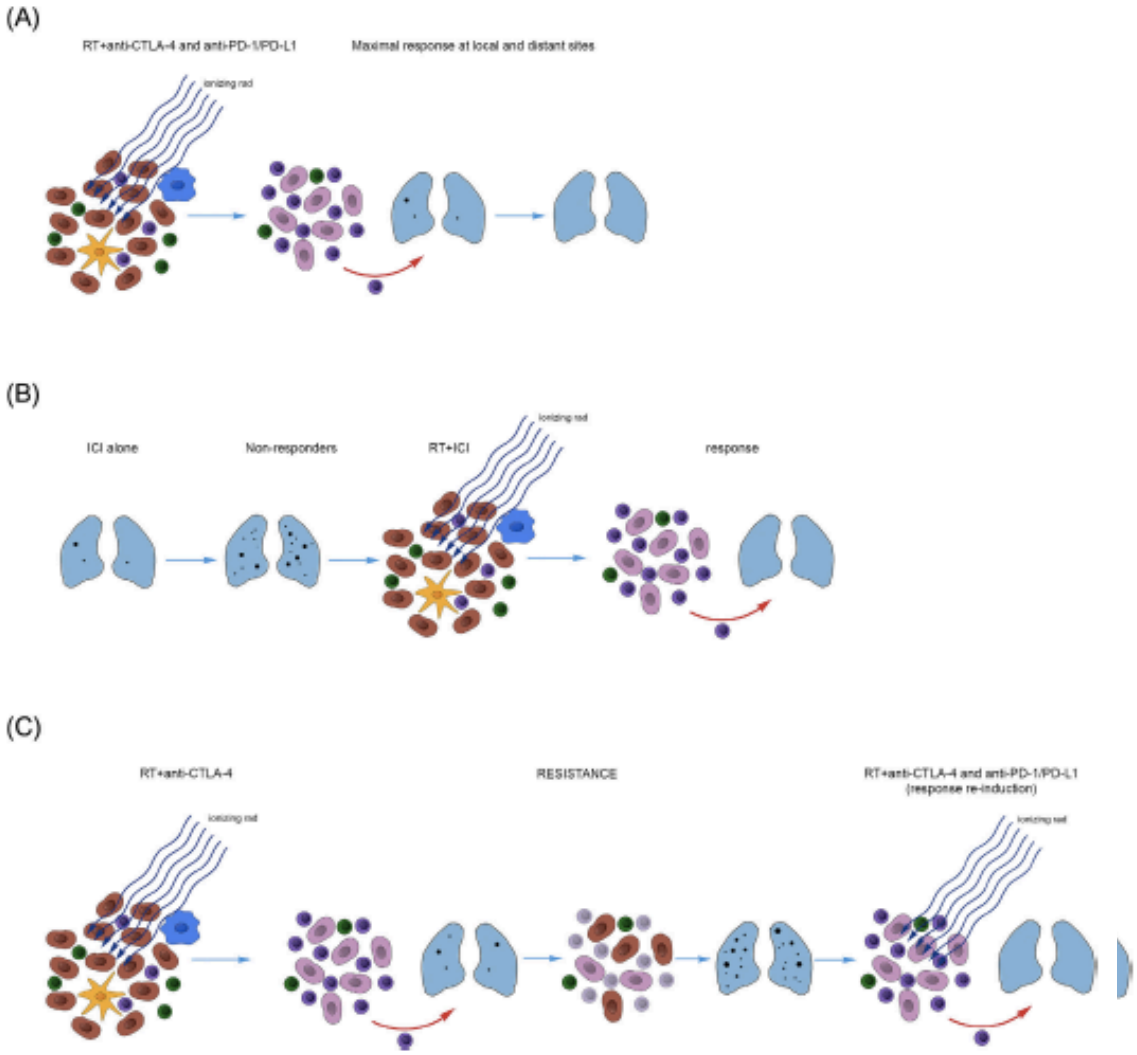
Low-dose radiation?



Trends in Cancer

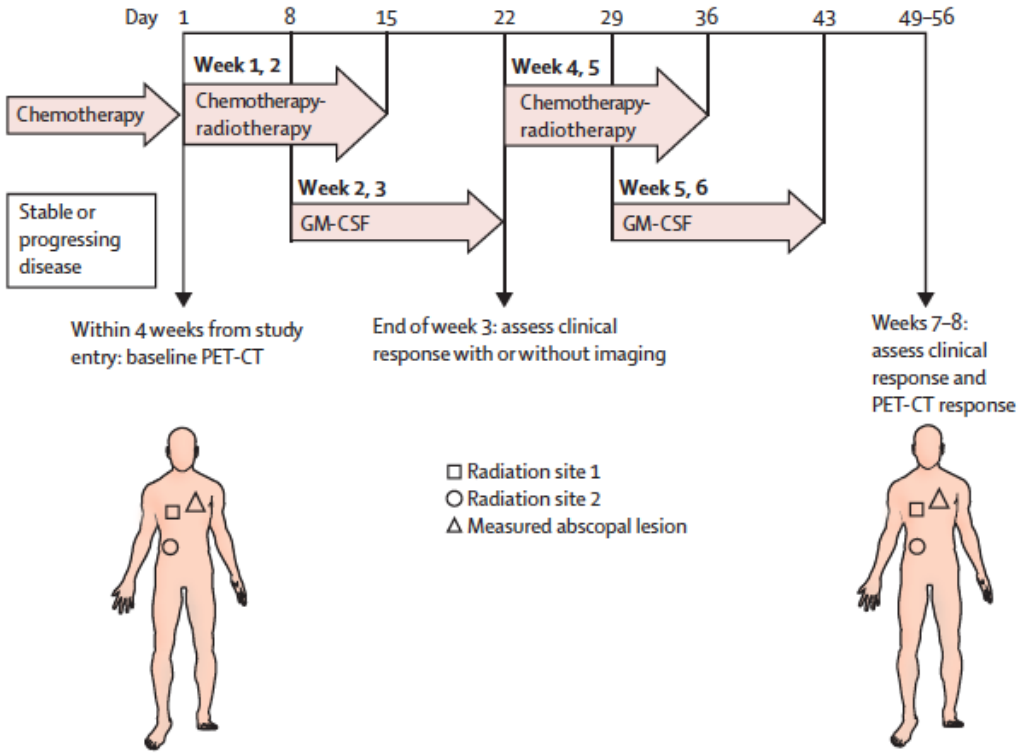
Demaria S et al, Trends in Cancer 2016

Different clinical strategies: overcoming resistance?



Filippi et al, Radiother Oncol 2016

RT + GM-CSF in metastatic solid tumors



	Enrolled patients (n=41)
Age (years)	62·0 (54·5–69·5)
Sex	
Male	8 (20%)
Female	33 (80%)
Number of previous therapies	
Radiotherapy	1 (0–3)
Chemotherapy	3 (2–4)
Number of measurable lesions	
Chest	2 (1–3)
Abdomen	0 (0–0·5)
Pelvis	0 (0–0)
Any site	3 (2–4)
Number of patients with lesions	
3 lesions	21 (51%)
4–6 lesions	15 (37%)
>6 lesions	5 (12%)

Data are n (%) or median (IQR).

Table 1: **Baseline patient characteristics**

Golden et al, Lancet Oncol 2015

RT + GM-CSF in metastatic solid tumors

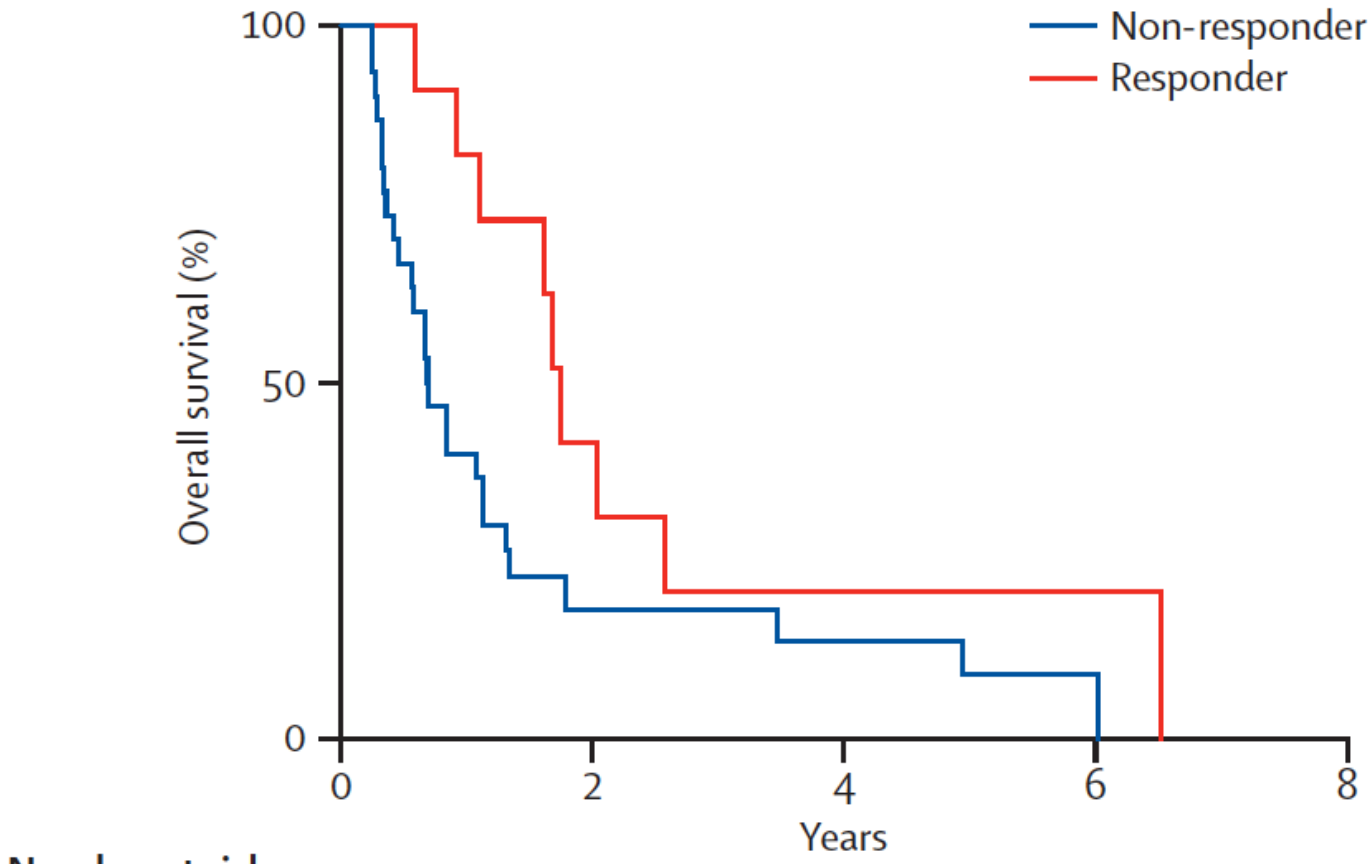
	Patients diagnosed	Patients completing scheduled therapy	Patients not assessable for best abscopal response	Patients assessable for best abscopal response				Patients assessable for best abscopal response who completed their scheduled therapy			
				PD	SD	PR	CR	PD	SD	PR	CR
Non-small-cell lung cancer	18 (44%)	13 (32%)	2 (5%)	2	10	2	2	1	7	2	2
Breast cancer	14 (34%)	11 (27%)	1 (2%)	2	6	5	0	2	4	4	0
Thymic cancer	2 (5%)	2 (5%)	..	0	0	2	0	0	0	2	0
Urothelial cancer	2 (5%)	0	..	0	2	0	0	0	0	0	0
Ovarian cancer	2 (5%)	0	1 (2%)	0	1	0	0	0	0	0	0
Eccrine cancer	1 (2%)	1 (2%)	..	0	1	0	0	0	1	0	0
Cervical cancer	1 (2%)	1 (2%)	..	0	1	0	0	0	1	0	0
Small-cell lung cancer	1 (2%)	1 (2%)	..	1	0	0	0	1	0	0	0
Total	41 (100%)	30 (73%)	4 (10%)	5	21	9	2	4	13	8	2

PD=progressive disease. SD=stable disease. PR=partial response. CR=complete disease.

Table 2: **Best abscopal responses based on patient diagnoses and completion of scheduled therapy**

Golden et al, Lancet Oncol 2015

RT + GM-CSF in metastatic solid tumors



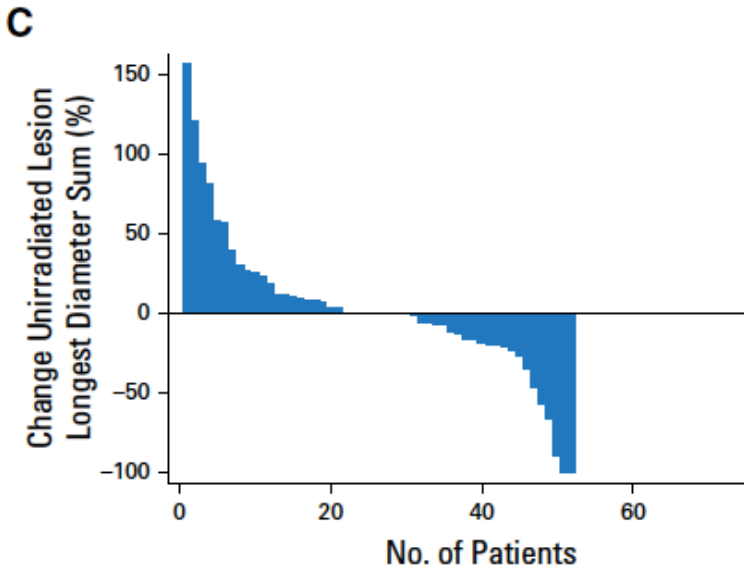
Number at risk

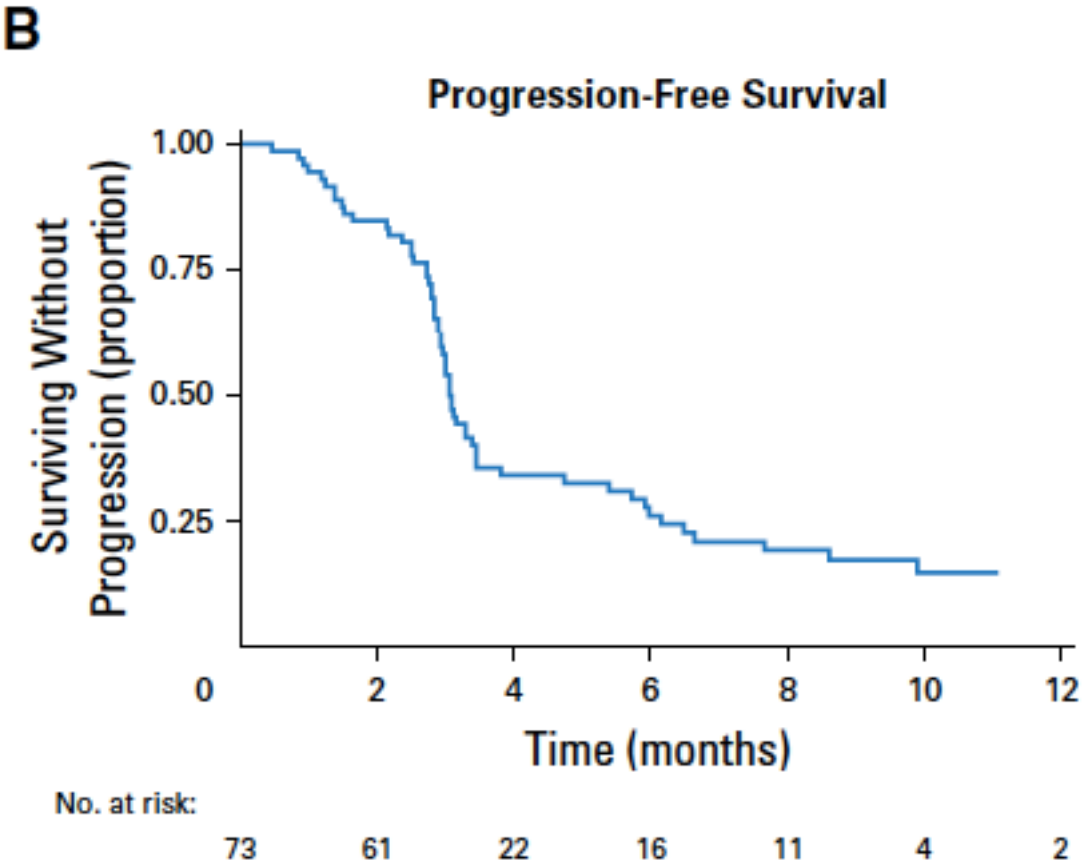
Non-responder	30	4	3	1	..
Responder	11	4	2	1	..

Golden et al, Lancet Oncol 2015

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

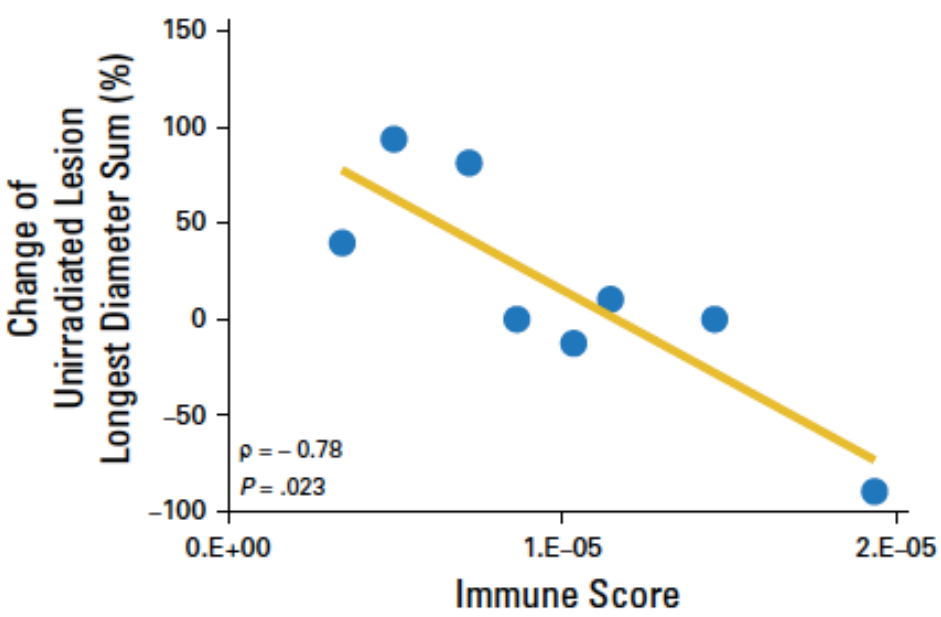
Jason J. Luke, Jeffrey M. Lemons, Theodore G. Karrison, Sean P. Pitroda, James M. Melotek, Yuanyuan Zha, Hania A. Al-Hallaq, Ainhoa Arina, Nikolai N. Khodarev, Linda Janisch, Paul Chang, Jyoti D. Patel, Gini F. Fleming, John Moroney, Manish R. Sharma, Julia R. White, Mark J. Ratain, Thomas F. Gajewski,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

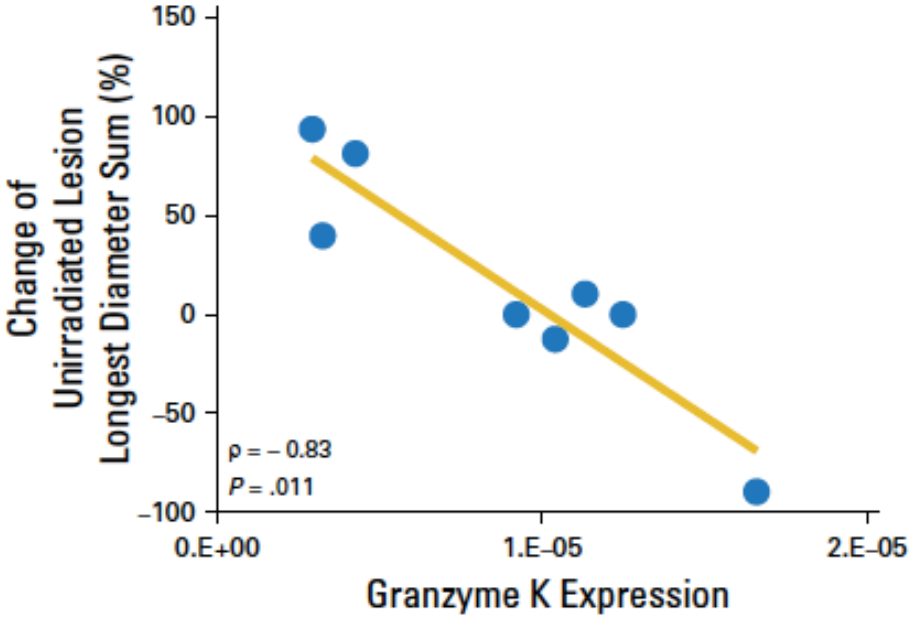




Luke et al, JCO 2018

Correlation between IFN-related immuno-score and non-irradiated tumor response





Luke et al, JCO 2018

How to potentiate RT-immunotherapy combination?

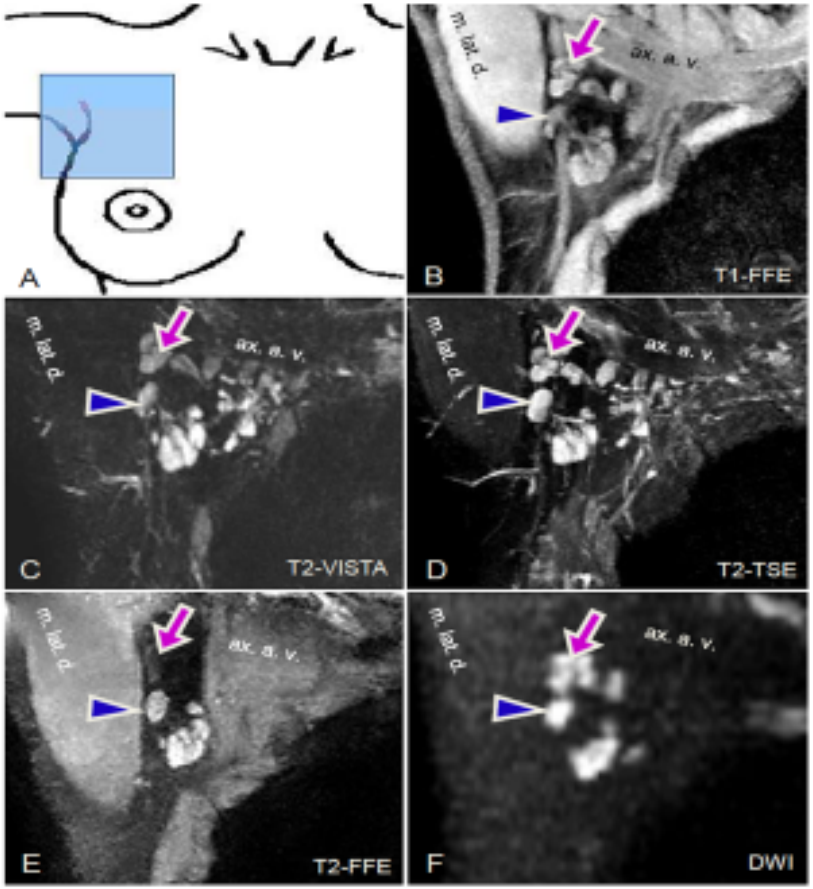
1. Overcome barriers to antigen release and antigen-presentation at treated site (appropriate RT dose, type I IFN release)
2. Enable T-cells trafficking and cytotoxic T-cells killing in non-irradiated tumors
3. By-pass antigenic heterogeneity among different metastases (broadening of TCR repertoire)
4. Counterbalance the immunosuppressive effects/T-cell exhaustion (suppress PD-1 axis)

RT on Immunological Compartments?

In room MRIgRT Clinical Examples

› Imaging breast lymph nodes

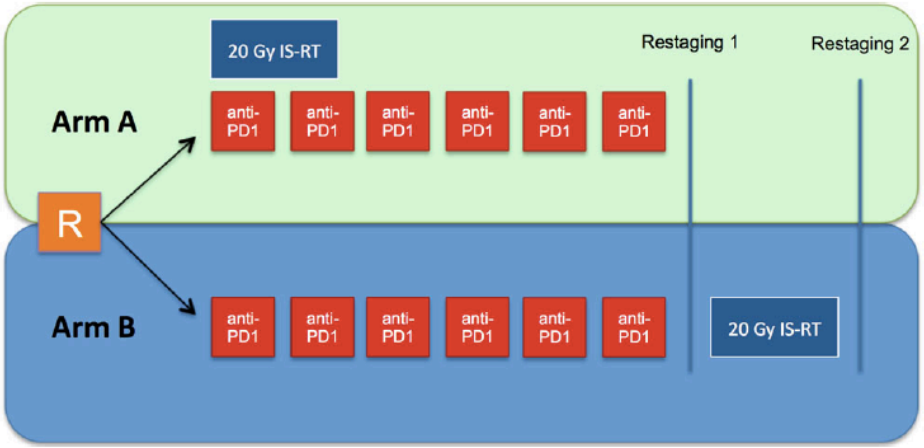
(B) T1-FFE (water-only image)
(C) T2-VISTA
(D) T2-TSE (water-only image)
(E) T2-FFE
(F) DWI (b = 1000 s/mm^2)



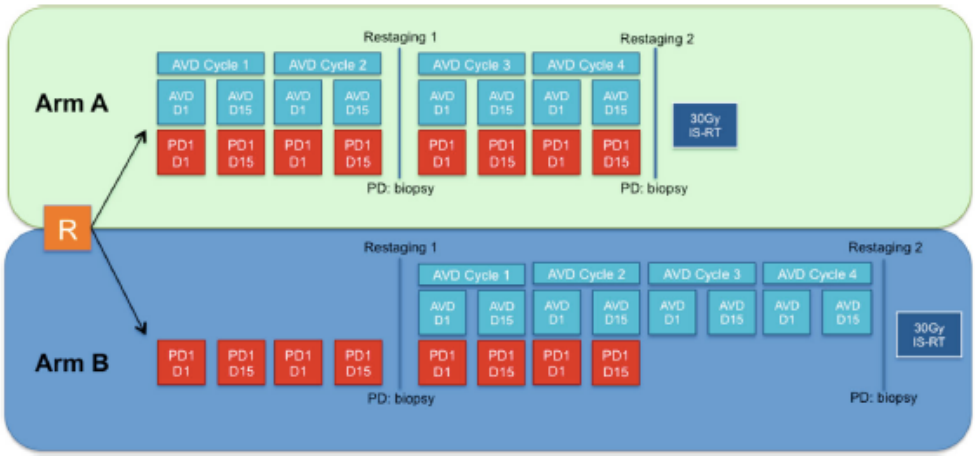
Courtesy Jan Lagendijk

GHSG study on early stage HL

FAV



UNFAV



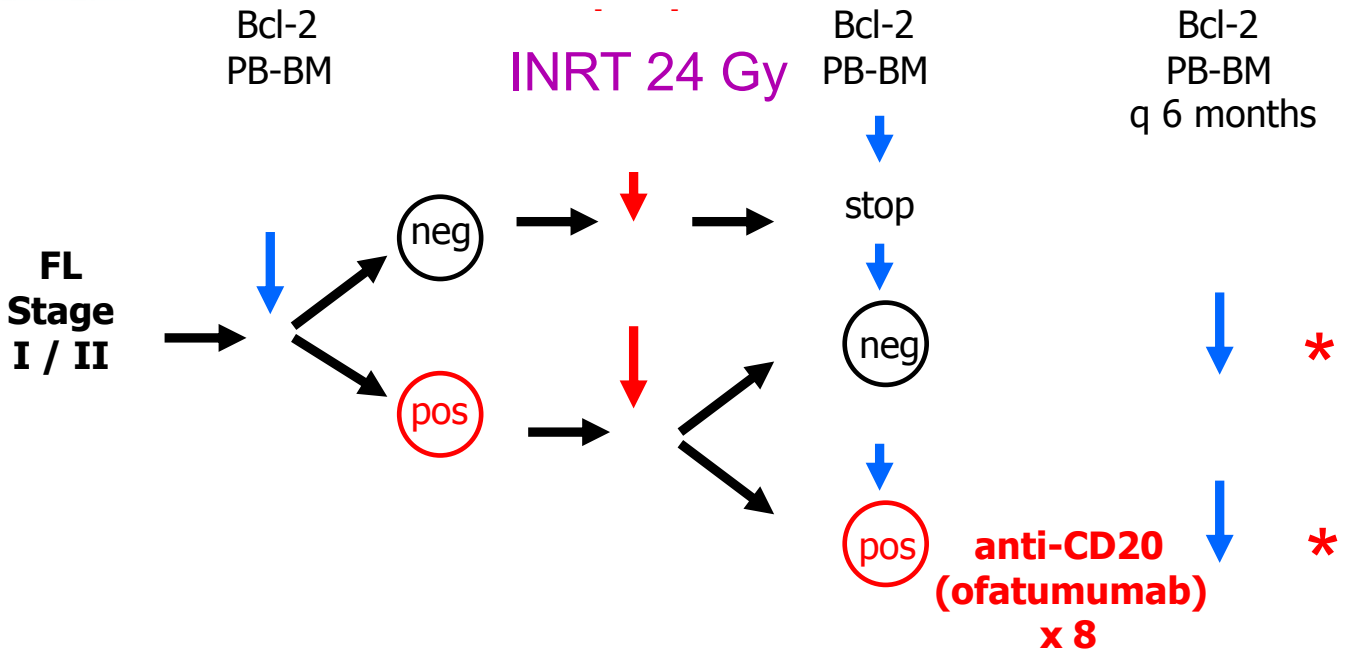
Stage I/II follicular lymphoma: spread of bcl-2/IgH+ cells in blood and bone marrow from primary site of disease and possibility of clearance after involved field radiotherapy

Pt	Baseline	Treatment	I FU	II FU	III FU	IV FU	V FU	VI FU	VII FU	VIII FU	IX FU	X FU
1	■Δ	RT	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ
2	□▲	RT	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ
3	□Δ	RT	□Δ									
4	■▲	RT	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ			
5*	■▲	RT	■▲	■▲	■▲	■▲	■▲	■▲	■▲			
6	■Δ	RT	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ			
7	■▲	RT	□Δ	□Δ	□Δ	□Δ	□Δ	□Δ				
8	□Δ	RT										
9*	■▲	RT	□Δ	□Δ	□Δ	□Δ	□Δ					
10	■▲	RT	■▲	■▲	■▲	■▲	■▲	■▲	■▲			
11**	■▲	RT										
12	■▲	RT	■▲	■▲	■▲							
13	■▲	RT	□Δ	□Δ	□Δ							
14	□Δ	RT										
15	□Δ	RT										
16	■▲	RT	■▲	■▲	■▲	■▲	■▲					
17	□Δ	RT										
18	□Δ	RT										
19*	■▲	RT	■▲	■▲	■▲	■▲						
20	■▲	RT	□Δ	□Δ	□Δ	□Δ	□Δ					
21	□Δ	RT										
22	■▲	RT	□Δ	□Δ	□Δ							
23	■▲	RT	■▲	■▲	■▲							
24	□Δ	RT										

Pulsoni et al, BJH 2007

"MIRO'" study (Molecularly Immuno-Radiotherapy Oriented)

FLOW CHART



* In case of conversion from neg to pos → **anti-CD20 (ofatumumab) x 8**

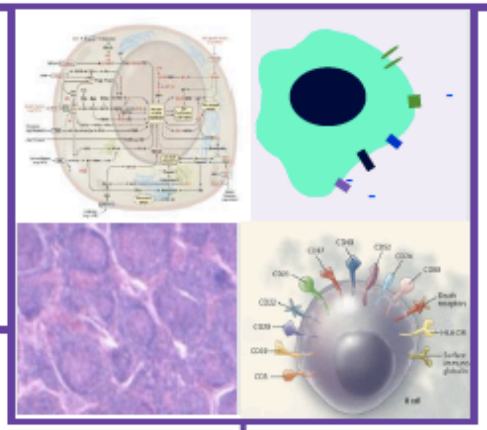
Courtesy A. Pulsoni, FIL Follicular Lymphoma Group

Microenvironment

- Lenalidomide
- T-cell exhaustion

Actionable mutations

- EZH2 — E7438
- CD79a/b — AEB071



Surface markers

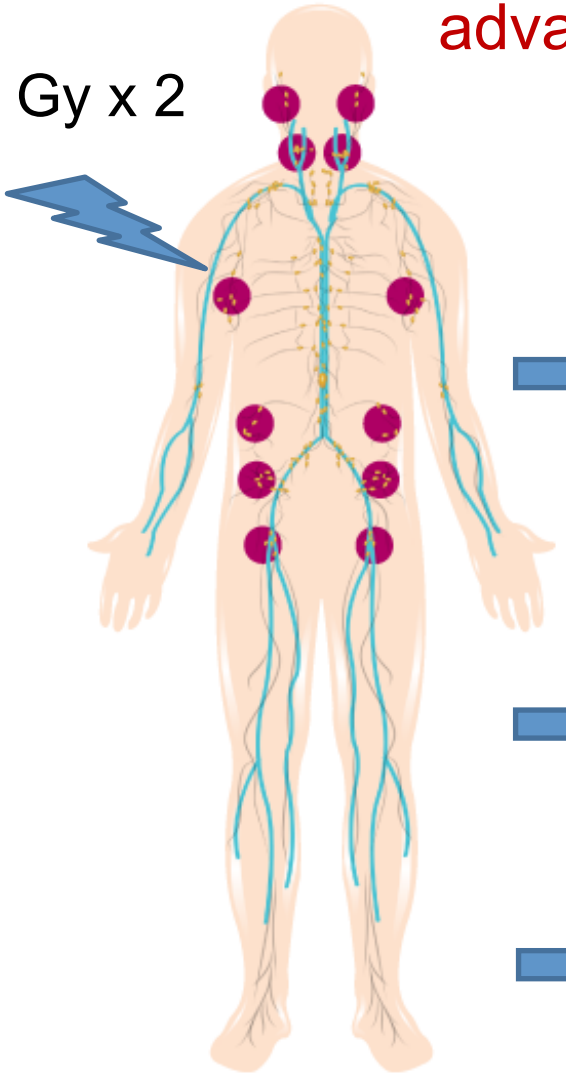
- Anti CD20 moAb — Ofatumumab, GA-101
- Anti CD40 moAb — Dacetuzumab
- Anti CD22 — Epratuzumab, Inotuzumab Ozogamicin, polatuzumab

Pathways

- Proteosome inhibitors — Bortezomib
- Bcl-2 family inhibitors — ABT-263
- Survivin inhibitors — YM155
- Syk inhibitors — Fostamatinib + others
- mTOR inhibitors — Everolimus, Temsirolimus
- PI3K inhibitors — Idelalisib, Copanlisib, Duvelisib, TGR-1202
- Btk inhibitors — Ibrutinib, ONO/GS-4059, ACP-196
- Hsp 90 inhibitors — KW 2478
- HDAC inhibitors — Vorinostat, Panobinostat
- PKC inhibitors — Enzastaurin
- Aurora kinase inhibitors
- Nedd8-activating enzyme inhibitors — MLN4924

Possible innovative uses of low dose RT for advanced stage FL

2 Gy x 2



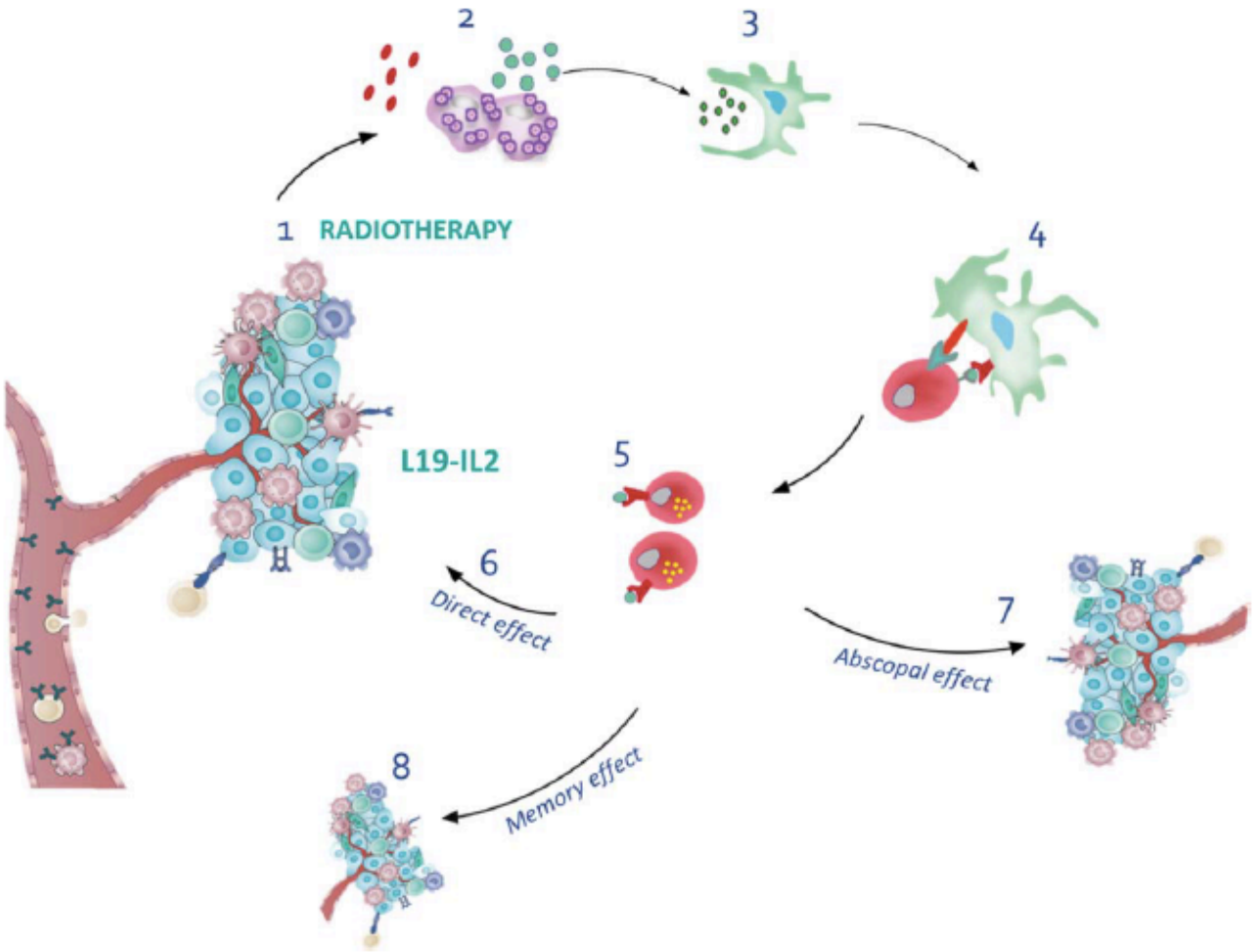
→ Immunecheckpoint inhibitors +/- Rituximab?

→ Lenalidomide +/- Rituximab?

→ Repeated RT?

The immunocytokine L19-IL2: An interplay between radiotherapy and long-lasting systemic anti-tumour immune responses

Nicolle H. Rekers [a,*], Veronica Olivo Pimentel [a,*], Ala Yaromina [a], Natasja G. Lieuwes [a], Rianne Biemans [a], Catharina M. L. Zegers [a], Wilfred T. V. Germeraad [b], Evert J. Van Limbergen [a], Dario Neri [c], Ludwig J. Dubois [a,**], and Philippe Lambin [a,d,**]



Oncoimmunology 2018

285

Radiation Sensitizes Tumor Cells to CAR T Cell Immunotherapy

C.J. DeSelm,[1] M. Hamieh,[2] and M. Sadelain[2]; [1]*Memorial Sloan Kettering Cancer Center, New York, NY,* [2]*Memorial Sloan Kettering Cancer Center, New York, NY*

Results: Neoadjuvant radiation two days before CAR T cell treatment, even at a low dose of 2 Gy, dramatically increases the rate of tumor cell killing relative to no radiation (57% vs 96% tumor death at a ratio of 1:1 effector/tumor cell, $P<0.001$).
Although radiation alone results in significant tumor cell death, the tumor cells surviving RT are more sensitive to CAR T cell mediated killing, at a wide range of CAR T cell/tumor cell ratios.

RT&Immunotherapy: a bright future?