Radioterapia ed immunoterapia: quali frontiere

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Modulo dichiarazione conflitto di interessi

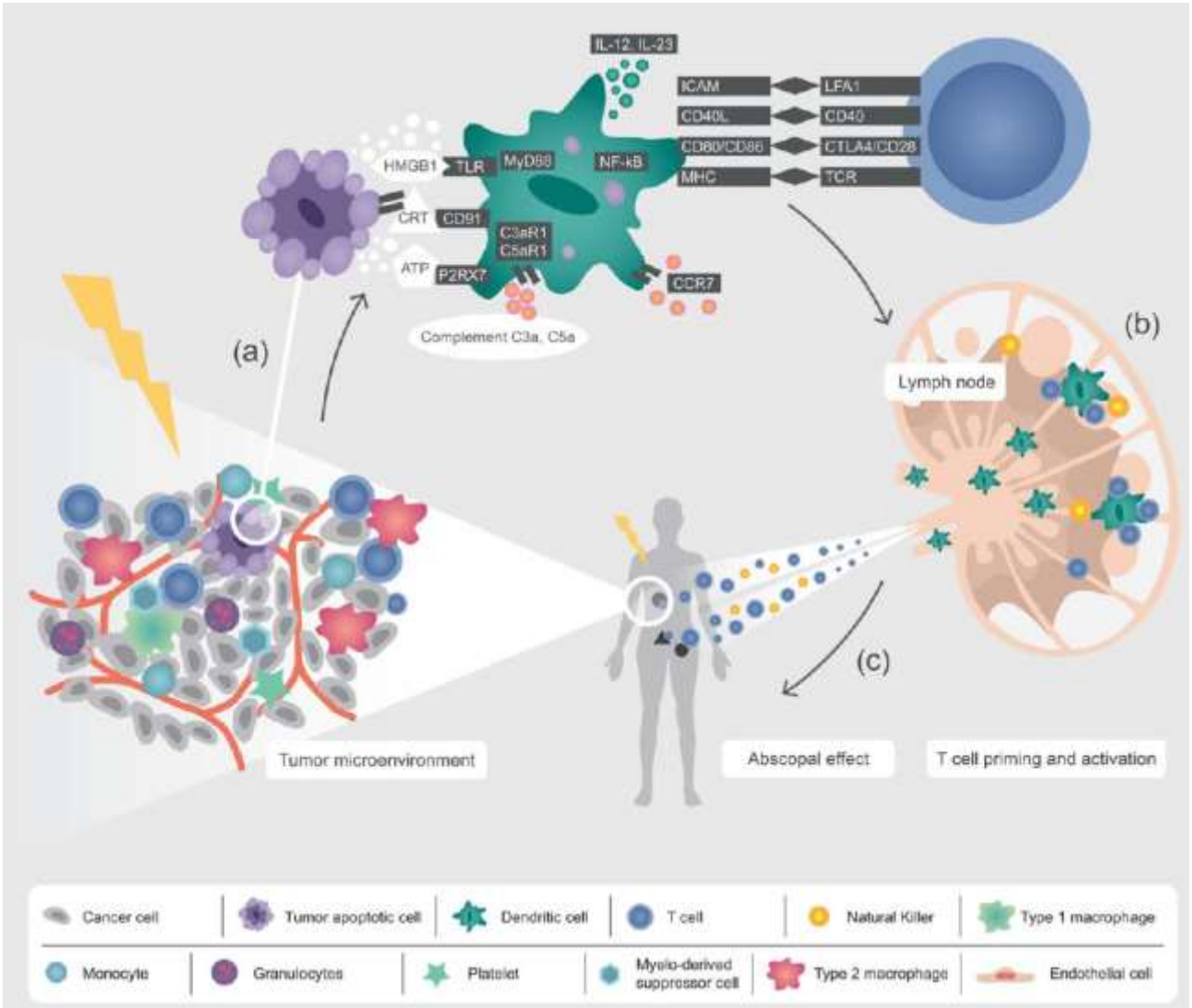
Tutti i rapporti finanziari intercorsi negli ultimi due anni devono essere dichiarati.

☐ Non ho rapporti (finanziari o di altro tipo) con le Aziende del farmaco

☒ Ho / ho avuto rapporti (finanziari o di altro tipo) con le Aziende del farmaco

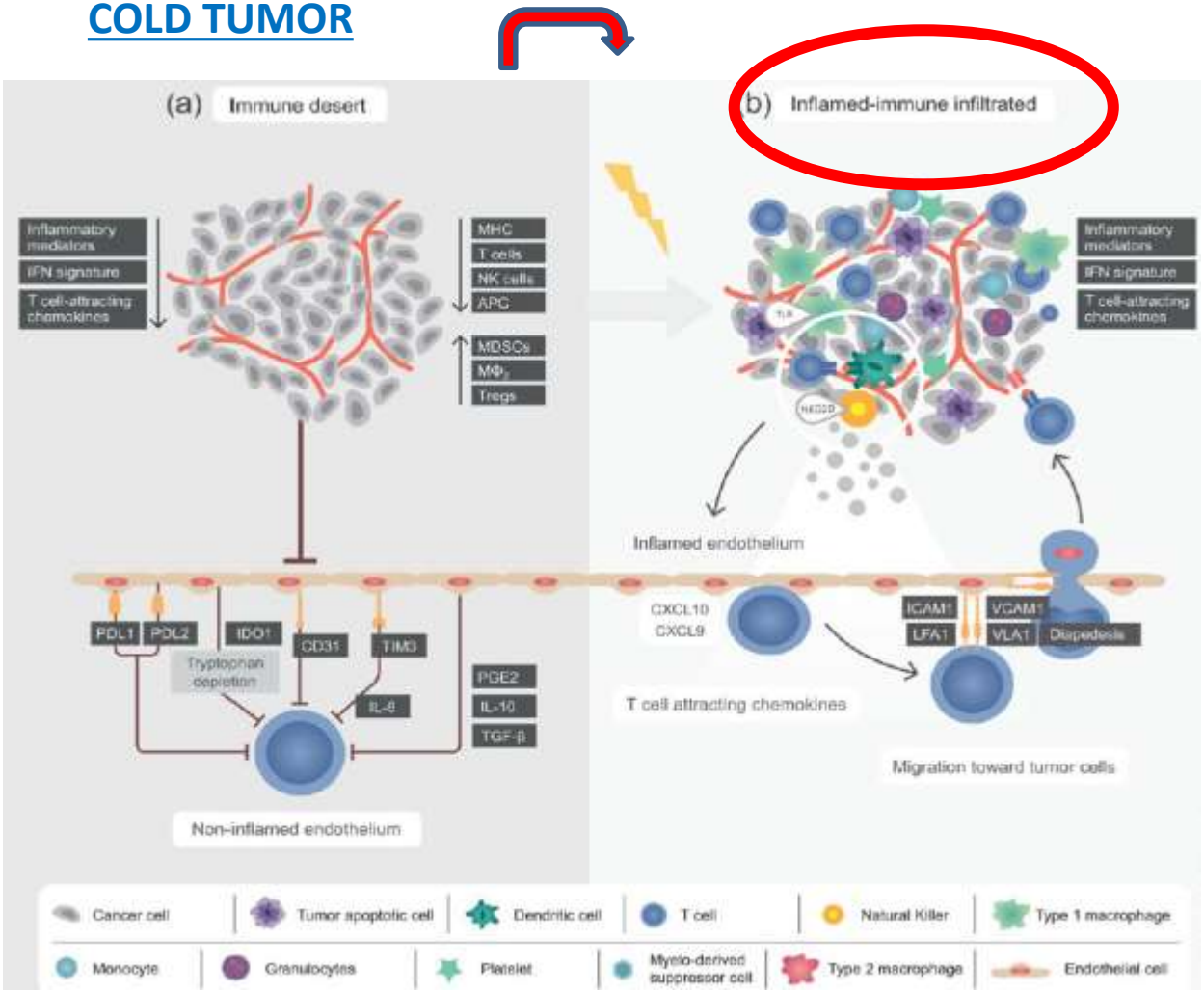
Relationship	**Company/Organization**
Clinical trials, speaker	Astra Zeneca, Pfeizer, MSD
Travel grants	Merck, Ipsen,MSD

RT→In situ vaccination



RT→Reprogramming of tumor microenvironment

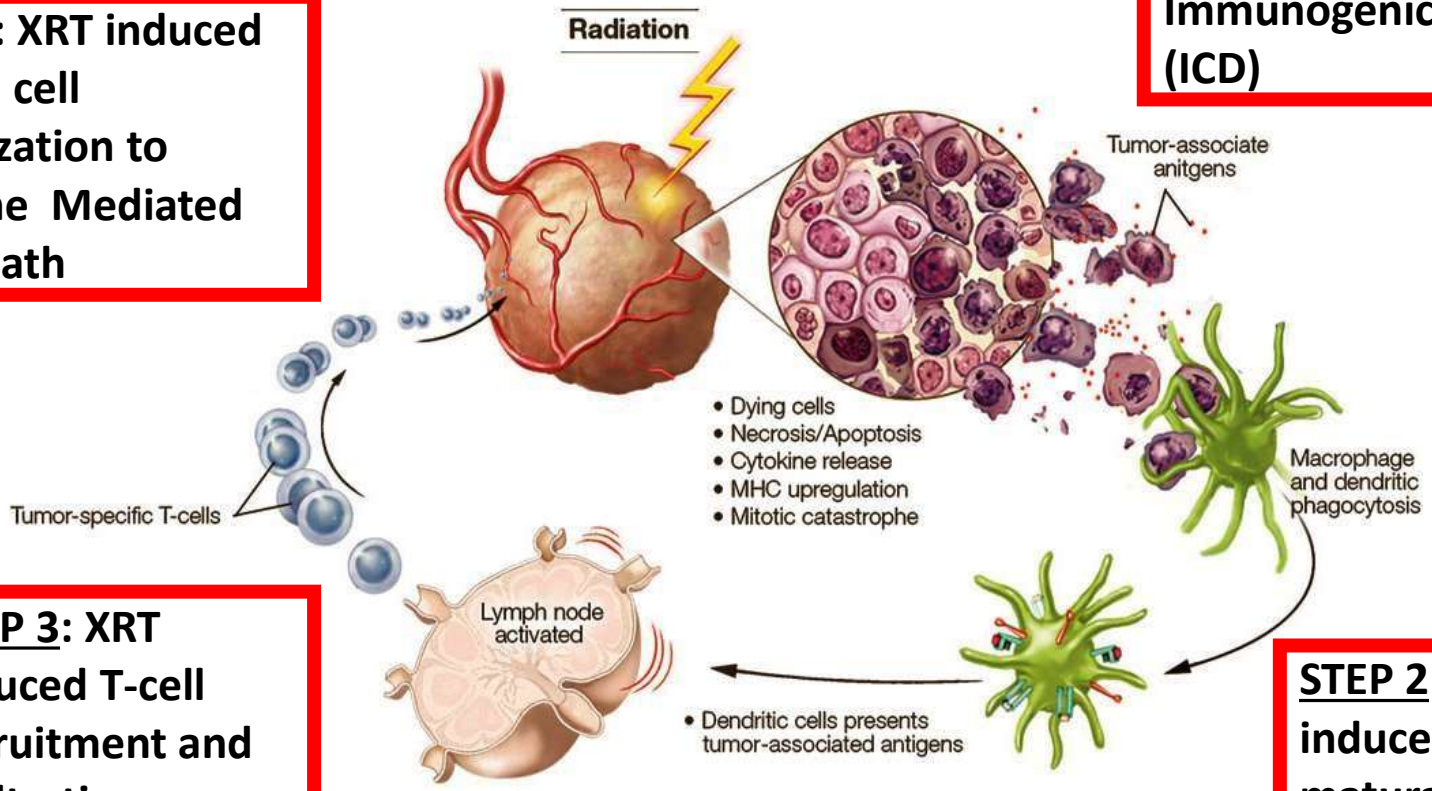
COLD TUMOR



Combination of radiotherapy and immunotherapy

STEP 1: Radiation Induced Antigen Release and Immunogenic Cell Death (ICD)

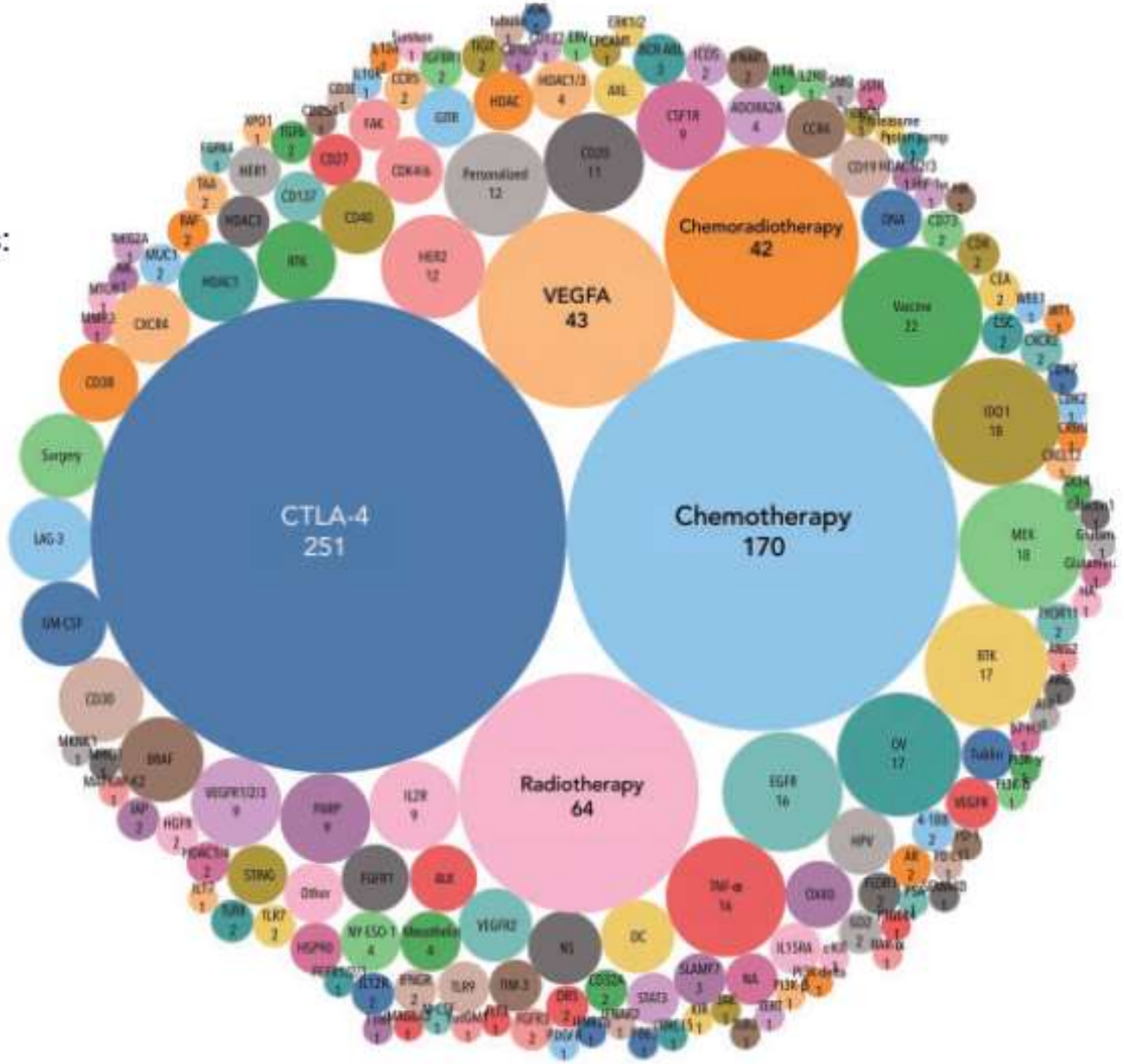
STEP 4: XRT induced Tumor cell Sensitization to Immune Mediated Cell Death



STEP 3: XRT induced T-cell recruitment and infiltration

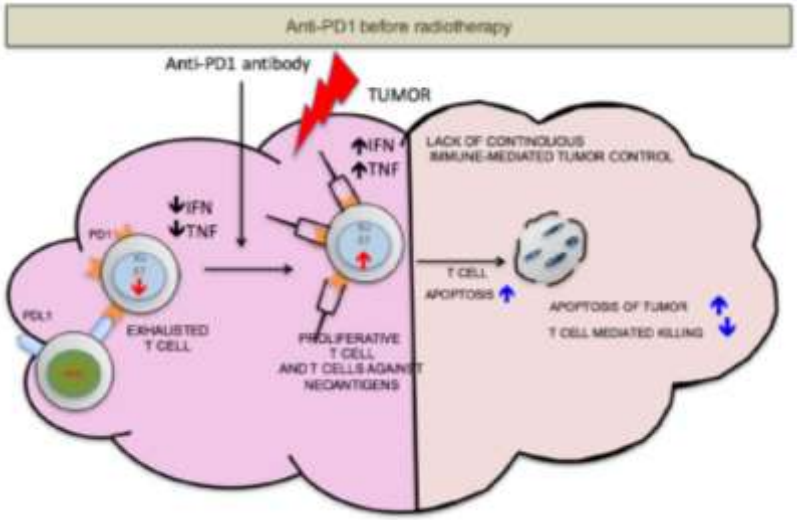
STEP 2: Radiation induced APC maturation and Antigen Presentation

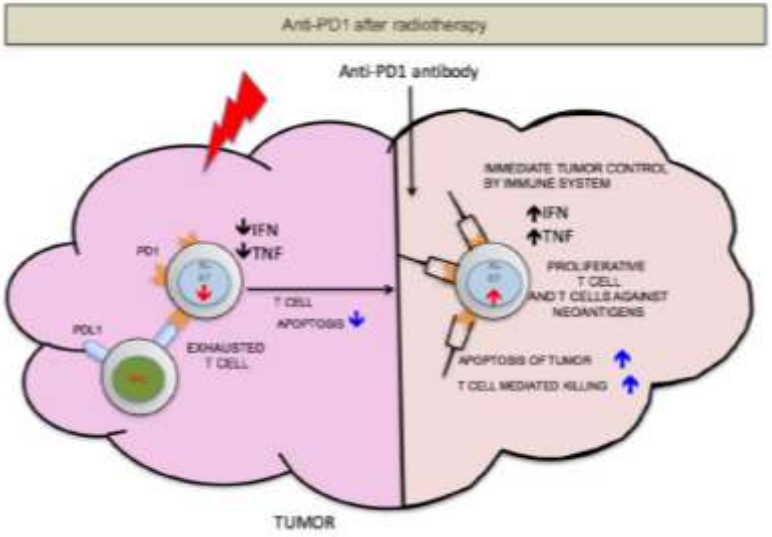
Kamrava M., Hodge JW., et al. Mol. BioSyst., 2009



J. Tang, Ann of Oncol 2018

The right way? Timing





RT just before Immunotherapy or concurrently…
But timing depends on the mechanism of action of the Immunotherapy (CTLA4 and OX40 agonist)

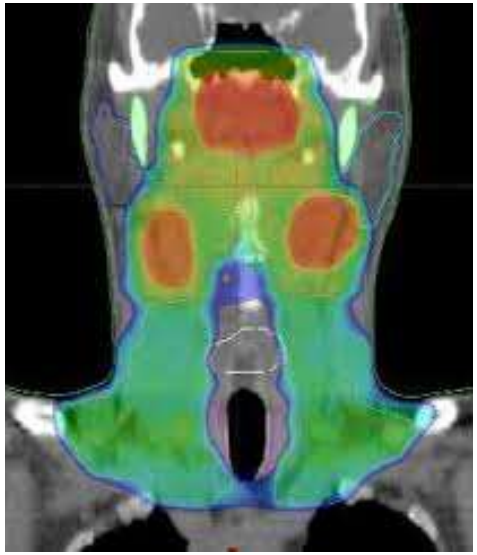
Simpson TR, J exp Med 2013; Evans D, J immunol 2001

The right way? Volume

Volume effect in …curative settings

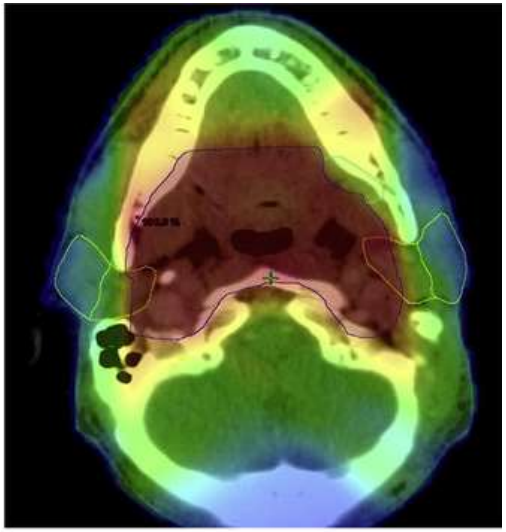
Is it useful elective nodal irradiation when combining radiotherapy with immunotherapy ?

Use of large radiation fields encompassing substantial volumes of bone marrow, pronounced reductions in blood counts were seen, thus reinforcing the notion that radiation is generally immunosuppressive



The right way?

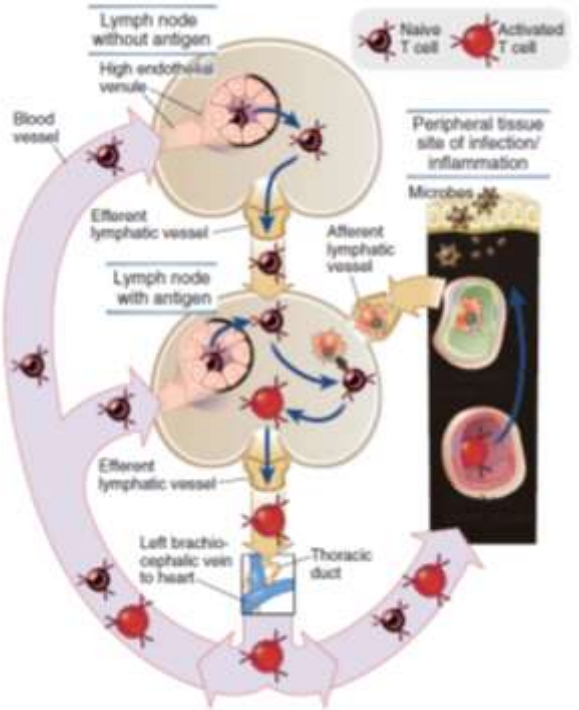
Volume effect in …curative settings



Low-dose bath to a large part of tissue

SKIN

LYMPHOCYTE



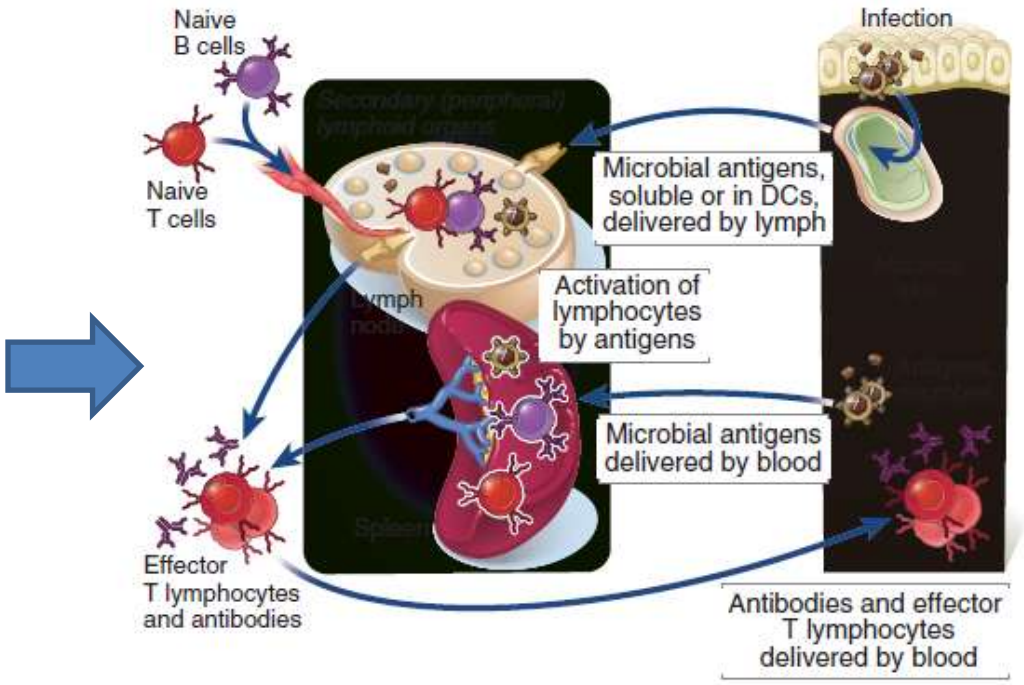
Dose is of less importance than field volume and hypofractionation generally **spares these cells by limiting time, i.e., volume blood passing through,** compared to a conventional 6-week delivery. (2Gy inactive LyT)

Dean et al., 1978; Hietanen et al., 1990; Yovino. Cancer Invest. 2013; Van Limbergen, Br J Radiol, 2017

The right way?

Volume effect in …curative settings

RT induced cross-presentation of tumor-associated epitopes by DCs **take place in the draining lymph nodes**



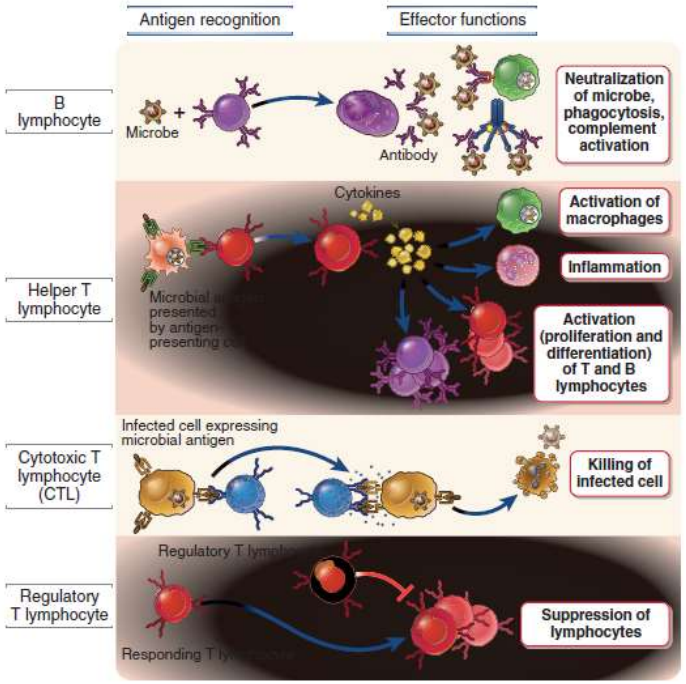
Sharabi A., Cancer Immunol Res, 2015

The right way?

Volume effect in …curative settings

In preclinical models RT reduce the proportion and absolute numbers **of tumor-infiltrating CD8+ T cells.**

Tregs, a sub-set of CD4+ T-cells involved in the **suppressive** microenvironment, are more radioresistants to fractionated schedules than other T-cell subsets, potentially mitigating the immune response induced by RT when **treating large volumes**



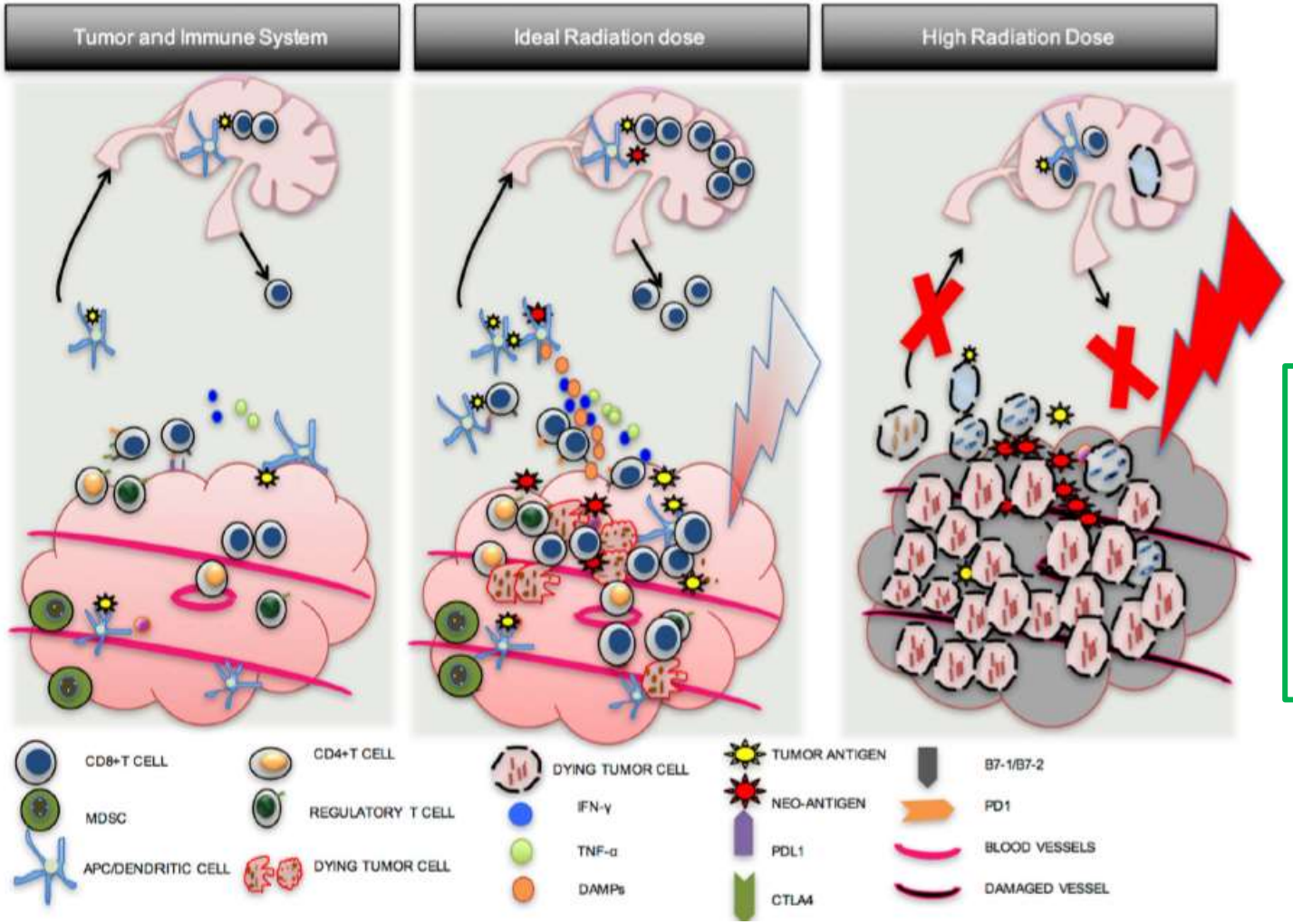
Hietanien T. Anticancer Res 2015

The right way? Dose and fractionation

1- meta-analysis of pre-clinical study showed that a BED>60Gy is associated to 50% probability of abscopal effect
2- in vivo? TME… so IED
3---no comparison different schedules
4---High dose per fraction induces tumor cell death…but
5---pre-clinical evidence dose greater 12 Gy is less immunogenic (citosol DNA increase until 12 Gy and this activate cGAS-STING complex and immune response) and induce vascular damage and reduced vascular flow…
5---repeated conventional dose: lymphopenia, increased TGFb and Treg, reduced IL-1b, increased expression PD-L1 and TIGIT….but normalizing tumor vasculature…
6---a dose and fractionation regimen optimized for a robust local response may be expected to differ from that optimized for a distant abscopal response

Lugade A, J immunol 2008; Vanpuille BoxC., Nat Commun 2017

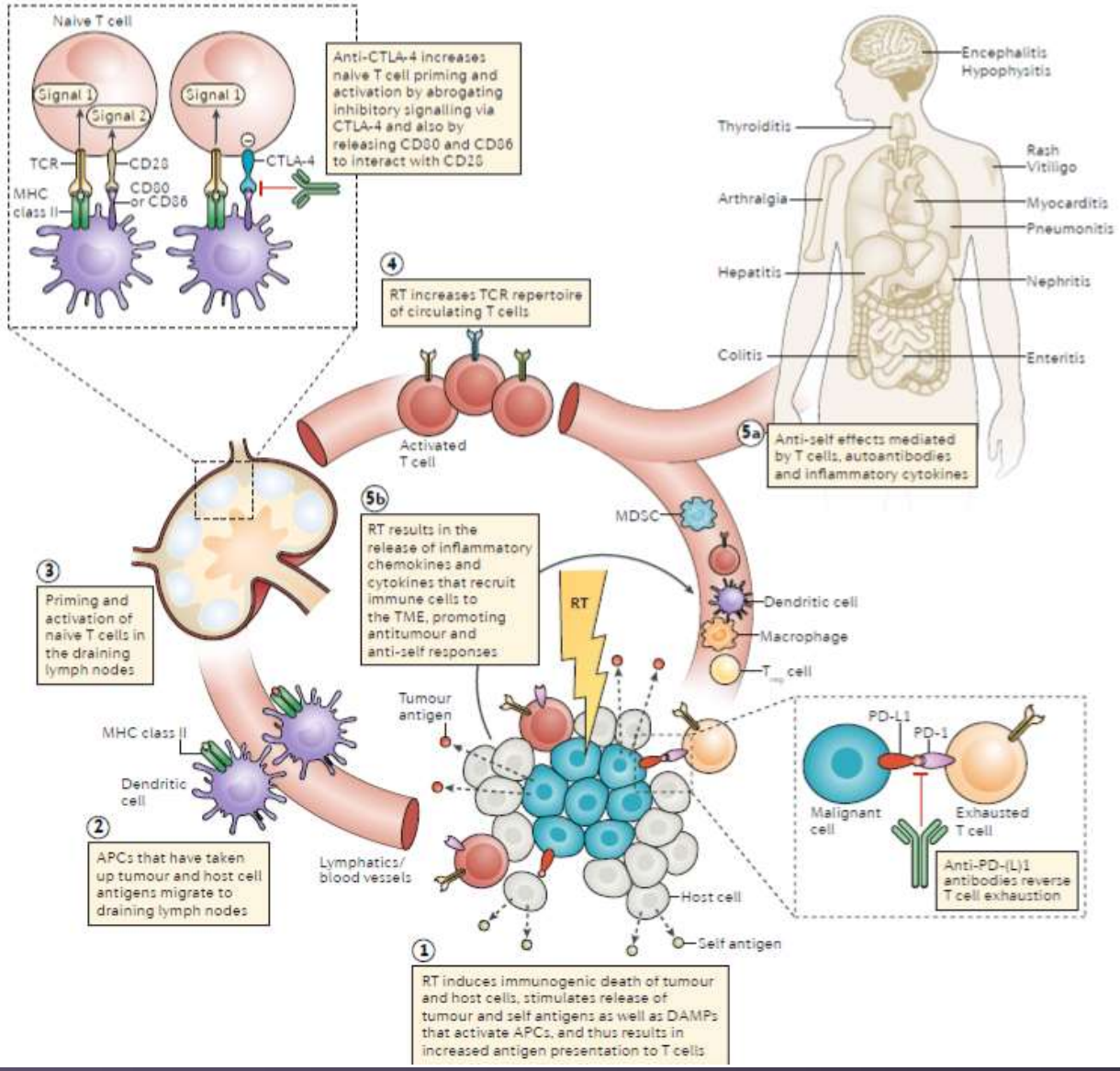
The right way? Dose and fractionation



8-10 Gy per fraction repeated 2-3 times…. in metastatic disease

Lugade A, J immunol 2008; Vanpuille BoxC., Nat Commun 2017

Safety for combination RT and ICI ??????

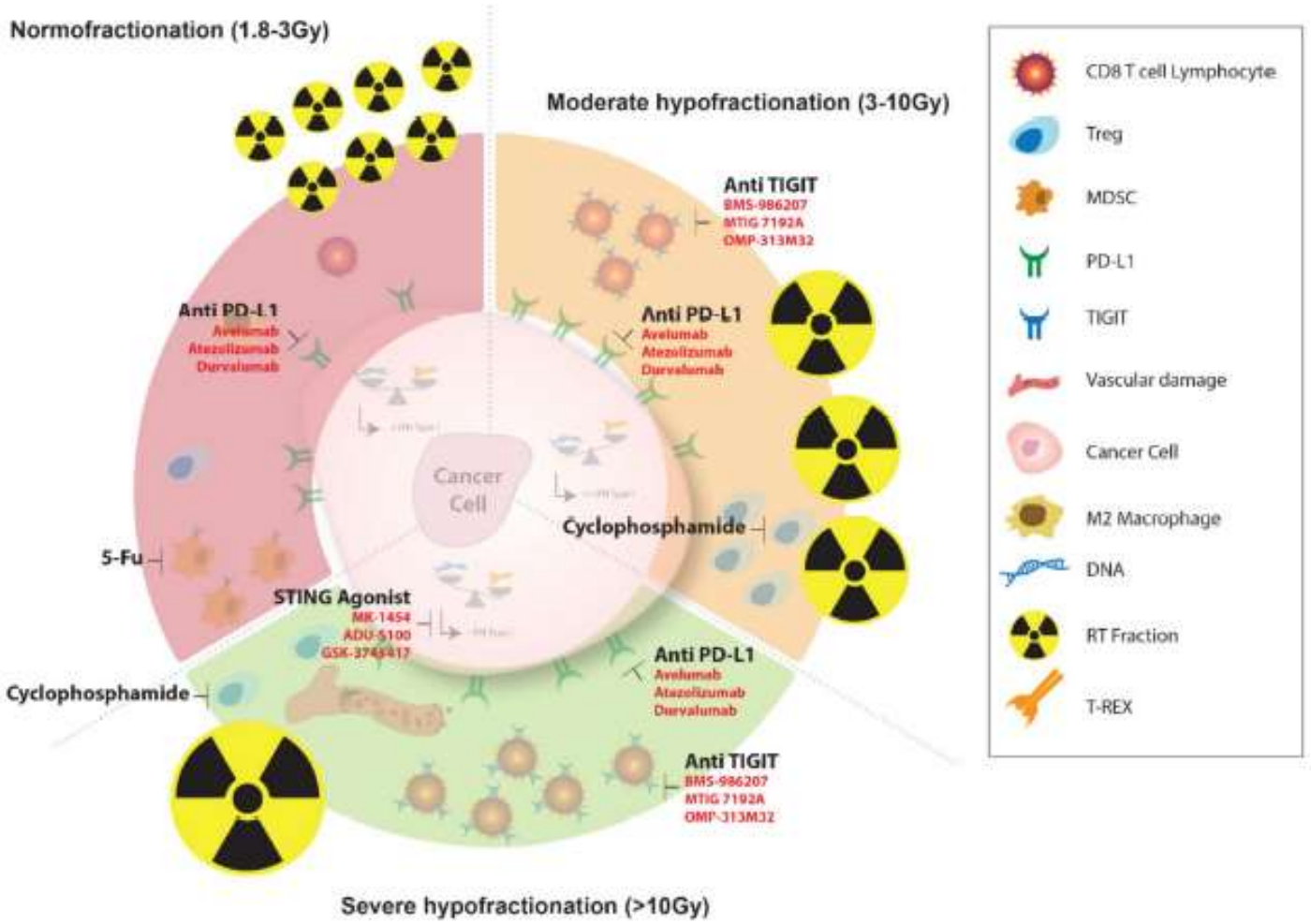


Hwang W., Nature rev 2018

Safety for combination RT and ICI ??????

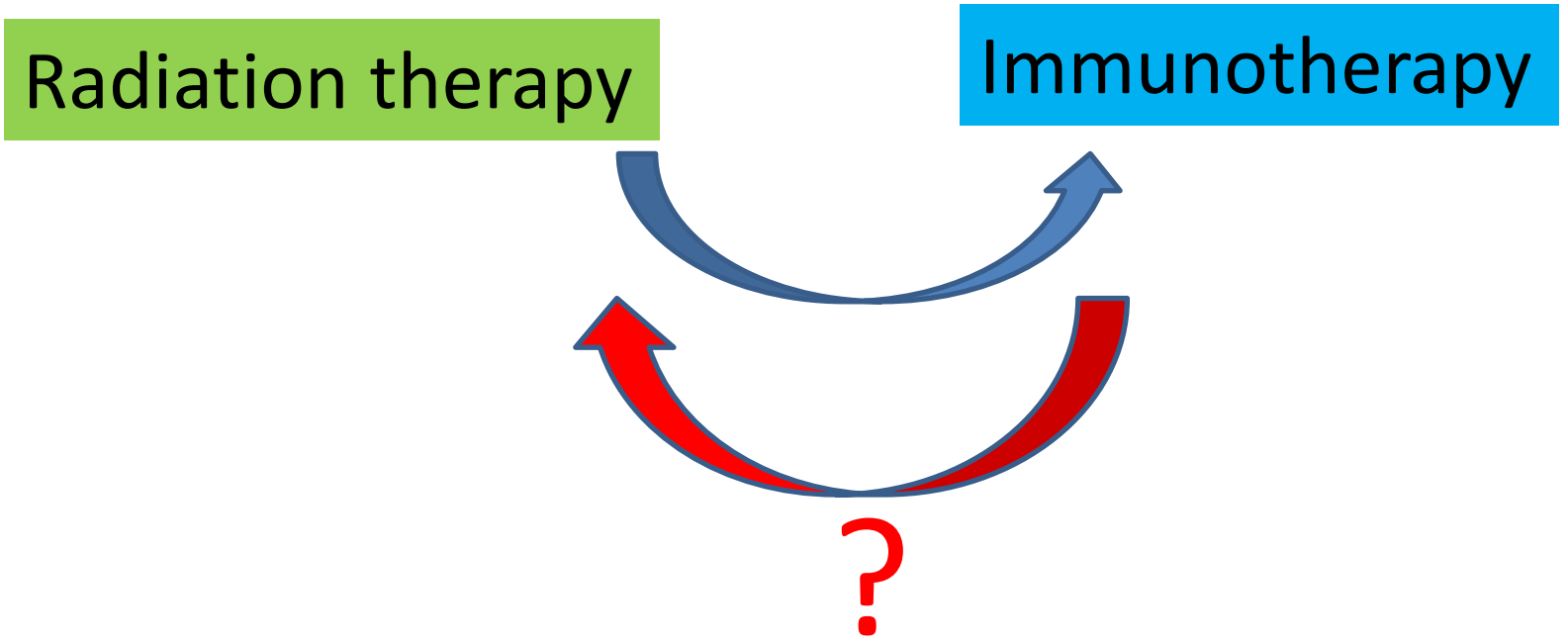
Study	characteristics	Exposure	Toxicity outcomes
Barker, 2013	Single- institution, retrospective study involving 29 patients with unresectable stage III–IV melanoma	Ipilimumab + concurrent extracranial RT	Grade ≥3 irAEs in 31% of patients including 0% of patients receiving an RT dose (EQD2) ≤100 Gy versus 44% in those receiving >100 Gyy; mFUP 11 mo
Fang, 2017	Single- institution, retrospective study involving 137 patients with brain metastases from melanoma	Intracranial SRT + CT and/or ICI	TABN in 27% on multivariate analysis, risk of RN was associated with CT < 6 months and with an increased number of lesions treated ,but was not associated with ICI type, ICI doses, or timing of ICI relative to SRT; mFUP 9.8 months
Antonia, 2017	Multicentre, randomized, placebocontrolled phase III trial involving 713 patients with locally advanced, unresectable NSCLC	Anti- PD-1 and/or anti- PD-L1 antibody ± thoracic RT (n = 73)	irAEs in 15.4% of patients receiving ICI vs 13.7% of patients receiving ICI + thoracic RT ; all- grade PNS in 5.5% of patients receiving ICI vs 8.2% of patients receiving ICI + thoracic RT; grade ≥2 PNS in 3.3% of patients receiving ICI ves 4.1% of patients receiving ICI + thoracic RT
Shaverdian, 2017	Single- institution, prospective secondary analysis involving 97 patients with advanced-stage NSCLC	Pembrolizumab ± preceding thoracic RT (n = 24)	All- grade PNS in 1% of patients receiving pembrolizumab vs 13% receiving pembrolizumab + thoracic); grade ≥3 PNS in 1% of patients receiving pembrolizumab versus 4% receiving pembrolizumab + thoracic RT ; mFUP 32.5 months in survivors

Quali frontiere?
Combination RT and biotherapies



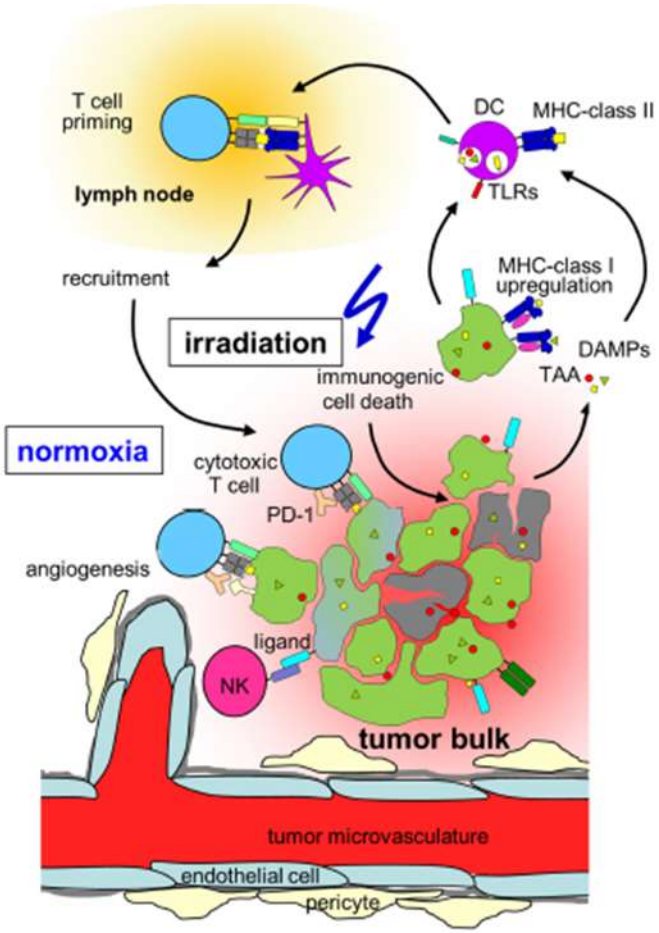
Boustani J, Cancers 2019

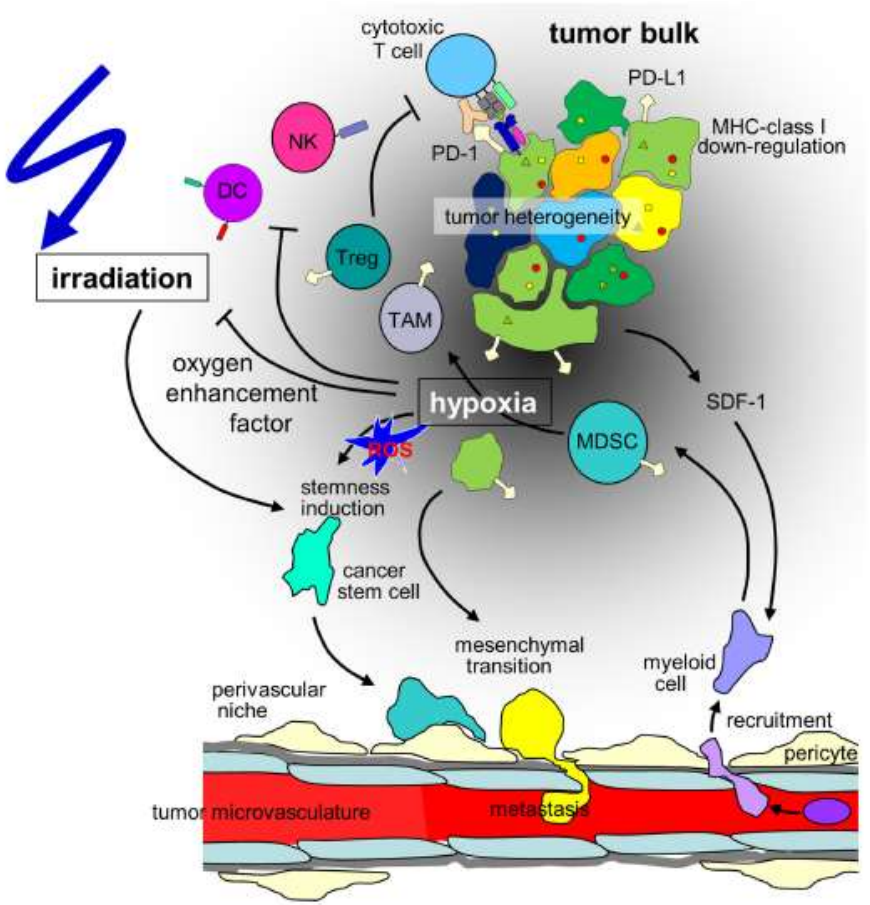
Quali frontiere?
Could immunotherapy be a radiation sensitizer?



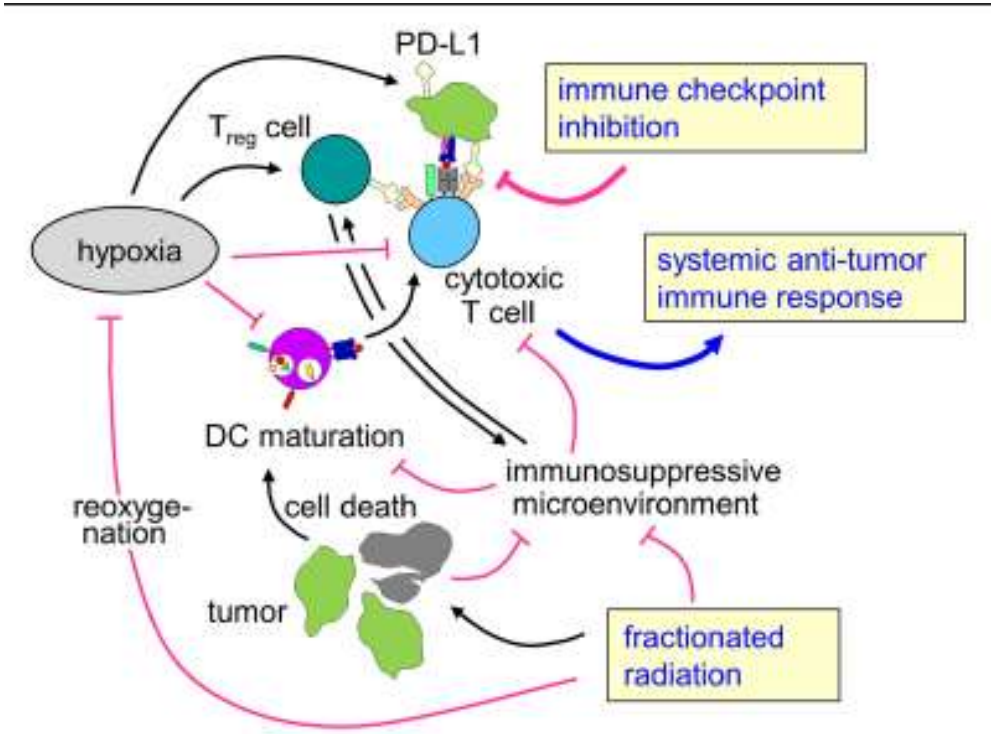
-----Regulators of both radiosensitivity and immune checkpoints have been identified (PARPinhibitors may act by upregulating PDL1 expression and inducing immunosuppression
-----ICI may influence the tumor microenvironment by regulating cytokine secretion and by remodeling tumor vasculature

Quali frontiere?
Ipoxyia





Quali frontiere? Rationale for combination RT and IO hypoxic tumors



Eckert S, Frontiers in immunol 2019

Multiple partial irradiation?

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

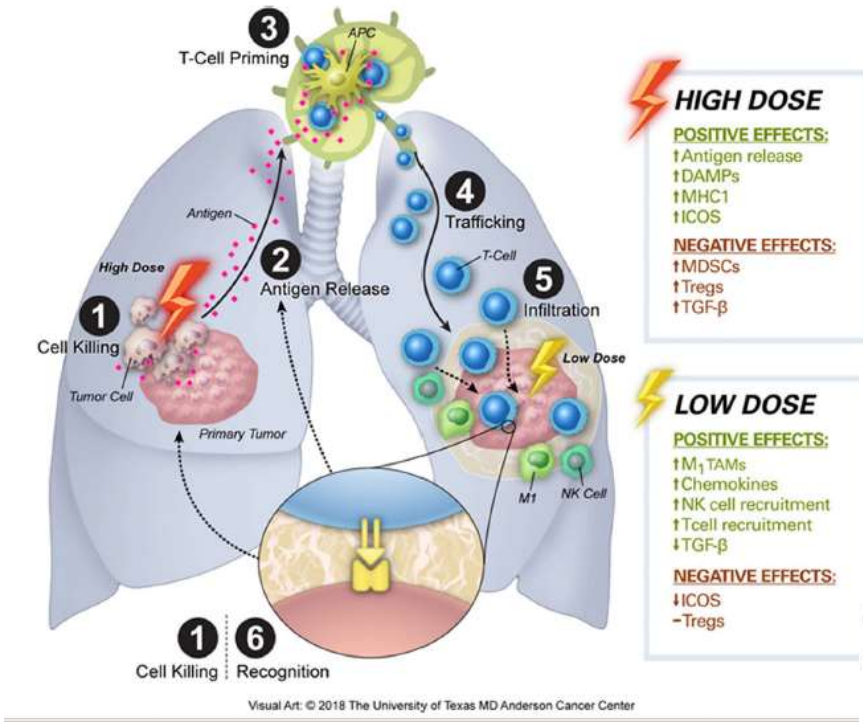
Anti-PD-1-treatment outcomes may be improved with lower disease burden

Patients progressing on standard treatment received SBRT to two to four metastases. Not all metastases were targeted, and metastases > 65 mL were partially irradiated. SBRT dosing varied by site and ranged from 30 to 50 Gy in three to five fractions with predefined dose de-escalation if excess dose-limiting toxicities were observed. Pembrolizumab was initiated within 7 days after completion of SBRT

Excellent local control, both in partially and full irradiated lesion; median overall survival of 9.6 months despite a PFS of 3.1 months

Luke JJ, J Clin Oncol 2018

Quali frontiere?
Low dose



HIGH DOSE

POSITIVE EFFECTS:
- ↑Antigen release
- ↑DAMPs
- ↑MHC1
- ↑ICOS

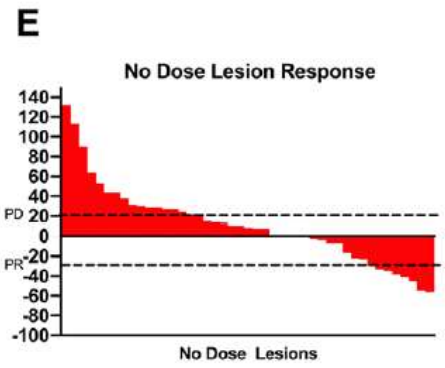
NEGATIVE EFFECTS:
- ↑MDSCs
- ↑Tregs
- ↑TGF-β

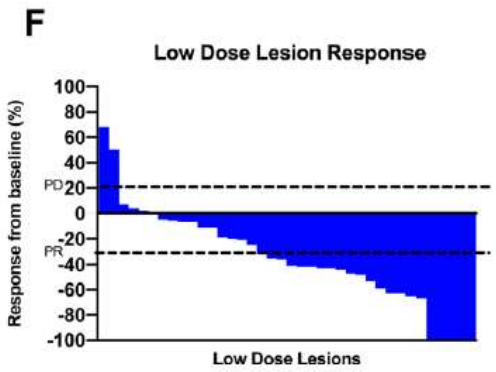
LOW DOSE

POSITIVE EFFECTS:
- ↑M_1 TAMs
- ↑Chemokines
- ↑NK cell recruitment
- ↑Tcell recruitment
- ↓TGF-β

NEGATIVE EFFECTS:
- ↓ICOS
- −Tregs

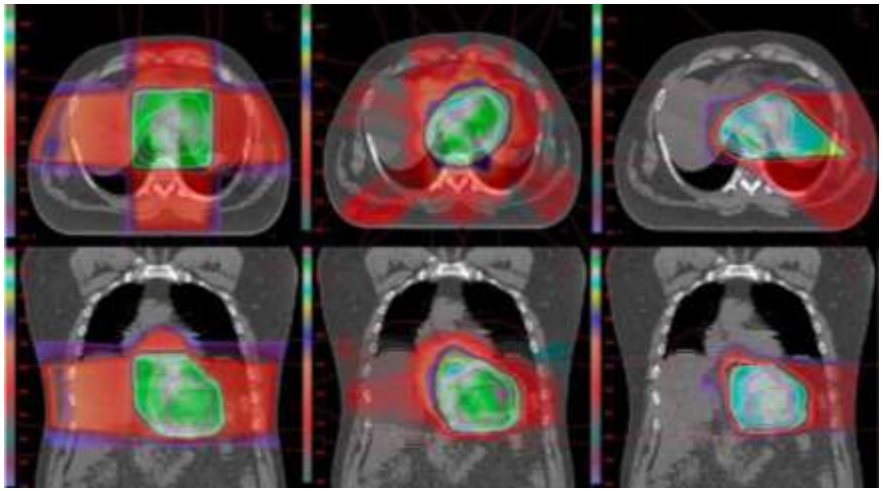
low-dose radiation may convert the stroma to a more favorable environment that induces homing of T lymphocytes, perhaps via reducing TGF-β signaling, which in turn results in decreased immunosuppressive cell signaling.

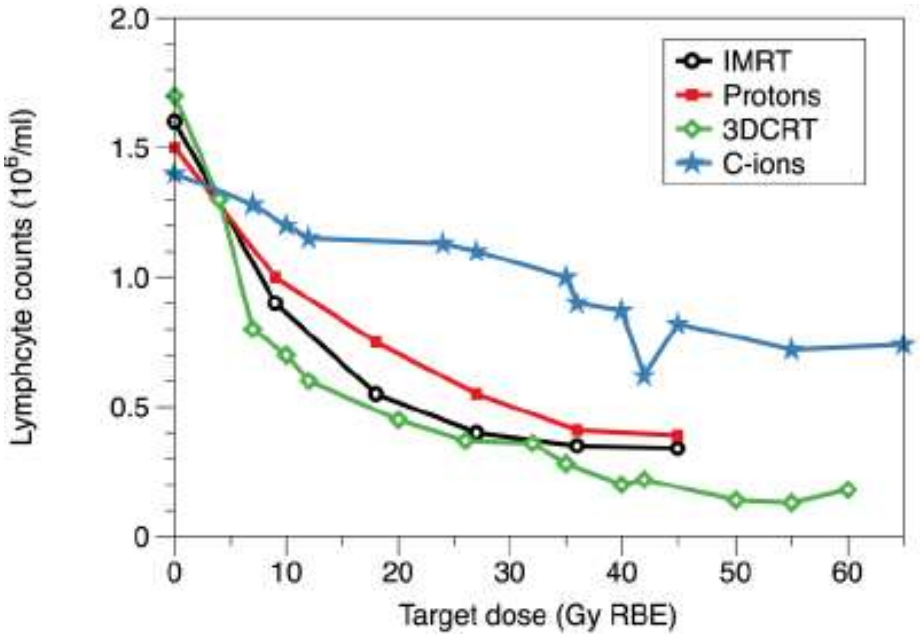




Barsoumian H, IJROBP 2018; Rodel F. Front oncol 2012; Menon H, J of Immunother Cancer 2019

Quali frontiere?
Particle radiation therapy is better?





Durante M., Br J Radiol 2019 and IJROBP 2000

Quale frontiera?
Radiotherapy is different from radioimmunotherapy

Dose escalation	Dose de-escalation
One dose fits all	Non-ablative personalised doses
Irradiate large volume	Minimise irradiated volume
Prophylactic lymph node irradiation	Spare lymph nodes
Whole pelvis radiotherapy	Spare small and large bowel for microbiome optimisation
Standard dose-volume histograms	Redefine dose-volume histograms
Include chemotherapy	Avoid chemotherapy?

Take home messages

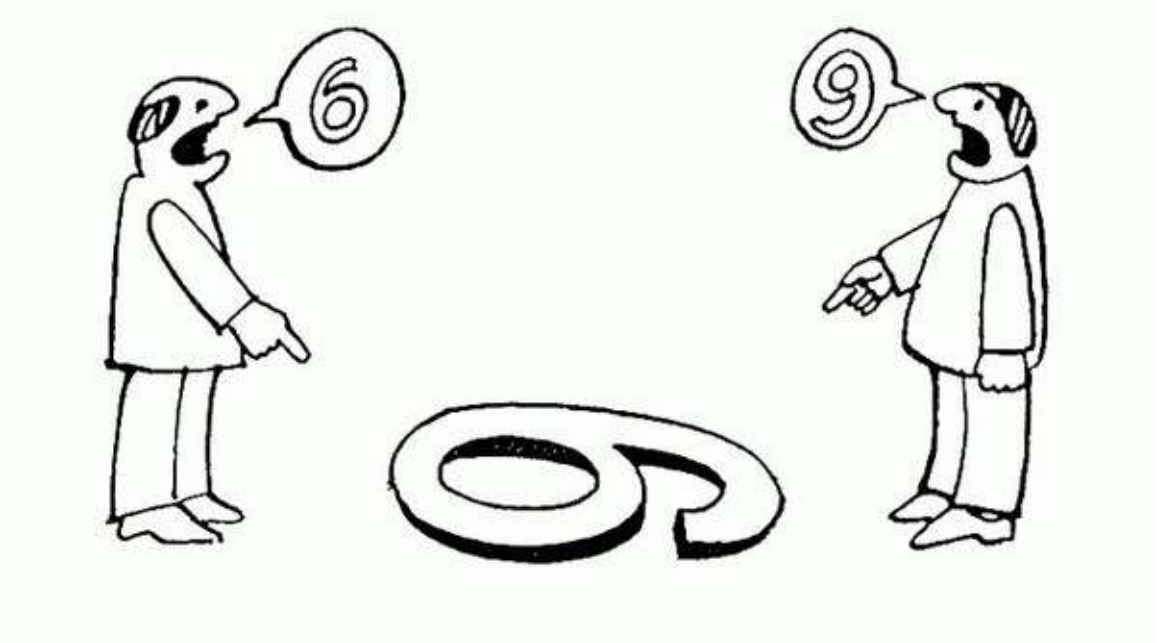
1. Setting (curative/oligometastic/polimetastatic)
2. Need for strong pre-clinic rationale: Know thy enemy and your friend
3. Disease are not equal
4. Site disease are not equal
5. Only for radiation oncologists: remember **radiobiology**
6. Immune system is equal…and dynamic
7. **Safety also for long term**

Need of «tumor»

What's future for postoperative radiation therapy?

Neoadjuvant perspective

A paradigm that needs to be reconsidered when associating RT and immunotherapy !



How far that little candle throws his beams!

W. Shakespeare

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