# Back to the future: Immunotherapy and Radiotherapy?

Philippe Lambin

# Disclosures

1. **Inventor: Licensed patents**: Two patents on radiomics (PCT/NL2014/050248, PCT/NL2014/050728) licensed to Oncoradiomics, patent on mtDNA (PCT/EP2014/059089) licensed to ptTheragnostic/DNAmito, patent on LSRT licensed to Varian & **non-patentable invention (softwares)** licensed to ptTheragnostic/DNAmito, Oncoradiomics and Health Innovation Ventures.
2. **Share holder & co-founder:** "Radiomics SA" (ex-Oncoradiomics SA), Convert pharmaceuticals SA, LivingMed Biotech and Comunicare Solutions SA
3. **Consulting/Speaker fees - Travel reimbursements**: Oncoradiomics, BHV, Convert Pharmaceuticals

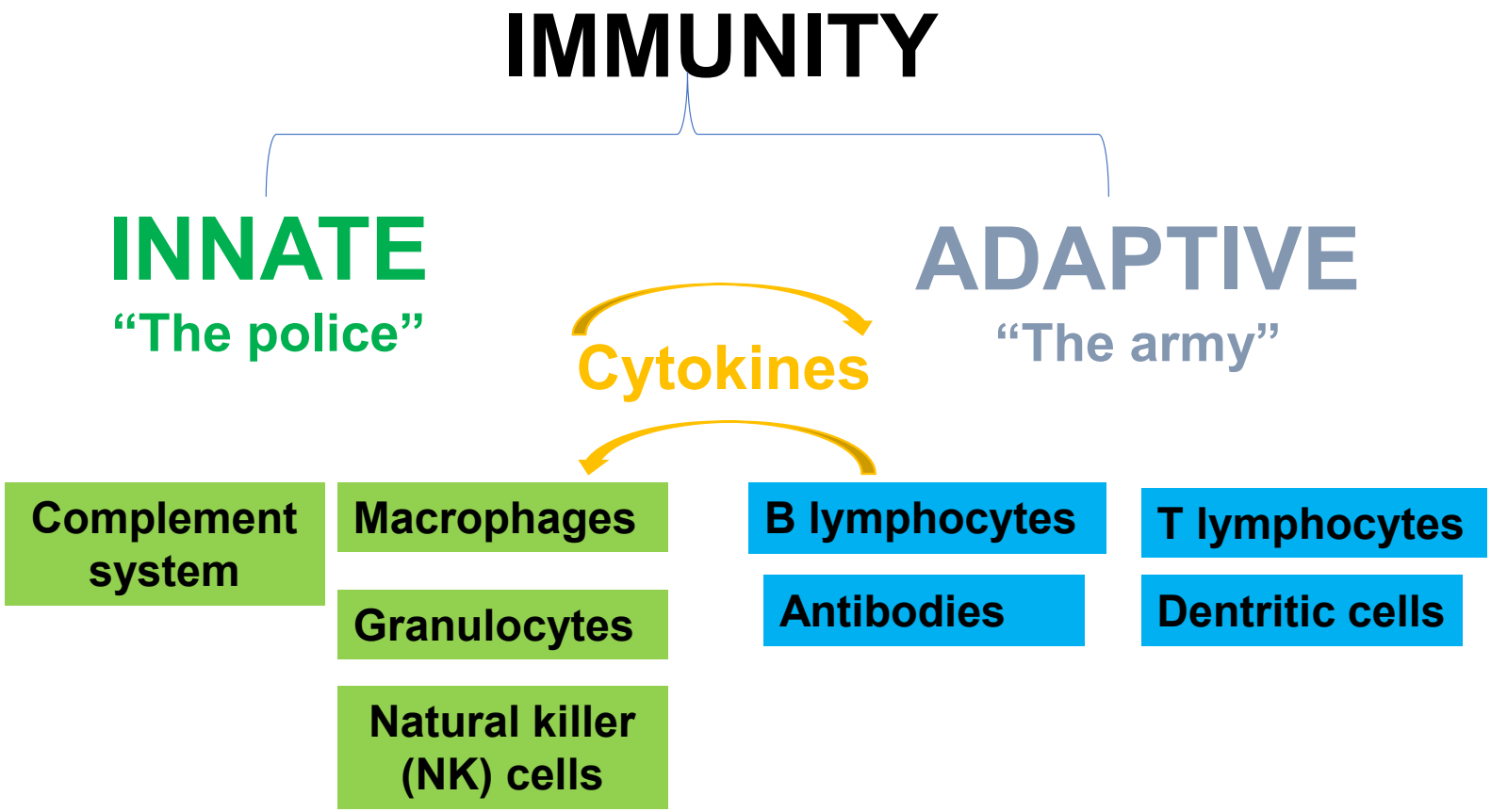
Cancer is a systemic disease

>90% of the cancer patients died of metastasis

James Ewing pro-radiation

William Coley pro-immunotherapy

# Immune System Components



# Cells and tissues of the immune system

The most important cells of adaptive immunity are **lymphocytes**.

**1. B lymphocytes** (so called because they mature in the ***b***one marrow) secrete proteins called **antibodies**, which bind to and eliminate extracellular microbes.

**2. T lymphocytes** (which mature in the ***t***hymus) function mainly to combat microbes that have learned to live inside cells (where they are inaccessible to antibodies)

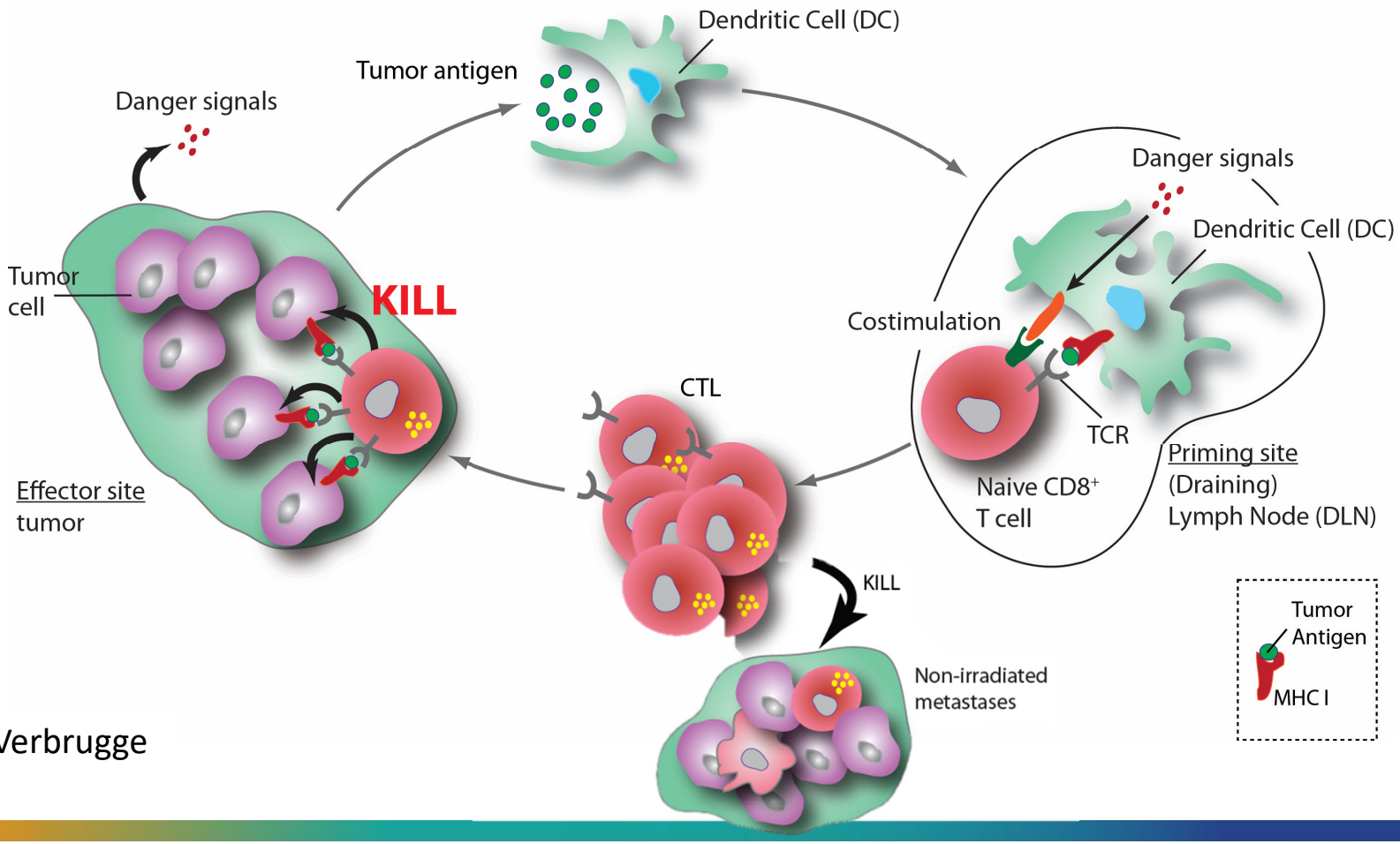
# T lymphocytes

Four main types of T lymphocytes:

1. **Cytotoxic (cytolytic) T lymphocytes (CTLs or CD8+)** kill infected host cells and thus serve to eliminate reservoirs of infection.
2. **Regulatory T cells (Treg)** control immune responses and prevent inappropriate reactions.
3. **Memory T cells (Tm)** ensure a long term protection
4. **Helper T cells** “help” B lymphocytes to make the most effective antibodies and “help” macrophages to kill ingested microbes

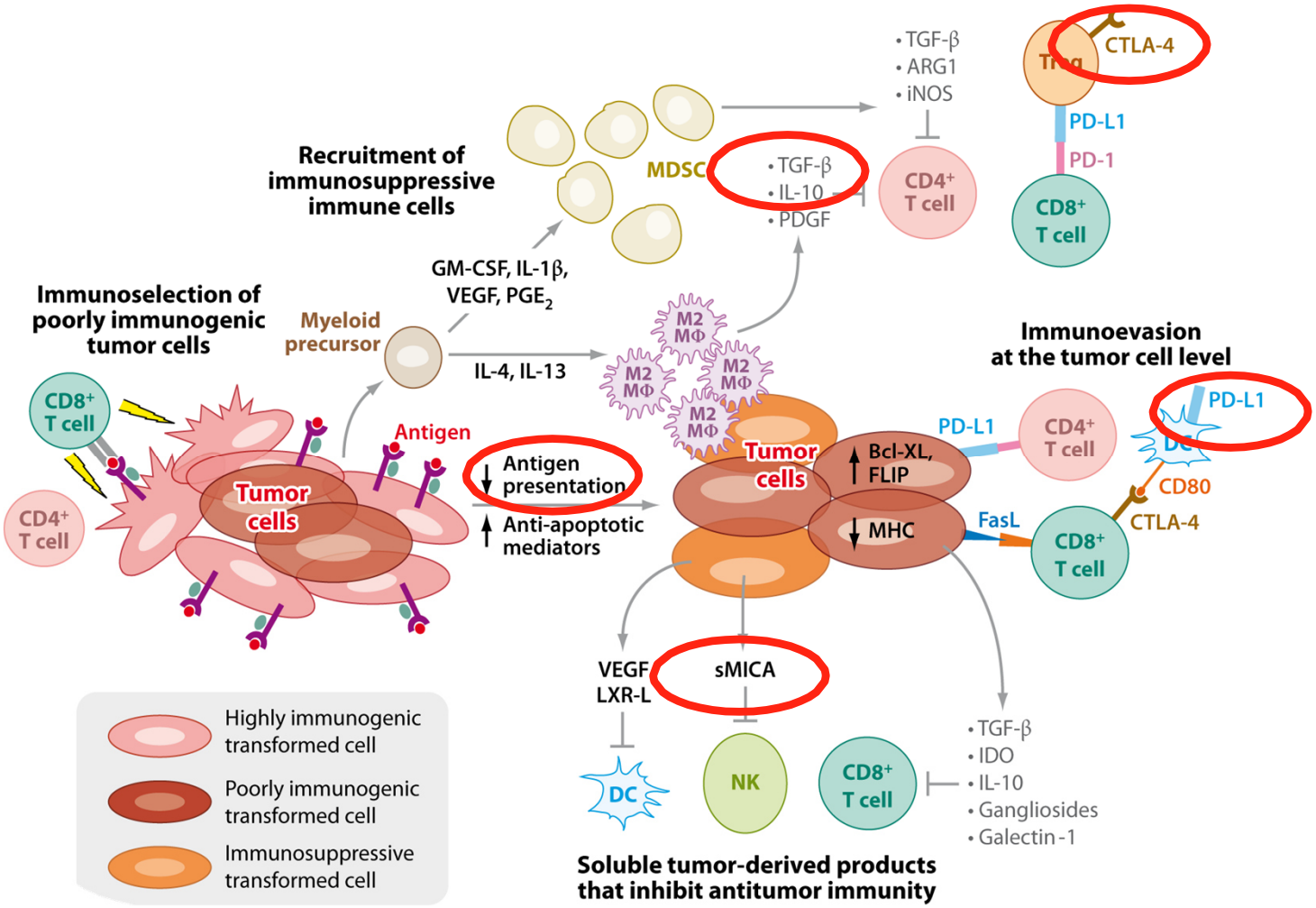
… And several other small populations of lymphocytes.

# -Ideal immune response




Courtesy: Inge Verbrugge

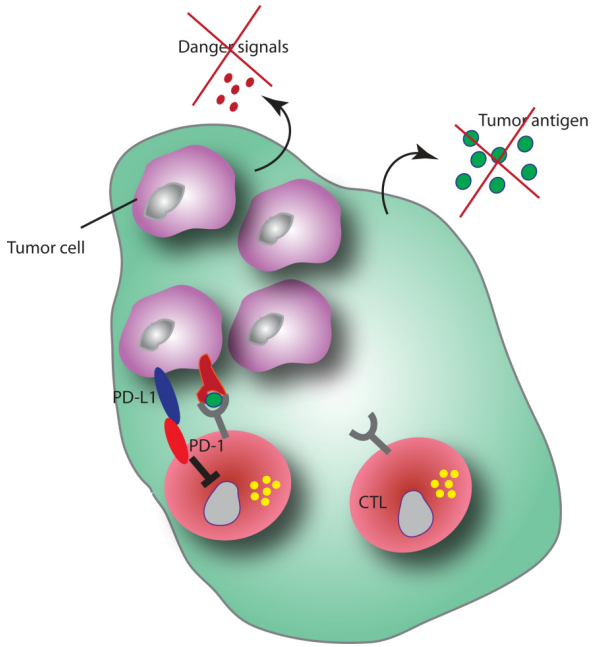
# Immunosuppression dominates in established tumours




*Vesely MD, 2011, Annu.Rev.Immunol 29:235-71*

# The immune system against cancer

- Immune response: problems
  - No danger signal
  - No tumor antigen
  - Tumor inhibits T cell
  - Not enough T cells

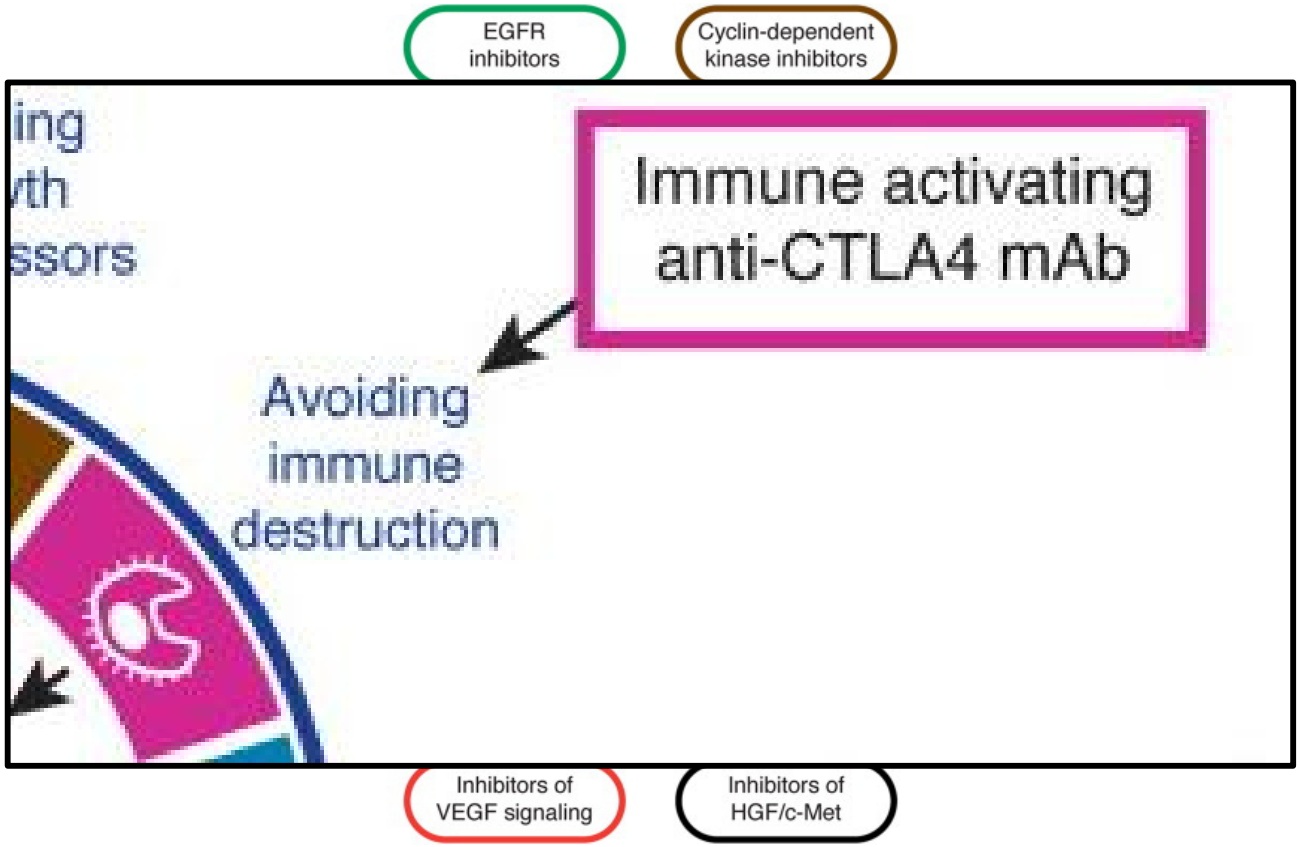



Barker al and Larson et al, Nat Rev Cancer 2015

# Discovery 1:

# Regulatory T cells: the *virtual firewalls* of the tumour

# The Hallmarks of Cancer

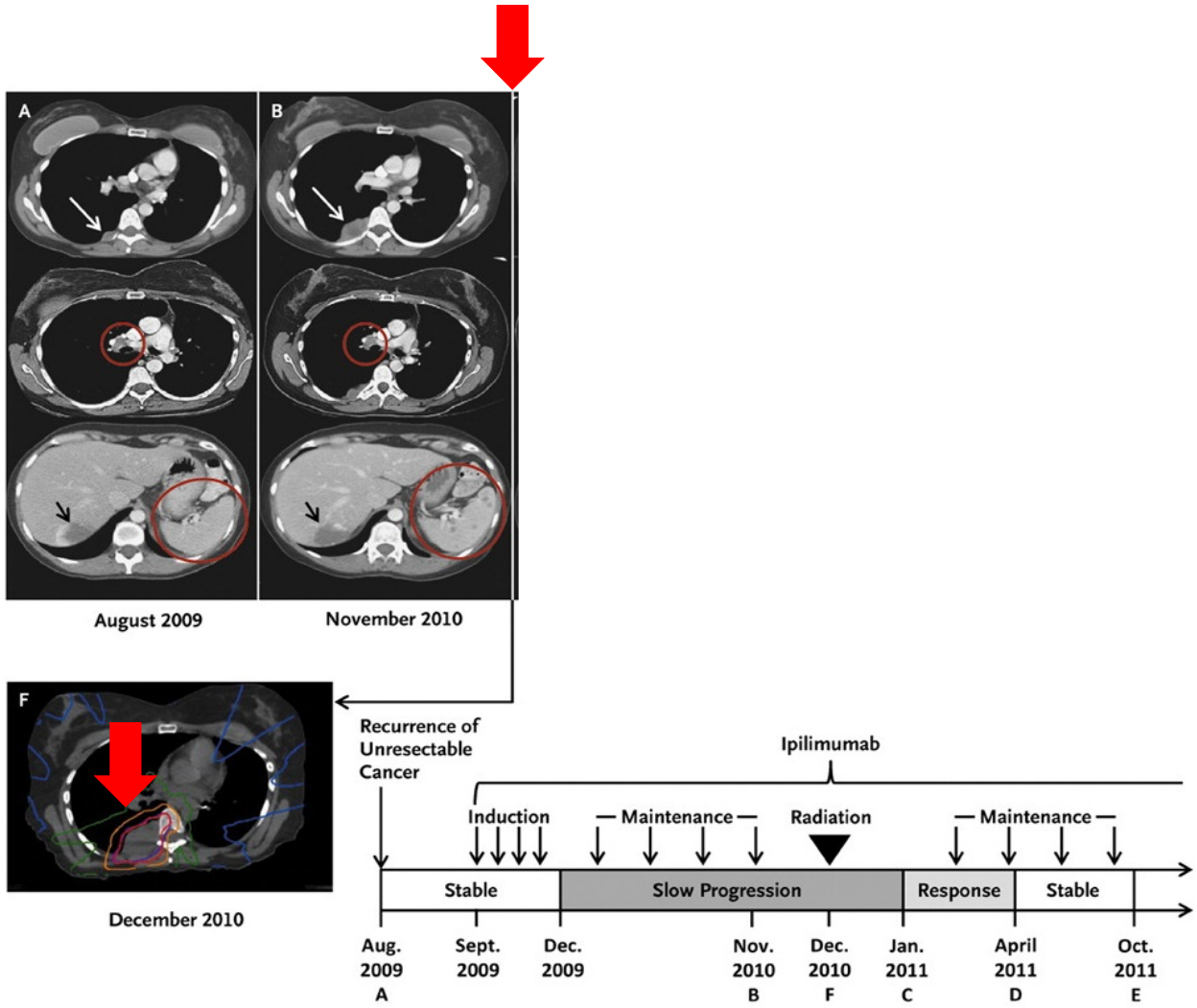



Hanahan D, Weinberg RA. Cell. 2011 Mar 4;144(5):646-74.

# Discovery 2: Radiotherapy will induce an *immunogenic* cell death

Formenti, Demaria et al.

# Abscopal Effect with RT and Ipilimumab (1)




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

Several trials: abscopal effect is clinically irrelevant (until now)

Effect on micrometastasis? Longer PFS?

# A breakthrough in the treatment of NSCLC

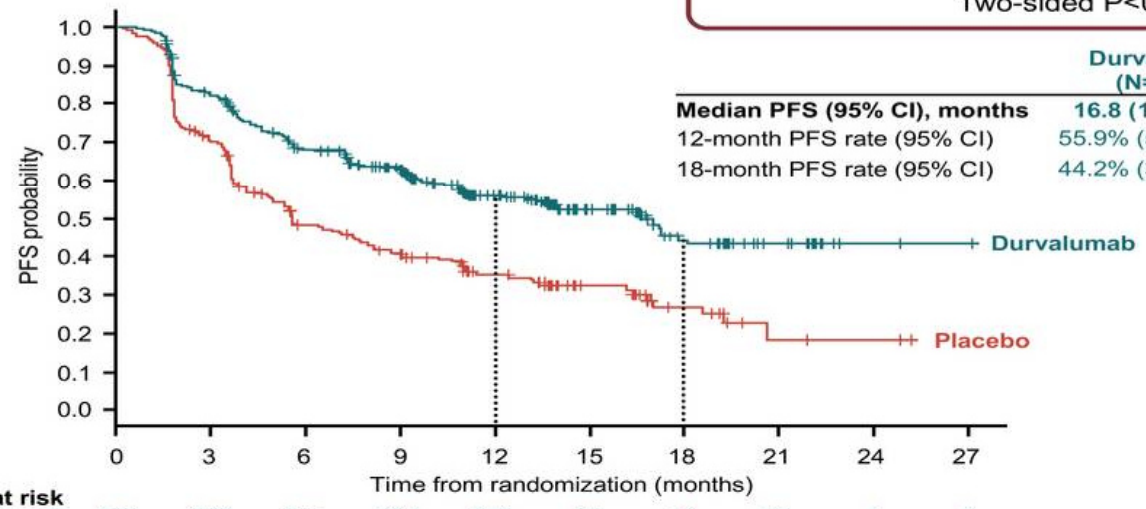
## PACIFIC trial

MADRID 2017 ESMO congress

### PFS by BICR (Primary Endpoint; ITT)

**Stratified hazard ratio, 0.52 (95% CI, 0.42–0.65)**
Two-sided P<0.0001

| | Durvalumab (N=476) | Placebo (N=237) |
|---|---|---|
| **Median PFS (95% CI), months** | **16.8 (13.0–18.1)** | **5.6 (4.6–7.8)** |
| 12-month PFS rate (95% CI) | 55.9% (51.0–60.4) | 35.3% (29.0–41.7) |
| 18-month PFS rate (95% CI) | 44.2% (37.7–50.5) | 27.0% (19.9–34.5) |




| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Durvalumab | 476 | 377 | 301 | 264 | 159 | 86 | 44 | 21 | 4 | 1 |
| Placebo | 237 | 163 | 106 | 87 | 52 | 28 | 15 | 4 | 3 | 0 |

BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival

26

Antonia et al. N Engl. J Med 2017

For comparison: Liao et al. J Clin Oncol. 2018

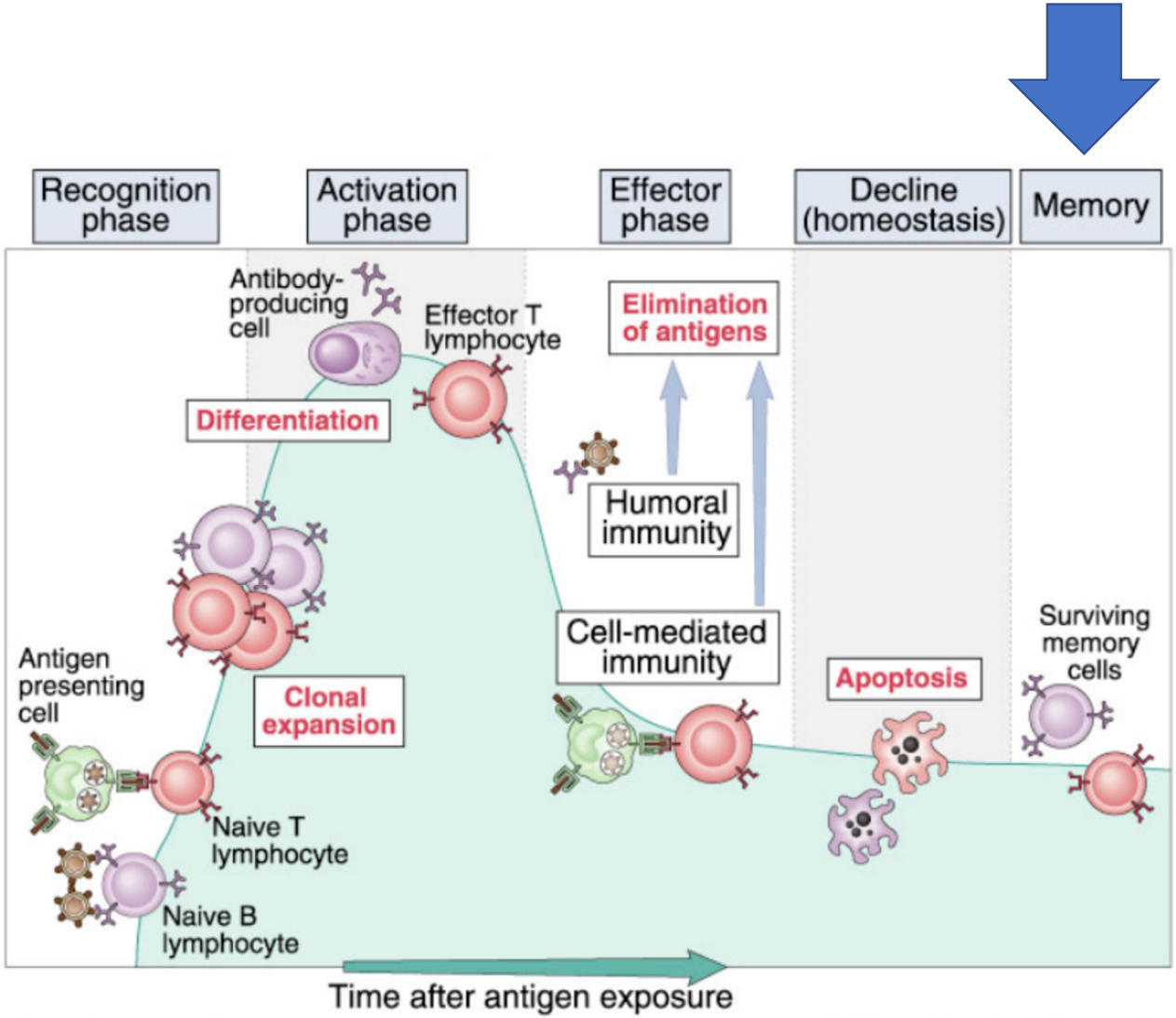
# wouldn’t it be nice …..

To have one treatment that had a therapeutic effect which lasted for several years , even if a new metastasis appeared ? A type of « virtuous circle »

Like a vaccination…

It is not called « memory effect »

# Steps in adaptive immune responses



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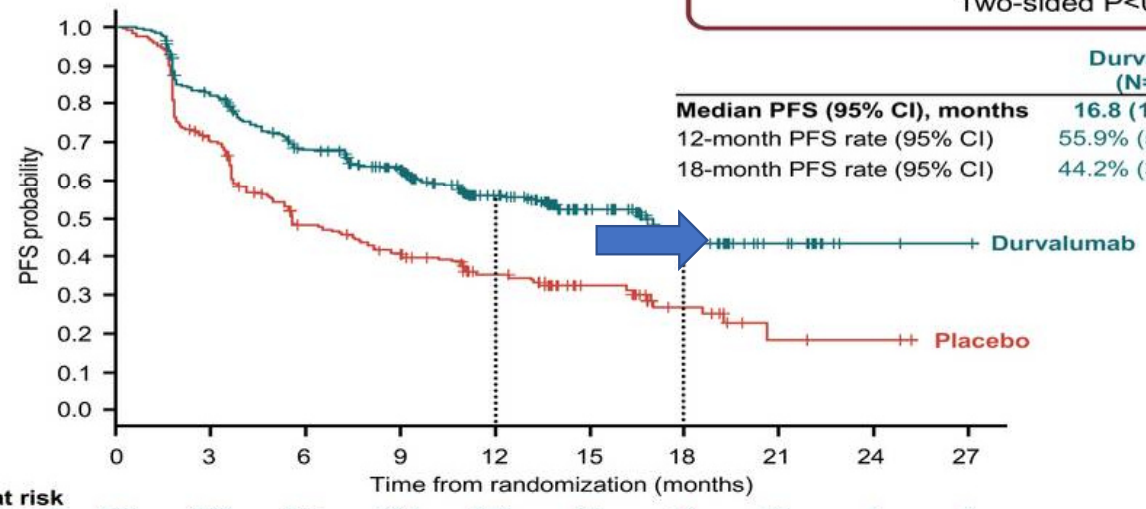


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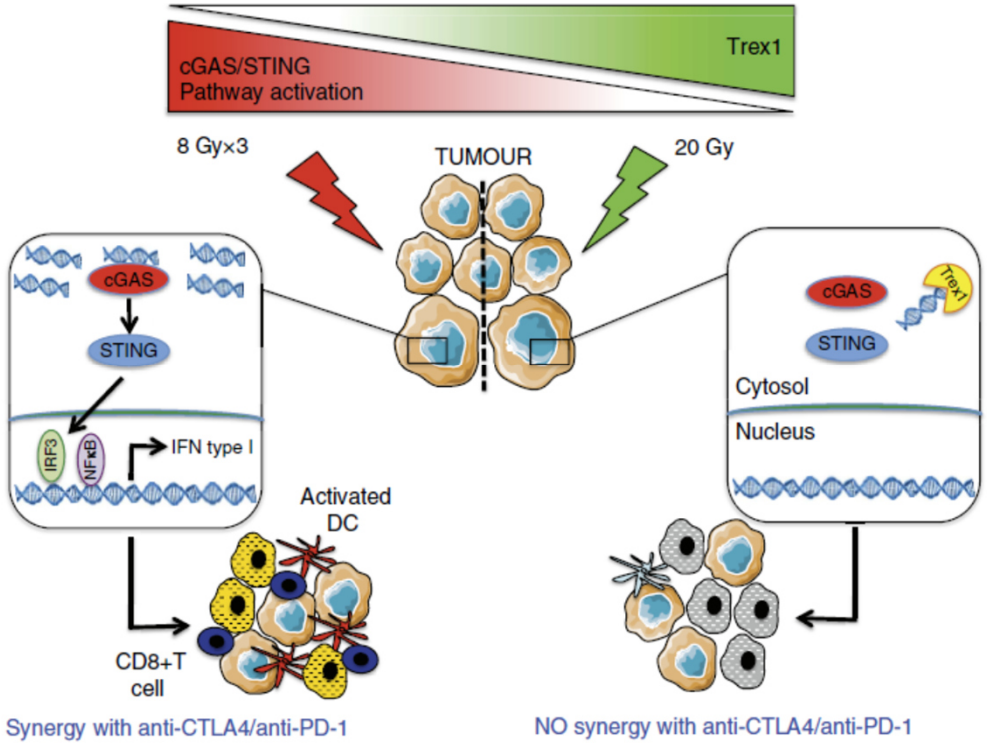
Antonia et al. N Engl. J Med 2017

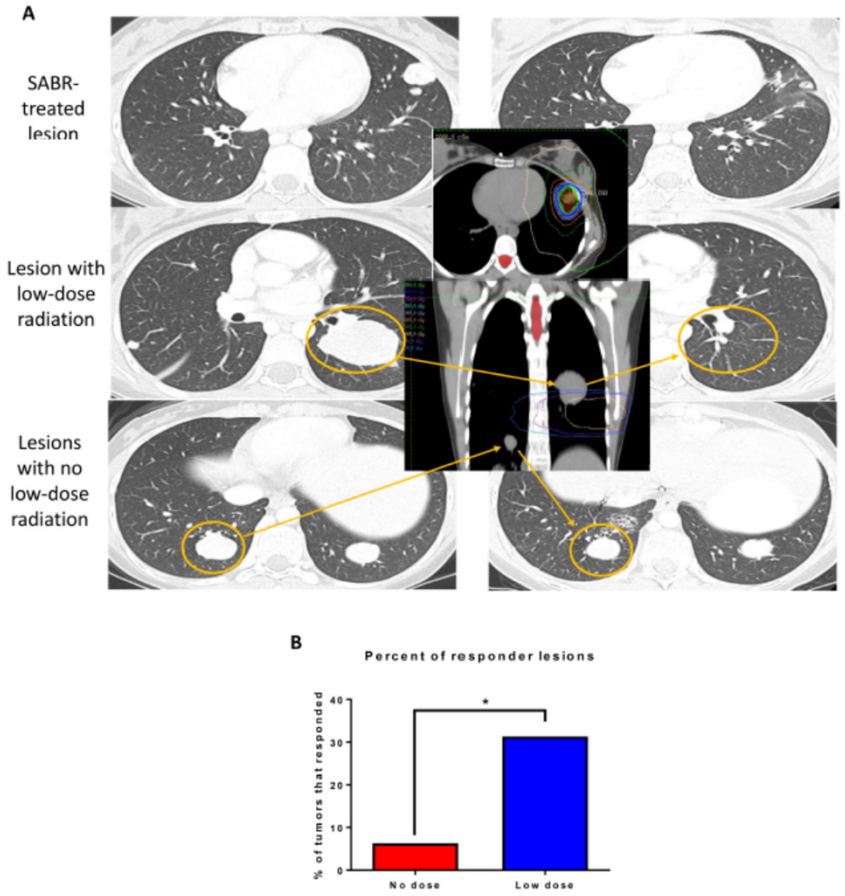
For comparison: Liao et al. J Clin Oncol. 2018

# Mechanism: Radiation Fraction Size, IFN-I and TREX1



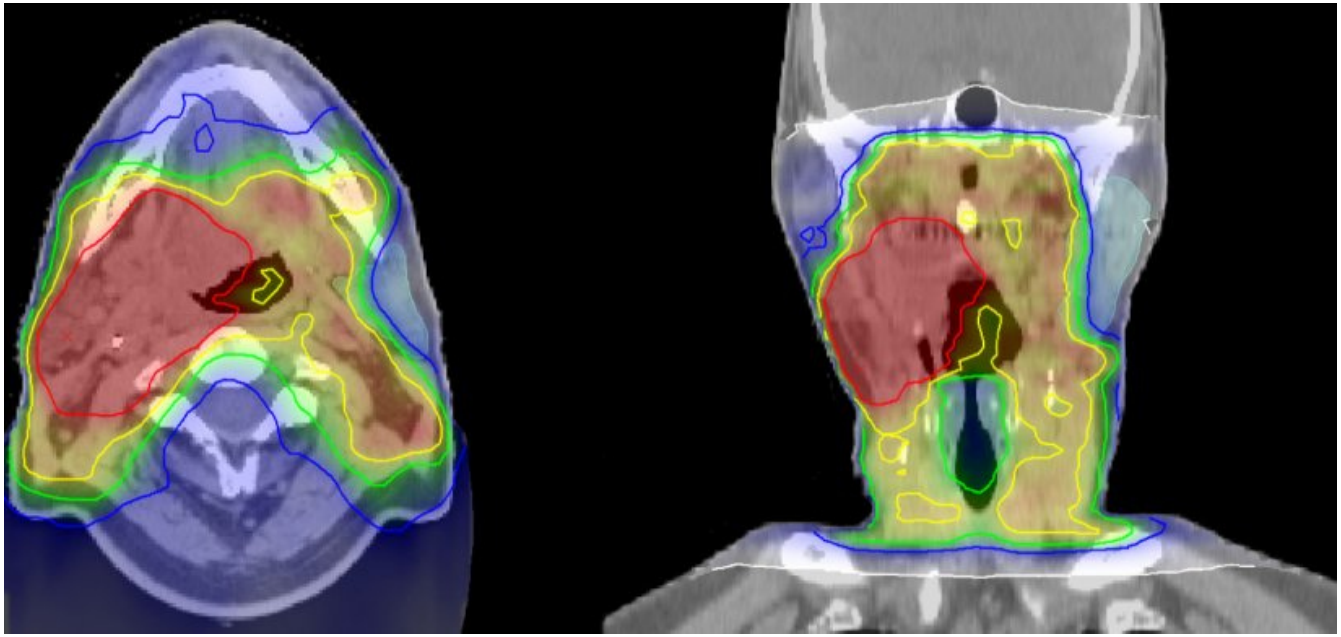

Vanpouille et al. Nat Commun 2017

# The Radscopal effect




Welsh et al Cancer Immunol Res 2019

# But the same approach does not work in head and neck cancer: why?



As radiation oncologist we will not administre IO but we can perhaps *optimize radiotherapy* to make it more friendly for IO

# LSRT

Seminars in RADIATION ONCOLOGY

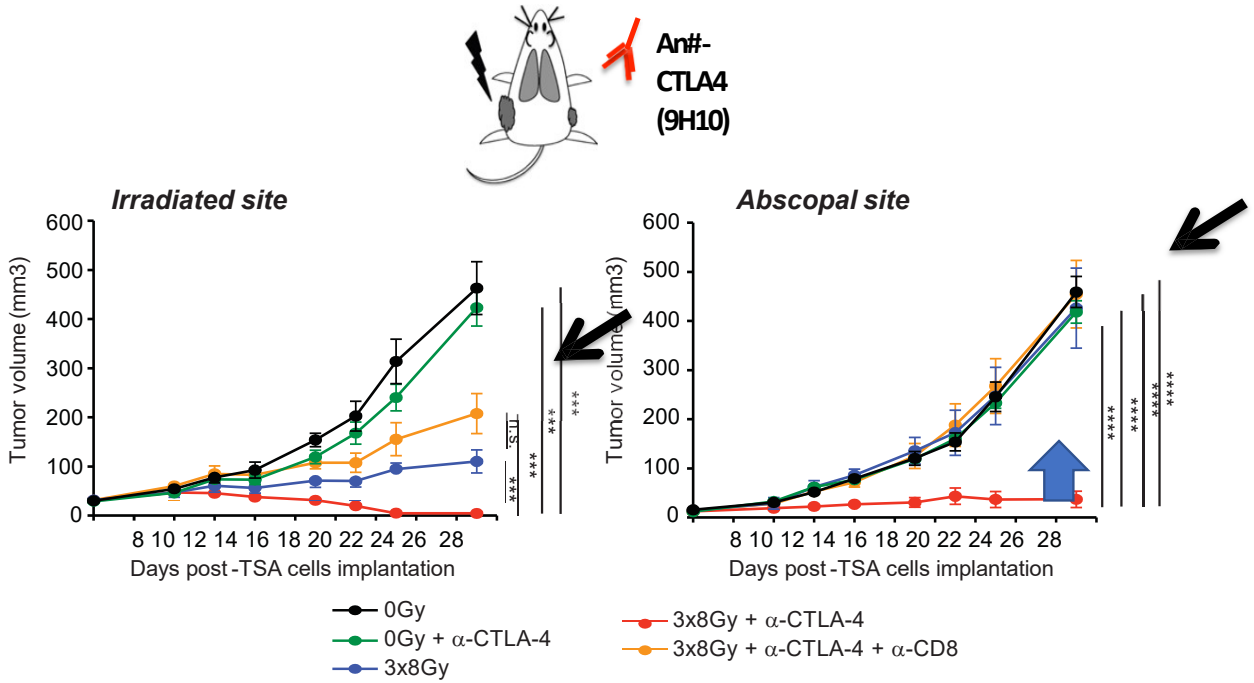
## Lymphocyte-Sparing Radiotherapy: The Rationale for Protecting Lymphocyte-rich Organs When Combining Radiotherapy With Immunotherapy

Philippe Lambin, MD, PhD,[*,1] Relinde I.Y. Lieverse, MD,[*,1] Franziska Eckert, MD,[†,1] Damiënne Marcus, MSc,[*] Cary Oberije, PhD,[*] Alexander M.A. van der Wiel, MSc,[*] Chandan Guha, MD PhD,[‡] Ludwig J. Dubois, PhD,[*] and Joseph O. Deasy, PhD[§]

Semin Radiat Oncol 30:187–193 © 2019 Published by Elsevier Inc.

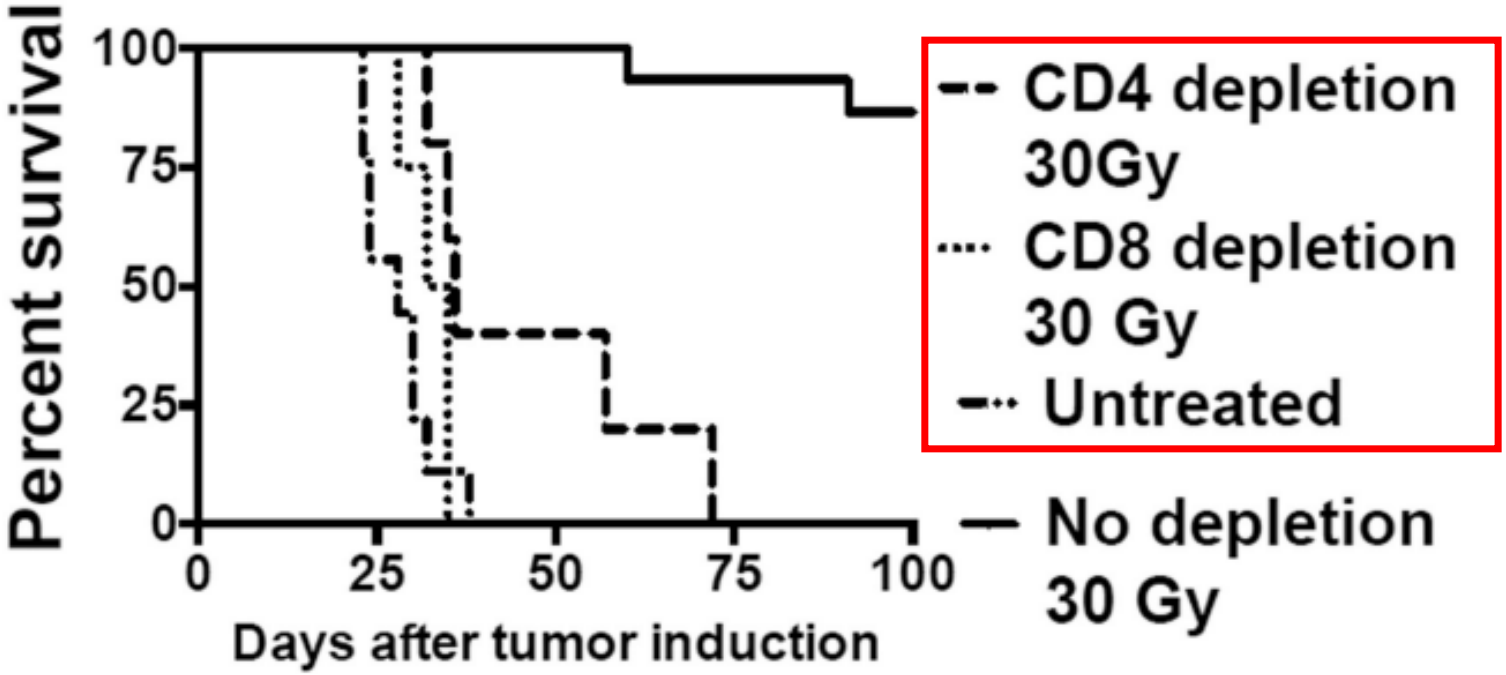
Disclosure: Co-inventor of a licensed LSRT patent

# The systemic anti-tumor response requires: CD8+ T cells



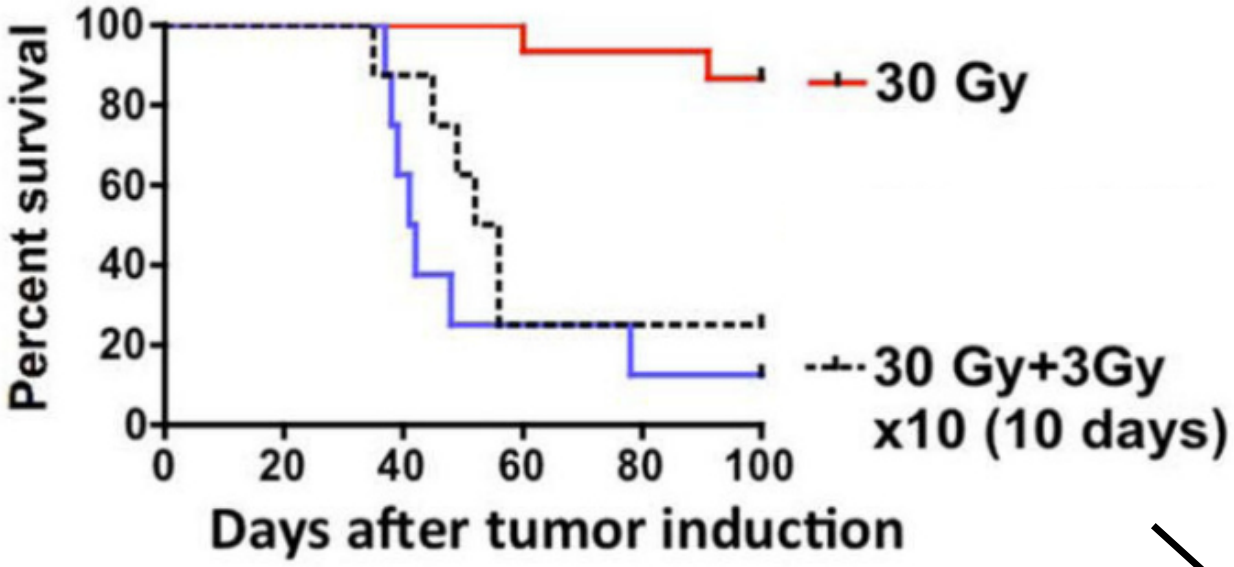

Vanpouille-Box et al., Nature Communications, June 2017

# For radiation to be effective, it requires the presence of CD8+ Lymphocytes.




Filatenkov et al. Clin Canc Res 2015

# Negative effect of Fractionation, depleting lymphocytes, in a preclinical model




Higher dose is worse when fractionated: an inverse dose response curve - related to CD8+ cells depletion

**= Physical dose of 60 Gy**

Filatenkov et al. Clin Canc Res 2015

# LSRT + rescue with IL7 in mice

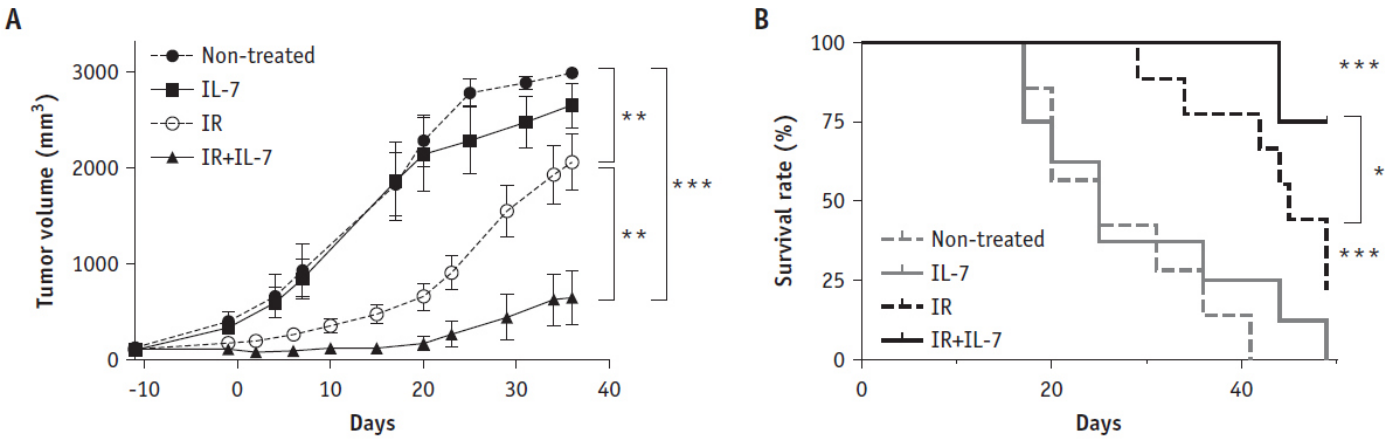
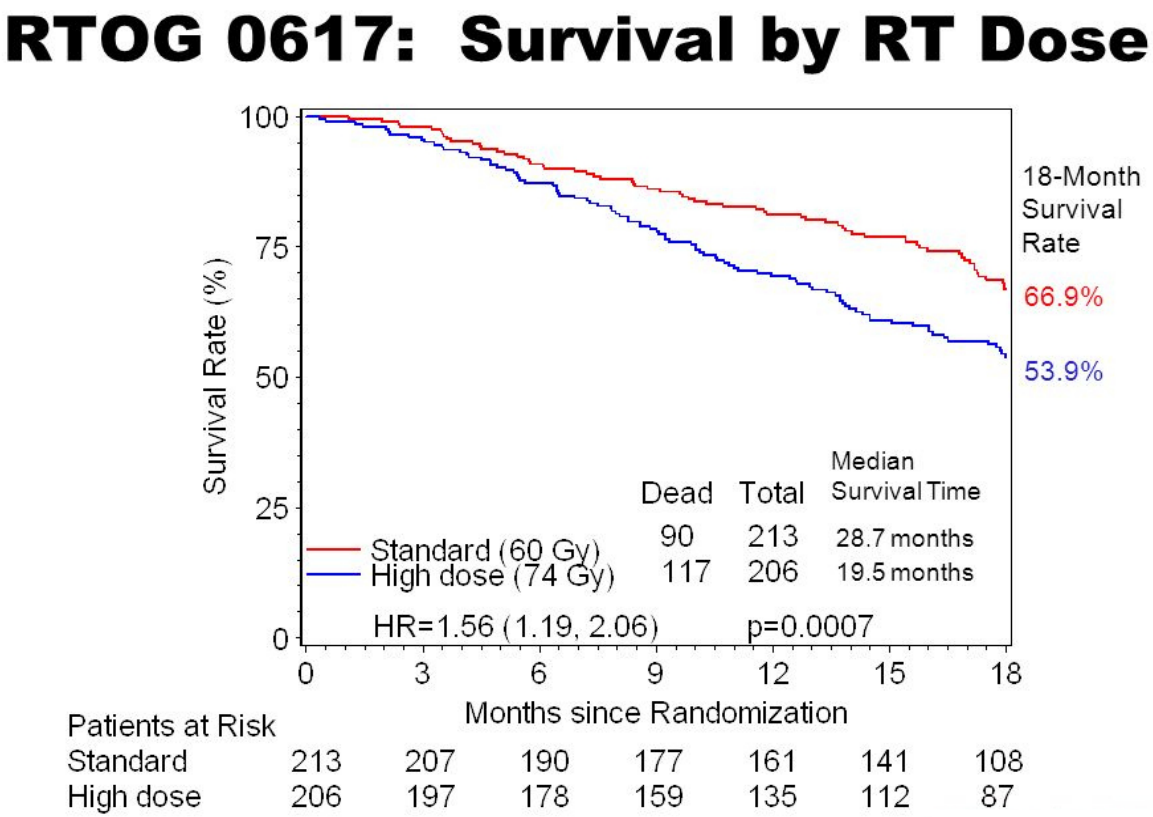



**Fig. 5.** Response of HCa-1 tumor to treatment. (A) Tumor growth in different groups of tumor-bearing mice. Statistical analysis was performed on day 36. (B) Survival curve in response to different treatments; n = 8 per group; stand-alone asterisks denote significance when compared with the nontreated group; $*P < .05$, $**P < .01$; and $***P < .001$; 2-tailed Mann-Whitney test and log-rank (Mantel-Cox) test; data are represented as mean ± standard error.

Hwa Kyung Byun et al. IJROBP 2021

# One of the enigma of modern RT

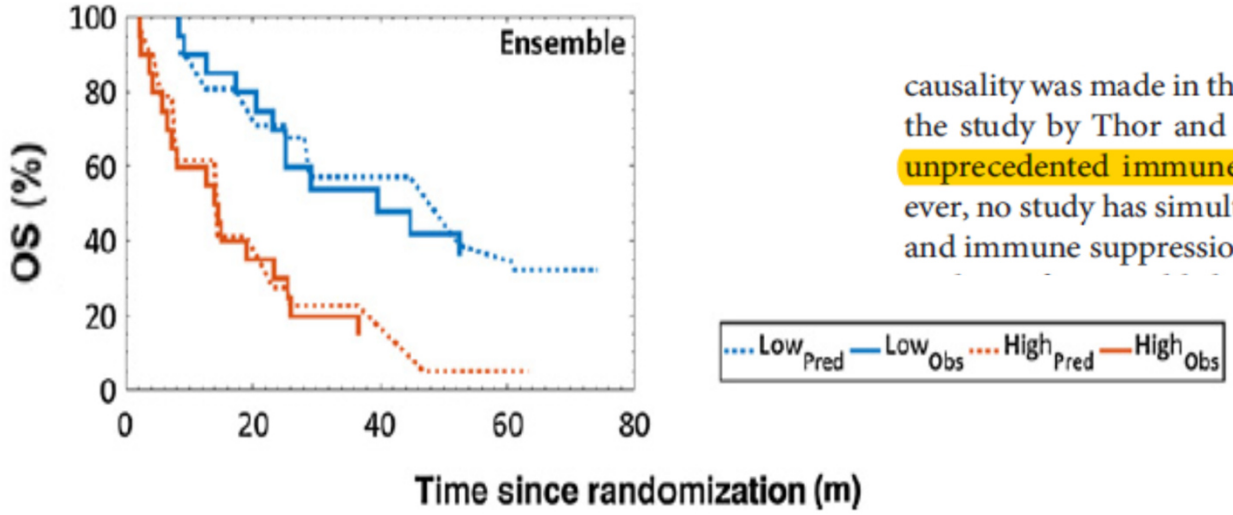


# Potential magnitude of the effect?

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

**Modeling the Impact of Cardiopulmonary Irradiation on Overall Survival in NRG Oncology Trial RTOG 0617**

Maria Thor[1], Joseph O. Deasy[1], Chen Hu[2], Elizabeth Gore[3], Voichita Bar-Ad[4], Clifford Robinson[5], Matthew Wheatley[6], Jung Hun Oh[1], Jeffrey Bogart[7], Yolanda I. Garces[8], Vivek S. Kavadi[9], Samir Narayan[10], Puneeth Iyengar[11], Jacob S. Witt[12], James W. Welsh[13], Cristopher D. Koprowski[14], James M. Larner[15], Ying Xiao[16], and Jeffrey Bradley[17]




Another attempt to untangle causality was made in the study by Contreras and colleagues (7) and in the study by Thor and colleagues (22) who found indications of an unprecedented immune suppression explaining OS. Thus far, however, no study has simultaneously explored cardiopulmonary function and immune suppression in the setting of OS.

For more conservative treatments, and if feasible, the upper limits for treatment planning could be defined by combining the intermediate- and the high-risk group (population average: Atria D45%[Gy] ≤ 30 Gy; Pericardium MOH55%[Gy] ≤ 39 Gy; Ventricles MOH5%[Gy] ≤ 41 Gy; and Lung Mean[Gy] ≤ 15 Gy).

Thor *et al* Clin Canc Res 2020

# The new paradim

Tumour + OAR

ARTICLE IN PRESS

Radiotherapy and Oncology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

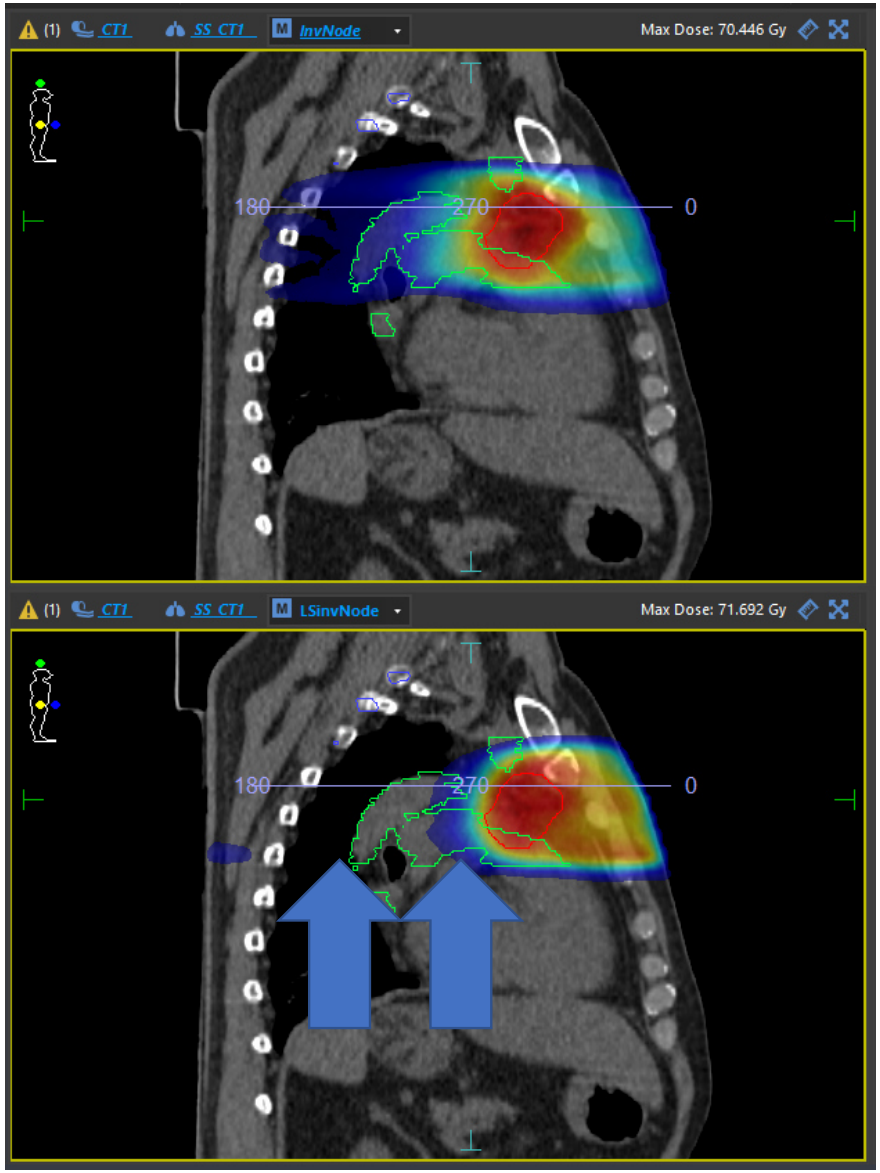

Original Article

# Mean cardiopulmonary dose and vertebral marrow dose differentially predict lineage-specific leukopenia kinetics during radiotherapy for esophageal cancer

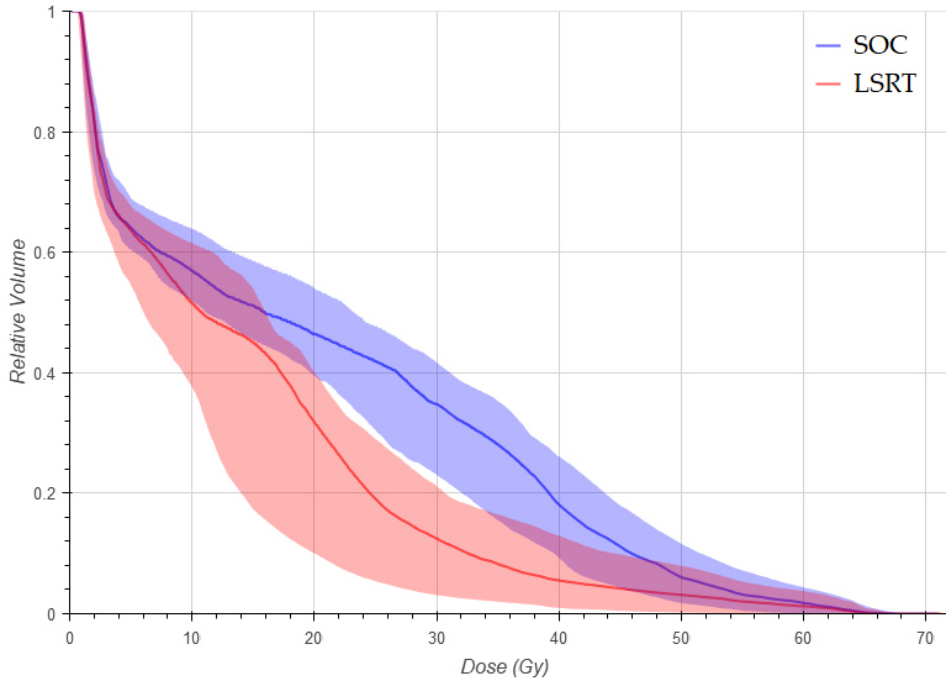
Joshua L. Anderson [a,1], Neil B. Newman [b], Chelsea Anderson [c], Alexander D. Sherry [a], Adam D. Yock [a], Evan C. Osmundson [b,*]

[a] Vanderbilt University School of Medicine; [b] Department of Radiation Oncology, Vanderbilt University Medical Center, Nashville; and [c] American Cancer Society, Atlanta, GA, United States

Taken together, these data highlight the complex immunomodulatory effect of radiotherapy and imply that off-target dose distribution to both central an peripheral hematological compartments could be optimized to promote a more favorable state of systemic anti-tumor immunity.




# + Hypofractionation = More lymphocyte sparing




Courtesy of Fernandes P., Jourani Y et al, Institut Jules Bordet, Brussels

# Vertebra sparing or heart-big vessels sparing?

Radiotherapy and Oncology 152 (2020) 169–176

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

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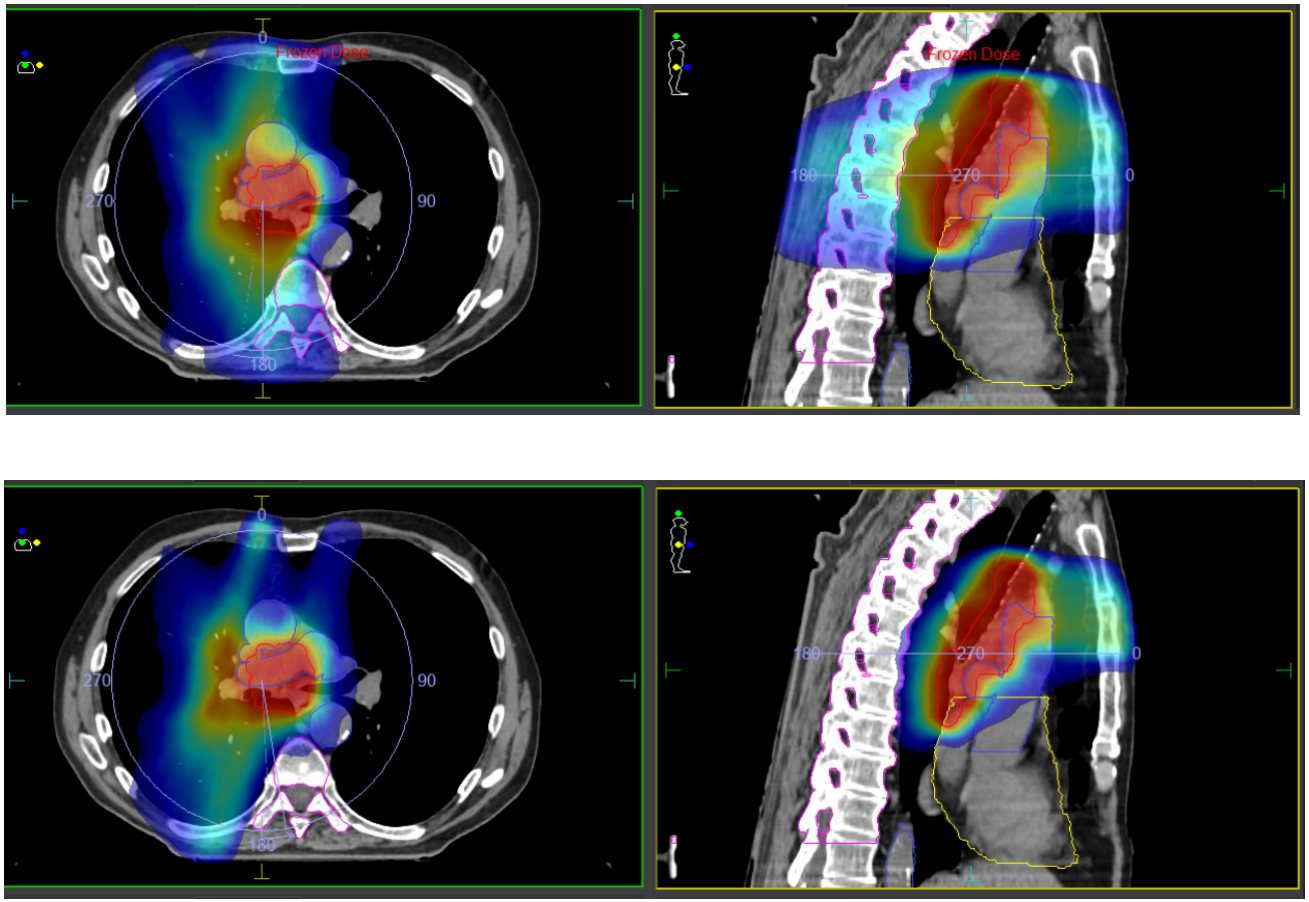
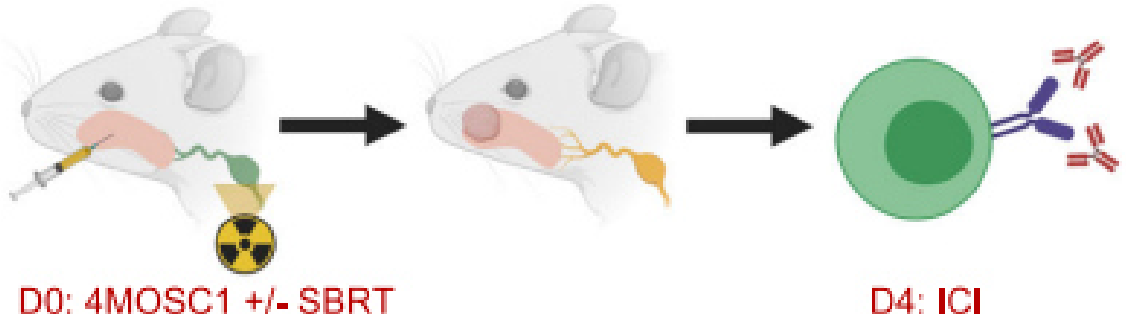
Mean cardiopulmonary dose and volume of thoracic marrow spared radiation differentially predict lineage-specific leukopenias during CRT for EC. mCPD is significantly associated with lower total WBC and neutrophil nadirs. In contrast, greater thoracic marrow spared radiation is associated with mitigation of lymphopenia during CRT.

# Possible? Example of planning SOC vs LSRT

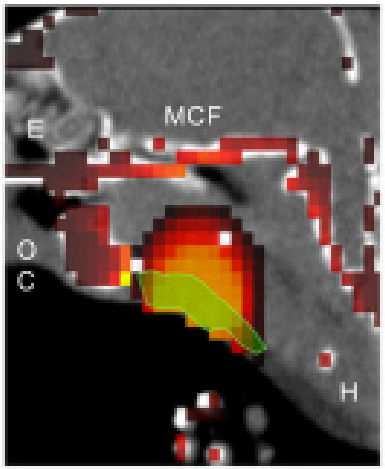


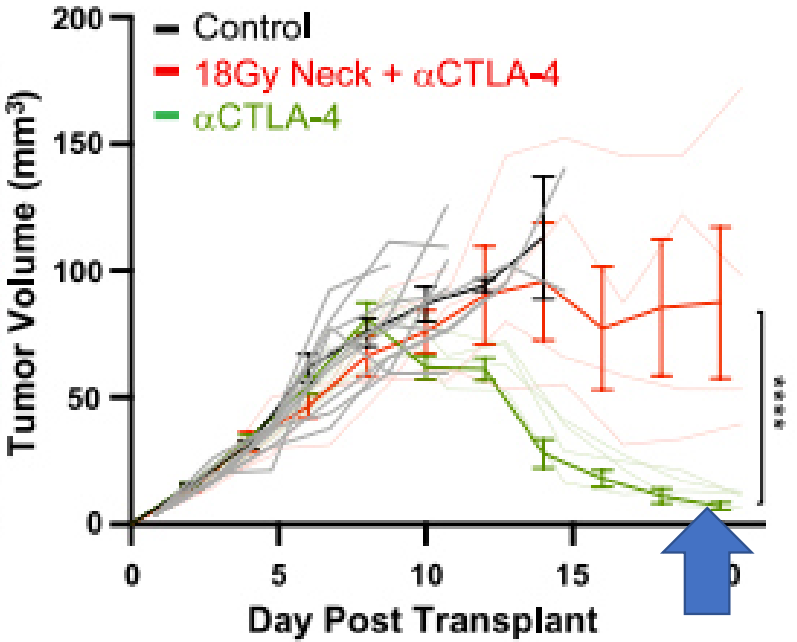

Courtesy of Fernandes P., Jourani Y et al

# LSRT: Draining nodes

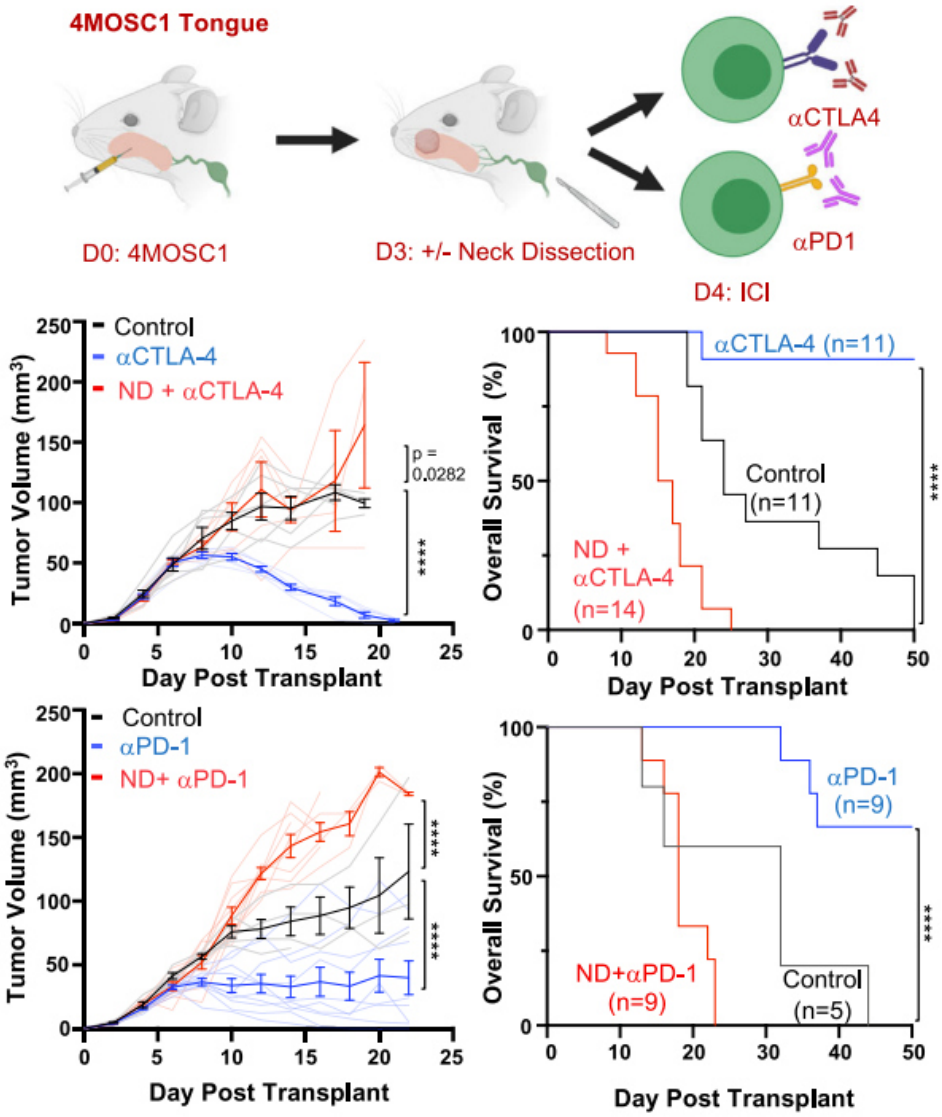



Mechanistically, within tumor-draining lymphatics, there is an upregulation of conventional type I dendritic cells and type I interferon signaling and show that both are necessary for the ICI response and lost with lymphablation (by surgery or by radiation)



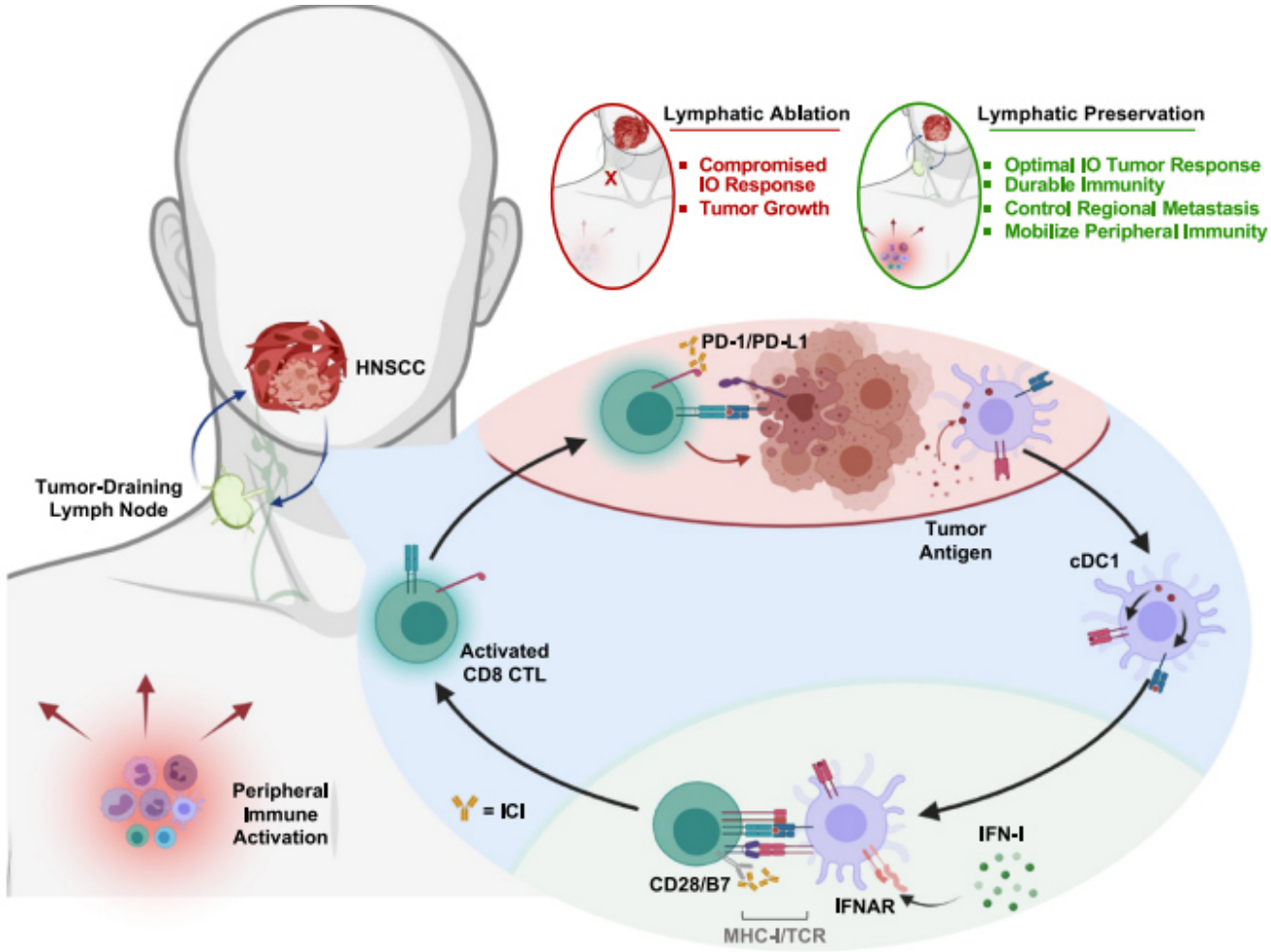




Robert Saddawi-Konefka et al. Nat Commun 2022


4MOSC1 Tongue
D0: 4MOSC1
D3: +/- Neck Dissection
αCTLA4
αPD1
D4: ICI
Control
αCTLA-4
ND + αCTLA-4
Tumor Volume (mm3)
p = 0.0282
****
Day Post Transplant
αCTLA-4 (n=11)
Control (n=11)
ND + αCTLA-4 (n=14)
Overall Survival (%)
Control
αPD-1
ND+ αPD-1
αPD-1 (n=9)
ND+αPD-1 (n=9)
Control (n=5)

# The efficacy of ICI may depend upon an intact tumor-lymphatic axis

Three-fold reduction in the incidence of occult regional lymphatic metastasis following therapy with αCTLA-4 therapy




***Solution?*** A rational treatment sequencing with *delayed* lymphatic ablation

(Leidner, R. et al . J. Immunother. Cancer 2021)

Robert Saddawi-Konefka et al. Nat Commun 2022

The ***Neoadjuvant Immuno-Radiotherapy Trial*** was an investigator-initiated single institution ***phase Ib clinical trial*** that enrolled patients with previously untreated locally advanced HPV-positive and HPV-negative HNSCC between 2018 and 2019. Eligible patients were treated with neoadjuvant SBRT at a total dose of either 40Gy in 5 fractions or 24Gy in 3 fractions, delivered in a 1-week timespan, with or without nivolumab, prior to definitive surgical resection.

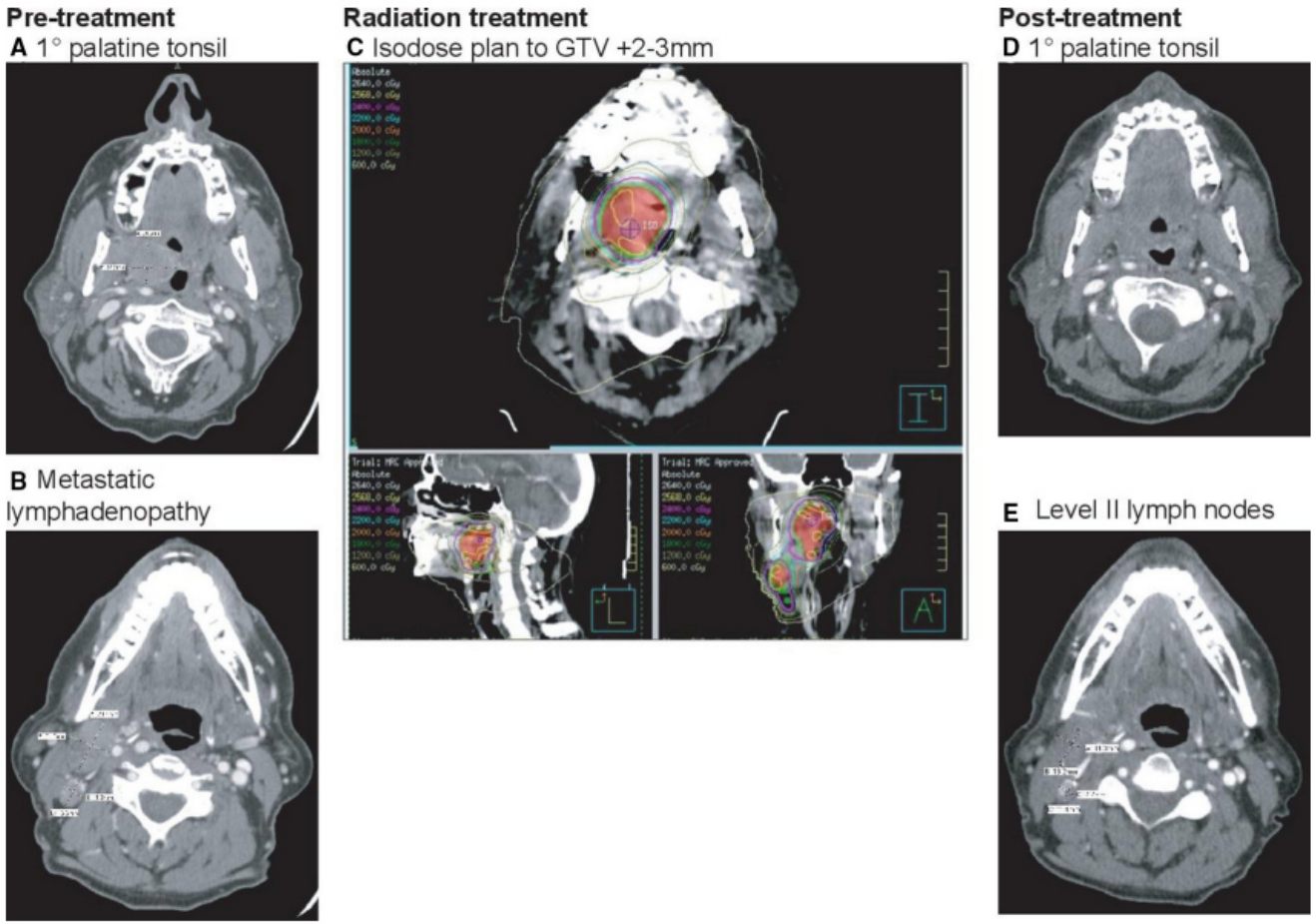
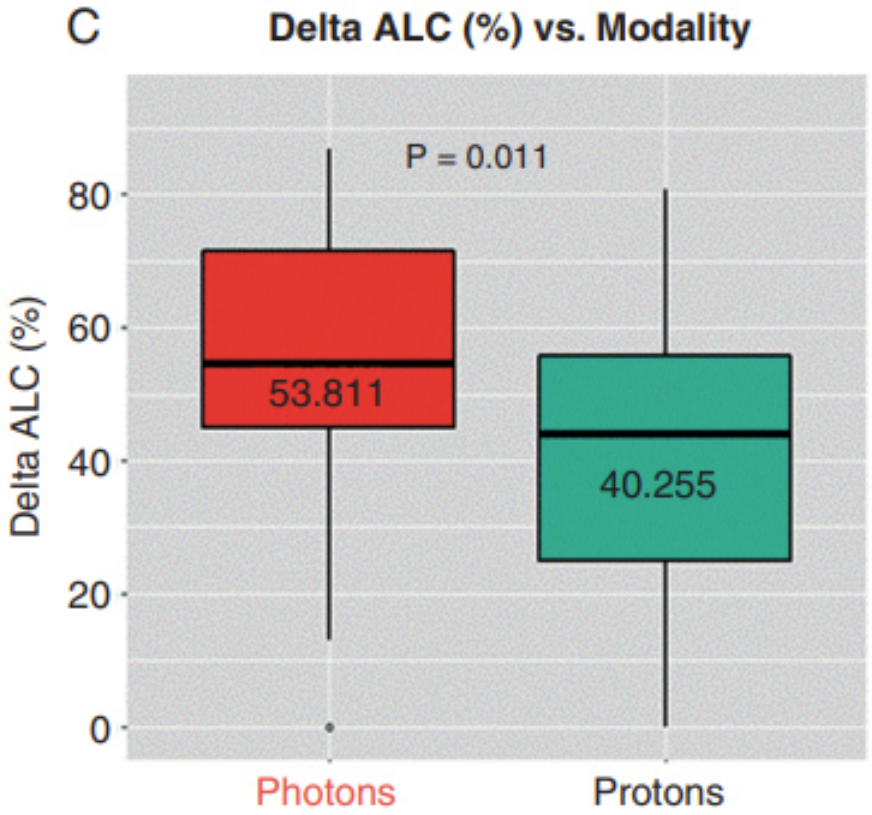



**Figure 3** CT imaging of a 63-year-old man (NIRT008) with cT2N1M0 HPV+ squamous cell carcinoma (SCC) of the tonsil. (A) Pretreatment axial image demonstrating primary tumor involving the palatine tonsil. (B) Pretreatment CT demonstrating right metastatic lymphadenopathy. (C) Radiation isodose plan to GTV+2–3 mm. (D) Post treatment CT demonstrating partial radiographic response by RECIST (–71%) with near complete resolution of the primary tumor. (E) Post treatment radiographic response in level II lymph nodes. Neoadjuvant treatment resulted in pathological complete response (pCR) in the primary and major pathological response (mPR) in the largest metastatic lymph node (<10% viable tumor cells).

Leidner R, et al. J Immunother Cancer 2021;9:e002485. doi:10.1136/jitc-2021-002485

# Evidence form a randomized phase 2 trial in GBM




Sex, baseline ALC, and whole-brain V20 were the strongest predictors of G3+L for patients with GBM treated with radiation and temozolomide. PT reduced brain volumes receiving low and intermediate doses and, consequently, reduced G3+L

Mohan et al. Neuro-Oncology 2021

# Part III

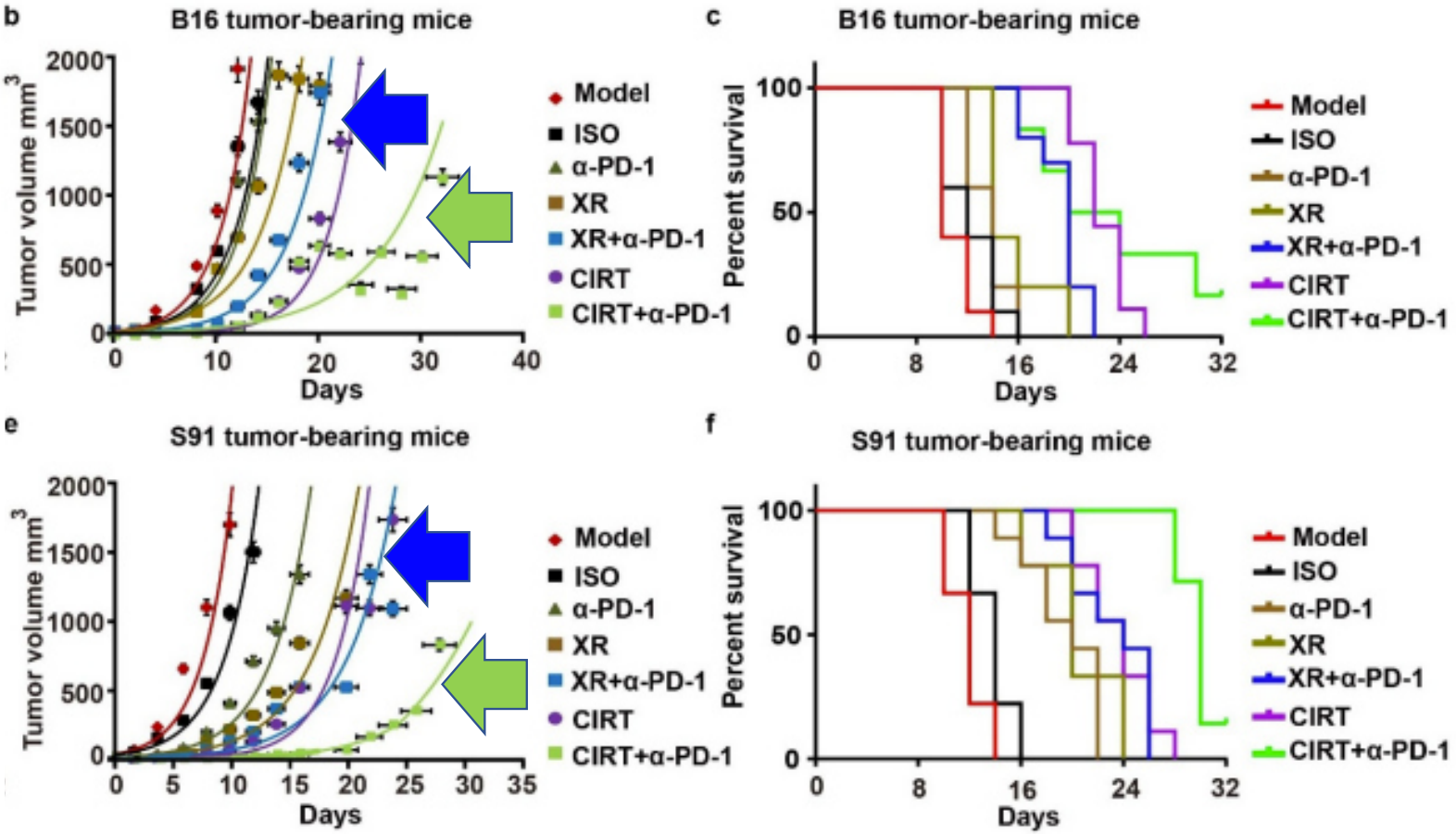
Is there a role for particle therapy in IO?

More specifically

1. Is particle therapy more immunogenic than X-rays?
2. Which immunotherapy works beter with particle therapy?

In collaboration with Amir Abdollahi's group  fromm Heidelberg

# Carbon ions more immunogenic then X-rays




Zhou *et al* Oncoimmunology 2022 (Gansu, China)

# At least two families of immumotherapies

Checkpoint inhibitors:
e.g. Anti CTLA4, anti PD1, anti PD-L1…

"Destroy the protective walls"
Or "release the break"

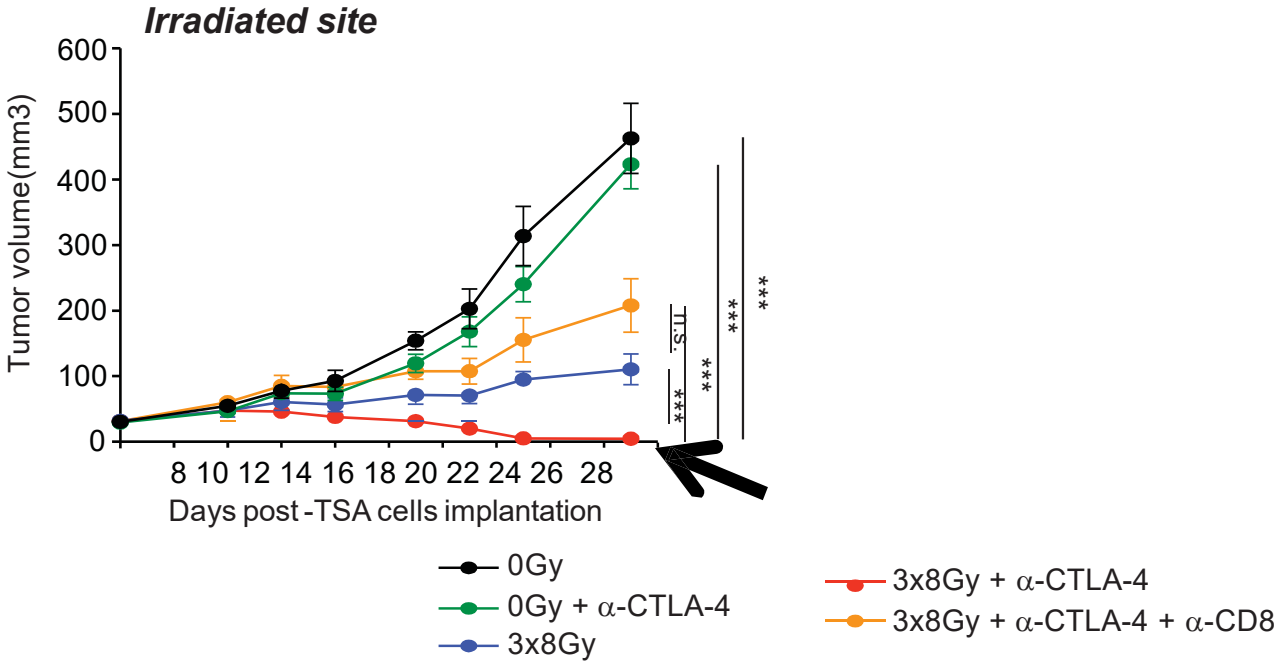
Twyman-Saint Victor et al, Nature 2015

Immunocytokines et al.
e.g. L19-IL2…

"Push the accelerator"

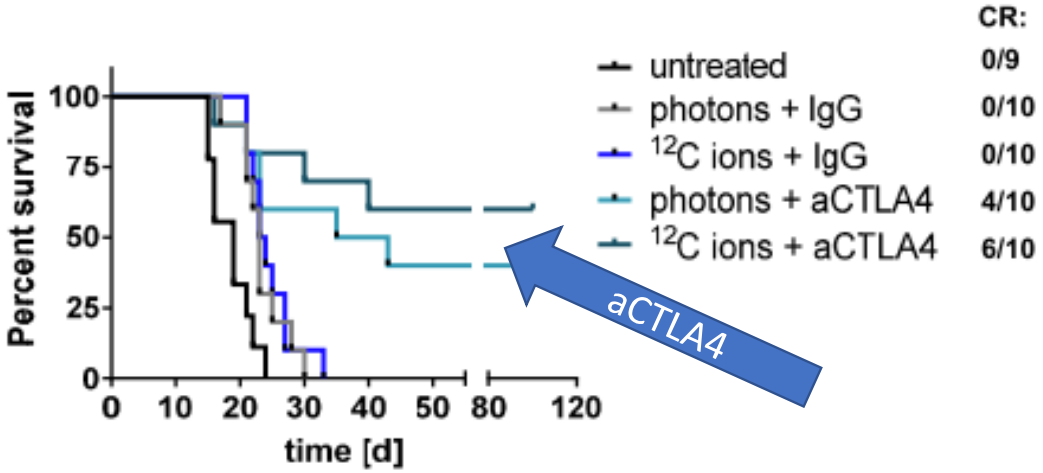
Zegers et al, Clin Cancer Res 2015

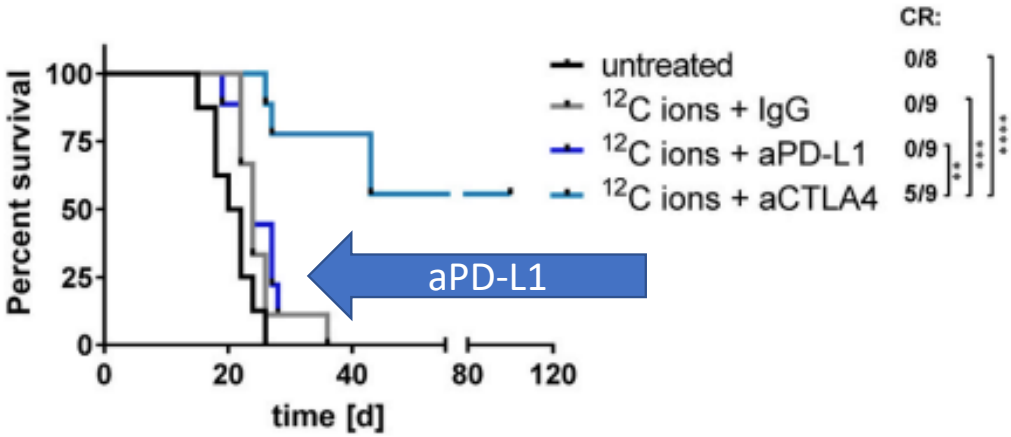
# Immunotherapeutics as radiosensitizers: aCTLA4


Vanpouille-Box et al., Nature Communications, June 2017

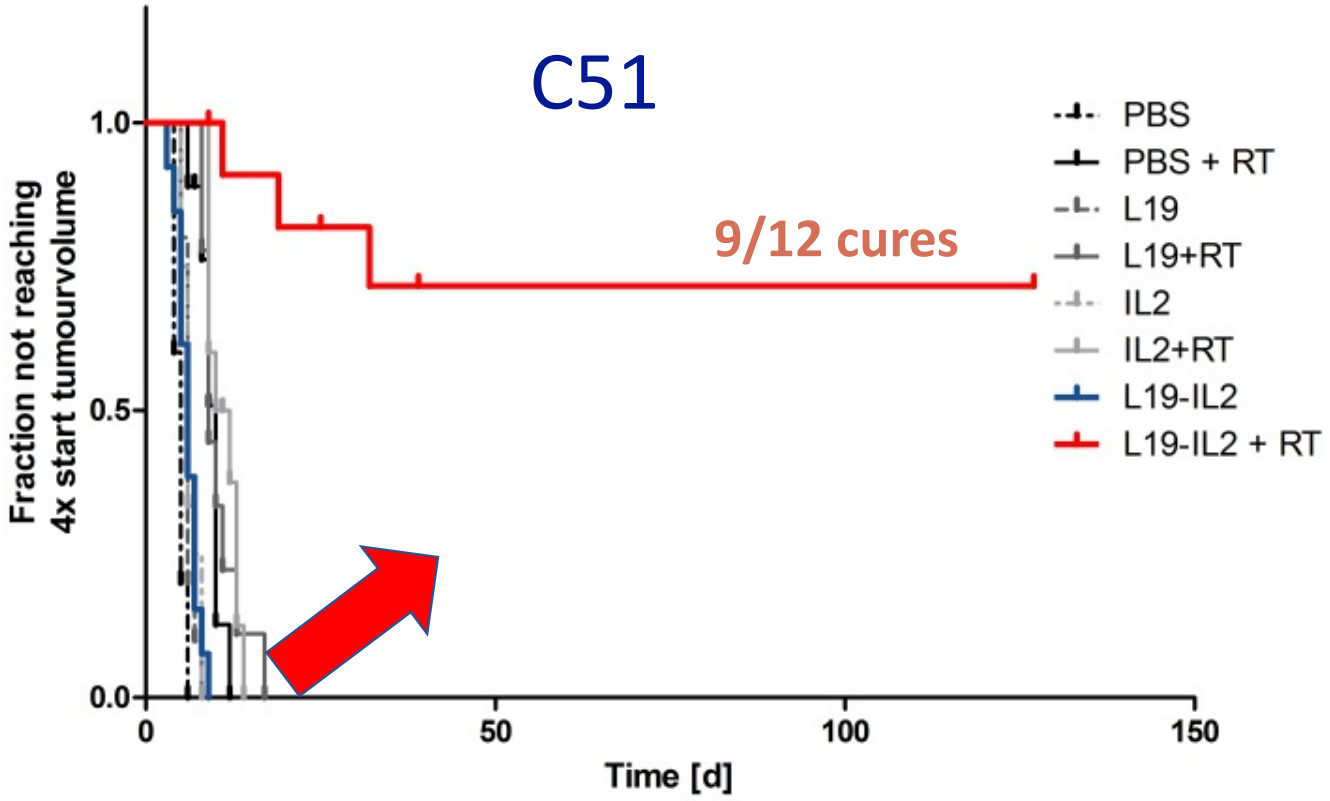
# The type of immunotherapy (aCTLA4 vs aPD-L1) does matter




Hartmann et al. Cancer letters 2022

# X-rays + immunocytokine (L19-IL2): synergistic effects




L19-IL2 must be given during or within 72 hours of RT

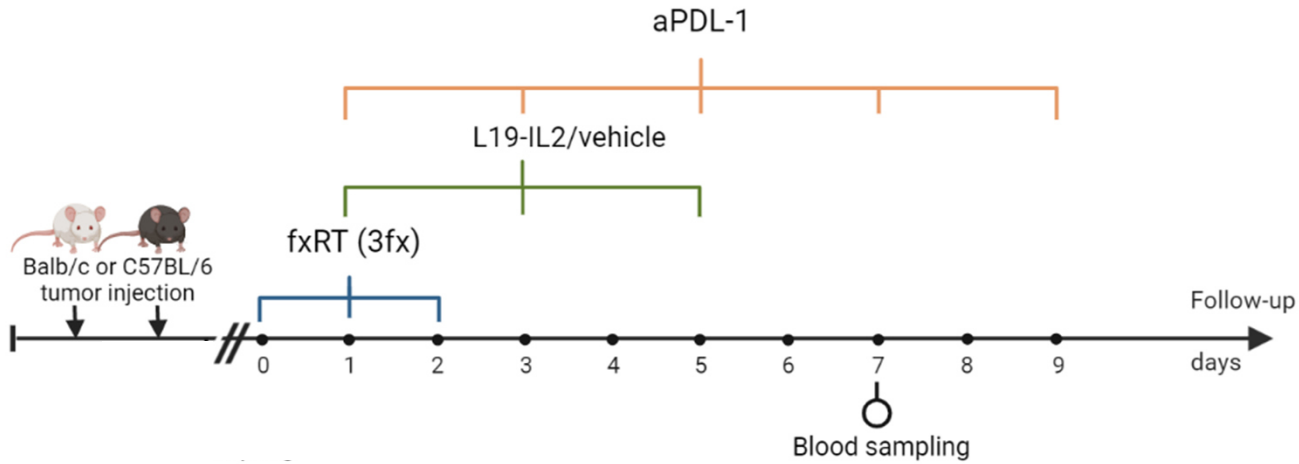
Zegers et al, Clin Cancer Res 2015; Phase 1 completed (van Limbergen et al. 2021), Randomized phase 2 ongoing: www.immunosabr.org

# Collaboration Heidelberg - Maastricht

Research questions:

1. Immunogenicity of protons versus Carbon ions
2. Immunocytokine versus checkpoint inhibitors
3. Status of immunological biomarkers

# Treatment scheme: Immunotherapy (checkpoint inhibitor or immunocytokine) and Radiation (electrons or protons or carbon ions)



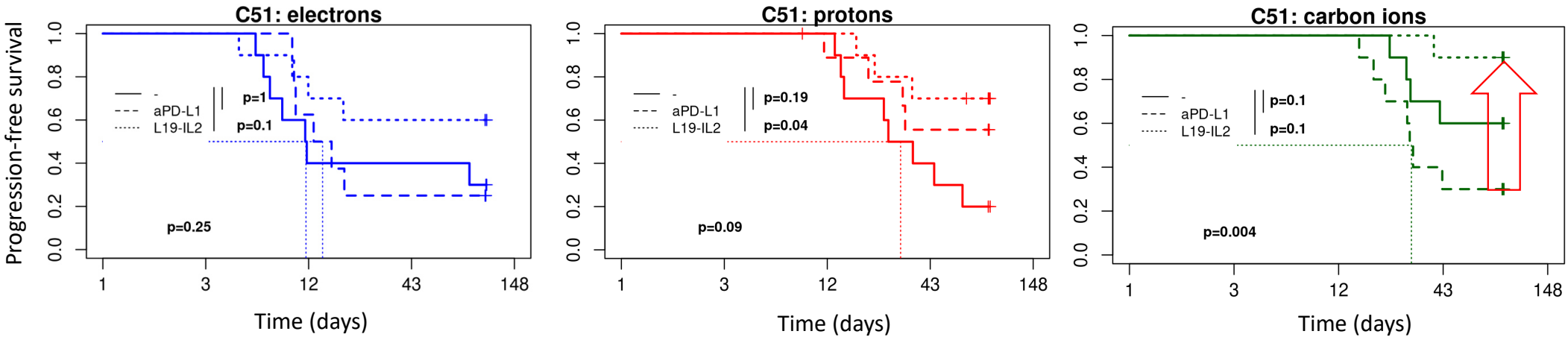

Tumor response to treatment depending on radiation quality and immunotherapy. A) Treatment scheme. Each mouse was injected with tumor cells (C51 or LLC) on the right flank. Tumors were irradiated with electrons (3x4 Gy), protons (C51: 3x2.9 Gy; LLC: 3x4 Gy) and carbon ions (C51: 3x1.8 Gy; LLC: 3x 2.1 Gy) combination with L19-IL2 or anti-PD-L1 or PBS control. Blood was withdrawn 7 days after the start of treatment for cytokine profiling.

Marcus D, Debus J, Lambin P, Ludwig Dubois L, Amir Abdollahi A, Yaromina A *et al.* , Unpublished

# Impact of linear energy transfer (LET) with Immunotherapy on tumor response *in vivo*

Conclusions: As far as the combo immunotherapy radiotherapy is concerned

1. Carbon ions > protons > electrons
2. Immunocytokine > checkpoint inhibitors




Progression-free survival (PFS) after different RT combinations in C51 tumor models. PFS rate was defined as percent of tumors not reaching 4 times start tumor volume. Kaplan-Meier survival curves. P-values calculated with parametric survival models (loglogistic distribution). LRT p-value (global), Wald type p-values for pairwise comparisons.

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Table 1. Estimated Odds Ratios of different treatments.

| **Treatment** | **Odds ratio* [95% CI], p-value** | |
|---|---|---|
| | C51 | LLC |
| Electrons | 1.44 [0.65-3.18], 0.364 | 0.6 [0.28-1.28], 0.183 |
| Protons | 0.47 [0.22-1.02], **0.056** | 1.36 [0.61-3.05], 0.456 |
| Carbon ions | 0.24 [0.11-0.55], **0.001** | 0.47 [0.22-1.00], **0.051** |
| L19-IL2 | 0.14 [0.06-0.35], **<0.001** | 0.27 [0.13-0.60], **0.001** |
| Anti-PD-L1 | 0.93 [0.44-2.00], 0.862 | 0.63 [0.29-1.35], 0.234 |

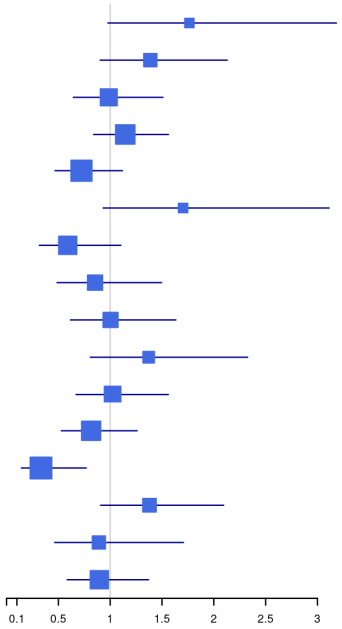
* Odds Ratio < 1 indicates that a specific treatment is more effective than all other treatments.

**Figure 4.** Cytokine profile in peripheral blood of mice bearing C51 tumors sampled 7 days after treatment start . **(A)** Forest plot showing the Hazard Ratio (HR) with 95% confidence interval (CI) and p-value for progression-free survival based on cytokine levels (multivariate analysis, Cox PH model). **(B)** Plasma IL5 levels induced by different treatments: electrons (e-), protons (H+), carbon ions (C) or untreated (ctrl). Boxplots represent the median, 25th and 75th percentiles and the whiskers the maximum and minimum values. Statistical significance was tested with linear models.

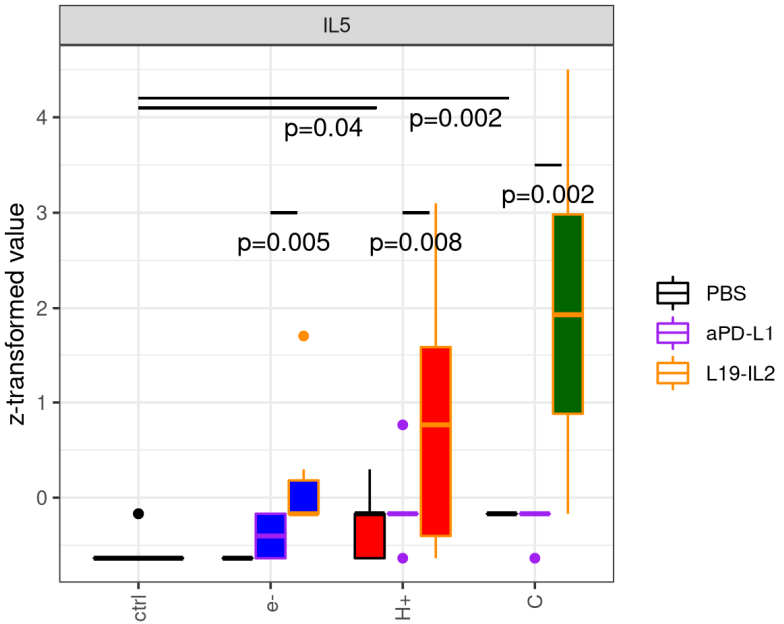
**A)**

**non-adjusted, multivariate**

| 69 / 43 | Hazard Ratio | 95% CI | p-value |
|---|---|---|---|
| CCL2 | 1.76 | 0.98-3.18 | 0.059 |
| G-CSF | 1.39 | 0.90-2.13 | 0.134 |
| IFNy | 0.99 | 0.65-1.51 | 0.951 |
| IL1b | 1.15 | 0.84-1.56 | 0.39 |
| IL4 | 0.72 | 0.47-1.12 | 0.145 |
| IL6 | 1.7 | 0.93-3.11 | 0.083 |
| TNFa | 0.59 | 0.32-1.10 | 0.099 |
| VEGF | 0.85 | 0.49-1.50 | 0.581 |
| CCL5 | 1 | 0.62-1.63 | 0.988 |
| GM-CSF | 1.37 | 0.81-2.33 | 0.241 |
| IL1a | 1.02 | 0.67-1.56 | 0.914 |
| IL2 | 0.82 | 0.53-1.26 | 0.36 |
| IL5 | 0.33 | 0.14-0.77 | **0.01** |
| IL10 | 1.38 | 0.91-2.09 | 0.132 |
| M-CSF | 0.89 | 0.46-1.71 | 0.727 |
| uPAR | 0.9 | 0.58-1.37 | 0.61 |




**B)**




Marcus D, Debus J, Lambin P, Ludwig Dubois L, Amir Abdollahi A, Yaromina A *et al.* , Unpublished

# Consistent picture with immunological biomarkers

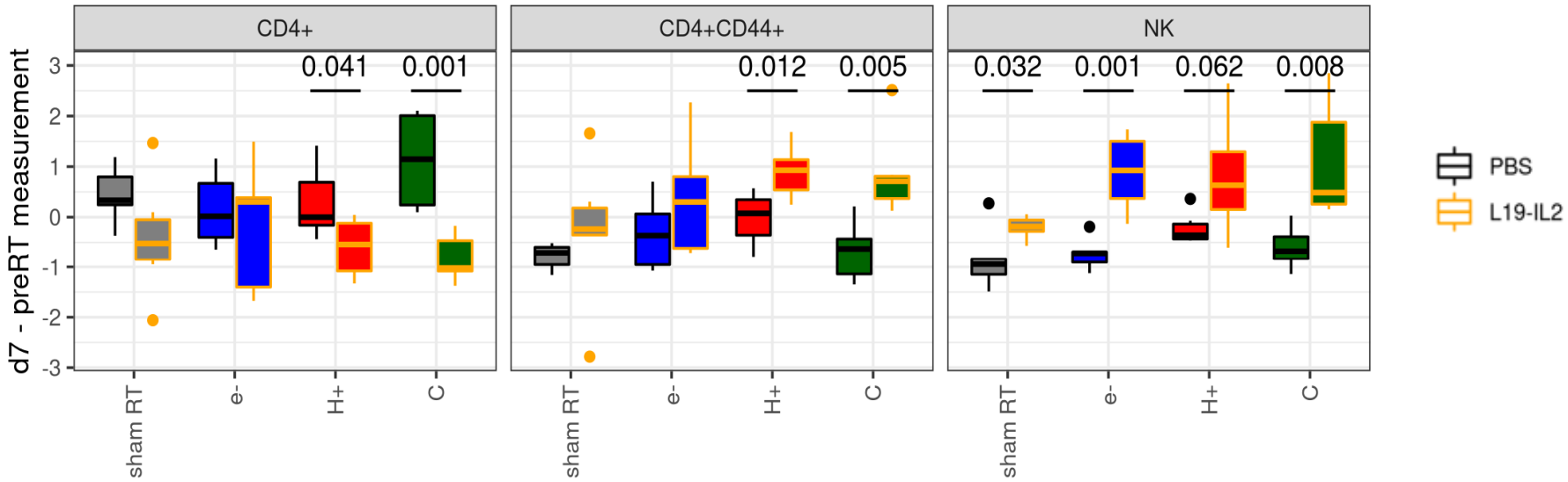



**Figure 5.** Immunological blood parameters assessed in mice bearing C51 tumors at day 7 after treatment start . **(A)** Treatment scheme. Each mouse was injected with C51 tumor cells on the right flank. Tumors were irradiated with electrons (3x4 Gy, e-), protons (3x2.9 Gy, H+), carbon ions (3x1.8 Gy, C) or sham irradiated (sham RT) in combination with L19-IL2 or PBS control. Blood was collected before treatment start and 7 days thereafter for the evaluation of immunological parameters. Tumors were excised at day 7 for transcriptome analysis and tumor infiltration. **(B)** Boxplots showing median changes (day 7 – preRT measurements), for CD4+, CD4+CD44+, CD8+ T cells and NK cells upon different treatments, with 25th and 75th percentiles .

Marcus D, Debus J, Lambin P, Ludwig Dubois L, Amir Abdollahi A, Yaromina A *et al.* , Unpublished

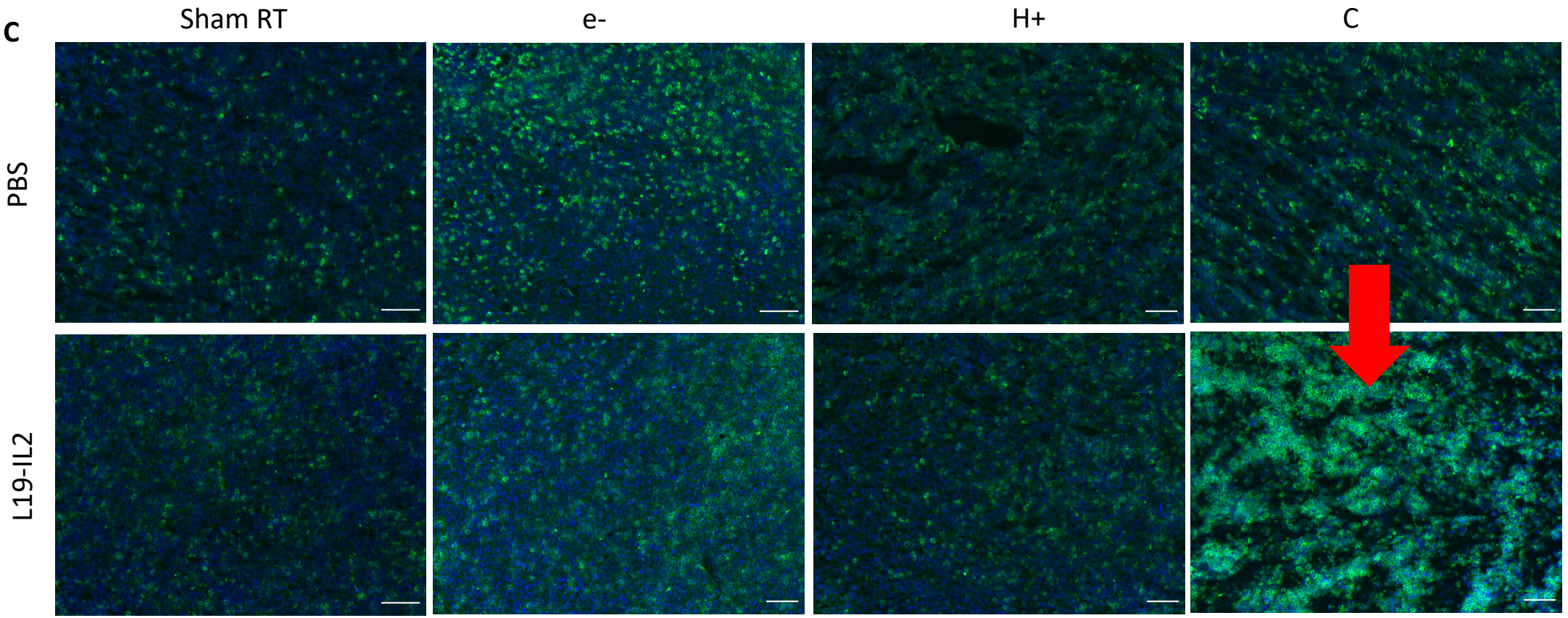



**Figure 5. (C)** Representative images showing CD8+ T cells (green) infiltration in tumor regions depending on the treatment. Scale bar represent 100 µm. Nuclei are depicted in blue (DAPI).

Marcus D, Debus J, Lambin P, Ludwig Dubois L, Amir Abdollahi A, Yaromina A *et al.* , Unpublished

# Interim conclusion: RT + IO

1. Effect of tumor targeted L19-IL2 immunotherapy increased with increasing LET achieving 90% local control when combined with carbon ions in C51 murine tumor model.
2. All types of radiation fueled L19-IL2 immunotherapy more effectively than checkpoint blockade with anti-PD-L1.

Marcus D, Debus J, Lambin P, Ludwig Dubois L, Amir Abdollahi A, Yaromina A *et al.* , Unpublished

| Condition or disease | Intervention/treatment |
| --- | --- |
| Non Small Cell Lung Cancer | Radiation: Carbon Ion Therapy |
| Head and Neck Squamous Cell Carcinoma | Drug: Immunotherapy (Pembrolizumab) |
| Melanoma | |
| Urothelial Carcinoma | |

Detailed Description:

This is a multicenter, open label, non-randomized phase II clinical trial aiming to assess the feasibility and the clinical activity of adding CIRT to ICIs in cancer patients that have obtained a disease stability (SD) with pembrolizumab administered as per standard of care. At stu
will be performed at Fondazione CNAO, Pavia

## Study Design

| | |
| --- | --- |
| Study Type : | Interventional (Clinical Trial) |
| Estimated Enrollment : | 27 participants |
| Allocation: | N/A |
| Intervention Model: | Single Group Assignment |
| Intervention Model Description: | Patient with solid cancer (NSCLC, HNSCC, melanoma, urothelial carcinoma) and a stable disease will be enrolled in the study. |
| Masking: | None (Open Label) |
| Primary Purpose: | Treatment |
| Official Title: | Immune Checkpoint Inhibitors and Carbon iON Radiotherapy In Solid Cancers With Stable Disease |
| Actual Study Start Date : | July 26, 2022 |
| Estimated Primary Completion Date : | August 2025 |
| Estimated Study Completion Date : | August 2026 |

**Sponsor:**
Peking University First Hospital

**Collaborator:**
YiZhou International Cancer Hospital

**Information provided by (Responsible Party):**
Xian-shu Gao, Peking University First Hospital

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

## Study Description

Brief Summary:
The purpose of this research study is to compare the effects (good and bad) on subjects and their cancer using **proton** radiation therapy in combination with **immunotherapy**(ie. Programmed cell death protein 1, also known as PD-1 antibody) in multiple metastases.

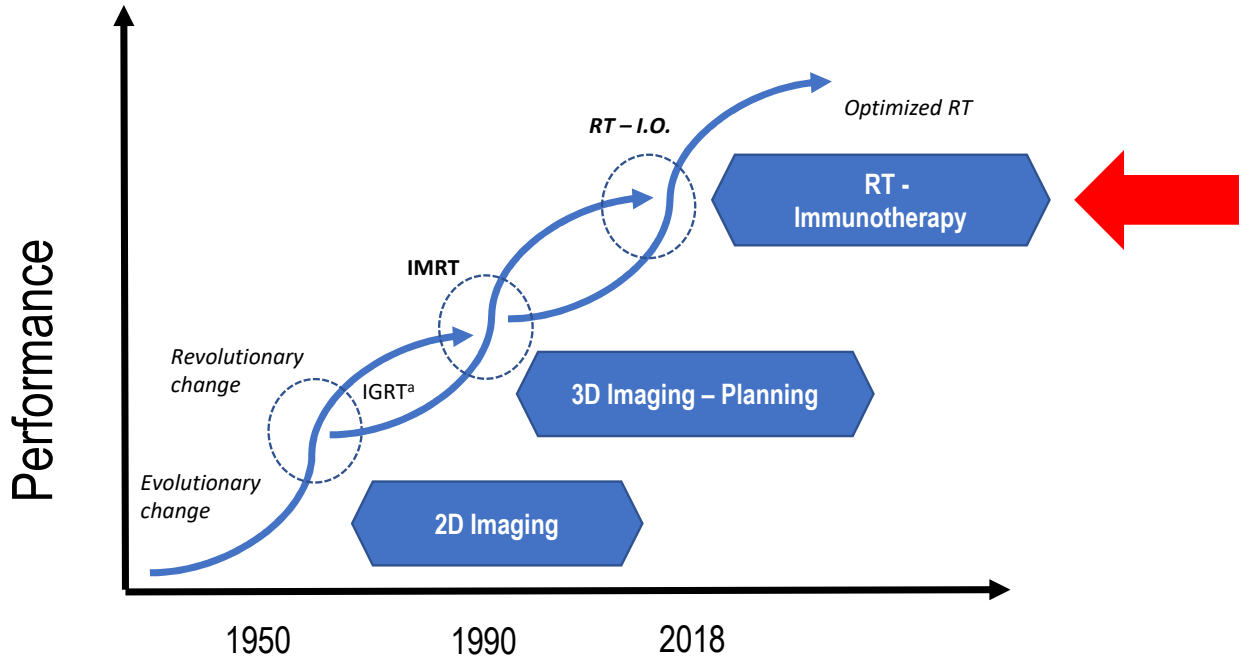
| Condition or disease | Intervention/treatment | Phase |
|---|---|---|
| **Proton Therapy**<br>**Immunotherapy**<br>**Neoplasm** Metastasis | Combination Product: Radiation: **Proton Therapy**+PD-1 Ab | Phase 1<br>Phase 2 |

Detailed Description:
As is known to all, the main treatment method for metastatic tumors is systemic chemotherapy and radiotherapy is merely for the purpose of palliative treatment. Recent studies have shown that tumors with no more than 5 metastatic sites can still achieve satisfactory overall survival by local treatments such as radiotherapy. However, for tumors with more meta
for photon radiotherapy due to the wide range of irradiation. Protons might be a safe treatment means for multiple metastases cancer because of the Brag peak, when the normal tissue dose can be significantly reduced. Combination of proton therapy with immunotherapy can be a research direction for multiple metastatic tumors. This study intends to observe
technique combined with immunotherapy in improving the overall anti- tumor effect for metastatic tumors.

## Study Design

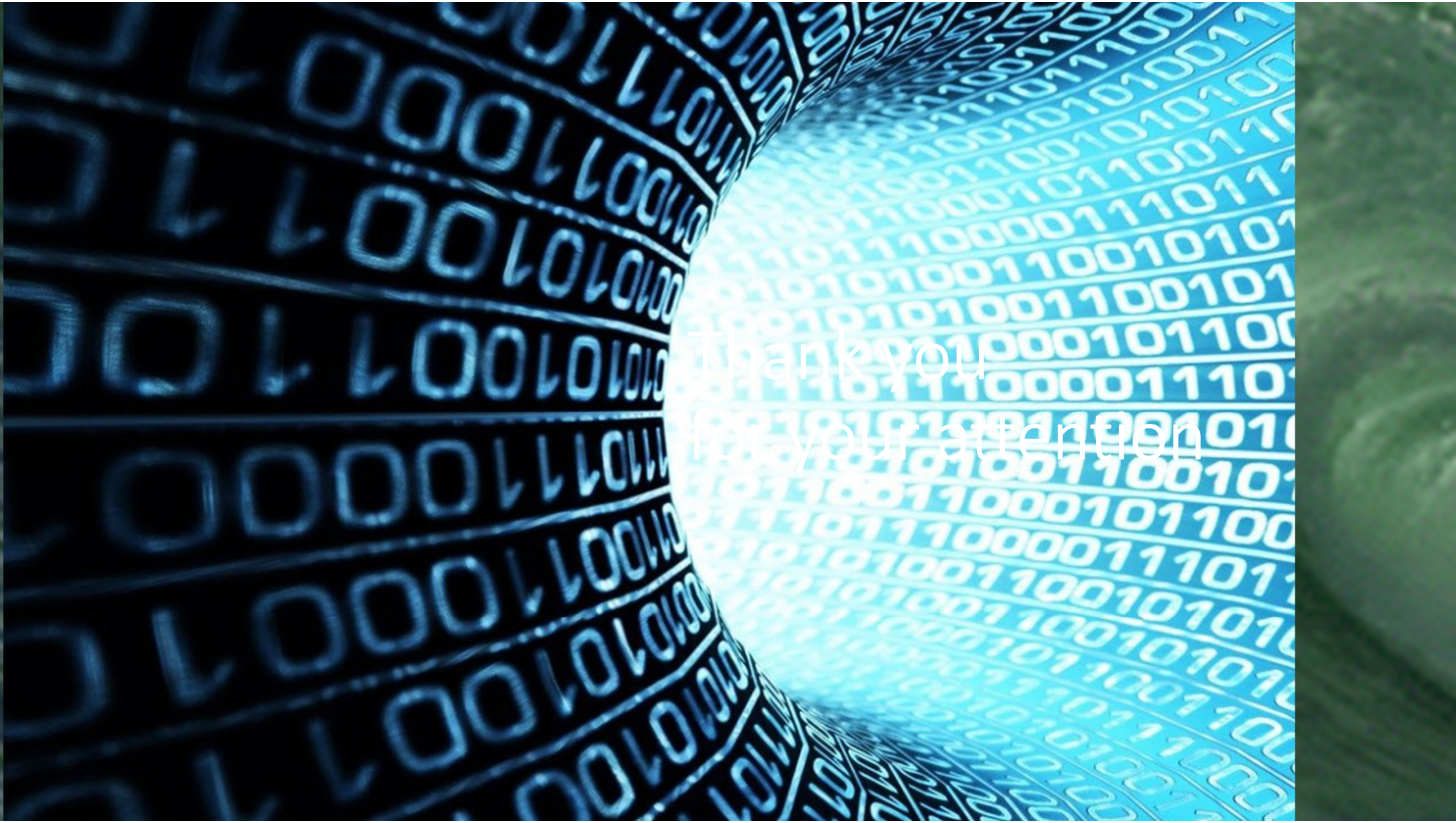
| | |
|---|---|
| Study Type : | Interventional (Clinical Trial) |
| Estimated Enrollment : | 30 participants |
| Allocation: | N/A |
| Intervention Model: | Single Group Assignment |
| Intervention Model Description: | Proton Therapy+PD-1 Ab |
| Masking: | None (Open Label) |
| Primary Purpose: | Treatment |
| Official Title: | A Phase I/II Study of Combination of **Proton Therapy** With **Immunotherapy** in Multiple Metastases **Cancer** |
| Estimated Study Start Date : | January 1, 2019 |
| Estimated Primary Completion Date : | January 1, 2022 |
| Estimated Study Completion Date : | December 1, 2022 |

# The disruptive moments in radiotherapy




precision medicine

Maastricht University


Thank you
for your attention

# Acknowledgments to our collaborators


**The Heidelberg group:**

Julian Schlegel, Mahmoud Moustafa, Maximillian Knoll, Jennifer Furkel, Carmen Klein, Marion Gijbels, Ivana Dokic, Sarah Meister, Stephan Brons, Juergen Debus, Amir Abdollahi

**The Maastricht group:**

Ala Yaromina, Ludwig Dubois, Damienne Marcus, Alex van der Wiel





# Thank you
# for your attention

philippe.lambin@maastrichtuniversity.nl

# LSRT + rescue with IL7 in mice

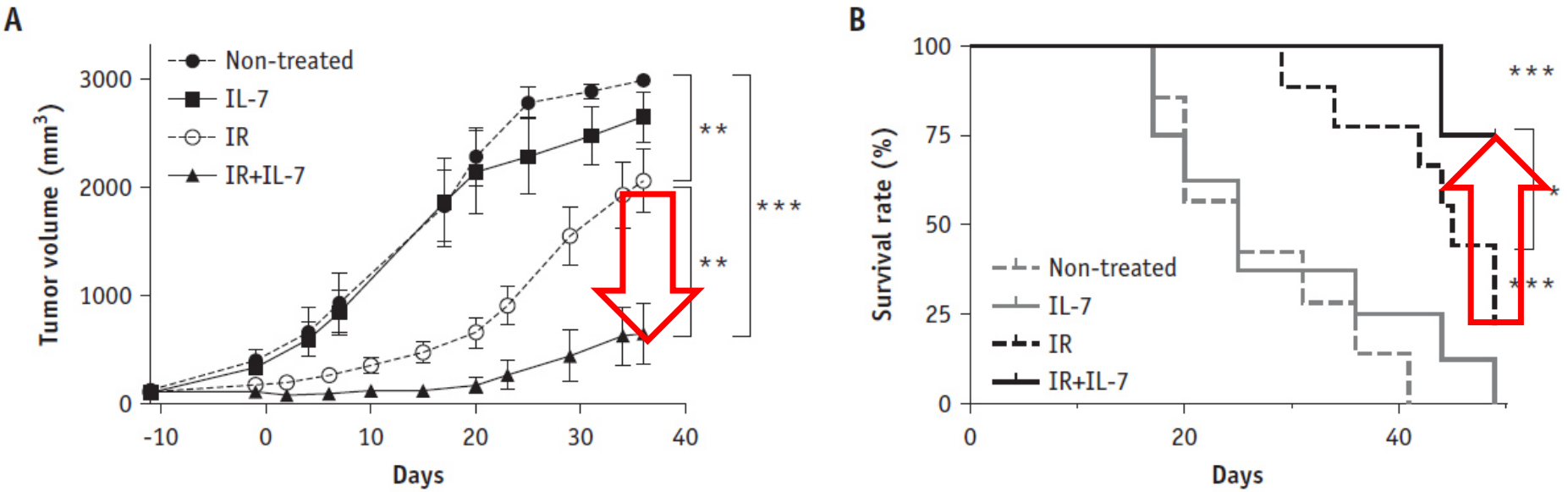
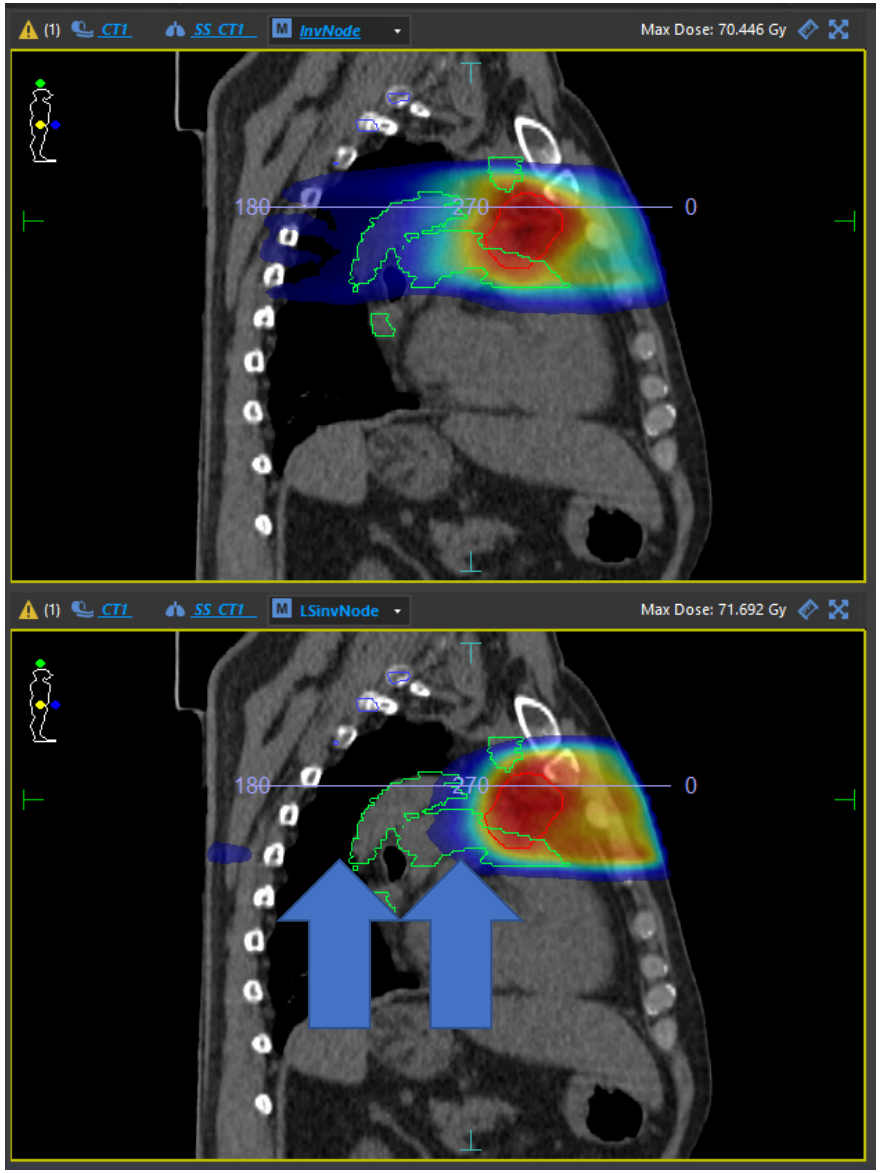
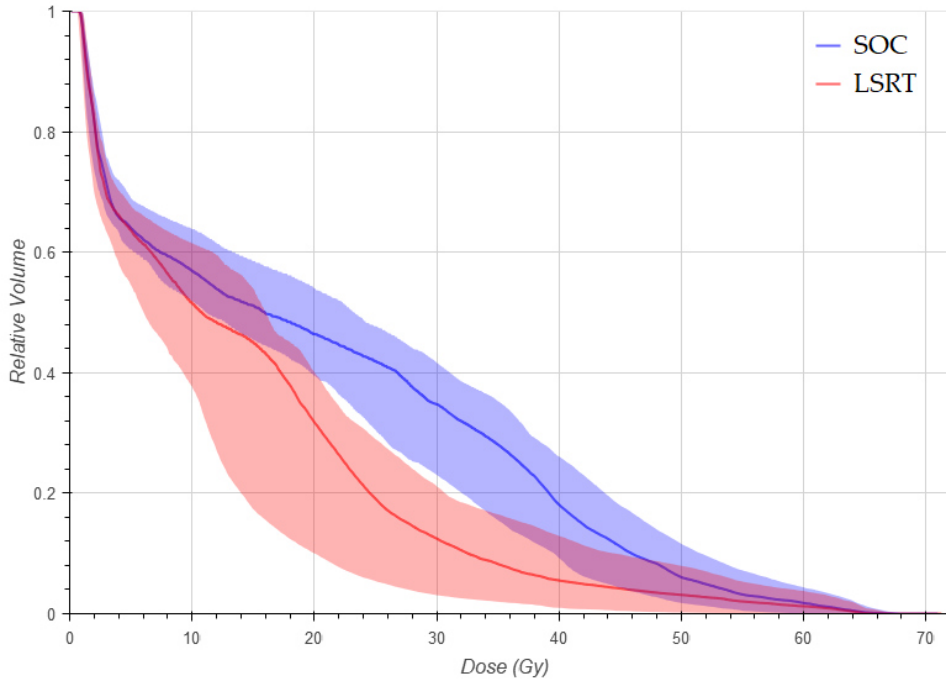



**Fig. 5.** Response of HCa-1 tumor to treatment. (A) Tumor growth in different groups of tumor-bearing mice. Statistical analysis was performed on day 36. (B) Survival curve in response to different treatments; n = 8 per group; stand-alone asterisks denote significance when compared with the nontreated group; $*P < .05$, $**P < .01$; and $***P < .001$; 2-tailed Mann-Whitney test and log-rank (Mantel-Cox) test; data are represented as mean ± standard error.

Hwa Kyung Byun et al. IJROBP 2021




# + Hypofractionation = More lymphocyte sparing




Courtesy of Fernandes P., Jourani Y et al, Institut Jules Bordet, Brussels