Radiotherapy and Immunotherapy

April 11, 2025

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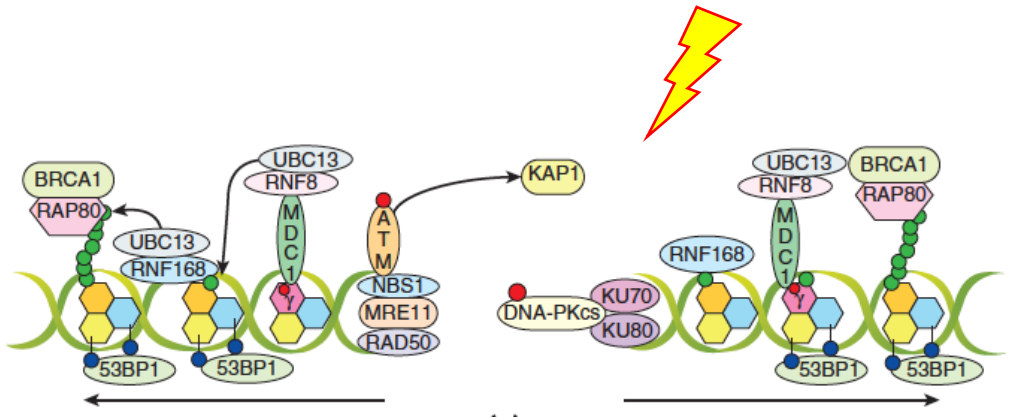
Learning Objectives

- Recognize the connections between RT-induced cellular responses and inflammatory signalling
- Appreciate how this signalling alters TME
- Gain insight to how these signals might manifest and be harnessed in the clinic

Damage responses are not compartmentalized



Minutes-to-Hours

Days

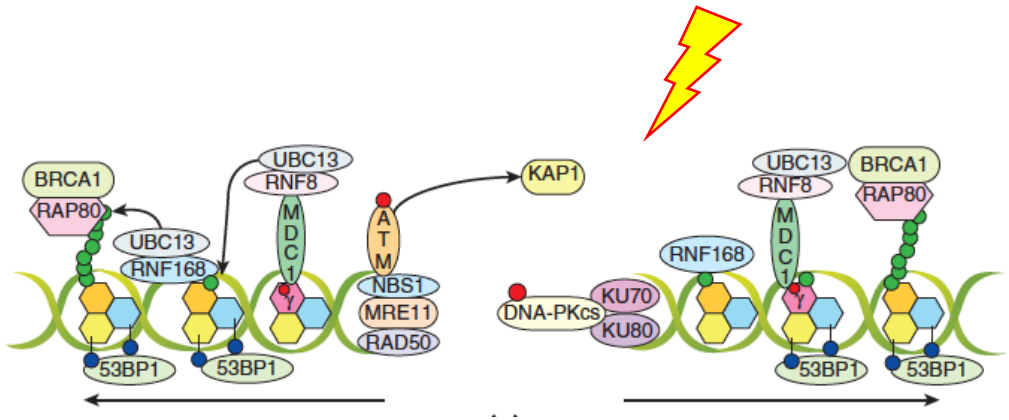
DNA Repair

Cell cycle checkpoints

Senescence

Cytokine production

Damage responses are not compartmentalized



DNA Repair

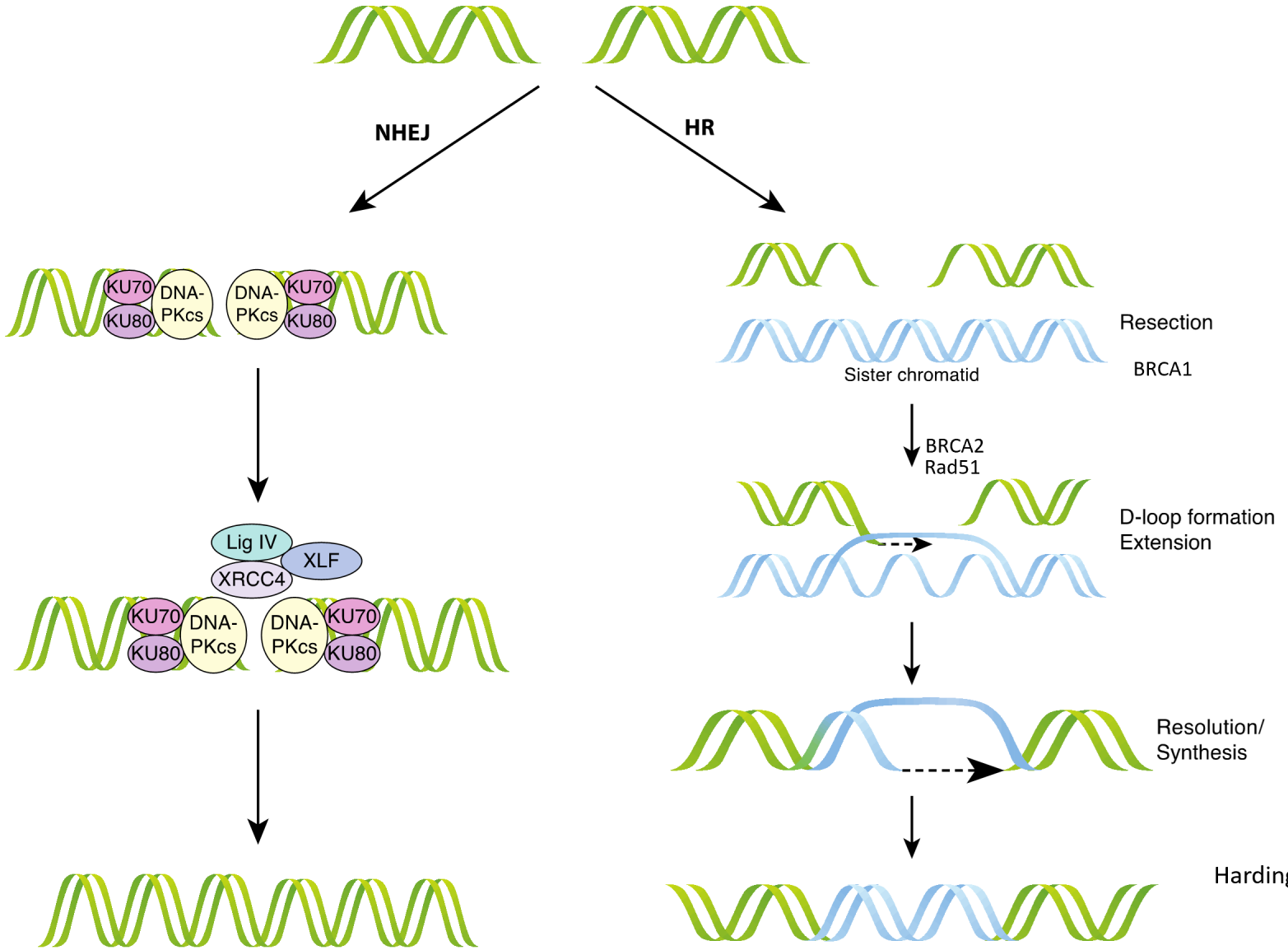
Cell cycle checkpoints

Metabolic Cell death

Cytokine production

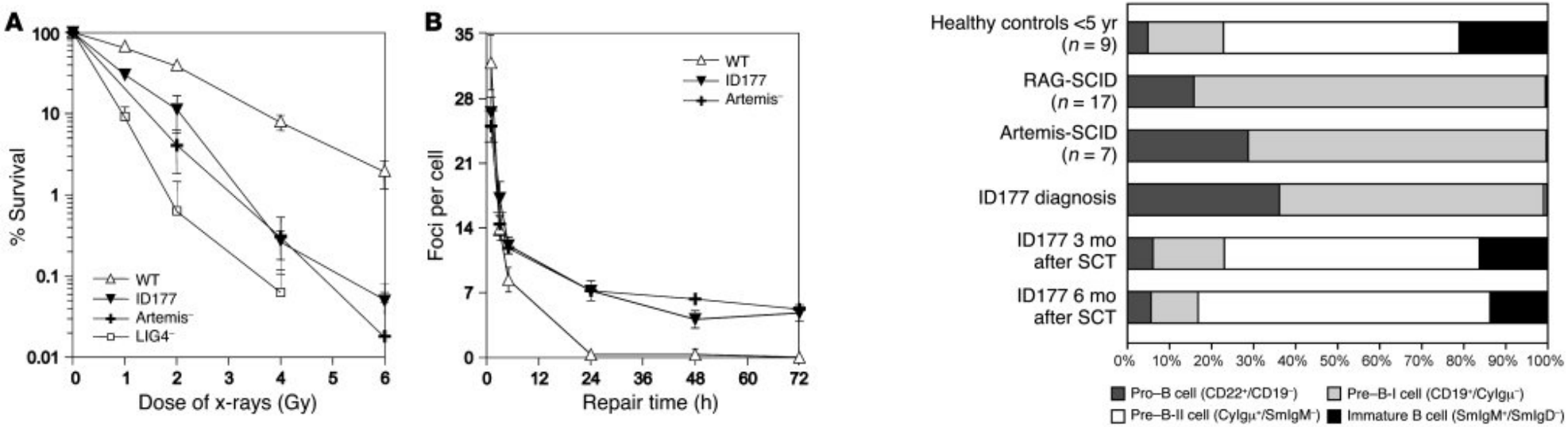
Senescence

Major DSB repair pathways: NHEJ and HR



Harding et al., BSO, 2012

Radiosensitivity, DNA repair and immunodeficiency

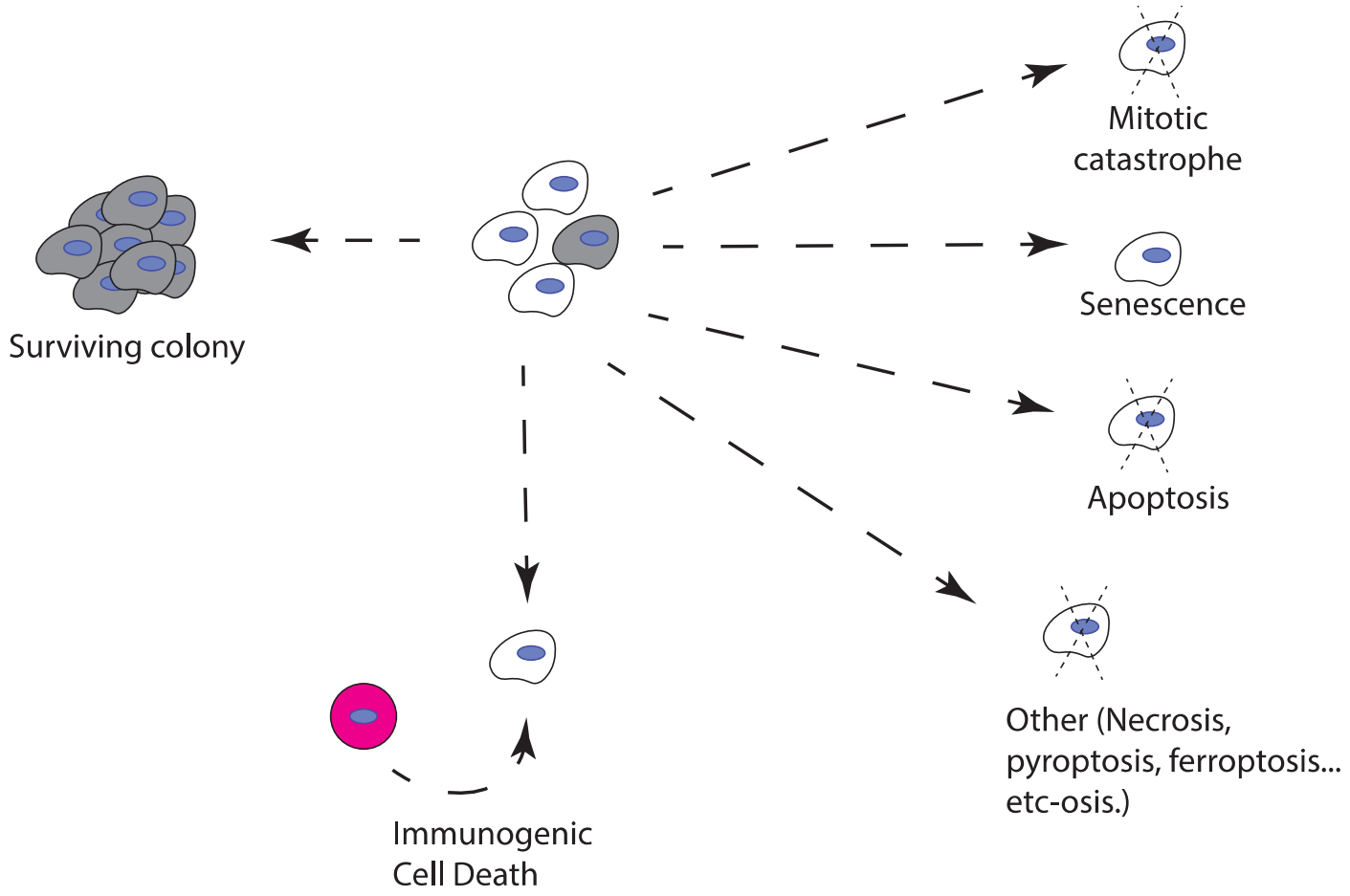


"A girl (patient ID177) from consanguineous parents…was clinically diagnosed with SCID when she was 5 months old. B and T cells were virtually absent from peripheral blood."

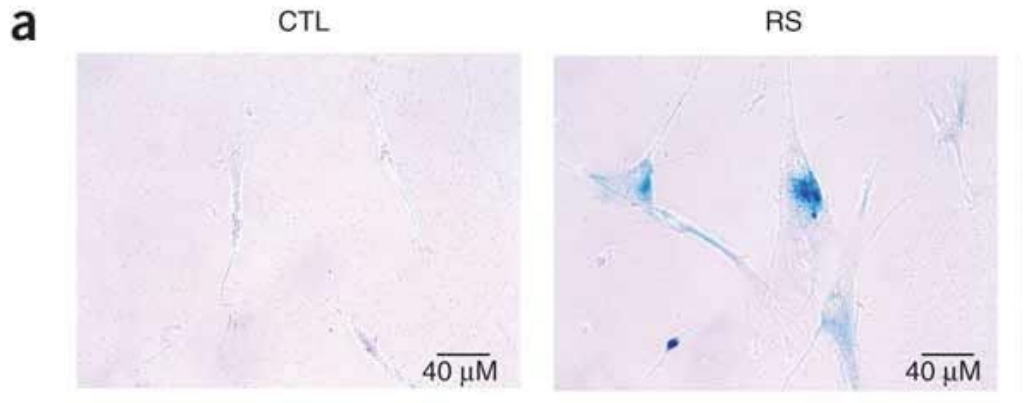
Patients who lack DSB repair through a pathway called non-homologous end-joining are radiosensitive and have defects in V(D)J recombination

van der Burg, JCI, 2008

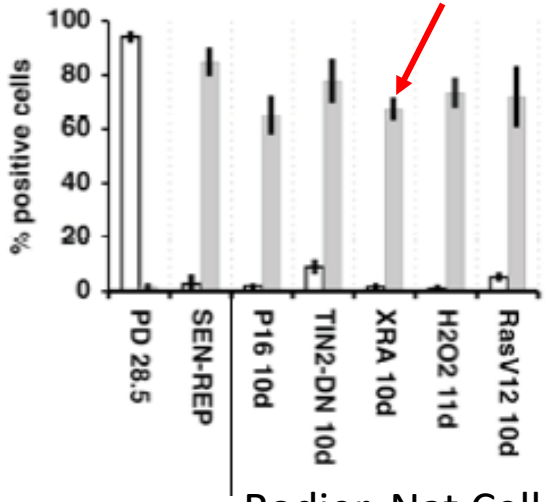
RT-induced cell death



Senescence and cytokine secretion are co-incident



Debacq-Chainiaux, Nat Prot., 2009

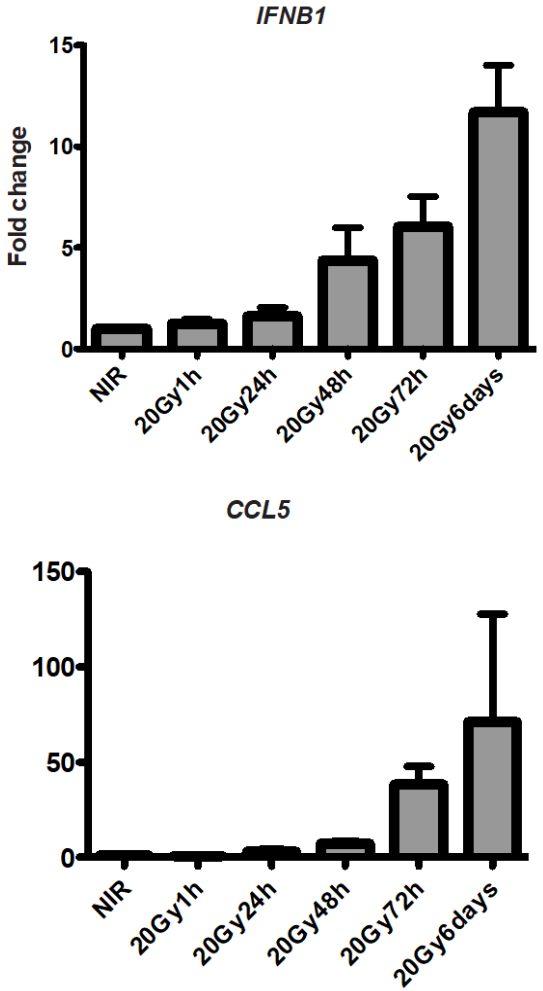


Rodier, Nat Cell Bio, 2009

Protein	Fold XRA/PRE	*P*-value
IL-6 / IL6	31.45	0.009
GRO / CXCL1-2-3	11.97	0.050
IL-8 / IL8	9.48	0.004
IGFBP-2 / IGFBP2	4.86	0.027
ICAM-1 / ICAM1	4.06	0.011
sgp130 / IL6ST	2.26	0.014
TRAIL-R3 / TNFRSF10C	2.10	0.003
Osteoprotegerin	2.03	0.031
TIMP-2 / TIMP2	2.03	0.032
sTNF RI / TNFRSF1A	1.85	0.024
MCP-1 / CCL2	1.83	0.030
IGFBP-3 / IGFBP3	1.73	0.022
IL-1 R1 / IL1R1	1.57	0.009
uPAR / PLAU	1.55	0.042
LIGHT / TNFSF14	0.58	0.018
IL-15 / IL15	0.47	0.033

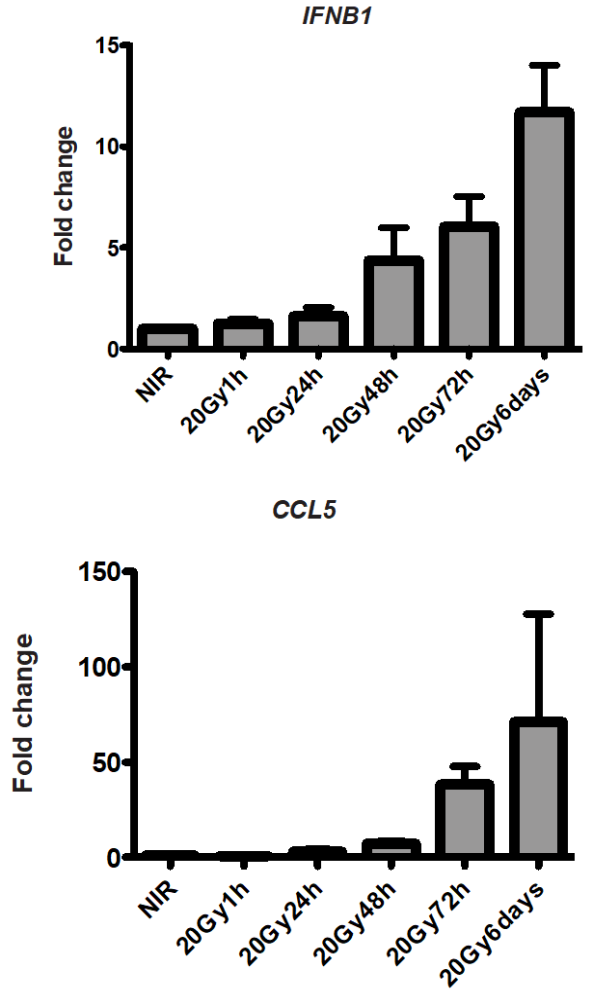
Rodier, Nat Cell Bio, 2009

Delayed cytokine response to RT

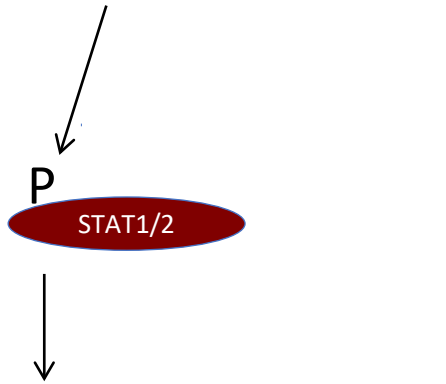


MCF10A cells

Delayed cytokine response to RT



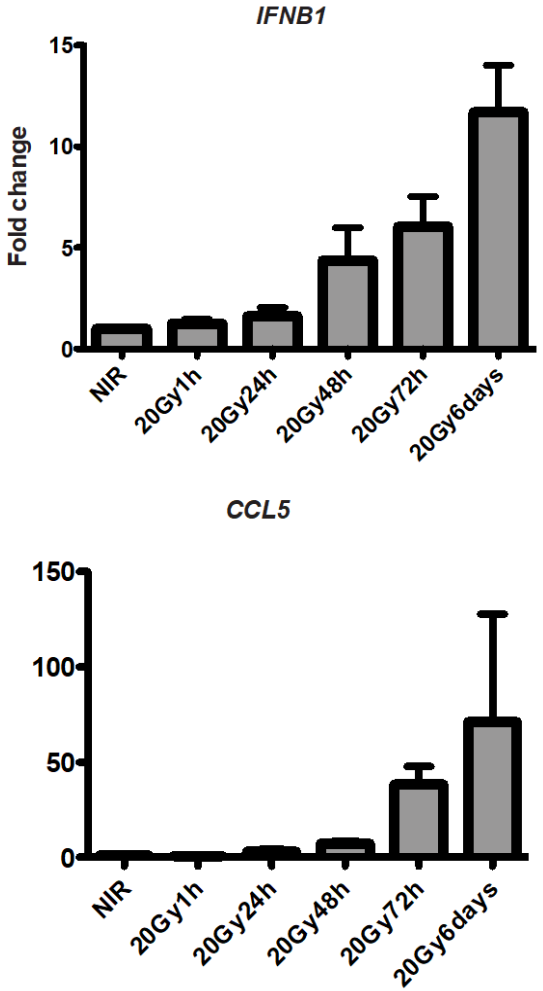
MCF10A cells



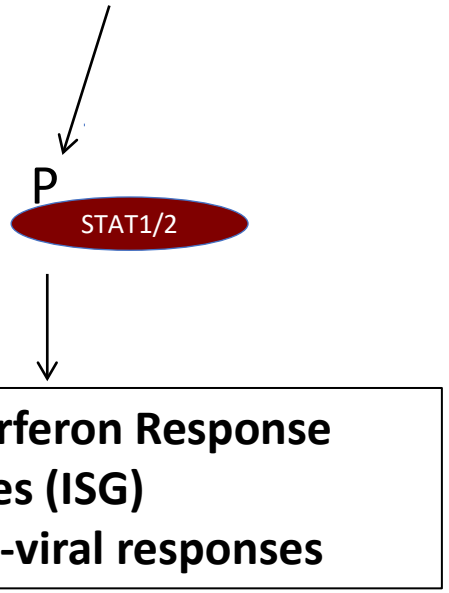
Interferon Response genes (ISG)
Anti-viral responses

Adapted from: Zheng, Cell Rep, 2013

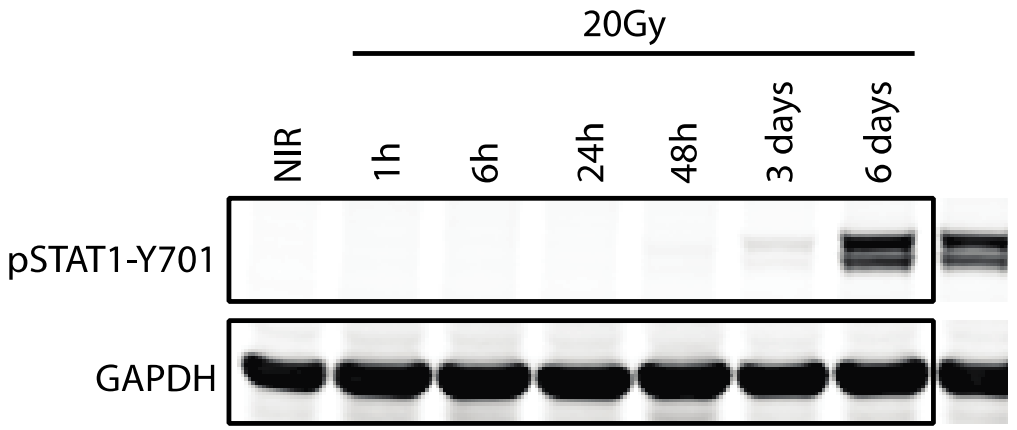
Delayed cytokine response to RT



MCF10A cells



Adapted from: Zheng, Cell Rep, 2013

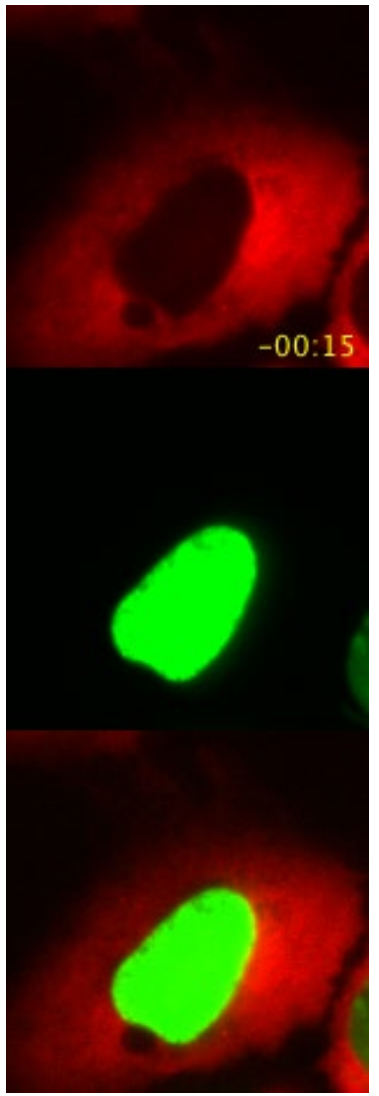


Harding, Nature, 2017

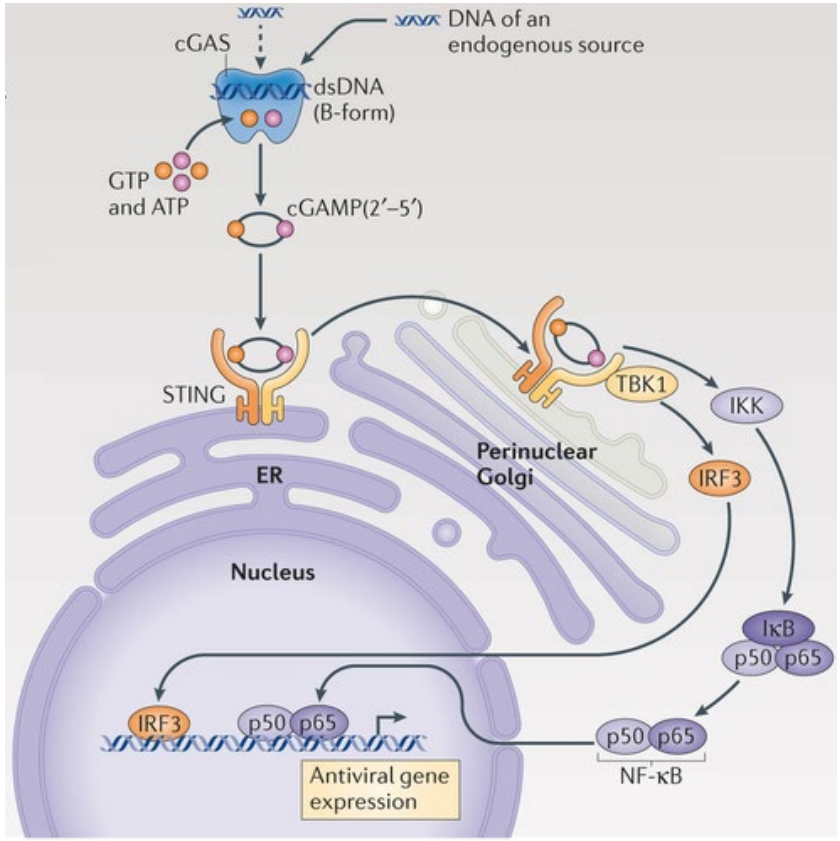
Micronuclei are a link between DSBs and cytokine induction

Percentage of nuclei

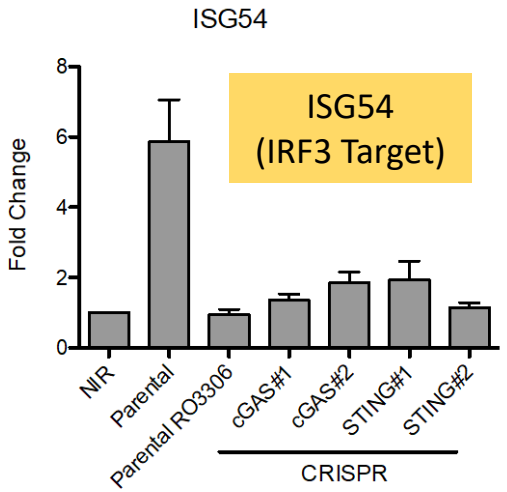
eated cells



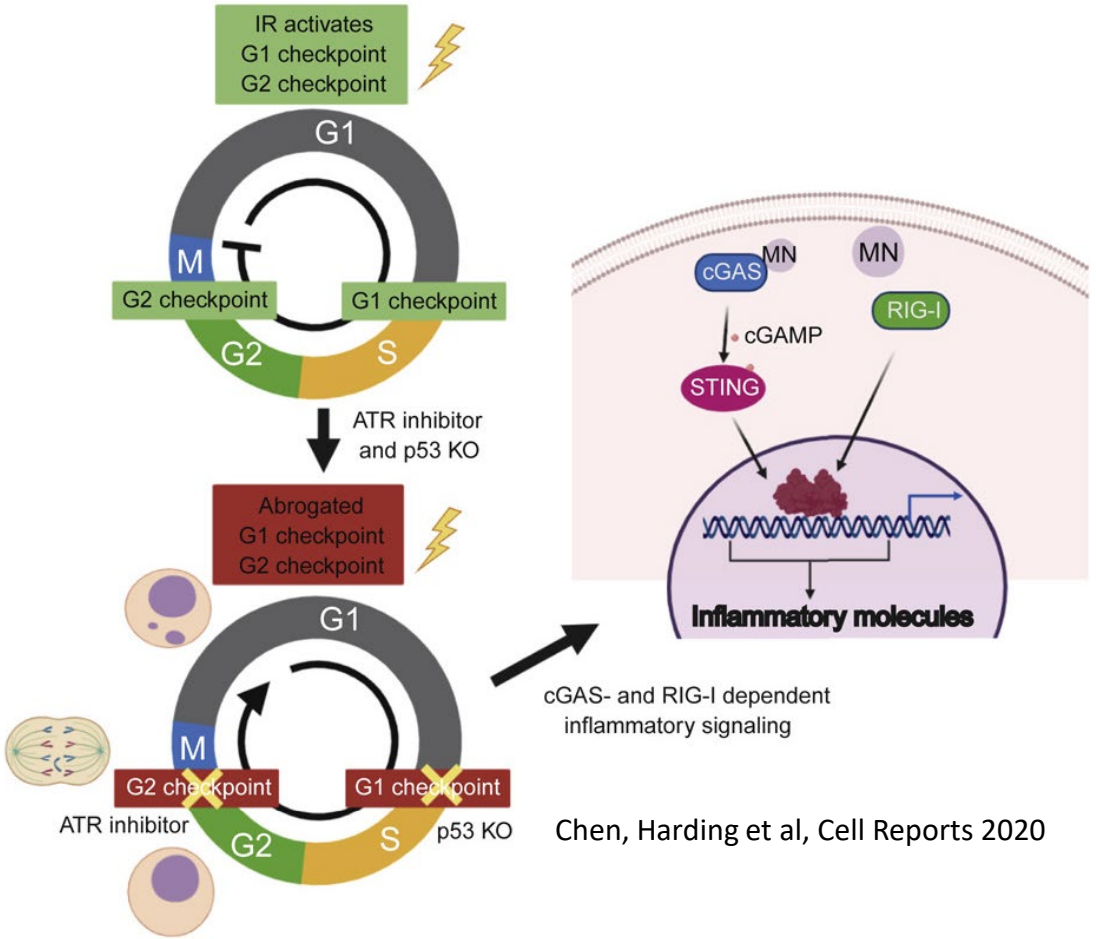
Innate viral sensing pathways are activated by RT



Adapted from: Hornung, Nat Rev Immun., 2014

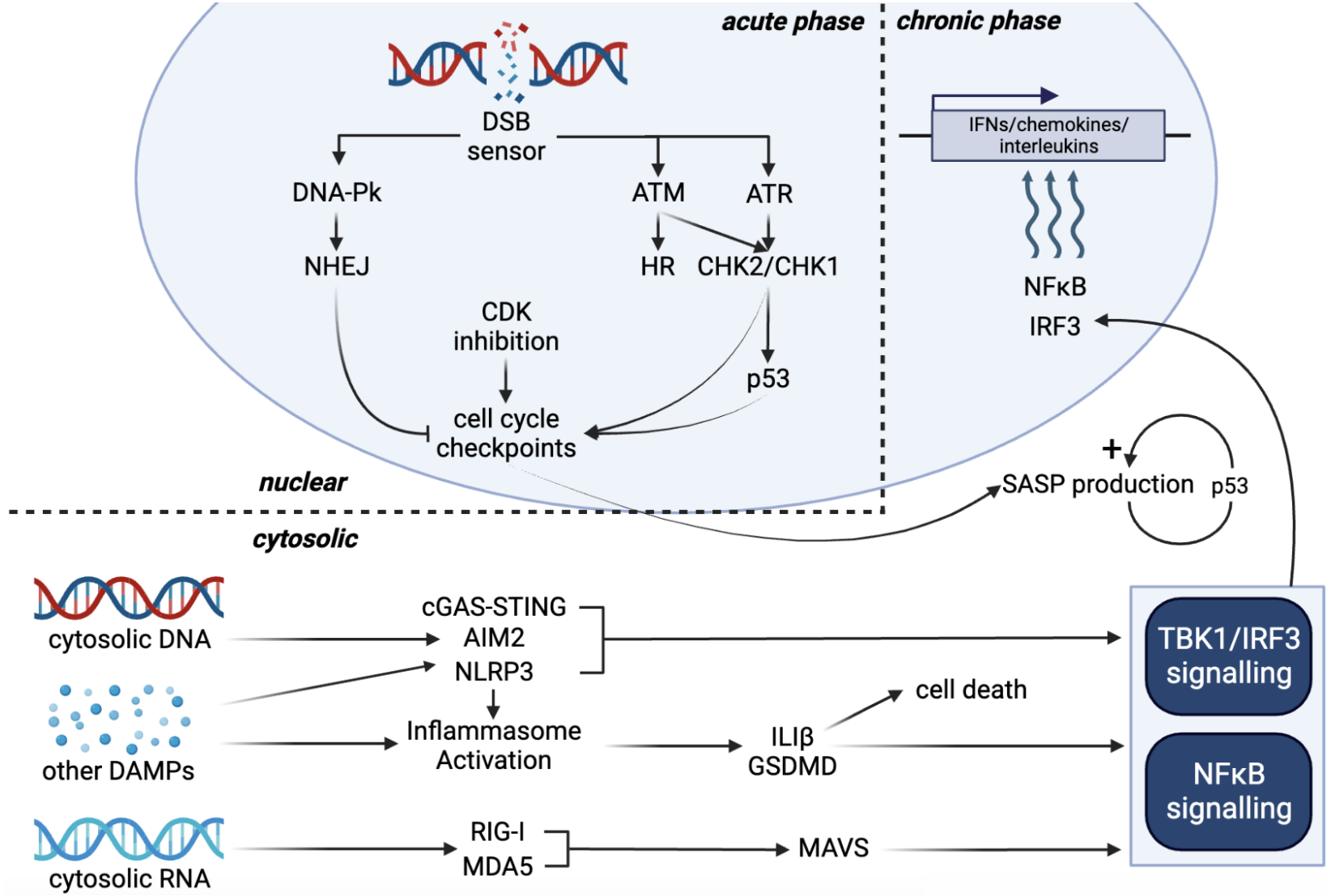


Contextual cell cycle regulation governs post-damage cytokine signaling



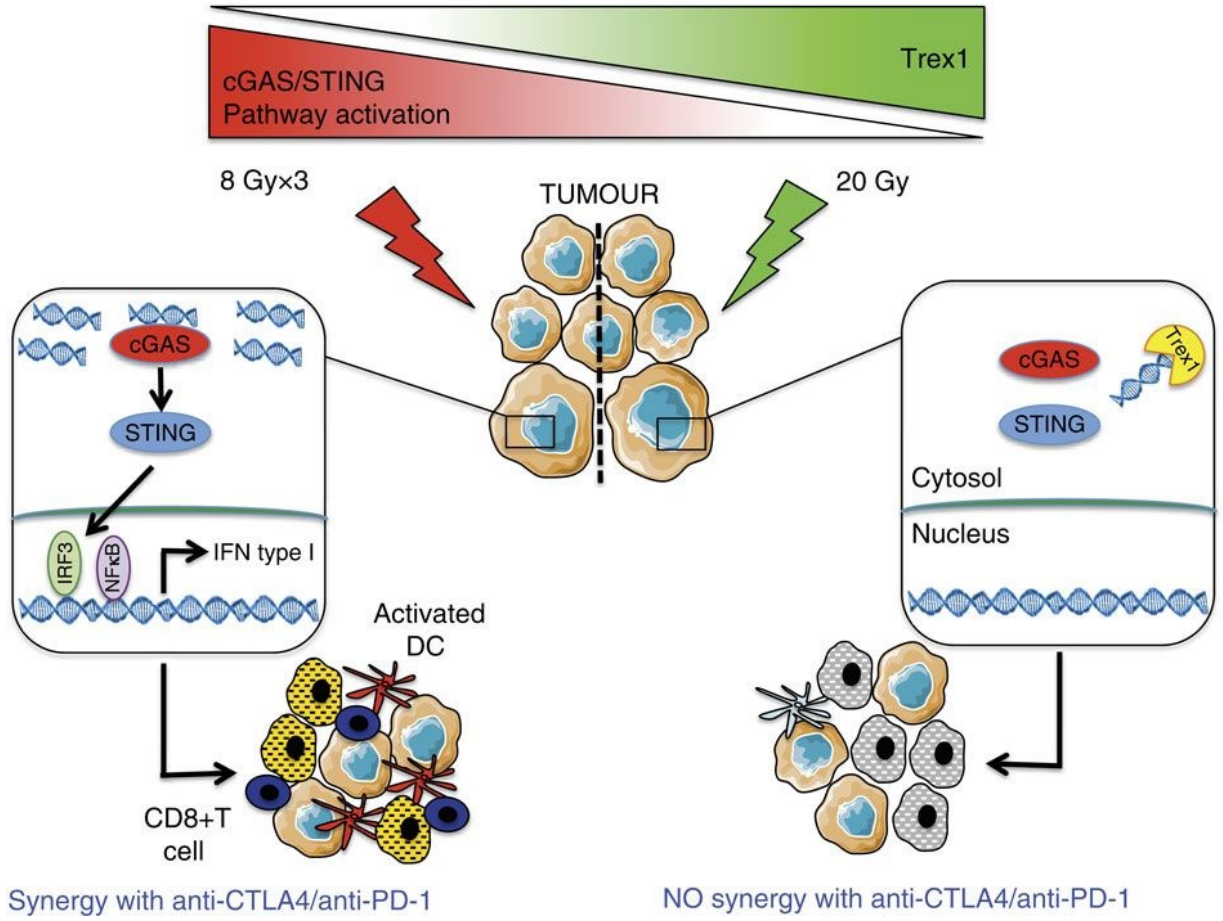
Chen, Harding et al, Cell Reports 2020

cGAS (and micronuclei) are not unambiguous IFN agonists



Ha, DNA Repair, 2023

TREX1 can counteract RT-induced cytoplasmic DNA



Vanpouille-Box, Nat Comm., 2017

Radiotherapy and inflammatory signaling

- Dermatitis was noted even in early experiments by Rontgen and others
- These short-term responses “burns”

  can lead to long-term changes

  in tissue structure
- Alterations in cellular signaling from RT

  can impact tumour responses

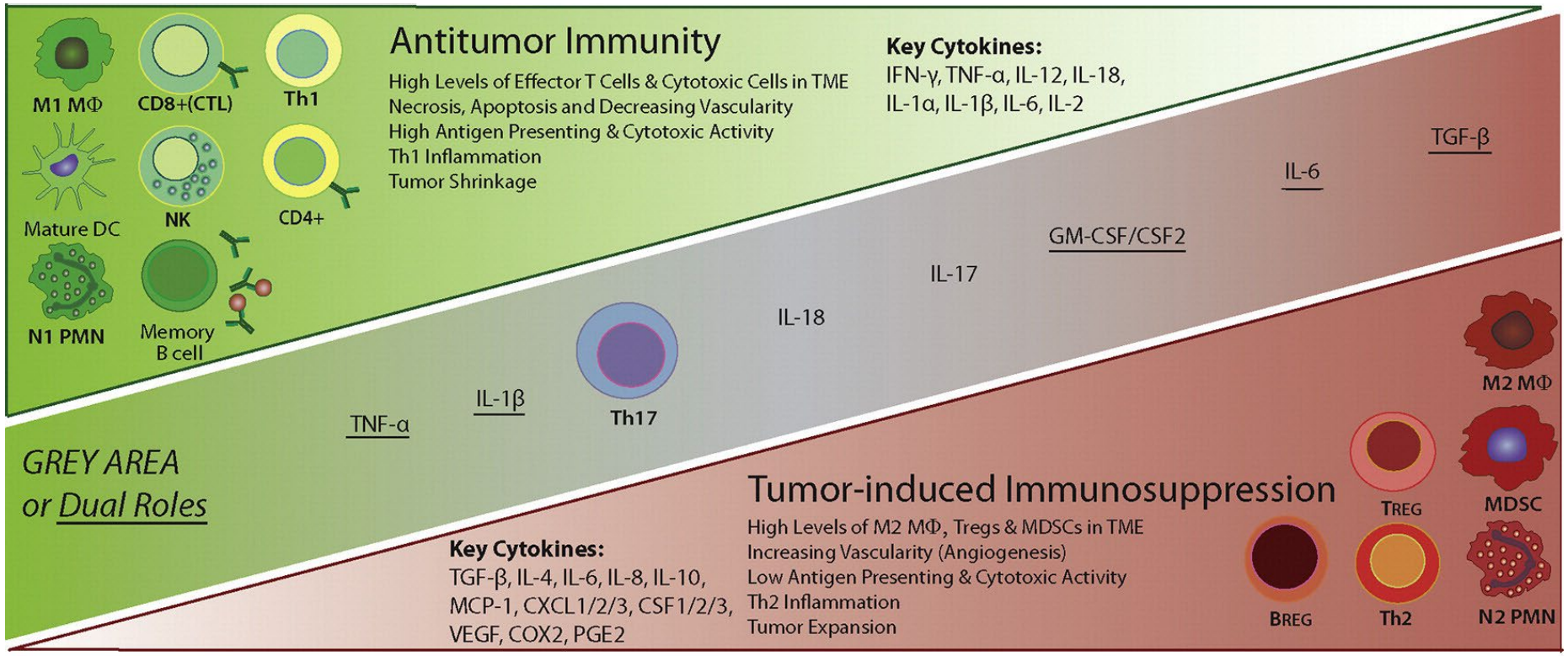
Fig. 51.

rofessor Curie's arm, showing a scar resulting fr
(Through the courtesy of the Success Company.)

RT and the immune system

- Lymphocytes are classically considered the most radiosensitive cells in the body, so RT is generally considered to be immunosuppressive
  - This has recently been called into question for tumour resident T-Cells (Arina, Nat Comm, 2019)
- In the lab, whole-body RT to animals is used to ablate bone-marrow before transplantation (sometimes in patients too)
- Despite this, multiple lines of evidence suggest that the immune system restricts tumour growth and contributes to positive therapy response after RT
- We use a lot of transplanted models in the laboratory, these are not ideal (Wisdom, Nat Comm, 2020)

RT impacts signaling in the TME in many ways



Elimination

Net loss of tumor cell number
Net tumor volume shrinkage
Net loss of tumor vascularity

Equilibrium

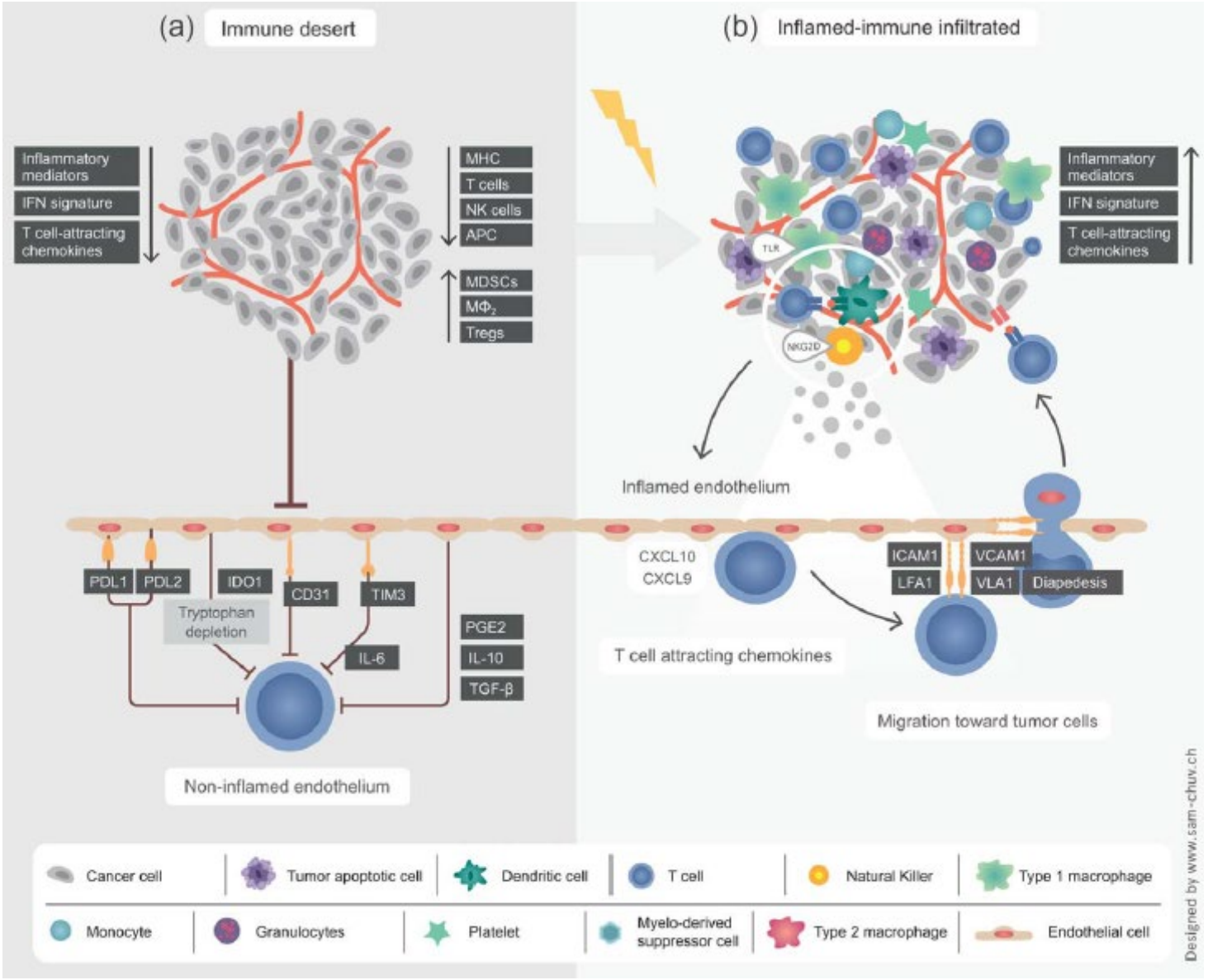
Little change in tumor cell number
Little change in tumor volume
Little change in tumor vascularity

Escape

Net gain of tumor cell number
Net gain in tumor volume
Net increase in tumor vascularity

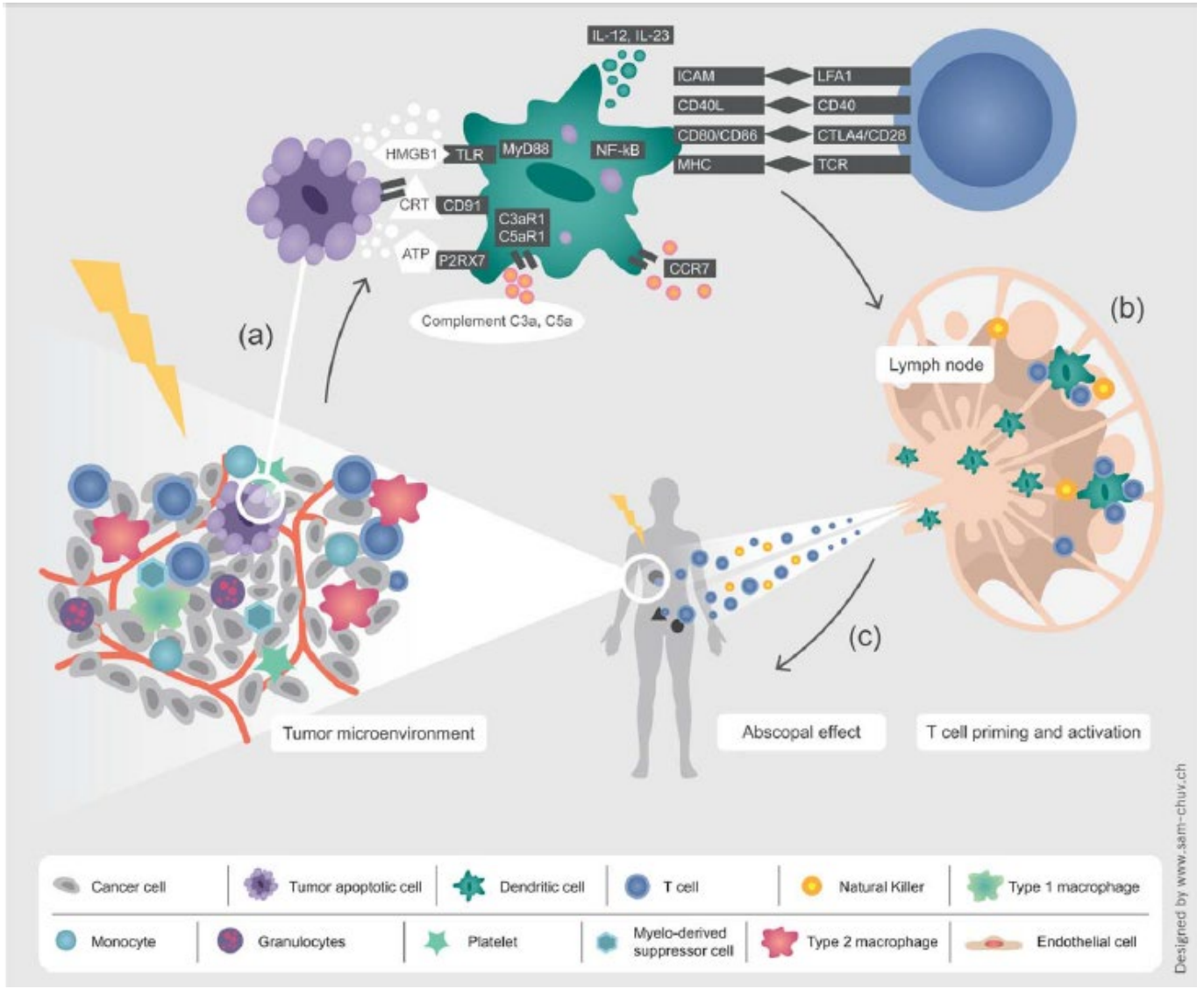
Burkholder, Biochimica et Biophysica Acta, 2014

RT impacts signaling in the TME in many ways



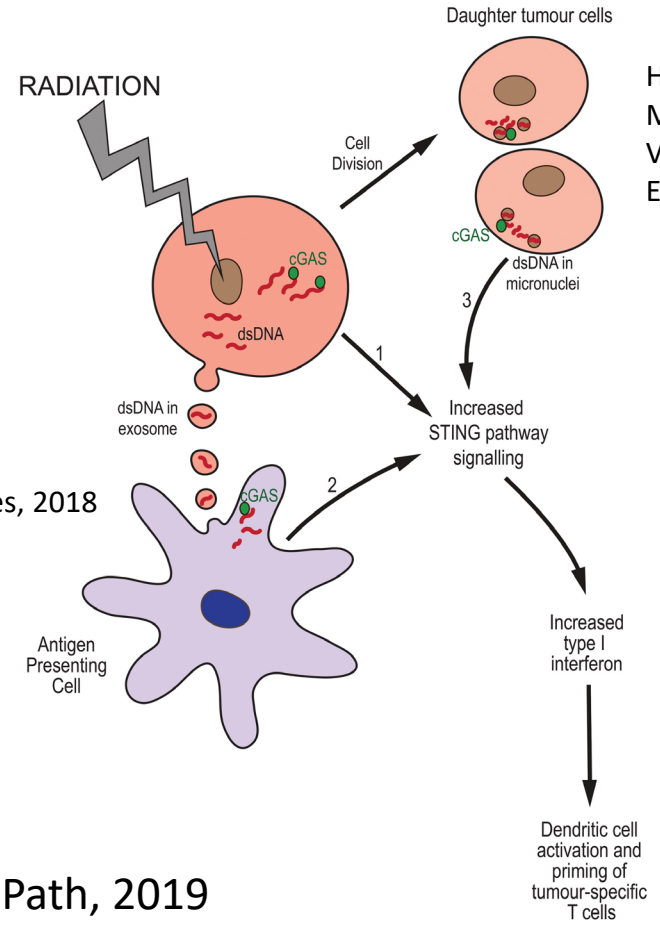
Herrera FG et al CA Cancer J Clin 2017

Immune mechanisms triggered by RT



Herrera FG et al CA Cancer J Clin 2017

DNA release after RT drives multiple immunogenic events

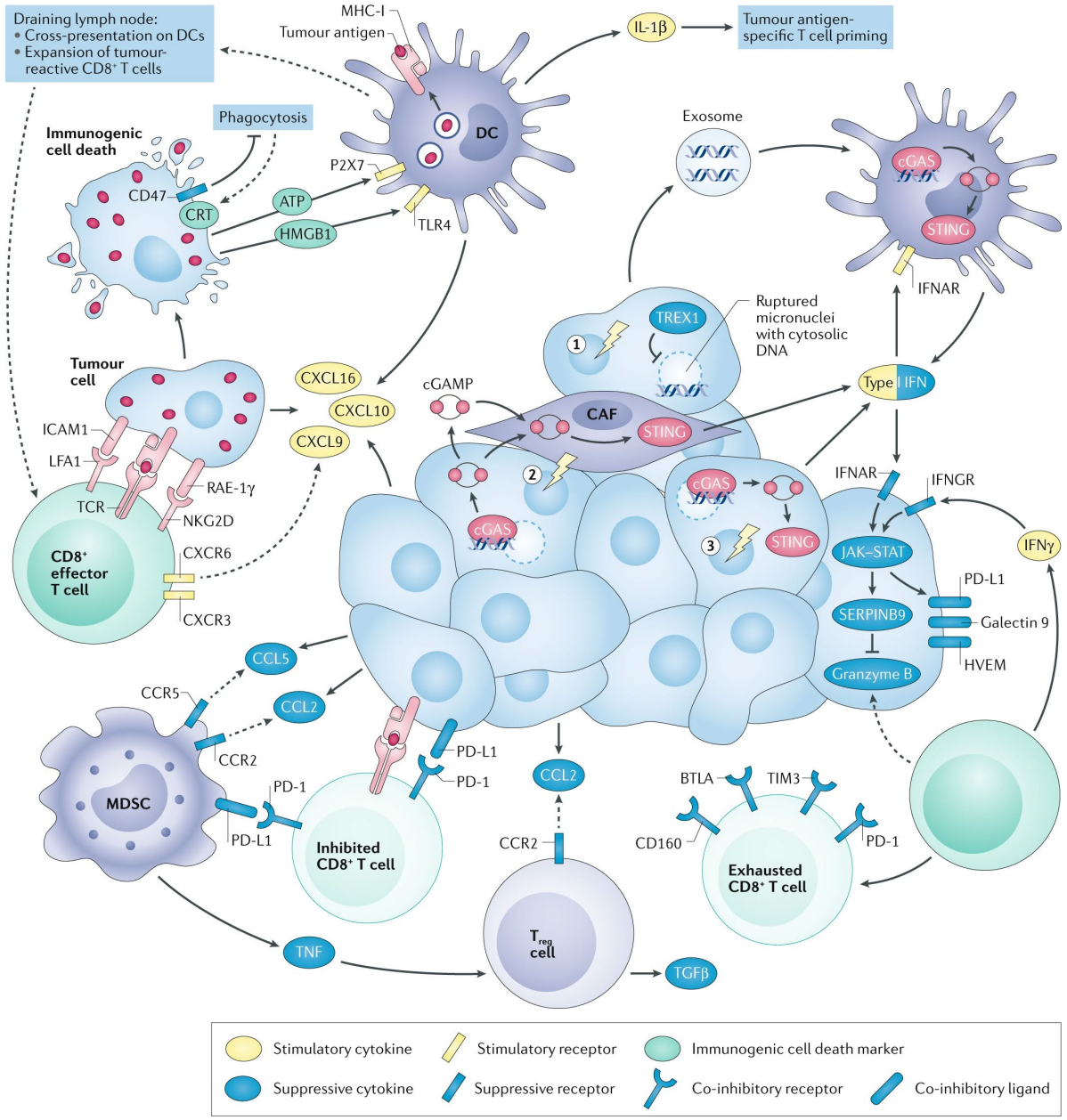


Harding, Nature, 2017
Mackenzie, Nature, 2017
Vanpouille-Box, Nat Comm, 2017
Etc.

Deng, Immunity, 2014
Woo, Immunity, 2014
Diamond, Cancer Immun Res, 2018

Wilkins, J of Path, 2019

Its not so simple immunologically…

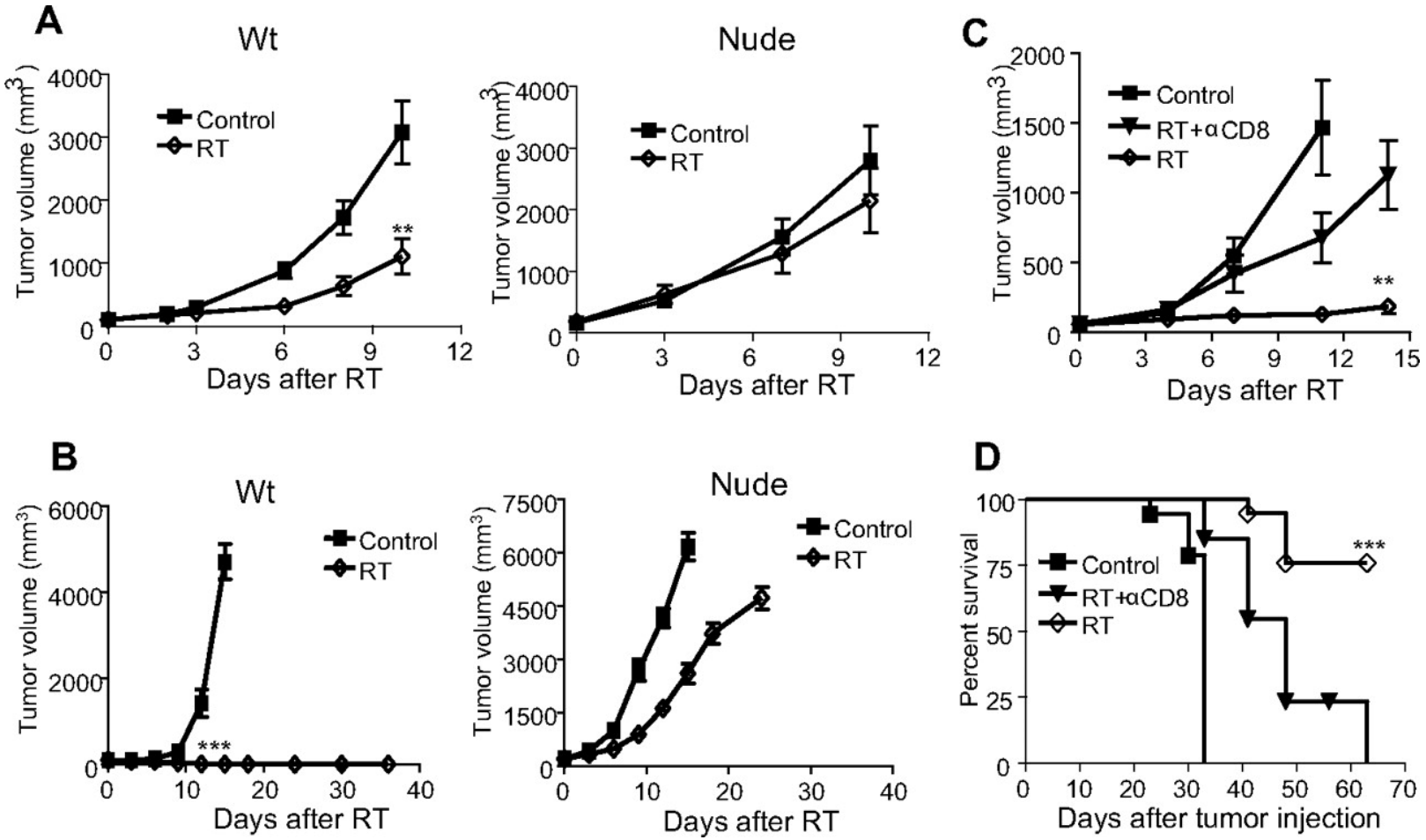


Plus…

-hypoxia
-cell death
-trafficking
-heterogeneity of tumour cells

McLaughlin, Nat Rev Cancer, 2020

Immune contributions to RT response

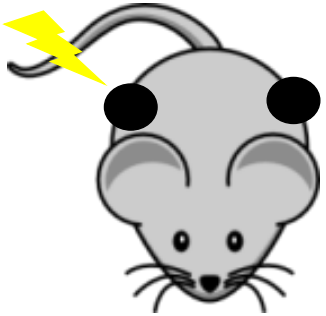


Lee, Blood, 2009

The abscopal effect

- An exceedingly rare clinical scenario where a tumour not subjected to therapy regresses as a result of local treatment to a distant tumour

Abscopal effect is driven by the immune system



Immune competent

Abscopal effect is driven by the immune system

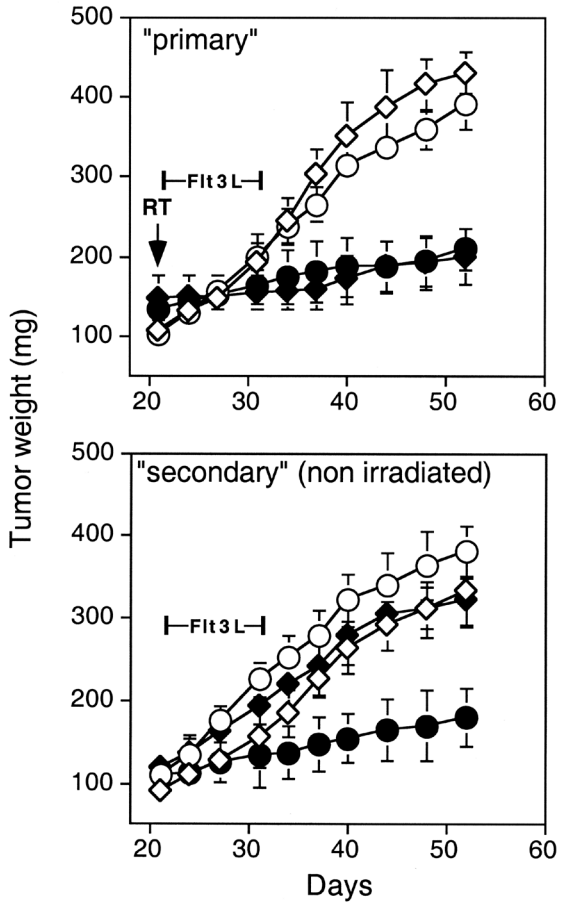
Immune competent

Abscopal effect is driven by the immune system

Immune competent

← Abscopal effect
RT + α-CTLA4
("Away From Target")

Dendritic cells are also important (as are MDSCs, NK, Tregs, etc.)



Demaria, IJROBP 2004

Clinical example of RT-IO combination

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Barker, M.D., Yoshiya Yamada, M.D., Jianda Yuan, M.D., Ph.D., Shigehisa Kitano, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasalan, B.S., Matthew Adamow, B.S., Erika Ritter, B.S., Christine Sedrak, B.S., Achim A. Jungbluth, M.D., Ramon Chua, B.S., Arvin S. Yang, M.D., Ph.D., Ruth-Ann Roman, R.N., Samuel Rosner, Brenna Benson, James P. Allison, Ph.D., Alexander M. Lesokhin, M.D., Sacha Gnjatic, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

N ENGL J MED 366;10 NEJM.ORG MARCH 8, 2012

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

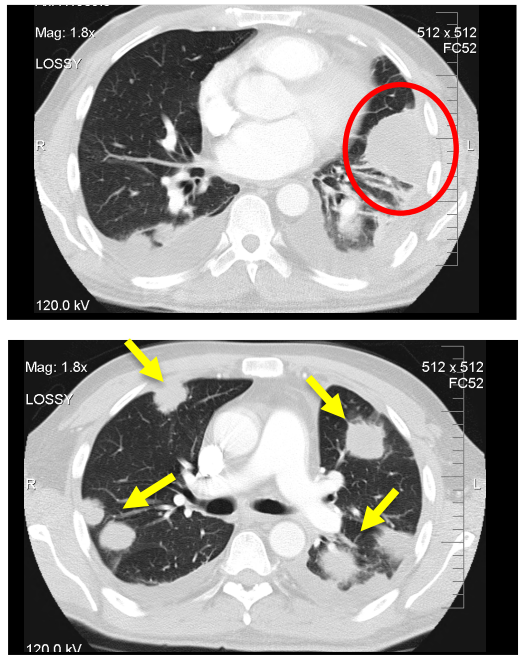
www.thelancet.com/oncology **Vol 16 July 2015**

UPenn Patient “0”

Irradiated Tumor

Abscopal Tumor

Baseline



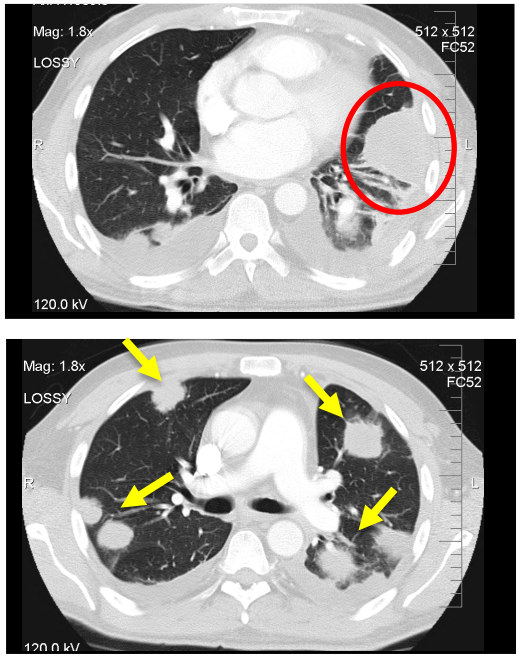
Slide courtesy of A. Minn (UPenn)
Postow, NEJM, 2012

UPenn Patient “0”

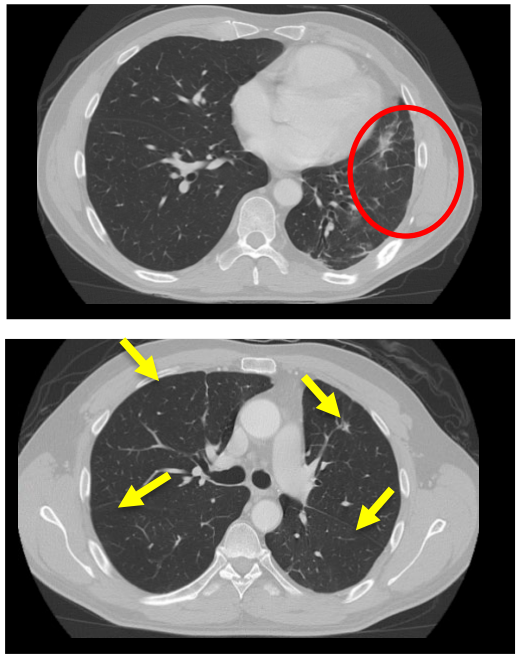
Irradiated Tumor

Abscopal Tumor

Baseline

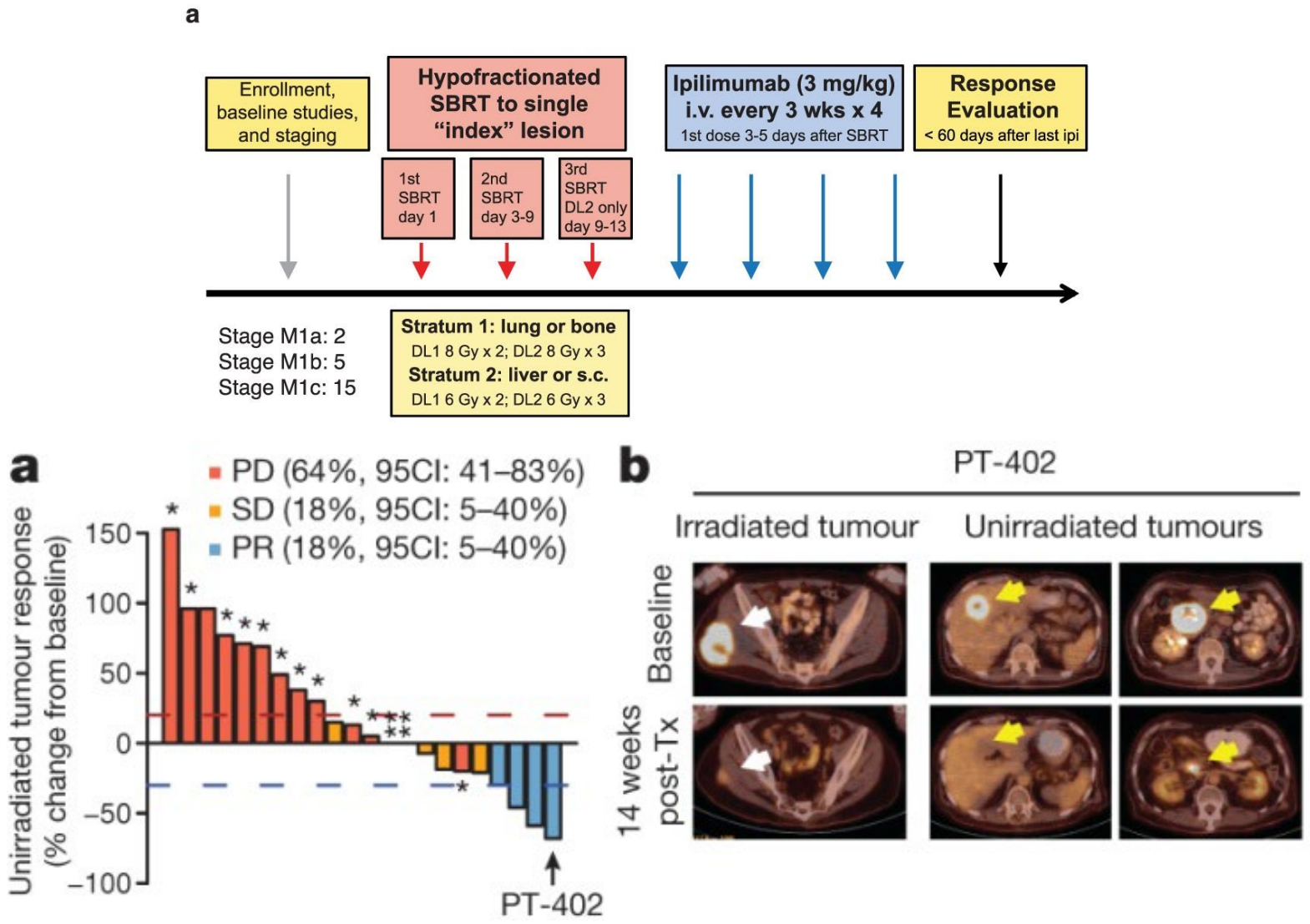


Post-Treatment



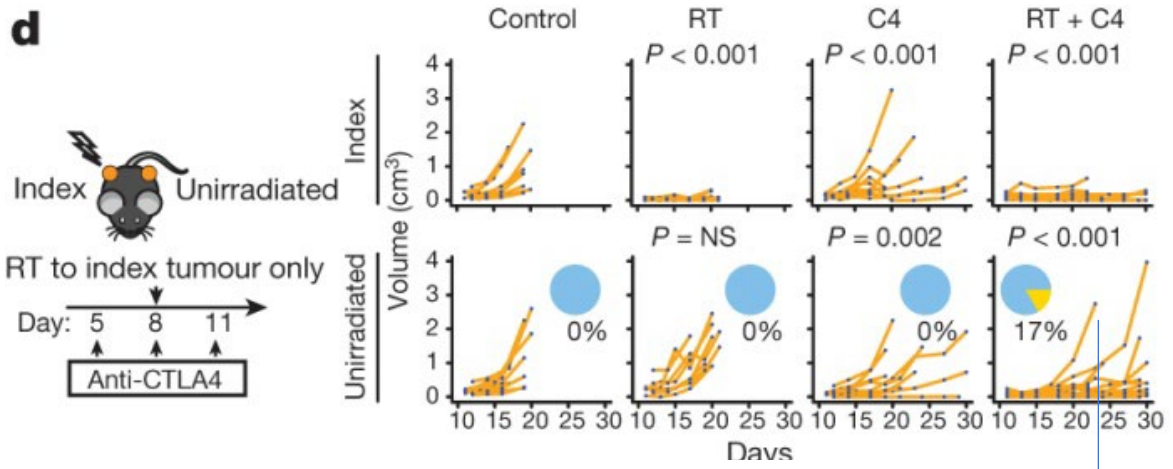
Slide courtesy of A. Minn (UPenn)
Postow, NEJM, 2012

Another UPenn example

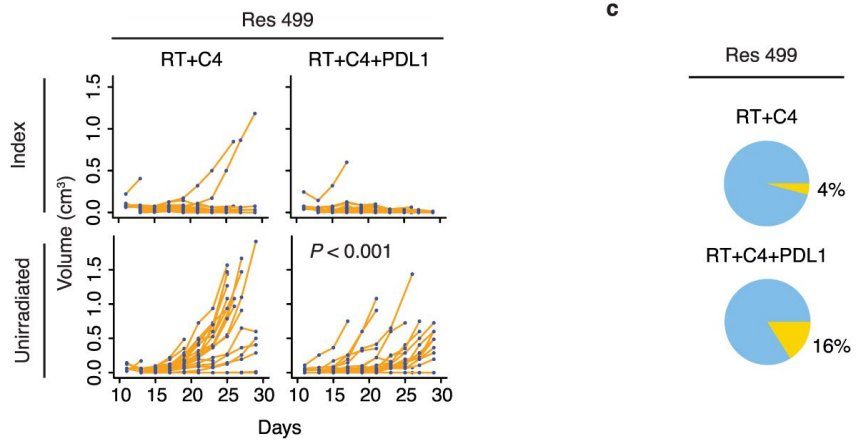


CT-S Victor *et al. Nature* doi:10.1038/nature14292

CTLA4 and PD1 combined ICB with RT



Derive resistant line (Res-499)
-Increased PD-L1



CT-S Victor *et al. Nature* doi:10.1038/nature14292

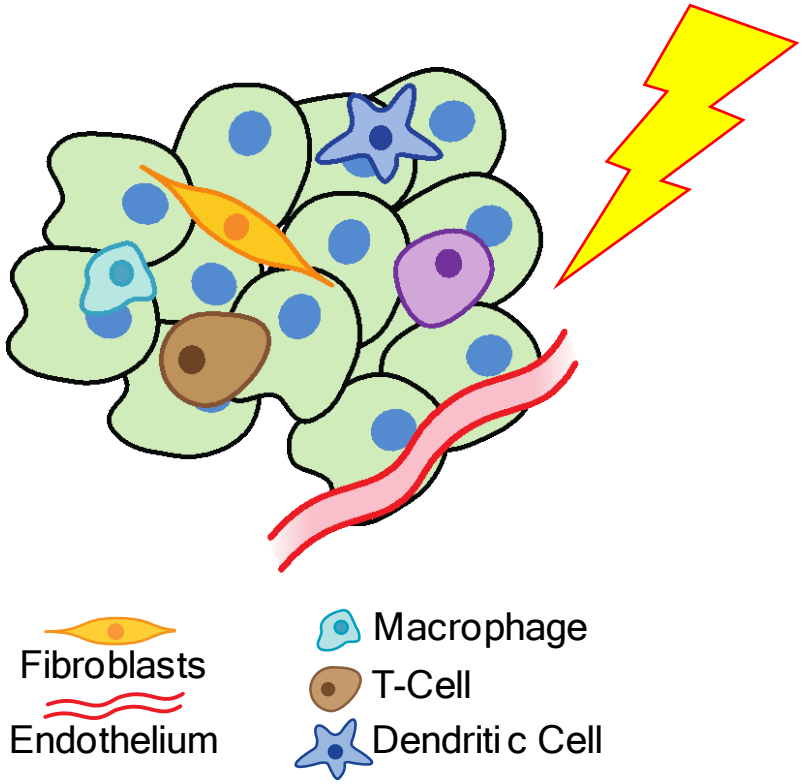
Notes on the abscopal effect

- Systemic response driven by RT+IO is tantalizing
  - This is an area that has received a huge amount of hype (>200 ongoing trials)
  - Evidence suggest abscopal effect remains rare in the clinic
    - Probably related to the models we use in the laboratory (Wisdom, Nat. Comm, 2020)

- Even if primary tumour responses are improved with RT+IO an opportunity to tailor treatment would be presented
  - (Lowering doses, less normal tissue, etc could all be explored)

Neoantigens

NEOANTIGENS are newly formed antigens that have not previously been recognized by the immune system

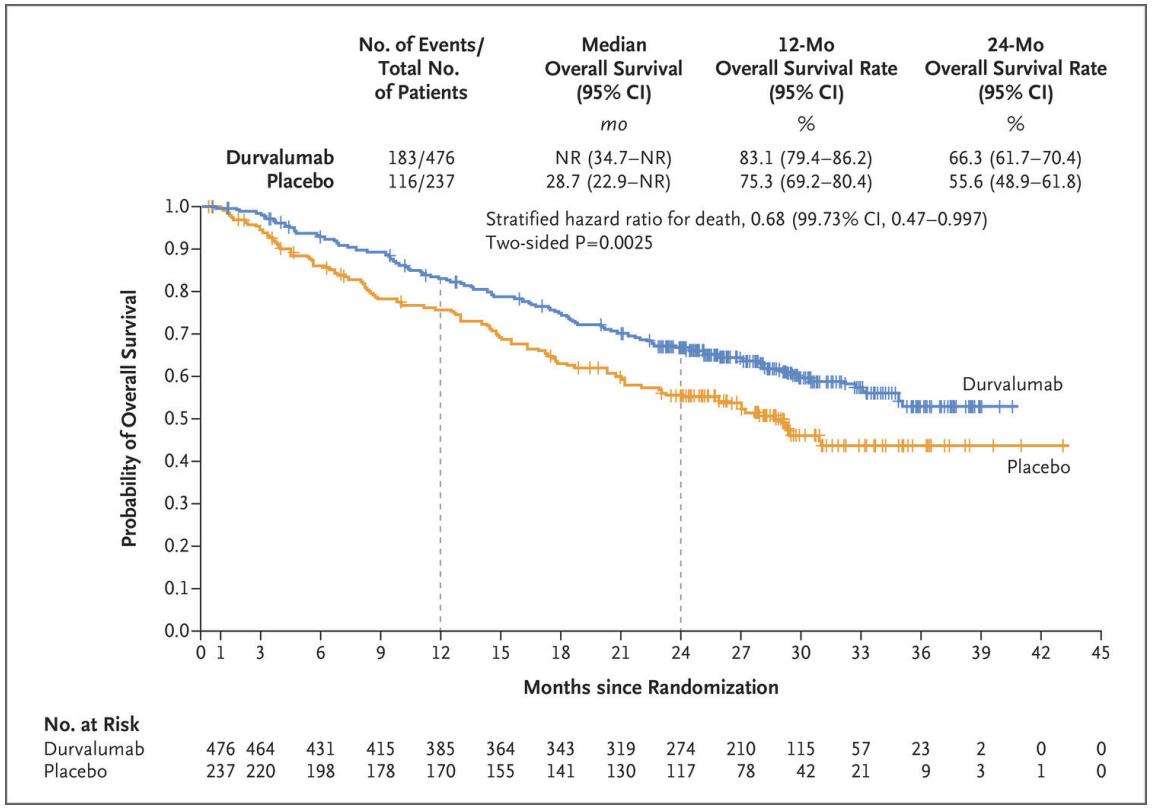


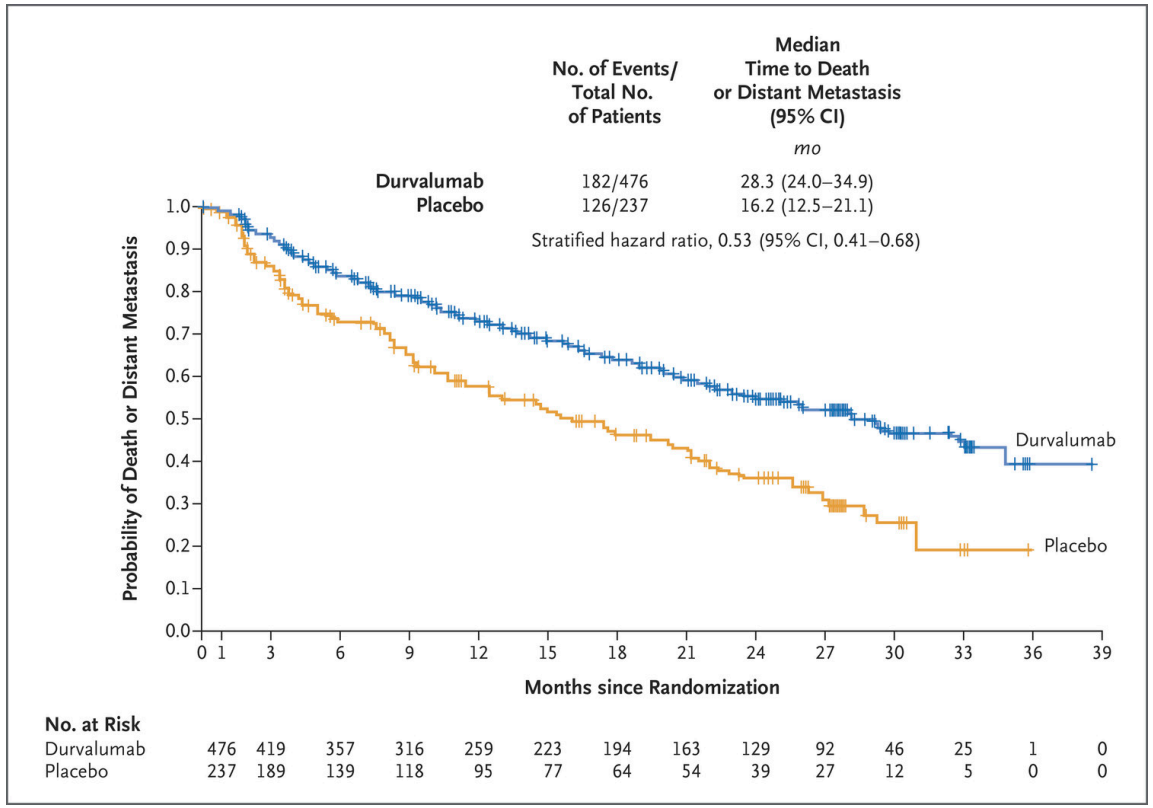
- We are irradiating tumour and normal tissues, where is specificity from?
- Idea is that tumour specific antigens are what drives the response because of central tolerance
- Open question as to whether RT induces novel antigens, improves presentation or just generates a favorable environment for immune activation (to pre-existing antigens)

Pacific trial

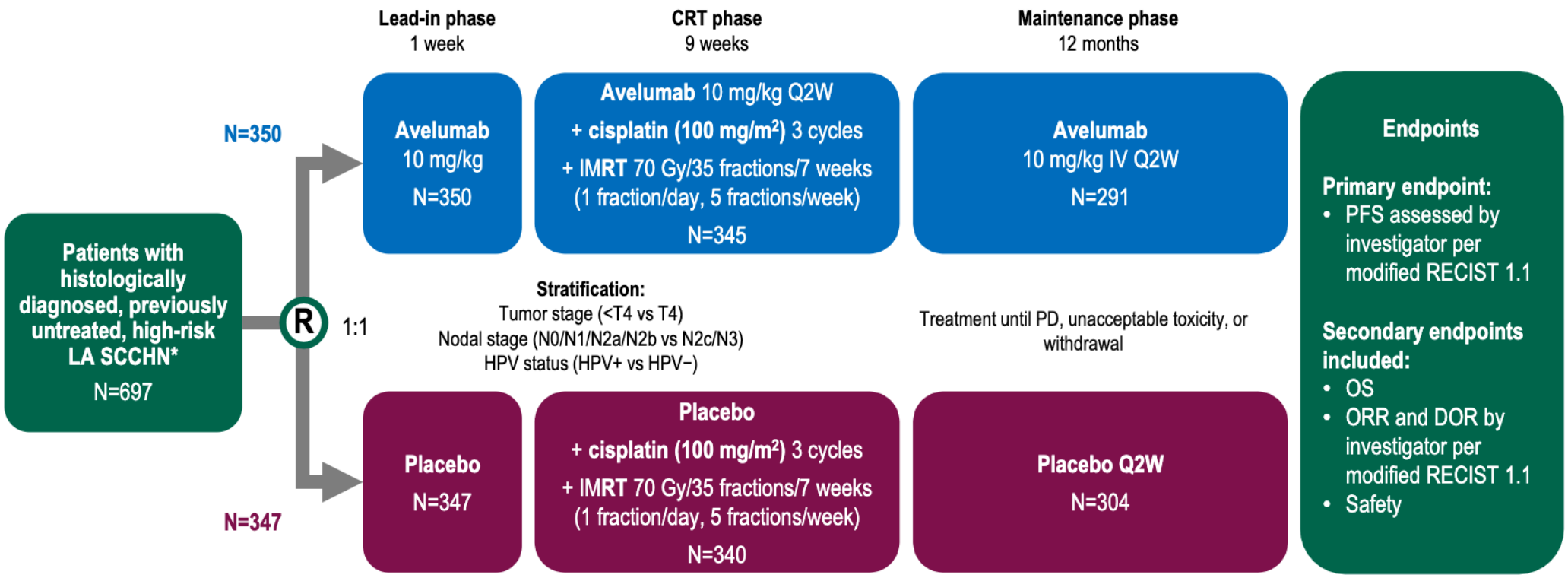
- Conducted in stage III NSCLC where standard of care is platinum-based chemotherapy + 60Gy fractionated RT
- Pacific is a randomized double-blind control trial in which Durvalumab (anti-PD1) was added to standard of care

Antonia, NEJM, 2018





Javelin H&N 100 study design



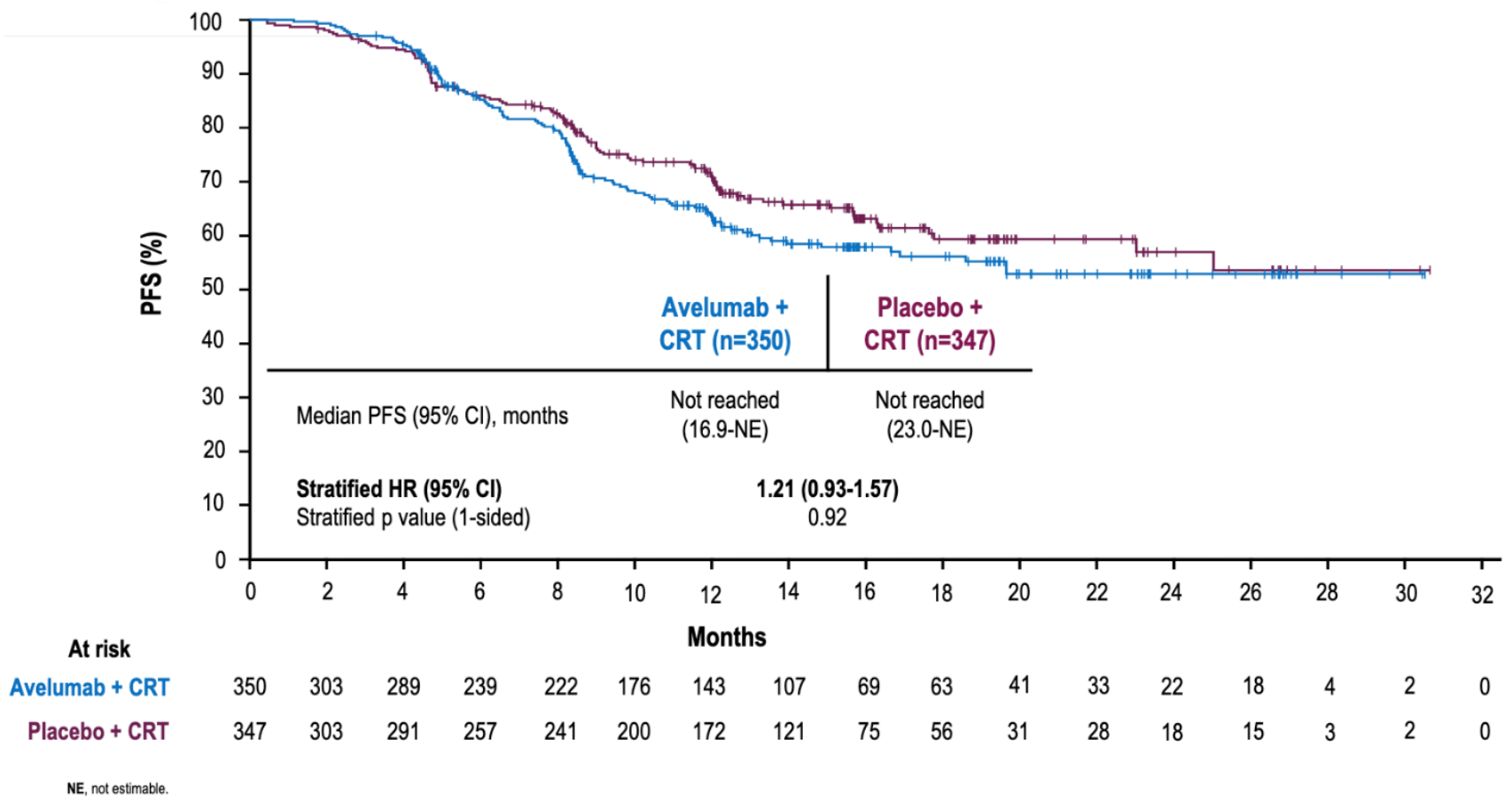
DOR, duration of response; **HPV**, human papillomavirus; **IMRT**, intensity-modulated radiation therapy; **IV**, intravenously; **ORR**, objective response rate; **OS**, overall survival; **PD**, progressive disease; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomized; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1.

* High-risk LA SCCHN (oral cavity, oropharynx, larynx, or hypopharynx): HPV-negative disease stage III, IVa, IVb; nonoropharyngeal HPV-positive disease stage III, IVa, IVb; HPV-positive oropharyngeal disease T4 or N2c or N3 (TNM staging per AJCC, 7th edition).

VIRTUAL 2020 ESMO congress

Javelin H&N 100 study design

Randomized, placebo-controlled, double-blind, phase 3 trial



NE, not estimable.

Javelin H&N 100 study design

Randomized, placebo-controlled, double-blind, phase 3 trial

Conclusions

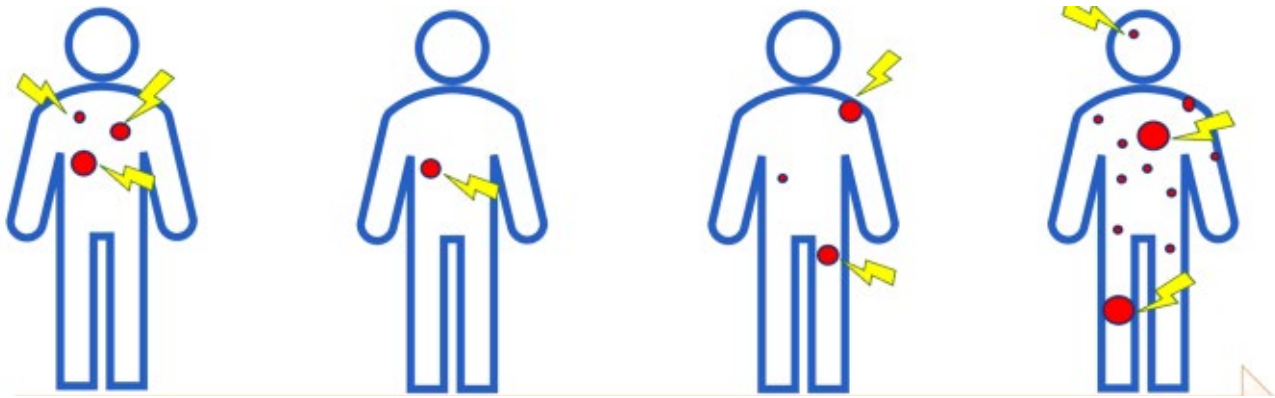
- JAVELIN Head & Neck 100 is the first randomized, phase 3 study of an immune checkpoint inhibitor combined with CRT in any tumor type
- The trial was stopped due to futility: avelumab + CRT followed by avelumab maintenance did not significantly improve PFS compared with placebo + CRT followed by placebo maintenance
- CRT exposure was consistent between the avelumab and placebo arms; a higher proportion of grade 3/4 TRAEs occurred in the avelumab arm (80%) vs the placebo arm (74%)
- Based on an exploratory analysis, the observed HR for PFS numerically favored avelumab + CRT in PD-L1–high tumors

Additional ongoing trials

- 200 ongoing (Arina, Nat Comm, 2019)
- Safety is a major consideration
  - In Pacific adverse events of grade 3-4 occurred in 30% and 26% of the Durvalumab and control groups, respectively.
  - 15% of patients in the durvalumab group and 10% in the controls had to discontinue the trial regime.
  - Nevertheless, in many settings toxicity is manageable and not necessarily worse than ICB alone
- Toxicity of RT can develop over many years, so full outcome including quality of life, is not likely for some time

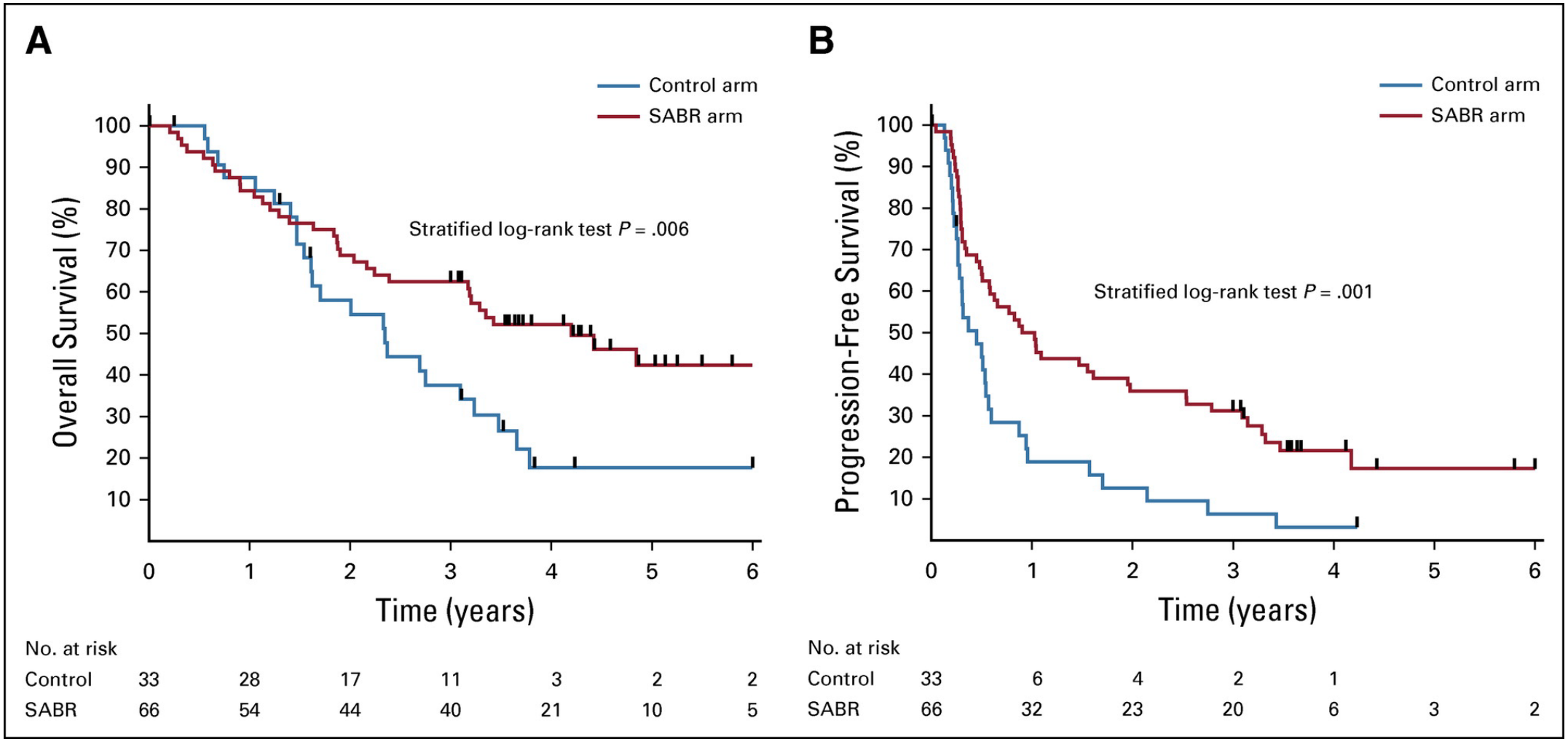
Oligometastatic disease

- In 1995 Hellman and Weichselbaum suggested that metastatic cancer is a spectrum of disease and that some forms may in fact be curable (JCI, 1995)
- Advances in RT mean that multiple lesions in the body can be targeted and potential eliminate cancer
- A means to reduce disease burden and suggested that this may be used in conjunction with IO to increase likelihood of cure (Pitroda, Lancet Oncology, 2019)



Beckham, BJC, 2020

SABR-COMET



Palma, Lancet, 2019 and JCO 2020

VOLUME 36 · NUMBER 16 · JUNE 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

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

ABSTRACT

Purpose

Stereotactic body radiotherapy (SBRT) may stimulate innate and adaptive immunity to augment immunotherapy response. Multisite SBRT is an emerging paradigm for treating metastatic disease. Anti-PD-1–treatment outcomes may be improved with lower disease burden. In this context, we conducted a phase I study to evaluate the safety of pembrolizumab with multisite SBRT in patients with metastatic solid tumors.

Patients and Methods

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. Pre- and post-SBRT biopsy specimens were analyzed in a subset of patients to quantify interferon-γ–induced gene expression.

Results

A total of 79 patients were enrolled; three patients did not receive any treatment and three patients only received SBRT. Patients included in the analysis were treated with SBRT and at least one cycle of pembrolizumab. Most (94.5%) of patients received SBRT to two metastases. Median follow-up for toxicity was 5.5 months (interquartile range, 3.3 to 8.1 months). Six patients experienced dose-limiting toxicities with no radiation dose reductions. In the 68 patients with imaging follow-up, the overall objective response rate was 13.2%. Median overall survival was 9.6 months (95% CI, 6.5 months to undetermined) and median progression-free survival was 3.1 months (95% CI, 2.9 to 3.4 months). Expression of interferon-γ–associated genes from post–SBRT tumor biopsy specimens significantly correlated with nonirradiated tumor response.

Conclusion

Multisite SBRT followed by pembrolizumab was well tolerated with acceptable toxicity. Additional studies exploring the clinical benefit and predictive biomarkers of combined multisite SBRT and PD-1–directed immunotherapy are warranted.

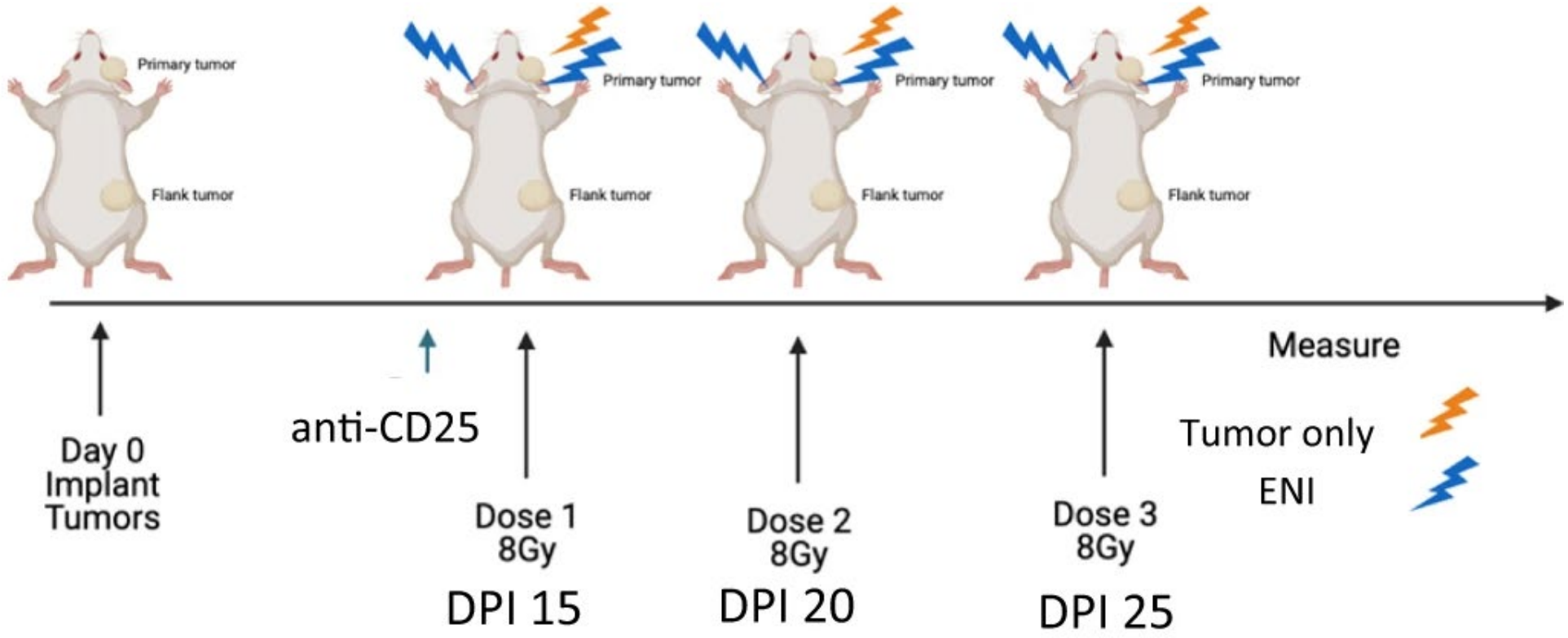
Neoplasia. 2022 Mar 15;27:100782. doi: 10.1016/j.neo.2022.100782

Table 2.

Ongoing and Future Phase III Trials Investigating the Addition of Metastasis-Directed Radiotherapy to Immune Checkpoint Blockade.

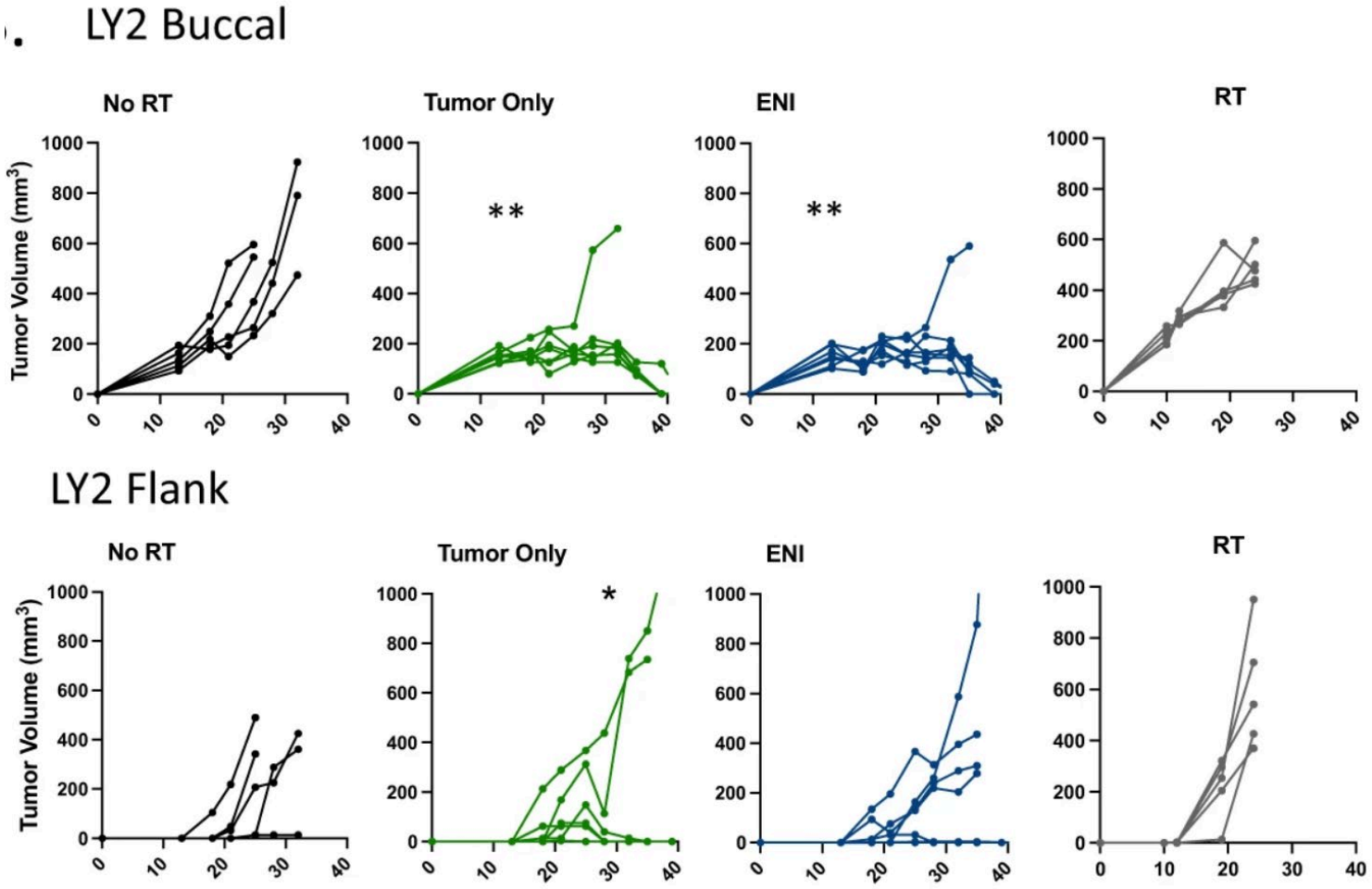
ClinicalTrials.gov Identifier	Cancer Type	Trial Design	Metastasis Details (Upper Limit; Stratification)	Projected Enrollment	Date Open -Est. Completion	Primary Endpoint
NCT03867175	NSCLC	Pembrolizumab ± RT	≤ 8; 1-3 vs. 4-6	112	Jun. 2019 - Dec. 2027	PFS
NCT04944914	NPX	Camrelizumab ± RT	≤ 5, ≤ 3 in one organ; –	188	Jun. 2021 - Jun. 2026	PFS
NCT04402788	SCLC	Atezolizumab ± RT	≤ 10, ≤ 3 hepatic; high vs. low burden[1]	138	Aug. 2020 - Aug. 2027	PFS, OS[2]
NCT04929041	NSCLC (PD-L1 < 1%)	Chemo-IO[3] ± RT	–; –	100	Jan. 2022 - Dec. 2027	PFS, OS[2]
NCT03391869	NSCLC	Ipilimumab, nivolumab ± LT[4]	–; oligometastatic[5]	360	Dec. 2017 - Dec. 2022	OS
NCT04747054	HNSCC	Pembrolizumab ± RT	–; –	130	Jun. 2021 - Jun. 2029	PFS
NCT03827577	NSCLC	Chemo-IO[6] ± LT[7]	–; 1 vs. 2-3, 1-3 vs. > 3	195	Oct. 2019 - Sep. 2022	OS
NCT03774732	NSCLC	Chemo-IO[8] ± RT	–; –	460	Mar. 2019-	OS

RT delivery: Nodes matter?



RT of only the tumour, sparing lymph nodes modestly increased response Darragh, Nat. Comm, 2022

RT delivery: Nodes matter?



Darragh, Nat. Comm, 2022

Also see:

Translational Cancer Mechanisms and Therapy

Clinical Cancer Research

Elective Nodal Irradiation Attenuates the Combinatorial Efficacy of Stereotactic Radiation Therapy and Immunotherapy

Ariel E. Marciscano[1], Ali Ghasemzadeh[2], Thomas R. Nirschl[2], Debebe Theodros[2], Christina M. Kochel[2], Brian J. Francica[2], Yuki Muroyama[2], Robert A. Anders[2,3], Andrew B. Sharabi[4], Esteban Velarde[1], Wendy Mao[2], Kunal R. Chaudhary[5], Matthew G. Chaimowitz[6], John Wong[1], Mark J. Selby[7], Kent B. Thudium[7], Alan J. Korman[7], David Ulmert[8], Daniel L.J. Thorek[2,9], Theodore L. DeWeese[1,2], and Charles G. Drake[2,6]

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CLINICAL INVESTIGATION

The Role of Elective Nodal Irradiation in Treating Clinically Node-Negative Sinonasal Squamous Cell Carcinoma

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Received May 31, 2023; Accepted for publication May 31, 2024

Purpose: This study aims to examine the role of elective nodal irradiation (ENI) in clinically node-negative (cN0) sinonasal squamous cell carcinoma (SNSCC) and to define the optimal radiation fields for ENI.

Methods and Materials: We retrospectively reviewed 368 patients with cN0 SNSCC treated between 2009 and 2021. The study evaluated the impact of ENI on overall survival, progression-free survival, regional failure–free survival, and distant metastasis–free survival, along with the coverage areas of ENI.

Results: The majority of patients underwent surgery (316/368, 85.9%), with 276 of 368 (75%) having tumors in the maxillary sinus or nasal cavity and 249 of 368 (67.7%) presenting with T4 disease. Additionally, in 119 of the 368 cases (32.3%), tumors were poorly differentiated. The 5-year overall survival, progression-free survival, regional failure–free survival, and distant metastasis–free survival rates were 59.3%, 54.0%, 57.6%, and 58.8%, respectively. ENI was performed in 217 patients (59%), with 16 experiencing neck relapse during follow-up. Although ENI did not enhance survival rates, it significantly reduced the overall regional failure rate (7.9% vs 1.8%; $\chi^2 = 7.98$; $P < .01$) and the cumulative incidence of regional failure ($P = .045$). Additionally, the subgroups with maxillary sinus origin (2.3% vs 13.5%; $P = .025$), T4 stage (1.8% vs 8.5%; $P = .028$), and poor differentiation (2.4% vs 13.5%; $P = .029$) had higher cumulative incidences of regional failure in patients without ENI. No significant difference was observed in survival and regional failure rates between patients treated with ENI to levels Ib and II with or without level III, as well as between cN0 patients with nonmidline crossing lesions receiving unilateral or bilateral ENI.

Conclusions: Despite no survival benefit, ENI significantly decreases the regional failure rate in patients with cN0 SNSCC. For primary lesions not crossing the midline, ipsilateral ENI targeting levels Ib and II proves to be an effective strategy.

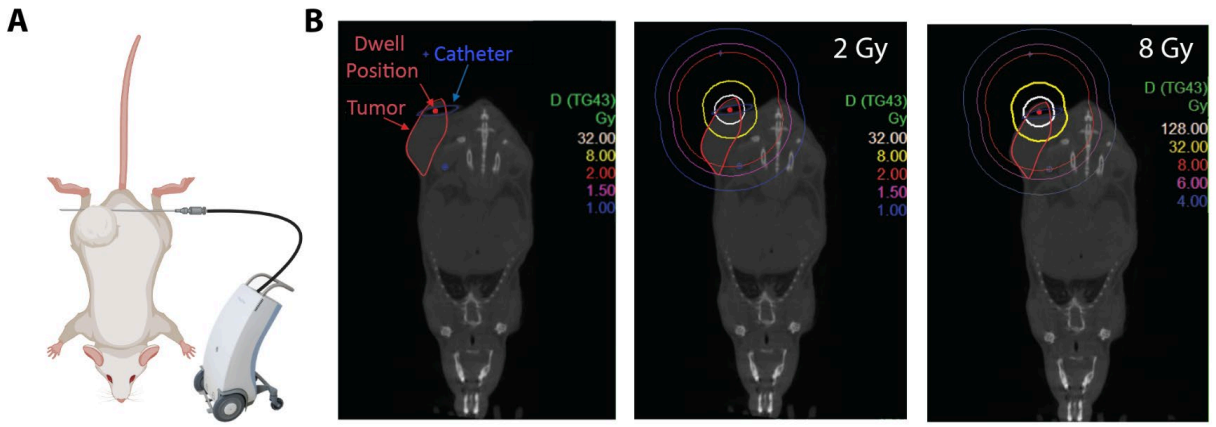
Spatial fractionation can preserve/enhance immune response

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

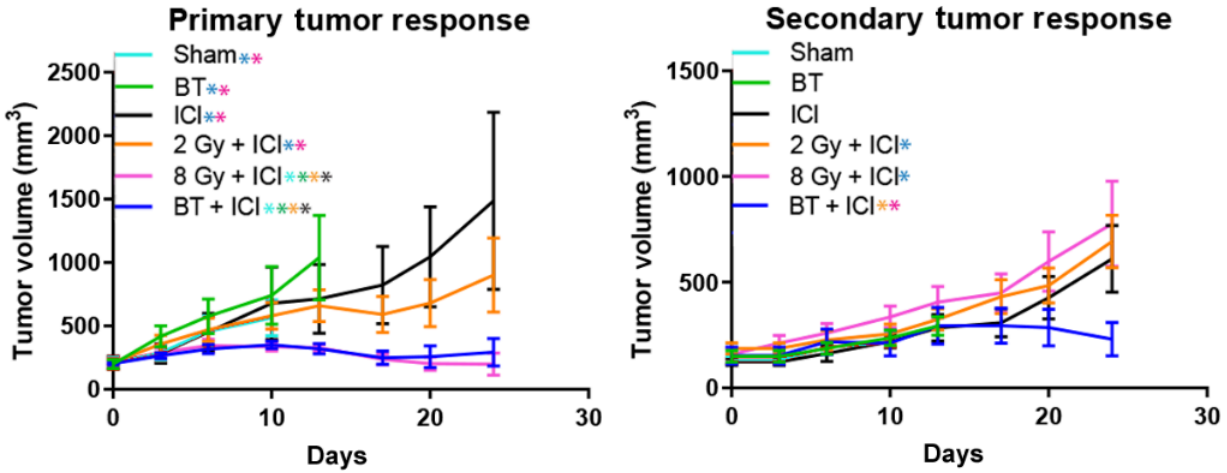
CANCER

Intratumoral radiation dose heterogeneity augments antitumor immunity in mice and primes responses to checkpoint blockade

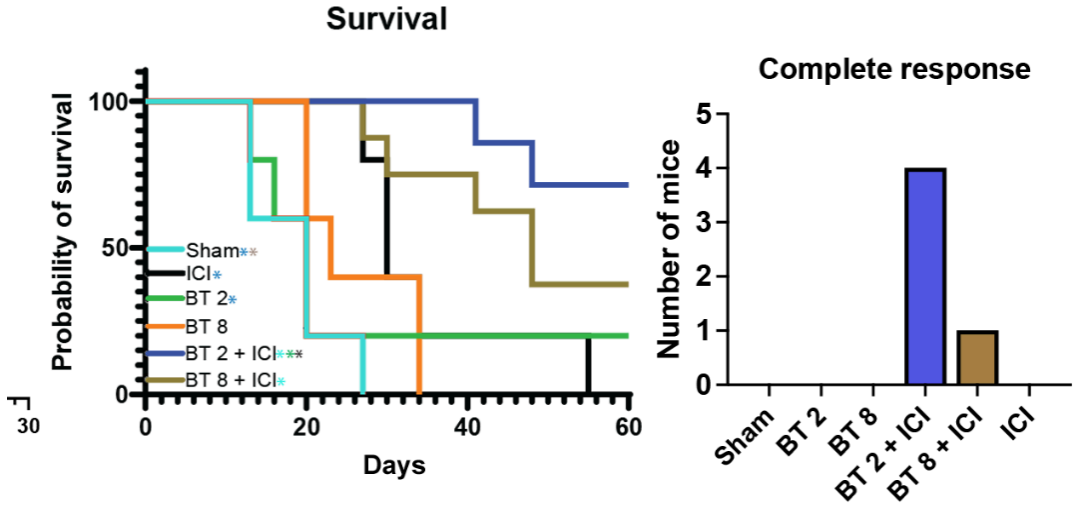
Justin C. Jagodinsky[1,2], Jessica M. Vera[3,4], Won Jong Jin[1], Amanda G. Shea[1], Paul A. Clark[1], Raghava N. Sriramaneni[1], Thomas C. Havighurst[3], Ishan Chakravarthy[1], Raad H. Allawi[1], KyungMann Kim[3], Paul M. Harari[1], Paul M. Sondel[1,5], Michael A. Newton[3], Marka R. Crittenden[6,7], Michael J. Gough[6], Jessica R. Miller[1], Irene M. Ong[3,8], Zachary S. Morris[1]*



B78 model



MyC-CaP model



Summary

- Classical DNA damage responses influence cytokine signalling post-RT
- RT-induced cytokines alter the TME in myriad (and variable) ways
- Signaling between components of the TME are important, but incompletely understood
- Abscopal responses remain rare in the “immunotherapy era”
- Tumour site(s), dose regime, drug choice all remain open areas of inquiry
- ICB is not like flicking a switch—there is plenty of promise here, but not universally effective today

Questions?