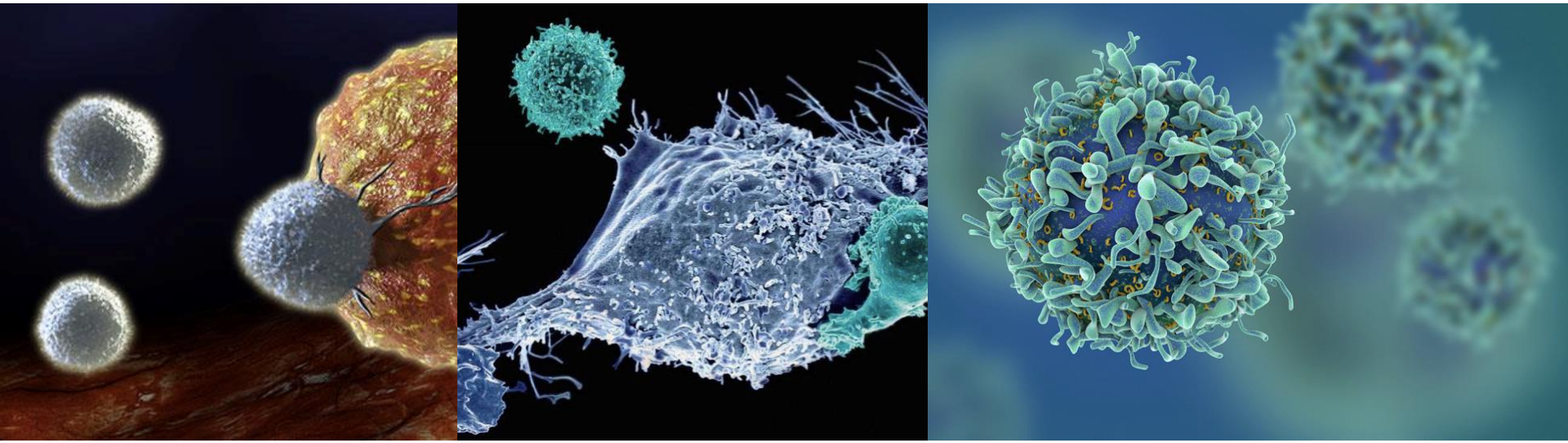
Optimizing Immunotherapy with Radiation



Megan E. Daly MD

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Megan Daly, MD

Optimizing Immunotherapy with Radiation

Relevant financial relationships in the past twelve months by presenter or spouse/partner.

Grant/research support: Research Funding, EMD Serono

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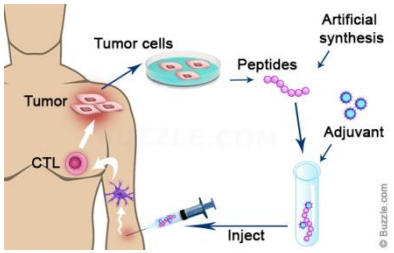
Overview

- Background: Rationale for Radiotherapy/Immunotherapy Combinatorial Strategies
  - Mechanisms of Synergy
- Radiation: Do target organ, sequencing with drug, dose, and fractionation matter?
- Current and Emerging Clinical Evidence
- Next Directions

Classes of Immunotherapy

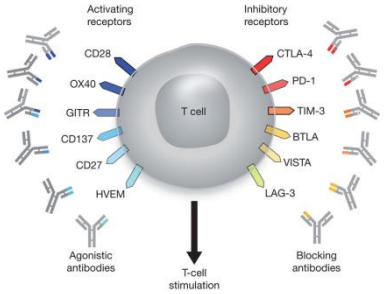
Vaccinations

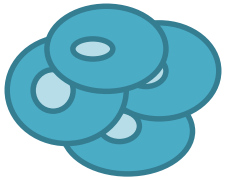
Similar to infection vaccines, retrains immune cells to recognize tumor associated antigens



Strong Immune Stimulants

General activation of the immune system in a non-specific manner

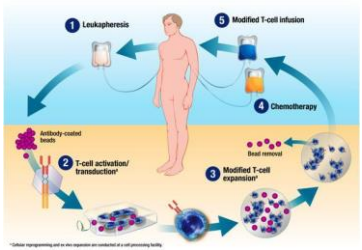




Tumor

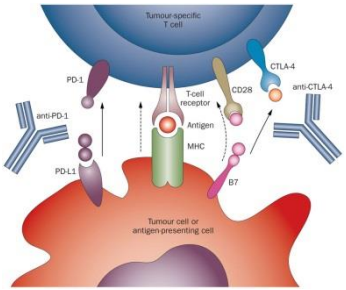
Chimeric Antigen Receptor (CAR) NK & T Cell Therapy

Empowering T cells and NK cells with engineered receptors to recognize cancer, then infuse back



Inhibitory Checkpoint Blockade

Releases the brakes of the immune system and/or steps on the gas



Nature Reviews Immunology 10, 580-593 (August 2010)

Immunotherapy Combinatorial Strategies

Approaches

- Dual Immunotherapy
  - Dual checkpoint blockade
  - Checkpoint blockade/stimulatory agonist
  - Other
- Immunotherapy/Chemotherapy
- Immunotherapy/Radiotherapy

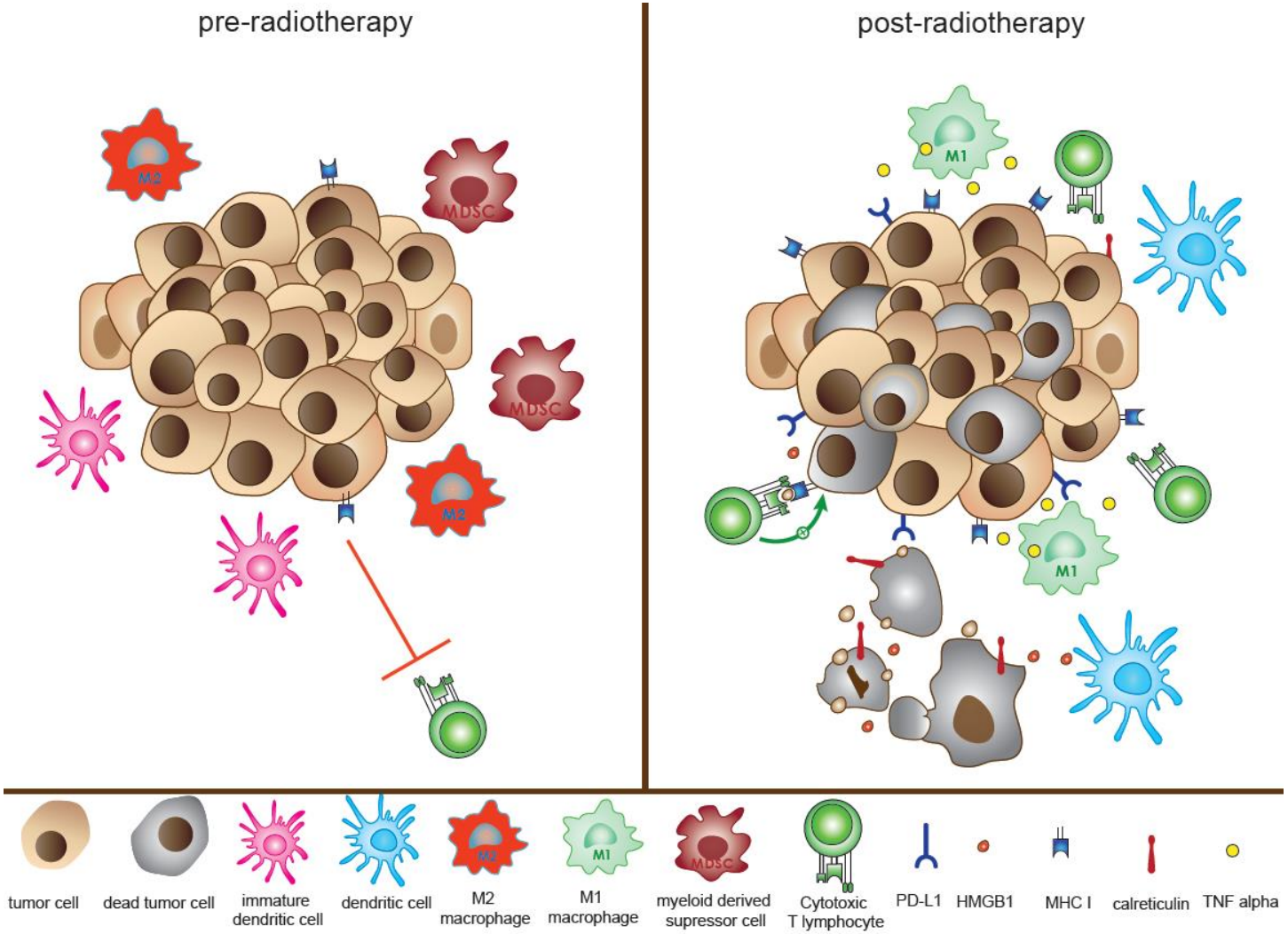
Open Questions for IO/RT strategies

- Sequencing/Timing
- Optimization
  - Radiation dose, fractionation, and site
- Synergistic toxicities

Rationale for Radiation/Immunotherapy Combinatorial Strategies

- Tumor debulking/release of tumor antigens
- Upregulation of immunogenic cell surface markers
- Secretion of cytokines/danger signals
- Induction of immunogenic cell death
- Increased homing of immune cells to tumor
- Improved antigen presentation by APCs
- Depletion of immunosuppressive cells
- Shifting TAM polarization to M1
- Up-regulation of cell-surface PD-L1

Mechanisms of Radiation-Induced Immune Activation



Daly ME, Monjazeb AM, Kelly K. Journal of Thoracic Oncology 2015

Immunotherapy/RT Combinatorial Strategies: Current Status

- Preclinical Data
  - Effects of RT on the immune system dependent on irradiated site
  - Data for dose and fractionation
  - Data for timing of IO and RT

- Retrospective Clinical Data
  - Case reports/series
  - Secondary analyses of prospective trials

- Prospective Clinical Trials
  - Metastatic Disease
  - Localized Disease

Effects of RT on the Immune System

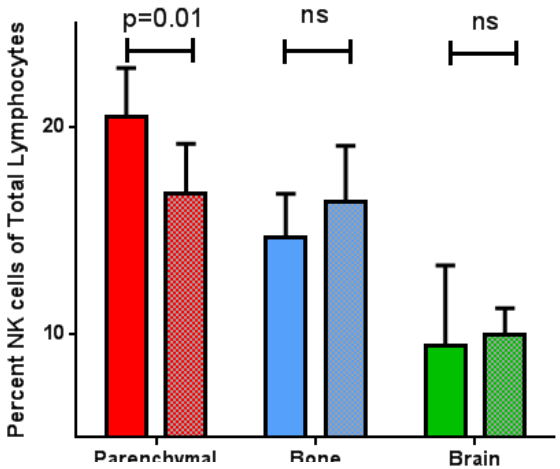
• RT traditionally thought of as immunosuppressive, related to irradiation of marrow and circulating blood

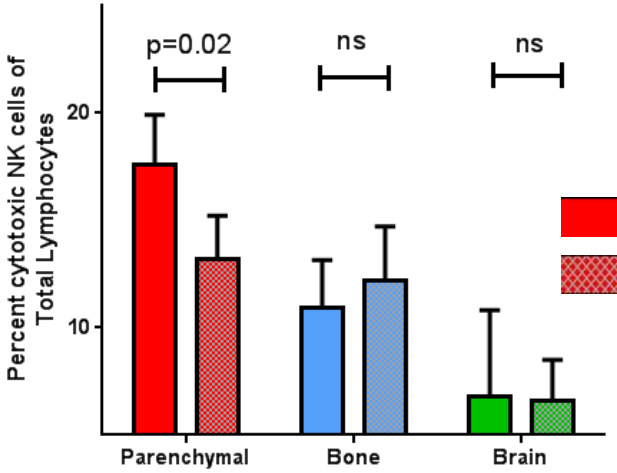
• However, effects of focal, high-dose radiation appear to be more complex

- Pilot study evaluating effects of SBRT on peripheral blood immunophenotype and cytokine/chemokine profiles from 40 patients treated with SBRT to lung, liver, bone, or brain identified changes in NK and T cell subsite that appear to related to irradiated site
- Obtained peripheral blood samples pre- and 1 week post-SBRT

McGee H et al. Stereotactic Ablative Radiation Therapy Induces Systemic Differences in Peripheral Blood Immunophenotype Dependent on Irradiated Site. IJROBP Aug 2018

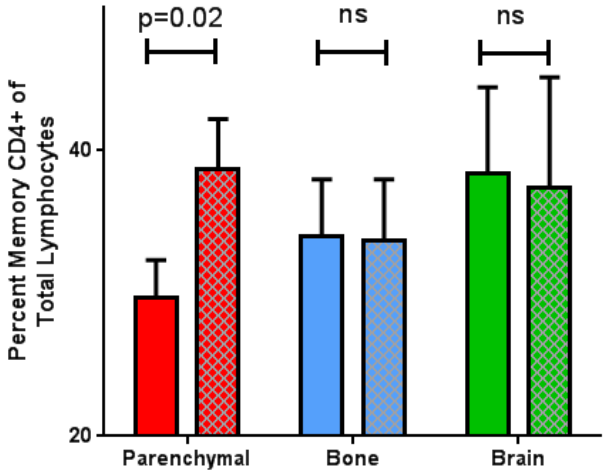
Effects of RT on the Immune System

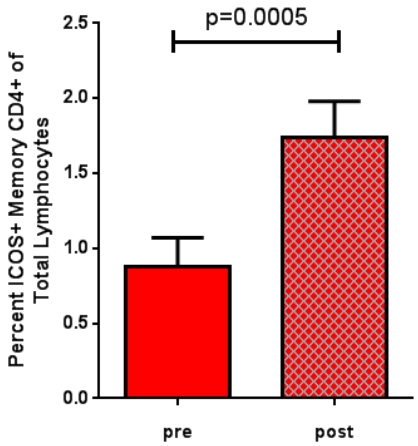


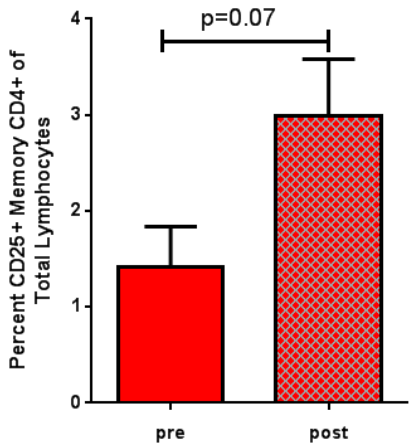


Pre-RT (solid)

Post-RT (hashed)







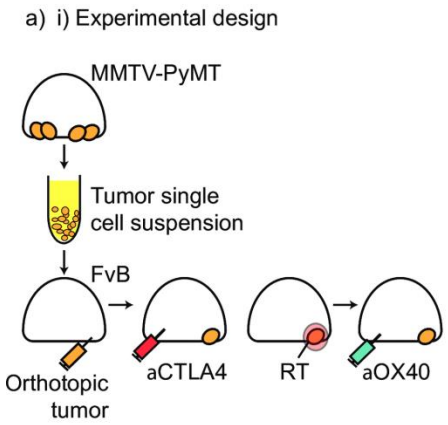
McGee H et al. Stereotactic Ablative Radiation Therapy Induces Systemic Differences in Peripheral Blood Immunophenotype Dependent on Irradiated Site. IJROBP Aug 2018

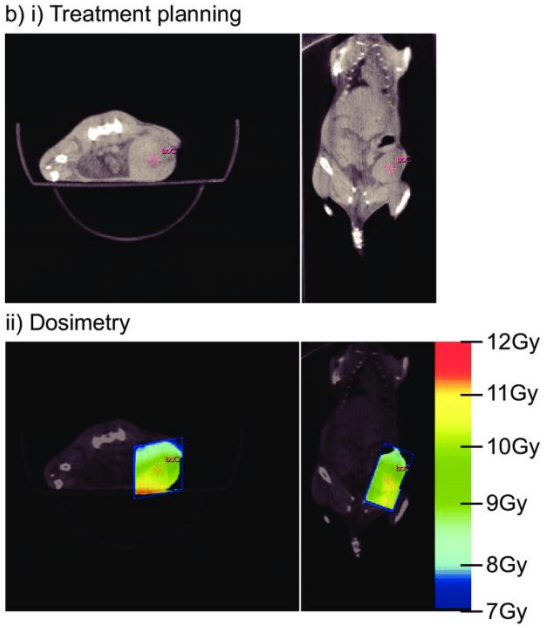
Does Dose/Fractionation Matter?

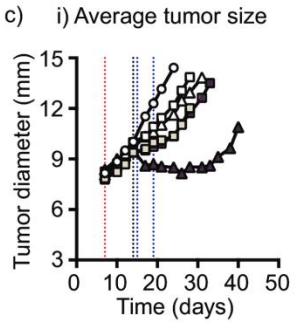
Study	Model	Dose/Treatment	Results
Lugade *et al*, 2005	Murine; heterotopic melanoma	• 15 Gy x 1 *or* • 3 Gy x 5	• Improved tumor control with 15 Gy • Increased immunogenic APCs with 15 Gy x 1 • Increased infiltration of immune cells at day 14 with 15 Gy x 1
Schaue *et al*, 2012	Murine; heterotopic melanoma	• 15 Gy in 1, 2, 3, or 5 fx • Single fx of 5, 7.5, 10, or 15 Gy	• 15 Gy in 2 fractions provided the best tumor control and tumor immunity while maintaining low Treg numbers.
Dovedi *et al*, 2013	Murine lymphoma model	TLR7 agonist + • 10 Gy x 1 *or* • 2 Gy x 5	• Fractionation enhanced tumor response mouse and survival as compared to single fraction
Dewan *et al*, 2009	Murine breast model, 2 sites	Anti-CTLA4 + • 20 Gy x 1 • 8 Gy x 3 • 6 Gy x 5	• Anti-CTLA4 + 8 Gy x 3 or 6 Gy x 5 generated abscopal effect in unirradiated tumor. • No effect for 20 Gy x 1
Verbrugge et al 2012	Murine triple negative breast model	• Anti CD137/anti-PD-1 • 4 Gy x 4 • 4 Gy x 5 • 12 Gy x 1	• 12 Gy x 1 100% response • 4 Gy x 4 40% response • 4 Gy x 5 80% response

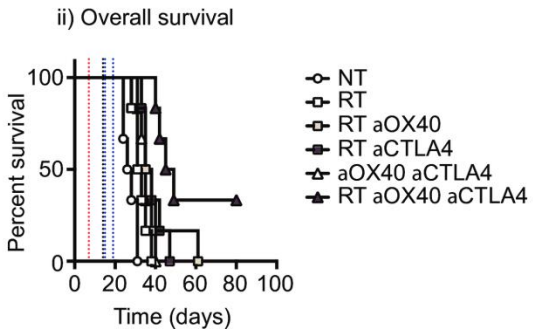
Does Timing Matter?

- Tumor bearing mice were treated with 20 Gy RT with either anti-CTLA-4 or OX40 agonist antibody
- Anti-CTLA-4 was most effective when given prior to RT
- OX40 agonist was most effective when delivered following RT
- Suggests optimal timing of immunotherapy and RT depends on mechanism of immunotherapy action





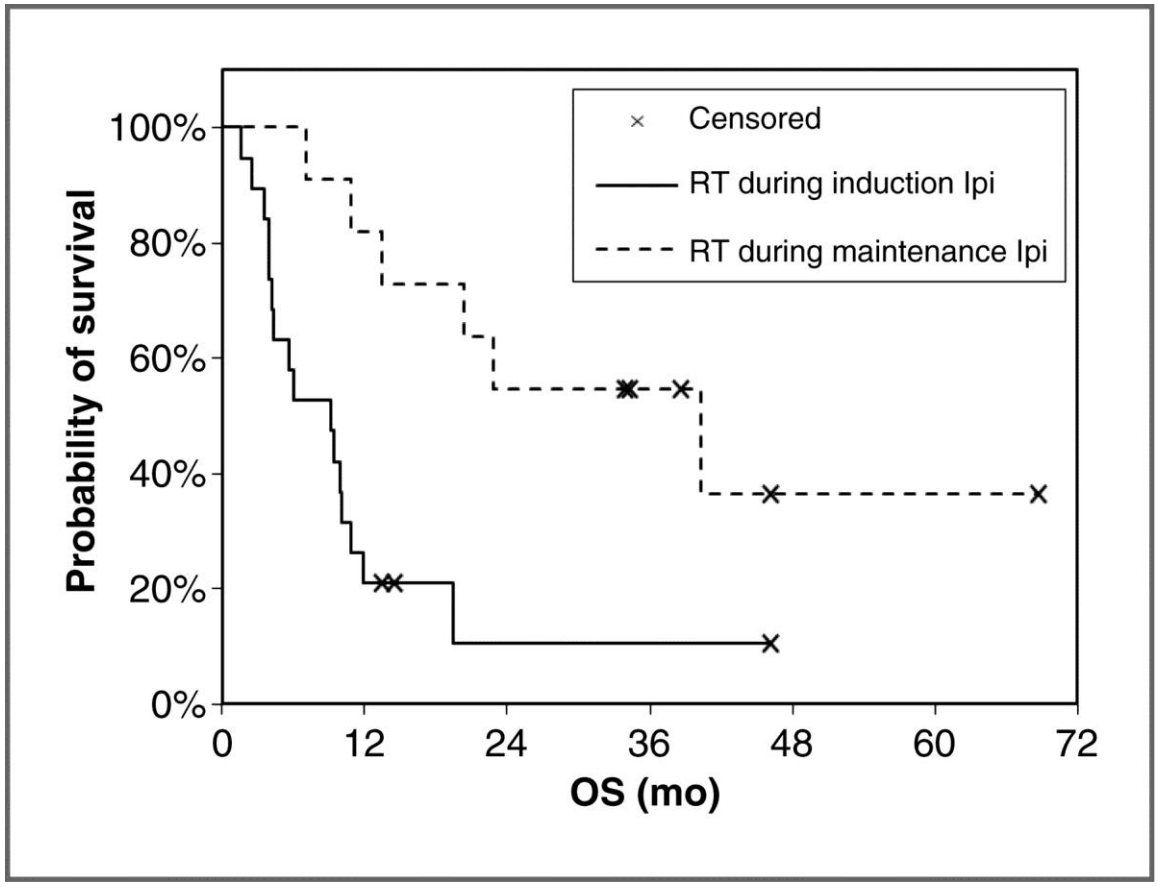




Young KH et al. Optimizing Timing of Immunotherapy Improves Control of Tumors by Hypofractionated Radiation Therapy. PLOS One. 2016 Jun 9;11(6):e0157164

Does Timing Matter?

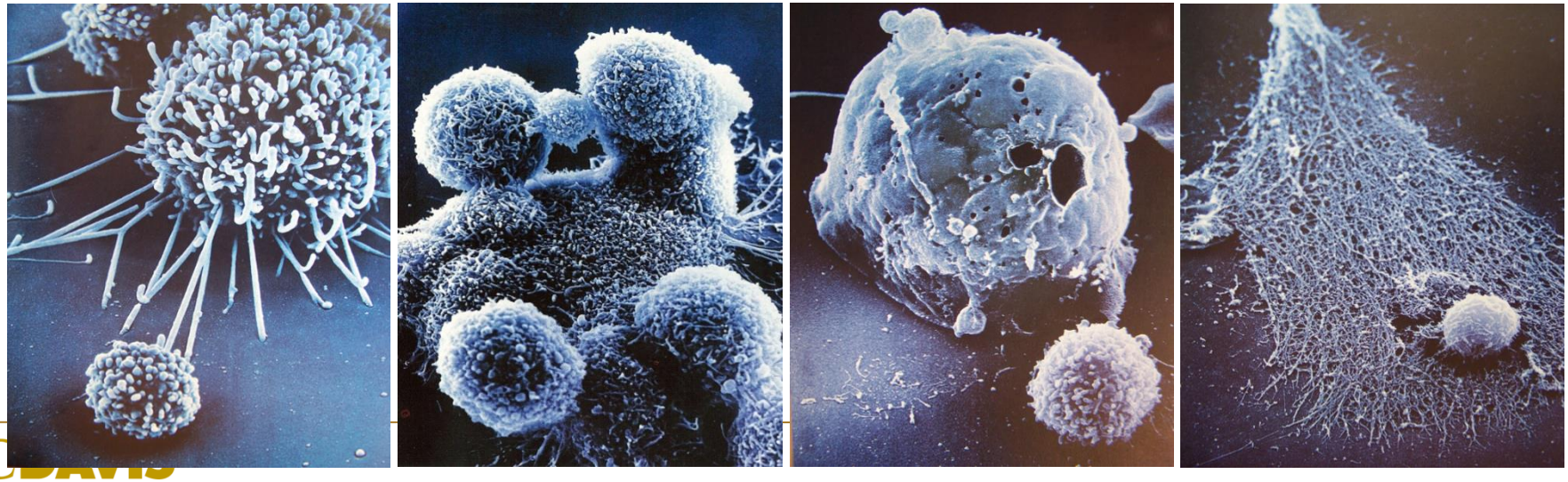
- Retrospective Review of patients treated with ipilimumab and non-brain directed RT for melanoma
- Median OS was 9 months for RT given during induction and 39 months for RT during maintenance
- Difference may be due to selection bias, but provocative



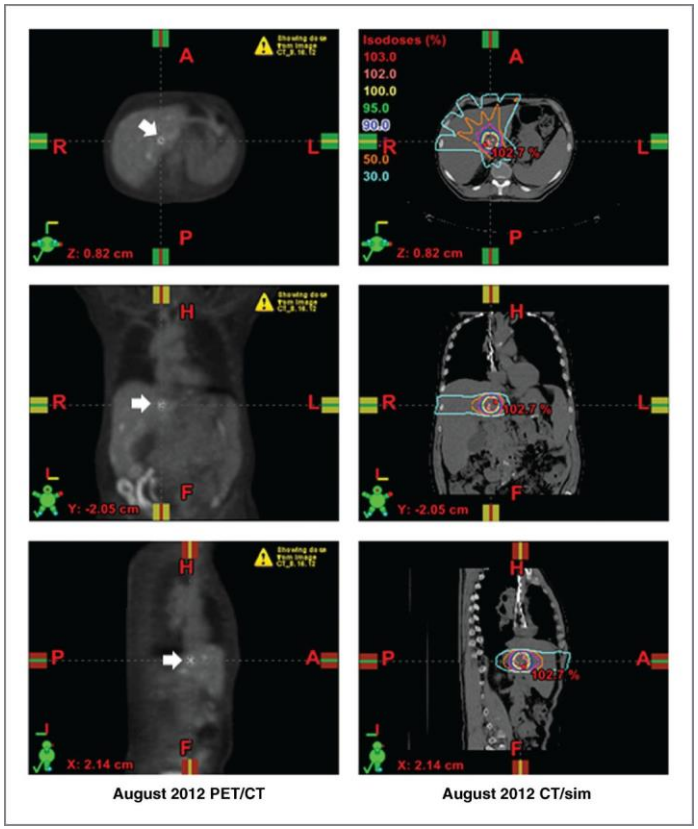
Barker CA et al. Concurrent radiotherapy and ipilimumab immunotherapy for patients with melanoma. Cancer Immunol Res. 2013 Aug;1(2):92-8.

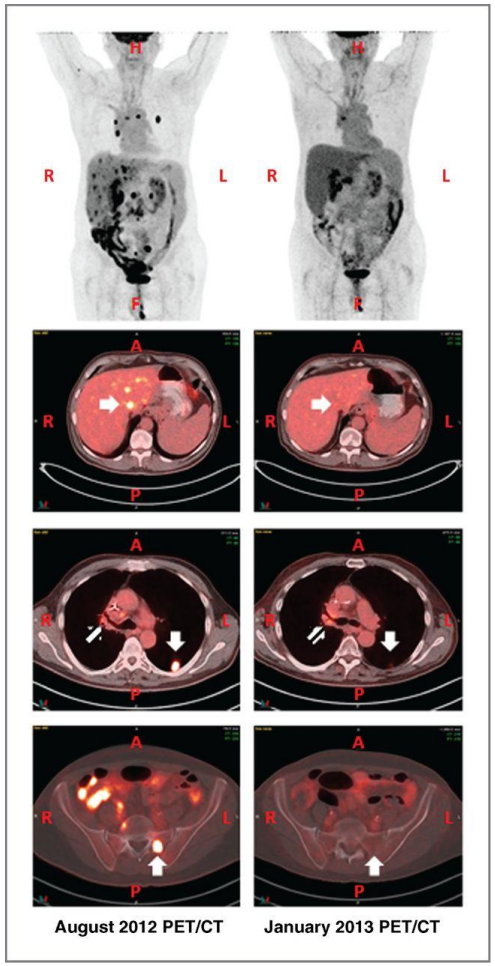
Clinical Data: Current Status

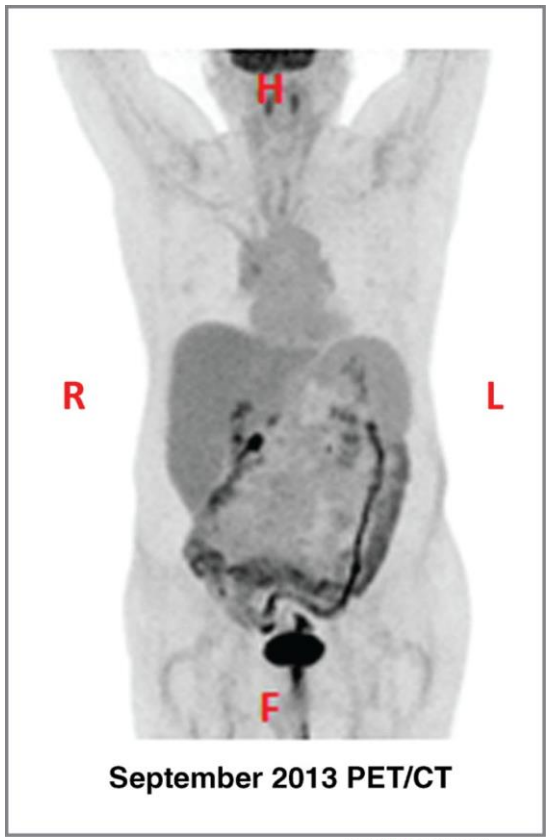
- Case reports/series
  - NYU, many other
- Secondary analyses of prospective trials
  - KEYNOTE 001
- Prospective trials
  - Few published, many ongoing



NYU Case Report: Ipilimumab + SBRT in NSCLC





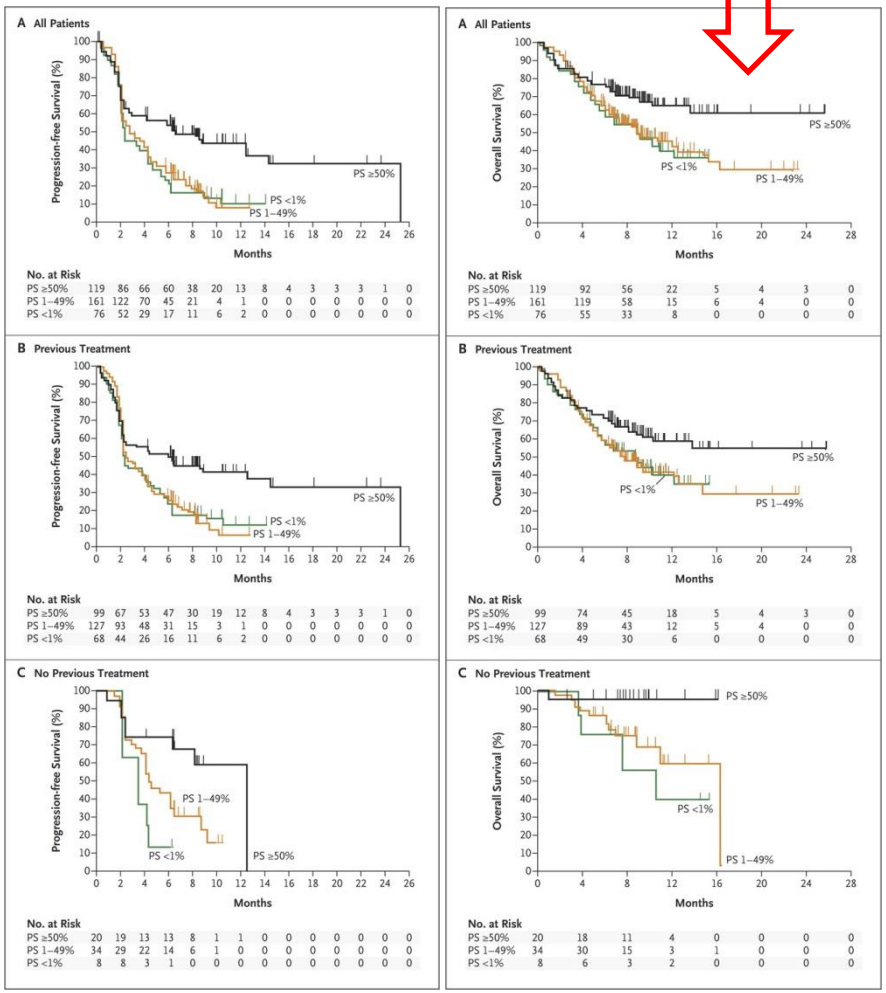


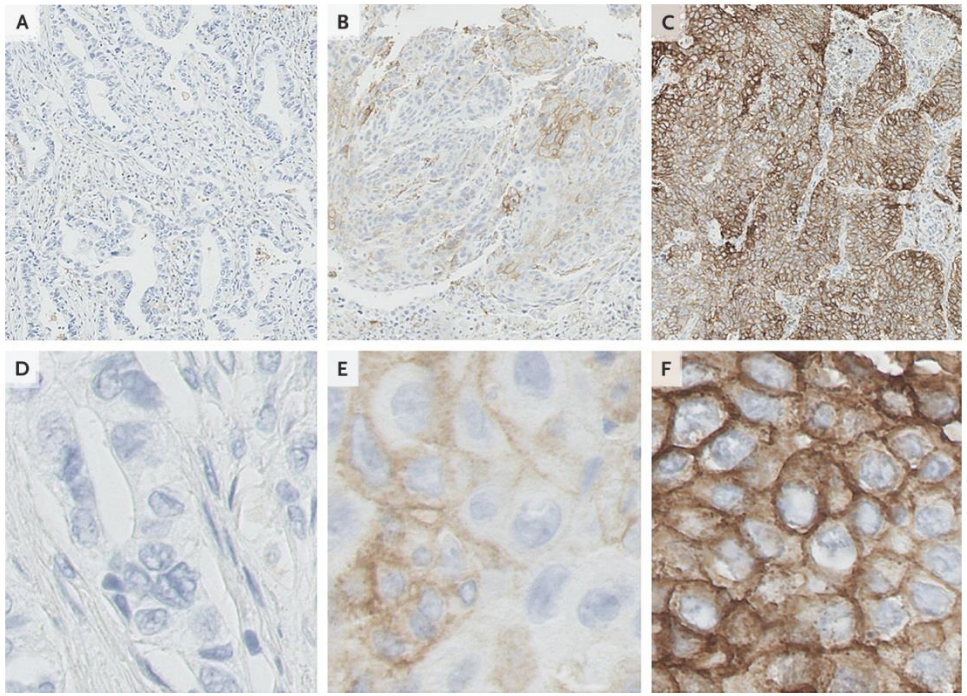
Cancer Immunology Research
AACR American Association for Cancer Research

Golden EB et al. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer Immunol Res 2013;1:365-372

KEYNOTE-001: Pembrolizumab for the Treatment of NSCLC

PFS **OS**





Tumor PD-L1 expression established as a biomarker for increased likelihood of response

The NEW ENGLAND JOURNAL of MEDICINE

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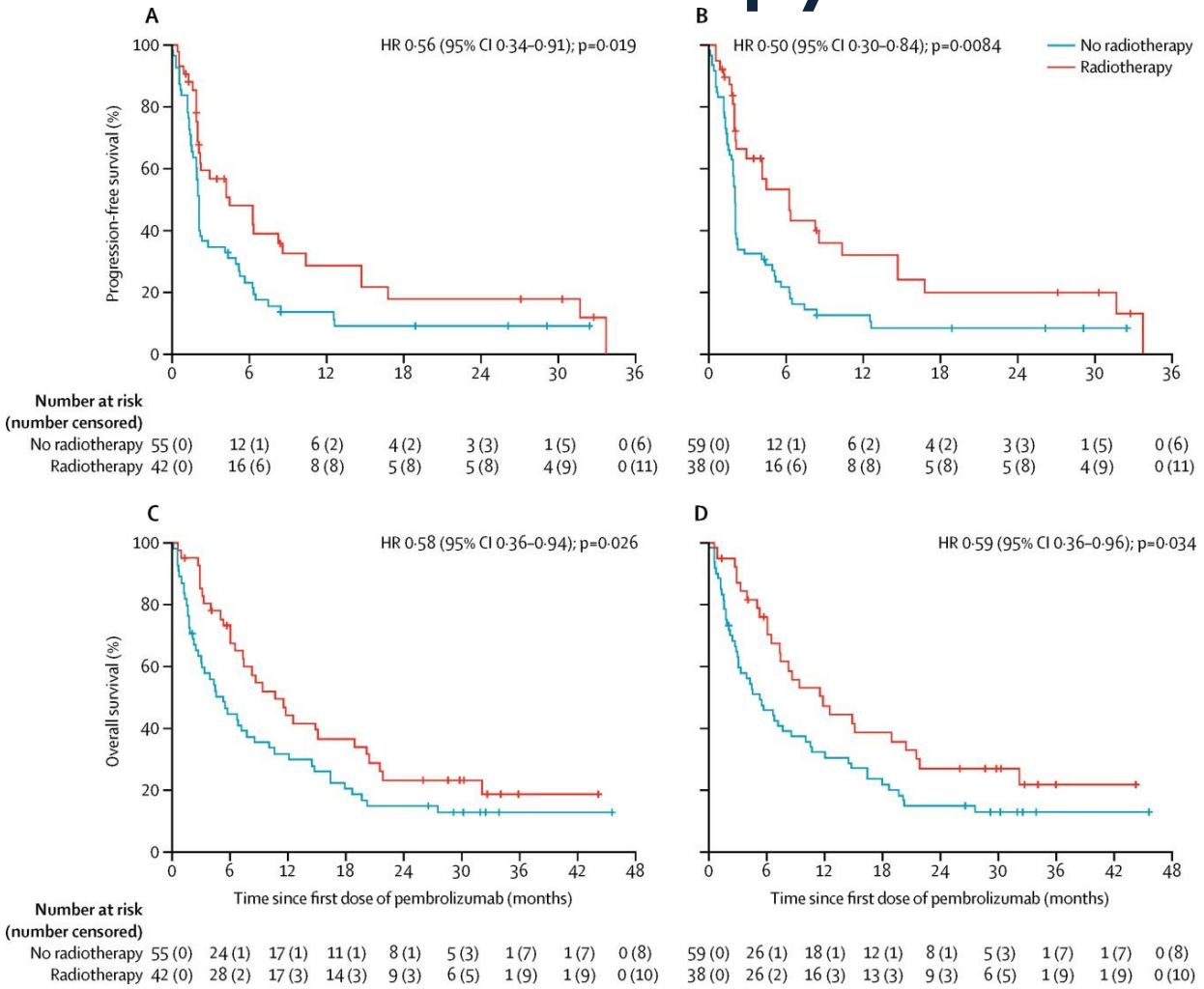
Garon EB et al. N Engl J Med 2015;372:2018-2028.

Secondary Analysis of KEYNOTE-001: Effect of Prior Radiotherapy on PFS and OS



Shaverdian N et al. Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial. The Lancet Oncology 2017 18, 895-903.

IO/RT Strategies: Prospective Clinical Trials

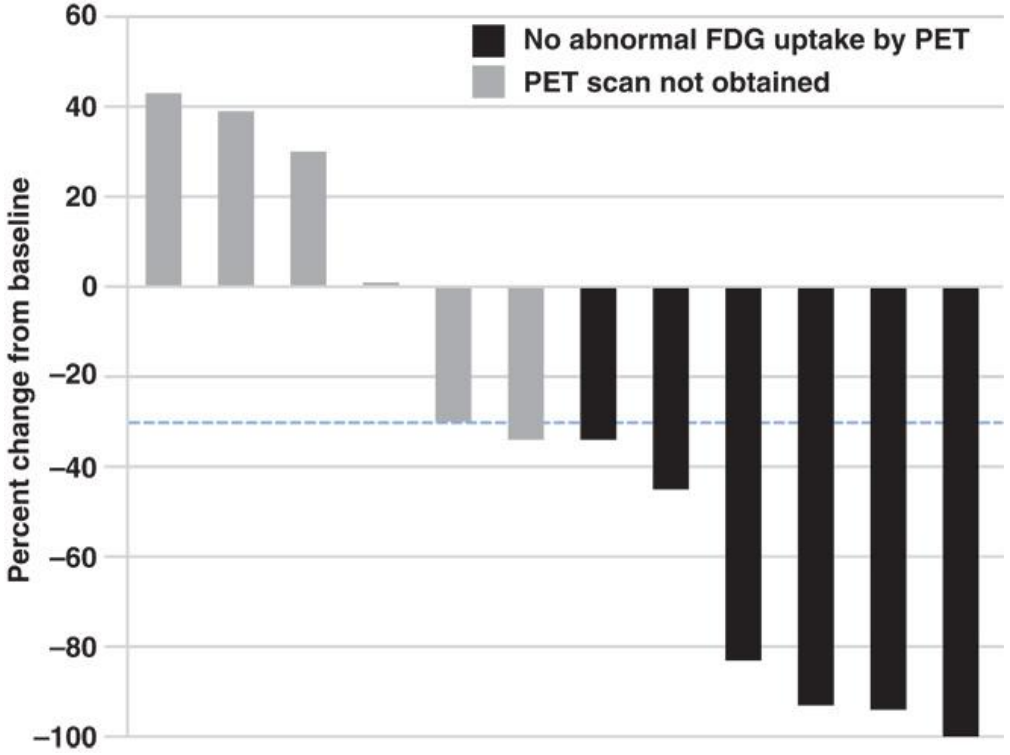
Hundreds of registered trials across most solid tumors/heme malignancies

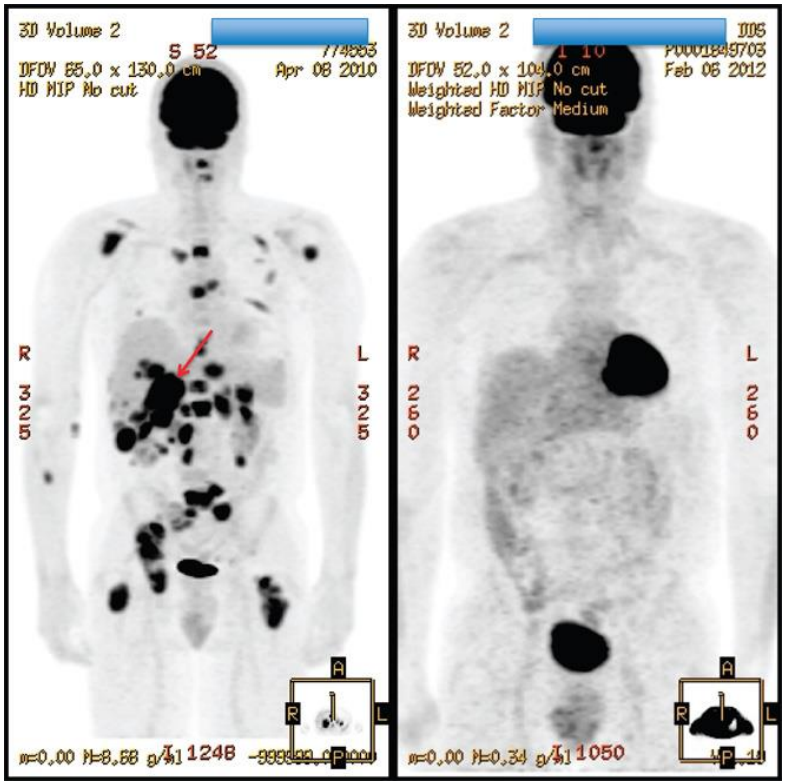
- NSCLC
- Breast Cancer
- Sarcoma
- Melanoma
- Urothelial Cancers
- Pancreatic Cancer
- Prostate Cancer
- Merkel Cell
- Mesothelioma
- Head and Neck Cancer
- Adenoid Cystic Carcinoma
- Glioblastoma
- Renal Cell
- Colorectal Cancer
- Follicular Lymphoma
- Cervical Cancer
- Ovarian Cancer
- Anaplastic thyroid
- Esophageal Cancer
- Primary CNS Lymphoma
- Solitary plasmacytoma
- Uterine Cancer

Published Prospective Clinical Trials using RT+IO agent in metastatic setting

Institution	Tumor Type	IO agent	RT	N	Primary outcome
NYU	Solid tumor	GM-CSF	35 Gy/10 fractions	41	Abscopal response rate
Yale	Melanoma (brain mets)	ipilimumab	WBRT 30/10 or single fx SRS	16	MTD and safety
MD Anderson	Solid tumor	ipilimumab	SBRT lung or liver 50/4 or 60/10	35	Safety
Stanford	melanoma	ipilimumab	Palliative RT, variety of schemas	22	Safety and efficacy
Earle A. Chiles Research Inst.	melanoma	IL-2	SBRT 20 Gy x 1, 2, or 3	12	MTD
Netherlands Cancer Institute	NSCLC	NHS-IL2	Palliative RT 20/5 to lung nodule	13	MTD
Stanford	Low grade lymphoma	CpG	2 Gy x 2	15	Clinical Response
U Penn	melanoma	ipilimumab	12-24 Gy in 2-3 fx	22	Toxicity and response

Phase I IL-2+SBRT in Melanoma and RCC



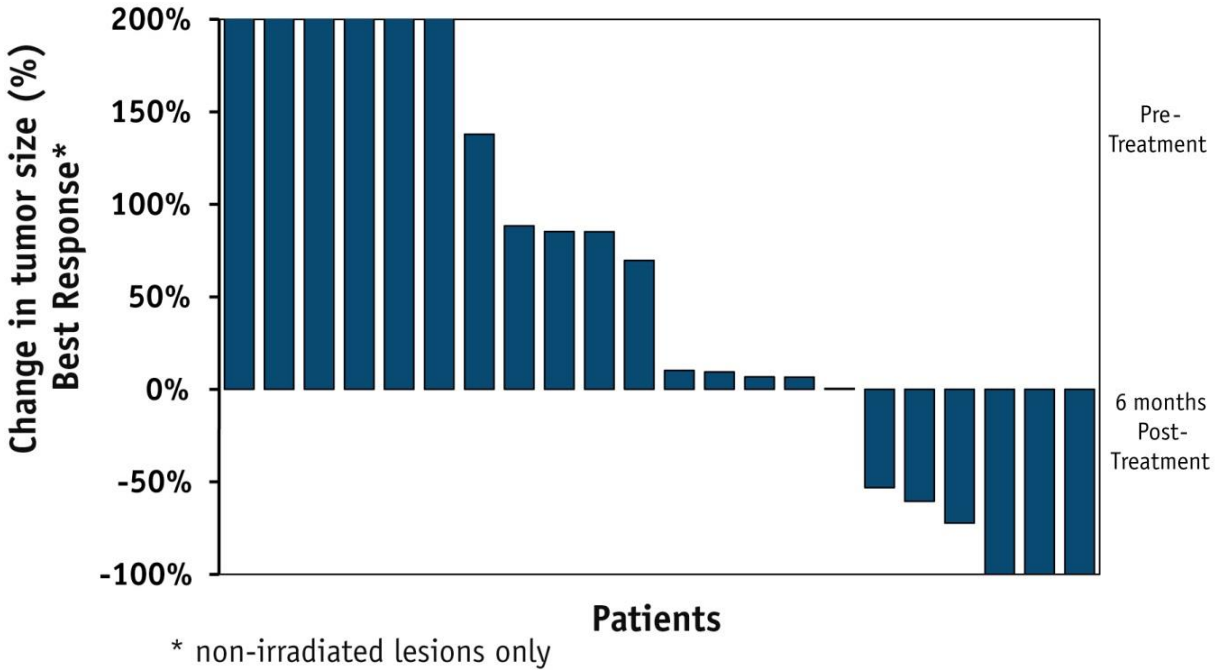


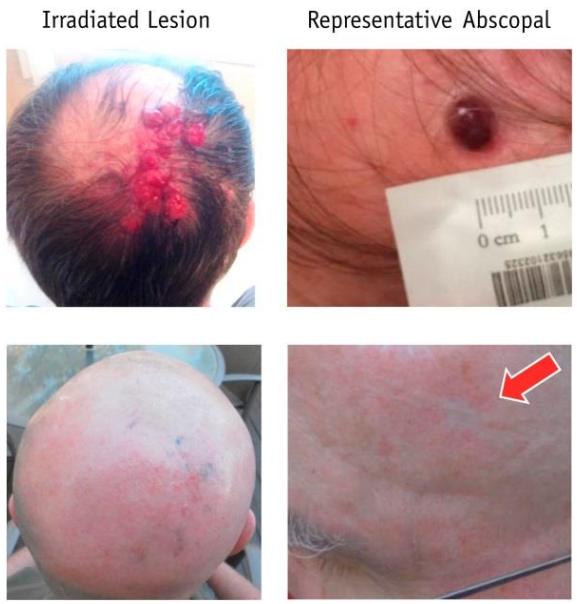
- 11 patients
- SBRT 20 Gy x 1-3 followed by high-dose IL-2
- 8/12 patients (66.6%) CR or PR

Seung SK et al. Phase 1 Study of Stereotactic Body Radiotherapy and Interleukin-2—Tumor and Immunological Responses. Sci Transl Med 2012;4:137ra74

Science Translational Medicine AAAS

Stanford Pilot Study: Ipilimumab+ Palliative RT in Metastatic Melanoma

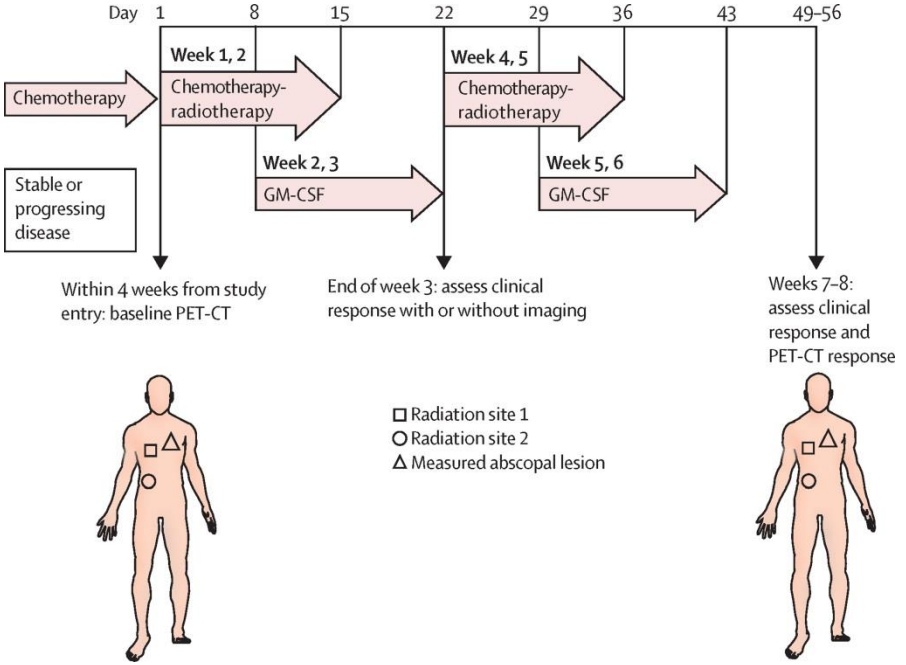


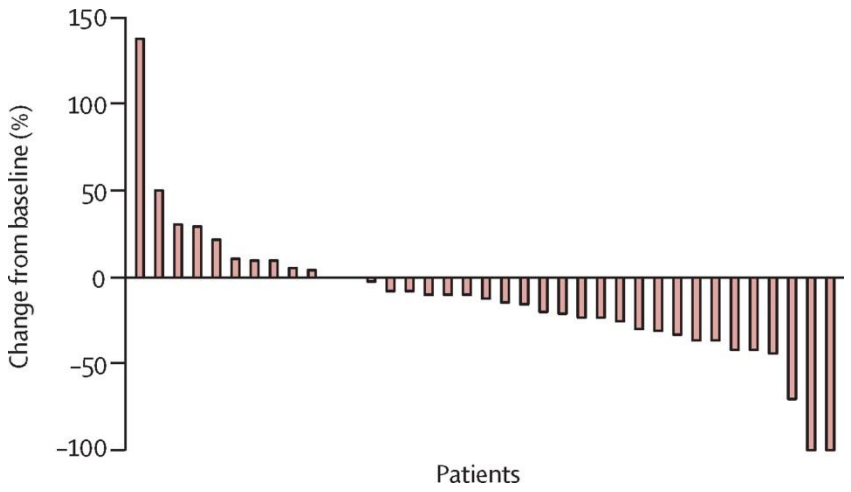


- 22 patients enrolled
- A variety of RT schedules were used, including SBRT in some patients
- 50% had clinical benefit, including CR, PR, and SD

Hiniker SM et al. A Prospective Clinical Trial Combining Radiation Therapy With Systemic Immunotherapy in Metastatic Melanoma. IJROBP Nov 2016.

NYU: GM-CSF+RT Pilot Trial in Metastatic Solid Tumors

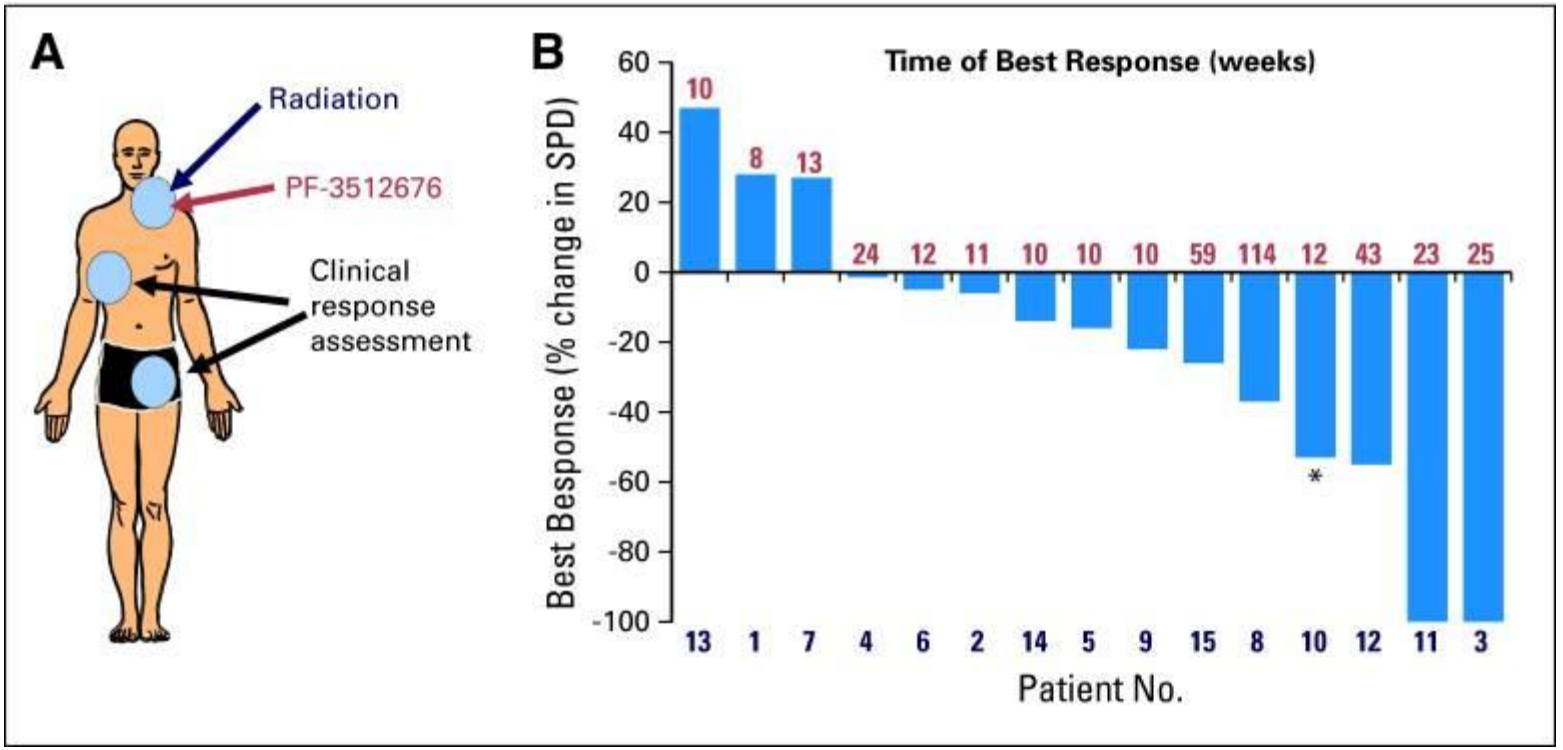




- 41 patients with stable or progressing solid tumors enrolled
- RT 35 Gy/10 fx delivered with GM-CSF sub-q daily for 2 weeks starting RT week 2
- Course repeated targeting a second site
- 11/41 patients had abscopal responses (out-of-field) (4 NSCLC, 5 breast, 2 thymic)

Golden EB et al. Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: a proof-of-principle trial. Lancet Oncology 2015

Intratumoral CpG with low dose RT for Low Grade Lymphoma



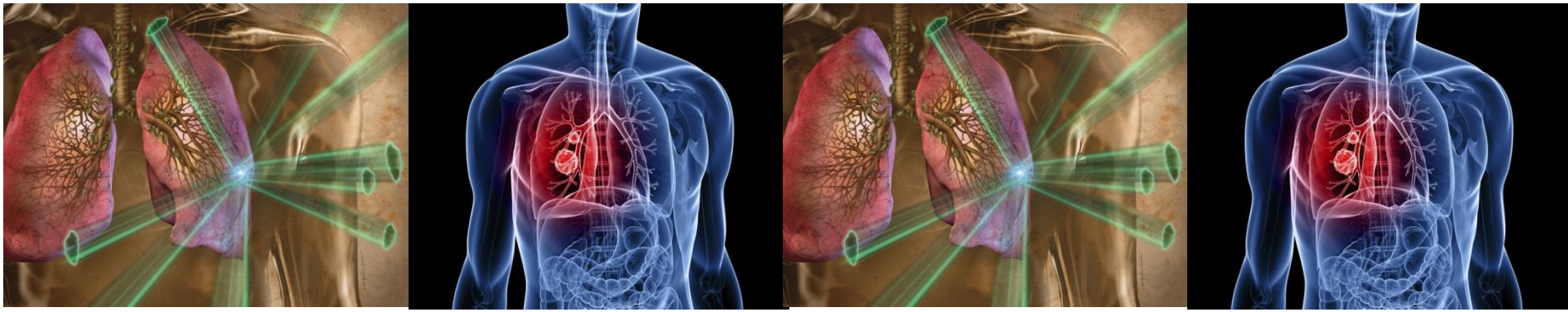
- 15 patients with refractory low grade lymphoma enrolled
- CpG given with low dose RT 2 Gy x2
- 1 CR, 3 PR, and 2 long-duration stable disease

Brody JG et al. In Situ Vaccination With a TLR9 Agonist Induces Systemic Lymphoma Regression: A Phase I/II Study. JCO Oct 2010.

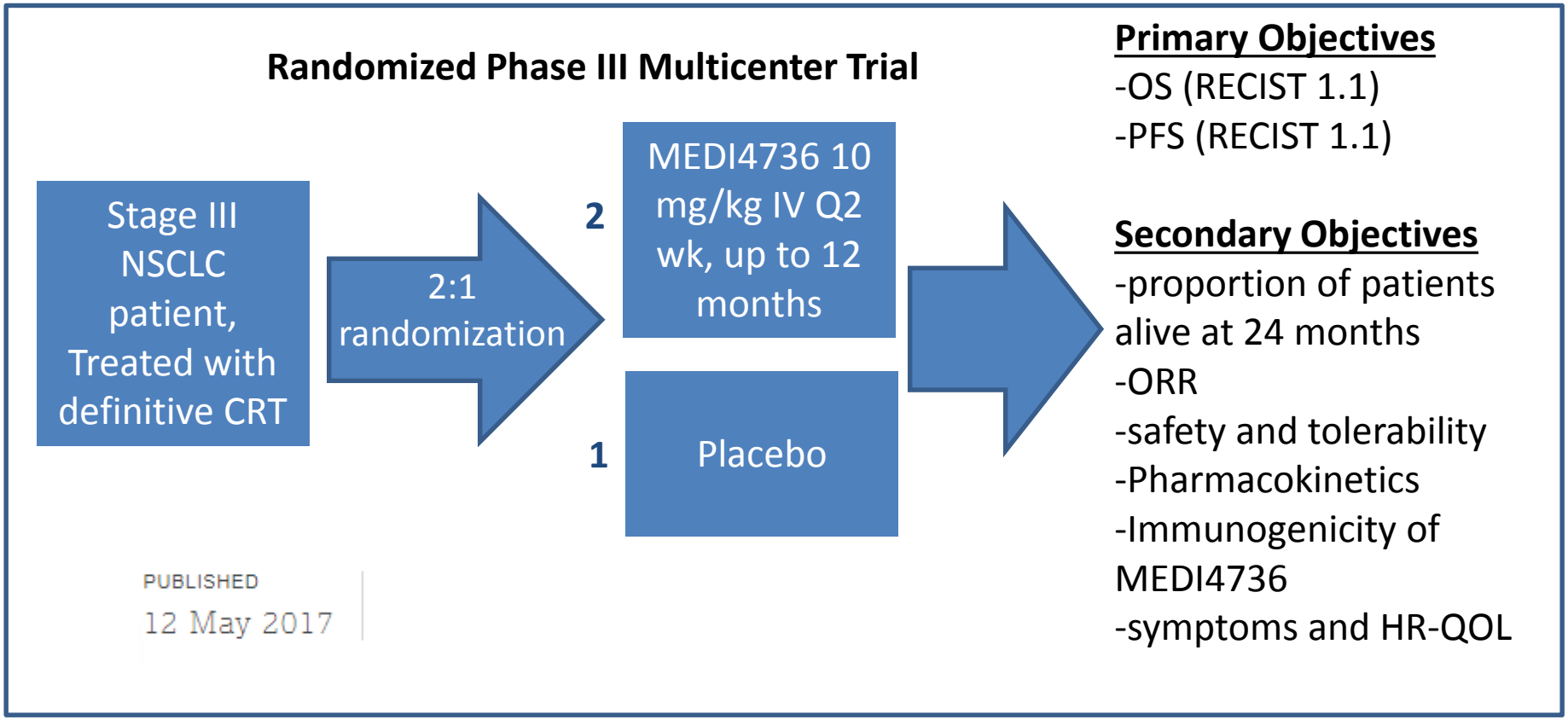
Moving Immunotherapy/RT Strategies to Earlier Stage Disease

Non-Small Cell Lung Cancer (NSCLC) as an example

- Locally Advanced disease
- Early Stage Disease

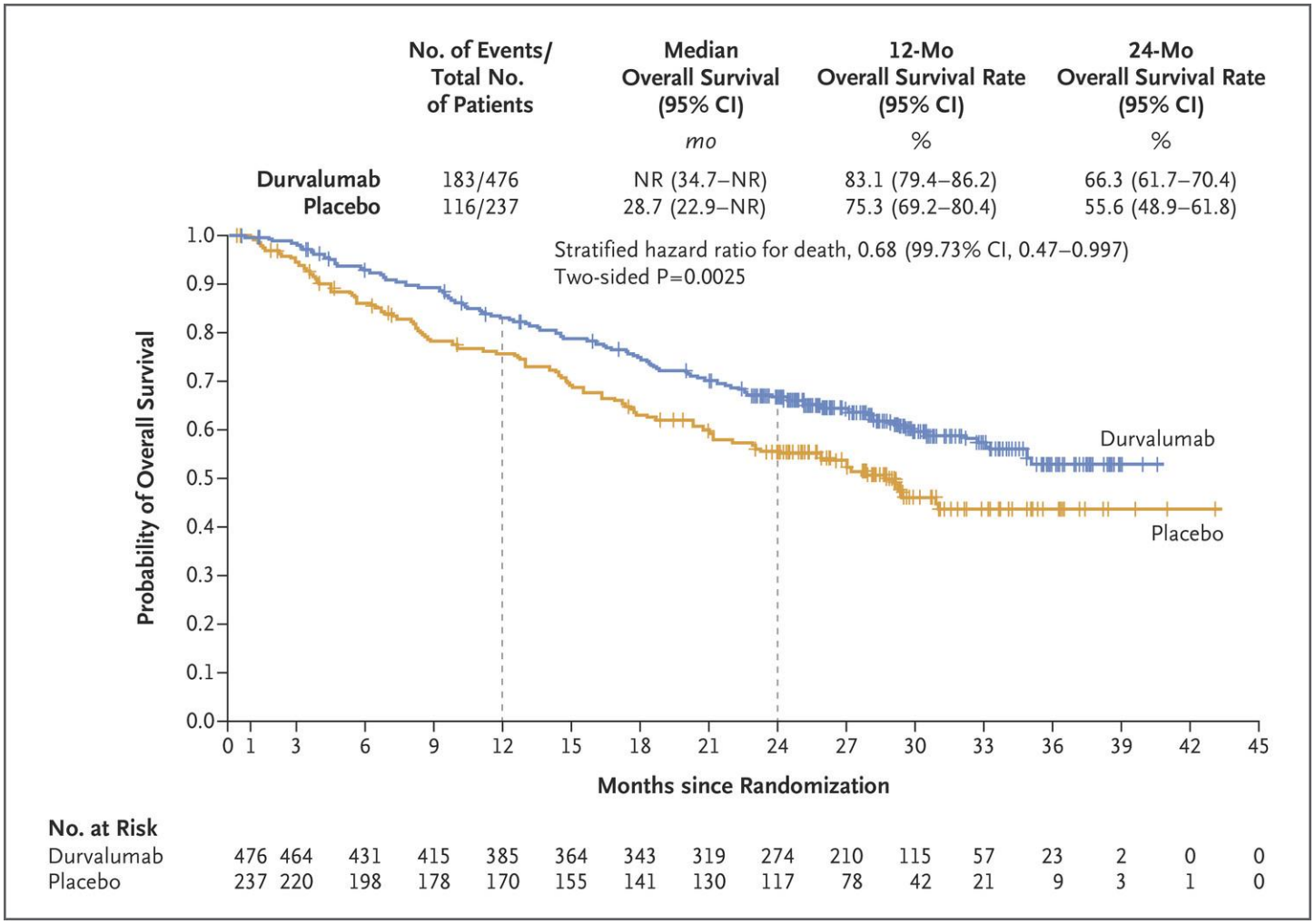


Moving Checkpoint Inhibitors to Earlier Stages: PACIFIC Trial: Stage III NSCLC



Durvalumab significantly reduces the risk of disease worsening or death in the Phase III PACIFIC trial for Stage III unresectable lung cancer

PACIFIC results: OS in the Intention-to-Treat Population.



SJ Antonia et al. N Engl J Med 2018. DOI: 10.1056/NEJM

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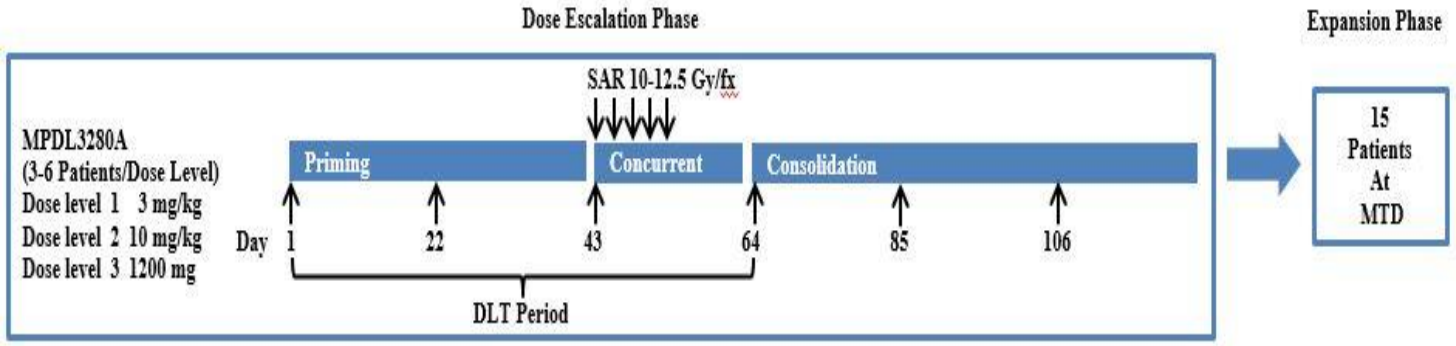
UC Davis Phase I: Atezolizumab+SAR for early stage, high-risk, medically inoperable NSCLC



Eligibility: T1-2N0 NSCLC, medically inoperable or refused surgery
One of more high risk feature:
Tumor diameter ≥ 2 cm
Tumor SUV max ≥ 6.2
Grade 3 histology

Primary Outcome: MTD of MPDL3280A that can be given with SAR in patients with inoperable stage I NSCLC.

Secondary Outcomes: Safety profile of this regimen using CTCAE v4
Preliminary efficacy data of the combination as determine by ORR and DFS using RECIST 1.1

Exploratory Objectives
To analyze serial blood for change in cytokine signatures, FACS and immunophenotyping of peripheral blood mononuclear cells (PBMCs) and tumor infiltrating immune cells.
To evaluate pre and post treatment tumor tissue (if available) for PD-L1 and other immune proteins in the tumor and tumor microenvironment and for molecular profiling in a subset of patient samples.

Summary/Next Directions

- Immuno-oncology strategies have altered the landscape of cancer therapies
- Radiation is an intriguing partner therapy
- Additional preclinical and clinical studies are needed to guide details of RT
  - Dose/fractionation
  - Site treated
  - Timing
- The vast array of actively accruing human clinical trials in this space should provide significant insights into this strategy once completed

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