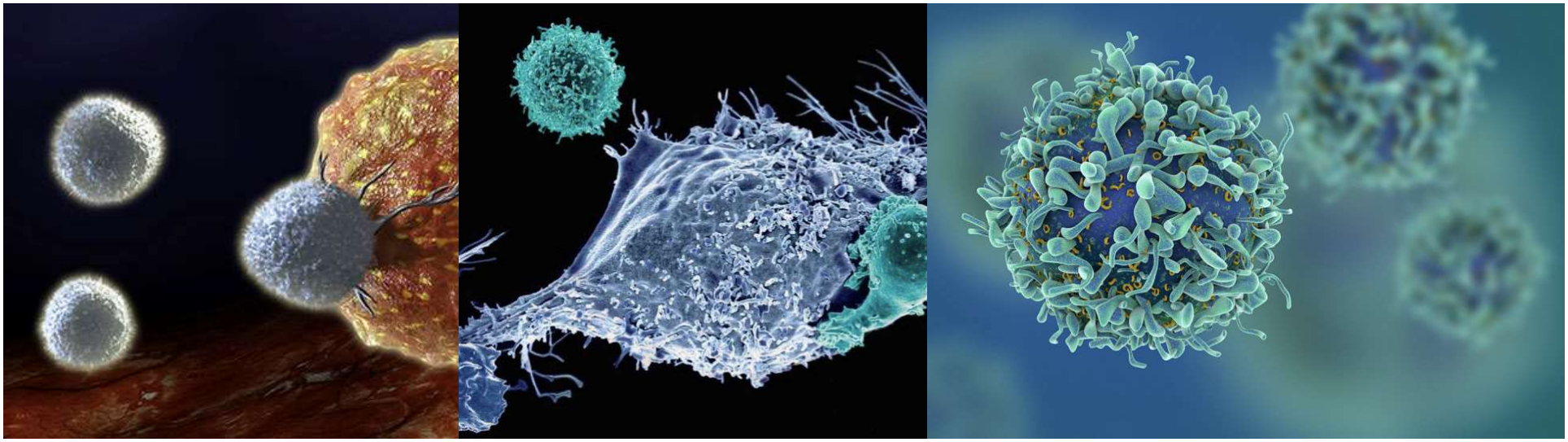
Combination Radiation and Immunotherapy



Megan E. Daly MD
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UCDAVIS COMPREHENSIVE CANCER CENTER

Megan Daly, MD

Combination Radiation and Immunotherapy

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

Grant/research support: Research Funding, EMD Serono, Genentech
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The Medical Educator Consortium

15th Annual California Cancer Conference Consortium
August 2019

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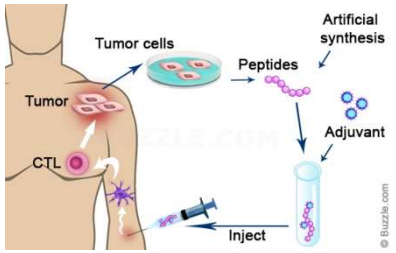
Overview

- Background: Rationale for radiotherapy/immunotherapy combinatorial strategies
  - Mechanisms of synergy
- Radiation: Do target, dose, and fractionation matter?
- Current and emerging clinical evidence
- Next directions

Classes of Immunotherapy

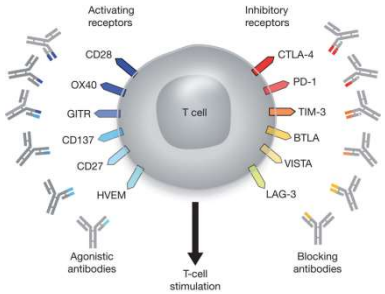
Vaccinations

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



Strong Immune Stimulants

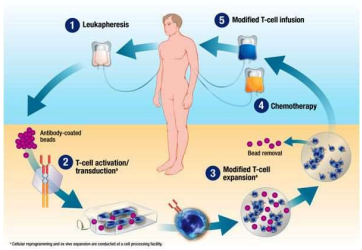
General activation of the immune system in a non-specific manner



Tumor

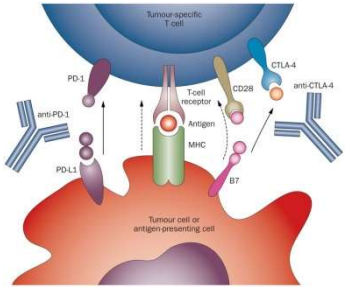
Chimeric Antigen Receptor (CAR) NK & T Cell Therapy

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

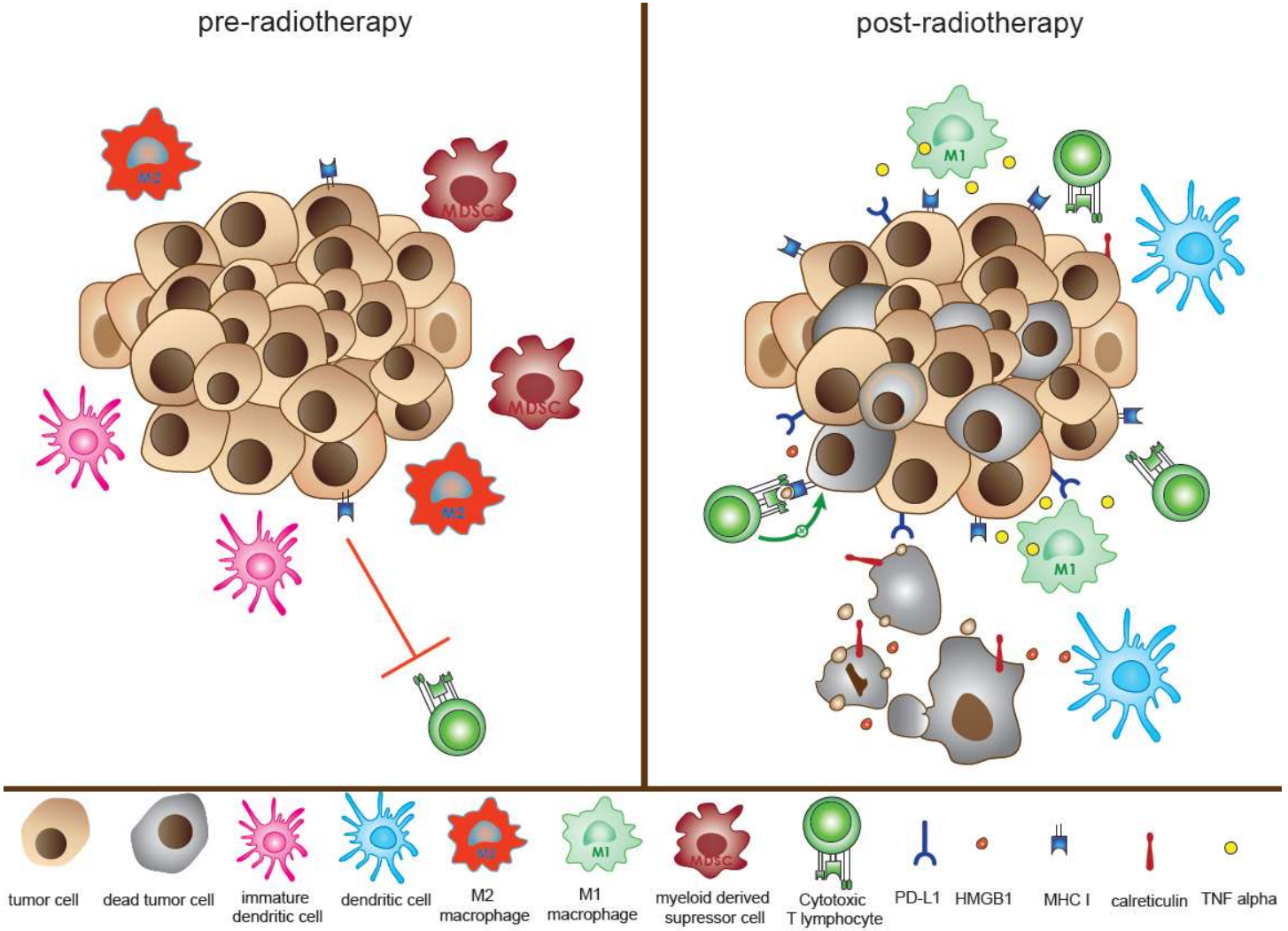
Immunotherapy/RT Combinatorial Strategies: Current Status

- Preclinical Data
  - Effects of RT on the immune system
  - Mouse models
  - Canine Models
- Retrospective Clinical Data
  - Case reports/series
  - Post-hoc analyses
- Prospective Clinical Trials
  - Metastatic Disease
  - Localized Disease

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

Effects of RT on the Immune System

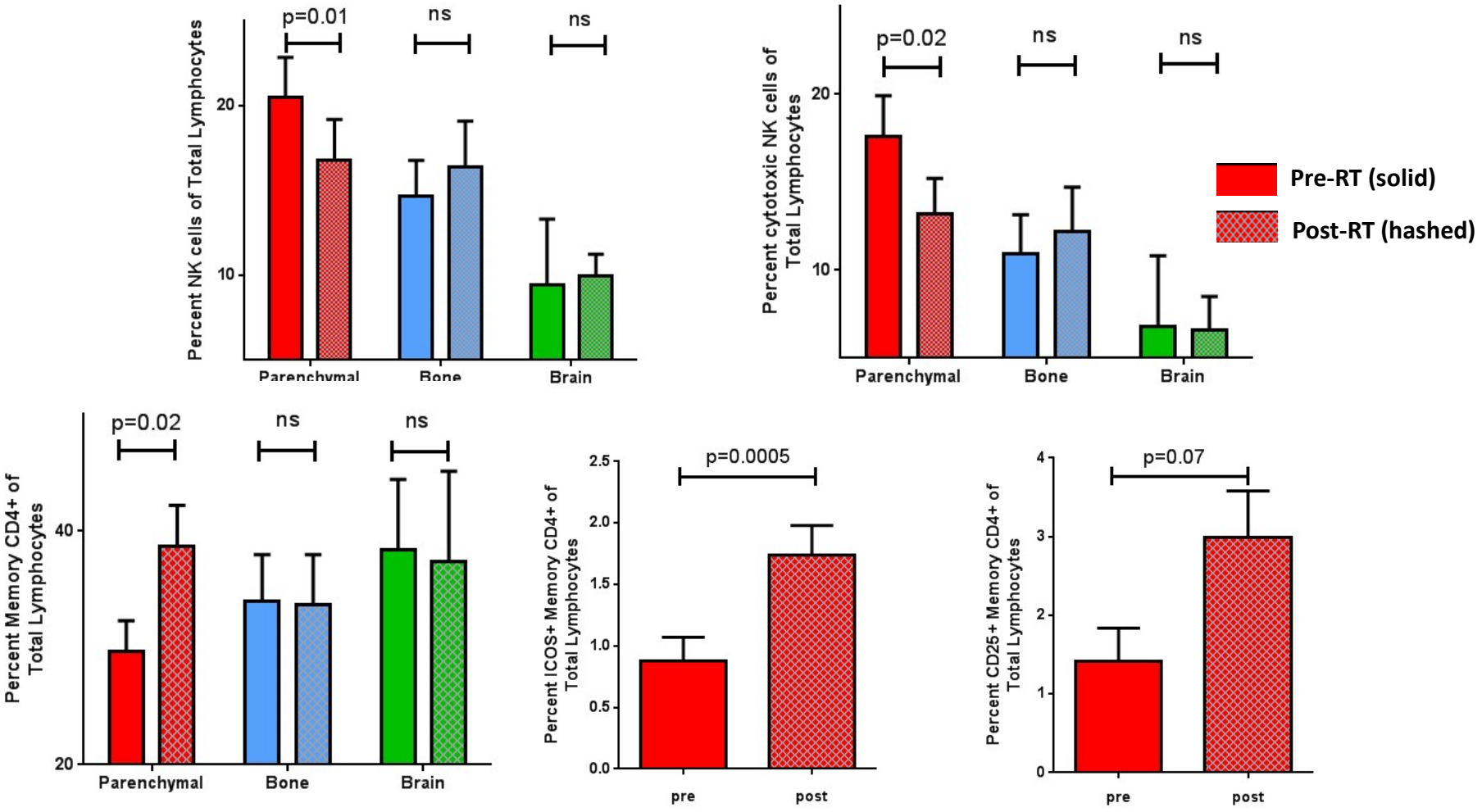
• RT traditionally thought of as immunosuppressive, related to irradiation of marrow and circulating blood

• 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

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



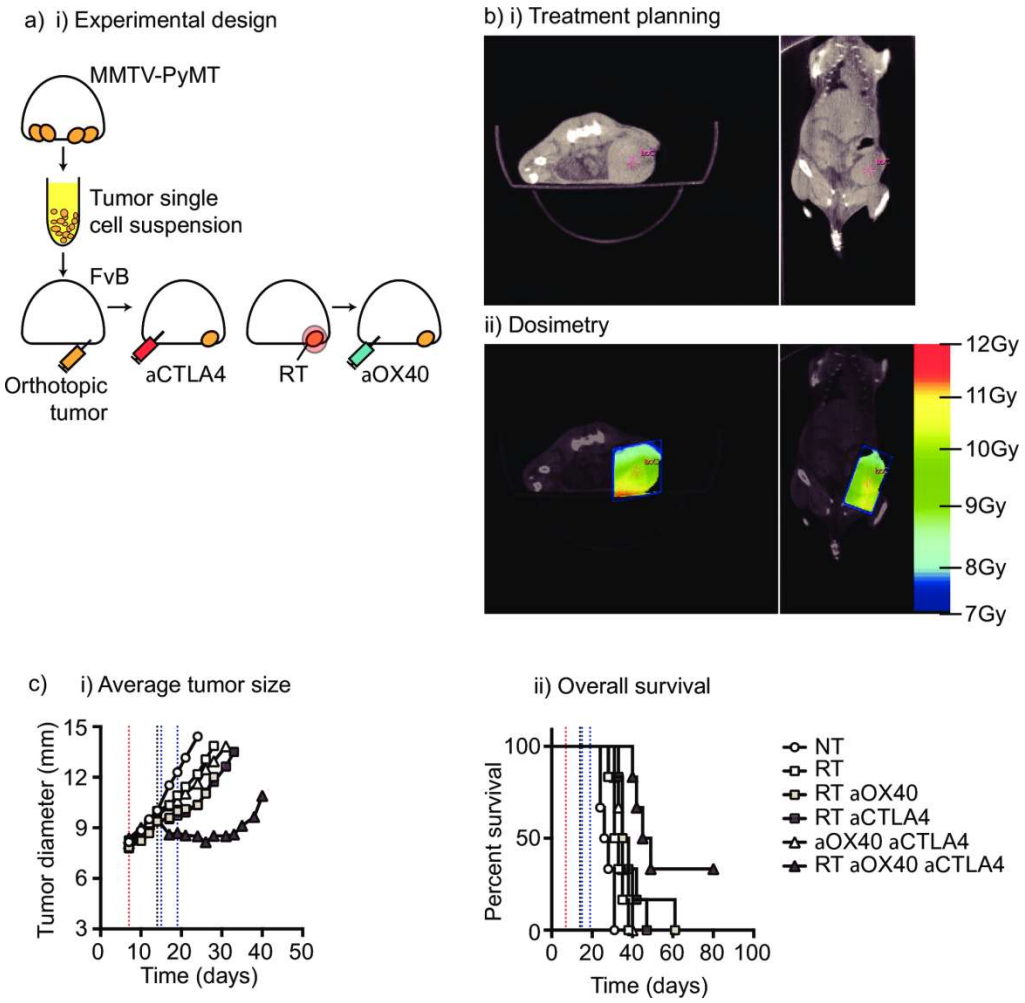
McGee H et al. Stereotactic Ablative Radiation Therapy Induces Systemic Differences in Peripheral Blood Immunophenotype Dependent on Irradiated Site. IJROBP Aug 2018

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?

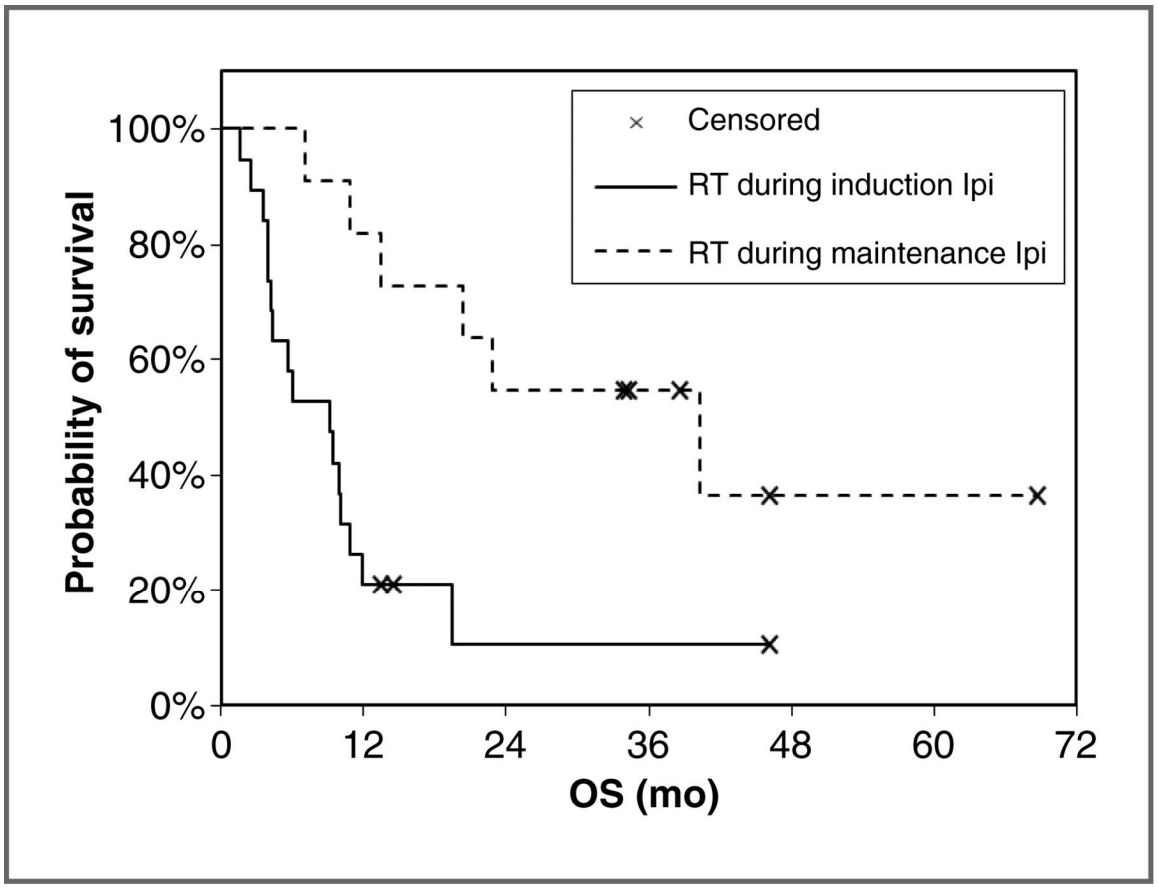
- Tumor bearing mice were treated with 20 Gy RT with either anti-CTLA-4 or OX40 agonist antibody
- Anti-CTLA-4 was most effective when given prior to RT
- OX40 agonist was most effective when delivered following RT
- Suggests optimal timing of immunotherapy and RT depends on mechanism of immunotherapy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



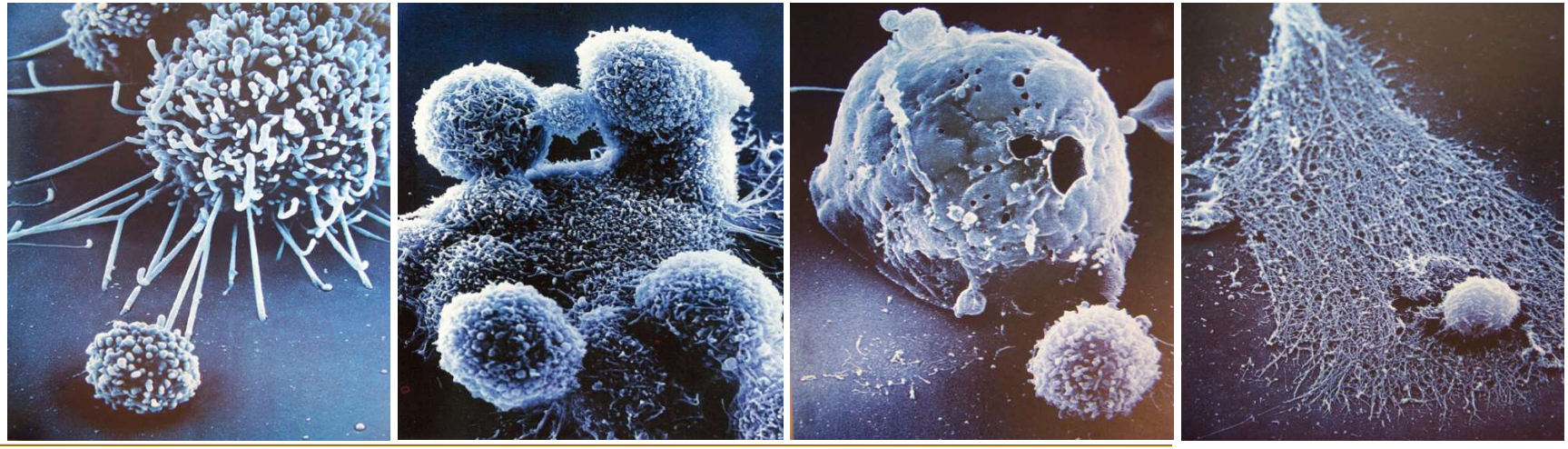
Barker CA et al. Concurrent radiotherapy and ipilimumab immunotherapy for patients with melanoma. Cancer Immunol Res. 2013 Aug;1(2):92-8.

Clinical Data: Current Status

- Case reports/series
  - many

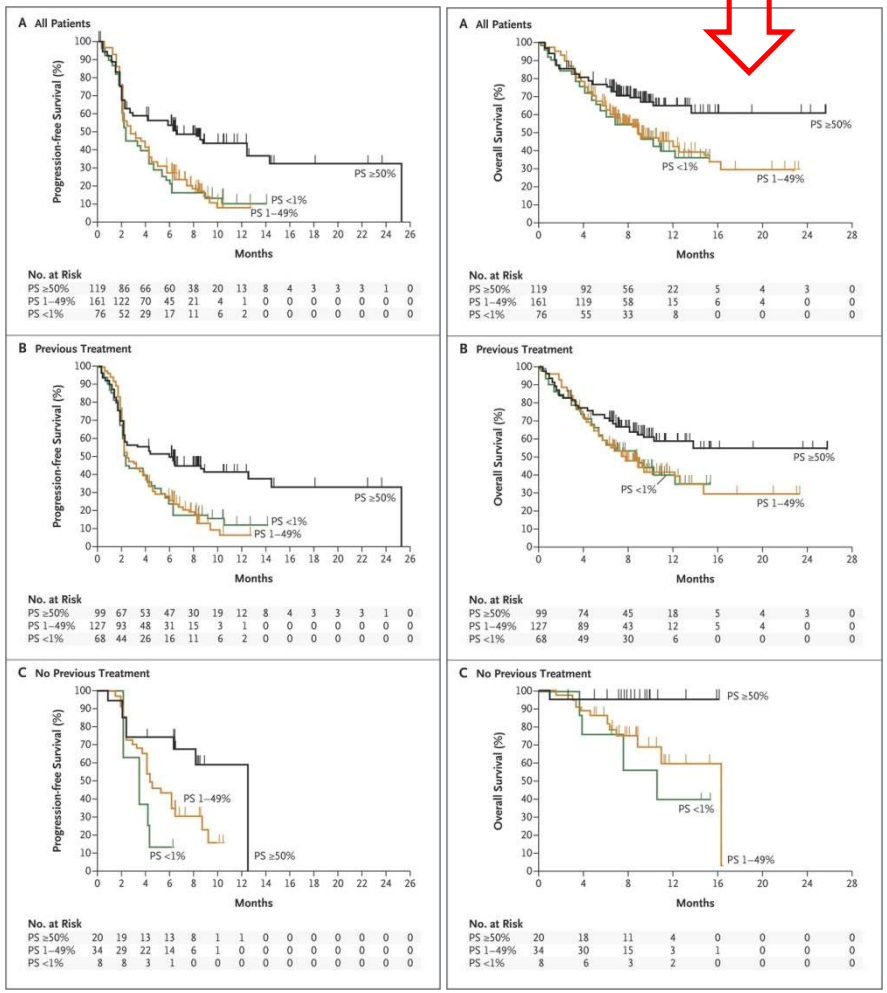
- Secondary analyses of prospective trials
  - KEYNOTE 001

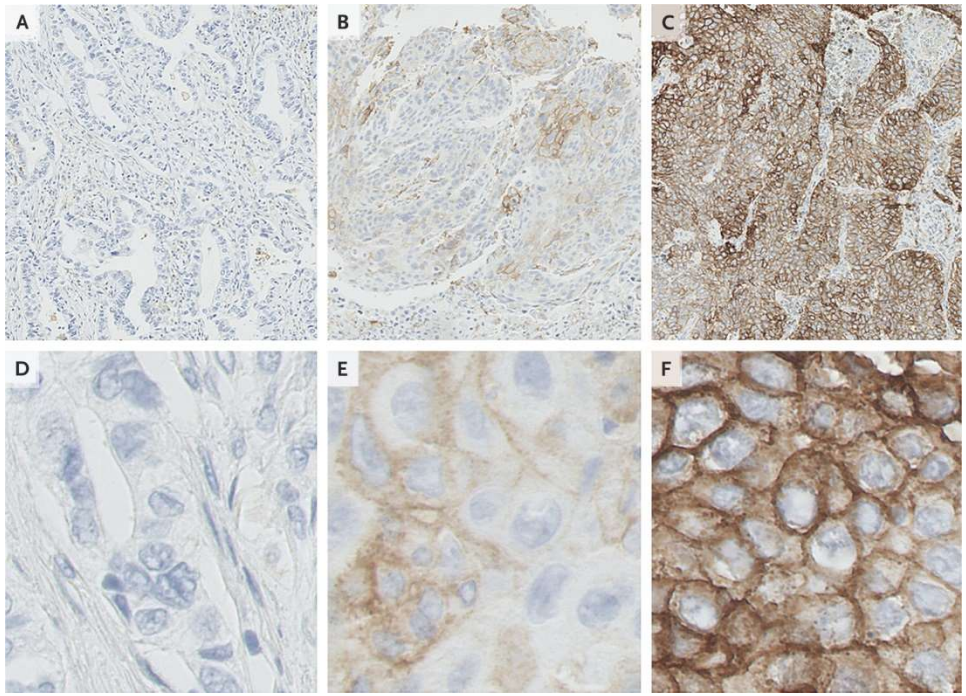
- Prospective trials
  - Few published (PEMBRO-RT)
  - Many ongoing



KEYNOTE-001: Pembrolizumab for the Treatment of NSCLC

PFS **OS**





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

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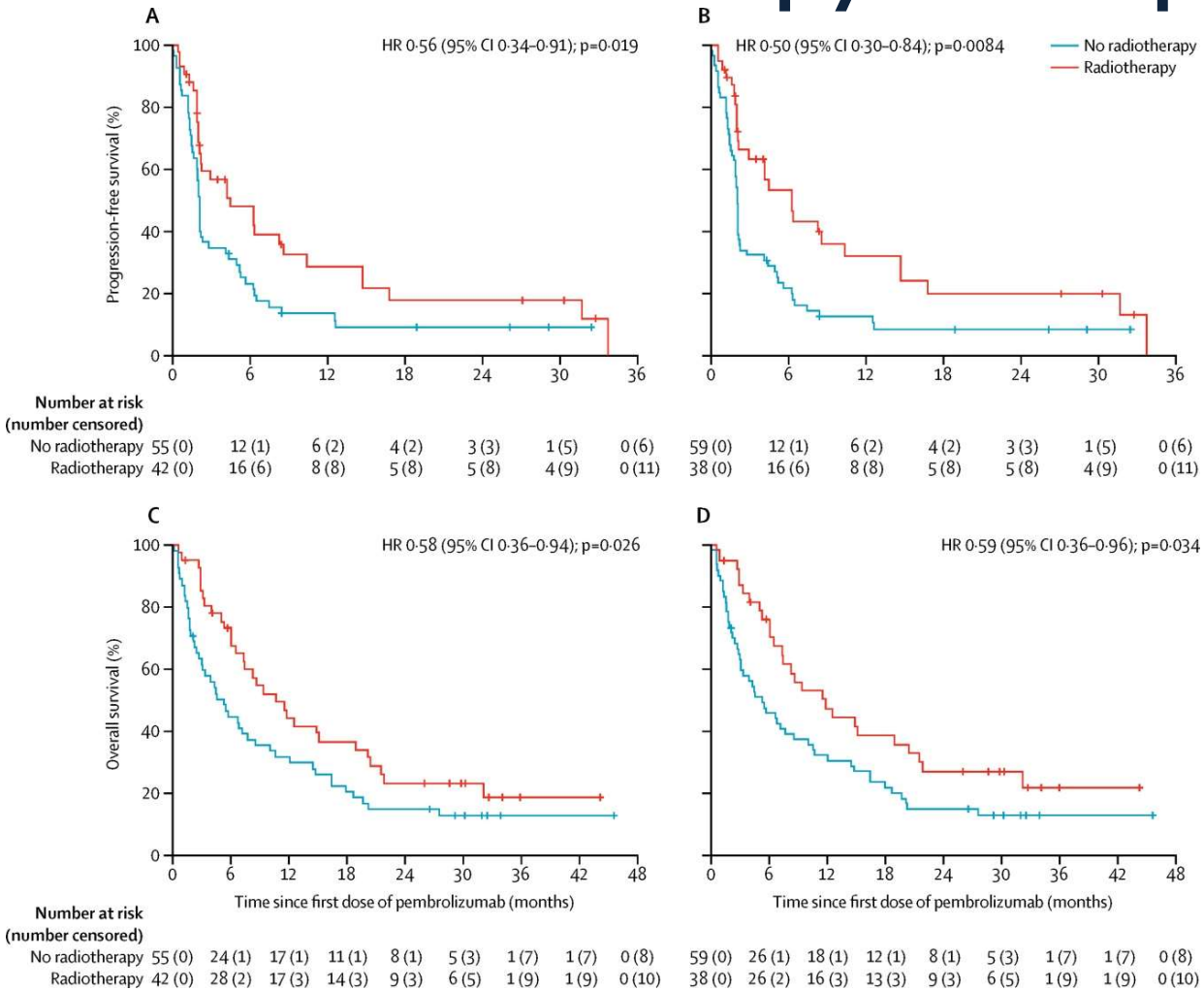
Garon EB et al. N Engl J Med 2015;372:2018-2028.

Secondary Analysis of KEYNOTE-001: Effect of Prior Radiotherapy on Response



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

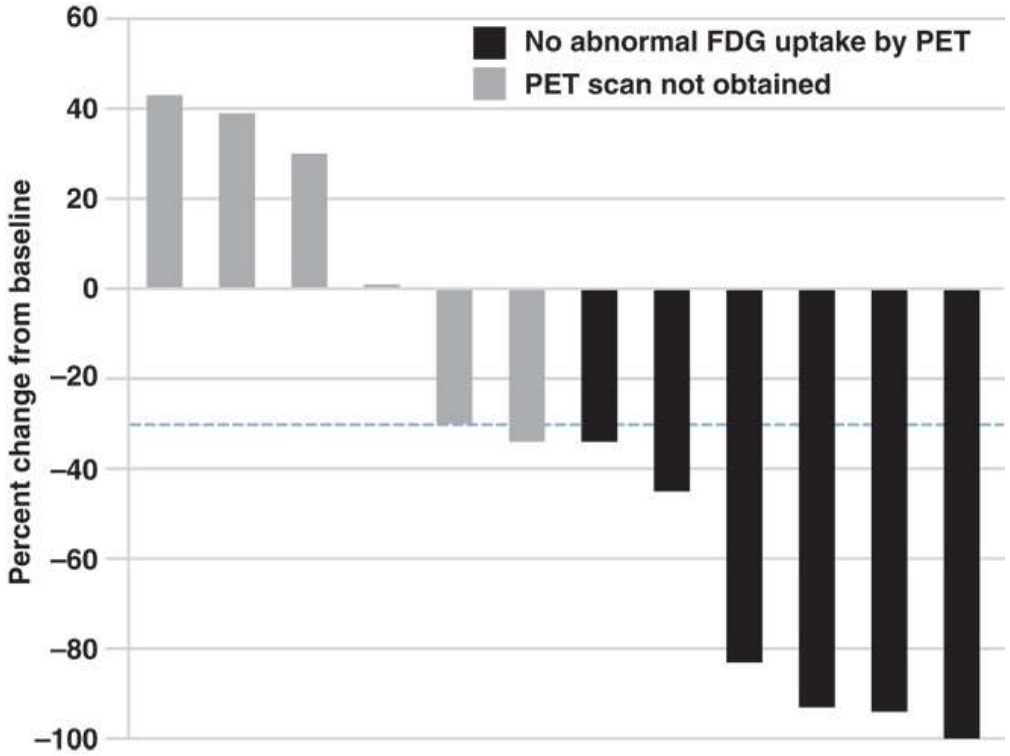
Hundreds of registered trials across most solid tumors/heme malignancies

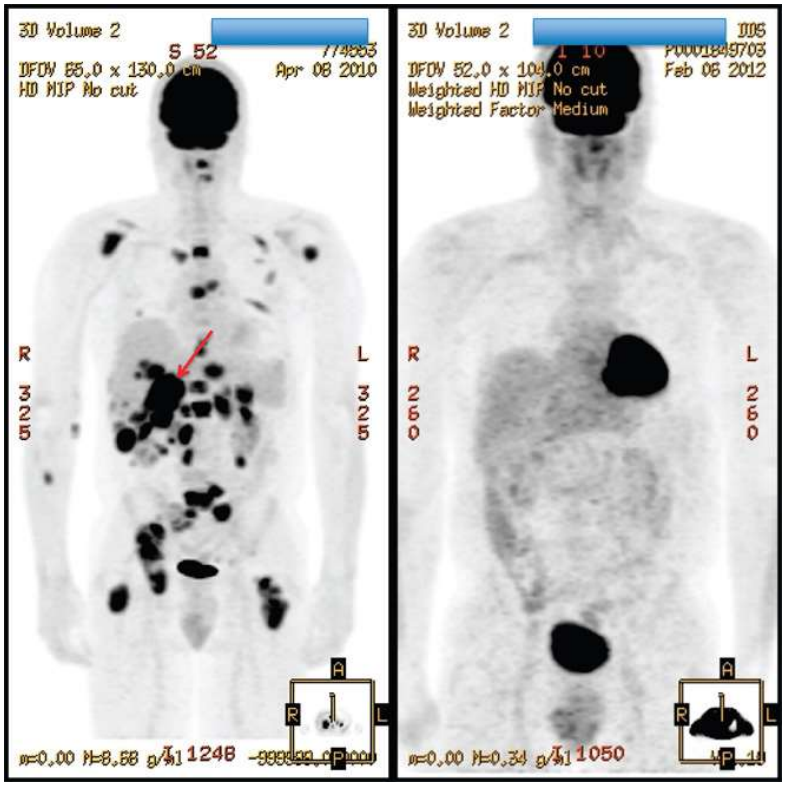
- NSCLC
- Breast Cancer
- Sarcoma
- Melanoma
- Urothelial Cancers
- Pancreatic Cancer
- Prostate Cancer
- Merkel Cell
- Mesothelioma
- Head and Neck Cancer
- Adenoid Cystic Carcinoma
- Glioblastoma
- Renal Cell
- Colorectal Cancer
- Follicular Lymphoma
- Cervical Cancer
- Ovarian Cancer
- Anaplastic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

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

Institution/ Trial	Tumor Type	IO agent	RT	N	Primary outcome
NYU	Solid tumor	GM-CSF	35 Gy/10 fractions	41	Abscopal response rate
Yale	Melanoma (brain)	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 Institute	melanoma	IL-2	SBRT 20 Gy x 1, 2, or 3	12	MTD
Netherlands Cancer Institute PMID:	NSCLC	NHS-IL2	Palliative RT 20/5 to lung nodule	13	MTD
PEMBRO-RT (Netherlands)	NSCLC	pembrolizumab	8 Gy x 3	92	ORR at 12 weeks
TONIC Trial (Netherlands)	Triple neg breast ca	nivolumab	8 y x 3	66 (total); 12 RT	ORR
PLUMMB Trial (Royal Marsden)	Bladder	pembrolizumab	36 Gy in 6 fractions	5	MTD

Phase I IL-2+SBRT in Melanoma and RCC





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

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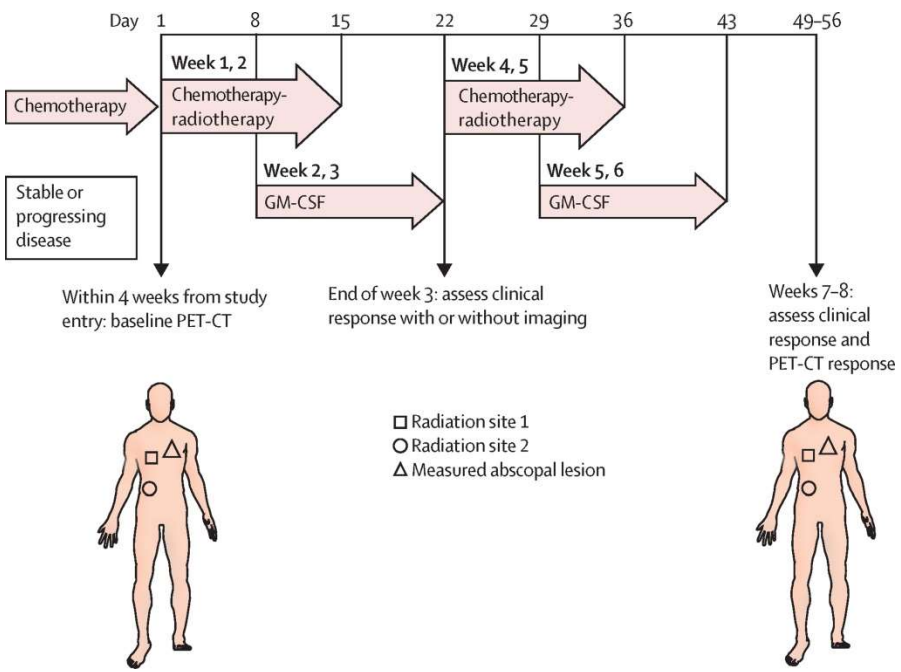
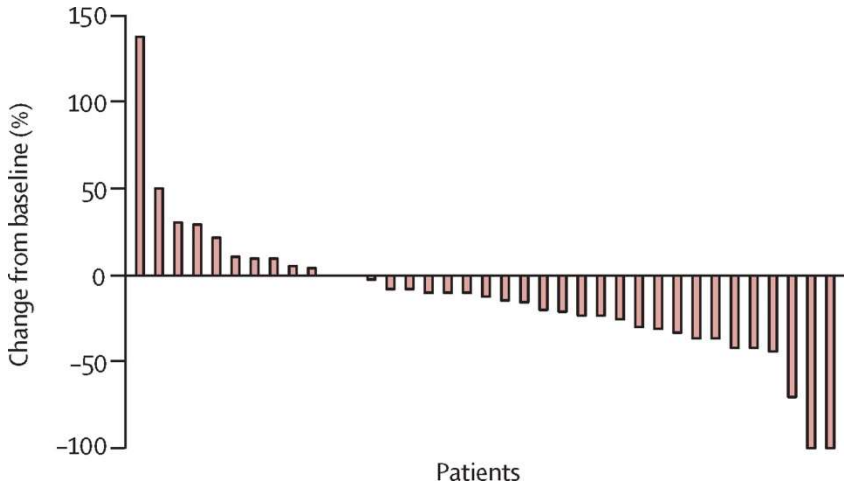
Science Translational Medicine AAAS

NYI GM-CSF+RT Pilot Trial



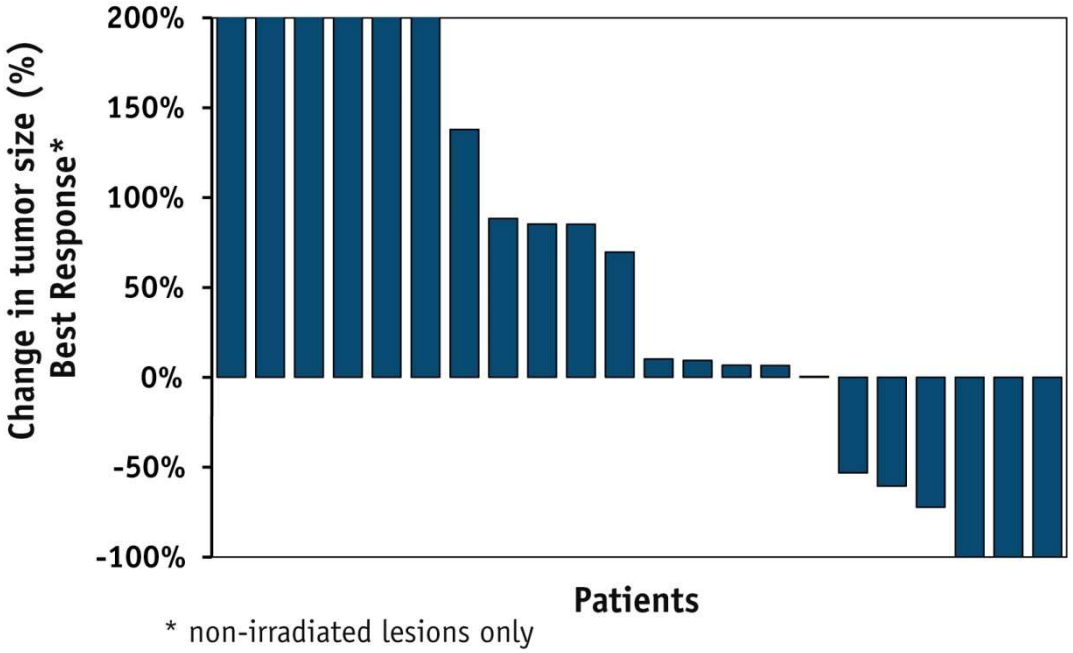


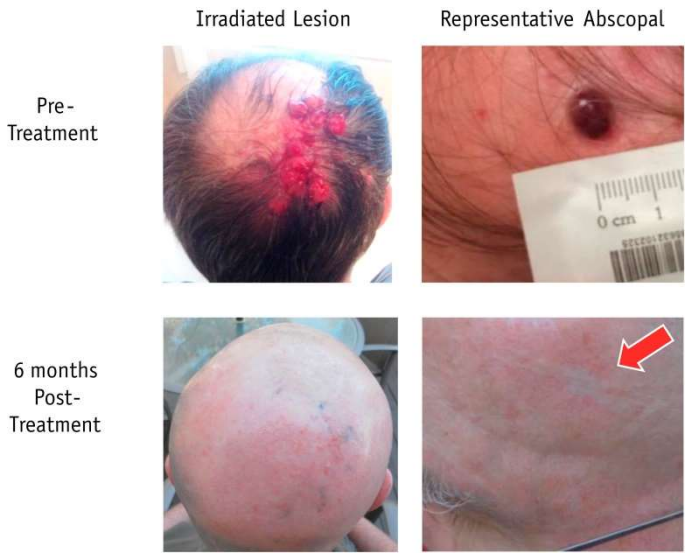
11/41 patients had abscopal responses (out-of-field)

-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

Stanford Pilot Study: Ipilimumab+ palliative RT



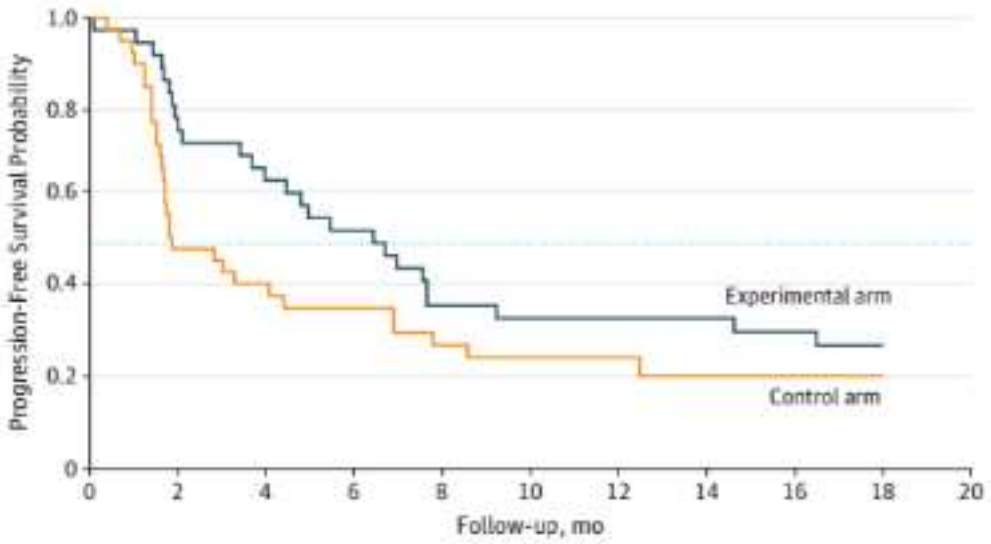


Hiniker SM et al. A Prospective Clinical Trial Combining Radiation Therapy With Systemic Immunotherapy in Metastatic Melanoma. IJROBP Nov 2016.

PEMBRO-RT Trial

-Multicenter phase II randomized trial of 92 metastatic NSCLC patients
-Primary outcome: Improvement in ORR at 12 weeks from 20% to 50% with p<0.10
-Trial did not meet pre-specified endpoint despite doubling of 12 week ORR (18% vs 36%)
-Median PFS 1.9 months versus 6.6 months

Response	Experimental Arm, No./Total No. (%) (n = 36)[a]	Control Arm, No./Total No. (%) (n = 40)[b]
Best overall response, No.		
Complete response	3	1
Partial response	14	8
Stable disease	9	10
Progressive disease	10	21
Objective response rate at 12 wk		
Overall[c]	13/36 (36)	7/40 (18)
PD-L1 TPS, %		
0	4/18 (22)	1/25 (4)
1-49	3/8 (38)	3/8 (38)
≥50	6/10 (60)	3/5 (60)
Disease control rate at 12 wk[d]	23/36 (64)	16/40 (40)

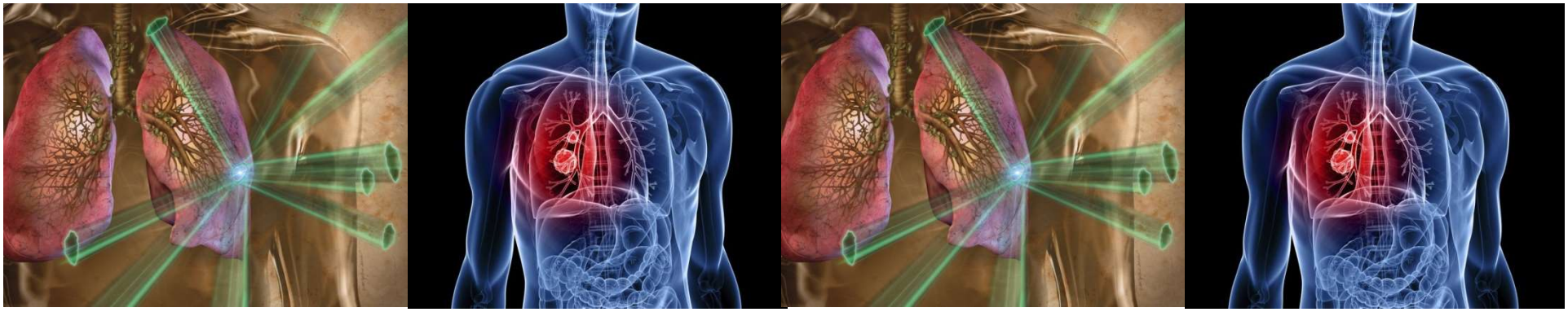


Theelen et al Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial. JAMA Oncol 2019

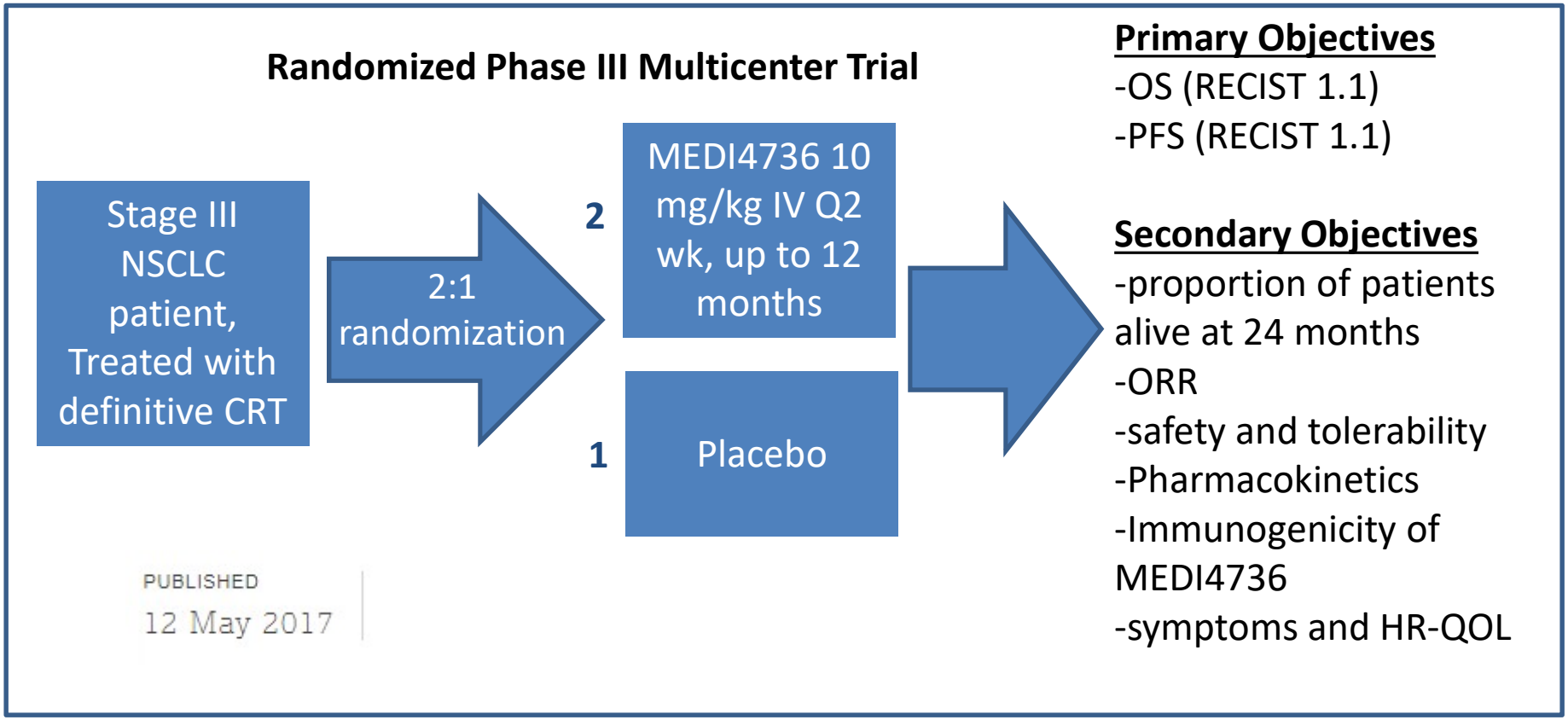
Moving Immunotherapy/RT Strategies to Earlier Stage Disease

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

- Locally Advanced disease
- Early Stage Disease

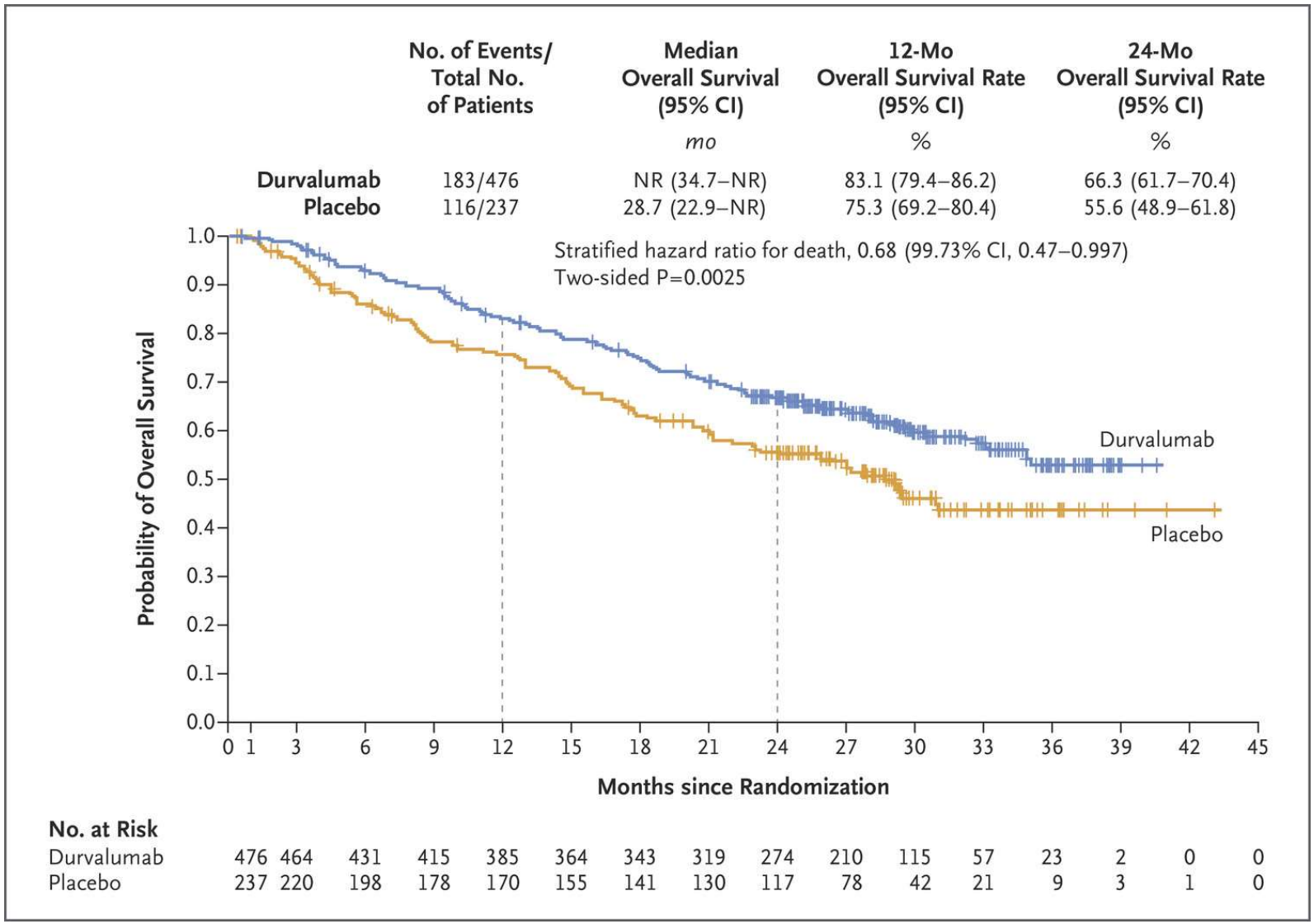


Moving Checkpoint Inhibitors to Earlier Stages: PACIFIC Trial: Stage III NSCLC



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.



Antonia SJ et al. N Engl J Med 2018

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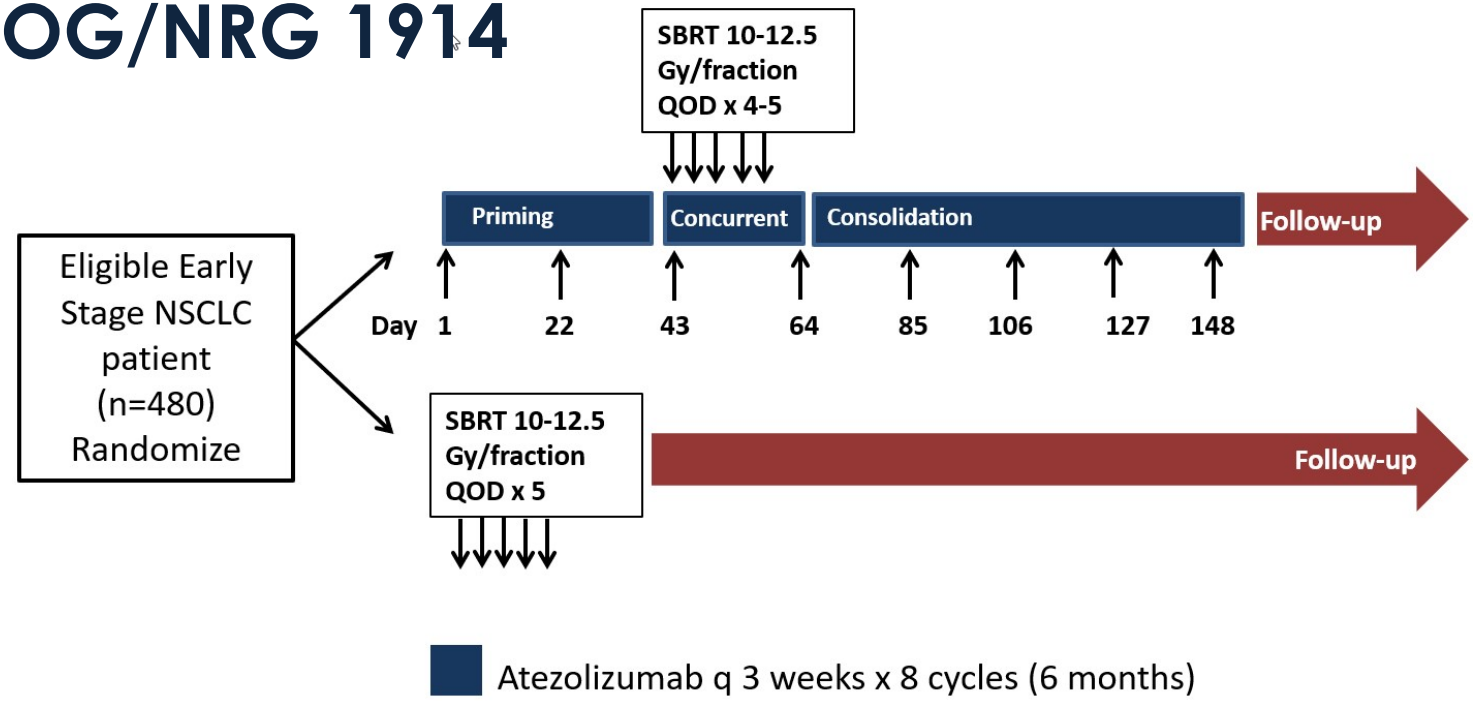


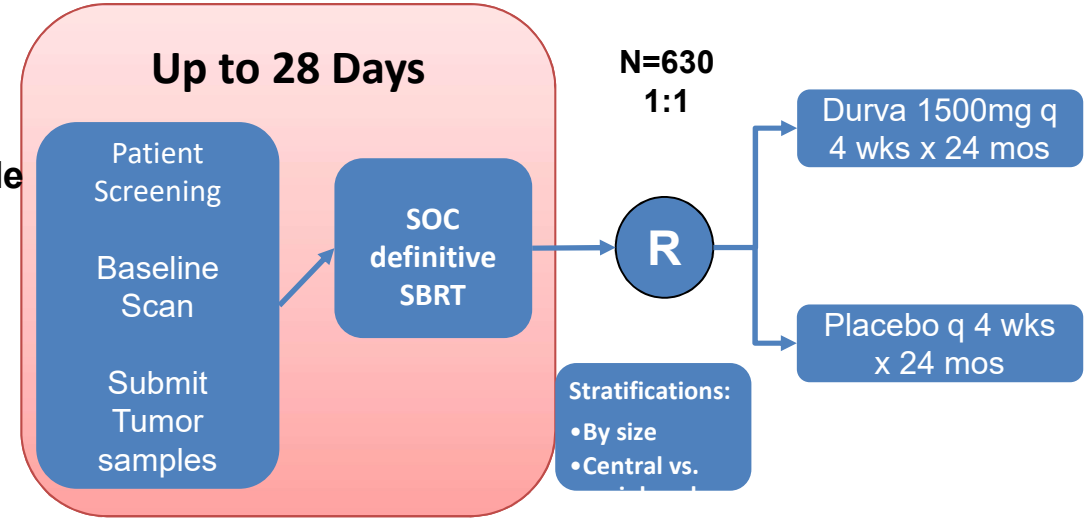
Eligibility: T1-2N0 NSCLC, medically inoperable or refused surgery
One of more high risk feature:
Tumor diameter ≥ 2 cm
Tumor SUV max ≥ 6.2
Grade 3 histology

Primary Outcomes: Overall Survival, Progression-Free Survival

PACIFIC 4 / RTOG 3515

Inclusion Criteria

- **Clinical Stage I/II node negative (T1 – T3 N0)**
- **Medically inoperable or refuse surgery**
- **ECOG PS 0-2**
- **All comers**



Primary Endpoint: PFS

Key Secondary Endpoint: OS

Lung Cancer Mortality

Additional Key points

- NSCLC proven by histology / cytology
- Tissue submission mandated – core preferred but will accept FNA samples for translational analysis
- SOC SBRT taking place during screening. SBRT planning can occur before study enrollment
- Randomization within **7 days of completion of SOC SBRT**

Slide Courtesy of Cliff Robinson MD

Safety Considerations: Synergistic Toxicity

Pneumonitis

PACIFIC trial: Pneumonitis requiring discontinuation of therapy: 4.8% in durvalumab group and in 2.6% in placebo group

Bladder and Bowel Toxicity

PLUMBB trial: Phase I trial stopped after 5 patients due to DLT with pembrolizumab and hypofractionated bladder RT

Three grade 3 urinary toxicities, attributable to therapy.

One grade 4 rectal perforation

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

Thank you!

Questions?