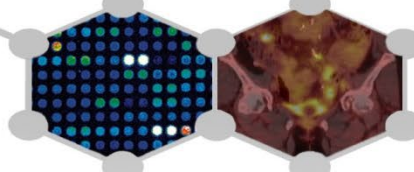

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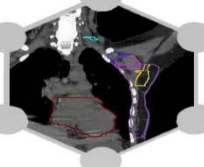

# A Randomized Phase III Trial of Induction/ Consolidation Atezolizumab + SBRT versus SBRT Alone in High risk, Early Stage NSCLC

## SWOG/NRG S1914

**Charles B. Simone, II, MD**

**July 23, 2022**

# Disclosures

- National Institutes of Health
  - R01-CA255748-01A1
  - R42-CA-199735-02
  - HHSN272201800011C
- Varian Medical Systems grants, honorarium

# Study Chairs

Principal Investigators:

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Co-Chairs:

Jeffrey Bradley, MD (NRG)

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Medical Oncology Co-Chair:

Jessica Bauman (NRG)

Translational Co-Chair:

Arta Monjazeb (NRG)

Physics Co-Chair:

Rojano Kashani (NRG)

QOL Co-Chair

Josephine Feliciano (NRG)

Statistician

Mary Redman (SWOG)

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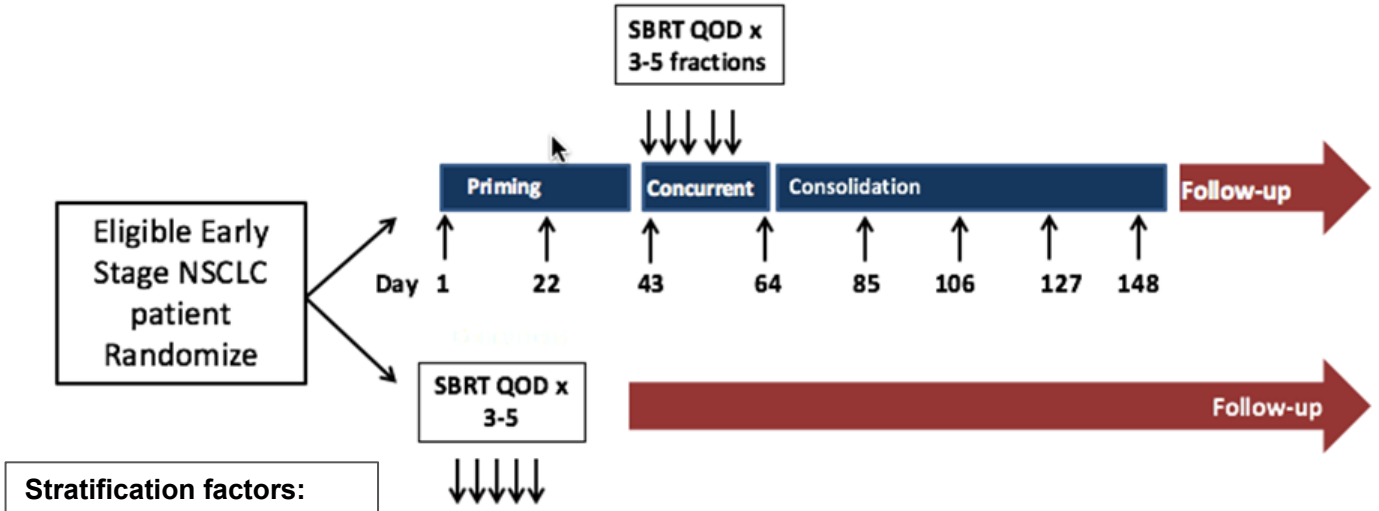
# Potential Benefits of Combining RT and Immunotherapy

- SBRT is less immunosuppressive than conventionally fractionated RT or sx
  - SBRT specifically can even be immunostimulatory and deplete immunosuppressive cells
- RT can improve antigen presentation by antigen presenting cells
  - SBRT specifically can release high levels of tumor antigens
- SBRT upregulates immunogenic cell surface markers (ie. MHC-1)
- SBRT can induce immunogenic cell death
- RT and especially SBRT can increase homing of immune cells to tumor
- RT can recruit regulatory T cells (Tregs)
- RT can shift tumor-associated macrophages polarization from M2 to M1
- RT can induce secretion of danger signals and cytokines (ie. TNFalpha)
- RT can upregulate cell-surface expression of PD-L1

# Rationale for Immunotherapy in Early Stage NSCLC

- Surgical lobectomy is standard-of-care for fit patients with early stage, resectable NSCLC
  - Adjuvant chemotherapy indicated for high-risk factors, improves OS
  - Adjuvant immunotherapy may further improve outcomes, reduce toxicity profiles
    - IMpower010 improved DFS, ECOG-ACRIN EA5142 ANVIL phase III trial completed accrual
- SBRT is standard-of-care for medically inoperable, early stage NSCLC and can achieve excellent local control (>90%), but regional and distant failures remain significant (15-25%)
  - Adjuvant chemotherapy is typically not used following SABR (limited data, chemo is not well tolerated in this typically frail, inoperable population with multiple comorbidities)
- Immunotherapy may allow for fewer nodal and distant failures and be well tolerated when given before, during, or after SBRT for early stage NSCLC

# S1914 Schema

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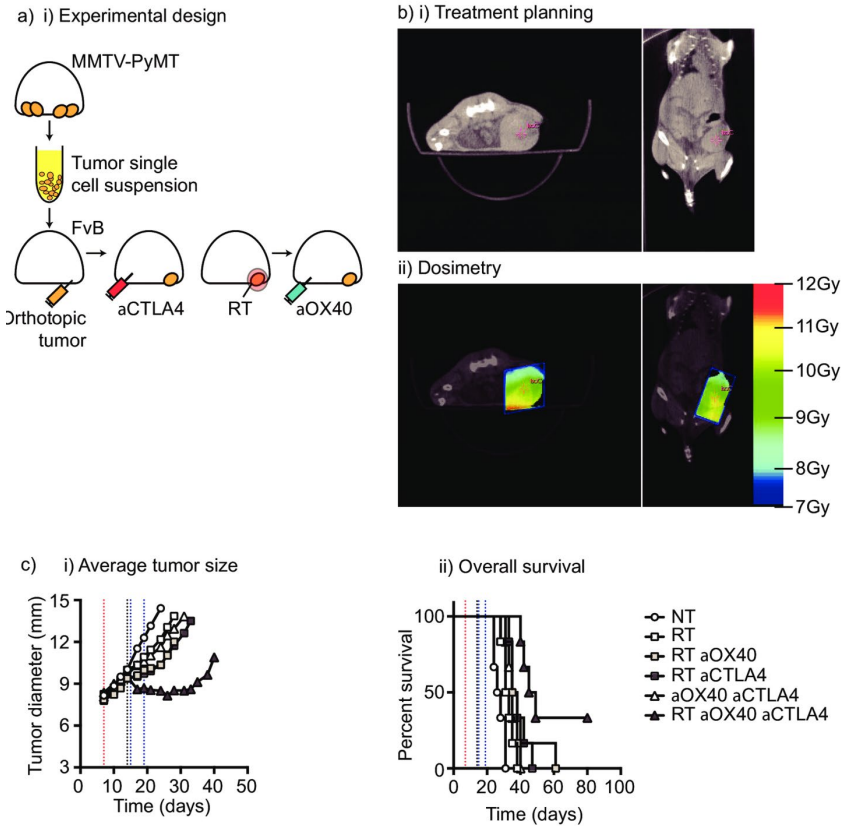
# SBRT + Immunotherapy: The Importance of Timing

- Tumor bearing mice treated to 20 Gy RT with either anti-CTLA-4 or OX40 agonist antibody
- Anti-CTLA-4 most effective when given prior to RT
  - Potentially due to regulatory T cell depletion
- OX40 agonist most effective when delivered following RT
- Optimal timing of immunotherapy and RT depends on mechanism of immunotherapy action

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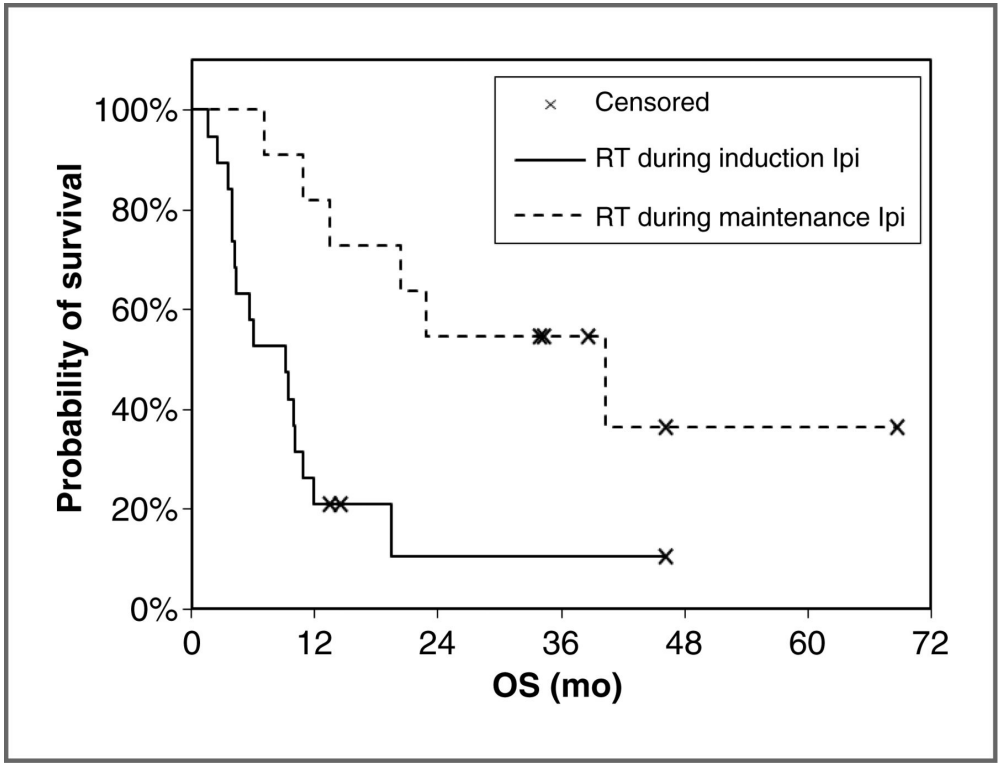
# RT + Immunotherapy: The Importance of Timing

- MSKCC retrospective study of melanoma patients treated with ipilimumab and extracranial RT
- Median OS: 9 months when RT given during induction vs. 39 months when RT given during maintenance

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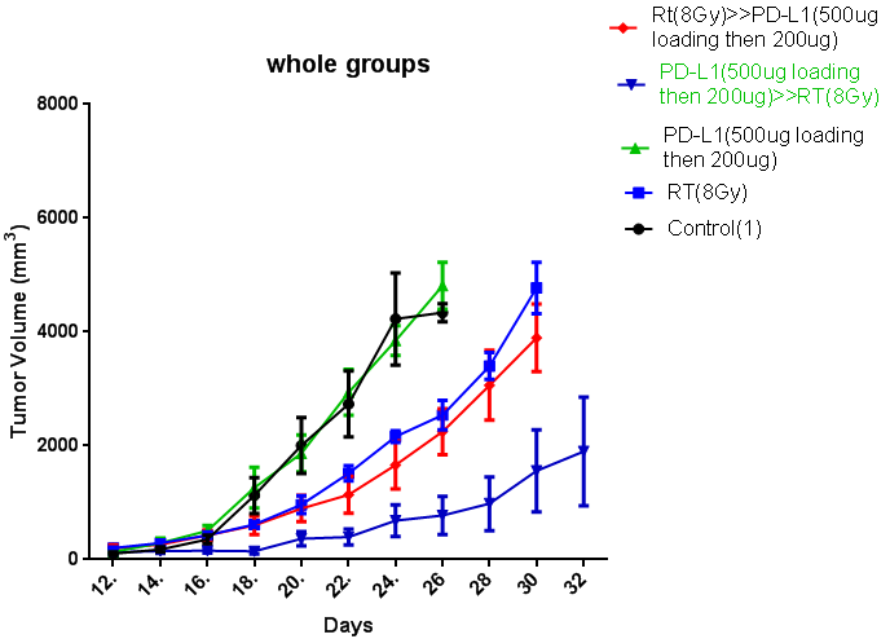
# Timing of Immunotherapy and SBRT




Significantly superior tumor control was achieved in Balb/c mice when the PD-L1 blockade was delivered prior to radiotherapy to 8 Gy

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# Objectives

- Hypothesis: the addition of atezolizumab to standard SBRT for early stage, medically inoperable NSCLC will improve overall survival and progression free survival as compared to SBRT alone
- Primary objective: compare overall survival in medically inoperable, early stage NSCLC patients randomized to SBRT with or without atezolizumab
- Secondary objectives:
  - Progression free survival
  - Distant, locoregional, and local failure rates
  - Frequency and severity of toxicities
  - Quality of life

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# Inclusion and Exclusion

Inclusion criteria

- Adults ≥18 years of age
- Histologically proven stage I-IIA or limited T3N0M0 (stage IiB) NSCLC ≤7 cm diameter without nodal or distant involvement
- Medically or surgically inoperable OR unwilling to undergo surgical resection
- Zubrod performance status score of 0-2
- FEV1 ≥ 700cc and a DLCO ≥ 5.5 m/min/mmHg
- Archival tumor sample available (FNA allowed, core needle biopsy preferred)
- One or more high-risk features identified:
  - Tumor diameter ≥ 2 cm
  - Tumor SUV max ≥ 6.2
  - Moderately or poorly differentiated or undifferentiated histology

Exclusion Criteria

- Uncontrolled concomitant disease
- Significant cardiovascular disease (NYHA Class II or greater); myocardial infarction within 3 months prior to randomization, unstable arrhythmias/angina, known left ventricular ejection fraction<40%
- Severe infection within four weeks prior to enrollment
- History of autoimmune disease other than stable hypothyroidism or controlled type II diabetes.
- HIV, Hepatitis B, Hepatitis C
- History of idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia
- Systemic immunostimulatory/immunosuppressive agents within 4 weeks or 5 half-lives of drug prior to enrollment

# Treatment Details

- SBRT (starts with cycle 3 [week 7] in Arm A)

| Dose per fraction | Number of Fractions | Total Dose | $BED_{10}$ | Tumor Sites |
|---|---|---|---|---|
| **18 Gy** | 3 | 54 Gy | 151.2 Gy | Peripheral |
| **12.5 Gy** | 4 | 50 Gy | 112.5 Gy | Peripheral or Central |
| **12 Gy** | 4 | 48 Gy | 105.6 Gy | Peripheral or Central |
| **12 Gy** | 5 | 60 Gy | 132 Gy | Peripheral or Central |
| **11 Gy** | 5 | 55 Gy | 115.5 Gy | Central |
| **10 Gy** | 5 | 50 Gy | 100 Gy | Central |

- Atezolizumab
  - 1200 mg IV over 60 min Q21 days for up to 8 cycles in Arm A

# Statistical Design and Accrual

- Primary Objective: OS
  - N=432 eligible patients (480 enrolled, assuming 10% ineligible)
  - 80% power to detect HR of 0.70 (43% improvement in OS), 1-sided 0.025 level
- Secondary Objective: PFS
  - 90% power to detect HR of 0.65, 1-sided 0.025 level
- Interim Analysis
  - Four annual interim analyses: all analyses will evaluate early stopping for futility (based on PFS), the 3rd and 4th will also evaluate early stopping for efficacy (based on OS)
- Accrual
  - 8 patients per month
  - Accrual duration 5 years

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# Laboratory Correlatives Planned

- We are collecting baseline tissue and baseline and on-treatment blood samples for banking

| Assay | Location | Methods |
|---|---|---|
| 1. Tumor-associated immune cell characterization | Genentech Dr. Schulze | Nanostring on RNA isolated from FFPE tissue |
| 2. PD-L1 | Dr. Hirsch's Lab | IHC - Dako 22c3 assay on FFPE tissue |
| 3. Circulating ICOS+ CD4+ T cells | UC Davis HIMC* Dr. Monjazeb | Multi-color flow cytometry on PBMCs |
| 4. Tumor mutation burden | Genentech / FM* | Foundation Medicine ACT assay on cell free DNA from blood |
| 5. ctDNA overall allele frequency | Genentech / FM* | Foundation Medicine ACT assay on cell free DNA from blood |
| 6. PBMC immune profiling | UC Davis HIMC* Dr. Monjazeb | Multi-color flow cytometry on PBMCs |
| 7. T cell receptor repertoire | UC Davis HIMC* Dr. Monjazeb | TCR deep sequencing on RNA extracted from PBMCs |
| 8. Plasma PD-L1 | Dr. Hirsch's Lab | NGS on cell free RNA obtained from plasma |

*HIMC – Human Immune Monitoring Core; FM – Foundation Medicine

# Important Study Amendments

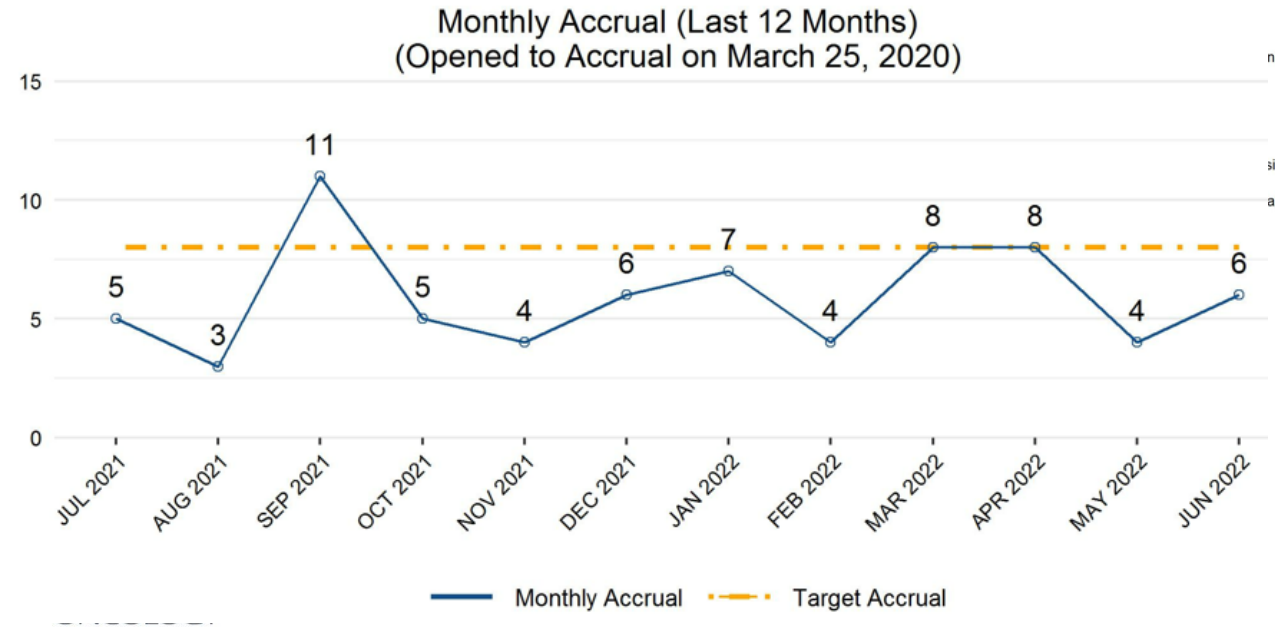
- May 2021 Amendment Highlights
  - Clarified normal tissue volume/volume constraints (ie. chest wall/ribs are guidelines rather than hard constraints)
  - Relaxed eligibility criteria around prior/concurrent malignancies (now only excludes prior/ concurrent malignancies if the treating investigator believes the malignancy or treatment has potential to interfere with the safety or efficacy assessment of the investigational regimen)
  - Added optional QOL questionnaire
  - Clarified the response assessment criteria after SBRT to aligned with prior cooperative group SBRT trials and to provided clarity on how to assess patients suspected of recurrence
- 2022 Amendment Highlights (conditional approval CTEP, under final review)
  - Clarifies eligibility (ie. 2 cm inclusion cutoff is inclusive of non-solid, ground glass component)
  - Allows up to 2 synchronous early stage primaries to be treated (previously limited to 1 lesion)
    - At least 1 must be biopsy confirmed
  - Allows 7.5 Gy x 8 for central tumors (previously required ≤5 fractions)

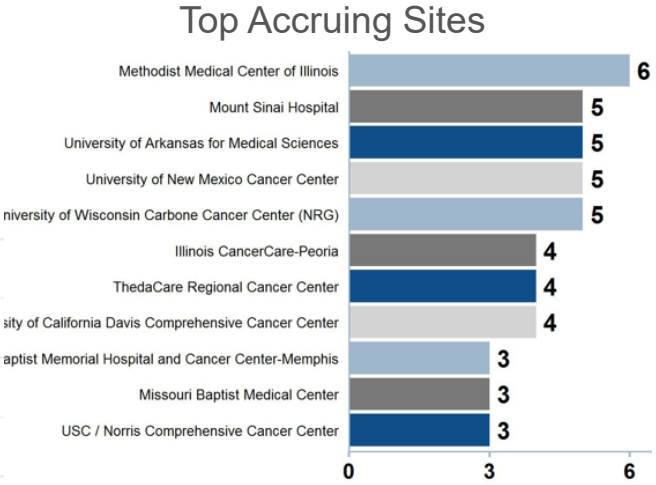
# Competing Trials

- Currently 2 competing trials for the same patient population, both industry sponsored (PACIFIC-4 and KEYNOTE-867)
  - S1914 uses **shorter duration immunotherapy** (6 months) vs. 24 months and 12 months, respectively
  - S1914 **does not require placebo** infusions
  - Timing of immunotherapy relative to SBRT in S1914 is **based on preclinical data** showing increase synergy between SBRT and immunotherapy when immunotherapy is delivered first to prime the immune response
  - S1914 allows sites to gain **accrual credit** with cooperative groups

# Study Status and Contact Information

- Study activation date: 5/28/20
- Current accrual: 109 of 480



# Questions or Suggestions

- Entire Study Team – S1914medicalquestion@swog.org
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- Megan Daly – medaly@ucdavis.edu