



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

SWOG/NRG S1914

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NRG Oncology



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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Medical Oncology Co-Chair:

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Translational Co-Chair:

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Rojano Kashani (NRG)

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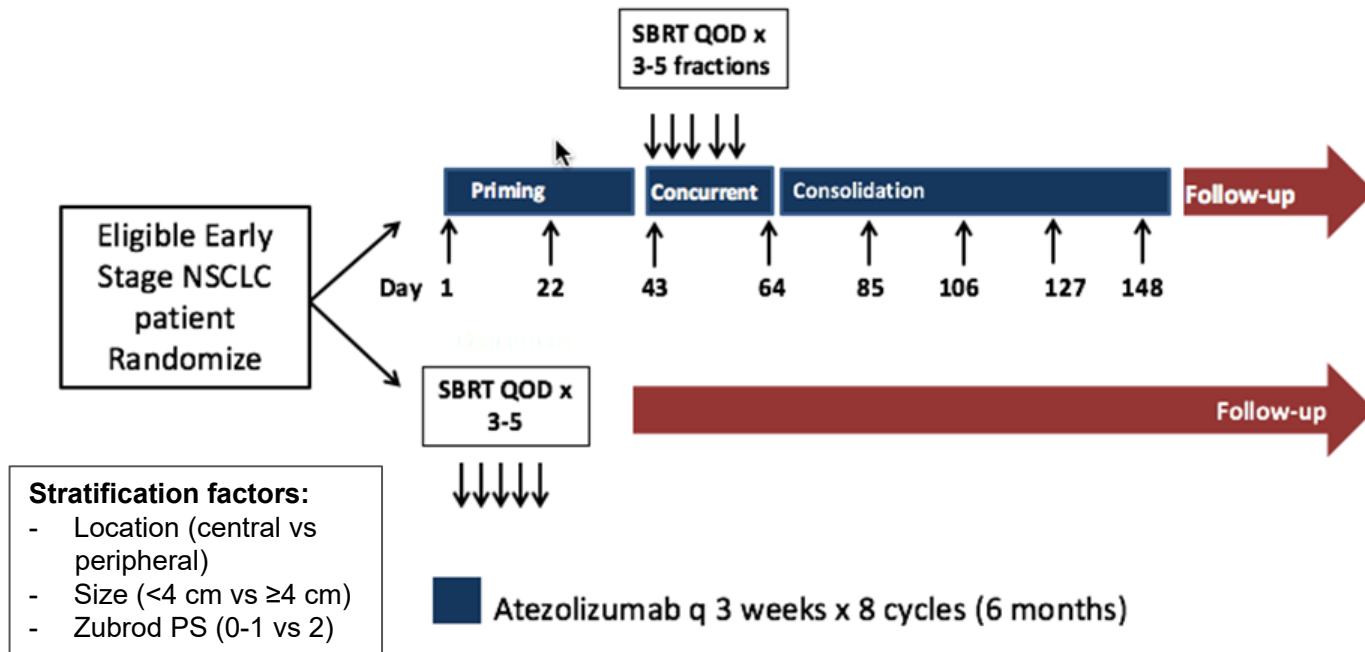
Potential Benefits of Combining RT and Immunotherapy

- 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

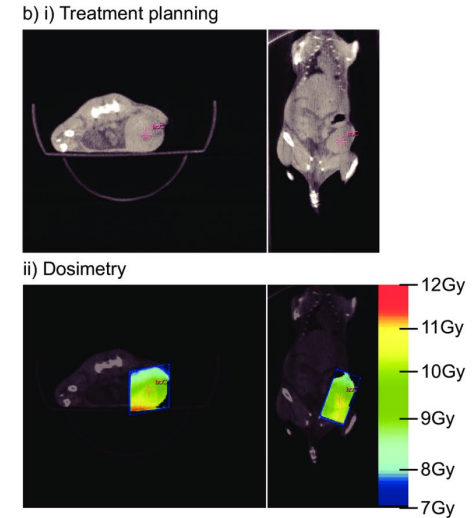
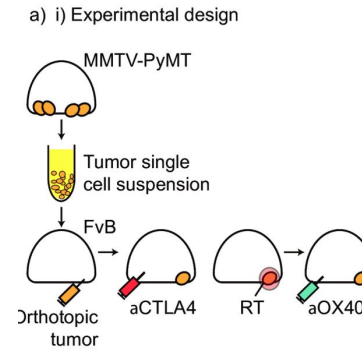
- Surgical lobectomy is standard-of-care for fit patients with early stage, resectable NSCLC
 - Adjuvant chemotherapy indicated for high-risk factors, improves OS
 - Adjuvant immunotherapy may further improve outcomes, reduce toxicity profiles
 - IMpower010 improved DFS, ECOG-ACRIN EA5142 ANVIL phase 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

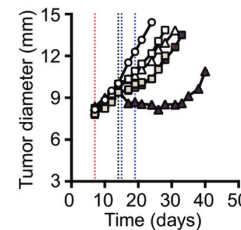


SBRT + Immunotherapy: The Importance of Timing

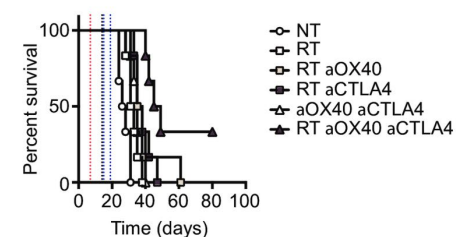
- Tumor bearing mice treated to 20 Gy RT with either anti-CTLA-4 or OX40 agonist antibody
- Anti-CTLA-4 most effective when given prior to RT
 - Potentially due to regulatory T cell depletion
- OX40 agonist most effective when delivered following RT
- Optimal timing of immunotherapy and RT depends on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



c) i) Average tumor size

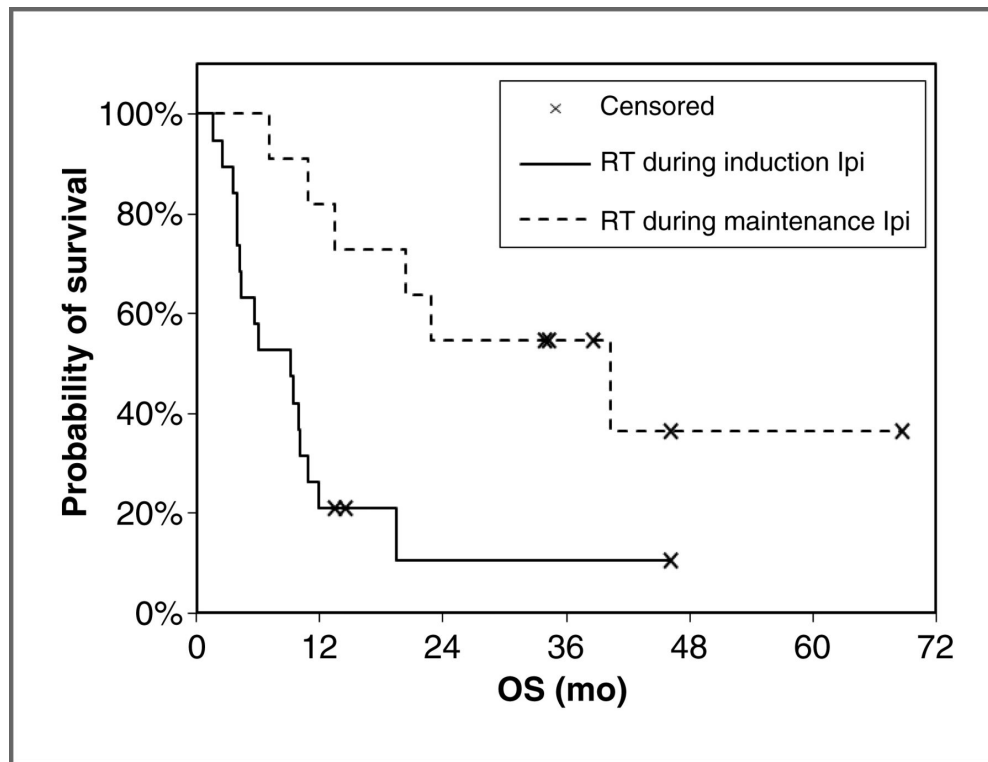


ii) Overall survival

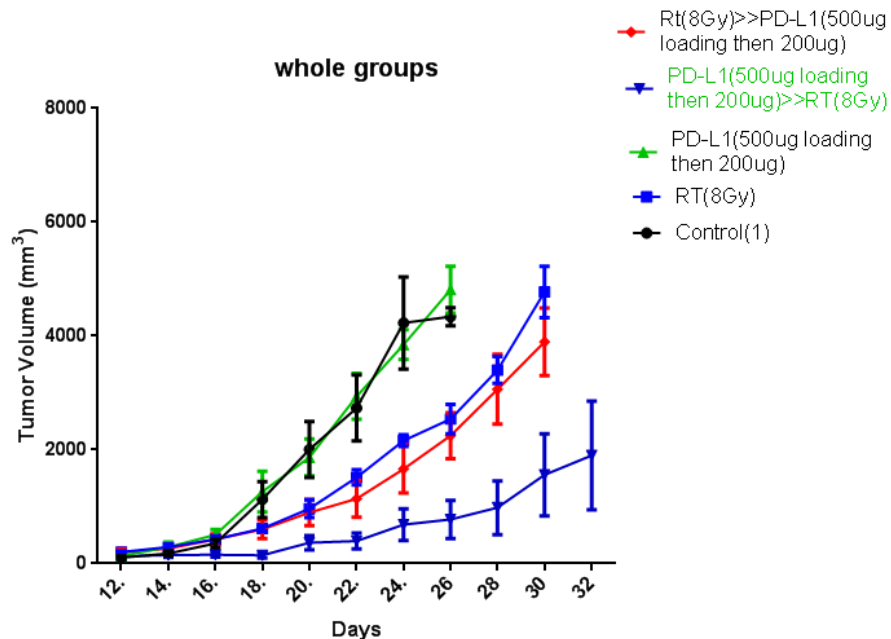


RT + Immunotherapy: The Importance of Timing

- 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



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

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

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 ≥ 700 cc 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

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)

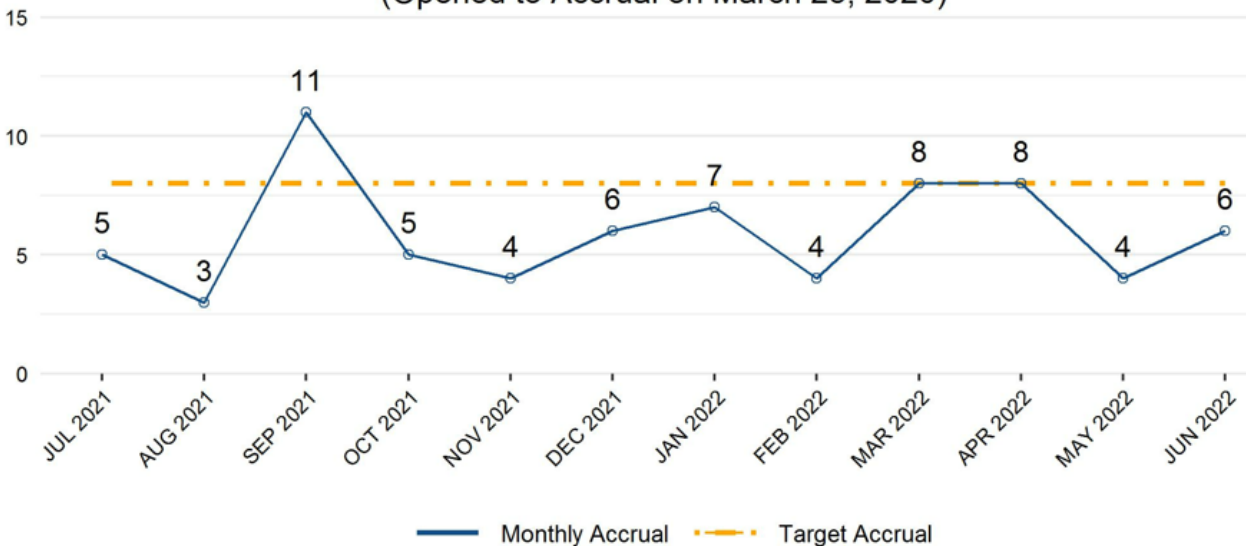
Competing Trials

- 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

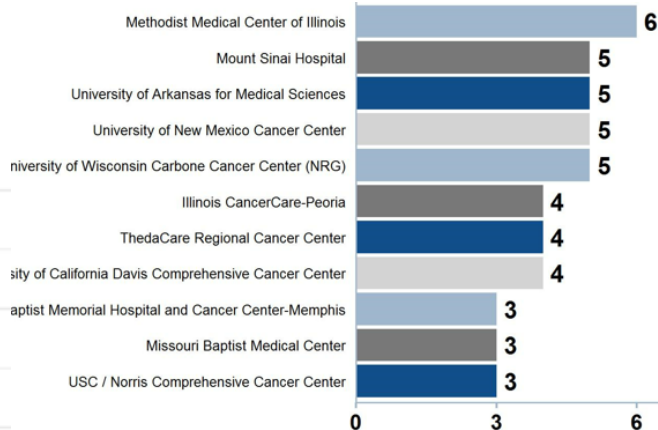
Study Status and Contact Information

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

Monthly Accrual (Last 12 Months)
(Opened to Accrual on March 25, 2020)



Top Accruing Sites



Questions or Suggestions

- Entire Study Team – S1914medicalquestion@swog.org
- Charles Simone – csimone@nyproton.com
- Megan Daly – medaly@ucdavis.edu