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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Disclosures

• National Institutes of Health
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  • R42-CA-199735-02
  • HHSN272201800011C

• Varian Medical Systems grants, honorarium
Study Chairs

Principal Investigators:
Charles B. Simone, II (NRG)
Megan Daly (SWOG)

Co-Chairs:
Jeffrey Bradley, MD (NRG)
Karen Kelly (SWOG)

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)
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

Stratification factors:
- Location (central vs peripheral)
- Size (<4 cm vs ≥4 cm)
- Zubrod PS (0-1 vs 2)

Eligible Early Stage NSCLC patient Randomize

Priming Concurrent Consolidation Follow-up

Day 1 22 43 64 85 106 127 148

SBRT QOD x 3-5

Follow-up

SBRT QOD x 3-5

Atezolizumab q 3 weeks x 8 cycles (6 months)
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
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
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 ≥ 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)

<table>
<thead>
<tr>
<th>Dose per fraction</th>
<th>Number of Fractions</th>
<th>Total Dose</th>
<th>BED_{10}</th>
<th>Tumor Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 Gy</td>
<td>3</td>
<td>54 Gy</td>
<td>151.2 Gy</td>
<td>Peripheral</td>
</tr>
<tr>
<td>12.5 Gy</td>
<td>4</td>
<td>50 Gy</td>
<td>112.5 Gy</td>
<td>Peripheral or Central</td>
</tr>
<tr>
<td>12 Gy</td>
<td>4</td>
<td>48 Gy</td>
<td>105.6 Gy</td>
<td>Peripheral or Central</td>
</tr>
<tr>
<td>12 Gy</td>
<td>5</td>
<td>60 Gy</td>
<td>132 Gy</td>
<td>Peripheral or Central</td>
</tr>
<tr>
<td>11 Gy</td>
<td>5</td>
<td>55 Gy</td>
<td>115.5 Gy</td>
<td>Central</td>
</tr>
<tr>
<td>10 Gy</td>
<td>5</td>
<td>50 Gy</td>
<td>100 Gy</td>
<td>Central</td>
</tr>
</tbody>
</table>

- 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

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

- Methodist Medical Center of Illinois: 6
- Mount Sinai Hospital: 5
- University of Arkansas for Medical Sciences: 5
- University of New Mexico Cancer Center: 5
- University of Wisconsin Carbone Cancer Center (NRG): 5
- Illinois CancerCare-Peoria: 4
- ThedaCare Regional Cancer Center: 4
- City of California Davis Comprehensive Cancer Center: 4
- Baptist Memorial Hospital and Cancer Center-Memphis: 3
- Missou Baptist Medical Center: 3
- USC / Norris Comprehensive Cancer Center: 3
Questions or Suggestions

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