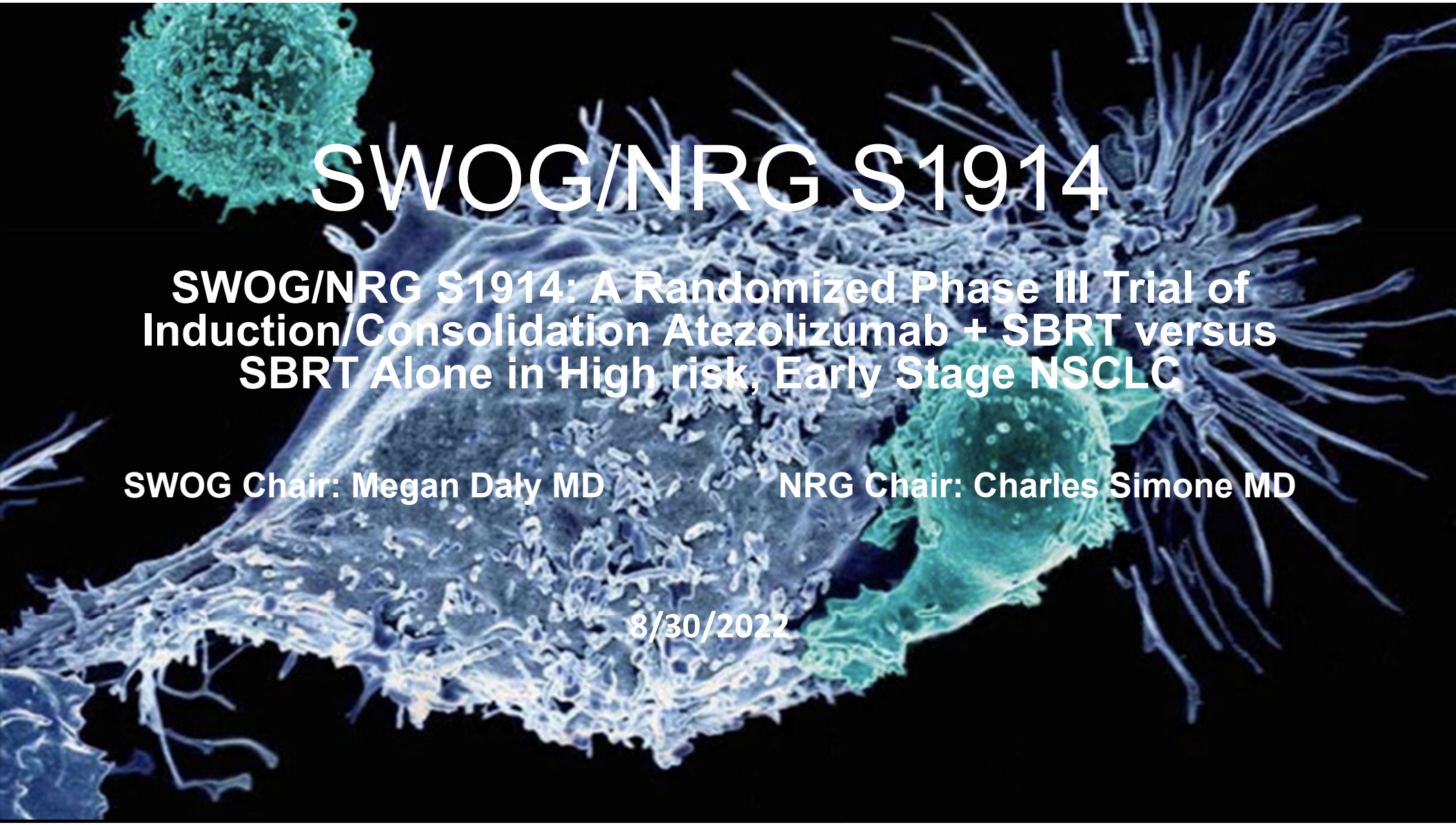

SWOG/NRG S1914

SWOG/NRG S1914: A Randomized Phase III Trial of Induction/Consolidation Atezolizumab + SBRT versus SBRT Alone in High risk, Early Stage NSCLC

SWOG Chair: Megan Daly MD **NRG Chair: Charles Simone MD**

8/30/2022

Study Chairs

Principal Investigators:

Megan Daly (SWOG)

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Co-Chairs:

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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)

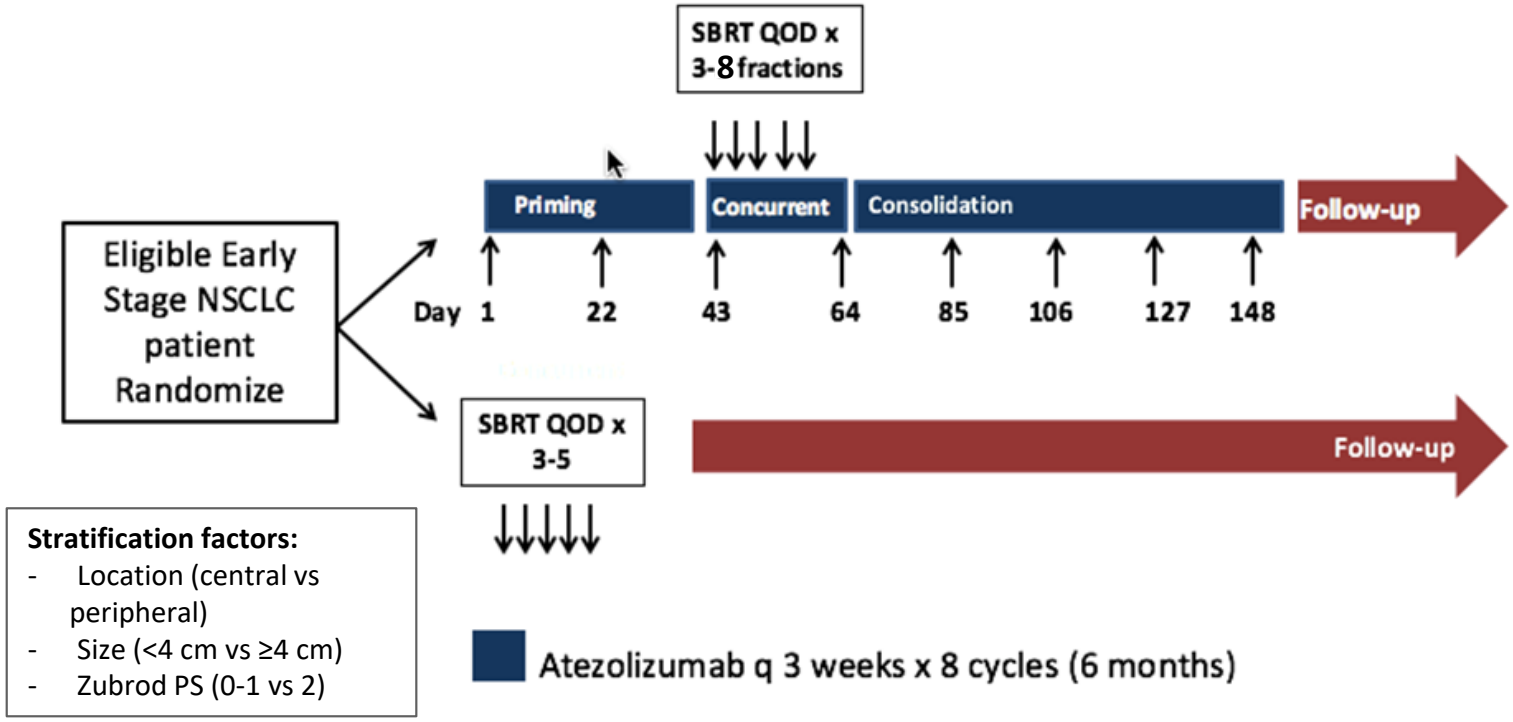
Potential Benefits of Combining RT and Immunotherapy

- 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

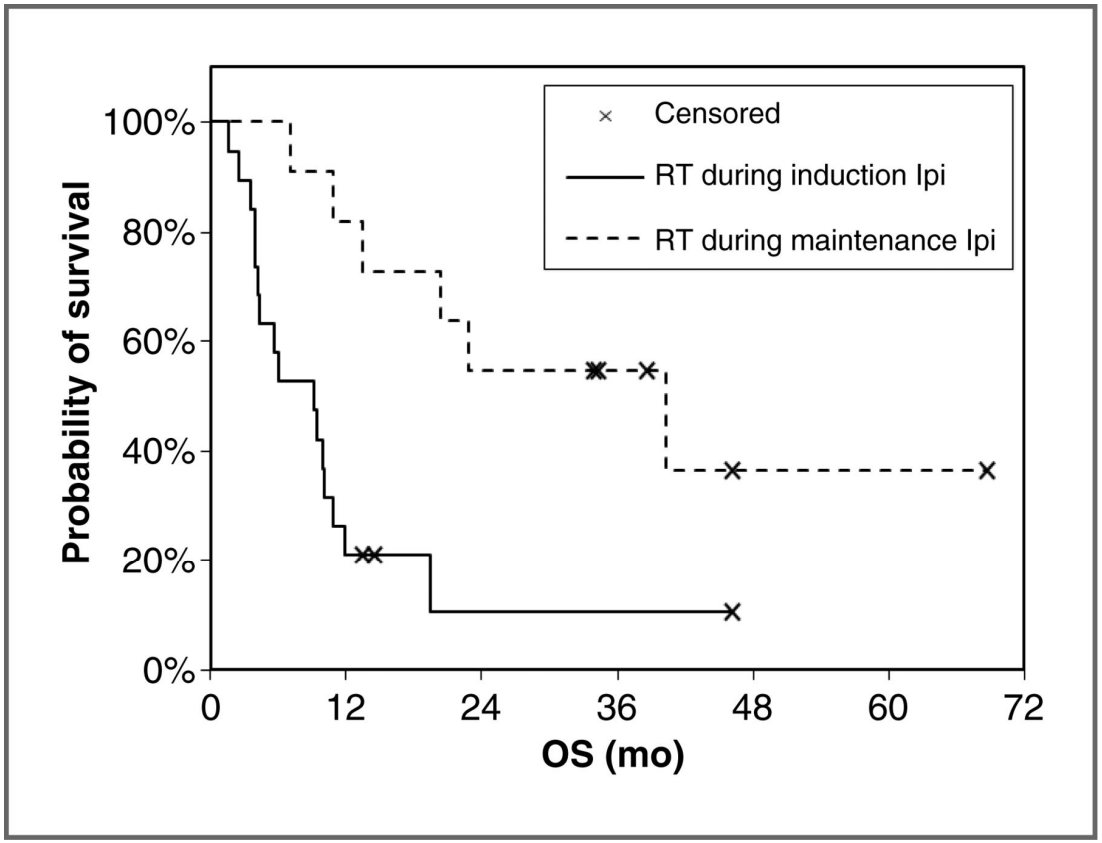
- Surgical lobectomy is standard-of-care for fit patients with early stage, resectable NSCLC
  - Adjuvant chemotherapy indicated for high-risk factors, improves OS
  - Adjuvant immunotherapy may further improve outcomes, reduce toxicity profiles
    - IMpower010 improved DFS, ECOG-ACRIN EA5142 ANVIL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



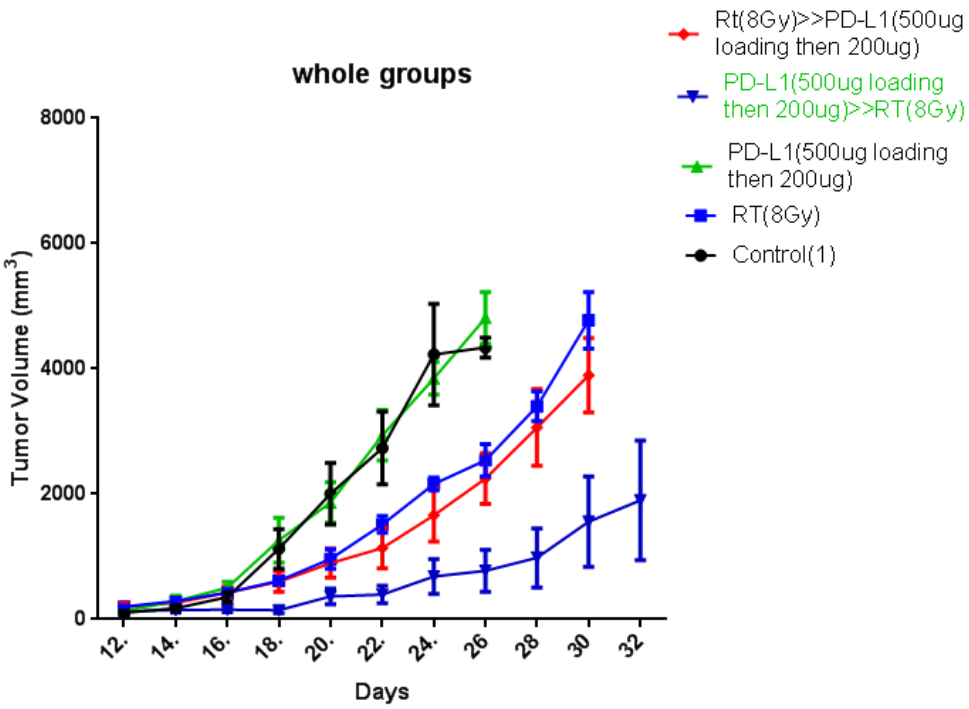
RT + Immunotherapy: The Importance of Timing

- 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



Barker CA, et al. *Cancer Immunol Res*. 2013;1(2):92-98.

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
- 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

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

July 2022 Amendment Highlights

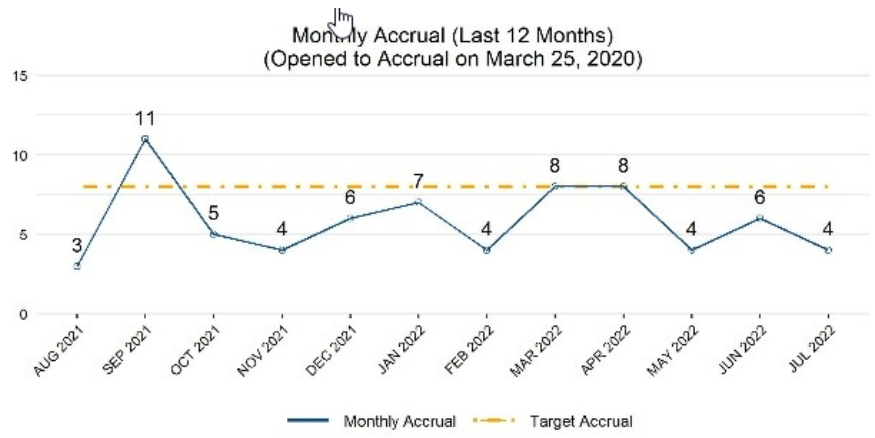
- Clarifies tumor diameter eligibility (ie. 2 cm inclusion cutoff **is inclusive of non-solid, ground glass component**)
- Allows **up to 2 synchronous early-stage primaries** to be treated (previously limited to 1 lesion)
  - At least 1 must be biopsy confirmed
- **Allows 7.5 Gy x 8 fx** for central tumors (previously required ≤5 fractions)
- Minimum PFT values no longer mandated
- Clarification that assessment timepoints are based on date of randomization

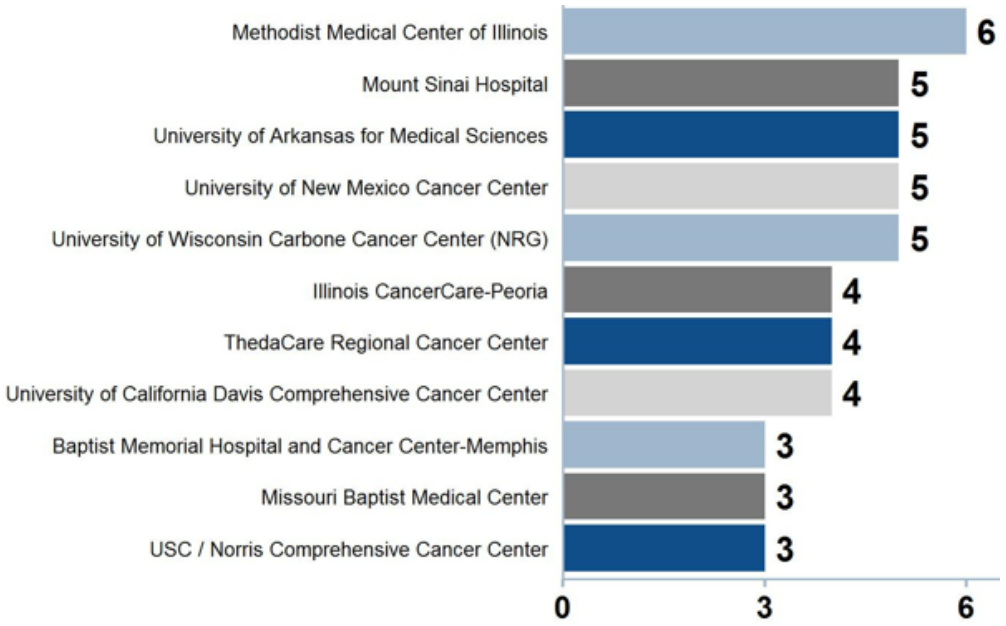
Competing Trials

- 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: 120 of 480 – 25% of target accrual





Questions or Suggestions

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