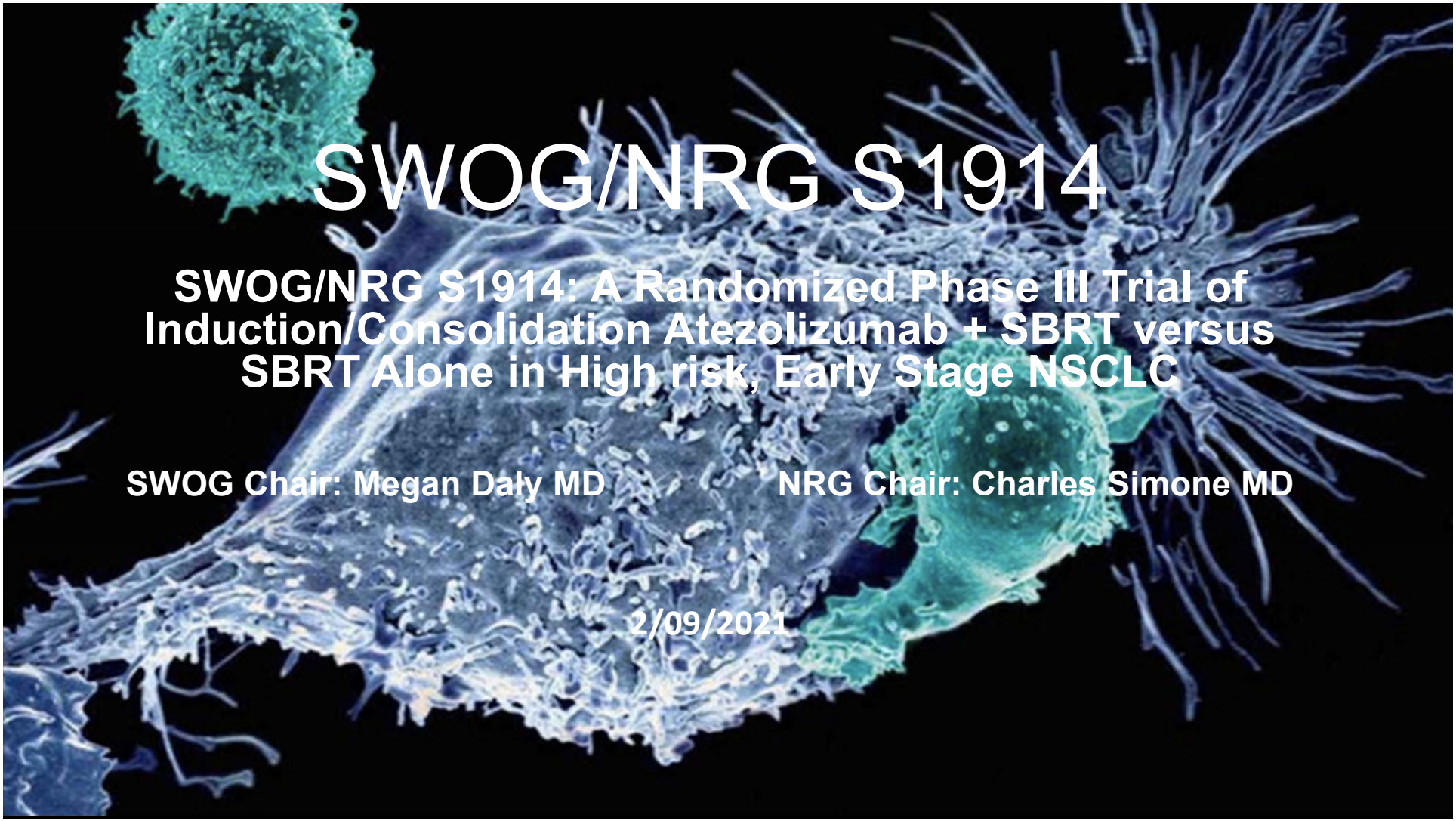

SWOG/NRG S1914

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

2/09/2021

Study Chairs

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Translational Co-Chair:

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Physics Co-Chair:

Rojano Kashani (NRG)

QOL Co-Chair

Josephine Feliciano (NRG)

Statistician

Mary Redman (SWOG)

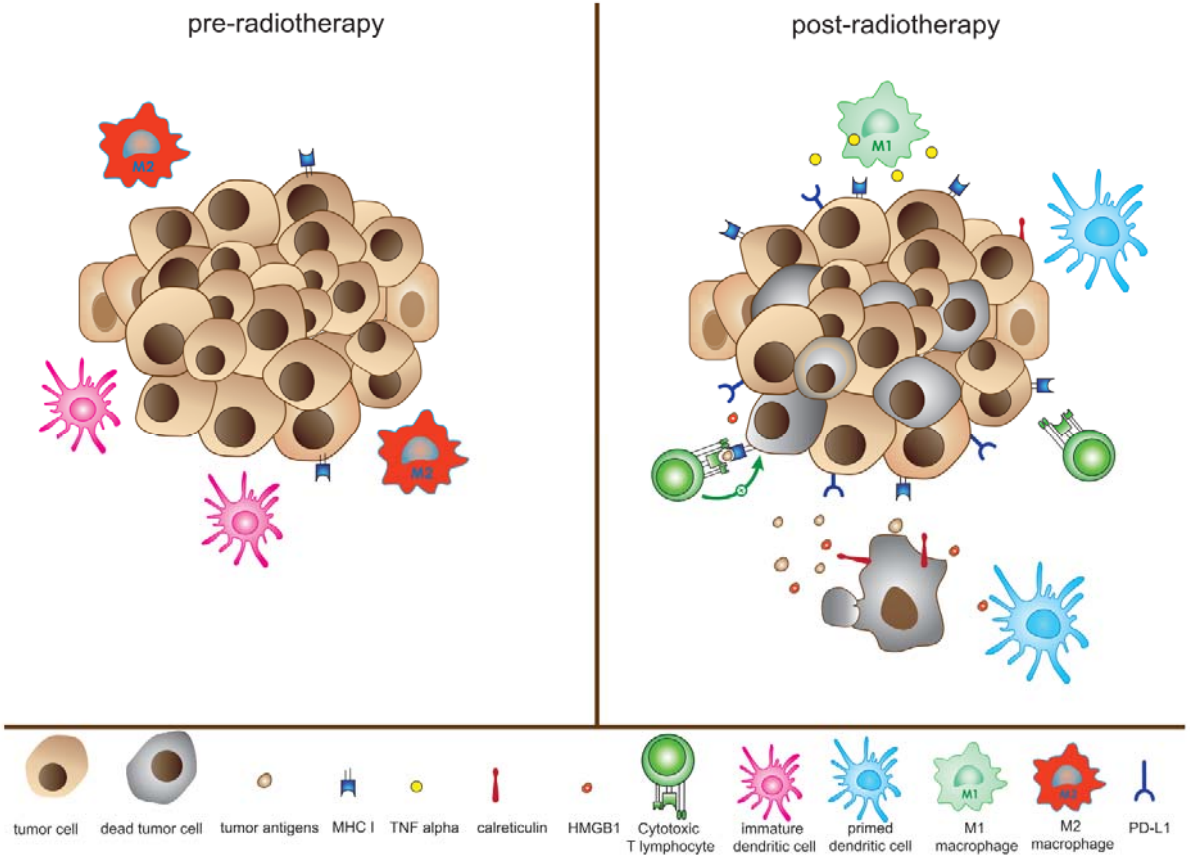
Rationale for Immunotherapy in Early Stage NSCLC

- 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 of interest to further improve outcomes, reduce toxicity profiles
    - 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 medical 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

Potential Benefits of Combining RT and Immunotherapy

- SBRT is less immunosuppressive than conventionally fractionated RT or surgery
  - 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

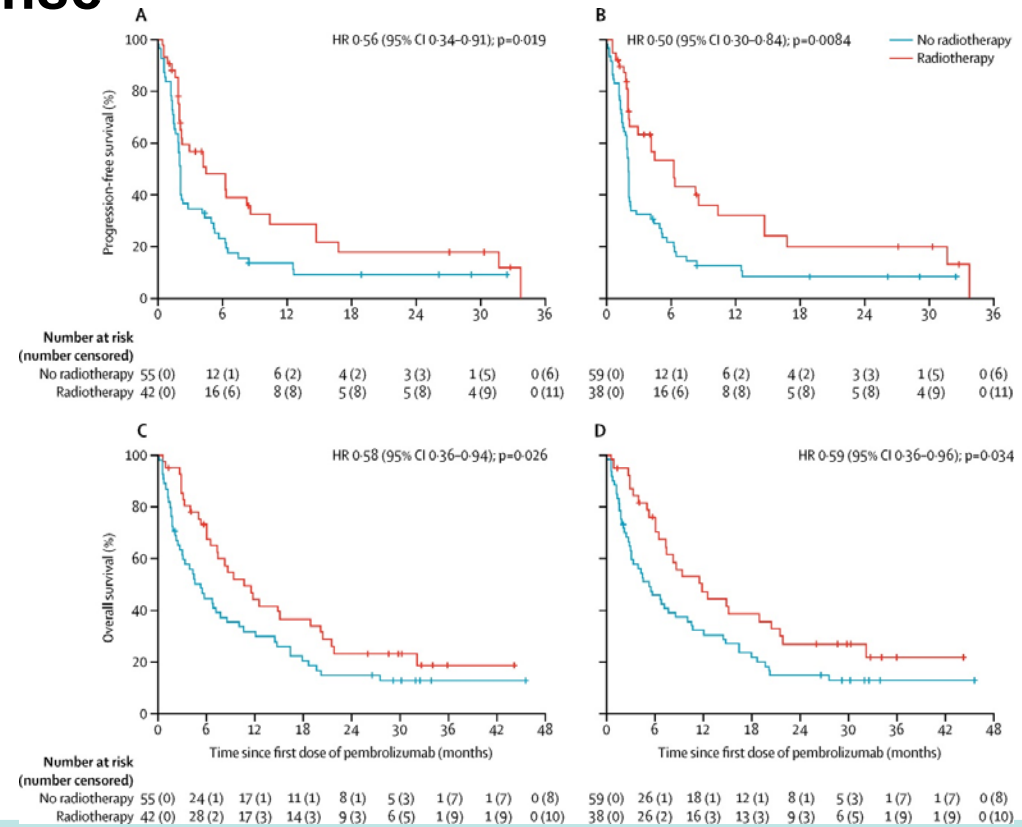
Radiation-Induced Immune Activation



- Homing of cytotoxic T lymphocytes to the tumor microenvironment
- Maturation of dendritic cells
- Down-regulation of immunosuppressive cells like myeloid derived suppressor cells
- Secretion of cytokines
- Shifting tumor associated macrophage polarization to M1

Daly ME, et al. *J Thorac Oncol*. 2015;10(12):1685-93.

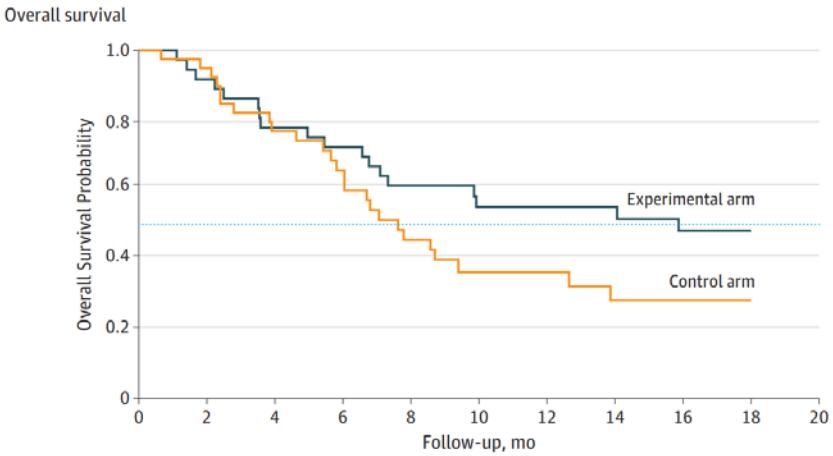
Lessons from Stage IV NSCLC: Secondary Analysis of KEYNOTE-001 (Pembro for Stage IV NSCLC) - Effect of Prior RT on Response



Shaverdian N, et al. *Lancet Oncol*. 2017;18(7):895-903.

Lessons Learned from Stage IV NSCLC – PEMBRO-RT Trial

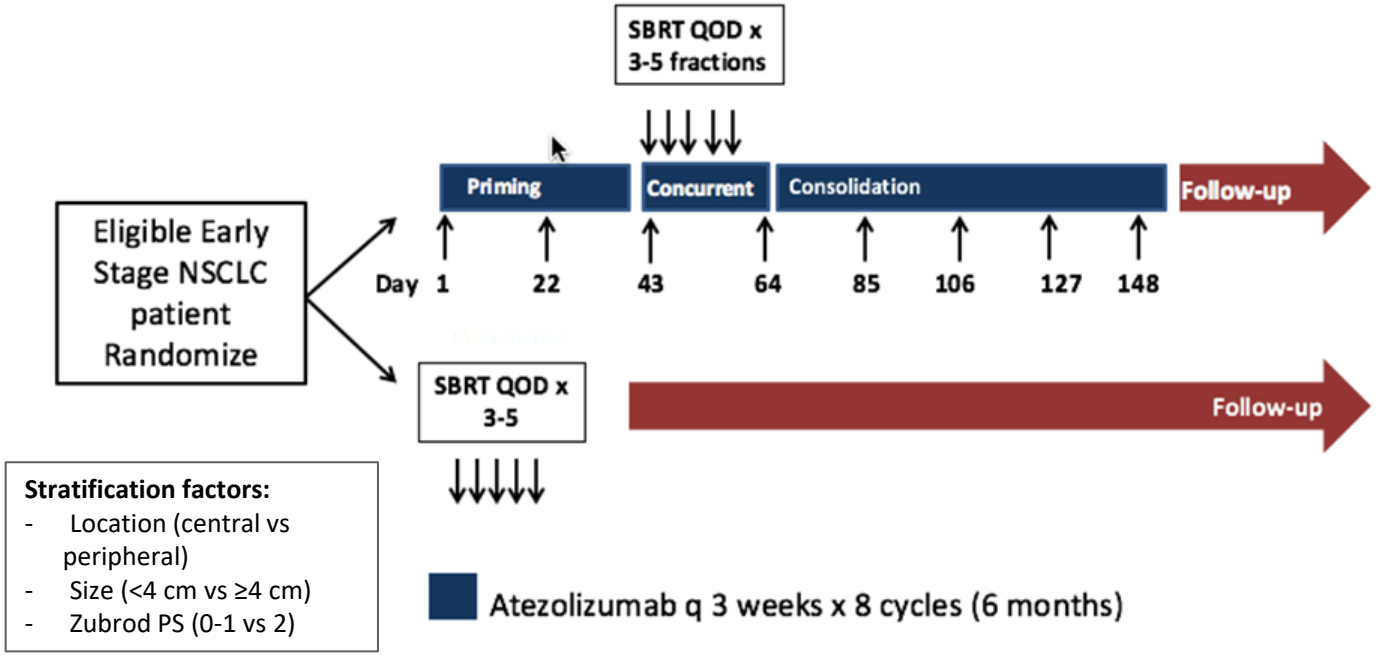
- Multicenter phase 2 study (PEMBRO-RT) of 76 patients with advanced NSCLC randomized to pembrolizumab (200 mg/kg Q3 wks x 24 months) alone or after SBRT (8 Gy x 3) to a single tumor
- Overall response rate 18% vs. 36% (p=0.07)
  - Disease control rate 48% vs. 72%
- Median PFS 1.9 vs. 6.6 months (p=0.19)
- PFS and OS significantly approved among PD-L1 negative subgroup
- Median OS 7.6 vs 15.9 months (p=0.16)
- No increase in treatment-related toxicities with SBRT



Early Phase Trials Evaluating SABR+ Checkpoint Blockade in Early Stage NSCLC

Study	Phase	N	Checkpoint inhibitor
Royal Marsden	II	31	Adjuvant nivolumab x 12 months
ASTEROID (Vastra Gotaland Region)	II	216	Adjuvant durvalumab x 12 months
UC San Diego	I/II	56	Concurrent + adjuvant durvalumab, 6 cycles
UCLA iSABR	I/IIR	105	Neoadjuvant, concurrent and adjuvant durvalumab x 5 cycles total (start 5 days prior to SABR)
MD Anderson	IIR	140	Concurrent and adjuvant nivolumab 4 cycles total
UC Davis	I	33	Neoadjuvant (2 cycles) concurrent and adjuvant atezolizumab, 6 cycles total

SWOG/NRG S1914 Schema



S1914 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 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 (whichever shorter) 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 30-60 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 interim analyses: analyses to be done annually. 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
  - Target 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

Accrual Challenges

- 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 is **based on preclinical data** showing increase synergy between SBRT and immunotherapy when immunotherapy is delivered first to prime the immune response
  - Allows sites to gain **accrual credit** with cooperative groups

Study Status and Contact Information

- Status
  - Study activation date: 5/28/20
  - QOL being added in study amendment
  - 131 sites with the trial IRB approved and activated, additional 465 additional sites in IRB/cancer center review process
  - Current accrual: 11/480
- Contact information
  - Entire Study Team – S1914medicalquestion@swog.org
  - Charles Simone – csimone@nyproton.com
  - Megan Daly – medaly@ucdavis.edu