Protocol Version Date: 06/13/2022

NCI National Clinical Trials Network

S1914

For Patients With Non-Small Cell Lung Cancer with High-risk Features

S1914 Available Through the CTSU

A Randomized Phase III Trial of Induction/Consolidation Atezolizumab (NSC #783608) + SBRT Versus SBRT Alone in High Risk, Early Stage NSCLC

Patient Population

See Section 5 for Full Eligibility Details

- Must have histologically or cytologically proven Stage I-IIA or limited T3N0M0 NSCLC, without radiographic evidence of nodal or distant involvement (N0M0). Patient may have T3 disease with the exclusion of pericardial involvement.
- Disease must have one or more of the following high-risk features:
  - Tumor diameter ≥ 2 cm as assessed by diagnostic CT.
  - Tumor SUV max ≥ 6.2 as assessed by FDG PET/CT.
  - Moderately differentiated, poorly differentiated, or undifferentiated histology.
- Must have undergone diagnostic chest CT with or without contrast within 42 days prior to randomization. PET-CT may be used if the CT portion is of comparable diagnostic quality to a stand-alone CT.
- Must have undergone FDG PET/CT of chest within 90 days prior to randomization.
- Must not have evidence of hilar or mediastinal nodal involvement.
- Must be medically or surgically inoperable OR patient's unwillingness to undergo surgical resection.
- Must not have received any prior treatment for the current NSCLC diagnosis.
- Must not have undergone prior radiation to overlapping regions of the chest.
- Must be ≥ 18 years old and have Zubrod PS of 0-2.
- Must not have a history of interstitial lung disease or active pneumonitis on the screening chest CT.

Treatment Plan

See Section 7 for Full Treatment Details

Arm A:
Atezolizumab:
- 1200 mg IV q 21 days x 8 cycles.
- One cycle = 3 weeks.

SBRT:
- Will begin on Day 1 of Cycle 3 of atezolizumab. 3-8 treatments starting in Week 7 (starts in week 7 and continuing into weeks 8 and 9, if necessary).

Arm B:
SBRT:
- 3-8 treatments beginning within 21 calendar days after randomization.

Number of Participants: 480

Study Chair:
Megan E. Daly, M.D.

NRG Study Chair:
Charles B. Simone, II, M.D.

ECOG-ACRIN Study Champion:
Conor Steuer, M.D.

Alliance Study Champion:
Apar Ganti, M.D.

Patient Enrollment

All Sites: Oncology Patient Enrollment Network (OPEN) https://open.ctsu.org/open

Protocol Information

CTSU Help Desk: 1-888-823-5923, CTSUcontact@westat.com, www.ctsu.org

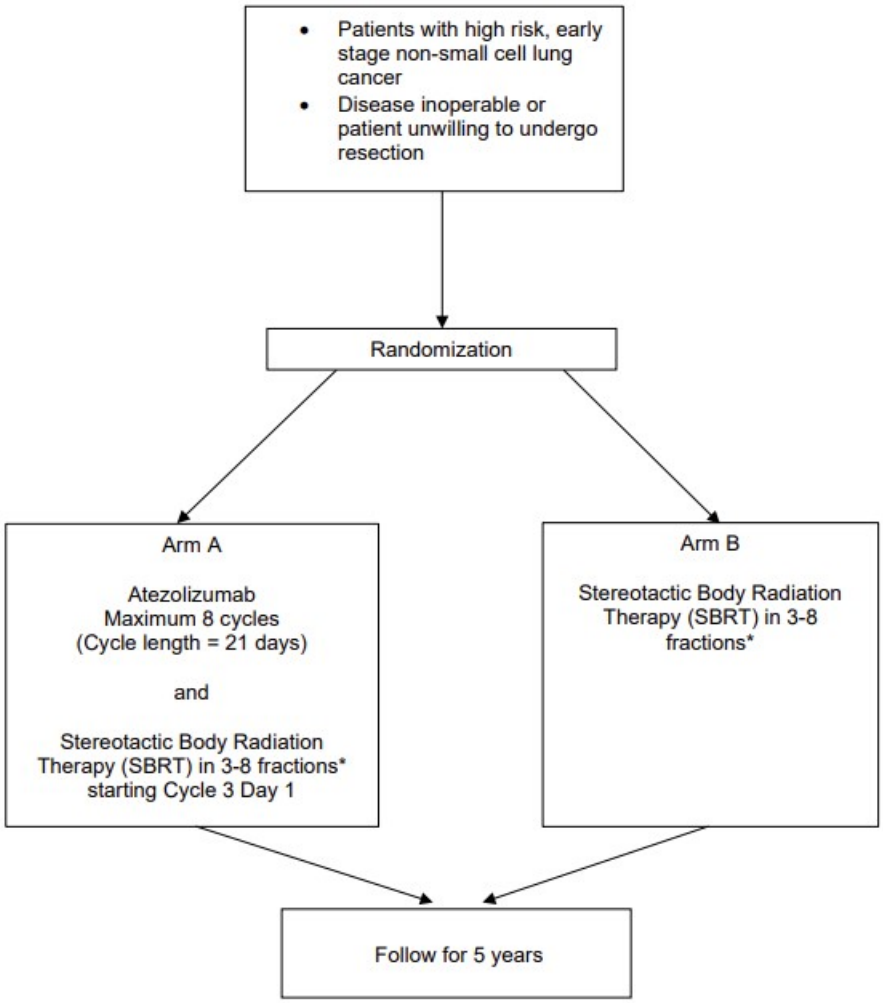
Please Enroll Your Eligible Patients!

S1914

S1914 Available Through the CTSU

A Randomized Phase III Trial of Induction/Consolidation Atezolizumab (NSC #783608) + SBRT Versus SBRT Alone in High Risk, Early Stage NSCLC

Schema



SWOG CANCER RESEARCH NETWORK

Version Date: November 2, 2022

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: SWOG Operations Office (Email: protocols@swog.org)

RE: **S1914**, "A Randomized Phase III Trial of Induction/Consolidation Atezolizumab (NSC #783608) + SBRT versus SBRT Alone in High Risk, Early Stage NSCLC"

REVISION #5

Study Chair: Megan E. Daly, M.D.
Phone number: 916/734-5428
E-mail: medaly@ucdavis.edu

Key Updates

(√) Drug Information changes
(√) Eligibility changes: The eligibility changes described below become effective 30 days after distribution of this notice through the CTSU Bi-Monthly Broadcast email. All patients registered more than 30 days after distribution of this notice must meet the revised eligibility criteria or they will be deemed ineligible.
(√) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
(√) Patient notification not required
(√) Editorial / Administrative changes

The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

REVISION #5

This amendment is in response to Matt Boron's notice regarding atezolizumab drug information updates. Additional administrative edits and clarifications have been made.

Throughout the protocol and consent, the Table of Contents, formatting, typographical errors, pagination, and cross-references have been corrected as needed.

Protocol Changes

1. The **version date** has been updated.

2. **Title Page**: Dr. Kelly's contact information has been updated.

3. **Section 3.1a**: The Mechanism of Action section has been modified per the CTEP Amendment Request for atezolizumab drug information updates.

4. **Section 3.1e**: The How Supplied section has been modified per the CTEP Amendment Request for atezolizumab drug information updates.

5. **Section 3.1f**: The Preparation, Storage, & Stability header has been re-ordered and this section has been modified per the CTEP Amendment Request for atezolizumab drug information updates.

6. **Section 5.3m and 5.3n**: These eligibility criteria regarding HBV and HCV have been updated as a requirement to test all patients within 28 days prior to randomization.

7. **Section 7.2**: The last sentence of this section has been updated to clarify funding source for image banking per CTEP comments attached from Revision 4.

8. **Section 7.3**: A bullet point regarding the administration of atezolizumab has been added to match the administration instructions in the paragraphs above.

9. **Section 7.4**: The first sentence has been modified to include the change to "≤8, oligofractionation."

10. **Section 7.4f**: Table **7. 4f.2** has been updated to indicate that daily treatment is permitted for the 8-fraction regimen.

11. **Section 7.4g Table 7.4g.3**: This table has been updated to clarify the delivery metric for 3-5 fractions and for 8 fraction.

12. **Section 8.5**: Under Endocrine Disorders, a clarification has been made to the management of symptomatic hyperthyroidism.

13. **Section 8.7i**: The Queries contact information has been updated for SAE reporting requirements.

14. **Section 8.8**: The Queries contact information has been updated for adverse events related to COVID-19.

15. **Sections 9.1 and 9.2:**
    - **Footnote J**: A clarification has been made for the 3-5 fraction regimens and the 8-fraction regimens.
    - **Footnote H**: A clarification has been made to the allowable windows.

16. **Section 9.1 Footnote O**: Magnesium has been added as a requirement to the chemistry panel. Phosphorous has been removed from the chemistry panel.

17. **Section 9.2 Footnote P**: Magnesium and phosphorous have been removed from the chemistry panel.

Model Consent Form Change

1. The **version date** has been updated.

2. **What exams, tests, and procedures are involved in this study?**: The bulleted list has been updated to include blood tests for hepatitis B and C as tests done to monitor safety and health, but are not included in usual care.

3. **Additional Drug Risks – Drug Interactions**: The timeframe for avoiding live attenuated vaccinations after last dose has been added per CTEP comments attached from Revision 4.

4. **What are the costs of taking part in this study?**: The second bullet point in the second set of bullets has been updated to include blood tests for hepatitis B and C as tests done for research purposes only that are covered by the study.

This study has been reviewed and approved by the NCI's Central Institutional Review Board (CIRB).

This memorandum serves to notify the NCI and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
J. Michelle Brockman, M.B.A.
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Matthew Novak
Tammy Bausinger

SWOG CANCER RESEARCH NETWORK

To: CTEP Protocol and Information Office

From: Megan Daly, MD and S1914 Study Team

Date: 11/02/2022

Re: **Study Team Responses to:** Review of Amendment #09 of Protocol #S1914: "A Randomized Phase III Trial of Induction/Consolidation Atezolizumab (NSC #783608) + SBRT Versus SBRT Alone in High Risk, Early Stage NSCLC"

I. Comments Requiring a Response– Administrative & Editorial Issues:

#	Section	Comments
1.	7.2	A 09, June 2022: In the last (revised) line of section 7.2, please re-write, to make clear the source of the funding and the various time-points, for example: Note that all scans must be submitted via TRIAD to IROC Ohio (see Section 15.3). All assessment imaging is considered standard of care for response assessment. All funding is provided by Genentech, not NCI, for banking of imaging at any / all time-points with IROC. **PI Response: This language has been added.**
2.	ICF – risks	Please add the 5-month post-treatment language for attenuated vaccines to the following: Throughout your treatment, you should inform your doctor about any medication changes. Do not receive any live attenuated vaccinations, such as shingles or influenza nasal spray, while you are taking part in this study and for 5 months after your last atezolizumab dose. **PI Response: This language has been added.**

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

SWOG CANCER RESEARCH NETWORK and NRG ONCOLOGY

A RANDOMIZED PHASE III TRIAL OF INDUCTION/CONSOLIDATION ATEZOLIZUMAB (NSC #783608) + SBRT VERSUS SBRT ALONE IN HIGH RISK, EARLY STAGE NSCLC

This is a potential FDA Registration Trial. Additional site requirements include maintenance of a Trial Master File (https://www.swog.org/sites/default/files/docs/2017-10/Guidance%20on%20FDA%20Inspection.pdf) and additional monitoring (see Section 18.3).

NCT#04214262

This study is being conducted under DCTD-sponsored IND #138328

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NCI-Supplied Investigational Agent:
Atezolizumab (IND #138328)

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PARTICIPANTS

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ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
NRG/NRG Oncology
SWOG/SWOG Cancer Research Network

TABLE OF CONTENTS

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Eligibility, RAVE, Data Submission	SWOG Statistics and Data Management Center lungquestion@crab.org 206/652-2267
Regulatory, Protocol, Informed Consent	SWOG Operations Office protocols@swog.org 210/614-8808
Quality of Life	NRG Oncology Data Management Center Matthew Novak and Tammy Bausinger NovakM@NRGOncology.org BausingerT@NRGOncology.org 215-574-3211 (M. Novak) 215-574-3223 (T. Bausinger)
RT Materials Submission to IROC Philadelphia (see Section 12.1)	Jennifer Presley, B.S., R.T.(R)(M)(T) IROC Philadelphia – RT QA Center jpresley@acr.org 215/574-3153
RT Credentialing	http://irochouston.mdanderson.org OR IROC-Credentialing@mdanderson.org
Image Submission to IROC Ohio (see Section 15.3)	SWOG1914@irocohio.org 614/293-2929
TRIAD	Triad-Support@acr.org
Specimen Tracking System (STS) Amendments, Errors, Connectivity Issues	technicalquestion@crab.org
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM)	CTEP-IAM account can be checked or new accounts can be created and updated: https://ctepcore.nci.nih.gov/iam/index.jsp
RAVE or Delegation of Task Log (DTL)	CTSU Help Desk ctsucontact@westat.com 1-888-823-5923
Central Monitoring & Source Document Portal	centralmonitorquestion@crab.org

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 866-651-CTSU (2878) for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG CRA Workbench via the SWOG website (www.swog.org).

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

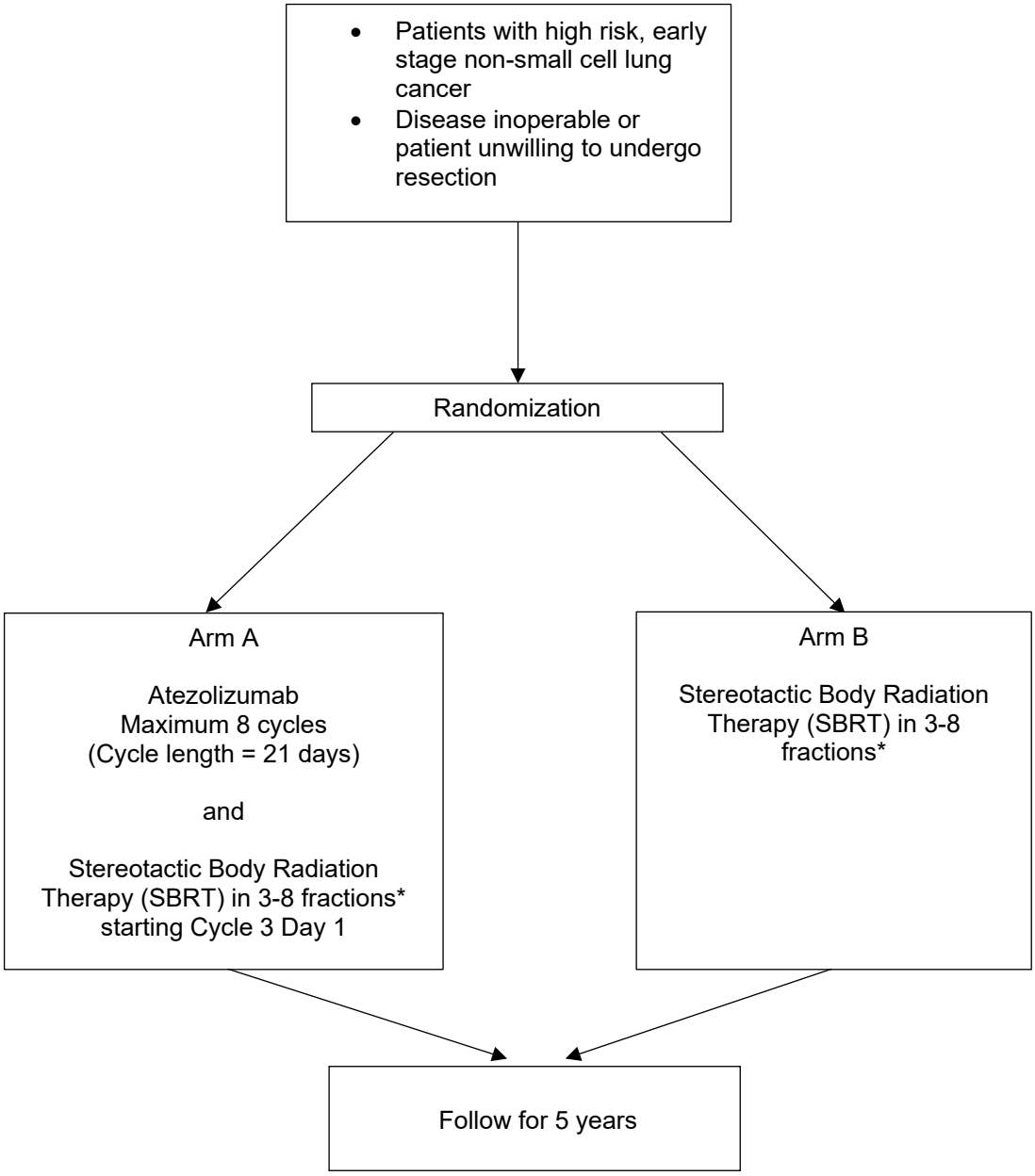
For patient eligibility or data submission questions contact the SWOG Statistics and Data Management Center (SDMC) by phone or email:
206/652-2267
lungquestion@crab.org

For treatment or toxicity related questions contact the Study Chair by phone or email:
S1914medicalquestion@swog.org
916/734-5428
646/968-9012

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Website is located at https://www.ctsu.org

SCHEMA



* See Section 7.4 for details

1.0 OBJECTIVES

1.1 Primary Objective

a. To compare overall survival (OS) in patients with inoperable, early stage non-small cell lung cancer (NSCLC) randomized to stereotactic body radiation therapy (SBRT) with or without atezolizumab.

1.2 Secondary Objectives

a. To compare investigator-assessed progression-free survival (IA-PFS) between the arms.

b. To compare PFS by blinded independent centralized review (BIRC) between the arms in a random subset of patients.

c. To evaluate distant, locoregional, and local failure rates within each treatment arm.

d. To evaluate the frequency and severity of toxicities within each treatment arm.

1.3 Additional Objectives

a. To collect specimens for banking.

1.4 Health-Related Quality of Life (HRQOL) Objectives

a. To assess quality of life as measured by the EORTC QLQ-30 and EORTC-QLQ-LC13 between the arms.

2.0 BACKGROUND

2.1 Management of Early Stage, Medically Inoperable Non-Small Cell Lung Cancer

Surgical resection is the standard of care for the treatment of medically operable, early stage (T1-2N0M0) non-small cell lung cancer (NSCLC). However, many patients with early stage lung cancer are ineligible for resection due to medical comorbidities or poor performance status. Stereotactic body radiotherapy (SBRT), which allows precise delivery of ablative radiation doses over 1-5 fractions to the target, has emerged as a potentially curative treatment option for patients with early stage, medically inoperable NSCLC. The first prospective North American trial, RTOG 0236, evaluated 3 fraction SBRT for peripherally located tumors, with 3 year in-field control of 97.6% and 5-year in-field control of 93%. *(1, 2)* Subsequent North American Cooperative Group trials have explored other fractionation regimens. RTOG 0813 tested 5 fraction SBRT for central tumors located within 2 cm of the proximal bronchial tree and found acceptable toxicity with Grade ≥3 acute toxicities in 13% and late toxicities in 10% among the 71 patients treated at the two highest dose levels, along with a 2-year overall survival of over 70% in this comorbid population. *(3)* RTOG 0915 was a Phase II randomized study comparing 48 Gy in 4 fractions to 34 Gy in a single fraction, and identified similar high rates of primary control and limited toxicity in the two arms. *(4)*

Despite impressive local control, distant failure remains problematic. Three-year and 5-year distant failure rates on RTOG 0236 were 22 and 31%, respectively, with higher rates of distant failure for T2 tumors as compared to T1 tumors (47% versus 15% at 3 years). Similar distant recurrence rates have been noted in other prospective studies. Overall survival outcomes for Stage I NSCLC remain relatively poor, with an estimated 5-year overall survival of 55.6% among all patients. *(5)* A systematic review of patterns-of-failure following SBRT identified regional failure of <5-11.3% and distant failure of 11.1-29.2% in

studies with median follow-up of at least 30 months, with T2-3 lesions, increasing tumor diameter, higher grade, non-squamous histology, and increased SUV (standardized uptake value) all associated with increased risk of distant metastases. *(6, 7, 8, 9, 10)* Various SUV thresholds have been evaluated as potential predictive features for recurrence following both surgical resection and SBRT for early stage NSCLC. A retrospective analysis of 130 patients treated with SBRT to 50 Gy in 4 fractions found that SUV >6.2 was associated with decrements in both PFS and OS. *(11)* Other studies have identified similar findings, with slightly varying SUV thresholds. *(12, 13, 14)*

Systemic therapy to decrease regional and distant failure in selected higher-risk patients is needed; however, the factors that lead to medical inoperability have precluded the evaluation of conventional platinum-based chemotherapy following SBRT due to toxicity concerns. This necessitates the integration of novel agents that have more mild toxicity profiles.

2.2 Immune Checkpoint Inhibitors in NSCLC

Immune checkpoint signaling pathways are important for switching CD8+ T cells on and off as necessary to defend against foreign stimuli; for example, the immune checkpoint inhibitory pathways naturally turn off CD8+ T cells by receptor-ligand interactions with other immune partners such as APC and Treg cells to prevent a state of chronic activation. *(15)* Tumors exploit these inhibitory pathways to avoid cell death by producing the cognate ligands that then bind to the inhibitory receptors on CD8+ T cells leading to CD8+ T cells inactivation and inability to attack. An inhibitory checkpoint pathway of great interest is Program death-1 (PD-1). The PD-1 protein is a co-T-cell regulatory receptor expressed on CD8+ T cells and Tregs that mediates immunosuppression by binding to its two ligands (Program death-Ligand 1) PD-L1 and PD-L2 (Program death-Ligand 2) that are expressed by partnering immune cells (APC) and tumor cells. *(16)* As a result, immune response is dampened and tumor cells survive. Several monoclonal antibodies have been developed to block the activation of the PD-1 inhibitory pathway and are FDA approved for the treatment of patients with advanced lung cancer in both the first and second line setting. Anti PD-1/PD-L1 antibodies are FDA approved for patients with advanced stage NSCLC in the second-line setting as monotherapy and in combination with pemetrexed and carboplatin in the first line setting. Based on the results of the randomized Phase III OAK trial, atezolizumab is the first anti-PD-L1 agent to be FDA approved for the treatment of relapsed NSCLC. Atezolizumab was found to have superior OS as compared to docetaxel in previously treated Stage IV disease [HR 0.73 [95% CI 0·62–0·87], p=0.0003). *(17)* The IMpower 150 study randomized 1202 patients to receive paclitaxel, carboplatin, bevacizumab (BCP), the same combination with atezolizumab (ABCP), or atezolizumab with carboplatin, and paclitaxel (ACP). The primary PFS endpoint was significantly superior for the ABCP arm as compared to the BCP arm, with a HR of 0.617 (95% CI 0.517-0.737; p<0.0001). *(18)* Overall survival was also significantly longer in the ABCP arm as compared to the BCP arm (median, 19.2 months vs. 14.7 months; stratified HR 0.78; 95% CI, 0.64 to 0.96; P=0.02). *(19)*

In locally advanced NSCLC, the recently published Phase III PACIFIC trial is the first to confirm benefit to checkpoint inhibition. The use of consolidation durvalumab, an anti PD-L1 antibody, after concurrent chemoradiotherapy in patients with Stage III NSCLC was associated with a marked improvement in the co-primary endpoints of PFS and OS. The median progression-free survival was 16.8 months (95% CI 13.0 to 18.1) with durvalumab versus 5.6 months (95% CI, 4.6 to 7.8) with placebo and a stratified hazard ratio (HR) for disease progression or death of 0.52 (95% CI, 0.42 to 0.65; P<0.001). *(20)* The 24 month OS was 66.3% (95% confidence interval [CI], 61.7 to 70.4) with durvalumab and 55.6% (95% CI, 48.9 to 61.8) with placebo, with a stratified HR for death of 0.68; 99.73% CI, 0.47 to 0.997; P=0.0025). *(21)* These results highlight the promise of checkpoint inhibitors to enhance disease control and survival for patients with earlier stages of disease.

Immune checkpoint inhibitors have also undergone preliminary study in earlier stage NSCLC. In a pilot study, patients with resectable stage I-IIIA NSCLC underwent 2 pre-operative doses of the PD-1 inhibitor nivolumab followed by surgical resection. A major pathologic response was noted in 9/20 (45%) of resected tumors and occurred in both PD-1 positive and negative tumors. *(22)* In a 19-patient multi-center phase I trial of locally advanced NSCLC patients receiving concurrent radiation therapy, platinum-based doublet chemotherapy, and pembrolizumab, no dose-limiting toxicities was seen in any patient. *(23)*

Several ongoing early-phase trials are testing the use of checkpoint inhibitors in tandem with SBRT in early stage, medically inoperable NSCLC. A Phase I dose escalation trial carried out at the University of California Davis treated early stage NSCLC patients with two cycles of induction atezolizumab with SBRT initiated with Cycle 3 (NCT02599454). Patients completed 6 total cycles, and atezolizumab doses were escalated up to a 1200 mg IV flat dose. One dose limiting toxicity, a Grade 3 dermatitis, was noted in a lower dose cohort (unpublished data). Multiple other single institution studies are also ongoing in this space. A currently accruing randomized phase III multi-center trial (ANVIL) is evaluating the impact on OS and DFS of adjuvant nivolumab following surgery and chemotherapy for stage IB-IIIA NSCLC (NCT02595944).

In the upcoming years, we can expect to see an increase in the number of patients with inoperable early stage lung cancer due to both our aging population and the increased implementation of low dose CT (computerized tomography) screening. The development of SBRT has provided these patients with a curative-intent local therapy with high rates of disease control at the primary site, but sub-optimal regional and distant disease control. As noted above, cytotoxic chemotherapy is often not medically suitable for this relatively frail patient population, and tolerable systemic treatment options are desirable.

2.3 Checkpoint Inhibitor/Radiation Combinations

Preclinical data suggest that radiotherapy can improve the efficacy of immunotherapy including checkpoint blockade. *(24, 25)* In addition to debulking tumor and releasing tumor antigens, radiotherapy has potent immunomodulatory effects and, as opposed to chemotherapy, is not systemically immunosuppressive. The immunomodulatory effects of radiotherapy are well established in the literature and include shifting tumor associated macrophage polarization, normalization of tumor vasculature, improving T-cell homing to tumor sites, destruction of immunosuppressive stromal cells in the tumor, microenvironment, induction of immunogenic cell death amongst many others. *(26, 27, 28, 29, 30, 31 ,32)*

Clinical data also suggest synergy between radiation and checkpoint inhibitors. Small clinical studies combining immunotherapy agents and SBRT in other diseases have also shown promise. A phase I trial combining one, two or three doses of local SBRT at 20 Gy per fraction with IL-2 (Interleukin-2) for metastatic melanoma did not demonstrated any dose limiting toxicities. A striking 71.4% systemic response rate, far superior to historical controls with IL-2 alone, was observed. *(33)* The majority of responders had long term durable responses and the toxicity was no higher than what was expected with IL-2 alone. A Phase I/II study of ipilimumab (another immune checkpoint inhibitor) at 3 or 10 mg/kg intravenously plus a single 8 Gy fraction to 1-3 bone lesions was evaluated in 41 patients with metastatic castrate resistant prostate cancer (MCRPC). *(34)* There was no DLT. In the entire group treatment related Grade 3 or 4 AEs occurred in 39% of patients and 22% were immune related. Six patients (15%) had confirmed declines in their PSA (prostate-specific antigen). One patient had a partial response and 15% of patients had stable disease. A recent unplanned secondary analysis of 98 patients enrolled on the KEYNOTE-001 Phase I trial found that patients who had received prior radiotherapy before treatment with pembrolizumab had better outcomes than those who had no prior radiotherapy, with superior overall survival (hazard ratio 0·58 [95% CI 0·36-0·94], p=0·026) and progression-free survival (hazard ratio 0·56 [95% CI 0·34-0·91], p=0·019). *(35)* A recent retrospective

analysis of 758 patients treated with checkpoint blockade and radiation also demonstrated that patients who received induction checkpoint blockade both as induction and concurrent with RT had superior OS as compared to those who received sequential therapy, and induction of >30 days was superior to shorter induction therapy, supporting the design of the present study with two cycles of checkpoint blockade delivered as induction. (36*)* A recent phase I/II trial demonstrates the safety of checkpoint blockade and SBRT in NSCLC.

Clinical data also strongly suggest concurrent delivery of thoracic radiation and checkpoint inhibitors is safe, with low risk of synergistic pneumonitis. In a toxicity evaluation of over 5000 patients treated with PD-1 or PD-L1 inhibitors, the incidence of pneumonitis was 4% vs 2% (p=0.01), respectively. *(37)* Decker et al enrolled patients with metastatic NSCLC who underwent treatment with pembrolizumab, and on disease progression received SBRT to one lesion. They report that SBRT during pembrolizumab treatment was safe, with no reported Grade 2 or higher treatment-related adverse events. *(38)* A phase I study in early stage, medically inoperable NSCLC combining atezolizumab with SBRT at UC Davis found no Grade 3+ thoracic toxicity with the combination (unpublished data).

2.4 Quality of Life

Quality of life is an important endpoint in this medically frail population. Increasingly, clinical trials are including measures of patient reported outcomes such as quality of life, as a factor that contributes to the value of a therapy in addition to the effectiveness of the therapy that is studied. Additionally, capturing patient reported outcomes can improve patient-physician communication, and can be prognostic and improve clinical outcomes.

While there are various quality of life tools that are validated and utilized in clinical trials, such as the FACT L and EORTC QLQ-C30 and QLQ-LC13, the EORTC QLQ-C30 and QLQ-LC13 appear to be the most widely utilized in both clinical trials with radiation and in clinical trials utilizing immunotherapy. *(39, 40)* Both tools have been extensively utilized and validated in lung cancer patients. *(41)*

We hypothesize that the addition of immunotherapy to this population of early stage lung cancer patients who are unable to undergo surgery, or decline surgery, will not result in clinically meaningful declines in Health related quality of life as measured by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 tool and QLQ-LC13 tools.

EORTC-QLQ

EORTC QLQ-C30 is a cancer specific questionnaire that can be completed by any cancer patient regardless of primary site of cancer and has been extensively tested and validated in cancer patients. *(42)* The EORTC QLQ-C30 takes approximately 10 minutes to complete, utilizes 30 items, and covers 9 domains. This tool captures functional, symptom, global health status, and quality of life domains. Minimally important differences are defined as 5-10 points. The scale is scored from 0-100. *(43)*

EORTC QLQ- LC13

This questionnaire is a lung-cancer specific supplement used with the QLQ-C30.[2] It is comprised of 13 items, that covers 2 domains including lung cancer-related symptoms and treatment side effects. *(44)* Most studies have measured time to deterioration of symptoms.

Together, the EORTC QLQ-C30 and the QLQ-LC13 are the most commonly utilized questionnaires used in lung cancer trials.

Quality of life with SRS
Stereotactic radiosurgery is frequently utilized in patients with early stage lung cancer who are medically inoperable, as it allows for high curative rates and local control rates comparable to historical rates in patients undergoing surgery. Although studies are small, SRS appears to be an effective therapy in medically inoperable patients without increased toxicity or negative impact on quality of life compared to patients who undergo surgery, or compared to baseline after SRS.

Videtic et al. successfully evaluated QOL in patients who have received SRS for medically inoperable lung cancer utilizing the FACT- L tool. *(45)* In this small study of 21 patients, quality of life was evaluated prospectively using the FACT-L tool. Investigators observed no significant changes in median total FACT-L scores between baseline and scores one year after therapy. *(46)*

The ROSEL study was a non-blinded phase III randomized controlled trial of SABR compared to surgery for stage IA NSCLC, which was closed prematurely after 22 patients were randomized due to low patient accrual. *(47)* Louie et al. reported an exploratory analysis of health related quality of life and patient reported outcomes measured by the EORTC QLQ-C30, and LC-13 measures. *(48)* Although the sample size was small, there were no significant differences in EORTC global health, pain, and dyspnea, or time to deterioration in global, functional, or symptoms scales in patients who received SRS versus surgery.

Furthermore, some investigators have started to report longer term quality of life in early stage lung cancer patients who undergo SRS. *(49)* In a prospective evaluation of quality of life in 45 patients who received SABR for early stage NSCLC, QOL was collected at long term follow up. Median follow up was 41 months and QOL was collected using EORTC QLQ-C30 and QLQ-LC13 at 2,6,12 months, and annually thereafter. This analysis demonstrated no statistically and clinically significant deterioration in QOL scores after SABR.

Although these evaluations may be limited by small sample sizes, SABR for inoperable early stage lung cancer does not appear to negatively impact a patient's quality of life from baseline.

Quality of life in previous NRG-RTOG / SWOG studies in lung cancer
Previous NRG-RTOG studies have successfully measured and reported quality of life. The NRG-RTOG 0617 study was a randomized phase III study to evaluate two doses of radiation therapy given concurrently with chemotherapy, with or without cetuximab therapy. A secondary analysis of the primary quality of life hypothesis was reported. *(50)* This study evaluated QOL using the FACT-LCS tool at baseline, 3 months, and 12 months and determined that more patients who received 74 Gy radiation compared to 60 Gy had a clinically meaningful decline in FACT-LCS, despite physician assessed toxicity being reported as similar between groups. Completion rates of the QOL data in all arms of the trial were similar between arms (57% and 53%, P = 0.57).

Quality of life with immunotherapy in lung cancer
Immunotherapies are a relatively new type of treatment modality for lung cancer, and are currently approved for patients with metastatic disease and for patients who have locally advanced disease and are not surgical candidates, after receiving concurrent chemoradiation. Various PD1 and PDL1 inhibitors have been approved for use in lung cancer patients including pembrolizumab, nivolumab, durvalumab, and atezolizumab. Quality of life measures are increasingly important to capture in clinical trials with

immunotherapy and a few reports from lung cancer trials comparing patients who received chemotherapy with those receiving immunotherapy have appeared.

In the KEYNOTE-024 study of pembrolizumab versus chemotherapy for patients with PDL1 expression of >50%, health related quality of life was measured using the EORTC QLQ-C30, EORTC-QLQ-LC13, and the EQ-5D-3L. *(51)* In this analysis, investigators measured PROs at baseline to week 15, and time to deterioration in the QLQ-LC13. Investigators found that pembrolizumab was associated with "a clinically meaningful improvement in HRQOL compared to chemotherapy" and that the time to deterioration was longer with pembrolizumab than with chemotherapy (HR 0.66, 95% CI .44-.97; p=0.029). *(52)*

Similarly, in a second line study of pembrolizumab versus docetaxel in previously treated patients with advanced lung cancer and PDL1> 1 %, HRQOL was evaluated using the EORTC QLQ-C30, EORTC-QLQ-LC13, and the EQ-5D-3L and similarly found improved quality of life at 12 weeks compared to docetaxel and significantly longer time to deterioration for the QLQ-LC13. *(53)* However, it is also recognized that patient reported outcomes designed specifically for patients receiving immunotherapy may be warranted in the future. *(54)*

Additionally, in an analysis of patient reported outcomes for the use of atezolizumab compared to docetaxel for previously treated patients with advanced lung cancer, EORTC QLQ-C30 and EORTC-QLQ-LC13 were utilized and assessed at every cycle and at treatment discontinuation. *(55)* Atezolizumab was associated with delayed time to deterioration in physical function and role function compared to docetaxel. *(56)*

Currently there are no fully published reports of patient reported outcomes of quality of life in patients who receive both radiation and immunotherapy. Although the majority of published results on patient reported outcomes in patients with lung cancer who receive immunotherapy demonstrate that immunotherapy agents maintain QOL relative to chemotherapy, there are many limitations to these analyses. Limitations to the measurement of patient reported outcomes in lung cancer patients receiving immunotherapy have included possible bias introduced by the open label study design. Additionally, PROs in these analyses were not collected very far beyond treatment discontinuation, which may limit the ability to capture long-term effects of immunotherapy on patient quality of life or long term toxicity. *(57, 58)* Furthermore, the commonly used QOL tools including the EORTC and the FACT-L may not accurately capture impacts on quality of life that may be unique to immunotherapy and development of PRO tools for patients receiving immunotherapy are underway.

An early analysis presented in abstract form of health related quality of life in patients who received durvalumab after chemoradiation for locally advanced lung cancer demonstrated no clinically significant worsening in symptoms, function, or health related quality of life. *(59)* However, further follow up and studies capturing the impact of immunotherapy to radiation are warranted.

2.5 Inclusion of Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	1	2	0	0	3
Asian	7	8	0	0	15
Native Hawaiian or Other Pacific Islander	4	5	0	0	9
Black or African American	20	24	0	0	44
White	172	183	14	15	383
More Than One Race	1	1	0	0	2
Total	205	222	14	15	456

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	9	10	0	0	19
More Than One Race	0	0	2	3	5
Total	9	10	2	3	24

3.0 DRUG INFORMATION

Investigator Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, atezolizumab is investigational and is being provided under an IND held by the National Cancer Institute (NCI). The current version of the Investigator Brochure for the agent will be accessible to site investigators and research staff through the PMB Online Agent Ordering Processing (OAOP) application: (http://ctep.cancer.gov/branches/pmb/agent_order_processing.htm). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via e-mail (IBCoordinator@mail.nih.gov).

3.1 Atezolizumab (NSC # 783608; IND #138328)

a. PHARMACOLOGY

Mechanism of Action: Atezolizumab is a humanized immunoglobulin (IgG1) monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). Atezolizumab targets human programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptor PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells. *(60)*

b. PHARMACOKINETICS

On the basis of available preliminary PK data (0.03-20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1 mg/kg and 20 mg/kg dose groups, the mean apparent CL and the mean Vss had a range of 3.20 to 4.44 mL/day/kg and 48.1 to 65.7 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

Serum atezolizumab concentrations exhibited a biphasic disposition with an initial rapid distribution phase followed by a slow elimination phase. Atezolizumab exhibited nonlinear pharmacokinetics at doses < 1 mg/kg (i.e., 0.03-0.3 mg/kg), likely due to target-mediated CL at lower concentrations. Atezolizumab exhibited linear pharmacokinetics at doses ≥ 1 mg/kg. At doses ≥ 1 mg/kg, the mean Cmax increased in a dose-proportional manner and was 26.0 mcg/mL for the 1-mg/kg dose group and 472 mcg/mL for the 20 mg/kg dose group. Similarly, at doses ≥ 1 mg/kg, the group mean AUC0-∞ had a range of 340-6050 Day x mcg/mL for 1 mg/kg and 20 mg/kg dose group and was approximately dose proportional, by similar CL across the dose range. The observed CL and Vss for atezolizumab at doses ≥ 1 mg/kg are consistent with these of a typical IgG1 antibody in humans.

Currently available PK and ATA data from Study PCD4989g suggest that the 15-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent) for Phase II and Phase III studies would be sufficient to both maintain trough concentration (Ctrough) ³ 6 µg/mL and further safeguard against both interpatient variability and the potential effect of ATAs that could lead to subtherapeutic levels of atezolizumab relative to the 10-mg/kg atezolizumab q3w regimen (or fixed-dose equivalent). From inspection of available observed Ctrough data, moving further to the 20-mg/kg atezolizumab q3w regimen does not appear to be warranted to maintain targeted Ctrough levels relative to the proposed 15-mg/kg atezolizumab q3w level.

Simulations (Bai et al. 2012) do not suggest any clinically meaningful differences in exposure following a fixed dose or a dose adjusted for weight. On the basis of this analysis, a fixed dose of 1200 mg has been selected when atezolizumab is administered q3w (equivalent to an average body weight-based dose of 15 mg/kg).

Refer to the atezolizumab Investigator's Brochure for details regarding nonclinical and clinical pharmacology of atezolizumab.

c. ADVERSE EFFECTS

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Atezolizumab (MPDL3280A, NSC 783608)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the

comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3,097 patients.* Below is the CAEPR for Atezolizumab (MPDL3280A).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, March 11, 2021[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Heart failure[2]	
		Myocarditis[2]	
		Pericardial effusion[2]	
		Pericardial tamponade[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes)[2]	
	Hyperthyroidism[2]		
		Hypophysitis[2]	
	Hypothyroidism[2]		
EYE DISORDERS			
		Eye disorders - Other (ocular inflammatory toxicity)[2]	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
	Dysphagia		
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		
	Flu like symptoms[3]		
HEPATOBILIARY DISORDERS			
		Hepatic failure[2]	
		Hepatobiliary disorders - Other (hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (systemic immune activation)[2]	
INFECTIONS AND INFESTATIONS			
Infection[4]			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased[2]		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased[2]		
		Creatinine increased	
	GGT increased[2]		
	Lipase increased*		
		Platelet count decreased	
	Serum amylase increased*		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Hyperglycemia[2]	
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		
	Back pain		
		Generalized muscle weakness	
	Myalgia		
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	
		Encephalopathy[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Guillain-Barre syndrome[2]	

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (meningitis non-infective)[2]	
		Myasthenia gravis[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Renal and urinary disorders - Other (nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Hypoxia		
	Nasal congestion		***Nasal congestion (Gr 2)***
		Pleural effusion[2]	
		Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis[2]	
		Erythema multiforme[2]	
	Pruritus		
	Rash acneiform		
	Rash maculo-papular		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])[2]	
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		
		Skin and subcutaneous tissue disorders - Other (exanthematous pustulosis)[2]	
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	

* Denotes adverse events that are <3%.

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Atezolizumab, being a member of a class of agents involved in the inhibition of "immune checkpoints," may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. Immune-mediated adverse reactions have been reported in patients receiving atezolizumab. Adverse events potentially related to atezolizumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of atezolizumab, administration of corticosteroids and supportive care.

[3] Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of atezolizumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of atezolizumab.

[4] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on atezolizumab (MPDL3280A) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that atezolizumab (MPDL3280A) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia
CARDIAC DISORDERS - Cardiac arrest; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Portal vein thrombosis
INVESTIGATIONS - Lymphocyte count decreased; Neutrophil count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp: Pain in extremity
NERVOUS SYSTEM DISORDERS - Headache
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Suicide attempt
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pulmonary hypertension; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin[2]; Hyperhidrosis
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: Atezolizumab (MPDL3280A) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

1. Pregnancy and Lactation: No developmental or reproductive toxicity studies have been conducted with atezolizumab as several nonclinical studies have already demonstrated that the PD-L1/PD-1 signaling pathway is essential in establishing maternal/fetal tolerance, which is necessary for embryo-fetal survival during gestation. Based on the critical role that PD-L1/PD1 pathway plays in the maintenance of maternal-fetal tolerance, atezolizumab should not be administered to pregnant women. The effects of atezolizumab on human reproduction or on the fetus or the developing infant are unknown but expected to have an adverse effect.

   It is not known whether atezolizumab is excreted in human milk. However, antibodies are known to cross the placenta and are excreted in breast milk during lactation. Atezolizumab should not be administered to nursing mothers.

2. Drug Interactions: Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

e. HOW SUPPLIED

Atezolizumab will be supplied free of charge.

It will be provided by Genentech/F. Hoffman-La Roche LTD and distributed by Pharmaceutical Management Branch, CTEP, NCI.

The agent is supplied in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Each 20 mL vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

f. PREPARATION, STORAGE, & STABILITY

Preparation:
The prescribed dose of atezolizumab should be diluted in 0.9% NaCl to a concentration between 3.2 mg/mL and 16.8 mg/mL and infused with or without a low-protein binding 0.2 or 0.22 micrometer in-line filter. The IV bag may be constructed of polyvinyl chloride (PVC), polyolefin (PO), or polyethylene (PE). The prepared solution may be stored at 2°C-8°C for up to 24 hours or at ambient ≤ 25°C (77°F) for 6 hours from the time of preparation. If the dose solution is stored at 2°C–8°C (36°F–46°F), it should be removed from refrigeration and allowed to reach room temperature prior to administration. These times include the storage and administration times for the infusion. Do not shake or freeze infusion bags containing the dose solution.

Storage:
2°C-8°C (36°F-46°F) Vial contents should not be frozen or shaken and should be protected from direct sunlight.

If a storage temperature excursion is identified, promptly return atezolizumab to 2°C-8°C (36°F-46°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability:
Stability studies are ongoing.

CAUTION: No preservative is used in atezolizumab; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug ordering: NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for

the study should be ordered under the name of one lead participating investigator at that institution.

Sites may order supplies of atezolizumab once a patient has been enrolled.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

2. Drug Handling and Accountability

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

3. Drug Return and/or Disposition Instruction

Drug Returns: All unused drug supplies should be recovered to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

4. Contact Information

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

h. PATIENT CARE IMPLICATIONS

Male patients and female patients of childbearing potential should utilize contraception and take active measures to avoid pregnancy while undergoing atezolizumab treatment and for at least 5 months (150 days) after the last dose of atezolizumab.

i. USEFUL LINKS AND CONTACTS

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov

- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

4.0 STAGING CRITERIA

4.1 Staging Criteria (AJCC 8th edition)

T	N	M	Stage
T1mi	N0	M0	IA1
T1a	N0	M0	IA1
T1b	N0	M0	IA2
T1c	N0	M0	IA3
T2a	N0	M0	IB
T2b	N0	M0	IIA
Limited T3 (see Section 5.1)	N0	M0	IIB

Primary Tumor (T)

T1mi Minimally invasive adenocarcinoma: adenocarcinoma (≤ 3 cm in greatest dimension) with a predominantly lepidic pattern and ≤ 5 mm invasion in greatest dimension
T1a Tumor ≤ 1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon.
T1b Tumor > 1 cm but ≤ 2 cm in greatest dimension.
T1c Tumor > 2 cm but ≤ 3 cm in greatest dimension.
T2a Tumor > 3 cm but ≤ 4 cm in greatest dimension.
T2b Tumor > 4 cm but ≤ 5 cm in greatest dimension.
Limited T3 Tumor > 5 cm but ≤ 7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus trials), phrenic nerve

Regional Lymph Nodes (N)

N0 No regional lymph node metastasis

Distant Metastases (M)

M0 No distant metastasis

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration in OPEN. Section 5 may be printed and used by the site but is not to be uploaded in RAVE (unless specially stated). For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG SDMC in Seattle at 206/652-2267 or lungquestion@crab.org prior to registration. **NCI policy does not allow for waiver of any eligibility criterion**

(http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. **If Day 14, 28, 42, or 90 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patient must have histologically or cytologically proven Stage I-IIA or limited T3N0M0 non-small cell lung cancer (NSCLC) as defined in Section 4.0, without radiographic evidence of nodal or distant involvement (N0M0). Patient may have T3 disease with the exclusion of pericardial involvement. Patients with multifocal tumors with no more than two lesions confirmed or suspected to be synchronous early stage NSCLCs are eligible provided at least one lesion is histologically or cytologically proven to be NSCLC and meets one or more high-risk features defined in Section 5.1.b.

b. Disease must have one or more of the following high-risk features:
- Tumor diameter ≥ 2 cm (inclusive of any non-solid, ground glass component) as assessed by diagnostic CT
- Tumor SUV max ≥ 6.2 as assessed by FDG PET/CT
- Moderately differentiated, poorly differentiated, or undifferentiated histology

c. Patient must have undergone diagnostic chest CT with or without contrast (IV contrast preferred) within 42 days prior to randomization. PET-CT may be used if the CT portion is of comparable diagnostic quality to a stand-alone CT. All disease must be assessed within 42 days prior to randomization.

d. Patient must have undergone FDG PET/CT of chest within 90 days prior to randomization.

e. Patient must not have evidence of hilar or mediastinal nodal involvement. Any patient with radiographically suspicious hilar or mediastinal nodes (including features such as non-calcified nodes with a short axis diameter > 1 cm, abnormal morphology, and/or elevated FDG avidity) must undergo cytologic sampling of suspicious nodes to rule out involvement prior to randomization. Mediastinal nodal sampling for other patients is optional. For cases in which the treating physician/multidisciplinary opinion is used to define nodes as “non-suspicious” (such as long-standing, stable enlarged nodes from other medical causes), the rationale must be clearly documented within the medical record.

f. Patient must have undergone history and physical examination within 28 days prior to randomization.

g. Patient must be medically or surgically inoperable as documented by a board certified thoracic surgeon or multi-disciplinary tumor board consensus OR patient’s unwillingness to undergo surgical resection must be clearly documented.

5.2 Prior/Concurrent Therapy Criteria

a. Patient must not have received any prior treatment for the current NSCLC diagnosis.

b. Patient must not have undergone prior radiation to overlapping regions of the chest that, in the opinion of the treatment physician, will interfere with protocol treatment.

c. Patient must not have received treatment with systemic immunostimulatory or immunosuppressive agents, including corticosteroids, within 14 days prior to randomization.

5.3 Clinical/Laboratory Criteria

a. Patient must be ≥ 18 years old.

b. Patient must have Zubrod Performance Status of 0-2 (see Section 10.3).

c. Patient must have adequate liver function defined as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x IULN within 28 days prior to randomization.

d. Patient must have adequate renal function defined as calculated creatinine clearance ≥ 30 mL/min using the following formula. The serum creatinine value used in the calculation must have been collected within 28 days prior to randomization.

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg})\ \dagger}{72 \times \text{serum creatinine}\ *}$$

Multiply this number by 0.85 if the patient is a female.

† The kilogram weight is the patient weight with an upper limit of 140% of the IBW.
* Actual lab serum creatinine value with a minimum of 0.8 mg/dL.

e. Patient must have ANC, platelets, and hemoglobin measured within 28 days prior to randomization. The purpose of these tests is to collect baseline values to compare with on-treatment values.

f. Patient must have TSH measured within 28 days prior to randomization. The purpose of this test is to collect baseline values to compare with on-treatment values.

g. Patient must not have significant cardiovascular disease (NYHA Class II or greater; see Appendix 18.2).

h. Patient must not have myocardial infarction within 90 days prior to randomization.

i. Patient must not have unstable arrhythmias or unstable angina.

j. Patient must not have known left ventricular ejection fraction (LVEF) <40% within 28 days prior to randomization.

NOTE: Assessment of LVEF by echocardiogram or MUGA is not an eligibility requirement, but if a standard of care echocardiogram or MUGA was clinically indicated, the LVEF must not be <40% within 28 days prior to randomization.

k. Patient must not have had an infection ≥ Grade 3 (CTCAE Version 5.0) within 28 days prior to randomization.

l. Patient must not have an active autoimmune disease that has required systemic treatment in past two years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or

pituitary insufficiency) is not considered a form of systemic treatment and is allowed.

m. Patient must be tested for hepatitis B within 28 days prior to randomization. Patient must not have active (chronic or acute) hepatitis B virus (HBV) infection. Patients may have past or resolved HBV infection.

Active HBV is defined as having a positive hepatitis B surface antigen (HBsAg) test.

Past or resolved HBV is defined as having a negative HBsAG test and a positive total hepatitis B core antibody (HBcAb) test.

n. Patient must be tested for hepatitis C within 28 days prior to randomization. Patient must not have active hepatitis C virus (HCV) infection.

Active HCV is defined as having a positive HCV antibody test followed by a positive HCV RNA test.

o. Patient must have pulmonary function testing documented within 90 days prior to randomization.

p. Patients with known human immunodeficiency virus (HIV) infection must be receiving anti-retroviral therapy and have an undetectable viral load at their most recent viral load test within **6 months** prior to randomization.

q. Patient must not have a history of clinically significant interstitial lung disease or evidence of active pneumonitis on the screening chest CT.

r. Patients must not have a prior or concurrent malignancy whose natural history or treatment has the potential (in the opinion of the treating physician) to interfere with the safety or efficacy assessment of the investigational regimen.

s. Patients must not be pregnant due to the potential teratogenic side effects of the protocol treatment. Women of reproductive potential and men must have agreed to use an effective contraception method for the duration of protocol treatment, and for 5 months (150 days) after the last dose of atezolizumab. A woman is considered to be of “reproductive potential” if she has had a menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with atezolizumab, breastfeeding must be discontinued prior to randomization.

t. Patients of reproductive potential must have a negative serum pregnancy test within 14 days prior to randomization.

u. Patients must not have known active tuberculosis.

v. Patients must not have received a live, attenuated vaccine within 28 days prior to randomization (for examples, see Section 18.7).

NOTE: All COVID-19 vaccines that have received FDA approval or FDA emergency use authorization are acceptable.

w. Patients must not have a known history of allergic reactions attributed to compounds of similar chemical or biologic composition to atezolizumab.

x. Patients must not have a known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric antibodies, fusion proteins, or Chinese hamster ovary cell products or to any component of the atezolizumab formulation.

5.4 Specimen Submission Criteria

a. Patient must agree to have specimens submitted for translational medicine and banking as outlined in Section 15.2.

5.5 Regulatory Criteria

a. Patients ***must*** be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

b. As a part of the OPEN registration process (see Section 13.3 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.6 Quality of Life Criteria

a. Patients who can complete quality of life instruments in English, French, or Spanish must agree to complete the questionnaires described in Section 15.4 at the protocol-specified time points.

6.0 STRATIFICATION FACTORS

Patients will be randomized between the treatment arms. Randomization will be stratified using a dynamic balancing algorithm based on the following stratification factors:

- Tumor size (< 4 cm versus ≥ 4 cm)
- Tumor location (central versus peripheral) *
- Zubrod Performance Status (0-1 versus 2)

*For detailed definition of tumor location, please see Section 18.6.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact S1914medicalquestion@swog.org. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

Initiation of treatment must be planned to start no more than 21 calendar days after randomization.

7.1 Treatment Summary

a. Arm A

Patients randomized to Arm A will receive stereotactic body radiation therapy (see Section 7.4) and atezolizumab (see Section 7.3). **SBRT will begin on Day 1 of Cycle 3 of atezolizumab.** If atezolizumab is delayed, also delay SBRT until beginning of Cycle 3. One cycle = 3 weeks.

Arm A Treatment	Schedule
Atezolizumab	Day 1 of Weeks 1, 4, 7, 10, 13, 16, 19 and 22
SBRT	3-8 treatments starting in Week 7 (continuing into Weeks 8 and 9, if necessary)

Atezolizumab Precautions:
Patients must not be planning to receive a live, attenuated vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab.

b. Arm B

Patients randomized to Arm B will receive stereotactic body radiation therapy (see Section 7.4). **SBRT should begin within 21 calendar days after randomization.**

Arm B Treatment	Schedule
SBRT	3-8 treatments beginning within 21 calendar days after randomization

7.2 Disease Assessments

Patients randomized to Arm A will have a chest CT within 42 days prior to randomization and within ± 3 calendar days of the following time points:

- at Week 4 (this scan will assess patient's ongoing suitability to undergo SBRT; growth of the target lesion on this scan prior to initiation of SBRT will not be considered progression; this diagnostic CT chest is separate from the simulation planning CT);
- then at Weeks 18, 30, 42, and 54;
- then every 6 months until progression for up to five years after randomization.

NOTE: Timepoints are from randomization.

Patients randomized to Arm B will have a chest CT within 42 days prior to randomization and within ± 3 calendar days of the following time points:

- Weeks 18, 30, 42, and 54;
- then every 6 months until progression for up to five years after randomization.

Disease assessment timing is to be based on calendar timing counted from the date of randomization, not based on cycles or drug administration. Every effort should be made to repeat the same modality of scanning and contrast administration.

Note that all scans must be submitted via TRIAD to IROC Ohio (see Section 15.3). All assessment imaging is considered standard of care for response assessment. All funding is provided by Genentech, not NCI, for banking of imaging at all timepoints with IROC.

7.3 Atezolizumab (Arm A Only)

Patients will receive intravenous atezolizumab (1200 mg) once every 21 days for a total of 8 doses.

Atezolizumab treatment may be administered up to three days before or after the protocol-specified dose administration date. Atezolizumab treatment will be administered on an outpatient basis.

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

Atezolizumab is administered as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab as an intravenous push or bolus. No premedication is indicated for administration of Cycle 1 of atezolizumab. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Atezolizumab	1200 mg	Intravenous over 60 minutes	1	q 21 days x 8 cycles*

* Patient may receive up to 8 doses

Atezolizumab Infusion-Related Reactions

For anaphylaxis precautions, see the management guidelines. Atezolizumab infusions will be administered per the instructions outlined in Table 7.3.

Table 7.3 Administration of First and Subsequent Atezolizumab Infusions

First Infusion	Subsequent Infusions
• No premedication is permitted prior to the atezolizumab infusion. • Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 60 (± 15) minutes. • If clinically indicated, vital signs should be measured every 15 (± 5) minutes during the infusion and at 30 (± 10) minutes after the infusion. • Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms. • Do not administer atezolizumab as an intravenous push or bolus.	• If the patient experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be measured within 60 minutes prior to the infusion. • Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) minutes if the patient experienced an infusion-related reaction with the previous infusion. • If the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (± 10) minutes after the infusion.

For anaphylaxis precautions, use the following procedure:

Equipment Needed

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intravenous, intramuscular, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

Procedures

In the event of a suspected anaphylactic reaction during atezolizumab infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
5. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
6. Continue to observe the patient and document observations.

7.4 Stereotactic body radiation therapy (SBRT)

Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SAbR), is a treatment strategy used to deliver highly focused and accurate radiation dose to demarcated targets outside of the brain where the entire course of therapy for an individual target is delivered in few fractions (≤8, oligofractionation). The definition of SBRT and its appropriate conduct have been extensively reviewed by several professional radiotherapy societies. For this protocol, the ACR/ASTRO consensus definition of SBRT and the related conduct guidelines for SBRT, along with guidelines from the AAPM Task Group 101 will be used. When and if there is a discrepancy between these professional society guidelines and this protocol, the protocol should be followed.

a. Treatment Technology Requirements

SBRT is a highly focused technique requiring many facets of modern technology in order to safely treat patients with large fractions of highly conformal doses. To successfully treat an SBRT patient, centers must satisfy a set of minimum technology requirements as well as use appropriate modalities for treatment.

General treatment technology requirements for SBRT are given in Table 7.4a.1. Questions regarding appropriate technology for this protocol can be directed to the protocol Study Chairs or medical physics co-chair.

Table 7.4a.1 Quick Reference Summary of Treatment Technology Requirements

Technology	Requirement	Comments
Beam Modality	MV Photons	MRgRT, including MR-Co60 and MR-linac allowed. Charged particle beams (including electrons, protons, and heavier ions) are not allowed

Beam Energy	1 to 10 MV preferred; >10-18 MV may be used in selected cases with >10 cm from skin to target so long as > 50% of target dose is delivered by beams with energy ≤10 MV	Minimize use of high energy in lung. 6 MV or lower energies should be predominately used in low-density tissue.
Treatment Technique	3DCRT (static, arc) or intensity-modulated techniques (IMRT, VMAT)	Tomographic and robotic techniques allowed.
Image Guidance	Treatment Machine must be equipped to provide daily kV,MV, or MR image guidance.	Non-ionizing guidance (RF transponders, optical surface imaging) is allowed, but kV or MV image verification is still required. On-table MR guidance is allowed.

b. Simulation

Proper immobilization and assessment and, if necessary, management of internal motion are essential for SBRT treatment. Quick reference guidelines for simulation are given in Table 7.4b.1 with additional details below.

Table 7.4b.1 Quick Reference Summary of General Simulation Guidelines

Topic/Parameter	Guideline
Immobilization	Proper immobilization with appropriate clinical devices to ensure reproducibility is required. Patient comfort should be prioritized.
Motion Assessment	Ascertain the characteristics of target (and normal tissue) motion with regard to magnitude (amplitude), timing (period), and regularity to determine the need or success of motion control. This is carried out both in simulation and treatment using real time monitoring (e.g., fluoroscopy, 4D CT, beacon tracking, cine MR, etc.)
Motion Control	Typical motion control maneuvers include inhibition strategies (e.g., abdominal compression and active breath hold), tracking based on a motion model, and gating to part of the breathing cycle, but others may be applicable. Recommended in cases where the extent of motion quantified on motion assessment exceeds 1 cm in any direction.
CT Slice Thickness	2 mm or less is recommended. No more than 3 mm shall be used. PTV size should be taken into consideration when choosing the slice thickness. Slices of 1-2 mm are recommended for tumors that are 1 cm or less in the largest dimension.
Use of Contrast	IV contrast is encouraged for better delineation between tumor, atelectasis, and vascular structures as well as better definition of normal tissue contours. Oral contrast can be used at the clinical discretion of the treating physician.

Immobilization

Patients should be positioned in a stable position capable of allowing accurate reproducibility of the target positions from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, including stereotactic frames that surround the patient on three sides and large, patient contoured rigid pillows (conforming to patients' external contours. At a minimum, patients should be uniformly supported with large cushions or patient contoured rigid pillows rather than simply lying on the treatment couch, which is uncomfortable for the period of time required for SBRT simulation, setup, and delivery. Arms should be supported and knees elevated. Patients with COPD often prefer that their head is elevated above their chest. Patient immobilization must be reliable enough to ensure that the gross tumor volume (GTV) does not deviate beyond the confines of the planning target volume (PTV) with any significant probability (i.e., < 5%) during the treatment.

Assessment and Management of Internal Organ Motion

Special considerations must be made to account for the effect of internal organ motion (e.g., primarily breathing associated motion but also bowel peristalsis motion) on target positioning and reproducibility. As a first step, it is required that the treatment team quantify the specific motion of a target so as to determine if management strategies listed in the next section are required to meet protocol guidelines. The patient should be in normal free breathing at the time of initial tumor motion assessment. Deep inspiration or expiration breath hold is not allowed for initial tumor motion assessment as such assessment generally overestimates free breathing tumor motion. Options for motion assessment include real time fluoroscopy and 4D CT scanning. Any strategy, including 4D CT should incorporate appropriate image review and quality assurance to ensure suitability for treatment planning and target delineation.

In some tumor locations, tumor motion measurement may demonstrate motion exceeding the required small tumor expansions per this protocol (resulting in marginal miss or excessive volume of irradiation) unless a motion management strategy is employed. Acceptable maneuvers for motion management include reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumor tracking, and active breath-holding techniques or other methods approved by the study committee. Internal organ management maneuvers must be reliable enough to ensure that the GTV does not deviate beyond the confines of the PTV with any significant probability (i.e., < 5%).

Table 7.4b.2 highlights the recommended and minimum requirements for motion assessment and treatment planning imaging.

Table 7.4b.2 Motion Assessment/Management Guidelines for Simulation

Treatment Technique	Recommended Method for Motion Assessment During Simulation	Minimum Method for Motion Assessment During Simulation	Scan(s) Recommended for Treatment Planning
Free breathing treatment using an internal gross target	4D CT or fluoroscopy as long as tumor can be directly visualized	Repeated slow acquisition CT scanning through the target (to sample motion)	Average intensity projection (AveIP) scan from a full field of view 4D CT for dose calculations; the

volume (IGTV) approach , including abdominal compression		fused to the planning CT dataset	maximum intensity projection (MIP) scan may be desirable to aid IGTV definition; Free-breathing scans are not recommended for treatment planning.
Gating with a gating window	4D CT	Exhale CT plus fluoroscopy (free-breathing + fluoroscopy strongly discouraged due to baseline shift)	Reconstructed average of gating window scans from 4D CT.
Breath hold (i.e. ABC)	Reproducibility of breath hold confirmed (examples: multiple low dose scans over tumor, repeat fluoroscopy or scout images)	N/A	Scan in breath hold position (inhale recommended since it maximizes lung volume)
Tracking	4D CT or breath hold CT	N/A	4D CT or breath hold CT

c. Imaging for Structure Definition, Image Registration/Fusion and Follow-up

Structure definition for SBRT may require multimodality imaging and image fusion. General guidelines on imaging for structure definition are given in Table 7.4c.1.

Table 7.4c.1 Summary of Imaging Guidelines for Structure Definition

Topic	Guidelines
Use of Multimodality Imaging	Multimodality imaging such as PET/CT or MRI can be used, as deemed appropriate by the treating physician, for structure definition.
Image Registration/Fusion	Multimodality imaging information should be able to be accurately and reliably registered/fused to the planning scan.

d. Definition of Target Volumes and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as “Required” in the table must be contoured and submitted with the treatment plan. Structures marked as “Required when applicable” must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated, including underscores, capitalization, etc.

If treating two tumors, these targets should be labeled as separate targets (GTV, ITV, PTV) using the Standard Names below. An additional identifier will be added to the end of the Standard Name as follows: Lesion 1: GTV_ddGyxF_1, IGTV_ddGyxF_1, PTV_ddGyxF_1; Lesion 2: GTV_ddGyxF_2, IGTV_ddGyxF_2, PTV_ddGyxF_2

Table 7.4d.1 Description and Naming of Required Target Volumes

Standard Name	Description	Validation Required/Required when applicable
GTV_ddGyxF	GTV to receive dd Gy per fraction for F fractions	**Required**
IGTV_ddGyxF	IGTV to receive dd Gy per fraction for F fractions	**Required**
PTV_ddGyxF	PTV to receive dd Gy per fraction for F fractions	**Required**
PTV20	PTV + 20 mm expansion defined to control intermediate dose spillage	**Required**

e.g., **dd = Gy** and **F = number of fractions**; If plan is for a central lung lesion prescribed to a total of 50 Gy delivered in 5 fractions, the PTV is to be named **PTV_10Gyx5**, where 10 Gy is to be given per fraction, for 5 fractions.

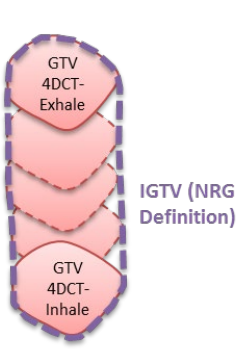
Detailed Specifications

Note: Instructions on IGTV and PTV creation based on treatment technique are given at the end of this section.

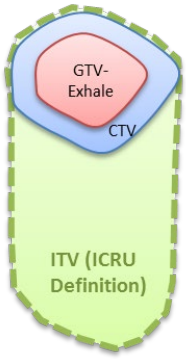
Targets in lung will generally be drawn using CT pulmonary windows; however, soft tissue windows, ideally with contrast, should be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. Information from fusion of multimodality imaging (e.g., PET) may be helpful in delineating tumor from normal tissue. For example, in the presence of large amounts of atelectasis or fibrotic changes, PET may be necessary to aid in GTV definition. IV contrast used with the planning CT is useful to differentiate more subtle atelectasis from tumor since atelectasis does not enhance. When a multimodality image serves as the primary image for GTV delineation, an additional margin to account for registration uncertainty should be considered when transferring the GTV to the primary image.

The clinical target volume (CTV) for lung SBRT targets is considered to be equivalent to the GTV. Thus, GTV targets will not be enlarged whatsoever for prophylactic treatment (including no “margin” for presumed microscopic extension); rather, include only abnormal imaging signal consistent with gross tumor (i.e., the GTV and CTV are identical).

The motion encompassing GTV will be defined at the IGTV. Note that the term “ITV” is explicitly avoided to prevent confusion between a motion encompassing CTV and GTV:



NRG defined IGTV = motion envelope for GTV



ICRU defined ITV = motion envelope for CTV

The PTV shall be defined as the IGTV (or GTV when strict motion control is applied) plus an uncertainty/set-up error margin. That uncertainty/set-up margin shall be 5 mm in all directions. Up to an additional margin of 2 mm in any direction is acceptable, if clinically warranted as determined by the treating physician. If institutional interfraction uncertainties suggest that this would not be a sufficient PTV margin for the workflow and equipment involved, please contact the protocol PIs and physics co-chair for additional guidance. Note that PTV margins are not to account for internal motion uncertainty (which is accounted for within the definition of the IGTV). The addition of an inverse planning optimization "helper" structure can be made to increase coverage to account for dose gradients (i.e., for coplanar VMAT in the cranial/caudal direction) as deemed necessary by the treating institution. General guidelines for IGTVs and GTVs based on treatment technique, as described in Table 7.4b.2, are summarized in Table 7.4d.2.

Table 7.4d.2 Guidelines for Definition of IGTV and PTV corresponding to Treatment Technique

Treatment Technique	Definition of IGTV	Definition of PTV
IGTV using 4DCT (includes abdominal compression)	Boolean union of GTV defined on all phases of 4DCT or a maximum intensity projection image (*)	IGTV plus 5 mm margin in all directions. Up to 7 mm in any direction is acceptable if warranted due to additional setup uncertainty in that direction.
Gating with a gating window	Boolean union of GTV defined on the gated phases of 4DCT	
Breath hold (i.e. ABC)	An appropriate margin (2-5 mm) to account for breath hold reproducibility or uncertainty is recommended	
Tracking	An appropriate margin (2-5 mm) to account for tracking reproducibility or uncertainty is recommended	

(*) If a Maximum intensity projection (MIP) dataset is used for IGTV delineation, care must be taken to verify the IGTV against the GTV defined above on each individual phase. In addition, the MIP is not appropriate for tumors located near boundaries with soft tissue density, such as near the diaphragm or mediastinum.

e. Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured

and submitted with the treatment plan. Structures marked as “Required when applicable” must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Table 7.4e.1 Description and Naming of Required Normal Tissue Volumes

Standard Name	Description
BrachialPlexus_L	Left Brachial Plexus
BrachialPlexus_R	Right Brachial Plexus
BrachialPlexus	Total Brachial Plexus (Right plus Left Brachial Plexus)
Bronchus	Carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus, right and left lower lobe bronchi
Bronchus+20	Bronchus expanded by 2 cm
Chestwall	Chest wall
Esophagus	Esophagus
External	Body surface
GreatVes	Great Vessels
Heart	Heart
Larynx	Larynx
Liver	Liver
Lung_L	Left Lung
Lung_R	Right Lung
Lungs	Combined Left and Right Lungs
Lungs-GTV	Combined Left and Right Lungs minus GTV
Skin	Outer 0.5 cm of the body surface (rind)
SpinalCord	Spinal cord
Trachea	Trachea

Critical structure contours will be drawn in axial planes of the primary planning dataset. In general, critical structures should be contoured if they are found within an axial slice within 5 cm in the craniocaudal direction of any PTV slice treated on protocol. As such, they may be further than 5 cm direct separation and still

required to be contoured. If a named critical structure is further than 5 cm from any PTV, then it need not be contoured or submitted.

Detailed Specifications

Spinal Cord
The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 5 cm above the superior extent of any PTV and continuing on every CT slice to at least 5 cm below the inferior extent of any PTV.

NOTE: For the spinal cord, constraints are absolute limits, and treatment delivery that exceeds defined limits will constitute a major protocol violation.

Esophagus
The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured over its entirety, or (at a minimum) starting at least 5 cm above the superior extent of any PTV and continuing on every CT slice to at least 5 cm below the inferior extent of any PTV.

Brachial Plexus
The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured. The brachial plexus will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib. If any PTV is more than 5 cm away from the brachial plexus, this structure does not need to be contoured.

Heart
The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aorto-pulmonary window) and extend inferiorly to the apex of the heart.

Trachea
The trachea and proximal bronchial tree will be contoured as two separate structures using mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. For this purpose, the proximal trachea will be contoured as one structure identified as Trachea, and the distal 2 cm of trachea will be included in the structure identified as Bronchus. Contouring of the Trachea should begin at least 5 cm superior to the extent of the PTV or 5 cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.

Bronchus
The proximal bronchial tree (Bronchus) will include the most inferior 2 cm of distal trachea and the proximal airways on both sides as indicated in the diagram above. The following airways will be included according to standard anatomic relationships: the distal 2 cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.

Lungs
Both the right and left lungs should be contoured individually (**Lung_L**, **Lung_R**) and also combined as one structure (**Lungs**). Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus as defined above should not be included for the structure created and labeled as **Lungs - GTV**.

PTV + 2 cm
As part of the QA requirements for "low dose spillage" listed above, a maximum dose to any point 2 cm away in any direction is to be determined (D2cm). To facilitate this QA requirement, an artificial structure 2 cm larger in all directions from the PTV is required. Most treatment planning systems have automatic contouring features that will generate this structure without prohibitive effort at the time of treatment planning. If possible, this structure should be constructed as a single contour that is 2 cm larger than the PTV and labeled as **PTV20.**

Skin
The skin will be defined as the outer 0.5 cm of the body surface. As such it is a rind of uniform thickness (0.5 cm) which envelopes the entire body in the axial planes. The cranial and caudal surface of the superior and inferior limits of the planning CT should not be contoured as skin unless skin is actually present in these locations (e.g., the scalp on the top of the head).

Chest wall
The chest wall should be contoured by first creating a structure that represents the lungs expanded by 2 cm. The lungs are then subtracted from this structure and the parts of the chest wall structure in the mediastinum and spinal canal are removed. If the GTV is adjacent to the chest wall, then the chest wall should be further inspected in this region to ensure tissues within a 2 cm expansion of the GTV are included.

Great Vessels
The great vessels (aorta and vena cava, not the pulmonary artery or vein) will be contoured using mediastinal windowing on CT to correspond to the vascular wall and all muscular layers out to the fatty adventitia. The great vessel should be contoured starting at least 5 cm above the superior extent of the PTV and continuing on every CT slice to at least 5 cm below the inferior extent of the PTV. For right sided tumors, the vena cava will be contoured, and for left sided tumors, the aorta will be contoured.

f. Treatment Planning Guidelines

Treatment planning for SBRT should be approached with care and experience is recommended for sites enrolling on an SBRT protocol. Table 7.4f.1 summarizes the general planning guidelines for this protocol.

Table 7.4f.1 General Treatment Planning Guidelines

Topic/Parameter	Guidelines
Planning Technique	3DCRT, conformal arc, and intensity-modulated techniques (IMRT, VMAT) allowed. Tomographic and robotic techniques also allowed. MR-guided RT is allowed.
Number of Beams	As planning dictates although approximately 7-11 beams are generally suitable for static beam plans. Note that dose should be properly distributed between beams due to skin toxicity considerations. Similarly, arcs should

Topic/Parameter	Guidelines
	cover an appropriate range so as to deliver a safe dose to the skin. Single arc plans may be suitable for simple geometries while additional arcs are preferred for more complex geometries.
Beam Arrangement	Coplanar or non-coplanar (non-coplanar are encouraged), non-overlapping, non-opposing beams or arc therapy (non-coplanar arcs encouraged to improve conformity and OAR sparing in complex geometries). Combination of static and arc beams allowed. Gantry clearance verification prior to treatment is recommended.
Beam Energy	As planning dictates although lower energies preferred for lung.
Block Margin (for 3DCRT)	Generally, 0 +/- 2 mm, but iterated to achieve coverage specifications. Negative margin blocks are frequently useful to create steep gradients along the axial limits of the PTV while positive margin (e.g., +2 mm) are often needed on the cranial and caudal limits of the PTV.
Minimum Field Size	As planning dictates although only the smallest field size accurately commissioned (e.g. small field output factors are within 5% of published standards or values) at the institution should be used. Because of concerns with small field dosimetry, field sizes above 2 cm x 2 cm are preferable.
Dataset for Dose Calculation	**IGTV Approach** – Average Intensity Projection (AveIP) CT from 4DCT or a slow acquisition CT which captures motion if 4DCT not available (free breathing CT is not appropriate). **Breath Hold Approach** – CT taken at treatment breath hold **Gated Approach** – Average from gating window phases from 4DCT or the median phase in the gating window **Tracking Approach–** 4D CT or breath hold CT Scans with contrast are generally acceptable for dose calculations. However, density/material overrides are recommended in areas of strong contrast when dose calculation accuracy may be affected (such as oral contrast in the esophagus). **Contrast CT scans** - In patients where the planning CT is acquired following contrast injection, density overrides may be needed in areas of strong contrast (such as oral contrast in esophagus)."
Dose Calculation Algorithm	Modern algorithms that accurately handle tissue heterogeneity and scatter should be used. IROC maintains an updated list of approved algorithms. Density corrections must be applied. Density overrides of the GTV are not recommended for photon treatment. For MR-guided treatment systems, dose calculation must account for the impact of the magnetic field.
Dose Grid Resolution	3 mm x 3 mm dose grid resolution or smaller is required. Use of 2 mm x 2 mm is recommended, especially for targets less than 2 cm in diameter.

Protocol specific fractionation details as well as prescription definition and compliance guidelines are given in Tables below.

Table 7.4f.2 Protocol Specific Fractionation Details

Item	Details
Number of Fractions	Patients will receive 3-8 fractions of radiation, on an every 2-day basis i.e., 2-3 treatments per week, so that the SBRT schedule is completed within 1-3 weeks. There should be a minimum of 40 hours and a maximum of 120 hours between each fraction for all 3-5 fraction regimens. For the 8-fraction regimen, daily treatment is permitted, and there should be a minimum of 16 hours and a maximum of 120 hours between each fraction.
Dose Per Fraction	The dose per fraction is to be prescribed to the prescription line at the edge of the PTV such that a minimum of 95% of the PTV receives the prescription dose.

NOTE: If two targets are being treated, the same dose and fractionation will be prescribed for both targets, based on the highest risk lesion location. Use of the same dose and fractionation is critical for accurate assessment of protocol compliance, particularly for normal tissue dose. Target coverage compliance will be assessed for each target and normal tissue compliance will be evaluated using a composite plan.

Table 7.4f.3 Allowable Fractionation Schemas

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
7.5 Gy	8	60 Gy	105 Gy	Central

Table 7.4f.4 Protocol Specific Target Dose Details and Guidelines

Metric	Guideline Value
D95% [Gy] for PTV	DOSE COVERING 95% OF THE PTV**
D99% [Gy] for PTV	DOSE COVERING 99% OF THE PTV.**
Typical normalization 60-90% with hotspot within GTV. For inverse planning techniques, effort should be made to design the cost function to mimic a 3DCRT dose distribution with a hotspot within the GTV.	
R100% (Rx Isodose volume/PTV)	<1.2 Desired. Exceptions can be made for small PTVs requiring a block margin to satisfy field size criteria. Effort should be made to avoid dose > 105% of the prescription dose outside of the PTV.

R50% (50% Rx Isodose volume/PTV)	Effort should be made to have the 50% isodose surface be as small as possible. Detailed tables of recommendations are given below for single targets.

Recommendations for Allowable Dose Spillage

PTV Volume (cc)	**Ratio of 50% Isodose Volume to the PTV, R50%**		**Maximum Dose at 2 cm from PTV in any direction as % of nominal Rx dose D2cm[%]**	
	Per Protocol	Acceptable Variation	Per Protocol	Acceptable Variation
1.8	<5.9	<7.5	<50.0	<57.0
3.8	<5.5	<6.5	<50.0	<57.0
7.4	<5.1	<6.0	<50.0	<58.0
13.2	<4.7	<5.8	<50.0	<58.0
22.0	<4.5	<5.5	<54.0	<63.0
34.0	<4.3	<5.3	<58.0	<68.0
50.0	<4.0	<5.0	<62.0	<77.0
70.0	<3.5	<4.8	<66.0	<86.0
95.0	<3.3	<4.4	<70.0	<89.0
126.0	<3.1	<4.0	<73.0	<91.0
163.0	<2.9	<3.7	<77.0	<94.0

g. Compliance Criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. A category called Deviation Unacceptable results when cases do not meet the requirements for either Per Protocol or Acceptable Variation. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended. Institutions are encouraged to contact the Study Chair or medical physics co-chair prior to submitting a case with a known unacceptable deviation.

Table 7.4g.1 Target Volume Constraints and Compliance Criteria

Name of Structure	**Dosimetric parameter**	**Per Protocol**	**Variation Acceptable**	**Notes**
PTV_ddGyxF	D99%[Gy]	90% of the prescription dose	85% of the prescription dose	
	D95%[Gy]	100% of the prescription dose	99% of the prescription dose	Can be reduced to 95% of the prescrip-tion dose to protect Spinal Cord or Brachial Plexus

Critical Organ Dose-Volume Limits

Table 7.4g.2 lists dose constraint limits to a volume within critical organs. All dose limits indicated as variation unacceptable must be met, and treatment delivery that exceeds these limits will constitute a major protocol violation. Other volumetric dose constraints are suggested guidelines, and while every effort should be made to achieve the recommended constraints, exceeding the suggested dose volume metrics will not constitute a protocol deviation.

Table 7.4g.2 Normal Tissue Dose Constraints

			3 Fractions	**4 Fractions**	**5 Fractions**	**8 Fractions**
Serial Tissue	**Volume**	**Priority**	**Limit**	**Limit**	**Limit**	**Limit**
Spinal Cord	D0.03cc [Gy]	Variation Unacceptable	18.0	24	28	32
	D0.35cc [Gy]	Variation Unacceptable	15.9	19	22	26.4
	D1.2cc [Gy]	Variation Unacceptable	13	13.6	15.6	16.8
Esophagus	D0.03cc (Gy)	Variation Unacceptable	27	30	105%	105%
	D0.03cc (Gy)	Variation acceptable	25.2	30	35	40
	D5cc [Gy]	Variation Acceptable	17.7	18.8	19.5	21.6
Brachial Plexus	D0.03cc [Gy]	Variation Unacceptable	24	27.2	32.0	38
	D3cc [Gy]	Variation Unacceptable	22	24.7	27	32.8
Heart	D0.03cc [Gy]	Variation Unacceptable	30 Gy	34 Gy	105%	105%
	D0.03cc [Gy]	Variation acceptable	NA	NA	38	40
	D15cc [Gy]	Variation acceptable	24	28	32	34
Great vessels	D0.03cc [Gy]	Variation Unacceptable	45	49	105%	105%
	D10cc [Gy]	Variation acceptable	39	43	47	55
Trachea	D0.03cc [Gy]	Variation Unacceptable	30	34.8	105%	105%
	D0.03cc [Gy]	Variation acceptable	NA	NA	40	44
	D5cc [Gy]	Variation acceptable	25.8	29.2	32	35
Proximal bronchial tree	D0.03cc [Gy]	Variation Unacceptable	30	34.8	105%	105%
	D0.03cc [Gy]	Variation acceptable	23.1	28	33	38
	D0.5cc [Gy]	Variation acceptable	18.9	20	21	23
Chest Wall	D0.03cc [Gy]	Variation acceptable	50	54	57	63

			3 Fractions	**4 Fractions**	**5 Fractions**	**8 Fractions**
	V30Gy [cc]	Variation acceptable	30 cc	30 cc	30 cc	30 cc
Skin	D0.03cc [Gy]	Variation acceptable	33	36	38.5	43
	D10cc [Gy]	Variation acceptable	31	33.2	36.5	38
Stomach	D0.03cc (Gy)	Variation Unacceptable	30	32.9	35	42
	D5cc[Gy]	Variation Unacceptable	22.5	24.8	26.5	31
Bile duct	D0.03cc [Gy]	Variation acceptable	36	39	41	48
Renal hilum	D15cc [Gy]	Variation Unacceptable	19.5	21.5	23	28

		Priority	3 Fractions	4 Fractions	5 Fractions	8 Fractions
Parallel Tissue	**Constraint**		**Limit (cc or %)**	**Limit (cc or %)**	**Limit (cc or %)**	
Lungs-GTV	CV10.5Gy [cc]	Variation acceptable	>1500			
	CV11.6Gy [cc]	Variation acceptable		>1500		
	CV12.5Gy [cc]	Variation acceptable			>1500	
	CV13.6Gy [cc]	Variation acceptable				>1500
	V11Gy[%]	Variation acceptable	<37			
	V13Gy[%]	Variation acceptable		<37		
	V13.5Gy[%]	Variation acceptable			<37	
	V20 Gy	Variation acceptable	<10%	<10%	<10%	<10%
	V20 Gy	Variation Unacceptable	<15%	<15%	<15%	<15%
Liver	CV17.1Gy [cc]	Variation acceptable	>700			
	CV19.2Gy [cc]	Variation acceptable		>700		
	CV21Gy[cc]	Variation acceptable			>700	
	CV24.8Gy [cc]	Variation acceptable				>700
Renal Cortex (Right + Left)	CV15Gy[cc]	Variation acceptable	>200			
	CV17[cc]	Variation acceptable		>200		
	CV18Gy[cc]	Variation acceptable			>200	
	CV20Gy [cc]	Variation acceptable				>200

Table 7.4g.3 Delivery Compliance Criteria

Delivery Metric		**Per Protocol**	**Variation Acceptable**	**Notes**
Overall Treatment time	3,4,5 Fraction (every other day)	≤14 days	≤16 days	Reason(s) for interruptions should be documented
	8 fraction (daily or	≤18 days	≤20 days	

	every other day)			
Interruptions		0	1	

h. Patient specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines. For intensity-modulated techniques, patient specific QA is highly recommended.

i. Daily Treatment Localization/IGRT

Daily image guidance is required for all SBRT treatments. Table 7.4i.1 lists details of IGRT and the minimum requirements for IGRT in lung. Techniques should be consistent with Tables 7.4b.2 and 7.4d.2. It is very strongly recommended that all calculated IGRT shifts of 1 mm and greater (using primary localization imaging) be applied.

Table 7.4i.1 Guidelines/Instructions for Acceptable IGRT

Treatment Technique	Acceptable Methods for Daily Image Guidance	Matching Instructions
ITV/free breathing (includes abdominal compression)	**Volumetric Imaging** Volumetric Imaging (i.e. CBCT, CT on rails, or in-room MR) is strongly recommended.	Initial rigid alignment followed by soft tissue match with average CT and slow CBCT. 4D CT to 4D CBCT can be used when capability exists.
	Planar Imaging If volumetric imaging is not available, then an appropriate tumor surrogate (i.e. implanted fiducials) must be able to be accurately imaged in the treatment position with 2D imaging. The patient surface is not an appropriate surrogate for tumor setup although surface based imaging may be used during treatment to assess unexpected patient motion. Note that when orthogonal 2D imaging (with or without implanted fiducials) is employed for sites where respiratory motion is expected and	Rigid alignment to bony anatomy. Repeat imaging to ensure tumor surrogate is within ITV. Repeat imaging at each treatment port to ensure tumor surrogate remains within the ITV is very strongly recommended.

Treatment Technique	Acceptable Methods for Daily Image Guidance	Matching Instructions
	not controlled via motion management techniques, care must be taken to ensure accurate targeting of the ITV within the treatment. For example, static kV imaging at an undetermined breath hold position would not be adequate IGRT for treating a free-breathing lung tumor. Repeat imaging during treatment is recommended to verify that the tumor is in the ITV. If any significant baseline shifts are noted, resimulation should be strongly considered.	
Gating with a gating window	The baseline gating position/phase should be verified using appropriate imaging techniques Volumetric Imaging (i.e. CBCT, CT on rails, or in-room MR) is strongly recommended for the initial localization to verify isocenter and tumor trajectory.	Initial rigid alignment followed by soft tissue match for baseline gating position.
Breath hold (i.e. ABC)	Volumetric imaging recommended; planar at breath hold position acceptable – repeated imaging recommended to ensure reproducibility of breath hold. All imaging should be done at breath hold treatment position.	Initial rigid alignment followed by soft tissue match of tumor or surrogate.
Tracking	Volumetric imaging or real-time fluoroscopic imaging, or cine MR of tumor surrogate required based on treatment machine capabilities.	Initial rigid alignment followed by soft tissue match of tumor or surrogate in baseline position.

j. Quality Assurance and Imaging Dose

Management of Radiation Dose to the Patient from IGRT

SWOG and NRG Oncology are concerned about the estimated doses given from IGRT and is committed to limiting the imaging dose when IGRT is used in any of its protocols. It is recommended that patients demonstrating severe set up problems during the first 1-2 fractions be moved to a treatment with larger margins.

Case Review

The Study Chairs will perform ongoing remote RT Quality Assurance Review after all cases enrolled have been received at IROC Philadelphia.

7.5 Criteria for Removal from Protocol Treatment

a. Disease progression (as defined in Section 10.0). Note: Disease progression before SBRT that maintains the ability to undergo the planned SBRT is not criteria for removal from protocol treatment.

b. Symptomatic deterioration (as defined in Section 10.0).

c. Unacceptable toxicity.

d. For patients on Arm A: Atezolizumab treatment delay > 84 days for any reason after completion of SBRT. If atezolizumab is being held due to an adverse event and the AE resolves within 84 days and the patient is receiving corticosteroid therapy for the event, atezolizumab may be held for up to 28 additional days in order to allow tapering of the steroid dose to ≤10 mg oral prednisone or equivalent.

e. Completion of treatment.

f. Patients may withdraw from protocol treatment at any time for any reason.

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.7 Follow-Up Period

All patients will be followed until death or 5 years after randomization, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 General Dose Modification Guidelines

a. Missed atezolizumab doses can be made up. Patient may receive up to 8 doses.

b. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

c. If patient on Arm A has to permanently discontinue atezolizumab, protocol treatment may continue on SBRT alone.

d. If patient on Arm A has to permanently discontinue SBRT, protocol treatment may continue on atezolizumab alone.

e. The maximum dose delay for any reason is 84 days. If patient is receiving corticosteroid therapy for an adverse event, the maximum dose delay could be 112 days in order to allow tapering of the steroid dose to ≤ 10 mg oral prednisone or equivalent.

8.3 SBRT adverse event management and dose modification guidelines

No SBRT dose modifications for toxicity are permitted, as SBRT-induced side effects typically do not manifest during a course of treatment. Any patient manifesting Grade 3 or higher pulmonary toxicity during the course of SAR treatment will be discontinued from protocol treatment.

Lung Injury: Radiation pneumonitis is a subacute (weeks to months from treatment) inflammation of the end bronchioles and alveoli. Radiation fibrosis is a late manifestation of radiation injury to the irradiated lung. Given the small amount of lung that typically receives high radiation doses with SBRT, lung toxicity has not been as dose-limiting as in conventionally fractionated large field RT. However, it is nevertheless seen, can be symptomatic, and may be confused with other causes of respiratory deterioration, including infections and tumor recurrence. It is very important that a radiation oncologist participate in the care of the patient, as the clinical picture may be very similar to acute bacterial pneumonia, with fatigue, fever, shortness of breath, nonproductive cough, and a pulmonary infiltrate on chest x-ray. The infiltrate on chest x-ray should include the area treated to high dose, but may extend outside of these regions. Patients reporting symptoms as above will be promptly evaluated and treated. Mild radiation pneumonitis may be treated with nonsteroidal anti-inflammatory agents or steroid inhalers. More significant pneumonitis will be treated with systemic steroids, bronchodilators, and pulmonary toilet. Supra- and concurrent infections should be treated with antibiotics. Consideration of prophylaxis of opportunistic infections should be considered in immunocompromised patients.

Central Airway/Bronchial Injury: This bronchial injury with subsequent focal collapse of lung may impair overall pulmonary status. It also makes further assessment of tumor response more difficult as the collapsed lung approximates the treated tumor. Because atelectatic lung and tumor have similar imaging characteristics, radiology reports will often describe the overall process as progressive disease while the actual tumor may be stable or shrinking. Investigators are referred to the strict criteria for progressive disease in Section 10 of this protocol to avoid such mischaracterization. The consequences of bronchial toxicity, e.g., cough, dyspnea, hypoxia, impairment of pulmonary function test parameters, pleural effusion or pleuritic pain (associated with collapse), should all be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Hemoptysis should be promptly evaluated bronchoscopically as fatal hemoptysis is a rare but established complication following SBRT for centrally located tumors.

Cardiac and Pericardial Injury: Serious cardiac complications following SBRT are rare. Symptoms suggestive of pericarditis, including pleuritic chest pain, pericardial friction rub on auscultation, fevers, and unexplained pericardial effusions should be evaluated with EKG and referral to an appropriate specialist.

Gastrointestinal/Esophageal Injury: The radiation effects on the esophagus can be acute: esophagitis (i.e., dysphagia, causing pain on swallowing, typically relatively soon after RT course is completed, and typically resolves on its own within days to a week or

longer), or chronic, typically manifesting with dysphagia due to stenosis, or esophageal ulceration, with perforation in the extreme cases. Acute mild to moderate esophagitis can be managed conservatively with viscous lidocaine solutions, Maalox, dietary modifications, and/or analgesics.

Chest wall/rib injury: Chest wall and/or rib pain or fractures are typically late manifestations, occurring months to several years after radiation. Treatment can include NSAIDS or for more severe cases short courses of steroids.

8.4 Atezolizumab adverse event management and dose modification guidelines

There will be no dose reduction for atezolizumab in this study.

Patients may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for >84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in this protocol. If the AE resolves within 84 days and the patient is receiving corticosteroid therapy for the event, atezolizumab may be held for longer than 84 days (up to 4 weeks) in order to allow tapering of the steroid dose to ≤10 mg oral prednisone or equivalent.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the Study Chair in consultation with CTEP.

The primary approach to grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade irAEs, atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent grade 2 irAEs may also mandate withholding atezolizumab or the use of steroids. Assessment of the benefit risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life threatening irAEs.

8.5 Management of Specific AEs

Management of certain AEs of concern, including immune-related pneumonitis, hepatitis, colitis, endocrinopathies, pancreatitis, neuropathies, meningoencephalitis, and potential ocular toxicities are presented in the atezolizumab Investigator's Brochure. See Section 7.3 for atezolizumab administration guidelines, including the "Administration of First and Subsequent Atezolizumab Infusions" table for guidelines for the management of infusion related reactions and anaphylaxis.

Atezolizumab has been associated with risks such as the following: IRRs and immune–related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, meningoencephalitis, myocarditis, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome.

Pleural and pericardial effusion

Patients experiencing dyspnea, chest pain, or unexplained tachycardia should be evaluated for the presence of a pericardial effusion. Patients with pre-existing pericardial effusion should be followed closely for pericardial fluid volume measurements and impact on cardiac function. When intervention is required for pericardial or pleural effusions,

atezolizumab should be held, and appropriate workup includes cytology, lactate dehydrogenase (LDH), glucose, cholesterol, protein concentrations (with pleural effusions), and cell count.

Pulmonary events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in the table below.

Event	Management
Pulmonary event, Grade 1	● Continue atezolizumab and monitor closely. ● Re-evaluate on serial imaging. ● Consider patient referral to pulmonary specialist. ● For Grade 1 pneumonitis, consider withholding atezolizumab
Pulmonary event, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] ● For recurrent events, or events with no improvement after 48-72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	● Permanently discontinue atezolizumab. [c] ● Bronchoscopy or BAL is recommended. ● Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day IV methylprednisolone. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL = bronchoscopic alveolar lavage

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or appropriate delegate).

Hepatic events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Patients eligible for study treatment must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in the table below.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of >5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Gastrointestinal events

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in the table below.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (*e.g.*, increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).

Endocrine disorders

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in the table below.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes, should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests (e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels, and ACTH stimulation test) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH closely. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. • Consider patient referral to endocrinologist. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism. • Consider patient referral to endocrinologist.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab if symptoms are not controlled or held >12 weeks. [c]

Event	Management
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. In the absence of corticosteroids or diabetes medication non-adherence may be an indication of beta-cell destruction and atezolizumab-induced diabetes. If patient has Type 1 diabetes (e.g., new-onset diabetes in the absence of corticosteroids or another inciting medication), treat as a Grade 3 event. • Exercise caution in utilizing non-insulin hypoglycemic agents in this setting, as new-onset hyperglycemia in the absence of corticosteroids may be an indication of beta-cell destruction and atezolizumab-induced diabetes. After a thorough investigation of other potential causes which may involve a referral to an endocrinologist, follow institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Strongly consider referral to endocrinologist, particularly if patient is deemed to have atezolizumab-induced diabetes; if so, obtain C-peptide level paired with glucose, autoantibody levels (e.g., GAD65, islet cell autoantibodies), and hemoglobin A1C level. • If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (e.g., anion gap, ketones, blood pH, etc.) reported. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b]

Event	Management
	• If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events).
Management guidelines for ocular events are provided in the table below.

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone.

Event	Management
	• If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Immune-mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g., B-type natriuretic peptide) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis and should be managed accordingly. Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below.

Management Guidelines for Immune-mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2-4	• Permanently discontinue atezolizumab. [a] • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

Event	Management

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on the investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).

Infusion-Related Reactions and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, anti-pyretics, and/or analgesics (*e.g.*, acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee *et al*., 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also been reported with immunotherapies that target PD-1 or PD-L1 (Rotz *et al*., 2017; Adashek and Feldman 2019) including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in the table below.

Severe COVID-19 appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin, 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include COVID-19, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator judgment. If a diagnosis of COVID-19 is confirmed, the disease should be managed as per local or institutional guidelines.

Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1[a] Fever [b] with or without constitutional symptoms	● Immediately interrupt infusion. ● Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. ● In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. ● For subsequent infusions, consider administration of oral premedication with

	antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2 [a] Fever [b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen [d] by nasal cannula or blow-by	● Immediately interrupt infusion. ● Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment.[c] ● For hypotension, administer IV fluid bolus as needed. ● Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this protocol. ● Consider IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy. ● Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab.[e] ● If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. ● If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the investigator.
Grade 3 [a] Fever [b] with hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen [d] by nasal cannula, face mask, non-rebreather mask, or Venturi mask	● Permanently discontinue atezolizumab. [e] ● Administer symptomatic treatment.[c] ● For hypotension, administer IV fluid bolus and vasopressor as needed. ● Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated, and manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this protocol. ● Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy. ● Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
Grade 4 [a] Fever [b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure	● Permanently discontinue atezolizumab. [e] ● Administer symptomatic treatment.[c] ● Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS as described in this protocol. ● Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours).

(*e.g.*, CPAP, BiPAP, intubation and mechanical ventilation)	● Consider anti-cytokine therapy. For patients who are refractory to anti-cytokine therapy, experimental treatments [f] may be considered at the discretion of the investigator. ● Hospitalize patient until complete resolution of symptoms.

ASTCT= American Society for Transplantation and Cellular Therapy; BiPAP= bi-level positive airway pressure; CAR= chimeric antigen receptor; CPAP= continuous positive airway pressure; CRS= cytokine-release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic Case Report Form; HLH= hemophagocytic lymphohistiocytosis; ICU = intensive care unit; IRR = infusion-related reaction; MAS= macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

a. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE v5.0 should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

b. Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

c. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

d. Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min.

e. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate). For subsequent infusions, administer oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio.

f. Refer to Riegler *et al*. (2019).

Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in the table below.

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase >1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (*e.g.*, >3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase >2.0–5.0 × ULN:** • Treat as a Grade 3 event.

Event	Management
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab. [c]
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab. [c]
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on the investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).

Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are

provided in the table below.

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve. • If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab. [c]
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).

Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in the table below.

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology.
Immune-rmediated neuropathy, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Investigate etiology and refer patient to neurologist. • Initiate treatment as per institutional guidelines. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to below Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).

Immune-mediated Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below.

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab. [a] • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).

Renal Events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below.

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).

Immune-Mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy. Patients with possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in table below.

Event	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.

Event	Management
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (*e.g.*, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (*e.g.*, cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit-risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re-challenge patients with atezolizumab should be based on investigator's assessment of benefit-risk and documented by the investigator (or an appropriate delegate).

Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS), which are considered to be potential risks for atezolizumab.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count < 100 × 10^9/L (100,000/mcL)
  - ANC < 1.0 × 10^9/L (1000/mcL)
- Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin >500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli *et al*. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin >684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181 × 10^9/L (181,000/mcL)
  - AST ≥48 U/L
  - Triglycerides >1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in below.

Event	Management
Suspected HLH or MAS	● Permanently discontinue atezolizumab. ● Consider patient referral to hematologist. ● Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. ● Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. ● If event does not respond to treatment within 24 hours initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al., 2019). ● If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH= hemophagocytic lymphohistiocytosis; MAS= macrophage activation syndrome.

8.6 Dose Modification Contacts

For treatment or dose modification questions, please contact S1914medicalquestion@swog.org.

8.7 Serious Adverse Event Reporting Requirements

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave.**

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period and is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the Last Administration of the Investigational Agent/Intervention are collected using the Late Adverse Event form.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301/897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU members' website:

- Study specific documents: *Protocols* > *Documents* > *Protocol Related Documents* > *Adverse Event Reporting*; and
- Additional resources: *Resources* > *CTSU Operations Information*> *User Guides & Help Topics*.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

If you have questions about this process, please contact the SAE Program Manager 210-614-8808 or email adr@swog.org.

a. Definition and Purpose

Definition: Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. (FDA, 21 CFR 312.32). See the tables below for definition of a Serious Adverse Event (SAE) and reporting requirements.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported to SWOG Operations Office using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to the tables below) via CTEP-AERS.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

When the adverse event requires expedited reporting, submit the report via CTEP-ARS within the number of calendar days of learning of the event specified in the tables below.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

d. Other recipients of adverse event reports

CTEP will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table 8.7a. The investigational agent used in this study is atezolizumab. If there is any question about the reportability of an adverse event or if Internet connectivity is disrupted please telephone or email the SAE Program Manager at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 8.7a.

Table 8.7a:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Atezolizumab

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

○ "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. ○ "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.
[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: **Expedited 24-hour notification followed by complete report within 5 calendar days for:** • All Grade 4, and Grade 5 AEs **Expedited 10 calendar day reports for:** • Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization • Grade 3 adverse events May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a CTEP IND:**

1. **Group-specific instructions**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the SWOG Operations Offices in order to complete the evaluation of the event. If requested by the SAE Program Manager, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006.

2. **Adverse events of special interest (AESI)**

The following adverse events are considered adverse events of special interest (AESI) for this protocol and require expedited reporting via CTEP-AERS. Unless otherwise specified in the list below, events are to be reported regardless of grade or attribution:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
  - Treatment-emergent ALT or AST > 3 x ULN (or > 3 x baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin > 2 x ULN (of which ≥ 35% is direct bilirubin)
  - Treatment-emergent ALT or AST > 3 x ULN (or > 3 x baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below:
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that

indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, macrophage activating syndrome and hemophagocytic lymphohistiocytosis
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 8.7b. If the patient has received SBRT but no atezolizumab, follow these guidelines. If there is any question about the reportability of an adverse event or if Internet connectivity is disrupted please telephone or email the SAE Program Manager at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table 8.7b.

Table 8.7b. Expedited reporting requirements for adverse events experienced by patients within 30 days of the last SBRT treatment

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

2. Supporting documentation should be submitted to CTEP by fax at 301-897-7404 in accordance with instructions provided by the CTEP-AERS system. A copy of supporting documentation must also be submitted to SWOG Operations Office by fax 210-614-0006.

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Pregnancy Loss, and Death Neonatal**

1. **Pregnancy.** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Pregnancy Loss.** Pregnancy loss is defined in CTCAE as "Death in utero." Pregnancy loss should be reported expeditiously as **Grade 4 "pregnancy loss under the Pregnancy, puerperium and perinatal conditions** SOC.

   A Pregnancy loss should **NOT** be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

3. **Death Neonatal.** "Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth." A neonatal death should be reported expeditiously as **Grade 4 "Death Neonatal"** under the **General disorders and administration** SOC.

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently CTEP-AERS recognizes this event as a patient death.

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-897-7404. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

Queries:

Technical CTEP-AERS Questions/Help:	**SAE Reporting Questions/Help:**
Email: ctephelpdesk@nih.gov	Email: adr@swog.org
Phone: 1-888-283-7457	Phone: 210-614-8808

8.8 Adverse Events Related to COVID-19

Infections occurring in participants on clinical trials are considered adverse events and should be reported per protocol guidelines via normal procedures (on CRFs/Rave and via CTEP-AERS if serious).

Please document COVID-19 related adverse events as follows:

Infections and infestations - Other, specify
Specify = COVID-19

Additionally, please record (and if applicable, report via CTEP-AERS) any other Adverse Events the subject experiences such as Dyspnea, Acute respiratory distress syndrome, etc.

CTEP-AERS specific instructions:

- **Narrative:** Identify all pertinent facts related to the COVID-19 infection including, but not limited to the following:

  - Presumptive vs confirmed diagnosis. If presumptive, please update your narrative if/when diagnosis is confirmed, including timelines.
  - Treatment information
  - Recovery information, including timelines
  - Outcome information/status
- **Supporting documentation:** Please fax supporting documentation including admission notes, progress notes, clinical visits, and discharge summary if/when available.
  - Fax Number: 301-897-7404, include protocol number, ticket number and subject ID on the fax cover sheet and each page faxed.

Queries:

CTEP-AERS Questions/Help:
Email: ctephelpdesk@nih.gov
Phone: 1-888-283-7457

9.0 STUDY CALENDAR

9.1 Arm A: SBRT + Atezolizumab

		Cycle Length = 21 days											
	PRE-REGISTRATION [A]	Cycle 1	Cycle 2	Cycle 3		Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	At Off Tx [Q]	Follow-up prior to prog [G]	At Prog	Follow-up after prog [H]
		Day 1	Day 1	Day 1	Days 2-21	Day 1	Day 1	Day 1	Day 1	Day 1				
PHYSICAL														
History & Physical Exam	X		X	X		X	X	X	X	X	X	X		X
Weight & Zubrod Performance Status	X		X	X		X	X	X	X	X	X	X		X
Toxicity Notation			X	X		X	X	X	X	X	X [K]	X [K]		X [K]
Baseline Abnormalities	X													
LABORATORY														
Hepatitis B and C testing	X [N]													
HIV viral load test	X [N]													
Chemistry Panel [O]	X	X [E]	X	X		X	X	X	X	X	X			
ANC, platelets, hemoglobin	X	X [E]	X	X		X	X	X	X	X	X			
TSH with reflex to Free T3/Free T4 if abnormal	X	X [E]	X	X		X	X	X	X	X	X			
Serum pregnancy test [T]	X													
PROCEDURES AND SCANS														
Chest CT (see Section 7.2 Disease Assessment) [D]	X		X						X [S]			X		
FDG PET/CT of chest	X [C]													
Cytologic sampling	X [F]													
FEV1 and DLCO	X [C]											At 6 months ± 21 days post-SBRT		

Calendar 9.1 continued on next page. Click here for Footnotes.

		Cycle Length = 21 days												
	PRE-REGISTRATION [A]	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 3 Days 2-21	Cycle 4 Day 1	Cycle 5 Day 1	Cycle 6 Day 1	Cycle 7 Day 1	Cycle 8 Day 1	At Off Tx [Q]	Follow-up prior to prog [G]	At Prog	Follow-up after prog [H]
SPECIAL INSTRUCTIONS														
Submit CT images to IROC Ohio (see Section 15.3)		X (base line CT)							X			X	X	
Submit RT materials to IROC Philadelphia (see Section 12.1)				X										
Archival tissue (see Section 15.2)		X												
Whole blood (see Section 15.2) [L]		X			X [R]				X [P]				X	
EORTC QLQ-C30 and EORTC QLQ-LC13 (see Section 15.4) [M]		X		X (w/in 1 wk prior to starting SBRT)								X		
TREATMENT														
Atezolizumab		X	X	X		X	X	X	X	X				
SBRT [J]				See Sections 7.1 & 7.4										

Note: Unless otherwise indicated, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection, and follow-up activities) must follow the established SWOG guidelines as outlined in the Best Practices document located at https://www.swog.org/clinical-trials/protocol-workbench.

Note: Forms are found on the protocol abstract page on the SWOG website (www.swog.org) and on the CTSU website (www.ctsu.org). Submission guidelines are found in Section 14.0.

Click here for Footnotes

Footnotes for Calendar 9.1

A To be performed within 28 days prior to randomization, except as otherwise indicated.

B This footnote has been removed.

C To be performed within 90 days prior to randomization

D To be performed within 42 days prior to randomization and within ±3 days of the following time points, counted from the date of randomization: at Week 4 (this scan will assess patient's ongoing suitability to undergo SBRT, growth of the target lesion on this scan prior to initiation of SBRT will not be considered progression; this diagnostic CT chest is separate from the simulation planning CT); then at Weeks 18, 30, 42, and 54; then every 6 months until progression for up to five years after randomization. Every effort should be made to repeat the same modality of scanning and contrast administration on successive imaging. See Section 7.2.

E If pre-registration labs were obtained within 14 days prior to Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1.

F For patients with radiographically suspicious hilar or mediastinal nodes, required prior to randomization to rule out involvement (see Section 5.1e.). NOTE: There is no specific timeframe for performing cytologic sampling prior to randomization (i.e., footnote "A" does not apply to this procedure).

G After off treatment prior to progression, patients should be followed by repeating the indicated tests within ±3 days of the following time points, counted from the date of randomization: Weeks 18 (if off treatment prior to this timepoint), 30, 42, and 54, then every 6 months for up to 5 years from randomization until progression.

H After off treatment after progression, patients should be followed by repeating the indicated tests at the following time points, counted from the date of randomization, if applicable: within ±3 days of Weeks 18, 30, 42, and 54, then within ±7 days of every 6 month assessment for 2 years, and then within ±14 days of every 12 month assessment for 2 years.

J SBRT to begin on Day 1 of Cycle 3. SBRT will be delivered to a total dose of 48-60 Gy over 3-8 fractions with a minimum interval of 40 hours and a maximum of 120 hours between fractions for 3-5 fraction regimens, and with a minimum interval of 16 hours and a maximum of 120 hours between fractions for 8 fraction regimens.

K Assessments should continue until 30 days after last dose of atezolizumab or until resolution of all acute adverse events, whichever is later.

L See Section 15.2 for details. If venipuncture for routine care clinical lab work is planned for the same day as venipuncture for research blood draws, the blood for research should be drawn at the same time. If patient is not scheduled for any routine care clinical lab work at the time of a protocol-specified research blood draw timepoint, it is acceptable to schedule blood collection for research only.

M To be completed at the following time points: after registration within 2 weeks prior to starting atezolizumab (must be completed on paper); within 1 week prior to starting SBRT; at week 30 and week 54 from atezolizumab start date (±4 weeks); and at week 80 from atezolizumab start date (± 8 weeks).

N See Section 5.3 for details.

O Chemistry panel (non-fasting) must include standard of care AST, ALT, calculated creatinine clearance, sodium, potassium, and magnesium.

P Collect at Week 18 counted from randomization (± 1 week).

Q Collect tests and procedures at end of Cycle 8 (i.e., Cycle 8 Day 21) or at end of the last cycle of treatment for patients who go off treatment prior to Cycle 8.

R Collect at 1 week after completion of SBRT (± 2 days but preferably ± 1 day if possible), per Section 15.2. NOTE: This activity may fall within the timeframe indicated on the calendar depending on patient's schedule.

S Collect at Week 18 counted from randomization (±3 days).

T For patients of reproductive potential, as defined in Section 5.3s and Section 5.3t.

9.2 Arm B: SBRT

	PRE-REGISTRATION [A]	Day 1	Days 2-21	Day 43	Follow-up prior to prog [G]	At prog	Follow-up after prog [H]
PHYSICAL							
History & Physical Exam	X				X		X
Weight & Zubrod Performance Status	X				X		X
Toxicity Notation		X [N]			X [K]		X [K]
Baseline Abnormalities	X						
LABORATORY							
Hepatitis B and C testing	X[O]						
HIV viral load test	X[O]						
Chemistry Panel [P]	X						
ANC, platelets, hemoglobin	X						
TSH with reflex to Free T4/Free T3 if abnormal	X						
Serum pregnancy test	X						
PROCEDURES AND SCANS							
Chest CT (see Section 7.2 Disease Assessment) [D]	X				X		
FDG PET/CT of chest	X [C]						
Cytologic sampling	X [F]						
FEV1 and DLCO	X [C]				At 6 months ± 21 days post-SBRT		
SPECIAL INSTRUCTIONS							
Submit CT images to IROC Ohio (see Section 15.3)		X (baseline CT)			X	X	
Submit RT materials to IROC Philadelphia (see Section 12.1)		X					
Archival tissue (see Section 15.2)		X					
Whole blood (see Section 15.2) [L]		X	Also submit one week after completion of SBRT and at Week 18 [Q]			X	
EORTC QLQ-C30 and EORTC QLQ-LC13 (see Section 15.4) [M]		X		X	X		

SBRT [J]		See Sections 7.1 & 7.4				

Note: Forms are found on the protocol abstract page on the SWOG website (www.swog.org) and on the CTSU website (www.ctsu.org). Submission guidelines are found in Section 14.0.

Note: Unless otherwise indicated, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection, and follow-up activities) must follow the established SWOG guidelines as outlined in the Best Practices document located at https://www.swog.org/clinical-trials/protocol-workbench.

Footnotes for Calendar 9.2

A To be performed within 28 days prior to randomization, except as otherwise indicated

C To be performed within 90 days prior to randomization

D To be performed within 42 days prior to randomization, then within ±3 days of the following time points, counted from the date of randomization: Weeks 18, 30, 42, and 54; then every 6 months until progression. Every effort should be made to repeat the same modality of scanning and contrast administration on successive imaging. See Section 7.2.

F For patients with radiographically suspicious hilar or mediastinal nodes, required prior to randomization to rule out involvement (see Section 5.1e.). NOTE: There is no specific timeframe for performing cytologic sampling prior to randomization (i.e., footnote "A" does not apply to this procedure).

G After off treatment prior to progression, patients should be followed by repeating the indicated tests within ±3 days of the following time points, counted from the date of randomization: Weeks 18, 30, 42, and 54, then every 6 months for up to 5 years from randomization until progression.

H After off treatment after progression, patients should be followed by repeating the indicated tests at the following time points, counted from the date of randomization, if applicable: within ±3 days of Weeks 18, 30, 42, and 54, then within ±7 days of every 6 month assessment for 2 years, and then within ±14 days of every 12 month assessment for 2 years.

J SBRT will be delivered to a total dose of 48-60 Gy over 3-8 fractions with a minimum interval of 40 hours and a maximum of 120 hours between fractions for 3-5 fraction regimens, and with a minimum interval of 16 hours and a maximum of 120 hours between fractions for 8 fraction regimens.

K Assessments should continue until resolution of all acute adverse events.

L See Section 15.2 for details. If venipuncture for routine care clinical lab work is planned for the same day as venipuncture for research blood draws, the blood for research should be drawn at the same time. If patient is not scheduled for any routine care clinical lab work at the time of a protocol-specified research blood draw timepoint, it is acceptable to schedule blood collection for research only.

M To be completed at the following time points: after registration within 2 weeks prior to starting SBRT (must be completed on paper); Day 43 from SBRT start date (± 1 week); at week 30 and week 54 from SBRT start date (±4 weeks); and at week 80 from SBRT start date (± 8 weeks).

N Toxicity Notation (AE assessment) is to occur on the last day of SBRT. Sites should also document any other toxicity brought to their attention following SBRT.

O See Section 5.3 for details.

P Chemistry panel (non-fasting) must include standard of care AST, ALT, calculated creatinine clearance, sodium, and potassium.

Q Collect at 1 week after completion of SBRT (± 2 days but preferably ± 1 day if possible) and at Week 18 counted from randomization (± 1 week), per Section 15.2.

R For patients of reproductive potential, as defined in Section 5.3s and Section 5.3t.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Measurability of Lesions

a. **Measurable disease**:

Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

a. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

b. The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. It is strongly recommended that CT slice of 0.5 cm be used. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

c. Lymph nodes are to be considered measurable if it measures ≥ 1.5 cm in SHORT AXIS (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Notes on measurability**

a. For CT and MRIs, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to prior scans. It is no longer necessary to distinguish between spiral and conventional CT.

b. Body scans should be performed with breath-hold scanning techniques, if possible.

c. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with stand-alone CT. The slice thickness of 0.5 cm or less is highly recommended. If CT scans have slice thickness > 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

d. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

e. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

f. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0 cm should be recorded.

10.2 Disease Status at each disease evaluation

The tumor longest diameter measurement must be provided for the primary tumor, if measurable. Otherwise, presence/absence must be noted.

10.3 Investigator-Assessed Progression

One or more of the following must occur: 20% increase in the longest diameter of the primary lung tumor over smallest measurement observed using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm, accompanied by confirmatory study (unequivocal PET findings or biopsy). Appearance of any new lesion/site. Death due to disease without prior documentation of progression. Unequivocal PET findings and/or biopsy confirming malignancy in the absence of growth is also sufficient to confirm progression.

Notes on progression and new lesions:

a. Progression of disease before SBRT that maintains the ability to undergo the planned SBRT is not counted as a progression event.

b. For increases in the primary tumor diameter meeting the criteria above, progression is confirmed if the primary tumor is avid on Positron Emission Tomography (PET) imaging with uptake of a similar or greater intensity as the pretreatment staging PET, OR the lesion is biopsied confirming viable carcinoma.

c. For increases in the primary tumor diameter meeting the criteria above, if a confirmatory PET scan or biopsy was not performed, this will not be considered progression unless determined to be unequivocal progression by the treating investigator and confirmation by PET or biopsy is not clinically possible. If the growth occurred greater than 6 months from completion of SBRT, PET or biopsy evaluation is strongly recommended, if clinically feasible. If PET or biopsy evaluation is not done and it is within 54 weeks from randomization, it is recommended to continue disease assessments per protocol (see Section 7.4 and 9.0). If PET or biopsy evaluation is not done and it is greater than 54 weeks from randomization, a 12-week interval CT chest for re-assessment is recommended.

d. For new sites of disease, if a confirmatory PET scan or biopsy was not performed, radiographically convincing metastatic or regional lesion will be assumed to be progression.

e. For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in the primary tumor), treatment or surveillance may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

f. A normal lymph node at baseline (<1.0 cm) that subsequently becomes pathologic is considered a new lesion and should be considered progression.

g. If a single enlarged lymph node is driving the progression event, continuation of treatment/follow-up and confirmation by a subsequent exam should be contemplated. If it becomes clear that the new lymph node has not resolved, or has increased in size, the date of progression would be the date the new lymph node was first documented.

h. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions.

i. For patients with multifocal tumors with two lesions, if either lesion meets above progression, it will be considered as progression.

10.4 Symptomatic deterioration

Global deterioration of health status during active protocol treatment requiring discontinuation of protocol treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

10.5 Performance Status

Patients will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.6 Investigator-assessed Progression-free survival (IA-PFS)

From date of randomization to date of first documentation of progression or death due to any cause. Patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression. Patients on Arm A (Atezolizumab + SBRT), who are reported to have progression/recurrence prior to beginning SBRT will be assigned the progression time of 18 weeks (126 days) and an IA-PFS equal to the minimum of 126 days or time to death.

10.7 PFS by blinded independent centralized review (PFS-BICR)

From date of randomization to date of first documentation of progression assessed by BICR, or death due to any cause. PFS-BICR-1 for patients last known to be alive without report of progression are censored at date of last disease assessment. For patients with a missing scan (or consecutive missing scans) whose subsequent scan determines progression, the expected date of the first missing scan (as defined by the disease assessment schedule) will be used as the date of progression.

10.8 Time to treatment failure

From date of randomization to date of first documentation of investigator-assessed progression or symptomatic deterioration (as defined above), early discontinuation of

treatment, or death due to any cause. Time to treatment failure for patients last known not to have failed treatment are censored at the date of last contact.

10.9 Overall Survival

From date of randomization to date of death due to any cause. Overall survival for patients last known to be alive are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Overview

The primary objective of this study is to compare overall survival between patients with inoperable, T1, T2, limited T3, N0M0 (early stage) non-small cell lung cancer (NSCLC) randomized to stereotactic body radiation therapy (SBRT) with or without atezolizumab.

Based on historical information, we assume that the 2-year historical rate for OS is approximately 68%, which results in the assumption of an average monthly hazard rate of 0.016. *(61, 62, 63)* Based on these studies, we believe that OS (and PFS) can be assumed to be exponentially distributed and employ that assumption in our sample size calculations. We also assume a uniform accrual rate of 8 patients per month (7.2 eligible patients per month). With 432 eligible patients accrued over 60 months with 36 months of follow-up, this study would have 80% power to rule out no difference in OS between the arms at the 1-sided 0.025 level (using a stratified log-rank test), if the true hazard ratio is 0.7 (43% improvement in OS). The final analysis would take place upon the observation of 245 deaths (57% of patients with events) or a maximum of 42 months after completion of accrual (whichever comes first). Assuming 90% of patients meet the eligibility criteria (see Section 5.0), the total sample size to be accrued is 480. The observation of an HR equal to 0.78 or smaller would be consistent with ruling out the null at the 0.025 level (based on design assumptions).

A HR of 0.70 for OS is thought to be a clinically meaningful improvement in OS based on prior studies. The PACIFIC trial resulted in a HR of 0.68 for OS favoring the use of durvalumab. However, the event rate is expected to be lower with early stage disease, hence a somewhat higher HR for OS is expected. In studies evaluating adjuvant chemotherapy for resected early stage disease, hazard ratios for OS between 0.69-0.86 have been observed in several large randomized studies. *(64, 65, 66)* In aggregate, a HR of 0.70 was felt to be realistic and clinically significant based primarily on the results of PACIFIC and results in an achievable patient accrual target.

11.2 Safety evaluation

The rate of patients randomized to Arm A unable to receive SBRT will be closely monitored. Within this arm, if the percentage of patients unable to receive SBRT exceeds 10% after at least 20% have been accrued, then the study chair, co-chairs, Lung committee chair, and study statistician will evaluate the specific details to determine if the study should continue accruing patients. This information will be provided to the study leadership on a monthly basis and included in the biannual reports.

In addition, this the trial will include monthly adverse event monitoring by the study leadership and Lung committee chair.

Radiation pneumonitis is considered the most probable and concerning synergistic toxicity. We will require real-time (within 48 hours) reporting of all Grade 3+ pneumonitis events to the study team.

11.3 Analysis Description, including details of interim analyses

The primary analysis population will include all randomized and eligible (meeting all criteria in Section 5) patients. As stated above, the primary objective is to compare OS between the arms. If the study makes it to full accrual and is not closed at an interim analysis, upon the observation of 245 deaths or at a maximum of 3 years of follow-up (whichever comes first), OS (as the sole primary endpoint) will be compared at the 0.0242 level (Lan-DeMets alpha spending function) to account for the effects of interim testing to preserve the study-wide 0.025 level. The comparison will be done using a stratified log-rank test with stratification based on the stratification factors as listed in Section 6.0.

A key secondary objective is to evaluate if the investigational treatment improves PFS (investigator-assessed PFS). This analysis will take place after completion of accrual, all patients are off treatment, and at least 6 months have elapsed after the completion of accrual, when an estimated 225 PFS events have been reported. The estimated time of this analysis is 12 months after completion of accrual. The results of this analysis will be released prior to the analysis of the primary objective comparing OS between the arms. To evaluate this secondary objective, PFS will be compared between the arms using a stratified log-rank test 1-sided 0.025 level. No adjustment for of type I error due to interim testing is needed for this comparison as the PFS comparison is a secondary objective and the interim analysis plan does not include early stopping for efficacy based on a PFS comparison.

With 225 PFS events and testing at the 1-sided 0.025 level, this design has 90% power (adjusted to 88% power, accounting for the effects of interim futility testing) to rule out no difference between the arms if the true HR is 0.66. Based on historical information, the estimated 2-year PFS rate is 50%. The observation of an HR equal to 0.77 or smaller would be consistent with ruling out the null at the 0.025 level.

A HR of 0.66 is thought to be a clinically meaningful improvement in PFS based on prior studies. The PACIFIC trial resulted in a HR of 0.52 for PFS favoring the use of durvalumab. However, the event rate is expected to be lower with early stage disease, hence a somewhat higher HR for PFS is expected. In studies evaluating adjuvant chemotherapy for resected early stage disease, hazard ratios for PFS between 0.60-0.83 have been observed in several large randomized studies. *(67, 68 ,69)* In aggregate, a HR of 0.66 was felt to be realistic and clinically significant based primarily on the results of PACIFIC and results in an achievable patient accrual target.

The trial will include four interim analyses:

Interim #1 (futility only):
This analysis will evaluate early stopping for futility alone at 36 months after study activation when it is estimated that 70 PFS and 40 OS events have been reported. The assessment of futility will be based on comparisons of OS and PFS. If either comparison suggests futility, the recommendation will be to close the study to further accrual under the conclusion of futility. Futility evaluations will be based on using testing the target hazard ratio for PFS (HR = 0.66) at the 1-sided 0.0025 level and the target hazard ratio for OS (HR = 0.70) for OS, at the 1-sided 0.005 level using a modified log-rank test.

Interim #2 (futility only):
This analysis will evaluate early stopping for futility alone at 48 months after study activation when it is estimated that 117 PFS and 91 OS events have been reported. The assessment of futility will be based on comparisons of OS and PFS. If either comparison suggests futility, the recommendation will be to close the study to further accrual under the conclusion of futility. Futility evaluations will be based on using testing the target hazard ratio for PFS (HR = 0.66) at the 1-sided 0.0025 level and the target hazard ratio for OS (HR = 0.70) for OS, at the 1-sided 0.005 level using a modified log-rank test.

Interim #3 (futility and efficacy):

This analysis will evaluate early stopping for futility and efficacy at 60 months after study activation when it is estimated that 172 PFS and 135 OS events have been reported. The assessment of futility will be based on comparisons of OS and PFS. The assessment of stopping for efficacy will be based on OS alone. For the assessment of futility, if either comparison suggests futility, the recommendation will be to close the study to further accrual under the conclusion of futility. Futility evaluations will be based on using testing the target hazard ratio for PFS (HR = 0.66) at the 1-sided 0.0025 level and the target hazard ratio for OS (HR = 0.70) for OS, at the 1-sided 0.005 level using a modified log-rank test.

Efficacy testing will be based on testing the null hypothesis for OS at the 1-sided 0.0025 level using a stratified log-rank test.

Interim #4 (efficacy only):
The 4th and final interim analysis will evaluate early stopping for efficacy based on a comparison of OS and evidence to support accelerated approval submission based on a comparison of PFS at 72 months after study activation when it is estimated that 225 PFS and 176 OS events have been reported. Efficacy testing will be based on testing the null hypothesis for OS at the 1-sided 0.0025 level using a stratified log-rank test. As the study is expected to have completed accrual at this time point, and all patients should have completed protocol treatment, this analysis will not include an assessment of futility. The comparison of PFS will proceed as described above (2nd paragraph, Section 11.3)

Table 1 describes the interim and primary analysis plan for the study including the estimated number of PFS and OS events at the interim analyses, the estimated hazard ratio boundary associated with testing the null and target(alternative) HRs, as described above, and the probability of stopping the study under the null and alternative based on PFS and OS alone These probabilities do not take into account the joint assessment of futility that would recommend early stopping for futility if either the PFS or OS assessment met the criteria to suggest futility.

Table 1. Interim and Primary Analysis Summary

Analysis	Analysis Time (months)	Estimated Accrual (eligible)	Estimated Number of Events		PFS: Estimated HR boundary	Probability of stopping based on PFS		OS: Estimated HR boundary		Probability of stopping for on OS	
			PFS	OS	Futility	HR: 1.0	HR: 0.66	Futility	Efficacy	HR: 1.0	HR: 0.70
Interim #1	36	259	70	54	1.29	14%	0.25%	1.41	N/A	10%	0.5%
Interim #2	48	345	117	91	1.09	20%	0.25%	1.18	N/A	14%	0.5%
Interim #3	60		172	135	0.99	22%	0.25%	1.06	0.62	17%	24%
Interim #4*	72	432	225	176	0.77*	N/A	99%	N/A	0.66	0.14%	13%
OS Analysis	96		N/A	245	N/A	N/A		0.78		N/A	

*While this is an interim analysis for the study overall with OS as the primary endpoint. This is the primary analysis of PFS to potentially support accelerated approval. Estimated HR to reject null and conclude PFS significant.

The futility evaluation is using the modified Haybittle-Peto approach based on testing the alternative hypothesis on the fixed-sample p-value scale. Translating the p-value thresholds to the scale testing the null, for PFS this is equivalent to recommending stopping for futility if the observed p-value exceeds 0.8562, 0.68, 0.475 at the 1st, 2nd, or 3rd analyses, respectively. For OS, this is equivalent to recommending stopping for futility if the observed p-value testing the null exceeding 0.897, 0.78, 0.63 at the 1st, 2nd, or 3rd analyses, respectively. If the null for OS is rejected at either the 3rd or 4th interim analysis, then the conclusion will be that the study has met the criteria to conclude significance and the study results will be released, including the PFS data. If the study does not meet the criteria for early release of OS data, the study would continue follow-up until the OS data reached the full sample number of events of 245.

Distributions for time-to-event outcomes (PFS, OS) will be evaluated using the method of Kaplan-Meier. For point estimates at landmark times, the associated 95% confidence interval (CI) will be calculated using Greenwood's formula and based on a log-log transformation applied on the survival function. Hazard ratios for these outcomes will be estimated using a Cox Proportional Hazards regression model and estimated using a stratified Cox regression model.

Evaluation of the types of failures, e.g. distant, local-regional and in-field failures will be analyzed as competing risks data, where deaths without respective failure are considered as competing events. The cumulative incidences for each arm will be estimated by Aalen-Johansen estimator, and compared using log-rank tests based on cause-specific hazard.

With 216 patients per arm, binary proportions (including frequency of toxicities) can be estimated to within 7% with 95% confidence. Any toxicity with at least 5% prevalence is likely to be observed (with >99% probability)

11.4 Estimate of Accrual Rate

Based on data from previous studies, the estimated monthly average accrual rate for this study is 8 patients/ month. The accrual duration is estimated to be 60 months. With this joint SWOG NRG collaboration and participation of the entire NTCN network, we do not anticipate any difficulties in achieving this accrual rate.

11.5 Data and Safety Monitoring

The SWOG Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

Statistical considerations for quality of life endpoints are located in Section 18.5.

12.0 DISCIPLINE REVIEW

12.1 Radiation Therapy Review

a. Registration Procedures

1. Access requirements for OPEN and TRIAD

Site staff will need to be registered with CTEP and have a valid and active CTEP Identity and Access Management (IAM) account. This is the same account (user id and password) used for the CTSU members' web site. To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

Institutions that have been previously credentialed for 3DCRT or IMRT on prior NCTN protocols and that have successfully irradiated a phantom and been approved by IROC Houston need not perform additional credentialing for **S1914**. However, institutions may administer only that treatment for which they have been previously credentialed (i.e., an institution credentialed for 3DCRT only may not administer IMRT on this

study without completing the IMRT credentialing process). Credentialing requirements for IMRT and 3DCRT are specified in sections below.

2. Pre-Registration Requirements for Intensity Modulated Radiation Therapy (IMRT) Treatment Approach

   In order to utilize IMRT on this study, the institution must have met specific technology requirements and have provided baseline physics information. Instructions for completing these requirements or determining if they already have been met are available on the IROC Houston web site. See the credentialing table for requirements.

3. Pre-Registration Requirements for 3-D Conformal Radiation Therapy (3DCRT) Treatment Approach

   Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in Quality Assurance Guidelines may enter patients onto this study. See the credentialing table for requirements.

RT Credentialing Requirements	Web Link for Procedures and Instructions: http://irochouston.mdanderson.org		
	Treatment Modality		
	Photon		**Key Information**
Facility Questionnaire	X		The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X		To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website (http://irochouston.mdanderson.org)
Phantom Irradiation	X		A thorax phantom study provided by the IROC QA Center Houston must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Note that only the most sophisticated technique needs to be credentialed (e.g., if credentialed for IMRT, 3DCRT may be used).
Credentialing Notification Issued to:			
Institution	X		IROC Houston QA Center will notify the institution that all desired credentialing requirements have been met.

b. Digital RT Data Submission to IROC Philadelphia Using TRIAD

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

1. TRIAD Access Requirements:

   - A valid Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) (CTEP-IAM) account.
   - Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
   - TRIAD Site User role on an NCTN or ETCTN roster.

   All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD, and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

2. TRIAD Installations:

   To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

   This process can be done in parallel to obtaining your CTEP-IAM account username and password and RCR registration.

   For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

c. RT Quality Assurance Reviews

The Radiation Oncology Study Chairs and/or their designees will perform RT Quality Assurance Reviews.

1. Radiation therapy quality assurance case reviews will be ongoing and performed remotely. The Study Charis and/or their designees will perform the RT Quality Assurance Reviews after IROC-Philadelphia RT has received complete data in TRIAD. These reviews will be on-going and performed remotely. The final cases will be reviewed within 6 months after this study has reached the target accrual or as soon as IROC-Philadelphia RT has received complete data for all cases enrolled, whichever occurs first. The scoring mechanism is: Per Protocol, Variation Acceptable, and Deviation Unacceptable.

2. Within 7 calendar days after the initiation of treatment, the following data must be submitted to TRIAD:

Required Submission to TRIAD		**Post Treatment Review**
DICOM DIGITAL RTDATA	DICOM CT Data Set DICOM RT Structure DICOM RT Dose DICOM RT Plan	**Due within 1 week after RT Start**

Required Submission to TRIAD		Post Treatment Review
	Note: Digital Data for all treatment fields must be included in one TRIAD submission only.	TRIAD submission time point = RT DIGITAL PLAN

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Initiation of treatment must be planned to start no more than 21 calendar days after randomization.

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✔	✔			
Financial Disclosure Form	✔	✔	✔		
NCI Biosketch (education, training, employment, license,	✔	✔	✔		

and certification)					
GCP training	✔	✔	✔		
Agent Shipment Form (if applicable)	✔				
CV (optional)	✔	✔	✔		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

b. CTSU Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

a. **IRB Approval**

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site

preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an Active CTEP status;
- Active status at the site(s) on the IRB/REB approval *(applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all protocol-specific requirements (PSRs)

Protocol Specific Requirements (PSR) for S1914 Site Registration

a. Training

A member of each institution (CRA or investigator, etc.) must complete training prior to patient registration. The training can be completed online at https://www.swog.org/required-S1914-training.

To receive credit, submit a saved copy or printout of the training verification form via the CTSU Regulatory Submission Portal. The SWOG Operations Office and CTSU will be notified of completion. There is a turn-around time of three business days for processing this training requirement at CTSU after submission of the verification form before the first registration may occur. However, if a registration is pending, please notify the CTSU Regulatory staff at CTSURegOffice@ecogchair.org so they may be prompted to process the training completion as a priority.

b. PSR for Radiation and/or Imaging (RTI) Component

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must

be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on a treating site roster can update the provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU website.

c. PSR for RT Modality Credentialing (IROC-Houston)

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

d. PSR for Radiation or Imaging (RT/I) Provider Credentialed (IROC Integration suite)

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory Support System (RSS) to comply the protocol specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification. IROC will continue to copy the provider and/or enrolling site on modality approvals.

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

For questions, contact IROC-Credentialing@mdanderson.org.

Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

The individual initiating the DTL for the site should upload the above listed training documentation when making the task assignment. The designated

reviewer will accept or reject the documentation. A note regarding rejection of any training documents will display on the Site DTL Browser next to the task assignment. The DTL cannot be submitted for CI sign-off until the minimum number of persons are assigned to the task and have met the training requirements.

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select **SWOG**, and protocol number **S1914**
- Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org at 1-866-651-2878 in order to receive further instruction and support.

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of your screen;
- Click on *Site Registration*; and
- Enter the sites 5-character CTEP Institution Code and click on Go:
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

13.3 Oncology Patient Enrollment Network (OPEN) Registration Requirements

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or

Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

OPEN will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for ALL patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

14.2 Master Forms

Master forms can be found on the protocol page on the CTSU website (www.ctsu.org).

14.3 Data Submission / Data Reporting Procedures

a. Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:
- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:
- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website (www.swog.org).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

d. Central Monitoring Review Using the CTSU Source Document Portal

Central Monitoring (CM) is required for this protocol for 2 patients randomized at each site. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients' charts (i.e., source data verification).

Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP). This application is available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with the CRA or Investigator roles in Rave can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional technical information on the SDP is available on the CTSU members' website under Auditing & Monitoring > Source Document Portal in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

e. Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Report modules.

14.4 Data Submission Overview and Timepoints

Please reference the ***ORP Manual*** on the CRA Workbench (www.swog.org) for detailed General Forms and Guidelines, as well as some disease-specific and study-specific forms. There are also many other chapters available in the manual to be used for regular reference of SWOG processes and procedures. Non-SWOG sites can access the

Workbench with their CTEP-IAM credentials here: https://crawb.crab.org/TXWB/ctsulogon.aspx

a. WITHIN 15 DAYS AFTER RANDOMIZATION, submit:

S1914 Eligibility Criteria Form, including upload of the paper Eligibility Checklist form signed by the Registering Investigator

S1914 Onstudy Forms

Baseline Abnormalities Form

Pathology Report (NOTE: Upload report via the Source Documentation: Baseline form in Rave®).

Radiology reports from all scans performed to assess disease at baseline, including diagnostic chest CT and FDG-PET/CT of chest (NOTE: Upload reports via the Source Documentation: Baseline form in Rave®).

Materials to IROC Ohio via TRIAD for Central Radiology Review as specified in Section 15.3.

Quality of Life Forms (via the NRG QOL Substudy **S1914-E01** in Rave®)

b. AT TIME POINTS SPECIFIED IN SECTION 15.2, submit:

Specimens as described in Section 15.2

c. WITHIN 15 DAYS FOLLOWING COMPLETION OF PAPER QOL FORMS (FOR PATIENTS WHO CHOOSE NOT TO COMPLETE ELECTRONICALLY) AT THE TIME POINTS LISTED IN SECTION 15.4, submit:

Quality of Life Forms (via the NRG QOL Substudy **S1914-E01** in Rave®)

d. FOR PATIENTS ON ARM A, WITHIN 15 DAYS AFTER EACH CYCLE OF TREATMENT, submit:

Vital Status Form

For Cycle 1 only: submit the **S1914** Pre-Treatment Laboratory Values Form

S1914 Atezolizumab Treatment Form

S1914 Laboratory Values Form

Adverse Events Form (NOTE: For last cycle of treatment, include all adverse events occurring within 30 days after the last treatment)

Concomitant Medications Form

e. WITHIN 15 DAYS AFTER EACH FOLLOW-UP DISEASE ASSESSMENT UNTIL PROGRESSION, submit:

Vital Status Form

S1914 Disease Assessment Form

Radiology reports from all scans performed to assess disease (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®).

Materials to IROC Ohio via TRIAD for Central Radiology review as described in Section 15.3

f. WITHIN 7 DAYS AFTER BEGINNING RADIATION THERAPY, submit:

Materials to IROC Philadelphia via TRIAD as described in Section 12.1.

g. WITHIN 15 DAYS AFTER COMPLETING RADIATION THERAPY, submit:

Vital Status Form

S1914 Radiation Therapy Summary Form

Upload the record of each daily treatment administered to the Source Documentation: RT form within Rave.

For patients on Arm B, in the Radiation Therapy (Arm B) folder:

Adverse Events Form

Concomitant Medications Form

h. WITHIN 15 DAYS AFTER DISCONTINUATION OF TREATMENT, submit:

Vital Status Form

Off Treatment Notice

For patients on Arm A, forms in last cycle folder:

S1914 Atezolizumab Treatment Form

S1914 Laboratory Values Form

Adverse Events Form

Concomitant Medications Form

i. AT SIX MONTHS POST RADIATION THERAPY, submit:

S1914 Post-SBRT Pulmonary Function Tests

j. WITHIN 15 DAYS AFTER PROGRESSION/RELAPSE, submit:

S1914 Disease Assessment Form

Lung Site(s) of Progression or Relapse Form

Radiology reports from all scans performed to assess disease (NOTE: Upload reports via the Source Documentation: Follow-up form in Rave®).

Materials to IROC Ohio via TRIAD for Central Radiology review as described in Section 15.3

Vital Status Form and the forms listed in Section 14.4g (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment).

k. WITHIN 30 DAYS AFTER EVERY FOLLOW-UP, submit:

Vital Status Form

Lung Follow Up Form

Late Adverse Events Form (if the patient experiences any severe [Grade ≥ 3] adverse event that is possibly, probably, or definitely related to protocol treatment, or a Serious Adverse Event [SAE] of any grade/attribution, that has not been previously reported).

Initial Post-Protocol Treatment Form (if the patient received their first regimen of post-protocol therapy).

Non-Protocol Radiation Therapy Form (if the patient received radiation to sites other than the brain since last follow-up).

Brain Metastases Form (if the patient developed new brain metastases since last follow-up).

l. WITHIN 30 DAYS OF DECLARATION OF LOST TO FOLLOW-UP, REFUSAL OF ANY FOLLOW-UP, OR A MAXIMUM FOLLOW-UP OF 5 YEARS, submit:

Vital Status Form

End of Study Form

m. WITHIN 30 DAYS AFTER KNOWLEDGE OF DEATH, submit:

Notice of Death and the forms listed in Section 14.4g (if the patient was still on protocol treatment) or the forms listed in Section 14.4j (if the patient was off protocol treatment) documenting death information.

End of Study Form

15.0 SPECIAL INSTRUCTIONS

15.1 Study-specific training

Prior to registering a site's first patient, a CRA or investigator must complete the study-specific training located at https://www.swog.org/required-S1914-training.

To receive credit, submit a saved copy or printout of the training verification form via the CTSU Regulatory Submission Portal. The SWOG Operations Office and CTSU will be notified of completion. There is a turn-around time of three business days for processing this training requirement at CTSU after submission of the verification form before the first registration may occur. However, if a registration is pending, please notify the CTSU Regulatory staff at CTSURegOffice@ecogchair.org so they may be prompted to process the training completion as a priority.

15.2 Specimen Submission

a. Tissue (REQUIRED IF AVAILABLE)

If available, the following specimens are required to be submitted for all patients. Kits are not provided for tissue submission; sites must use their own supplies.

Within 28 days after randomization, submit either:

- 1-2 formalin fixed paraffin embedded (FFPE) tissue blocks

  OR

- 1 H&E slide and 10 unstained slides containing freshly cut, serial sections

Follow the packaging and shipping instructions located at https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures. If collection/submission instructions differ from those in the protocol, the protocol instructions should be followed; otherwise, the website instructions should be followed.

Specimens will be banked until a protocol revision is approved and funding is obtained for translational medicine studies such as those described in Appendix 18.1.

b. Whole blood (REQUIRED)

Streck BCT cf-DNA tubes will be provided. Specimen collection kits may be ordered by using the SWOG Specimen Repository Management Application at https://kits.bpc-apps.nchri.org.

NOTE: Roche BCT cf-DNA tubes were previously provided for this study. Sites may use unexpired Roche BCT cf-DNA tubes if they have any leftover.

Sites will use institutional supplies for all other collections.

Collect the following:

- Prior to beginning protocol treatment (after randomization)
  - Three 10-mL purple-top EDTA tubes
  - Two Streck BCT cf-DNA tubes
- One week after completion of SBRT (+/- 2 days but preferably +/- 1 day if possible)
  - Three 10-mL purple-top EDTA tubes
  - Two Streck BCT cf-DNA tubes
  - NOTE: Patients that go off protocol treatment are not required to continue to submit whole blood at this time point.
- Week 18 (+/- 1 week)*
  - Three 10-mL purple-top EDTA tubes
  - Two Streck BCT cf-DNA tubes
  - NOTE: Patients that go off protocol treatment are not required to continue to submit whole blood at this time point.
- Progression
  - Two Streck BCT cf-DNA tubes (Note: do not collect EDTA tubes at this time point)

Ship overnight on same day as collection.

Follow the packaging and shipping instructions located at https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures. If collection/submission instructions

differ from those in the protocol, the protocol instructions should be followed; otherwise, the website instructions should be followed.

Specimens will be banked until a protocol revision is approved and funding is obtained for translational medicine studies such as those described in Appendix 18.1.

c. Specimen tracking and additional instructions

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. For instructions on using the Specimen Tracking system, visit the SWOG Specimen Submission webpage located here:

https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures)

Ship specimens to Lab #201 (SWOG Biospecimen Bank, Solid Tissue, Myeloma & Lymphoma Division).

15.3 Submission of images to IROC Ohio for central review **(REQUIRED)**

CT images must be locally read and interpreted by the local site radiology service. **All imaging exams** must then be submitted within 15 days to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD. A subset of the scans will be reviewed for PFS (see Section 1.2b).

a. The following are recommended guidelines for CT scan quality:

1. Neutral contrast
    a. Water or Volumen
    b. NO POSITIVE ORAL CONTRAST
2. 16- 64-detector MDCT
3. INTRAVENOUS CONTRAST (if used):
    a. 150 ml (or weight based), 60ml saline
    b. Bolus Tracking technique
    c. Rate of contrast: at least 3-4 ml/sec
4. 0.6 mm collimation (thinnest collimation)
5. Diagnostic Images:
    a. 3 mm slice thickness, 3 mm recon interval
    b. 2 recon: 1 mm x 0.8 mm recon (smallest slice with overlap)
    c. Reconstructions: 3 mm x 3 mm coronal MPRs for all phases.

b. TRIAD Digital Image Submission

See Section 12.1b for instructions regarding TRIAD.

Questions regarding image submissions should be directed to SWOG1914@irocohio.org or call IROC Ohio at 614/293-2929.

15.4 Quality of Life **(REQUIRED)**

Patients who can complete quality of life instruments in English, French, or Spanish must do so as described in this section. NOTE: Patients enrolled to **S1914** prior to revision #2 are not eligible for the QOL study.

a. Quality of life Instruments to be administered:
- General HR QOL – EORTC QLQ-C30
- Lung cancer related QOL – EORTC QLQ-LC13

b. Patients will be assessed according to the following schedule.

For patients on Arm A:
- after registration within 2 weeks prior to starting atezolizumab (must be completed on paper)
- within 1 week prior to starting SBRT
- at week 30 from atezolizumab start date (±4 weeks)
- at week 54 from atezolizumab start date (±4 weeks)
- at week 80 from atezolizumab start date (± 8 weeks)

For patients on Arm B:
- after registration within 2 weeks prior to starting SBRT (must be completed on paper)
- Day 43 from SBRT start date (± 1 week)
- at week 30 from SBRT start date (±4 weeks)
- at week 54 from SBRT start date (±4 weeks)
- at week 80 from SBRT start date (± 8 weeks)

The questionnaires combined are made up of 43 questions and will take approximately 10 minutes to complete at each time point.

c. Optional Online Completion of Patient-Reported QOL Assessments

Missing data are a significant problem, particularly for QOL assessments. Unlike data for traditional endpoints, such as survival, QOL data can never be obtained retrospectively if it is not provided by the patient at the appropriate time point. This limits researchers' ability to accurately perform QOL statistical analyses and negatively impacts the clinical relevance of this effort. Typically, QOL forms are filled out in hardcopy (paper). To provide a more convenient method of completing QOL assessments, NRG Oncology is working with VisionTree Software, Inc., San Diego, CA. VisionTree offers patients on this study the option of completing their QOL forms online from any location that has a computer with Internet access, including the patient's home, and provides reminders to patients to complete the assessments.

VisionTree has developed a tool, VisionTree Optimal Care (VTOC), a HIPAA-secure, user friendly, web-based software system. *(70,71,72)* The VTOC tool contains a web-based system for global patient and trial administration access, which allows improved compliance and accuracy of data collection, validation, and reporting. It is compliant with the Title 21, Code of Federal Regulations, Part 11 statistical process control system and provides a mobile solution for clinical trials. QOL data are collected with Microsoft Excel and PDF export of reports. VTOC also has mobile messaging and e-mail reminders. Surveys can be "pushed" to patients for completion at timed intervals (see http://www.visiontree.com for details). This

technology allows consenting patients on this study to fill out their QOL forms online from any location and to receive e-mail reminders to complete assessments. E-mail reminders also can be sent to research associates (RAs) at the appropriate institutions to remind them that a QOL time point window is about to close so that a patient can be contacted to fill out QOL information on time, before it becomes "missing data".

In a pilot RTOG study (RTOG 0828), the compliance rate of patients completing QOL assessments at 6 months significantly improved using electronic technology. Based on this pilot data, NRG Oncology is offering VisionTree as an option in other studies, including this one. Patients preferring to complete hardcopy QOL assessments can do so. The QOL forms completed via VTOC are identical to the hardcopy forms; this technology does not add to or change the QOL assessments in this study.

For this trial, the baseline QOL forms must be completed in hardcopy prior to the start of treatment. To complete subsequent QOL forms online, patients will be asked for an e-mail address that they consent to use so that e-mail reminders may be sent to them. The patient's e-mail address also will be used for password-protected access to VTOC. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g. Yahoo!, Hotmail, or AOL). Note: The site RA is responsible for setting up the patient's account on VTOC. The RA may do so by logging on the VTOC portal at the following link: https://rtog.optimalcare.com - medical team. RA login information will be provided by VTOC after the patient is randomized to the study. The patient's VTOC account must be set up within 14 days after randomization.

Patients will receive a login card (either printed or sent via e-mail) with which to log in using the secure, web-based VTOC portal. VTOC meets all HIPAA guidelines and is encrypted (via 128-bit SSL) for the security, privacy, and confidentiality of QOL information. It is similar to the secure login commonly used when performing online banking. The login card can then be kept and maintained by the patient.

The patient's e-mail address only will be used by NRG Oncology for this purpose. Patients will be sent e-mail reminders to complete QOL forms. A typical e-mail reminder would read: "Your Quality of Life forms for the study, S1914, are now due. Please go to http://www.optimalcare.com, use your secure login, and complete the online forms. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. If you have any questions, please e-mail or call your research associate at [insert RA e-mail address] or [insert RA telephone number]. Thank you for participating in this study." The reminders will be created by NRG Oncology and placed into a study template that will be sent to patients at customized intervals (at the time points when QOL forms are due). Reminders will be sent for each of the QOL time points (following the baseline QOL forms, which are completed in hardcopy) until the form(s) is completed or the time window on that time point ends. After a patient has completed all forms in the VTOC portal, a dialogue box will appear that says, "Thank you for completing your Quality of Life forms," and the patient will no longer receive any remaining notices for that time point. The site RA or study administrator will be informed through the VTOC "At-A-Glance" form management system when QOL forms have been completed.

d. If the patient chooses to complete the questionnaires on paper instead of via VTOC, the site must enter the data in the QOL forms via the NRG QOL Substudy **S1914-E01** in Rave®.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Federal Register Vol. 82, No. 12, January 19, 2017) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agent in this study:

a. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

b. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    1. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

    2. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to

allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

3. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

c. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

d. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

e. Any data provided to the Collaborator(s) for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

f. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Light reporting consists of Patient Demographics, On/Off Treatment Status, Abbreviated Treatment and Course information, and Adverse Events as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (https://ctep.cancer.gov/protocolDevelopment/dmu.htm).

Note: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

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18.0 APPENDIX

18.1 Translational Medicine

Specimens described in Section 15 will be banked until a protocol revision is approved and funding is obtained for translational medicine analyses such as the following.

a. Tumor-Associated Immune Cell Characterization

Objective: To evaluate the association between gene expression profiles characteristic of selected immune cell populations in the tumor microenvironment (TME) and clinical outcome as measured by progression free survival (PFS), overall survival (OS), and local and distant failure rates (LRF and DF).

Hypothesis: Higher gene expression levels of selected immune cell subsets indicating a T-cell inflamed TME are associated with better clinical outcomes in both treatment arms.

b. PD-L1

Objective: To evaluate the association between PD-L1 expression levels in the TME and clinical outcome as measured by PFS,OS, and LRF/DF rates.

Hypothesis: Higher levels of PD-L1 expression are associated with improved clinical outcomes in patients treated with SBRT + Atezolizumab but not patients treated with SBRT.

c. Circulating ICOS+ CD4+ T cells

Objective: To evaluate changes in circulating levels of ICOS+CD4+ T cells pre- versus post-treatment and to evaluate the association of these changes with clinical outcome as measured by PFS, OS and DF rates.

Hypothesis: The circulating levels of ICOS+CD4+ T cells will increase after therapy but to a greater extent in the SBRT + Atezolizumab arm. Higher levels of ICOS+CD4+ T cells post treatment are associated with improved clinical outcomes in both treatment arms.

d. Tumor Mutation Burden in circulating tumor DNA (ctDNA)

Objective: To correlate the tumor mutational burden (TMB) in ctDNA with patient treatment outcome as measured by PFS and distant failure rates.

Hypothesis: Patients with high TMB will have improved outcomes compared to those with lower mutational burden.

e. Serial ctDNA Analysis

Objective: To serially monitor ctDNA overall allele frequencies as a surrogate for disseminated disease burden to assess treatment activity and early progression.

Hypothesis: ctDNA will be an early indicator of tumor response and progression such that decreases in ctDNA from baseline will indicate disease response and increases in ctDNA will indicate disease progression.

f. PBMC Immune Phenotyping

Objective: To evaluate changes in circulating levels of immune cell subsets and their expression of activation / inhibitory markers pre- versus post-treatment and to evaluate the association of these changes with clinical outcome as measured by PFS and local and distant failure rates.

Hypothesis: The circulating levels of activated CD4+ T cells and CD8+ T cells will increase after therapy but to a greater extent in the SBRT + Atezolizumab arm. Increased activated circulating T cells post-therapy will correlate with improved clinical outcomes.

g. T cell Receptor Repertoire

Objective: To evaluate changes in the clonal diversity and expansion of circulating T cells pre- versus post-treatment and to evaluate the association of these changes with clinical outcome as measured by PFS and local and distant failure rates.

Hypothesis: T cell clonal diversity and proliferation will increase after therapy but to a greater extent in the SBRT + Atezolizumab arm. Increased T cell clonal diversity and proliferation post-therapy will correlate with improved clinical outcomes

h. Plasma PD-L1 circulating tumor RNA (ctRNA) expression levels

Objective: To quantify circulating tumor PD-L1 ctRNA at baseline and assess changes in pre- vs. post treatment collected plasma specimens as an indirect, non-invasive measure of tumor PD-L1 expression relative to disease burden.

Hypothesis: Circulating tumor RNA PD-L1 levels will correlate with tumor PD-L1 expression levels. A decrease in PD-L1 ctRNA post-therapy will be associated with improved clinical outcomes.

i. Instructions for SWOG Biospecimen Bank

Samples will not be distributed to researchers until funding is obtained for translational medicine studies.

18.2 New York Heart Association Criteria

Class	Cardiac Symptoms	Need for Limitations	Physical Ability Additional Rest*	To Work**
I	None	None	None	Full Time
II	Only moderate	Slight or occasional	Usually only slight	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.
** At accustomed occupation or usual tasks.

18.3 Quality Assurance Auditing and Monitoring

The Quality Assurance Program of the Groups participating in the NCTN was developed to enhance the reliability and validity of clinical trials data through the use of routine monitoring procedures which includes auditing as one component. The purpose of an audit is to document the accuracy of data submitted to the Data Operations Center and to verify compliance with protocol and regulatory requirements. The program also surveys data management practices at each institution in order to provide educational support to the sites regarding issues related to data quality, data management, and other aspects of quality assurance.

Audits are conducted according to FDA regulations and NCI guidelines for Auditing Clinical Trials for the National Clinical Trials Network (NCTN) Program, NCI Community Oncology Research Program (NCORP) and Research Bases: http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ctmbauditguidelines.pdf.

Each institution is audited at least once every three years, but remains at annual risk of an audit. Routine monitoring of Institutional Performance Review reports and timeliness of reporting of Serious Adverse Events is conducted to identify institutions that may require more frequent audits.

The audit team consists of qualified individuals capable of providing a medical assessment of the patient cases (Quality Assurance staff, physician, nurse or experienced clinical research associate [CRA]). A number of patients equal to 10% of the accrual since the last audit with a minimum of three are randomly selected for review at each institution. In addition, a limited review of eligibility and consent only is conducted for at least one unannounced case at each on site audit.

The major objective of the audit process is to verify study data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data against the source documents. Primary source documentation reviewed during an audit includes the following: research records, hospital charts, clinic charts, lab reports, x-rays, scans, radiotherapy reports, operative reports, pathology reports and other special studies required by protocol.

By comparing the data collection forms submitted to the Statistics and Data Management Center with the primary records and referring to the protocol, the audit team reviews the records to determine compliance with protocol requirements for eligibility, treatment administration, response assessment, toxicity reporting, and general data quality. Auditors verify that the current IRB-approved version of the consent form was signed prior to registration and that subjects were informed of new findings that could affect their willingness to participate in the study. NCTN investigators and institutions are expected to follow the protocol and lead Group policies in treating patients registered on Group protocols. Among other requirements, investigators/institutions must follow SWOG's policies for dosing principles, reporting of Serious Adverse Events, and follow-up of all patients.

The audit team also verifies that the protocol and its amendments received initial and continuing IRB review and approval and that safety reports and serious adverse events were submitted to the IRB. Investigational drug accountability record forms (DARFs) are reviewed and random patients are cross referenced against the medical record. A tour of the pharmacy is conducted to verify security and storage conditions as well as the physical inventory.

The audit report is comprised of three components: 1) conformance to IRB and informed consent requirements, 2) the pharmacy and use of NCI DARFs, and 3) patient case review. An acceptable rating requires no deficiencies, few lesser deficiencies, or major deficiencies that were addressed prior to the audit. Institutions found to be "unacceptable" or

"acceptable, but requires follow-up" on any component are required to submit a written response and/or corrective and preventive (CAPA) action plan. Failure to submit a written response including a corrective and preventive action plan within the required timeframe will result in suspension of registration privileges. A re-audit of any component rated as unacceptable will be conducted within one year after the unacceptable audit. An unacceptable rating for the same audit component on two consecutive audits will result in probation. Accrual will be suspended pending submission of a site improvement plan that addresses key infrastructural issues contributing to poor performance. An unacceptable rating at the second re-audit may result in termination from the Group. If systematic misrepresentation of data is identified, an immediate repeat audit is scheduled by the representatives from the Group with the NCI and/or the FDA present.

In some cases, non-compliance for issues such as timeliness of data submission, SAE reporting and submission of specimens is monitored off site rather than scheduling a re-audit. Failure to show improvement may result in scheduling of a re-audit or other disciplinary action.

Results of all Quality Assurance Audits are entered into the CTMB-AIS database and reported to the NCI, the Principal Investigator of the institution that was audited, and Group leadership. Protocol specific audit results are also sent to the Statistics and Data Management Center to inform the statisticians, data chairs and study chairs of any significant discrepancies involving eligibility, treatment, toxicity or response assessment.

The Quality Assurance Program performs its educational role through several mechanisms including presentations during the Group Meetings, online Clinical Trials Training Courses, collaboration with others such as the Pharmacy Committee and Statistics and Data Management Center to develop training tools, and memos and newsletter articles that are distributed to all Group institutions to educate research staff about changes in regulatory and quality assurance issues and audit procedures.

Additional Monitoring

In addition to the standard auditing process outlined above, the following additional requirements will be implemented for this study:

- Routine monitoring by Data Coordinators at the Statistics and Data Management Center.
- Risk-based monitoring by Monitors at the Statistics and Data Management Center.
- Additional on-site audits by Quality Assurance Auditors at the Operations Office.

Routine Monitoring at the SWOG Statistics and Data Management Center

Data Coordinators at the SWOG Statistics and Data Management Center (SDMC) will perform routine monitoring with the following actions:

Monitor data quality through routine review of submitted data such as on-study, baseline and follow up tumor assessment, lab, treatment, off treatment, and follow up case report forms to identify and follow-up on missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors in data collection and reporting at a site.

- Analyze site characteristics, performance metrics and clinical data to identify trial sites with characteristics correlated with poor performance or noncompliance through the SWOG Institutional Performance Reporting mechanism and other available reports.

- Verify critical source data remotely via the collection and review of pathology, radiology and applicable lab reports. This includes the review and confirmation of appropriate disease classification as determined by the pathology report, and assessment of response to treatment based on scan reports uploaded to the Electronic Data Capture (EDC) system and submitted disease assessment forms.

- To assure data are as consistent, complete and accurate as possible, all subject data must undergo careful review by Data Coordinators (DCs). After verifying that all data forms required to determine eligibility have been received or at a time point designated when all the required forms should have been received, the DC reviews the data and completes an initial evaluation.

The initial review includes the following:

- Determine that all required data fields on each form were completed and are consistent with other data.
- Determine if all prestudy tests and exams were performed within protocol specified time limits.
- Determine if each eligibility criterion was met and properly documented.
- Review and confirm pathology based on the pathology report uploaded to the EDC system.
- Verify that stratification and/or descriptive factors (if applicable) were correctly identified at registration.
- Verify that the subject received the assigned study treatment and correct dose(s).
- Verify that the treatment was started within the time limit indicated in the protocol (if applicable).
- Determine if adverse events reported are consistent with other data and entered as required by study specifications.
- Post internal notes to add additional information which may be useful to the study sponsor, monitors, or statisticians, but which do not require action by site personnel.
- Use the query tool to request additional data classifications and corrections of the CRA.

The DC will perform subsequent review of data when new data become available or queries are answered. Regular review will also occur while patients are still on-study, at the time of progression, once they are removed from study and at the time of death.

Subsequent reviews include the following:

- Determine if all required data fields on each newly submitted form were completed and consistent with other data.
- Evaluate all new treatment documentation for correct treatment and dose.
- Conduct assessment of response to treatment based on scan reports uploaded to the EDC and submitted disease assessment forms.
- Review and code any new concomitant medications as required by study specifications.
- Evaluate if the subject is or should be off protocol treatment per protocol criteria.
- Review and evaluate death if death of subject is reported.
- Use the query tool to request additional data classifications and corrections.
- Post internal query notes to add additional information that may be useful to the study sponsor, monitor, or statisticians but which do not require action by site personnel.
- Review site responses to the queries and the corrected or amended eCRF pages. When corrections and responses are considered satisfactory, queries are closed by the data coordinators. Unsatisfactory responses are re-queried and tracked.
- Perform re-evaluations promptly after responses to queries are received.

Centralized Risk-based Monitoring at the Statistics and Data Management Center (SDMC)

Monitors at the Statistics and Data Management Center (SDMC) will support the risk-based monitoring approach for this trial with the following actions:

Off-site monitoring to include auditable elements for eligibility, through administration of treatment and the week 18 disease assessment for the first 2 patients randomized at each site where an on-site audit has not yet occurred. The review is to include eligibility, the administration of treatment through cycle 2 (Arm A only), and disease assessment at week 18. Within one month of randomization, the Head CRA (or Data Manager) at the study site will be contacted by a SDMC monitor via email with instructions for uploading the auditable elements. This will allow ample time to gather and upload source documents. All source documents will be uploaded to the Source Document Portal (SDP), which can be accessed directly through CTSU.org by going to the Auditing and Monitoring tab and selecting Source Document Portal.* The SDP can also be accessed through Medidata Rave.

Documents required for uploading to the SDP:

Informed Consent Pages:
- Title Page
- Response to Future Contact Question
- Responses to Samples for Future Research Studies questions
- Signature Page

Eligibility:
- **S1914** Registration Worksheet

Source Documents to support:
- H&P to include weight and performance status, concomitant medication, treatment records
- Onstudy: Patient and Disease Description
- Onstudy: Laboratory Values
- Onstudy: Prior Treatment
- Baseline Abnormality Form

Treatment (Arm A) - Upload source documents to support the following forms:
- **S1914** Atezolizumab Treatment Form (For patients on atezolizumab + SBRT
- Adverse Events Form
- **S1914** Pre-Treatment Laboratory Values form
- **S1914** Laboratory Value Form
- **S1914** Concomitant Medication Form

Disease Assessment - Upload source documents to support the following forms:
- **S1914** Disease Assessment Form
  (Arm A= Pre-Registration, Cycle 2 & Week 18)
  (Arm B= Pre-Registration & Week 18)
- Vital Status Form

Please note:
- The **S1914** Registration Worksheet and **S1914** Eligibility Criteria form must be signed and dated by the Registering Investigator
- Treatment records must include physician orders and administration records/logs including reasons for dose modifications

* The Source Document Portal (SDP) in CTSU provides a tool to redact PHI. Please ensure all source documents are properly and completely redacted and free of PHI.

CTSU recommends that users complete the training “CTSU Central Monitoring Using the Source Document Portal (SDP)” which is posted on the CTSU website under Resources -> Educational Multimedia -> Webinars.

Onsite Audits

In addition to the standard auditing process outlined above, the following additional requirements will be implemented for this study:

- The first on-site audit will be conducted within 6 months of the first patient registration at each site.
- Audits will be combined with other routine audits whenever possible. The initial monitoring visit may be postponed up to 3 months to coincide with a routine audit or to coincide with a routine audit of another institution in the same geographic area. Audits may also be postponed if no accrual or activity has occurred beyond the timeframe covered by the off-site central monitoring.
- Subsequent monitoring visits will be conducted according the following criteria:
  - If > 5 patients per year (~ 10% of sites) – annually
  - < 5 patients per year – a minimum of every 3 years
- More frequent audits to a site may be scheduled in response to several factors – high rate of accrual, unacceptable audit results, centralized monitoring outcome, turnover in staff, etc.
- All sites that receive and dispense investigational agents must be audited on site to allow at least one visit to the pharmacy while patients remain on treatment with the following exceptions:
  - Sites that use a centralized pharmacy may be monitored at this central location.
  - After an initial onsite visit, NCORP sites and LAPS/Main Member Affiliates may be monitored at a central location.
  - Pharmacies monitored during SWOG site visits for other studies will suffice for the onsite auditing requirement.
  - The need for subsequent onsite visits will be determined on a case by case basis including past audit results, number of patients on the investigational agent, etc.

Communication of Monitoring Results

The monitoring team will meet routinely to share all aspects of monitoring (on site, centralized, safety, for-cause). When needed, the SWOG Executive Officer for Quality Assurance will be consulted.

All audit results will be reported according to NCI-CTMB requirements via the CTMB-AIS data base and regularly reviewed by SWOG monitoring staff.

Summarized results of all audits will be provided semi-annually to the SWOG Board of Governors and the study team. Any problems or issues of concern will be reported to the Data and Safety Monitoring Committee on an as-needed basis.

Safety Specific Centralized Monitoring at the Operations Office

Each Serious Adverse Event (SAE) report submitted (via CTEP-AERS) will be reviewed by the SWOG SAE Manager. Supporting documentation for any deaths on study will be requested and compiled with the report and sent to the Physician Reviewer. As mentioned below all sites will undergo mandatory training and this will include training regarding SAE reporting. SWOG regularly monitors timeliness of SAE reporting and addresses any issues of poor performance with individual sites.

The study will be monitored for under reporting/missed Serious Adverse Events: The SWOG SAE Manager receives a weekly report from the data base that includes all adverse events that are submitted through routine submission that potentially also meet expedited reporting criteria but for which no CTEP-AERS report is found. The Coordinator

is responsible for following up with the responsible site to ensure that SAEs are not missed/under-reported.

The study will be monitored for trends in Serious Adverse Events: A "new SAE on study" report is generated each time a new Serious Adverse Event is entered into the SWOG data base. It is a cumulative report that lists all SAEs reported for the protocol. This allows those who review the report to identify concerning trends in reported events; events that may be occurring at greater intensity (higher toxicity grade) or frequency than expected. The SAE Manager, Physician Reviewer, Study Chair, and assigned Statisticians are responsible for regularly monitoring this report.

Additional Approaches to be Used

- Mandatory training of key site personnel prior to first patient registration.
- Timely review of all monitoring reports to identify sites that require additional training, monitoring, disciplinary action, etc.
- Mentoring visits and additional communication between monitor and site staff to assess potential problem areas, provide feedback on data submission quality and timeliness, identify staff turnover, etc.
- Additional mandatory centralized training to be provided to all sites if major changes to the protocol occur or common problem areas are identified.

Management of Noncompliance

Issues of particular concern related to patient safety and questions of site fraud will be managed according to SWOG standard policies and the policies of the NCI CTMB for auditing of clinical trials under the NCI National Clinical Trials Network (NCTN) Program.

Where important deviations are discovered, additional site training components will be developed and implemented.

As with standard NCTN procedures, sites will be required to develop and implement corrective action plans in response to any deficiencies identified at a monitoring visit.

Ensuring Quality Monitoring

All staff involved in monitoring are required to undergo training in the principles of clinical investigations and human subjects protection. They are also required to complete the same protocol specific training required of the site staff.

All monitoring and auditing processes for the study will be reviewed by study leadership annually to ensure conformance to the monitoring plan.

Monitoring Plan Amendments

At each formal review of the monitoring plan and conformance to it, the study leadership will make a recommendation regarding the need for amendments to the monitoring plan. These amendments will be reviewed and approved by the NCI and provided in this protocol section and will be submitted to the FDA.

18.4 Additional Criteria for Evaluation and Endpoint Analysis

a. **Categories of failure related to SBRT**

1. Primary Tumor Failure (PTF)

One of the following must occur:

- 20% increase in the longest diameter of primary tumor after SBRT over smallest measurement observed using the same techniques as pre-SBRT disease assessment AND FDG-PET scan is performed of the primary tumor and SUV_{max} is avid with uptake of similar intensity as the pre-SBRT PET or biopsy confirming tumor.
- Other suspicious CT findings after SBRT leading to PET or biopsy of primary tumor confirming tumor
- Unequivocal progression of the primary tumor in the opinion of the treating physician unable to be confirmed with PET or biopsy.

2. Marginal Failure

New measurable lesion after SBRT appearing within 1.0 cm of the treated PTV (see Section 7.4) AND, one of the following must occur:

- FDG-PET scan is performed of this new lesion and SUV_{max} is avid with uptake of similar intensity as the pre-SBRT PET OR a biopsy of the new lesions confirms viable carcinoma.
- Unequivocal progression of the new measurable lesion after SBRT appearing within 1.0 cm of the treated PTV in the opinion of the treatment physician unable to be confirmed with PET or biopsy.

3. In-field Failure

Primary Tumor Failure (see Section 18.4a.1) or Marginal Failure (see Section 18.4a2)

b. **For lesions not targeted by SBRT**

1. Involved Lobe Failure (ILF)

New measurable lesion(s) within the anatomical boundaries of the lobe in which the primary tumor arose (involved lobe) which meets either of the following definitions for unconfirmed or confirmed ILF.

- If an FDG-PET scan is performed of the new lesion and SUV_{max} is avid with uptake highly suspicious for cancer (e.g., SUV>3-5) or viable tumor is detected on biopsy of this lesion, then the new lesion will be considered a confirmed ILF.
- If the new lesion is determined to be an unequivocal new lesion by the treating physician but is not able to be confirmed by PET or biopsy (e.g., due to medical reasons or rapidly progressing disease), then the lesion will be considered an unconfirmed ILF.

2. Regional Failure (RF)

New measurable lesion within lymph nodes along the natural lymphatic drainage typical for the location of the GTV, with SHORT AXIS measurement of at least 1.5 cm on imaging studies (preferably CT scans) or suspicious morphology (confirmed pathologically) within the lung,

bronchial hilum or the mediastinum. Equivocally appearing enlarged lymph nodes should be positive on PET imaging or biopsied to confirm involvement with carcinoma. If the new lesion is determined to be an unequivocal new lesion by the treating physician but is not able to be confirmed by PET or biopsy (e.g., due to medical reasons or rapidly progressing disease), then the lesion will be considered an unconfirmed RF.

3. Distant Failure (DF)

Development of metastatic disease outside the involved hemithorax or regional nodal regions (hilar, mediastinal, and supraclavicular) after SBRT.

c. **Failure of either SBRT targeted or non-targeted lesions**

1. Local Failure (LF)

Primary tumor failure or involved lobe failure or both.

2. Locoregional failure (LRF)

Primary tumor failure, marginal failure, involved lobe failure, or regional failure

18.5 Statistical Considerations for Quality of Life Endpoints

a. Objectives

1. To compare clinically meaningful decline of general health related quality of life (HRQOL) between patients receiving immunotherapy with stereotactic radiation versus stereotactic radiation alone as measured by the EORTC QLQ-C30 and EORTC-QLQ-LC13.

2. To evaluate the longitudinal changes in HRQOL, as measured by the EORTC QLQ-C30 and EORTC-QLQ-LC13, between arms.

b. Power calculations

The primary QOL endpoint is whether a patient experiences a clinically meaningful deterioration of EORTC QLQ-C30 (defined as a decline of 15 points or more from baseline) at 12 months post-randomization, e.g., a binary endpoint. The null primary QOL hypothesis is that the ratio between the proportion of patients in the experimental arm who will experience clinically meaningful deterioration (CMD) at 12 months after randomization (p_2) and that in the control arm (p_1) is greater than a margin $\sigma(>1)$, e.g., $p_1/p_2 > \sigma$.

By definition, only participants who are alive at 12 months after randomization could potentially be analyzable for QOL analysis. The QOL endpoint assessed at 12-month (54 weeks) post-randomization is a patient-level measurement, which is expected to occur while the parent trial is active, whose primary analysis will be occurred upon 245 deaths or a maximum of 3 year of follow-up (from the last accrued patients). The choice of time point of assessment is a consensus between NRG Oncology and Genentech after considering clinical relevance and interest, and patients' convenience. Furthermore, this time point is chosen because it will allow for disease recurrence events to occur. We hypothesize that the QOL in the atezolizumab arm with SRS will be superior compared to the control arm at 54 weeks. We hypothesize the improved quality of life will be due to improved disease control and reduced recurrences or metastases in the atezolizumab arm.

Based on the primary hypothesis of OS, the survival rate at 12 months after randomization is approximately 82% under H_0, and 87% under H_1. We define patients as analyzable if they are randomized and have assessments at both timepoints (baseline and 12 months). To our best knowledge, there are limited data, as measured in EORTC QLQ-C3- and EORTC-QLQ-LC13, available in this patient population. Therefore, it is not reasonable to perform a rigorous power analysis. If 90% of patients alive at 12 months are analyzable, we will have approximately 170 and 160 analyzable cases in Arm 1 and 2 respectively. Using a one-sided Score test (Farrington & Manning) at the level of 0.05, we have 76% power to detect a ratio (p_1/p2) of 1.0 when the non-inferiority ratio is 1.3 if p_2=0.50. *(1)*

c. Statistical analysis plan

The QOL analyses for any changes between two timepoints will be performed based on all randomized patients with assessments at both timepoints. The primary QOL endpoint, CMD rate at 12 months after randomization, is defined as the proportion of randomized subjects who have a 15 point or greater decrease from baseline at 12 months. The CMD rates and associated 95% confidence interval will be calculated for each treatment group. Clopper-Pearson method will be used for calculating 95% CI.

The QOL completion rates will be summarized at each assessment point as the proportion of assessments actually received out of the expected number (i.e., the number of subjects still in follow-up).

QOL measurements (EORTC QLQ-C30 and EORTC-QLQ-LC13) at baseline and at each subsequent assessment, as well as their change from baseline will be summarized using descriptive statistics by treatment group as randomized. The summary at baseline and at each time point is based on all randomized subjects with a measurement at respective time point. The change from baseline analysis will only include subjects who have an assessment at baseline and at the subsequent time point. The scores at baseline and subsequent time points, as well the changes from baseline at each time point for each treatment group will be analyzed as continuous variables and compared using the two-sample t-test. If the parametric assumptions are not met, then the Mann-Whitney test will be used. Effect size of EORTC QLQ-C30 and EORTC-QLQ-LC13 changes at different time points will be calculated based on Cohen's d, i.e., dividing the difference between arms in mean score changes by the pooled standard deviation of the baseline score means.

A longitudinal analysis will also be conducted with a focus on the patterns of scores over time points of EORTC QLQ-C30 and EORTC-QLQ-LC13. Following the descriptive statistics on assessments, a linear mixed model will also be used to analyze the QOL/PRO outcomes collected over time using all available data while adjusting for stratification variables and other baseline characteristics as appropriate. Mixed models are a general class of models for analyzing repeated measures data, which allow modeling of the covariance among the repeated measures as well as random effects such as patient-specific intercepts and slopes, and can incorporate fixed and time-varying covariates. Fixed effects will consist of stratification factors and potentially other baseline covariates that may be prognostic to QOL/PRO or efficacy. Since missing data is expected, patients with missing data will be compared to patients with complete data at each follow-up time with respect to baseline characteristics. If any of these characteristics are found to be significantly different, then they will be incorporated into the mixed effects model.

Completion of all scheduled assessments is part of the routine delinquency assessment. NRG SDMC statisticians will monitor the proportions of missing quality of life information in each treatment arm at different assessment points. In spite of these efforts, missing data is expected. The information from patients with missing data will be reviewed to determine whether the data analyses will be biased. Patients with missing data will be reviewed for the distributions of treatment arms and patient characteristics. Mean scores by assessment time for cohorts stratified by baseline score quartile will also be compared to investigate if the missingness is consistent with an ignorable missing data process (missing at random). If a missing-at-random (MAR) mechanism is reasonable, the data will be analyzed with appropriate likelihood-based analysis methods such as linear mixed effect models. If a MAR mechanism is not strongly supported, multiple imputations for missing values and sensitivity analyses will be conducted to control for the potential bias. The possible strategies for imputation and analyses will depend on the severity of the missing data problem and may include: worse-case scenario, use of mean response for individuals who withdraw from the trial from either all or similar (matched) patients remaining in the trial, last observation carried forward, or multiple imputations. A joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR (missing not at random) due to the high number of patient deaths or dropouts. *(2)* Other options for MNAR data are pattern mixture and selection models. *(3,4)* Sensitivity analyses will be performed to compare the results of different analytic strategies. *(5)*

d. QOL Study Data Management and Sharing

This is a shared protocol between two NCTN groups (NRG Oncology and SWOG) and therefore collaboration between the two statistical centers is required. SWOG will be responsible for the analysis of the clinical comparison of the two study arms with respect to clinical efficacy endpoints. The QOL study will be analyzed by NRG. SWOG will be responsible for data quality control of all data except QOL data. Forms collected as part of the QOL component will be entirely the responsibility of NRG. While one NCTN group may lead certain parts of the analysis, results and data will be shared between both and publications authored collaboratively.

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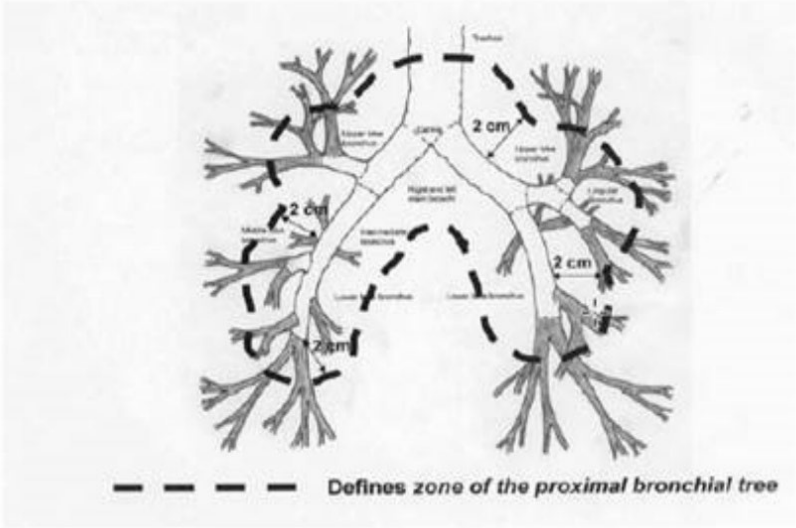
18.6 Zone of the Proximal Bronchial Tree

Tumor within or touching the zone of the proximal bronchial tree, defined as a volume 2 cm in all directions around the proximal bronchial tree (carina, right and left main bronchi, right and left upper lobe bronchi, intermedius bronchus, right middle lobe bronchus, lingular bronchus right and left lower lobe bronchi). [See figure on next page] Tumors that are immediately adjacent to mediastinal or pericardial pleura (PTV touching the pleura) also are considered central tumors and are eligible for this protocol.

Figure 1



18.7 Live Vaccines Examples

Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.