NRG ONCOLOGY and
THE ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY
NRG-LU005
(ClinicalTrials.gov NCT #03811002)

LIMITED STAGE SMALL CELL LUNG CANCER (LS-SCLC): A PHASE III RANDOMIZED STUDY OF CHEMORADIATION VERSUS CHEMORADIATION PLUS ATEZOLIZUMAB (02-JUNE-2021)

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology in collaboration with The Alliance for Clinical Trials in Oncology, and with the participation of the network of NCTN organizations; ECOG-ACRIN Medical Group; and SWOG.

This is a potential FDA Registration Trial. Additional site requirements include enhanced central monitoring (see protocol Section 13.5).

Coordinating Center:
NRG Oncology
Four Penn Center; 1600 JFK Blvd; Suite 1020; Philadelphia, PA 19103

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For questions concerning RT data submission	IROC Philadelphia – RT QA Center ACR Center for Research and Innovation 50 South 16th Street, Suite 2800 Philadelphia, PA 19102 [redacted]
RT Credentialing	http://irochouston.mdanderson.org OR IROC-Credentialing@mdanderson.org
TRIAD Support – issues pertaining to installation, performance, login access, or other technical issues	Triad-Support@acr.org Additional installation and user guidance is available at https://triadhelp.acr.org
Protocol-related matters or issues involving crediting in Rave or receipt of diagnostic images	IROCImagearchive@acr.org For a timely response, please reference the trial number in the subject line.
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Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Cisplatin	Commercial	119875	[redacted]	DCTD, NCI
Carboplatin	Commercial	241240		
Etoposide	Commercial	141540		
Atezolizumab (MPDL3280A)	NCI/PMB	783608		

Participating Sites (22-FEB-2021)

☒ U.S.
☒ Canada
☒ Japan

Document History

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Amendment 13	**July 10, 2024**
Amendment 12	December 19, 2023
Amendment 11	November 13, 2023
Amendment 10	October 17, 2023
Amendment 9	November 3, 2022
Amendment 8	August 3, 2022
Amendment 7	October 26, 2021
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Amendment 3	September 18, 2020
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Initial	March 18, 2019

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CTSU CONTACT INFORMATION (17-OCT-2023)		
For regulatory requirements:	**For patient enrollments:**	**For 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 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 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is 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. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). 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 Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the study data manager listed on the NRG Oncology contact information table on the protocol cover page.		
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.		

For imaging data submission questions:
IROCimagearchive@acr.org; please include trial number in the email subject line

For TRIAD access and installation support:
TRIAD-Support@acr.org
Triadhelp.acr.org

TRIAD Software Installation:
https://triadinstall.acr.org/triadclient/

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NRG-LU005
SCHEMA (03-AUG-2022)

PATIENT POPULATION:
Limited stage (Tx, T1-T4, N0-3, M0) small cell lung cancer (LS-SCLC)

STRATIFICATION

- Radiation schedule, BID (3 weeks) vs daily (6.5 weeks)
- Chemotherapy (cisplatin vs carboplatin)
- Sex (male vs female)
- ECOG Performance Status (0/1 vs 2)

RANDOMIZE*

Arm 1	**Arm 2**
Platinum**/etoposide q3 weeks x 4 cycles + Thoracic RT 45 Gy bid or 66 Gy daily beginning with cycle 2 of chemotherapy***	Platinum**/etoposide q3 weeks x 4 cycles + Thoracic RT 45 Gy bid or 66 Gy daily beginning with cycle 2 of chemotherapy*** + Atezolizumab q3 weeks x 1 year (17 doses), beginning with cycle 2 of chemotherapy

* Randomization is 1:1.

** First cycle of chemotherapy must be given prior to study entry for a total of 4 cycles, 3 given on study. Chemotherapy doublets delivered concurrently, cisplatin/etoposide or carboplatin/etoposide, is required. The site/investigator must declare the chemotherapy regimen that the patient will receive prior to the patient's randomization. Patients who develop a contraindication to cisplatin after beginning therapy may receive carboplatin in subsequent cycles. See Section 5.1 and 6 for details.

*** All patients with a complete or near complete response are strongly recommended to receive prophylactic cranial irradiation (PCI), planned within 4-6 weeks from completion of chemoradiotherapy**. Significant chemoradiotherapy toxicities should be resolved to grade 2 or less before beginning PCI.** Patients on Arm 2 who receive PCI will receive it concurrent with atezolizumab.

1.0 OBJECTIVES

1.1 Primary Objective (02-JUNE-2021)

To compare overall survival (OS) for patients with LS-SCLC treated with chemoradiation +/- atezolizumab.

1.2 Secondary Objectives (10-JUL-2024)

- To compare progression free survival (PFS) for patients with limited stage small cell lung cancer (LS-SCLC) treated with chemoradiation +/- atezolizumab.
- To determine overall response rate (ORR), rates of local control, and distant metastases free survival with chemoradiation +/- atezolizumab
- To characterize immune mediated and non-immune mediated toxicity from chemoradiotherapy plus atezolizumab
- To compare quality of life, as measured by the FACT-TOI, for patients undergoing chemoradiation +/- atezolizumab
- To evaluate the quality-adjusted survival, using scores from the EQ-5D-5L, of chemoradiation +/- atezolizumab for patients with LS-SCLC
- To characterize fatigue, as measured by the PROMIS, following chemoradiation +/- atezolizumab
- To determine the association of SCLC molecular subtypes with clinical outcomes

1.3 Exploratory Objectives (10-JUL-2024)

- To collect biospecimens at baseline, Day 1 and 3 months after the end of chemoradiotherapy, to allow for future analyses
- To characterize patient-reported symptomatic toxicities measured by the PRO-CTCAE
- To characterize the concordance between tumor and cfDNA-determined molecular subtypes

2.0 BACKGROUND

2.1 Rationale

Patients with LS-SCLC respond to chemoradiotherapy with substantial decrease in tumor burden the vast majority of the time, but relapse occurs early and often, limiting long-term survival to about 25% of the LS-SCLC population. We hypothesize that the unmasking of hidden tumor antigens and creation of immunologic space during and after chemoradiotherapy will enhance immune stimulation by atezolizumab thus increasing efficacy of therapy, duration of response and overall survival.

Immunotherapy is already established in extensive stage (ES) SCLC. In the phase 1/2 Checkmate 032 trial (Antonia et al, 2016, https://clinicaltrials.gov/ct2/show/NCT01928394), response rates were 10% for nivolumab and 23% for nivolumab plus ipilimumab independent of PD-L1 expression and with grade 3/4 adverse events occurring in approximately 20%. Nivolumab or nivolumab plus ipilimumab are now compendia listed for relapsed SCLC, and are included in the National Comprehensive Cancer Network guidelines for patients who have progressive disease within 6 months of completion of initial chemotherapy. Further, the IMpower133 study (Horn et al 2017, https://clinicaltrials.gov/ct2/show/NCT02763579), a phase III double-blinded, placebo

controlled study of carboplatin/etoposide +/- atezolizumab in chemotherapy naïve extensive stage small cell lung cancer, recently reported improved PFS and OS in patients receiving atezolizumab concurrently with chemotherapy.

In LS-SCLC, the European Thoracic Oncology Platform phase II randomized study compares chemoradiation with platinum/etoposide and PCI alone or followed by adjuvant nivolumab and ipilimumab (https://clinicaltrials.gov/ct2/show/NCT02046733). NRG-LU005 differs in agent used as well as in timing of immunotherapy which begins concurrent with chemoradiotherapy to take advantage of the salutary effects of radiation on both tumor antigen exposure and reduction in immunosuppressive T-cells.

NRG-LU005 will randomly assign patients to standard etoposide and platinum chemotherapy plus thoracic radiation alone or with concurrent and adjuvant atezolizumab. The hypothesis that chemoradiotherapy plus atezolizumab will be superior to chemoradiotherapy alone is based on known chemotherapy and radiation effects on both tumor cells and host immune system. Adding concurrent checkpoint inhibitors to radiation was synergistic in xenograft models of pancreatic, colon, and breast cancer (Blanquicett et al, 2005, Deng et al, 2014). Radiation upregulates PD-L1 expression on tumor and stromal cells. Both chemotherapy and radiation affect immune response to cancer by decreasing T-regulatory cells and by increasing expression of hidden tumor neoantigens during immune reconstitution after treatment. Radiation to a primary tumor leads to tumor-antigen release and a tumor specific adaptive immune response, which is enhanced by immune-stimulating agents. Thus, while radiation induces a local tumor response at the site of radiation, it may also lead to regression of micrometastatic disease (the abscopal effect) (Tang et al, 2015).

Dovedi et al reported that low doses of fractionated radiation given concurrently with anti PD-1 antibodies enhanced local tumor control and elicited out of field responses in a mouse model of colon cancer, with a >70% complete response rate. Sequential delivery of checkpoint inhibitors did not improve response to radiotherapy at local or distant sites. Next generation sequencing of T cell receptors showed that while radiation increased T cell infiltration at the irradiated tumor only, radiation + anti PD-1 increased T cell infiltration/expansion at both irradiated and out-of-field tumors. Additionally, radiation + anti-PD-1 increased T-cell receptor diversity more than radiation or anti PD-1 alone (Dovedi et al, 2017).

Reports from the phase III PACIFIC trial in NSCLC showed substantial improvements in PFS, one of the co-primary end-points, with consolidative durvalumab after concurrent chemoradiation (Antonia et al, 2017, https://clinicaltrials.gov/ct2/show/NCT02125461). An unplanned subset analysis suggested better PFS for patients who began durvalumab within 14 days after the last radiation treatment compared with those randomized later. This finding supports the hypothesis that concurrent or early adjuvant immunotherapy may augment radiation response.

Incorporating concurrent and consolidative immunotherapy in the definitive setting as studied here is a rational approach, given the preclinical evidence for synergy of

checkpoint inhibitors with radiation and chemotherapy and clinical evidence from similar patient populations with NSCLC. This study incorporates early checkpoint inhibitor therapy with standard curative intent chemoradiotherapy to enhance the systemic polyclonal T-cell response and address systemic micrometastatic disease as early as possible during the treatment course.

2.2 Study Significance

SCLC accounts for approximately 15% of lung cancer cases in the US (12% in men and 18% in women) and has a poor prognosis despite rapid and significant initial response to chemoradiotherapy. Standard chemoradiotherapy for LS-SCLC cures some patients, but at least 70% will relapse within 2 years with no available curative strategy at progression. The unmet need in LS-SCLC – the ability to cure more than a small fraction of these early stage patients – has not changed in decades of chemoradiotherapy and targeted therapy trials. The median overall survival reported in the most contemporary phase III trial in limited stage small cell lung cancer, testing once daily compared to twice-daily radiation therapy, was 25 and 30 months, respectively, and the median progression-free survival was 14.3 and 15.4 months, respectively (Faivre-Finn et al, 2017, https://clinicaltrials.gov/ct2/show/NCT00433563).

Checkpoint inhibitors represent an opportunity to improve cure rates by establishing immunologic control over local and disseminated residual cancer after chemoradiotherapy. Etoposide-platinum plus thoracic radiation is the standard of care in these patients and cures 25 to 35% of patients. Thus, this backbone provides a platform upon which to add novel agents such as immunotherapy. The exposure of hidden antigens and the depletion of immune cells, especially T-regs, by chemotherapy and radiation, allows broader antigen exposure to repopulate effector T cells and NK cells. While toxicity is a concern when combining radiotherapy, to the chest and/or brain particularly, with checkpoint inhibitors, excessive toxicity has not been reported in ongoing trials in which patients have received radiation and immunotherapy concurrently. Even so, comparatively few patients have been treated thus far, so NRG-LU005 is designed with real-time monitoring for safety especially for potentially significant immune related pneumonitis, esophagitis, neurotoxicity and myocarditis.

Integrative biomarker studies will help to develop tools to identify patients who may benefit most from immunotherapy. This study has the potential to create a new treatment paradigm for a deadly disease.

This study will randomize patients to chemoradiation +/- atezolizumab, given concurrently and in the consolidative setting for 12 months total. Patients will be stratified by sex, performance status (PS 0&1 vs.2) radiation fractionation schema (once vs. twice daily fractionation) and cisplatin vs. carboplatin chemotherapy. For limited stage small cell lung cancer (LS-SCLC), the strongest prognostic factors include good performance status and female sex. These variables have been shown to be highly prognostic in LS-SCLC based upon an analysis of over 1000 patients treated on Southwest Oncology Group clinical trials (Albain et al, J Clin Oncol. 1990 Sep;8(9):1563-74). Radiation fractionation and carboplatin vs. cisplatin will also be stratification factors in order to

avoid any potential treatment imbalances between the study arms.

2.3 Context for Chemoradiation in LS-SCLC in Combination with Immunotherapy

Radiation dose and schedule for LS-SCLC have been previously studied. The CONVERT trial (Faivre-Finn et al, 2017, https://clinicaltrials.gov/ct2/show/NCT00433563) showed no statistically significant difference in overall survival between 45 Gy twice daily or 66 Gy daily. In patients assessed for radiotherapy toxicity, the rates of grade 3 or 4 esophagitis and radiation pneumonitis were similar. The concurrent radiation schedule in this trial will, therefore, allow either 45 Gy twice daily or 66 Gy daily and will stratify for radiation option. PCI will be encouraged for patients who achieve a complete or near complete response.

Preliminary safety data from combined immunotherapy and radiation trials is reassuring. Hwang et al reported clinically significant pneumonitis in 5.3% of 164 patients treated with thoracic radiation before, during, or after checkpoint inhibitors. Hubbeling et al reported no difference in toxicity of brain radiation whether or not patients received immunotherapy, nor did the timing of immunotherapy and brain radiation influence side effects. Additionally, the IMpower133 study of carboplatin/etoposide +/- atezolizumab as first line treatment of extensive stage small cell lung cancer allowed PCI and there was no increase in neurologic toxicities in patients receiving atezolizumab (Horn et al, 2017).

A phase I/II MD Anderson trial utilizing MK-3475 (pembrolizumab, anti-PD1 Merck) concurrently with chemoradiation (CRT) and for 12 months following CRT in LS-SCLC, reported tolerable toxicity profiles. Patients received PCI in this study at the discretion of the treating physician. Table 1 below summarizes steroid use, and number of patients with grade 3 and higher adverse events in this study (https://clinicaltrials.gov/ct2/show/NCT02402920).

Table 1. Summary of Immune-mediated Grade 3 and Higher AEs, MDA Phase I Study

# of patients (%)	Grade 3&4 AEs	Steroid Use
1 (4%)	Pericarditis	0/1
4 (14%)	Respiratory (pneumonitis, pneumonia, hypoxia)	4/4
0	Neurologic (cognitive decline, encephalitis)	Not applicable

The MD Anderson investigators found that grade 3 and higher adverse events were manageable and not excessive. Four patients (14%) developed grade 3 and higher respiratory toxicities that were possibly attributed to protocol treatment, and were treated with steroids while patients remained on study. Of these 4 patients, 3 had toxicity that resolved within 3 weeks from onset. One patient developed grade 3 fatigue. No patients developed grade 3 or higher esophagitis. No patients developed encephalitis or other grade 3 or higher neurologic toxicities possibly attributable to immunotherapy in the setting of PCI, of which 11 of 28 patients received PCI (unpublished data, personal communication from Dr. [redacted]).

A phase I study of chemoradiation + pembrolizumab for stage III non-small cell lung cancer is underway at Rutgers University (https://clinicaltrials.gov/ct2/show/NCT02621398). This study delivers 60 Gy thoracic radiation with weekly carboplatin/paclitaxel + pembrolizumab, introduced at varying time points of chemoradiation dependent upon the specific dose cohort. One grade 3 pneumonitis has been reported, attributed to pembrolizumab, with no grade 4 or 5 toxicities related to immunotherapy. This trial is ongoing (unpublished data, personal communication from Dr. [redacted]).

2.4 Quality of Life

Health-related quality of life (QOL) is an important endpoint in clinical trials to assess the overall disease burden and treatment effect from the patient's perspective using patient reported outcomes (PROs). If the atezolizumab arm shows superior OS, a new standard of care will be defined for limited stage SCLC.

The effects of atezolizumab immunotherapy on CRT in lung cancer on QOL are currently unknown. Hence, this study will provide a unique opportunity to characterize the effects of this novel treatment on QOL. It is anticipated that concurrent and consolidative atezolizumab will improve OS with minimal overlapping acute toxicities of atezolizumab and CRT. Obtaining QOL data at baseline, during treatment, and follow up after treatment provides baseline prognostic data as well as reporting the effect of treatment on HRQOL from the patient's perspective. Baseline QOL data was found to be a prognostic variable in addition to clinical factors in predicting survival in cancer patients (Quinten 2014, Urba 2012) in a pooled analysis of 7417 cancer patients entered on randomized trials. These data suggest that obtaining baseline QOL data are of superior prognostic significance than obtaining physician graded performance scale scores such as Karnofsky performance scales or ECOG scales prior to initiation of treatment.

3.0 PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

3.1 Patient Selection Guidelines (13-NOV-2022)

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Administration of atezolizumab, platinum/etoposide chemotherapy, and external beam radiation may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Women of child-bearing potential and men must agree to use

adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study treatment, and for 5 months (150 days) after the last dose of study agent or for patients on arm 1, after completion of chemoradiation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.3 Submission of an H&E stained slide from primary tumor is required for all patients. Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. (See Section 10 for details.)

3.2 Eligibility Criteria (26-OCT-2021)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1 Pathologically (histologically or cytologically) proven diagnosis of limited stage small cell lung cancer (Stage Tx, T1-T4, N0-3, M0, AJCC Staging, 8th Ed.), within 60 days prior to registration;

3.2.2 Patients must have received one cycle of platinum/etoposide chemotherapy pre-registration (prior to study entry). Study registration must be within 21 days from day 1 of the pre-registration cycle of chemotherapy.

3.2.3 Patients must have had measurable disease (per RECIST, version 1.1) prior to the required pre-registration cycle of platinum/etoposide chemotherapy.

3.2.4 Minimal staging requirements include:

- History/physical examination within 30 days prior to registration;
- PET/CT scan for staging within 60 days prior to registration;
- CT chest and CT abdomen with IV contrast (unless contraindicated based on kidney function*) within 60 days prior to registration; MRI abdomen with IV contrast allowed in place of CT abdomen.
  ***Note:** If contrast allergy exists, premedication per institutional guidelines should be performed prior to obtaining CT with contrast. The only exception to this is a documented life-threatening allergy.
- MRI scan of the brain with contrast (preferred) or CT scan of the brain with contrast (allowable if there is a contraindication with MRI with contrast) within 30 days prior to registration;

3.2.5 Age ≥ 18;

3.2.6 ECOG Performance Status of 0-2 within 30 days prior to registration;

3.2.7 Required Initial Laboratory Values (prior to pre-registration cycle):

ANC	≥1,500/cells/mm^3
Platelet Count	≥100,000 cells/mm^3
Hemoglobin	≥9 g/dL
Total Bilirubin	≤1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤2.0 x ULN

3.2.8 Adequate renal function within 30 days prior to registration defined as follows:
Creatinine clearance ≥ 30 mL/min by the Cockcroft-Gault (C-G) equation:

CrCl (mL/min) =	[140 – age (years)] x weight (kg) / 72 x serum creatinine (mg / dL)	{x 0.85 for female patients}

3.2.9 Patients presenting with a pleural effusion will be eligible if thoracentesis is cytologically negative and non-bloody or if pleural fluid is too small a volume to effectively sample by thoracentesis and does not show increased metabolic activity on CT/PET imaging.

3.2.10 Negative serum pregnancy test within 14 days of registration for pre-menopausal women of childbearing potential.

3.2.11 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.2.12 Hepatitis B/C testing prior to enrollment for patients that have not been tested before. Note: This is required even if the patient has never shown or had symptoms of hepatitis.

3.2.13 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.3 Ineligibility Criteria (03-NOV-2022)

Patients with any of the following conditions are NOT eligible for this study.

3.3.1 Definitive clinical or radiologic evidence of metastatic disease;

3.3.2 Definitive surgical resection of small cell lung cancer;

3.3.3 Prior invasive malignancy (except non-melanomatous skin cancer, localized prostate cancer, or any early stage cancer treated with curative intent resection) unless disease free for a minimum of 2 years (carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

3.3.4 More than 1 cycle of prior platinum-based chemotherapy for SCLC prior to enrollment; note that prior chemotherapy for a different cancer is allowable;

3.3.5 Any prior Atezolizumab or other immunotherapy agent;

3.3.6 Prior radiotherapy to the lungs or mediastinum that would result in clinically significant overlap of radiation therapy fields; prior tangent fields for breast cancer with minimal overlap with target volumes are allowed per approval of study PIs.

3.3.7 Patients with cytologically positive pleural or pericardial fluid are not eligible.

3.3.8 An active, known or suspected autoimmune disease. Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

3.3.9 Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)

3.3.10 History of allogeneic organ transplant

3.3.11 History of primary immunodeficiency

3.3.12 Severe, active co-morbidity defined as follows:

- Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis, cirrhosis, fatty liver, and inherited liver disease;
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications;
- Active tuberculosis;
- Active hepatitis B (chronic or acute) or hepatitis C infection. Note that if hepatitis status is unknown, hepatitis B/C testing is required.

- Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen (HBsAg) test, a positive anti-HBc [antibody to hepatitis B core antigen], and a negative viral DNA test (only obtained if HBsAg is found positive) **are eligible**.
- Patients positive for HCV antibody **are eligible** only if polymerase chain reaction (PCR) is negative for HCV RNA. (The HCV RNA test must be performed for patients who have a positive HCV antibody test.)

- Known immunosuppressive disease, for example history of bone marrow transplant or CLL;
- COPD requiring chronic oral steroid therapy of > 10 mg prednisone daily or equivalent at the time of registration. Inhaled corticosteroids are not exclusionary;
- Unstable angina and/or congestive heart failure requiring hospitalization within the last 3 months;
- Transmural myocardial infarction within the last 3 months;
- Clinically significant interstitial lung disease

3.3.13 A condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

3.3.14 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception for the duration of study treatment and for 150 days after the last dose of study drug (Arm 2); this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP (10-JUL-2024)

PRE-TREATMENT ASSESSMENTS

Timepoint	*Procedure/test*	*Notes*
60 days Prior to Registration	☐ Pathologic proof of SCLC ☐ PET/CT for staging (including tumor measurements) ☐ CT chest and abdomen with IV contrast; MRI abdomen with IV contrast allowed in place of CT abdomen	Radiographic tumor measurements should be obtained via Chest CT. See RECIST 1.1 (https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf, Appendix II) for allowable imaging modalities used to assess disease at baseline and subsequent visits. All diagnostic imaging is to be submitted to TRIAD. NOTE: Submission of imaging via TRIAD is not possible until patient is enrolled.
30 days Prior to Registration	☐ Brain MRI with contrast or Brain CT with contrast (allowable if there is a contraindication to MRI with contrast) ☐ Medical history ☐ Physical Exam ☐ ECOG Performance Status ☐ Vital signs	To include heart rate, blood pressure, pulse Ox, and weight, additional baseline cardiac monitoring (e.g. ECG, troponin) as clinically indicated
Prior to Pre-registration Cycle	☐ CMP and CBC with differential ☐ Serum Pregnancy Test (if applicable)	For chemotherapy cycle prior to study enrollment
Within 14 days of Registration	☐ Serum Pregnancy Test (if applicable)	Required only if test above is > 14 days prior to Registration
60 days Prior to Protocol Treatment	☐ Pulmonary Function Tests (FEV1 and DLCO)	
Within 7 days Prior to Protocol Treatment	☐ FACT-TOI ☐ PROMIS fatigue short form ☐ EQ-5D-5L ☐ PRO-CTCAE *	The study-specific PRO-CTCAE items can be found on the forms section of the CTSU protocol webpage and is titled “NRG-LU005 NCI PRO-CTCAE Item Library”
Pre-treatment (prior to enrollment)	☐ Hepatitis B/C testing*	*Required only if hepatitis status is unknown. See sections 3.2.11 and 3.3.12 for Hepatitis testing requirements. The HCV RNA test must be performed for patients who have a positive HCV antibody test.
Pre-treatment (prior to protocol treatment)	☐ Mandatory H&E stained slide submission ☐ Optional specimen submissions (For patients who consent to biobanking)	See Section 10

ASSESSMENTS DURING TREATMENT

- Cycle 1 is the first cycle of chemotherapy following study entry
- Premedications must be administered per institutional guidelines
- Standard intravenous hydration must be administered in conjunction with cisplatin.
- Routine premedications are not allowed for 1st cycle of atezolizumab, but may be added per standard institutional protocols if indicated for subsequent cycles.
- Dose modifications found in Section 6 of protocol
- Atezolizumab must be administered within 8 hours of preparation
- Radiation will be administered at 45 Gy bid (in 30 fractions) or 66 Gy daily (in 33 fractions). See Section 5

Timepoint	*Procedure/test/treatment*	*Notes*
Cycles 1-3*		
Cycles 1-3 day 1 (the start of the cycle has a window of +/- 3 days, but once the cycle starts, Etoposide must be given consecutively)	☐ History/Physical exam ☐ ECOG Performance Status ☐ Vitals signs ☐ CMP ☐ CBC with differential ☐ TSH ☐ Adverse event evaluation ☐ Cisplatin (60mg/m^2) and Etoposide (120mg/m^2/d) OR Carboplatin AUC = 5 mg/min/mL and Etoposide (100 mg/m^2/d) ☐ Atezolizumab 1200 mg (Arm 2 Only)	VS to include heart rate, blood pressure, pulse Ox, and weight, additional cardiac monitoring (e.g. ECG, troponin) as clinically indicated CMP to include creatinine clearance, AST, ALT, and bilirubin CBC to include ANC, platelets, hemoglobin TSH with reflex to T4, then T3 as clinically indicated (Arm 2 only) Assessments can be performed up to 3 days prior to day 1 of Cycle. Atezolizumab may be given on day 1 or 2 of the cycle
Cycles 1-3 days 2-3	☐ Etoposide (120 or 100 mg/m^2/d)	Etoposide must be given over 3 consecutive days.
Cycles 1-3 days 8 &15 (+/- 3 days)	☐ History/Physical exam ☐ ECOG Performance Status ☐ Vitals signs ☐ CMP ☐ CBC with differential ☐ Adverse event evaluation ☐ PRO-CTCAE	VS to include heart rate, blood pressure, pulse Ox, and weight, additional cardiac monitoring (e.g. ECG, troponin) as clinically indicated CMP to include creatinine clearance, AST, ALT, and bilirubin CBC to include ANC, platelets, hemoglobin
Cycle 4-17 Consolidative Immunotherapy (Arm 2 only)		
Every 3 weeks (+/- 3 days)	☐ History/Physical exam ☐ ECOG Performance Status ☐ Vital Signs	VS to include heart rate, blood pressure, pulse Ox, and weight; additional cardiac monitoring (e.g.

	☐ Adverse event evaluation ☐ CMP ☐ CBC with differential ☐ TSH	ECG, troponin) as clinically indicated CMP to include creatinine clearance, AST, ALT, and bilirubin CBC to include ANC, platelets, hemoglobin TSH with reflex to T4, then T3 if clinically indicated

*Cycle 1-3 of protocol treatment corresponds to cycles 2-4 of platinum/etoposide given in total; the first cycle of chemotherapy is given before protocol treatment.

ASSESSMENTS IN FOLLOW UP

Follow-up Assessments from End of CRT, defined as the end of the last cycle of chemotherapy (e.g. day 21, cycle 3 of platinum/etoposide protocol infusion)		
Timepoint	***Procedure/test/treatment***	***Notes***
End of CRT (+/- 1 week)	☐ Tumor measurements ☐ CT scan chest (through adrenals) with contrast ☐ FACT-TOI ☐ PROMIS fatigue short form ☐ EQ-5D-5L ☐ PRO-CTCAE* ☐ Optional Specimen submission	Unless contraindicated QOL assessments must be done at each timepoint indicated in this table Optional specimens: day 1 after completion of CRT
Q 3 mos. x 2 years (+/- 2 weeks†)	☐ History and Physical Exam ☐ ECOG Performance status ☐ Vital Signs ☐ Adverse Event evaluation ☐ CT scan of chest (through adrenals)/CT abdomen with contrast (unless contraindicated) ☐ Brain MRI with and without contrast or brain CT with contrast (allowable if there is a contraindication to MRI)** ☐ Tumor measurements, if applicable ☐ CMP (if clinically indicated) ☐ CBC with differential (if clinically indicated) ☐ TSH ☐ FACT-TOI ☐ PROMIS fatigue short form ☐ EQ-5D-5L ☐ PRO-CTCAE * ☐ Optional Specimen submission	Vital signs include heart rate, blood pressure, pulse Ox, and weight; additional cardiac monitoring (e.g. ECG, troponin) as clinically indicated **Brain MRI in follow up – Q3 mos. in year 1; Q6 mos. in year 2. Then as clinically indicated All diagnostic imaging is to be submitted to TRIAD. TSH until returns to baseline and then as clinically indicated (Arm 2 only); TSH with reflex to T4, then T3 if clinically indicated †Quality of Life assessments: at 3 and 6 months (+/- 2 weeks), and 15 and 21 months (+/- 6 weeks) after completion of CRT then every other year;

		PRO-CTCAE at 6 months (+/- 2 weeks) and 15 months (+/- 6 weeks) after completion of CRT Optional specimens at Day 1 after completion of CRT, and 3 months after completion of CRT
Q6 mos in year 3 (+/- 3 weeks)	☐ History and Physical Exam ☐ ECOG Performance status ☐ Vital Signs ☐ Adverse Event evaluation ☐ CT scan of chest (through adrenals)/CT abdomen with contrast ☐ Brain MRI with and without contrast (if clinically indicated) or brain CT with contrast (allowable if there is a contradiction to MRI) ☐ Tumor measurements, if applicable ☐ CMP (if clinically indicated) ☐ CBC with differential (if clinically indicated)	
Then annually (+/- 4 weeks), unless otherwise indicated	☐ History and Physical Exam ☐ ECOG Performance status ☐ Vital Signs ☐ Adverse Event evaluation ☐ CT scan of chest (through adrenals)/CT abdomen with contrast ☐ Brain MRI with and without contrast (if clinically indicated) or brain CT with contrast (allowable if there is a contraindication to MRI) ☐ Tumor measurements, if applicable ☐ CMP (if clinically indicated) ☐ CBC with differential (if clinically indicated)	

* This study uses Medidata Patient Cloud ePRO. (ePRO is not available in Japanese.) Remember to register the patient to the Patient Cloud ePRO. For instructions on registering the patients, please refer to Appendix III. The study-specific PRO-CTCAE items for this protocol can be found on the CIRB tab of the CTSU protocol webpage and is titled "NRG-LU005 Participant Questionnaire (PRO-CTCAE)".

Please note that the end of CRT, defined by the end of the 4th cycle of chemotherapy, was chosen to standardize this timepoint for all patients as radiation schedule will vary depending on whether patients received daily or twice daily radiation. Additionally, please note that follow-up assessments including QOL/PRO measurements occurring at 6 months after the end of CRT will be during immunotherapy for patients randomized to the experimental arm.

Definition of Disease Assessments

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eisenhauer 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

5. TREATMENT PLAN/REGIMEN DESCRIPTION (03-AUG-2022)

This randomized phase III trial will compare etoposide and platinum chemotherapy plus standard thoracic radiation with or without concurrent and adjuvant atezolizumab. The first cycle of chemotherapy must be given prior to study entry (i.e. pre-registration cycle). Participants will receive three cycles (i.e. Cycles 1-3) of chemotherapy on study for a total of four cycles. **Protocol treatment begins with concurrent chemotherapy and radiation.**

Participants randomized to Arm 1 will receive Standard CRT (45 Gy bid or 66 Gy daily) plus platinum/etoposide chemotherapy (cisplatin preferred) given every 3 weeks for 3 cycles (for a total of 4 cycles of chemotherapy that includes the cycle given prior to registration). Radiation must start within +/- 2 business days of protocol chemotherapy.

Participants randomized to Arm 2 will receive Standard CRT (45 Gy bid or 66 Gy daily) plus platinum/etoposide chemotherapy (cisplatin preferred) given every 3 weeks for 3 cycles (for a total of 4 cycles of chemotherapy that includes the cycle given prior to registration) plus concurrent atezolizumab, 1200 mg IV every 3 weeks x 1 year (17 doses). Radiation must start within +/- 2 business days of protocol chemotherapy.

Note: PCI is strongly recommended after completion of chemotherapy for patients who have a complete or near complete response, 25 Gy in 10 fractions, planned within 4-6 weeks from completion of chemoradiotherapy. Toxicities from chemoradiotherapy should be resolved to grade 2 or less before initiation of PCI. Patients on Arm 2 who receive PCI will receive it concurrent with atezolizumab.

NOTE: Radiation therapy protocol treatment (45 Gy bid or 66 Gy daily) must begin within +/- 2 business days of protocol platinum/etoposide chemotherapy. It is preferred for radiation to start in the early part of the week, Monday-Wednesday.

	Treatment Week								
	Pre-study registration		1	2	3	4	5	6	Weeks 7-49
RT (45 Gy bid* or 66 Gy daily♦)			*	*	*				
			♦	♦	♦	♦	♦	♦	♦ (week 7)
platinum/etoposide (cisplatin 60 mg/m^2 on day 1 with etoposide 120 mg/m^2 on days 1-3 OR carboplatin	X**		X			X			X (week 7)

[AUC = 5] on day 1 with etoposide 100 mg/m^2 on days 1-3)									
Arm 2 Only: atezolizumab 1200 mg IV q3 weeks x 1 year (17 doses)			X			X			X (q3 weeks x 17 cycles total)

**** The pre-registration cycle of chemotherapy is given prior to study entry. On-study protocol treatment begins with concurrent chemoRT +/- atezolizumab**

5.1 Systemic Treatment (03-AUG-2022)

5.1.1 Platinum/etoposide

A platinum/etoposide doublet will be administered as follows: Cisplatin will be dosed at 60 mg/m^2 day 1 with etoposide 120 mg/m^2 days 1-3 of each 21 day cycle. If using carboplatin, carboplatin will be dosed at AUC = 5 day 1 with etoposide 100 mg/m^2 days 1-3 for each of four 21-day cycles. Variations in dosing in the pre-registration cycle, initiated prior to study entry, are acceptable provided they are within the standard of care for platinum/etoposide administration. Antiemetic premedications including standard dexamethasone should be administered per institutional standards. Either the cisplatin/etoposide or carboplatin/etoposide doublet is allowed per the treating physician's discretion with cisplatin preferred unless contraindicated. If a contraindication to cisplatin develops during therapy, carboplatin may be substituted if the patient remains otherwise eligible to continue treatment.

Protocol treatment is designed to begin 21 days after initiation of pre-registration cycle; however, if patient has not recovered from pre-registration cycle chemotherapy toxicities, then an additional 14 days is permitted from start of treatment.

One of the following recognized standard, protocol-allowed regimens must be given with radiation therapy:

THIS REGIMEN PREFERRED:
Cisplatin (60 mg/m^2/d) intravenous on day 1 and
Etoposide (120 mg/m^2/d) intravenous on days 1 to 3

Standard antiemetic premedications must be administered per individual institutional guidelines. Standard intravenous hydration must be administered in conjunction with cisplatin.

OR

Carboplatin AUC = 5 mg/min/mL intravenous day 1 and
Etoposide (100 mg/m^2/d) intravenous on days 1 to 3

Standard premedications must be administered per individual institutional guidelines.

5.1.2 Atezolizumab

Atezolizumab 1200 mg will be administered IV over 60 minutes (first dose) or 30 minutes (subsequent doses) on day 1 or 2 of each chemotherapy cycle and continued every 3 weeks for one year or until loss of clinical benefit (defined as disease progression or excessive toxicity requiring stopping of study drug (see Section 6.1.2), whichever is earlier.

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.

The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion associated AEs, the second infusion may be delivered over 30 (±10) minutes. If the 30 minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before the infusion. If clinically indicated, vitals should be measured every 15 [±5] minutes, and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion. If patient experienced an infusion-related reaction with previous infusion or if clinically indicated, vital signs should be measured during the infusion and at 30 (±10) minutes after the infusion.

Premedication is not permitted for the first dose of atezolizumab. Premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) may be administered for subsequent infusions at the discretion of the treating physician. See Section 6 for the management of Infusion Related Reactions.

On the day of infusion, there is not a specified sequence of administration of chemotherapy and atezolizumab; this can be performed per institutional preference.

5.2 Radiation Therapy

NOTES: FOR THIS STUDY, EITHER IMRT OR 3D-CRT IS REQUIRED. IGRT IS REQUIRED.

PRE-TREATMENT REVIEW is required for the first 3 patients enrolled from each institution PRIOR TO DELIVERY of radiation treatment. The patient cannot start treatment until they have received approval from the Imaging and Radiation Oncology Core (IROC)-Philadelphia RT. The Pre-Treatment Review process requires 3 business days from the receipt of complete data via TRIAD.

5.2.1 Treatment Technology Requirements

Three-dimensional conformal radiation therapy (3D-CRT) or Intensity Modulated Radiation Therapy (IMRT) is required. Proton Beam Therapy is not allowed. IMRT

techniques delivered from equipment using Tomotherapy, ViewRay and VMAT are allowed. For photons, beam energy of 6-10 MV will be used. ViewRay with Cobalt 60 source and ViewRay MRIdian are permitted. Daily image guided radiation therapy (IGRT) using orthogonal X-ray, cone beam CT, CT on rails, or MR guidance must be used for all patients, regardless of radiation techniques. Multi-leaf collimation will be used to spare normal tissues outside of the target volume. 4DCT is required. Use of PET/CT for treatment planning is strongly encouraged.

5.2.2 Immobilization and Simulation

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices. Alpha Cradles or Vac-lok devices are used for shoulder immobilization. Arms are abducted bilaterally with hands above the head (preferably in all cases unless patients are incapable of doing so but setup must be reproducible daily and treatment planning will accommodate for the deviation).

Simulation Imaging

Simulation CTs should be CT slices of ≤ 3 mm slice thickness starting from the level of the cricoid cartilage (or further cranially) and extending inferiorly through the entire liver (or further caudad) volume. Administration of intravenous (I.V.) contrast during simulation CT is optional provided a diagnostic CT with contrast has been done to help delineate the major blood vessels. If such diagnostic CT is not available, I.V. contrast should be given during the treatment planning CT. The simulation should be performed after the first cycle of chemotherapy to account for any significant shrinkage of the primary tumor.

Motion Management Technique

The use of four-dimensional radiation treatment planning is required to assess for respiratory motion in the treatment planning process. Use of a MIP image is acceptable to aid in contouring the IGTV, but care should be taken in areas of uniform density such as mediastinum, chestwall and diaphragm. If normal tissue tolerances are exceeded, or MLC interplay effects are of concern, motion limiting techniques may be considered. Permitted methods include active breath hold, gated treatment and abdominal compression.

5.2.3 Imaging for Structure Definition and Image Registration

A volumetric treatment planning CT study as described above under Simulation Imaging will be required to define gross tumor volume (IGTV), clinical target volume (CTV), and planning target volume (PTV) (see definitions below). The IGTV, CTV, and PTV and critical structures will be outlined on all appropriate CT slices. A treatment planning FDG PET/CT scan (or FDG-PET alone) with the patient in the treatment position is encouraged for treatment planning. In the case where the PET/CT is obtained in the treatment position, the CT from this study may be used as the planning CT scan. Otherwise, a diagnostic PET/CT used for staging could be used for target delineation with image co-registration with the planning CT.

5.2.4 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.

Once Per Day RT Option: 2 Gy x 33 fractions = 66 Gy		
DICOM Standard Name	**Description**	**Validation** (Required/Required when applicable)
IGTV_6600	GTV to receive 66 Gy	Required
CTV_6600	CTV to receive 66 Gy	Required
PTV_6600	PTV to receive 66 Gy	Required
BID RT Option: 1.5 Gy BID x 30 fractions = 45 Gy		
DICOM Standard Name	**Description**	**Validation** Required/Required when applicable
IGTV_4500	IGTV to receive 45 Gy	Required
CTV_4500	CTV to receive 45 Gy	Required
PTV_4500	PTV to receive 45 Gy	Required

Detailed Specifications

Target volumes: The definitions of volumes will be in accordance with the ICRU 50 (1999) for 3DCRT and ICRU 83 (2010) for IMRT.

IGTV_6600 or IGTV_4500: The primary tumor and clinically positive lymph nodes seen either on the planning CT
(> 1cm short axis diameter) or pre-treatment PET scan (SUV > 3) will constitute the IGTV. This volume(s) may be disjointed. If the primary tumor/lymph nodes have changed significantly after the first cycle of chemotherapy, the IGTV should reflect the

tumor seen on planning CT and not a larger pre-chemotherapy volume. In the event of a collapsed lobe or lung segment, the use of PET to distinguish tumor from fluid/atelectasis is encouraged.
CTV_6600 or CTV_4500: The CTV is defined to be the IGTV plus a 0.5 cm margin as appropriate to account for microscopic tumor extension. The CTV should be adjusted to not expand into other organs such as esophagus, heart, major blood vessels, or bone unless clinically indicated.
PTV_6600 or PTV_4500: The PTV will be equal to the CTV+0.5 cm setup margin (SM) in all directions.

5.2.5 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.

Standard Name	**Description**	**Validation** Required/Required when applicable
SpinalCord	Spinal Cord	Required
Lungs-IGTV	Combined lungs minus IGTV	Required
Esophagus	Esophagus	Required
Heart	Heart	Required
BrachialPlexus	Brachial Plexus	Required for upper lobe tumors or high mediastinal nodal involvement

Detailed Specifications

SpinalCord: Boundaries: Cranial: 1st slice of CT; Caudal: last slice of CT

Esophagus: Boundaries: Cranial: Bottom of cricoid; Caudal: GE junction

Lungs-IGTV: Boundaries: Cranial: From apex bilaterally; Caudal: to bottom of L2; Right + Left Lung Combined but excluding IGTV

Heart: Boundaries: Base: Bottom of the aortic arch; Inferior: Apical most of the ventricle

BrachialPlexus: C5, C6, C7, C8, T1 nerve roots and cord extensions

5.2.6 Dose Prescription

1. 66 Gy in 6.5 weeks

Patients will receive treatment 5 days per week, in once daily fractions, 2 Gy per fraction. The total dose will be 66 Gy in 33 fractions. Radiation will begin concurrently with the second cycle of chemotherapy

2. 45 Gy in 3 weeks **(preferred)**

Patients will receive treatment 5 days per week, in twice daily fractions, 1.5 Gy per fraction. The total dose will be 45 Gy in 30 fractions. For IMRT, the same treatment plan will be delivered for each treatment. There will be a minimum of 6 hours between the morning and afternoon fractions. Radiation will begin concurrently with the second cycle of chemotherapy.

For patients with a complete or near complete response to therapy, PCI is recommended. The dose will be 25 Gy, delivered at 2.5 Gy per fraction for 10 fractions, to be started 4-6 weeks from completion of CRT. (Patients on Arm 2 who receive PCI will receive it concurrent with atezolizumab.)

Once Daily RT: 2 Gy x 33 fractions = 66 Gy					
Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Frequency**	**Dose specification technique**
PTV_6600	66	2	33	Daily 1 fraction per day	Covering at least 95% of PTV

BID RT: 1.5 Gy x 30 fractions = 45 Gy					
Target Standard Name	**Dose (Gy)**	**Fraction Size** (Gy)	**# of fractions**	**Frequency**	**Dose specification technique**
PTV_4500	45	1.5	30	BID (>=6 hours apart)	Covering at least 95% of PTV

5.2.7 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. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall

at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

Normalization of Dose: The plan is normalized such that 95% of the PTV volume receives prescription dose.

Once Daily RT 66 Gy: Target Volume Constraints and Compliance Criteria

Once Daily RT 2 Gy x 33 Fractions = 66 Gy			
Name of Structure	**Dosimetric Parameter**	**Per Protocol**	**Variation Acceptable**
PTV_6600	D95%[Gy]	66	64.7 to 67.3 (excluding 66 Gy)
	D0.03cc[Gy]	<= 79.2	<= 82.5

Once Daily RT 66 Gy: Normal Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
Lungs-IGTV	V5 [%]	<=60	<=70
	V20[%]	<=35	<=37
	Mean[Gy]	<=18	<=20
SpinalCord	D0.03cc[Gy]	<=48	<=50
Esophagus	D0.03cc[Gy]	<=72.6	<=75.9
	Mean[Gy]	<=34	<=40
BrachialPlexus	D0.03cc[Gy]	<=60	<=66
Heart	V30[%]	<=50	<=55
	D0.03cc[Gy]	<=70	<=75
	Mean [Gy]	<=20	<=22

Per Protocol range is excluded from Variation Acceptable range
Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met.

Once Daily RT 66Gy: Delivery Compliance Criteria

	Per Protocol	Variation Acceptable
Start Date: with Cycle 2 platinum/etoposide	<=22 days	<=23 days
Overall Treatment Time	<= 45 days	<=47 days
Interruptions (other than holidays)	none	<=2 days

BID RT 45 Gy: Target Volume Constraints and Compliance Criteria

BID RT 1.5 Gy x 30 Fractions = 45 Gy			
Name of Structure	**Dosimetric Parameter**	**Per Protocol**	**Variation Acceptable**

PTV_4500	D95%[Gy]	45	42.75 to 47.25 (excluding 45 Gy)
	D0.03cc[Gy]	<=54	<=56.25

BID RT 45 Gy: Normal Structure Constraints and Compliance Criteria

Name of Structure	Dosimetric Parameter	Per Protocol	Variation Acceptable
Lungs-IGTV	V5 [%]	<=50	<=58
	V20[%]	<=29	<=31
	Mean[Gy]	<=15	<=17
SpinalCord	D0.03cc[Gy]	<=41	none
Esophagus	D0.03cc[Gy]	<=49.5	<=51.75
	Mean[Gy]	<=28	<=33
BrachialPlexus	D0.03cc[Gy]	<=50	<=55
Heart	V30[%]	<=42	<=46
	D0.03cc[Gy]	<=48	<=51
	Mean [Gy]	<=18	<=20

Per Protocol range is excluded from Variation Acceptable range
Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met.

BID RT 45Gy: Delivery Compliance Criteria

	Per Protocol	Variation Acceptable
Start Date: with Cycle 2 platinum/etoposide	<=22 days	<=23 days
Overall Treatment Time	<=20 days	<=22 days
Interruptions (other than holidays)	none	<=2 days

5.2.8 Treatment Planning Priorities and Instructions

1. Spinal Cord
2. PTV
3. Lungs
4. Heart
5. Esophagus
6. Brachial Plexus

- Required algorithms
Acceptable choices of algorithm are listed at http://irochouston.mdanderson.org. Any algorithm used for this study must be credentialed by IROC Houston.

For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided. Dm, computed inherently by these algorithms, should be reported. These principles hold for Pencil Beam type algorithms and for homogeneous dose calculations

when allowed for a clinical trial (e.g., conical collimators in stereotactic radiosurgery).

- Primary dataset for dose calculation
The primary dataset for dose calculation must be an average intensity pixel CT (AveIP) generated from the 4DCT or the breath-hold/gated CT. Maximum Intensity Pixel (MIP) generated images from 4DCTs may not be used as the primary dose calculation dataset.

-Dose matrix resolution
Dose grid size should be ≤ 3 mm in all directions.

5.2.9 Patient specific QA
Any patient-specific QA that needs to be acquired should follow institutional guidelines and AAPM task group report recommendations. IMRT/VMAT patient-specific QA is highly recommended.

5.2.10 Daily Treatment Localization/IGRT
Image-guided radiation therapy (IGRT) is radiation therapy using imaging to facilitate accuracy and precision throughout its entire process from target and normal tissue delineation, to radiation delivery, to adaptation of therapy to anatomic and biological changes over time in individual patients. In this section we use the terminology IGRT to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment.

Daily image guidance that allows for 3D shifts is the minimum requirement for this trial. Most advanced imaging techniques can be utilized, as long as they also allow for 3D shifts. The setup margin in this trial is tied to the use of daily image guidance. When able to localize using soft tissue, the target will be most effective for localization. Other soft tissues in the lung such as the carina can help for mediastinal alignment. Fiducial markers can be used for localization as needed. Any linear shifts seen that are ≥2 mm should be applied prior to treatment.

-Minimal IGRT requirements

Location	No Fiducials	With Fiducials**
Lung*	Imaging that allows for 3D shifts	Imaging that allows for 3D shifts

*Registration using a soft tissue surrogate for the tumor is recommended. Free-breathing CTs are not to be used as reference images for 4D CBCT IGRT process
**Clearly visible anatomical markers are acceptable as fiducials, e.g. inserted radio opaque markers.

5.3 General Concomitant Medication and Supportive Care Guidelines (22-FEB-2021)

5.3.1 Permitted Supportive/Ancillary Care and Concomitant Medications
Concomitant therapy includes any prescription medications or over the counter preparations used by a patient between the 7 days preceding, the screening evaluation and the treatment discontinuation visit.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice (for sites outside the United States, equivalent medications may be substituted per local practice). Serious infusion associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and ß$_2$-adrenergic agonists; see Section 6.1.2).

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for atezolizumab Cycles ≥2 at the discretion of the treating physician. The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as appetite stimulant is acceptable while the patient is enrolled in the study.

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or warfarin at a stable dose level) should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

5.3.2 Prohibited Therapies

Any concomitant therapy intended for the treatment of cancer, whether health authority approved or experimental, is prohibited unless it is specifically included in the treatment regimen described in this protocol. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, or investigational agents (except for maintenance therapies outlined in Section 5.3.1).
    - After Cycle 1, certain forms of radiotherapy may be considered for pain palliation if patients are deriving benefit (e.g., treatment of known bony metastases); atezolizumab administration may be suspended during radiotherapy.

Initiation or increased dose of granulocyte colony stimulating factors (e.g., granulocyte colony stimulating factor, granulocyte/macrophage colony stimulating factor, and/or pegfilgrastim) is prohibited during radiotherapy for this trial.

Patients are not allowed to receive immunostimulatory agents, including, but not limited to, IFN-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

Patients should also not be receiving immunosuppressive medications, including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids and anti-TNFα agents may attenuate potential beneficial immunologic

effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered.

5.3.3 Herbal and Nutritional Supplements

The concomitant use of herbal therapies is not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However the use of general nutritional foundation supplements will be allowed including: calcium with vitamin D and/or minerals, Omega3's (fish oil), Vitamin B6, Vitamin B12, a basic multivitamin, L-glutamine, or probiotic oral supplements as long as the supplement(s) is at or below the FDA approved recommended dose allowance (RDA) by a healthcare provider. Herbal-based multivitamins are not allowed. Any additional supplements will need prior review and approval by Study Chair.

5.3.4 Participation in Other Trials

- Patients are not to participate in other therapeutic trials. However, trials that do not add experimental agents are allowed (e.g. imaging trials, quality of life, biobanking, etc).

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or for a total of one year or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6,
- Patient decides to withdraw consent for treatment or participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

Chemotherapy doses and schedules may be modified per standard institutional protocols due to toxicity.

When systemic therapy related toxicity is observed, dose delays and/or reductions in drug administration are allowed per package insert and institutional standards as described below. Please note that the table below shows suggested starting dosing, though treatment dosing and dose modification is permitted in accordance with local institutional guidelines. Dose rounding is also permitted per local institutional practice. Weight or BSA changes of >10% would require recalculation of doses. In general, if a subject misses a treatment, the next dose should be administered at the next scheduled time, e.g, no more than 2 dose reductions will be permitted for any patient.

6.1 Management of Atezolizumab-Related Toxicity (17-OCT-2023)

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

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.	• 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, 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. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.

4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observation.
6. Draw serum/plasma samples for immunogenicity testing.
7. Ask participant to return for washout immunogenicity sample if appropriate.

6.1.1 General AE 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 PI 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.

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 **the Agent Administration Guidelines** in this document, 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.
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. ● For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	● Permanently discontinue atezolizumab. ● Bronchoscopy or BAL is recommended. ● 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.

Event	Management

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 determined by the investigator and the Medical Monitor.

[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.

Hepatic events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients 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.
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. • 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.

Event	Management

[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 determined 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.

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.
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.
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. • 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.

Event	Management
	• 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 determined 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.

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 experiencing one or more unexplained AEs possibly indicative of endocrine dysfunction (including headache, fatigue, myalgias, impotence, mental status changes, and constipation) 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 T3 and T4 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] and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency. The table below describes dose management guidelines for hyperthyroidism, hypothyroidism, symptomatic adrenal insufficiency, and hyperglycemia.

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • 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. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.

Event	Management
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.
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.
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • 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.

Event	Management
	• 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. • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab. • 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 determined 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.

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.
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Event	Management

[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 determined 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.

Immune-mediated myocarditis and pericarditis have been associated with the administration of atezolizumab. Management guidelines for cardiac events are provided in the table below.

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-NP [B-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 or associated with pericarditis (see section on pericardial disorders below) 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 electrocardiogram (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.

Immune-mediated Pericardial Disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be

considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Event	Management
	•
Immune-mediated myocarditis, Grade 2–4 Immune-mediated pericardial disorders, Grade 2–4	• Permanently discontinue atezolizumab. • 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 symptoms resolve to below Grade 2, taper corticosteroids over ≥1 month.

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

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, antipyretics, 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.

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 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 atezolizumab 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. ● Consider IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] ● 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. ● 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 Principal 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. ● 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. ● Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] ● 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 (*e.g.*, CPAP, BiPAP, intubation and mechanical ventilation)	● Permanently discontinue atezolizumab. ● 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. ● Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] 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; HLH= hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS= macrophage activation syndrome.

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 (version as specified in the protocol) 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. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz *et al*. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.
f. Refer to Riegler *et al*. for information on experimental treatments for CRS.

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.
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.
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist.

Event	Management
	• 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. • For recurrent events, permanently discontinue atezolizumab.
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab. • 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 determined 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.

Dermatologic events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. 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.

Event	Management
	● Initiate treatment with topical corticosteroids. ● Consider treatment with higher-potency topical corticosteroids if event does not improve.
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.
Dermatologic event, Grade 4	● Permanently discontinue atezolizumab.
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 determined 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.

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 work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders, and specific guidelines for myelitis, are provided in the table below.

Event	Management
Immune-related neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Immune-related neuropathy, including facial paresis, 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.
	• For general immune-mediated neuropathy:
	• If symptoms resolve to below Grade 2, resume atezolizumab. [b]
	• If symptoms do not resolve to below Grade 2 while withholding atezolizumab, permanently discontinue atezolizumab.
	• For facial paresis:
	  • If event resolves fully, resume atezolizumab. [b]
	  • If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab. [c]

Immune-related neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab. • 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 determined 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.

Event	**Management**
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

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. • 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.

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, 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 determined 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.

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 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.
Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.

Event	Management
	• 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 and contact Medical Monitor.
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • 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 and contact Medical Monitor. • For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • 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 agreed upon by the investigator and the Medical Monitor.

[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.

- 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).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2017). 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 below.

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent.

Event	Management
	● 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.

HLH= hemophagocytic lymphohistiocytosis; MAS= macrophage activation syndrome.

6.2 Dose Modifications During Concurrent Chemoradiotherapy With Cisplatin and Etoposide

Please note that institutions are permitted to follow their local institutional standards for dose modifications as standard of care, and in accordance with package insert guidelines for these agents.

If cisplatin or etoposide doses are reduced, all future doses are reduced.

6.3 Dose Modifications for During Concurrent Chemoradiotherapy With Carboplatin and Etoposide

Please note that institutions are permitted to follow their local institutional standards for dose modifications as standard of care, and in accordance with package insert guidelines for these agents

If carboplatin or etoposide doses are reduced, all future doses are reduced.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agent administered in NRG-LU005, atezolizumab (NSC #783608) (MPDL3280A) is being made available under an IND sponsored by DCTD, NCI. For atezolizumab, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.9.2, Arm 1 of the protocol.

Commercial Agents

The commercial agents in NRG-LU005 are cisplatin, etoposide and carboplatin.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

Clinician graded CTCAE is the AE (adverse event) safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no directed action will be taken. Patient responses to the PRO-CTCAE may lead to additional assessment by the clinician; the responses should be reviewed. The specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled "NRG-LU005 NCI PRO-CTCAE Item Library". PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

NOTE: PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action. PRO-CTCAE may lead to additional evaluation by the clinician; their response should not be overlooked.

7.3 Comprehensive Adverse Events and Potential Risks (CAEPR) List for Investigational Study Agent Atezolizumab (MPDL3280A) (17-OCT-2023)

For atezolizumab, expectedness of adverse events is based on the current NCI Specific Protocol Exceptions to Expedited Reporting (SPEER).

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 3097 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 2.4, September 14, 2023[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			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
	Dysphagia		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
	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 [immune related hepatitis])[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS))[2]	
		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]		
	Aspartate		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
	aminotransferase increased[2]		
	Blood bilirubin increased[2]		
		Creatinine increased	
	GGT increased		
	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]	
		Guillain-Barre syndrome[2]	
		Myasthenia gravis[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	
		Nervous system disorders - Other (facial paresis)[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Nervous system disorders - Other (immune-mediated myelitis)[2]	

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
		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		
		Skin and subcutaneous tissue disorders - Other (Drug reaction with eosinophilia with systemic symptoms [DRESS])[2]	
		Skin and subcutaneous tissue disorders - Other (Exanthematous pustulosis)[2]	
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
		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.

7.4 Adverse Events of Special Interest for Atezolizumab (18-SEPT-2020)

Adverse events of special interest (AESIs), including potential drug-induced liver injury and suspected transmission of an infectious agent by the study drug, must be reported expeditiously within 24 hours regardless of grade. Report all instances of AESIs during protocol treatment and for 90 days from last dose of atezolizumab:

Drug-Induced Liver Injury
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:

- Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x ULN
- Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice

Suspected transmission of an infectious agent by the study drug
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 the study drug is suspected.

Additional Adverse Events of Special Interest

- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, macrophage activating syndrome, 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)

7.5 Adverse Events for Cisplatin
Refer to the package insert for detailed pharmacologic and safety information

7.6 Adverse Events for Carboplatin
Refer to the package insert for detailed pharmacologic and safety information

7.7 Adverse Events for Etoposide
Refer to the package insert for detailed pharmacologic and safety information

7.8 Adverse Events and PRO-CTCAE (22-FEB-2021)
PRO-CTCAE

The PRO-CTCAE instrument will be used to assess patient reported toxicity outcomes.

PRO-CTCAE is a validated instrument developed by the National Cancer Institute to assess clinical trial toxicity outcomes by patient report; it complements information collected by physician-reported CTCAE. PRO-CTCAE is available in English, French and Spanish for this study. The PRO-CTCAE assessment can be completed on paper or using an electronic device, but patients participating in the electronic patient-reported outcomes assessment (Medidata Patient Cloud ePRO) will only have the option to complete the English and Spanish language PRO-CTCAE. French and Japanese language PRO-CTCAE is not currently available on ePRO. French and Japanese-speaking patients will have to complete the PRO-CTCAE on paper.

Assessments will be collected before, during and at the end of treatment and in follow-up as specified in the Section 4 assessment tables.

The patient-reported AEs that will be assessed using PRO-CTCAE are listed in the table below. These adverse events are considered expected and, if reported, should also be clinician graded using the CTCAE v.5.0.

CTCAE v.5.0	**PRO-CTCAE Items With Attributes**
Esophagitis Dysphagia	Difficulty swallowing (Severity)
Anorexia	Decreased appetite (Severity)
Nausea	Nausea (Severity)
Vomiting	Vomiting (Severity)
Constipation	Constipation (Severity)
Colitis	Diarrhea (Frequency)

Diarrhea	
Dyspnea	Shortness of breath (Severity & Interference)
Cough	Cough (Severity)
Palpitations	Heart palpitations (Severity)
Rash acneiform Rash maculo-papular	Rash (Presence)
Pruritus	Itching (Severity)
Dermatitis radiation	Radiation skin reaction (Severity)
Peripheral sensory neuropathy	Numbness & tingling (Severity)
Dizziness	Dizziness (Severity)
Blurred vision	Blurred vision (Severity)
Tinnitus	Ringing in ears (Severity)
Concentration impairment	Concentration (Severity)
Memory Impairment	Memory (Severity)
Headache	Headache (Severity)
Fatigue	Fatigue (Severity)
Insomnia	Insomnia (Severity)

7.9 Expedited Reporting of Adverse Events

All adverse events (AEs) are submitted for expedited reporting protocol-specific rules evaluation using the Medidata Rave data management system. All AEs will be evaluated by the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) to determine whether expedited reporting is recommended based on a set of programmed expedited reporting rules. AEs identified as meeting the programmed expedited reporting requirements can then be submitted in CTEP-AERS. A deep link in Rave will take the user directly to CTEP-AERS where the expedited report may be completed and submitted via CTEP-AERS.

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the link in RAVE. CTEP-AERS is also accessed via the CTEP web site, but all expedited reports must be initiated in RAVE
https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP by telephone at 301-897-7497 and NRG Oncology by phone at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.9.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS-24-Hour Notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by CTEP as the IND sponsor for this study and NRG as needed to complete adverse event review. Supporting source

documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page. Fax source documents to CTEP at 301-897-7404. Contact NRG Oncology at 1-215-574-3191 for source documentation assistance.

- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.9.2 Expedited Reporting Requirements for Adverse Events

Arm 2 Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 90 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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 90 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite, and adverse events of special interest (AESI) that occur more than 90 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

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Protocol-Specific Instructions to Expedited Reporting Requirements:
Adverse events of special interest (AESIs), including potential drug-induced liver injury and suspected transmission of an infectious agent by the study drug, must be reported expeditiously within 24 hours regardless of grade. Report all instances of AESIs during protocol treatment and for 90 days from last dose of atezolizumab.

Arm 1 Expedited Reporting Requirements [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **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.

Attribution	Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected
Unrelated Unlikely			10 day	10 day
Possible Probable Definite	24-h/5 day		24-h/5 day	24-h/5 day

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:

- Unexpected Grade 4 and all Grade 5 AEs

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The study-specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled "NRG-LU005 NCI PRO-CTCAE Item Library"

7.9.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.9.4 Secondary Malignancy (01-OCT-2019)

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 during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS . In addition, secondary malignancies following radiation therapy must 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 AE reporting unless otherwise specified.

7.10 Routine Reporting Requirements for Adverse Events (01-OCT-2019)

Arm 2 (atezolizumab) AE Reporting Requirements:

- Report all adverse events regardless of relationship to protocol treatment starting at initiation of protocol treatment

- Report all other AEs for 90 days after end of treatment regardless of relationship to protocol treatment; then only report AEs reasonably related to protocol treatment

Arm 1 AE Reporting Requirements: report all adverse events regardless of relationship to protocol treatment starting at initiation of protocol treatment and for 30 days after end of treatment; then only report AEs reasonably related to protocol treatment.

All Adverse Events must be reported in routine study data submissions.

7.10.1 Reporting PRO-CTCAE

Symptomatic Adverse Events reported by patients through PRO-CTCAE are not safety reporting and should also be clinician graded using the CTCAE v.5.0 and reported as routine AE data.

7.11 Pregnancy (26-NOV-2019)

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 6 months after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

8.0 REGISTRATION AND STUDY ENTRY PROCEDURES (10-JUL-2024)

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain Cancer Therapy Evaluation Program (CTEP) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems.. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);

- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- 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)	✓	✓	✓		

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;
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit Registration Requirements (10-JUL-2024)

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support System Unit (CTSU) members' website.

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

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (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. 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 through 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 email (CTSURegPref@ctsu.coccg.org) or by calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have 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);
- Delegation and Task Log (DTL)
- Compliance with all applicable protocol-specific requirements (PSRs).

RTI Provider
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, 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. Only 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 members' website.
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.
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 and Roster Maintenance applications to comply with 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 the Regulatory application, the enrolling site may access Oncology Patient Enrollment Network (OPEN) to complete enrollments. If the study is using the IROC integration suite, 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.

Downloading Site Registration Documents:
Download the site registration forms from the NRG-LU005 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and it 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);
- Click on *Protocols* in the upper left of the screen;
    - Enter the protocol # in the search field at the top of the protocol tree, or

- Click on the By Lead Organization folder to expand, then select *NRG* and protocol # *NRG-LU005*;
- 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 using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select 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 to receive further instruction and support.

Checking Your Site's Registration Status:

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

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 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 within the protocol. 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.

Delegation of Tasks 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 to 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 describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master

Task List.

8.2 Additional Pre-Registration Requirements FOR CANADIAN INSTITUTIONS (17-OCT-2023)

Prior to clinical trial commencement, Canadian institutions must also complete and submit via the Regulatory Submission portal on the CTSU website:

- Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form
- IRB/REB approved consent (English and native language versions*)
  ***Note**: Canadian Institutions must submit their consent form to NRG Regulatory (regulatory-phl@NRGOncology.org) prior to IRB submission (initial and amendments). Certification/verification of IRB/REB consent translation is also required (described below).
- Protocol Signature Form
- Investigator Brochure Signature Form
- List of Laboratories

The following items are collected by NRG Oncology Regulatory on a yearly or biyearly basis.

- IRB/REB Membership Roster
- Laboratory Certificates and Normal Values
- CVs for Qualified Investigator and Sub-Investigators noted on the DTL log
-

8.2.1 Additional Pre-Registration Requirements FOR INTERNATIONAL INSTITUTIONS

- IRB/REB approved consent (English and native language versions*). English version must be submitted to NRG Regulatory (regulatory-phl@NRGOncology.org) for review prior to IRB/REB/IEC submission.

***Note**: International Institutions must provide certification/verification of IRB/REB/IEC consent translation to NRG Oncology (described below).

* Non-English Speaking Canadian and International Institutions:

Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational/letterhead stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

- 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 of the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Site 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 members' website.

- 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

8.3 RT-Specific Pre-Registration Requirements (17-OCT-2023)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, IROC Houston will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. IROC will automatically send the approval to the Regulatory Support System (RSS) to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**	
	Treatment Modality	
	Photon	Key Information
Credentialing Status Inquiry Form	**x**	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
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.
Phantom Irradiation	**x**	A Thorax phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (**http://irochouston.mdanderson.org**).
Credentialing Notification Issued to:		
Institution	**x**	Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.

8.4 Digital Radiation Therapy Data Submission Using Transfer of Images and Data (17-OCT-2023)

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.

TRIAD Access Requirements:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;

- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). 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, ETCTN, or other relevant 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.

TRIAD Installation:
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 and RCR registration.

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

8.5 Patient Enrollment (10-JUL-2024)

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, informed consent is obtained, and the study site is listed as 'approved' in the CTSU RSS.
Patients must have signed and dated all applicable consents and authorization forms.

Informed Consent: Patients must be aware of the neoplastic nature of their disease and informed of the procedure(s) to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts prior to signing the informed consent in accordance with institutional and federal guidelines. Current IRB/REB/REC approval of this protocol and a consent form is required prior to patient consent and registration. The model consent form created for this study adheres to the NCI informed consent template requirements.

8.5.1 Oncology Patient Enrollment Network (OPEN)

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 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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- 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;
- 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, or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA) 1572 in the Registration and Credential Repository (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
- 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. You may 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 at https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: websupport@acr.org or call the NRG Registration Desk at 215-574-3191, Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

8.5.2 Medidata Patient Cloud ePRO Registration

This study includes the use of Medidata Patient Cloud ePRO (electronic patient-reported outcomes). (ePRO is not available in Japanese.) After the patient is registered to the trial via OPEN, and if the patient can read or understand English, French, or Spanish and is willing to participate in electronic data collection, the site staff will then complete a registration for the patient to the Patient Cloud ePRO through iMedidata. Note: Site staff must have already completed required eLearning for the Patient Cloud ePRO application to register a patient and information about the training is in the ePRO Appendix. The registration to the Patient Cloud ePRO will create a unique patient registration code that the site staff will provide to the patient. The patient (with assistance from the site staff) should be instructed to download the Patient Cloud ePRO app onto his/her own device (IOS, Android, phone or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient reported outcomes electronically for the trial. There are multiple versions of the app available. The **Patient Cloud** App (the version with the cloud logo) will be used on this study. Ensure that the patient downloads the correct version of the

ePRO app. Note only 1 version of the app is active per protocol.

For sites providing a shared institutional device for use by multiple patients on site:

- The site staff should assist the patient with access and registration to the Patient Cloud ePRO app, and the patient can then complete the electronic data submission independently. Site staff may need to assist patients with logging on to the device at each visit.

8.5.3 CRA Patient Registration Instructions for ePRO

Please visit the CTSU website for reference information on Patient Cloud ePRO for CRAs.

- The subject registration process starts in iMedidata. Begin by selecting the Patient Cloud ePRO Registration link for your study.
- The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.
- Now you can register your first patient. Create a subject ID and select a Country / Language from the drop down, (these are the only required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.
- The subject added and will include the date the patient was added, the subject ID, subject initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered. When the patient has registered the status will change from "invited" to "registered".

Reminder- site staff must have already completed the Medidata Patient Cloud training in order to register study participants. Please visit the Medidata Learning Tool for reference information on Patient Cloud ePRO for CRAs. https://learn.mdsol.com/patient-cloud/en/video-library-for-providers-102101952.html.

9.0 DRUG INFORMATION

9.1 Investigational Study Agent: Atezolizumab (IND #[redacted] NSC #783608) (10-JUL-2024)

Other Names: Tecentriq™, MPDL3280A

Classification: monoclonal antibody

M.W.: 150 KD

Mode of Action: anti-PD-L1

Description:
Atezolizumab is a humanized IgG1 monoclonal antibody consisting of two heavy chains

(448 amino acids) and two light chains (214 amino acids). Atezolizumab targets human 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 (Butte et al. 2007).

How Supplied:
Atezolizumab is provided by Genentech/F.Hoffmann-La Roche LTD and distributed by the 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.

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.

Route of Administration: IV infusion

Method of Administration:
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 premedications with subsequent infusions.

Potential 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.

Patient Care Implications:
Female patients of childbearing potential should utilize contraception and take active measures to avoid pregnancy while undergoing atezolizumab treatment and for at least 150 days after the last dose of atezolizumab.

9.1.1 Agent Ordering and Agent Accountability

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 they have a patient in screening.

Submit agent requests through the PMB Agent Inventory Management System (AURORA) application. Access to AURORA 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.

Agent Inventory Records
The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability
The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB AURORA. Access to AURORA requires the

establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

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 *Agent Inventory Management System (AURORA) application: https://ctepcore.nci.nih.gov/aurora*
- 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)

9.2 Commercial Agent: Cisplatin (22-FEB-2021)

Sites in the US and Japan must refer to the package insert and site-specific pharmacy for detailed pharmacologic and safety information. Sites in Canada must refer to the product monograph for pharmacologic and safety information.

9.2.1 Adverse Events

Sites in the US and Japan please refer to the package insert. Sites in Canada refer to the product monograph.

9.2.2 Availability/Supply

Please see Section 5.1.1 for administration instructions. US sites please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage. Sites in Canada must refer to the product monograph for this information.

9.3 Commercial Agent: Carboplatin (22-FEB-2021)

Sites in the US and Japan must refer to the package insert and site-specific pharmacy for detailed pharmacologic and safety information. Sites in Canada must refer to the product monograph for pharmacologic and safety information.

9.3.1 Adverse Events

Sites in the US and Japan please refer to the package insert. Sites in Canada refer to the product monograph.

9.3.2 Availability/Supply

Please see Section 5.1.1 for administration instructions. US sites please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for

toxicity information and instructions for drug preparation, handling, and storage. Sites in Canada must refer to the product monograph for this information.

9.4 Commercial Agent: Etoposide (22-FEB-2021)

Sites in the US and Japan must refer to the package insert and site-specific pharmacy for detailed pharmacologic and safety information. Sites in Canada must refer to the product monograph for pharmacologic and safety information.

9.4.1 Adverse Events

Sites in the US and Japan please refer to the package insert. Sites in Canada refer to the product monograph.

9.4.2 Availability/Supply

Please see Section 5.1.1 for administration instructions. US sites please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage. Sites in Canada must refer to the product monograph for this information.

10. PATHOLOGY/BIOSPECIMENS

10.1 Central Pathology Review Guidelines (01-OCT-2019)

In this study, retrospective central review for confirmation of non-metastatic small cell lung cancer (Stage Tx, T1-T4, N0-3, M0) will be performed by the NRG Oncology Biospecimen Bank–San Francisco (NRGBB-SF) utilizing standard pathologic criteria. The primary reviewer of each case will be the Pathology Co-Chair, Dr. [redacted] Submission of biospecimens for this review is mandatory for all patients. See Section 10.3.1 for specimen collection and shipping details.

10.2 Biospecimen Selection for Integrated Marker Testing: (10-JUL-2024)

Tumor molecular subtyping:

In a recent publication by Gay et al., investigators used tumor expression data and a bioinformatics approach to demonstrate that SCLC is a group of heterogeneous molecular subtypes. They identified 4 subtypes largely based on transcription factors, including SCLC-A, SCLC-N, SCLC-P, and SCLC-I. SCLC-A, occurring in about 51% of cases, and SCLC-N (occurring in about 23% of cases) are neuroendocrine subtypes and share high chromogranin and synaptophysin staining. SCLC-A is characterized by ASCL1 expression, high TTF-1, and is more epithelial. SCLC-N is more neuroendocrine driven by NEUROD1, but lacks TTF-1, while SCLC-P is driven by POU2F3. SCLC-I is a subtype characterized by more mesenchymal features (higher vimentin, AXL, lower E-cadherin), and occurring in about 18% of cases. Interestingly, SCLC-I is characterized by higher CD8 expression and immune cell infiltrate (including T cells, NK cells, and macrophages). In addition, SCLC-I demonstrates a higher T-cell gene expression signature score, higher STING pathway gene expression features, and higher immune checkpoints (CD38, IDO-1, TIGIT, VISTA, ICOS, LAG3), suggesting this subtype is an immune inflamed subtype. This transcriptional subtype analysis was performed utilizing a non-negative matrix factorization (Skoulidis et al, 2015, PMID 26069186) to previously published RNAseq

data from 81 surgically resected, limited stage SCLC samples (George et al, 2015). Concordant with the above findings, SCLC-I experiences the greatest benefit from the addition of anti-PD-L1 therapy to chemotherapy in IMPower133 (comparing first-line atezolizumab plus chemotherapy vs chemotherapy alone for extensive stage SCLC). SCLC-I patients had a median overall survival of 18.2 months with atezolizumab and chemotherapy , compared to 9.6-10.9 months for the other 3 subtypes. Eighteen percent of patients were classified as SCLC-I in this analysis (Gay et al, 2021, PMID 33482121) These results suggest molecular subtyping can identify patients most likely to respond to atezolizumab and chemotherapy.

RNA-Seq is a next-generation sequencing platform that measures various levels of RNA transcripts and provides sequencing information. We will perform RNA-Seq on available baseline archival tumor tissue from the NRGBB-SF. After extracting RNA, we will perform RNA-Seq on tumor tissue samples and perform bioinformatics analysis to subtype tumors from patients enrolled on NRG-LU005 into the 4 subtypes (SCLC-A, SCLC-N, SCLC-P, and SCLC-I). This testing will be done at a Genentech-designated third party vendor laboratory, Expression Analysis (a Q2 Solutions laboratory). We hypothesize that patients bearing tumors with the "inflamed" SCLC-I signature will have the highest response to atezolizumab and chemoradiation therapy leading to improved PFS compared to the other subtypes or a grouping of all 3 subtypes (SCLC-A, SCLC-N, and SCLC-P).

SCLC subtypes identified from public data (Gay et al, Cancer Cell 2021) and IMpower133 (Nabet et al, Cancer Cell 2024) will be assigned from bulk RNA-seq data from NRG-LU005. A previously developed and locked bioinformatic protocol will be used for this approach as described (Motzer et al, Cancer Cell 2020). A random forest machine learning algorithm was trained on data from IMpower133 to develop a classifier to predict each of the subtypes in prospectively collected data. As input, the classifier uses gene expression of the most variable genes identified in IMpower133 to predict classes in subsequent data. Input data are first normalized (z-score transformed) to ensure similar scale as the training data (IMpower133) and the classifier assigns each new sample (NRG-LU005) a probability of each SCLC subtype. The SCLC subtype with the maximum probability is then assigned to the sample. This algorithm has been previously trained on IMpower133 and tested on SKYSCRAPER-02 and SKYSCRAPER-02C and is fully locked for deployment on additional data.

<u>Blood SCLC molecular subtyping:</u>
Due to the challenges in obtaining tumor biopsies for molecular profiling, there is an urgent need to develop non-invasive diagnostic methods that can identify patients who are more likely to benefit from anti-PD-L1 therapies. Recently, Chemi and colleagues reported on a genome-wide DNA methylation profiling method to detect the different transcription factor molecular subtypes via liquid biopsy (e.g. plasma). They found that their cfDNA methylation method discriminated between transcription factor SCLC subtypes.

We will test their methylome profiling assay by performing unsupervised DNA methylation analysis from cfDNA isolated from patient plasma (stored at Foundation Medicine). Batch effect removal pre-processing using the limma R package (or similar software) will be performed before centering beta-values and applying PCA. Then, bioinformatics analysis will be completed to assign SCLC subtypes to each patient's plasma (e.g. ASCL1, NEUROD1, POU2F3 subtypes). We hypothesize that the ASCL1 (SCLC-A), NEUROD1 (SCLC-N), and POU2F3 (SCLC-P) subtypes will benefit less from atezolizumab and chemoradiation compared to SCLC-I (or "triple-negative" molecular subtype) by demonstrating lower PFS.

SCLC subtypes will be assigned using a cell-free DNA methylation-based assay from plasma samples from NRG-LU005. The final assay and bioinformatic pipeline will be fully trained and tested using samples from IMpower133 using the RNA-seq based subtype assignment as ground truth prior to application to samples from NRG-LU005. As previously demonstrated by several groups cell-free DNA assays can accurately identify SCLC subtypes from plasma (Heeke et al, Cancer Cell 2024; Chemi et al Nature Cancer 2022). We are currently training and testing an approach that uses, but is not limited to, cfDNA methylation to predict SCLC subtypes non-invasively. cfDNA is enzymatically converted to identify methylated regions and differentially methylated genomic regions between SCLC subtypes are used to develop a machine learning based classifier to prospectively assign samples. Additional analytes from the same plasma samples that may boost classification performance are also being assessed, such as cfDNA whole genome sequencing to identify differentially fragmented genomic regions as well as circulating proteomics. Using match tissue and plasma samples from IMpower133, a suite of machine learning algorithms (LASSO, random forest, ridge regression, elastic net) are being tested to assess classification performance using the cfDNA methylation-based assay. Once an optimal classifier has been developed, this algorithm will be locked for deployment on subsequent samples (NRG-LU005). NRG-LU005 samples with matched tissue and plasma samples will be the first validation of this approach.

The current plan is to perform the methylome assay at Freenome (San Francisco, CA). This testing will require blood samples that sites will collect and ship ambient overnight. The plasma will be isolated and stored temporarily at Precision for Medicine until the primary analysis.

Correlation (and degree of agreement) between tumor (RNA-Seq) and blood (methylome) molecular subtyping will also be determined.

10.3 Biospecimen Submission Tables (10-JUL-2024)

10.3.1 Mandatory Specimen Submissions

This study includes mandatory collection of biospecimens for future integrated analyses. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate

background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

See detailed specimen collection/processing/shipping instructions on the protocol-specific page of the CTSU website.

Mandatory Specimen Collection #1: Central Confirmation of Tumor and integrated correlative studies on tissue. After central review of tumor tissue is performed, for patients who consent to tissue banking, the following assays may be performed using available/ remaining FFPE tissue: RNA sequencing (first 112 patients only), for tissue molecular subtyping.

- H&E stained slide with tumor must be submitted and will be used to retrospectively confirm the diagnosis of small cell carcinoma, as well as be used for correlative tissue studies.
- If review of submitted H&E slide is inadequate, a new H&E slide may be requested from the corresponding tissue block and immunohistochemical stains may need to be performed including use of standard neuroendocrine markers to confirm a diagnosis of small cell lung cancer.
- If sending an FFPE block, tumor cell content should be >20% and at least 50 tumor cells in the specimen (as assessed by a corresponding H&E slide cut from the block). If punch cores are sent instead, please ensure that these cores are taken from viable, non-necrotic portions of tumors (as assessed with a corresponding H&E slide cut from the block).
- Required Forms: ST form and pathology reports with study and case number date of procedure, pathology accession number; any other personal health information (PHI) should be redacted by sites before sending.
- Shipping costs: Submitting site pays cost of shipping FFPE samples, and pays for returns. Sites can ship FFPE material Monday-Friday.
- Residual Material: H&E slides and blocks will be retained at the bank unless needed for immediate patient care.

Ship all FFPE biospecimens for central review for this trial to:
NRG Oncology Biospecimen Bank–San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115

415-476-7864; FAX 415-476-5271
NRGBB@ucsf.edu

QUESTIONS: Call or email the NRGBB-SF.

Mandatory Specimen Type	Collection Time Points	Collection Information and	Shipping

		Requirements	
One H&E slide from primary tumor - can be from a lymph node or an FNA only if a corresponding FFPE block is available.	Pre treatment	H&E Slides can be diagnostic or duplicate cut slides. Bank retains all slides unless otherwise requested for patient care.	Slides shipped ambient temperature to NRGBB-SF
FFPE Block (required only for patients who consent to banking)	Pre treatment	Corresponding FFPE Block (recommended). If site is unable to submit a Block then the following alternative is acceptable Two or three 2mm (or 3mm) punches (tumor size dependent) embedded in paraffin* with a corresponding H&E (punch kits available from NRG BB-San Francisco) Unstained slides are not acceptable.	Ship by overnight carrier to NRGBB-SF (use cold packs during warm weather)

*For sites with the capability to do so, the two to three mm punch biopsies should be embedded into one new paraffin block from which an H&E slide should be obtained. The constructed block containing the punch and the H&E slide must then be submitted to the NRGBB-SF along with the original H&E slide. Alternatively, sites can either 1) send the block to the Biospecimen Bank, and the bank will punch and embed the blocks for the sites before returning them, or 2) send the two to three punches to the bank to be embedded by the Biospecimen Bank.

<u>Mandatory Specimen Collection #2:</u> For integrated blood molecular subtyping and frozen whole blood for sequencing control.

- Specimen #1: 20 mL blood in BCT tubes must be collected (minimum 10 mL) and sent within 24 hours of collection, to Precision for Medicine (PM) (see Appendix V below for details). Plasma will be isolated, stored temporarily at PM and shipped back to the NRG biospecimen bank for all patients. Specimens will be used to identify whether tumor molecular subtyping from blood (cfDNA methylome profiling) can predict response to atezolizumab.
- Specimen #2: 5 mL whole blood as a control will need to be collected in K2-EDTA tubes, aliquoted into cryovials on the same day as collection, and stored frozen. Frozen whole blood will be shipped to the NRGBB-SF in batches.
- Required Forms: Study-specific ST form for Specimen #1, regular NRG ST form for Specimen #2.

- Materials: For Specimen #1 - BCT tubes and kits and shipping labels can be requested from PM. For Specimen #2 - whole blood kits can be requested from the NRGBB-SF at NRGBB@ucsf.edu. Allow 10 business days for materials to arrive. Sites must have IRB approval before requesting materials. US and Canadian sites will receive one prepaid return label provided for each case (for batch shipping of frozen biospecimens only). Sites in Japan are to provide their own shipping containers and should store Specimen #2 at -80°C and then batch ship samples from multiple patients.
- Shipping costs: None. Genentech covers all shipping costs.
  Ship Specimen #1 (per instructions in Appendix V below) to:

US Sites:

ATTN: [redacted]
Precision for Medicine (PM)
8425 Precision Way
Frederick, MD 21701
RepositoryServices.Mailbox@precisionformedicine.com

Sites in Japan:

National University Hospital (S) Pte Ltd
c/o NUH Tissue Repository
5 Lower Kent Ridge Road
Main Building Level 3
Singapore 119074
Precision-APAC@precisionformedicine.com

Samples can be shipped to Precision for Medicine on Friday for Saturday Delivery. Please do not ship samples on Saturday, Sunday, or the day before a nationally recognized holiday.

Ship Specimen #2 to:
NRG Oncology Biospecimen Bank–San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
415-476-7864; FAX 415-476-5271
NRGBB@ucsf.edu

****NOTE: Ship whole blood specimen #2 to NRG Biobank on Monday to Wednesday. Do NOT ship days before a nationally recognized holiday. Check NRG broadcasts for other closures.**

Mandatory Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
WHOLE BLOOD (Specimen #1): 20 mL of	Pre treatment	Forms: Study-specific ST form	**US Sites:** Ship ambient by

fresh blood (to yield ~10 mL of plasma after processing by Precision for Medicine) in BCT tubes and shipped within 24 hrs of collection.		Kits: request from PM **Shipping:** **US Sites:** One prepaid FedEx label provided by PM. Can be shipped with optional specimens in 10.3.2 **Sites in Japan:** Instructions for shipping via QuickStat to be included in Precision for Medicine lab manual. Lab manual will be provided electronically to the sites. Can be shipped with optional specimens in 10.3.2.	Priority Overnight Courier to Precision for Medicine (for details, see Appendix V below) **Sites in Japan:** Ship ambient by QuickStat to National University Hospital for details, see Appendix V below)
WHOLE BLOOD (Specimen #2): 5 mL of anticoagulated whole blood in K2-EDTA tubes	Pre treatment	Forms: ST Form Specimens: Whole blood samples containing a minimum of 1.5 mL per aliquot in three 2 mL cryovials, frozen and stored at -80°C. Can be batch shipped to NRGBB-SF.	**All sites:** Ship frozen on dry ice by Priority Overnight Courier to NRGBB-SF **Sites in Japan:** Batch ship samples from multiple patients

10.3.2 Optional Specimen Submissions

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

This study includes optional collection of biospecimens for future analyses, for example to assess biomarkers in association with treatment complications. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

See detailed specimen collection/processing/shipping instructions at on the protocol-specific page of the CTSU website.

Optional Specimen Collection #1 for Tissue Biobanking for Potential Future Research
Forms: ST Form, pathology report with accession number and date of procedure visible. All other PHI information should be redacted.

- For patients who consent to banking, the tumor block that corresponds to the mandatory H&E stained slide, lymph node block, or FNA cell block is required and can be returned upon request for immediate patient care.
- Two to three punch biopsies (2-3 mm in size) of the paraffin block may be substituted in place of the FFPE block. The punches should be embedded into a new block and submitted with a new H&E. Original H&E must still be submitted for central review.
- An FFPE cell block from fine needle aspiration of the primary tumor or from lymph node tissue may be submitted instead of primary tumor block if sufficient tumor cells are present.

FFPE Punch Kits: can be requested at the same time as blood kits from the NRGBB-SF at NRGBB@ucsf.edu. Allow 5-10 business days for kits. Sites must have IRB approval before requesting kits.
Shipping: Sites pay for FFPE shipments. Sites can ship FFPE samples Monday-Friday.

Ship specimens to:
NRG Oncology Biospecimen Bank – San Francisco
UCSF – Dept of Radiation Oncology
2340 Sutter Street- Room S341
San Francisco, CA 94115

For questions, please contact the San Francisco Bank at:
Email: NRGBB@ucsf.edu
415-476-7864/Fax 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements/ Instructions for Site	Shipping

H&E slide(s) of primary tumor	Pre treatment	Can be same material as for central review in Section 10.1	Ship ambient temperature to NRGBB-SF by overnight courier
FFPE Block of primary tumor (same as H&E)	Pre treatment	Site should make every effort to submit the block for this study. Can be same material as for central review in Section 10.3.1 If site is unable to submit a Block then the following alternative is acceptable: Two or three 2mm (or 3mm) punches (tumor size dependent) embedded in paraffin* with a corresponding H&E (punch kits available from NRG BB-San Francisco) Note: Unstained slides are not acceptable.	Ship ambient temperature by overnight carrier to NRGBB-SF (use cold packs during warm weather)

*The NRGBB-SF can embed the punches for sites without the facilities to embed punches into blocks.

Optional Specimen Collection #2 for Plasma and PBMC Biobanking for Potential Future Research

Sample Size: Testing will be performed on materials from 90 patients who contribute samples at all three timepoints (baseline, day one after CRT and at three months post CRT). To ensure that we have 90 patients with submissions at all three timepoints we will collect specimens from the first 180 patients that consent to participate in this optional collection.

Forms: Study-specific ST form.

Kits and Shipping: All necessary materials for shipping (including blood collection tubes and prepaid FedEx labels) can be obtained from Precision for Medicine. Please contact [redacted]) to arrange for delivery of materials. Sites must have IRB approval prior to requesting kits.

Ship samples (per instructions in Appendix V below) to:

US Sites:
ATTN: [redacted]
Precision for Medicine

8425 Precision Way
Frederick, MD 21701
RepositoryServices.Mailbox@precisionformedicine.com

Sites in Japan:

National University Hospital (S) Pte Ltd
c/o NUH Tissue Repository
5 Lower Kent Ridge Road
Main Building Level 3
Singapore 119074
Precision-APAC@precisionformedicine.com

For questions, please contact Precision for Medicine at the email above.

Samples can be shipped on Friday for Saturday Delivery. Please do not ship samples on Saturday, Sunday, or the day before a nationally recognized holiday.

Specimen Type	Collection Time Points	Collection Information and Requirements/ Instructions for Site	Shipping
WHOLE BLOOD FOR PLASMA ISOLATION Approximately 20 mL in BCT tubes and shipped within 24 hrs of collection	Pre treatment Day 1 after completion of CRT** 3 months after end of CRT**	Forms: Study-specific ST form Kits: request from PM Shipping: **US Sites:** One prepaid FedEx label provided by PM. **Sites in Japan:** Instructions for shipping via QuickStat to be included in Precision for Medicine lab manual. Lab manual will be provided electronically to the sites.	**US Sites:** Ship ambient by Priority Overnight Courier to Precision for Medicine (for details, see Appendix V below). **Sites in Japan:** Ship ambient by QuickStat to National University Hospital (for details, see Appendix V below).
WHOLE BLOOD FOR PBMC ISOLATION: ~10 mL of whole blood in K2 EDTA tubes and shipped within 24 hrs of collection	Pre treatment Day 1 after completion of CRT** 3 months after end of CRT**	Forms: Study-specific ST form. Kits: request from PM Shipping: **US Sites:** One prepaid FedEx label provided by PM. Can be shipped with optional specimens in 10.3.2.	**US Sites:** Ship ambient by Priority Overnight Courier to PM. For details, see Appendix V below. **Sites in Japan:** Ship ambient by QuickStat to National University Hospital (for details, see

		Sites in Japan: Instructions for shipping via QuickStat to be included in Precision for Medicine lab manual. Lab manual will be provided electronically to the sites.	Appendix V below).

Completion of CRT defined as the end of the last cycle of chemotherapy (e.g. day 21, cycle 3 of platinum/etoposide protocol infusion). **NOTE: do not collect/submit samples from patients who do not have a baseline sample.

11. SPECIAL STUDIES (NON-TISSUE)

11.1 Quality of Life (QOL) and Patient-Reported Outcomes (PROs)

11.1.1 Background

Health-related QOL is an important endpoint in clinical trials to assess treatment effect from the patient's perspective using PROs. In this study, atezolizumab will be given concurrently with chemoradiation and will continue for a full year. If the atezolizumab arm shows superior OS, a new standard of care will be defined for limited stage small cell lung cancer. The effects of atezolizumab combined with CRT on QOL are currently unknown. This study provides a unique opportunity to study the effects of immunotherapy on QOL. It is anticipated that atezolizumab will improve OS while maintaining a reasonable toxicity profile. Given the high degree of symptom burden of small cell lung cancer, characterized by central and often obstructing primary tumors, improvements in PFS and OS with immunotherapy are likely to correlate with QOL with less cancer-related symptomatology. The hypothesis for this study is that long-term QOL using FACT-TOI at 15 months from the end of CRT (~ 3 months from completion of immunotherapy for patients receiving atezolizumab) will be superior in the CRT plus atezolizumab arm compared to the CRT alone arm as the addition of atezolizumab is expected to improve tumor response to CRT and thereby improve QOL.

11.2 Assessments (01-OCT-2019)

FACT-TOI

In order to analyze the difference in QOL between all arms, we plan to use a brief, validated instrument that is user friendly and has clinical relevance. FACT-TOI is a measure of 21 items that sums the functional well-being (FWB), physical well-being (PWB), and the lung cancer subscale (LCS) of the Functional Assessment of Cancer Therapy – Lung (FACT-L) QOL instrument, which has been extensively used for measuring QOL in patients with lung cancer. In a review of literature reported that the FACT-L scale has been used in more than 5,000 patients and has been found to be sensitive to changes in performance status, treatment response. FACT has been translated into many languages and is available free of charge to institutions with the completion of an agreement to share data, accessible at http://www.facit.org/translation/licensure.aspx. This instrument has not only been shown to be prognostic for survival, but also sensitive to changes in QOL on serial evaluations throughout treatment. Importantly, the FACT-TOI has been associated with clinically meaningful changes in patients with lung cancer. The lung cancer sub-scale (LCS) consists of 9 items, involving lung cancer specific symptoms. All items are rated

on a 5-item (point) Likert Scale, from 0 (not at all) to 4 (very much). It has been determined that a 5-point difference on the FACT-TOI is associated with a meaningful difference in clinical and subjective indicators. Thus, a difference of 5 points will be considered clinically significant. Handling of missing data will be in accordance with the FACIT Administration and Scoring Guidelines, described at www.facit.org.

The full FACT-L questionnaire can be completed in less than 10 minutes. Patients will complete the FACT-TOI at the time points described in Section 4.

Fatigue in NSCLC patients receiving CRT and immunotherapy

In clinical studies investigating immunotherapy, the most common toxicity described is fatigue. Other toxicities include dermatologic toxicity, gastrointestinal, symptoms (diarrhea/colitis, decreased appetite). Rare immunologic mediated toxicities from immunotherapy have been described and include pneumonitis and endocrinopathies (pituitary, hypothalamus, thyroid, and adrenal disease). These immune-mediated toxicities may present with nonspecific symptoms such as fatigue, headache, mental status changes, abdominal pain, change in bowel habits, or hypotension. In lung cancer, fatigue is one of the most common and distressing symptoms affecting up to 60% of patients. With concurrent chemoradiation, the majority of patients experience fatigue usually peaking during the first and second weeks after completion of CRT, which can remain higher than baseline in approximately half of patients long-term. Because approximately 25% of patients undergoing immunotherapy alone experience fatigue, the effect of immunotherapy with CRT on patient-reported fatigue warrants study.

Hence a secondary objective is to evaluate patient reported fatigue using the PROMIS fatigue short form in patients receiving atezolizumab concurrently and following chemoradiation for lung cancer. We acknowledge that the data around fatigue in patients undergoing chemoradiation plus immunotherapy is minimal, and we believe measuring fatigue in a systematic way will inform future trials that study chemoradiation and immunotherapy combinations.

PROMIS-Fatigue: A Novel Short Form Fatigue Scale

The National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) Roadmap initiative (www.nihpromis.org) was initiated. PROMIS is a 5-year cooperative group program of research designed to develop, validate, and standardize item banks to measure patient-reported outcomes (PROs) relevant across common medical conditions, including cancer [Cella, 2007; Garcia, 2007]. Integral to the work of this group is the creation of a PROMIS-derived fatigue short form (using limited questions to minimize patient burden) that was developed for ease of use in oncology populations. While the psychometric properties of this 7-question short fatigue scale have been validated in the general population [Garcia, 2007; Lai, 2008], validation in patients with cancer is ongoing. A “cross-walk” has been successfully developed between the PROMIS fatigue item bank and the PROMIS-Cancer fatigue item bank that produced the short form measure. These two item banks, sharing 54 common items, were linked by equating item parameters using items that held stable psychometric properties between the cancer and general population

populations in which they were tested. Results showed that cancer patients reported more severe fatigue (1/3 standard deviation more severe, but the same scale characteristic curve slope) than the general population, which matches clinical expectations [Cella, 2008].

This 7-question short fatigue scale can be completed in a few minutes. The PROMIS fatigue will be completed at the time points described in Section 4.

EuroQol (EQ-5D-5L)

The EuroQol (EQ-5D) is a well-accepted instrument to measure generic health status and QOL and has been used widely for economic evaluation that compares the cost and benefit of health care interventions (Pickard 2007). The EQ-5D-5L will be used to assess quality-adjusted life-year (QALY) and potentially for future cost-utility analysis for this study. The EQ-5D-5L is a two-part questionnaire and has been translated into multiple languages. The first part is the descriptive system and consists of 5 items covering 5 dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension can be graded on 3 levels including: 1-no problem, 2-moderate problems, and 3-extreme problems. The score from the descriptive system will be converted into a single index value to compare the health status. The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20 cm, 10 point-interval scale. Either the index score or the VAS score can be used in the QALY analysis that will inform economic evaluation of interventions (Wu 2002). Additionally, the benefit of using QALY is that the QALY can be compared to the outcomes of other interventions across disease sites and can be used by health policy makers to rank interventions.

Protocol-eligible patients will be included in the quality-adjusted survival analysis only if they have provided baseline and at least 1 subsequent measurement.

The EQ-5D-5L can be completed in 5 minutes (Schulz 2002). Patients will complete the EQ-5D-5L version at the time points described in Section 4.

Form QOL should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. Once the questionnaires are completed by the patient, the staff member should review it to ensure that no items were unintentionally left blank. When absolutely necessary, it may also be administered by mail or phone. Upload the completed form onto the Quality of Life Completion Form in Medidata Rave.

Quality of Life (QOL) and Patient-Reported Outcome instruments will be assessed at time points described in Section 4. Note the baseline assessment in the context of QOL/PRO component is defined as prior to study entry, occurring within 7 days prior to initiation of protocol treatment.

11.3 Administration of NRG-LU005 Patient-Completed Questionnaires

11.3.1 Time Points for Administration: See Section 4.

11.4 Patient Population (22-FEB-2021)

All patients enrolled in NRG-LU005 who read English, French, Spanish, or Japanese and who have completed the baseline questionnaire will be required to participate in the QOL study.

11.5 Additional Toxicity Monitoring with PRO-CTCAE (03-AUG-2022)

Patient-reported symptomatic AEs will be evaluated using select PRO-CTCAE items. Twenty-one PRO-CTCAE items have been selected based on literature, including the most common side effects of concurrent chemoradiation for lung cancer patients (Koming et al., 2013; Verma et al., 2017), the most common and potential side effects of Atezolizumab (Ramos-Esquivel et a., 2017), and a core set of symptoms recommended by the NCI's Symptom Management and Health-Related Quality of Life Steering Committee for adult cancer patients (Reeve et al., 2014). Please refer to the Section 7.7 for the list of the PRO-CTCAE items.

11.6 Administration of PRO-CTCAE

Time points for Administration

Patients will complete the PRO-CTCAE at the time points described in Section 4.

Recall period

A 1-week recall period (time period over which patient recalls specific symptoms) will be used for all PRO-CTCAE data collected.

11.7 PRO-CTCAE Patient Population (22-FEB-2021)

All patients enrolled in NRG-LU005 who read English, French, Spanish, or Japanese and who have completed the baseline PRO-CTCAE questionnaire will be required to participate in the PRO-CTCAE study. After responding to the initial baseline questions, patients will have the option to complete the remainder of the survey by paper or electronic device (except patients who read French or Japanese who must complete the PRO-CTCAE on paper.)

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews (18-SEPT-2020)

The Principal Investigator, Kristin Higgins, MD, or Radiation Oncology Co-Chairs [redacted] MD or [redacted] MD, PhD will perform an RT Quality Reviews.

Pre-treatment reviews of the first 3 patients enrolled from each institution are required PRIOR TO DELIVERY of radiation treatment. The patient cannot start treatment until the site has received approval from the Imaging and Radiation Oncology Core (IROC)-Philadelphia RT. The Pre-Treatment Review process requires 3 business days from the receipt of **complete data** via TRIAD.

The Principal Investigator or Radiation Oncology Co-Chairs will perform an RT Quality Assurance Review on an ongoing basis once complete RT data is received at NRG Headquarters for the remainder of enrolled cases.

12.2 Medical Oncology Modality Quality Assurance Reviews (18-SEPT-2020)

The Medical Oncology Co-Chairs, [redacted] MD and [redacted] MD PhD, will perform a Modality Quality Assurance Review of all patients who receive or are to receive systemic treatment in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of systemic treatment data. The scoring mechanism is: **1) Per Protocol, 2) Acceptable Variation, 3) Unacceptable Deviation, and 4) Not Evaluable**.

Drs. [redacted] will perform a Quality Assurance Review after NRG Headquarters has received complete data for the first 20 cases enrolled. Dr. [redacted] and [redacted] will perform the next review after NRG Headquarters has received complete data for the next 20 cases enrolled. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as NRG Headquarters has received complete data for all cases enrolled, whichever occurs first.

13. DATA AND RECORDS

13.1 Data Management/Collection (10-JUL-2024)

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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; 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 a 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 individuals 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 the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. 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.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user) will be automatically accepted and study access in Rave will be automatically granted for the site user. Account activation instructions are located on the CTSU website in the *Data Management* section under the Data Management Help Topics >Rave resource materials (*Medidata Account Activation and Study Invitation*). Additional information on iMedidata/Rave is available on the CTSU members' website in the *Data Management > Rave* section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

PRO-CTCAE items will be collected using ePRO for patients who read English or Spanish. The patient will use personal hand-held devices or tablets. Once a patient submits the responses, the data goes directly from the device into the Rave database. There are no documents to audit. The electronic responses are the source documentation. Patients who read French or Japanese will complete the PRO-CTCAE on paper.

13.2 Data Quality Portal (13-NOV-2023)

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 who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data using via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on

the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

13.3 Rave-CTEP-AERS Integration (03-NOV-2022)

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.**

Pre-existing medical conditions (formerly referred to as baseline AEs) identified during baseline assessment are not considered AEs and therefore should not be reported on the Adverse Event form. If these pre-existing conditions worsen in severity, the investigator must reassess the event to determine if an expedited report is required. Whether or not an expedited report is required, the worsened event should be reported as a routine AE.

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 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.

13.4 Summary of Data Submission (22-FEB-2021)

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 the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Sections 7.9 and 7.10 for information about expedited and routine reporting. PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

Summary of Data Submission: Refer to the CTSU website.

See Section 8.4 for TRIAD account access and installation instructions. See table below for RT data submission details.

DICOM files to export from Treatment Planning System to TRIAD	• DICOM Planning CT • DICOM Baseline PET or PET/CT (used for tumor volume delineation) • DICOM RT Structure • DICOM RT Dose • DICOM RT Plan	**Due Within 1 week of start of RT unless pre-treatment review is required for first 3 cases enrolled** **TRIAD Time Point:** ***RT Digital Plan***
All required structures must be labeled per the tables in Sections 5.2.4 and 5.2.5		
Upon submission of the RT digital data via TRIAD, complete an online **Digital Data Submission Information Form (DDSI)**: https://www.irocqa.org/Resources/TRIAD		
NOTE: ALL SIMULATION AND PORTAL IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.		

See Diagnostic Imaging submission table for TRIAD below.
All Diagnostic Imaging Submissions require **Clinical Image Submission Form (CISF)** completion in iMedidata RAVE for corresponding timepoints**.**

DICOM files to export to TRIAD	**Pre-Treatment Assessment Imaging**	**TRIAD Time Point:**
	• **PET/CT** for staging (including tumor measurements) • **CT Chest/CT Abdomen with IV contrast** • **Brain MRI with contrast** (preferred) or **Brain CT with contrast** (allowable if there is a contraindication to MRI)	• **Baseline**
	End of CRT Imaging	
	CT Chest with IV Contrast (through adrenals)	• **End of CRT**
	F/U Imaging*	
	• **CT chest** (through adrenals)/ **CT abdomen with contrast** • **Brain MRI with and without contrast or brain CT with contrast (allowable if there is a contraindication to MRI)****	• **Post CRT** o Months or Years
***Follow Up Imaging:** Q 3 mos x 2 years (+/- 2 weeks) then Q6 mos in year 3 (+/- 3 weeks). Then annually (+/- 4 weeks), unless otherwise indicated. Please refer to section 4. ****Brain MRI in follow up** – Year 1: Q3 mos. Year 2: Q6 mos. Then as clinically indicated.		

***Note*:** **Please refrain from anonymizing the DICOM header of any exam prior to uploading into the TRIAD application.** Custom DICOM editing can exclude an exam from final analysis, due to the omission of technical data elements. These elements include, but are not limited to: study/series name, study date, unit station name, unit serial number, and all image acquisition parameters. TRIAD has been uniquely configured to locate and de-identify all PHI from the NRG-LU005 DICOM headers, prior to the image transfer to ensure the anonymity of our trial patients.

13.5 Enhanced Centralized Data Monitoring (22-FEB-2021)

In addition to the NCI guidelines for auditing clinical trials for the National Clinical Trials Network (NCTN) Program, NRG will perform enhanced centralized monitoring of the components listed below.

13.5.1 Quality Assurance Enhancements

- *Site Initiation Visit*

The study initiation will be conducted via video/webinar. The link to a secure web site is posted on the CTSU website and available for all NCTN Member Institutions. It is mandatory that the Principal Investigator (PI) (the PI on the IRB documentation) and at least one research associate (RA) view the initiation video.

During the site initiation video, at a minimum, the following activities are included:

- An in-depth review of the protocol using a lecture format.
- Presentation of study requirements and procedures including, but not limited to: study objectives, study design, eligibility criteria, enrollment procedures, schedule of evaluations, criteria for patient discontinuation, adverse event reporting (definitions, SAE reporting procedures), study drug administration, study time frame, drug ordering, blood and tumor sample submission requirements (if applicable), and laboratory procedures;
- Discussion of the structure of the auditing/monitoring process for the Study;
- Discussion of the patient enrollment procedures;
- Discussion of the importance of maintaining adequate source and regulatory documents;
- Review of Electronic Case Report Forms and completion guidelines including visit-specific pages, correction procedure, patient identification numbers, and the data query resolution process;
- Review of the NRG Oncology contact list;
- Discussion of the Drug Accountability Log requirements;
- Documentation of all attendees by obtaining a signed confirmation of completion from the attendees

13.5.2 Centralized Monitoring (CM)

Central Monitoring (CM) Review is required for this protocol. 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). **All source documents must be provided in English.** 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 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).

Eligibility
The source records which document the eligibility for the first two patients randomized to each arm (e.g., Arm 1 and Arm 2), then every 10th patient randomized to each arm enrolled from each site (as identified by a unique NCI identifier) will be reviewed for 100% completeness and consistency with the eligibility criteria, the data reported during the enrollment process and the data reported on the case report forms (CRFs). Documents are to be submitted within two weeks of subject enrollment.

In the event that this monitoring identifies unacceptable enrollment procedures or significant deviations from eligibility criteria, then the site will need to submit a corrective action plan within two weeks of being notified of the findings of the centralized monitoring. The source records for the eligibility and treatment for the next individual enrolled to the study from the site are again to be submitted and reviewed. In the event of significant repeated deviations from the protocol, accrual at the site may be suspended per discretion of the overall Study Chair.

The pretreatment documents to be reviewed include:

- Pathology Report to document the stage and histology of the primary tumor.
- Documentation of dates and agents administered for the first cycle of chemotherapy pre study registration
- Documentation of baseline tumor measurements per RECIST
- All Baseline imaging reports to confirm the presence of RECIST measurable disease.
- Medical history to include history of prior malignancy, prior radiotherapy to lungs, mediastinum prior corticosteroid use and other chronic/acute conditions and/or comorbidities. physical examinations records and laboratory results, including all blood and urine tests,
- Documentation pleural effusion absence/presence with cytological findings if present
- Signed and dated informed consent form. In addition to review of signatures, version, and patient responses to consent form questions, the first consent form for each site will be reviewed for content. If a new version of the protocol results in modifications to the consent form, then the first consent form for a patient enrolled under the new version will also be reviewed for content.

Drug Accountability, Drug-Dose Compliance and Adverse Events
As in the eligibility review, the source records and adverse events (AEs) during *the **first two cycles*** of treatment for the patients enrolled from each site (as identified by a unique NCI identifier) will be reviewed for compliance with the protocol, completeness and consistency with the data reported on the case report forms, and drug accountability records. The documents listed below should be submitted at two time-points: (1) within two weeks of beginning the second cycle of treatment (for records and AEs during the first cycle of treatment), and (2) within two weeks of beginning the third cycle of treatment (for records and AEs during the second cycle of treatment).

In the event that this monitoring identifies unacceptable procedures or significant deviations from protocol procedures, then the site will need to submit a corrective action plan within two weeks. The source records for the first two cycles of treatment for the

next individual enrolled to the study from the site should then again be submitted and reviewed. In the event of significant repeated deviations from the protocol, accrual at the site may be suspended per discretion of the overall Study Chair.

The documents to be reviewed include:

- Study drug orders treatment dose calculations and administration records.
- Reports from protocol-directed laboratory studies.
- Reports from any additional tests performed to document an adverse event.
- All progress notes relating to AE assessments
- Pharmacy drug accountability records.
- Summaries of hospital admissions and discharge for hospitalizations.

13.5.3 Enhanced Consent Form Review **(01-OCT-2019)**

Central review of the consent form for the essential elements of informed consent (as defined by the Department of Health and Human Services Office for Human Research Protection) for the first signed consent form and signed amended consent forms (when required by protocol amendment) submitted from each site (as identified by a unique NCI identifier) will be performed in real time after first patient entry.

13.5.4 Enhanced Record Review - Audit Visits **(01-OCT-2019)**

The enhanced record review will be conducted by the NRG SDMC at any NCTN institution which enrolled a patient on the Study.

- *Time of Site Visit Audits*

  During the audit visits that occur under the CTEP audit procedures, additional cases will be reviewed to ensure that all sites that enrolled patients to the Study will be selected for review.

- *Additional On-Site Audit*

  In addition to the regularly scheduled audit per CTMB guidelines, an additional audit will be conducted within two years of the anticipated date when the study is expected to mature for the final analysis. Sites that enrolled fewer than eight subjects may be audited remotely.

13.6 Global Reporting/Monitoring (01-OCT-2019)

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP website http://ctep.cancer.gov/reporting/cdus.html).

This study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design (13-NOV-2023)

The study is an open-label, randomized, phase III trial to evaluate the addition of

atezolizumab to standard chemoradiation for limited stage small cell lung cancer. Randomization will occur in a 1:1 ratio through use of a permuted-block randomization method. Patients will be randomly assigned to one of two treatment arms: chemoradiation alone (Arm 1) or chemoradiation plus atezolizumab (Arm 2). The randomization scheme is designed to ensure that an approximately equal number of patients will be enrolled in each treatment arm within the baseline characteristics of the following stratification factors:

- Radiation schedule, BID (3 weeks) vs daily (6.5 weeks)
- Chemotherapy (cisplatin vs carboplatin)
- Sex (male vs female)
- ECOG Performance Status (0/1 vs 2)

14.2 Study Endpoints (10-JUL-2024)

14.2.1 Primary Endpoint

The primary endpoint is overall survival (OS), which is defined as the time from randomization to the date of death due to any cause.

14.2.2 Secondary Endpoints

- Progression-free survival
- Toxicities as measured by the CTCAE v.5.0
- Objective response rate
- Local control
- Distant metastases free survival
- Quality of life as measured by the FACT-TOI
- Quality-adjusted survival using scores from the EQ-5D-5L
- Fatigue as measured by the PROMIS

Molecular subtyping as integrated markers

14.2.3 Exploratory Endpoints

- Patient-reported symptomatic toxicities (PRO-CTCAE)

14.3 Primary Objectives Study Design (03-AUG-2022)

14.3.1 Primary Hypothesis and Endpoints

The primary objective of this randomized phase III trial is to determine whether addition of atezolizumab to concurrent chemoradiotherapy will improve OS compared to standard chemoradiotherapy for patients with LS-SCLC.

Based on the CONVERT trial (Faivre-Finn et al, 2017) and the most recent data for combined modality therapy outcomes, we assume the median OS in the control arm will be 27 months. In regards to the effect size, a hazard ratio (HR) of 0.71 is hypothesized for OS (approximately equivalent to improving the median OS from 27 months to 38 months [H1]). We believe the effect size for OS is supported by prior immunotherapy studies utilizing atezolizumab in NSCLC. The phase III OAK study, which compared atezolizumab versus docetaxel in patients with stage IIIB or IV NSCLC with disease progression after platinum-based therapy and which established the role of atezolizumab in stage IV NSCLC, demonstrated an improvement in OS with atezolizumab compared with docetaxel, with a HR of 0.73; 95% CI, 0.62-0.87 (p=0.0003).

14.3.2 How Primary Endpoints Will Be Analyzed

OS is defined as the time from randomization to death due to any cause. Patients without documented death at the time of analysis will be censored at the date of last known contact. The primary analysis for OS will be performed on an intent-to-treat (ITT) basis, such that all randomized cases will be included in the treatment arm to which they were randomized regardless of what treatment the patients actually received. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, and efficacy outcome research.

The definitive phase III analysis of OS will occur when at least 315 deaths are available, and the study will be considered as positive if the log-rank test statistics Z-value > 2.01 ($p < 0.022$), which is the threshold adjusted for type 1 error using group sequential methods.

The survival rates at various timepoints (e.g., every 6 months after randomization) and median OS for each arm will be estimated using the Kaplan-Meier method (1958). 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. In addition, the treatment hazard ratio will be estimated using a stratified Cox regression model (stratifying for randomization stratification factors). If one stratum has less than 10 events, the stratification factor which contains the level with the smallest number of patients will be removed from the stratified analyses. Results from an unstratified analysis will also be provided.

14.3.3 Sample Size and Power Calculations:

The final analysis for OS will occur when at least 315 deaths (full OS information) have been observed. The study will provide at least 85% power to detect a hazard ratio of 0.71 at a 1-sided significance level of 0.025. Assuming exponentially distributed OS and a monthly accrual rate of 10 eligible patients per month (see Section 14.5 below), a study that enrolls a total of 480 eligible patients (uniformly) over 48 months with an additional follow-up of 26 months after the last patient accrual will have ~85% power to detect an improvement in median OS of 27 months in the control arm to 38 months in the experimental arm, using a 1-sided 0.025 level log-rank test. As of June 24, 2022, the study is closed to accrual for sites in the U.S. and Canada, and only open to accrual for sites in Japan. The trial will enroll a total of 545 patients, after accounting for ineligibility or lack-of-data, as well as regulatory requirements in Japan.

14.4 Study Monitoring of Primary Objectives (03-AUG-2022)

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. An interim study summary report will be prepared at each meeting accordingly until the initial study results have been released. In general, the interim reports will contain information about patient accrual rate, a projected completion date for the accrual phase, distributions of pretreatment characteristics and important prognostic baseline variables, and the frequencies and severity of adverse events. The interim reports will not contain the results from the treatment comparisons with respect to the primary or any secondary endpoints, with the

exception of reporting of adverse events. The DMC also will review the study on an "as needed" basis.

To allow adequate protection of the patients in the experimental arm in the event that the experimental regime is clearly harmful, an early "harm" look will be conducted at 25% of the full OS information (corresponding to the time when a total of **79 OS events** have been observed) (Freidlin, Korn and Gray, 2010). Specifically, at this time, we consider the experimental regimen is likely to be safe with respect to OS if the log-rank test statistics Z-value > -1.645 when at least 79 deaths are available. In other words, the trial will stop when the null hypothesis can be rejected in favor of superior efficacy of the *control* arm at the one-sided 0.05 level.

Two interim analyses for both efficacy and futility of OS will occur when approximately 127 and 222 deaths are available (corresponding to 40% and 70% information). The efficacy early stopping boundary is based on the Lan-DeMets implementation of O'Brien-Fleming boundary, and the futility early stopping boundary is based on Freidlin et al (2010) (using the LIB20 criterion). The table below summarizes the analyses to be conducted and the criteria for possible early stopping for efficacy or futility for the primary endpoint.

Analysis	Information Fraction	Cumulative OS Events (Both Arms)	Efficacy Boundary*		Futility Boundary*		Projected analysis time from study activation (months)
			Z >	P <	Z <	P >	
Interim 1	40%	127	3.178	0.0007	-0.0103	0.504	46
Interim 2	70%	222	2.402	0.0082	0.248	0.402	61
Final	100%	315	2.010	0.022	--	--	82

* one-sided p-value

If there are any deviations from the assumptions, group sequential methods will be used to properly adjust for the stopping boundary based on cumulative information. Unless the study is terminated prior to the final analysis, the interim analyses results will not be available to the investigators, sponsor or industry collaborator, nor used to modify the study design or sample size. The results of this analysis will be reported to the NRG DMC for review.

14.5 Accrual/Study Duration Considerations (02-JUNE-2021)

During the first 6 months following activation, little accrual is anticipated while the trial is being approved by institutional review boards (IRBs). We assume a uniform monthly accrual rate of 10.5 patients (10 eligible patients to be randomized) and minimal accrual in the first 6 months for ramp-up. Accrual rates are based on observed enrollment patterns in completed and ongoing RTOG/NRG and Alliance trials in this disease setting.

In the ongoing Alliance CALGB 30610/RTOG 0538, a phase III randomized trial for limited stage small cell lung cancer, the average monthly accrual is approximately 6-7 patients. In the closed RTOG 0212, a phase II/III randomized trial for limited stage small cell lung cancer focusing the use of prophylactic cranial irradiation, the monthly accrual was approximately 4-5 patients. Therefore, with the collective efforts from both NRG Oncology and Alliance, the NCTN accrual infrastructure, as well as patient/caregiver desires for access to immunotherapy, we believe a monthly accrual of 10 patients is a reasonable projection.

Under the alternative hypothesis (H1), the entire study is projected to take approximately 80 months (= 6 months ramp-up + 48 months accrual + 26 months follow-up = ~6.7 years) from study initiation to reach the required 315 deaths.

The above projected study duration is based on the hypothesized design parameters. If the actual study parameters deviate from the hypothesized ones, the actual study duration may be different from the projection. For example, from the results of the CONVERT trial (with a median follow-up of 45 months), it appeared that there may be plateaus in the OS curve beyond 5-years. Should such phenomenon occur, the required number of OS events for the final analysis will not change, but the projected study duration may be longer than currently anticipated. To account for this possibility yet ensuring sufficient OS follow-up, the final OS analysis will occur after observing at least 315 deaths or 5 years after accrual completion, whichever occurs first.

14.6 Secondary or Exploratory Endpoints (10-JUL-2024)

14.6.1 Secondary Hypotheses and Endpoints:

- Progression-free survival
- Toxicities as measured by the CTCAE v.5.0
- Objective response rate
- Local control
- Distant metastases free survival
- Quality of life as measured by the FACT-TOI
- Quality-adjusted survival using scores from the EQ-5D-5L
- Fatigue as measured by PROMIS
- Molecular subtyping as integrated markers

14.6.2 Exploratory Endpoints

- Patient-reported symptomatic toxicities (PRO-CTCAE) Concordance between tumor and cfDNA molecular subtypes

14.7 Definitions of Secondary Endpoints and How These Will Be Analyzed (10-JUL-2024)

14.7.1 Statistical Analysis Plan: Toxicity

The As-Treated (AT) patient population will be used for the analysis of safety data in this study. The AT population consists of all randomized subjects based on the treatment they actually received; patients who do not receive any protocol treatment will not be included

in these analyses.

For each patient, the maximum severity reported for both immune mediated and non-immune mediated adverse events will be used in the summaries. Adverse events will be summarized regardless of relationship to protocol treatment as assessed by the investigator. All adverse events, adverse events leading to withdrawal, interruption or modification of protocol treatment, Grade ≥ 3 adverse events, and serious adverse events will be summarized. Deaths and cause of death will be summarized. The rate of treatment-related adverse events using NCI Common Terminology Criteria for Adverse Events (CTCAE, v.5.0) will be reported with the frequency and severity (e.g., type, grade, and attribution) by arm; the analysis will be performed at the time of the primary endpoint analyses. All adverse events will be classified as either immune or non-immune mediated.

14.7.2 Statistical Analysis Plan: Progression-free survival, Distant metastases-free survival, Local control, Objective response rate

The analyses for all efficacy secondary endpoints will be performed on an intent-to-treat (ITT) basis, and conducted at the time of primary analysis after study closure. The primary analysis occurs when OS meets its final analysis goal (e.g., at least 315 deaths observed if not terminated early), or OS efficacy boundary is crossed and the trial stops early at one of the planned interim analysis.

Progression-free survival (PFS) is defined as the time between the date of randomization and the first date of documented progression as determined by the investigator according to RECIST v1.1, regardless of discontinuation of study drug, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have the PFS event on the date of their death. Subjects who do not progress or die will be censored on the date of their last evaluable tumor assessment as determined with radiographic evidence. Subjects who do not have any on-study tumor assessments and do not die will be censored on the second day of their date of randomization. The rates at various timepoints (e.g., every 6 months after randomization) and medians of PFS for each arm will be estimated using the Kaplan-Meier method (1958). 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. Stratified log-rank test will be used to compare PFS between the treatment arms. Cox proportional hazards model, stratified by the protocol-defined stratification factors, will be used to estimate the HR between the two treatment arms and its 95% confidence interval (CI). Results from an unstratified analysis will also be provided as sensitivity analysis. If >5% of patients receive palliative local therapy or initiate systematic anti-cancer therapy (aka new therapy) without a prior reported progression confirmed by RECIST 1.1, , a sensitivity analysis will be conducted by censoring these patients on the date of their last tumor assessment as determined with radiographic evidence prior to the permanent discontinuation of treatment or the initiation of subsequent anti-cancer therapy or palliative local therapy.

Distant metastases-free survival (DMFS) is defined as the time between the date of

randomization and the first date of documented distant metastases (or failures in a different lung lobe) or death due to any cause, whichever occurs first. Patients with no post-baseline tumor assessment and do not die will be censored on the date of randomization. Local progression occurred prior to distant metastases will be censored on the date of local progression. The rates at various timepoints (e.g., every 6 months after randomization) and medians of DMFS for each arm will be estimated using the Kaplan-Meier method (1958). 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. Stratified log-rank test will be used to compare DMFS between the treatment arms. Cox proportional hazards model, stratified by the protocol-defined stratification factors, will be used to estimate the HR between the two treatment arms and its 95% confidence interval (CI). Results from an unstratified analysis will also be provided. Patients who have not experienced distant metastases (or failures in a different lung lobe) and have not died by the data cutoff date will be censored at the date of the last tumor assessment as determined with radiographic evidence. Local control is analyzed based on time to local progression, defined as the time from randomization to first date of documented local progression, in which a failure is defined as intrathoracic tumor progression (failure in the lobe of the primary tumor or mediastinal lymph nodes) by RECIST 1.1 criteria determined by the investigator. Time to local progression is analyzed as time-to-event competing risks data, where both non-local progression (i.e., distant metastasis or failure in a different lung) and death (without local progression/failure) will be considered as "competing risks". The probability of local progression will be estimated by treatment using Aalen-Johansen estimator of cumulative incidence function. The rates at various timepoints (e.g., every 6 months after randomization) for each arm will be estimated. To account for the competing risks inherent in the comparison of time to local progression between treatment arms, a stratified log-rank test will be computed based on a cause-specific hazard function. HR and 95% CI based on stratified cause-specific Cox regression model will also be estimated.

Objective response rate (ORR) is defined as the proportion of all randomized subjects whose best overall response (BOR) is a confirmed objective response (i.e., Complete Response or Partial Response on two consecutive occasions ≥4 weeks apart) as determined by the investigator according to RECIST v1.. ORR will be compared using a two-sided 5% level Cochran-Mantel Haenszel (CMH) test stratified by the same stratification factors used for randomization. The 95% CI for the difference in confirmed ORRs between the two treatment arms will be computed using the normal approximation to the binomial distribution . The 95% CI of the confirmed ORR will be calculated for each treatment arm using the Clopper-Pearson method

If one stratum has less than 10 events, the stratification factor which contains the level with the smallest number of patients will be removed from the stratified analyses.

14.7.3 Multiplicity Strategy for Primary Endpoint and Secondary Endpoints

To meet regulatory requirements, a multiple testing strategy will be implemented to control the family-wise type 1 error (alpha) for the entire trial. Specifically, upon

achieving statistical significance on the primary endpoint OS, testing of each of the secondary endpoints in the following order sequentially: 1) progression-free survival (PFS); 2) objective response rate (ORR); 3) local control (LC); 4) distant metastases free survival (DMFS); 5

14.7.4 Interim Analysis for Toxicity

In addition to monitoring severe adverse events and unexpected adverse events closely and having them reviewed at the semi-annual DMC meetings, as part of routine study monitoring effort, the following adverse events of interest will be closely monitored by the study team: pneumonitis, pericarditis, esophagitis, and encephalitis. For the first 40 eligible patients randomized to Arm 2 who receive at least one cycle of atezolizumab, the frequency of grade 3 or higher pneumonitis, pericarditis, esophagitis, and encephalitis will be continuously monitored during the safety evaluation.

Special safety interim analyses of grade 3 or higher pneumonitis, pericarditis, esophagitis, and encephalitis that remain unresolved for more than 4 weeks will be conducted when 10, 20, 30 and 40 patients become analyzable (e.g., patients who have been treated with atezolizumab and have been observed for at least 4 weeks). Based on the following Bayesian toxicity monitoring rule, if the rate is considered as concerning, the study team and group leaders will discuss with CTEP about the most appropriate actions to mitigate the potential risks, including a possible major modification to study design or accrual suspension. We assume a priori that Arm 2 has an average toxicity rate of approximately 15% and that there is an approximately 18% chance that the risk will be 30% or higher, which corresponds to a Beta (0.15, 0.85) prior distribution. We then consider the rate of toxicity to be concerning if the posterior probability of the toxicity rate ≥30% is more than 70%. Table 14.1 summarizes the Bayesian monitoring rule when the 10^{th}, 20^{th}, 30^{th} and 40^{th} patients become analyzable.

Table 14.1 Bayesian Toxicity Monitoring Rule

Total # of analyzable patients	10	20	30	40
# patients with AE of interest	5	8	11	14

Table 14.2 summarizes the operating characteristics based on 5,000 simulations with 40 patients in terms of how frequent Arm 2 may be considered "alarming" for accrual suspension.

Table 14.2 Operating characteristics of the monitoring rule

Underlying risk	0.2	0.25	0.3	0.35	0.4	0.45
% of time stopping considered	7.2%	20.4%	42.1%	67.1%	84.2%	94.5%

14.7.5 Power Calculations for Quality of Life (QOL) Research Based on Expected Sample Sizes

The primary QOL endpoint is whether a patient experiences a clinically meaningful deterioration of FACT-TOI (defined as a decline of 5 points or more from baseline) at 15 months after the end of the 4^{th} cycle of chemotherapy, e.g., a binary endpoint. The primary QOL hypothesis is that the proportion of patients in the experimental arm will experience clinically meaningful deterioration (CMD) at 15 months after completion of CRT (p_2) is smaller than that in the control arm (p_1), e.g., $p_2<p_1$. Based on Section

14.7.3, this hypothesis will be tested if and only if the 1-sided type 1 error of 2.5% are passed over from other secondary endpoints with higher rank. In this case, Fisher's exact test will be used to compare the proportions of patients experiencing CMD between the two arms.

By definition, only participants who are alive at 15 months after completion of CRT (approximately 18 months after randomization) could potentially be analyzable for FACT-TOI analysis. Based on the primary hypothesis of OS, the survival rate at 15 months after completion of the 4th cycle of chemotherapy (approximately 18 months after randomization) is approximately 63% under H_0, and 72% under H_1. We define patients are analyzable if they are randomized and have assessments at both timepoints (baseline and 15 months after CRT completion). While great efforts will be made to minimize patients' attrition such that the number of analyzable cases can be maximized, it is well acknowledged that uncertainty still exists in the total number of analyzable cases. Furthermore, to our best knowledge, there are no existing data available in LS-SCLC that can be used for the control group, nor a widely accepted difference in patients experiencing CMD. Therefore, we argue the sample size of the QOL component should not be determined by detecting a fixed difference between patients' proportions of experiencing CMD. Instead, we demonstrate that, under reasonable assumptions, it is reasonable and justifiable to offer QOL to all patients, and the entire study will provide reasonably good power to detect non-trivial differences in proportions of patients experiencing CMD. The following table assumes 80% patients are analyzable. When the attrition rate is lower, e.g., smaller than 20%, greater powers are expected to detect same differences in CMD proportions.

Table 14.3: Power of Comparing FACT-TOI Deterioration

% Experienced CMD in Arm 2 (p_2)	% Experienced CMD in Arm 1 (p_1)	Power (Under H0 for OS)	Power (Under H1 for OS)
10%	30%	96%	97%
20%	40%	91%	92%
30%	50%	86%	88%
40%	60%	85%	87%
15%	30%	75%	78%
25%	40%	65%	68%
35%	50%	60%	64%
45%	60%	59%	63%

14.7.6 Statistical Analysis Plan: Quality of Life and Fatigue

The QOL analyses for any changes between two timepoints will be performed based on all randomized patients with assessments at both timepoints (section 11.1).

The primary QOL endpoint, FACT-TOI deterioration rate at 15 months after the end of the 4th cycle of chemotherapy, is defined as the proportion of randomized subjects who have a 5 point or greater decrease from baseline in FACT-TOI at 15 months after chemotherapy completion. FACT-TOI deterioration rates and associated 95% confidence interval will be calculated for each treatment group, based on all randomized subjects.

Clopper-Pearson method will be used for calculating 95% CI. The deterioration rates of each arm will also be compared using Fisher's exact Test.

FACT-TOI 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).

FACT-TOI at baseline (note this timepoint is defined as prior to study entry, occurring within 7 days prior to initiation of protocol treatment) 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 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 FACT-TOI 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. It is noted that patients in this study will receive either twice daily or daily radiation, which is a stratified variable. Given the hypothesis for the quality of life analysis addresses quality of life at 15 months after CRT completion, which corresponds to 3-4 months after consolidative immunotherapy has ended, it is felt that the radiation schema will not impact the quality of life analysis.

Baseline and PROMIS 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 change from baseline to subsequent timepoints may be compared between treatment arms using a t-test, or Wilcoxon test if the data is non-normal.

A longitudinal analysis will also be conducted with a focus on the patterns of scores over time points of FACT-TOI and PROMIS. 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. 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 for institutions with patients participating. 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 to a certain extent 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 (patient exclusion is not considered as missingness). 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 missing-at-random (MAR) mechanism is suspected, 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 due to the high number of patient deaths or dropouts (Rizopoulos 2012). Other options for MNAR data are pattern mixture and selection models (Fairclough 2010, Little 2014). Sensitivity analyses will be performed to compare the results of different analytic strategies (Fairclough 1998).

EQ-5D-5L consists of the descriptive system and the visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state.

Subjects' overall health state on a visual analog scale (VAS) at each assessment time point will be summarized using descriptive statistics by treatment group, as randomized. Proportion of subjects reporting problems for the five EQ-5D-5L dimensions at each assessment time point will be summarized by level of problem and by treatment group, as randomized. Percentages will be based on number subjects assessed at assessment time point.

Quality-adjusted survival can be defined by the weighted sum of different time episodes added up to a total quality-adjusted life-year [U= sum of quality (qi) of health states K times the duration (si) spent in each health state] (Glasziou 1990):

$$\mathbf{U} = \sum_{\mathbf{i=1}}^{\mathbf{K}} \mathbf{q}_{\mathbf{i}} \mathbf{s}_{\mathbf{i}}$$

The area under the EQ-5D curve yields predicted Quality-Adjusted Life Years (QALYs) (Glick 2007). QALY differences of 0.03 are considered important, and QALY differences of as little as 0.01 are considered potentially meaningful and important for several prevalent diseases, including cancer, diabetes, and heart disease (Samsa 1999; Walters 2003). We will use Glasziou's multiple health-state (Q-TwiST) models to use the repeated measures of EQ-5D. Because Glasziou's method incorporates longitudinal QOL data into an analysis of quality-adjusted survival, the health state model must be constructed on the following assumptions:

A1) QOL is independent from treatment.
A2) A health state is independent from previous states.
A3) Proportionality of quality-adjusted duration and duration of the actual state of health

Assumption A1 can be checked by plotting QOL scores over time according to treatment, and the t-test can be used to compare the mean QOL scores of each treatment arm. Assumption A2 can be checked by comparing the QOL scores for patient groups in a given health state where the groups are defined by duration of previous health state experience using a regression model. A suitable check for assumption A3 at a minimum would be a simple plot. If data do not support these assumptions, we will use a method that uses the longitudinal QOL data directly. The remaining time points at which the EQ-5D is collected will also be assessed using similar longitudinal analysis techniques as described for the other QOL endpoints.

14.7.7 Statistical Considerations: Tumor and cfDNA Molecular Subtyping as Integrated Markers

All translational research that correlate biomarkers and clinical outcomes will occur concurrently with or after the final analysis, as specified in Section 14.3.2. Tumor and cfDNA molecular subtyping will be determined per protocol section 10.2 and reference within. We hypothesize that patients bearing tumors with the "inflamed" SCLC-I signature will have improved PFS compared to the other subtypes or a grouping of all 3 subtypes (SCLC-A, SCLC-N, and SCLC-P) when treated with atezolizumab. In Gay et al, SCLC-I subtype based on tumor occurred in about 18% of cases.

For cfDNA molecular subtyping analysis using methylation analysis, we project there will be at least 219 PFS events from both arms and 102 PFS events from atezolizumab arm (under H1) available at the time of cfDNA molecular subtyping. Assuming SCLC-I subtype prevalence will be at least 20%, the following table summarizes the minimal HR which can be detected at a 2-sided significance level of 0.05 with at least 80% power.

Table 14.4 Minimum Effect Size (HR) to detect cfDNA SCLC-I subtype as a prognostic factor

Population	# of PFS events	Prevalence	Min PFS HR
Atezolizumab arm	102	0.2	2.00
		0.3	1.83

Based on this table, patients treated with Atezolizumab alone will have a reasonably good power (at least 80%) to detect cfDNA SCLC-I subtype as a prognostic factor (HR>2), with respect to PFS, when the prevalence is 20%. If the prevalence is higher than 20% or observing more than 102 PFS events, we will have an even greater power to detect such a relationship for patients treated with atezolizumab alone.

If we observe a statistically significant and clinically meaningful prognostic effect of cfDNA SCLC-I subtype for patients treated with atezolizumab, we will then evaluate if cfDNA SCLC-I subtype is a predictive biomarker by using patients from both arms. Based on the design parameters and the method proposed by Peterson and George [Peterson 1993], we summarize the statistical power to detect interaction effects (ratio of hazard ratios) of 0.33 when the marker positive prevalence is 20%, at 2-sided significance level of 0.05. We denote monthly hazard rates as λ, expected number of events of respective subgroups as E[N], and the hazard ratio between marker + and - as Δ. The subscripts indicate the corresponding treatment arms. The assumed monthly hazard rates and associated expected number of events are listed in the following Table accordingly. When the prevalence of cfDNA SCLC-I subtype is larger than 20%, the power to detect such interaction (predictive marker) will be even larger.

Table 14.5 Power Analysis for cfDNA SCLC-I subtype as Predictive Marker

Prevalence of Marker +/-		Arm 1			Arm 2			Interaction	
		Marker -	Marker +	Δ_1	Marker -	Marker +	Δ_2	$\Delta_{21}=\Delta_2/\Delta_1$	Power
0.2	λ	0.0533	0.0533	1.0	0.0332	0.0129	0.39	0.33	84.0%
	E[N]	94	24		87	13			
	λ	0.0491	0.0736	1.5	0.0372	0.0184	0.5	0.33	88.0%
	E[N]	92	25		85	16			
	λ	0.0462	0.0925	2.0	0.0356	0.0235	0.67	0.33	90.0%
	E[N]	91	26		84	18			

For tumor molecular subtyping analysis, we anticipate roughly 40% of cases will have sufficient tumor tissues to conduct this analysis. We project there will be at least 41 PFS events from atezolizumab arm (under H1) and at least 88 PFS events available from both arm at the time of tumor molecular subtyping analysis. The tumor SCLC-I subtype analysis will be descriptive in nature and should be interpreted collectively with cfDNA analysis. In the following we show the minimal effect size we may be able to detect using tumor tissue alone. Assuming tumor SCLC-I subtype prevalence will be at least 20%, the following table summarizes the minimal HR which can be detected at a 2-sided significance level of 0.05 with at least 80% power.

Table 14.6 Minimum Effect Size (HR) to detect tumor SCLC-I subtype as a prognostic factor

Population	# of PFS events	Prevalence	Min PFS HR
All patients	88	0.2	2.11
		0.3	1.92
Atezolizumab arm	41	0.2	2.98
		0.3	2.60

SCLC-I subtyping based on cfDNA and tumor analysis will be also correlated with other clinical outcomes, such as overall survival.

The aforementioned analysis will be performed based on the treatment patients actually receive. The rates of OS/PFS at various timepoints (e.g., every 6 months after randomization) and median OS/PFS for each SCLC-I subtype will be estimated using the Kaplan-Meier method (1958). 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. The prognostic value of SCLC-I subtype, based on either cfDNA or tumor analysis, will be evaluated using a Cox regression model. If applicable, the predictive value of SCLC-I subtype will be evaluated using a Cox regression model including the status of SCLC-I subtype, treatment received, and their interaction. In addition, the treatment hazard ratios (95% CI) for each SCLC subtype (i.e., subgroup analysis by SCLC subtypes) will be estimated using an unstratified Cox regression model.

14.8 Exploratory Hypothesis and Endpoints (10-JUL-2024)

14.8.1 Exploratory Endpoints

- Patient-reported symptomatic toxicities (PRO-CTCAE)
- Concordance between tumor and cfDNA molecular subtypes

14.8.2 Statistical Analysis Plan: PRO-CTCAE

Adverse events will also be assessed using PRO-CTCAE items. The PRO-CTCAE is a patient-reported outcome measurement system developed to characterize the frequency, severity and interference of symptomatic treatment toxicities (Basch et al., 2014). Items are scored on a Likert scale (e.g., for severity, 0=none, 1=mild, 2=moderate, 3=severe, and 4=very severe). The specific symptoms to be evaluated for this study are listed in Section 7.8 above. Assessments will be collected as specified in the Section 4 assessment tables. For each symptom and each domain (i.e., frequency, severity, and interference), counts and frequencies will be summarized for the worst score experienced by the patient by treatment arm.

14.8.3 Concordance Between Tumor and cfDNA Molecular Subtypes

The concordance between molecular subtypes (SCLC-A, SCLC-N, SCLC-P, and SCLC-I) obtained via RNAseq on tumor tissue and methylation analysis on cfDNA will be assessed among patients who have both evaluable RNAseq and methylation results, where Cohen's

Kappa and corresponding 95% confidence interval will be reported. In addition, the sensitivity and specificity of dichotomized cfDNA molecular subtypes, e.g., SCLC-I vs. SCLC-A/N/P (considering RNAseq as reference standard), along with the associated 95% confidence intervals, will be reported. Spearman rank correlation and associated 95% confidence intervals based on bootstrap between RNAseq and methylation will be reported.

14.9 Other Pre-specified Outcomes: NIH Required Analyses for Trials with Phase III Components (10-JUL-2024)

Estimates of treatment effect and the corresponding 95% confidence intervals (CIs) will be provided as follows (with an understanding that sometimes the CI or estimate will not be computable because of scant data).

- Estimates of the primary outcome treatment effect and the corresponding 95% confidence intervals (CIs) by sex.
- Estimates of the primary outcome treatment effect and the corresponding 95% confidence intervals (CIs) by race.
- Estimates of the primary outcome treatment effect and the corresponding 95% confidence intervals (CIs) by ethnicity.

14.10 Sex/Ethnicity/Race Distribution (10-JUL-2024)

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	2	1	1	2	6
Asian	3	7	0	0	10
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	30	20	0	0	50
White	207	207	9	9	432
More Than One Race	1	1	0	0	2
Total	243	236	10	11	500

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	23	22	0	0	45

Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More Than One Race	0	0	0	0	0
Total	23	22	0	0	45

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APPENDIX I
PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	**100**	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX II
Collaborative Agreements Language

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company(ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

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(s) in this study:

1. Agent(s) may not be used for any purpose 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.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other 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"):

    a. NCI will provide all Collaborators with prior 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 that would tend to restrict NCI's participation in the proposed combination protocol.

    b. 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 Agent.

    c. 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.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available 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.

4. 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.

5. Any data provided to Collaborator(s) for Phase 3 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.

6. 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 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:

   Email: ncicteppubs@mail.nih.gov

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

APPENDIX III (18-SEPT-2020)
Medidata Patient Cloud ePRO Operational Instructions

Introduction

Electronic collection of patient-reported outcomes (ePRO) through Medidata Patient Cloud ePRO is preferred but not mandatory. Traditional paper submission is the other option. Patients who will be submitting PRO data via Patient Cloud ePRO must be registered to Patient Cloud ePRO by an authorized site user after the patient has been registered to the study. Patients may use their own device or one provisioned by the site.

Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to Patient Cloud ePRO with their passwords or their PIN codes on the same device.

CRA Site Users

Site users of Patient Cloud ePRO require the same access as Rave. Access to the trial in the Patient Cloud ePRO is granted through the iMedidata. Site users will receive an invitation to Patient Cloud ePRO and the site user must accept the invitation to begin patient registration. Users who have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Please note, site users will not be able to access the study in the Patient Cloud ePRO until all required Rave and study specific trainings are completed.

Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail.

CRA Instructions for Setting the Patient Cloud ePRO App to Multi-User Mode

Sites conducting studies entirely on-premise, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to Patient Cloud with their passwords or their PIN codes on the same device. If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the Patient Cloud ePRO app to the device and set the Patient Cloud ePRO App to multi-user mode if applicable.
To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode**, then select **Multi-User**.
4. Tap **Yes** to confirm.

5. Tap the back arrows to return to the log in screen.

Note: If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

For a video demonstration, see Show Me How to Switch to Multi-User Mode.

Patient Users

To use the Patient Cloud ePRO, patients will need to use their own device (IOS, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Sites can provide a site-specific tablet for multiple study participant use on site. If a site-specific tablet is used, study staff need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log into Patient Cloud ePRO with their passwords or their PIN codes on the same device. **Refer to Appendix E on Setting the Patient Cloud ePRO App to Multi-User Mode.**

Patient Instructions for Accessing the Patient Cloud Using Your Personal Device

Downloading the Patient Cloud ePRO App
If you are using your personal device, and you do not have the Patient Cloud ePRO app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud ePRO app is already on the device, or if you are using a provider's device, you can skip this section.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud ePRO app.
2. Tap the *App Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Note: Patient Cloud ePRO is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud ePRO app
2. Tap the *Play Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud ePRO app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud ePRO app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud ePRO app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud ePRO app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the Patient Cloud ePRO app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud ePRO app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.

2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password
You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms
Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.
There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a + icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

Patient Compliance

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

Security

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks "Submit," the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The email address is stored for what purpose? The patient's email links the device (used) and (ePRO) account to where the data is stored. The patient's email is not visible to anyone in the system.

The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and LPOs.

The Patient Cloud ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud ePRO are encrypted and therefore this information cannot be read if intercepted while in transit.

Site checklist for activities prior to consenting a patient

- ☐ Site staff must have already completed required eLearning for the Patient Cloud ePRO application. See last bullet with hyperlink to training video library. Contact the LPO to request appropriate Rave access to register patients in Patient Cloud ePRO
- ☐ Accept study invitation at iMedidata.com
    - Note: you must be rostered in RSS and have received an invitation to Patient Cloud ePRO
- ☐ Verify the IOS or Android operating system is using the most current version
- ☐ Verify Patient Cloud ePRO app is using the most current version
- ☐ If using institutional shared devices, first patient only: Verify Patient Cloud ePRO app is in Multi-User mode
- ☐ Refer to Review Quick Reference Guides for videos and other procedural information

APPENDIX IV (26-OCT-2021)
PROPOSED EXPLORATORY CORRELATIVE STUDIES

Flow cytometry immunophenotyping:
Cellular characterization by multi-color flow cytometric analysis is an analytical cytometry method to detect different populations of immune cells in peripheral blood. The main objective of flow-based analysis for this study is to understand the basal composition and status of the immune cell repertoire and most importantly changes in the composition and status of the repertoire induced by therapy. Both the basal state and perturbed state of the immune cell repertoire can be measured by comprehensive evaluation of peripheral blood subsets. Such analysis should include not only cell type (e.g. helper/suppressor/regulatory T cells, natural killer, alpha/beta, gamma delta, dendritic cells, myeloid-derived suppressor cells) but also their maturity (naïve, naïve in transition, memory, quiescent memory, activated memory, senescent, etc.), their activation status (early, mid, mid late, late and very late activation) and degranulation status.

Our underlying research hypotheses of this study are that the composition and status of the immune cell repertoire at baseline correlates with clinical characteristics (including histological grade, tumor mutational load, predicted neo-antigen load, patient clinical TNM stage, patient age, patient gender, smoking status etc.), but also with response to therapy and clinical outcomes. In addition, changes and degree of changes in immune cell repertoire composition and status induced by therapy (by comparing baseline and serial during therapy samples) will allow us to determine which subset of cells are most important in positive and negative response to therapy.

Peripheral blood samples will be collected in K2-EDTA tubes at various timepoints and PBMCs will be processed in real time by Precision for Medicine. Upon conclusion of this clinical trial, the frozen PBMCs will be sent to a partnering lab for analysis. Changes in the immune cell repertoire will be detected from blood samples.

This testing will measure changes in immune cell subsets in 100 patients (50 control arm, 50 experimental arm).

Tissue/Blood Selection for Future Research (exploratory endpoints using banked blood and tissue):
If sufficient tissue/blood remains after integrated analyses are complete (or optional biospecimen submission), other potential exploratory correlative assessments (not integrated) may include, but are not limited to:

Whole exome sequencing (WES) in patients with progression (tumor): As mentioned above, we plan to perform whole exome sequencing on archival tumor samples from 112 patients. In addition, we will perform WES on tumor tissue on 10% of these patients (~12 patients) who develop progressive disease. This will serve as an exploratory analysis to identify potential mechanisms of resistance or progression compared to WES data from baseline tumor tissue. If patients consent to optional biobanking, tissue from

archival or a fresh tumor biopsy at progression will be requested for this analysis. Similar to the WES at baseline, either an FFPE block, or 2-3 punch cores (each core 2-3 mm thick) from an FFPE block should be sent to the NRG biobank for this future analysis.

Circulating tumor DNA (ctDNA): Circulating tumor DNA (ctDNA) is a sensitive and specific way to measure presence of tumor DNA in the blood and ctDNA correlates with prognosis and response to treatment, and therefore may be a predictive biomarker. Many studies show that changes in ctDNA can predate changes in imaging. We will access ctDNA from peripheral blood. We hypothesize that we can identify presence of ctDNA mutations in circulating free DNA of peripheral blood, and that changes in ctDNA during/after therapy will serve as an early predictor of treatment outcomes (e.g. progression-free and overall survival).

PD-L1 immunohistochemistry: PD-L1 (programmed death-ligand 1, or B7-H1) is a transmembrane protein that plays a role in suppressing the immune system. Through binding of PD-L1 on tumor cells to PD-1 on T cells, an inhibitory signal is transmitted to T cells. There is data suggesting that high PD-L1 expression may predict benefit in the setting of immunotherapy for NSCLC. However, the role for PD-L1 as a predictive biomarker in SCLC to checkpoint inhibitors in SCLC has not demonstrated the same predictive power. From available (remaining) tumor tissue submitted for whole exome sequencing integrated analysis, we may perform PD-L1 immunohistochemistry and quantify tumor PD-L1 expression patterns. We hypothesize that high PD-L1 expression in tumor cells will predict benefit from protocol therapy.

T cell receptor (TCR) sequencing/phenotyping: High-throughput sequencing of T cell receptors has now provided the opportunity for accurate identification and quantification of every distinct T cell clone. It allows the assessment of the diversity of the TCR repertoire and the kinetics of each antigen-specific T cell clone over time. We may perform TCR sequencing on genomic RNA isolated from PBMCs from peripheral blood and tumor (using RNA-Seq), in order to determine how protocol therapy alters TCR repertoire diversity and clones of neoantigen-specific T cells. We hypothesize that the addition of immunotherapy to standard chemoradiation will result in changes in T cell receptor repertoire and clonal diversity.

Cytokine assays: We will perform multiplex enzyme linked immunoadsorbent assays to measure cytokines, chemokines, or inflammatory markers in blood samples. We hypothesize that the addition of immunotherapy to standard chemoradiation therapy will alter cytokine/inflammatory marker levels and that reproducible changes in cytokine levels will correlate with improved response from the protocol therapy.

RNA-Seq (tumor): RNA-Seq is a next-generation sequencing platform that measures various levels of RNA transcripts and provides sequencing information, including T cell receptor (TCR) sequences. Preliminary data suggest that an RNA signature measuring levels of T cell effector presence/activity may predict response to immunotherapy. We hypothesize that a high T cell effector signature will correlate with response to protocol

therapy. We will perform RNA-Seq on available tumor tissue remaining after the whole exome sequencing integrated analysis above.

RNA-Seq (blood): Preliminary data suggest that transcripts, particular those relevant to inflammatory and antiviral signaling pathways, may be associated with the development of cancer-related fatigue. We may perform RNA-Seq on RNA isolated from PBMCs from available blood remaining in the biobank. TCR sequences will also be derived from RNA-Seq data obtained from blood and potentially correlated to tumor response to immunotherapy. We hypothesize that transcripts generated from RNA-Seq will be associated with fatigue levels over the course of immunotherapy.

DNA methylation (blood): Preliminary data indicate that DNA methylation changes secondary to cancer treatment may be associated with the development of cancer-related fatigue. We hypothesize DNA methylation changes will be associated with fatigue levels over the course of immunotherapy. We may perform DNA methylation on DNA isolated from PBMCs from available blood remaining in the biobank.

APPENDIX V: CLINICAL BLOOD SAMPLE SHIPMENT PREPARATION AND TRANSPORTATION FOR PBMC AND PLASMA PROCESSING AT PRECISION FOR MEDICINE (22-FEB-2021)

1. Instructions for sites

Precision for Medicine (PM) will provide PBMC and plasma processing and sample storage services to NRG Oncology, as described below. The purpose of this document is to describe the procedure for handling, packaging, and shipping blood samples from study participants to PM.

NOTE: PM also will distribute a study-specific lab manual electronically to all participating sites. The lab manual details the contents of the kit, how to use all of the kit components, how to correctly use the included shipping materials for optimal sample integrity during transport and to ensure conformance to the International Air Transport Association (IATA) regulations. The Lab manual also contains email addresses for the PM Biorepository as well as contact numbers if help is required with the kits or manual. PM provides Laboratory Manuals electronically to sites. Hard copies can be provided upon client request.

Table 1: Materials Shipping to PM

VISIT	SAMPLE TYPE
Baseline	~20-25 mL (mandatory) Whole Blood in Roche BCT tubes
	~20-25 mL (optional) Whole Blood in Roche BCT tubes
	10 mL (optional) Whole Blood in K2-EDTA tubes
On treatment visits	~20-25 mL (optional) Whole Blood in Roche BCT tubes
	10 mL (Optional) Whole Blood in K2-EDTA tubes

2. Number of Collection Kits

Below chart represents the Kit Type that the site should request for each visit.

To request kits, contact the following

[redacted]

NRGLU005@precisionformedicine.com

Table 2: Number of Kits by Type

VISIT	KIT TYPE (PLASMA AND PBMCS)	KIT TYPE (PLASMA ONLY)	TOTAL PER PATIENT	# OF PATIENTS
Baseline	Kit Type 1	Kit Type 3	1	280
Day 1 After CRT	Kit Type 2	Kit Type 4	1	280
3 Months After End of CRT	Kit Type 2	Kit Type 4	1	280

Only one (1) kit is needed for each patient/timepoint. All kit types include the Roche BCT Tubes. Kit Type 1 and 2 contains the optional K2-EDTA vacutainer while Kit Type 3 and 4 do

not contain the K2-EDTA vacutainer.

PM will monitor site initiation and the expected schedule of events (SOE) to ensure that the kits are available at the clinical sites as needed, and to minimize kits being shipped that will remain unused. However, each kit will also contain a requisition form for additional kits, and the PM provided laboratory manual will also contain contact details should more kits or supplies be required.

Table 3: Kit Components by Kit Type

KIT TYPE 1: BASELINE	KIT TYPE 2: ON TREATMENT VISITS
1 - Kit box 1 - Requisition Form 1 - Ambient shipper 1 - 2" bag n bag 7 - Labels	1 - Kit box 1 - Requisition Form 1 - Ambient shipper 1 - 2" bag n bag 5 - Labels
Blood Collection Tubes	**Blood Collection Tubes**
6 - 8.5 mL Roche RUO CELL-FREE DNA tube (BCT) 1 – 10 mL K2-EDTA tube	3 - 8.5 mL Roche RUO CELL-FREE DNA tube (BCT) 1 - 10mL K2-EDTA tube
Kit Type 3: BASELINE	**Kit Type 4: ON TREATMENT VISITS**
1 - Kit box 1 - Requisition Form 1 - Ambient shipper 1 - 2" bag n bag 7 - Labels	1 - Kit box 1 - Requisition Form 1 - Ambient shipper 1 - 2" bag n bag 5 - Labels
Blood Collection Tubes	**Blood Collection Tubes**
6 - 8.5 mL Roche RUO CELL-FREE DNA tube (BCT)	3 - 8.5 mL Roche RUO CELL-FREE DNA tube (BCT)

3. Outgoing and Return Kit Shipments

PM will provide sample collection kits that contain collection tubes and materials, as well as return shipping supplies, as described in the table below. Three "kits" will fit into one box for shipment, such that one outgoing shipment will contain supplies for 3 participant visits.

Upon arrival of kits at PM, samples for PBMC isolation and plasma processing will be transported to PM's central laboratories for processing.

SHIPPING ADDRESS:

US Sites:

ATTN: [redacted]

Precision for Medicine
8425 Precision Way
Frederick, MD 21701
RepositoryServices.Mailbox@precisionformedicine.com

Sites in Japan:

National University Hospital (S) Pte Ltd
c/o NUH Tissue Repository
5 Lower Kent Ridge Road
Main Building Level 3
Singapore 119074
Precision-APAC@precisionformedicine.com

APPENDIX VI: CARBOPLATIN DOSE CALCULATION INSTRUCTIONS

1) The Cockcroft-Gault formula will be used in NRG Oncology trials.

Dosing of Carboplatin:

1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using creatinine clearance (mL/min) from the Cockcroft-Gault formula.

2) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using **a minimum value of 0.7 mg/dL.**

3) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin will not need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

4) Carboplatin doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

5) At the time of dose modification, if the patient's age had changed (the patient has had a birthday), the site can use the current age.

CALVERT FORMULA:
Carboplatin dose (mg) = target AUC x (GFR [or estimated CrCl] + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.
Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

The maximum allowed doses of carboplatin are:
AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (mL/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (yrs)] x actual body Weight* (kg)}}{\textbf{72 x serum creatinine (mg/dl)}} \textbf{\{x 0.85 } \textbf{\textit{if female}}\textbf{\}}$$

Notes:
1) Weight in kilograms (kg):
   a. Body Mass Index (BMI) should be calculated for each patient.

b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**

d. Adjusted weight calculation:
Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) (+ 45.5 females) or (+ 50 for men)
Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight

At the time of a dose modification for toxicity:
If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.