ALLIANCE FOUNDATION TRIALS (AFT)

PROTOCOL NUMBER
AFT – 16

Protocol title
Phase II trial of induction immunotherapy with atezolizumab for patients with unresectable stage IIIA and IIIB NSCLC (AJCC 7th Edition) eligible for chemoradiotherapy with curative intent.

Protocol Version:
Protocol Version Date: 08-19-2019

Investigational Product: Atezolizumab
IND Sponsor: AFT

ClinicalTrials.gov Identifier: NCT03102242

Study Principal Investigator
[redacted]

PROTOCOL SIGNATURE PAGE

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US Sponsor Name: Alliance Foundation Trials (AFT), LLC

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, all applicable regulations, ICH Good Clinical Practice (GCP) and Declaration of Helsinki.

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First Name, Last Name Date, Signature

I. Synopsis

Study Title	Phase II trial of induction immunotherapy with atezolizumab for patients with unresectable stage IIIA or IIIB NSCLC (AJCC 7th Edition) eligible for chemoradiotherapy with curative intent
Study Number	AFT-16
Study Type/Phase	Phase II
Clinical Indication	Stage III NSCLC eligible for chemoradiotherapy with curative intent
ClinicalTrials.gov Identifier	NCT03102242
IND Number	N/A
Number of Trial Patients	63
Estimated Duration of Trial	3 years
Rationale	Lung cancer remains the leading cause of cancer death in the US. While advances in diagnosis and treatment have improved survival, these improvements have been gradual and the overall case fatality rate remains greater than 80%. Most US patients are diagnosed with locally advanced or advanced disease with an estimated more than 40,000 cases per year of stage III NSCLC. These patients are of particular interest in that they can be treated with curative intent although only approximately 25% will be cured by conventional chemoradiotherapy. Their generally better health compared to patients with metastatic NSCLC makes these patients ideal candidates for an immunologic approach. The combination of checkpoint inhibition to counter tumor related immunosuppression along with standard chemoradiotherapy that depletes T-regulatory cells might create immunologic "space" to facilitate clonal expansion of effector T-cells in an environment that has potentially improved tumor immunogenicity by blocking PD-L1. Further, both chemotherapy and radiation may expose otherwise hidden antigens that can present additional targets to the reconstituting immune system. Immunotherapy has come to the forefront of promising new modalities of care over the past few years. Immunotherapies have

	been successful enough in melanoma that several drugs are now FDA approved in this disease. Similar strategies have shown promise in advanced NSCLC and checkpoint inhibitors targeting PD-1 and PD-L1 are of particular interest given their apparently manageable toxicity and the long response durations that have been seen in early clinical trials.[i, ii] Nivolumab and atezolizumab are FDA approved in second line therapy for metastatic squamous and non-squamous lung cancer based on the activity seen in the Checkmate 017 and 057 trials and the POPLAR and OAK trials.[iii] Pembrolizumab is approved for patients with metastatic NSCLC progressing after initial platinum based chemotherapy and whose tumors express PD-L1 based on the Keynote clinical trials. It is also approved for front-line therapy in high PD-L1 expressers. Expanded approvals of several immune agents in locally advanced and metastatic NSCLC are occurring rapidly. PD-1 is a T-cell co-receptor found on activated T-cells. Some tumors, including a substantial minority of NSCLC, seem to be able to exploit this receptor through expression of the inhibitory PD-L1 ligands whose interaction with PD-1 can suppress the antitumor immune response. Expression of PD-L1 within lung cancers is thought to contribute to activated T-cell down-regulation and to the immunosuppressed state of lung cancer patients.[i] Initial trials in advanced lung cancer patients have reported response rates in the 20% range overall but with response durations that can be significantly longer than would be expected with chemotherapy. Many studies suggest that response correlates with degree of PD-L1 expression, but optimal biomarkers are not yet known and some non-expressers have responded well. Despite the clinical uncertainties, the checkpoint inhibition strategy is promising and is particularly attractive in patients with the possibility of cure such as those with stage III NSCLC in whom reversal of cancer mediated immunosuppression might reasonably be hoped to improve long-term survival rates. An estimated 30-50% of late-stage NSCLC patients may express PD-L1. Preclinical data suggest that an even higher percentage of tumors from stage III patients are PD-L1 positive *(Genentech personal communication),* hence these patients are likely to be the best candidates for neoadjuvant trials of checkpoint inhibition. This trial is intended to lead directly into a phase III trial of neoadjuvant atezolizumab followed by combined chemoradiotherapy/immunotherapy compared to chemoradiotherapy followed by adjuvant immunotherapy.

	Radiotherapy can affect host immune response and impact tumor control and spread. In preclinical studies, Formenti and colleagues demonstrated that the abscopal effect of radiotherapy is, in part, immune mediated and that T cells are required for regression of distant metastases after radiotherapy. Lee and Weichselbaum demonstrated that CD-8+ T cells are required for distant radiotherapy effects. Radiation therapy (RT) can increase tumor expression of PD-L1, and combined RT plus PD-1-pathway targeting results in synergistic decrease in suppressor T-cells, thereby promoting anti-tumor immunity. These pre-clinical data combined with recent case reports of immune checkpoint inhibitor mediated abscopal effects provide support for a trial combining anti-PD-L1 therapy with atezolizumab before and after definitive chemoradiotherapy.
Primary Objective	Determine the disease control rate (DCR) of neoadjuvant atezolizumab therapy in the study population. The goal of the primary objective of the phase II trial is to determine whether neoadjuvant anti-PDL-1 therapy with atezolizumab is worthy of further investigation in the target population. The primary endpoint will test the disease control rate (DCR), i.e., the rate of complete/partial response and stable disease, in response to neoadjuvant atezolizumab. If the disease control rate after neoadjuvant therapy is high, and in the absence of clinically significant toxicity, further study of this approach in locally advanced NSCLC will be merited.
Secondary Objectives	Determine progression-free survival (PFS) after neoadjuvant atezolizumab therapy followed by standard chemoradiotherapy, consolidation and adjuvant atezolizumab in the study population. Evaluate safety of neoadjuvant atezolizumab therapy combined with standard chemoradiotherapy followed by adjuvant atezolizumab. Determine response rates (RR) to neoadjuvant atezolizumab and to the overall treatment regimen. Determine overall survival (OS) at 12 and 18 months.
Translational Science Objectives	Principal: Define the role of PD-L1 biomarker testing in selecting the population most likely to respond to neoadjuvant and adjuvant immunotherapy together with standard chemoradiotherapy. Additional: Study the association of biomarkers, including immunologic signatures, and outcomes. Analyses may include,

	but are not limited to, multipanel immunohistochemistry, gene expression profiling by Nanostring, RNAseq or RT-PCR, whole exome and T cell receptor sequencing, cytokine/chemokine analysis, flow cytometry, and T cell function analysis. Specimens will include blood, serum, whole blood/plasma for additional evaluation of circulating tumor DNA (ctDNA), and FFPE tissue.
Other Correlative Sciences Objectives	Quality of life endpoints will be assessed during induction atezolizumab, during chemoradiotherapy, and during adjuvant atezolizumab at 3 month intervals and will be measured by the EORTC QLQ-30.
Trial Design and Schema	Induction immunotherapy: atezolizumab 1200 mg IV q 21 days x 4 cycles. Restaging after cycle 2 and cycle 4 induction: patients with progression of disease (PD) at the post-cycle 2 assessment will stop atezolizumab and go immediately to chemoradiotherapy if still stage III and eligible for curative intent therapy. Subjects may remain on study despite proceeding directly to chemoradiotherapy due to PD on restaging after cycle 2 induction if, in the investigator's view, the subject may benefit clinically. Chemoradiotherapy: carboplatin AUC = 2 + paclitaxel 50 mg/m2 IV weekly x 6 weeks concurrent with radiation to a total dose of 60 Gy given in 2 Gy fractions daily M-F x 30 fractions Consolidation chemotherapy: Carboplatin AUC = 6 + paclitaxel 200 mg/m2 IV q 21 days x 2 cycles beginning 3-5 weeks after completion of radiation. Adjuvant immunotherapy: atezolizumab 1200 mg IV q 21 days to complete one year of therapy (from start of induction). If, as anticipated, this study leads into a phase III trial, the comparator arm will be standard chemoradiotherapy followed by immunotherapy. Study Design: This phase II trial will combine neoadjuvant immunotherapy with atezolizumab q 21 days for 12 weeks followed by standard chemoradiotherapy with curative intent for good PS patients with unresectable stage IIIA/B NSCLC. Because of the consequences of progression in this curative-intent population, restaging CT scans will be obtained after the first 2 cycles of neoadjuvant therapy. Real-time monitoring will be used to provide reassurance that there is not an unacceptable rate of early PD in PD-L1 negative patients. Non-progressing patients will complete a total of one year of anti-PD-L1 therapy with an interruption during chemoradiotherapy. Assumptions include: • DCR of at least 70% with neoadjuvant immunotherapy, • That 85% of the study population will complete radiation,

	• That 60% of the study population will complete the entire treatment course including consolidation chemotherapy and adjuvant immunotherapy with atezolizumab. If the pilot study reaches its preplanned endpoints, a randomized phase III trial is planned in which patients will be randomized 2:1 to neoadjuvant immunotherapy followed by chemoradioimmunotherapy and adjuvant immunotherapy vs standard chemoradiotherapy and adjuvant immunotherapy. A key component of the successful completion of this study will be quality assurance of the radiotherapy delivery. Augmentation of the immune system by immune checkpoint inhibition has the potential to increase risk of pulmonary, cardiac and esophageal toxicity. Data on the use of PD-1/PD-L1 pathway agents in sequence with radiotherapy are limited. Out of 129 patients with NSCLC on a phase I trial for the PD-1 inhibitor nivolumab, 75 (58%) had previously received RT although the site of RT, dosing parameters and timing are not known. Out of the 129 NSCLC cases, there were 9 cases of pneumonitis (7.0%) and 3 cases of grade 3-4 pneumonitis (2.3%). There is some suggestion from early trials that the risk of pneumonitis may be less with atezolizumab than previously seen with nivolumab. Recent trials of the anti-PD-L1 BMS agent 936559 reported no cases of pneumonitis. However, given the possibility that the immune mediated risk of pneumonitis could be higher in a lung cancer population being treated with definitive thoracic radiotherapy, tight quality control through the cooperative group process will be critical. In multiple datasets, the quality of radiotherapy has been integral to the outcome in combined modality therapy trials.
Inclusion Criteria	Patients must meet the following criteria for study entry: 1) Newly diagnosed stage IIIA/B (per AJCC 7) NSCLC, PS 0-1. 2) No active autoimmune disease or uncontrolled infection; normal bone marrow, renal, hepatic function; FEV1 ≥ 1.2L; no significant underlying heart or lung disease. 3) Pathologically proven diagnosis of NSCLC. 4) Measurable Stage IIIA or IIIB disease per AJCC 7. 5) Patients must be considered unresectable or inoperable. Patients with nodal recurrence after surgery for early-stage NSCLC are eligible if the following criteria are met:

	• No prior chemotherapy or radiation for this lung cancer. • Prior curative-intent surgery at least 3 months prior to the nodal recurrence. 6) Stage III A or B disease (per AJCC 7) with minimum diagnostic evaluation within 6 weeks to include: • History/physical examination • Contrast enhanced CT of the chest and upper abdomen • MRI of the brain with contrast (or CT with contrast if MRI is medically contraindicated) • PET/CT 7) If pleural fluid is visible on CT scan thoracentesis to exclude malignancy should be obtained. Patients with effusions that are too small to tap are eligible. 8) Patients must be at least 4 weeks from major surgery and must be fully recovered. 9) Age ≥ 18 years. 10) Availability of representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks are preferred) or at least 4 (preferably 20) unstained slides, with an associated pathology report, for central testing of tumor PD-L1 expression. • If an archived tumor block exists, then either the block (preferred) or at least 4 (preferably 20) unstained slides from the block should be submitted. Tumor tissue should be of good quality based on total and viable tumor content, i.e. at least 50 viable tumor cells and intact tissue architecture. Fine-needle aspiration, brushing, and lavage samples are not acceptable. If the block is tissue from a core-needle biopsy, then the block should

	contain tissue from at least three cores to be sufficient for evaluation. • Patients who do not have existing (archived) tissue specimens meeting eligibility requirements may undergo a biopsy during the screening period. Acceptable samples include core-needle biopsies for deep tumor tissue (minimum of three cores) or excisional, or forceps biopsies for endobronchial or nodal lesions. The tissue should be fixed in formalin and embedded on site and sent as a block. 11) Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1; if repeat labs are obtained on or prior to C1D1 they must re-meet eligibility criteria to treat the subject): • ANC ≥ 1500 cells/μL • WBC counts > 2500/μL • Lymphocyte count ≥ 300/μL • Platelet count ≥ 100,000/μL • Hemoglobin ≥ 10.0 g/dL • Total bilirubin ≤ 1.5 × upper limit of normal (ULN) with the following exception: - Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled. • AST and ALT ≤ 3.0 × ULN • Alkaline phosphatase ≤ 2.5 × ULN • Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation: - $\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$

	12) Measurable disease per RECIST v1.1 (see Appendix 3). 13) For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use highly effective form(s) of contraception (i.e., one that results in a low failure rate [< 1% per year] when used consistently and correctly, such as hormonal or barrier method of birth control, or abstinence) and to continue its use for 150 days after the last dose of atezolizumab. 14) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (see Appendix 5).
Exclusion Criteria	**General Exclusion Criteria:** 1) Active autoimmune disease. 2) Greater than minimal, exudative, or cytologically positive pleural effusions. 3) Involved contralateral hilar nodes. 4) 10% weight loss within the past month. 5) Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years; non-invasive conditions such as carcinoma in situ of the breast, localized prostate cancer or thyroid nodules, carcinoma in situ of the oral cavity or cervix are all permissible. 6) Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable. 7) Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields. 8) Prior severe infusion reaction to a monoclonal antibody. 9) Severe, active co-morbidity, defined as follows: 10) Significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, myocardial infarction within the last 6 months, uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction.

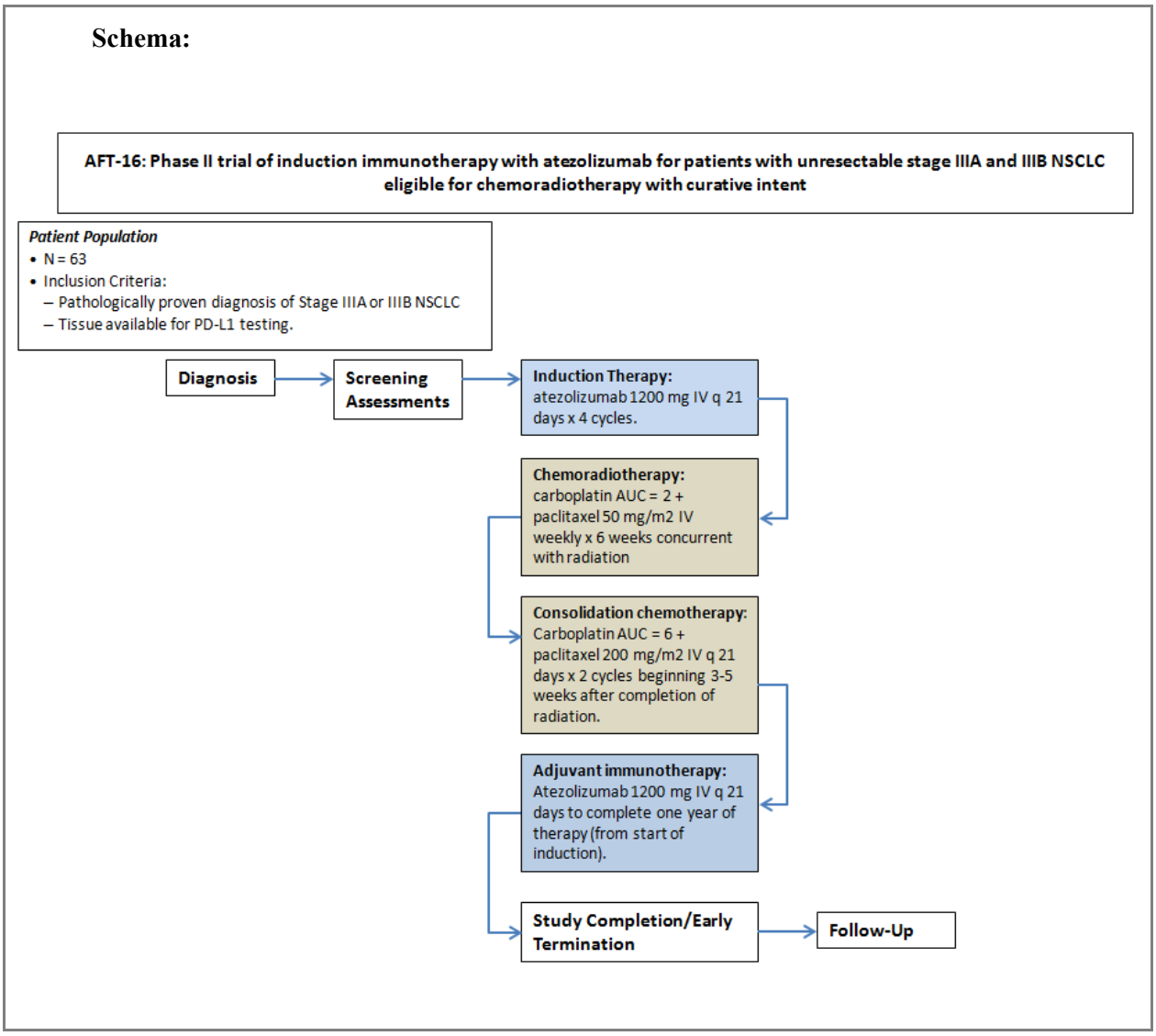
	11) Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration or within 2 weeks of cycle 1 day 1. Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration. 12) Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects. 13) Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, HIV testing is required for entry into this protocol due to the immunologic basis for induction treatment. 14) Pregnancy, lactation or inability or unwillingness to use medically acceptable forms of contraception if pregnancy is a risk 15) Any history of allergic reaction to paclitaxel or other taxanes, or to carboplatin 16) Uncontrolled neuropathy grade 2 or greater regardless of cause 17) Any approved anticancer therapy, including chemotherapy, hormonal therapy, or radiotherapy, within 3 weeks prior to initiation of study treatment; however, the following are allowed: i. Hormone-replacement therapy or oral contraceptives ii. Herbal therapy > 1 week prior to Cycle 1, Day 1 (herbal therapy intended as anticancer therapy must be discontinued at least 1 week prior to Cycle 1, Day 1) 18) Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease. 19) Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive

	anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible 20) Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA. 21) Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies. 22) Inability to comply with study and follow-up procedures. 23) History of active autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis. 24) Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible 25) Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible 26) Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions: Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations. Rash must cover less than 10% of body surface area (BSA). Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate

	0.1%, fluocinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%). No acute exacerbations of underlying condition within the last 6 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids). 27) History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. 28) 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. 29) Active tuberculosis. 30) Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study. 31) Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study. 32) Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study **Medication-Related Exclusion Criteria:** 33) Prior treatment with anti–PD-1, or anti–PD-L1 therapeutic antibody or pathway-targeting agents. 34) Treatment with systemic immunostimulatory agents (including but not limited to interferon

	[IFN]-α or interleukin [IL]-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1. 35) Treatment with investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer). 36) Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, or anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1. 37) Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled. 38) The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. 39) History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins. 40) Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation.

Schema:


AFT-16: Phase II trial of induction immunotherapy with atezolizumab for patients with unresectable stage IIIA and IIIB NSCLC eligible for chemoradiotherapy with curative intent
Patient Population
• N = 63
• Inclusion Criteria:
– Pathologically proven diagnosis of Stage IIIA or IIIB NSCLC
– Tissue available for PD-L1 testing.
Diagnosis
Screening Assessments
Induction Therapy: atezolizumab 1200 mg IV q 21 days x 4 cycles.
Chemoradiotherapy: carboplatin AUC = 2 + paclitaxel 50 mg/m2 IV weekly x 6 weeks concurrent with radiation
Consolidation chemotherapy: Carboplatin AUC = 6 + paclitaxel 200 mg/m2 IV q 21 days x 2 cycles beginning 3-5 weeks after completion of radiation.
Adjuvant immunotherapy: Atezolizumab 1200 mg IV q 21 days to complete one year of therapy (from start of induction).
Study Completion/Early Termination
Follow-Up

II. Table of Contents

Protocol

III. List of Tables

IV. Abbreviations and Terms

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AFT	Alliance Foundation Trials
AIDS	Acquired immunodeficiency syndrome
anti-HBc	antibody to hepatitis B core antigen
anti-TNF	Anti-tumor necrosis factor
ATA	anti-therapeutic antibody
AUC	area under the concentration-time curve
BSA	body surface area
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CNS	central nervous system
CL	Clearance
CR	complete response
CRF	Case Report Form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTMS	Clinical Trial Management System
DCR	Disease control rate
DL_{CO}	diffusion capacity of the lung for carbon monoxide
DLT	dose-limiting toxicity
DVH	Dose volume histograms
EBV	Epstein-Barr virus
EBNA	Epstein-Barr nuclear antigen
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EORTC QLQ C30	The European Organization for Research and Treatment of Cancer QLQ-C30
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation	Definition
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IF	Immunofluorescence
IFN	Interferon
IHC	immunohistochemistry
Ig	Immunoglobulin
IL	Interleukin
IMP	investigational medicinal product
IND	Investigational New Drug (application)
irAE	immune-related adverse event
IRB	Institutional Review Board
IRF	independent review facility
IRR	infusion-related reaction
irRC	immune-related response criteria
ITF	internal target volume
IV	Intravenous
LFT	liver function test
LPLV	last patient, last visit
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PES	Polyethersulfone
PET	positron emission tomography
PFS	progression-free survival
PI	Package Insert
PK	Pharmacokinetic
PR	partial response

Abbreviation	Definition
PRO	Patient reported outcomes
PUVA	psoralen plus ultraviolet A radiation
PVC	Polyvinylchloride
QOL	Quality of life
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RR	Response rate
RT	Radiation Therapy
SAE	serious adverse event
SD	stable disease
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
US	United States

1. Background

1.1. Overview of Disease and Patient Population

Lung cancer remains the leading cause of cancer death in the US. While advances in diagnosis and treatment have improved survival, these improvements have been gradual and the overall case fatality rate remains greater than 80%. Most US patients are diagnosed with locally advanced or advanced disease with an estimated more than 40,000 cases per year of stage III NSCLC.

These patients are of particular interest in that they can be treated with curative intent although only approximately 25% will be cured by conventional chemoradiotherapy. Their generally better health compared to patients with metastatic NSCLC lends this population to an immunologic approach. The combination of immune regulation with checkpoint inhibition plus standard treatments that deplete T-regulatory cells (radiation and chemotherapy) may create immunologic "space" to facilitate clonal expansion of effector T-cells. Further, both chemotherapy and radiation may expose otherwise hidden antigens that can present additional targets to the reconstituting immune system after chemoradiotherapy.

Immunotherapy has come to the forefront of promising new modalities of care over the past few years. Immunotherapies have been successful enough in melanoma that several drugs are now FDA approved in this disease. Similar strategies have shown promise in advanced NSCLC and checkpoint inhibitors targeting PD-1 and PD-L1 are FDA approved for NSCLC and are of particular interest given their apparently manageable toxicity and the long response durations that have been seen in early clinical trials.[i, ii]

Nivolumab and atezolizumab are approved in second line therapy for metastatic squamous and non-squamous lung cancer based upon results of the CheckMate Poplar, Birch and Oak Trials.[iii] Pembrolizumab is approved for advanced NSCLC patients whose disease has progressed after platinum doublet chemotherapy and whose tumors express PD-L1 and in the first line for stage IV

NSCLC patients whose tumors highly express PD-L1 based on the Keynote trials. Other approvals for advanced NSCLC are expected.

PD-1 is a T-cell co-receptor found on activated T-cells. Some tumors, including a substantial minority of NSCLC, seem to be able to exploit this receptor through expression of the inhibitory PD-L1 ligands whose interaction with PD-1 can suppress the antitumor immune response. Expression of PD-L1 within lung cancers is thought to contribute to activated T-cell down-regulation and to the immunosuppressed state of lung cancer patients. Initial trials in advanced lung cancer patients have shown response rates in the 20-30% range but with response durations that can be significantly longer than would be expected with chemotherapy. Most studies suggest that response is correlated with degree of PD-L1 expression, but the optimal biomarkers are not known and a few non-expressers have responded well. Despite the clinical uncertainties, the approach is promising and is particularly attractive in patients with the possibility of cure such as those with stage III NSCLC.

An estimated 30-50% of late-stage NSCLC patients may express PD-L1. Preclinical data suggest that an even higher percentage of tumors from stage III patients are PD-L1 positive (Genentech personal communication) hence these patients are likely to be the best candidates for initial trials of checkpoint inhibition. This trial is intended to lead directly into a phase III trial of the combined chemoradiotherapy/immunotherapy approach compared to standard chemoradiotherapy.

Radiotherapy can affect the host immune response and impact tumor control and spread. In preclinical studies, Formenti and colleagues demonstrated that the abscopal effect of radiotherapy is, in part, immune mediated and that T cells are required for regression of distant metastases after radiotherapy. Lee and Weichselbaum demonstrated that CD-8+ T cells are required for distant radiotherapy effects. Radiation therapy can increase tumor expression of PD-L1, and combined RT plus PD-1-pathway targeting results in synergistic reduction of suppressor T-cells, thereby promoting anti-tumor immunity. These pre-clinical data combined with recent case reports of immune checkpoint inhibitor mediated abscopal effects form the basis for studying anti-PD-L1 therapy with atezolizumab in sequence with definitive chemoradiotherapy.

1.2. Study Drug Mechanism of Action

Atezolizumab is a human immunoglobulin G1 (IgG1) monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and prevents Fc-effector function at expected concentrations in humans. Atezolizumab targets human programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptor, programmed death-1 (PD-1). Atezolizumab also blocks binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells.

Atezolizumab (Tecentriq™) is approved in the United States for the treatment of locally advanced or metastatic urothelial cancer (UC) and for second line treatment of advanced NSCLC. Atezolizumab is being investigated in a wide spectrum of solid tumors and hematologic malignancies in humans, please see IB or drug label for approved indications.

1.3. Preclinical Data

The nonclinical strategy of the atezolizumab program was to demonstrate in vitro and in vivo activity, to determine in vivo pharmacokinetic (PK) behavior, to demonstrate an acceptable safety profile, and to identify a Phase I starting dose. Comprehensive pharmacology, PK, and toxicology evaluations were thus undertaken with atezolizumab.

The safety, pharmacokinetics, and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, pharmacokinetics, and toxicokinetics of atezolizumab.

Overall, the nonclinical pharmacokinetics and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed Phase I starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down-modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients.

Refer to the atezolizumab Investigator's Brochure for details on the nonclinical studies.

1.4. Clinical Pharmacokinetics and Immunogenicity

On the basis of available preliminary PK data (0.03–20 mg/kg), atezolizumab appeared to show linear pharmacokinetics at doses ≥ 1 mg/kg. For the 1-mg/kg and 20-mg/kg dose groups, the mean clearance (CL) and the mean volume at steady state (V_{ss}) had a range of 3.20–4.43 mL/kg and 48.1–64.1 mL/kg, respectively, which is consistent with the expected profile of an IgG1 antibody in humans.

The development of ATAs has been observed in patients in all dose cohorts and was associated with changes in pharmacokinetics for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg). The development of detectable ATAs has not had a significant impact on pharmacokinetics for doses from 10–20 mg/kg. Patients dosed at the 10-, 15-, and 20-mg/kg dose levels have maintained the expected target trough levels of drug despite the detection of ATAs. To date, no clear relationship between detection of ATAs and AEs or IRRs has been observed.

1.5. Clinical Data

1.5.1. Ongoing Clinical Studies

Current studies of atezolizumab include one ongoing Phase Ia monotherapy study, three ongoing combination studies, five Phase II studies, and one Phase III study. Details of all ongoing studies can be found in the Atezolizumab Investigator's Brochure.

Phase Ia Study PCD4989g
Study PCD4989g is a multicenter, first-in-human, open-label, dose-escalation study evaluating the safety, tolerability, immunogenicity, pharmacokinetics, exploratory pharmacodynamics, and preliminary evidence of biologic activity of atezolizumab administered as a single agent by IV infusion every 3 weeks to patients with locally advanced or metastatic solid malignancies or hematologic malignancies. Ongoing expansion cohorts are studying the efficacy in patients with pancreatic cancer, bladder cancer, breast cancer,

esophageal cancer, prostate cancer, small-cell lung cancer, malignant lymphoma, multiple myeloma, and other less common tumor types.

Phase Ib Study GP28328
Ongoing Phase Ib Study GP28328 is evaluating the safety and pharmacology of atezolizumab administered with bevacizumab alone (Arm A) or with bevacizumab plus leucovorin, 5-fluorouracil, and oxaliplatin (FOLFOX; Arm B) in patients with advanced solid tumors. Additional cohorts have been included to investigate atezolizumab in combination with carboplatin plus paclitaxel, in combination with carboplatin plus pemetrexed, and in combination with carboplatin plus nab paclitaxel, pemetrexed, and cisplatin in patients with advanced or metastatic non-small cell lung cancer (NSCLC).

Phase Ib Study GP28384
Ongoing Phase Ib Study GP28384 is evaluating the safety and pharmacology of atezolizumab administered in combination with vemurafenib in patients with previously untreated $BRAF^{V600}$-mutation–positive metastatic melanoma.

Phase Ib Study GP28363
Ongoing Phase Ib Study GP28363 is evaluating the safety and pharmacology of atezolizumab administered in combination with cobimetinib (MEK inhibitor) in locally advanced or metastatic solid tumors.

Phase II Study GO28625 (FIR)
Ongoing, single-arm, Phase II Study GO28625 is evaluating the safety and efficacy of atezolizumab monotherapy in PD-L1–positive patients with NSCLC. In particular, this study is evaluating whether archival or fresh tumor tissue is more predictive of response to atezolizumab. Safety and efficacy data are not yet available for this study.

Phase II Study GO28753 (POPLAR)
Study GO28753 is a randomized, open-label, Phase II study in patients with locally advanced or metastatic NSCLC who have failed a prior platinum-containing regimen. Patients in the control arm of Study GO28753 will receive docetaxel alone. Eligible patients will be enrolled regardless of PD-L1 status and will be stratified by PD-L1 expression. The primary endpoint is overall survival (OS) for both the PD-L1–positive population and the overall study population.

Phase II Study GO28754 (BIRCH)
Ongoing, single-arm, Phase II Study GO28754 is evaluating the safety and efficacy of atezolizumab monotherapy in PD-L1–positive patients with NSCLC. As of the 1 December 2015 data cutoff date, 659 patients with NSCLC have been treated with atezolizumab as a fixed dose of 1200 mg IV q3w. In Study GO28754, 93.8% patients experienced at least one adverse event, 65% of patients experienced one treatment-related adverse event, and 12% of patients experienced Grade ≥3 treatment-related adverse event.

Phase II Study WO29074
Ongoing Phase II Study WO29074 is evaluating the safety and efficacy of atezolizumab monotherapy or the combination of atezolizumab and bevacizumab versus sunitinib in treatment-naïve patients with renal cell carcinoma (RCC). Safety and efficacy data are not yet available for this study.

Phase II Study GO29293
Ongoing Study GO29293 is a single-arm, open label, Phase II study to assess the clinical benefit of atezolizumab as a single agent in patients with locally advanced or metastatic UBC. The co-primary endpoints of this study are independent review facility (IRF)–assessed objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1) and investigator-assessed ORR according to modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Phase III Study GO28915 (OAK)
Study GO28915OAK was a randomized, Phase III, open-label study assessing the clinical benefit of atezolizumab as a single agent versus docetaxel in PD-L1-unselected patients with locally advanced or metastatic NSCLC that has progressed during or following treatment with a platinum-containing regimen

At the primary analysis, there were 850 efficacy-evaluable patients (ITT population), 425 in the docetaxel arm and 425 in the atezolizumab arm. Median OS in the ITT population was 13.8 months for atezolizumab compared with 9.6 months for docetaxel (HR of 0.73; 95% CI: 0.62, 0.87, p=0.0003). OS benefit was seen regardless of PD-L1 expression (HR 0.75 in <1% PD-L1 expression population; 0.41 in ≥50% TC or ≥10% IC expression population) and was consistent across subgroups, including histology (HR 0.73 for both), patients with asymptomatic CNS mets (HR 0.54) and never smokers (HR 0.71). Atezolizumab was well tolerated with a favorable safety profile compared to docetaxel. No new safety signals were identified. The rate of immune-mediated AEs was low (Barlesi et al. 2016).

1.5.2. Clinical Activity

Single-Agent Clinical Safety in Patients with Non-Small Cell Lung Cancer in Study PCD4989g

Study PCD4989g is a Phase Ia dose escalation and expansion study, in which atezolizumab is being used as a single agent in patients with locally advanced or metastatic solid tumors or hematologic malignancies, and provides significant data (with 629 safety-evaluable patients across all cancer types as of the data cutoff date of 15 December 2015) for the safety profile of atezolizumab as monotherapy.

Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of adverse events have been determined.

The safety profile of atezolizumab as a single agent is observed to be consistent across different indications, including small-cell lung cancer, NSCLC, urothelial bladder cancer (UBC), renal cell carcinoma (RCC), melanoma, gastric cancer, colorectal cancer, head and neck cancer, breast cancer, and sarcoma.

Of the 629 patients across all cancer types in Study PCD4989g, 619 patients (98.4%) experienced at least one adverse event, including 444 patients (70.6%) who experienced one treatment-related adverse event. Commonly reported events (reported in ≥ 10% of all patients) included fatigue, nausea, decreased appetite, diarrhea, constipation, dyspnea, pyrexia, and cough.

A total of 89 safety-evaluable patients with NSCLC received atezolizumab in Study PCD4989g. A total of 88 patients (98.9%) experienced at least one adverse event, including 67 patients (75.3%) with treatment-related adverse events, 35 (39.3%) patients with Grade 3–4 adverse events, 36 patients (40.4%) with serious adverse events, 5 patients (5.6%) who discontinued study drug due to an adverse event, and 1 death (1.1%).

The safety profile of the NSCLC cohort was consistent with the overall safety profile of all safety-evaluable patients in Study PCD4989g, as well as with the safety-evaluable patients with NSCLC who received atezolizumab monotherapy in other studies.

Analyses of tumor-infiltrating immune cells for PD-L1 expression on baseline tumor tissue have been performed for Study PCD4989g. Preliminary results from Study PCD4989g suggest that PD-L1 expression in tumor-infiltrating immune cells is likely to be associated with response to atezolizumab.

Efficacy in NSCLC Patients

The POPLAR trial is a randomized, phase II comparison between standard second line docetaxel and atezolizumab in good performance status patients with NSCLC that had progressed after a platinum based chemotherapy regimen (. The study screened over 500 patients at 61 centers in 13 countries including the USA and Europe and randomized 144 patients to atezolizumab and 143 to docetaxel between August 2013 and March 2014. Patients had normal organ function and measurable disease and were stratified by PD-L1 status, tumor infiltrating immune cells as well as by histology and prior therapy. The primary study endpoint was overall survival in the ITT population and the PD-L1 prespecified subgroups. Survival was similar to docetaxel in patients lacking PD-L1 expression and improved with atezolizumab in both responders and non-responders.

Overall survival of the participants in the POPLAR study was 12.6 months (95% CI 9.7 – 16.4) for atezolizumab and 9.7 months (95% CI 8.6 – 12.0) for docetaxel (HR 0.73, p= 0.04). Survival improvement with atezolizumab compared to docetaxel was associated with the degree of PD-L1 expression.

Atezolizumab was well tolerated. 11 (8%) patients discontinued treatment due to AEs compared to 30 (22%) for docetaxel. 16 (11%) patients in the atezolizumab arm had grade 3/4 AEs compared to 52 (39%) for docetaxel. There was one treatment related death in the atezolizumab group and 3 in the docetaxel group.[iv]

For further details, see the atezolizumab Investigator's Brochure.

1.6. Clinical Safety

The presented safety data for atezolizumab have been derived mainly from the treatment of patients in Phase Ia Study PCD4989g. As of 10 May 2014, atezolizumab has been administered to approximately 775 patients with solid and hematologic malignancies. No dose-limiting toxicities (DLTs) have been observed at any dose level, and no maximum tolerated dose (MTD) was established. Fatigue was the most frequently reported adverse event (AE).

Adverse Events
The following safety data are from PCD4989g, in which atezolizumab is being used as single-agent therapy in patients with locally advanced or metastatic solid tumors or hematologic malignancies. In 412 treated patients, 97.1% reported an AE while on study. Of these AEs, 48.8% were Grade 1 or 2 in maximum severity on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0). The most frequently observed AEs (occurring in ≥ 10% of treated patients) included fatigue, nausea, decreased appetite, pyrexia, dyspnea, diarrhea, constipation, cough, headache, back pain, vomiting, anemia, arthralgia, rash, insomnia, asthenia, abdominal pain, chills, pruritus, and upper respiratory tract infection.

Grade ≥ 3 AEs were reported by 199 of 412 patients (48.3%). There were 51 patients (12.4%) who reported Grade ≥ 3 AEs that were assessed as related to study drug by the investigators. The most frequently reported related Grade ≥ 3 AEs included fatigue (5 patients [1.2%]), increased ALT and increased AST (each reported in 4 patients [1.0%]); and asthenia, autoimmune hepatitis, and hypoxia (each reported in 3 patients [0.7%]).

Immune-Related Adverse Events
Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program. These include potential dermatologic, hepatic, endocrine, and respiratory events as well as events of hepatitis/elevated liver function tests (LFTs) and influenza-like illness. Expected adverse drug reactions associated with atezolizumab include the following: hepatitis/transaminitis, hypothyroidism, infusion-related reactions (IRRs), pneumonitis, influenza-like illness, and dermatologic reactions. Potential adverse drug reactions include the following: anti-therapeutic antibodies (ATAs), colitis, endocrine disorders, hypersensitivity, neurologic disorders, and pericardial effusion.

For further details, see the Atezolizumab Package Insert[v].

1.7. Study Design Rationale and Significance

1.7.1. Study Design

This phase II pilot trial will combine neoadjuvant immunotherapy with atezolizumab q 21 days for 12 weeks with standard chemoradiotherapy with curative intent for good PS patients with unresectable stage IIIA/B NSCLC. Because of the consequences of progression in this curative-intent population, restaging CT scans will be carried out after the first 2 cycles of neoadjuvant therapy. Non progressing patients will complete a total of one year of anti-PDL1 therapy with an interruption during chemoradiotherapy. Patients with evidence of progression at the first restaging evaluation will proceed immediately to chemoradiotherapy if still eligible for curative intent therapy.

Assumptions include a DCR of at least 70% to neoadjuvant immunotherapy, that 85% of the study population will complete radiation, and that 60% of the study population will complete the entire treatment course including consolidation chemotherapy and adjuvant immunotherapy with atezolizumab. If the pilot study reaches its preplanned endpoints, a randomized phase III trial is planned in which patients will be randomized 2:1 to induction

immunotherapy followed by chemoradiotherapy with immunotherapy and adjuvant immunotherapy vs standard conventional chemoradiotherapy followed by immunotherapy.

A key component of the successful completion of this study will be quality assurance of the radiotherapy delivery. Augmentation of the immune system by immune checkpoint inhibition has the potential to increase risk of pneumonitis. To date, there are limited data on the use of PD-1/PD-L1 pathway agents in sequence with radiotherapy. Out of 129 patients with NSCLC on a phase I, dose-escalation, cohort expansion trial for the PD-1 inhibitor nivolumab, 75 (58%) had previously received RT. Without knowing the precise details of radiotherapy treatment, out of the 129 NSCLC cases, there were 9 cases of pneumonitis (7.0%) and 3 cases of grade 3-4 pneumonitis (2.3%), suggesting that the incidence of radiation mediated toxicity was not increased by the immunotherapy in that small cohort. There is some suggestion that the risk of pneumonitis will be less with atezolizumab than previously seen with nivolumab. Recent trials of the anti-PD-L1 BMS agent 936559 reported no cases of pneumonitis. However, given the possibility that the immune mediated risk of pneumonitis could be higher in a lung cancer population being treated with definitive thoracic RT, tight quality control through the cooperative group process will be critical. In multiple datasets, the quality of radiotherapy has been integral to the outcome in combined modality therapy trials. Reports of immune mediated myocarditis have been occasional but reports of fatal myocarditis surfaced in 2016. This complication appears very rare and more common in patients treated with combined immunotherapy with an anti-CTLA4 agent plus a checkpoint inhibitor. Cardiac function will be followed with echocardiography and all care will be taken to minimize heart dose in the radiation field[vi].

1.7.2. Rationale for Study and Patient Population

Lung cancer remains the leading cause of cancer death in the US. While advances in diagnosis and treatment have improved survival, these improvements have been gradual and the overall case fatality rate remains greater than 80%. Most US patients are diagnosed with locally advanced or advanced disease with an estimated more than 40,000 cases per year of stage III NSCLC.

Stage III NSCLC patients are of particular interest in that they can be treated with curative intent with chemoradiotherapy although only approximately 25% will be cured. Their generally better health compared to patients with metastatic NSCLC lends this population to an immunologic approach. The combination of checkpoint inhibition immunotherapy with standard treatments that deplete T-regulatory cells (radiation and chemotherapy) may create immunologic “space” to facilitate clonal expansion of effector T-cells. Further, both chemotherapy and radiation may expose otherwise hidden antigens that can present additional targets to the recovering immune system.

PD-1 is a T-cell co-receptor found on activated T-cells. Some tumors, including a substantial minority of NSCLC, seem to be able to exploit this receptor through expression of the inhibitory PD-L1 ligands whose interaction with PD-1 can suppress the antitumor immune response. Expression of PD-L1 within lung cancers is thought to contribute to activated T-cell down-regulation and to the immunosuppressed state of lung cancer patients. Initial trials in advanced lung cancer patients report response rates in the 20-30% range but with response durations that can be significantly longer than would be expected with chemotherapy. Most studies suggest that response correlates with the degree of PDL1 expression, but the optimal biomarkers are not known and a few non-expressers have responded well. Despite the clinical

uncertainties, the approach is promising and is particularly attractive in patients with the possibility of long term survival such as those with stage III NSCLC in whom the curative fraction may be increased by this strategy.

An estimated 30-50% of late-stage NSCLC patients may express PD-L1. Preclinical data suggest that an even higher percentage of tumors from stage III patients are PD-L1 positive (*Genentech personal communication*) hence these patients are likely to be the best candidates for induction trials of checkpoint inhibition. This trial is intended to lead directly into a phase III trial of combined chemoradiotherapy/immunotherapy compared to standard chemoradiotherapy.

1.7.3. Trial Significance

Patients with stage III lung adenocarcinoma are treated with chemoradiotherapy with curative intent, but the vast majority of patients will relapse and die of disease. This patient population is healthier and more likely to have an intact immune system than patients with more advanced disease and with heavy cytotoxic pretreatment. The opportunity to add immune modulation with checkpoint inhibitors neoadjuvantly and adjuvantly in this patient population would be expected to improve overall survival significantly and may increase the proportion of patients who can be cured.

1.7.4. Rationale for Dose Selection and Duration of Treatment

Chemoradiotherapy will be the Alliance standard carboplatin + paclitaxel concurrent with RT as most recently used in the 0617 clinical trial. This regimen has shown the best survival statistics to date with a weekly low dose carboplatin and paclitaxel chemotherapy backbone and a radiation dose of 60 Gy. The duration of atezolizumab therapy of one year with an interruption during chemoradiotherapy is based on previous trials with the agent.

1.7.5. Rationale for Endpoints

1.7.5.1 Primary - Induction immunotherapy may not produce early tumor shrinkage so the traditional tumor response measurement method, such as RECIST, may not accurately capture the immunotherapy efficacy. In this trial, we elected to use disease control rate as the primary endpoint, rather than response rate (CR+PR) defined in RECIST 1.1. The decision was intended to better capture the immunotherapy effect among those patients who may respond to immunotherapy without early tumor shrinkage.[vii]

1.7.5.2 Secondary - The secondary endpoints of PFS, OS, RR and safety are standard. The proportion of patients completing induction chemoradiation and consolidation chemotherapy is of particular importance in a stage III NSCLC population. - The denominator will be the total number of patients who register to the trial and start the induction immunotherapy. The numerator will be the number of the patients who complete induction immunotherapy, chemoradiation therapy and consolidation chemotherapy. These data are vital to compare the study therapy with recent multimodality trials in stage III NSCLC patients without the immunotherapy component.

1.7.5.3 Translational Research. The primary correlative analysis for this trial will be the correlation of PD-L1 expression in tumor specimens with changes in immune system

function and response to atezolizumab. Please refer to the correlative sciences manual for the study for additional detail.

1.7.5.4 Correlative biomarkers
Please refer to specimen management manual for additional information and to Appendix 11 for correlative science objectives.

1.7.5.5 Patient reported outcomes/QoL
Questionnaires will be collected at the following time points: on Cycle 1 Day One of Induction Therapy, Day 1 of Concurrent Therapy, Cycle 1 Day of Consolidation Therapy and at 3 month intervals throughout adjuvant therapy. The EORTC QLQ-C30 is a well-validated cancer-specific measure[73]. It is comprised of six functional scales (physical, role, emotional, cognitive, social, and global health status/quality of life); three symptom scales (fatigue, pain, and nausea and vomiting); and six single items (appetite loss, constipation, diarrhea, dyspnea, sleep disturbance, and economic consequences of the disease and treatment). Functional and symptom scales/items are combined into a newly developed single health-related QOL (HRQL) summary measure. The summary score and all scales and single items range from 0-100. A high score for the summary measure and all functional scales indicates a high/better level of QOL or functioning, whereas a high score on a symptom scale/item represents a higher level of symptoms/problems.

2. Objectives

2.1. Primary Objective

The primary objective of this single arm phase II trial is to determine whether neoadjuvant and adjuvant anti-PD-L1 therapy bracketing standard chemoradiation therapy and consolidation therapy is worthy of further investigation in NSCLC patients treated with curative intent for stage IIIA and IIIB disease (AJCC 7th edition). The primary endpoint will be the disease control rate (DCR) after 12 weeks induction immunotherapy.

2.2. Secondary Objectives

Secondary endpoints include objective response rate (ORR), progression free survival (PFS), overall survival (OS) and the proportion of patients who complete induction immunotherapy, chemoradiation therapy and consolidation chemotherapy. Toxicity including immune related adverse events will be assessed for all patients receiving any study therapy.

2.3. Translational Science Principal Objective

Assess the utility of PD-L1 as a biomarker for DCR, ORR, PFS, OS in the study population.

2.4. Translational Science Additional Objectives

Study the association of biomarkers, including immunologic signatures, and clinical outcomes. Analyses may include, but are not limited to, multipanel immunohistochemistry, gene expression profiling by Nanostring, RNAseq or RT-PCR, whole exome and T cell receptor sequencing, cytokine/chemokine analysis, flow cytometry, and T cell function. Specimens will include blood and FFPE tissue. Time-points are: at baseline, after atezolizumab induction, after chemoradiotherapy,

during adjuvant atezolizumab monotherapy, at treatment completion, and during follow-up. Please see appendix 11 for detailed correlative science description and procedures.

2.5. Other Correlative Science Objectives

Quality of life endpoints will be measured by the EORTC QLQ-30 assessed during induction, during chemoradiotherapy, during adjuvant atezolizumab at 3 month intervals.

2.6. Study Design

Single arm phase II trial of induction immunotherapy with anti-PD-L1 for patients with unresectable stage III NSCLC and PS 0-1.

The phase II trial will register a total 63 patients. Assuming 5% ineligibility and cancelation, 60 eligible patients are expected to receive at least one cycle of the experimental agent. PD-L1 status will be determined by Ventana assay (TC/IC). Of 60 patients, we expect approximately 40 and 20 patients are PD-L1 positive (≥1% expression in tumor cells or tumor-infiltrating immune cells) and PD-L1 negative (otherwise), respectively. The DCR in PD-L1 negative patients in particular is a topic of great interest and will be assessed in real time by study staff in order to avoid harm to this particular population.

2.7. Sample Size

The disease control rate (DCR) is assumed the same for PD-L1 positives and negatives. With 60 eligible and treated patients, the study has approximately 90% power to detect H0:P</=0.50 versus H1: P>/= 0.67, where p is the disease control rate (DCR) after 12 weeks neoadjuvant anti-PD-L1 therapy, with a one-sided binomial test at a significance level of 0.10. In particular, if 35 or fewer of these patients remain disease controlled, it will be concluded that the treatment regimen is not worthy of further investigation. Otherwise, it will be concluded that the treatment regimen has sufficient efficacy to warrant further investigation. Under the design, the probability of erroneously concluding that the treatment regimen is worthy of further investigation when the DCR is truly 50% or less is 0.0775. The probability of erroneously concluding that the treatment regimen is NOT worthy of further investigation when the true DCR is 67% or greater is 0.0999.

2.8. Accrual Rate and Accrual Duration

A total of 63 patients will be registered to the trial. The trial will be open for patient enrollment in 15 Alliance institutions selected for their experience and prior good enrollment in clinical trials of chemoradiotherapy for NSCLC. We expect approximately 4 unresectable stage III NSCLC patients who meet the eligibility criteria will be enrolled per month. It will take approximately 16 months to reach the target accrual. Follow up of at least 18 months will be required for all patients for progression free survival and overall survival.

2.9. Primary Endpoint Completion Date

Approximately two years after the first enrollment.

2.10. Data Safety Monitoring

If 5 or more of the first 20 treated patients experience grade 4/5 non-hematologic adverse events that are probably, possibly, or definitely related to study treatments, OR if the rate of treatment-

related deaths within the first 60 days exceeds 4 among the first 20 patients at any time, accrual to the study will be suspended to allow for investigation. If the true rate of grade 4/5 non-hematologic AEs is 10%, 20%, 30%, 33%, 40%, 50%, the corresponding probability of accrual suspension is 0.043, 0.370, 0.762, 0.848, 0.949, 0.994, respectively. The safety stopping rule will allow trial suspension with considerable probability when excessive AE events occur in an initial cohort of treated patients, e.g. >84.8% if the true SAE is ≥30%. After consideration by the study team, a decision will be made as to whether accrual can be resumed, potentially with modifications to entry criteria and/or study conduct.

2.11. Analytic Methods

The analysis cohort will be the patients who meet eligibility criteria and receive at least one cycle of the experimental agent.

The primary endpoint is disease control rate (DCR), which is defined as the proportion of patients who reach complete/partial response and stable disease after 12 weeks of neoadjuvant atezolizumab therapy. Binomial exact test will be used for testing. The 90% exact confidence interval for DCR will be provided.

For the analysis of secondary endpoints, the primary analysis cohort will be used. Objective response rate (ORR) is the rate of best overall response (complete or partial response) after 12 weeks of neoadjuvant atezolizumab therapy. ORR and its 95% confidence interval will be estimated. Progression-free survival (PFS) is defined as the time from the start of neoadjuvant therapy to disease progression or recurrence (first disease recurrence or death, whichever comes first). The Kaplan-Meier estimator will be used to estimate median PFS, PFS at 12 months, and their confidence intervals. Similar analysis will be conducted to estimate median overall survival (OS) and OS at 12 and 18 months. The frequencies of metastases by site will be tabulated.

The proportion of patients who complete induction immunotherapy, chemoradiation therapy and consolidation chemotherapy will be estimated. Its 95% confidence interval will be provided.

Overall treatment-related adverse events will be summarized by phase of protocol treatment (Induction immunotherapy, Chemoradiotherapy, Consolidation chemotherapy, Adjuvant immunotherapy), type and grade for all patients who received at least one cycle of atezolizumab therapy.

Blood based biomarkers will be evaluated before and after the protocol treatment. The association of the baseline value and the changes of these biomarkers with clinical outcomes, such as objective response, overall survival and progression free survival, will be evaluated using logistic regression and Cox models.

QoL will be measured by the EORTC QLQ-30. The QoL scores, including mean, standard deviation, range, for each scale will be summarized at the following time points: induction at 6 & 12 weeks, chemoradiotherapy at completion of concurrent phase + after consolidation, during adjuvant atezolizumab at 3 month intervals.

3. Patient Selection

3.1. Inclusion Criteria

Patients must meet the following criteria for study entry:

1) Newly diagnosed stage IIIA/B (per AJCC 7) NSCLC, PS 0-1.
2) No active autoimmune disease or uncontrolled infection, normal bone marrow, renal, hepatic function, FEV1 ≥ 1.2L, no significant underlying heart or lung disease.
3) Pathologically proven diagnosis of NSCLC.
4) Measurable Stage IIIA or IIIB disease per AJCC 7.
5) Patients must be considered unresectable or inoperable. Patients with nodal recurrence after surgery for early-stage NSCLC are eligible if the following criteria are met:
    - No prior chemotherapy or radiation for this lung cancer
    - Prior curative-intent surgery at least 3 months prior to the nodal recurrence
6) Stage III A or B disease (per AJCC 7) with minimum diagnostic evaluation within 6 weeks to include:
    - History/physical examination
    - Contrast enhanced CT of the chest and upper abdomen
    - MRI of the brain with contrast (or CT with contrast if MRI is medically contraindicated)
    - PET/CT
7) If pleural fluid is visible on CT scan, thoracentesis to exclude malignancy should be obtained. Patients with effusions that are too small to tap are eligible.
8) Patients must be at least 4 weeks from major surgery and must be fully recovered.
9) Age ≥ 18 years.
10) Availability of representative formalin-fixed paraffin-embedded (FFPE) tumor specimens in paraffin blocks (blocks are preferred) or at least 4 (preferably 20) unstained slides, with an associated pathology report, for central testing of tumor PD-L1 expression.
    - If an archived tumor block exists, then either the block (preferred) or at least 4 (preferably 20) unstained slides from the block should be submitted. Tumor tissue should be of good quality based on total and viable tumor content, i.e. at least 50 viable tumor cells and intact tissue architecture. Fine-needle aspiration, brushing, and lavage samples are not acceptable. If the block is tissue from a core-needle biopsy, then the block should contain tissue from at least three cores to be sufficient for evaluation.
    - Patients who do not have existing (archived) tissue specimens meeting eligibility requirements may undergo a biopsy during the screening period. Acceptable samples include core-needle biopsies for deep tumor tissue (minimum of three cores) or excisional, or forceps biopsies for endobronchial or nodal lesions. The tissue should be fixed in formalin and embedded on site and sent as a block.

11) Adequate hematologic and end organ function, defined by the following laboratory results obtained within 14 days prior to the first study treatment (Cycle 1, Day 1; if repeat labs are obtained on or prior to C1D1 must re-meet eligibility criteria to treat the subject):

- ANC ≥ 1500 cells/μL
- WBC counts > 2500/μL
- Lymphocyte count ≥ 300/μL
- Platelet count ≥ 100,000/μL
- Hemoglobin ≥ 10.0 g/dL
- Total bilirubin ≤ 1.5 × upper limit of normal (ULN) with the following exception:
  - Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.
- AST and ALT ≤ 3.0 × ULN
- Alkaline phosphatase ≤ 2.5 × ULN
- Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:
  - $\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$

12) Measurable disease per RECIST v1.1 (see Appendix 3).

13) For female patients of childbearing potential and male patients with partners of childbearing potential, agreement (by patient and/or partner) to use highly effective form(s) of contraception (i.e., one that results in a low failure rate [< 1% per year] when used consistently and correctly, such as hormonal or barrier method of birth control, or abstinence) and to continue its use for 150 days after the last dose of atezolizumab.

14) Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (see Appendix 5).

3.2. Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.

General Exclusion Criteria:

1) Active autoimmune disease.
2) Greater than minimal, exudative, or cytologically positive pleural effusions.
3) Involved contralateral hilar nodes.
4) 10% weight loss within the past month.
5) Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years; non-invasive conditions such as carcinoma in situ of the breast, localized prostate cancer or thyroid nodules, carcinoma in situ of the oral cavity or cervix are all permissible.

6) Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable.

7) Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields.

8) Prior severe infusion reaction to a monoclonal antibody.

9) Severe, active co-morbidity, defined as follows:

10) Significant history of uncontrolled cardiac disease; i.e., uncontrolled hypertension, unstable angina, myocardial infarction within the last 6 months, uncontrolled congestive heart failure, and cardiomyopathy with decreased ejection fraction.

11) Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration or within 2 weeks of cycle 1 day 1.

    Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days before registration.

12) Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects.

13) Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, HIV testing is required for entry into this protocol due to the immunologic basis for induction treatment.

14) Pregnancy, lactation, or inability or unwillingness to use medically acceptable forms of contraception if pregnancy is a risk.

15) Any history of allergic reaction to paclitaxel or other taxanes, or to carboplatin.

16) Uncontrolled neuropathy grade 2 or greater regardless of cause.

17) Any approved anticancer therapy, including chemotherapy, hormonal therapy, or radiotherapy, within 3 weeks prior to initiation of study treatment; however, the following are allowed:

    i. Hormone-replacement therapy or oral contraceptives

    ii. Herbal therapy > 1 week prior to Cycle 1, Day 1 (herbal therapy intended as anticancer therapy must be discontinued at least 1 week prior to Cycle 1, Day 1)

18) Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease.

19) Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.

20) Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

21) Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

22) Inability to comply with study and follow-up procedures.

23) History of active autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

24) Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.

25) Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.

26) Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:

    Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations.

    Rash must cover less than 10% of body surface area (BSA).

    Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, fluocinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%).

    No acute exacerbations of underlying condition within the last 6 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids).

27) History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan.

28) 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.

29) Active tuberculosis.

30) Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study.

31) Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study.

32) Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study.

Medication-Related Exclusion Criteria:

33) Prior treatment with anti–PD-1, or anti–PD-L1 therapeutic antibody or pathway-targeting agents.

34) Treatment with systemic immunostimulatory agents (including but not limited to interferon [IFN]-α or interleukin [IL]-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1.

35) Treatment with investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer).

36) Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, or anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1.

37) Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.

38) The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

39) History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

40) Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation.

4. Patient Enrollment

4.1. Site Enrollment Requirements

Site must submit all required essential documents including:

- IRB/Regulatory Approval
- Investigator 1572(s)
- Institutional informed consent form
- Following regulatory and ethical approval for each participating site, it is the responsibility of the Sponsor to formally activate sites according to local obligations. Sites will only be able to enroll patients once formal site activation has been performed by the Sponsor.

4.2. Patient Enrollment Procedures

Informed consent: The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and enrollment.

Patient enrollment will be facilitated using the AFT web-based RAVE EDC (electronic data capture) system.

Patients must be enrolled prior to submission of biospecimens. After written informed consent has been obtained, the study site will obtain a unique patient identifier which will stay the same throughout the entire study. Patients enrolled but not treated for any reason have to be documented as a Screening Failure in IRT.

Prior to accessing AFT EDC, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form.

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5. Schedule of Assessments

Assessment	**Screening**				**Registration**	**Induction Immunotherapy (Cycle=21 Days)**				**Concurrent Therapy** (weekly during radiation):						**Consolidation** (1 cycle = 21 days, 2 cycles total)		Adjuvant Immuno-therapy (Q21days to complete 1 Year)	Treatment Completion/ ET Visit[e]	Follow-up visit (months after the termination of treatment)		
																					3	6	12
Day	-60	-42	-28	-16	0	C1D1	C2D1	C3D1	C4D1	D1	D8	D15	D22	D29	D36	C1D1	C2D1					
Informed consent		X																				
Demographic data		X																				
General med history & baseline conditions		X																				
Vital signs[a]			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Height			X																			
Weight			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Physical examination			X			X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Hematology[b]				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Chemistry[c]				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X			
TSH				X				X		X						X		X	X			
Toxicity Assessment						X	X	X	X						X		X	X	X			
CT Scan for Tumor Measurement[h]			X					X		X						X		X – q 3 months	X	X	X	X
PET/CT Scan			X																	X	X	X
Brain MRI (CT if MRI is contraindicated)		X																				
HIV Test				X																		
Pregnancy Test				X																		

Assessment	Screening				Registration	Induction Immunotherapy (Cycle=21 Days)				Concurrent Therapy (weekly during radiation):						Consolidation (1 cycle = 21 days, 2 cycles total)		Adjuvant Immuno-therapy (Q21days to complete 1 Year)	Treatment Completion/ ET Visit[e]	Follow-up visit (months after the termination of treatment)		
																				3	6	12
Day	-60	-42	-28	-16	0	C1D1	C2D1	C3D1	C4D1	D1	D8	D15	D22	D29	D36	C1D1	C2D1					
Other laboratory tests[k]				X																		
Drug administration						X	X	X	X	X	X	X	X	X	X	X	X	X				
Response assessment[i]								X		X						X		X – q 3 months	X	X	X	X
Concomitant medications					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Adverse events					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ECG				X															X			
Echocardiogram[j]		X																X (prior to first infusion)	X			
PFTs[d]	X									X									X			
QoL Assessments[i]						X				X						X		X – q 3 months				
Tumor Tissue[f]	X																					
ACD and heparin tubes for correlative research[g]						X				X						X		X – q 3 months	X			
Whole Blood Streck[g]						X				X						X		X – q3 months	X	X	X	X

Abbreviation: ECG= electrocardiogram; ET= Early termination; PFT= pulmonary function tests; QoL= quality of life;

[a] Heart rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[b] Hemoglobin, hematocrit, platelet count, WBC count, percent and absolute differential count. If obtained during screening within 7 days of C1D1, need not be repeated on C1D1.

[c] Sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase. If obtained during screening within 7 days of C1D1, need not be repeated on C1D1.

[d] Pulmonary Function Tests will be completed at the following time intervals and shall include spirometry and diffusion capacity testing: Prior to enrollment as pre-screening, between completion of induction immunotherapy and start of chemoradiotherapy, at 12 months after study entry

[e] Treatment completion refers to a subject's completion of 12 months of study treatment, or early discontinuation of study treatment. For those who complete study treatment, the treatment completion visit should occur within 21 days of the last dose.

[f] FFPE blocks (preferred) or slides, see section 3.1.11.

[g] 10 ml in two Streck tubes, 5 ml in two ACD tubes and 10 ml in two heparin tubes. C1D1 draw may be performed any time after registration and prior to study drug infusion. Samples should only be drawn M-Th per shipment requirements.

[h] CT scan for tumor measurements – This will be a CT of the chest with IV contrast (unless contra-indicated). These scans will occur within 28 days prior to registration, after completion of the second cycle of induction immunotherapy but prior to the third cycle starting, and at least seven days after the completion of the last cycle of induction immunotherapy but no later than Day 1 of concurrent chemoradiotherapy. CT of the entire chest with IV contrast obtained for radiotherapy simulation may serve as the third scan provided it is of diagnostic quality and read by a radiologist. The CT scan at the after the completion of concurrent chemoradiotherapy will occur at least 14 days after the completion of chemoradiotherapy but no later than Day 1 of the consolidative chemotherapy. During adjuvant immunotherapy, CT scans will be completed every 3 months, starting 3 months after the prior scan.

[i] These assessments during adjuvant immunotherapy should be performed in the same timeframe as the CT scans.

[j] Echocardiogram – Required at screening, otherwise as clinically indicated at other timepoints.

[k] Thyroid function testing (free T3 and free T4), Epstein-Barr virus (EBV) serology (EBNA IgG), hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen), and HCV serology (anti-HCV) as clinically indicated. HBV DNA test is required for patients who have known positive serology for anti HBc. HCV RNA test is required for patients who have known positive serology for anti HCV.

6. Study Assessments and Procedures

The flowchart of scheduled study assessments is provided in Section 5. Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly. Systemic therapy visits with be within 3 days except within 1 day for the concurrent chemoradiotherapy portion.

6.1. Medical History

Medical history includes clinically significant diseases within the previous 5 years, smoking history, cancer history (including tumor characteristics such as hormone receptor status), prior cancer therapies and procedures, and all medications used by the patient within 7 days before the screening visit (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies).

6.2. Physical Examination and Vital Signs

A complete physical examination will be performed at screening and at the treatment discontinuation visit and should include the evaluation of head, eye, ear, nose, and throat and cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems.

A limited physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as AEs if appropriate.

All patients should be monitored for symptoms of brain metastases. Symptoms suggestive of new or worsening CNS metastases should prompt a full neurological examination. A CT or magnetic resonance imaging (MRI) scan of the head should be done as clinically indicated to confirm or refute new or worsening brain involvement.

Vital signs will include measurements of heart rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature.

For the first infusion, the patient's vital signs (heart rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

6.3. Laboratory Assessments

Samples for hematology, serum chemistries, coagulation, urinalysis, and the pregnancy test will be analyzed at the study site's local laboratory. Analysis of biomarkers on tumor and blood samples will be performed at a central laboratory.

Local laboratory assessments will include the following:

- Hematology (CBC, including RBC count, hemoglobin, hematocrit, WBC count with differential, and platelet count)
- Serum chemistries (glucose, BUN, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total bilirubin, ALT, AST, alkaline phosphatase, LDH, total protein, and albumin)
- TSHHIV test
- Pregnancy test, either serum or urine (for women of childbearing potential, including women who have had a tubal ligation)
- Thyroid function testing (free T3, and free T4), Epstein-Barr virus (EBV) serology (EBNA IgG), hepatitis B virus (HBV) serology (HBsAg, antibodies against HBsAg, hepatitis B core antigen), and HCV serology (anti-HCV) as clinically indicated

HBV DNA test is required for patients who have known positive serology for anti-HBc

HCV RNA test is required for patients who have known positive serology for anti-HCV

- Echocardiograms:
    - Echocardiograms will be obtained at the following time intervals:
        - Prior to enrollment as pre-screening (required)
        - Between completion of chemoradiotherapy and start of adjuvant immunotherapy (as clinically indicated)
        - At study completion (as clinically indicated)
- Pulmonary Function Testing:
    - Pulmonary Function tests will be completed at the following time intervals and shall include spirometry and diffusion capacity testing:
        - Prior to enrollment as pre-screening
        - Between completion of induction immunotherapy and start of chemoradiotherapy
        - At 12 months after start of study therapy.

7. Data and Specimen Submission

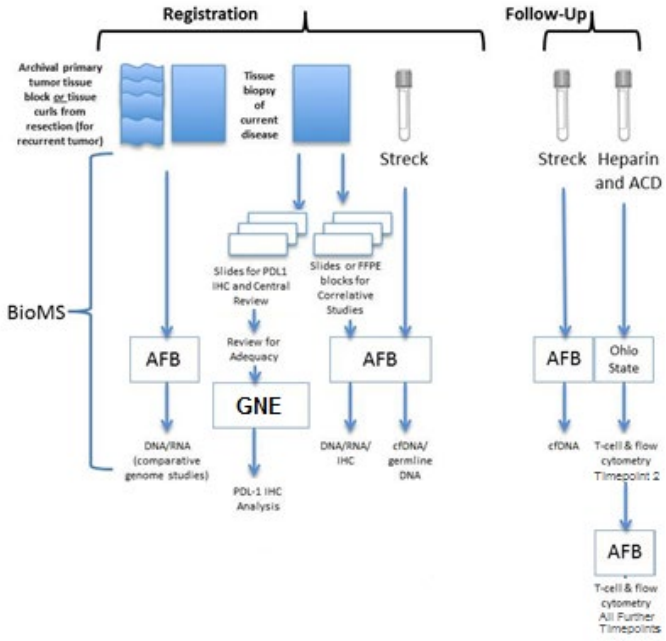
7.1. Data Collection and Submission

Data collection for this study will be done through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in AFT CTMS System. See Study Manual of Operations/Data Entry Guidelines for additional instructions.

7.2. Biospecimen Collection, Shipping and Processing

Tissue from a formalin-fixed biopsy of a tumor lesion not previously irradiated must be collected for integrated correlative PD-L1 biomarker analysis. A fine needle aspirate or cytologic specimen will not be accepted. Core needle or excisional biopsies, or resected tissue is required. For core needle biopsies, 3 full cores are required to be submitted. Only patients with an adequate tissue biopsy submission are eligible for enrollment (see section 3.1.9).

7.3. Biospecimen Collection Schemas



7.4. Biospecimen Logging and Tracking (AFT BioMS)

Use of the AFT Biospecimen Management System (AFT.BioMS) is mandatory and all specimens must be logged and shipped via this system. AFT BioMS is a web-based system for logging and tracking all biospecimens collected on AFT trials. Authorized individuals may access AFT.BioMS through the AFT single sign on portal, using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the AFT.BioMS system, please refer to the 'Help' links on the BioMS webpage to access the on-line user manual, FAQs, and training videos. [redacted] Staff

members should familiarize themselves with the AFT.BioMS system and confirm that they are able to log into the system, prior to registering patients to the trial.

After logging collected specimens in AFT.BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

7.5. Biospecimen Shipping

Biospecimen shipping kits will be available for collecting and shipping biospecimens at baseline and follow up collection time points. Kits must be requested using the AFT.BioMS application. Instructions for using the AFT.BioMS kit request system may be found on the AFT.BioMS web site.

Please note that:

1. Tumor tissue for PD-L1 biomarker analysis **MUST** be submitted within 14 days of registration.
2. A formalin fixed tissue block is preferred, but if a block cannot be sent then unstained tissue section slides may be sent as a substitute.
3. If the tumor tissue (either newly obtained or from a previous diagnostic procedure) consists of needle core biopsy specimens, the block or slides submitted should contain at least three independent needle cores to ensure sufficient tumor and tumor representation for biomarker analysis.
4. Whole blood collected in heparin and ACD tubes must be shipped within 24 hours of collection. Also note that blood in Heparin and ACD tubes will be shipped to an independent location (Ohio State University) and NOT the AFT biorepository at Washington University in St. Louis. Proper use of the AFT.BioMS system will guide the user to ensure that the correct samples are shipped to the correct location.
5. Whole blood collected in BCT (Streck) tubes must be shipped within 72 hours of collection.

All submitted biospecimens must be physically labeled with the AFT patient number, patient's initials and date of specimen collected. A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens. A printed, de-identified copy of the institutional surgical pathology report should also be included with the shipment of surgical pathology tissue samples. Please be sure to use a method of shipping that is secure and traceable. Ship specimens on Monday through Thursday only. Shipping by overnight service to assure receipt is required. Do not ship specimens on Fridays or Saturdays. All specimens should be sent as directed by the address printed on each AFT.BioMS shipment manifest.

7.6. Biospecimen Collection

Specific instructions for biospecimen collection can be found in the correlative sciences manual.

Screening/Registration

The following biospecimens will be collected at screening:

A. MANDATORY- Slides for PD-L1 staining. Four 4 micron, unstained tumor tissue sections from a formalin fixed / paraffin embedded (FFPE) tissue block containing tumor

tissue should be serially cut and mounted onto positively charged glass slides, with at least 50 viable tumor cells. Slides must not be older than 60 days (freshly cut) although the FFPE blocks from which they originate may be older. Slides should be labeled with the patient study ID, institutional surgical pathology number, and serial cut number, i.e. 1-4. These must be submitted within 14 days of registration.

B. REQUIRED- Tumor tissue for additional correlative studies.

C. REQUIRED (if available)- For recurrent cases, tumor tissue from the primary case. If the patient is presenting with a recurrent tumor, and a tumor tissue block is available from the primary presentation case, a representative tumor tissue block from the original case or 1 H/E stained slide and tissue curls from that block should be submitted for correlative, comparative genomic studies. The total number of tissue curls to submit will depend upon the cross sectional area of the tissue face. Slide, block, or tissue curls should be labeled with the patient study ID and institutional surgical pathology number.

D. REQUIRED- Whole blood in two ACD yellow tubes (10 ml). Collect 5 mL of whole blood by standard venous phlebotomy into each of two ACD yellow tubes provided. Tube should be labeled with patient study number, patient initials, and date / time of collection. After collection, invert the tube 10 times to ensure adequate mixing and anticoagulation. ACD tubes must be shipped within 24 hours of collection.

E. REQUIRED- Whole blood in two cell stabilization (Streck) tubes (20 ml). Collect 10 mL of whole blood by standard venous phlebotomy into each of two BCT (Streck) tubes provided. Tube should be labeled with patient study number, patient initials, and date / time of collection. After collection invert the tube 10 times to ensure adequate mixing and preservation. Store tube at room temperature until ready for shipment. Whole blood collected in BCT (Streck) tubes must be shipped within 72 hours of collection.

F. REQUIRED- Whole blood in two heparin tubes (20 ml). Collect 10 mL whole blood in each of two heparin tubes. Tube should be labeled with patient study number, patient initials, and date / time of collection. After collection invert the tube 10 times to ensure adequate mixing and preservation. Store tube at room temperature until ready for shipment. Heparin tubes must be shipped within 24 hours of collection.

Whole blood biospecimens will be collected at each of these 9 time points:
Baseline (pre-treatment on C1D1 of induction immunotherapy) / D1 of concurrent chemoradiation therapy / D1 of consolidation chemotherapy / 3 months after consolidation chemotherapy during adjuvant immunotherapy / 6 months after consolidation chemotherapy during adjuvant immunotherapy / end of study
Streck tubes only during follow-up: 3 months after end of treatment / 6 months after end of treatment / 12 months after end of treatment

8. Study Treatment

8.1. Treatment Plan

Protocol treatment is to begin within 21 days of registration. Questions regarding treatment should be directed to the ALLIANCE Study Chair.

Protocol therapy will consist of induction (neoadjuvant) atezolizumab 1200 mg IV every 21 days for 4 cycles followed by radiotherapy given with concurrent chemotherapy for six weeks. Consolidative chemotherapy will be given for two cycles after the completion of concurrent therapy. Adjuvant atezolizumab will be administered as in the neoadjuvant portion of the trial every 21 days to complete a total of one year of therapy.

Concurrent Therapy (1 cycle = 36 days):
Concurrent Chemoradiotherapy will begin 21 to 28 days after completion of the last dose of induction immunotherapy. Chemotherapy and radiotherapy should be started within 1 day of each other.
Patients will receive paclitaxel 50 mg/m^2 by IV over 1 hour weekly with standard premedication followed by carboplatin AUC 2 by IV over 30-60 minutes for 6 weeks (days 1,8,15,22,29,36).

Consolidation (1 cycle = 21 days): 3-5 weeks following the end of radiotherapy, patients will receive paclitaxel 200 mg/m^2 by IV over 3 hours followed by carboplatin AUC 6 by IV over 30-60 minutes on day 1 of each 21 day cycle for a total of 2 cycles (days 1 and 22).

8.2. Radiotherapy

All patients will receive a radiotherapy course using single daily fractions of 2 Gy for a total dose of 60 Gy. Conformal 3-dimensional or IMRT treatment planning will be utilized. CT scans for radiotherapy simulation should be performed within 16 days of start of radiotherapy. All treatment plans must be reviewed by the IROC Rhode Island Quality Assurance Review Center (QARC) prior to initiating therapy. **NOTE:** Digital submission of treatment plans is required on this study.

8.2.1. Target Volume Definitions

The nomenclature and definitions of ICRU Reports 50 and 62 shall be followed in this study.

The GTV will be the volume of tumor visible on CT or PET imaging or biopsy proven sites. This will in general include lymph nodes within the mediastinum ≥ 1.0 cm in short diameter and/or PET positive lymph nodes. Information from PET imaging should be used to determine occult nodal areas as well as to accurately contour gross disease within areas of atelectasis. For areas within or near inflated lung tissue, lung window settings will be utilized for contouring. For disease within or abutting the mediastinum, soft tissue window settings will be used.

The GTV will be expanded based on motion assessment imaging to account for target motion and thus an internal target volume (ITV) will be created.

A 0.5 cm (CTV) expansion of the ITV will be utilized to account for potential occult tumor involvement. This can be edited back from areas were extension cannot occur (blood vessels, bone, chest wall, etc.) unless there is imaging evidence that inclusion would be logical. Elective nodal irradiation of lymph nodes is not allowed on this study. Only areas of gross disease as determined by contrast enhanced CT and PET imaging will be targeted.

The CTV will be expanded an additional uniform 5mm minimum to create a planning target volume (PTV) to which the radiotherapy dose will be prescribed. This can be adjusted to no more than 1.0 cm if patient specific uncertainty requires additional planning margin.

If patients have a complete response (CR) to induction immunotherapy, the target volume will be modified such that a CTV will be delineated to include the pre-immunotherapy nodal stations in the hilum and mediastinum and as best as possible, the location of the original primary tumor. The size of this CTV should take into account anatomic changes as a result of the response to therapy, i.e. diminishment in mediastinal width due to response. This CTV will be expanded by 5mm to create a PTV.

8.2.2. Treatment Techniques

3D Conformal Planning or IMRT is required on this protocol. Both planar and non-coplanar field arrangements are acceptable. If IMRT is used, patient specific IMRT QA will be required prior to treatment with the IMRT plan.

- Patient Position

  A custom immobilization cast is encouraged but not required. All components of immobilization must, in conjunction with the image guidance being used, ensure that both interfraction set-up uncertainty and unaccounted for intrafraction motion be limited to less than 5mm (PTV margin). Patients must be treated in the supine position.

- Inhibition of effects of internal organ motion:

  Motion management with respiratory gating, active breathing control (ABC), or breath hold and monitoring techniques will be encouraged. IMRT will be restricted to patients with less than 1cm of tumor motion on 4D imaging or utilizing of gating, ABC, or breath hold methods. Abdominal compression as a method of minimizing respiratory motion is allowed. The Motion Management Reporting Form shall be submitted to document the method used.

- Image Guidance:

  A reliable method of daily image guidance will be utilized. This can include but is not limited to daily conebeam imaging, fiducial marker tracking systems, kV – kV matching.

8.2.3. Equipment

- **Modality** - 3D Conformal or IMRT Radiotherapy
- **Energy** - Megavoltage quality radiation will be used with a nominal energy of 4-12 MV. C0-60 treatment is not allowed on this protocol. Proton therapy is not allowed on this protocol.
- **Geometry** - The distance from the radiation source to the isocenter should not be less than 100 cm.

3.3.1 Target Dose

- Prescribed Dose: 60 Gy in 30 fractions of 2.0 Gy per fraction given once daily.

- Dose Uniformity: The prescribed isodose volume will cover at least 95% of the PTV. The minimum PTV dose must not fall below 95% of the prescription dose. The maximum dose must not exceed a value that is 125% of the prescribed dose. The minimum and maximum doses will be defined as the dose to a 0.1cc volume of the PTV.
- Acceptable and Unacceptable Variations: Deviations from the above target coverage are not desirable, but are acceptable for treatment situations in which the target to critical structure geometry is challenging. Variations Acceptable include: The prescribed dose can cover as little as 90% of the PTV. The minimum dose to the PTV can likewise fall to 90% of the prescribed dose. The maximum dose cannot exceed 130% of the prescribed dose. Unacceptable deviations occur if the variation acceptable limits are exceeded. Additionally, a deviation unacceptable is assigned if more than 1 cc of tissue outside the PTV receives > 120% of the prescribed dose.
- Tissue Heterogeneity: All dose calculations will account for the density differences within the irradiated volume.
- Approved Dose Algorithms: Planning must be performed using an approved dose calculation algorithm. Approved algorithms include: convolution superposition, collapsed cone convolution, and Monte Carlo. Contact QARC [redacted] for information regarding approved dose algorithms.
- Additionally, the treatment planning system PlanUNC, which uses a Clarkson's-integration with a 2-source model and modified Batho correction dose algorithm, will be allowed as part of this protocol based on successful irradiation of the standardized lung phantom in 2009.

8.2.4. Imaging Requirements

Computed tomography will be the primary image platform for targeting and treatment planning. The planning CT scans are encouraged to be done with *IV* contrast unless the patient has allergic problems with contrast or has renal insufficiency. Contrast will allow better distinction between tumor and adjacent normal tissue or atelectasis. Axial acquisitions with gantry 0 degrees will be required with spacing ≤ 3.0 mm between scans in the region of the tumor. Images will be transferred to the treatment planning computers via direct lines, disc, or tape.

- The additional exception to the use of IV contrast with the CT planning scan will be if the restaging diagnostic CT of the chest at the completion of the induction immunotherapy occurs within 10 days (before or after) of the planning CT in such a way that it can be timely incorporated into the planning process and that the patient can start on time. This will minimize the possibility of close-proximity contrast injections.

Four-dimensional CT (4D-CT) is permitted and encouraged for the study. There are many valid approaches to defining target volumes and margins using multiple datasets representing different phases of the breathing cycle. These include but not limited to:

a. the ITV (Internal Target Volume) concept from ICRU 62 with an appropriate margin accounting for geometric uncertainties (uniform 5 mm recommended) to define the PTV; this method is preferred for purposes of this protocol.

b. the mean target position with an appropriate margin to account for target motion and geometric uncertainties to define the PTV;

c. two helical scans, one scan with the patient at inhale breath-hold and the second scan with patient at exhale breath-hold.

Options B and C have inherently more uncertainty and the PTV margin will be a minimum of 7 mm with a maximum of 1 cm based on discretion of treating physician. The following will be required in terms of documenting target motion:

1. For particular method of target motion suppression (abdominal compression, breath hold, etc.), keep a tally of target motion range for each patient treated. Describe clearly the method utilized in the measurement of range of target motion and provide estimated error of measurement. Justify the estimation of error.
2. It is preferable to have information on range of motion along each axis of the patient's body (sup-inf, ap-pa, lt-rt). In case such information is not available, provide range of motion in 1 or 2 directions with clear indication of the orientation of the axis along which the motion range is evaluated.
3. In case of multiple measurements of ranges of motion (at simulations and/or at treatments, possibly pre- and post-treatments) provide information about the day and time when the data have been collected.
4. When data for some patients/treatment fractions is not collected the record of the missing measurement has to be kept and reported. If there is a clinical reason for not collecting data, it needs to be reported as well.
5. The reported range of motion has to be separated from setup errors.

A treatment planning FDG PET/CT scan (or FDG-PET alone) with the patient in the treatment position may be utilized to aid in treatment planning. If no dedicated treatment planning PET imaging is available then the staging PET imaging must be reviewed by the treating physician in order to accurately contour the target areas.

8.2.5. Time-dose Considerations

Treatment will be delivered in single daily fractions, 5 fractions per week.

Adjustments for Treatment Interruptions: There are no planned radiotherapy rests. Treatment interruptions are strongly discouraged. The Study Chair should be notified for treatment interruptions > 3 days not including weekends and traditional holidays.

8.2.6. Contouring of Normal Tissue Structures

Spinal Cord

The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at the level of the cricoid cartilage and extending to the level of the GE junction. In short, this should include the same contouring range as that for the esophagus.

Esophagus

The esophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The esophagus should be contoured starting at the cricoid cartilage and extend inferiorly to the level of the GE junction.

Brachial Plexus

The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from C5 to T2. The brachial plexus will consist of the actual roots and trunks of the brachial plexus without including the surrogate vasculature. The plexus will be outlined starting from the C5 nerve root and ending at the sublavian neurovascular bundle. Please refer to Kong et al IJROBP 2010 thoracic radiotherapy contouring atlas for description of contouring techniques.[36]

Heart

The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the root of the great vessels and extend inferiorly to the apex of the heart.

Whole Lung

Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated and collapsed lung should be contoured; however, gross tumor (GTV) and trachea/ipsilateral bronchus when contouring structure should not be included in this structure.

Chest Wall

Although no specific dose constraints will be used, the dose to the chest wall is of interested and will be required. The chest wall is defined as 3cm thick expansion of the lung contour toward the periphery of the patient subtracting the lung and mediastinal contents.

Bronchial Tree

The dose to the proximal bronchial tree will not be restricted but recorded for this protocol in order to potentially learn some dose constraint for hypofractionated therapy with regard to this organ. The bronchial tree will be defined as the distal 2 cm of trachea and include the mainstem bronchi, and lobar bronchi to the level of the segmental bronchi. Please refer to Kong et al IJROBP thoracic contouring atlas for detailed descriptions.[36]

8.2.7. Normal Tissue Sparing

The following dose constraints will be followed:

Lung

V20 > **35**% will be a minor deviation, V20 > **40**% will be a major deviation. Mean Lung Dose will be recorded and in general should be kept below 20 Gy

although the V20 constraints will be utilized as the dose limitations for purposes of this protocol.

Heart

The heart will be treated with the following limits: V50 < 25% and mean heart dose < 20 Gy.

Spinal Cord

The maximum cumulative dose to any contiguous volume ≥ 0.03 cc in the spinal cord will be: 50.0 Gy.

Esophagus

The esophagus is in general located in close proximity to nodal areas involved in stage 3 NSCLC and therefore is challenging to limit the total dose without sacrificing tumor coverage. In general < 30% of the contoured esophagus will be allowed to receive a dose > 55 Gy. This is also not an absolute requirement but maximum dose to a contiguous 5cc of the esophagus will be limited to ≤ 105% of the prescription dose when feasible.

Brachial Plexus

The maximum cumulative dose to any contiguous volume ≥ 0.03 cc in the brachial plexus will be: 62.1 Gy.

8.2.8. Quality Assurance Documentation

Digital Submission: Submission of treatment plans in digital format as DICOM RT is required. Digital data must include CT scans, structures, plan and dose files. Submission may be either by SFTP or CD. Instructions for data submission are on the QARC web site at [redacted] Any items on the list below that are not part of the digital submission may be submitted as screen captures along with the digital data.

Prior to the start of radiotherapy, the following data should be submitted for pre-treatment review:

Treatment Planning System Output

- RT treatment plan including CT, structures, dose, and plan files. These items are included in the digital plan.
- Dose volume histograms (DVH) of the GTV, spinal cord, chest wall, heart, esophagus, and liver. When using IMRT, a DVH shall be submitted for a category of tissue called "unspecified tissue." This is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure. DVH's are included in the digital plan.
- Digitally reconstructed radiographs (DRR) for each treatment field. DRR's are not required for IMRT.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.

Supportive Data

- Copies and reports of CT scans, PET scans, and other diagnostic materials used for planning target volumes.
- Prescription Sheet for Entire Treatment
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by QARC and the radiation oncology reviewers.

Forms

- RT-1 Dosimetry Summary Form
- Motion Management Reporting Form

Within one week of the completion of radiotherapy the following data shall be submitted.

- The RT-2 Radiotherapy Total Dose Record form.
- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas, critical organ and reference points
- Documentation listed above showing any modifications from original submission.

Supportive Data and Forms may be included with the transmission of the digital RT data via sFTP or submitted separately via e-mail. [redacted]

Questions regarding the dose calculations or documentation should be directed to: [redacted]

8.2.9. Definitions of Deviations in Protocol Performance

Prescription Dose

- **Variation Acceptable:** The dose to the prescription isodose surface differs from that in the protocol by between 6% and 10%.
- **Deviation Unacceptable:** The dose to the prescription isodose surface differs from that in the protocol by more than 10%.

Dose Uniformity

- **Variation Acceptable:** The prescribed dose covers between 90% and 95% of the PTV or the minimum dose to 1 cc of the PTV is between 90% and 95% of the prescribed dose or the maximum dose to 1 cc of the PTV exceeds 130% of the prescribed dose.
- **Deviation Unacceptable:** The prescribed dose covers less than 90% of the PTV or the minimum dose to 1 cc of the PTV is less than 90% of the prescribed dose or the maximum dose to 1 cc of tissue outside the PTV exceeds 120% of the prescribed dose.

Volume

- **Variation Acceptable:** Margins less than specified, or field(s) excessively large as deemed by the study chair.
- **Deviation Unacceptable:** GTV incorrectly defined resulting in fields that transect tumor.

Critical Organ

- **Variation Acceptable:** The lung V20 exceeds 35%; the dose to the heart, esophagus, or brachial exceeds the limits specified in Section 9.2.8.
- **Deviation Unacceptable:** The maximum dose to the spinal cord exceeds the limits specified in Section 9.2.8 or the lung V20 exceeds 40%.

8.3. Chemotherapy and immunotherapy

Patients will receive induction and adjuvant immunotherapy as well as concurrent chemoradiotherapy followed by consolidation chemotherapy (cycles 1 and 2).

Induction immunotherapy: Atezolizumab 1200 mg IV every 21 days for 4 cycles following the manufacturer's instructions for mixing and administration.

8.3.1. Concurrent Chemoradiotherapy (1 cycle = 36 days)

Paclitaxel* at 50 mg/m^2 by IV over 1 hour on days 1, 8, 15, 22.29, 36

Carboplatin** AUC 2 by IV over 30 minutes on days 1, 8, 15, 22.29, 36 following the paclitaxel administration

*Premedications for Paclitaxel and carboplatin should be given as per institutional standards of the treating institution

1.

** The Calvert equation (Dose = AUC X [GFR + 25]) will be used to calculate carboplatin dose. The GFR will be estimated by the Crockoft-Gault formula as follows:

$$\frac{\text{(140-age) x wt. in kg.}}{\text{72 x serum creatinine}} \times \begin{matrix}\text{0.85 for females}\\ \text{1.0 for males}\end{matrix}$$

A maximum calculated GFR of 125 ml/min will be used for both men and women.

Institutional standard may be used for paclitaxel and carboplatin dosing calculations.

8.3.2. Consolidation Chemotherapy (1 cycle = 21 days, 2 cycles to be administered)

Consolidation chemotherapy will begin 3-5 weeks after completion of radiotherapy. If the patient is unable to begin chemotherapy by the 5 week time point following radiotherapy, the chemotherapy may be delayed up to an additional 4 weeks. If the chemotherapy cannot be given during this time interval, the patient will be considered off protocol treatment. Patients will be required to have ANC $\geq$ 1,500/mm^3 and platelet count $\geq$100,000 mm^3 to start consolidation chemotherapy.

Paclitaxel* at 200 mg/m^2 by IV over 3 hours on day 1 of each 21 day cycle

Carboplatin** AUC 6 by IV over 30-60 minutes on day 1 of each 21 day cycle, following the paclitaxel administration

*Premedications for Paclitaxel and carboplatin should be given as per institutional standards of the treating institution

** The Calvert equation (Dose = AUC X [GFR + 25]) will be used to calculate carboplatin dose. The GFR will be estimated by the Crockoft-Gault formula as follows:

$$\frac{\text{(140-age) x wt. in kg.}}{\text{72 x serum creatinine}} \times \begin{matrix}\text{0.85 for females}\\ \text{1.0 for males}\end{matrix}$$

A maximum calculated creatinine clearance of 125 ml will be used for both men and women. Serum CR 0.7 minimum for calculating.

At the treating physician's discretion, institutional standard dosing for carboplatin and paclitaxel may be used, using actual body weight in the calculation of drug doses.

8.3.3. Adjuvant Immunotherapy

Adjuvant atezolizumab will be administered as in the neoadjuvant portion of the trial every 21 days to complete a total of one year of therapy.

8.4. Study drug - Investigational Product (IP)

8.4.1. Study Drug: Atezolizumab

8.4.2. Once marketing authorization is received commercial atezolizumab will be used and will not be provided by Genentech for "on-label" studies. For studies done before marketing authorization and/or "out of label", atezolizumab will be provided free of charge by Genentech but switched to commercial drug once marketing authorization is received. Genentech will replace any atezolizumab drug that is not reimbursed. For studies done "out of label," atezolizumab will be provided free of charge by Genentech. The Sponsor-investigator of the study will ensure maintenance of complete and accurate records of the receipt, dispensation, and disposal or return of all study drug in accordance with 21 Code of Federal Regulations (CFR), Part 312.57 and 312.62, and Genentech requirements.
Formulation

The atezolizumab drug product is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid

solution intended for IV administration. 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. The atezolizumab drug product is formulated as 60 mg/mL atezolizumab in 20 mM histidine acetate, 120 mM sucrose, 0.04% polysorbate 20, pH 5.8.

Atezolizumab must be refrigerated at 2°C - 8°C (36°F - 46°F) upon receipt until use. Atezolizumab vials should not be used beyond the expiration date provided by the manufacturer. No preservative is used in the atezolizumab drug product; therefore, each vial is intended for single use only. Discard any unused portion of drug left in a vial. Vial contents should not be frozen or shaken and should be protected from direct sunlight.

For further details, see the Atezolizumab Investigator's Brochure.

8.4.3. Dosage, Administration, and Storage

The dose level of atezolizumab to be tested in this study is 1200 mg (equivalent to an average body weight–based dose of 15 mg/kg) administered by IV infusion every 3 weeks (21 [± 2] days). Atezolizumab will be delivered in infusion bags with IV infusion lines that have product contacting surfaces of polyvinyl chloride (PVC) or polyolefin and 0.2 μm in-line filters (filter membrane of polyethersulfone [PES]). No incompatibilities have been observed between ATEZOLIZUMAB and PVC or polyolefin infusion materials (bags or infusion lines).

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, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician. The management of IRRs will be according to severity as follows:

a. In the event that a patient experiences a mild (NCI CTCAE Grade 1) IRR, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced

rate. If tolerated, the infusion rate may then be increased to the original rate.

b. In the event that a patient experiences a moderate IRR (NCI CTCAE Grade 2) or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the IRR.

c. For severe or life-threatening IRRs (NCI CTCAE Grade 3 or 4), the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated. Patients experiencing severe or life-threatening IRRs will not receive further infusion and will be further managed as clinically indicated until the event resolves.

For anaphylaxis precautions, see Appendix 6.

Guidelines for dosage modification, treatment interruption, or discontinuation and the management of specific adverse events are provided in Section 12 and Section 9, respectively.

8.5. Non-Investigational Product (Non IP)

Carboplatin, paclitaxel and all routine pre-medications will be obtained from standard commercial sources and administered according to the manufacturers' and institutional guidelines.

8.6. Dose and Treatment Modifications

8.6.1. General Guidelines

Monitoring

Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to NCI CTCAE v4.0. Patients will be assessed for safety (including laboratory values) according to the schedule in Protocol Section 5. Patients will be followed for safety for 90 days following the last dose of study treatment or until receipt of another anticancer therapy, whichever comes first.

General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries and blood counts (see Protocol Section 5for the list and timing of study assessments). All serious adverse events (SAEs) and protocol-defined events of special interest (see Section 12.3.2.10) will be reported in an expedited fashion (see Section 12.3.3.3). In addition, the investigators will review and evaluate observed AEs on a regular basis.

Patients who have an ongoing study treatment–related AE upon study completion or at discontinuation from the study will be followed until the event has resolved to

baseline grade, the event is assessed by the investigator as stable, new anticancer treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE.

8.6.1.1. Management of Specific Safety Concerns with Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology.

Although most immune-related adverse events (irAEs) observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect and, in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNFα inhibitors.

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.

Please refer to the IB for management of specific irAEs and guidelines for dose modifications in specific circumstances.

8.6.2. Dose Modifications

Atezolizumab treatment will be given as long as the patient continues to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation listed in Section 9.

There will be no dose reduction for atezolizumab in this study. Patients may temporarily suspend study treatment for up to 84 days 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 Section 12.1.

If a patient must be tapered off steroids used to treat AEs, atezolizumab may be held for additional time beyond 84 days from the scheduled dose until steroids are discontinued or reduced to a prednisone dose (or dose equivalent) of ≤ 10 mg/day. The acceptable length of interruption will be at the discretion of the investigator.

Dose holds do not affect dosing or assessment schedules.

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 Sponsor.

Any toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most irAEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNFα inhibitors.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to atezolizumab occurs at any time during the study, treatment with atezolizumab should be discontinued.

Management of hepatitis/transaminitis, colitis, rash, and hypothyroidism are presented in this section as they have been observed in this study and are potentially immune related. See appendix 4 for guidelines for the management of IRRs (see Appendix 6 for precautions for anaphylaxis).

8.6.2.1. Gastrointestinal Toxicity

Immune-mediated colitis has been associated with the administration of atezolizumab.

Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild.

If the event is of significant duration or magnitude, or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased CRP or platelet count or bandemia), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy with three to five specimens for standard paraffin block be performed. If possible, one or two biopsy specimens should be snap frozen and stored.

Treatment may be restarted following the resolution of colitis. In addition, if the patient is being managed with corticosteroids, treatment should not be restarted until the steroids have been tapered down to a prednisone dose ≤ 10 mg/day. Patients who resume treatment should be monitored closely for signs of renewed diarrhea. Table 1 provides a summary of dose modification guidelines for gastrointestinal toxicities.

Table 1 Dose Modification Guidelines for Gastrointestinal Toxicity

Toxicity	Description	Management
Diarrhea	Grade 2 (4–6 stools per day over baseline) < 5 days	Hold atezolizumab and discontinue NSAIDS (or other medications known to exacerbate colitis). Investigate for etiology. Restart atezolizumab once at baseline stool frequency.
	Grade 2 (4–6 stools per day over baseline) > 5 days	Hold atezolizumab and discontinue NSAIDS (or other medications known to exacerbate colitis) while etiology is being investigated. Consider referral to a gastroenterologist. Administer anti-diarrheal agent (e.g., Imodium®). Consider oral budesonide, mesalamine, or 10 mg oral prednisone equivalent per day. Restart atezolizumab once at baseline stool frequency.
	Abdominal pain Blood or mucus in stool OR Grade ≥ 3 (≥ 7 stools/day over baseline) with peritoneal signs, ileus, or fever	Hold atezolizumab and discontinue NSAIDS (or other medications known to exacerbate colitis). Rule out bowel perforation. Consider administering prednisone 60 mg/day or 1-2 mg/kg/day or equivalent. Taper steroids over 1 month. Restart atezolizumab if diarrhea is resolved and systemic steroid dose is ≤ 10 mg oral prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related diarrhea or colitis.

NSAID = nonsteroidal anti-inflammatory drug.

8.6.2.2. Hepatotoxicity

Immune-mediated hepatitis has been associated with the administration of atezolizumab.

While in this study, patients presenting with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately, and LFTs should be reviewed before administration of the next dose of study drug.

If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder, and biliary tree should be performed to rule out neoplastic or other causes of increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered.

Patients with LFT abnormalities should be managed according to the guidelines in Table 2.

Table 2 Dose Modification Guidelines for Hepatotoxicity

Toxicity	Description	Management
LFT abnormalities	AST/ALT (> ULN to 3 × ULN) with total bilirubin < 2 × ULN	Continue with the standard monitoring plan (i.e., LFTs every 3 weeks before dosing).
	AST/ALT (> 3 × ULN to < 10 × ULN) with total bilirubin < 2 × ULN	Continue atezolizumab. Monitor LFTs at least weekly. Consider referral to a hepatologist.
	AST/ALT > 10 × ULN	Hold atezolizumab. Consider administering IV steroids for 24–48 hours (prednisone 60 mg/day or 1-2 mg/kg/day or equivalent) followed by an oral prednisone (or equivalent) taper over 2–4 weeks. If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNFα antagonist) to the corticosteroid regimen may be considered. Monitor LFTs every 48–72 hours until decreasing and then follow weekly. Restart atezolizumab if AST/ALT ≤ 3 × ULN with bilirubin < 2 × ULN and steroid dose is ≤ 10 mg oral prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related hepatic events.

Table 2 Dose Modification Guidelines for Hepatotoxicity (cont.)

Toxicity	Description	Management
LFT abnormalities (cont.)	AST/ALT ≥ 3 × ULN with bilirubin > 2 × ULN	Hold atezolizumab. Consult a hepatologist. Consider administering IV steroids for 24–48 hours (prednisone 60 mg/day or 1-2 mg/kg/day or equivalent) followed by oral taper over 1 month. If LFTs results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g., mycophenolate or TNFα antagonist) to the corticosteroid regimen may be considered. Monitor LFTs every 48–72 hours until decreasing and then follow weekly. Restart atezolizumab if AST/ALT ≤ 3 × ULN with bilirubin < 2 × ULN and steroid dose is ≤ 10 mg oral prednisone equivalent per day.

IV = intravenous; LFT = liver function test; TNFα = tumor necrosis factor alpha; ULN = upper limit of normal.

8.6.2.3. Dermatologic Toxicity

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. A biopsy should be performed unless contraindicated. Low-grade rash and pruritus irAEs have been treated with symptomatic therapy (e.g., antihistamines). Topical or parenteral corticosteroids may be required for more severe symptoms.

Dermatologic toxicity and rash should be managed according to the guidelines in Table 3.

Table 3 Dose Modification Guidelines for Dermatologic Toxicity

Toxicity	Description	Management
Dermatologic toxicity/rash (e.g., maculopapular or purpura)	Grade 1: Mild < 10% BSA	Continue atezolizumab symptomatic therapy with antihistamine PRN. Consider topical steroids and/or other symptomatic therapy (e.g., antihistamines).
	Grade 2: Moderate 10%–30% BSA	Continue atezolizumab. Consider dermatologist referral. Administer topical steroids. Consider higher potency topical steroids if rash is unresolved.
	Grade 3: Severe > 30% BSA	Hold atezolizumab. Consult dermatologist. Administer oral prednisone 10 mg or equivalent. If the rash is unresolved after 48–72 hours, administer oral prednisone 60 mg or 1-2 mg/kg/day or equivalent. Restart atezolizumab if rash is resolved and systemic dose is ≤ 10 mg oral prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related dermatologic toxicity.

BSA = body surface area; PRN = as needed.

8.6.2.4. Endocrine Toxicity

Hypothyroidism has been associated with the administration of atezolizumab.

Patients with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies, as well as for hyponatremia or hyperkalemia. An endocrinologist should be consulted if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T4 levels should be obtained to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Hypothyroidism should be managed according to the guidelines in Table 4.

Table 4 Dose Modification Guidelines for Endocrine Toxicity

Toxicity	Description	Management
Hypothyroidism	TSH elevated, asymptomatic	Continue atezolizumab. Start thyroid-replacement hormone. Monitor TSH weekly.
	TSH elevated, symptomatic	Hold atezolizumab. Consider referral to an endocrinologist. Restart atezolizumab when symptoms are controlled by thyroid replacement and TSH levels are decreasing.

TSH = thyroid-stimulating hormone.

8.6.2.5. Pulmonary Toxicity

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab and have primarily been observed in patients with underlying NSCLC.

Mild-to-moderate events of pneumonitis have been reported with atezolizumab. All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension and the following should be performed:

a. Measurement of oxygen saturation (i.e., arterial blood gas)

b. High-resolution CT scan of the chest

c. Bronchoscopy with bronchoalveolar lavage and biopsy

d. Pulmonary function tests (with diffusion capacity of the lung for carbon monoxide [DL_{CO}])

Patients will be assessed for pulmonary signs and symptoms throughout the study. Patients will also have CT scans of the chest at every tumor assessment (see Section 10.3.2).

Pulmonary toxicity should be managed according to the guidelines in Table 5.

Table 5 Dose Modification Guidelines for Pulmonary Toxicity

Toxicity	Description	Management
Pulmonary toxicity	GGO or non-infectious infiltrate in absence of hypoxia, or dyspnea	Hold treatment with atezolizumab. Re-evaluate after 1 week. If no worsening in GGO/infiltrates and patient still asymptomatic, resume treatment with atezolizumab. If GGO/infiltrates worsen and patient is still asymptomatic, continue to hold atezolizumab and refer for bronchoscopy. Consider starting low-dose oral prednisone 10 mg or equivalent. Re-evaluate after 1 week. Resume atezolizumab if GGO/infiltrates improving.
	Hypoxia or dyspnea in presence of GGO or infiltrate without alternative etiology	Hold atezolizumab. Consult a pulmonologist. Investigate for other etiologies and consider bronchoscopy. If bronchoscopy is consistent with immune-related etiology, start 60 mg or 1-2 mg/kg prednisone equivalent per day followed by taper over 2 weeks. Restart atezolizumab if symptomatically improved, infiltrates are resolved, and steroid use is ≤ 10 mg prednisone equivalent per day. Permanently discontinue atezolizumab for life-threatening, immune-related pulmonary events.

GGO = ground glass opacities.

8.6.2.6. Pericardial and Pleural Effusions

Pericardial and pleural involvement with associated effusions is common in patients with cancer and has the theoretical potential to be exacerbated by inflammation associated with anti-tumor immunity following PD-L1 blockade. Patients presenting with 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, appropriate workup includes cytology, LDH, glucose, cholesterol, protein concentrations (with pleural effusions), and cell count. For patients with a pericardial effusion causing end-diastolic right ventricular collapse, treatment may be restarted following the placement of a pericardial window, demonstration of hemodynamic stability, and resolution of right ventricular dysfunction.

8.6.2.7. Potential Pancreatic Toxicity

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests (see also Section 8.6.2.4).

8.6.2.8. Potential Eye Toxicity

An ophthalmologist should evaluate visual complaints. Uveitis or episcleritis may be treated with topical corticosteroid eye drops. Atezolizumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

Ocular toxicity should be managed according to the guidelines in Table 6.

Table 6 Dose Modification Guidelines for Eye Toxicity

Toxicity	Description	Management
Eye toxicity (autoimmune uveitis, iritis, or episcleritis)	Symptomatic	Hold atezolizumab. Consult ophthalmologist and start topical corticosteroid eye drops. Atezolizumab may be restarted following resolution of the events. Permanently discontinue atezolizumab for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

8.7. Concomitant Medications

8.7.1. Concomitant Therapy

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 β_2-adrenergic agonists; see Appendix).

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 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. Megastrol 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), or other allowed maintenance therapy should continue their use. Males and females of reproductive potential should use highly effective means of contraception.

8.7.2. Excluded Therapy

Any concomitant therapy intended for the treatment of cancer, whether health authority-approved or experimental, is prohibited. This includes but is not limited to the following:

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy

It is strongly recommended that:

- Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity
- The use of a RANKL inhibitor (denosumab) be discontinued during the study; this agent could potentially alter the activity and the safety of atezolizumab

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 for patients with solid malignancies.

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.

In addition, all patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

9. Dose Modifications and Management of Toxicity

9.1. Dose Modifications During Concurrent Chemoradiotherapy

9.1.1. Hematologic Toxicities

- For ANC <1,000 or platelets <75,000 on day of treatment, delay carboplatin and paclitaxel until ANC ≥1,000 and platelets ≥75,000, then resume at the previous doses. If treatment is delayed for ≥ 3 weeks, discontinue the drugs for the duration of concurrent therapy.
- For febrile neutropenia occurring at any time during a cycle, hold therapy.
- Doses that are missed will not be made up.
- Radiation therapy will be held for grade 4 hematologic toxicity.

9.1.2. Non-hematologic Toxicities

Radiation therapy should continue to be delivered for ≤ grade 3 non-hematologic toxicities in or outside the radiation treatment field. RT should be held for all Grade 4 non-hematologic toxicity in or outside the treatment field and resumed only when toxicity ≤ grade 2.

Neurotoxicity:

- **Grade 2:** Hold paclitaxel until ≤ Grade1, then resume at full dose. If paclitaxel is held ≥ 3 weeks, discontinue paclitaxel permanently. Continue carboplatin at full dose.
- **Grade 3:** Discontinue palictaxel permanently, continue carboplatin.

Renal Toxicity: A ≥10% change in the serum creatinine, based on weekly calculated creatinine clearance, will require a recalculation of the carboplatin dose.

Ototoxicity: For ≥ grade 3 toxicity discontinue carboplatin permanently.

Hypersensitivity: For grade 3 reactions, in the subsequent cycle, use double dose steroids pretreatment and decrease the paclitaxel infusion rate for the first 1/3 of the

infusion. For the last 2/3 of the infusion, double the rate of the infusion. For documented Grade 4 hypersensitivity reactions to paclitaxel, discontinue paclitaxel.

Cardiotoxicity: If a patient develops chest pain, hypotension, or arrhythmia other than asymptomatic sinus brachycardia, the paclitaxel infusion should be stopped and patients should not receive further paclitaxel. For asymptomatic sinus brachycardia, the infusion need not be stopped, but the patient should be followed carefully.

Hepatic Dysfunction: Give the following % of full dose for paclitaxel:

AST		**Bilirubin**	**Paclitaxel**
<2.0 x ULN	and	<1.5 mg/dl	100%
2.0-5.0 x ULN	and	<1.5 mg/dl	50%
>5.0 x ULN	or	≥1.5 mg/dl	0*

* Hold paclitaxel for one week (radiation therapy may continue), repeat labs, and evaluate for etiology. If progressive disease is found, take the patient off protocol treatment. If disease progression is not found and labs return to normal (AST <2.0 x ULN and Bili<1.5 mg/dl) within three weeks, reinstitute paclitaxel at 100%. IF AST >5.0 x ULN or bilirubin >1.5 mg/dl after three weeks, discontinue paclitaxel for all subsequent cycles but continue treatment with carboplatin.

Other toxicities: For all other toxicities that exceed grade 3 (except alopecia, nausea, vomiting, fatigue and anorexia), hold carboplatin and paclitaxel until toxicity resolves to ≤ grade 2.

9.1.3. Radiotherapy Related Toxicity

Esophagus/pharynx

- **Grade 3:** If day of chemotherapy hold until ≤ grade 2. Hold radiotherapy ≤ 5 days.
- **Grade 4:** Hold radiation and chemotherapy until toxicity has resolved to ≤ grade 2, then resume therapy at previous dose.
- If IV support is needed insertion of a feeding tube should be considered.
- If treatment is interrupted ≥ 3 weeks discontinue all protocol therapy.

Pulmonary Toxicity

- **Grade 3:** Hold treatment with carboplatin, paclitaxel and radiation therapy. Once toxicity has resolved to ≤ grade 2 restart chemotherapy and radiotherapy at previous dose.
- **Grade 4:** Discontinue all further radiotherapy. Hold treatment with carboplatin and paclitaxel until toxicity resolves to ≤ grade 2.
- If treatment is interrupted ≥ 3 weeks discontinue all protocol therapy.

9.2. Dose Modifications During Consolidation Chemotherapy

- If more than one of the dose modifications apply, use the most stringent (i.e., the greatest dose reduction).
- The following dose levels are used for dose modifications. If dose reduction below level -1 is required, discontinue the drug causing the toxicity, and continue the other drug.
- If treatment is delayed for ≥ 3 weeks, discontinue all protocol treatment.

Dose Level	Carboplatin	Paclitaxel
0	AUC = 6	200 mg/m^2
-1	AUC = 4.5	150 mg/m^2

9.2.1. Hematologic Toxicity

- For ANC <1,500 or platelets <100,000 on day 1, delay treatment with carboplatin and paclitaxel until ANC ≥1,500 and platelets ≥100,000, then resume at the previous doses if fully recovered in 1 week. If not, decrease by 1 dose level when recovered.
- For ANC <500 or platelets <25,000, hold therapy then decrease carboplatin and paclitaxel by one dose level for all subsequent doses once ANC ≥1,500 and platelets ≥100,000.

9.2.2. Non-hematologic Toxicities

Neurotoxicity:

- **Grade 2:** Hold paclitaxel until ≤ Grade1, then resume at full dose. If paclitaxel is held ≥ 3 weeks, discontinue paclitaxel permanently. Continue carboplatin at full dose.
- **Grade 3:** Discontinue paclitaxel permanently, continue carboplatin.

Renal Toxicity: A ≥10% change in the serum creatinine, based on weekly calculated creatinine clearance, will require a recalculation of the carboplatin dose.

Ototoxicity: For ≥ grade 3 toxicity discontinue carboplatin permanently.

Hypersensitivity: For grade 3 reactions, in the subsequent cycle, use double dose steroids pretreatment and decrease the paclitaxel infusion rate for the first 1/3 of the infusion. For the last 2/3 of the infusion, double the rate of the infusion. For documented Grade 4 hypersensitivity reactions to paclitaxel, discontinue paclitaxel.

Cardiotoxicity: If a patient develops chest pain, hypotension, or arrhythmia other than asymptomatic sinus brachycardia, the paclitaxel infusion should be stopped and patients should not receive further paclitaxel. For asymptomatic sinus brachycardia, the infusion need not be stopped, but the patient should be followed carefully.

Hepatic Dysfunction: Give the following % of full dose for paclitaxel:

AST		**Bilirubin**	**Paclitaxel**
<2.0 x ULN	and	<1.5 mg/dl	100%
2.0-5.0 x ULN	and	<1.5 mg/dl	50%
>5.0 x ULN	or	≥1.5 mg/dl	0*

* Hold paclitaxel for one week, repeat labs, and evaluate for etiology. If progressive disease is found, take the patient off protocol treatment. If disease progression is not found and labs return to normal (AST <2.0 x ULN and Bili<1.5 mg/dl) within three weeks, reinstitute paclitaxel at 100%. IF AST >5.0 x ULN or bilirubin >1.5 mg/dl after three weeks, discontinue paclitaxel for all subsequent cycles but continue treatment with carboplatin.

Other toxicities: For all other toxicities that exceed grade 3 (except alopecia, nausea, vomiting, fatigue and anorexia), hold carboplatin and paclitaxel until toxicity resolves to ≤ grade 2.

9.2.3. Failure to Complete Consolidation Chemotherapy

Based on available data of consolidation chemotherapy (34-35), it is expected that not all patients will either start or complete the consolidation chemotherapy portion of the trial. These patients will still be evaluable for toxicity and outcome endpoints. Toxicities will be scored as outlined above. Not completing consolidation therapy will not in and of itself constitute a dose limiting toxicity. For purposes of follow-up assessment, imaging will be timed to start as outlined in the calendar based on the anticipated Cycle 5 Day 1 date.

Patients with contraindications to consolidation therapy may be allowed to proceed directly to adjuvant atezolizumab, only with prior approval from the sponsor.

9.3. Dosing for Obese Patients

There is no clearly documented adverse impact of treatment in obese patients when actual body weight is used to calculate doses which are defined in terms of body surface area (BSA) considerations. Accordingly, paclitaxel dosing, defined on the basis of BSA, will be calculated on the basis of the patient's actual body weight. This will eliminate the risk of calculation error and the possible introduction of variability in dose

administration. Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol violation.

AUC dosing will be used to determine carboplatin dosing. The protocol permits use of the Cockcroft-Gault formula to estimate creatinine clearance. However, in markedly obese patients, the Cockcroft-Gault formula will tend to overestimate the creatinine clearance. (Adipose tissue tends to contribute little creatinine requiring renal clearance). The actual body weight (in kilograms) will be utilized in the Cockcroft-Gault formula. However, if the calculated creatinine clearance exceeds an upper limit for creatinine clearance, as specified below, then this ceiling value for creatinine clearance, rather than the calculated creatinine clearance, will be used in the Calvert formula to calculate the dose of carboplatin.

At the treating physician's discretion, institutional standard dosing for carboplatin and paclitaxel may be used, using actual body weight in the calculation of drug doses.

The maximum CrCl that can be used in this calculation, for both women and men, is 125 mL/min.

Alternatively, at the treating physician's discretion, a measured 24 hour creatinine clearance can be obtained. In this case, the measured creatinine clearance can be used to calculate the carboplatin dose in the Calvert formula.

10. Measurement of Effect

Any evaluable or measurable disease must be documented at screening and reassessed at each subsequent tumor evaluation. For solid malignancy patients with measurable disease, response will be assessed by the investigator per RECIST v1.1 (see Appendix) and immune-related response criteria (irRC; see Appendix).

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) guidelines (version 1.1). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the short axis measurements in the case of lymph nodes are used in the RECIST guideline[viii].

10.1. Schedule of Evaluations:

For the purposes of this study, patients should be reevaluated for response and survival every 6 weeks during induction immunotherapy, 3 weeks after completion of concurrent combined modality therapy, 3 weeks after completion of consolidation chemotherapy and every 3 months during adjuvant immunotherapy.

10.2. Definitions of Measurable and Non-Measurable Disease

10.2.1. Measurable Disease

A non-nodal lesion is considered measurable if its longest diameter can be accurately measured as ≥2.0 cm with chest x-ray, or as ≥1.0 cm with CT scan, CT component of a PET/CT, or MRI.

A superficial non-nodal lesion is measurable if its longest diameter is ≥ 1.0 cm in diameter as assessed using calipers (e.g. skin nodules) or imaging. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

A malignant lymph node is considered measurable if its short axis is ≥1.5 cm when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

10.2.2. Non-Measurable Disease

All other lesions (or sites of disease) are considered non-measurable disease, including pathological nodes (those with a short axis ≥ 1.0 to < 1.5 cm).

Note: 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions. In addition, lymph nodes that have a short axis < 1.0 cm are considered non-pathological (i.e., normal) and should not be recorded or followed.

10.3. Guidelines for Evaluation of Measurable Disease

10.3.1. Measurement Methods

- All measurements should be recorded in metric notation (i.e., decimal fractions of centimeters) using a ruler or calipers.
- The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. For patients having only lesions measuring at least 1 cm to less than 2 cm must use CT imaging for both pre- and post-treatment tumor assessments.
- Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation to assess the antitumor effect of a treatment.

10.3.2. Acceptable Modalities for Measurable Disease

- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.
- As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- **PET-CT:** If the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time.
- **FDG-PET:** FDG-PET scanning is allowed to complement CT scanning in assessment of progressive disease [PD] and particularly possible 'new' disease. A 'positive' FDG-PET scanned lesion is defined as one which is FDG avid with an update greater than twice that of the surrounding tissue on the attenuation corrected image; otherwise, an FDG-PET scanned lesion is considered 'negative.' New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  a. Negative FDG-PET at baseline with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up:
     1) If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
     2) If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT at the same evaluation, additional follow-up CT scans (i.e., additional follow-up scans at least 4 weeks later) are needed to determine if there is truly progression occurring at that site. In this situation, the date of PD will be the date of the initial abnormal PDG-PET scan.
     3) If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, it is not classified as PD.

10.3.3. Measurement at Follow-up Evaluation

- The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.
- Cytologic and histologic techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain.)

10.4. Measurement of Treatment/Intervention Effect

10.4.1. Target Lesions & Target Lymph Nodes

- Measurable lesions up to a maximum of 5 lesions, representative of all involved organs, should be identified as "Target Lesions" and recorded and measured at baseline. These lesions can be non-nodal or nodal, where no more than 2 lesions are from the same organ and no more than 2 malignant nodal lesions are selected.

Note: If fewer than 5 target lesions and target lymph nodes are identified (as there often will be), there is no reason to perform additional studies beyond those specified in the protocol to discover new lesions.

- Target lesions and target lymph nodes should be selected on the basis of their size, be representative of all involved sites of disease, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion (or malignant lymph node) does not lend itself to reproducible measurements in which circumstance the next largest lesion (or malignant lymph node) which can be measured reproducibly should be selected.
- **Baseline Sum of Dimensions (BSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the baseline sum of dimensions (BSD). The BSD will be used as reference to further characterize any objective tumor response in the measurable dimension of the disease.
- **Post-Baseline Sum of the Dimensions (PBSD):** A sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes will be calculated and reported as the post-baseline sum of dimensions (PBSD). If the radiologist is able to provide an actual measure for the target lesion (or target lymph node), that should be recorded, even if it is below 0.5 cm. If the target lesion (or target lymph node) is believed to be present and is faintly seen but too small to measure, a default value of 0.5 cm should be assigned. If it is the opinion of the radiologist that the target lesion or target lymph node has likely disappeared, the measurement should be recorded as 0 cm.
- **The minimum sum of the dimensions (MSD)** is the minimum of the BSD and the PBSD.

10.4.2. Non-Target Lesions & Non-Target Lymph Nodes

Non-measurable sites of disease (Section 12.2.2) are classified as non- target lesions or non-target lymph nodes and should also be recorded at baseline. These lesions and lymph nodes should be followed in accord with 12.4.3.3.

10.4.3. Response Criteria

All target lesions and target lymph nodes followed by CT/MRI/PET-CT must be measured on re-evaluation at evaluation times specified in Section 11.1. Specifically, a change in objective status to either a PR or CR cannot be done without re-measuring target lesions and target lymph nodes.

Note: Non-target lesions and non-target lymph nodes should be evaluated at each assessment, especially in the case of first response or confirmation of response. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

10.4.3.1. Evaluation of Target Lesions

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all target lesions.
  b. Each target lymph node must have reduction in short axis to < 1.0 cm.
- **Partial Response (PR):** At least a 30% decrease in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the BSD (see Section 11.4.1).
- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. At least a 20% increase in PBSD (sum of the longest diameter for all target lesions plus the sum of the short axis of all the target lymph nodes at current evaluation) taking as reference the MSD (Section 11.4.1). In addition, the PBSD must also demonstrate an absolute increase of at least 0.5 cm from the MSD.
  c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD taking as reference the MSD.

10.4.3.2. Evaluation of Non-Target Lesions & Non-target Lymph Nodes

- **Complete Response (CR):** All of the following must be true:
  a. Disappearance of all non-target lesions.
  b. Each non-target lymph node must have a reduction in short axis to <1.0 cm.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesions or non-target lymph nodes.
- **Progression (PD):** At least one of the following must be true:
  a. At least one new malignant lesion, which also includes any lymph node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up.
  b. Unequivocal progression of existing non-target lesions and non-target lymph nodes. (NOTE: Unequivocal progression should not normally trump target lesion and target lymph node status. It must be representative of overall disease status change.)
  c. See Section 11.3.2 for details in regards to the requirements for PD via FDG-PET imaging.

10.4.4. Overall Objective Status

The overall objective status for an evaluation is determined by combining the patient's status on target lesions, target lymph nodes, non-target lesions, non-target lymph nodes, and new disease as defined in the following tables:

For Patients with Measurable Disease

Target Lesions & Target Lymph Nodes	**Non-Target Lesions & Non-Target Lymph Nodes**	**New Sites of Disease**	**Overall Objective Status**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	CR Non-CR/Non-PD	No	PR
CR/PR	Not All Evaluated*	No	PR**
SD	CR Non-CR/Non-PD Not All Evaluated*	No	SD
Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	No	Not Evaluated (NE)
PD	Unequivocal PD CR Non-CR/Non-PD Not All Evaluated*	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	Unequivocal PD	Yes or No	PD
CR/PR/SD/PD/Not all Evaluated	CR Non-CR/Non-PD Not All Evaluated*	Yes	PD

10.4.5. Symptomatic Deterioration

Patients with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not either related to study treatment or other medical conditions, should be reported as PD due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment due to symptomatic deterioration.

11. End of Treatment and Follow-up

11.1. Duration of Treatment

11.1.1. CR, PR, or SD

Patients who are in CR, PR or SD will continue on therapy for a total of 12 months. After treatment is discontinued, patients will be followed per the study calendar in Section 5.0 and 6.0.

11.1.2. Disease Progression

Remove from protocol therapy any patient with disease progression. Document details, including tumor measurements, on data forms.

After disease progression, patients should be followed for survival per the study calendar (Section 5.0 and 6.0).

11.2. Managing ineligible patients and registered patients who never receive protocol intervention

Definition of ineligible patients: A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible. Patients who are deemed ineligible may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Study participants who are registered to the trial but never receive study intervention (for a reason other than because they were deemed ineligible) must still complete follow-up requirements as specified below.

11.3. Extraordinary Medical Circumstances

If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

11.4. Follow-up

After the end of treatment visit, patients will be required to attend follow-up visits. These visits will occur 3, 6 and 12 months after the end of treatment visit. Patients will have tumor response evaluation by RECIST and imaging. Blood samples will be collected for assessment of circulating tumor cells as well (See Section 5 for details).

12. Safety Instructions and Guidance

12.1. Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and initiation of any study procedures and ends 30 days following the last administration of study treatment or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

12.2. Assessment of Adverse Events

All AEs and SAEs, whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means, will be reported appropriately. Each reported AE or SAE will be described by its

duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of atezolizumab, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to atezolizumab; and/or the AE abates or resolves upon discontinuation of atezolizumab or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than atezolizumab (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to atezolizumab administration (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected AEs are those AEs that are listed or characterized in the Package Insert (PI) or current Investigator's Brochure.

Unexpected AEs are those not listed in the PI or current Investigator's Brochure or not identified. This includes AEs for which the specificity or severity is not consistent with the description in the PI or Investigator's Brochure. For example, under this definition, hepatic necrosis would be unexpected if the PI or Investigator's Brochure only referred to elevated hepatic enzymes or hepatitis.

12.3. Procedures for Eliciting, Recording, and Reporting Adverse Events

12.3.1. Eliciting Adverse Events

A consistent methodology for eliciting AEs at all patient evaluation timepoints should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

12.3.2. Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

12.3.2.1. Diagnosis versus Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a

single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

12.3.2.2. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 12.1), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths that occur during the protocol-specified adverse event reporting period (see Section 12.1) that are attributed by the investigator solely to progression of disease should be recorded only in the study eCRF.

12.3.2.3. Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

12.3.2.4. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions,
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study, or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

12.3.2.5. Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 90 days after the last dose of study drug. A Pregnancy Report CRF should be completed by the investigator immediately (i.e., no more than 24 hours after

learning of the pregnancy) and submitted via fax. A pregnancy report will automatically be generated and sent to Genentech Drug Safety. Pregnancy should not be recorded on the Adverse Event CRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event CRF.

A Clinical Trial Pregnancy Reporting Form should be completed in the AFT-EDC (Rave) system within 24 hours after learning of the pregnancy. AFT will forward to Genentech Drug Safety within 24 hours of receipt.

12.3.2.6. Pregnancies in Partners of Male Patients

Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after completing treatment with Atezolizumab. Male patients who received study treatment should not attempt to father a child until end of study. A Pregnancy Report CRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) in the AFT-EDC (Rave) system. AFT will forward to Genentech Drug Safety within 24 hours of receipt.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

12.3.2.7. Abnormal Liver Functions Tests Reported as Hy's Law

Investigators must report as a serious adverse event the occurrence of either of the following:

- 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

The finding of an elevated ALT or AST (>3 x ULN) in combination with either an elevated total bilirubin (>2 x ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the safety department of AFT (US sites) or ABCSG (Non-US sites) immediately (i.e., no more than 24 hours after learning of the event) using the study specific SAE reporting way.

12.3.2.8. Abortions

Any spontaneous abortion should be classified as an SAE (as the Sponsors consider spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to AFT immediately (i.e., no more than 24 hours after learning of the event; see Section 12.3). AFT will forward to Genentech Drug Safety within 24 hours of receipt.

12.3.2.9. Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event CRF, and reported to AFT immediately (i.e., no more than 24 hours after learning of the event). AFT will forward to Genentech within 24 hours of receipt.

12.3.2.10. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior atezolizumab exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

12.3.2.11. Adverse Events of Special Interest

Adverse events of special interest (AESIs) are defined as a potential safety problem, identified as a result of safety monitoring of the IMP.

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) via the AFT-EDC (Rave) system.

The following AEs are considered of special interest and must be reported to the Genentech Drug Safety expeditiously, irrespective of regulatory seriousness criteria:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:

- Treatment-emergent ALT or AST ≥ 3 × baseline value in combination with total bilirubin ≥ 2 × ULN (of which > 35% is direct bilirubin)
- Treatment-emergent ALT or AST ≥ 3 × baseline value in combination with clinical jaundice

- Suspected transmission of an infectious agent by the study treatment, as defined below
  - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism and hypophysitis
- Hepatitis, including AST or ALT > 10 x ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome and systemic immune activation
- Nephritis
- Ocular toxicities (e.g. uveitis, retinitis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥2 cardiac disorders (e.g. atrial fibrillation, myocarditis, pericarditis)

12.3.3. Adverse Events Reporting

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. The CTCAE is available at [redacted] Attribution

to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms, using the codes provided.

12.3.3.1. Routine Adverse Event Reporting

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 will be recorded after informed consent is obtained and initiation of any study procedures through 30 days following cessation of treatment. Adverse events are reported in a routine manner at scheduled times according to the study calendar in Section 6. All adverse events are entered into the Adverse Event eCRF in Rave.

12.3.3.2. Expedited Adverse Event Reporting

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Investigators are required to notify the AFT and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and **grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for AE reporting.** The CTCAE is identified and located on the CTEP website at: [redacted] All appropriate treatment areas should have access to a copy of the CTCAE. All reactions determined to be "reportable" in an expedited manner must be reported via the Adverse Event eCRF in the Rave.

Note: All deaths on study require both routine and expedited reporting via the AFT-EDC (Rave) system, regardless of causality. Attribution to treatment or other cause should be provided.

12.3.3.3. Serious Adverse Event (SAE)

Investigators **MUST** immediately report to the sponsor (AFT) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

Table 7. Serious Adverse Event Reporting Requirements

REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS

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 patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
7) Or is a new cancer (that is not a condition of the study).
8) Or is associated with an overdoes

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to AFT via the AFT-EDC (Rave) system.

Hospitalization	**Grade 1 Timeframes**	**Grade 2 Timeframes**	**Grade 3 Timeframes**	**Grade 4 & 5 Timeframes**
Resulting in Hospitalization > 24 hrs	Enter into AFT-EDC (Rave) as an SAE within 24 hours of the site's awareness of the event			
Not resulting in Hospitalization ≥ 24 hrs	Not required to enter as an SAE in AFT-EDC (Rave).		Enter into AFT-SRS as an SAE within 24 hours of the site's awareness of the event	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AFT-EDC (Rave) ≤ 24 hours of learning of the AE, followed by a complete expedited report ≤ 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted ≤ 10 calendar days of learning of the AE.

All 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 or any SAE that occurs through 90 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the investigational product, require reporting into AFT-EDC (Rave) within 24 hours of awareness of the event.

NOTE: Deaths occurring outside of the serious adverse event reporting period that are clearly due to progressive disease should **NOT** be reported as an SAE, but rather should be reported via routine reporting methods in the AFT-EDC (Rave) system. For deaths occurring within the reporting window, even if considered to be related to disease progression, the cause of death should be reported as an SAE within the AFT-EDC (Rave) system with death noted as the outcome of the event.

13. Statistical Considerations and Methodology

13.1. Overview of the Study Design

This phase II pilot trial will combine neoadjuvant immunotherapy with atezolizumab q 21 days for 12 weeks with standard chemoradiotherapy with curative intent for good PS patients with unresectable stage IIIA/B NSCLC. Because of the consequences of progression in this curative-intent population, restaging CT scans will be carried out after the first 2 cycles of neoadjuvant therapy. Responding patients will complete a total of one year of anti-PDL1 therapy with an interruption during chemoradiotherapy and consolidation chemotherapy. Patients with evidence of progression at the first restaging evaluation will proceed immediately to chemoradiotherapy if still eligible.

Assumptions include a DCR of at least 70% to neoadjuvant immunotherapy, that 85% of the study population will complete radiation, and that 60% of the study population will complete the entire treatment course including consolidation chemotherapy and adjuvant immunotherapy with atezolizumab.

13.2. Endpoints

13.3. Primary Objective

The primary objective of this single arm phase II trial is to determine whether neoadjuvant and adjuvant anti-PD-L1 therapy bracketing standard chemoradiation therapy and consolidation therapy is worthy of further investigation. The primary endpoint will be the disease control rate (DCR) after 12 weeks induction immunotherapy.

13.4. Secondary Objectives

Secondary endpoints are objective response rate (ORR), progression free survival (PFS) and overall survival (OS), the proportion of patients who complete induction immunotherapy, chemoradiation therapy and consolidation chemotherapy. Toxicity including immune related adverse events will be assessed for all patients receiving any study therapy.

13.5. Translational Science Principal Objective

Assess the utility of PD-L1 as a biomarker for DCR, ORR, PFS, OS in the study population.

13.6. Translational Science Additional Objectives

Examine the role of immunologic signatures for positive and negative predictive value and to identify selective biomarkers. Multi-panel immunohistochemistry, NanoString/RNA-Seq/RT-PCR expression profiling, whole exome and T cell receptor sequencing, flow cytometry, and cytokine and chemokine markers will be assessed in blood and in FFPE tissue. Additionally, whole blood and serum will be obtained at study entry and at crucial time-points for additional evaluation of circulating tumor DNA (ctDNA). Whole blood will be obtained at 3 crucial timepoints (at baseline, after induction atezolizumab, after chemoradiotherapy.

13.7. Other Correlative Science Objectives (e.g., QoL, PRO, etc)

Quality of life endpoints will be assessed during induction, during chemoradiotherapy, during adjuvant atezolizumab at 3 month intervals and will be measured by the EORTC QLQ-30.

13.8. Sample Size, Accrual time, and Study Duration

13.8.1. Sample Size

The disease control rate (DCR) is assumed the same for PD-L1 positives and negatives. With 60 eligible and treated patients, the study has approximately 90% power to detect H0: $p \leq 0.50$ versus H1: $p \geq 0.67$, where p is the disease control rate (DCR) after 12 weeks neoadjuvant anti-PD-L1 therapy, with a one-sided binomial test at a significance level of 0.10. In particular, if 35 or fewer of these patients remain disease controlled, it will be concluded that the treatment regimen is not worthy of further investigation. Otherwise, it will be concluded that the treatment regimen has sufficient efficacy to warrant further investigation. Under the design, the probability of erroneously concluding that the treatment regimen is worthy of further investigation when the DCR is truly 50% or less is 0.0775. The probability of erroneously concluding that the treatment regimen is NOT worthy of further investigation when the true DCR is 67% or greater is 0.0999.

13.8.2. Accrual Rate and Accrual Duration

The phase II trial will register a total 63 patients. Assuming 5% ineligibility and cancelation, 60 eligible patients are expected to receive at least one cycle of the experimental agent. PD-L1 status will be determined by Ventana assay (TC/IC). Of them, we expect approximately 40 and 20 patients are PD-L1 positive (≥1% expression) and PD-L1 negative (otherwise), respectively.

A total of 63 patients will be registered to the trial. The trial will be open for patient enrollment in 15 Alliance institutions selected for their experience and prior good enrollment in clinical trials of chemoradiotherapy for NSCLC. We expect approximately 4 unresectable stage III NSCLC patients who meet the eligibility criteria will be enrolled per month. It will take approximately 16 months to reach the target accrual. Follow up of at least 18 months will be required for all patients for progression free survival and overall survival.

13.9. Study Team - Safety Monitoring

In addition to the collection of the treatment-related toxicity forms (radiotherapy and chemotherapy), the status of patients will be monitored by the study chairs via telephone conversations with the treating sites. The monitoring will occur at least twice monthly during therapy and monthly after treatment. The goal is for real time understanding of potential toxicity issues, treatment delivery challenges, accrual barriers, and study retention.

14. Correlative Sciences

See Appendix 11.

15. General Regulatory and Other considerations

15.1. Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow patients to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

15.2. Regulatory and ethical compliance

By signing the Protocol the investigator agrees to treat all of the information that is provided with the strictest confidentiality and to require the same of his personnel as well as the IRB. Study documents (protocols, investigator`s brochures, eCRFs, etc.) provided by the AFT will be stored in an appropriate manner in order to ensure confidentiality. The information provided to the investigator by AFT must not be made available to other parties without a direct written authorization by the aforesaid parties, with the exception of the extent to which disclosure is necessary in order to obtain informed consent from the patients who wish to participate in the study.

15.3. Ethics and Good Clinical Practice

This study will be conducted in compliance with the study protocol, subsequent amendment(s) and with the study-specific manuals/guidelines, if applicable. These documents ensure that the ICH E6 guideline for Good Clinical Practice is maintained as well as compliance with the principles of the Declaration of Helsinki (World Medical Association), or the laws and regulations of the country in which the research is conducted, whichever afford the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulation and applicable local, state and federal laws.

By signing the study protocol the investigator agrees to comply with the instructions and procedures described therein and thus to adhere to the principles of good clinical practice, which these instructions and procedures reflect.

15.4. Confidentiality

Patient medical information both, associated with biologic specimens or not, is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law. Data derived from biologic specimen analysis on

individual patients will in generally not be provided to study investigators unless a request for research use is granted. The overall results of any research conducted using biologic specimens will be available in accordance with the effective AFT policy on study data publication.

15.5. Protocol Amendments

Any modifications to the protocol or the Informed Consent Form which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be released by AFT, agreed by the investigator(s) and approved by relevant IRBs prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents and the Informed Consent Form have been approved by relevant IRBs must be provided to AFT before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the AFT, agreed by the investigator(s) and notified to the IRB.

15.6. Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Informed Consent from each patient participating in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. This information must be provided to the patient prior to undertaking any trial-related procedure which is not part of the routine clinical management of the patient (i.e. would not be indicated outside the study).

For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patients and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. The Investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

Furthermore, it is the investigator's responsibility to obtain the signed Informed Consent Form, and a signature from the person conducting the informed consent discussion, prior to undertaking any trial-related procedure. The proposed Informed Consent Form must accomplish with the ICH GCP guideline and regulatory requirements.

15.7. Financial Disclosure

Investigators will provide AFT with adequate and accurate financial information in accordance with local regulations and laws in order to allow AFT to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing updated information on financial interests during the course of the study as well as for 1 year after completion of the study.

15.8. Protocol Deviations

The investigator is responsible to document and explain any deviations from the approved protocol. The investigator should promptly report any deviations that might impact patient safety and data integrity to AFT and if locally applicable, to the respective IRB in accordance with local IRB policies and procedures. Deviations should also be recorded in the AFT-EDC (Rave).

15.9. Retention of Records

Any records and documents relating to the conduct of this study and the distribution of investigational drug, including ICFs, eCRFs, PRO data, laboratory test results, and medication inventory records, must be retained by the Principal Investigator until notification by AFT, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of AFT. Written notification should be provided to AFT prior to transferring any records to another party or moving them to another location.

16. References

Attached as endnotes.

17. Appendices

Appendix 1 Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine Clearance (men)} = \frac{(140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine Clearance (women)} = \frac{0.85 \times (140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Reference:

Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992;62:249.

Appendix 2 Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

P[redacted]

[redacted]

Appendix 3 Response Evaluation Criteria in Solid Tumors (RECIST)

[redacted]

Appendix 4 Immune-Related Response Criteria

INTRODUCTION

Increasing clinical experience indicates that traditional response criteria (e.g., Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to characterize fully activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria[1] (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab). (Note: The irRC only index and measurable new lesions are taken into account.)

GLOSSARY

Term	Definition
SPD	sum of the products of the two largest perpendicular diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	minimally recorded tumor burden
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irBOR	immune-related best overall response

BASELINE ASSESSMENT USING irRC

Step 1. Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

Step 2. Calculate the SPD of all of these index lesions:

$$\text{SPD} = \sum_{i} \text{(Largest diameter of lesion i)} \times \text{(Second largest diameter of lesion i)}.$$

[1] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res. 2009;15:7412–20.

Appendix 4 Immune-Related Response Criteria (cont.)

POST-BASELINE ASSESSMENTS USING irRC

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions (≥ 5 × 5 mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

Step 3. Calculate the SPD of the new, measurable lesions.

Step 4. Calculate the tumor burden:

Tumor burden = $SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$

Step 5. Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

Step 6. Derive the overall response using the table below.

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥ 4 weeks from the date first documented
irPR	Decrease in tumor burden ≥ 50% relative to baseline confirmed by a consecutive assessment ≥ 4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden ≥ 25% relative to nadir confirmed by a consecutive assessment ≥ 4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

DETERMINATION OF irBOR

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

Appendix 5 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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

Appendix 6 Anaphylaxis Precautions

EQUIPMENT NEEDED

i. Tourniquet
j. Oxygen
k. Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
l. Antihistamines
m. Corticosteroids
n. Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

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

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
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.

Appendix 7 Safety Reporting Fax Cover Sheet

Genentech
A Member of the Roche Group

GENENTECH SUPPORTED RESEARCH

[redacted]

Page 1 of ___

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	
Initial Report Date	_____/_____/_____ dd / mmm / yyyy
Follow-up Report Date	_____/_____/_____ dd / mmm / yyyy
Patient Initials (Please enter a dash if the patient has no middle name)	____ - ____ -____

[redacted]

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET.

Appendix 8 FDA MedWatch 3500 Form

This form is included in the study start-up zip file to be sent to sites via email, and can also be found on the FDA website.

Appendix 9 Carboplatin Package Insert

Bristol-Myers Squibb Company

Rx only

BRISTOL-MYERS SQUIBB ONCOLOGY

PARAPLATIN®
(carboplatin aqueous solution) INJECTION

WARNING

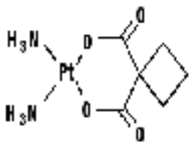
PARAPLATIN (carboplatin aqueous solution) INJECTION should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate treatment facilities are readily available.

Bone marrow suppression is dose related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug-related side effect.

Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of PARAPLATIN administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

DESCRIPTION

PARAPLATIN® (carboplatin aqueous solution) INJECTION is supplied as a sterile, pyrogen-free, 10 mg/mL aqueous solution of carboplatin. Carboplatin is a platinum coordination compound. The chemical name for carboplatin is platinum, diammine [1,1-cyclobutane-dicarboxylato(2-)-0,0']-,(SP-4-2), and carboplatin has the following structural formula:



Carboplatin is a crystalline powder with the molecular formula of $C_6H_{12}N_2O_4Pt$ and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14

Appendix 10 Paclitaxel Package Insert

TAXOL® (paclitaxel) INJECTION
(Patient Information Included)

Rx only

WARNING

TAXOL® (paclitaxel) should be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H_2 antagonists. (See **DOSAGE AND ADMINISTRATION**.) Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug.

TAXOL therapy should not be given to patients with solid tumors who have baseline neutrophil counts of less than 1500 cells/mm^3 and should not be given to patients with AIDS-related Kaposi's sarcoma if the baseline neutrophil count is less than 1000 cells/mm^3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving TAXOL.

DESCRIPTION

TAXOL (paclitaxel) Injection is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. TAXOL is available in 30 mg (5 mL), 100 mg (16.7 mL), and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremophor® EL* (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

*Cremophor® EL is the registered trademark of BASF Aktiengesellschaft.
Cremophor® EL is further purified by a Bristol-Myers Squibb Company proprietary process before use.

Appendix 11 Correlative Sciences

Correlative Sciences information to be maintained in a separate correlative sciences manual, housed outside of the study protocol.

REFERENCES

[i] *Immunologic checkpoint blockade in lung cancer. Reck M, Paz-Ares L. Semin Oncol. 2015 Jun;42(3):402-17.*

[ii] *Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, Horn L, Lena H, Minenza E, Mennecier B, Otterson GA, Campos LT, Gandara DR, Levy BP, Nair SG, Zalcman G, Wolf J, Souquet PJ, Baldini E, Cappuzzo F, Chouaid C, Dowlati A, Sanborn R, Lopez-Chavez A, Grohe C, Huber RM, Harbison CT, Baudelet C, Lestini BJ, Ramalingam SS. Lancet Oncol. 2015 Mar;16(3):257-65.*

[iii] *Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WE, Poddubskaya E, Antonia S, Pluzanski A, Vokes EE, Holgado E, Waterhouse D, Ready N, Gainor J, Arén Frontera O, Havel L, Steins M, Garassino MC, Aerts JG, Domine M, Paz-Ares L, Reck M, Baudelet C, Harbison CT, Lestini B, Spigel DR. N Engl J Med. 2015 Jul 9;373(2):123-35.*

[iv] *Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open label, phase 2 randomised controlled trial. Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J, Park K, Smith D, Arta-Cortes A, Lewanski C, Braiteh F, Waterkamp D, He P, Zou W, Chen DS, Yi J, Sandler A, Rittmeyer A. Lancet. 2016 Apr 30;387(10030):1837-46.*

[v] *Tecentriq Package Insert, 06 May 2016*
http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761034s000lbl.pdf

[vi] *Fulminant Myocarditis with Combination Immune Checkpoint Blockade. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, Becker JR, Slosky DA, Phillips EJ, Pilkinton MA, Craig-Owens L, Kola N, Plautz G, Reshef DS, Deutsch JS, Deering RP, Olenchock BA, Lichtman AH, Roden DM, Seidman CE, Koralnik IJ, Seidman JG, Hoffman RD, Taube JM, Diaz LA Jr, Anders RA, Sosman JA, Moslehi JJ. N Engl J Med. 2016 Nov 3;375(18):1749-55.*

[vii] *Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Clin Cancer Res. 2013 Jul 15;19(14):3936-43.*

[viii] *New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eisenhauer EA, Therasse P, Bogaert J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. Eur J Cancer. 2009 Jan;45(2): 228-47.*