

ALLIANCE FOUNDATION TRIALS (AFT)

PROTOCOL NUMBER

AFT – 46

**CHIO3 Trial: CHemotherapy Combined with Immune Checkpoint Inhibitor for Operable Stage IIIA/B
Non-Small Cell Lung Cancer**

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Protocol Signature Page

Protocol Title: CHIO3 Trial: CHemotherapy Combined with Immune Checkpoint Inhibitor for Operable Stage IIIA/B Non-Small Cell Lung Cancer

Protocol Number: AFT-46

Protocol Version: 6.0

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.

Full Name (printed)

Signature, Date

Study Resources

The following study resource sites are accessible via the AFT website: https://alliancefoundationtrials.org/ Adverse Event Reporting via Medidata Rave→ iMedidata Portal
BiOMS AFT Resource Site https://cbmiapps.wustl.edu/confluence/x/TaETAO

Protocol-related questions may be directed as follows:

<u>Questions</u>	<u>Contact</u>
Questions regarding patient eligibility, treatment, and dose modification Questions related to IRB issues, model consent revisions, site regulatory documents, and data submissions in RAVE	AFT-46 General Inbox [REDACTED]
Questions related to AE/SAE reporting	IQVIA Safety Safety Management [REDACTED]

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Protocol Synopsis and Study Schema

Study Number/Title	AFT-46/CHIO3: CH emotherapy Combined with Immune Checkpoint Inhibitor for O perable Stage IIIA/B (T1-4,N2) Non-Small Cell Lung Cancer
Study Type/Phase	Single Arm Phase II
Clinical Indication	Stage IIIA and IIIB (T1-4,N2) Non-Small Cell Lung Cancer (NSCLC)
Number of Study Patients	55
Estimated Duration of Study	5 years
Primary Objective	To increase N2 nodal clearance (N2NC) to 50% or greater for combined platinum doublet chemotherapy with durvalumab induction therapy from historical rate of 30% for platinum doublet chemotherapy alone in patients with potentially resectable stage IIIA/B (N2) NSCLC.
Secondary Objectives	• To evaluate the safety and tolerability of neoadjuvant platinum doublet chemotherapy and durvalumab followed by surgery followed by adjuvant radiation and durvalumab. • To assess the radiographic response rate of neoadjuvant platinum doublet chemotherapy and durvalumab. • To evaluate the rate of major pathologic response and pathologic complete response in the resected primary tumor and lymph nodes following neoadjuvant combination therapy. • To evaluate the event free survival from the time of registration to one of the following events, whichever comes first: a) radiographic disease progression, b) local progression as defined by lymph node progression precluding surgery, c) inability to resect the tumor, d) local or distant recurrence, e) death due to any cause. • To assess overall survival rate from the time of registration to death of all causes. • To assess the rate of complete resection. • To assess post-operative complications (within 30 days of surgery).

Exploratory Objectives:	- To assess the rate of pneumonitis after neoadjuvant platinum doublet chemotherapy and durvalumab, surgery, and adjuvant radiation. - To assess the failure pattern (local versus distant) of patients treated with neoadjuvant platinum doublet chemotherapy and durvalumab followed by surgery followed by radiation and durvalumab.
Correlative Objectives:	To investigate the potential association of pre-treatment and on-treatment candidate biomarkers in peripheral blood and in tumor tissues.
Study Design	This is a single arm, phase II trial of combined neoadjuvant platinum doublet chemotherapy plus durvalumab followed by surgery, postoperative radiation and adjuvant durvalumab for 13 cycles for patients with potentially resectable stage IIIA and IIIB (T1-4, N2) NSCLC (per the 8th International Association for the Study of Lung Cancer classification). In the preoperative period, patients who have undergone adequate mediastinal evaluation and are considered operable will be treated with durvalumab 1500 mg IV every 3 weeks (Q3W) in combination with platinum doublet chemotherapy (cisplatin with pemetrexed or docetaxel, depending upon histology). Patients will undergo postoperative radiation (54Gy) within 4-10 weeks after surgery at discretion of treating physician and if a positive margin from surgery occurs. One to 6 weeks after completion of radiation, patients will receive adjuvant durvalumab 1500 mg IV every 4weeks (Q4W) for 1 year (13 cycles in total). Patients who do not have surgery due to refusal, physician decision, or local and distant progression will have to discontinue study treatment. All participants will have imaging assessment prior to surgery after Cycle 2 (Week 6) and after Cycle 4 (Weeks 13 15). Patients will undergo potentially curable surgery as per standard of care. Patients will undergo imaging assessment approximately every 12 weeks after surgery for 2 years, then every 6 months for a total of 5 years.

Key Eligibility Criteria	• Patients who are at least 18 years of age and have previously untreated, histologically or cytologically confirmed stage IIIA or IIIB (T1-4, N2) NCSLC. • Have ECOG performance status of 0 to 1. • Must have life expectancy of at least 12 weeks. • Have adequate organ function. • No history of noninfectious pneumonitis/interstitial lung disease requiring oral steroids. • No active infection requiring systemic therapy. • No allogenic tissue/solid organ transplant. • No known hypersensitivity to study chemotherapy or durvalumab. • No active autoimmune disease that has required systemic treatment in the last 2 years. • No known HIV. No HIV testing is required. • No known history of Hepatitis B (as defined by Hepatitis B surface antigen reactive) or known active Hepatitis C virus (defined as HCV RNA detected) infection. • Has not received prior systemic anticancer therapy including investigational agents for the current malignancy. Has no known additional malignancy that is progressing or requires active treatment within the past 3 years with the exception of noninvasive basal and squamous cell skin cancer. • Patients with known EGFR mutation are excluded.
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Figure 1: AFT-46 Study Schema

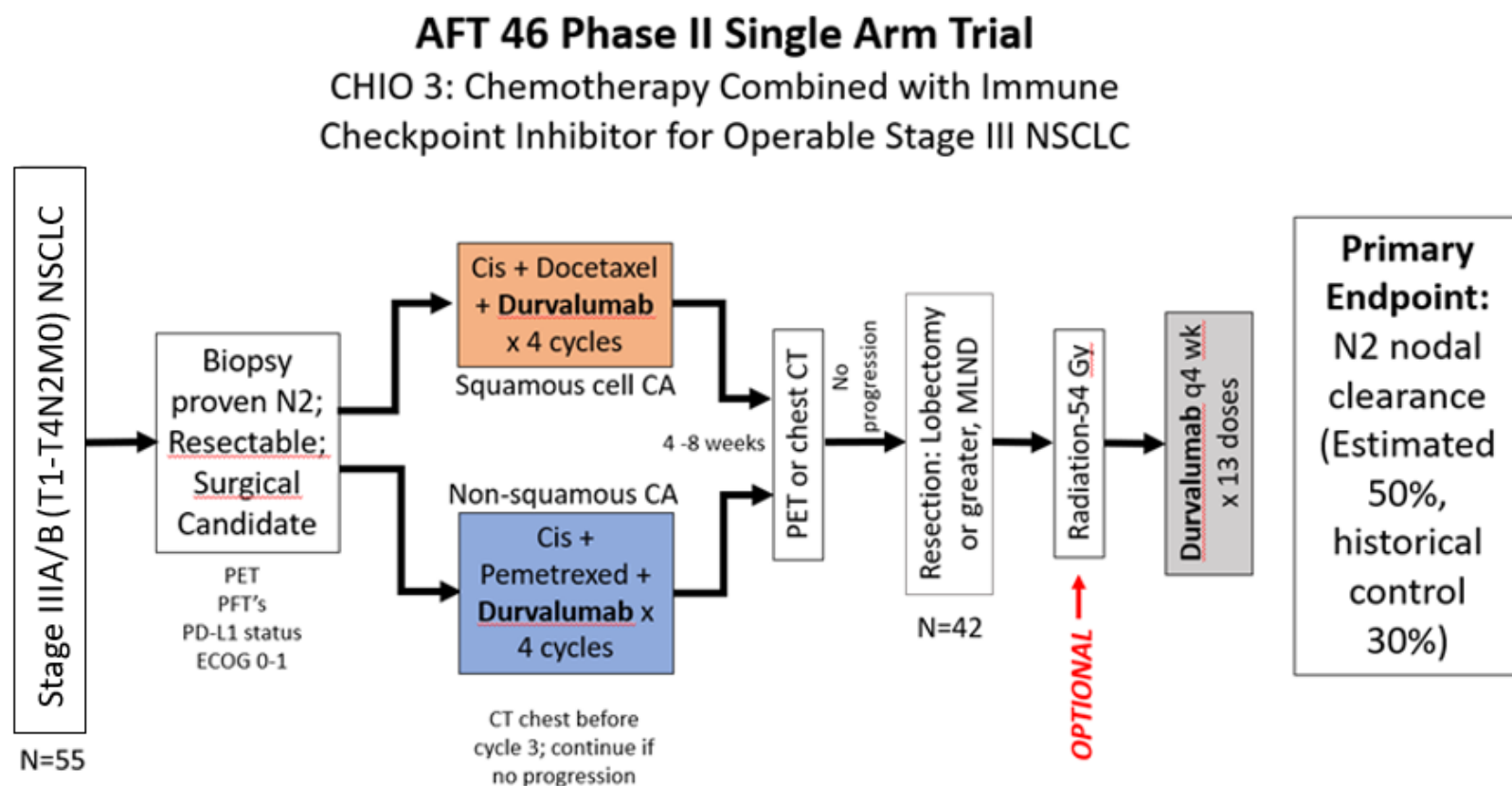


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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
AFB	Alliance Foundation Biorepository
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
CrCl	creatinine clearance
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
DRR	digitally reconstructed radiographs

Abbreviation	Definition
DVH	dose volume histograms
EBUS	endobronchial ultrasound
EBUS-TBNA	Endobronchial Ultrasound Transbronchial Needle Aspiration
EBV	Epstein-Barr virus
EBNA	Epstein-Barr nuclear antigen
EC	Ethics Committee
ECOG	Eastern Cooperative Oncology Group
EKG	electrocardiogram
EFS	event-free survival
ENE	extranodal extension
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GTV	gross tumor volume
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IF	Immunofluorescence
IFN	Interferon
IHC	Immunohistochemistry
Ig	Immunoglobulin
IL	Interleukin
ILD	interstitial lung disease
IMP	investigational medicinal product

Abbreviation	Definition
IMRT	Intensity-modulated radiation therapy
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
mPR	major pathological response
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
N2NC	N2 nodal clearance
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
pCR	pathological complete response
PD	progressive disease
PD-1	programmed death-1
PD-L1	programmed death-ligand 1
PES	polyethersulfone
PET	positron emission tomography
PFS	progression-free survival

Abbreviation	Definition
PI	Package Insert
PK	pharmacokinetic
PORT	postoperative radiotherapy
PR	partial response
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
VATS	video-assisted thoracoscopic surgery
WOCBP	women of childbearing potential

1. Background Information

1.1. Overview of Disease and Patient Population

1.1.1. Overview of Disease

Stage IIIA/B (T1-4, N2) non-small cell lung cancer (NSCLC) continues to be a clinical challenge with 5 year survival on the order of 15%-40%.¹ Both local and distant recurrence plagues this population. Optimal management remains uncertain, in part because of the heterogeneity of the disease burden and performance status of this group of patients. Divergent opinions exist on the role of surgery, despite Intergroup 0139 results showing a doubling in survival for lobectomy versus nonsurgical patients (36% vs. 18%, 5 year survival, $p=0.002$).² Opinions also vary on whether there is a preferred sequence of dual or tri-modality treatment. There have not been many significant advances in this stage of disease with the exception of nuances in managing side effects of systemic therapy, toxicity of both radiation and surgery, and improvements in patient selection. Fortunately, the promising efficacy of immune checkpoint inhibition in lung cancer may represent a much needed breakthrough for operable stage III lung cancer.

Patients who potentially can benefit from surgery for stage IIIA/B NSCLC (ie, those with discrete ipsilateral mediastinal nodal involvement [N2] and sufficient cardiopulmonary reserve to undergo aggressive therapy) do stand to benefit from some combination of systemic therapy, radiation, and surgery. Locoregional recurrence rates with definitive chemoradiation are around 51% compared with 34% when surgery is part of the treatment.³ Median survival increased from 1.7 years to 4.2 years with the addition of surgery to chemoradiation in a retrospective Canadian study. Thus, locoregional control and survival may indeed be better when resection is performed in concert with multimodality therapy.

Developing novel preoperative therapies has been challenging, and the standard remains platinum doublet chemotherapy. Platinum doublet chemotherapy alone for induction achieves pathologic complete response (CR) in only 2% to 8%, and objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) criteria in the range of 40%-50%.⁴ It is rare that it converts an unresectable lung cancer to a resectable case, or a pneumonectomy to a lobectomy. Several studies, some retrospective, and at least one prospective Swiss study, have failed to show enhanced survival or resection rates comparing induction chemotherapy to chemoradiation.^{4,5} RTOG 0839, a phase II study investigating preoperative chemoradiation alone or with panitumumab followed by surgery in stage IIIA,⁶ closed due to excessive toxicity in the panitumumab arm, prompting further interest in revisiting a less toxic neoadjuvant approach.

1.1.2. Current Treatment Approach Indication

An induction strategy with an enhanced response rate is appealing for many reasons, including the goal of allowing more patients to undergo surgery, as well as the potential for better systemic disease control. There is good reason to believe that combining platinum doublet chemotherapy with an immune checkpoint inhibitor could further augment the response rate. In Keynote 189, a double blind phase III randomized trial, use of a PD-1 inhibitor with platinum doublet chemotherapy in stage IV nonsquamous NSCLC yielded a substantially greater 1 year survival compared with platinum doublet chemotherapy alone (69.2% vs. 49.4%, hazard ratio 0.49, 95% CI, 0.38 0.64; $p<0.001$). Again, this effect was significant regardless of PD-L1 status.⁷ Pembrolizumab in addition to chemotherapy also improves outcome in patients with squamous NSCLC as demonstrated in Keynote 407,⁸ improving response rate from 35% to 58% with triplet therapy. Moreover, recently published data on the use of immune checkpoint inhibitors as neoadjuvant monotherapy have demonstrated feasibility and safety.⁹ Twenty of

21 stage I IIIA patients were completely resected, and major pathologic response was observed in 9 of 20 resected patients. PD-L1 status did not influence response rates.

The patient population targeted in this proposal is operable stage IIIA/B NSCLC, in which N2 disease has been documented histologically. This trial seeks to determine the feasibility and clinical impact of using combined platinum doublet chemotherapy with durvalumab for operable stage III NSCLC as neoadjuvant therapy, anatomic resection, followed by postoperative radiation to 50-54 Gy in select situations, and subsequently durvalumab 1500 mg IV q 4 weeks for 1 year.

1.1.3. Study Rationale and Significance

Immune checkpoint inhibitors have revolutionized the treatment approach to advanced NSCLC. Among patients with a tumor proportion score for programmed death ligand 1 (PD-L1) of 50% or greater, pembrolizumab has replaced cytotoxic chemotherapy as the first-line treatment of choice.¹⁰ In addition, combination therapy of pembrolizumab and chemotherapy for patients with nonsquamous NSCLC was associated with higher response rate (47.6% versus 18.9%), progression free survival (PFS; 8.8 versus 4.9 months), overall survival (OS) at 12 months (69.2% versus 49.4%) in a large phase III trial.⁷ Moreover, press releases and presentations confirming a benefit to the combination of another immune checkpoint inhibitor, atezolizumab, with chemotherapy have also been reported^{11,12} as well as pembrolizumab with chemotherapy in squamous NSCLC.⁸

In addition, Forde, Chaft, and colleagues reported a pilot study of single agent neoadjuvant nivolumab in early stage NSCLC. In this study, two doses of preoperative nivolumab were associated with high rates of pathologic complete response (CR, 9 of 21 cases).⁹

Radiation is part of stage III lung cancer management in most cases. One tactic is to defer radiation to the adjuvant setting, potentially reducing toxicity pre- and perioperatively. With a more impactful induction strategy, disease control and response potentially will be similar to induction chemoradiation, with surgery and radiation still to follow.

We hypothesize that the combination of platinum doublet chemotherapy with immune checkpoint inhibitor in earlier stage lung cancer will lead to improvements in N2 nodal clearance (N2NC). Moreover, we hypothesize that the N2NC rates will be similar to patients treated with chemoradiation, but with less toxicity, such that a greater fraction of patients would be able to undergo complete resection. Radiation can then be minimized to only cases needing enhancement of local control after surgery.

Postoperative radiotherapy (PORT) in patients with completely resected (R0) NSCLC with N2 disease has been shown to improve the control of disease in the thorax based on phase III studies and meta-analyses.^{13,14,15,16} The most recent update in 2010 of the British Medical Research Council meta-analysis demonstrated no clear adverse impact of PORT on survival when N2 nodes were present as opposed to a significant detrimental effect on patients with N0 or N1 disease. In addition, patients with N2 disease demonstrated an absolute 24% reduction in local recurrence.¹⁷

In 2020, the first report of the long anticipated LungART trial occurred. This study randomized patients to adjuvant radiation or no adjuvant radiation for resected Stage III NSCLC. The trial included patients with proven N2 nodal disease and a complete resection. No difference was shown overall survival but a non-statistically significant 15% improvement in DFS with PORT. This study result is already swaying the standard of care to exclude many patients from undergoing PORT at many centers. However, this study had several weaknesses leaving room for uncertainty in many clinical scenarios. First, the trial took 11 years to accrue 500 patients suggesting the potential for a substantial selection for patients that the treating team would have equipoise to randomization. This group might include patients with relatively small nodal burden, lower T stage, response to neo-adjuvant treatment, or favorable resection

parameters. In addition, the radiation technology used was a 3D conformal approach with generous exposure of the normal anatomy to a relatively high radiation dose which could influence the toxicity of treatment and potentially the survival outcome of patients. Because of the uncertainties remaining it is reasonable to allow latitude for clinical discretion in determining if a patient will require adjuvant radiation therapy. Certain instances such as positive margins, which were excluded from LungART, will be included per protocol.

Because 4 cycles of platinum based therapy will be given neoadjuvantly, there is no need for adjuvant chemotherapy when complete resection has been accomplished. Thus, radiation would be the next phase of treatment, given 4 to 10 weeks after surgery. Consolidation therapy with an immune checkpoint inhibitor has not been studied in this population; however, the PACIFIC trial utilized a strategy of 1 year of consolidation durvalumab after definitive chemoradiation in nonoperative stage III NSCLC, with significant improvement in PFS.¹⁸ This has raised considerable interest in applying a similar strategy for operable stage III NSCLC patients. Because this strategy remains experimental, when applicable radiation would be given first postoperatively followed by 1 year of adjuvant durvalumab.

Nodal clearance has been felt to be a surrogate for outcome in stage 3 NSCLC. It was recently used as primary endpoint in 2 major cooperative group trials (RTOG 0229¹⁹ and RTOG 0839⁶). In the Intergroup 0139 trial in patients undergoing thoracotomy with ypN0 status, the median survival was 34.4 months and 5-year overall survival rate was 41%, which was significantly longer than patients with N1-3 status or not undergoing surgery ($p<0.0001$).² Cancer and Leukemia and Group B 8935 was a single arm phase II trial that investigated induction chemotherapy in pathological N2 disease and revealed a pathological clearance rate of N2 disease of 21%.²⁰ Patients with pathological clearance of N2 compared with patients with residual N2 disease had a superior survival (median failure-free survival of 47.8 versus 8.2 months, $p=0.01$). A similar study of induction therapy performed in Switzerland in resectable N2 disease revealed a rate of N2 clearance of 43% (50/115 by intention to treat [ITT] analysis) in the chemotherapy group. Patients with downstaging to N0-1 compared with persistent N2 disease had a superior overall survival ($p<0.001$), and the improvement was persistent on multivariable analyses (HR=0.22, $p=0.0003$).²¹ In the German Lung Cancer Cooperative study, which included N2 and N3 disease, patients with chemotherapy converted to ypN0-1 in 29% of the chemotherapy arm, and 46% of the chemoradiotherapy group. The 5 year survival for downstaged patients was 48% versus 13% (HR 2.07, $p=0.003$).²² It is worthy to note that nodal clearance rates are tracked only in the patients who go on to surgery, which is typically 80% to 85% of ITT analysis;^{2,4,5,19} so it is a more selected population enriched with responders. Pathologic N2 clearance, as determined at the time of resection, historically occurs 20% to 40% of the time in chemotherapy induction strategies^{5,20,22,23,24} and approximately 40% to 65% of the time in resected patients following chemoradiation induction.^{2,4,6,19}

1.2. Study Design

We propose a single arm phase II trial for potentially resectable pathologically proven N2 disease in clinical stage IIIA/B NSCLC patients (per the 8th International Association for the Study of Lung Cancer classification), with 4 cycles of combined platinum doublet chemotherapy and durvalumab, followed by anatomic surgical resection (lobectomy or greater) and adjuvant postoperative radiation therapy to 50-54Gy in select situations. This will subsequently be followed with 1 year of adjuvant durvalumab.

Our hypothesis is that N2NC will be substantially higher (50% or greater) for combined platinum doublet chemotherapy with adjuvant durvalumab than for platinum doublet chemotherapy alone (historically 20%-40%, about 30% on average) for patients with potentially resectable stage IIIA/B (T1-4, N2) NSCLC. The N2NC rate will be the primary endpoint for those who complete neoadjuvant therapy and have nodal clearance status evaluated.

Secondary endpoints will include:

- To evaluate the safety and tolerability of neoadjuvant platinum doublet chemotherapy and durvalumab followed by surgery followed by adjuvant radiation and durvalumab.
- To assess the radiographic response rate of neoadjuvant platinum doublet chemotherapy and durvalumab.
- To evaluate the rate of major pathologic response and pathologic complete response in the resected primary tumor and lymph nodes following neoadjuvant combination therapy.
- To evaluate the event-free survival from the time of registration to one of the following events, whichever comes first: a) radiographic disease progression, b) local progression as defined by lymph node progression precluding surgery, c) inability to resect the tumor d) local or distant recurrence e) death due to any cause.
- To evaluate overall survival rate from the time of registration to death of all causes.
- To assess the rate of complete resection.
- To assess postoperative complications (within 30 days of surgery).

1.3. Study Design Rationale

We propose a single arm phase II trial for pathologically proven N2 disease in clinical stage IIIA/B NSCLC patients, with 4 cycles of combined platinum doublet chemotherapy and adjuvant durvalumab, followed by anatomic surgical resection (lobectomy or greater) and adjuvant postoperative radiation therapy to 50-54 Gy in select situations. This will subsequently be followed with 1 year of adjuvant durvalumab.

Our hypothesis is that N2NC will be substantially higher (50% or greater) for combined platinum doublet chemotherapy with durvalumab than for platinum doublet chemotherapy alone (historically 20%-40%, about 30% on average) for patients with potentially resectable stage IIIA/B (T1-4, N2) NSCLC. The N2NC rate will be the primary endpoint for those who complete neoadjuvant therapy and have nodal clearance status evaluated.

Nodal clearance has been felt to be a surrogate for outcome in stage III NSCLC. We will collect information regarding pathologic response, radiographic response, efficacy, feasibility, and toxicity.

1.4. Study Agents

1.4.1. Investigational Agent: Durvalumab

Durvalumab is a programmed cell death ligand 1 (PD-L1) blocking antibody.

Please refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on durvalumab.

1.1.4. Other Agents

Patients will receive standard of care neoadjuvant chemotherapy in addition to durvalumab. The ongoing phase 3 PACIFIC trial is combining durvalumab with chemotherapy. No unexpected adverse events (AEs) have been noted thus far.

1.5. Risks and Benefits

The purpose of this study is to evaluate the safety and efficacy of durvalumab in the perioperative setting. As the administration of durvalumab with chemotherapy as so far proven safe (personal

communication, AstraZeneca), we have chosen to administer durvalumab with each of the preoperative chemotherapy cycles.

Durvalumab is approved for use in patients with NSCLC after definitive chemoradiation. We have chosen to administer durvalumab for 52 weeks (1 year; a total of 13 cycles) after postoperative radiation therapy.

Risks with durvalumab include, but are not limited to, cough/productive cough, pneumonitis, interstitial lung disease (ILD), dysphonia, ALT/AST increased, hepatitis, diarrhea, abdominal pain, colitis, hypothyroidism, hyperthyroidism, adrenal insufficiency, Type 1 diabetes mellitus (which may present with diabetic ketoacidosis), hypophysitis/hypopituitarism, diabetes insipidus, blood creatinine increased, dysuria, nephritis, rash, pruritus, night sweats, dermatitis, pemphigoid, myocarditis, pyrexia, oedema peripheral, upper respiratory infections, pneumonia, oral candidiasis, dental and oral soft tissue infections, influenza, myalgia, myositis, polymyositis, immune-mediated arthritis, myasthenia gravis, Guillain-Barre syndrome, infusion-related reactions, immune thrombocytopenia, pancreatitis, noninfective encephalitis, and uveitis.

Potential immune-mediated adverse events for durvalumab include other rare or less frequent events with a potential immune-mediated etiology such as pericarditis, sarcoidosis, cholangitis sclerosing, immune-mediated cystitis, and other events involving the eye (keratitis, optic neuritis), skin (scleroderma, vitiligo), hematologic events (hemolytic anemia, immune-mediated neutropenia), rheumatologic events (polymyalgia rheumatic), neuropathy/neuromuscular toxicities, vasculitis, non-infectious meningitis, psoriasis, and hypersensitivity reactions (anaphylaxis and allergic reaction or cytokine release syndrome).

For information on all identified and potential risks with durvalumab, please refer to the current version of the durvalumab IB. Further information on these risks can be found in the current version of the durvalumab IB.

In monotherapy clinical studies, AEs (all grades) reported very commonly ($\geq 15\%$ of patients) are fatigue, decreased appetite, cough, nausea, dyspnea, constipation, diarrhea, and arthralgia. Approximately 9.4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6.6% of patients experienced a serious adverse event (SAE) that was considered to be related to durvalumab by the study investigator. The most common AEs leading to treatment discontinuation were pneumonitis, pneumonia, dyspnea, general physical health deterioration, ILD, radiation pneumonitis, sepsis, anemia, and respiratory failure.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated reactions ([Appendix 1](#)). A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

It cannot be guaranteed that participants in clinical trials will directly benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of investigation therapies.

2. Objectives and Endpoints

2.1. Primary Objectives

- To increase N2 nodal clearance (N2NC) to 50% or greater for combined platinum doublet chemotherapy with durvalumab induction from an historical rate of 30% for platinum doublet chemotherapy alone in patients with potentially resectable stage IIIA/B (N2) NSCLC.

2.2. Secondary Objectives

- To evaluate the safety and tolerability of neoadjuvant platinum doublet chemotherapy and durvalumab followed by surgery followed by adjuvant radiation and durvalumab.
- To assess the radiographic response rate of neoadjuvant platinum doublet chemotherapy and durvalumab.
- To evaluate the rate of major pathologic response and pathologic complete response in the resected primary tumor and lymph nodes following neoadjuvant combination therapy.
- To evaluate the event-free survival from the time of registration to one of the following events, whichever comes first: a) radiographic disease progression, b) local progression as defined by lymph node progression precluding surgery, c) inability to resect the tumor, d) local or distant recurrence, e) death due to any cause.
- To evaluate overall survival rate from the time of registration to death of all causes.
- To assess the rate of complete resection.
- To assess post-operative complications (within 30 days of surgery).

2.3. Exploratory Objectives

- To assess the rate of pneumonitis after neoadjuvant platinum doublet chemotherapy and durvalumab, surgery, and adjuvant radiation.
- To assess the failure pattern (local versus distant) of patients treated with neoadjuvant platinum doublet chemotherapy and durvalumab followed by surgery followed by radiation and durvalumab.

2.4. Correlative Objectives

- To investigate the potential association of pre-treatment and on-treatment candidate biomarkers in peripheral blood and in tumor tissues.

2.5. Endpoints

The N2NC rate will be the primary endpoint for those who complete neoadjuvant therapy and have nodal clearance status evaluated.

This trial will use safety, response rate, major pathologic response, complete pathologic response rate (pCR), event-free survival (EFS), and overall survival (OS), rate of complete resection, and postoperative complication rate as secondary endpoints.

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence, causality, and outcome of adverse events (AEs)/serious adverse events (SAEs); and changes in vital signs and laboratory values. Adverse events will be assessed as defined by Common Terminology Criteria for Adverse Events (CTCAE), version 5.

Response rate will be based upon RECIST criteria.

Pathological complete response (pCR) will be evaluated as an exploratory endpoint. Although no neoadjuvant therapy for NSCLC has been approved on the basis of major pathological response (mPR) or pCR, there is support among physicians for using these endpoints, defined as follows:

- Major Pathological Response (mPR) for this trial is defined as $\leq 10\%$ viable tumor cells in primary resected tumor and all resected lymph nodes.
- Pathological complete response (pCR) for this trial is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the resected lung specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy (ie, ypT0/Tis ypN0).

Event-free survival (EFS) is a common surrogate endpoint for OS that is used to evaluate the efficacy of neoadjuvant and adjuvant cancer therapy and is sometimes used as primary endpoint.

Overall survival (OS) is a standard assessment of clinical benefit in participants with NSCLC.

Surgical complications that will be considered as SAEs include broncho-pleural fistulas, re-operation, supraventricular arrhythmia, pneumonia, and respiratory failure. This list is not exhaustive and other serious surgical complications should be reported.

2.6. Biomarker/Correlative Studies

Tumor tissue, peripheral leukocytes, and blood plasma specimens at baseline and during therapy will be collected as part of this study. PD-L1 assessment will be performed on pretreatment tissue as per local standards. To ensure comparability of data across all studies of durvalumab and to gain real world experience on the performance of this assay, it is strongly encouraged that all studies that include PD-L1 testing utilize the Ventana SP263 assay.

The Ventana SP263 assay is a fully, analytically validated test characterized through to the completion of reader precision studies in NSCLC and squamous cell carcinoma of the head and neck (SCCHN). For these tumors, the Ventana SP263 assay has a full reproducibility data package supporting cut-off and scoring algorithm. Following completion of ATLANTIC and HAWK clinical trials, the assay will be associated with clinical utility. In other cancer types (ie, bladder, pancreatic, gastric, hepatocellular, triple negative breast, ovarian, esophageal, nasopharyngeal, glioblastoma, soft tissue sarcoma, cholangiocarcinoma, small cell lung, melanoma, and cervical HPV+ cancers), the Ventana SP263 assay has only limited clinical performance data.

- Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (ie, >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.

In addition to analysis of PD-L1 expression by IHC, collected tissue biospecimens will be further used to perform genomic, epigenomic, gene expression, and/or proteomic analyses to identify candidate biomarkers of treatment response and outcome. Serial, peripheral blood plasma biospecimens will be used to evaluate nucleic acid, proteomic, and/or metabolic biomarkers of response and outcome.

2.7. Future Biomedical Research

See [Section 13.4](#).

3. Eligibility Criteria

For entry into the study, subjects must meet all of the inclusion, and none of the exclusion criteria.

AFT does not grant eligibility waivers. Investigators must carefully consider any condition that in the opinion of investigator would interfere with participation in the study. Please contact the study chairs for eligibility questions.

3.1. Operability Criteria

A patient is considered functionally operable if the following criteria are met:

1. ECOG Performance Status 0-1.
2. Absence of major associated comorbidities that increase the surgery risk to an unacceptable level.
3. Pulmonary function capacity capable of tolerating the proposed lung resection. FEV1 at least 2 L. If less than 2 L, the predicted postoperative forced expiratory volume in 1 second (FEV1) must be >0.8 L or be >35% of the predicted value. Postoperative predicted DLCO ≥35% is required.
4. R0 resection deemed to be possible by a board (ABTS) certified, or equivalent, study-approved thoracic surgeon.

3.2. Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Patients who are at least 18 years of age.
2. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-1.
3. Life expectancy of at least 12 weeks.
4. Patients with potentially resectable IIIA/B (T1-4, N2) NSCLC (per the 8th International Association for the Study of Lung Cancer classification) who are candidates for surgery with intent of R0 resection. Invasive T3 disease (eg, phrenic nerve, pericardium, chest wall other than Pancoast superior sulcus) may be included if the surgeon and study team deem it to be resectable. T4 based on size alone, >7 cm, that is deemed resectable CAN be included in the trial. T4 disease based on any criteria other than size alone per AJCC 8th edition staging system is excluded given the lack of benefit of surgery in these patients.
5. Patients must be evaluated by a thoracic surgeon within 4 weeks of registration.
6. Operability is defined as having adequate pulmonary, cardiac, renal, nutritional, musculoskeletal, neurologic, and cognitive capacity to undergo major pulmonary resection with acceptable morbidity and mortality.
7. N2 nodes must be discrete (ie, not invading surrounding structures) and less than 3 cm in maximum diameter.
8. Measurable disease according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).²⁵
9. Pathologically proven N2 disease (tissue must be collected within 4 weeks of registration if archival tissue is not available). PET/CT positivity in the ipsilateral mediastinal nodes will not be sufficient to establish N2 nodal status. Mediastinal lymph node sampling biopsy is required preoperatively by at least one of the following:
 - a. Endobronchial Ultrasound Transbronchial Needle Aspiration (EBUS-TBNA);
 - b. Mediastinoscopy;
 - c. Mediastinotomy (Chamberlain procedure);
 - d. Endoscopic ultrasound guided node aspiration (EUS);

- e. Video-assisted thoracoscopy; OR
- f. Fine needle aspiration by image guidance.

Endobronchial ultrasound (EBUS) or mediastinoscopy or other tissue sampling (at least 2 stations must be biopsied, with at least one station positive for N2 disease). If there are any mediastinal nodes suspicious by CT (>1.5 cm) or PET in N3 stations, they must be biopsied. If biopsy proven involvement in an N3 station, the patient is excluded. In the event that there is only 1 station that contains one or more nodes for sampling, out of at least 2 stations that are assessed, sites can use that 1 station for eligibility.

10. Mediastinal nodal biopsy or aspiration can only be omitted in the special circumstance in which ALL of the following are true:

- a. The tumor is left sided;
- b. The only mediastinal nodal involvement is a node visible in the AP (level 5) region on CT scan;
- c. Distinct primary tumor separate from the nodes; AND
- d. Biopsy proven non-small cell histology from the primary tumor.

11. No prior history of thoracic radiation.

12. Organ and marrow function definitions (example below)

- | | |
|-----------------------------|---|
| - Leukocytes | ≥ 3,000/mcL |
| - absolute neutrophil count | ≥ 1,500/mcL |
| - platelets | ≥ 100,000/mcL |
| - Hemoglobin | > 9.0 g/dL |
| - total bilirubin | within normal institutional limits |
| - AST(SGOT)/ALT(SGPT) | ≤ 2.5 × institutional upper limit of normal |
| - creatinine | within normal institutional limits |
| OR | |
| - creatinine clearance | ≥ 60 mL/min/1.73 m ² for participants with creatinine levels above institutional normal. |

13. Patients are capable of giving informed consent and/or have an acceptable surrogate capable of giving consent on the subject's behalf.

14. Nonpregnant and non-nursing. The effect of durvalumab on the fetus is unknown.

15. Women of childbearing potential (WOCBP) must be willing to use 2 methods of birth control and at least 1 highly effective method of contraception or be surgically sterile, or abstain from heterosexual activity for the course of the study through 3 months after the last dose of study medication. Patients of childbearing potential are those who have not been surgically sterilized or have not been free of menses > 1 year.

16. Evidence of postmenopausal status or negative urinary or serum pregnancy test for female premenopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
 - a. Women < 50 years of age would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the postmenopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
 - b. Women ≥ 50 years of age, but ≤ 65 years of age, would be considered postmenopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses > 1 year ago, had chemotherapy-induced menopause with last menses > 1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).
 - c. Women > 65 years of age are deemed to not be of childbearing potential.
17. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
18. Male patients with female partners of childbearing potential must agree to use 2 methods of birth control and at least 1 highly effective method of contraception (see Section 8.2 for highly effective methods) starting with the first dose of study therapy through 90 days after the last dose of study therapy.
19. No history of noninfectious pneumonitis/interstitial lung disease requiring oral steroids.
20. No known hypersensitivity to study chemotherapy or durvalumab.
21. No known HIV. No HIV testing is required.
22. No known history of Hepatitis B (as defined by Hepatitis B surface antigen reactive) or known active Hepatitis C virus (defined as HCV RNA detected) infection

3.3. Exclusion Criteria

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

1. Any prior treatment for NSCLC.
2. Prior thoracic radiation.
3. Patients with ≥ Grade 2 peripheral neuropathy.
4. Any active or history of autoimmune disease (including any history of inflammatory bowel disease) or history of a syndrome that required systemic steroids or immunosuppressive medications, except for patients with vitiligo or resolved childhood asthma/atopy.
5. Patients requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses <10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

6. Patients with previous malignancies (except nonmelanoma skin cancers, in situ bladder, gastric, breast, colon or cervical cancers/dysplasia) are excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.
7. History of solid organ transplant unless corneal transplantation.
8. N3 nodal disease.
9. Mixed small cell/NSCLC will be excluded.
10. Pregnant or breastfeeding.
11. History of allogenic organ transplantation.
12. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], active diverticulitis with the exception of diverticulosis, systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]. The following are exceptions to this criterion:
 - a. Patients with vitiligo or alopecia.
 - b. Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.
 - c. Any chronic skin condition that does not require systemic therapy.
 - d. Patients without active disease in the last 5 years may be included but only after consultation with the study physician.
 - e. Patients with celiac disease controlled by diet alone.
13. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
14. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥ 470 ms calculated.
15. Patients with known EGFR mutation are excluded.

3.4. Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this study.

4. Patient Enrollment

4.1. Site Enrollment Requirements

Sites must submit all required essential documents including:

- AFT Investigator Agreement.
- Curriculum Vitae(s) of the Principal Investigator.
- Medical License(s) from all investigators.

- Completed Financial Disclosure Form(s) from all investigators.
- Investigator Brochure Signature Page(s).
- Documentation of Good Clinical Practice (GCP) Training.
- Protocol Signature Page.
- A copy of the dated and signed, written IRB approval of the protocol, amendments, ICF, and any recruiting materials, if applicable.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Documentation of protocol training.
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable.
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable.
- Any other documentation required by local regulations.

Essential documents must be submitted to the AFT electronic Trial Master File, SiteZone, accessible via the AFT website: <https://alliancefoundationtrials.org/>. Sites will receive site selection correspondence with detailed requirements for site activation.

4.2. Patient Enrollment

Patient enrollment will be facilitated using the Medidata Rave® iMedidata Portal, accessible via the AFT Web site: <https://alliancefoundationtrials.org/>. After written informed consent has been obtained, the study site will obtain a unique patient identifier by entering the patient in Medidata Rave®. The patient identifier will stay the same throughout the entire study. Patients must receive this identifier prior to submission of biospecimens.

Prior to accessing the patient enrollment system, 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.

Patients screened but not registered for any reason should be documented as a screen failure in Medidata Rave®.

5. Treatment Plan

5.1. Treatment Regimen—Preoperative Period

The preoperative treatment to be used in the trial is outlined below in **Table 1**.

Table 1: Preoperative Treatment Regimen

Study Treatment	Dose/Route of Administration	Frequency
Durvalumab	1500 mg IV	Every 3 weeks × 4, prior to surgery

Pemetrexed	500 mg/m ² IV	Every 3 weeks × 4, prior to surgery
Docetaxel	75 mg/m ² IV	Every 3 weeks × 4, prior to surgery
Cisplatin	75 mg/m ² IV	Every 3 weeks × 4, prior to surgery

Abbreviation: IV=intravenous

Participants are to begin study treatment within 14 calendar days of registration. Participants are to receive durvalumab 1500 mg IV plus histology dependent platinum doublet chemotherapy every 3 week treatment cycle up to a maximum of 4 cycles:

- Non-squamous NSCLC: durvalumab 1500 mg, followed by pemetrexed at a dose of 500 mg/m² IV over 10 minutes or per institutional standard with cisplatin at a dose of 75 mg/m² IV over 120 minutes or per institutional standard, every 3-week treatment cycle, for up to 4 cycles.
- Squamous NSCLC: durvalumab 1500 mg, followed by docetaxel at a dose of 75 mg/m² IV over 60 minutes or per institutional standard with cisplatin at a dose of 75 mg/m² IV over 120 minutes or per institutional standard, every 3-week treatment cycle, for up to 4 cycles.

Dosing calculations for chemotherapy should be based on the body surface area (BSA) calculation assessed as per standard of care. The dose should remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight. All doses should be rounded up or to the nearest milligram or per institutional standard.

When study drugs (durvalumab and chemotherapy) are to be administered on the same day, durvalumab is to be administered first. Durvalumab infusion must be promptly followed by a saline flush to clear the line of durvalumab before starting the chemotherapy infusion. The time in between infusion of durvalumab and chemotherapy is expected to be approximately 30 minutes but may be more or less depending on the situation.

There will be no dose escalations or reductions of durvalumab allowed. Participants may be dosed no less than 18 days from the previous dose.

Participants should be carefully monitored for infusion reactions during durvalumab administration. If an acute infusion reaction is noted, participants should be managed according to [Appendix 1](#).

The dose of durvalumab may be interrupted, delayed, or discontinued depending on how well the participants tolerates the treatment.

Dose delay criteria can be found in [Section 7.3.1](#), and discontinuation criteria can be found in [Appendix 1](#). Criteria to resume treatment can be found in [Section 7.3.1](#).

Refer to instructions below for pemetrexed/cisplatin and docetaxel/cisplatin administration.

Doses of pemetrexed and/or cisplatin may be modified, delayed, or discontinued depending on how well the participant tolerates the treatment. Dose modifications for toxicity will be performed according to [Section 7.0](#). Dose delay and discontinuation criteria can be found in [Section 7.3.2](#). Caution should be used when administering nonsteroidal anti-inflammatory drugs (NSAIDs) concurrently with pemetrexed to patients with mild to moderate renal insufficiency (creatinine clearance from 45 to 79 mL/min). Pemetrexed should not be administered if the calculated CrCl is < 45 mL/min.

Doses of docetaxel and/or cisplatin may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. Dose modifications for toxicity will be performed according to [Section 7.0](#). Dose delay and discontinuation criteria can be found in [Section 7.3.3](#).

If a participant who is receiving durvalumab and platinum doublet chemotherapy experiences an AE and the investigator can attribute it to either durvalumab or chemotherapy, then either durvalumab or the chemotherapy agents can be discontinued, and the other agent(s) can be continued. For any questions regarding this, please contact the AFT study team to confirm.

5.2. Surgery—Operative Period

Evaluation for Surgery

5.2.1. Mediastinal Sampling

N2 status must be pathologically confirmed to be positive within 4 weeks prior to registration.

Investigators are strongly encouraged to biopsy multiple stations of mediastinal lymph nodes at the time of invasive staging in addition to those nodes that are abnormal on PET/CT scan. At least 2 stations must be biopsied, with at least one station positive for N2 disease. If there are any mediastinal nodes suspicious by CT (> 1.5 cm) or PET in N3 stations, they must be biopsied. If biopsy proven involvement in an N3 station, the patient is excluded. In the event that there is only 1 station that contains one or more nodes for sampling, out of at least 2 stations that are assessed, the site can use that 1 station for eligibility. N2 status must be pathologically confirmed to be positive within 4 weeks prior to registration by at least one of the following methods:

- Mediastinoscopy;
- Mediastinotomy (Chamberlain procedure);
- Transesophageal needle biopsy using endoscopic ultrasound (EUS);
- Endobronchial ultrasound biopsy using endoscopic ultrasound guidance (EBUS-TBNA);
- Video-assisted thoracoscopy;
- Transbronchial needle biopsy by Wang technique (TBNA); OR
- Fine needle aspiration under CT guidance.

PET/CT positivity in the ipsilateral mediastinal lymph nodes will not be sufficient to establish N2 nodal status.

- Nodal Documentation

Review of pre-treatment studies (PET/CT, CT, pathologic results of mediastinal staging) will define mediastinal lymph node status for appropriate analysis, as follows:

- Number of Stations Involved
 - If, on review of the pathology report only one station has been biopsied and that station is positive for cancer, the patient will be classified as N2LX (nodes not evaluable); patients with a paralyzed vocal cord and enlarged aorto-pulmonary window nodes also will fall into this category.
 - If, on review of the pathology report more than one station has been biopsied and only one station is positive for cancer the patient will be classified as N2L1 (one station involved).

- If, on review of the pathology report more than one station has been biopsied and two or more stations are positive for cancer, the patient will be classified as N2L2 (two or more stations involved).
- Nodal Micrometastases and Lymph Node Size
 - Patients with either any non-subcarinal nodes with a short axis diameter on CT > 1 cm or subcarinal nodes with a short axis diameter on CT > 1.2 cm shall be classified as cN2 (clinically involved lymph nodes);
 - Patients in whom all non-subcarinal nodes are ≤ 1 cm and subcarinal nodes ≤ 1.2 cm shall be classified as mN2 (microscopically involved lymph nodes).
- If lymph nodes in the contralateral (opposite the primary) mediastinum and neck are visible on the contrast CT scan of the chest and are > 1.0 cm in short axis or if contralateral involvement is suggested by PET/CT scan, then the nodes must be confirmed to be negative by one of the diagnostic procedures listed in [Section 5.2.1](#).

5.3. Pre- Surgical Assessment After Completion of Induction Therapy

Upon completion of neoadjuvant therapy (start of Week 13) and prior to anticipated surgery (Weeks 16-20), all patients will be re-evaluated as follows to assure that their medical condition has not deteriorated to the point that the patient is no longer medically fit to withstand resection.

Reassessments include the following:

- History and physical by medical oncologist;
- Evaluation by thoracic surgeon;
- Electrocardiogram (EKG);
- Pulmonary Function Tests with diffusion capacity; the quantitative V/Q scan or split functions need not be repeated unless the FEV1 is worse than pre-study;
- Repeat laboratory evaluations for bone marrow and hepatic function (repetition of the creatinine clearance is not necessary);
- Imaging:
 - Chest and upper abdominal CT scan to include entire liver; OR
 - Whole body FDG-PET scan (preferred; recommended but not required). This PET/CT scan should ideally be performed at the same facility as the pre-treatment PET/CT scan so that the data can be used for analysis of the secondary objective.

Note: To be included in this analysis, the patient's PET/CT studies must be performed with a dedicated BGO, LSO, or GSO PET or PET/CT scanner; PET scanners with sodium iodide (NaI) detectors are not acceptable. A bone scan is not required unless there is new bone pain or new elevation of the alkaline phosphatase or LDH.
- Repeat bronchoscopy is performed at the discretion of the surgeon. It is recommended in those patients who have disease near the carina or in another position where small amounts of progression which may not be well visualized on CT scan may impact resectability.
- Radiographic response determinations (CR, PR, SD, PD) will be required for this study (see [Section 13.8](#)). Whenever possible, a biopsy should be obtained to confirm distant progression.

All patients who fit the criteria for no progression in the chest or elsewhere, including all patients who have stable disease on re-evaluation, are eligible to proceed to surgery.

If there is progressive disease (PD) or distant disease identified, protocol treatment will be discontinued. Further treatment is at the discretion of the treating medical oncologist. Patients with progressive disease will receive further nonoperative, non-protocol therapy at the discretion of their treating physician(s).

Patients who have not progressed but are inoperable for medical or anatomic reasons, should proceed to consolidation therapy as detailed in the protocol. Sites will submit the Pre-Surgical Assessment Form.

If it is the opinion of the attending thoracic surgeon that the patient has developed a problem that makes surgery medically or technically unsafe, or if the patient refuses surgery, the Thoracic Surgery Co-Chair, [REDACTED], or, in her absence, the Medical Oncology Co-Chair, [REDACTED], should be notified and this information documented.

Surgery will be performed 4 to 8 weeks after completion of induction therapy. Occasionally, an extra week will be required to recover from toxicity of induction therapy. If longer than a week is deemed necessary, [REDACTED] or [REDACTED] should be notified immediately. The site will document the reason(s) for delay on the Pre-Surgical Assessment Form. If the delay is approved by [REDACTED], the delay will not be considered a protocol deviation.

5.4. Surgical Guidelines/Extent of Resection

A lobectomy, bilobectomy, sleeve lobectomy or other extended resection, or a pneumonectomy will be performed at the discretion of the attending thoracic surgeon. A sublobar resection (eg, a wedge or segmentectomy) will be considered a major protocol deviation. The type of resection chosen should provide complete removal of the primary lesion with negative gross margins; this is not subject to quality assurance review. Documentation of margins by frozen section at surgery is strongly recommended.

Lesions with direct extension into parietal pleura or chest wall should be resected with an en bloc chest wall resection. Lesions with direct extension into pericardium or diaphragm should have en bloc resection of those structures with an attempt made to achieve a minimum of 2 cm gross or 1 cm microscopic margins. These are recommendations subject to quality assurance review (i.e., if it is not a chest wall lesion but a pleura invasion, this must be reviewed).

A formal systematic mediastinal lymph node dissection will be performed in all cases. The primary endpoint of this trial is clearance of disease from mediastinal lymph nodes at the time of resection. Numbering and/or nomenclature outlined in the Lymph Node Map will be used (see [Appendix 2](#)).²⁶ Mediastinal lymph nodes removed at thoracotomy should include nodes from the following regions, as defined in the Operative Standard for Cancer Surgery²⁷:

- For right sided lesions: 4R, 7, 9R, 10R; and if accessible, 2R. If the 4R, 7, 9R, and 10R levels are not performed, it will be considered a major protocol deviation. 2R is recommended but is not subject to quality assurance review. If nodes are not identified in required stations, this should be documented in the operative report. If exploration of a nodal station is documented, and no nodes are found, this is NOT a protocol deviation.
- For left sided lesions: 5, 6, 7, 9L, 10L; and if accessible, 4L. If the 5, 6, 7, 9L, and 10L levels are not performed, it will be considered a major protocol deviation. 4L is recommended but is not subject to quality assurance review. If nodes are not identified in required stations, this should

be documented in the operative report. If exploration of a nodal station is documented, and no nodes are found, this is NOT a protocol deviation.

The attending thoracic surgeon and medical oncologist must review and sign all postsurgical forms.

At the time of surgical resection, after the completion of the anatomic resection, it is optional for a soft tissue flap (muscle or thymic or pericardial fat flap) to be placed on the bronchial stump to buttress the bronchus to prevent air leak, bronchopleural fistula, or infection.

In the case of an anticipated lobectomy, it is recommended that an intercostal muscle flap made up of the fifth intercostal muscle with neurovascular pedicle be harvested at the time of the thoracotomy before placing the rib spreader. The flap should then be protected with gauze soaked in saline and/or papaverine.

In the case of a pneumonectomy, the serratus anterior muscle is recommended and should be harvested in its anterior and inferior portions. It can be left attached to the scapula superiorly but is generally detached posteriorly. This is then placed through the second or third intercostal space anteriorly. It is suggested that the flaps then be secured with interrupted 4-0 vicryl sutures to the adventitia overlying the bronchus, 2 anteriorly and 2 posteriorly. Performing a resection without soft tissue flap will not be considered a major protocol deviation.

The use of video-assisted thoracoscopic surgery (VATS) techniques for resection are discouraged but not prohibited in this trial because of the extensive pretreatment and need for thorough mediastinal nodal dissection.

5.5. Postoperative Period

During the post-operative period the use of minimal IV fluids is recommended. After pneumonectomy, a strict fluid restriction of < 1500 cc/day adhered to for the first 4 days is recommended. In addition, diuretic therapy is strongly encouraged (typically, Lasix 20 mg bid is used daily), and additional doses of Lasix are used if blood transfusions are necessary.

5.5.1. Surgical Adverse Events

All acute and late AEs from protocol surgery will be reported and scored for severity using the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5 for grading all adverse events. CTCAE, v.5 is identified and located on the CTEP Web site at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

See [Section 11.8](#) for Adverse Event Reporting.

5.5.2. Post-Operative Complications

Major morbidities are scored as any event occurring within 30 days following surgery. The complications of surgery will be documented on the Surgical Evaluation Form (S1) as part of the secondary objectives of this study. All patients undergoing surgical resection will be included in the analysis of surgical AEs. Data collection also will include Surgical Operative (S2) and Surgical Pathology (S5) Reports documenting duration of surgery, estimated blood loss, blood transfusions required intra- and peri operatively, and number of postoperative days intubated. The AEs attributed to surgery will include any of the following complications listed below:

- Bronchial, pleural, and lung infections: includes pneumonia and empyema that was diagnosed during the postoperative period; specify the organism causing the infection.
- Infection (other than pulmonary).

NOTE: This includes wound infection of surgical incisions for thoracotomy. When there is a wound infection, specify the organism causing the infection in the space provided, and record which wound was infected.

- Atelectasis: includes collapse of either an entire lung or a lobe of the lung or atelectasis severe enough to require medical/operative intervention.

NOTE: Do not include instances of incidental post-operative basilar atelectasis.

- Pneumothorax: Includes lung collapse that is due to air leakage from the lung into the pleural space). The pneumothorax must be severe enough that treatment (ie, insertion or reinsertion of a chest tube) is required.
- Bronchopleural fistula: Includes bronchial stump leaks, includes any fistula that developed within the postoperative period.

NOTE: A patient with a bronchopleural fistula associated with an intrathoracic infection should be reported as having both the intrathoracic infection and a fistula, pulmonary/upper respiratory.

- Pleural effusion (nonmalignant): Includes any effusion within the postoperative period that requires treatment (ie, pleural tap).
- Chylothorax.
- Myocardial infarction, Acute coronary syndrome: includes any myocardial infarction that occurred within the postoperative period.
- Thromboembolic event: Includes any pulmonary embolus that occurred within the postoperative Period.
- Atrial fibrillation, atrial flutter: Includes any new atrial arrhythmia that developed within the postoperative period that requires treatment.
- Ventricular arrhythmia: Includes any new ventricular arrhythmia that developed within the post-operative period that requires treatment.
- Postoperative hemorrhage: Postoperative period is defined as ≤ 72 hours after surgery; includes hemorrhage that required reoperation for control.
- Death: Any grade 5 AE occurring within 30 days of surgery, regardless of attribution.
- Other: Includes any surgical or medical complication that occurred during the postoperative period (eg, cerebrovascular accident). Specify details.

5.5.3. Surgical Quality Assurance Reviews

The Thoracic Surgery Co-Chair, [REDACTED] will review surgical staging prior to induction therapy and at surgical resection (ie, the Operative and Surgical Pathology reports for the initial evaluation of lymph nodes and the surgical resection). [REDACTED] will perform a Quality Assurance Review after complete data for the first 15 cases enrolled has been received by AFT. [REDACTED] will perform the next review after complete data for the next 15 cases enrolled has been received. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as complete data for all cases enrolled has been received, whichever occurs first.

5.5.3.1. Goals of Surgical Quality Assurance

The goals of surgical quality assurance are:

- To assure eligibility and correct surgical staging of patients prior to Induction Therapy;
- To assure safety of patients undergoing resection after Induction Therapy;
- To assure adequate resection of primary and lymph node dissection after Induction Therapy.

5.5.3.2. *Surgical Protocol Compliance Criteria*

- Deviations Minor:
 - Surgical resection outside the defined window (unless prior approval from the Thoracic Surgery Co-Chair was obtained);
- Deviations Unacceptable: Those deviations that affect patient safety/outcome, which will result in an institution being suspended from further participation in the study, such as:
 - Inadequate nodal dissection and/or numbering at thoracotomy;
 - No documentation of post neoadjuvant/pre-operative PFTs or evidence of calculated post-resection FEV 1 < 800 cc.

5.6. Postoperative Treatment: Radiation

5.6.1. Radiotherapy

Radiation treatment will be required for patients with a positive margin. All other patients can be treated with radiation therapy at the discretion of the treating institution. If radiation is included in the treatment course for the patients, the protocol techniques showed be followed.

Patients will receive a radiotherapy course using single daily fractions. Radiotherapy should begin no sooner than 4 weeks after completion of surgery and no later than 10 weeks after completion of surgery.

Conformal 3-dimensional or Intensity-modulated radiation therapy (IMRT) treatment planning will be utilized. Proton therapy using Intensity-modulated proton therapy will be allowed (IMPT). All treatment plans must be sent to the IROC Rhode Island Quality Assurance Review Center (QARC) prior to initiating therapy.

NOTE: Digital submission of treatment plans is required on this study.

5.6.1.1. *Target Volume Definitions*

rCTV (resected Clinical Target Volume). This corresponds to lymph nodes involved in the mediastinum and hilum according to the pathological report of the lymph node exploration. The bronchial stump, the ipsilateral hilar node region, as well as the eventual extension to mediastinal pleura adjacent to the completely resected tumor bed will **always** be included in the rCTV.

CTV (Clinical Target Volume). In the CTV, will be included the rCTV plus a margin for micro-extensions of nodal disease, which is 1.0 cm (**CTV = rCTV + 1 cm**). We recommend the vertebral body, and large adjacent organ structures such as the mainstem bronchi, large blood vessels, heart, and adjacent lung be excluded from the 1 cm rCTV expansion. In addition, if not encompassed in the 1 cm rCTV expansion, the upper and lower lymph node station adjacent to the involved lymph node regions should be included in the CTV. **The volumes delineated for the CTV (CTV = rCTV + 1 cm) should not exceed the maximal upper and lower limits as shown in Table 2. All the lymph nodes that lie between 2 noncontiguous node stations that are involved will be included in the CTV.** Because of the frequent involvement of subcarinal (LN7) and the ipsilateral paratracheal nodes (LN4) on surgical series, these stations will always be systematically included in the CTV.

The ipsilateral supraclavicular region will NOT be routinely included systematically in CTV.

The lymph nodes can be delineated according to the atlas from the University of Michigan²⁸ corresponding to a CT-based definition of thoracic lymph node stations.

Table 2 provides CTV delineation according to LN involvement.

Table 2: CTV Delineation According to LN Involvement

Surgically Involved Mediastinal Nodes	LN Stations to be Included in the CTV
1-2R	1-2R ¹ , 4R, 7, 10R Maximal upper limit: 1 cm above sternal notch but ipsilateral subclavicular node station may be treated if needed. Maximal lower limit: 4 cm below the carina ²
1-2L	1-2L, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch but homolateral subclavicular node station may be treated if needed. Maximal lower limit: 4 cm below the carina ²
3 (Right-sided Tumor)	3, 4R, 7, 10R Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina ²
3 (Left-sided Tumor)	3, 4L, 7, 10L Maximal upper limit: 1 cm above the sternal notch Maximal lower limit: 4 cm below the carina ²
4R	4R, 7, 10R Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina ²
4L	4L, 7, 10L Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina ²
5	4L, 5, 7, 10L Maximal upper limit: Top of aortic arch Maximal lower limit: 4 cm below the carina ²

Surgically Involved Mediastinal Nodes	LN Stations to be Included in the CTV
6	4L, 6 , 7, 10L Maximal upper limit: sternal notch Maximal lower limit: 4 cm below the carina ²
7 (Right-sided Tumor)	4R, 7 , 10R Maximal upper limit: Top of aortic arch Maximal lower limit: 5 cm below the carina ²
7 (Left-sided Tumor)	4L, 7 , 10L Maximal upper limit: Top of aortic arch Maximal lower limit: 5 cm below the carina ²
8 (Right-sided Tumor)	4R, 7, 8 , 10R. Maximal upper limit: Top of aortic arch The maximal lower limit should be the gastro- esophageal junction.
8 (Left-sided Tumor)	4L, 7, 8 , 10L Maximal upper limit: Top of aortic arch The maximal lower limit should be the gastro- esophageal junction.

¹ Text in bold is meant to specify a station containing the pathologically involved nodes).

² Unless other nodes are involved.

Motion Management: 4D CT imaging will be obtained at the time of simulation, and the CTV shall be expanded to encompass the range of motion from the 4D CT dataset. This target volume will create an ITV.

The ITV will be expanded to create a planning target volume (PTV) to which the radiotherapy dose will be prescribed. The description of the PTV expansion is outlined in [Section 5.6.5](#) based on the motion management and assessment techniques used and outlined in that section.

Special Cases:

1. Pathologic Complete Response

- a) Multiple N2 Stations on pre-op assessment: The bronchial stump, the ipsilateral hilar node region, as well as the eventual extension to mediastinal pleura adjacent to the completely resected tumor bed will be included as the rCTV. The CTV will be created to include the rCTV + the pre-immunotherapy nodal stations in the hilum and mediastinum and as best as possible based on any pre-operative imaging (PET/CT and/or CT) and available mediastinal assessment from bronchoscopy, esophageal endoscopic ultrasound, or mediastinoscopy. The size of this CTV should take into account anatomic

changes as a result of the response to therapy (ie, diminishment in mediastinal width due to response). This CTV will be expanded to create a PTV as outlined below.

- b) Single N2 Station on pre-op assessment: If patients have a complete response (CR) to induction immunotherapy in both the single known lymph node station and the primary tumor (ypT0N0) then post-operative radiotherapy should be withheld.
 - c) Residual disease in primary tumor but ypN0: The bronchial stump, the ipsilateral hilar node region, as well as the eventual extension to mediastinal pleura adjacent to the completely resected tumor bed will be included as the rCTV. The CTV will be created to include the rCTV + the pre-immunotherapy nodal stations in the hilum and mediastinum and as best as possible based on any pre-operative imaging (PET/CT and/or CT) and available mediastinal assessment from bronchoscopy, esophageal endoscopic ultrasound, or mediastinoscopy. This will be for either single or multistation N2 disease at pre-immunotherapy assessment. The size of this CTV should take into account anatomic changes as a result of the response to therapy (ie, diminishment in mediastinal width due to response). This CTV will be expanded to create a PTV as outlined below.
2. Positive Margins or Extranodal extension (ENE)
- a) In the event of a positive surgical margin or extranodal extension, an additional CTV will be contoured, labeled hrCTV to include as best as possible the area of concern based on surgical reports, pathologic assessment, and any pre or postoperative imaging. The area at risk shall be contoured and then expanded by 5 mm to include possible microscopic extent of disease with appropriate adjustment for anatomic boundaries to spread such as bone or major blood vessels. An hrITV will be created to encompass the motion of the target region based on 4DCT. The ITV will be expanded to include the hrCTV. Finally, a hrPTV will be created using a 5 mm expansion from the hrITV.

5.6.2. Treatment Techniques

3D Conformal Planning, IMRT, or IMPT is required on this protocol. Both planar and non-coplanar field arrangements are acceptable. If IMRT/IMPT 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 5 mm (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 are permissible. IMRT will be restricted to patients with less than 1 cm 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 cone beam imaging, fiducial marker tracking systems, kV – kV matching. Daily cone beam (CBCT) imaging is the preferred method; CBCT imaging should be registered to the target tissue when aligning the CBCT and the reference imaging.

5.6.3. Equipment

- **Modality:** 3D Conformal, IMRT Radiotherapy, or IMPT
- **Energy:** For X-ray techniques, megavoltage quality radiation will be used with a nominal energy of 4-12 MV. Co-60 treatment is not allowed on this protocol. Proton energy ranges suitable for treatment of the target at depth should be chosen.
- **Geometry:** The distance from the radiation source to the isocenter should not be less than 100 cm for x-ray techniques

5.6.4. Target Dose

- **Prescribed Dose:** 54 Gy (RBE) in 30 fractions of 1.8 Gy per fraction given once daily to the PTV. For patients required to include an additional hrPTV due to positive margin or extra-nodal extension, the hrPTV will be treated to 60 Gy in 30 fractions of 2.0 Gy per fractions given once daily using a simultaneous integrated boost technique. For proton planning the dose will be prescribed to the CTV with evaluation of beam robustness criteria based on beam specific range/set-up uncertainty.
- **Dose Uniformity:** The prescribed isodose volume will cover at least 95% of the respective 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 0.1 cc volume of the PTV. For proton planning this criteria will be applied to the CTV.
- **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. (CTV for proton planning)
 - 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. (CTV for proton planning)
- **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 () 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.

5.6.5. 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.

- Exception: 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 Internal Target Volume (ITV) 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 a 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.

5.6.6. Time-dose Considerations

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

5.6.6.1 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.

5.6.7. Contouring of Normal Tissue Structures

5.6.7.1 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.

5.6.7.2 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.

5.6.7.3 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 subclavian neurovascular bundle. Please refer to Kong et al IJROBP 2010 thoracic radiotherapy contouring atlas for description of contouring techniques.²⁹

5.6.7.4 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.

5.6.7.5 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 volume (GTV) and trachea/ipsilateral bronchus when contouring structure should not be included in this structure.

5.6.7.6 Chest Wall

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

5.6.7.7 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 main stem bronchi, and lobar bronchi to the level of the segmental bronchi. Please refer to Kong et al IJROBP thoracic contouring atlas for detailed descriptions.²⁹

5.6.8 Normal Tissue Sparing

The following dose constraints will be followed:

5.6.8.1 Lung

V20 >31% will be a minor deviation in the case of a lobectomy, V20 >22% will be a minor deviation after a pneumonectomy. V20 >37% will be a major deviation after a lobectomy, V20 >28% will be a major deviation after a pneumonectomy. Mean Lung Dose will be recorded and in general should be kept below 18 Gy although the V20 constraints will be utilized as the dose limitations for purposes of this protocol.

5.6.8.2 Heart

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

5.6.8.3 Spinal Cord

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

5.6.8.4 Esophagus

The esophagus is, in general, located in close proximity to nodal areas involved in stage 3 NSCLC; therefore, it 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 5 cc of the esophagus will be limited to $\leq 105\%$ of the prescription dose when feasible.

5.6.8.5 Brachial Plexus

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

5.6.9 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 QARC SUBMIT. Instructions for data submission are in the Radiation Therapy Quality Assurance (RTQA) Manual or 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 U Treatment.
- If the recommended doses to the organs at risk are exceeded, an explanation should be included for review by the radiation oncology reviewers.

Forms

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

Within 1 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.

Send e-mail to [REDACTED] to indicate that you have uploaded protocol case data. Please identify the study group, protocol, and case number for the submission. or mailed to:

IROC – Rhode Island
640 George Washington Highway
Building B, Suite 201
Lincoln, RI 02865
[REDACTED]

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

ALLIANCE Protocol Dosimetrist
IROC – Rhode Island
640 George Washington Highway
Building B, Suite 201
Lincoln, RI 02865
[REDACTED]

5.6.10 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 5.6.8](#).
- **Deviation Unacceptable:** The maximum dose to the spinal cord exceeds the limits specified in [Section 5.6.8.3](#) or the lung V20 exceeds 40%.

5.7. Postoperative Treatment: Adjuvant Therapy

Durvalumab: Upon completion of postoperative radiation, durvalumab 1500 mg IV every 4 weeks will be administered for 13 cycles (**Table 3**). Durvalumab should begin between 1-6 weeks after completion of radiation after toxicities of radiation therapy are grade 0 or 1.

Table 3: Postoperative Adjuvant Therapy

Study Treatment	Dose/Route of Administration	Frequency
Durvalumab	1500 mg IV	Every 4 weeks × 13

5.7.1. Pre-Treatment Criteria

On Cycle 1 Day 1 (C1D1; within 72 hours) of postoperative adjuvant therapy, patients must meet the following criteria:

1. ECOG PS 0-1

2. Organ and marrow function definitions:

- Leukocytes $\geq 3,000/\text{mCL}$
- absolute neutrophil count $\geq 1,500/\text{mCL}$
- platelets $\geq 100,000/\text{mCL}$
- Hemoglobin $> 9.0 \text{ g/dL}$
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT) $\leq 2.5 \times$ institutional upper limit of normal
- creatinine within normal institutional limits

OR

- creatinine clearance $\geq 60 \text{ mL/min/1.73 m}^2$ for participants with creatinine levels above institutional normal.

5.7.2. Cycle 1 Day 1

Patients must undergo Cycle 1 Day 1 (C1D1; within 72 hours) laboratory and performance status assessment prior to start of treatment and meet above parameters.

5.7.3. Subsequent Cycles

Please see dose reduction guidelines for subsequent preoperative Cycles 1-4 in [Sections 7.3.4](#). Toxicities should be resolved to grade 0 or 1 prior to retreatment. If the last dose of study drug is delayed >7 but <11 days, while it is recommended that this dose be skipped, if the investigator feels that it is appropriate to administer the last dose, discuss with the AFT Study Team before administering the last dose of study drug. Patients should meet the following parameters:

1. ECOG PS 0-1

2. Organ and marrow function definitions:

- Leukocytes $\geq 3,000/\text{mCL}$
- absolute neutrophil count $\geq 1,500/\text{mCL}$
- platelets $\geq 100,000/\text{mCL}$
- Hemoglobin $> 9.0 \text{ g/dL}$
- total bilirubin within normal institutional limits
- AST(SGOT)/ALT(SGPT) $\leq 2.5 \times$ institutional upper limit of normal
- creatinine within normal institutional limits

OR

- creatinine clearance $\geq 60 \text{ mL/min/1.73 m}^2$ for participants with creatinine levels above institutional normal.

6. Study Treatment

All study treatments will be administered on an outpatient basis.

6.1. Durvalumab

A population PK model was developed for durvalumab using monotherapy data from a phase I study (study 1108; N = 292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of approx. 75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similar findings have been reported by others.³³ Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies.³¹ In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/PD parameters.³²

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg every 3 weeks (Q3W) or every 4 weeks (Q4W) durvalumab (equivalent to 20 mg/kg Q4W) are included in the current study.

6.2. Docetaxel

Premedication with corticosteroids will be given to participants receiving docetaxel. The recommended premedication is dexamethasone 8 mg PO twice daily given 1 day before, on the day of, and 1 day after administration of chemotherapy. For institutions that have established an equivalent premedication regimen consistent with local docetaxel labeling, such premedication regimens will be permitted.

6.3. Pemetrexed

Pemetrexed premedications may be used as per institutional standard. The following guidelines may be considered.

- Folic acid: Start a low-dose oral folic acid preparation or multivitamin with folic acid at least 1 week before the first pemetrexed dose and continue for 21 days after the last dose of pemetrexed.
- Vitamin B12: Vitamin B12 1000 µg IM injection. A vitamin B12 injection must be administered at least 1 week before the initial pemetrexed dose and repeated every 3 cycles while on pemetrexed.
- Dexamethasone: Dexamethasone (4 mg orally or equivalent) should be administered twice daily.

6.4. Cisplatin

Cisplatin 75 mg/m² as a 120 minute or per institutional standard IV infusion will be administered to participants as the second infusion. Dosing calculations for cisplatin should be based on the BSA calculation and may be capped per local standards. The dose may remain the same if the participant's weight is within 10% of the baseline weight or prior dose weight.

Pretreatment hydration for cisplatin can follow local standard of care or use 1 to 2 liters of fluid infused IV for 8 to 12 hours prior to cisplatin infusion is recommended. Adequate hydration and urinary output must be maintained for at least 24 hours following cisplatin administration.

Administration and monitoring should be performed according to local standards. Use of mannitol following the cisplatin infusion should also follow local standards of care. Participants who will be receiving cisplatin may have audiometric testing performed prior to initiation of therapy and prior to subsequent doses of cisplatin, as per local or institutional standards of care. Participants considered to be at higher risk for ototoxicity with cisplatin have the option to receive carboplatin-based chemotherapy regimen after discussion with AFT Study Team.

For participants who are unable to tolerate cisplatin, the reasons for intolerability should be documented. If the investigator would like to use a carboplatin-based regimen, the investigator should discuss this with and obtain approval from the AFT Study Team prior to utilization.

Carboplatin will be administered at a dose of AUC 6 as a 30-minute or as per institutional standard IV infusion, on Day 1 of each 3-week cycle.

Carboplatin should be given following docetaxel or pemetrexed on Day 1 of each cycle, and the carboplatin dose (mg) will be calculated using the Calvert formula as follows:

$$= \text{Target AUC} \times [\text{CrCl (mL/min)} + 25]$$

Creatinine clearance (CrCl) calculation is based on the Cockcroft-Gault formula and should include the most recent serum creatinine and most recent weight.

NOTE: If calculation of the CrCl by the Cockcroft-Gault formula yields a result of >125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.

The dose of carboplatin may be capped per local standards.

7. Dose Modifications of Chemotherapeutic Agents

Dose modifications of chemotherapeutic agents are provided in **Table 4**.

Table 4: Dose Modifications of Chemotherapeutic Agents

Dose	Docetaxel	Pemetrexed	Cisplatin	Carboplatin
Starting dose	75 mg/m ²	500 mg/m ²	75 mg/m ²	AUC 6
First dose reduction	75% of starting dose	75% of starting dose	75% of starting dose	AUC 5
Second dose reduction	50% of starting dose	50% of starting dose	50% of starting dose	AUC 3
Third dose reduction	Discontinue	Discontinue	Discontinue	Discontinue

Note: Follow local regulations if they are different than what appears in this table. Any participants with 2 prior dose reductions for 1 agent who experiences a toxicity that would cause a third dose reduction must be discontinued from that agent.

Note 2: Carboplatin is only used after documented inability to tolerate cisplatin and with study chair approval. Carboplatin dose reductions are listed in **Table 6** and will be per institutional standard.

7.1. Platinum Doublet Chemotherapy - Dose Reductions for Hematologic Toxicity

Dose modifications for hematologic toxicities (according to CTCAE version 5) are summarized in **Table 5**. Dose adjustments are based on nadir blood counts (assessed as per local standards) since the preceding drug administration. Dose level adjustments for platinum doublet chemotherapy are relative to that of the preceding administration. Generally, both chemotherapy agents in the platinum doublet chemotherapy regimen should be dose reduced together for hematologic toxicity. After the first cycle, growth factors may be used to assist hematologic recovery. Use local standards of care in the use of these supportive measures. Additionally, prophylactic antibiotics may be used according to local standards of care. Please report any antibiotic or growth factor use on the electronic case report form (eCRF).

Table 5: Dose Modifications for Hematologic Toxicity (Based on Nadir Counts)

Toxicity ^a	Docetaxel	Pemetrexed	Cisplatin
Neutrophil Count Decreased			
Grade 4 (<500/mm ³ or <0.5 × 10 ⁹ /L)	Reduce one dose level and consider prophylactic G-CSF in subsequent cycles	Reduce one dose level and consider prophylactic G-CSF in subsequent cycles	Reduce 1 dose level and consider prophylactic G-CSF in subsequent cycles
Platelet Count Decreased			
Grade 3 (25,000 to < 50,000/mm ³ ; 25.0 to <50.0 × 10 ⁹ /L)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Grade 4 (< 25,000/mm ³ ; <25.0 × 10 ⁹ /L)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Hemoglobin Decreased			
Grade 3 (< 8.0 g/dL; < 4.9 mmol/L, <80 g/L)	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Grade 4 ^{SEP} (Life threatening consequences)	Hold drug	Hold drug	Hold drug

^a Based on Nadir Counts

Doses of docetaxel will be modified for participants who experience docetaxel-related events of febrile neutropenia, neutrophils <500 cell/mm³ for >7 days, severe or cumulative cutaneous reactions, or other

Grade 3/4 nonhematological toxicities during docetaxel treatment. Participants should have treatment delayed according to [Section 7.3.3](#) and then resumed at 1 dose level reduction (75% of starting dose). Should these AEs occur after the first dose reduction, then a second dose reduction to (50% of starting dose) is permitted. If a third dose reduction is required, then the participants should discontinue docetaxel treatment.

7.2. Platinum Doublet Chemotherapy - Dose Reductions for Non Hematologic Toxicities

Dose adjustments for platinum doublet chemotherapy for nonhematologic toxicities during treatment are described in [Section 7.2](#). All dose reductions should be made based on the worst grade toxicity. Participants experiencing any of the toxicities detailed in **Table 6** during the previous cycle should have their chemotherapy delayed until retreatment criteria are met and then reduced for all subsequent cycles by 1 dose level or discontinued as appropriate. Dose levels for the 2 drugs in the platinum doublet chemotherapy regimen are not linked and may be reduced independently.

Table 6: Dose Modifications for Nonhematologic Toxicity

Toxicity ^{a,b}	Docetaxel	Pemetrexed	Cisplatin	Carboplatin
Febrile Neutropenia Grade ≥ 3	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level	Reduce 1 dose level
Diarrhea Grade ≥ 3	Reduce 1 dose level	Reduce 1 dose level	No change	No change
Allergic reaction ^c Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue
Neuropathy Grade 2	No change	No change	Reduce one dose level ^d	No change
Neuropathy Grade ≥ 3	Discontinue	Discontinue	Discontinue	Discontinue
Calculated creatinine clearance < 50 mL/min	No change	Discontinue if creatinine clearance < 45 mL/min	Discontinue	Discontinue if creatinine clearance < 20 mL/min
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated	Adjust as medically indicated

^a If local standard for dose adjustments differ from those outlined, please discuss with AFT Study Team.

^b Please see local drug label for additional adjustments.

^c Only the drug(s) causing the hypersensitivity reaction or acute infusion reaction ($\geq$ Grade 3) require(s) discontinuation. All other drugs may be continued.

^d When given with pemetrexed, cisplatin should be reduced 2 dose levels (ie, by 50% for Grade 2 neuropathy. Participants receiving docetaxel who develop Grade > 3 peripheral neuropathy, or who otherwise meet criteria specified in, should discontinue docetaxel treatment.

7.3. Dose Delays

7.3.1. Durvalumab Dose Delay Criteria

Durvalumab administration should be delayed for the following:

- Grade 2 non-skin, drug-related AE, with the exception of fatigue
- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities
- Grade 3 drug-related laboratory abnormality, with the exception of the following:
 - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay

Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication. Participants who require delay of durvalumab should be re-evaluated weekly or more frequently if clinically indicated and resume durvalumab dosing when re-treatment criteria are met.

If an AE requiring Durvalumab dose hold has not returned to baseline level by Day 1 of the next planned cycle, Durvalumab should be delayed according to guidelines within this section:

- IP dose can be held for up to 6 weeks in the neoadjuvant phase
- and up to 8 weeks in the adjuvant phase

Patients should not hold or discontinue other chemotherapy for side effects potentially or likely related to study IP.

In case other chemotherapy agents are held/ discontinued due to an AE, the Durvalumab dose should also be delayed/ discontinued until all other chemotherapy agents are resumed.

Table 7 provides a summary of dosing modification and toxicity criteria. Please see [Appendix 1](#) for full dosing modification and toxicity criteria graded per NCI CTCAE v5.0.

Table 7: Dosing Modification and Toxicity Criteria

General Considerations	
Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: - Inability to reduce corticosteroid to a dose of ≤ 10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/study regimen	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: - It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. - Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a

General Considerations

Dose Modifications	Toxicity Management
- Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing	possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow.
Grade 1 No dose modification	- Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.
Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤ 1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤ 10 mg/day or equivalent.	- For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥ 3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. - If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper).
Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	- More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the iMAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids.
Grade 4 Permanently discontinue study drug/study regimen.	Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. - With long-term steroid and other immunosuppressive use, consider need for <i>Pneumocystis jirovecii</i> pneumonia (PJP, formerly

Note: For asymptomatic amylase or lipase levels of $> 2X$ ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed.

General Considerations

Dose Modifications	Toxicity Management
	known as <i>Pneumocystis carinii</i> pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. - Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper

Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).

Abbreviations: AE= adverse event; CTC=Common Toxicity Criteria; CTCAE=Common Terminology Criteria for Adverse Events; imAE=immune-mediated adverse event; IV=intravenous; NCI=National Cancer Institute; PO=per os, by mouth.

7.3.2. Dose Delay Criteria for Platinum Doublet Chemotherapy

Dosing of both drugs in the platinum doublet chemotherapy regimen selected should be delayed for any of the following on the Day 1 of each cycle:

- Absolute neutrophil count (ANC) <1500/ μ L
- Platelets <100,000/ mm^3
- Any Grade 2 nonskin, nonhematologic, drug-related AE (excluding Grade 2 alopecia, Grade 2 fatigue, and Grade 2 laboratory abnormalities)
- Any Grade 3 skin, drug-related AE

- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin:
 - Grade 3 lymphopenia does not require dose delay.
 - If a participant has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade 2 toxicity.
 - If a participant has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade 3 toxicity
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

Investigators should consult local labeling for the chemotherapy drugs being administered to any given participant for additional guidance on dose delays. If any nonhematologic AE event meeting the dose delay criteria above is felt to be related to only 1 particular agent in the platinum doublet chemotherapy regimen, then that agent alone may be omitted for that cycle while the other agent is given. In order to maintain synchronized dosing of the regimen, the omitted agent should be resumed with the next scheduled cycle once the AE has improved and retreatment criteria are met.

7.3.3. Docetaxel Dose Delay Criteria

Docetaxel administration should be delayed for the following:

- Any Grade 2 nonskin, drug-related AE, with the following exceptions:
 - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay.
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, neutrophil count, AST, ALT, or total bilirubin:
 - Grade 3 lymphopenia does not require dose delay.
 - Should not be given if neutrophil counts are $< 1500 \text{ cells/mm}^3$
 - Should not be given if total bilirubin $>$ upper limit of normal (ULN), or if AST and/or ALT $> 1.5 \times \text{ULN}$ concomitant with alkaline phosphatase $> 2.5 \times \text{ULN}$
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the Investigator, warrants delaying the dose of study medication. Participants receiving docetaxel may receive growth factors (including G-CSF) at the discretion of the Investigator.

7.3.4. Durvalumab Modification and Toxicity Management

Durvalumab dose reductions are not permitted. Durvalumab treatment may be interrupted or discontinued due to toxicity.

Adverse events (AEs) associated with durvalumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of durvalumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Most irAEs are reversible and are often managed with interruptions of durvalumab, administration of corticosteroids and or/other supportive care. Patients with suspected irAEs should have adequate evaluation to confirm etiology or

exclude other causes. Consultation with appropriate specialists for evaluation and procedures such as bronchoscopy, endoscopy, or colonoscopy may be necessary as part of the evaluation and management. Based on the severity of the irAEs, withhold or permanently discontinue durvalumab and administer corticosteroids.

Dose modification and toxicity management guidelines for durvalumab are provided in [Appendix 1](#).

Durvalumab will be withheld for drug-related Grade 4 hematologic toxicities (**Table 8**), nonhematological toxicity $\geq$ Grade 3 including laboratory abnormalities, and severe or life threatening AEs as per [Appendix 1](#).

Table 8: Durvalumab Dose Modification Guidelines for Drug-Related Hematologic Adverse Events

Toxicity	Grade	Hold Treatment	Timing for Restarting Treatment	Dose/Schedule for Restarting Treatment	Discontinue Patient (after consultation with Sponsor)
Hematological	1, 2	No	NA	NA	NA
	3 ^a	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last infusion
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week	Permanent discontinuation should be considered for any severe or life-threatening event

Abbreviation NA = not applicable

^a Excluding Grade 3 neutropenia, anemia, and thrombocytopenia

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Study PI. With Investigator and Study PI agreement, patients with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

Patients who experience a recurrence of the same severe or life-threatening AE at the same grade or greater with re-challenge of durvalumab should be discontinued from trial treatment.

Supportive care and evaluation of toxicity from durvalumab should be as per ASCO guidelines.³⁴

8. End of Treatment

8.1. Duration of Participation

Duration of participation is 5 years from the date of registration. Participants will have CT scans every 3 months for the first two years from surgery date, every 6 months for the third, fourth, and fifth years, and then annually as per National Comprehensive Cancer Center guidelines.

Biopsies are strongly recommended at progression of disease, and are considered standard of care; tissue will be requested, though not required, when/if this occurs.

Patients who do not undergo surgery will be followed for survival only every 6 months for years 1-3 and every 1 year for years 4 and 5 years after registration, or until death, whichever comes first.

8.2. Use in Pregnancy and Nursing Women (if applicable)

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after. At the time of registration, confirmation of adequate contraceptive method(s) should be documented in the medical record.

- Female patient of child-bearing potential
 - Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use 2 methods of birth control and at least 1 **highly** effective method of contraception (**Table 9**) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy).
 - Non-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.
- Male patients with a female partner of childbearing potential
 - Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
 - Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (**Table 9**).
 - Two methods of birth control and at least 1 **highly** effective method of contraception must be used.

In the case of paternal exposure, the investigator must obtain permission from the subject's partner in order to collect any pregnancy information.

Note: Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered postmenopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women < 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥ 50 years of age, but ≤ 65 years of age, would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

- Women > 65 years of age are deemed to not be of childbearing potential.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in **Table 9**. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; noncopper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel, which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 9: Highly Effective Methods of Contraception (< 1% Failure Rate)

Barrier/Intrauterine methods	Hormonal Methods
Copper T intrauterine device	Implants: Etonogestrel-releasing implants: eg, Implanon® or Norplant®
Levonorgestrel-releasing intrauterine system (eg, Mirena®) ^a	Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: eg, NuvaRing®
	Injection: Medroxyprogesterone injection: eg, Depo-Provera®
	Combined Pill: Normal and low dose combined oral contraceptive pill
	Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: eg, Ortho Evra®
	Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

^a This is also considered a hormonal method.

9. Supportive Care and Concomitant Medications

Antiemetic premedication will be administered according to local standards. Recommended antiemetic treatments are dexamethasone (dosing according to local standards; an equivalent dose of another corticosteroid may be substituted) and a 5-HT₃ receptor antagonist (type per Investigator discretion and local standards-of-care). Additional use of antiemetic premedications may be employed at the discretion of the Investigator.

9.1. Permitted Concomitant Medications

Table 10: Supportive Medications

Supportive Medication/Class of Drug	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care,	To be administered as prescribed by the Investigator

Supportive Medication/Class of Drug	Usage
except for those medications identified as “prohibited,” as listed above	
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc.])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

9.2. Excluded Concomitant Medications

Table 11: Prohibited Medications

Prohibited Medication/Class of Drug	Usage
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding >10 mg of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor- α blockers	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs, • Short term premedication for pemetrexed or docetaxel permitted • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc.).
EGFR TKIs	Should not be given concomitantly.

Prohibited Medication/Class of Drug	Usage
	Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based, Clinical Practice guideline.³⁵

- Epoetin (EPO): Use of epoetin in this protocol is prohibited OR permitted at discretion of the treating physician.
- Filgrastim (G-CSF) and sargramostim (GM-CSF): Filgrastim (G-CSF)/pegfilgrastim and sargramostim (GM-CSF) treatment for patients on protocols that do not specify their use is discouraged.
- Filgrastim/pegfilgrastim and sargramostim may not be used: To avoid dose reductions, delays, or to allow for dose escalations specified in the protocol.
- For the treatment of the febrile neutropenia the use of CSFs should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSFs may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSFs in this setting. The use of CSF (filgrastim/pegfilgrastim or sargramostim) must be documented and reported (eg, on CRFs per protocol requirements).
- If filgrastim/pegfilgrastim or sargramostim are used, they must be obtained from commercial sources.

10. Study Assessments and Procedures

10.1. Schedule of Assessments

Study procedures and timing are summarized in the Schedule of Assessments (**Table 12**).

Table 12: Schedule of Assessments

Visit	Screening ¹	Induction therapy: Combined Platinum Doublet with Durvalumab ²	Pre-Surgical Assessment	Surgery and Post-Surgical Assessment ³	Radio-therapy ⁵	Adjuvant Durvalumab ⁶	End of Treatment ⁷	Post-Treatment Follow-up ^{8,9}
Frequency		every 3 weeks (+/- 3 days) for 4 cycles ¹⁵			6 weeks of treatment (54Gy)	every 4 weeks (+/- 3 days) for 13 cycles	30-45 days after completion of protocol therapy	Every 6 months post registration
Medical History	X							
Physical Exam	X	X	X	X		X	X	X
Height	X							
Vital Signs, Weight	X	X	X	X		X	X	X
ECOG Performance Status	X	X	X	X		X	X	
CT chest/upper abdomen ⁴	X	X (prior to administration of C3)	X	X ³		X		X ⁸
PET/CT	X		X ¹⁰					
Brain MRI or head CT with contrast	X							

Visit	Screening ¹	Induction therapy: Combined Platinum Doublet with Durvalumab ²	Pre-Surgical Assessment	Surgery and Post-Surgical Assessment ³	Radio-therapy ⁵	Adjuvant Durvalumab ⁶	End of Treatment ⁷	Post-Treatment Follow-up ^{8,9}
Frequency		every 3 weeks (+/- 3 days) for 4 cycles ¹⁵			6 weeks of treatment (54Gy)	every 4 weeks (+/- 3 days) for 13 cycles	30-45 days after completion of protocol therapy	Every 6 months post registration
PFTs (spirometry, DLCO)	X		X					
EKG ¹¹	X		X					
Hematology Panel (CBC with diff)	X	X	X	X		X	X	
Chemistry Panel Blood Test	X	X	X			X	X	
Pregnancy Test	X							
Proven N2 disease	X							
Evaluation by a thoracic surgeon	X		X	X ¹²				
Review of Concomitant Medications	X	X	X	X	X	X	X	
Archival/Fresh Biopsy	X ¹⁴			X			X ¹³	

Visit	Screening ¹	Induction therapy: Combined Platinum Doublet with Durvalumab ²	Pre-Surgical Assessment	Surgery and Post-Surgical Assessment ³	Radio-therapy ⁵	Adjuvant Durvalumab ⁶	End of Treatment ⁷	Post-Treatment Follow-up ^{8,9}
Frequency		every 3 weeks (+/- 3 days) for 4 cycles ¹⁵			6 weeks of treatment (54Gy)	every 4 weeks (+/- 3 days) for 13 cycles	30-45 days after completion of protocol therapy	Every 6 months post registration
Research Blood Samples	X		X				X	
Study Drug Administration		X				X		
Review of Adverse Events (CTCAE v5)		X	X	X	X	X	X	X
RECIST determination (with CT C/A)	X	X (prior to administration of C3)	X					
Submission of Radiotherapy dose records					X			

¹ Screening tests must be performed within 28 days of registration Pregnancy test should be completed within 72 hours of first dose of study drug. PFTs can be within 6 months of registration (date of enrollment) MRI, CT, and PET/CT Scans must be performed within 6 weeks of registration (date of enrollment).

² D1 of each cycle for up to 4 cycles. Induction therapy should start within 4 weeks of registration (date of enrollment).

³ Surgery must take place 4-8 weeks after completion of induction therapy; all post-surgical assessments must be completed within 12 weeks of surgery. The post-surgical CT scan should occur 12 weeks after surgery.

- ⁴ After surgery, CT scans (-7 to 0 days before C3) will be performed on the following schedule until a documented recurrence, death, or 5 years post registration (date of enrollment), regardless of the treatment or follow-up phase:
- Surgery – 2 years post-surgery: every 3 months
 - 2 years post-surgery – 5 years post registration (date of enrollment): every 6 months
 - 5 years post-registration (date of enrollment) – onward: once per year as per National Comprehensive Cancer Center guidelines.
- ⁵ A 6-week (54Gy) treatment period; must start 4-10 weeks post-surgery. Radiation treatment will be required for patients with a positive margin. All other patients can be treated with radiation therapy at the discretion of the treating institution.
- ⁶ D1 of each cycle for up to a total of 13 cycles; must start 1-6 weeks after completion of the prior phase of treatment (radiation, or surgery if no radiation).
- ⁷ If the patient completes all treatment per protocol, the end of treatment visit must take place 30-45 days after completion of adjuvant therapy. If the patient does not complete treatment per protocol, the end of treatment visit must take place as soon as possible after treatment is discontinued.
- ⁸ Patients who DO undergo surgery but DO NOT complete protocol treatment are followed up with annually from the last on-study scan for survival, once there has been disease progression. If there has NOT been disease progression, patients should be followed with scans every 3 months for years 1-2, then every 6 months for years 3-5 then every year, same as patients on protocol therapy (as described in Note 4). Follow-up scans are scheduled from the last scan on-study. After documentation of progression, CT scan collection for investigational use will discontinue.
- ⁹ Patients who DO NOT undergo surgery are followed for survival every 6 months starting from their last on study scan for years 1-3, and then every year for years 4-5.
- ¹⁰ PET/CT is preferred at pre-surgical assessment (either PET/CT OR CT chest /abdomen).
- ¹¹ EKG is generally performed preoperatively, not prior to initiating treatment, unless needed for QTC for chemotherapy.
- ¹² Monitoring for surgical AEs.
- ¹³ Biopsy at progression is optional, but may be done as standard of care. If collected, tissue should be submitted to AFT Biorepository.
- ¹⁴ Archived/ freshly obtained tissue. See the study correlative science manual for further details
- ¹⁵ C1D1 assessments do not have to be repeated if they were performed for screening within 3 days (72 hours) of the first dose. Only exception is TSH which does not have to be repeated if performed within 14 days.

10.1.1. Efficacy Assessments

The primary efficacy assessments will be mediastinal nodal clearance rate, and a key secondary endpoint is mPR rate (defined as number of participants with < 10% residual tumor in lung and lymph nodes).

Surgery should be performed within 4 to 8 weeks after completing up to 4 cycles (last dose) of neoadjuvant treatment (surgery is between Weeks 16-20 after first dose of neoadjuvant treatment).

The following lymph node levels should be resected at the time of definitive surgery:

- For right-sided tumor: Levels 4, 7, 9R, 10R, and 2R if accessible. 2R is recommended but is not subject to quality assurance review. If nodes are not identified in required stations, this should be documented in the operative report.
- For left-sided tumor: Levels 5, 6, 7, 9L, 10L; and if accessible, 4L. If the 5, 6, 7, 9L, and 10L levels are not performed, it will be considered a major protocol deviation. 4L is recommended but is not subject to quality assurance review. If nodes are not identified in required stations, this should be documented in the operative report.

Tumor and lymph node collection from definitive surgical resection and sampling of fresh tumor sample for biomarker studies (as applicable dependent on the size of residual tumor) is mandatory on the day of surgery. Processing of the remainder of the specimens for histopathologic analysis should be performed within 72 hours of the procedure.

Gross examination on the entire specimen should be performed which includes all tumor, associated lymph node tissue, and uninvolved parenchyma. The specimen should be sectioned at 0.5 cm intervals, and blocks should be submitted for the full cross section for every other 0.5 cm interval. When estimating viable tumors, in situ carcinoma should not be included. For very large tumors with no gross evidence of response, a minimum of 1 slide/cm is required for assessment of major pathologic response.

Radiographic assessments will be performed with the Schedule of Assessments (**Table 12**).

Disease recurrence, change in tumor measurements, and tumor response will be assessed using the RECIST 1.1 criteria.²⁵

10.1.2. Imaging Assessment Collection Plan

Study evaluations will take place in accordance with the Schedule of Assessments (**Table 12**).

Screening (baseline) assessments are to be performed within 28 days prior to registration. A separate CT with contrast of the chest, abdomen, and other suspected areas (as well as the PET/CT) is required if the CT component of a PET/CT is not of sufficient diagnostic quality for RECIST 1.1 measurements. Participants must also undergo MRI/CT of the brain pre- and post-contrast prior to registration.

Tumor assessments should be performed following RECIST 1.1 criteria.²⁵

A preoperative PET/CT with contrast should be acquired within 28 days of surgery. A separate CT with contrast of the chest, abdomen, and other suspected areas (as well as the PET/CT) is required if the CT component of a PET/CT is not sufficient diagnostic quality for RECIST 1.1 measurements.

Postoperative assessments with CT with contrast of the chest including the adrenal glands and CT or MRI of other additional suspected/known sites of disease. The first tumor assessment should occur 12 weeks (± 7 days) after definitive surgery per RECIST 1.1 and then should occur every 3 months (12 weeks ± 7 days) for the first 2 years from the surgery date, then every 6 months (24 weeks ± 7 days) until 5 years from the date of registration, and then annually as per National Comprehensive Cancer Center guidelines until disease recurrence or progression is confirmed. The same imaging method should be used as the screening/baseline.

10.1.3. Laboratory Assessments

The following clinical laboratory tests will be performed (**Table 13**, **Table 14**, see the Schedule of Assessments (**Table 12**)).

Table 13: Hematology Laboratory Tests

Basophils ^a	Mean corpuscular volume
Eosinophils ^a	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 0 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 0), and as clinically indicated.

^a Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by DM if entered as percentage. Total white cell count, therefore, has to be provided.

Table 14: Clinical Chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase

Alanine aminotransferase	Lipase ^a
Amylasea	Magnesium ^b
Aspartate aminotransferase	Potassium
Bicarbonate ^b	Sodium
Calcium	Total bilirubin
Chloride ^{c, b}	Total protein
Creatinine ^{b, c}	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase ^b	Uric acid
Thyroid-stimulating hormone ^d	

Note: Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is $\geq 2 \times$ upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

^a It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

^b Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at baseline, on Day 0 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 0), and if clinically indicated.

^c Creatinine clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).

^d If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day 1. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

If a patient shows an AST or ALT $\geq 3 \times$ ULN together with total bilirubin $\geq 2 \times$ ULN, refer to [Appendix 1](#) for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 30 days (± 3 days), 2 months (± 1 week) and 3 months (± 1 week) after permanent discontinuation of IP (see **Table 14**).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in [Section 11](#).

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IP must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

11. Safety and Tolerability Assessments

11.1. Definitions

Adverse Events

Per the International Conference of Harmonisation (ICH) guidelines, an adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure.

Serious Adverse Events

An AE or suspected adverse reaction is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death,
- Life-threatening adverse event,
- Inpatient hospitalization,
- Prolongation of existing hospitalization,
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

- An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of an SAE/Reaction.

- Qualifies for expedited IND safety reporting to the FDA, Competent Authorities, and other regulatory bodies by meeting all 3 definitions of suspected adverse reaction, serious, and unexpected.
- Expected adverse reactions and related serious adverse reactions to study drugs are listed in the IB/package insert(s). A serious adverse reaction that is not included in the IB/package insert(s) should be evaluated and reporting on the study specific SAE form by the site Investigator as a SUSAR within 24 hours after learning of the event.

Adverse Events of Clinical Interest

Adverse events of clinical interest are events that the drug manufacturer or the Sponsor of the study, AFT, are actively monitoring as a result of a previously identified signal (even if non-serious).

11.2. Expected Adverse Events

11.2.1. Cisplatin

Adverse Reactions > 10%:

Central nervous system: Neurotoxicity (peripheral neuropathy is dose and duration dependent)

Gastrointestinal: Nausea and vomiting (76% to 100%)

Genitourinary: Nephrotoxicity (28% to 36%; acute renal failure and chronic renal insufficiency)

Hematologic and oncologic: Anemia ($\leq 40\%$), leukopenia (25% to 30%; nadir: Day 18 to 23; recovery: By Day 39; dose related), thrombocytopenia (25% to 30%; nadir: Day 18 to 23; recovery: By Day 39; dose related)

Hepatic: Increased liver enzymes

Otic: Ototoxicity (children 40% to 60%; adults 10% to 31%; as tinnitus, high frequency hearing loss)

Adverse Reactions 1% to 10%:

Local: Local irritation

Adverse Reactions < 1%:

Postmarketing, and/or case reports: Alopecia (mild), ageusia, anaphylaxis, autonomic neuropathy, bradycardia, bronchoconstriction, cardiac arrhythmia, cardiac failure, cerebral arteritis, cerebrovascular accident, dehydration, diarrhea, dysgeusia, extravasation, heart block, hemolytic anemia (acute), hemolytic-uremic syndrome, hiccups, hypercholesterolemia, hyperuricemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypotension, increased serum amylase, ischemic heart disease, leukoencephalopathy, Lhermitte's sign, myocardial infarction, neutropenic enterocolitis optic neuritis, papilledema, peripheral ischemia (acute), phlebitis, reversible posterior

leukoencephalopathy syndrome, seizure, SIADH, skin rash, tachycardia, tetany, thrombosis (aortic; Fernandes 2011), thrombotic thrombocytopenic purpura, vasospasm, vision color changes, vision loss.

11.2.2. Docetaxel

Percentages reported for docetaxel monotherapy; frequency may vary depending on diagnosis, dose, liver function, prior treatment, and premedication.

Adverse Reactions > 10%:

Central nervous system: Neurotoxicity (23% to 58%; severe: 4% to 6%)

Dermatologic: Alopecia (56% to 76%), dermatological reaction (20% to 48%; severe: 5%), nail disease (11% to 41%; severe: 1% to 4%)

Endocrine and metabolic: Fluid retention (includes edema and effusion; 26% to 60%; severe: 3% to 9%)

Gastrointestinal: Stomatitis (26% to 53%; severe 6% to 8%), diarrhea (23% to 43%; severe: 5% to 6%), nausea (34% to 42%), vomiting (22% to 23%)

Hematologic and oncologic: Neutropenia (84% to 99%; grade 4: 75% to 86%; grades 3/4: 65%; nadir [median]: 7 days, duration [severe neutropenia]: 7 days), leukopenia (84% to 99%; grades 3/4: 49%; grade 4: 32% to 44%), anemia (87% to 97%; grades 3/4: 8% to 9%), thrombocytopenia (7% to 12%; grades 3/4: 3%; grade 4: 1%), febrile neutropenia (5% to 14%)

Hepatic: Increased serum transaminases (4% to 19%)

Hypersensitivity: Hypersensitivity reaction (6% to 21%; severe: 1% to 4%)

Infection: Infection (22% to 34%; severe: 6%)

Neuromuscular and skeletal: Weakness (53% to 66%; severe: 13% to 18%), myalgia (6% to 23%; severe: 2%), neuromuscular reaction (16%)

Respiratory: Pulmonary reaction (41%)

Miscellaneous: Fever (31% to 35%)

Adverse Reactions 1% to 10%:

Cardiovascular: Hypotension (3%)

Central nervous system: Peripheral motor neuropathy (4%; severe; mainly distal extremity weakness)

Gastrointestinal: Dysgeusia (6%; severe: 1%)

Hepatic: Increased serum bilirubin (9%), increased serum alkaline phosphatase (7%)

Infection: Severe infection (2% to 6%)

Local: Infusion site reaction (4%)

Neuromuscular and skeletal: Arthralgia (3% to 9%)

11.2.3. Pemetrexed

Percentages reported for pemetrexed monotherapy; frequency may vary depending on diagnosis, dose, liver function, prior treatment, and premedication.

Adverse Reactions > 10%:

Dermatologic: Rash (10%)

Gastrointestinal: Nausea (19%), anorexia (19%), vomiting (9%)

Hematologic and oncologic: Anemia (15%)

Hepatic: Increased serum transaminases (10%)

Miscellaneous: Fatigue (25%)

Adverse Reactions 1% to 10%:

Gastrointestinal: Vomiting (9%), mucositis/stomatitis (7%), diarrhea (5%)

Infection: Infection (5%)

Neuromuscular and skeletal: Neuropathy (9%)

Renal: Decreased creatinine clearance (1-5%)

11.2.4. Durvalumab

Adverse Reactions > 10%:

Cardiovascular: Peripheral edema (15%)

Central nervous system: Fatigue (34% to 39%)

Dermatologic: Dermatitis ($\leq 26\%$), skin rash ($\leq 26\%$; including immune-mediated rashes), pruritus (12%)

Endocrine and metabolic: Hyperglycemia (52%), hypocalcemia (46%), hyponatremia (33%), hyperkalemia (32%), increased gamma-glutamyl transferase (24%), hypothyroidism (11% to 12%)

Gastrointestinal: Constipation (21%), decreased appetite (19%), colitis ($\leq 18\%$), diarrhea ($\leq 18\%$), nausea (16%), abdominal pain (10% to 14%)

Genitourinary: Urinary tract infection (15%)

Hematologic and oncologic: Lymphocytopenia (43%; grades 3/4: 11%)

Hepatic: Increased serum ALT (39%), increased serum AST (36%), hepatitis (12%)

Infection: Infection (38% to 56%)

Neuromuscular and skeletal: Musculoskeletal pain (24%)

Respiratory: Cough ($\leq 40\%$), productive cough ($\leq 40\%$), pneumonitis ($\leq 34\%$), radiation pneumonitis ($\leq 34\%$), upper respiratory tract infection (26%), pneumonia (17%), dyspnea ($\leq 13\%$), dyspnea on exertion ($\leq 13\%$)

Miscellaneous: Fever ($\leq 15\%$; including tumor-associated fever)

Adverse Reactions 1% to 10%:

Central nervous system: Voice disorder ($< 10\%$)

Dermatologic: Night sweats ($< 10\%$)

Endocrine and metabolic: Hyperthyroidism (7%), hypermagnesemia (grades 3/4: 4%), dehydration (grades 3/4: $\geq 3\%$), hypercalcemia (grades 3/4: 3%), hypoalbuminemia (grades 3/4: 1%), hypokalemia (grades 3/4: 1%)

Genitourinary: Dysuria ($< 10\%$)

Hematologic and oncologic: Anemia (grades 3/4: 8%), neutropenia (grades 3/4: 1%)

Hepatic: Increased serum alkaline phosphatase (grades 3/4: 4%), hyperbilirubinemia (grades 3/4: 1%)

Immunologic: Antibody development (3%)

Infection: Increased susceptibility to infection ($< 10\%$)

Renal: Nephritis (6%; immune-mediated), increased serum creatinine (grades 3/4: 1%)

Miscellaneous: Infusion-related reaction (2%)

Adverse Reactions Frequency Not Defined:

Endocrine and metabolic: Hypophysitis

Hepatic: Hepatic injury

Infection: Sepsis

Renal: Acute renal failure

Adverse Reactions < 1%:

Postmarketing, and/or case reports: Adrenocortical insufficiency, aseptic meningitis (immune-mediated), hemolytic anemia (immune-mediated), immune thrombocytopenia, myocarditis (immune-mediated), myositis (immune-mediated), ocular toxicity (immune-mediated; including uveitis and keratitis), pituitary insufficiency, thyroiditis, type 1 diabetes mellitus, vitiligo. cholangitis sclerosing immune- mediated cystitis, immune mediated neutropenia

11.3. Adverse Event of Special Interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or nonserious.

If the Investigator has any questions in regards to an event being an AESI, the Investigator should promptly contact AFT.

AESIs observed with durvalumab include:

- Diarrhea /Colitis and intestinal perforation
- Pneumonitis /ILD
- Hepatitis /transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash/Dermatitis
- Nephritis/Blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Myocarditis
- Myositis/Polymyositis
- Neuropathy/neuromuscular toxicity (eg, Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to: pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, hematological, and rheumatological events.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see [Appendix 1](#)). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

11.4. Events of Clinical Interest

Pregnancy

If a patient inadvertently becomes pregnant while on treatment with durvalumab, the subject will immediately be removed from the study. The site will contact the patient at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to AFT without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to AFT. If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to AFT and followed as described above.

11.5. Overdose

Any known or perceived overdose from protocol defined therapy must be reported within 24 hours to AFT.

11.6. Hepatic function abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to AFT. AFT will report these events to AstraZeneca Patient Safety using the designated Safety e-mailbox within 7 calendar days or sooner when required, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) $\geq 3 \times$ Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) $\geq 2 \times$ ULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study patient will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by AFT and its pharmaceutical partner.

11.7. Adverse Event Reporting Exceptions

The following are NOT considered AEs:

- **Baseline condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Disease Progression:** The term disease progression should not be reported as an adverse event term. As an example, “worsening of underlying disease” or the clinical diagnosis that is associated with disease progression should be reported.
- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not to be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- Deaths occurring outside of the serious adverse event reporting period that are clearly due to progressive disease should be reported via routine reporting methods in the Rave data capture system. Deaths occurring within the reporting window, even if considered to be related to disease progression as the cause of death should be reported as a Serious Adverse Event with death noted as the outcome of the event.

11.8. Adverse Event Reporting

Adverse event (AE) data collection and reporting, which are required as part of every clinical study 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. AEs will be recorded from the time of the first study related procedure through 90 days following cessation of treatment or until the initiation of alternative anticancer therapy. Any increase of a documented baseline condition from screening/history will be reported as an adverse event. Adverse events are entered into the Adverse Events eCRF in RAVE Electronic Data Capture (EDC) system.

11.9. Serious Adverse Event Reporting

Serious adverse events (SAEs) will be recorded from the time of the first study related procedure through 90 days following cessation of treatment. SAEs and serious AESIs are also entered into the SAE eCRF in RAVE. In the event that RAVE is not available and an SAE must be reported, a paper SAE report form should be submitted.

11.10. Events of Clinical Interest Reporting

All deaths that occur during the study, or within the protocol defined 90 day post last dose of durvalumab safety follow up period must be reported in the Rave data capture system as follows:

- Death that is clearly the result of disease progression should be documented and reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported in the Rave data capture system as a SAE within 24 hours (see [Section 11.8](#) for further details). The report should contain a comment regarding the co involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

Deaths that occur following the protocol-defined 90-day post-last-dose of durvalumab safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE. However, if an Investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the Investigator should notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

11.11. Other Events Requiring Reporting

11.11.1. Overdose

An overdose is defined as a patient receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study patient with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox . If the overdose results in an AE, the AE must also be recorded as an AE (see [Section 11.7](#)). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see [Section 11.8](#)). There is currently no specific treatment in the event of an overdose of durvalumab.

The Investigator will use clinical judgment to treat any overdose.

11.11.2. Pregnancy Reporting

All pregnancy events must be reported to the sponsor according to expedited reporting timelines (see [Section 11.4](#)). The timeframe for capturing pregnancies is 90 days after the subject's last dose.

11.12. Assessment of Severity of Adverse Events

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE):

The AE severity grading scale for the NCI CTCAE (version 5) will be used for assessing AE severity. **Table 15** will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE. All appropriate treatment areas should have access to a copy of the CTCAE version 5. A copy of the CTCAE version 5 can be downloaded from the CTEP Web site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Table 15: Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age appropriate instrumental activities of daily living ^a
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities ^b
4	Life-threatening consequences or urgent intervention indicated d Assessment of Severity of Adverse Events ^c
5	Death related to adverse event ^d

Note: Based on the most recent version of NCI CTCAE (version 5).

^a Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^b Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

^c If an event is assessed as a "significant medical event," it must be reported as an SAE (see [Section 11.8](#) for reporting instructions), per the definition of SAE in [Section 11.1](#).

^d Grade 4 (only if immediately life threatening) and Grade 5 events must be reported as SAEs (see [Section 11.8](#) for reporting instructions), per the definition of SAE in [Section 11.1](#).

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to AFT (or designee) using the same procedure used for transmitting the initial SAE report.

All AEs should be followed to resolution or stabilization.

11.13. Assessment of Causality of Adverse Events

An assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must document the causal relationship in the eCRF and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable. A suspected adverse reaction is any AE for which there is reasonable possibility that the investigational product caused the AE. An Investigator's causality assessment should determine if there exists a reasonable possibility that the investigational product caused or contributed to an AE.

The relationship of the AE to the study treatment will be assessed following the definitions below:

- **No (unrelated):** Any event that does not follow a reasonable temporal sequence from administration of investigational product and is likely to have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- **Yes (related):** Any reaction that follows a reasonable temporal sequence of administration of investigational product and followed a known response pattern to the suspected investigational product and recurs with re-challenge, and/or is improved by stopping the investigational product or reducing the dose.

11.13.1. Expedited Adverse Event Reporting

As this study is IND exempt, AFT will not be submitting SUSAR reports to the FDA or other regulatory authorities. However, AFT will still send safety reports to AstraZeneca following the FDA SUSAR timelines within 15 calendar days of AFT awareness of the event and all SUSARs resulting in life-threatening, or death within 7 calendar days of AFT awareness.

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is from the time of the first study related procedure through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The Investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

Note: All serious or unexpected adverse events must be reported to AstraZeneca regardless of the country where the study is conducted.

If a nonserious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca.

11.14. Emergency Unblinding of Treatment Assignment

Not applicable.

12. Study Treatment

12.1. Investigational Product

12.1.1. Formulation

Durvalumab (MEDI4736) will be supplied by Medimmune as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The nominal fill volume is 10.0 mL.

12.1.2. Storage and Stability

Unopened vials of durvalumab must be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

12.1.3. Availability

Study drug will be managed by Alliance Foundation Trials (AFT), LLC, through a third party warehousing group. Durvalumab will be provided to investigators free of charge, and is provided for the study by AstraZeneca.

12.1.4. Administration

Durvalumab will be administered as an approximately 60 minute IV infusion per institutional standard. A fixed dose of 1500 mg durvalumab every 3 weeks (Q3W) in the pre-operative setting and every 4 weeks (Q4W) in the post-operative setting will be used in the current study.

Preparation of durvalumab (MEDI4736) doses for administration with an IV bag

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

For patients > 30kg in weight, a dose of or 1500mg Q3W or Q4W will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. For the 1500 mg dose, add 30.0 mL of durvalumab (MEDI4736) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If patient weight falls to ≤ 30 kg, weight-based dosing at 20 mg/kg (Q3W or Q4W) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

Standard infusion time is one hour, however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered.

If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

12.1.5. Ordering

A drug resupply form will be provided to all sites as part of their study document package. Resupply forms must be submitted to AFT for processing. Please provide at least 1 week advance notice for drug resupply. Initial shipments of study drug will be sent at site activation.

12.1.6. Accountability

Site investigators or designated responsible parties must maintain a record of the inventory of distribution of the study drug using the appropriate documentation method (eg, drug accountability log).

The Investigator is responsible for keeping accurate records of the clinical supplies received from AFT or designee, the amount dispensed to patients and the amount remaining at the conclusion of the study.

12.1.7. Destruction and Return

Sites may destroy unused study drug according to their institutional policies. If any study drug is lost or damaged, its disposition should be documented in the source documents. Patients will be instructed to return empty containers (if applicable) and unused investigational product to the clinic site.

13. Data Collection and Management/Data and Specimen Submission

13.1. Data Collection and Submission

Data collection for this study will be done through the Medidata Rave EDC system.

13.2. Specimen Collection and Submission

Biospecimen collection information will be provided in the study's correlative science manual.

13.3. Correlative Science

See [Section 2.6](#).

13.4. Future Biomedical Research

All collected biospecimens will be stored in the Alliance Foundation Biorepository (AFB), a CAP accredited biorepository at Washington University in St. Louis, until biospecimen accrual and clinical follow-up is sufficiently complete to allow for the design and execution of specific correlative analyses using ‘state-of-the-art’ analytical platforms that will be available at that time.

Such biomarker research will address emergent questions not described elsewhere in this protocol and will only be conducted on specimens from appropriately consented patients. The objective of collecting specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of disease and/or their therapeutic treatments in the context of this study. Proposals for future correlative research will undergo rigorous scientific, programmatic, and statistical review by AFT, and biospecimens will only be released to those investigators who have obtained appropriate regulatory approval and demonstrate adequate funding to successfully complete proposed research aims. AFT will ensure that all collected specimens are used only for approved research protocols.

Anonymized (de-identified) data generated from biospecimens used for future correlative research, including somatic and constitutional (germline) genomic data, may be shared with other researchers or deposited in a publicly accessible or controlled-access data repositories. Correlative study results and data will never be returned to individual patients.

13.5. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria¹

13.5.1. Definitions

- Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least 1 cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below.

Note: Participants who exhibit objective disease progression prior to the end of Cycle 1 will also be considered evaluable.

- Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least 1 cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

13.6. Disease Parameters

13.6.1. Measurable Disease

- **Measurable disease.** Measurable lesions are defined as those that can be accurately measured in at least 1 dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥ 10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

- **Malignant lymph nodes.** To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
- **Non-measurable disease.** All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

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

'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 participant, these are preferred for selection as target lesions.

- **Target lesions.** All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.
- **Non-target lesions.** All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

13.7. Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.
- Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. 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. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. 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.

- FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). 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: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will

be the date of the initial abnormal FDG-PET scan). 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, this is not PD.

- c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

- PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (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.

Note: The PET portion of the CT introduces additional data that may bias an Investigator if it is not routinely or serially performed.

- Meta-iodobenzylguanidine (MIBG). The following is recommended, to assure high quality images are obtained:

Patient preparation: Iodides, usually saturated solution of potassium iodide (SSKI), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop 3 times daily is sufficient, for adolescents 2 drops 3 times daily, and for adults 3 drops 3 times daily. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling IV line is established. The dose of MIBG is administered by slow IV injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123 MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (approx. 150 μ Ci/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

SPECT: Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

- Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.
- Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.^{36,37,38} In addition, the Gynecologic Cancer Intergroup has developed CA 125 progression criteria, which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.³⁹
- Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

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.

13.8. Response Criteria

13.8.1. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Note: The appearance of 1 or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

13.8.2. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

13.8.3. Evaluation of New Lesions

The finding of a new lesion should be unequivocal (ie, not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size, etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

13.8.4. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (**Table 16, Table 17**).

Table 16: Overall Response for Participants with Measurable Target Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required ^a
CR	CR	No	CR	≥ 4 weeks Confirmation

CR	Non-CR/Non-PD	No	PR	≥ 4 weeks Confirmation ^b
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥ 4 weeks from baseline ^b
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD ^c	Yes or No	PD	
Any	Any	Yes	PD	

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.

^a See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

^b Only for nonrandomized trials with response as primary endpoint.

^c In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Table 17: Overall Response for Participants with Non-measurable, Non-Target Disease

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD ^a
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

^a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

13.8.5. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.8.6. Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from registration to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from registration to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from registration to progression, or censored at date of last disease evaluation for those without progression reported.

14. Statistical Considerations

14.1. Overview of the Study Design

This is a single arm, phase II trial with the primary objective to determine an increase in N2 nodal clearance (N2NC) rate to 50% for combined platinum doublet chemotherapy with durvalumab from 30% for platinum doublet chemotherapy alone for patients with potentially resectable stage IIIA/B (N2) NSCLC. The N2NC rate is the primary endpoint and it is calculated from the patients who complete neoadjuvant therapy and have nodal clearance status evaluated. Patients will have mediastinal staging documenting N2 pathologic involvement. At surgery, mediastinal nodal dissection will be performed. N2 nodal disease will be tabulated as YES or NO. The primary endpoint tabulates the percentage of patients with persistent N2 disease at the time of resection.

Secondary objectives are: 1) to evaluate the safety and tolerability of neoadjuvant platinum doublet chemotherapy and durvalumab followed by surgery followed by adjuvant radiation and durvalumab; 2) to evaluate the radiographic response rate of neoadjuvant platinum doublet

chemotherapy and durvalumab; 3) to evaluate the rate of major pathologic response and pathologic complete response in the resected primary tumor and lymph nodes following neoadjuvant combination therapy; 4) to evaluate the event-free survival from the time of registration to one of the following events, whichever comes first: a) radiographic disease progression, b) local progression as defined by lymph node progression precluding surgery, c) inability to resect the tumor d) local or distant recurrence e) death due to any cause; (5) to evaluate overall survival rate from the time of registration to death of all causes; (6) to evaluate the rate of complete resection; and (7) to assess post-operative complications within 30 days of surgery.

14.2. Sample Size, Accrual Time and Study Duration

Approximately 55 patients will be enrolled. Assuming 95% of registered patients meet eligibility criteria and of them 80% will receive surgery and have nodal clearance status evaluated, the trial will yield 42 N2NC evaluable patients that are used to estimate nodal clearance rate. All patients will be followed for a maximum of 5 years from registration.

14.2.1. Sample Size Determination

The N2NC rate is the primary endpoint for this study. For the purpose of sample size determination, we assume if the true rate of N2NC is 50% or greater, there is an interest in concluding that neoadjuvant chemotherapy with durvalumab could significantly improve nodal clearance rate. On the other hand, if the true rate of N2NC is 30% or less there is an interest in concluding that neoadjuvant chemotherapy with durvalumab is not worthy of further investigation. In other words, we are interested to test the following hypothesis:

$$H_0: p \leq 0.30 \text{ versus } H_1: p \geq 0.50,$$

where p is the true N2NC rate. Forty-two (42) patients with evaluable N2NC status after treated with platinum doublet chemotherapy with durvalumab will be needed.

We will use an admissible 2-stage design to evaluate the N2NC rate of the experimental therapy.^{41, 42} The 2-stage design allows a futility test after stage I patients has been evaluated for N2NC status. The specific design satisfies the requirements of type I error of 0.10 and type II error of 0.10, and it has the same maximal sample size as Simon's minmax design and an expected sample size under the null close to Simon's optimal design. Specifically, the first stage of this trial will enroll 21 patients with evaluable N2NC status. If 6 or less patients have N2NC among the 21 patients, the trial will be terminated for futility; otherwise, the trial will move forward to enroll additional 21 patients with evaluable N2NC status. If 16 or fewer patients among the total of 42 patients have N2NC, the experimental therapy will be concluded as not worthy of further investigation; otherwise it will be conducted that the experimental therapy has sufficient activity worthy of further investigation. The above design has expected sample size 30.44 under the null hypothesis and a maximum sample size of 42. The early stopping probability at stage I is 0.5505 under the null and 0.0392 under the alternative. The actual type I and type II errors are 0.09 and 0.0988, respectively.

We assume that 95% of registered patients meet eligibility criteria and of them 80% are treated by the experimental regimen and surgery and have nodal clearance status evaluated. Therefore, approximately 55 patients will be enrolled to this study.

14.2.2. Stratification Factors

Not applicable. This is a single arm, phase II study.

14.3. Primary Endpoint

The N2NC rate is the primary endpoint for this study. For the purpose of sample size determination, we assume if the true rate of N2NC is 50% or greater, there is an interest in concluding that neoadjuvant chemotherapy with durvalumab could significantly improve nodal clearance rate. On the other hand, if the true rate of N2NC is 30% or less there is an interest in concluding that neoadjuvant chemotherapy with durvalumab is not worthy of further investigation. The null hypothesis will be rejected if 17 or more patients have N2NC at the end of the trial among the total of 42 patients with evaluable N2NC status after the experimental therapy. The N2NC rate will be estimated using the UMVUE method and its 80% confidence interval will be calculated (Kayoma and Chen, 2008).

14.4. Secondary Efficacy Endpoints

All patients who received at least 1 cycle of neoadjuvant therapy will be included in the assessment for safety and tolerability of neoadjuvant platinum doublet chemotherapy and durvalumab followed by surgery followed by adjuvant radiation and durvalumab. The AEs, including toxicity related to neoadjuvant therapies and radiotherapy as well as surgery related complication within 30 days of surgery will be tabulated by type, grade, and treatment phase (neoadjuvant, surgery and adjuvant) in term of frequency and percentages. The rate of complete resection after neoadjuvant therapy will be estimated as well as its confidence interval (CI) will be estimated from the patients who receive at least 1 cycle of neoadjuvant therapy.

The analysis for secondary efficacy endpoints will be based on all registered patients who are deemed eligible and complete at least 1 cycle of the neoadjuvant therapy. The radiographic response rate of neoadjuvant platinum doublet chemotherapy and durvalumab will be estimated as well as its 95% exact CI. The rate of major pathologic response (mPR) and pathologic complete response (pCR) will be estimated as well as their 95% exact CIs in the patients with resected primary tumor and lymph nodes following neoadjuvant combination therapy. The event-free survival (EFS) will be estimated using Kaplan-Meier product estimator. EFS is defined as the time from registration to 1 of the following events, whichever comes first: a) radiographic disease progression, b) local progression as defined by lymph node progression precluding surgery, c) inability to resect the tumor d) local or distant recurrence e) death due to any cause. Patients without these events will be censored at the last known contact. Overall survival (OS) and overall survival rate at 3 years will be similarly estimated using Kaplan-Meier estimator. OS is defined as the time from registration to death of all causes. Patients without documented death at the time of analysis will be censored at the date of last known contact.

Pre-treatment and on-treatment candidate biomarkers will be measured with the samples collected at baseline and during the treatment for every 3 weeks. The changes (mean, SD, etc.) of these biomarkers relative to baseline will be summarized by collection time. The trajectory of the changes and the effects of baseline risk factors on the trajectory will be evaluated in linear mixed models. The association of pre-treatment and on-treatment candidate biomarkers in peripheral blood and in tumor tissues with clinical outcomes, including N2NC rate, tumor response rate,

EFS and OS, will also be evaluated univariately through Chi-square test for binary endpoints or log-rank test for survival endpoints and multivariately through logistic regression model for binary endpoints or Cox PH regression model for survival endpoints.

14.5. Adverse Event Stopping Rule

Adverse events (AEs) will be closely monitored by the study team for the first 20 patients after 4 cycles of treatment. If 5 or more of the first 20 treated patients experience grade 3 or higher serious adverse events (SAEs) that are related to study treatments, accrual to the study will be suspended to allow for investigation. 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. Under this safety monitoring rule, there are 59% and 76% probability of accrual suspension if the true SAE rates are 25% and 30%, respectively. In the entire trial period, severe adverse events and unexpected adverse events will be summarized and reviewed at the semi-annual AFT DSMB meetings.

The analysis for safety will include all patients treated with at least one cycle of protocol treatment. Treatment-related toxicity will be summarized by grade, type and system organ class. The type of adverse events, the frequency of each type and its grade will be summarized. The percentage of each grade of adverse events will be presented in bar charts over treatment cycles to describe the change of adverse event severity over time.

14.6. Accrual Monitoring Stopping Rule

See [Section 14.5](#).

14.7. Missing Data

Not applicable.

14.8. Primary Endpoint Completion Time

The primary endpoint will be available within days of surgery, and thus should be available approximately 3 months after initiation of treatment of the last enrolled patient.

14.9. Criteria for Taking a Patient Off Protocol Therapy

Subjects are to remain on treatment for the duration of the 1- to 1.5 year treatment plan. Subjects will follow the study calendar through follow up. Subjects discontinuing early will continue into follow up from the date of discontinuation.

14.10. Criteria for Taking a Patient Off Study

Patients may withdraw consent at any time for any reason or be dropped from the study at the discretion of the Investigator should any untoward effect occur. In addition, a patient may be withdrawn by the Investigator or the Sponsor if enrollment into the study is inappropriate,

the study plan is violated, or for administrative and/or other safety reasons. 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.

A patient must be discontinued from the study for any of the following reasons:

- The patient or legal representative (such as a parent or legal guardian) withdraws consent.
- The patient does not undergo surgery as required in the protocol.
- Unacceptable adverse experiences.
- Intercurrent illness that prevents further administration of treatment.
- Investigator's decision to withdraw the patient.
- The patient has a confirmed positive serum pregnancy test.
- Noncompliance with study treatment or procedure requirements.
- The patient is lost to follow-up.

14.11. Data and Safety Monitoring

Interim reports from the statistical team will be generated for the Data and Safety Monitoring Board (DSMB). See [section 15.12](#) for further details.

15. General Regulatory Considerations

15.1. Compliance with Study Enrollment 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 study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, [REDACTED]. Information posted will allow patients to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study 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, IBs, 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.

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 (GCP), which these instructions and procedures reflect.

15.3. 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 study-related procedure which is not part of the routine clinical management of the patient (ie, 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 study, 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 (ICF), and a signature from the person conducting the informed consent discussion, prior to undertaking any study-related procedure. The proposed ICF must comply with the ICH GCP guideline and regulatory requirements.

15.4. Responsibilities of the Investigator/IRB/IEC/REB

The regulatory requirements for the Investigator can be found in Subpart D of 21CFR312 (21CFR 312.60: General Responsibilities of Investigators) and in ICH E6 Section 4.

Additional requirements are also outlined in the Statement of Investigator Agreement and the Site Services Agreement. Alliance Foundation Trials, LLC (AFT) will supply the protocol and subsequent amendments.

The Investigator is responsible for ensuring all patients and/or parents or legal guardian of each patient, if applicable, are informed about the study and that written consent is obtained prior to the conduct of any study related procedures.

In addition, the Investigator is responsible for reviewing all health related information collected for each study patient in order to identify any safety related issues/AEs. All SAEs are to be reported within 24 hours.

As specified in 21CFR 312.62(Investigator Record Keeping and Record Retention) and ICH E6 Section 4.9 and Section 8, the Investigator is responsible for ensuring that their study staff maintains and retains all study related documentation, including but not limited to: signed Informed Consent forms, medical records that are applicable for this study and source documents, the AFT-46 protocol, IRB approvals, relevant IRB and Sponsor correspondence, and assorted regulatory documents. The Investigator is responsible for retaining and keeping safe all patient related documentation. In order to do this, the site staff will complete eCRFs in a timely manner.

15.5. Financial Disclosures

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.

15.6. 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.

A deviation is a departure from the protocol. If deviations are discovered by the monitor or data manager, other member of study staff or otherwise, they will be discussed with the Investigator and study staff. AFT does not provide waivers for protocol deviations.

15.7. Protocol Amendments

Any modifications to the protocol or the ICF, which may impact 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 ICF 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.

15.8. Retention of Records (Study Documentation, Record Keeping, and Retention of Records)

Any records and documents relating to the conduct of this study and the distribution of investigational product must be retained by the 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.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), AFT should be prospectively notified. The study records must be transferred to a designee acceptable to AFT, such as another investigator, another institution, or to AFT itself.

15.9. Data Confidentiality

Patient medical information, including information associated with biologic specimens, 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 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.

Data collected during this study may be used to support the development, registration, or marketing of an investigational product. All data collected during the study will be controlled by the Sponsor (AFT). AFT will abide by all relevant data protection laws. After a patient has consented to take part in the study, their medical records and the data collected during the study will be reviewed by representatives of the Sponsor to confirm that the data collected are accurate and for the purpose of analyzing the results. These records and data may be additionally reviewed by auditors or by regulatory authorities. The patient's name, however, will not be disclosed outside the hospital. They will be known by a unique patient number.

Written Authorization is to be obtained from each patient prior to enrollment into the study, and/or from the patient's legally authorized representative in accordance with the applicable privacy requirements (eg, Health Insurance Protection and Portability Act [HIPAA]), and any other state and country privacy requirements.

15.10. Database Management and Quality Control

The Site Principal Investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study.

Rave EDC will be used for this study. The study data will be transcribed by study-site personnel from the source documents onto an eCRF.

The Clinical Research Coordinator (CRC) or designated study site personnel will complete the eCRFs in a timely manner after the information is collected. The Investigator will review and approve the completed eCRFs. Patients will not be identified by name in the study database or on any study documents to be collected by the AFT (or designee), but will be identified by a site number, subject number.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto eCRFs.

At study completion, when the database has been declared to be complete and accurate, the database will be locked.

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis.

AFT will review eCRFs for accuracy and completeness; any discrepancies will be resolved with the investigator or designee, as appropriate. Queries are entered, tracked, and resolved through the EDC system directly. All changes to the study database will be documented.

15.11. Site Monitoring

Monitoring visits will be conducted by representatives of the AFT according to the US CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to AFT (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.12. Data and Safety Monitoring Board

The Alliance Foundation Trials Data Safety Monitoring Board (DSMB) will be monitoring this study to ensure objectivity and the safety of participants. The DSMB will meet twice a year either at a face-to-face meeting or by teleconference. At each meeting, the study will be reviewed for safety and progress toward completion. When appropriate, the DSMB will also review formal interim analyses of the outcome data. If necessary, the DSMB will recommend study closure or modifications. Any DSMB recommendations for changes to the study will be circulated to investigators in the form of an addendum to this protocol document.

The DSMB will include accrual data, AEs, and results of interim analyses when available. In determining whether the study should be continued, the DSMB will consider the results of each interim analysis, as described above. The DSMB will also consider the evidence regarding safety (AEs and the feasibility of completing the study, ie, the accrual rate). Weighing the AEs and the feasibility of study completion is complex and, therefore, no particular cut-offs of these measurements are provided in advance. The DSMB will use its discretion in weighing these measurements.

15.13. Regulatory Reporting

It is the responsibility of the Investigator and the research team to ensure that SAEs are reported according to the Code of Federal Regulations, GCPs, the protocol guidelines, AFT's guidelines, and IRB policy.

15.14. Audits and Inspections

Investigator sites may be audited by AFT under the AFT site audit program. Affiliate and satellite sites are subject to audit by AFT but in most cases will be centrally audited at the main member site. To enable evaluations and/or audits from health authorities or AFT, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., eCRFs and hospital records), all original signed informed consent forms, copies of all eCRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). In the event that the investigator or other site personnel are notified of a Health Authority's intent to inspect the site(s), notification will be sent to [REDACTED] immediately upon awareness.

15.15. Early Discontinuation of the Study

- Early study termination will be the result of the criteria specified below:
- Poor adherence to protocol and regulatory requirements.
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects.
- Plans to modify or discontinue the development of the study drug.

15.16. Publication of Study Protocol and Results

Alliance Foundation Trials, LLC prioritizes the timely presentation and publication of study results. Publications and any kind of presentations of results from the study shall be in accordance with accepted scientific practice, academic standards and customs and must be approved in writing by AFT as the sponsor of this study. No investigator may present or publish any portion of this study without written approval from AFT.

16. List of References

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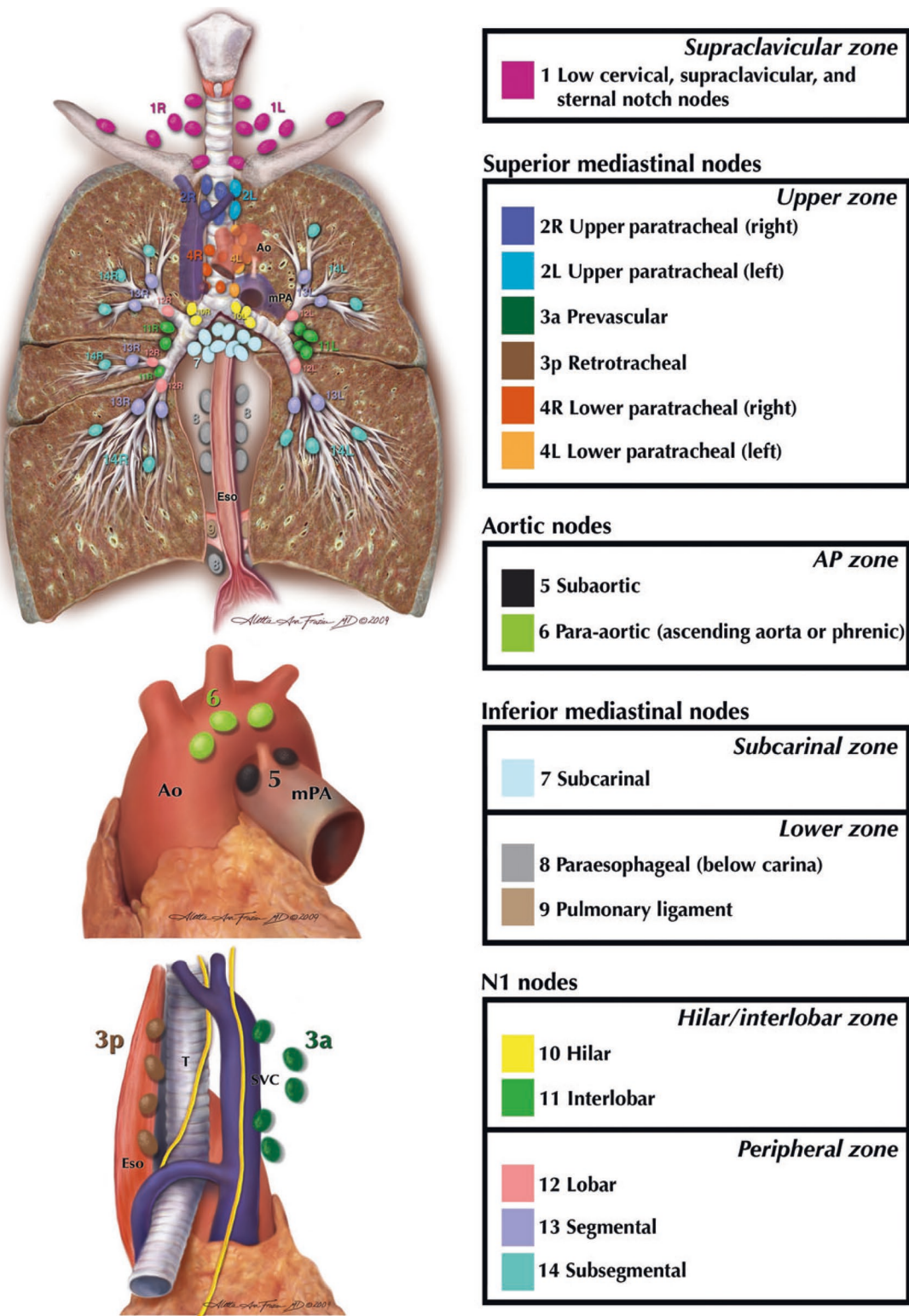
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17. Appendices

17.1. Appendix 1

Figure 2: IASLC Lymph Node Map



17.2 Appendix 2 – ANNEX TO PROTOCOL (attached)

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy,
Durvalumab in Combination with other Products, or Tremelimumab Monotherapy – Version 21-
September-2023