Summary of Changes- Protocol

#	Section	Comments
1.	Title Page	Protocol version and date revised. Updated study contact information for CROCC lead Coordinator and Lead UAD Coordinator. Removed CROCC Program Manager Contact.

Neoadjuvant Immunoradiation for Stage III Resectable Non-Small Cell Lung Cancer

JHU Protocol #: J1772 / IRB00127418

AstraZeneca Reference #: ESR1612244

Study Phase: II

Study Products:

Durvalumab (MEDI4736)

Tremelimumab

IND #: 134339

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Confidential Information

Protocol Revision Record

Version 9.0: March 2, 2022

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Protocol Synopsis

Name of Sponsor/Company: AstraZeneca/MedImmune		
Name of Finished Product: Durvalumab (MEDI4736) Tremelimumab		
Name of Active Ingredient: Durvalumab (MEDI4736) Tremelimumab		
Title of Study: Neoadjuvant Immunoradiation in Patients with Resectable Stage III Non-Small Cell Lung Cancer		
Investigators: Principal Investigator: Patrick Forde, MB BCH		
Study Center(s): Johns Hopkins University		
Anticipated Study Period (years): 2	**Phase of Development:** II	

Objectives:

Primary Objectives:

1. Safety: To evaluate whether durvalumab (cohort 1) or durvalumab plus tremelimumab (cohort 2) delivered concurrent with thoracic radiation (RT) and in the pre-surgical window prior to surgical resection, will be safe and tolerable to administer, in patients with stage III resectable NSCLC.
2. Feasibility: To evaluate whether durvalumab (cohort 1) or durvalumab plus tremelimumab (cohort 2) delivered concurrent with thoracic radiation (RT) and in the pre-surgical window prior to surgical resection, will not delay the time to surgery beyond the planned date of surgical resection, in patients with stage III resectable NSCLC.

Secondary Objective(s):

1. Pathologic Response

To determine whether durvalumab (cohort 1) or durvalumab plus tremelimumab (cohort 2) delivered concurrent with thoracic radiation (RT) and in the pre-surgical window prior to surgical resection, will induce a pathologic response in patient's primary tumors and draining lymph nodes, in patients with stage III resectable NSCLC.

2. Radiologic Response
To determine whether durvalumab (cohort 1) or durvalumab plus tremelimumab (cohort 2) delivered concurrent with thoracic radiation (RT) and in the pre-surgical window prior to surgical resection, will induce a radiologic response in in patient's primary tumors and draining lymph nodes, in patients with stage III resectable NSCLC.

3. Recurrence-Free Survival (RFS)
To determine whether durvalumab (cohort 1) or durvalumab plus tremelimumab (cohort 2) delivered concurrent with thoracic radiation (RT) and in the pre-surgical window prior to surgical resection, will delay the development of local or distant recurrent non-small cell lung cancer, in patients with stage III resectable NSCLC.

4. Surgical morbidity and mortality
To determine whether durvalumab (cohort 1) or durvalumab plus tremelimumab (cohort 2) delivered concurrent with thoracic radiation (RT) and in the pre-surgical window prior to surgical resection, will lead to unacceptable rates of postoperative morbidity or mortality when compared to historical controls, in patients with stage III resectable NSCLC.

5. Overall Survival
To determine whether durvalumab (cohort 1) or durvalumab plus tremelimumab (cohort 2) delivered concurrent with thoracic radiation (RT) and alone in the pre-surgical window prior to surgical resection, will result in an overall survival improvement in comparison to historical controls, in patients with stage III resectable NSCLC.

Exploratory Objective(s):
1. Genomic and neoantigen correlates.
To identify dynamic changes in the genomic and neoantigen landscape of cancer cells that are associated with pathologic response in patients with stage III resectable NSCLC, treated with preoperative durvalumab (cohort 1) or durvalumab plus tremelimumab (cohort 2) alongside thoracic radiation, and alone in the pre-surgical window. To determine whether changes in the T cell receptor (TCR) repertoire by means of TCR sequencing as well as in circulating cell-free tumor DNA (ctDNA) dynamics can predict response to these therapies.
2. Immunologic correlates
To evaluate markers of immune reactivity in the tumor microenvironment or peripheral blood in pre and post therapy tumor tissue and serially obtained blood samples in patients with stage III resectable NSCLC, treated with preoperative durvalumab (cohort 1) or durvalumab plus tremelimumab (cohort 2) alongside thoracic radiation, and alone in the pre-surgical window.

Methodology:
This is a pilot study of neoadjuvant 'immunoradiation' (durvalumab or durvalumab plus tremelimumab) administered every 4 weeks for 2 doses, concurrently with standard thoracic radiation (RT) (45Gy in 25 fractions), with one dose of immunotherapy alone delivered in the pre-surgical

window, prior to surgical resection, for patients with stage III NSCLC that is deemed resectable with a lobectomy by a thoracic surgeon. If preliminary safety of the durvalumab/thoracic RT combination is established, a second cohort investigating the combination of durvalumab/tremelimumab/thoracic RT prior to surgical resection will be opened. After surgical resection, patients may receive standard adjuvant chemotherapy, as deemed appropriate by the treating investigator.

Patients with a history of prior thoracic radiation or interstitial lung disease/pneumonitis will be excluded. Patients who would require a pneumonectomy will be excluded. This study aims to determine if immunoradiation will be safe, tolerable and feasible to administer prior to surgical resection for patients with stage III NSCLC. Safety will be determined by the number of dose-limiting toxicities that delay the time to surgery by >8 weeks from the date of completion of thoracic RT, and pre-defined grade 3+ pulmonary toxicities that occur during the DLT observation period in comparison to historic norms of pulmonary toxicities seen with chemoradiation prior to surgery . Feasibility will be defined as the number of patients who undergo surgery within the planned surgical window: 6-8 weeks after completion of thoracic RT. The DLT observation window will start from the day of commencement of immunotherapy, until 30 days after thoracic surgery or 100 days after the last dose of immunotherapy, whichever is longer.

From a translational perspective, this study will allow investigators to collect pre- and post-treatment tumor and lymph node tissue and serial blood and related biospecimens, aimed at examining potential mediators of response and resistance to immunoradiation. Other endpoints of clinical interest will include: pathologic response, radiologic response, recurrence-free survival (RFS), overall survival (OS) and surgical morbidity and mortality. Patients will undergo routine screening investigations including CBC, CMP, Hepatitis B/C/HIV assessment, urine, pregnancy test, and standard radiologic body imaging and brain imaging at least 28 days prior to enrollment. Patients will be monitored with a clinical visit with a study doctor, AE assessment and routine laboratory tests (CBC, CMP, endocrine labs) at each week of thoracic RT and dose of immunotherapy and at a pre-surgical and post-surgical visits. After completion of study therapy, patients will be followed every 12 weeks (+/-7 days) for 12 months with standard radiologic imaging, laboratory tests and an AE assessment, and then every 12 weeks (+/-7 days) for years 2 and 3 to assess survival status.

# of Patients (planned):

Cohort 1: Identify 20 eligible and evaluable subjects, enroll 16 subjects. Cohort 2: Identify 20 eligible and evaluable subjects, enroll 16 subjects.

Inclusion Criteria:

- Written informed consent and any locally-required authorization obtained.
- Histologically-confirmed diagnosis of stage III non-small cell lung cancer (NSCLC)
- Age≥18 years
- Life expectancy ≥6 months
- Body weight >30kg
- Subjects with non-small cell lung cancer deemed surgically resectable by an attending thoracic surgeon with lobectomy
- ECOG Performance Status 0-1
- Normal bone marrow and organ function on routine laboratory tests, as defined in section 4.1
- Evidence of post-menopausal status or negative urinary/serum pregnancy test for female pre-menopausal subjects. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause.
- Ability to understand and willingness of sign consent form
- Willingness to comply with the protocol for the duration of the study

Exclusion Criteria:

- Involvement in the planning and/or conduct of the study (includes AstraZeneca staff and staff at the study site)
- Prior investigational therapy within 28 days/at least 5 half-lives before study drug administration
- Prior chest radiation
- Prior history of interstitial lung disease or pneumonitis requiring corticosteroids, or active non-infectious pneumonitis
- Patients only suitable for surgical management with pneumonectomy, deemed by an attending thoracic surgeon
- Prior therapy with PD-1, PD-L1, CTLA-4 or anti-cancer vaccines, including durvalumab and tremelimumab
- Participation in another clinical study with an investigational product in the last 4 weeks or equivalent of 5 half-lives of the first dose of study treatment, whichever is shorter
- History of another primary malignancy that requires active ongoing treatment or, in the opinion of the investigator, is likely to require treatment within 6 months of trial enrollment
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
    - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

- Any unresolved toxicity (>CTCAE grade 2) from previous anti-cancer therapy

- Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy)
- Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable
- Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
- Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable
- History of allogenic organ transplantation.
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], 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 (vitiligo or alopecia; hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement; any chronic skin condition that does not require systemic therapy; active disease in the last 5 years may be included but only after consultation with the study physician; celiac disease controlled by diet alone.)
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
- Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab or tremelimumab
- Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.
- Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study result.
- Known allergy or hypersensitivity to IP or any excipient
- Uncontrolled psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written consent

• Any condition that, in the opinion of the investigator would interfere with evaluation of study treatment or interpretation of patient safety or study results.
Investigational Product(s), Dose, and Mode of Administration: Durvalumab 1500 mg via IV infusion Q4W for 3 doses in patients > 30 kg Durvalumab 1500 mg plus tremelimumab 75 mg via IV infusion Q4W for 3 doses in patients >30 kg *N.B If a patient's weight falls to 30kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W and 1mg/kg tremelimumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500mg plus tremelimumab 75 mg Q4W).*
Study Population: Subjects in this study will be males or females 18 years of age or older. Subjects must have histologically confirmed stage III NSCLC deemed surgically resectable by a thoracic surgeon with lobectomy, have adequate organ and marrow function, no prior history of active autoimmune disease or active infections, and have an ECOG performance status of 0-1. Patients with a prior history of chest radiation, interstitial lung disease/pneumonitis, or who would require a pneumonectomy, will be excluded.
Study Assessments and Criteria for evaluation:

Safety Assessments:

1. Safety:
   All adverse events (including serious and non-serious, as well as adverse events of special importance AESIs) will be recorded from commencement of therapy until 30 days after surgical resection or 100 days after the last dose of immunotherapy, whichever is longer. Adverse events will be collected and recorded according to CTCAE version 4.03
2. Feasibility:
   The number of dose-limiting toxicities that delay the time of planned surgery beyond the planned surgical window (>8 weeks) after completion of thoracic RT. DLTs will be collected and recorded according to CTCAE version 4.03
3. Surgical Morbidity and Mortality:
   All adverse events (including serious and non-serious, as well as adverse events of special importance AESIs) or deaths that occur from the time of surgery until 30 days post-surgery or 100 days after the last dose of immunotherapy, whichever is longer.

Efficacy Assessments:

1. Pathologic Response Rate:
   Pathologic response evaluated by two thoracic pathologists as described by Pataer et al (J Thorac Oncol 2012), and stratified into major pathologic response (MPR), partial response (PR) and no response (NR).
2. Radiologic Response:
   Radiologic response by RECIST 1.1 and immune-related RECIST criteria.
3. Recurrence-Free Survival:
   The time from study enrollment until radiologic evidence of local or distant recurrent NSCLC.
4. Overall Survival
   The time from study enrollment until death from any cause.

Statistical methods:

This is an open-label pilot study aimed at establishing the safety and feasibility of neoadjuvant immunoradiation prior to surgical resection of stage III NSCLC, which is deemed surgically resectable by a thoracic surgeon with lobectomy. Thoracic RT will be given at standard doses and using standard methods, as per published phase III data (45Gy: Albain et al, Lancet 2009). Thoracic surgery will consist of lobectomy with mediastinal lymph node sampling.

In cohort 1, the safety, tolerability and feasibility of durvalumab with concurrent thoracic RT, will be assessed. In this cohort, durvalumab will be administered at the standard dose of 1500mg IV every 4 weeks for 3 doses, two doses of which will be administered concurrently with thoracic RT and one dose will be delivered in the pre-surgical window. If preliminary safety is established in cohort 1, the study will expand to include cohort 2, which will test the safety and feasibility of durvalumab plus tremelimumab with concurrent thoracic RT. In this cohort, durvalumab will be administered at the standard dose of 1500mg IV every 4 weeks for 3 doses, and tremelimumab will be administered at the standard dose of 75 kg every 4 weeks for 3 doses, two doses of which will be administered concurrently with thoracic RT (45Gy in 25 fractions)

and one dose will be delivered in the pre-surgical window. The doses of these therapies are in keeping with ongoing phase III studies of both single agent durvalumab and the combination of durvalumab plus tremelimumab.

The co-primary endpoints of this study are safety, tolerability and feasibility in cohort 1, followed by safety and feasibility in cohort 2. Safety will be monitored through the rate of all treated patients that develop adverse events (including serious and non-serious, as well as adverse events of special importance AESIs) and dose-limiting toxicities from commencement of durvalumab/RT or durvalumab/tremelimumab/RT until 30 days postoperatively or 100 days after the last dose of immunotherapy whichever is longer, or any pre-defined pulmonary DLTs that occur from the date of surgery until 30 days postoperatively. The DLT observation window will be defined as the time from the date of commencement of immunotherapy until 30 days post-surgery or 100 days after last immunotherapy dose, whichever is longer. Safety will be monitored continuously for all patients. A Bayesian safety monitoring rule will be used to evaluate the rate of adverse events of interest continuously, from the 3rd evaluable patient, and accrual will be suspended at any time if there is sufficient evidence of excessive toxicity. Specifically, the Bayesian toxicity monitoring rule suspends accrual anytime if the posterior probability of adverse event of interest being larger than 25%, is 70% or higher. The following table gives the corresponding stopping rule for the 16 evaluable patients:

#Patients with DLT	2	3	4	5	6
Out of total #patients treated	3-4	5-7	8-11	12-13	16

Feasibility will be monitored through the proportion of patients who undergo surgery within the planned surgical window: 6-8 weeks after completion of thoracic RT. We will use a probability-based decision rule to decide if the probability of successfully proceeding to surgery as planned is convincingly less than 75%. A Bayesian monitoring rule would apply and suspend the accrual if there is at least 90% probability that less than 75% of patients can continue to surgery without treatment-related delays, as shown in the following table:

#Patients planned for surgical resection	1	2	3	5	6	7	8
Out of total # evaluable patients	6	7	8-9	10	13	14-15	16

Exploratory analyses as detailed in the biomarker table/summary will be presented descriptively, and are detailed in the researcher comments section.

Sample Size Determination:

We will aim to accrue 20 patients to each cohort, with anticipation of 16 evaluable and operable patients in each. It is estimated that JHH sees between 25-35 patients with stage III resectable NSCLC that would be suitable for enrollment onto this study. We conservatively estimate accrual of 2 patients every month. Accounting for an approximate 10% drop-out rate, we estimate a target accrual of 40 patients in 20-24 months. Additional study sites have been identified that will contribute to accrual, if needed.

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List of Abbreviations and Definition of Terms

Abbreviation	Definition
Abbreviation or special term	Explanation
AChE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response

Abbreviation	Definition
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response

Abbreviation	Definition
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure

Abbreviation	Definition
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous

Abbreviation	Definition
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1

Abbreviation	Definition
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate

Abbreviation	Definition
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

FIGURE 1: SCHEDULE OF ASSESSMENTS

Trial Period:	**Screening Phase**	**Treatment Phase (Treatment Cycles)**			**End of Treatment Phase**				
		Thoracic Radiation Week 1-5±2							
Treatment Cycle/Title:	**Study Screening (Visit 1)**	**1**	**2**	**3**	**Pre-Surgery 1**	**Pre-Surgery 2**	**Time of Surgery**	**Safety Follow-up**	
Day	**-1 to -28**	**1**	**30**	**60**					
Scheduling Window (Days):	**-28 to -1**	**± 3**	**± 3**	**± 3**	**Within 7 days of planned surgery**	**Within 72 hours of planned surgery**		**30 days post-Surgery** (± 3)**	**100 days post-Surgery** (± 7)**
Week	**-4 to -1**	**1**	**4**	**8**	**11-15**	**11-15**		**4 weeks post Surgery**	**3 months post surgery**
Administrative Procedures									
Written Informed consent/ assignment of subject identification number	X								
Inclusion/Exclusion Criteria	X								
Formal verification of eligibility criteria	X								
Clinical Procedures/Assessments									
Demographics including alcohol and tobacco use	X								
Medical and Surgical History	X							X	X

Trial Period:	**Screening Phase**	**Treatment Phase (Treatment Cycles)**			**End of Treatment Phase**				
		Thoracic Radiation Week 1-5±2							
Treatment Cycle/Title:	**Study Screening (Visit 1)**	**1**	**2**	**3**	**Pre-Surgery 1**	**Pre-Surgery 2**	**Time of Surgery**	**Safety Follow-up**	
Day	**-1 to -28**	**1**	**30**	**60**					
Scheduling Window (Days):	**-28 to -1**	**± 3**	**± 3**	**± 3**	**Within 7 days of planned surgery**	**Within 72 hours of planned surgery**		**30 days post-Surgery** (± 3)**	**100 days post-Surgery** (± 7)**
Week	**-4 to -1**	**1**	**4**	**8**	**11-15**	**11-15**		**4 weeks post Surgery**	**3 months post surgery**
Prior and Concomitant Medication Review	X	X	X	X	X	X		X	X
Review Adverse Events	X	X	X	X	X	X		X	X
Full Physical Examination	X	X	X	X	X				
Survival Status Assessment (Telephone)									
Vital Signs (pre-, during and post-infusion vital signs assessments)[1]	X	X	X	X	X	X		X	X
Weight	X	X	X	X	X				
ECOG Performance Status	X	X	X	X	X				
EKG[2]	X	X	X[2]	X[2]	X[2]				
Durvalumab Administration		X	X	X					

Trial Period:	**Screening Phase**	**Treatment Phase (Treatment Cycles)**			**End of Treatment Phase**				
		Thoracic Radiation Week 1-5±2							
Treatment Cycle/Title:	**Study Screening (Visit 1)**	**1**	**2**	**3**	**Pre-Surgery 1**	**Pre-Surgery 2**	**Time of Surgery**	**Safety Follow-up**	
Day	**-1 to -28**	**1**	**30**	**60**					
Scheduling Window (Days):	**-28 to -1**	**± 3**	**± 3**	**± 3**	**Within 7 days of planned surgery**	**Within 72 hours of planned surgery**		**30 days post-Surgery** (± 3)**	**100 days post-Surgery** (± 7)**
Week	**-4 to -1**	**1**	**4**	**8**	**11-15**	**11-15**		**4 weeks post Surgery**	**3 months post surgery**
Tremelimumab Administration (cohort 2 only)									
Laboratory Procedures/Assessments[3]									
Hepatitis B, C, HIV	X								
Pregnancy Test – Urine or Serum -HCG[4]	X	X	X		X		X	X	X
Serum Chemistries, Thyroid Function Tests, Liver Function Tests	X	X	X	X	X	X	X	X	X
Coagulation parameters (PT/INR and aPTT)	X					X	X	X	X
Hematology	X	X	X	X		X	X	X	X
Thyroid function tests (TSH and fT3 and fT4)[5]	X		X			X	X	X	X

Trial Period:	**Screening Phase**	**Treatment Phase (Treatment Cycles)**			**End of Treatment Phase**				
		Thoracic Radiation Week 1-5±2							
Treatment Cycle/Title:	**Study Screening (Visit 1)**	**1**	**2**	**3**	**Pre-Surgery 1**	**Pre-Surgery 2**	**Time of Surgery**	**Safety Follow-up**	
Day	**-1 to -28**	**1**	**30**	**60**					
Scheduling Window (Days):	**-28 to -1**	**± 3**	**± 3**	**± 3**	**Within 7 days of planned surgery**	**Within 72 hours of planned surgery**		**30 days post-Surgery** (± 3)**	**100 days post-Surgery** (± 7)**
Week	**-4 to -1**	**1**	**4**	**8**	**11-15**	**11-15**		**4 weeks post Surgery**	**3 months post surgery**
Urinalysis	X								
Pulmonary Function Tests (including FEV1, FVC, DLCO)	X[9]								
Radiologic Assessments									
PET/CT with contrast[6]	X*				X*				
MRI Brain with contrast	X[10]								
CT chest/abdomen/pelvis with contrast with recist read[6]	X*				X*				
Correlative Analyses									
Pre-treatment Tissue Collection[7]	X								
Blood collection	X	X	X	X		X		X	X
Post-treatment Tissue[7]							X		

NOTE: *In order to minimize the need for research-only in-person visits, telemedicine visits may be substituted for in-person clinical trial visits or portions of clinical trial visits where determined to be appropriate and where determined by the investigator not to increase the participants risks. Prior to initiating telemedicine for study visits the study team will explain to the participant, what a telemedicine visit entails and confirm that the study participant is in agreement and able to proceed with this method. Telemedicine acknowledgement will be obtained in accordance with the Guidance for Use of Telemedicine in Research. In the event telemedicine is not deemed feasible, the study visit will proceed as an in-person visit. Telemedicine visits will be conducted using HIPAA compliant method approved by the Health System and within licensing restrictions.*

[*] All assessments to be performed pre-infusion unless stated otherwise ** If patients do not proceed to surgery, they will proceed to the safety follow-up visit at a time point 100 days after commencement of immunotherapy. [1] Subjects will have their blood pressure and pulse measured before, during, and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes), At 30 minutes during the infusion (±5 minutes), At the end of the infusion (at 60 minutes ±5 minutes)
- In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (i.e., 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.

[2]EKG during screening and at Day1 – baseline. Thereafter as clinically indicated. Baseline and abnormal EKG at any time in triplicate others single.

[3] If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated.

[4] Pre-menopausal female subjects of childbearing potential only. If urine test is positive or not evaluable, serum test is required

[5] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[6]CT of the Chest/Abdomen/Pelvis is required between days -1 to days -28. A PET/CT may be substituted for a CT Chest/Abdomen/Pelvis if it done within 3 months prior to Cycle 1 Day 1. Either a PET/CT or CT of the Chest/Abdomen/Pelvis may be used for Preoperative imaging within 3 weeks of planned surgical resection date.

[7]Pre-treatment and post-treatment tissue will be collected as in section 8.

[8]Blood collection for correlative analysis will be taken at 12 month time point only during follow-up

[9]Assessment of lung function can be done within 3 months of treatment start as it is considered standard of care in the staging evaluation of patients with resectable NSCLC

[10] MRI Brain imaging within 3 months of treatment start as it is considered standard of care in the staging evaluation of patients with NSCLC

LONG TERM FOLLOW UP

Evaluation	Time Since Last Dose of MEDI4736 for those who did not proceed to surgery per SOC For those who did proceed to surgery, LT follow up would be scheduled from surgery date following SOC						
	Months (±2 weeks) Long term follow up visits can be done via telehealth						Every 12 weeks (+/- 2 weeks) or per SOC for years 2 and 3
	4	6	8	9	10	12	
Physical examination[a]		X		X		X	
Vital signs (temperature, respiratory rate, blood pressure, pulse)		X		X		X	
Weight		X		X		X	
AE/SAE assessment		X		X		X	X
Concomitant medications		X		X		X	X
Palliative radiotherapy	As clinically indicated →						
ECOG performance status[b]		X		X		X	
Subsequent anti-cancer therapy	X	X	X		X		X
Survival status: (telephone if patient refuses to return during year 1)	X	X	X		X		X
Urine hCG or serum βhCG							
Hematology							

LONG TERM FOLLOW UP

Evaluation	**Time Since Last Dose of MEDI4736 for those who did not proceed to surgery per SOC** **For those who did proceed to surgery, LT follow up would be scheduled from surgery date following SOC**						
	Months (±2 weeks) Long term follow up visits can be done via telehealth						**Every 12 weeks (+/- 2 weeks) or per SOC for years 2 and 3**
	4	**6**	**8**	**9**	**10**	**12**	
Serum chemistry		X**		X**		X**	
Thyroid function tests (TSH, and fT3 and fT4)[c]							
Tumour assessment (CT or MRI)	For subjects who **discontinue MEDI4736 following confirmed progression**, **scans should be conducted according to local clinical practice**.						

[a] Full physical exam

[b] PS to be collected if available at the 2 monthly calls to obtain subsequent anti-cancer therapy and survival status

[c] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[d] For patient questionnaires different approaches based on indication and study design

* For subjects who have discontinued Durvalumab and Tremelimumab Treatment due to confirmed Progression of Disease at the Investigator Discretion only.

** For subjects who have completed Durvalumab and Tremelimumab and Achieved Disease Control (until confirmed Progressive Disease) and Subjects who Discontinued Durvalumab or Tremelimumab due to Toxicity in the Absence of Confirmed Progressive Disease

1. Introduction

1.1. Disease Background

Immune responses directed against tumors are one of the body's natural defence against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung[1], renal[2]; pancreatic[3]; ovarian cancer[4], and hematologic malignancies[5, 6] tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis.

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell[7]. This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination[8].

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. T cells play a critical role in antitumor immunity and their infiltration and activity have been linked to improved prognosis in a number of cancers[9-11]. Immune evasion, primarily through suppression of T-cell activity, is now recognized as one of the hallmarks of cancer. Such evasion can occur via a range of mechanisms including production of suppressive cytokines such as IL-10, secretion of chemokines and growth factors that recruit and sustain suppressive regulatory T cells (Tregs) and inflammatory macrophages, and expression of inhibitory surface molecules such as B7-H1. Tumor types characterized as being responsive to immunotherapy-based approaches include melanoma[12, 13], renal cell carcinoma[14], bladder cancer[15], and malignant mesothelioma[16]. Inhibition of CTLA-4 signaling is a validated approach to cancer therapy, as shown by the approval in 2011 of ipilimumab for the treatment of metastatic melanoma based on statistically significant and clinically meaningful improvement in OS[12].

In general, tumor response rates to anti-CTLA-4 therapy are low (~10%). However, in patients who respond, the responses are generally durable, lasting several months even in patients with aggressive tumors such as refractory metastatic melanoma. Because these agents work through activation of the immune system and not by directly targeting the tumor, responses can occur late and some patients may have perceived progression of their disease in advance of developing disease stabilization or a tumor response. In some cases, early growth of pre-existing

lesions or the appearance of new lesions may have been due to immune-cell infiltration into the tumor and not due to proliferation and extension of neoplastic cells, per se[17]. Overall, although the impact on conventionally-defined PFS can be small, durable response or stable disease seen in a proportion of patients can lead to significant prolongation of OS. The melanoma data with ipilimumab clearly demonstrate that a small proportion of patients with an objective response had significant prolongation of OS, supporting the development of this class of agents in other tumors. Although Phase 2 and Phase 3 studies of tremelimumab in metastatic melanoma did not meet the primary endpoints of response rate and OS, respectively, the data suggest activity of tremelimumab in melanoma[18, 19]. In a large Phase 3 randomized study comparing tremelimumab with dacarbazine (DTIC)/temozolomide in patients with advanced melanoma, the reported median OS in the final analysis was 12.58 months for tremelimumab versus 10.71 months for DTIC/temozolomide (HR = 1.1416, p = 0.1272)[19].

1.1.1. Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors[20]. PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor[7]. PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by the immune system. In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. Binding of CTLA-4 to CD80 or CD86 on IC leads to inhibition of T-cell activation[21]. Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (eg, IFNγ) and can be found on both tumor cells (TC) and tumor infiltrating IC. The binding of PD L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, preventing them from killing target TC, and protecting the tumor from immune elimination[8] PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated[21, 22].

In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell-dependent mechanism[23] PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. In some cancers, (eg, renal cell carcinoma), taking into consideration the limitations of published literature, the expression of PD-L1 seems associated with reduced survival and an unfavorable prognosis[2]. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients[24-28] with responses that tend to be more pronounced in patients with tumors that express PD-L1[29, 30]. In addition, high mutational burden eg, in bladder carcinoma[31] may contribute to the responses seen with immune therapy.

The levels of tumour-infiltrating cells, and more specifically cytotoxic T-cells, have been correlated to improved prognosis in a number of cancers including colorectal, melanoma, and lung cancers[9] suggesting that an anti-tumour immune response is beneficial to patients. In contrast to PD-L1, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells. In addition, blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies whilst nivolumab and pembrolizumab, two anti-PD-1 agents and atezolizumab, an anti PD-L1 agent have been granted approvals by agencies such as the United States of America Food and Drug Administration and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, data from agents in the anti-PD-1/PD-L1class shows clinical activity in a wide range of tumor types

1.2. **Durvalumab**

The non-clinical and clinical experience is fully described in the current version of the durvalumab (MEDI4736) Investigator's Brochure.

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFNγ; Stewart et al. 2015).

To date durvalumab has been given to more than 1800 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 1.13.1. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.3. **Tremelimumab**

The non-clinical and clinical experience is fully described in the current version of the tremelimumab Investigator's Brochure.

Tremelimumab is a human immunoglobulin (Ig) G2 mAb that is directed against CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells and whole blood (Tarhini and Kirkwood 2008). Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

To date tremelimumab has been given to more than 1000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.13.1. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.4. **Durvalumab in combination with Tremelimumab**

Because the mechanisms of action of CTLA-4 and PD-1 are non-redundant targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity[32] therefore, in addition to evaluating both agents in the monotherapy setting in a number of cancer indications AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish the safety, PK/pharmacodynamics, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 or 4 weeks (Q2W, Q4W) up to 12 months, combined with tremelimumab Q4W up to Week 24 for 7 doses then every 12 weeks (Q12W) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue. In addition, other clinical studies have since started looking at the combination in both NSCLC and other oncology indications.

To date more than 800 patients have received the combination using a number of doses and dosing schedules. Details on the safety profile of durvalumab + tremelimumab combination therapy are summarized in Section 1.13.3. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK and efficacy.

1.5. **Research Hypothesis**

Neoadjuvant durvalumab (cohort 1) or durvalumab + tremelimumab (cohort 2) during and after thoracic radiation therapy and prior to surgery, will be safe and feasible to administer in patients with stage III resectable NSCLC. This combination may lead to pathologic responses that can be correlated with clinical outcomes; as well as immunologic changes that can be quantitatively measured to assess immune reactivity, which may be enhanced with this combination through antigen release and increased priming of anti-tumor T cells.

1.6. **Rationale for Conducting Study**

1.6.1. Current Management of Locally Advanced NSCLC

Approximately 80% of lung cancer cases are NSCLC with most patients presenting with late stage disease. Of patients with NSCLC, 20% present with stage I or II disease, whereas 30% present with stage III disease and 50% with stage IV disease (SEER database)[33]. Patients with pathologic stage I NSCLC have approximately a 60% 5-year survival. Stage II NSCLC patients have approximately 25% to 40% 5-year survival. Surgical resection remains the mainstay of treatment for stage I and II patients and selected patients with stage III NSCLC, however despite apparently curative surgery approximately 50% of stage IB, 70% of stage II, and 75% of stage III NSCLC patients will relapse and eventually die of their disease.

Optimum management of stage IIIA NSCLC is a controversial area in lung cancer medicine. In selected patients with stage III NSCLC who are deemed resectable by a thoracic surgeon, surgical resection remains a treatment option[34]. In these patients who do not require a pneumonectomy, tri-modality therapy with radiation, chemotherapy and surgery are all recommended, while the optimum sequence and modalities of therapy are debated[35].

1.6.2. Perioperative Systemic Therapy in Stage III NSCLC

A rational approach to eradicate micrometastatic disease and minimize the risk of relapse for patients with locally advanced NSCLC, is treatment with adjuvant or neoadjuvant chemotherapy. Many adjuvant studies have been performed and these trials are summarized in Table 1.

Although there are some conflicting results, the overall evidence from these studies suggests that adjuvant platinum doublet chemotherapy is beneficial for good performance status patients with stage II-IIIA disease[36-41]. The LACE meta-analysis of modern adjuvant and neoadjuvant trials, all of which used cisplatin-based chemotherapy, suggested a 5% survival advantage at 5 years from adjuvant chemotherapy with the benefit

being greatest for stage II and IIIA patients. A 2010 meta-analysis including both older and more recent trials confirmed the survival benefit shown in the LACE meta-analysis and suggested a benefit of adjuvant chemotherapy for stage IB disease patient[42, 43]

TABLE 1: SELECTED NSCLC STUDIES OF ADJUVANT CHEMOTHERAPY

Trial	Stage	Treatment	n	5 year OS	HR	p-value
ALPI	I-III	Surgery MVP	603 601	45% 50%	0.96	0.59
IALT	I-III	Surgery Cisplatin-based	935 932	40% 44.5%	0.86	<0.03
ANITA	IB-IIIA	Surgery Cisplatin+ Vinorelbine	433 407	43% 51%	0.80	0.017
BLT	I-IIIA	Surgery Cisplatin-based	189 192	58% 60%	1.02	0.90
NCIC/JBR10	IB-II	Surgery Cisplatin+ Vinorelbine	240 242	54% 69%	0.69	0.03
CALGB	IB	Surgery	171	57%	0.80	0.10

		Carboplatin+ Paclitaxel	173	59%		
OS= overall survival, HR= hazard ratio, ALPI: Adjuvant Lung Cancer Project Italy, IALT= International Adjuvant Lung Cancer Trial, ANITA= Adjuvant Navelbine Trialist Association, BLT= Big Lung Trial, NCIC= National Cancer Institute Canada, CALGB: Cancer and Leukemia Group, MVP= Mitomycin ,Vindesine, Cisplatin.						

1.6.3. Neoadjuvant Systemic Therapy in Resectable NSCLC

Preoperative chemotherapy has been assessed in a number of trials for patients with resectable NSCLC, though most were closed early when the adjuvant chemotherapy data revealed a survival advantage. A meta-analysis based upon seven trials involving 988 patients suggested that neoadjuvant chemotherapy improved overall survival when given preoperatively (5-year survival 20% versus 14 % without neoadjuvant chemotherapy), this improvement in survival being similar to that noted in the meta-analyses of predominantly adjuvant chemotherapy[43]. Neoadjuvant approaches may benefit patients by providing an *in vivo* assessment of anti-tumor response, improved rates of therapy completion, and early theoretical eradication of micrometastatic disease[43]. From a research standpoint, neoadjuvant therapy allows investigators to assess pre and post-therapy tumor tissue and serial blood samples to identify candidate biomarkers, as well as potential surrogate endpoints predictive of clinical outcome. This is in contrast with adjuvant studies, where no on-treatment tumor tissue is assessable, and studies may take decades to result. Several studies have shown preoperative systemic therapy to be safe prior to surgical resection of NSCLC with no difference in extent of surgical procedures performed, operative morbidity and mortality[36, 44, 45].

1.6.4. Neoadjuvant Radiation in Stage IIIA NSCLC

Preoperative chemoradiation in patients with resectable stage III NSCLC where surgery involves a lobectomy and mediastinal sampling, is currently a category 1 NCCN recommendation for treatment of stage III resectable NSCLC (Albain et al, 2009). This approach is also used for patients with superior sulcus tumors that are surgically resectable[46, 47]. Preoperative chemoradiation has been associated with improved pathologic complete response and negative mediastinal lymph nodes in comparison with induction systemic therapy alone[48], and thus may be a preferred approach in a subset of patients. The optimum dose of thoracic radiation administered concurrent with systemic therapy and prior to

surgical resection is unknown, but ranges from 45Gy-54Gy in 1.8-2Gy daily fractions, delivered over 5-7 weeks. Radiation pneumonitis with higher doses of thoracic radiation may be up to 20%, whereas rates are <10% with lower doses[49].

Optimum methods by which thoracic radiation should be administered are also controversial, however recent data suggests that newer methods using intensity-modulated radiation therapy (IMRT) as opposed to three-dimensional (3D) conformational radiation therapy are associated with improved clinical outcomes (Wang et al, Oncologist 2016). Other available advanced technologies include but are not limited to: 4D-CT and/or PET/CT simulation, IMRT, volumetric modulated arc therapy (VMAT), image-guided radiation therapy (IGRT), motion management, and proton therapy. Non-randomized comparisons of selected advanced technologies versus older techniques, demonstrate potential for reduced toxicity and improved survival outcomes with newer approaches, depending on the availability of these approaches at selected institutions[50, 51].

1.6.5. Surgical Considerations in Stage III Resectable NSCLC

Surgical resection for patients with superior sulcus NSCLCs as mentioned above, involves induction chemoradiation and en-bloc resection via an extended posterolateral thoracotomy. The largest series to explore this approach, examined 225 patients from Memorial Sloan-Kettering Cancer Center[52, 53]. In these patients, there was an operative mortality of 4%, and locoregional recurrence was the most common form of relapse. Surgical resection with lobectomy in these patients was associated with improved survival outcomes, compared with limited pulmonary resection[52, 53]. In patients with stage III NCLC treated with induction chemoradiation followed by surgical resection with both lobectomy or pneumonectomy, 16 (7.9%) patients died of causes not due to cancer, 10 of which occurred within 30 days of thoracotomy. Of these 16 deaths, 14 occurred after pneumonectomy, while only 1 occurred following surgical resection with lobectomy (0.5%), and 1 occurred in a patient who did not undergo thoracotomy. Causes were ARDS, 9; other respiratory, 4; cardiac, 2; hemorrhage, 1[49].

The use of induction chemoradiation prior to surgery for stage III NSCLC remains controversial, particularly for patients with N2 disease. Two randomized studies in this population failed to demonstrate an overall survival benefit for surgery. However, this population is anatomically heterogenous and thus the NCCN guidelines support consideration of surgical resection in subsets of patients that are deemed resectable by an attending thoracic surgeon, such as those with non-bulky N2 disease, where the largest lymph node larger is <3cm in size[34]. Guidelines support rigorous staging workup in this subset of patients and evaluation by an attending thoracic surgeon in a multidisciplinary setting before surgery in this clinical setting is undertaken. Additionally, a large multi-institutional trial demonstrated that surgery with pneumonectomy after neoadjuvant chemoradiation my result in unacceptable patient morbidity and mortality[49].

1.7. Rationale for Neoadjuvant Immunotherapy plus Radiation Therapy in Stage III NSCLC

1.7.1. Anti-PD-1/PD-L1 is Safe and Effective in NSCLC

With ~20% response rates (RR) in pre-treated NSCLC and durable responses in a subset of patients, anti-PD-1/PD-L1 agents including durvalumb (anti-PD-L1) are efficacious in NSCLC[54-58]. Combined anti-PD-L1 plus CTLA-4 inhibition with durvalumab plus tremelimumab has also resulted in remarkable RRs of up to 23% in pre-treated NSCLC[59], and is being studied in front-line NSCLC trials (NCT02453282, NCT02542293).

1.7.2. Neoadjuvant Anti-PD-1 is Safe and Feasible in Early Stage NSCLC

In a JHH investigator-initiated study[60] 18 patients with stage IB-IIIA(N1) NSCLC treated with 2 doses of neoadjuvant anti-PD-1 prior to surgical resection proceeded to surgery and demonstrated no high-grade AEs, delays to surgery, or surgical complications. Additionally, ~50% of patients exhibited major pathologic responses in resection specimens (MPR: >90% reduction in tumor cells)[61, 62], ~15% had partial responses (10-90% reduction), while ~35% had no pathologic response (<10% reduction). MPRs also showed dramatic increases in tumor-specific T cells. Importantly, patients with stage III (N2) were excluded from this study due to the potential benefit of TRT in this population. Interestingly, this study also demonstrated that anti-PD-1 expands T-cell clones both in the tumor and in peripheral blood, suggesting that it can enhance systemic immunity that can identify and kill micrometastatic tumor, thereby potentially conferring an ability to delay or mitigate relapse.

1.7.3. Radiation Therapy and Anti-PD-1/PD-L1 may have Immunologic Synergy

Preclinical models have demonstrated that RT may have immunologic effects that support an anti-tumor response, including: increased antigen presentation, chemokine release, effector T cell recruitment into the tumor microenvironment, and induction of immunogenic cell death[63-65] In addition, combining RT and immune checkpoint blockade may generate an anti-tumor effect outside the irradiated field, termed the abscopal effect[66] thought to be mediated by cross-priming of cytotoxic T-cells[66, 67]. The benefit of immune checkpoint blockade may also be affected by the diversity of the T cell receptor (TCR) repertoire, assessable through next-generation sequencing methods. In prior studies, it has been shown that CTLA-4 blockade diversifies the TCR repertoire[68], and that the maintenance of this diversity is associated with improved OS[69]. From here, preclinical models combining RT and immune checkpoint blockade, have demonstrated TCR diversification both systemically and in tumor-infiltrating lymphocytes[70]. Conversely, activated proliferating T cells are also known to be exquisitely radiosensitive, and preclinical models have shown that RT may impair their proliferation[71, 72]. In mouse models, RT to primary tumors together with checkpoint inhibition had significant effects on micrometastases[73].

1.8. **Rationale for Anti-PD-1/PD-L1 plus Anti-CTLA-4 in NSCLC**

As an antibody that blocks the interaction between PD-L1 and its receptors, durvalumab may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of anti-tumor T-cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile[24, 28]. Responses have been observed in patients with PD-L1-positive tumors and patients with PD-L1-negative tumors. In addition, durvalumab monotherapy has shown durable responses in NSCLC[59].

The rationale for combining durvalumab and tremelimumab is that the mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity[32]. In fact, combining immunotherapy agents has been shown to result in improved response rates (RRs) relative to monotherapy. For example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma induced higher objective response rates (ORRs) than those obtained with single-agent therapy. Importantly, responses appeared to be deep and durable[13]. Similar results have been observed in an ongoing study of durvalumab + tremelimumab in NSCLC[59], with further updated details presented in this clinical study protocol, with >20% RRs in pre-treated NSCLC[59]. This combination is currently being studied in front-line NSCLC trials (NCT02453282, NCT02542293).

1.9. **Durvalumab + tremelimumab combination therapy dose rationale**

The durvalumab + tremelimumab doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

Pharmacokinetics/Pharmacodynamics data

Study D4190C00006 included dose cohorts with both a Q4W and a Q2W schedule of durvalumab in combination with a Q4W schedule of tremelimumab. The Q4W schedule was included to align with the Q4W dosing of tremelimumab. PK simulations from durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W dosing with durvalumab. The observed durvalumab PK data from the D4190C00006 study were in line with the predicted monotherapy PK data developed pre-clinically and in line with that seen in the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. This demonstrates similar exposure of durvalumab 20 mg/kg Q4W and 10 mg/kg Q2W, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median maximum plasma concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg Q4W (approximately 1.5 fold) and median trough

concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg Q2W (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data. Monotonic increases in PDx activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy. There was evidence of augmented PDx activity relative to durvalumab monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both the 15 and 20 mg/kg durvalumab plus 1 mg/kg tremelimumab combinations.

Clinical data

In Study D4190C00006 various dose combinations have been explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of durvalumab ranging from 3 to 20 mg/kg. Tremelimumab was given on a Q4W schedule whilst durvalumab was explored in both a Q4W and Q2W schedule, with the goal of identifying the dose combination that best optimizes the risk:benefit profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the 3 or 10 mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of durvalumab with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of durvalumab may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of durvalumab. In Study D4190C00006, of all treatment cohorts, the cohort of patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had a tolerable safety profile, but still showed strong evidence of clinical activity. No dose-limiting toxicities (DLTs) were reported in this cohort. Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses. Efficacy data suggested that the 20 mg/kg durvalumab +

1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. Of the 14 patients in this cohort, there were 4 patients (29%) with PR, 4 patients (29%) with SD, and 2 patients (14%) with PD. Two patients were not evaluable for response. Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information on the durvalumab + tremelimumab combination, including safety, efficacy and pharmacokinetics

1.10. **Rationale for fixed dosing**

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 ~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-subject variability with fixed dosing regimen. Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) (Wang et al, 2014). Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others[74-77]. 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[74]. 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-subject variability in pharmacokinetic/pharmacodynamics parameters[77]. 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 Q4W durvalumab (equivalent to 20 mg/kg Q4W) and a fixed dose of 75 mg Q4W tremelimumab (equivalent to 1mg/kg Q4W) is included in the current study.

1.11. **Benefit/risk and ethical assessment**

Durvalumab monotherapy is safe and tolerable in advanced NSCLC, with only 9% of patients experiencing grade 3-4 (>G3) adverse events (AEs), and 1% developing treatment-related pneumonitis with durvalumab in a large phase IB study in these patients[58]. Moreover, >G3 pneumonitis was only seen in 4% of those treated with durvalumab plus tremelimumab in a phase I study of the combination, in 102 NSCLC patients[59]. Thus, the incidence of high-grade pneumonitis with PD-1/PD-L1 pathway inhibitors[78] is similar to standard cytotoxic chemotherapy[79] or tyrosine kinase inhibitors[80, 81] investigated in the neoadjuvant setting. Since radiation pneumonitis/pulmonary toxicity may also occur in up to 15% of patients treated with TRT (45Gy)[46-49], and 1-3% of patients who undergo lobectomy or sublobar resection for NSCLC may develop acute lung injury[82], the incidence and severity of potential pulmonary toxicity in patients planned to receive immunoradiation before surgery merits special attention. To this end, special measures (patient selection and monitoring, as per below) have been taken in my proposed study to limit the risk associated with pneumonitis as investigation of immunoradiation is undertaken in the neoadjuvant setting. Greater experience and use of management algorithms for anti-PD-1/PD-L1 pneumonitis, appear to have substantially mitigated this toxicity since early phase studies[83]. Reassuringly, a phase III study of maintenance durvalumab administered after definitive chemoradiation in patients with stage IIIB NSCLC, has also recently reported no preliminary evidence of excessive toxicity (NCT02125461).

1.12. **Potential Benefits:**

1.12.1. Durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first time in-human, single-agent study (Study 1108) in patients with advanced solid tumors. Data from Study 1108 were presented at the European Society for Medical Oncology 2014 Congress. Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%)[84].

1.12.2. Tremelimumab

In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, an RR of 7% and a median OS of 10 months in the second-line setting (as compared to approximately 6 months with best supportive care reported from a retrospective analysis were observed[18, 85]. In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg every 90 days) versus chemotherapy (dacarbazine or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed an RR of 11% and a median OS of 12.58 months in this first-line setting as compared to 10.71 months with standard chemotherapy; however, these results were not statistically significant[19]. Additionally, a Phase II maintenance study (Study A3671015) in patients with Stage IIIB or IV NSCLC who had responded or remained stable failed to achieve statistical significance. The primary endpoint of PFS at 3 months was 22.7% in the tremelimumab arm (15 mg/kg) compared with 11.9% in the best supportive care arm (Study A3671015).

1.12.3. Durvalumab + tremelimumab

The preclinical and clinical justification for this combination as noted in Section 1.1.4 also supports the synergy of this combination. Available data, such as those presented by Wolchok et al, suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma[13]. Of the 102 subjects with advanced NSCLC treated with durvalumab in combination with tremelimumab in Study D4190C00006, 63 subjects with at least 16 weeks of follow-up were evaluable for response (defined as measurable disease at baseline and at least 1 follow-up scan; this included discontinuations due to disease progression or death without follow-up scan). Of the 63 evaluable subjects, 17 (27%) had a best overall response of PR, 14 (22%) had SD, 22 (35%) had PD, and 10 (16%) were not evaluable. The ORR (confirmed and unconfirmed CR or PR) was 27% and the DCR (CR, PR, or SD) was 49% as assessed by RECIST v1.1.

Current experience with single-agent IMT studies suggests that clinical responses may be restricted to a subset of any given patient population and that it might be beneficial to enrich the patient population by selecting patients likely to respond to therapy. To date, no assay has been established or validated, and no single approach has proven accurate, for patient enrichment for IMTs. However, independent data from multiple sources using different assays and scoring methods suggests that PD-L1 expression on tumor cells and/or tumor infiltrating cells may be associated with greater clinical benefit.

Data from ongoing studies with durvalumab and other agents targeting the PD-1/PD-L1 pathway suggest, as shown in a number of tumor types (e.g., NSCLC, renal cell carcinoma, and melanoma), that monotherapy may be more efficacious (in terms of ORR) in patients who are PD-L1-positive.

Given these findings, a number of ongoing studies are assessing the activity of agents in patients with PD-L1–positive tumors. There is also an unmet medical need in patients with PD-L1–negative tumors that needs to be addressed. Data, as of 27 January 2015 from Study 006 show that with the addition of tremelimumab to durvalumab, the ORR can be increased to 25% in patients with PD-L1 negative NSCLC. As patients with PD-L1 positive disease can also have an increase in ORR, from 25% with durvalumab monotherapy, to 36% with the combination of durvalumab and tremelimumab, the study will enroll all patients with NSCLC, with an emphasis on those determined to be PD-L1 negative.

1.13. **Identified and Potential Risks**

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. Potential risks are events with a potential inflammatory mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine replacement therapy. These risks include gastrointestinal AEs such as colitis and diarrhoea, pneumonitis, nephritis and acute renal failure, hepatic AEs such as hepatitis and liver enzyme elevations, dermatitis, and endocrinopathies such as hypo- and hyper-thyroidism, hypophysitis and adrenal insufficiency.

1.13.1. Durvalumab

Identified risks with durvalumab are diarrhea, increases in transaminases, pneumonitis and colitis. Potential risks include endocrinopathies (hypo- and hyper-thyroidism, hypophysitis and adrenal insufficiency) hepatitis/hepatotoxicity, neurotoxicities, nephritis, pancreatitis, dermatitis, infusion-related reactions, anaphylaxis, hypersensitivity or allergic reactions, and immune complex disease. 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 (≥ 10% of subjects) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 10% of subjects experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 3.5% of subjects experienced an SAE that was considered to be related to durvalumab by the study investigator.

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 toxicity (see the Dosing Modification and Toxicity Management Guidelines in Appendix 1.)

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

1.13.2. Tremelimumab

Potential risks, based on the mechanism of action of tremelimumab and related molecules (ipilimumab) include potentially immune-mediated gastrointestinal (GI) events including enterocolitis, abdominal pain, dehydration, nausea and vomiting, and decreased appetite (anorexia); dermatitis including urticaria, skin exfoliation, and dry skin; endocrinopathies including hypophysitis, adrenal insufficiency, and hyperthyroidism and hypothyroidism; pancreatitis including autoimmune pancreatitis and lipase and amylase elevation; respiratory tract events including pneumonitis and interstitial lung disease (ILD); nervous system events including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barré syndrome; cytopenias including thrombocytopenia, anemia, and neutropenia; infusion-related reactions; anaphylaxis; and serious allergic reactions. The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma). Overall, 944 of the 973 patients (97.0%) treated with tremelimumab monotherapy as of the data cutoff date of 12 November 2014 (for all studies except D4190C00006 that has a cutoff date of 04 December 2014 and not including 497 patients who have been treated in the ongoing blinded Phase IIb Study D4880C00003) experienced at least 1 AE. The events resulted in discontinuation of tremelimumab in 10.0% of patients, were serious in 36.5%, were Grade ≥3 in severity in 49.8%, were fatal in 67.7%, and were considered to be treatment related in 79.1% of patients. The frequency of any AEs and Grade ≥3 AEs was generally similar across the tremelimumab dose groups. However, a higher percentage of patients in the 10 mg/kg every 28 days and 15 mg/kg every 90 days groups compared with the All Doses <10 mg/kg group experienced treatment-related

1.13.3. Durvalumab + tremelimumab

The safety of durvalumab + tremelimumab combination therapy is being evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and has so far shown a manageable safety and tolerability profile.

The potential risks with the combination of durvalumab + tremelimumab are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study 006 and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these potential immune-mediated toxicities.

In durvalumab + tremelimumab combination studies AEs (all grades) reported very commonly (≥ 10% of patients) are diarrhea, fatigue, nausea, dyspnea, pruritus, rash, increased amylase, decreased appetite, pyrexia, increased ALT, cough, colitis, and increased lipase.

A detailed summary of durvalumab + tremelimumab combination AE data can be found in the current version of the durvalumab IB.

2. Study Objective

2.1. **Primary Objective(s)**

(1) Evaluate the safety and tolerability of preoperative 'immunoradiation' with durvalumab (cohort 1) +/- durvalumab plus tremelimumab (cohort 2) concurrent with and after thoracic radiation (45Gy in 25 fractions), followed by surgery, in patients with resectable stage III NSCLC.

(2) Evaluate the feasibility of preoperative 'immunoradiation' with durvalumab (cohort 1) +/- durvalumab plus tremelimumab (cohort 2) concurrent with and after thoracic radiation, followed by surgery, in patients with resectable stage III NSCLC.

2.2. **Secondary Objective(s)**

(1) Examine pathologic responses in post-treatment resection specimens, in patients with resectable stage III NSCLC treated with preoperative immunoradiation followed by surgery.

(2) Examine radiologic responses in stage III resectable NSCLC treated with preoperative immunoradiation, using RECIST 1.1 and immune-related (ir) RECIST criteria

(3) Evaluate recurrence-free survival (RFS) in patients with stage III resectable NSCLC treated with preoperative immunoradiation followed by surgery, where RFS is defined as the time from commencement of therapy until the development of local or distant recurrent disease.

(4) Evaluate surgical morbidity and mortality in patients with stage III resectable NSCLC treated with preoperative immunoradiation followed by surgery, where morbidity is defined as the number treatment-related AEs, and mortality is the number of deaths, from the day of surgery until 30 days postoperatively or 100 days after the last dose of immunotherapy, whichever is longer.

(5) Evaluate overall survival (OS) in patients with stage III resectable NSCLC treated with preoperative immunoradiation followed by surgery, where OS is defined as the time from commencement of therapy until death from any cause.

2.3. **Exploratory Objective(s)**

Examine changes in the genomic and neoantigen landscapes, TCR repertoire, ctDNA and immune reactivity pre and post immunoradiation both systemically and in the tumor microenvironment, in patients with stage III resectable NSCLC treated with preoperative immunoradiation followed by surgery.

3. Study Design

3.1. **Overview of Study Design**

This is a two-cohort study that will be conducted at SKCCC.

3.1.1. Screening

Eligible subjects will be consented to receive the investigational treatment. The study sample size will consist of 16 patients in cohort 1 and 16 patients in cohort 2. Study staff will arrange drug supply and treatment. All study drug will be supplied by AstraZeneca Pharmaceuticals.

3.1.2. Determination of Eligibility

After eligibility is established, the study staff will register participants. The following are required to be submitted for successful registration:

Registration forms

Copy of subject consent

Copies of the following documents:

- Diagnostic pathology report(s)
- PET/CT or CT scan report, MRI or CT brain with contrast report
- Laboratory reports including:

o Complete blood count (CBC) with differential (including absolute lymphocyte count) and direct platelet count.

o Chemistry: Albumin, SGOT (AST), SGPT (ALT), Bilirubin (direct and total), Calcium, Creatinine, Glucose, Total protein, Urea nitrogen, Uric Acid, Electrolytes (including sodium, potassium, chloride and bicarbonate).

o Liver function tests (AST, ALT, Total bilirubin, alkaline phosphatase)

o Urinalysis (routine)

o Baseline thyroid immune safety assay: Thyroid Stimulating Hormone (TSH). Abnormal endocrine results should be followed up per standard of care, and may require an endocrine consult and additional testing.

o Pulmonary function report

o Other documents, if requested.

Study treatment cannot begin until the patient is registered. Subjects who sign a consent form, but do not initiate protocol treatment for any reason (e.g., subjects who are screen failures), will be replaced and will not count towards our accrual goal. Also patients who do not stay enrolled through the DLT period, will be replaced and not count towards our accrual goal.

3.1.3. Diagnostic and Surgical Evaluation of Subjects

All patients enrolled on this protocol must be surgical candidates with stage III NSCLC, deemed to be resectable with lobectomy by an attending thoracic surgeon. Patients will have undergone radiographic evaluation indicating no evidence of distant disease and no evidence of unresectable loco-regional tumor extension before surgical resection. Any further preoperative testing that is recommended by the surgeon or anesthesiologist will be performed as part of standard of care.

3.1.4. Treatment and Collection of Biological Specimens

Sixteen patients with resectable IIIA NSCLC (squamous and non-squamous) will receive preoperative durvalumab on days 1, 30 and 60, (week 1, 4, 8), concurrently with thoracic radiation weeks 1-5 (+/-2) before planned surgery on 6-8 weeks after completion of thoracic radiation. Thoracic radiation will be performed as part of standard of care, to a total of 45Gy in 25 fractions using standard radiation methods employed at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University. Serial peripheral blood samples for exploratory analyses will be collected prior to each dose of study drug(s), once within 3 days prior to surgery, and at a timepoint 30 days (+/- 7 days) after surgery, as detailed in Figure 1. Preoperative core biopsy of the primary tumor, and optional preoperative mediastinal lymph node biopsies, will be

obtained. Archived or new tissue specimens will fulfill these criteria. Details of sample requirements are detailed in section 8.3. Specific procedures for accessioning specimens are outlined in detail in the laboratory manual. Patients will have one tumor imaging of the chest during the 7 days prior to surgery to re-assess tumor status and potential pulmonary inflammation following neoadjuvant treatment. Surgery for patients enrolled on this protocol will be according to generally accepted standards of care. It is advised that patients have at least 3 mediastinal and hilar lymph node stations sampled during surgery. The treatment plan is outlined in section 6.0

3.1.5. Toxicity assessments

Safety will be monitored continuously by the study investigators for patients in both cohort 1 and cohort 2 through day 90 following the last dose of study therapy or 30 days after the day of surgery, whichever happens later. Details of safety assessments as detailed in

section 9.0 of this protocol. A detailed statistical analysis plan for safety and feasibility is contained in section 11 of this protocol.

Dose Delays due to Toxicity:

If patients, after receiving the first dose of study therapy (Day 1) are unable to receive the second dose on Day 30 (+/-3 days), therapy may be deferred as long as the second dose is received during the time period of thoracic radiation. If this is not possible, they will be discontinued from study therapy and will proceed to surgery after standard preoperative evaluation.

If patients, after receiving the second dose of study therapy (Day 30) are unable to receive the

third dose on Day 60 (+/-3 days), therapy may be deferred as long as the third dose is received during the pre-surgical window prior to planned surgery. If this is not possible, they will be discontinued from study therapy and will proceed to surgery after standard preoperative evaluation.

Prior to surgery any treatment-related toxicity should have resolved to ≤grade 1.

3.1.6. Postoperative Treatment of Subjects

3.1.6.1. Adjuvant Chemotherapy

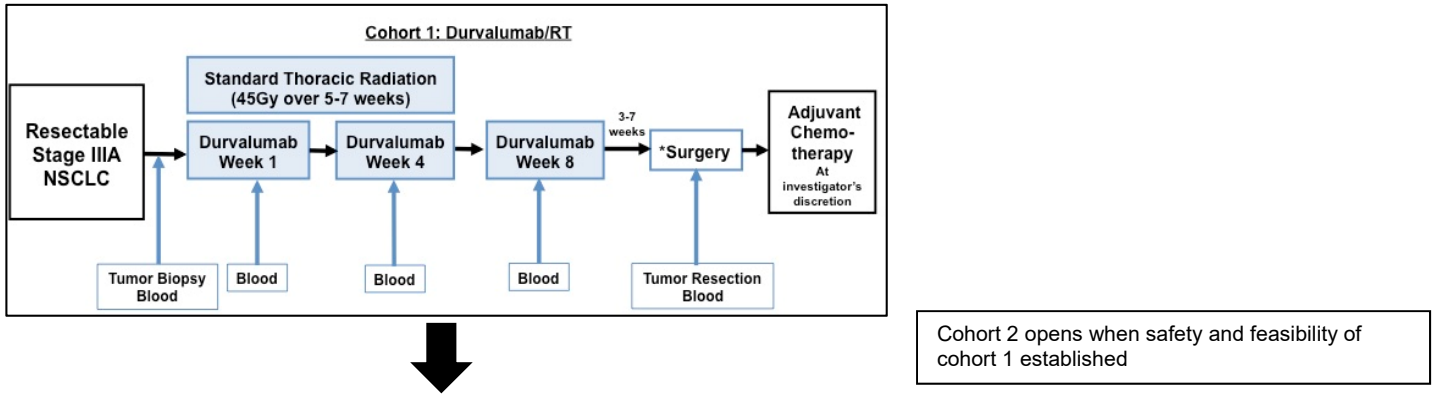
Postoperative chemotherapy will be administered at the discretion of the treating oncologist based on established standard indications. Postoperative chemotherapy will start at a time based on the standard of care approach taking into account postoperative recovery time for the subject. Postoperative chemotherapy should not commence until any study drug-related toxicity has resolved to <grade 2.

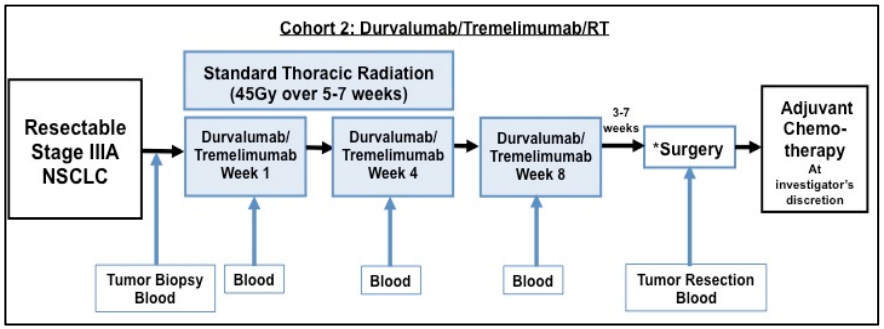
3.1.6.2. **Evaluation of Perioperative Safety**

The subject's medical record will be reviewed on a weekly basis from the start of therapy until 100 days after the last dose of study therapy or 30 days following surgery, whichever occurs later. The medical record will be reviews for information regarding operative complications including delay in planned surgery and in particular potential immune related toxicities (Note: Only those subjects who initiate study therapy will be followed). Toxicities will be reviewed at regular meetings of study investigators and minutes of these meetings will be documented by the clinical research staff. In the event that a subject does not continue his or her peri-operative care at the institution, every attempt will be made to collect this information either by direct contact or through communication with the subjects outside physician(s).

Deaths that occur during the DLT period will be assessed for their relationship to study therapy. As per section 1.6.5, historical norms for perioperative mortality with preoperative chemoradiation are in the order of 4%. If there is an early death in the study that is deemed related to study therapy such that the perioperative mortality rate exceeds that of historical norms, the study will be closed. If an early death occurs that is not deemed to be related to study therapy, the study may be allowed to continue in conjunction with safety assessments outlined in section 9.0.

FIGURE 2: STUDY SCHEMA





3.2. **Study Oversight for Safety Evaluation**

Early trial termination will be the result of the criteria specified below:

Quality or quantity of data recording is inaccurate or incomplete.

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.

In the event of an AstraZeneca decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

4. Patient Selection, Enrollment, Restrictions, Discontinuation and Withdrawal

Each patient must meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances will there be exceptions to this rule.

4.1. **Inclusion Criteria**

For inclusion in the study, patients should fulfill the following criteria:

1. Written informed consent and any locally-required authorization (e.g., HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
2. Age ≥ 18 years at time of study entry or Adult male or female (according to age of majority as defined as ≥18 years).
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
4. Life expectancy of ≥ 6 months
5. Body weight >30kg
6. Adequate normal organ and marrow function as defined below:
7. Haemoglobin ≥ 9.0 g/dL
8. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
9. Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)
10. Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). <<This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
11. AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN
12. Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

    Males:

    $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}.$$

    Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

13. Subjects with a histologically-confirmed diagnosis of stage III non-small cell lung cancer.
14. Subjects with non-small cell lung cancer that has been deemed surgically resectable with lobectomy, by an attending thoracic surgeon.
15. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal subjects. 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:
    - 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 or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    - Women ≥50 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, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
16. Subject 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.

4.2. **Exclusion Criteria**

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
2. Participation in another clinical study with an investigational product during the last 4 weeks or the equivalent of 5 half-lives of the first dose of study treatment, whichever is shorter.

3. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
4. Any previous treatment with a PD1 or PD-L1 agent including durvalumab or an CTLA-4 drug, including tremelimumab.
5. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
6. Subjects with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
7. Subjects with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.
8. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
9. Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug.
10. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
11. History of allogenic organ transplantation.
12. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], 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: Subjects with vitiligo or alopecia, Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement, Any chronic skin condition that does not require systemic therapy, Subjects without active disease in the last 5 years may be included but only after consultation with the study physician, Subjects 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. History of another primary malignancy that requires active ongoing treatment or, in the opinion of the investigator, is likely to require treatment within 6 months of trial enrollment
15. History of active primary immunodeficiency
16. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), **hepatitis B** (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
17. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion: Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection). Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent, Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
18. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Subjects, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.
19. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
20. Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.
21. Has history of (non-infectious) pneumonitis that required steroids, evidence of interstitial lung disease or active, non-infectious pneumonitis.
22. Prior history of thoracic irradiation for any indication.
23. Subjects who are only deemed suitable for surgical management of stage III NSCLC with pneumonectomy, as determined by an attending thoracic surgeon.
24. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results

25. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ or employing an effective method of birth control from screening to180 days after the last dose of durvalumab + tremelimumab combination therapy or 100 days after the last dose of durvalumab monotherapy, whichever is the longer time period
26. Uncontrolled psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written consent
27. Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.3. If a patient withdraws from participation in the study, then his or her enrollment code cannot be reused. Withdrawn patients will not be replaced.

4.3. **Withdrawal of Subjects from Study Treatment/On Study**

If incorrectly enrolled, subjects should discontinue study treatment and enrollment. Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

4.4. **Permanent Discontinuation of Study Therapy**

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

Withdrawal of consent or lost to follow-up

Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing

Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk

Pregnancy or intent to become pregnant

Any AE that meets criteria for discontinuation as defined in Section 9.3.

- Serious Adverse event related to thoracic radiation, with the exception of toxicities that do not meet the criteria for discontinuation as defined in Section 9.3.
- Dose-limiting toxicity (See Section 6.3 for definition of DLT).
- Grade ≥ 3 infusion reaction

- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits
- Initiation of alternative anticancer therapy including another investigational agent
- Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab + tremelimumab

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 9.0 and Appendix 2 or 3, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled I another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

4.5. **Withdrawal of Consent**

Subjects are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

Subjects who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A subject who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- all further participation in the study including any further follow up (eg, survival contact telephone calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

4.6. **Replacement of Subjects**

If subject withdraws from the study, that subject will be replaced.

4.7. **Registration Procedures: General Guidelines**

Eligible patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the CROCC Lead Study Coordinator. All sites should call/email the coordinating center at crocc@jhmi.edu for registration. The Registration Form and Eligibility Worksheet will be supplied to each participating site.

Subjects who sign a consent form, but do not initiate protocol treatment for any reason (e.g., subjects who are screen failures), will be replaced and will not count towards our accrual goal. The Coordinating Center should be notified as soon as possible.

4.8. **Registration Process**

To register a patient, the following documents should be completed by the Research Nurse or Study Coordinator and emailed to crocc@jhmi.edu and the CROCC Lead Study Coordinator to the Coordinating Center:

- Registration Form
- Signed patient consent form
- Eligibility Screening Checklist
- Copy of required screening tests (e.g., vitals, labs, EKGs) and scans

Study treatment cannot begin until the patient is registered. The Research Nurse or Study Coordinator at the participating site will then e-mail (crocc@jhmi.edu and the CROCC Lead Study Coordinator) the Coordinating Center to verify eligibility. To complete the registration process, the Coordinating Center will:

- Assign a patient study number
- Register the patient on the treatment portion of the study
- Email confirmation of enrollment and the patient study number to the participating site

5. Investigational Product(s)

5.1. Durvalumab and tremelimumab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab and tremelimumab to the investigator as solutions for infusion after dilution.

5.1.1. Formulation/Packaging/Storage

Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca 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 density of 1.054 g/mL. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg vial solution for infusion after dilution or a 25-mg vial solution for infusion after dilution. The solution contains 20 mg/mL of tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dehydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5 and density of 1.034 g/mL. The nominal fill volume is 20.0 mL for the 400-mg vial and 1.25 mL for the 25-mg vial. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original container until use to prevent prolonged light exposure.

5.2. Dose and Treatment Regimens

5.2.1. Durvalumab monotherapy (cohort 1)

Patients in the durvalumab (MEDI4736) monotherapy group will receive 1500 mg durvalumab via IV infusion every 4 weeks for up to 3 doses/cycles. Doses 1 and 2 will be administered on the same days as concurrent thoracic radiation. Dose 3 will be administered after completion of thoracic radiation, in the pre-surgical window. Dosing outside the window should be discussed with the Study Physician. Duration of durvalumab infusion will be approximately 1 hour. A 1-hour observation period is required after the first infusion of durvalumab. If no

clinically significant infusion reactions or dose-limiting toxicities are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after durvalumab infusion).

5.2.2. Durvalumab + tremelimumab combination therapy (cohort 2)

Patients in the durvalumab (MEDI4736) + tremelimumab combination therapy group will receive 1500 mg durvalumab (MEDI4736) via IV infusion every 4 weeks for up to 3 doses/cycles and 75 mg tremelimumab via IV infusion every 4 weeks for up to 3 doses/cycles. Doses 1 and 2 will be administered on the same days as concurrent thoracic radiation. Dose 3 will be administered after completion of thoracic radiation, in the pre-surgical window. Dosing outside the window should be discussed with the Study Physician. Tremelimumab will be administered first. Durvalumab (MEDI4736) infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions or dose-limiting toxicities are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

5.2.3. Study Drug Preparation of Durvalumab and Tremelimumab

Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab and 75 mg Q4W tremelimumab is included in the current study for patients > 30 kg. For patients $\leq$ 30 kg, weight-based dosing equivalent to 20mg/kg Q4W durvalumab and 1mg/kg Q4W tremelimumab should be utilized.

5.2.4. Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab 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 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

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration

ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (i.e., 1500 mg of durvalumab) to an appropriately sized IV bag such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

For patients ≤30kg, calculate the dose volume of durvalumab and number of vials needed for the subject to achieve the accurate dose. The appendix includes an example of a weight-based dose calculation. Patient weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2 or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

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 and document if the line was not flushed.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes time allowances and temperatures.

5.2.5. Durvalumab hold and infusion times

Maximum time from needle puncture to start of administration	**4 hours at room temperature, 24 hours at 2˚C to 8˚C**
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits outlined in the table, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

5.2.6. Preparation of tremelimumab doses for administration with an IV bag

The dose of tremelimumab for administration must be prepared by the Investigator's designated IP manager using aseptic technique. Total time from needle puncture of the tremelimumab 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

If storage time exceeds these limits, a new dose must be prepared from new vials. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature prior to administration.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. A dose of 75 mg tremelimumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% dextrose, with a final tremelimumab concentration ranging from 0.1 mg/mL to 10 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line filter. Add 3.8 mL of tremelimumab (i.e., 75 mg of tremelimumab) to an appropriately sized IV bag such that the final concentration is within 0.1 mg/mL to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

For patients ≤30 kg, calculate the dose volume for tremelimumab and number of vials needed for subject to achieve the accurate dose. The appendix includes an example of a weight based dose calculation. Patient weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

Tremelimumab will be administered at room temperature (approximately 25°C) by controlled infusion into a peripheral or central vein. Following preparation of tremelimumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2 or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

The IV line will be flushed with a volume of 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 and document if the line was not flushed.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes time allowances and temperatures.

5.2.7. **Tremelimumab hold and infusion times**

Maximum time from needle puncture to start of administration	**4 hours at room temperature, 24 hours at 2°C to 8°C**
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits outlined in the table, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

5.2.8. Monitoring of Dose Administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site , must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary

5.2.9. Accountability and Dispensation

Drug accountability and treatment compliance will be recorded and monitored by reviewing the subject's medical record and documentation in the CRF.

5.2.10. Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

6. Treatment Plan

6.1. **Subject Enrollment**

Eligible patients will be reviewed at the weekly Johns Hopkins Multidisciplinary Lung Cancer Clinic (MDC) for unbiased confirmation of diagnosis and treatment candidacy prior to enrollment. Eligible patients will be entered on study at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the Lead Study Coordinator.

Following registration, patients should begin protocol treatment within 5 days. Issues that would cause treatment delays should be discussed with Dr. Naidoo or Dr. Hales. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

6.1.1. Patient Registration Procedures

All patients entered on any Johns Hopkins clinical trial, whether treatment, companion, or cancer control trial, must be registered with the Sidney Kimmel Comprehensive Cancer Center and complete Informed Consent. Patients will be registered through CRMS and must be registered prior to the initiation of treatment.

6.1.2. Recruitment

- Patients will be recruited through the Upper Aerodigestive Division (UAD) in the Department of Oncology at the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins Medicine. Patients will be recruited from 1-2 other participating sites if accrual is slow.
- Patient referrals will be accepted from other Johns Hopkins Medicine sites which include The Johns Hopkins Hospital, Johns Hopkins Bayview Medical Center, Howard County General Hospital, Sibley Memorial Hospital, and Suburban Hospital, and other sites.
- In addition, Johns Hopkins coordinates the Johns Hopkins Clinical Research Network (JHCRN) which was founded in 2009 as an integrated network of select academic and community-based medical institutions established within the Johns Hopkins Institute for Clinical and Translation Research. The JHCRN is comprised of the 6 hospitals within the Johns Hopkins Medicine, Anne Arundel Medical Center, Greater Baltimore Medical Center, INOVA Health Systems, Peninsula Regional Medical Center and Reading Hospital and Health System.
- Referrals from clinicians at these or other facilities will be accepted. In such a case, communication will be directed to the Principal Investigator of the study. This contact may be in the form of telephone, email, etc. The Principal Investigator may inquire as to patient age, diagnosis, prior treatment, timing of prior treatment, and extent of current disease to determine whether the patient would meet global criteria for the study. This information will not be collected, maintained or stored in any way. Patients referred in such a manner will be required to meet in person for review of eligibility, registration and informed consent. These patients will be referred to the study team members in the UAD Program to review eligibility.

- Additional potential participants will be identified during routine clinic visits to the UAD Program at Johns Hopkins. Individuals will be approached by the provider or study team to determine willingness to learn more about a study for which they may be eligible. Discussions regarding study participation will take place privately and individuals will be provided with the IRB approved consent form.
- In addition, potential participants may contact the study team directly. This contact may be in the form of telephone, email, etc. Initial discussions regarding study.

6.2. **Dosage and Administration**

6.2.1. Durvalumab monotherapy or Durvalumab and Tremelimumab

Dosage of study therapy to be administered in this protocol is outlined below in Table 2.

In cohort 1: Three doses of durvalumab monotherapy will be administered to enrolled patients on Days 1, 30 and 60 (+/- 3 days) concurrently with standard thoracic radiation from day 1 until days 25-28, prior to planned surgery. Thoracic surgery will take place 6-8 weeks after completion of thoracic radiation.

In cohort 2: Three doses of durvalumab + tremelimumab will be administered to enrolled patients on Days 1, 30 and 60 (+/- 3 days) concurrently with standard thoracic radiation from day 1 until day 25-28 prior to planned surgery. Thoracic surgery will take place 6-8 weeks after completion of thoracic radiation.

Dosing of study therapy is flat dosing.

TABLE 2: TRIAL TREATMENT

Drug	Dose/Potency*	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Durvalumab	1500 mg	Q4W	IV infusion	Day 1 of each 4 week cycle	Experimental
Tremelimumab (cohort 2 only)	75mg	Q4W	IV infusion	Day 1 of each 4 week cycle	Experimental

* Weight-based dosing should be utilized for patients ≤ 30 kg equivalent to 20 mg/kg durvalumab Q4W and 1 mg/kg tremelimumab Q4W

The rationale for dosing is outlined in sections 1.0 and 5.0. Trial treatment should begin on the day of registration or as close as possible to the date on which treatment is allocated/assigned. Refer to Section 5.0 for the administration and monitoring of administration of durvalumab and tremelimumab.

6.2.2. Thoracic Radiation

6.2.2.1. Contemporary RT simulation and planning:

- **CT simulation:** Patients will be positioned in a stable position capable of allowing accurate reproducibility of the target position from treatment to treatment. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be used, including using an alpha-cradle or vac-bag.
- Simulation CT scans of the chest will cover whole lung with an adequate margin for generation of digitally reconstructed radiographs (DRRs). Scans will be performed either under free breathing with multiple-phased 4D CT scans at a fixed breathing phase for motion management.
- Thoracic radiation will be planned and delivered using contemporary RT planning techniques
- CT-based conformal planning with 4D CT is required for this study
- The use of intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) is mandatory Image guidance using conebeam beam CT or similar technology will be used for daily radiotherapy.

6.2.2.2. Target Dose

- Prescription Point: Dose is to be prescribed to an isodose line that encompasses the PTV with at least 92% coverage
- CTV is to be covered by 99% of the dose; iGTV is to be covered by 100% of the prescription isodose line

6.2.2.3. Prescription Dose and Fractionation

- Patients will receive treatment 5 days per week in once daily fractionation, 1.8-2.0 Gy per fraction. The total dose will be 45Gy in 25 fractions.

- A plan for potential definitive radiation therapy prior to therapy administration (i.e. to 60-70Gy) will be generated concurrently with the neoadjuvant treatment plan to 45 Gy to ensure that patients who may no longer be found to be surgical candidates, may be offered a potentially curative course of treatment without significant delay.

6.2.2.4. Target Volumes

- Gross Target Volume (GTV): is the volume occupied by known disease based by FDG-PET imaging, biopsy results or suspicion on CT; Elective nodal irradiation will not be used.
- Clinical Target Volume (CTV): is the GTV plus a 5-7mm expansion to encompass microscopic disease. The CTV expansion may be pulled away from normal tissues that are not at risk for tumor invasion.
- Planning Target Volumes (PTV): is the CTV plus an added margin determined by the institution to account for variability in treatment planning, breathing or motion during treatment. Daily image guidance is recommended to minimize the CTV to PTV expansion.

6.2.2.5. Normal Structures

Normal organs will be contoured as avoidance structures for treatment planning and will include: the spinal canal, the esophagus, the total lung-GTV, and the pericardium

- Spinal Canal: The treatment plan will avoid >50 Gy delivery to the spinal canal
- Esophagus: The treatment plan will keep the mean esophageal dose <34 Gy
- Pericardium: The treatment plan will keep the mean pericardial dose <26 Gy; the point max will be less than 50 Gy.
- Total lung: The total lung-GTV V20 will be <30 Gy. The mean total lung-GTV dose will be <16 Gy. It is strongly encouraged to minimize low dose bath to the total lung, ideally by keeping the V05<55 and the V10<40 to the total lung-GTV. However, these V05 and V10 constraints are not mandatory as situations may arise that required exceeding these constraints to maintain target coverage.

Thoracic radiation will be delivered as per standard of care. If a subject does not complete all planned doses of radiation therapy. The subject will be replaced, but will continue to be followed for safety.

6.2.3. Thoracic Surgery

6.2.3.1. Surgical Procedure

- Subjects must be suitable for surgical resection with lobectomy, by an attending thoracic surgeon.
- Subjects only deemed surgically resectable with pneumonectomy by an attending thoracic surgeon, will be excluded from the study.
- If after completion of study therapy a subject is only suitable for surgical resection with a pneumonectomy, the subject will be replaced, but will continue to be followed for safety.

6.2.3.2. Surgical Technique

- Subjects may undergo surgical resection with either VATS-assisted or an open surgical approach, as deemed suitable by the attending thoracic surgeon

6.2.3.3. Mediastinal Lymph Node Sampling

- Subjects must have at least 3 mediastinal and hilar lymph node stations sampled during surgery.

If a subject does not receive all planned doses of study therapy and proceeds to surgery, the subject will be replaced, but will continue to be followed for safety.

6.3. **Definition of Dose Limiting Toxicity (DLT)**

Dose-limiting toxicities (DLTs) will be evaluated from the first day of administration of durvalumab (cohort 1) or durvalumab+tremelimumab (cohort 2), in this trial. The period for evaluating DLTs will be from the day of first administration of study therapy until 30 days after surgical resection or 100 days following the last dose of study therapy, whichever occurs later. Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. A patient who experiences a DLT will be permanently discontinued from treatment and will proceed to surgery after standard preoperative evaluation by a surgeon and anesthesiologist. Prior to surgery any treatment related toxicity should have resolved to ≤grade 1.

A DLT will be defined as any Grade 3 or higher toxicity that occurs during the DLT evaluation period. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs:

- Any Grade 4 irAE
- Any ≥ Grade 3 colitis
- Any Grade 3 or 4 non-infectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management

- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days
- Grade 3 esophagitis secondary to radiation therapy

Immune-related AEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT

6.4. **Dose Modification and Toxicity Management**

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

6.4.1. Durvalumab + tremelimumab

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy and durvalumab + tremelimumab are provided in the Dosing Modification and Toxicity Management Guidelines in Appendix 1.**Error! Reference source not found.**

In addition, there are certain circumstances in which durvalumab and/or tremelimumab should be permanently discontinued.

Following the first dose of durvalumab +/- tremelimumab, subsequent administration of durvalumab +/- tremelimumab can be modified based on toxicities observed (see Appendix 1).

Based on the mechanism of action of durvalumab or tremelimumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 9.1.3. All toxicities will be graded according to NCI CTCAE v4.0

7. Restrictions During the Study and Concomitant Treatment(s)

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Female patient of child-bearing potential

Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 3) from the time of screening and must

agree to continue using such precautions for 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female subjects should also refrain from breastfeeding throughout this period.

Male subjects with a female partner of childbearing potential

- Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + any drug combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male subjects must also use a highly effective method of contraception throughout this period (Table 3).

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

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:

- 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 or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥50 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, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

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 3. Note that some contraception methods are not considered highly effective (e.g., male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper 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 3. HIGHLY EFFECTIVE METHODS OF CONTRACEPTION (<1% FAILURE RATE)

Barrier/Intrauterine methods	Hormonal Methods
Copper T intrauterine device	Etonogestrel implants: eg Implanon or Norplant
Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	Intravaginal device: eg ethinylestradiol and etonogestrel
	Medroxyprogesterone injection: eg Depo-Provera
	Normal and low dose combined oral contraceptive pill
	Norelgestromin/ethinylestradiol transdermal system
	Cerazette (desogestrel)

[a] This is also considered a hormonal method

Blood donation

Subjects should not donate blood while participating in this study.

7.1. Concomitant Therapy and Supportive Care Guidelines

The Principal Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the CRF.

Restricted, prohibited, and permitted concomitant medications are described in the following tables.

7.2. Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed in Tables 4 and 5.

TABLE 4: SUPPORTIVE MEDICATIONS

Supportive medication/class of drug:	**Usage:**

Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed below.	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management.	Should be used, when necessary, for all subjects
Inactivated viruses, such as those in the influenza vaccine	Permitted

7.3. **Excluded Concomitant Medications**

TABLE 5. PROHIBITED CONCOMITANT 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
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly. (Use of immunosuppressive medications for the management of IP-related AEs, or in subjects with contrast allergies is acceptable). In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study

Prohibited medication/class of drug:	Usage:
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly. 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.

8. Study Procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedule of Assessments during the screening and treatment period (Figure 1) is provided following the Protocol Synopsis.

8.1. Schedule of Study Procedures

8.1.1. Screening Phase

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics

- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead EKG (in triplicate [2-5 minutes apart] where applicable)
- Tumor biopsy
- Review of prior/concomitant medications
- Tumor Imaging
- Pulmonary Function Tests
- Clinical laboratory tests for:
- Hematology (see Table 5)
- Clinical chemistry (see Table 6)
- Liver function tests
- TSH
- Coagulation (PT, PTT, INR)
- Creatinine Clearance
- Serum pregnancy test (for women of childbearing potential only)
- Hepatitis serologies
- Urinalysis (see Table 8)

All patients enrolled on this protocol must be surgical candidates with stage III NSCLC deemed resectable with a lobectomy, by an attending thoracic surgeon. Patients will have undergone radiographic evaluation indicating no evidence of distant disease and no evidence of unresectable loco-regional tumor extension before surgical resection, as part of the screening procedures above. Any further preoperative testing that is recommended by the surgeon or anesthesiologist will be performed as part of standard of care. Surgery for patients enrolled on this protocol will be according to generally accepted standards of care.

8.1.2. Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Screening procedures performed within 28 days of Cycle 1 Day 1 (C1D1) do not need to be repeated.

8.1.3. End of Treament

The End of Treatment phase will consist of 2 pre-surgical visits and a safety visit, as defined in the Schedule of Assessments (Figure 1). For subjects who discontinue durvalumab or durvalumab + tremelimumab prior to completion of planned therapy, end of treatment will be considered the last visit where the decision is made to discontinue treatment, and subjects will return for the safety follow-up visit, after which they will enter the Follow-Up phase.

Assessments for subjects who have completed durvalumab monotherapy or durvalumab plus tremelimumab treatment, or have discontinued study therapy due to toxicity in the absence of confirmed progressive disease are provided in APPENDIX 2.

Assessments for subjects who have discontinued durvalumab monotherapy or durvalumab plus tremelimumab treatment due to confirmed PD are presented in APPENDIX 3.

All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

8.1.4. Follow-up Phase

Procedures to be conducted during the follow-up phase of the study are presented in the Schedule of Assessments. Subjects will be seen every 12 weeks (+/- 7 days) by a study doctor for a clinical assessment and tumor imaging for the first year after completion of therapy. Thereafter, subjects will be contacted every 12 weeks (+/- 7 days) for an assessment of survival status.

8.2. Description of Study Procedures

8.2.1. Medical history and physical examination, electrocardiogram, weight and vital signs

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examinations will be performed on study days noted in the Schedule of Assessments. The timing of assessments will be performed as detailed in the Schedule of Assessments (Figure 1).

8.2.2. Physical Examination

Physical examinations will be performed according to the assessment schedule. Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at Screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 9.

8.2.3. Electrocardiograms

Resting 12-lead EKGs will be recorded at screening and as clinically indicated throughout the study. EKGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

At Screening, a single EKG will be obtained on which QTcF must be <470 ms.

In case of clinically significant EKG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead EKGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

Situations in which EKG results should be reported as AEs are described in Section 9.0.

8.2.4. Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules Body weight is also recorded at each visit along with vital signs.

First infusion

On the first infusion day, patients in both the durvalumab + tremelimumab combination therapy cohort and the durvalumab monotherapy cohort will be monitored and vital signs collected/recorded in the CRF prior to, during and after infusion of IP as presented in the bulleted list below.

BP and pulse will be collected from patients in the I-O arms before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab and tremelimumab.

Subsequent infusions

BP, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

8.2.5. Clinical laboratory tests

The following clinical laboratory tests will be performed at the study sites of local laboratories, as deemed appropriate by the study investigator (see the Schedule of Assessments). Laboratory values outside of reference ranges will be reported to the study investigator, and treatment may be held, deferred or discontinued if necessary.

- Coagulation parameters: Activated partial thromboplastin time and International normalized ratio to be assessed at baseline and as clinically indicated
- Pregnancy test (female subjects of childbearing potential only)
- Urine human chorionic gonadotropin
- Serum beta-human chorionic gonadotropin (at screening only)
- Thyroid Stimulating Hormone
- free T3 and free T4 only if TSH is abnormal

- Serum Chemistries
- Liver function tests
- Other laboratory tests
  - Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
  - HIV antibody

TABLE 6. HEMATOLOGY LABORATORY TESTS

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

TABLE 7. CLINICAL CHEMISTRY (SERUM OR PLASMA) LABORATORY TESTS

Albumin	Lipase[b]
Alkaline phosphatase	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Bicarbonate[c]	Total protein
Calcium	TSH
Chloride[c]	T3 free[c] (reflex)
Creatinine clearance[c]	T4 free[c] (reflex)

Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyl-transferase[c]	
Glucose	
Lactate dehydrogenase	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

[b] 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.

[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at screening, on Day 0 (unless screening laboratory assessments are performed within 3 days prior to Day 0), and if clinically indicated.

[d] 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

ALT Alanine aminotransferase; AST Aspartate aminotransferase, TSH Thyroid Stimulating Hormone

TABLE 8. URINALYSIS TESTS[A]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells

8.3. **Biological Sampling Procedures**

Patients enrolled on this study will be required to have pre-treatment primary tumor biopsy material available for diagnosis and exploratory studies. This may consist of diagnostic biopsies that have been previously performed, or biopsies conducted by the study team in the case of inadequate pre-existing material. Excisional biopsies, or at least 4 core needle biopsies (≤21 gauge diameter) of the primary tumor are required; fine needle aspirates will not be adequate. A minimum of ten 5-micron paraffin tissue sections is required. Biopsies may be obtained by the following approaches: transbronchial, radiographically guided transthoracic approach, or video- assisted thoracoscopy. Biopsies that are formalin-fixed and paraffin embedded (FFPE) are required. Fresh frozen biopsy specimens may be

analyzed in addition to, but not in place of, FFPE specimens. Pretreatment biopsies of draining lymph nodes are desirable but not required; fine-needle aspirations of lymph nodes (>21 gauge diameter) are allowable. Primary tumor, draining lymph nodes and normal lung specimens will be collected from patients who undergo surgical resection, after receiving neoadjvant durvalumab +/- tremelimumab and thoracic radiation. After removal of tissue necessary for clinical assessment, remaining tissue specimens for research purposes will be divided in surgical pathology into 1) Fresh tissue that will be transported to the laboratory for viable cell isolation, 2) Fixation and paraffin embedding (FFPE), and 3) flash frozen for DNA and RNA analysis. If additional tissue remains, frozen blocks in OCT (Optimal Cutting Temperature) compound will also be prepared. Specific procedures for accessioning specimens are outlined in detail in the laboratory manual.

8.4. Biomarker Evaluation and methods

All patients will undergo the same laboratory correlate studies on tumor biopsy, resection specimen and blood samples as subsequently enrolled patients.

8.4.1. Tumor Tissue Samples

8.4.1.1. Collection of Pretreatment Tumor and Lymph Node Biopsies

New biopsies will be performed for this study. At least 6-8 core needle biopsies of the primary tumor will be required at the time of diagnosis (prior to first dose of study therapy); fine needle aspiration or biopsy is sufficient for hilar or mediastinal lymph node sampling by either endobronchial ultrasound or mediastinoscopy, but not for primary tumor biopsy.Where possible, and after a consent form has been signed, attempts will be made to coordinate diagnostic and study biopsies.

8.4.1.2. Pretreatment Biopsy Handling, Transportation, Storage, and Processing

Please see the laboratory manual for details of procedures. The study staff will be notified when a biopsy is taking place. The following procedures will be followed:

- If a core needle biopsy is being performed specifically for entry to the study, then at least 6-8 core-biopsy specimens will be obtained, the first three will be snap frozen and the remainder will be suspended in 10% neutral buffered formalin.
- After 24 hours of fixation in formalin, the cores will be embedded in paraffin.
- Tumor tissue will be processed for the appropriate studies listed below.
- For fine needle aspiration biopsies of draining lymph nodes, cells will be collected by centrifugation, fixed in formalin and embedded in a paraffin block using standard pathology procedures.

- The study coordinator will keep a log with the study number, the patient's study number, the date and time, and a consecutive sample number; thus, the samples will be numbered serially and will not contain identifying information.

8.4.1.3. **Operative specimens (tumor, normal lung, draining lymph nodes)**

Tissue specimens will be snap frozen or fixed in formalin and embedded in paraffin blocks, for genomic, transcriptomic and protein analyses as described in detail in the laboratory manual. Additional specimens obtained at the time of surgery will be dissociated enzymatically into single cell suspensions and will be viably cryopreserved according to a protocol provided in a companion laboratory manual.

8.5. **Blood Samples**

8.5.1. Collection Schedule

Blood samples will be drawn at the time points identified in Figure 1. Time points include:

- Day 1 (prior to study drug administration): 80 ml whole blood for peripheral blood mononuclear cell (PBMC), 20ml whole blood for plasma isolation, and 20 ml whole blood for serum isolation.
- Day 30 (+/- 3 days) (prior to study drug administration): 50 ml whole blood for PBMCs, 20ml whole blood for plasma and 10 ml whole blood for serum.
- Day 60 (+/- 3 days) (prior to study drug administration): 50 ml whole blood for PBMCs, 20ml whole blood for plasma and 10 ml whole blood for serum.
- Pre-surgical visit (72 hours prior to surgery): 50 ml whole blood for PBMCs, 20ml whole blood for plasma and 10 ml whole blood for serum.
- Safety and Follow-up visits (30 days, 100 days +/- 3 days after surgery and 12 month follow-up visit): 80 ml whole blood for peripheral blood mononuclear cell (PBMC), 20ml whole blood for plasma isolation, and 20 ml whole blood for serum isolation.

8.5.2. **Specimen Handling, Transportation, Storage, and Processing**

Serum samples: Whole blood will be collected in serum separator tubes (Becton- Dickinson SST tube or equivalent), processed per manufacturer's instructions and stored at -70°C or below until transfer for analysis.

PBMCs and plasma: Whole blood will be collected into EDTA tubes and processed per the laboratory manual. Viable PBMCs will be stored in cryopreservation medium, at 5e6-1e7 per vial, in liquid nitrogen.

These processes are outlined in full in the study Laboratory Manual

8.6. **Biomarker Evaluation methods**

8.6.1. **Immunohistochemistry**

We will discern phenotypes of immune cell populations in tumor and lymph node biopsy and resection tissue using immunohistochemistry, including but not limited to: CD3, CD4, CD8, CD25, CD45RO, CD56, CD20, CD68, granzyme B, FOXP3, TIM-3, LAG3, TIGIT, PVR-Ig, PD-1, PD-L1, eomesodermin, Tbet, phosphor-S6K and Egr2 (anergy marker) using validated commercially available or locally-developed antibodies to evaluate changes in the immune composition of the tumor microenvironment. Pathologists will assign an intratumoral and peritumoral immune cell infiltrate grade of (0) none, (1) rare lymphocytes (2) focal lymphohistocytic aggregates or (3) severe diffuse infiltration[86]. Pathologists will designate 3 representative fields to be evaluated by image analysis, which will allow for the data to be reported as a percentage of area with positive staining. These studies will provide a comprehensive view of cellular subsets and immune checkpoint molecule expression in tumors from untreated patients and how cellular subsets and key immune regulatory molecules are impacted intratumorally after treatment with anti-PD-L1+/- CTLA-4 and thoracic radiation. PD-L1 expression in FFPE specimens will be assessed as detailed below.

8.6.2. RNA Analysis

RNA analyses may be performed by means of RNAseq on fresh frozen samples as well as Nanostring or qRT-PCR on FFPE samples. Laser Capture Microdissection (LCM) may be performed to enrich for areas of tumor versus lymphocytic infiltrates, and in 20 ml whole blood for serum isolation as per the study schema. Genes to be probed may include but will not be limited to: specific cytokines, such as IFN-g, IL-17, IL-10, IL- 22, TGF-b, IL-4, TNF-a and certain chemokines. These studies will provide information on functional capacity of cancer cells and tumor infiltrating lymphocytes**.** Genes and pathways that are significantly altered in post-therapy tumor tissues as compared to stage-matched untreated tumor tissues or pre-therapy tissues will be assessed using bioinformatic platforms**.**

8.6.3. Flow Cytometric Analysis of Tumor and Lymph Nodes

Cryopreserved viable single cell suspensions will be thawed, and cells will be stained with specific monoclonal antibodies to assess coordinate expression of co-regulatory molecules by tumor infiltrating lymphocytes, draining lymph node cells and tumor cells. Multicolor flow cytometric analyses will be conducted. We will enumerate and characterize T cell subsets (e.g., CD4, CD8, CD25, HLA-DR, CD45RO, FoxP3, LAP, PD-1, PD-L1, PD-L2, LAG-3, ICOS, OX40, 41BB, central memory, effector memory), B cells (e.g., CD19, CD20, PD-1, PD-L2, ICOSL), dendritic cells and macrophages (e.g., CD68, CD83, CD1a, PD-L2, HLA-DR) and natural killer cells (CD56). Functional data and further demonstration of relevant T cell subsets will be gained from intracellular cytokine staining on T cells before and after non-specific CD3/28 activation (e.g., IFN-g, TNF-a, granzyme, IL-4, IL-10, and IL-17). The importance of these specific cytokines is that they mark distinct subsets of T cells with specific roles in pro- vs. anti-cancer immunity. In addition, blood samples will also be analyzed for the same

markers, and for cytokines by multiplex assays. Multi-parameter flow cytometry (for surgical resections) and multispectral immunofluorescence (IF) will also evaluate geographical relationships between immune cell population.

8.6.4. PBMC analysis

Assessments of coordinate expression of co-regulatory molecules by PBMCs will be performed using multicolor flow cytometric analyses. T cell subsets (including CD4, CD8, and Treg with CD25 and Foxp3) will be analyzed as well as co-stimulatory and co- inhibitory molecule expression and markers for T cell activation state (e.g., CD25, HLA- DR, CD45RO, LAP, PD-1, PD-L1, LAG-3, ICOS, OX40, 41BB, central memory, effector memory). B cells (CD19, CD20, PD-1, PD-L1, PD-L2, ICOSL), dendritic cells and macrophages (CD68, CD83, CD1a, PD-L1, PD-L2, 4-1BB, 4-1BBL, ICOSL, HLA-DR) and natural killer cells (CD56) will be enumerated and characterized. Myeloid derived suppressor cells (MDSCs) will be enumerated by staining for CD14, CD11b, and HLA-DR expression. Further cytokines produced by T cells, will be analyzed by intracellular cytokine staining and multiplex assay. In certain cases, tetramer staining for populations of antigen-specific T cell populations may be performed.

8.6.5. Pharmacodynamic Assessment

Approximate quantitation of infused study drug bound to PD-1 receptors on the surface of T cells in the peripheral blood and within the resected tumor and lymph node specimens will be performed in Dr. Topalian's laboratory, according to published procedures[87]. This will provide information about tissue penetration of the study drug(s), which has not been obtainable in prior studies.

8.6.6. Genomic and Mutation-associated neoantigen (MANA) Analyses

Genomic analyses will be performed by whole-exome sequencing in pre and post-treatment tumor tissue and matched normal tissue, to assess dynamics in the mutational landscape using described methods[88, 89]. A multi-dimensional neoantigen prediction algorithm that incorporates MHC binding affinity, epitope processing, self-similarity and gene expression to generate neoantigen candidates tailored to each individual's HLA haplotype will be used as previously described[89]. The TCR repertoire will be assessed serially by means of TCR sequencing as previously described[89].

8.6.7. Immune Functional Assays

To assess functional recognition of MANAs, we will complete immune functional assays on PBMC and TIL where applicable, using a new assay called MANAFEST (MANA Functional Expansion of Specific T-cells), developed at the Bloomberg-Kimmel Institute. This assay assesses expansion of T-cell clones based on deep sequencing of TCRbeta CDR3 regions. MANAFEST antigens will be validated by multiplex tetramer staining.

8.6.8. Liquid Biopsy Analysis

ctDNA dynamics will be assessed by targeted sequencing of serial plasma samples collected at the time intervals specified in the study timeline. For these analyses, we will use a custom capture and

sequencing approach called targeted error correction sequencing (TEC-Seq) that allows for sensitive and specific detection of low abundance sequence alterations using next generation sequencing[90].

8.6.9. Serum Analysis

Serum will be assessed for immunological factors which may include antibodies, cytokines and chemokines, as well as potentially for circulating tumor DNA.

8.6.10. Leftover Samples

Any leftover study blood and tissue samples will be stored in the Immunology Laboratories at Johns Hopkins for future research studies. These samples may be released for use in future studies after approval by the principal investigator and other regulatory bodies, as appropriate. Subjects will be asked to consent to the future use of samples in the consent document.

8.6.11. Additional Information

The study coordinator will keep a log (separate logs will be kept for the blood and tissue samples) that includes the study number, a specimen serial number, the patient's name, time point in therapy, and the date and time that the sample was drawn. The sample will be labeled with a serial number only. The laboratory technician will keep a log with the specimen number, conditions, processing and storage information. The laboratory investigators will be blinded to the subject identifiers and clinical data while generating the research data; additionally, the reported results will not disclose any unique patient identifiers.

Note: The correlative sample collection schedules outlined above are based on an ideal subject. The sample schedule should be followed as closely as is realistically possible; however, the schedule may be modified due to problems such as scheduling delays or conflicts (e.g., clinic closure, poor weather conditions, vacations, etc.)

8.6.12. PD-L1 Testing

To ensure comparability of data across all studies of durvalumab and/or tremelimumab 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. Testing should be restricted to the Ventana SP263 assay and should be performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT).

The Ventana SP263 assay is fully analytically validated test characterized through to the completion of reader precision studies in the non-small cell lung cancer (NSCLC) and squamous cell carcinoma of the head & neck (SCCHN). For these tumors, the Ventana SP263 assay has a fully 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 (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.

Sample collection for PD-L1 testing

- The preferred tumor sample for the determination of a patient's PD-L1 status is the one taken following the completion of the most recent prior line of therapy. Samples taken at this time reflect the current PD-L1 status of the tumor and considered clinically most relevant.
- In AstraZeneca studies, the preferred sample for PD-L1 testing was less than or equal to 3 months old. In cases where a sample a less than 3 months old was not available, patients were asked to undergo a new biopsy if considered clinically appropriate by their treating physician.
- 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.
- When the collection of a new sample is not clinically appropriate, archival samples may be utilized provided the specimen it is not older than 3 years of age. When archival samples are used to assess PD-L1 status, the age of the sample/date of collection should be captured.
- Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for PD-L1 analysis.

Sample data collection for PD-L1 testing

The following fields of data should be collected from the site/institution collecting and if, indicated shipping of the samples:

- Patient identifier (ecode or unique identifier)
- Specimen identifier (written on the specimen)
- Site identifier
- Specimen collection date
- Type of specimen submitted
- Quantity of specimen
- Date of sectioning
- Archival or new biopsy/tissue
- Tumor type

- Primary tumor location
- Metastatic tumor location (if applicable)
- Fixative

The following fields of data should be collected from PD-L1 testing laboratory:

- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells
- Total percent positivity of PD-L1 in infiltrating immune cells

The Ventana SP263 assay to measure PD-L1 in tumors is experimental. As with all tests, there is a chance of false positive (the test shows high PD-L1 when it is not there) or false negative (the test does not show PD-L1 when it is there) results may occur.

Sample processing and if indicated submission process for PD-L1 testing

Preparing Stored samples for testing

Where samples already exist, they should be retrieved from the Bio-Bank storage location. These blocks should undergo quality review, prior to evaluation or shipment. Where it is not possible or indicated to ship the block to a testing laboratory, unstained slides should be prepared from the paraffin-embedded tumor sample block (described below) prior to evaluation or shipment.

Preparing newly acquired samples for PD-L1 testing

If patients are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample should be used to determine PD-L1 status, from one core biopsy that is inidividually processed into am FFPE block.

It is recommended that core needle tumor biopsies are collected using an 18 gauge or larger needle and the process should be image-guided. Excisional or incisional samples are also adequate. If this is not per the institutions normal practice and a smaller gauge needle is used then the number of cores collected should be increased to allow sufficient material for successful PD-L1 testing (>100 tumor cells) and embedded in the same block. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for PD-L1 testing

Previously frozen tissue is not acceptable for processing to FFPE for PD-L1 testing. To fix newly acquired tissue, place immediately (within 30 min of excision) into an adequate volume of 10% v/v

neutral buffered formalin (NBF). Core biopsies and resection specimens should remain in fixative for 24 and 48 hours respectively at room temperature.

It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10 volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

Embedding in paraffin for PD-L1 testing

An overnight processing schedule into paraffin wax is recommended

Storage of tumor blocks for PD-L1 testing

FFPE blocks and 20 ml whole blood for serum isolation should be stored at -20 degrees Celsius and protected from light until shipment by courier at, as detailed at timepoints In the study schema when tissue is obtained.

Quality control of samples to be used for PD-L1 testing

Tissue should be assessed by the site pathologist prior to PD-L1 testing.

Each sample should be reviewed for:

- Adequate fixation
- Good preservation of morphology
- Presence of tumor tissue
- Histopathology consistent with indication
- Greater than 100 tumor cells are required to determine PD-L1 status – tumor cell content must be reviewed prior to testing in order for PD-L1 obtain a valid result.

If indicated, shipping samples to a PD-L1 testing laboratory

When submitting sample to for PD-L1 testing the recommendation is to ship the block in order for sectioning to occur at the laboratory. Blocks should be shipped - containing enough material to be provided to allow a minimum of 5, and preferably 10, sections to be cut (each 4 microns thick) to be used for PD-L1 testing.

Sectioning instructions

- Where it is not possible or indicated to ship the block to laboratory for PD-L1 testing, unstained slides should be prepared from the paraffin-embedded tumor sample block as described below:
- A minimum of 4 x 5 micron (µm) thick, unstained sections should be provided for PD-L1 testing
- A new disposable microtome blade must be used for each block to prevent contamination between patient samples

- Apply one section per slide to positively-charged Superfrost glass slides
- The sections should be dried overnight between room temperature and 37°C. Do not dry sections at temperatures above 37°C.

Sections should be stored at -20 degrees Celsius and protected from light until use or shipment to testing lab by courier at ambient temperature. It is recommended that slides are cut freshly prior to PD-L1 testing and they are used within 90 days of being cut to obtain PD-L1 status.

8.6.13. Estimate of volume of blood to be collected

The total volume of blood that will be drawn from each subject in this study is as follows:

TABLE 9. VOLUME OF BLOOD TO BE DRAWN FROM EACH SUBJECT

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	**Clinical chemistry**	5ml	7	35ml
	Hematology	5ml	7	35ml
Biomarker		120ml	3	360ml
Biomarker		80ml	3	240ml
Total				670mLs

8.7. **Withdrawal of informed Consent for Donated Biological Samples**

As collection of required biological samples is an integral part of the study, then the subject is withdrawn from further study participation. If a subject withdraws consent for the use of leftover samples, the samples will be disposed of/destroyed, and the action documented. The Principal Investigator will ensure:

- Biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- The laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- The subject is informed about the sample disposal.

9. Assessment of Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

9.1. Safety Parameters

9.1.1. Definition of Adverse Events (AE)

An adverse event is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

9.1.2. Definition of Serious Adverse Event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the subject
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above:
- Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

Adverse Events (AEs) for malignant tumours reported during a study should generally be assessed as Serious AEs. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a Non-Serious

AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy. The above instruction applies only when the malignant tumour event in question is a new malignant tumour (i.e., it is not the tumour for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

9.1.3. Definition of Adverse Events 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 and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for durvalumab ± tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

<< The following should be added if applicable. In the event of imAE or suspected imAE, the AstraZeneca study team may request relevant clinical information (including images) for those subjects who demonstrate the event, and may request the independent review by external experts based on the acquired clinical information.>>

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab ± tremelimumab 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 (e.g. Guillain-Barré, and myasthenia gravis)
- Intestinal Perforation

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to:

- Pericarditis
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin
- Hematological events
- Rheumatological events
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

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

Further information on these risks (e.g., 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.

9.1.4. Thoracic Radiation Adverse Events of Special Interest

Esophagitis

Inflammation of the esophagus can happen as a recognized adverse event with thoracic radiation. Diagnostic workup and management is outlined in Appendix 8.

Radiation-related Toxicities

Adverse events associated with therapeutic radiation will be graded weekly and coded using common terminology criteria for adverse events CTCAE 4.03 definitions. Treatment management will be determined by grade of toxicity using the treatment modifications listed in Appendix 7.

9.1.5. Immune-related Adverse Events

Based on the mechanism of action of durvalumab and tremelimumab leading to T-cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies[12, 24, 28]. These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include irAEs could potentially occur at higher frequencies than with either durvalumab or tremelimumab monotherapy. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided in Table 1, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab[91]. These guidelines recommend the following:

- Patients should be evaluated to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
- More potent immunosuppressives should be considered for events not responding to systemic steroids (e.g., infliximab or mycophenolate).
- If the Investigator has any questions in regards to an AE being an irAE, the Investigator should immediately contact the Study Physician.

9.2. Assessment of Safety Parameters

9.2.1. Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of

AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.0. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below:

Grade 1 (mild): An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Grade 2 (moderate): An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3 (severe): An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.

Grade 4 (life threatening): An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc.)

Grade 5 (fatal): Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria above. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

9.2.2. Assessment of Relationship

The relationship of all adverse events and serious adverse events to study medication will be assessed

by an investigator and assigned as follows:

Definitely: An adverse event which has a timely relationship to the administration of the investigational drug/agent, follows a known pattern of response, for which no alternative cause is present.

Probably: An adverse event, which has a timely relationship to the administration of the investigational drug/agent, follows a known pattern of response, but for which a potential alternative cause may be present.

Possibly: An adverse event, which has a timely relationship to the administration of the investigational

drug/agent, follows no known pattern of response, but a potential alternative cause does not exist.

Unlikely: An adverse event which does not have a timely relationship to the administration of the investigational drug/agent, follows no known pattern of response, does not reappear or worsen after re administration of the investigational drug/agent (if applicable), and for which there is evidence that it is related to a cause other than the investigational drug/agent.

Unrelated: An adverse event, for which there is evidence that it is definitely related to a cause other than the investigational drug/agent. In general, there is no timely relationship to the administration of the investigational drug/agent, or if there is a timely relationship, the event does not follow a known pattern of response, and there is an alternative cause.

9.3. **Recording of Adverse Events and Serious Adverse Events**

Adverse events will be recorded on written or electronic case report forms (CRFs) or serious adverse event forms (SAE) and the data stored in Johns Hopkins Clinical Research Database (CRMS) using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety.

The following variables will be collected for each AE:

- AE (verbatim)
- Date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against durvalumab +/- tremelimumab (as outlined in section 9.3.2)
- Action taken with regard to durvalumab +/- tremelimumab
- Outcome

In addition, the following variables will be collected for SAEs as applicable:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Date of hospitalization

- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Study Drug

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

9.3.1. Study Recording Period and Follow-up for Adverse Events and Serious Adverse Events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period. During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

9.3.2. Causality Collection

The Investigator will assess causal relationship between the IPs and each AE and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?” For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as “yes.” A guide to the interpretation of the causality question is found in Appendix 1.

9.3.3. Relationship to Protocol Procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment–emergent (ie, SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.
- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

9.3.4. Adverse Events based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

9.3.5. Adverse Events based on Examinations and Tests

The results from protocol-mandated laboratory tests and vital signs measurements will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IPs.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting Investigator should use the clinical rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

9.3.6. Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix 1 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

9.3.7. Disease Progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

9.3.8. New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

9.3.9. Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be 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 to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

AstraZeneca/MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

9.3.10. Reporting of Serious Adverse Events

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 the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab + tremelimumab 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.

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE or pregnancy occurs in the course of the study, it will be reported promptly to the Coordinating Center (email: crocc@jhmi.edu and CROCC Lead Study Coordinator) within 24 hours of recognition of the event. If this falls on a weekend or holiday, an email notification is acceptable but must be followed by an SAE reporting form on the next business day.

Coordinating Center

The CRO Coordinating Center is the central location for the collection and maintenance of documentation of adverse events and is responsible for submitting adverse event reports to the Protocol Chair promptly. The CROCC will maintain documentation of all adverse event reports for each participating site. Adverse event reports submitted to the CROCC must be signed and dated by the participating site's Principal Investigator. The CROCC will provide appropriate forms to be used by all participating sites for reporting adverse events. Information to be provided must include:

- Subject ID number, and initials
- Date of the event
- Description of the event
- Description of site's response to the event
- Assessment of the subject's condition
- Subject's status on the study (on study, off study, etc.)
- Attribution of event to study drug

Participating Sites

Participating sites are responsible for reporting adverse events to their IRB according to its specific requirements and to the CRO Coordinating Center as follows:

Fatal Events whether anticipated or unanticipated, and whether or not related to the study must be reported to the CRO Coordinating Center within 24 hours of the participating site Principal Investigator's learning of the event.

Serious and Unanticipated Adverse Events as defined above must be reported to the CRO Coordinating Center within 24 hours of the participating site Principal Investigator's learning of the event.

Other Serious Adverse Events which may result in a change to the protocol, informed consent, or risk to subjects as specified in the protocol must be reported within three (3) working days of the participating site Principal Investigator's learning of the event.

Adverse Events which result in no change to protocol, informed consent, or risk to subjects must be reported to the CRO Coordinating Center on a monthly basis.

Adverse event reports are to be emailed (use fax as a back-up) to the CRO Coordinating Center at SKCCC. Follow-up reports are faxed, mailed, or sent electronically to the CROCC as necessary.

The investigator must also report follow-up information about SAEs within the same time frames.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided within the same time frames described above.

All SAEs must be collected whether or not they are considered causally related to the investigational product. Investigators and other site personnel are responsible for reporting all casually related SAEs to their IRB and the Protocol Chair.

The principal investigator will notify the appropriate regulatory agencies of any serious adverse event due to any cause during the course of this investigation. These include the Johns Hopkins Cancer Center Data and Safety Monitoring Committee, and the Johns Hopkins Medical Institutional Review Board (JHM-IRB) of The Johns Hopkins Medical Institutions. The required reporting time period is 3 days for fatal events, and 10 days for all other events.

For studies conducted under an Investigator IND, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and **no later than 7 days** (for a death or life-threatening event) or **15 days** (for all other SAEs) **after the investigator's or institution's initial receipt of the information.** BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs should be reported via a MedWatch Form 3500A or similar form. It MUST include the institutional **AND** AZ reference number.

MedWatch SAE forms and coversheet should be sent to the FDA at:
MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

The CRO Coordinating Center shall fax or email SAEs to AstraZeneca at:

AstraZeneca
SAE email address: AEMailboxClinicalTrialTCS@astrazeneca.com

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

9.3.11. Reporting of Deaths to AstraZeneca

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab + tremelimumab safety follow-up period must be reported to AstraZeneca as follows:

- Death that is clearly the result of disease progression should be documented but should not be 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 to AstraZeneca as a SAE within **24 hours** (see Section 9.3.2 **Error! Reference source not found.**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 occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

9.3.12. Other Events Requiring Reporting

9.3.12.1. Overdose

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

Any overdose of a study subject with durvalumab +/- tremelimumab, 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 (see Section 10.3.2 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 9.3). 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 9.3.2). There is currently no specific treatment in the event of an overdose of durvalumab+/- tremelimumab.

The investigator will use clinical judgment to treat any overdose.

9.3.12.2. Hepatic Function Abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic

function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 9.3.2 for contact information), unless a definitive underlying diagnosis for the abnormality (eg, 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) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN 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 subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject 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 the sponsor and AstraZeneca/MedImmune.

9.3.12.3. Pregnancy

9.3.12.3.1. Maternal Exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study. If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, ie, immediately, but no later than 24 hours of when he or she becomes aware of it. The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

9.3.12.3.2. Paternal Exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab +/- tremelimumab or 90 days after the last dose of durvalumab +/- tremelimumab, whichever is the longer time period.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab +/- tremelimumab or 90 days after the last dose of durvalumab +/- tremelimumab, whichever is the longer time period should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

10. Disease Evaluation and Methods

10.1. Safety Variables

10.1.1. Safety

Safety data will be collected as in section 9.0. Safety will be monitored continuously by the study investigators for every subject through day 90 following the last dose of study therapy or until 30 days post-surgery, whichever happens first. Safety data will be collected and stored in CRMS. A detailed statistical analysis plan for safety including stopping rules is contained in section 11 of this protocol.

10.1.2. Feasibility

The feasibility of neoadjuvant immunoradiation will be based on subjects proceeding to surgery without extended treatment-related delays. A treatment related delay will be considered "extended" if it is greater than 8 weeks (56 days) following the initially planned surgery date. For feasibility, a drug-related toxicity of any grade, that in the judgment of the investigator or surgeon could adversely impact perioperative morbidity or mortality, should delay the planned operative date.

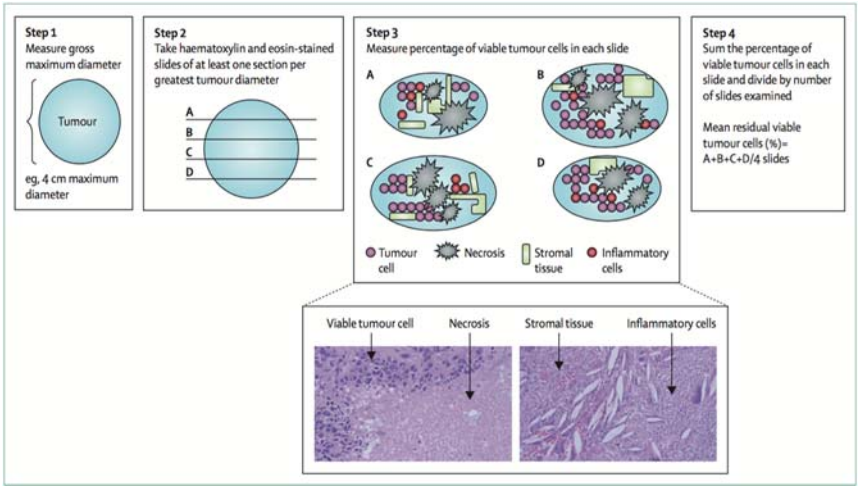
10.1.3. Surgical Morbidity and Mortality

Adverse events of any grade that occur in the postoperative period (day of surgery until 30 days post surgery), will be collected. These data will be obtained by weekly review of the subject's medical record by study investigators. The attributions of these AEs will also be recorded, as per section 9.3. Deaths that occur in the postoperative period will be recorded, and the attribution of any subject death will be recorded.

10.2. **Efficacy Variables**

10.2.1. Pathologic Response

Schematic of Pathologic Response Assessment



In patients who proceed to surgical resection, pathologic response in resection specimens will be evaluated by two thoracic pathologists, and stratified into major pathologic response (MPR: 90% reduction in tumor cells), partial response (PR: 10-90% reduction) and no response (NR:0-10% reduction), as per published methods[61, 62] (Figure 3). The rate of MPR, PR and NR will be recorded. Pathologic responses will be correlated with clinical outcomes, including RFS. In the neoadjuvant study of single agent anti-PD-1 in patients with early stage (stage IB-IIIA (N1) NSCLC discussed earlier by Forde et al, approximately ~50% of patients exhibited major pathologic responses in resection specimens (MPR: >90% reduction in tumor cells). We anticipate that the same number of patients or greater will exhibit MPRs, to the combination of anti-PD-L1+/-CTLA-4 together with thoracic radiation, in this study.

10.2.2. Radiologic Response

Radiologic response will be evaluated by RECIST 1.1 and immune-related RECIST criteria. Radiologic responses will be correlated with pathologic responses and clinical outcomes, including RFS. Radiologic responses to combined chemoradiation prior to surgery are seen in approximately 60-65% of patients. We anticipate that neoadjuvant immunoradiation will yield similar response rates, although this is unknown.

10.2.3. Immune-related RECIST

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following[17, 92]:

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after PD by conventional criteria
- The appearance of new lesions may not represent PD with immunotherapy
- SD while on immunotherapy may be durable and represent clinical benefit.

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anti-cancer

medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anti-cancer compounds, the study may wish to implement the following in addition to standard RECIST 1.1 criteria:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration.
- **Therefore, in patients with PD by RECIST 1.1 on CT scan prior to surgery, a second CT can be performed 4 weeks later to confirm PD.**

Modification of RECIST as described may provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anti-cancer therapy other than durvalumab +/- tremelimumab or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

10.2.4. Recurrence-free Survival

Recurrence-free survival (RFS) will be defined as the time from commencement of therapy until the development of local or distant recurrent disease. The development of local or distant recurrent disease will be detected radiologically by CT scan performed as per the Schedule of Assessments (Figure 1), by RECIST 1.1 criteria. RFS will be correlated with pathologic response and radiologic response to study therapy. Progression-free survival for patient treated with neoadjuvant chemoradiation prior to surgery in patients with stage III NSCLC was a median of 12.8 months as reported by Albain and colleagues. We anticipate to see similar or potentially improved results in this study. Subject deaths without recurrence will be censored.

10.2.5. Overall Survival

OS will be defined as the time from commencement of therapy until death from any cause. Patients will be followed with a telephone call or clinic visit every 3 months for years 1-3 for survival status. The cause of death will be documented if known and relationship to study drug as per section 9.3.2. OS for patient treated with neoadjuvant chemoradiation prior to surgery in patients with stage III NSCLC was a median of 23.6 months as reported by Albain and colleagues. We anticipate to see similar or potentially improved results in this study.

11. Study Drug Information

11.1. Durvalumab and Tremelimumab

12. Statistical Methods and Sample Size Determination

12.1. Study Design

This is an open-label pilot study aimed at establishing the safety and feasibility of neoadjuvant immunoradiation prior to surgical resection of stage III NSCLC, that is deemed surgically resectable by a thoracic surgeon with lobectomy. Thoracic RT will be given at standard doses and fractionation to a total dose of 45Gy in 25 fractions, as per published phase III data[49], and using standard methods. In cohort 1, the safety and feasibility of durvalumab with concurrent thoracic RT, will be assessed. In this cohort, durvalumab will be administered at the standard dose of 1500mg IV every 4 weeks for 3 doses, as per ongoing phase III studies. If preliminary safety is established in cohort 1, the study will expand to include cohort 2, which will test the safety and feasibility of durvalumab plus tremelimumab with concurrent thoracic RT. In this cohort, durvalumab will be administered at the standard dose of 1500mg IV every 4 weeks for 3 doses, and tremelimumab will be administered at the standard dose of 75mg every 4 weeks for 3 doses. The primary endpoints of this study are safety and feasibility in cohort 1and cohort 2 (if applicable). Patients will be observed for perioperative grade 3-4 adverse events through day 90 following the last dose of immunotherapy or until 30 days post-surgery, whichever is longer. Safety and feasibility will be monitored continuously throughout the study through weekly meetings with investigators, as well as the planned Bayesian monitoring rules (see below). A set of markers of immune reactivity measured in lung tumor resection specimens, draining lymph nodes, and peripheral blood will be evaluated. Feasibility will be evaluated as the proportion of evaluable patients who successfully complete preoperative treatment and proceed to surgery without any extended treatment related delays. Extended treatment-related delay will be defined as >8 weeks from the day of completion of thoracic RT. For each cohort, we aim to accrue 16 evaluable patients, defined as those who receive at least one dose of durvalumab or durvalumab/tremelimumab administration and have complete toxicity follow-up. We plan to accrue 20 patients to ensure 16 evaluable patients are available for analysis. If less than 16 evaluable patients are available after accruing 20 patients, we will amend the protocol to ensure at least 16 evaluable patients are available for analysis.

12.2. Study Endpoints Definition

12.2.1. Primary Endpoints

Safety of durvalumab monothererapy (cohort 1) +/- durvalumab+tremelimumab (cohort 2) administered preoperatively together with thoracic radiation in stage III NSCLC.

Safety will be measured by the frequency of any of the following events:

• Drug-related adverse events occurring up to 100 days after the last dose of immunotherapy or 30 days after surgery (whichever is longer).

• Serious adverse events occurring up to 100 days after the last dose of immunotherapy or 30 days after surgery (whichever is longer).

• Clinical laboratory test by worst toxicity grade (as assessed at the time intervals outlined in the Schedule of Assessments, Figure 1.)

Feasibility of preoperative administration of durvalumab monothererapy (cohort 1) +/- durvalumab+tremelimumab (cohort 2) concurrently with thoracic radiation in stage III NSCLC

Feasibility will be evaluated through the proportion of evaluable patients who successfully complete preoperative treatment and proceed to surgery without any extended treatment-related delays defined as >8 weeks from the last day of thoracic radiation.

12.2.2. Safety Endpoint

Safety stopping rule:

To minimize the risks of adding durvalumab monotherapy (cohort 1) or durvalumab+tremelimumab (cohort 2) to thoracic radiation prior to surgery, safety will be monitored by a Bayesian stopping rule for the rate of adverse events of interest (Section 9.2). Previous experience with single and multiple dose schedules of durvalumab and durvalumab+tremelimumab demonstrated that the incidence of grade 3-4 toxicities in advanced NSCLC and other solid tumors is low. The primary DLTs of concern for safety monitoring will be grade 3-4 toxicities of the types listed in section 6.3. These include liver, GI, renal, pneumonitis and any other grade 3-4 toxicity that in the opinion of the investigator significantly interfered with the subjects' optimal perioperative management. They will be monitored continuously for sixteen patients through day 90 following the last dose of immunotherapy (or day 30 post-surgery, whichever is longer).

AEs will be monitored continuously for all patients. A Bayesian safety monitoring rule will be used to evaluate the rate of the AE of interest continuously, from the 3rd evaluable patient, and will suspend accrual at any point if there is sufficient evidence of excessive toxicity. Specifically, the Bayesian toxicity monitoring rule will suspend accrual anytime if the posterior probability of AE of interest being larger than 25%, is 70% or higher. We assume a priori that the experimental regimens has an average risk around 5% and there is about 7% chance that the risk will be 25% or higher. This corresponds to a Beta (0.05,0.95) prior distribution. Table 10.1 summarizes the continuous stopping rule for the 16 evaluable patients for each regimen. For example, if 2 patients out of the first 3 or 4 evaluable patients experience adverse events of interest, we will stop accrual. Furthermore, to cautiously assess the toxicity profiles of experimental regimens in the event that accrual is relatively "fast" comparing to the safety assessment duration, the accruals of each cohort will be suspended when 6 eligible patients have been accrued to allow the continuous safety evaluations to be done among the first 6 evaluable patients before further accruals. The accrual would resume only if the following Bayesian stopping rule being used is not met. At any time if the stopping criterion is met, accrual to the trial will be temporarily suspended and the

principle investigators and study team will review the toxicity data and recommend either modification or termination of the trial.

TABLE 10.1 STOPPING RULE FOR SAFETY

# patients with DLT	2	3	4	6
Out of total # patients treated	3-4	5-7	8-11	16

Table 10.2 summarizes the operating characteristics based on 5,000 simulations with 16 evaluable patients in terms of how frequent the study would stop based on the stopping rule under different hypothetical toxicity rates, as well as the average sample sizes.

TABLE 10.2 OPERATING CHARACTERISTICS OF THE STOPPING RULE FOR SAFETY

Underlying risk	0.15	0.20	0.25	0.30	0.35
% of time study stops	15.8%	29.3%	43.1%	60%	72.8%
Expected sample size	14.3	13	11.7	10	8.6

Early Stopping Plan for Treatment-related Grade 5 AE

We will also evaluate the rate of treatment-related grade 5 AE if it's convincingly greater than 10%. Specifically, the Bayesian toxicity monitoring rule that suspends the accrual anytime if the posterior probability of treatment-related grade 5 AE being larger than 10% is 70% or higher. We assume a priori that the experimental regimens has an average risk 5% and there is about 14% chance that the risk will be 10% or higher. This corresponds to a Beta (0.1,1.9) prior distribution. Table 10.3 summarizes the continuous stopping rule for the 16 evaluable patients for each regimen.

TABLE 10.3 EARLY STOPPING RULE FOR GRADE 5 ADVERSE EVENT

# patients with grade 5 AE	1	2	3
Out of total # evaluable patients	1-3	4-10	11-16

Table 10.4 summarizes the operating characteristics based on 5,000 simulations with 16 evaluable patients in terms of how frequent the study would stop based on the stopping rule under different hypothetical grade 5 AE rates, as well as the average sample sizes.

TABLE 10.4 OPERATING CHARACTERISTICS OF THE STOPPING RULE FOR GRADE 5 AE

Underlying risk	0.04	0.08	0.10	0.12	0.16	0.20
% of time study stops	6.4%	21.5%	32.2%	38.8%	57.5%	72.4%
Expected sample size	15.5	14.4	13.6	13.1	11.6	10.4

12.2.3. Feasibility Endpoint

Stopping guideline for feasibility

The feasibility of neoadjuvant durvalumab monotherapy (cohort 1) or durvalumab+tremelimumab (cohort 2) together with thoracic radiation prior to surgery will be based on the proportion of evaluable patients proceeding to surgery without extended treatment-related delays. A treatment-related delay will be considered "extended" if it is greater than 8 weeks following completion of thoracic radiation. For feasibility, drug-related toxicity of any grade, that in the judgment of the investigator or surgeon could adversely impact perioperative morbidity or mortality, should delay the planned operative date.

We would consider the experimental regimen is "infeasible" if the probability of not proceeding to surgery as planned is convincingly (more than 70%) more than .25, i.e., the probability of proceeding to surgery as planned is convincingly less than 75%. We assume about 10% of patients will have their surgery delayed and there is about 14% chance that the risk will be 25% or more. This corresponds to a Beta (0.1,0.9) prior distribution. Table 10.5 summarizes the continuous stopping rule for the 16 evaluable patients for each regimen. The feasibility stopping rule calls for the study to be paused for a review if the number of patients successfully proceeding to surgery is too low, starting from the 6th evaluable patient.

Table 10.5 Stopping Rule for Feasibility

# patients with delay in planned surgery	3	4	5	6
Out of total # evaluable patients	6-7	8-10	11-14	15-16

Table 10.6 summarizes the operating characteristics based on 5,000 simulations with 16 evaluable patients in terms of how frequent the study would stop based on the stopping rule under different hypothetical feasibility rates, as well as the average sample sizes.

Table 10.6 Operating characteristics of the stopping rule for feasibility

Underlying feasibility	0.65	0.7	0.75	0.8
% of time study stops	37.9%	13.9%	6.4%	2.1%

Expected sample size	13.8	15.2	15.6	15.9

If the feasibility stopping boundary is reached, we will re-evaluate the clinical advantages of the treatment, pathological tumor response and prolonged RFS, against the risks and consider re-designing the regimen to allow more time between the last dose of immunotherapy and surgery to better manage potential side effects.

12.3. **Statistical Analysis Plan**

12.3.1. Analysis Plan for Primary Endpoints

The proportion of adverse events of interest and feasibility will be reported along with the associated exact binomial 95% confidence intervals. Adverse events for each regimen will also be tabulated by type, grade, and attribution of adverse event.

12.3.2. Analysis Plan for Secondary Endpoints

Pathologic response will be stratified as showing MPR (>90% reduction in tumor cells), PR (10-90%) or NR (0-10%).The proportion of patient's whose tumor samples achieve MPR, PR and NR will be tabulated. The relationship between pathologic response in post-treatment resection specimens and clinical outcomes such as RFS, OS and surgical morbidity/mortality will be assessed through log-rank test and Cox proportional hazards (PH) model. Radiologic response will be evaluated by RECIST 1.1 and immune-related RECIST criteria at time points specified in the Schedule of Assessments (Figure 1). The relationship between radiologic response in post immunoradiation CT scans and clinical outcomes including RFS, OS and surgical morbidity/mortality will be assessed using log-rank and Cox PH model. RFS will be defined as time from commencement of study therapy until the date of radiologic evidence of local or distant recurrent NSCLC. OS) will be defined as the time from commencement of protocol treatment until death due to any cause. RFS and OS will be calculated using the Kaplan-Meier method, and will be analyzed as time-to-event data. All adverse events that occur from the time of surgery until 30 days post-surgery or from the last dose of immunotherapy until 100 days, will be similarly summarized by type and grade. Any deaths that occur in this time period will be recorded. Attributions to the development of AEs or death in this time period will be recorded as either definitely related, possibly related, probably related or unrelated to study therapy.

12.4. **Exploratory Endpoints**

12.4.1. **Markers of Immune Reactivity to Immunoradiation**

Markers of immune reactivity will be prospectively measured in lung tumor resection specimens, draining lymph nodes (DLNs) and serial peripheral blood samples from 16 stage III NSCLC patients who receive 3 doses of preoperative immunotherapy concurrently with thoracic radiation, prior to planned surgery. All samples will be analyzed using whole exome sequencing, multicolor flow cytometry, immunohistochemistry +/- multicolor IF for candidate surrogate markers of immune response to

immunoradiation, including frequency of coordinate expression of co-regulatory molecules by peripheral blood lymphocytes, tumor infiltrating lymphocytes, DLN cells and tumor cells. PD-L1, CD3, CD4, CD8, granzyme B, CD20, and CD56 staining will be performed on biopsy and resection specimen and frequency of expression tabulated. Additional molecules may be assessed as well.

12.4.2. **Analysis of Exploratory Endpoints**

These exploratory analyses will be descriptive/graphical in nature, and are designed to generate new hypotheses to be tested in future clinical studies. When parameters of immune response are measured, continuous variables will be summarized with means and standard deviations. Dichotomous and categorical variables will be summarized using proportions with exact 95% confidence intervals and counts, respectively. These summaries will be computed for each treated patient at multiple time points before and after immunotherapy administration as indicated in the study schema. Plots will be used to show the changes in immune response over time both for each individual. For each patient, comparisons in the pre and post-durvalumab (cohort 1) or durvalumab+tremelimumab (cohort 2) responses will be compared using paired t-tests (or Wilcoxon signed rank tests if appropriate) for continuous variables and McNemar's test for dichotomous or categorical variables. Associations between immune responses will be explored graphically (e.g. scatterplots, boxplots) and numerically (e.g. correlations, $\chi 2$ tests). Similar comparisons will be performed between immunoradiation-treated patients, and control patients with stage III resectable NSCLC who do not receive immunoradiation, but are enrolled on a companion tissue collection protocol

12.5. **Patient Accrual**

The accrual rate for this study is expected to be 1-2 patients per month. It is estimated that JHH sees between 25-35 patients with stage III resectable NSCLC per year that would be suitable for enrollment onto this study. For each cohort, it is projected to complete full accrual within 2 years if the experimental regimen is tolerable and feasible.

13. Ethical and Regulatory Requirements

13.1. **Ethical conduct of the study**

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection.

13.2. **Ethics and Regulatory Review**

Institutional Review Board Information regarding study conduct and progress will be reported to the Johns Hopkins Institutional Review Board (IRB).

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that the correct version of the protocol is used.
- Taking responsibility for the overall conduct of the study and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE).
- Reviewing data from all sites.

13.3. **Informed consent**

An investigator will explain to each subject the nature of the study, its purpose, procedures involved, expected duration, potential risks and benefits. Each subject will be informed that participation in the study is voluntary and that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment. This informed consent will be given by means of a standard written statement and will be submitted for IRB approval prior to use. No patient will enter the study before her informed consent has been obtained. In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.4. **Changes to the protocol and informed consent form**

Any changes to the protocol or informed consent form will be made in the form of an amendment and must be approved by the IRB before implementation. The Principal Investigator is responsible for the coordination and development of all protocol amendments.

14. Study Management

14.1. **Training of study site personnel**

Study staff at the Sidney Kimmel Comprehensive Cancer Center Upper Aerodigestive Division will be trained in the details of this protocol and accompanying protocol materials prior to commencement of this study. Standard instructional materials will be supplied to study staff at a site initiation visit. Details of biospecimen acquisition, workflow and processing will be detailed in the study lab manual. Details of the study agents will be available in the study pharmacy manual.

14.2. **Monitoring of the study**

Evaluation of safety will be monitored continuously through day 90 following the last dose of study therapy or 30 days post surgery, whoever comes first. The evaluations will be conducted under the direction of Dr. Julie Brahmer, Dr. Patrick Forde, and the study statistician; additional information may be found in the statistical section.

14.3. **Study timetable and end of study**

We conservatively estimate accrual of 1-2 patients every month. Accounting for an Approximate 10% drop-out rate, we estimate a target accrual of 40 patients in 20-24 months (cohorts 1 and 2). Additional study sites have been identified will contribute to accrual, if needed.

15. Data Management

Eligible patients will be entered on study centrally at the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University by the CROCC Lead Study Coordinator. All sites should email the CRO Coordinating Center at crocc@jhmi.edu as well as the Lead CROCC Study Coordinator. The Registration Form, and Eligibility Worksheet will be supplied to each participating site.

If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Coordinating Center should be notified of cancellations as soon as possible.

All sties must maintain the electronic case report forms in the Clinical Research Management System (CRMS). All data must be entered into the CRMS eCRFs within 2 weeks of the visit dates. For participating sites, de-identified source documents must be uploaded into CRMS.

At the time of registration:

- Registration Form
- Informed Consent Form (signed by the subject)
- Eligibility Checklist
- Source documents related to eligibility and randomization

Within 2 weeks after registration:

- Baseline study case report forms
- Pertinent source documents

Within 2 weeks after final dose of study medication:

- On study case report forms
- Pertinent source documents

The Study Coordinator at the participating site will then e-mail (crocc@jhmi.edu and the CROCC Lead Study Coordinator) to verify eligibility. To complete the registration process, the CRO Coordinating Center will:

- Assign a patient study number
- Register the patient on the treatment portion of the study
- Email the patient study number to the participating site
- Email the research nurse or data manager at the participating site

The investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study related documents. The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

The SKCCC Compliance Monitoring Program will provide external monitoring for JHU-affiliated sites in accordance with SKCCC DSMP (Version 6.0, 02/21/2019). The SMC Subcommittee will determine the level of patient safety risk and level/frequency of monitoring.

The PI is responsible for internally monitoring the study and establishing additional external data & safety monitoring oversight, as required. The PI will also monitor the progress of the trial, review safety reports, and confirm that the safety outcomes and response assessments favor continuation of the study.

Data monitoring of this protocol will occur on a quarterly or annual at minimum basis with the frequency dependent on the rate of subject accrual and the progress of the study. The protocol will be monitored internally (Johns Hopkins East Baltimore and Bayview Medical Center Campuses) at SKCCC by the Principal Investigator and externally by the SKCCC CRO QA in accordance with SKCCC guidelines. Trial monitoring and reporting will be done through the Safety Monitoring Committee (SMC) at SKCCC. The Johns Hopkins SKCCC CRO Coordinating Center will be responsible for data monitoring at AHN and any other participating sites.

Interim analysis of toxicity, outcome, and ongoing scientific investigations will be performed every 6 months by the Sidney Kimmel Comprehensive Cancer Center Data Safety Monitoring Board (SKCCC DSMB). The SKCCC DSMB will review aspects of this trial that are outlined in the responsibilities section of the Data and Safety Monitoring Board (DSMB) Guidance. If the committee decides that amendments should be made to this trial, recommendations will be made in writing to the Study Principal Investigator. The study team will submit modifications to the IRB within 60 days of receipt from the DSMB. The Associate Director of Clinical Research, will arbitrate any disagreements between the DSMB and the study Principal Investigator. These changes may include early termination of accrual if deemed appropriate.

15.1. **Meetings**

Teleconferences of all investigators, research nurses and other study staff involved in the study will take place, starting once both sites have enrolled a subject. The following study team members involved with the conduct of the trial will be included as appropriate: study coordinators, data managers, research nurses, sub-investigators, collaborators (if applicable), and statistician. During these meetings matters related to the following will be discussed: enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), validity and integrity of the data, toxicities, acquisition of serum samples and transfer to lab, and progress of data for objectives.

15.2. **Study governance and oversight**

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

15.3. **Multicenter Guidelines**

Protocol Chair

- The Protocol Chair is responsible for performing the following tasks:
- Coordinating, developing, submitting, and obtaining approval for the protocol
- as well as its subsequent amendments
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE)
- Reviewing data from all sites

Coordinating Center

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

Participating Sites

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center via CRMS eCRFs.
- Providing redacted source documentation.
- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.

16. Investigational Product and Other Treatments

16.1. Identity of investigational product(s)

TABLE 11. LIST OF INVESTIGATIONAL PRODUCTS FOR THIS STUDY

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	50 mg/mL solution for infusion after dilution	MedImmune
Tremelimumab	20 mg/mL solution for infusion after dilution	MedImmune

17. APPENDICES

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy 17 November 2020 Version (CTCAE v4.03)

General Considerations regarding Immune-Mediated Reactions

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 v4.03 (unless indicated otherwise). 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** of the start of the immune-mediated adverse event (imAE) • Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing	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 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. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – 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., myo-carditis, 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). – 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. 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
Grade 1 No dose modification **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. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy 17 November 2020 Version (CTCAE v4.03)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications		Toxicity Management
Grade 4	Permanently discontinue study drug/study regimen. Note: For asymptomatic amylase or lipase levels of >2.0×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. 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).	– when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* 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.

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 By mouth.

Pediatric Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** of the start of the immune-mediated event	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for steroid dosing (i.e., mg/kg/day) that are provided for adult patients should also be used for pediatric patients. – The recommendations for IVIG and plasmapheresis use provided for adult patients may be considered for pediatric patients

Pediatric Considerations regarding Immune-Mediated Reactions	
Dose Modifications	**Toxicity Management**
	– The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Other Immune Mediated Reactions		**Dose Modifications (Any Grade): *Note it is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines** **Dose Modifications (Grade 1):** No dose modifications **Dose Modifications (Grade 2):** Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. 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. Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper **Dose Modification (Grade 3):** Hold study drug/study regimen **Dose Modification (Grade 4):** Discontinue study drug/study regimen	**Any Grade** − Thorough evaluation to rule out any alternative etiology (e.g. disease progression, concomitant medications and infections) − Consultation with relevant specialist − Treat accordingly, as per institutional standard **Grade 1** − Monitor as clinically indicated Grade 2,3,4 − Treat accordingly as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)

Amylase/Lipase increased		**Dose Modifications (General Guidance):** None **Dose Modifications (Grade 1):** No dose modifications **Dose Modifications (Grade 2, 3 or 4):** In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	**For Any Grade:** – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g, abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
Acute Pancreatitis		**Dose Modifications (General Guidance):** None **Dose Modifications (Grade 1):** No dose modifications **Dose Modifications (Grade 2):** Hold study drug/study regimen dose until resolution to Grade ≤1. Consider resumption of study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase in consultation with relevant pancreatic specialist **Dose Modification (Grade 3 or 4):** Permanently discontinue study drug/study regimen	**For Any Grade:** – Consider gastroenterology referral **For Grade 1:** – IV hydration – Manage per amylase/lipase increased (asymptomatic) **For Grade 2,3 or 4:** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent – IV hydration
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and

		pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan. – Consider Pulmonary and Infectious Disease Consults.
Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious Disease consults.
Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider Chest CT with contrast and repeat in 3-4 weeks. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to

			infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a] – Consider Pulmonary and Infectious Disease consults. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Disease consults; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a]
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus).

		– **When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist consider checking lactoferrin; if positive treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: symptomatic; medical	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm

intervention indicated*) * "medical intervention" is not invasive		colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider. [a] **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated)	– **Grade 3** -Hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper. Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days. -Permanently discontinue discontinue study drug for 1) Grade 3 colitis in	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 2 days continue steroids and promptly add further immunosuppressives (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without delay. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of

	(Grade 3 Perforation: severe symptoms, elective* operative intervention indicated; Grade 4 Perforation: life-threatening consequences, urgent intervention indicated) *This guidance anticipates that Grade 3 operative interventions of perforations are usually not elective	patients treated with CTLA-4 inhibitors or 2) Any grade large intestine perforation/Intestinal perforation in any patient treated with ICI. **Grade 4** Permanently discontinue study drug/study regimen.	cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
		• No dose modifications. • If it worsens, then treat as described for elevations in the row below.	–
	AST or ALT >3.0×ULN and ≤5.0 if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN	• Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal. • If toxicity worsens, then treat as described	Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to AST or ALT≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>2 to 3 days) or worsens, promptly start

	and ≤3.0×ULN if baseline normal, >1.5-3.0×baseline if baseline abnormal	for elevation in the row below. • If toxicity improves to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, resume study drug/study regimen after completion of steroid taper.	prednisone 1 to 2 mg/kg/day PO or IV equivalent .
	AST or ALT >5.0×ULN if baseline normal, >5×baseline if baseline abnormal; and/or TB >3.0×ULN if baseline normal; >3.0×baseline if baseline abnormal	For elevations in transaminases ≤8×ULN and/or in TB ≤5×ULN if baseline normal, or for elevations in transaminases ≤8×baseline and/or TB ≤5×baseline if baseline abnormal: • Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade as described in bullet above within 14 days For elevations in transaminases >8×ULN or	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil 0.5-1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Request Hepatology consult, and perform abdominal workup and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

		elevations in TB >5×ULN if baseline normal, or for elevations in transaminases >8×baseline and/or TB >5×baseline if baseline abnormal, permanently discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above

Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline **Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose untilresolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper.	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetilg 0.5-1 g every 12 hours then taper in

			consultation with hepatology consult).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR):			

		- **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase riseFor example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)** - **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**	
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted.

		• If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	– Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN); (Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup and prompt treatment with an immunosuppressive in consultation with a nephrologist. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – Hold study drug if Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or other severe cutaneous adverse reaction (SCAR) is suspected.

			– Permanently discontinue study drugs if SJS, TEN or SCAR is confirmed.
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain Dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event persists for >1 week or recurs.
	Grade 3 or 4	**For Grade 3:** -Hold study drug/study regimen until resolution to Grade ≤1 or baseline. -If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper. -If toxicity worsens, then treat as Grade 4. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult Dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – Consider, as necessary, discussing with study physician.

Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** − Consider consulting an endocrinologist for endocrine events. − Consider, as necessary, discussing with study physician. − Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). − Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). − Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study. − If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** − Monitor patient with appropriate endocrine function tests. − For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and

		prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) 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 ≤10 mg/day or equivalent.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. - Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy and without corticosteroids. Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory

			assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) 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 ≤10 mg/day or equivalent.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy and without corticosteroids. Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and	**Any Grade** (depending on the type of neurotoxicity,	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections,

autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	refer to NCI CTCAE v4.03 for defining the CTC grade/severity)		metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with Neurology consult as appropriate. – FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.
	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. -Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days. -If toxicity worsens, then treat as Grade 3 or 4.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain Neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG or other immunosuppressive depending on the specific imAE).
	Grade 3 or 4	**For Grade 3:** Permanently discontinue study drug/ study regimen	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain Neurology consult. – Consider hospitalization.

		For Grade 4: Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG or other immunosuppressive depending on the specific imAE). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a Neurology consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a Neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not

		typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult.
Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such

		therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.

			○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory e.g., BNP or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated.

		drug/study regimen is held, resume after complete resolution to Grade 0.	- Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up.

		– If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation.

	activities of daily living [ADLs])	drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	– Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no

	For Grade 4: - Permanently discontinue study drug/study regimen.	improvement within 2 to 3 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.
AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

APPENDIX 2: DURVALUMAB WEIGHT-BASED DOSE CALCULATION

For durvalumab dosing done depending on subject weight. Weight-based dosing should be utilized for patients $\leq$ 30 kg:

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

3. Dose for subject: XY mg = X (mg/kg) × Y (kg)

4. Dose to be added into infusion bag:

Dose (mL) = XY mg / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration.

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5. The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1. Cohort dose: 20 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 600 mg = 20 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL

5. The number of vials required for dose preparation:

Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

APPENDIX 3: TREMELIMUMAB WEIGHT-BASED DOSE CALCULATION

For tremelimumab dosing done depending on subject weight. Weight-based dosing should be utilized for patients $\leq$ 30kg:

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

3. Dose for subject: XY mg = X (mg/kg) × Y (kg)

4. Dose to be added into infusion bag:

Dose (mL) = XY mg / 20 (mg/mL)

where 20 mg/mL is tremelimumab nominal concentration.

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5. The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 20.0 (mL/vial)

Example:

1. Cohort dose: 1 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 30 mg = 1 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 30 mg / 20 (mg/mL) = 1.5 mL

5. The number of vials required for dose preparation:

Number of vials = 1.5 (mL) / 20.0 (mL/vial

APPENDIX 4: MANAGEMENT OF RADIATION ESOPHAGITIS

Esophageal complaints are common with combined modality therapy. Esophagitis does not constitute a reason to interrupt or delay radiotherapy or chemotherapy provided oral intake is sufficient to maintain hydration. Patients should be advised to avoid alcoholic, acidic, or spicy foods or beverages. Viscous xylocaine, carafate, or other medications should be used for symptomatic relief. In some cases, narcotics may be required. It is not necessary to biopsy acute esophagitis in the first 2 weeks of combined therapy since it is rarely due to underlying viral or fungal disease. Acute esophagitis may persist for 4-6 weeks. If grade 4 esophagitis occurs, radiation treatment can be held until esophagitis improves to grade 2 or less. Every effort should be made to limit the interruption to ≤ 3 treatment days. Patients requiring hospitalization because of esophagitis may have their treatment interrupted. In this event, please notify the principal investigator.

Esophagitis should be graded according to CTCAE, v. 4.0 as follows: **Grade**	**Clinical Scenario**
1	Asymptomatic; pathologic, radiographic or endoscopic findings only
2	Symptomatic; altered eating/swallowing (e.g. altered dietary habits, oral supplements), IV fluids indicated < 24 hrs
3	Symptomatic and severely altered eating/swallowing (e.g. inadequate oral caloric or fluid intake), IV fluids, tube feeding, or TPN indicated > 24 hrs.
4	Life-threatening consequences
5	Death

APPENDIX 5: MANAGEMENT OF RADIATION-RELATED TOXICITIES

Radiation Associated Toxicity	**Grade**	**Action**
Esophagitis	4	Hold treatment until ≤ grade 2
	3	No change or hold ≤5 days (depending on patients KPS)
	2	No change
Pneumonitis	4	Discontinue therapy
	3	Hold treatment until ≤ grade 2
	2	No change
Dermatitis	4	Hold treatment until ≤ grade 2
	3	No change
	2	No change

18. LIST OF REFERENCES

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