Investigational Drug Substance(s)	Durvalumab (MEDI4736) Sirolimus (Rapamune)
Study Number	19-20015
Version Number	4
Date	11 February 2022

A Phase 1b Neoadjuvant Trial of Sirolimus Followed by Durvalumab (MEDI4736) in Resectable Non-small Cell Lung Cancer

Supporter: AstraZeneca/MedImmune

PROTOCOL SYNOPSIS

Clinical Protocol ESR 19-20015

Study Title: A Phase 1b Neoadjuvant Trial of Sirolimus followed by Durvalumab (MEDI4736) in Resectable Non-small Cell Lung Cancer
Protocol Number: 19-20015
Clinical Phase: Ib
Study Duration: 4 years, which will include survival follow-up for up to 2 years after the last patient receives the last dose of neoadjuvant durvalumab
Investigational Product(s) and Reference Therapy: Durvalumab (MEDI4736) solution for infusion after dilution will be supplied in glass vials containing 500 mg of liquid solution durvalumab at a concentration of 50 mg/mL infusion after dilution. Sirolimus (Rapamune) will be supplied in 1 mg, white, triangular-shaped tablets marked "RAPAMUNE 1 mg" on one side; bottle containing 100 tablets.
Research Hypothesis We hypothesize that administration of sirolimus, an mTOR inhibitor, followed by durvalumab, an engineered human IgG1 kappa monoclonal antibody targeting PD-1, will demonstrate a good safety profile and produce objective responses in clinical Stage I-IIIA NSCLC. We plan to assess established markers that correlate with response including PD-L1 expression in the tumors and tumor mutation burden by next generation sequencing. As these markers are not perfect and some patients with low PD-L1 and mutational burden may derive benefit, additional study of immune mechanisms is needed. Moreover, there is significant interest in developing combination therapy regimens that enhance the immune system response to cancer of patients that are PD-L1 and mutational burden low. Our focus on biomarkers of response will help identify patients who will benefit from this treatment strategy.
Objectives: **Co-Primary Objectives:** • To evaluate the safety and tolerability of sirolimus followed by durvalumab as neoadjuvant treatment

• To evaluate the efficacy of sirolimus followed by durvalumab as neoadjuvant treatment for Stage I, II, and IIIA NSCLC

Secondary Objective(s):

• To evaluate the efficacy of sirolimus followed by durvalumab as neoadjuvant treatment for Stage I, II, and IIIA NSCLC
• To evaluate response to sirolimus followed by durvalumab in patients with PD-L1 positive vs. PD-L1-negative tumors
• To evaluate the association between blood mutation burden and response to sirolimus followed by durvalumab

Exploratory Objective(s):

• To evaluate the immune-mediated effects of sirolimus followed by durvalumab
• To investigate tumor and immune microenvironment changes in tissue samples

Study Design:

Up to 31 patients with NSCLC will be enrolled in this study at Emory University Winship Cancer Institute and associated clinical sites. Eligible patients will complete 3 weeks of daily oral sirolimus followed by 2 cycles of durvalumab treatment prior to proceeding to standard of care surgical resection. Durvalumab will be administered at a dose of 1500mg Q 3 weeks starting on C1D1 for up to 2 cycles that are 21 days in length. Pharmacodynamic analysis will be done using PD samples collected at baseline (tissue) and with blood samples on day 1, day 22 C1 prior to durvalumab, day 43 C2 durvalumab, and at the time of surgery (blood and tissue). Additional post surgery blood samples will be collected at 1-, 3-, and 6-months post-surgery. See Appendix D for schedule of Biomarker collection. Patients will proceed to surgery within a 2–3-week period post 2nd dose of durvalumab but not earlier than two weeks after the administration of durvalumab i.e. not earlier than C2D14. Additionally, as an optional study, patients will self-administer heavy water (D2O) 50ml orally three times a day from day 22 C1 through day 27 followed by 50ml orally twice a day through the day prior to surgery in order to label dividing cells for research tracking purposes.

Number of Centers: Emory University Winship Cancer Institute and affiliated hospitals

Number of Patients: 31

Study Population: Resectable Stage 1-3A NSCLC

Inclusion Criteria:

- Pathologically documented NSCLC who are candidates for surgical resection
- Capable of signing informed consent

- Age ≥ 18 years at time of study entry.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Life expectancy of ≥ 26 weeks
- Body weight >30 kg
- Adequate normal organ and marrow function as defined in protocol
- Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients.
- Measurable disease defined by RECIST v 1.1.
- Patient is able to take oral medications
- Patient consents to heavy water (D2O) self-administration, if enrolling in optional heavy water study
- Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

Exclusion Criteria:

- Prior therapy for lung cancer including chemotherapy, hormonal therapy, or radiotherapy.
- Concurrent enrolment in another clinical study, unless it is observational
- Prior treatment with anti-PD-1, anti-PDL-1, including durvalumab other PD-1/PDL-1 pathway targeting agents, or mTOR inhibition.
- History of allogenic organ transplantation.
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). Exceptions listed in protocol below.
- Uncontrolled intercurrent illness
- History of another primary malignancy with exceptions noted in protocol
- QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms
- History of active primary immunodeficiency
- Active infection including tuberculosis, hepatitis B, hepatitis C
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. There are exceptions to this criterion listed below in the protocol
- Receipt of live attenuated vaccine within 30 days prior to the first dose of study medications

- Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab
- Known allergy or hypersensitivity to any of the study drugs or excipients.
- Patients with a history of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan
- Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

Investigational Product(s), Dose and Mode of Administration:

Patients will receive 1500 mg durvalumab via IV infusion Q3W for up to a maximum of 2 cycles prior to curative resection surgery. Weight-based dosing (20 mg/kg) should be utilized for patients whose body weight falls to <30 kg while on study.

Patient will self-administer sirolimus 6 mg orally once on day 1, followed by once daily dosing of 2mg, continuously through day 21, which is one day prior to C1 of durvalumab. The dose should be taken each morning, with or without food.

Study Assessments and Criteria for Evaluation:

Safety Assessments:

• Incidence of adverse events, with severity per NCI CTCAE v5.0
• Length of hospital stay after surgery

Efficacy Assessments:

• Complete pathologic response, scored by a pathologist, based on surgical resection as defined by prior studies
• Investigator-assessed response rate per RECIST v1.1
• DFS and OS
• Pathological response in PD-L1-positive and PD-L1-negative groups
• Overall response rate in PD-L1-positive and PD-L1-negative groups based on mutational burden

Statistical Methods and Data Analysis:

Safety Analyses:

All enrolled patients will be evaluable for safety analyses from the time of their first treatment with sirolimus. After study complete, DLTs will be summarized and tabulated by type and grade. DLT rate

by dose level will be calculated as proportion (Patients with DLT/Total patients) along with 95% confidence intervals using the Clopper-Pearson method. Chi-square test or Fisher's exact test will be used to compare the probability of DLT between the different other factors, such as PD-L1 status, dose levels, etc. respectively.

Other adverse events (toxicity) will be listed and summarized overall and by dose level. Adverse events will also be listed by severity, seriousness, and by system organ class. The number and percentage of subjects who experience AEs will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. No formal statistical comparison between the dose levels or PD-L1 will be performed. AEs will be presented with and without regard to causality based on the investigator's judgment. The frequency of overall toxicity, categorized by toxicity grades 1 through 5, will be described. Additional summaries will be provided for AEs that are observed with higher frequency.

Efficacy Analyses:

The primary and secondary efficacy analyses will include all enrolled patients who have received at least one dose of durvalumab, underwent resection and who do not have EGFR mutant tumors (efficacy population).

Primary Efficacy Endpoint

The effectiveness of sirolimus followed by durvalumab will be assessed by complete pathologic response rate in the efficacy population. If the null hypothesis is rejected then this is evidence that the response rate exceeds 10% when sirolimus followed by durvalumab is given before resection. The one-sided 95% confidence interval (CI) for complete pathologic response will be reported. Exact binomial test will be used to compare the estimated complete pathologic response rate to the historical reference.

Secondary Efficacy Endpoints

The complete pathologic response rates for PDL-1 negative and PDL-1 positive patients in the *efficacy population* will be presented separately.

A comparison of both the *complete pathologic response* and investigator assessed response rates per RECIST v1.1 rate*s* between the PD-L1 positive and PD-L1 negative groups will be performed by calculating the lower bound of a one-sided 80% CI for the difference, complete pathologic response for PDL-1 positive patients − complete pathologic response for PDL-1 negative patients. Chi-square test or Fisher's exact test will be used to compare the efficacy in term of response rate between the different groups stratified by other factors, respectively. Logistics regression model will be further employed to test the adjusted effect of each other factor on the response rate after adjusting for other clinical factors and demographic factors, respectively. Correlation of response will be performed for tumor mutation burden using spearman correlation coefficient and tested with Wald's test.

Sample Size Determination:

Pathologic complete response is rare following neoadjuvant chemotherapy but was reported in 0-8% of cases[39]. The current study is designed to test improved rate of pathologic complete response from 10% to 25% with sequential treatment with sirolimus and durvalumab. Using a MinMax 2-stage design, a total of 31 patients will be enrolled in 2 stages. At the end of stage I, at least 2 of 16 patients must achieve complete pathologic complete response in order for the study to enroll 15 additional patients. The regimen of sirolimus followed by durvalumab will be considered to have sufficient efficacy to warrant further testing in this patient population if 6 or more of the 31 patients achieve a pathologic CR at the end of stage II. The study has 80% power at a 1-sided alpha of 0.1 to show a compelling 25% pCR compared to a less compelling rate of 10%. Because this is a signal finding study, an alpha of 0.1 is considered reasonable since any promising signal will be confirmed in a larger follow-up study.

SCHEDULE OF STUDY ASSESSMENTS

	Screening	**Sirolimus**	**Durvalumab C1**	**Durvalumab C2**	**Pre-surgery**	**Surgery**	**Study DC**	**Follow-up**	
Week	**-4 to 0**	**0**	**3**	**6**	**8-9**		**Post Surgery 30 +/- 7 days**	**Every 3 months for 2 years**	**For details see Section**
Day	**-28 to 0**	**1-21**	**22 +/- 3 days[a]**	**43 +/- 3 days[a]**	**57-64 +/- 10 days**				
Informed Consent									
Informed consent: study procedures[b]	X								**Error! Reference source not found. Error! Reference source not found.**

	Screening	**Sirolimus**	**Durvalumab C1**	**Durvalumab C2**	**Pre-surgery**	**Surgery**	**Study DC**	**Follow-up**	
Week	**-4 to 0**	**0**	**3**	**6**	**8-9**		**Post Surgery 30 +/- 7 days**	**Every 3 months for 2 years**	**For details see Section**
Day	**-28 to 0**	**1-21**	**22 +/- 3 days[a]**	**43 +/- 3 days[a]**	**57-64 +/- 10 days**				
Consent: genetic sample and analysis (optional)	X								**Error! Reference source not found.**
Study Procedures									
Physical exam (full)	X								**Error! Reference source not found.**
Targeted physical exam (symptom driven)		X	X	X	X		X		**Error! Reference source not found.**

	Screening	**Sirolimus**	**Durvalumab C1**	**Durvalumab C2**	**Pre-surgery**	**Surgery**	**Study DC**	**Follow-up**	
Week	**-4 to 0**	**0**	**3**	**6**	**8-9**		**Post Surgery 30 +/- 7 days**	**Every 3 months for 2 years**	**For details see Section**
Day	**-28 to 0**	**1-21**	**22 +/- 3 days[a]**	**43 +/- 3 days[a]**	**57-64 +/- 10 days**				
Vital signs[c]	X	X	X	X	X		X		**Error! Reference source not found.**
ECG[d]	X	As clinically indicated							**Error! Reference source not found.**
Concomitant medications		<----------						---------->	**Error! Reference source not found.**

	Screening	**Sirolimus**	**Durvalumab C1**	**Durvalumab C2**	**Pre-surgery**	**Surgery**	**Study DC**	**Follow-up**	**For details see Section**
Week	**-4 to 0**	**0**	**3**	**6**	**8-9**		**Post Surgery 30 +/- 7 days**	**Every 3 months for 2 years**	
Day	**-28 to 0**	**1-21**	**22 +/- 3 days[a]**	**43 +/- 3 days[a]**	**57-64 +/- 10 days**				
Demography, including baseline characteristics and tobacco use	X								**Error! Reference source not found.**
Eligibility criteria	X								**Error! Reference source not found.** and **Error! Reference source not found.**
Laboratory Assessments									

	Screening	**Sirolimus**	**Durvalumab C1**	**Durvalumab C2**	**Pre-surgery**	**Surgery**	**Study DC**	**Follow-up**	
Week	**-4 to 0**	**0**	**3**	**6**	**8-9**		**Post Surgery 30 +/- 7 days**	**Every 3 months for 2 years**	**For details see Section**
Day	**-28 to 0**	**1-21**	**22 +/- 3 days[a]**	**43 +/- 3 days[a]**	**57-64 +/- 10 days**				
Clinical chemistry[e]	X	X[f]	X	X	X		X		**Error! Reference source not found.**
Hematology[e]	X	X[f]	X	X	X		X		**Error! Reference source not found.**
TSH[g], (reflex free T4[h])	X			X	X		X		**Error! Reference source not found.**

	Screening	**Sirolimus**	**Durvalumab C1**	**Durvalumab C2**	**Pre-surgery**	**Surgery**	**Study DC**	**Follow-up**	**For details see Section**
Week	**-4 to 0**	**0**	**3**	**6**	**8-9**		**Post Surgery 30 +/- 7 days**	**Every 3 months for 2 years**	
Day	**-28 to 0**	**1-21**	**22 +/- 3 days[a]**	**43 +/- 3 days[a]**	**57-64 +/- 10 days**				
Hepatitis B and C and HIV	X								**Error! Reference source not found.**
Pregnancy test[i]	X		X						**Error! Reference source not found.**
Sirolimus level for batch analysis			X						8.1.2
Monitoring									
WHO/ECOG performance status	X	X	X	X	X		X		10.1.1

	Screening	**Sirolimus**	**Durvalumab C1**	**Durvalumab C2**	**Pre-surgery**	**Surgery**	**Study DC**	**Follow-up**	
Week	**-4 to 0**	**0**	**3**	**6**	**8-9**		**Post Surgery 30 +/- 7 days**	**Every 3 months for 2 years**	**For details see Section**
Day	**-28 to 0**	**1-21**	**22 +/- 3 days[a]**	**43 +/- 3 days[a]**	**57-64 +/- 10 days**				
AE/SAE assessment [j]		<----------							**Error! Reference source not found.**
IP administration									
Sirolimus		X							5.1
Durvalumab[k]			X	X					5.2
Optional Heavy Water (D2O)			X	X	X				

	Screening	**Sirolimus**	**Durvalumab C1**	**Durvalumab C2**	**Pre-surgery**	**Surgery**	**Study DC**	**Follow-up**	
Week	**-4 to 0**	**0**	**3**	**6**	**8-9**		**Post Surgery 30 +/- 7 days**	**Every 3 months for 2 years**	**For details see Section**
Day	**-28 to 0**	**1-21**	**22 +/- 3 days[a]**	**43 +/- 3 days[a]**	**57-64 +/- 10 days**				
Other assessments and assays									
Blood biomarker samples for immunologic analysis		X	X	X	X		X	X[m]	**Error! Reference source not found.Error! Reference source not found.**

	Screening	**Sirolimus**	**Durvalumab C1**	**Durvalumab C2**	**Pre-surgery**	**Surgery**	**Study DC**	**Follow-up**	
Week	**-4 to 0**	**0**	**3**	**6**	**8-9**		**Post Surgery 30 +/- 7 days**	**Every 3 months for 2 years**	**For details see Section**
Day	**-28 to 0**	**1-21**	**22 +/- 3 days[a]**	**43 +/- 3 days[a]**	**57-64 +/- 10 days**				
Tumor biopsy (newly acquired/fresh if amenable to core biopsy)	X								**Error! Reference source not found.Error! Reference source not found.**
Tumor biopsy (archival, required for diagnosis and PD-L1 assessment)	X								**Error! Reference source not found.**
Fresh tumor and lymph node samples for immunologic analysis						X			
Efficacy evaluations									

	Screening	**Sirolimus**	**Durvalumab C1**		**Durvalumab C2**		**Pre-surgery**	**Surgery**	**Study DC**	**Follow-up**	
Week	**-4 to 0**	**0**	**3**		**6**		**8-9**		**Post Surgery 30 +/- 7 days**	**Every 3 months for 2 years**	**For details see Section**
Day	**-28 to 0**	**1-21**	**22 +/- 3 days[a]**		**43 +/- 3 days[a]**		**57-64 +/- 10 days**				
Tumor evaluation (CT or MRI) (RECIST 1.1)[l] within 6 weeks of C1D1	X[n]						X				**Error! Reference source not found.**
Pathologic response assessment								X			

[a] If cycle 2 day 1 visit is delayed, all subsequent visits will be delayed accordingly

[b] Informed consent of study procedures and tumor biopsy sample may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization. The collection of tumor biopsies at the time of progression prior to retreatment is mandated; the Investigator must consult with the Study Physician if such sampling is not feasible. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of study assignment.

[c] Body weight is recorded at each visit along with vital signs

[d] Any clinically significant abnormalities detected require triplicate ECG results.

[e] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.

[f] If screening clinical chemistry and haematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1.

[g] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day 1.

[h] Free T4 may only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[i] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion

[j] For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed

[k] Results for LFTs, electrolytes, full blood count and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.

[l] RECIST assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands) and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before the date of randomization and, ideally, should be performed as close as possible to and prior to the start of IP. Repeat assessments will be performed as close as possible to surgery date.

[m] Peripheral blood collection for biomarker analysis will be obtained at 3- and 6-months post-surgery

n Screening/Baseline Cross-sectional Imaging (CT, PET, or MRI) for RECIST should be within 6 weeks of starting C1D1 of trial therapy

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

C Cycle; ECG Electrocardiogram; IM Intramuscular; LFT Liver function test; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

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ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	Anti-drug antibody

Abbreviation or special term	Explanation
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APC	Antigen-presenting cells
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CL	Clearance
C_{max}	Peak concentration
$C_{max,ss}$	Peak concentration at steady state
C_{min}	Trough concentration
$C_{min,ss}$	Trough concentration at steady state
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DC	Disease control
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Disodium edetate dihydrate

Abbreviation or special term	Explanation
Fc	Fragment crystallizable
FFPE	Formalin fixed paraffin embedded
FSH	Follicle-stimulating hormone
FTIH	First-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HCl	Hydrochloride
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IGF	Insulin-like growth factor
IgG1	Immunoglobulin G1
IgG2	Immunoglobulin G2
IGSF	Immunoglobulin superfamily
IHC	Immunohistochemistry
IL	Interleukin
imAE	Immune-mediated adverse event
IRB	Institutional Review Board
IV	Intravenous(ly)
MAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro ribonucleic acid
MRI	Magnetic resonance imaging

Abbreviation or special term	Explanation
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural killer
NOAEL	No-observed-adverse-effect level
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
PVC	Polyvinyl chloride
Q2W	Every 2 weeks
Q3M	Every 3 months
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q12W	Every 12 weeks
QoL	Quality of life

Abbreviation or special term	Explanation
QTc	Time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable disease
SID	Subject identification
sPD-L1	Soluble programmed cell death ligand 1
SOCS3	Suppressor of cytokine signaling 3
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Half life
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocyte
T_{max}	Time to peak concentration
$T_{max,ss}$	Time to peak concentration at steady state
TNF-α	Tumor necrosis factor alpha
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
USA	United States of America
WFI	Water for injection
WHO	World Health Organization

1. INTRODUCTION

1.1 Disease background

Lung cancer is the number one cause of cancer-related death in men and women in the United States. Based on Surveillance Epidemiology and End Results Program (SEER) data, there will be an estimated 222,500 new cases and 155,870 lung cancer deaths in the United States in 2017[1]. Unfortunately, only 16% of patients are diagnosed with localized disease, and despite this early stage, 5-year survival is less than 60%. Another 22% of patients are diagnosed with lymph-node positive disease and again despite the potential for cure, less than 30% are alive five years later[1]. Non-small cell lung cancer (NSCLC), accounts for over 80% of lung cancer diagnoses, and adenocarcinoma and squamous cell carcinoma are the two most common histologic subtypes.

In an effort to reduce the risk of local and distant recurrences after resection, both adjuvant and neoadjuvant systemic therapies have been tested in NSCLC. Adjuvant cisplatin-based doublet chemotherapy for up to 4 cycles has been shown in multiple trials to provide a benefit to patients with stage II-III NSCLC[2-4]. The LACE meta-analysis of 5 large trials showed there was an absolute 5-year overall survival benefit of 5.4%[5]. Patients without nodal involvement, but large tumors ≥ 4 cm in diameter were also found to have a statistically significant survival advantage[6], indicating patients with stage Ib disease can also benefit from systemic therapy. There is fewer data on neoadjuvant chemotherapy because the positive adjuvant data led to the early closure of some neoadjuvant studies[7]. A meta-analysis of 13 trials in 2010 demonstrated survival benefit with chemotherapy[8] and a more recent meta-analysis of 15 randomized studies with over 2000 patients with NSCLC showed a survival benefit similar to the adjuvant chemotherapy trials[9].

1.1.1 Immunotherapy in NSCLC

Currently, there are ongoing trials testing immunotherapy as a potential neoadjuvant +/- adjuvant treatment for resectable NSCLC[10, 11], based on the benefit of such treatment seen in patients with unresectable or metastatic disease. Four phase III randomized clinical trials demonstrated improved overall survival with immunotherapy targeting the Programmed death 1 (PD-1)/Programmed death ligand 1 (PD-L1) immune checkpoint when compared to docetaxel as second line therapy for advanced NSCLC[12-15]. While some patients have a remarkable clinical response, the majority of NSCLC patients treated with single agent immunotherapies do not benefit; response rates ranged from 18%-30% in the metastatic setting[12-15]. In the neoadjuvant setting major pathologic response (MPR) rates have ranged from 45% with nivolumab[10] and 21% with atezolizumab[11]. Combination neoadjuvant regimens are also being tested; in a phase 2 trial of neoadjuvant nivolumab or nivolumab + ipilimumab, combination

PD-1 and CTLA-4 blockade was associated with numerically higher MPR and side effects than PD-1 blockade alone[16]. Ongoing research efforts are underway to both identify biomarkers that can predict response to checkpoint inhibitor therapy in NSCLC and develop novel combination treatment strategies that enhance the therapeutic efficacy of cancer immunotherapy.

Useful but not entirely predictive or prognostic markers established to date include PD-L1 expression on the tumor and tumor mutation burden. Comparison across trials of PD-L1 expression is complicated by different companion diagnostic tests that have been developed along with technical variables including biopsy source, processing, detection antibodies, and immunohistochemistry cutoffs[17]. In general, patients with higher tumor PD-L1 expression showed improved response rates and overall survival compared to patients with low PD-L1 expression[18]. However, patients with low or no PDL-1 expression can still derive a benefit, and therefore other markers are being studied. Interestingly, the number of mutations identified in the tumor may predict response. Rizvi et al. demonstrated with whole exome sequencing that improved response rates and PFS were seen in patients with higher mutational burdens treated with pembrolizumab[19]. Similar findings were seen using next generation sequencing of patients treated with PD-1 or PD-L1 directed monotherapy or combination immunotherapy[20]. The development of reliable biomarkers would further improve the ability to interrogate the effectiveness of combination therapies in both preclinical and clinical studies.

Ideal agents to combine with PD-1/PDL-1 checkpoint inhibitor therapy would include well-tolerated, easy to administer drugs with single agent anti-cancer activity that have a complementary effect on the immune system. The mammalian target of rapamycin (mTOR) is one such therapeutic target in cancer based on its diverse roles in cell proliferation, metabolism, and survival. There are currently three FDA approved inhibitors of mTOR: rapamycin (sirolimus) and two rapamycin analogs or rapalogs, everolimus and temsirolimus. Sirolimus has long been used as an immunosuppressant in organ transplantation, temsirolimus is approved for use in renal cell carcinoma[21] and everolimus has FDA indications for multiple solid organ malignancies including the treatment of hormone receptor positive HER-2 negative breast cancer, neuroendocrine tumors of the pancreas[22], lung, or GI tract, and renal cell carcinoma (RCC)[23]. Additionally, single agent neoadjuvant everolimus was tested in resectable NSCLC. In this window of opportunity study 23 patients were treated with everolimus (5 or 10mg daily) for 3 to four weeks, followed by resection, with evidence of dose dependent, metabolic, and anticancer activity[24].

1.1.2 Potential role of mTOR inhibition in NSCLC and immunologic effects

Pharmacological inhibition of the mTOR pathway can modulate both innate and adaptive immunity. Modulation of the innate immune system by mTOR inhibition can be seen in the known inflammatory side effects including fever, pneumonitis, anemia of inflammation as well as the promotion of inflammatory cytokines IL-1B and IL-12[25]. Rapamycin has been shown to decrease plasmacytoid dendritic cell production of interferon[26]. Additionally, there is accumulating understanding of rapamycin and rapalogs impact on T cell activation and differentiation. Using a well described mouse model, Araki et al. showed increased numbers of virus specific memory CD8 T-cells following treatment with rapamycin. Low doses of rapamycin led to increased numbers of memory T cell precursors and regulation of memory T cell differentiation occurs through the mTORC1 pathway[27]. The mTOR pathway is involved in the regulation of FOXP3 expression in regulatory T cells[28, 29]. In a study of metastatic RCC patients on everolimus, better clinical responses were seen in patients that developed high expression of tumor specific Th1 cells and lower regulatory T cells (Tregs)[30].

The interaction of mTOR inhibition with PD-1/PDL-1 pathway has been studied in preclinical models. In genetically engineered mouse models of lung cancer, mTOR inhibition led to decreased tumor growth, increased tumor-infiltrating lymphocytes (TILSs) and decreased Tregs[31], but there is some controversy over the mechanism. In that paper mTOR activation reportedly up-regulated PD-L1 while mTOR pathway inhibition with rapamycin decreased PD-L1[31]. A subsequent study using a murine model of RCC and human RCC cells showed that everolimus in combination with anti-PDL1 therapy up-regulated PD-L1 on the cell surface, indicating this mechanism underlies the therapeutic benefit of combination therapy[32]. Additionally, rapamycin was shown to enhance anti-PD-L1 treatment with durable tumor control in an immunogenic model of oral cavity cancer[33]. These preclinical studies provide evidence of significantly enhanced antitumor activity with combined mTOR plus PD-1/PD-L1 targeted therapy over single agent immunotherapy in 3 different solid tumor models (RCC, NSCLC, and oral cancer).

The purpose of this study is to evaluate the ability of the mTOR inhibitor sirolimus given prior to durvalumab, an engineered human IgG1 kappa monoclonal antibody targeting PD-L1, to produce pathologic responses in the neoadjuvant setting in patients with early stage NSCLC who have a pretreatment biopsy. Clinical staging of NSCLC is based on computed tomography (CT) of the chest and upper abdomen, positron emission tomography (PET) and brain CT or magnetic resonance imaging (MRI) to rule out metastatic disease. These studies and any necessary additional functional assessments by attending thoracic surgeons will be used to assess the potential for curative-intent resection. The study will only include patients with surgically resectable early stage NSCLC (I, II, or IIIA disease) and who are deemed suitable for surgical resection without metastatic disease and have sufficient initial biopsy material to

analyze biomarkers. The subsequent surgical tumor resection from these patients will allow determination of pathologic response rates and investigation of potential predictive biomarkers from the pretreatment biopsy. Additional peripheral blood immune-phenotyping by flow cytometry will describe the evolution of immune related markers associated with response in the tumor biopsy specimen after treatment.

1.2 Durvalumab background/non-clinical and clinical experience

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

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and 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).). The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ[49]. *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism[49]. Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date durvalumab has been given to more than 8000 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 0 and Section 6.3. 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 Sirolimus background/non-clinical and clinical experience

Sirolimus inhibits mTOR, a highly conserved serine-threonine kinase that is a master regulator of protein synthesis, cell growth, cell proliferation, angiogenesis and cell survival. mTOR forms two distinct complexes (mTORC-1 with raptor and mTORC-2 with rictor)[36]. Signaling via mTORC-1 leads to activation of p70 S6 kinase and suppression of 4EBP1, initiating translation

of cyclin D1, C-myc, and Mcl-1, which are known oncogenic proteins. The mTORC-2 complex is known to be involved in survival via AKT/PI3 kinase pathways as well as cytoskeletal regulation via protein kinase C[36]. Sirolimus binds to FK Binding Protein-12 (FKBP-12), which then binds to and inhibits mTOR thereby preventing T cell activation and suppresses cytokine-driven T cell proliferation. Additionally, mTOR blockade with sirolimus may up regulate AKT via a negative feedback loop[37].

Rapamycin is currently FDA approved for the prophylaxis of kidney transplant rejection and the treatment of lymphangioleiomyomatosis. Dosing as an immunosuppressant for the aforementioned indications ranges from 6-15 gm loading dose and 2-5 mg daily doses thereafter, with adjustments made based on trough levels for goal 12-20ng/ml[34]. Interestingly, a dosing scheme on the higher range was recently studied for its direct anti-cancer effects in a window of opportunity head and neck cancer trial[35]. Patients received a loading dose of 15mg followed by 5mg daily dosing, with down titration if troughs were > 20 ng/ml for 21 day treatment prior to curative intent surgery in 15 patients and chemo-radiation in 1 patient. Five patients experienced a > 25% tumor shrinkage including one complete response, and there were no significant changes in CD3, CD4, CD8 or CD19+ circulating lymphocytes[35]. This dose led to dramatic reduction in pS6 and pAKTS473 and was well tolerated with mostly grade 1-2 thrombocytopenia and neutropenia, and only one grade three adverse event, hypokalemia[35].

1.4 Research hypothesis

We hypothesize that administration of sirolimus, an mTOR inhibitor prior to durvalumab, an engineered human IgG1 kappa monoclonal antibody targeting PD-1, will demonstrate a good safety profile and produce objective responses in clinical Stage I-IIIA NSCLC. We plan to assess established markers that correlate with response including PD-L1 expression in the tumors and tumor mutation burden by next generation sequencing. As these markers are not perfect and some patients with low PD-L1 and mutational burden may derive benefit, additional study of immune mechanisms is needed. Moreover, there is significant interest in developing combination therapy regimens that enhance the immune system response to cancer of patients that are PD-L1 and mutational burden low. Our focus on biomarkers of response will help identify patients who will benefit from this treatment strategy.

1.5 Rationale for conducting this study

Given the significant mortality associated with potentially resectable NSCLC, additional treatment options are desperately needed. Checkpoint inhibitor therapy has shown remarkable efficacy in some patients, but unfortunately the majority of patients do not benefit from this modality of therapy. Recent murine models and translational studies suggest that mTOR

pathway inhibition can enhance immunity and may increase PD-L1 targets on cancer cells. Furthermore, sirolimus, an FDA approved mTOR inhibitor, is safe and well tolerated. These findings lay the foundation for the use of sequential therapies that enhance the function of PD-1/PDL-1 targeted therapies. We therefore propose to conduct a phase Ib trial to evaluate the safety and tolerability as well as efficacy of sirolimus followed by durvalumab for neoadjuvant treatment of resectable NSCLC.

1.5.1.1 Role of neo-adjuvant studies in biomarker discovery

Neoadjuvant treatment protocols such as this allow a unique window of opportunity to assess biologic effects of novel combination or sequential therapies and limit confounding effects. Commonly, patients with heavily pre-treated or refractory disease are treated with new agents or regimens, but prior therapy may induce cellular and immunologic alterations that impact treatment responses. We have shown at the Winship Cancer Institute that this neoadjuvant paradigm is feasible, from a patient willingness perspective to delay surgery as well as logistically keeping to defined timelines for biopsy, staging, treatment, and surgical resection[24]. Furthermore, there is institutional expertise in the areas of T cell exhaustion, checkpoint inhibitor therapy, and chronological immune assessment of peripheral blood and tissue. As such, neoadjuvant trials will enable us to evaluate sequential therapies utilizing checkpoint inhibitors where one can assess the immune environment before and after treatment. It is critical to develop highly predictive biomarkers of response and to study the evolution of immune-related markers with treatment with sirolimus followed by durvalumab.

1.5.1.2 Correlative studies rationale

Cancer can escape the immune system through multiple mechanisms including the manipulation of cells with immunosuppressive phenotypes. In addition, it has been shown that elements of both the innate and adaptive immune systems have anti-tumor functions. Therefore, it is necessary to study the global immune modulatory effects of combination durvalumab and sirolimus therapy to further elucidate mechanisms of action in different patients with lung cancer.

Tumor based and systemic markers have been evaluated, but no definitive biomarker has been established. The predictive value of PDL-1 expression on the tumor as measured by immunohistochemistry (IHC) varies across tumor types, line of therapy, and even among trials with similar patients[40]. Furthermore, PDL-1 expression may: change over time, not be uniform across the tumor, and be influenced by other cancer therapies. Tissue samples will be obtained pre-treatment and at resection for immunohistochemistry, immunofluorescence microscopy, and RNA sequencing.

Peripheral blood will be collected at baseline, and pre-specified time-points during treatment, at resection, and at follow-up in order to perform multiple investigational assays. Flow cytometric analysis of peripheral blood of patients on checkpoint inhibitor therapies has shown promise in interrogating mechanisms of response. Specifically, a significant transient rise in Ki67+ PD1+ CD8 T-cells has been correlated with clinical response to pembrolizumab in metastatic melanoma patients[41]. Similar findings were seen in NSCLC patients that responded to anti-PD-1 therapy[42] and additional study elucidated the importance of the co-stimulatory receptor CD28 in mediating this response[43]. The role of inflammatory cytokines as predictive and/or prognostic variables is also being studied and high levels correlated with poor response in melanoma patients on pembrolizumab[41].

Recent murine studies have furthered our understanding of the proliferative burst that occurs in CD8 T-cells after PD1 blockade. Im et al. showed that the proliferative burst is dependent on a stem-like CD8 T cell population[44]. When the stem-like cells are activated, they both self-renew, and undergo differentiation into a Tim3+ effector cell that has high expression of effector molecules. Importantly, treatment with anti-PD1 greatly enhances the rate of this differentiation process, and without the stem-like CD8 T-cell, no expansion of the T-cell pool occurs[44]. We plan to localize and characterize the phenotype and function of analogous stem-like CD8 T-cells present in NSCLC by analyzing resected tissue and peripheral blood from patients with stage I-III disease.

Additionally, the novel technique of *in vivo* deuterium labeling (also termed heavy water) may be used to evaluate T cell dynamics in study patients. This technique, pioneered by Dr. Hellerstein at the University of California Berkley, uses the naturally occurring stable, non-radioactive isotope deuterium (^2H) to measure DNA replication and hence cell proliferation in humans. This method has been effectively utilized at Emory University to understand CD8 T cell homeostasis. Healthy subjects consumed deutierated water during the first two weeks after vaccination with yellow fever virus (YFV)[45]. Deuterium was incorporated into the DNA of dividing YFV-specific effector CD8 T cells thus marking all the YFV-specific CD8 T cells responding to the vaccine virus. Tracking the deuterium label in these marked cells revealed that substantial CD8 T cell proliferation continues to occurs after viral genomes are no longer seen in the blood and YFV-specific memory CD8 T cells exhibited a long-intermitotic interval, dividing approximately once in ~500 days[45]. This novel method will enable us to track the dynamics of T cell populations in NSCLC patients treated with combination mTOR and Durvalumab therapy *in vivo* as part of an optional labelling study.

1.5.1.3 Durvalumab dose rationale

A durvalumab dose of 20 mg/kg Q4W is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 17 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on immunogenicity, please see the current IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W[47]. Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab Investigator's Brochure for a complete summary of clinical information including safety, efficacy and pharmacokinetics at the 20mg/kg Q4W regimen.

1.5.1.4 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-patient variability with fixed dosing regimen.

Similar findings have been reported by others[48, 50, 51, 52]. 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[50]. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters[51].

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 Q3W durvalumab is included in the current study. A 3 week interval is chosen to keep within neoadjuvant window.

1.5.1.5 Sirolimus dose rationale

Rapamycin is currently FDA approved for the prophylaxis of kidney transplant rejection and the treatment of lymphangioleiomyomatosis. Dosing as an immunosuppressant for the aforementioned indications ranges from 6-15 gm loading dose and 2-5 mg daily doses thereafter, with adjustments made based on trough levels for goal 12-20ng/ml[34]. Interestingly, a dosing scheme on the higher range was recently studied for its direct anti-cancer effects in a window of opportunity head and neck cancer trial[35]. Patients received a loading dose of 15mg followed by 5mg daily dosing, with down titration if troughs were > 20 ng/ml for 21 day treatment prior to curative intent surgery in 15 patients and chemo-radiation in 1 patient. Five patients experienced a > 25% tumor shrinkage including one complete response, and there were

no significant changes in CD3, CD4, CD8 or CD19+ circulating lymphocytes[35]. This dose led to dramatic reduction in pS6 and pAKTS473 and was well tolerated with mostly grade 1-2 thrombocytopenia and neutropenia, and only one grade three adverse event, hypokalemia[35].

1.6 Benefit/risk and ethical assessment

1.6.1 Potential benefits

1.6.1.1 Durvalumab

Durvalumab is currently FDA approved for use in patients with unresectable stage III NSCLC who completed at least two cycles of concurrent platinum-based chemotherapy and definitive radiation within 42 days, based on the PACIFIC study (NCT02125461). This was a multicenter, double-blind, placebo-controlled study of patients with WHO performance status of 0-1 and no prior documented autoimmune disease or need for systemic immunosuppression, and excluded those who progressed following concurrent chemotherapy and radiation. Patients were randomized 2:1 to receive durvalumab or placebo every 2 weeks for up to 12 months, unacceptable toxicity or progression. Durvalumab was well tolerated and improved both progression free[53] and overall survival[54].

1.6.1.2 Sirolimus

There are no known benefits of sirolimus in patients with NSCLC.

1.6.1.3 Heavy Water

There are no known benefits of low dose heavy water in patients with NSCLC.

1.6.2 Overall 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. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects can occur in nearly any organ system,

and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

Neo-adjuvant studies additionally pose the risk of delaying or preventing surgery due to treatment related toxicities that may make surgery not feasible. Neoadjuvant PD-1 pathway targeting therapies have not significantly precluded surgery in ongoing single agent studies. Furthermore, neoadjuvant everolimus was well tolerated prior to surgery in NSCLC and neoadjuvant sirolimus was well tolerated prior to surgery in head and neck squamous cell carcinoma patients. However, the risks of combination durvalumab and sirolimus are not known. The dose limiting toxicity assessment of combination therapy portion of this study must be completed as outlined in section 5.1. Furthermore, a low dose of sirolimus, which corresponds to the target immunologic dose, will be administered.

1.6.2.1 Risk associated with durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions, and infections/serious infections.

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

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 15% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9.4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6.5% of patients 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 adverse events (Appendix 1)

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

1.6.2.2 Risk associated with Sirolimus

The safety profile of sirolimus differs based on indication (renal transplant or lymphangioleiomyomatosis) and goal trough range. As there are added complicating medical factors in the post-transplant population, detailed below are the reported side effects in patients with lymphangiolyomyomatosis.

Safety was assessed in a controlled trial involving 89 patients with lymphangioleiomyomatosis, 46 of whom were treated with Rapamune. The adverse drug reactions observed in this trial were consistent with the known safety profile for renal transplant patients receiving Rapamune, with the addition of weight decreased which was reported at a greater incidence with Rapamune when compared to placebo. Adverse reactions occurring at a frequency of ≥ 20% in the Rapamune treatment group and greater than placebo include stomatitis, diarrhea, abdominal pain, nausea, nasopharyngitis, acne, chest pain, peripheral edema, upper respiratory tract infection, headache, dizziness, myalgia, and hypercholesterolemia.

Additional warnings and precautions in the FDA package insert based on clinical trials and post marketing experience include but are not limited to the following:

• Increased Susceptibility to Infection and the Possible Development of Lymphoma:

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression. Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections such as tuberculosis, fatal infections, and sepsis.

• Lung Transplantation Patients– Bronchial Anastomotic Dehiscence
Cases of bronchial anastomotic dehiscence, most fatal, have been reported in de novo lung transplant patients when Rapamune has been used as part of an immunosuppressive regimen.

• Hypersensitivity Reactions:

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis and hypersensitivity vasculitis, have been associated with the administration of Rapamune

• Angioedema:
The concomitant use of Rapamune with other drugs known to cause angioedema, such as angiotensin-converting enzyme (ACE) inhibitors, may increase the risk of developing angioedema. Elevated sirolimus levels (with/without concomitant ACE inhibitors) may also potentiate angioedema. In some cases, the angioedema has resolved upon discontinuation or dose reduction of Rapamune.

• Fluid Accumulation and Impairment of Wound Healing:
There have been reports of impaired or delayed wound healing in patients receiving Rapamune, including lymphocele and wound dehiscence. mTOR inhibitors such as sirolimus have been shown in vitro to inhibit production of certain growth factors that may affect angiogenesis, fibroblast proliferation, and vascular permeability. Appropriate measures should be considered to minimize such complications. Patients with a body mass index (BMI) greater than 30 may be at increased risk of abnormal wound healing based on data from the medical literature. There have also been reports of fluid accumulation, including peripheral edema, lymphedema, pleural effusion, ascites, and pericardial effusions (including hemodynamically significant effusions and tamponade requiring intervention in children and adults), in patients receiving Rapamune.

•Hyperlipidemia:
Increased serum cholesterol and triglycerides requiring treatment occurred more frequently in patients treated with Rapamune compared with azathioprine or placebo controls in clinical studies. There were increased incidences of hypercholesterolemia (43-46%) and/or hypertriglyceridemia (45-57%) in patients receiving Rapamune compared with placebo controls (each 23%). The risk/benefit should be carefully considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including Rapamune.

Any patient who is administered Rapamune should be monitored for hyperlipidemia. If detected, interventions such as diet, exercise, and lipid-lowering agents should be initiated as outlined by the National Cholesterol Education Program guidelines. During Rapamune therapy with or without cyclosporine, patients should be monitored for elevated lipids, and patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

•Interstitial Lung Disease/Non-Infectious Pneumonitis

Cases of interstitial lung disease [ILD] (including pneumonitis, bronchiolitis obliterans organizing pneumonia [BOOP], and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the ILD was reported with pulmonary hypertension (including pulmonary arterial hypertension [PAH]) as a secondary event. In some cases, the ILD has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the trough sirolimus concentration increases.

Additional risks that pertain to the renal transplant population include declines in renal function, proteinuria, increased risk of calcineurin associated thrombotic microangiopathy, and additional opportunistic infections such as PCP and latent viral infections with BK or others. Please refer to full prescribing information in the FDA package insert.

Absorption

"The mean time to peak concentration after ingestion of the oral solution is approximately 1 hour and 2 hours in healthy subjects and renal transplant patients, respectively. The systemic availability of sirolimus is low, and was estimated to be approximately 14% after the administration of Rapamune Oral Solution. In healthy subjects, the mean bioavailability of sirolimus after administration of the tablet is approximately 27% higher relative to the solution. Sirolimus tablets are not bioequivalent to the solution; however, clinical equivalence has been demonstrated at the 2 mg dose level. To minimize variability in sirolimus concentrations, both Rapamune Oral Solution and Tablets should be taken consistently with or without food."

Distribution

"The mean (± SD) blood-to-plasma ratio of sirolimus was 36 ± 18 in stable renal allograft patients, indicating that sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution (Vss/F) of sirolimus is 12 ± 8 L/kg. Sirolimus is extensively bound (approximately 92%) to human plasma proteins, mainly serum albumin (97%)."

Metabolism

"Sirolimus is a substrate for both CYP3A4 and P-gp. Sirolimus is extensively metabolized in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen. Inhibitors of CYP3A4 and P-gp increase sirolimus concentrations. Inducers of CYP3A4 and P-gp decrease sirolimus concentrations."

Excretion

"After a single dose of [14C] sirolimus oral solution in healthy volunteers, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine. The mean ± SD terminal elimination half-life (t1⁄2) of sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours."

Patients with Renal Impairment

"The effect of renal impairment on the pharmacokinetics of sirolimus is not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites in healthy volunteers. The loading and the maintenance doses of Rapamune need not be adjusted in patients with renal impairment."

Patients with Hepatic Impairment

"Rapamune was administered as a single, oral dose to subjects with normal hepatic function and to patients with Child-Pugh classification A (mild), B (moderate), or C (severe) hepatic impairment. Compared with the values in the normal hepatic function group, the patients with mild, moderate, and severe hepatic impairment had 43%, 94%, and 189% higher mean values for sirolimus AUC, respectively, with no statistically significant differences in mean Cmax. As the severity of hepatic impairment increased, there were steady increases in mean sirolimus t1/2, and decreases in the mean sirolimus clearance normalized for body weight (CL/F/kg). The maintenance dose of Rapamune should be reduced by approximately one third in patients with mild-to-moderate hepatic impairment and by approximately one half in patients with severe hepatic impairment. It is not necessary to modify the Rapamune loading dose in patients with mild, moderate, and severe hepatic impairment. Therapeutic drug monitoring is necessary in all patients with hepatic impairment."

Effects of Age, Gender, and Ethnicity

"Clinical studies of Rapamune did not include a sufficient number of patients > 65 years of age to determine whether they will respond differently than younger patients. After the administration of Rapamune Oral Solution or Tablets, sirolimus trough concentration data in renal transplant patients > 65 years of age were similar to those in the adult population 18 to 65 years of age. Sirolimus clearance in males was 12% lower than that in females; male subjects had a significantly longer t1/2 than did female subjects (72.3 hours versus 61.3 hours). Dose adjustments based on gender are not recommended. In the phase 3 trials for the prophylaxis of organ rejection following renal transplantation using Rapamune solution or tablets and cyclosporine oral solution and/or cyclosporine capsules there were no significant differences in mean trough sirolimus concentrations over time between Black (n = 190) and non-Black (n = 852) patients during the first 6 months after transplantation."

1.6.2.3 Risks associated with heavy water

Deuterium (2H) is a naturally occurring, stable, non-radioactive isotope. Occasional cases of transient dizziness have been reported on the first day of drinking heavy water and participants are warned not to drive for 30 minutes following the intake of the first dose. No other known side effects have been reported.

1.6.2.4 Overall benefit-risk

Standard of care therapy for resectable stage I-IIIA NSCLC, namely post-operative chemotherapy in those patients with at least stage II disease, is associated with significant risk of recurrent disease. Multiple ongoing single agent and combination therapy trials of immunotherapy are on-going and of a similar design to this trial. Both neoadjuvant agents are well tolerated individually and care will be given to close monitoring with safety assessments. Overall this study has a good risk-benefit profile to both benefit enrolling patients and inform future combination therapies.

2. STUDY OBJECTIVES

2.1 Co-Primary objective(s)

- To evaluate the safety and tolerability of sirolimus followed by durvalumab as neoadjuvant treatment by incidence of adverse events, with severity per NCI CTCAE v5.0.

- To evaluate the efficacy of sirolimus followed by durvalumab as neoadjuvant treatment for Stage I, II, and IIIA NSCLC by complete pathologic response at surgical resection scored by a pathologist.

2.2 Secondary objective(s)

- To evaluate the efficacy of sirolimus in combination with durvalumab as neoadjuvant treatment for Stage I, II, and IIIA NSCLC by Investigator-assessed response rate per RECIST v1.1, disease free survival and overall survival

- To evaluate response to sirolimus in combination with durvalumab in patients with PD-L1-positive vs. PD-L1-negative tumors by complete pathologic response rate

- To evaluate the association between blood mutation burden and response to sirolimus and durvalumab by overall response rate in PD-L1-positive and PD-L1-negative groups based on mutational burden.

- To evaluate impact of neoadjuvant durvalumab and sirolimus on post-surgical recovery by length of hospital stay after surgery

2.3 Exploratory objective(s)

- To evaluate the immune-mediated effects of combination sirolimus and durvalumab by assessment of immune responses by flow cytometry, cytokine analysis, and genetic assessments in serial blood and tissue samples and correlate with clinical outcome

- To investigate tumor and immune microenvironment changes in tissue samples by pathological analyses (which may include immunohistochemistry immunofluorescence) of tissue samples pre- and post- neoadjuvant therapy

3. STUDY DESIGN

3.1 Overview of study design

This is a Phase Ib open-label, single-arm study in newly diagnosed stage I-IIIA NSCLC patients, to test sirolimus in combination with durvalumab as neoadjuvant treatment prior to curative-intent surgical resection. The safety and tolerability as well as efficacy of combination sirolimus with durvalumab will be evaluated in this treatment setting. The study is also designed to investigate a number of laboratory correlative studies to define mechanisms of anti-tumor activity of sirolimus + durvalumab and several potential predictive biomarkers, which will help identify patients who are more likely to respond to treatment. Finally, the study will also include DFS and OS as secondary endpoints.

Up to 31 patients with NSCLC will be enrolled in this study at Emory University Winship Cancer Institute and affiliated sites. Enrollment will occur in 2 parts based on simon 2 stage design, in which at least 2 of the first 16 patients must achieve pathologic complete response in order for the study to enroll 15 additional patients.

Eligible patients will complete 2 cycles of outpatient study treatment prior to proceeding to standard of care surgical resection. In order to allow a reliable assessment of the contribution of sirolimus versus durvalumab to the observed clinical and PD outcome, treatment will start with sirolimus 6mg orally for one loading dose followed by 2mg orally once daily three weeks prior to the start of durvalumab. Durvalumab will be administered at a dose of 1500mg Q 3 weeks starting on C1D1 for up to 2 cycles that are 21 days in length. Pharmacodynamic analysis will be done using PD samples collected at baseline (tissue) and with blood samples on day -7, C1D1 prior to durvalumab, C1D8, C2D1, C2D8 and at the time of surgery (blood and tissue). Additional post surgery blood samples will be collected at 1, 3, and 6 months post-surgery. See **study schedule of assessments** for schedule of Biomarker collection. Patients will proceed to surgery within a 4-week period post 2nd dose of durvalumab but not earlier than one week after the administration of durvalumab i.e. not earlier than C2D8. Additionally, patients will self-administer heavy water (D2O) 50ml orally three times a day from C1D1 through C1D5 followed by 50ml orally twice a day through the day prior to surgery in order to label dividing cells for research tracking purposes.

The dose of sirolimus chosen for this study is based on our pre-clinical data that indicate that a lower dose is most likely to result in the desirable pharmacodynamics effects on the immune system. For clinical use in the renal transplant setting and high immunologic risk transplants, sirolimus is recommended at an initial loading dose of 15 mg followed by 5mg/day maintenance, with adjustments based on trough level. In lymphangiolyomyomatosis (LAM), the recommended dose is 2 mg daily to block mTOR pathway activation; median whole blood

sirolimus trough concentration after 3 weeks of receiving sirolimus tablets at a dose of 2 mg/day was 6.8 ng/mL (interquartile range 4.6 to 9.0 ng/mL; n = 37). As the sirolimus treatment phase will be only 3 weeks, a single loading dose of 6mg on day 1 will be followed by 2mg daily. No dose changes will be made for individual patients given this short term low dose regimen designed to reach levels of 5-15 ng/ml, which was noted in pre-clinical studies to correlate with proliferation of memory T cells. This lower dose is also likely to be tolerated better by patients.

As an added safety measure, the first 6 patients will be monitored through hospital discharge following surgical resection to assess for dose limiting toxicities (DLTs) related to sirolimus followed by durvalumab therapy. DLTs and safety analysis are described in section 6.4.

Patients will be closely monitored for safety and tolerability throughout the study. Safety assessments will include collection and monitoring of adverse events and laboratory abnormalities graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0). Tumor tissue samples, normal lung parenchyma, whole blood samples, and optional lymph node samples will be collected for biomarker assessments.

After study treatment discontinuation, patients will be followed per SOC, but information on recurrence and survival will be collected every 6 months for up to 2 years after the last patient receives the last dose in the study (in person or by phone). Patients who discontinue the study due to adverse events will be followed until resolution or stabilization of the adverse event. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

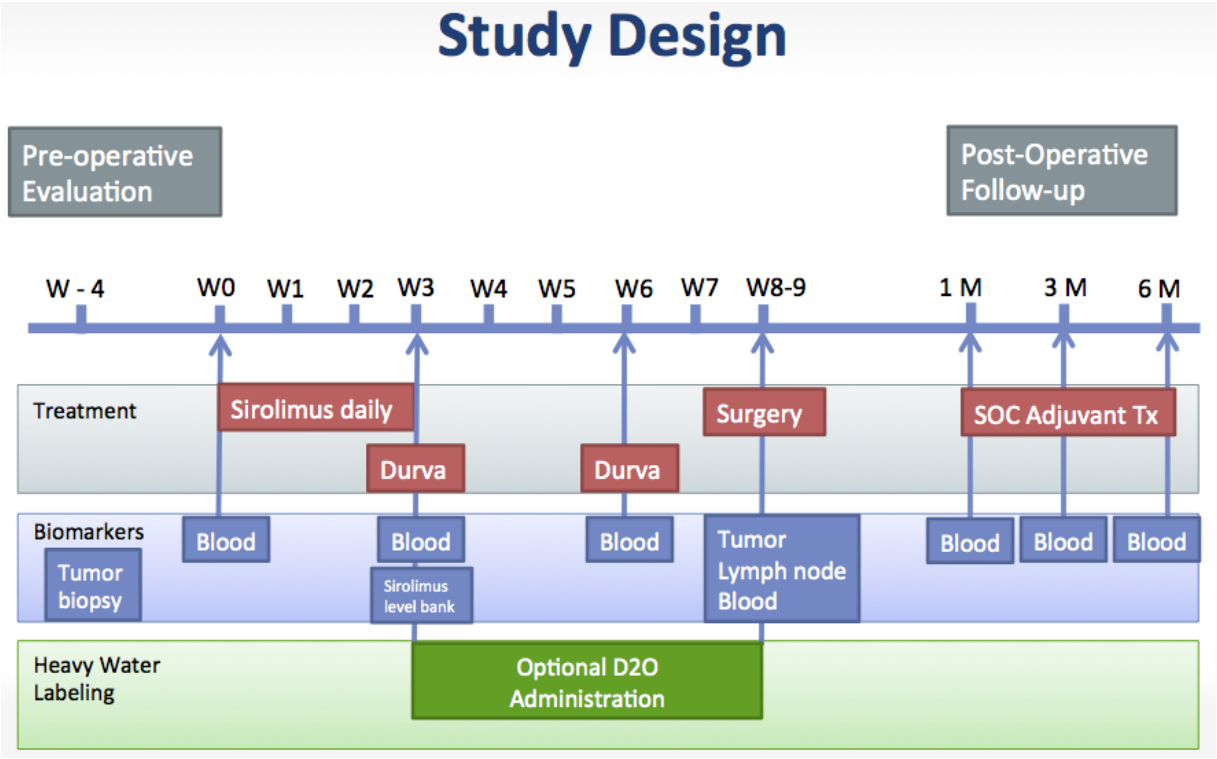
Table 1: Neoadjuvant Study Treatment dosing regimen

Regimen Description					
Agent	**Premedications Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Sirolimus	Take with or without food	6 mg on day 1, followed by 2mg	PO	Once daily Start on day 1	21 days (3 weeks)

		daily on days 2-21			
Durvalumab	None required	1500 mg in NS or D5W	IV over 1 hr	Once every 3 weeks, starting on day 22	

3.2 Study schema

Figure 1. Study Schema



Durva: 1500mg of durvalumab

W: week; M: month; SOC: standard of care; Tx: treatment

3.3 Surgical Resection

Following neoadjuvant systemic treatment described above, patients will undergo surgical resection of the primary tumor and associated lymph nodes. Repeat chest CT scan and/or PET/CT scan will be obtained prior to surgical resection. Resection may be accomplished via an open or minimally invasive procedure (i.e., thoracotomy, sternotomy, video assisted thoracic surgery (VATS) or robotically assisted VATS.)

Anatomic resection via segmentectomy, lobectomy, bilobectomy or pneumonectomy is strongly preferred although wedge resection is acceptable for very small (2 cm or less) tumors located peripherally where wedge resection permits a wide margin (at least 1 cm in all directions).

Hilar and mediastinal lymph node dissection or sampling should be performed whenever possible. For right sided resections, the recommended sampling includes lymph nodes from levels 4R, 7, 10R, and 11R. For left sided resections, the recommended sampling includes lymph nodes from levels 5/6, 7, 10L, and 11L.

Pathologic specimens will undergo standard histopathologic and immunohistochemical evaluation for lung cancer. Sections of tumor and normal tissue specimens will be fresh frozen and formalin-fixed for correlative studies. Sections of lymph nodes will be freshly prepared in media and formalin-fixed for correlative studies. Whole blood samples will be collected at the time of surgical resection for correlative studies. The blood will be processed for PBMC, plasma, and serum for correlative studies.

At the postoperative follow-up visit, patients whose tumors have not demonstrated evidence of pathologic response and who have radiographic progression will have an end-of-study treatment visit, after which they will be followed per SOC, as deemed clinically appropriate. Whole blood will be collected at postoperative follow-up visit and will be processed for plasma, serum, and PBMC for correlative studies.

3.4 Study oversight for safety evaluation

There will be a planned safety assessment of the first 6 patients, who will be monitored through hospital discharge following surgical resection to assess for dose limiting toxicities (DLTs) related to sirolimus followed by durvalumab therapy. If $\geq$ 2/6 patients have a DLT then additional enrollment will be halted until safety assessment is completed.

4. PATIENT SELECTION

4.1 Inclusion criteria

For inclusion in the study patients must fulfill all of the following criteria:

1. Patients with pathologically documented NSCLC who are deemed to be candidates for definitive surgery: Stage will be categorized based on 8th edition of American Joint Committee on Cancer (AJCC) Non-small cell Lung Cancer Staging system; see Appendix 3.

2. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

3. Age ≥ 18 years at time of study entry.

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

5. Life expectancy of ≥ 26 weeks

6. Body weight >30 kg

7. Adequate normal organ and marrow function as defined below:

   - Haemoglobin ≥9.0 g/dL
   - Absolute neutrophil count (ANC) 1.5 x 10^9/L (≥ 1500 per mm^3)
   - Platelet count ≥100 x 10^9/L (≥100,000 per mm^3)
   - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN).
   - 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
   - Measured creatinine clearance (CL) >40 mL/min or Calculated 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:

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

8. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

   – 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).

9. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

10. Patients must consent to pre-treatment research biopsy and study peripheral blood collection.

11. Patients must have measurable disease, defined by RECIST v 1.1.

12. Patient is able to take oral medications

13. Patient consents to heavy water (D2O) self-administration if on optional heavy water labelling study

4.2 Exclusion criteria

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

1. Patients who have had prior therapy for lung cancer including chemotherapy, hormonal therapy, or radiotherapy.

2. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study

3. Prior treatment with anti-PD-1, anti-PDL-1, including durvalumab other PD-1/PDL-1 pathway targeting agents, or mTOR inhibition.

4. History of allogenic organ transplantation.

5. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

    a. Patients with vitiligo or alopecia

    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement

    c. Any chronic skin condition that does not require systemic therapy

    d. Patients without active disease in the last 5 years may be included but only after consultation with the study physician

    e. Patients with celiac disease controlled by diet alone

6. 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

7. History of another primary malignancy except for

a. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence

b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

c. Adequately treated carcinoma in situ without evidence of disease

8. QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms. Patient safety and the cardiac SKG should be consulted as needed.

9. History of active primary immunodeficiency

10. 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.** Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

11. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

    a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)

    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

12. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

13. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy.

14. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

15. Prior randomisation or treatment in a previous durvalumab clinical study regardless of treatment arm assignment.

16. Patients with a history of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia, or evidence of active pneumonitis on screening chest CT scan

17. Inability to stop prohibited concomitant medications listed in Section 7.7.2.

18. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.3

4.3 Withdrawal of patients from study treatment and/or study

Stopping Rules:

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Radiographic and/or symptomatic deterioration attributed to disease progression disease as determined by the investigator
- Intolerable toxicity related to sirolimus and/or durvalumab, including development of an irAE determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues on study treatment
- Use of another non-protocol-specified anti-cancer therapy

The primary reason for study treatment discontinuation should be documented on the appropriate CRF.

Additional reasons for patient discontinuation include:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

Permanent discontinuation of study treatment

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. A patient who decides to discontinue durvalumab or sirolimus will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see the SoAs).

All patients will be followed for survival until the end of the study.

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in the SoAs as an alternative.

Patients who have permanently discontinued from further receipt of IP will need to be discontinued from the IVRS/IWRS.

Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

In order to support key end points of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up."

- Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable CRF modules will be updated.)

- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

Withdrawal of consent

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

Patients 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 patient 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 to the use of any samples

4.4 Replacement of patients

Patients who withdraw consent prior to administration of durvalumab will be replaced. Patients who discontinue study treatment prematurely will not be replaced.

5. INVESTIGATIONAL PRODUCT(S)

5.1 Durvalumab

5.1.1 Formulation/packaging/storage

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 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 Investigational Product should be kept in original packaging until use to prevent prolonged light exposure.

5.1.2 Durvalumab doses and treatment regimens

Regimen Description					
Agent	**Premedications Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Durvalumab	None required	1500 mg in NS or D5W	IV over 1 hr	Once every 3 weeks, starting on day 22	21 days (3 weeks)

5.1.3 Study drug preparation

Patients will receive 1500 mg durvalumab via IV infusion q3w for a maximum of 2 doses. Weight based dosing (20 mg/kg) will be utilized for any patient whose body weight drops below to 30 kg or below (≤30 kg) while on study.

Preparation of durvalumab doses for administration with an IV bag

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

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

A dose of 1500 mg (for patients >30 kg in weight) 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 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add

30.0 mL of durvalumab (i.e., 1500 mg of durvalumab) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If weight falls to ≤ 30 kg weight-based dosing at 20 mg/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 15mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

Standard infusion time is 1 hour.In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

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

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered or complete the infusion according to institutional policy to ensure the full dose is administered. If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

5.1.4 Monitoring of dose administration

Patients will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Patients are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

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 (up to 4 hours) 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. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature (otherwise requires new infusion preparation). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in **Error! Reference source not found.**.

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.

5.1.5 Accountability and dispensation

Administration will occur at the study site (Winship Cancer Institute) or Grady Memorial Hospital and recorded in medical record as well as study specific event sheet.

5.1.6 Disposition of unused investigational study drug

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

5.2 Sirolimus

5.2.1 Formulation/packaging/storage

Sirolimus (Rapamune) is supplied as in both an oral solution and tablets for oral administration. This study will preferentially use the tablet formulation from commercial supply:

Rapamune Tablets are available supplied in bottle or blister cards as follows:

- NDC 0008-1040-05, 0.5 mg, tan, triangular-shaped tablets marked “RAPAMUNE 0.5 mg” on one side; bottle containing 100 tablets.
- NDC 0008-1040-10, 0.5 mg, tan, triangular-shaped tablets marked “RAPAMUNE 0.5 mg” on one side; in of 100 tablets (10 blister cards of 10 tablets each).
- NDC 0008-1041-05, 1 mg, white, triangular-shaped tablets marked “RAPAMUNE 1 mg” on one side; bottle containing 100 tablets.
- NDC 0008-1041-10, 1 mg, white, triangular-shaped tablets marked “RAPAMUNE 1 mg” on one side; in of 100 tablets (10 blister cards of 10 tablets each).
- NDC 0008-1042-05, 2 mg, yellow-to-beige triangular-shaped tablets marked “RAPAMUNE 2 mg” on one side; bottle containing 100 tablets.

Rapamune Tablets should be stored at 20° to 25°C [USP Controlled Room Temperature] (68° to 77°F). Use cartons to protect blister cards and strips from light. Dispense in a tight, light-resistant container as defined in the USP.

5.2.2 Doses and treatment regimens

The dose of sirolimus for this study is 6mg orally daily once on day 1, followed by 2mg orally daily from day 2 through 21.

5.2.3 Dose administration

Patients will self-administer on a continuous once daily dosing schedule. Patients should be instructed to take the dose of sirolimus daily in the morning with or without food at approximately the same time each day. However, dietary habits around the time of sirolimus intake should be as consistent as possible throughout the study. Patients should swallow the tablets as a whole and not chew them.

If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted as an adverse event. If the patient forgets to take her/his dose and does not remember before 6:00 PM, then the dose should be withheld that day and sirolimus resumed the following day.

Patients must avoid consumption of St. John's Wort, Seville oranges, grapefruit or grapefruit juice, grapefruit hybrids, pummelos and exotic citrus fruits from 7 days prior to the first dose of study medication and during the entire study treatment period due to potential CYP3A4 interaction with the study medication. Patients must avoid concomitant intake of strong and moderate CYP3A4/5 inhibitors and inducers. Orange juice is allowed.

5.2.4 Monitoring of dose administration

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

5.2.5 Disposition of unused investigational study drug

Patients will return any unused medication to their study site for disposal by investigaional pharmacy services.

5.3 Heavy Water (D2O)

Deuterated water is 70% D2O and 30% normal H2O and is manufactured and supplied by Cambridge Isotope Laboratories. The Emory research pharmacy will sterilely portion out individually labeled 50ml conical tubes and provide to trial patients who agree to optional heavy water labelling study. Patients will self-administer 50 ml orally TID for the first 5 days to serve as

a loading dose (Day 22, C1 Durvalumab). Subsequently, patients will self-administer 50 ml orally BID from day 27 until the day prior to surgery. Previous and ongoing studies have shown high compliance among donors. Since compliance with drinking the heavy water is critical to achieve adequate deuterium enrichment of body water, participants will be encouraged and rewarded for completing the memory aid provided (See **Appendix 5**) to help keep track of the heavy water consumption.

6. TREATMENT PLANT

6.1 Patient enrollment

Patients will be enrolled following screening procedures on the open label study. Those patients who withdraw consent and discontinue the study prior to a dose of durvalumab will be replaced.

6.2 Dosage and administration

Refer to Section 5.1.4 and 5.1.5 for the administration and monitoring of administration of durvalumab

Refer to Section 5.2.3 and 0 for the administration and monitoring of any additional study drug(s)

6.3 Definition of DLT

Dose-limiting toxicities (DLTs) will be evaluated in the first 6 patients enrolled on the trial. The period for evaluating DLTs will be from the time of first administration of durvalumab until discharge from the hospital following surgical resection. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Continued enrollment of subsequent patients will be allowed during the DLT monitoring period.

If and when ≥2 DLTs are identified in the first 6 patients, then subsequent enrollment will be halted until safety review. Patients already started on therapy will continue per protocol.
A DLT is defined as the occurrence of an adverse event (AE) that is **at least possibly related to the investigational product (IP) or investigational regimen (IR)**, with two exceptions: any grade of vitiligo or alopecia will not qualify as a DLT. AEs that are **at least possibly related to durvalumab-containing regimens** shall be assessed as DLTs if they meet any of the following criteria:

Hematologic toxicity:

- Grade ≥3 neutropenia complicated by fever >38.3°C
- Grade 4 neutropenia (lasting more than 7 days)
- Grade ≥3 thrombocytopenia with significant bleeding
- Grade 4 thrombocytopenia (regardless of duration)
- Grade 4 anemia (regardless of duration)

Non-hematologic toxicity:

- Any Grade 4 non-immune-mediated AE
- Any Grade 4 immune-mediated AE, excluding endocrinopathies
- Any Grade 3 non-immune mediated AE that does not resolve to ≤Grade 1 or baseline within 30 days with optimal medical management
- Any Grade 3 immune-mediated AE – excluding diarrhea/colitis, pneumonitis, hepatitis, rash, neurotoxicity, myocarditis, myositis/polymyositis, endocrinopathies and nephritis – that does not resolve to ≤Grade 1 or baseline within 30 days after onset of the event despite optimal medical management including systemic corticosteroids
- Grade 3 diarrhea or colitis that does not resolve to ≤Grade 1 within 14 days [*both* immune- *and* non-immune-mediated indicated here; the same is the case if not specified in remaining bullet points below]
- Grade 3 noninfectious pneumonitis
- Grade 2 noninfectious pneumonitis that does not resolve to ≤Grade 1 within 3 days of the initiation of maximal supportive care
- **Aspartate** aminotransferase (AST) or **alanine** aminotransferase (ALT) ≥3×ULN with concurrent increase in total bilirubin (TBL) ≥2×ULN without evidence of cholestasis or alternative explanations (e.g., viral hepatitis, disease progression in the liver; i.e., "Hy's Law")
- ALT or AST >8×ULN or TBL>5×ULN
- Grade 3 immune-mediated rash that does not resolve to ≤Grade 1 or baseline within 30 days
- Grade 2 rash covering > 30% BSA that does not resolve to ≤Grade 1 or baseline within 30 days
- Any grade of immune-mediated rash with bullous formation
- Grade 3 immune-mediated neurotoxicity (excluding Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 30 days
- Grade 2 or 3 immune-mediated peripheral neuromotor syndrome (such as Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 30 days or that exhibits signs of respiratory insufficiency or autonomic instability
- Grade 3 immune-mediated myocarditis
- Any symptomatic immune-mediated myocarditis that does not become asymptomatic within 3 days of initiating optimal medical management including systemic corticosteroids

- Grade 2 or 3 immune-mediated myositis/polymyositis that does not resolve to Grade ≤1 within 30 days of initiating optimal medical management including systemic corticosteroids or that exhibits signs of respiratory insufficiency regardless of optimal medical management
- Immune-mediated increase in creatinine >3×ULN, or >3×baseline for patients with a baseline creatinine elevated above ULN
- Delay in administration of scheduled doses of sirolimus greater than 2 weeks because of drug-related toxicity of any grade.

Any treatment-related toxicities that first occurred during the DLT period must be followed for resolution to determine if the event qualifies as a DLT as specified in the DLT criteria above.

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 Toxicity management guidelines

6.4.1 Durvalumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the durvalumab Toxicity Management Guidelines (TMGs). Please see APPENDIX 1.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see section **Error! Reference source not found.** of this protocol and the Dosing Modification and Toxicity Management Guidelines in **Error! Reference source not found.**).

Following the first dose of IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in **Error! Reference source not found.**. These guidelines have been prepared 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 durvalumab monotherapy by the reporting investigator.

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

All toxicities will be graded according to NCI CTCAE, Version5.0.

6.4.2 Sirolimus

Table 2 Criteria for interruption and re-initiation of Sirolimus

Stomatitis	Description	Management/Next Dose for Sirolimus
Grade 1	Minimal symptoms, normal diet	No modifications necessary. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day
Grade 2	Symptomatic but can eat and swallow modified diet	Manage with topical analgesic mouth treatments (e.g. benzocaine, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)
Grade 3	Symptomatic and unable to adequately aliment or hydrate orally	Temporary dose interruption until recovery to grade ≤1. Manage with topical analgesic mouth treatments (e.g. benzocaine, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)
Grade 4	Symptoms associated with life-threatening consequences	Discontinue Sirolimus and treat with appropriate medical therapy.
*Patients requiring a delay of >2 weeks should go off protocol therapy.		

Other Non-hematologic toxicities	Management/Next Dose for Sirolimus
≤ Grade 1	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor.
Grade 2	If toxicity is tolerable, no dose adjustment required. Initiate appropriate medical therapy and monitor. If toxicity becomes intolerable, temporary dose interruption until recovery to grade ≤1. Re-initiate sirolimus at the same dose. If toxicity recurs at grade 2, interrupt sirolimus until recovery to grade ≤1. Re-initiate sirolimus at the same dose.

Other Non-hematologic toxicities	**Management/Next Dose for Sirolimus**
Grade 3	Temporary dose interruption until recovery to grade ≤1. Initiate appropriate medical therapy and monitor. Consider re-initiating sirolimus. If toxicity recurs at grade 3, consider discontinuation.
Grade 4	Discontinue sirolimus and treat with appropriate medical therapy.
*Patients requiring a delay of >2 weeks should go off protocol therapy.	

Hematologic Toxicities (anemia, neutropenia, thrombocytopenia)	**Management/Next Dose for Sirolimus**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose.
Grade 3	Hold until < Grade 2. Resume at same dose. *
Grade 4	Off protocol therapy
* Patients who develop grade 3 neutropenia associated with temperature higher than 38.3 C should go off protocol therapy. Patients requiring a delay of >2 weeks should go off protocol therapy	

6.4.3 Potential Overlapping Toxicites

Based on the pharmacological properties of a large monoclonal antibody and oral small molecule inhibitor, there are not anticipated overlapping toxicities.

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

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

- Female patients of childbearing potential who are not abstinent and intend to be 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 throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Non-sterilised male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential

- Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 3).

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

Women will be considered 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.

- 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.

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 • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

[a] This is also considered a hormonal method

Blood donation

Patients should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab.

7.2 Concomitant treatment(s)

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 7 days prior to initiation of study drug to the study completion/ discontinuation visit. Because there is a potential for interaction of sirolimus with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Appendix 4 presents guidelines for identifying medications/substances that could potentially interact with the study agent(s).

7.2.1 Permitted concomitant medications

Table 4. Permitted 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 above	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 [including palliative radiotherapy to non-target lesions, etc.])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted
Inhaled steroids for COPD, mineralocorticoids (eg fludrocortisone for adrenocortical insufficiency), and prednisone < 10mg daily	Permitted

Standard-of-Care Chemotherapy (with or without Radiation) after Surgical Resection

After surgical resection of their tumor, patients may receive SOC chemotherapy (with or without radiation) after surgical resection of their tumor. Choice of SOC adjuvant therapy will be at the discretion of the treating physician, depending on the stage of their disease, as deemed clinically appropriate.

7.2.2 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 [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., 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, or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs, • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).

Prohibited medication/class of drug:	Usage:
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 (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor
Seville orange, star fruit, grapefruit and their juices	Should not be used concomitantly as they affect P450 and P glycoprotein (P-gp) activity.
Strong inhibitors of CYP3A4 or P-GP	Should not be given concomitantly, see table 5
Strong inducers of CYP3A4	Should not be given concomitantly, see table 5
Moderate CYP3A4 inhibtors	Should be used with caution, see table 5

Table 6. List of CYP3A4 strong and moderate inhibitors and inducers

Strong CYP3A4,5,7 inhibitors	Moderate CYP3A4,5,7 inhibitors	CYP3A4 inducers
clarithromycin	aprepitant	Barbiturates
Conivaptan	atazanavir	Carbamazepine
grapefruit juice	cimetidine	Efavirenz
Indinavir	ciprofloxacin	Modafenil
Itraconazole	darunavir	Nevirapine
Ketoconazole	diltiazem	Oxcarbazepine
Lopinavir	erythromycin	Phenobarbital
Mibefradil	fluconazole	Phenytoin
Nefazodone	tofisopam	pioglitazone
Nelfinavir	verapamil	Rifabutin
Posaconazole	amprenavir	Rifampin
Ritonavir	fosamprenavir	St. John's wort
Saquinavir		Topiramate

Strong CYP3A4,5,7 inhibitors	**Moderate CYP3A4,5,7 inhibitors**	**CYP3A4 inducers**
Telithromycin		troglitazone
Troleandomycin		
Voriconazole		
This database of CYP inhibitors was compiled from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database based on *in vitro* studies. Strong inhibitors are predicted to increase BKM120 AUC > 5-fold, and moderate inhibitors are predicted to increase BKM120 AUC ≥ 2-fold but < 5-fold. This database of CYP inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table; and from (Pursche et al. 2008).		

8. STUDY PROCEDURES

8.1 Schedule of 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 Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

- Tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of surgery.
- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc. required for dosing should be performed within 3 days prior to dosing.
- Patients may delay durvalumab dosing under certain circumstances.
  - Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible

8.1.1 Screening phase

Screening procedures will be performed up to 35 days before Day -7, unless otherwise specified. All patients must first read, understand, and sign the IRB approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, patients 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 ECG (in triplicate [2-5 minutes apart])
- Tumor biopsy for fresh tissue if not already obtained
- Review of prior/concomitant medications
- Imaging by CT/MRI
- Clinical laboratory tests for:
    - Hematology (see Table 7)
    - Clinical chemistry (see Table 8)
    - TSH
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum pregnancy test (for women of childbearing potential only)
    - Hepatitis serologies
    - Urinalysis (see Table 9)

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 72 hours of cycle 1 day 1 do not need to be repeated on cycle 1 day 1.

1. Sirolimus dosing: will be given 6mg po once on day 1, followed by 2mg po daily on days 2-21. Steady state trough levels will be collected on day 23 and stored for batch analysis.

2. Heavy water dosing: first dose to be taken in clinic on day 23 and a 6 week supply for self- administration will be dispensed in labeled conical tubes. The patients will also be shown how to collect salivate samples.

3. Durvalumab dosing: starting on Day 22 q 3 weeks for 2 doses

4. Restaging imaging prior to surgery

5. Standard of care surgical resection

6. Peripheral blood research tube collection per study calendar

8.1.3 End of treatment

End of treatment is defined as the 30 day post hospital discharge/surgery follow-up. All required procedures may be completed within ±7 days of the end of treatment visit. See Appendix 2.

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

8.2 Biological sampling procedures

8.2.1 Biomarker/pharmacodynamic sampling and evaluation methods

Assessment of secondary and exploratory biomarker objectives on tumor tissue, lymph node tissue, and whole blood that may include, but is not limited to, immunohistochemistry, immunofluorescence microscopy, RNA sequencing, DNA sequencing, flow cytometry, and mass spectrometry. Additionally, blood samples will be banked for future analyses related to NSCLC, sirolimus followed by durvalumab's mode of action, and/or understanding of response and may include, but is not limited to, DNA sequencing.

PD-L1 testing

To ensure comparability of data across all studies of durvalumab and to gain real world experience on the performance of this assay, it is strongly encouraged that all studies that include PD-L1 testing utilize the Ventana SP263 assay. 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 (i.e., >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 (e-code 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 of fresh tumor
- 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

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. Where clinically acceptable, a minimum of 2 core biopsies should be collected and processed to FFPE in a single block. The provision of 2 cores is advised in order to provide sufficient tissue for PD-L1 assessment.

- 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). Samples should remain in fixative for 24 – 48 hours 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 should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period.

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-micron 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 5-10 x 4 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
    - Slides are stable under these conditions for 6 months.

- 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 ambient temperature 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.

Next Generation Sequencing of the tumor Either an internal or external validated platform to test for a wide panel of genes including those known to have prognostic or predictive impact on lung cancer outcomes will be tested as per standard institutional protocol.

8.2.2 Blood-based Studies for immunologic analysis

Collection:
Approximately 12-16 ml of blood will be collected into two, 8 ml Cell Preparation Tubes (CPT) at study specified time points. The CPT tubes will be labeled and logged at Emory's Winship Cancer Institute by a skilled nurse or phlebotomist.

Handling:
They will be maintained at room temperature until they are transported to an Emory immunology laboratory for processing for flow cytometry, cytokine, DNA, and RNA analysis. Plasma and PBMC may be used fresh or will be frozen and banked for future batch analyses. All blood-based samples will be handled in biosafety hoods with the handling personnel wearing protective safely gear (lab coat, gloves, and safety glasses when required).

Storage:
Frozen PBMC and plasma samples will be stored at minus 80 degrees Celsius or on liquid nitrogen per standard laboratory protocols.

Flow Cytometry
Detailed phenotypic analysis will be performed on peripheral blood mononuclear cells using standard flow cytometry methods. Fluorescent antibody stains may be used to assess various T cell markers including: CD3, CD4, CD8, CD45RA, CCR7, CD28, PD1, FoxP3, and Tbet. Additional phenotypic B cell analysis may include CD19, IgD, CD38, and CD27 markers. Other markers may be added based on the mechanism of action of the immunologically active agent and growing cancer immunology research findings.

Cytokine Analyses

Cytokine levels will be assessed using commercially available multiplex kits (such as the Luminex and Legendplex platforms). Cytokines of interest may include, but not limited to TNF-alpha, IFN-gamma, IL1-beta, IL-2, IL-6, IL-10, IL17a, and others.

HLA Typing

Patient peripheral blood sample will be used for HLA typing.

DNA and RNA Analyses

Investigational germline and tumor genetic analysis may include RNA isolation and sequencing, DNA extraction and sequencing (including but not limited to whole exome sequencing), and assessment of tumor mutation burden.

Deuterium Label Analysis

Deuterium enrichment in the body water can be determined by collection of saliva, urine or blood samples. CD8 T cells, CD4 T cells and regulatory T cell populations will be sorted from the blood and post-surgical tissues at the Emory flow cytometry core, cell pellets frozen and sent to Dr.Hellerstein's laboratory for DNA extraction and analysis of 2H enrichment. Specifically, we will analyze how much deuterium incorporation has occurred in various sorted subsets to measure the level of proliferation in the cell types in the window of deuterium incorporation.

Sample Prioritization

Pre- and Post-Treatment FFPE Biopsy Samples
1. Pathology analyses
2. PD-L1 IHC analysis
3. Multiplex IF analysis
4. Banking for additional non-protocol-specified exploratory analyses

Pre-Treatment Fresh Frozen Biopsy Samples
1. RNA isolation and sequencing
2. Back-up for RNA and banking for additional non-protocol-specified exploratory analyses

Post-Treatment Fresh Frozen Biopsy Samples
1. RNA sequencing
2. DNA extraction and WES

8.2.3 Sirolimus Level Collection

Sirolimus levels should be collected as troughs to facilitate intra-patient comparison.

Step 1: The level is scheduled to be drawn on day 22, which is C1D1 Durvalumab and the last dose is on day 21. Therefore this timing should be appropriate for trough level. If there are anticipate delays in durvalumab, then appotintment should be made for this lab draw. The coordinator should call the patient 1-2 days before the appointment to remind them about trough level and for patient to bring that am dose to clinic.

Step 2: Collection Tube details:
Whole Blood (EDTA**)**: One 5 mL lavender (EDTA) tube. Minimum volume needed 250 µL whole blood (EDTA), single test, with no repeat.

Step 3: Specimen Preparation: Whole blood. Do not spin. Samples obtained from Winship (either at Emory University or other site such as Emory St. Joseph's Hospital) should be submitted the same day to special chemistry lab. Samples obtained at Grady should be be couriered over to Winship at Clifton road for analysis (along with the CPT tube for immunologic analysis).

- Unacceptable conditions include serum or plasma collection or clotted specimens and will be discarded. Patient should be scheduled for repeat lab
- Storage/Transport Temperature
  Stable at room temperature, 15-30^{o}C for up to 7 days. Stable refrigerated at 2-8^{o}C for up to 14 days.
- Performed only on day shift. Must be in Special Chemistry lab by 13:00 pm M-F and 11:00 am on weekends and holidays for same day results.

8.2.3 Estimate of volume of blood to be collected

The total volume of blood that will be drawn from each patient in this study is as follows: See Table 10. Additional blood may need to be drawn for follow-up of sirolimus trough levels.

Table 10. Volume of Blood to be Drawn From Each Patient

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	**Clinical chemistry**	12	6	72
	Hematology	4	6	24
	Sirolimus Level	4	1	4
	Fasting Lipid Panel	4	1	4
Research Cell Preparation Tubes		16	9	144
Total				248

8.2.4 Archival tumor samples and fresh tumor biopsies use beyond PD-L1

8.2.5 Archival tumor samples

Core biopsy blocks may be requested for immunofluorescent staining of 2-4 unstained slides if sufficient tissue is available. This is not a required analysis.

8.2.5.1 Fresh tumor biopsies

If patients have lesions amenable to core biopsy, then they will be asked to consent to an additional research biopsy to obtain 2-3 image guided fresh core samples prior to any study treatment for baseline immune analysis. These will be kept in a patient labelled sterile container at room temperature and transported to the Ahmed laboratory by courier during the same business day. Once in the lab, the samples will be processed for analysis by flow cytometry, and may include RNA and DNA analysis.

8.2.6 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal Investigator:

- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures 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
- Ensures that the patient is informed about the sample disposal.

9. DISEASE EVALUATION AND METHODS

9.1.1 Pathologic Response Assessment

A detailed pathological evaluation will be performed on the surgically resected samples to obtain data described below.

1. Tumor size (3 measurements)
2. Tumor diagnosis using the 2015 World Health Organization (WHO) classification

3. Predominant differentiation of the tumor (well, moderately, or poorly differentiated), and for adenocarcinoma histology, the histology subtypes present
4. Lowest degree of tumor differentiation
5. Angiolymphatic invasion
6. Neural invasion
7. Margin status in mm
8. Degree of response International Union Against Cancer (UICC) pathological T and N stage
9. Total percentage of areas of necrosis
10. Total percentage of areas of fibrosis
11. Total percentage of viable tumor tissue
12. Total percentage of viable malignant cells
13. Evidence of field effect.

9.1.2 Radiographic Response Assessment of Anti-tumor effect

For the purposes of this study, patients should be re-evaluated for response prior to surgical resection.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[46]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with sirolimus.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of Durvalumab, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

Disease Parameters

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

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold

scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers will not be used in this study to assess response.

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

Response Criteria

Evaluation of Target Lesions

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

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

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

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

Evaluation of Non-Target Lesions

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

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

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

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

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

Evaluation of Best Overall Response

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

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	

SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

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

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

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).
The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

10. ASSESSMENT OF SAFETY

10.1.1 Clinical laboratory tests

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see the SoAs). Samples will be run at the clinic/hospital site utilized by each patient. Laboratory values outside reference ranges will be reviewed by a study investigator.

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables to be measured are presented in Table 7 (hematology), Table 8 (chemistry), and Table 9 (urinalysis).

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, and HIV antibodies.

The following laboratory variables will be measured:

Table 7. 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	

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

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

Table 8. Clinical Chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase	Uric acid

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] gamma glutamyltransferase, and magnesium testing are to be performed at baseline, on Day 0 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 0), and if clinically indicated.

[d] Creatinine Clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).

[e] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day 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

Table 9. 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

If a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to **Error! Reference source not found.** for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at the post-surgery, end of treatment visit.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 10.5.

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

10.1.2 Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, 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 10.5.

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

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

Situations in which ECG results should be reported as AEs are described in Section 10.5

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

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

Situations in which ECG results should be reported as AEs are described in Section 10.

10.1.3 Vital signs

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

First infusion

On the first infusion day, patients will be monitored and vital signs collected/recorded in eCRF 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 [i.e., 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.

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.

10.1.4 Early patient review for safety

Patients will be seen in close interval follow-up (Cycle 1 Day 8, Cycle 2 Day 8, and during surgical window to ensure early identification and management of toxicities.

10.1.5 WHO/ECOG performance status

ECOG performance status will be assessed at the times specified in the assessment schedules (see the SoAs) based on the following:

0. Fully active; able to carry out all usual activities without restrictions

1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (e.g., light housework or office work)

2. Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.

3. Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4. Completely disabled; unable to carry out any self-care and totally confined to bed or chair

5. Dead

Any significant change from baseline or screening must be reported as an AE.

10.1.6 Other safety assessments

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 1) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc.) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

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

10.2 Safety parameters

10.2.1.1 Definition of adverse events

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a patient's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the patient has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the patient being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

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

10.2.2 Definition of serious adverse events

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 patient
- 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.

10.2.3 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. An AESI may be serious or non-serious.

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 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)

- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the skin of the eyes, haematological and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please 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.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see **Error! Reference source not found.**) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc.) will be captured in <<specify where this information will be recorded e.g. eCRF, CRF, etc.)>>

It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:

(i) ILD Markers (KL-6, SP-D) and β-D-glucan

(ii) Tumor markers: Particular tumor markers which are related to disease progression.

Additional Clinical chemistry: CRP, LDH

10.2.4 Safety data to be collected following the final DCO of the study

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Appendix 1). All data post the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving durvalumab treatment (or within the 90 days following the last dose of durvalumab treatment) post the final DCO and database closure must be reported as detailed in Section 10.5

10.3 Assessment of safety parameters

10.3.1 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 v5.0.
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 patient.
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 patient.
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 patient 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 in Section 10.1.2. 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 non-serious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.4 Recording of adverse events and serious adverse events

AEs and SAEs will be collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of durvalumab). <<teams to include required follow up period for the comparator agent>>). If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study drug or the study has completed.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF.

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

The following variables will be collected for each AE:

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

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

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

- Date the AE met criteria for SAE

- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 10.4.2
- Description of the SAE

The grading scales found in the NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

10.4.1 Study recording period and follow-up for adverse events and serious adverse events

If a patient discontinues from treatment and 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 patient 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.

10.4.2 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 **Error! Reference source not found.**.

10.4.3 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 (i.e., 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 (e.g., 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.

10.4.4 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 CRF.

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.

10.4.5 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 (e.g., 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.

10.4.6 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 **Error! Reference source not found.** for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

10.4.7 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.

10.4.8 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.

10.4.9 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 CRF 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 CRF.
- 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 CRF.
- 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.

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 patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

10.4.10 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF.

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

10.4.11 Post-study events

After the patient has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study patients after the 90-day safety follow-up period for patients treated with durvalumab. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Patient Safety.

10.5 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 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 serious, related and unexpected adverse events must be reported to AstraZeneca regardless of the country where the study is conducted.

For those events requiring expedited reporting to the regulatory authorities, the investigator and/or sponsor must inform all applicable regulatory authorities (e.g. FDA), via a MedWatch/AdEERs or applicable required regulatory form (e.g. CIOMS), of any serious, related and unexpected adverse events in accordance with reporting obligations (e.g. FDA21 CFR 312.32) and will concurrently forward all such reports to AstraZeneca in English. A copy of the MedWatch/AdEERs report must be emailed to AstraZeneca at the time the event is reported to the regulatory authorities (e.g. FDA). It is the responsibility of the sponsor to compile all necessary information and ensure that the regulatory authorities receive a report according with the applicable reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

***** A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-19-20015)

***** Sponsor must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

**** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:*** AEMailboxClinicalTrialTCS@astrazeneca.com
If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

Serious adverse events that do not require expedited reporting to the regulatory authorities still need to be reported to AstraZeneca 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.

10.5.1 Reporting of deaths to AstraZeneca

All deaths must be recorded and reported as outlined in Section 10.5. In addition, all SAEs resulting in death or death of unknown cause must be reported to AstraZeneca via AEMailboxClinicalTrialTCS@astrazeneca.com within 7 calendar days of awareness or sooner when required (See Section 10.5).

10.5.2 Other events requiring reporting

10.5.3 Overdose

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

Any overdose of a study patient with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor. The sponsor must report these to AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 10.5 for contact information) within 7 calendar days or sooner when required (see Section 10.5). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.5). 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 10.5). There is currently no specific treatment in the event of an overdose of durvalumab.

An overdose of sirolimus is required to be reported within 24 hours of knowledge of the event to the sponsor.

The investigator will use clinical judgment to treat any overdose.

10.5.4 Hepatic function abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor. The Sponsor must report these events to AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 10.5 for contact information) within 7 calendar days or sooner when required, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct

obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥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 patient will be based on the clinical judgment of the investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune.

10.5.5 Pregnancy

10.5.6 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 sponsor within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The sponsor will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days. The Sponsor must report to AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 10.5 for contact information) within 7 calendar days or sooner when required (see Section 10.5), for pregnancies with SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

10.5.7 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy, 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 + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy, 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.

10.6 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration

- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those that lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs Sponsor within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The Sponsor works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days. The Sponsor must report to AstraZeneca Patient Safety using the designated Safety e-mailbox (see Section 10.5 for contact information) within 7 calendar days or sooner when required (see Section 10.5) if there is an SAE associated with the medication error and within 30 days for all other medication errors.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

11.1.1 Safety analysis set

All enrolled patients will be evaluable for safety analyses from the time of their first treatment with sirolimus and/or durvalumab.

11.1.2 Efficacy analysis set

The primary and secondary efficacy analyses will include all enrolled patients who have received at least one dose of durvalumab, underwent resection and who do not have EGFR mutant tumors (efficacy population).

11.2 Methods of statistical analyses

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. Demographic information such as age and race will be tabulated. Descriptive statistics, including means, standard deviations, and ranges for continuous parameters, as well as percentages and frequencies for categorical parameters, will be presented. Adverse events, Grade 3/4 adverse events, and serious adverse events will be tabulated.

11.2.1 Safety analyses

After study complete, DLTs will be summarized and tabulated by type and grade. DLT rate will be calculated as proportion (Patients with DLT/Total patients) along with 95% confidence intervals using the Clopper-Pearson method. Chi-square test or Fisher's exact test will be used to compare the probability of DLT between the different other factors, such as PD-L1 status, , etc. respectively.

Other adverse events (toxicity) will be listed and summarized.Adverse events will also be listed by severity, seriousness, and by system organ class. The number and percentage of subjects who experience AEs will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. AEs will be presented with and without regard to causality based on the investigator's judgment. The frequency of overall toxicity, categorized by toxicity grades 1 through 5, will be described. Additional summaries will be provided for AEs that are observed with higher frequency.

11.2.2 Efficacy analyses

Primary Efficacy Endpoint

The effectiveness of sirolimus followed by durvalumab will be assessed by complete pathologic response rate in the efficacy population. If the null hypothesis is rejected then this is evidence that the response rate exceeds 10% when sirolimus followed by durvalumab is given before resection. The one-sided 95% confidence interval (CI) for complete pathologic response will be reported. Exact binomial test will be used to compare the estimated complete pathologic response rate to the historical reference.

Secondary Efficacy Endpoints

The complete pathologic response rates for PDL-1 negative and PDL-1 positive patients in the *efficacy population* will be presented separately.

A comparison of both the *complete pathologic response* and investigator assessed response rates per RECIST v1.1 rate*s* between the PD-L1 positive and PD-L1 negative groups will be performed by calculating the lower bound of a one-sided 80% CI for the difference, complete pathologic response for PDL-1 positive patients − complete pathologic response for PDL-1 negative patients. Chi-square test or Fisher's exact test will be used to compare the efficacy in term of response rate between the different groups stratified by other factors, respectively. Logistics regression model will be further employed to test the adjusted effect of each other factor on the response rate after adjusting for other clinical factors and demographic factors, respectively. Correlation of response will be performed for tumor mutation burden using spearman correlation coefficient and tested with Wald's test.

11.2.3 Exploratory analyses

Exploratory biomarker analyses will be performed to explore the relationship between the clinical outcomes and the immunological, pathological and genomic characteristics of the cancers. Biomarker analyses may include, but may not be limited to, the analyses described below.

- A detailed pathological evaluation will be performed on the surgically resected samples.
- Immunologic analyses by IHC, IF, and flow cytometry
- Genomic analaysis may include DNA sequencing (NGS or WES) and RNA sequencing from tumor tissue and normal blood/tissue, to identify mutations, mutation burden, gene expression profiles and associations with treatment response.

11.2.4 Interim analyses

There will be a safety assessment following the completion of surgery for the first six patients on the protocol. Both the DLT assessment and Enrollment will continue during this time. There will be an analysis of the pCR rate of the 16 patients included in the first stage of the design.

11.3 Determination of sample size

Pathologic complete response is rare following neoadjuvant chemotherapy but was reported in 0-8% of cases[39]. The current study is designed to test improved rate of pathologic complete response from 10% to 25% treatment with sirolimus followed by durvalumab. Using a MinMax 2-stage design, a total of 31 patients will be enrolled in 2 stages. At the end of stage I, at least 2 of 16 patients must achieve complete pathologic complete response in order for the study to enroll 15 additional patients. The regimen of sirolimus followed by durvalumab will be considered to have sufficient efficacy to warrant further testing in this patient population if 6 or more of the 31 patients achieve a pathologic CR at the end of stage II. The study has 80% power at a 1-sided alpha of 0.1 to show a compelling 25% pCR compared to a less compelling rate of 10%. Because this is a signal finding study, an alpha of 0.1 is considered reasonable since any promising signal will be confirmed in a larger follow-up study.

Planned total number of patients is 31 over 2 years, with an estimated accrual rate of approximately 1-2 patients/month. Racial, ethnic, and gender accrual estimates below are based on 2010 Atlanta Census demographic information.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	1	+	1	=	2
Not Hispanic or Latino	14	+	14	=	28
Ethnic Category: Total of all subjects	15 (A1)	+	15 (B1)	=	30 (C1)
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	1	+	1	=	2
Black or African American	6	+	6	=	12

Native Hawaiian or other Pacific Islander	1	+	1	=	2
White	7	+	7	=	14
Racial Category: Total of all subjects	15 (A2)	+	15 (B2)	=	30 (C2)
	(A1 = A2)		(B1 = B2)		(C1 = C2)

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 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 Patient data protection.

12.2 Ethics and regulatory review

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the Emory IRB by the Principal Investigator and reviewed and approved by the Emory IRB before the study is initiated.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB. Investigators are also responsible for promptly informing the IRB of any protocol amendments.

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor.

12.3 Informed consent and confidentiality

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and

disclosure of personal health information) signed by the patient, unless permitted or required by law.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of the analyses, data derived from exploratory biomarker specimens will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication

12.4 Changes to the protocol and informed consent form

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by the sponsor and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at Emory. A copy of the written approval of the IRB must be provided to AstraZenica. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects,
2. significant changes in the study design (e.g. addition or deletion of a control group),
3. increases in the number of invasive procedures,
4. addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by AstraZeneca in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons AstraZeneca must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials
2. minor changes in the packaging or labeling of study drug.

12.5 Audits and inspections

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

13. STUDY MANAGEMENT

13.1 Training of study site personnel

Each of the Emory University Affiliated Study sites will undergo training sessions for the sub-investigators and the clinical study staff, utilizing a standardized PowerPoint presentation that will highlight pertinent details of the protocol.

13.2 Monitoring of the study

13.2.1 Source data

Source data will be logged onto Oncore per Winship Standard procedures.

13.3 Study timetable and end of study

The end of this study is defined as Last Patient Last Visit, which is expected to when the last patient completes the survival follow-up (which may occur in person or by phone). This is expected to occur approximately 2 years after the last patient receives the last dose of neoadjuvant durvalumab. The treatment period of this study will end when the last data point required for primary efficacy analysis (i.e., pathology evaluation at time of surgery) is obtained. This is expected to occur approximately 30 days after the last patient's surgery.

After completing treatment with sirolimus + durvalumab, patients will be followed for survival for up to 2 years after the last patient receives the last dose of durvalumab (by phone or in person). Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. The recruitment period is expected to last 1.5 to 2 years. The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4 years.

14. DATA MANAGEMENT

Data will be collected using an institutional electronic data recording system, Oncore. Electronic case report forms and study calendar will be generated prior to study activation. Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The Investigator will permit study-related audits by AstraZenica or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator‟s staff, must be available at some time during audits to review data and resolve any queries and to allow direct access to the subject‟s records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available so that the accuracy and completeness may be checked.

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the protocol therapy, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject‟s diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval).

15. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

15.1 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 at flat dose 1500mg*	MedImmune/AstraZeneca
Sirolimus	*2 mg oral tablet by mouth*	Pfizer

16. LIST OF REFERENCES

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Appendix 2:
End of Study and Follow-up Evaluations

	Day (+/-7)	**Every 3 Months (±4 weeks)**		
	30	**3**	**6**	**Chart follow-up**
Full Physical examination	X			
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X			
Weight	X			
Urine hCG or serum βhCG				
AE/SAE assessment	X			
Concomitant medications	X			
Post-operative chemotherapy and/or radiotherapy as clinically indicated	→			
ECOG performance status	X	X	X	
Subsequent anticancer therapy		X	X	
Survival status: phone contact with patients who agree to be contacted and chart review		X	X	X (every 6 months)
Hematology	X			
Serum chemistry	X			
Research blood collection	X	X	X	
Tumor assessment (CT or MRI) per standard of care	→			

Appendix 3: American Joint Committee on Cancer Non-small cell Lung Cancer Staging, 8th Edition

T: Primary tumor	
Tx	Primary tumor cannot be assessed or tumor proven by presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤3 cm in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a(mi)	**Minimally invasive adenocarcinoma**[b]
T1a	**Tumor ≤1 cm in greatest dimension**[a]
T1b	**Tumor >1 cm but ≤2 cm in greatest dimension**[a]
T1c	**Tumor >2 cm but ≤3 cm in greatest dimension**[a]
T2	Tumor >3 cm **but ≤5 cm** or tumor with any of the following features[c]: - **Involves main bronchus regardless of distance from the carina but without involvement of the carina** - Invades visceral pleura - **Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung**
T2a	**Tumor >3 cm but ≤4 cm in greatest dimension**
T2b	**Tumor >4 cm but ≤5 cm in greatest dimension**
T3	**Tumor >5 cm but ≤7 cm in greatest dimension** or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	**Tumor >7 cm in greatest dimension** or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: **diaphragm,** mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina
N: Regional lymph node involvement	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis present
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion[d]
M1b	**Single extrathoracic metastasis**[e]
M1c	**Multiple extrathoracic metastases in one or more organs**

Note: Changes to the seventh edition are in bold.
[a]The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.
[b]Solitary adenocarcinoma, ≤ 3cm with a predominately lepidic pattern and ≤ 5mm invasion in any one focus.
[c]T2 tumors with these features are classified as T2a if ≤4 cm in greatest dimension or if size cannot be determined, and T2b if >4 cm but ≤5 cm in greatest dimension.
[d]Most pleural (pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor and the fluid is nonbloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.
[e]This includes involvement of a single distant (nonregional) lymph node.

		N categories			
		Overall stage			
Descriptor in 7th edition	Proposed T/M	N0	N1	N2	N3
T1 ≤ 1 cm	T1a	**IA1** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 1-2 cm	T1b	**IA2** (IA)	**IIB** (IIA)	IIIA	IIIB
T1 > 2-3 cm	T1c	**IA3** (IA)	**IIB** (IIA)	IIIA	IIIB
T2 > 3-4 cm	T2a	IB	**IIB** (IIA)	IIIA	IIIB
T2 > 4-5 cm	T2b	**IIA** (IB)	**IIB** (IIA)	IIIA	IIIB
T2 > 5-7 cm	T3	**IIB** (IIA)	**IIA** (IIB)	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 structures	T3	IIB	IIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 > 7 cm	T4	**IIIA** (IIB)	IIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 diaphragm	T4	**IIIA** (IIB)	IIA	**IIIB** (IIIA)	**IIIC** (IIIB)
T3 endobronchial: location/atelectasis 3-4 cm	T2a	**IB** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T3 endobronchial: location/atelectasis 4-5 cm	T2b	**IIA** (IIB)	**IIB** (IIIA)	IIIA	IIIB
T4	T4	IIIA	IIIA	IIIB	**IIIC** (IIIB)
M1a	M1a	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1b single lesion	M1b	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)	**IVA** (IV)
M1c multiple lesions	M1c	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)	**IVB** (IV)

[a]Where there is a change, the resultant stage groupings proposed for the eighth edition are in bold, and the stage in the seventh edition is given in parenthesis.
T, tumor; M, metastasis.

Appendix 4: Information on Possible Drug Interactions

Information on Possible Interactions with Other Agents for Patients and Their Caregivers and Non-Study Healthcare Team

The patient _____ is enrolled on a clinical trial using the investigational agents sirolimus followed by durvalumab. This clinical trial is supported by AstraZenica. This form is addressed to the patient, but includes important information for others who care for this patient.

Sirolimus interacts with many drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or herbal supplements such as St. John's wort.

Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you and keep the attached information card in your wallet**. These are the things that you and they need to know:

Sirolimus interacts with (a) certain specific enzyme(s) in your liver.

- The enzyme(s) in question is/are ***CYP3A4 isoenzyme***
- Sirolimus must be used very carefully with other medicines that need these liver enzymes to be effective or to be cleared from your system.
- Other medicines may also affect the activity of the enzyme.
    - Substances that increase the enzyme's activity ("inducers") could reduce the effectiveness of the drug, while substances that decrease the enzyme's activity ("inhibitors") could result in high levels of the active drug, increasing the chance of harmful side effects.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.
- Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of ***CYP3A4 isoenzyme***.
- Your prescribers should look at this web site http://medicine.iupui.edu/clinpharm/ddis/table.aspx or consult a medical reference to see if any medicine they want to prescribe is on a list of drugs to avoid.
- Please be very careful! Over-the-counter drugs have a brand name on the label—it's usually big and catches your eye. They also have a generic name—it's usually small

and located above or below the brand name, and printed in the ingredient list. Find the generic name and determine, with the pharmacist's help, whether there could be an adverse interaction.

- Be careful:
  - If you take acetaminophen regularly: You should not take more than 4 grams a day if you are an adult or 2.4 grams a day if you are older than 65 years of age. Read labels carefully! Acetaminophen is an ingredient in many medicines for pain, flu, and cold.
  - If you drink grapefruit juice or eat grapefruit: Avoid these until the study is over.
  - If you take herbal medicine regularly: You should not take St. John's wort while you are taking Sirolimus

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctors can be contacted at:

Emory University Winship Cancer Center 404-778-1900

INFORMATION ON POSSIBLE DRUG INTERACTIONS	
You are enrolled on a clinical trial using the experimental agent **_____.** This clinical trial is sponsored by the NCI. _____ interacts with drugs that are processed by your liver. Because of this, it is very important to: ➢ Tell your doctors if you stop taking regular medicine or if you start taking a new medicine. ➢ Tell all of your prescribers (doctor, physicians' assistant, nurse practitioner, pharmacist) that you are taking part in a clinical trial. ➢ Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.	_____ interacts with a specific liver enzyme called **CYP_____**, and must be used very carefully with other medicines that interact with this enzyme. ➢ Before you start the study, your study doctor will work with your regular prescriber to switch any medicines that are considered "strong inducers/inhibitors or substrates of **CYP_____**." ➢ Before prescribing new medicines, your regular prescribers should go to http://medicine.iupui.edu/clinpharm/ddis/table.aspx for a list of drugs to avoid, or contact your study doctor. ➢ Your study doctor's name is _____ and can be contacted at _____**.**

Appendix 5: Memory Aid for Heavy Water

Patient Initials:
Patient ID#

Take all doses of heavy water at least 4 hours apart

Day of Heavy Water	Date	Heavy Water Intake	Salivette	Time Dose 1 taken (am)	Time extra dose taken (midday)	Time dose 2 taken (pm)
1		50 ml x 3				
2		50 ml x 3				
3		50 ml x 3				
4		50 ml x 3				
5		50 ml x 3				
6		50 ml x 2				
7		50 ml x 2	Chew 2 hours after HW			
8		50 ml x 2				
9		50 ml x 2				
10		50 ml x 2				
11		50 ml x 2				
12		50 ml x 2				
13		50 ml x 2				

14		50 ml x 2	Chew 2 hours after HW			
15		50 ml x 2				
16		50 ml x 2				
17		50 ml x 2				
18		50 ml x 2				
19		50 ml x 2				
20		50 ml x 2				
21		50 ml x 2				
22		50 ml x 2				
23		50 ml x 2				
24		50 ml x 2				
25		50 ml x 2				
26		50 ml x 2				
27		50 ml x 2				
28		50 ml x 2				
29		50 ml x 2				
30		50 ml x 2				

31		50 ml x 2				
32		50 ml x 2				
33		50 ml x 2				
34		50 ml x 2				
35		50 ml x 2				
36		50 ml x 2				
37		50 ml x 2				
38		50 ml x 2				
39		50 ml x 2				
40		50 ml x 2				
41		50 ml x 2				
42		50 ml x 2				

Appendix 6: Trial outline patient handouts

Please usepertinent flow sheet for patient pending D2O and use full sized copies loaded into oncore/Complion.