A Phase 2 Open-label, Multicenter, Randomized, Multidrug Platform Study of Neoadjuvant Durvalumab Alone or in Combination with Novel Agents in Subjects with Resectable, Early-stage (I [> 2 cm] to IIIA) Non-small Cell Lung Cancer (NeoCOAST)

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Investigational Products: Durvalumab (MEDI4736) and novel oncology therapies (oleclumab [MEDI9447], monalizumab [IPH2201], and danvatirsen [AZD9150])

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PROTOCOL SYNOPSIS

TITLE

A Phase 2 Open-label, Multicenter, Randomized, Multidrug Platform Study of Neoadjuvant Durvalumab Alone or in Combination with Novel Agents in Subjects with Resectable, Early-stage (I [> 2 cm] to IIIA) Non-small Cell Lung Cancer (NeoCOAST)

HYPOTHESES

Primary Hypothesis: Neoadjuvant durvalumab alone or in combination with novel agents administered over a 28-day treatment period to subjects with resectable, early-stage (Stage I [> 2 cm] to IIIA) non-small cell lung cancer (NSCLC) will lead to a pathological response within the resected tumor specimen.

Secondary Hypothesis: Neoadjuvant durvalumab alone or in combination with novel agents will demonstrate an acceptable safety profile and will not result in a delay in surgery in subjects with resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC.

OBJECTIVES AND ASSOCIATED ENDPOINTS

Type	Primary Objective	Primary Endpoint
Efficacy	Assess the antitumor activity of durvalumab alone and/or in combination with novel agents	MPR rate

MPR = major pathological response.

Type	Secondary Objectives	Secondary Endpoints
Safety	Assess the feasibility of receiving the planned surgical resection	Feasibility, defined as having the planned surgical resection within Day 29 to Day 42 after Week 1, Day 1
Safety	Assess the safety and tolerability of durvalumab alone and/or in combination with novel agents	Presence of AEs, SAEs, laboratory abnormalities, and vital signs
Efficacy	Assess the antitumor activity of durvalumab alone and/or in combination with novel agents	pCR rate
Pharmacokinetics	To describe the PK of durvalumab alone and/or in combination with novel agents	Concentration of durvalumab or novel agents in plasma or serum
Immunogenicity	(a) To assess the immunogenicity of durvalumab alone or in combination with novel agents	ADA incidence of durvalumab or novel biologic agents
	(b) To assess the immunogenicity of novel biologic agents in combination with durvalumab	

ADA = antidrug antibody; AE = adverse event; pCR = pathological complete response; PK = pharmacokinetics; SAE = serious adverse event.

STUDY DESIGN

Study D9108C00002 (NeoCOAST) is a Phase 2, open-label, multicenter, randomized, multidrug platform study of durvalumab alone or in combination with novel agents in subjects with resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC. Subjects will be enrolled and randomized into the durvalumab alone or combination treatment arms. Up to approximately 25 sites globally will participate in this study. Treatment arms may be opened sequentially or in parallel. Subjects will be treated with durvalumab alone or in combination with novel agents for up to 28 days. After the 28-day treatment period (starting from Week 1, Day 1), surgical resection will be planned within ≤ 14 days (Day 29 to Day 42). After surgical resection, subjects will be followed up to Day 105 (starting from Week 1, Day 1). Study treatment will be discontinued upon disease progression, unacceptable toxicity, or other reason, eg, subject decision or noncompliance with study procedures. New durvalumab combination therapy arms may be added based on emerging nonclinical and clinical data via a protocol amendment.

TARGET SUBJECT POPULATION

Resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC

TREATMENT GROUPS AND REGIMENS

Durvalumab monotherapy, Arm A: [redacted] durvalumab intravenously (IV) every 4 weeks (Q4W; on Week 1, Day 1) over a 28-day treatment period

Durvalumab + Oleclumab, Arm B: [redacted] durvalumab IV Q4W (on Week 1, Day 1) and [redacted] oleclumab IV every 2 weeks (Q2W; on Week 1, Day 1 and Week 3, Day 1) over a 28-day treatment period

Durvalumab + Monalizumab, Arm C: [redacted] durvalumab IV Q4W (on Week 1, Day 1) and [redacted] monalizumab IV Q2W (on Week 1, Day 1 and Week 3, Day 1) over a 28-day treatment period

Durvalumab + Danvatirsen, Arm D: Seven-day danvatirsen lead-in period (200 mg danvatirsen IV on Days 1, 3, and 5 [Week 0]), followed by [redacted] durvalumab IV Q4W (on Week 1, Day 1) and [redacted] danvatirsen IV every week (on Week 1, Day 1; Week 2, Day 1; Week 3, Day 1; and Week 4, Day 1) over a 28-day treatment period

STATISTICAL METHODS

Sample size: At the onset, subjects will be randomized with equal ratios into each treatment arm. A total of up to 40 subjects per arm may be enrolled. An interim analysis will be performed in any given arm, once a respective arm enrolls at least 20 efficacy evaluable subjects.

Statistical analyses:

Efficacy

The final efficacy analyses will be based on the Intent-to-treat Population. The interim analyses will be based on the Efficacy Evaluable Population. Major pathological response rate (defined as proportion of subjects with ≤ 10% residual viable tumor cells) and pathological complete response rate (defined as proportion of subjects with no viable tumor cells), and the corresponding 95% confidence interval will be reported for each arm. In addition, the difference between any durvalumab combination therapy arm and the durvalumab monotherapy arm will be evaluated. Comparison of each of the combination therapy arms with the monotherapy arm will be obtained from the Chi-square or Fisher's exact test.

Safety

Summary statistics will be provided for adverse events (AEs), serious adverse events, and AE grade, severity, and relationship to study drug, clinical laboratory parameters, physical examinations, and vital signs. In addition, feasibility to surgery will be evaluated. Feasibility to surgery is defined as the proportion of subjects in each arm with no delay in the planned surgery (no later than 42 days after Week 1, Day 1). AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Pharmacokinetics

Only subjects who receive at least 1 dose of durvalumab and/or other combination study drug, and provide at least 1 post-treatment sample, will be evaluated. For each treatment arm, individual durvalumab and individual study drug concentrations will be tabulated with descriptive statistics.

Immunogenicity

Only subjects who receive at least 1 dose of durvalumab and/or other combination study drug, and provide at least 1 post-treatment sample, will be evaluated. For each treatment arm, the immunogenic potential of durvalumab will be assessed by summarizing the number and percentage of subjects who develop detectable antidrug antibodies (ADAs) to durvalumab. For treatment arms that include a novel biologic agent, the immunogenic potential of the novel biologic agent will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs to the novel biological agent.

Interim analyses: Interim analyses will be conducted during the course of the study to evaluate the clinical activity and safety of any treatment arm. The first planned interim analysis will be initiated once at least 1 treatment arm has enrolled 20 efficacy evaluable subjects. Across all treatment arms, subject accrual beyond 20 subjects will be determined based on interim data. Bayesian predictive probabilities will be used to evaluate clinical activity. In addition, for any treatment arm, enrollment will be stopped if more than 2 out of the first 20 enrolled subjects failed the feasibility to surgery.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMP	adenosine monophosphate
AUC	area under the curve
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BOR	best overall response
CD	cluster of differentiation
CI	confidence interval
C_{max}	maximum serum concentration
CR	complete response
CSR	clinical study report
CT	computed tomography
DCO	data cutoff
DEHP	bis (2-ethylhexyl) phthalate
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
FAAN	Food Allergy and Anaphylaxis Network
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HLA-E	major histocompatibility complex E
IB	Investigator's Brochure
IBW	ideal body weight
ICH	International Council for Harmonisation

Abbreviation or Specialized Term	Definition
IEC	Independent Ethics Committee
Ig	immunoglobulin
IL	interleukin
imAE	immune-mediated adverse event
IRB	Institutional Review Board
IRR	infusion-related reaction
ITT	Intent-to-treat
IV	intravenous
IXRS	interactive voice/web response system
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MPR	major pathological response
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
NIAID	National Institute of Allergy and Infectious Diseases
NK	natural killer
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
pCR	pathological complete response
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
PET	positron emission tomography
PI	Package Insert
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
PVC	polyvinyl chloride
QTc	QTc interval
Q2W	every 2 weeks
Q4W	every 4 weeks

Abbreviation or Specialized Term	Definition
QW	every week
RECIST v1.1	Response Evaluation Criteria for Solid Tumors version 1.1
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SID	subject identification
SOC	system organ class
SRC	Safety Review Committee
STAT3	signal transducer and activator of transcription 3
SUSAR	suspected unexpected serious adverse reaction
SUV	standardized uptake values
TBL	total bilirubin
TV	target value
US	United States
w/v	weight per volume

1 INTRODUCTION

Study D9108C00002 (NeoCOAST) is a platform study assessing the efficacy and safety of neoadjuvant durvalumab alone or in combination with novel agents in subjects with resectable, early-stage (Stage I [> 2 cm] to IIIA) non-small cell lung cancer (NSCLC). New combination treatment arms can be added during the course of the study via a protocol amendment, as novel agents of interest become available for testing in this population of patients (Section 1.6.3).

1.1 Disease Background

Lung cancer is the second most common cancer in both men and women, with an estimated 234,030 new cases of lung cancer in the United States (US) in 2018, and remains the main cause of cancer-related deaths worldwide. NSCLC represents approximately 85% of all lung cancers, and 30% of patients present with resectable NSCLC at diagnosis (American Cancer Society, 2018). Resectable, early-stage NSCLC is considered a potentially curable disease, and the standard of care is surgery alone or surgery with adjuvant or neoadjuvant platinum-based doublet chemotherapy (National Comprehensive Cancer Network, 2018). However, up to 55% of patients eventually relapse after surgery and die from NSCLC (Uramoto and Tanaka, 2014).

Based on the National Cancer Data Base dataset, patients had 5-year survival rates ranging from approximately 70% for Stage IA1 NSCLC to 20% for Stage IIIA NSCLC (Chansky et al, 2017). The use of adjuvant chemotherapy with a platinum-based regimen has been shown to provide survival benefit in patients with resected, early-stage NSCLC; a quantitative meta-analysis of multiple clinical trials evaluating adjuvant chemotherapy demonstrated a 4% to 5% improvement in overall survival (OS) with the use of adjuvant chemotherapy following surgery compared to surgery alone (Burdett et al, 2015). In addition, preoperative neoadjuvant chemotherapy has also been studied in several trials in patients with resectable NSCLC (Burdett et al, 2006). A meta-analysis of 7 trials showed that neoadjuvant chemotherapy improved OS versus surgery alone (5-year OS rate of 20% vs 14%, respectively). Furthermore, the use of a neoadjuvant approach offers the possibility for assessing clinical and molecular biomarkers that may correlate with sensitivity to therapy and possibly, long-term outcomes.

Compared with adjuvant chemotherapy in early-stage NSCLC, the use of neoadjuvant chemotherapy resulted in a higher proportion of patients receiving the planned chemotherapy regimen, which supports the notion that early-stage NSCLC patients have a more favorable clinical condition before compared to after a major surgical lung resection (Felip et al, 2010). In addition, patients with resectable NSCLC treated with neoadjuvant chemotherapy have higher rates of pathological tumor response (complete response and/or ≤ 10% residual viable tumor cells) within the resected specimen compared to patients who underwent surgery alone,

which may predict clinical benefit and correlates with improved outcomes (Cascone et al, 2018; Felip et al, 2010; Machtay et al, 2004; Pataer et al, 2012). In other tumor types, such as early-stage breast cancer, pathological complete response (pCR) after neoadjuvant chemotherapy correlates with OS, and is considered a valid and widely used endpoint in clinical studies (Bear et al, 2006; Rastogi et al, 2008).

In the subset of patients with Stage IIIA and N2 disease, the role of surgery remains controversial. In general, for unselected patients with Stage IIIA-N2 NSCLC, both chemotherapy alone or in combination with radiation followed by surgery or concurrent chemoradiotherapy have shown to be equivalent, but neither showed an OS benefit with the use of surgery (Albain et al, 2009; Eberhardt et al, 2015; van Meerbeeck et al, 2007). However, a critical appraisal of these studies demonstrates that the Stage IIIA-N2 population is heterogeneous and a subset of patients such as those requiring only a lobectomy/bilobectomy instead of a total pneumonectomy, or those with a single lymph node (N2 single station) smaller than 3 cm can be considered candidates for surgery (Decaluwé et al, 2009; Martins et al, 2012; Pless et al, 2015; van Meerbeeck et al, 2007). Furthermore, it is recommended that Stage IIIA-N2 (single nodal station, ≤ 3 cm in size) disease be rigorously confirmed (ie, both radiologically and invasively) and the presence of N3 disease be clearly excluded (Vansteenkiste et al, 2010).

Recently, the role of programmed cell death-1 (PD-1)/programmed cell death ligand-1 (PD-L1) inhibition has been evaluated for the treatment of resectable, early-stage NSCLC in the neoadjuvant setting. In a single-arm pilot study, a total of 21 subjects with resectable, early-stage NSCLC received one month of neoadjuvant treatment with nivolumab (OPDIVO®). After 1 month of treatment with neoadjuvant nivolumab, radiologic responses were observed in 2 (9.5%) subjects, and major pathological responses (MPRs) were observed in 45% of the resected tumors (Forde et al, 2018). In another small Phase 2, single-arm study evaluating neoadjuvant atezolizumab (TECENTRIQ®) alone, MPRs were observed in 10 of 50 (20%) subjects, including 3 subjects who had pCRs in the primary tumor. Three subjects had partial responses (PRs) per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1; Rusch et al, 2018). Overall, both studies concluded that neoadjuvant nivolumab and atezolizumab were safe and did not delay the planned surgical resection. These studies also demonstrated the potential for using pathologic changes within the tumor as an objective measure of antitumor activity.

Overall, early-stage NSCLC, despite being potentially curable, has a high risk of relapse and death due to disease progression. Thus, new therapies are needed to further improve the long-term prognosis for patients with resectable, early-stage NSCLC.

1.1.1 Immunotherapy

1.1.1.1 Programmed Cell Death Ligand-1

PD-1, PD-L1, and programmed cell death ligand-2 (PD-L2) are part of a complex system of receptors and ligands that control T-cell activation. PD-L1 expression helps tumors evade detection and elimination by the immune system (Chen and Mellman, 2013; Juneja et al, 2017; Keir et al, 2008; Ohaegbulam et al, 2015). The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal preventing T cells from killing target tumor cells (Pardoll, 2012; Zou and Chen, 2008; Zou et al, 2016). Monoclonal antibodies (mAbs) targeting PD-1 (nivolumab, pembrolizumab [KEYTRUDA®]) and PD-L1 (atezolizumab, durvalumab) have shown evidence of antitumor activity and a manageable safety profile in patients with NSCLC and have been granted approvals by the US Food and Drug Administration and/or the European Medicines Agency for the treatment of NSCLC (IMFINZI® US Package Insert [PI], 2018; KEYTRUDA US PI, 2018; OPDIVO US PI, 2018; TECENTRIQ US PI, 2018).

1.1.1.2 CD73

Adenosine is a regulatory autocrine and paracrine factor that accumulates in the tumor microenvironment, influencing immune activity, angiogenesis, and metastasis. Upon apoptotic or necrotic cell death, tumor cells release adenosine triphosphate (ATP) into the extracellular space. ATP has been shown to lead to a pro-inflammatory response. To prevent an immune overactivation, tissues express cluster of differentiation (CD)39 and CD73 to enzymatically convert ATP to adenosine, which induces a localized immunosuppressive response through multiple immune cell types. In the extracellular space, CD39 and CD73 in tandem metabolize ATP to adenosine monophosphate (AMP), and AMP to adenosine, respectively, and are a major source of extracellular adenosine. Extracellular adenosine impairs the proliferation and effector function of cytotoxic T lymphocytes while simultaneously contributing to the immunosuppressive effects of both regulatory T cells and myeloid-derived suppressor cells, among others (Vijayan et al, 2017). The rate limiting step in the generation of extracellular adenosine is the dephosphorylation of AMP by CD73.

One mechanism by which tumors may have evolved to evade the immune system is via overexpression of CD73. Overexpression of CD73 has been associated with poor prognosis in multiple cancer types (Inoue et al, 2017; Turcotte et al, 2015; Vijayan et al, 2017). Notably, high CD73 expression in NSCLC was associated with poor OS and recurrence free survival in a multivariate analysis (Inoue et al, 2017). It is hypothesized that blocking CD73 activity will reduce adenosine production, thus augmenting host and/or immunotherapy response to tumor.

1.1.1.3 NKG2a

Major histocompatibility complex E (HLA-E) is a non-classical major histocompatibility complex class I molecule, over-expressed by malignant cells in a variety of tumor types. HLA-E can present antigens to the CD94/NKG2a receptors on the surface of some types of lymphocytes. Activation of CD94/NKG2a receptors induces inhibitory signals that suppress

cytokine secretion and direct cytotoxicity of cytotoxic T lymphocytes or natural killer (NK) cells against stressed, infected, or "transformed" cells. Such activity has been described as a possible mechanism in immune escape of cancer cells (Borrego et al, 1998; Braud et al, 1998). Conversely, the blockade of CD94/NKG2a by an antagonist mAb restores the response of NK cells, enhancing notably their cytotoxicity against tumor cells expressing HLA-E. Furthermore, blockade of CD94/NKG2a may enhance NK-mediated antibody-dependent cellular cytotoxicity (Denis et al, 2017). NK cells can also decrease metastasis through immunosurveillance (López-Soto et al, 2017; Malladi et al, 2016)

Expression of CD94/NKG2a has been documented by subsets of cytotoxic T lymphocytes and NK cells infiltrating solid tumors. CD94/NKG2a appeared to be over-expressed in tumor-infiltrating NK cells as compared to NK cells present in the non-tumoral areas of the same tissue or in the blood. Hyper-expression of CD94/NKG2a by infiltrating NK cells appeared to be associated with diminished cytotoxic potential (Mamessier et al, 2011; Platonova et al, 2011; Sheu et al, 2005) and has been documented in a variety of solid tumors including NSCLC, colorectal, ovarian, endometrial, pancreatic, and prostate cancers (Aparicio-Pages et al, 1991; Gooden et al, 2011; Iannone et al, 2015; Pasero et al, 2015; Peng et al, 2014; Tarle et al, 1993; Zeestraten et al, 2014). In addition, expression of HLA-E has been shown to correlate with a poor outcome in colorectal, ovarian, or endometrial carcinoma (Emens et al, 2017; Gooden et al, 2011; Guo et al, 2015; Versluis et al, 2017).

1.1.1.4 STAT3

Interactions between tumor cells, immune cells and other cell types within the tumor microenvironment have a significant impact on the progression of cancer. Inflammatory cells, fibroblasts and endothelial cells in the microenvironment release cytokines, chemokines and growth factors to stimulate tumor growth and to modulate the invasive potential of tumor cells. These signals also create immunosuppressive networks that enable immune evasion of tumor cells (Yu et al, 2007). Signal transducer and activator of transcription 3 (STAT3) drives the production of interleukin (IL)-6, IL-10 and vascular endothelial growth factor from tumor cells, and also regulates the production of pro-tumorigenic and anti-tumorigenic cytokines, as well as immune suppressive signaling in immune cells. Thus, STAT3 establishes a critical crosstalk between tumor cells and tumor-associated immune cells and is a central component of a 'feed-forward loop' that shifts the tumor microenvironment to a more pro-tumorigenic phenotype (Kortylewski et al, 2009; Yu et al, 2007).

1.2 Study Drug Background

1.2.1 Durvalumab

Durvalumab is a human immunoglobulin (Ig) G1 kappa mAb that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T cells and CD80 (B7.1) on immune cells, and is

engineered to reduce antibody-dependent cell-mediated cytotoxicity and complement activation. Refer to the current durvalumab Investigator's Brochure (IB) for details.

1.2.2 Oleclumab

Oleclumab (MEDI9447) is a human IgG1 lambda mAb that selectively binds to CD73, and leads to a reduction in CD73 expression through internalization, thus contributing to decreased adenosine production (Geoghegan et al, 2016; Hay et al, 2016). It contains a triple mutation in the heavy chain constant region for reduced effector function. The enzymatic blockade of CD73 and decreased expression caused by binding of oleclumab to CD73 may lead to increased antitumor immunity. Refer to the current oleclumab IB for details.

1.2.3 Monalizumab

Monalizumab (IPH2201) is a humanized mAb of the IgG-4 subtype produced in Chinese hamster ovary cells. It has a non-depleting and purely blocking activity directed with high affinity and specificity against the CD94/NKG2a subunit of the heterodimeric inhibitory CD94/NKG2a receptor expressed by subsets of NK cells, activated αβ CD8+ T cells and γδ-T cells. By suppressing the inhibitory signal transduced by CD94/NKG2a, monalizumab enhances the antitumor functions, including cytolytic activity of these immune effector cells. Refer to the current monalizumab IB for details.

1.2.4 Danvatirsen

Danvatirsen (AZD9150) is a 16-nucleotide antisense oligonucleotide designed to reduce expression of STAT3 protein by targeted down-regulation of *STAT3* messenger ribonucleic acid (mRNA). STAT3 is a promising cancer drug target, because of its pleiotropic involvement in tumorigenesis, including roles in immune evasion, angiogenesis, and metastasis. Refer to the current danvatirsen IB for details.

1.3 Summary of Nonclinical Experience

1.3.1 Durvalumab Nonclinical Experience

[redacted]

1.3.2 Oleclumab Nonclinical Experience

[redacted]

[redacted]

1.3.3 Monalizumab Nonclinical Experience

[redacted]

1.3.4 Danvatirsen Nonclinical Experience

[redacted]

1.4 Summary of Clinical Experience

[redacted]

1.4.1 Clinical Experience - Durvalumab

[redacted]

1.4.2 Clinical Experience – Oleclumab Alone and in Combination with Durvalumab

[redacted]

[redacted]

1.4.3 Clinical Experience - Monalizumab Alone and in Combination with Durvalumab

[redacted]

1.4.4 Clinical Experience – Danvatirsen Alone and in Combination with Durvalumab

[redacted]

1.5 Rationale for Conducting the Study

Five-year survival rates in early-stage NSCLC ranges from approximately 70% for Stage IA1 disease to 20% for Stage IIIA disease, with the majority of patients experiencing post-surgical relapse and disease recurrence (Chansky et al, 2017; Goldstraw et al, 2007). Adjuvant platinum-based chemotherapy provides an approximate 5% increase in survival benefit compared to surgery alone, with rates of overall Grade 3 to 4 toxicity of 66%. Thus, there is an unmet medical need for more effective therapies for patients with early-stage NSCLC. Blockade of the PD-1/PD-L1 pathway in the neoadjuvant setting may provide clinical benefit by enhancing the antitumor response, and eradicating micrometastases prior to surgery, thereby reducing disease recurrence. Two recent clinical studies have shown that blockade of PD-l/PD-L1 in the neoadjuvant setting may yield clinically meaningful pathological response (MPR and pCR) in subjects with resectable, early-stage NSCLC without delaying planned surgical resection (Forde et al, 2018; Rusch et al, 2018).

In the NeoCOAST study, utilizing a neoadjuvant approach to assess the role of durvalumab alone or in combination with novel agents has several advantages. First, durvalumab alone or in combination with novel agents may result in pathological response and/or downstaging prior to surgery. Second, the resected tumors can be analyzed and provides a unique opportunity to perform correlative biomarker studies and investigate changes in the tumor microenvironment. Predictive biomarkers or underlying resistance mechanisms may be identified, which will help inform future durvalumab-based combination therapy studies. Additionally, nonclinical evidence supports that immune response to neoadjuvant immunotherapies may be more effective compared to an adjuvant approach because the total load of tumor associated antigens is higher during neoadjuvant immunotherapy, which may enhance the antitumor immune response (Liu et al, 2016). Further, in order to maximize the benefit-risk assessment, the treatment period duration will be short, which will minimize treatment exposure, potential AEs, and avoid delaying the planned surgical tumor resection.

The NeoCOAST study will utilize a platform study design, which will allow for the rapid evaluation of neoadjuvant durvalumab alone or in combination with novel agents in patients with resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC. Combining a platform study design with early efficacy endpoints (eg, MPR) will provide a more dynamic approach to

identifying the most efficacious durvalumab-based combination regimens. In comparison, executing multiple, individual, Phase 2 studies will require more time and a greater number of subjects. Combination therapy arms may be closed or opened during the study based on emerging nonclinical and clinical data. Potential new candidate study agents to be evaluated in combination with durvalumab in this platform study must have a known mechanism of action that could be additive or synergistic with durvalumab, an established recommended dose in combination with durvalumab with an acceptable safety profile, and preliminary evidence of clinical activity in combination with durvalumab in a solid tumor setting. As a starting point, oleclumab, monalizumab, and danvatirsen meet these criteria, and will be used in combination with durvalumab as the initial combination arms of this platform study.

1.5.1 Rationale for Inclusion of Durvalumab in Combination with Oleclumab

High CD73 expression in NSCLC is associated with poor OS and recurrence free survival in a multivariate analysis (Inoue et al, 2017). CD73 is known to contribute to the immunosuppressive effects of both cytotoxic T lymphocytes and myeloid-derived suppressor cells, among others (Vijayan et al, 2017). Nonclinical experiments have shown increased tumor growth inhibition and survival in tumor bearing mice treated with anti-CD73 antibody in combination with anti-PD-1/PD-L1 antibodies (Hay et al, 2016). As oleclumab selectively binds to CD73 and inhibits adenosine production as well as leads to a reduction in CD73 expression, the combination with durvalumab is hypothesized to have a synergistic effect on reversal of immune suppression in the tumor microenvironment. Oleclumab in combination with durvalumab had a manageable safety profile in Study D6070C00001 (see Section 1.4.2), further supporting exploration of this treatment combination.

1.5.2 Rationale for Inclusion of Durvalumab in Combination with Monalizumab

[redacted]

1.5.3 Rationale for Inclusion of Durvalumab in Combination with Danvatirsen

[redacted]

1.6 Benefit-risk and Ethical Assessment

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements. More detailed information about the known and expected benefits, risks, and reasonably expected AEs of durvalumab and each novel oncology therapy may be found in the respective IB for each molecule.

1.6.1 Potential Benefits

Two recent clinical studies have shown that blockade of PD-l/PD-L1 in the neoadjuvant setting may yield clinically meaningful MPR and pCR (Forde et al, 2018; Rusch et al, 2018), which have been shown to be associated with improved survival (Felip et al, 2010; Machtay et al, 2004; Pataer et al, 2012).

This protocol will allow subjects with resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC to receive durvalumab alone or in combination with novel therapies, and potentially achieve pathological response. Selection of the combination novel agents was based on nonclinical and clinical data supporting a potentially favorable interaction with durvalumab in this patient population, with a well-tolerated and manageable safety profile.

1.6.2 Potential Risks

1.6.2.1 Durvalumab

Durvalumab may boost endogenous immune responses leading to undesired AEs. Most adverse drug reactions seen with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/interstitial lung disease, endocrinopathies (ie, events of hypophysitis, adrenal insufficiency, hyper- and hypo-thyroidism, and type I diabetes mellitus), hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory

events including neurotoxicities, infusion-related reactions (IRRs), hypersensitivity reactions, and infections/serious infections.

[redacted]

1.6.2.2 Oleclumab Plus Durvalumab

Overall, oleclumab and durvalumab combination therapy has demonstrated an acceptable safety profile (Section 1.4.2). [redacted]

For oleclumab, important potential risks include arterial calcifications, arterial ischemic disorder, thrombosis, and increased microvascular permeability, and potential risks include joint calcifications. [redacted]

Other important potential risks associated with the administration of mAbs include IRRs, anaphylaxis, hypersensitivity or serious allergic reactions, and immune complex disease. Additional potential risks associated with any IV administration are localized infection, redness, swelling, pain, and induration at the administration site. Given the mode of action of oleclumab, the theoretical risk associated with removing the inhibition of adenosine on the microenvironment favors increased antitumor immunity when combined with durvalumab, as well as the risk of emergence of autoimmune phenomena.

[redacted]

1.6.2.3 Monalizumab Plus Durvalumab

Overall, durvalumab and monalizumab combination therapy has demonstrated an acceptable safety profile (Section 1.4.3). [redacted]

There is currently no identified risk with monalizumab alone and/or in combination with durvalumab therapies. Given the mode of action of monalizumab, however, there are theoretical risks that could be related to its administration. These risks include adverse effects on the immune system, such as emergence of autoimmune phenomena, increased risk of infection, acute generalized or delayed hypersensitivity reactions, immunogenicity, local injection-site reactions and AEs associated with the blocking effect on CD94/NKG2a

receptors. The theoretical risk of infections with monalizumab could be the overlapping toxicity when treated with durvalumab.

[redacted]

1.6.2.4 Danvatirsen Plus Durvalumab

Overall, danvatirsen and durvalumab combination therapy has demonstrated an acceptable safety profile (Section 1.4.4). [redacted]

For danvatirsen, important identified risks are thrombocytopenia and liver enzyme elevations (ALT/AST). Important potential risks include reduced absolute neutrophil counts and reduced hemoglobin. In addition, as danvatirsen is being studied in combination with durvalumab, the side effects of danvatirsen and durvalumab are to some degree overlapping (possible ALT/AST elevations [danvatirsen] and immune mediated hepatitis [durvalumab]), therefore careful consideration is required in the evaluation and monitoring of the liver function in subjects receiving both study drugs simultaneously. The combination therapy may have overlapping toxicities and different mechanisms leading to increased hepatic events.

[redacted]

1.6.3 Overall Benefit-risk

Clinical and nonclinical data to date have shown acceptable safety profiles and antitumor activity for the novel agents proposed in this study. Neoadjuvant durvalumab alone or in combination with novel therapies may provide clinical benefit by enhancing the antitumor response and reducing disease recurrence after surgery.

The design of the current study aims to minimize potential risks to subjects, including the inclusion and exclusion criteria (Section 4.1.2 and Section 4.1.3), restrictions on concomitant medications during the study (Section 4.7.2), safety monitoring (including review of all relevant data by the Safety Review Committee [SRC, Section 3.1.4]), toxicity management guidelines (Section 3.1.3), stopping criteria (Section 4.4), and rules and procedures to add new durvalumab combination therapy arms. Specific intensive safety monitoring is in place for those risks deemed to be most likely for durvalumab alone and for each of the durvalumab combination therapies.

Further design elements aim to specifically minimize the risks to subjects enrolled in a durvalumab combination therapy arm. Any new combination treatment arm must adhere to the following elements:

- A rationale for additive or synergistic activity of the potential new candidate agent in combination with durvalumab based on its mechanism of action and supported by nonclinical or clinical evidence.
- An established, recommended combination dose for the novel agent in combination with durvalumab with an acceptable safety profile for the target population in this study.
  - Description of the safety profile and adverse events of special interest (AESIs) for the novel agent alone and/or in combination with durvalumab based on previous Phase 1 expansion cohorts or Phase 2 studies.
- Preliminary evidence of clinical activity of the novel agent in combination with durvalumab in a solid tumor setting.
- Requirement of a protocol amendment and respective health authority and local Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approvals prior to implementing any new treatment arm.
- Updated informed consent form with relevant information on the new durvalumab combination therapy arm.

Thus, the benefit-risk assessment for this Phase 2 platform study is acceptable.

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

Neoadjuvant durvalumab alone or in combination with novel agents administered over a 28-day treatment period to subjects with resectable, early-stage NSCLC (Stage I [> 2 cm] to IIIA) will lead to a pathological response within the resected tumor specimen.

1.7.2 Secondary Hypotheses

Neoadjuvant durvalumab alone or in combination with novel agents will demonstrate an acceptable safety profile and will not result in a delay in surgery in subjects with resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC.

2 OBJECTIVES AND ENDPOINTS

Overall study objectives and endpoints applicable across treatment arms are presented below.

Each combination therapy arm will evaluate these objectives based on the respective novel agent. Secondary immunogenicity objective (b) is applicable only to novel biologic agents (Table 2).

2.1 Primary Objective and Associated Endpoint

Table 1 Primary Objective and Associated Endpoint

Type	Objective	Endpoint
Efficacy	Assess the antitumor activity of durvalumab alone and/or in combination with novel agents	MPR rate

MPR = major pathological response.

2.2 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Safety	Assess the feasibility of receiving the planned surgical resection	Feasibility, defined as having the planned surgical resection within Day 29 to Day 42 after Week 1, Day 1
Safety	Assess the safety and tolerability of durvalumab alone and/or in combination with novel agents	Presence of AEs, SAEs, laboratory abnormalities, and vital signs
Efficacy	Assess the antitumor activity of durvalumab alone and/or in combination with novel agents	pCR rate
Pharmacokinetics	To describe the PK of durvalumab alone and/or in combination with novel agents	Concentration of durvalumab or novel agents in plasma or serum
Immunogenicity	(a) To assess the immunogenicity of durvalumab alone or in combination with novel agents	ADA incidence of durvalumab or novel biologic agents
	(b) To assess the immunogenicity of novel biologic agents in combination with durvalumab	

ADA = antidrug antibody; AE = adverse event; pCR = pathological complete response; PK = pharmacokinetics; SAE = serious adverse event.

2.3 Exploratory Objectives and Associated Endpoints

[redacted]

3 STUDY DESIGN

3.1 Description of the Study

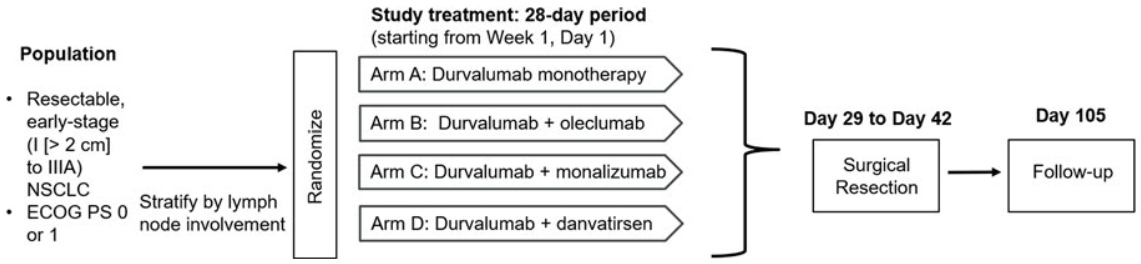
3.1.1 Overview

Study D9108C00002 (NeoCOAST) is a Phase 2, open-label, multicenter, randomized, multidrug platform study of durvalumab alone or in combination with novel agents in subjects with resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC.

Subjects will be enrolled and randomized into the durvalumab alone or combination treatment arms. Information on subject randomization and sample size is provided in Section 4.6.1 and Section 4.8.2, respectively. Up to approximately 25 sites globally will participate in this study.

Treatment arms may be opened sequentially or in parallel. Subjects will be treated with durvalumab alone or in combination with novel agents for up to 28 days, followed by surgical resection. After surgical resection, subjects will be followed up to Day 105 (Figure 1). New durvalumab combination therapy arms may be added based on emerging nonclinical and clinical data via a protocol amendment (Section 1.6.3). Interim futility analyses will be performed using Bayesian predictive probabilities (Section 4.8.7).

Figure 1 Study Flow Diagram

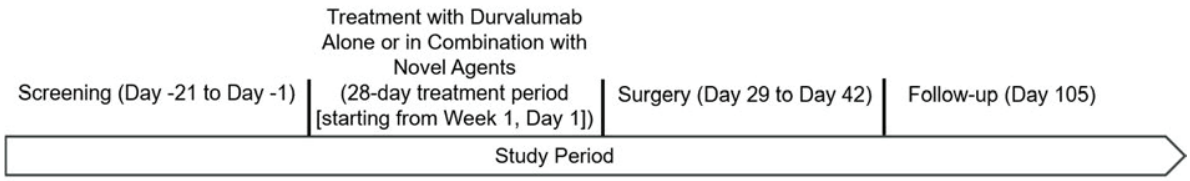


ECOG PS = Eastern Cooperative Oncology Group Performance Status; NSCLC = non-small cell lung cancer.
NOTE: Enrollment into treatment arms may be stopped if planned interim analyses show safety concerns or lack of efficacy (Section 4.8.7). New combination treatment arms may be added based on emerging nonclinical and clinical data via a protocol amendment.

3.1.2 Treatment Regimen

Subjects will be randomized to a treatment arm and will receive durvalumab alone or in combination with novel agents for a period of 28 days prior to surgical resection. Treatment arms may be opened sequentially or in parallel. Study treatment will be discontinued upon disease progression, unacceptable toxicity, or other reason, eg, subject decision or noncompliance with study procedures (Section 4.1.6). After the 28-day treatment period (starting from Week 1, Day 1), surgical resection will be planned within ≤ 14 days (Day 29 to Day 42). After surgical resection, subjects will be followed up to Day 105 (starting from Week 1, Day 1; Figure 2). If a subject receives adjuvant chemotherapy or radiotherapy as per standard clinical practice prior to Day 105, the subject will come off study and the end of study visit will be scheduled prior to start of adjuvant therapy.

Figure 2 Study Period Duration

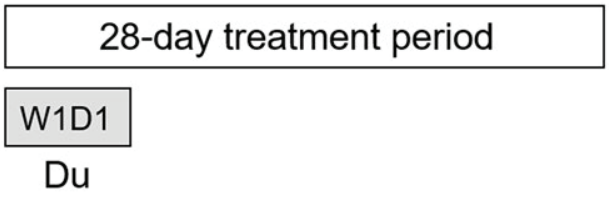


NOTE: See Figure 6 for details on the danvatirsen lead-in period (Week 0).

3.1.2.1 Durvalumab Monotherapy (Arm A)

Subjects randomized to durvalumab monotherapy will receive treatment as presented in Figure 3.

Figure 3 Treatment Regimen – Durvalumab Monotherapy

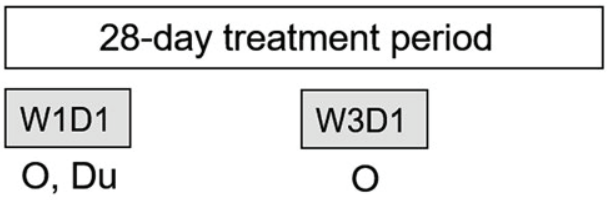


D = Day; Du = durvalumab; IV = intravenously; Q4W = every 4 weeks; W = Week.
Subjects will receive [redacted] durvalumab IV Q4W on Week 1, Day 1.

3.1.2.2 Durvalumab Plus Oleclumab (Arm B)

Subjects randomized to durvalumab in combination with oleclumab will receive treatment as presented in Figure 4.

Figure 4 Treatment Regimen – Durvalumab Plus Oleclumab

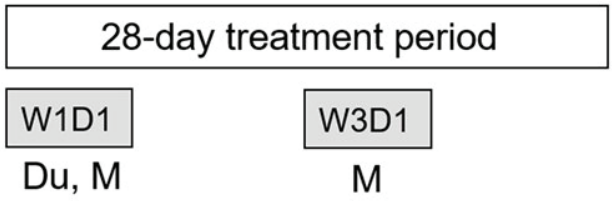


D = Day; Du = durvalumab; IV = intravenously; O = oleclumab; Q2W = every 2 weeks; Q4W = every 4 weeks; W = Week.
Subjects will receive [redacted] durvalumab IV Q4W on Week 1, Day 1 and [redacted] oleclumab IV Q2W on Week 1, Day 1 and Week 3, Day 1.

3.1.2.3 Durvalumab Plus Monalizumab (Arm C)

Subjects randomized to durvalumab in combination with monalizumab will receive treatment as presented in Figure 5.

Figure 5 Treatment Regimen – Durvalumab Plus Monalizumab

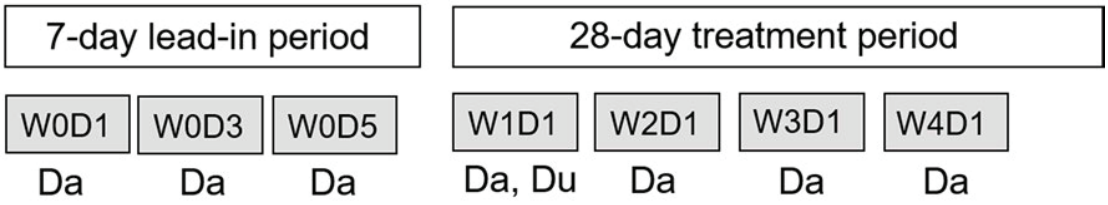


D = Day; Du = durvalumab; IV = intravenously; M = monalizumab; Q2W = every 2 weeks; Q4W = every 4 weeks; W = Week.
Subjects will receive [redacted] durvalumab IV Q4W on Week 1, Day 1 and [redacted] monalizumab IV Q2W on Week 1, Day 1 and Week 3, Day 1.

3.1.2.4 Durvalumab Plus Danvatirsen (Arm D)

Subjects randomized to durvalumab in combination with danvatirsen will receive treatment as presented in Figure 6.

Figure 6 Treatment Regimen – Durvalumab Plus Danvatirsen



D = Day; Da = danvatirsen; Du = durvalumab; IV = intravenously; Q4W = every 4 weeks; QW = every week; W = Week.
Subjects will undergo a 7-day danvatirsen lead-in period [redacted] danvatirsen IV on Days 1, 3, and 5 [Week 0]), followed by [redacted] durvalumab IV Q4W (Week 1, Day 1) and [redacted] danvatirsen IV QW (Week 1, Day 1, Week 2, Day 1, Week 3, Day 1, and Week 4, Day 1).

3.1.3 Management of Study Medication Related Toxicities

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

- Dose administration of the novel agent can be delayed up to 3 days, with the exception of the danvatirsen lead-in period as stated below. If delayed > 3 days, subjects will skip the planned dose.
  - For the danvatirsen lead-in period (Week 0), dose administration on Day 3 and Day 5 can be delayed up to 1 day. If delayed > 1 day, subjects will skip the planned dose.

- In the absence of clear alternative etiology, all events should be considered potentially immune mediated.
- In the event that an AE is considered related only to durvalumab or the combination novel therapy, both agents must be delayed.
- For subjects who develop ≥ Grade 2 pulmonary edema or ≥ Grade 3 peripheral edema after treatment with durvalumab plus oleclumab, doses should be omitted, and therapy may be discontinued at the discretion of the investigator.

If unsure how to manage a subject, contact the study medical monitor to discuss individual cases. Treatment for toxicities should be initiated prior to discussion with the study medical monitor.

Dose modifications are not allowed.

Guidelines for the management of immune-mediated reactions, IRRs, and non-immune-mediated reactions for durvalumab alone or in combination with the novel immunotherapies are provided in the Toxicity Management Guidelines. 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. Following the guidelines are expected, but changes due to local site procedures are allowed according to the physician's judgement.

The most current version of the Toxicity Management Guidelines is to be maintained within the Site Master File. In addition, a version of the current Toxicity Management Guidelines is available through the following link: https://tmg.azirae.com. Please contact the clinical study associate for information on how to gain access to this website.

3.1.4 Safety Review Committee

An SRC will conduct safety reviews of all enrolled subjects at least twice a year. The SRC may make recommendations regarding continuation, modification, or termination of any treatment arm for safety concerns. They may request additional data (eg, clinical efficacy) as needed. Additional safety reviews may be conducted at the discretion of the SRC.

An SRC will consist of the following:

- The sponsor study Medical Monitor, or delegate
- Global Safety Physician, or delegate
- Study Statistician
- Principal Investigators, or delegates, from a subset of active investigational sites. The number of sponsor representatives will not exceed the number of Principal Investigators.
- External physician not associated with the conduct of the study (SRC Chairperson)

The Clinical Pharmacology Scientist, Patient Safety Scientist, Clinical Operations Representative, and other delegates may also be invited as appropriate. Other internal and external experts may be consulted by the SRC as necessary. The membership, roles, responsibilities, and details on the process flow/communication plan are provided in the SRC Charter.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

3.2.1.1 Durvalumab

[redacted]

3.2.1.2 Oleclumab

[redacted]

3.2.1.3 Monalizumab

[redacted]

[redacted]

3.2.1.4 Danvatirsen

[redacted]

3.2.2 Rationale for Study Population

Surgery is the preferred and cornerstone treatment approach for patients diagnosed with resectable, early-stage (Stage I [> 2 cm] to IIIA) NSCLC. However, the majority of patients experience post-surgical relapse and disease recurrence (Section 1.5). Neoadjuvant durvalumab alone or in combination with novel agents may result in pathological response and/or downstaging prior to surgery.

3.2.3 Rationale for Endpoints

The primary objective of this platform study is to evaluate the efficacy of durvalumab alone and/or in combination with novel agents. The primary study goal is to assess the pathologic changes (eg, MPR) within the resected tumors, and identify promising durvalumab-based combination regimens for the treatment of patients with resectable, early-stage NSCLC. This study will use MPR, pCR, and BOR and ORR per RECIST v1.1 as efficacy endpoints to provide an early measure of antitumor activity. The safety and tolerability of each study treatment will be assessed by the standard safety endpoints, including AEs, SAEs, laboratory

abnormalities, and vital signs. Safety will also be assessed as feasibility to surgery, to capture any delays in the planned surgical resection. The development of ADA and its potential effect on safety and PK will also be assessed.

[redacted]

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Up to 40 subjects per treatment arm may be enrolled into the study. Across all treatment arms, subject accrual beyond 20 subjects will be determined based on interim data (Section 4.8.7). At the onset, subjects will be randomized with equal ratios into each treatment arm.

New durvalumab combination therapy arms may be added over time via a protocol amendment (Section 1.6.3). Details regarding the specifics of a new combination arm will be included in the protocol amendment. See also Section 4.6.1 for potential changes to the randomization scheme.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Written informed consent and any locally required authorization (eg, data privacy) obtained from the subject prior to performing any protocol-related procedures, including screening evaluation.
2 Age ≥18 years old
3 Body weight ≥ 35 kg
4 Subjects must have cytologically and/or histologically-documented NSCLC
   (a) Stage I (> 2 cm) to IIIA (for subjects with N2 disease, only those with 1 single nodal station ≤ 3 cm are eligible) NSCLC according to the 8th edition of American Joint Committee on Cancer staging classification
   (b) Considered amenable to complete surgical resection
   (c) Subjects have not received any other therapy for this condition (chemotherapy, biologic or radiotherapy)
5 Predicted FEV1 ≥ 50%
6 Predicted D_{LCO} ≥ 50%

7 Of the initial 20 subjects per treatment arm to be enrolled, a minimum of 10 subjects per arm must provide pretreatment biopsy tumor tissue. Archived biopsies (tissue block or unstained slides) collected within ≤ 6 months of study entry or undergoing a pretreatment tumor biopsy are both acceptable. Sites need to confirm the nature of archival tumor material (biopsy vs others [cytology, fine needle aspiration, unavailable]) before randomization. Refer to the Laboratory Manual for details.

8 Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1

9 Adequate organ and marrow function as defined in Table 4

Table 4 Criteria for Adequate Organ and Marrow Function

	Parameter	Value
Hematological	Hemoglobin [a]	≥ 9.0 g/dL (5.59 mmol/L)
	Absolute neutrophil count [a]	≥ 1.0×10^9/L (1,000 per mm^3)
	Platelet count [a]	≥ 100×10^9/L (100,000 per mm^3)
Hepatic	Total bilirubin	≤ 1.5 × ULN in the absence Gilbert's syndrome
		≤ 3 × ULN if the subject has Gilbert's syndrome
	Alanine transaminase and aspartate transaminase	≤ 2.5 × ULN
Renal	Calculated creatinine clearance [b]	≥ 40 mL/minute

ULN = upper limit normal.

[a] Hematological criteria cannot be met with ongoing or recent blood transfusions (within 14 days prior to the scheduled first dose of study treatment) or require growth factor support (within 21 days prior to the scheduled first dose of study treatment).

[b] As determined by Cockcroft-Gault formula using actual body weight (Cockcroft and Gault, 1976) or creatinine clearance based on 24-hour urine collection.

10 Females of childbearing potential and non-sterilized male subjects with female partners of childbearing potential must use effective methods of contraception from screening to 180 days after the final dose of study treatment (Appendix A).

4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1 Participation in another interventional clinical study within 90 days prior to enrollment.

2 Subjects with small-cell lung cancer or mixed small-cell lung cancer.

3 Subjects who require or may require pneumonectomy, as assessed by their surgeon, to obtain potentially curative resection of primary tumor.

4 Prior treatment with PD-L1, PD-L1, or cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitors.

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

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

(b) Systemic corticosteroids ≤ 12 mg/day of prednisone or its equivalent.

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

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

(a) Subjects with vitiligo or alopecia.

(b) Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement.

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

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

(e) Subjects with celiac disease controlled by diet alone

7 Pregnant or breast-feeding female.

8 Major surgical procedure as defined by the Principal Investigator within 30 days prior to the scheduled first dose of study treatment.

9 History of active primary immunodeficiency.

10 Active infection including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus.

11 History of allogenic organ transplantation.

12 Known allergy or hypersensitivity to investigational product formulation(s).

13 QTc interval (QTc) ≥ 470 ms. (NOTE: If prolonged, then 2 additional ECGs should be obtained and the average QTcF interval should be used to determine eligibility.)

14 Have moderate or severe cardiovascular disease:

(a) Presence of cardiac disease, including myocardial infarction or any other arterial thrombotic event including cerebrovascular accident, transient ischemic attack, or unstable angina pectoris within 6 months prior to study entry.

(b) New York Heart Association Class 3 or 4 congestive heart failure, or uncontrolled hypertension.

15 Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, 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 subject to give written informed consent.

16 Receipt of live attenuated vaccination within 30 days prior to study entry.

17 History of another primary malignancy except for:

(a) Curative-treated malignancy with no known active disease > 2 years before enrollment on the study.

(b) Curative-treated non-melanoma skin cancer and/or carcinoma in-situ.

18 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca/MedImmune staff and/or staff at the study site).

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice/web response system [IXRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and are not randomized), including the reason(s) for screening failure.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not be randomized or receive study treatment. Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened, only after discussion with and permission from the sponsor or its designee. Further details regarding randomization are detailed in Section 4.6.1.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (study treatment and assessments) at any time, without prejudice to further treatment. All study drug(s) should be returned by the subject. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

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

1 The subject or the subject's designee requests withdrawal of consent for further dosing.
2 Disease progression and investigator determination that the subject is no longer benefitting from treatment.
3 Any toxicity/AE that in the opinion of the investigator and/or the sponsor, warrants discontinuation of further dosing.
4 Any AE that meets criteria for discontinuation as defined in the Toxicity Management Guidelines (see Section 3.1.3)
5 Initiation of alternative anticancer therapy

6 Intercurrent illness or medical condition, in the judgment of the investigator and/or the sponsor warrants discontinuation of further dosing.
7 Pregnancy or intent to become pregnant (Section 5.6.2).
8 Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits)
9 The treating physician determines it is not in the best interest of the subject to continue treatment.

Subjects who are permanently discontinued from receiving study treatment will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn from further study participation (Section 4.1.5), disease progression, the subject starts alternative treatment/clinical study, or the subject is lost to follow-up.

4.1.7 Replacement of Subjects

Subjects who are dosed will not be replaced.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

MedImmune ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, MedImmune is not obliged to destroy the results of this research. As collection of the biological samples is an integral part of the study, if a subject decides to withdraw consent to the use of donated biological samples, then the subject will also be withdrawn from further study participation.

The Principal Investigator:

- Ensures subject's withdrawal of informed consent to the use of donated samples is notified immediately to MedImmune.
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site.
- Ensures that the subject and MedImmune are informed about the sample disposal.

MedImmune ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

4.2 Schedule of Study Procedures

The schedule of study procedures outlined in this section, with the exception of the study drug administration which are treatment-arm specific such as danvatirsen, will be followed for all treatment arms. The study drug treatment regimens for each treatment arm are presented in Section 3.1.2.

Table 5 Schedule of Screening, Treatment, and Follow-up Period Procedures

Procedure	Screening	Danvatirsen Only Arm (Lead-in) [a]	28-day Treatment Period			Surgical Resection [b]	Follow-up
	Day -21 to Day -1	Week 0, Day 1 (±3 days) [c]	Week 1, Day 1 (±3 days) [c]	Week 3, Day 1 (±3 days)	EoT Day 28 (±3 days)	Day 29 to Day 42	Day 105 (±21 days) [d]
Written informed consent	X						
Demographics	X						
Medical history [e]	X						
Verify eligibility criteria	X						
Physical examination [f]	X	X	X	X	X		X
Vital signs	X	X	X	X	X		X
ECG [g]	X	X		X	X		X
ECOG performance status	X	X	X	X	X		X
Tumor specimen [h]	X					X	
Serum chemistry	X	X [i]	X [i]	X	X		X
Thyroid function tests [j]	X	X [i]	X [i]	X	X		X
Hematology	X	X [i]	X [i]	X	X		X
Urinalysis	X	As clinically indicated					
Coagulation parameters	X	X [i]	X [i]	X	X		
Hepatitis B and C; HIV [k]	X						
Pregnancy test [l]	X				X		X
Concomitant medications	X	X	X	X	X		X
Assessment of AEs/SAEs	X	X	X	X	X		X
Disease assessments (scans) [m]	X				X		

Table 5 Schedule of Screening, Treatment, and Follow-up Period Procedures

Procedure	Screening	Danvatirsen Only Arm (Lead-in) [a]	28-day Treatment Period			Surgical Resection [b]	Follow-up
	Day -21 to Day -1	Week 0, Day 1 (±3 days) [c]	Week 1, Day 1 (±3 days) [c]	Week 3, Day 1 (±3 days)	EoT Day 28 (±3 days)	Day 29 to Day 42	Day 105 (±21 days) [d]
Brain MRI (preferred) or CT scan [n]	X						
PET scan	X						
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]
[redacted]		[redacted]	[redacted]		[redacted]		[redacted]
[redacted]		[redacted]	[redacted]				
[redacted]		[redacted]	[redacted]		[redacted]		[redacted]
[redacted]	[redacted]			[redacted] [p]			
Serum or plasma for PK		X [q]	X [q]	X [q]	X		X
Serum or plasma for ADA		X (predose) [r]	X (predose) [r]		X		X
Study drug administration [s]		According to each study-drug specific regimen					

ADA = antidrug antibody; AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CT = computed tomography; [redacted]; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; EoT = end of treatment; HBc = hepatitis B core antigen; HBsAg = hepatitis B virus surface antigen; HBs = hepatitis B surface; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; mRNA = messenger RNA; [redacted];

Note: All safety laboratory results must be reviewed by the investigator or physician designee prior to administration of any study treatment.

[a] On Week 0, Day 3 and Week 0, Day 5 (danvatirsen lead-in period), the dosing window for danvatirsen is ± 1 day. On Week 2, Day 1 and Week 4, Day 1 of danvatirsen administration, the dosing window for danvatirsen is ± 3 days.

[b] After surgical resection, the resected tumor will be sent to the sponsor as outlined in the Laboratory Manual.

Table 5 Schedule of Screening, Treatment, and Follow-up Period Procedures

Procedure	Screening	Danvatirsen Only Arm (Lead-in) [a]	28-day Treatment Period			Surgical Resection [b]	Follow-up
	Day -21 to Day -1	Week 0, Day 1 (±3 days) [c]	Week 1, Day 1 (±3 days) [c]	Week 3, Day 1 (±3 days)	EoT Day 28 (±3 days)	Day 29 to Day 42	Day 105 (±21 days) [d]

[c] Subjects will be randomized after completing the screening assessments. Study treatment must be administered within 3 days after the treatment arm is assigned; subjects may also be randomized on Week 0, Day 1 (danvatirsen only arm) or Week 1, Day 1 prior to dosing.

[d] If a subject receives subsequent anticancer treatment (eg, adjuvant chemotherapy or radiotherapy) prior to Day 105 (± 21 days), the follow-up visit can be scheduled earlier, prior to the start of adjuvant therapy.

[e] Diagnosis of active tuberculosis is defined by compatible clinical evaluation (medical history and physical examination), radiographic findings, and tuberculosis testing in line with local practice.

[f] A complete physical examination will be performed at screening. Abbreviated symptom-directed physical examinations will be conducted at subsequent visits post dosing.

[g] In cases when the first ECG shows clinically significant abnormalities, including a QTcF value ≥ 470 ms, 2 additional ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding based on the average of all 3 manually overread ECGs by a medically qualified delegate. On Week 0, Day 1 and Week 3, Day 1, ECGs will be performed predose and immediately after the end of danvatirsen infusion (prior to the start of durvalumab infusion). ECGs should also be performed as clinically indicated.

[h] Of the initial 20 subjects per treatment arm to be enrolled, a minimum of 10 subjects per arm must provide pretreatment biopsy tumor tissue. Archived biopsies (tissue block or unstained slides) collected within ≤ 6 months of study entry or undergoing a pretreatment tumor biopsy are both acceptable. Sites need to confirm the nature of archival tumor material (biopsy vs others [cytology, fine needle aspiration, unavailable]) before randomization.

[i] If screening laboratory assessments are performed within 3 days prior to Day 1, they do not need to be repeated at Day 1.

[j] TSH only. If TSH is abnormal, add T3 and T4 assessments.

[k] Active hepatitis B, hepatitis C, and HIV infections are defined by positive serologic test. Subjects positive for HBV infection are eligible if findings are compatible with past or resolved infection (HBsAg negative, anti-HBc positive and anti-HBs positive) or due to vaccination (HBsAg negative, anti-HBc negative and anti-HBs positive). Subjects positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

[l] Females of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study treatment. A urine or serum pregnancy test is acceptable; if urine test is positive or equivocal, then serum β-hCG testing should be performed for confirmation.

[m] CT scan of the chest and abdomen; an equivalent MRI scan is acceptable.

[n] A brain MRI (preferred) or CT scan is required only during the screening period.

[o] Samples will not be collected from subjects enrolled in the danvatirsen + durvalumab treatment arm on Week 1, Day 1.

[p] [redacted]

Table 5 Schedule of Screening, Treatment, and Follow-up Period Procedures

Procedure	Screening	Danvatirsen Only Arm (Lead-in) [a]	28-day Treatment Period			Surgical Resection [b]	Follow-up
	Day -21 to Day -1	Week 0, Day 1 (±3 days) [c]	Week 1, Day 1 (±3 days) [c]	Week 3, Day 1 (±3 days)	EoT Day 28 (±3 days)	Day 29 to Day 42	Day 105 (±21 days) [d]

[q] On Week 0, Day 1 (danvatirsen only arm [lead-in period]), Week 1, Day 1, and Week 3, Day 1, plasma or serum samples for PK will be collected predose (within 60 minutes prior to the start of infusion), and immediately post EOI (within 10 minutes after the EOI). In combination arms, PK predose and post EOI samples will be collected according to the administration time of each study drug. For example: PK predose Agent 1 collected → Agent 1 administration → PK EOI Agent 1 collected → PK predose Agent 2 collected → Agent 2 administration → PK EOI Agent 2 collected.

[r] In all treatment arms, ADA samples will be collected predose, within 60 minutes prior to administration of the first study drug only. For example: ADA predose Agent 1 and Agent 2 collected → Agent 1 administration → Agent 2 administration.

[s] Treatment regimens are described in Section 3.1.2.

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Evaluation of Response

Pathological tumor response will be assessed locally in the resected specimens. Hematoxylin and eosin-stained slides of sections of the gross residual tumor will be prepared by pathologists. At least 1 section per cm of tumor at its greatest diameter is recommended. The percentage of residual tumor will be estimated by comparing the estimated cross-sectional area of the viable tumor cells with estimated cross-sectional total tumor (including areas of necrosis, fibrosis, and/or inflammation). The results from all slides will be averaged together to determine the mean values for each subject. MPR is defined by ≤ 10% viable tumor cells in the resected specimen. pCR is defined as no residual viable tumor cells in the resected specimen. At the discretion of the sponsor, an independent, central review may be considered to evaluate pathological response.

RECIST v1.1 (Appendix F) will be used to assess subject response to treatment and allow calculation of ORR. Disease assessments will be performed according to the schedules in Section 4.2. Radiographical confirmation of a response is not feasible due to the length of the study (eg, a confirmatory scan will not be performed). Tumor assessments may include the following evaluations: cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and brain.

- MRI (preferred) or CT scans of the brain will be performed at screening for all subjects
- CT or MRI scan of the chest and abdomen will be performed at screening and with each disease assessment for all subjects.

The preferred method of disease assessment is CT with contrast; if CT with contrast is contraindicated, CT without contrast is preferred over MRI. The preferred method for central nervous system imaging is MRI; if CT scan is performed, CT with contrast is required. The same method is preferred for all subsequent tumor assessments.

Computed Tomography Scan

- CT (contrast preferred) scans of the chest and abdomen should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm. The same imaging device should be used for serial evaluations.

Magnetic Resonance Imaging Scan

- MRI scan of the chest and abdomen is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments.

- In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.

4.3.1.2 Baseline Disease Assessment by PET

Local changes and the presence of distal metastasis will be assessed by positron emission tomography (PET). The methods for assessing metabolic update by PET are summarized below (Plathow et al, 2008).

- PET requires measurement of the metabolically active lesions and background area. The FDG-distribution is rated visually and quantified as standardized uptake values (SUV).
- Any focal tracer uptake in lesions with SUV peak at least 1.5-fold greater than liver SUV mean is considered metastatic in absence of any alternative explanation. If liver is abnormal, primary tumor lesion should have uptake at least 2.0-fold greater than SUV mean of blood pool in descending thoracic aorta.
- For each lesion suspicious for malignancy in PET/CT, the site-based localization (lymph nodes, lung, liver, adrenal gland, brain, other viscera, and bone) is recorded.
- These parameters can be recorded as exploratory data on up to 5 measurable target lesions, typically the 5 hottest lesions, which are typically the largest, and no more than 2 per organ. Tumor size of these lesions can be determined per RECIST v1.1.
- Additional SUV measures including SUV mean, SUV peak or volumetric information may be measured to assess suspicious lesions

4.3.2 Lung Cancer Surgery

Feasibility to surgery will be evaluated (Section 4.8.4). General recommendations for the surgical therapy of subjects with resectable NSCLC include, where feasible:

- Anatomical resection consisting of at least a lobectomy
- Adequate collection of the margins of resection
- N1 and N2 node resection and mapping should be routine with a minimum of three N2 stations sampled or preferentially a complete mediastinal lymph node resection
- Complete ipsilateral mediastinal lymph node dissection is highly recommended for subjects undergoing resection for Stage IIIA-N2 disease
- A complete resection is the most important prognostic factor and should include free resection margins including mediastinal lymph node dissection
- Subjects who are eligible for an anatomic segmentectomy with formal ligation of the segmental artery and bronchus, and node dissection as described above can be considered after discussion with the medical monitor

4.3.3 Medical History, Physical Examination, Electrocardiogram, and Vital Signs

Medical History

Medical history will be collected at screening. Based on findings from medical history, ongoing current conditions will be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical Examinations

Physical examinations will be performed according to the schedules in Section 4.2. A complete physical examination will be performed at screening and should include assessments of the head, eyes, ears, nose, and throat, respiratory, cardiovascular, gastrointestinal, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, endocrine systems, weight to 0.1 kg, and height (screening only). Abbreviated symptom-directed physical examinations will be conducted at subsequent visits post dosing.

Vital Signs

Vital signs (blood pressure, pulse rate, and temperature) will be measured according to the schedules in Section 4.2. For all vital sign measurements, subjects should rest for at least 10 minutes in a supine or semi-recumbent position, and all vital sign measurements should be taken prior to any blood draws or other procedures whenever possible.

ECG

Resting 12-lead ECGs will be recorded as presented in Section 4.2. ECGs should be obtained after the subject has been in a supine position for 5 minutes and recorded while the subject remains in that position.

In cases when the first ECG shows clinically significant 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 based on the average of all 3 manually overread ECGs by a medically qualified delegate (eg, for initially prolonged QTcF value, the average QTcF value of all 3 manually overread ECGs should be ≥ 470 ms for the QTcF prolongation to be confirmed).

4.3.4 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed (see Section 4.2) for the schedule of tests:

Serum Chemistry

- Albumin
- Amylase
- ALP
- ALT
- AST
- Bicarbonate
- Blood urea nitrogen / urea
- Calcium
- Chloride
- Creatinine
- GGT
- Glucose
- Lactate dehydrogenase
- Lipase
- Magnesium
- Potassium
- Sodium
- Total bilirubin (TBL; direct bilirubin should be obtained if TBL is > ULN)
- Total protein
- C-reactive protein

ULN = upper limit of normal

Note: Tests for AST, ALT, ALP, and TBL must be conducted concurrently and assessed concurrently.

Hematology

- Absolute lymphocyte count [a]
- Absolute neutrophil count [a]
- Absolute leukocyte count
- Platelet count
- White blood cells count [a]
- Hemoglobin

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

Urinalysis

- Protein
- Blood

Pregnancy Test (females of childbearing potential only)

- Urine hCG
- Serum β -hCG (required if a urine hCG is equivocal or positive)

β -hCG = beta-human chorionic gonadotropin; hCG = human chorionic gonadotropin.

NOTE: A urine or serum pregnancy test is acceptable; if urine test is positive or equivocal, then serum β-hCG testing should be performed for confirmation.

Other Safety Tests

- Coagulation tests: activated aPTT and INR. If INR is not available, the sites may substitute a prothrombin time PT.
- Tuberculosis: Diagnosis of active tuberculosis is defined by compatible clinical evaluation (medical history and physical examination), radiographic findings, and tuberculosis testing in line with local practice.
- Hepatitis B, hepatitis C, and HIV: Active hepatitis B, hepatitis C, and HIV infections are defined by positive serologic test. Subjects positive for HBV infection are eligible if findings are compatible with past or resolved infection (HBsAg negative, anti-HBc positive and anti-HBs positive) or due to vaccination (HBsAg negative, anti-HBc negative and anti-HBs positive). Subjects positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Thyroid function tests: TSH only. If TSH is abnormal, add T3 and T4 assessments.

HBc = hepatitis B core; HBs = hepatitis B surface; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ration; PT = prothrombin time; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

4.3.5 Pharmacokinetic Evaluation and Methods

Blood samples will be collected to evaluate PK in plasma or serum when durvalumab is administered alone and/or in combination with novel agents. Additionally, PK of novel agents administered in combination with durvalumab will be evaluated; see Section 4.2 for collection time points. Evaluations will be performed using a validated immunoassay.

In combination arms, at visits when predose and end of infusion samples are required, PK predose (within 60 minutes prior to the start of infusion) and end of infusion (within 10 minutes post end of infusion) samples will be collected according to the administration time of each study drug. For example: PK predose Agent 1 collected → Agent 1 administration → PK end of infusion Agent 1 collected → PK predose Agent 2 collected → Agent 2 administration → PK end of infusion Agent 2 collected.

4.3.6 Immunogenicity Evaluation and Methods

Blood samples will be collected to evaluate antidrug antibody (ADA) responses to biological agents (durvalumab, oleclumab, monalizumab, and danvatirsen) when durvalumab is administered alone or in combination with novel agents; see Section 4.2 for collection time points. Evaluations will be performed using a validated immunoassay. Tiered analyses will be performed to include screening, confirmatory, and titer assay components, and the positive-negative cut points will be statistically determined from drug-naive validation samples. Samples may be utilized for further characterization of the ADA response.

In all treatment arms, ADA samples will be collected within 60 minutes prior to administration of the first study drug only. For example: ADA predose Agent 1 and Agent 2 collected → Agent 1 administration → Agent 2 administration.

4.3.7 [redacted]

[redacted]

4.3.7.1 [redacted]

[redacted]

4.3.7.2 [redacted]

[redacted]

4.3.8 Biomarker Evaluation and Methods

The subject's consent to the use of donated biological samples is mandatory.

Details on sample collection, processing, handling, shipment, and storage are provided in the Laboratory Manual.

4.3.8.1 Radiomics

CT or MRI scans will be performed as indicated in Section 4.2. Changes in radiomics signatures may be compared in pretreatment vs post-treatment scans, and correlation with pathological response may be evaluated.

4.3.8.2

[redacted]

4.3.8.3

[redacted]

4.3.8.4

[redacted]

4.3.8.5

[redacted]

4.3.8.6

[redacted]

4.3.8.7 [redacted]

4.3.8.8 Storage, Re-use and Destruction of Biological Samples

Samples will be stored for a maximum of 15 years or as per local regulations from the date of the last subject's last visit, after which they will be destroyed. The results of this biomarker research will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the study drug to generate hypotheses to be tested in future research.

4.3.9 Estimate of Volume of Blood to Be Collected

A total of no more than 35 mL of blood will be required for all screening tests. No more than 51 mL of blood will be drawn at any visit during the treatment period. During the follow-up visit, no more than approximately 36 mL of blood will be collected. The total volume to be collected will depend on the treatment arm, central laboratory used, and length of a subject's participation in the study. The Laboratory Manual may be referenced for test volume specifics.

4.4 Study or Study Component Suspension or Termination

MedImmune reserves the right to temporarily suspend or permanently terminate this study or component of the study at any time. The reasons for temporarily suspending or permanently terminating the study or component of the study may include but are not limited to the following:

1 Recommendation by the SRC, or the incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
2 Subject enrollment is unsatisfactory
3 Non-compliance that might significantly jeopardize the validity or integrity of the study
4 Sponsor decision to terminate development of durvalumab or any of the combination study treatments for this indication
5 Sponsor decision to terminate the study or component of the study based on a planned futility analysis
6 Regulatory, ethical or other reason consistent with applicable laws, regulations and GCP.

If MedImmune determines that temporary suspension or permanent termination of the study or component of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where

applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study or component of the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study or component of the study is suspended for safety reasons and it is deemed appropriate by MedImmune to resume the study or component of the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

For all the treatment arms, MedImmune will provide the investigators with study drug (Table 6) using designated distribution centers.

Table 6 Identification of Investigational Product

Investigational Product	Supplier	Concentration and Formulation as Supplied
Durvalumab (MEDI4736)	MedImmune	[redacted]
Oleclumab (MEDI9447)	MedImmune	[redacted]
Monalizumab (IPH2201)	MedImmune	[redacted]
Danvatirsen (AZD9150)	AstraZeneca	[redacted]

Table 6 Identification of Investigational Product

Investigational Product	Supplier	Concentration and Formulation as Supplied
[redacted]		

4.5.1.1 Investigational Product Handling

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational products will be returned to a MedImmune authorized depot or disposed of upon authorization by MedImmune according to the investigational site policy.

4.5.1.2 Investigational Product Inspection

Each vial selected for dose preparation should be inspected. See Section 4.5.1 for a description of investigational product presentation.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.9) for further instructions.

4.5.1.3 Durvalumab Dose Preparation and Administration

The dose of durvalumab for administration must be prepared by the investigator's or site's designated investigational product manager using aseptic technique.

Total time from needle puncture of a durvalumab vial to 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 [redacted] 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 [redacted] and delivered through an IV administration set with a 0.2- or 0.22-µm filter. [redacted] of durvalumab (ie, [redacted] of durvalumab) to the IV bag. The IV bag size should be selected such that the final concentration is within [redacted] Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

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

For treatment arms that require administration of durvalumab and the combination study drug on the same day, the total infusion time for both study drugs should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line. For IV flushing instructions, refer to Section 4.5.1.7.

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

4.5.1.4 Oleclumab Dose Preparation and Administration

The dose of oleclumab for administration must be prepared by the investigator's or site's designated investigational product manager using aseptic technique.

Total time from needle puncture of the oleclumab 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

No incompatibilities between oleclumab and polyvinylchloride or polyolefin IV bags have been observed.

A dose of [redacted] will be administered using an IV bag containing 0.9% (w/v) saline with a final oleclumab concentration of [redacted] and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time for oleclumab is 1 hour; however, if there are interruptions during infusion, the total allowed time should not exceed 4 hours at room temperature. If this duration is met, then the remainder of the dose should be abandoned and should not be completed with a second prepared dose.

On the day when both oleclumab and durvalumab are administered, durvalumab infusion will start no less than 15 minutes after the end of oleclumab infusion. See Section 4.5.1.3 for durvalumab administration. In the event that on the day when both oleclumab and durvalumab are administered there are interruptions during infusion for either oleclumab and/or durvalumab, the total infusion duration for both study drugs should not exceed 8 hours. Of the total 8-hour infusion duration, a maximum of 4 hours may correspond to oleclumab infusion.

Do not co-administer other drugs through the same infusion line. For IV flushing instructions, refer to Section 4.5.1.7

If preparation time exceeds the time limits outlined above, a new dose must be prepared from new vials. Oleclumab does not contain preservatives, and any unused portion must be discarded.

4.5.1.5 Monalizumab Dose Preparation and Administration

The dose of monalizumab for administration must be prepared by the investigator's or site's designated investigational product manager using aseptic technique.

Slowly add 7.4 mL of sterile Water for Injection by tilting the vial to one side such that the liquid stream is directed along the vial wall and not directly onto the lyophilized cake. Gently swirl the solution until all solids are dissolved. DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL. Visually inspect the solution to ensure that the entire content of the lyophilized cake is completely reconstituted. The reconstituted solution should appear clear to opalescent. A thin layer of bubbles on the surface of the liquid is normal.

Monalizumab should be protected from direct sunlight during preparation and handling. Total time from start of reconstitution to the start of monalizumab administration should not exceed:

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

No incompatibilities between monalizumab and polyolefin, polyethylene, polypropylene, or polyvinyl chloride (PVC) IV bags have been observed.

A dose of [redacted] will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final monalizumab concentration of [redacted] and delivered through an IV administration set with a 0.2- or 0.22 µm filter. Add [redacted] of monalizumab (ie, [redacted] of monalizumab) to the IV bag. The IV bag size should be selected such that the final concentration is within [redacted] Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard monalizumab infusion time is 1 hour, however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. The infusion rate should not be changed unless necessary to manage acute reactions.

On the day when both durvalumab and monalizumab are administered, durvalumab will be administered first. See Section 4.5.1.3 for durvalumab treatment administration.

Monalizumab infusion will start no less than 15 minutes after the end of the durvalumab infusion. In the event that on the day when both durvalumab and monalizumab are administered and there are interruptions during infusion for either durvalumab and/or monalizumab, the total infusion duration for both study drugs should not exceed 8 hours. Of the total 8-hour infusion duration, a maximum of 4 hours may correspond to durvalumab infusion.

Do not co-administer other drugs through the same infusion line. For IV flushing instructions, refer to Section 4.5.1.7

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

4.5.1.6 Danvatirsen Dose Preparation and Administration

The dose of danvatirsen for administration must be prepared by the investigator's or site's designated investigational product manager in a validated aseptic suite; it should not be prepared on the ward.

Vials must be used within the individually assigned expiry date on the label.

Remove two vials from the refrigerator and allow the vials to equilibrate to room temperature for 30 minutes prior to dose preparation.

Add [redacted] of danvatirsen to an IV infusion bag containing 250 mL of 0.9% (w/v) sodium chloride (normal saline) using a regular 18G to 22G stainless steel needle and latex-free syringe made of polypropylene or polycarbonate. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Saline IV bags (250 mL) must be latex-free and can be made of PVC or polyolefins, manufactured with bis (2-ethylhexyl) phthalate (DEHP) or DEHP-free. IV infusion lines made of PVC/DEHP-free or PVC/DEHP-containing are acceptable for use.

Label the IV bag per the institution's procedures. Record on the label the total volume contained in the IV bag. Include the total volume, the overfill (assume 25 mL unless otherwise known) and the volume of danvatirsen that was added.

Fully prime the infusion line with normal saline, prior to connecting it to the danvatirsen IV bag.

Following preparation of the dose, the entire contents of the IV bag should be administered at a constant rate over 1 hour.

Total time from needle puncture of a danvatirsen vial to end of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
  - Note: This represents the maximum storage time at 2°C to 8°C and will therefore be reduced by any time spent at room temperature.
- 4 hours at room temperature

The above storage times are based on chemical and physical stability; assignment of microbial shelf-life is the responsibility of the clinical center and should be aligned with local procedures for managing microbial risk, so long as the above are not exceeded.

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration, allow approximately 30 minutes for this.

If in-use time exceeds the stated limits outlined above, a new dose must be prepared from new vials.

Danvatirsen does not contain preservatives, and any unused portion of concentrate in vial must be discarded.

It is not necessary to protect the diluted infusion from light during the period of preparation and administration.

Do not co-administer other drugs or solutions through the same infusion line. For IV flushing instructions, refer to Section 4.5.1.7.

On the day when both durvalumab and danvatirsen are administered, danvatirsen will be administered first. See 4.5.1.3 for durvalumab treatment administration.

On the day when danvatirsen and durvalumab are infused, durvalumab will start approximately 1 hour after the end of the danvatirsen infusion.

4.5.1.7 Treatment Administration

The first day of dosing with durvalumab alone or in combination with novel agents is considered Week 1, Day 1 in all the treatment arms. In the durvalumab + danvatirsen treatment arm, the lead-in period for danvatirsen starts on Week 0, Day 1.

No specific premedication is required for durvalumab, oleclumab, monalizumab, or danvatirsen. Details of any premedication or concomitant medication given to manage or prevent AEs should be recorded on the electronic case report form (eCRF).

In all treatment arms, flush the IV line 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.

A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available.

4.5.1.8 Monitoring of Dose Administration

Subjects will be monitored during and after infusion(s) of investigational product(s). Vital signs will be measured according to the schedules described in Section 4.2.

As with any biologic product, allergic reactions to dose administration are possible. Therefore, 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.

4.5.1.9 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product

Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com
Phone: +1-301-398-2105
+1-877-MEDI-411 (+1-877-633-4411)
Fax: +1-301-398-8800
Mail: MedImmune
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, MD USA 20878

4.5.2 Additional Study Medications

No other study medications are specified for use in this clinical protocol.

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into local languages, as required.

4.5.4 Storage

All investigational products should be stored in a secure and dry place. Vials of investigational product for parenteral administration should be stored at 2°C to 8°C (36°F to 46°F; refrigerated) and must not be frozen. Investigational product supplied as oral tablet should be stored at 15°C to 30°C (59°F to 86°F). Drug product should be kept in original packaging until use to prevent excessive light exposure.

4.5.5 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

4.5.6 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

Once confirmed that the subject meets eligibility criteria, an IXRS will randomize the subject to a treatment arm according to the randomization scheme.

A randomization method with dynamically changing randomization ratios will be employed to account for fluctuation in the number of treatment arms open for enrollment over the course of the study. The randomization scheme will use an equal ratio to all study treatment arms open for enrollment (eg, if treatment arms are opened sequentially, a treatment arm is added/closed, or enrollment in a treatment arm is suspended). After 20 subjects have been enrolled into any treatment arm, the randomization ratio can be adjusted. Randomization will be stratified by lymph node involvement (Yes vs No). At the onset, the randomization scheme will use an equal ratio in all treatment arms. Study treatment must be administered within 3 days after the treatment arm is assigned. If there is a delay in the administration of study treatment such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

4.6.2 Methods to Ensure Blinding

This study is not blinded.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the final study visit. Any concomitant medication(s), including herbal and natural preparations, taken during the study will be recorded in the eCRF.

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as prohibited in Section 4.7.2.

4.7.2 Prohibited Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator. The following concomitant medications are prohibited:

- Any other investigational anticancer therapy
- Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.

- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 12 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-alpha blockers. The following are exceptions:
  - Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable.
  - Use of inhaled, intranasal, topical corticosteroids, or local steroid injections (eg, intra-articular injection) is permitted.
  - Temporary courses of corticosteroids for treatment of underlying or concurrent illness or in the setting of palliative radiotherapy may be permitted upon discussion with the medical monitor.
- Live attenuated vaccines during the study through 180 days after the last dose of study drug
- Herbal and natural remedies should be avoided

4.8 Statistical Evaluation

4.8.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. Additional details of statistical analyses will be described in the statistical analysis plan.

The Intent-to-treat (ITT) Population is defined as all subjects who are randomized and receive any amount of investigational product. Subjects will be analyzed according to randomized treatment assignment. All analyses will be performed on the ITT Population unless otherwise specified.

The As-treated Population is defined as all subjects who receive any investigational product. Subjects will be analyzed according to the treatment they actually received. All safety endpoints will be analyzed on the As-treated Population.

The Efficacy Evaluable Population includes subjects from the As-treated Population who have the opportunity to be followed for the planned surgery by the time of the data cutoff, and either have pathological tumor response data post-surgery and/or discontinued treatment due to death or disease progression. Interim analyses of efficacy will be performed on this population.

4.8.2 Sample Size

This study is designed to obtain preliminary clinical efficacy, safety, PK and immunogenicity data on durvalumab in combination with novel agents compared to durvalumab monotherapy. It is not designed to make explicit power and Type I error considerations for a hypothesis test.

At the onset, subjects will be randomized with equal ratios into each treatment arm. The initial arms included are: durvalumab monotherapy, durvalumab plus oleclumab, durvalumab plus monalizumab, and durvalumab plus danvatirsen. A total of up to 40 subjects per arm may be enrolled. An interim analysis will be performed in any given arm, once a respective arm enrolls at least 20 efficacy evaluable subjects (see Section 4.8.1).

Table 7 shows estimated differences in MPR between a durvalumab combination therapy arm compared to the durvalumab monotherapy arm, along with 95% Wald confidence intervals (CIs), with different assumptions and a sample size of 40 subjects each assuming an asymptotic normality. The assumed 30% MPR rate with the durvalumab monotherapy arm is based on a pooled analysis of data from two recently published clinical trials evaluating anti-PD-1/PD-L1 monotherapies in a similar patient population. One study (Forde et al, 2018) reported an MPR rate of 45% (9/20) for subjects who received nivolumab monotherapy; while another study (Rusch et al, 2018) reported an MPR rate of 20% (10/50) for subjects who received atezolizumab monotherapy. An arithmetic average of these two MPR rates is rounded to 30% as the assumed MPR rate for durvalumab. Forty subjects per treatment arm provides a 95% CI with reasonable width (~ ± [redacted]%) for the estimated difference between a durvalumab combination therapy arm and the durvalumab monotherapy arm. When the MPR rate for a durvalumab combination therapy arm is [redacted]%, the lower limit of the 95% CI for the difference between the durvalumab combination therapy arm and the durvalumab monotherapy arm is [redacted]%, which is greater than [redacted]% suggesting tha [redacted]

Table 7 Estimated Differences in MPR Rate Between Durvalumab Monotherapy and Each Durvalumab Combination Therapy Arm (40 Subjects Each)

Number (%) of Responders		Difference (%) in MPR (95% Wald CI)
Durvalumab Combination Therapy Arm (n = 40)	Durvalumab Monotherapy Arm (n = 40)	
16 (40%)	12 (30%)	10% (-11%, 31%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

CI = confidence interval; MPR = major pathological response.

4.8.3 Efficacy

The final efficacy analyses will be based on the ITT Population defined in Section 4.8.1. The interim analyses will be based on the Efficacy Evaluable Population. Response will be summarized and compared between the durvalumab combination therapy arm and Arm A

(durvalumab monotherapy). There will be no formal comparisons between any combination therapy arms. The following efficacy endpoints will be analyzed. More details will be provided in the statistical analysis plan.

4.8.3.1 Primary Efficacy Analysis

MPR rate, defined as the proportion of subjects with ≤ 10% residual viable tumor cells, and the corresponding 95% CI will be reported for each arm. In addition, the difference between any durvalumab combination therapy arm and the durvalumab monotherapy arm will be evaluated. Comparison of each of the combination therapy arms with the monotherapy arm will be obtained from the Chi-square or Fisher's exact test.

4.8.3.2 Secondary Efficacy Analyses

pCR rate, defined as the proportion of subjects with no viable tumor cells, and the corresponding 95% CI will be reported for each arm. In addition, the difference between any durvalumab combination therapy arm and the durvalumab monotherapy arm will be evaluated. Comparison of each of the combination arms with the monotherapy arm will be obtained from the Chi-square or Fisher's exact test.

4.8.3.3 [redacted]

[redacted]

4.8.4 Safety

Summary statistics will be provided for AEs, SAEs, and AE grade, severity, and relationship to study drug, clinical laboratory parameters, physical examinations, and vital signs.

In addition, feasibility to surgery will be evaluated. Surgical resection is to be performed approximately 29 to 42 days after Week 1, Day 1. Feasibility to surgery is defined as the proportion of subjects in each arm with no delay in the planned surgery (no later than 42 days after Week 1, Day 1).

The SRC will assess feasibility to surgery for all treatment arms during every meeting. The following general rules will apply: When more than 1 subject per treatment arm experiences a delay in the planned surgery outside of the exclusions provided below, randomization into the

concerned treatment arm may be paused. The SRC members will be notified and an SRC meeting will be planned within the next 14 days. During the SRC meeting all delays to surgery in the concerned arm will be reviewed, and the recommendation of the SRC will be discussed with the sponsor to make a final decision about stopping enrollment into the concerned arm.

Delays to surgery not considered for the feasibility analysis include:

- Weather or other local emergencies impacting normal hospital activities.
- Unforeseen causes not related to the disease under study such a car accident, family illness or unexpected travel.
- Withdrawal of consent to further participation on the study not related to AEs or study procedures.

4.8.4.1 Analysis of Adverse Events

AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) using the Medical Dictionary for Regulatory Activities (MedDRA) by system organ class (SOC) and preferred term (PT). Specific AEs will be counted once for each subject for calculating rates, but will be presented in total in subject listings. In addition, if the same AE occurs multiple times within a particular subject, the highest severity and level of causality will be reported. All treatment-emergent AEs will be summarized overall and by MedDRA SOC and PT, by severity and relationship to investigational product. In addition, summaries of deaths, SAEs and treatment discontinuations due to AEs will be provided. AEs before and after surgery will be summarized separately.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Laboratory parameters will be assessed at baseline as well as throughout the study. Frequencies of maximum observed grade will be presented for each laboratory parameter as well as the rates of subjects with Grade 3-4 toxicities. A shift table, presenting the 2-way frequency tabulation for baseline and post-baseline grade at scheduled time of evaluation as well as the worst post-baseline grade, will be provided for clinical laboratory tests. Also, laboratory parameters will be assessed by presenting tables containing information related to 2-grade (or greater) laboratory shifts.

4.8.4.3 Analysis of Vital Signs

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation and by treatment arm including end of treatment visit as well as for the maximum and minimum post-baseline values.

4.8.4.4 Analysis of ECOG Performance Status

Descriptive statistics will be provided for the ECOG Performance Status assessments and changes from baseline by scheduled time of evaluation and by treatment arm.

4.8.5 Analysis of Immunogenicity/Pharmacokinetics

4.8.5.1 Immunogenicity Analyses

Only subjects who receive at least 1 dose of durvalumab and/or other combination study drug, and provide at least 1 post-treatment sample, will be evaluated. For each treatment arm, the immunogenic potential of durvalumab will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs to durvalumab. For treatment arms that include a novel biologic agent, the immunogenic potential of the novel biologic agent will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs to the novel biologic agent.

4.8.5.2 Pharmacokinetic Analyses

Only subjects who receive at least 1 dose of durvalumab and/or other combination study drug, and provide at least 1 post-treatment sample, will be evaluated. For each treatment arm, individual durvalumab and individual combination study drug concentrations will be tabulated with descriptive statistics.

4.8.6 [redacted]

[redacted]

4.8.7 Interim Analysis

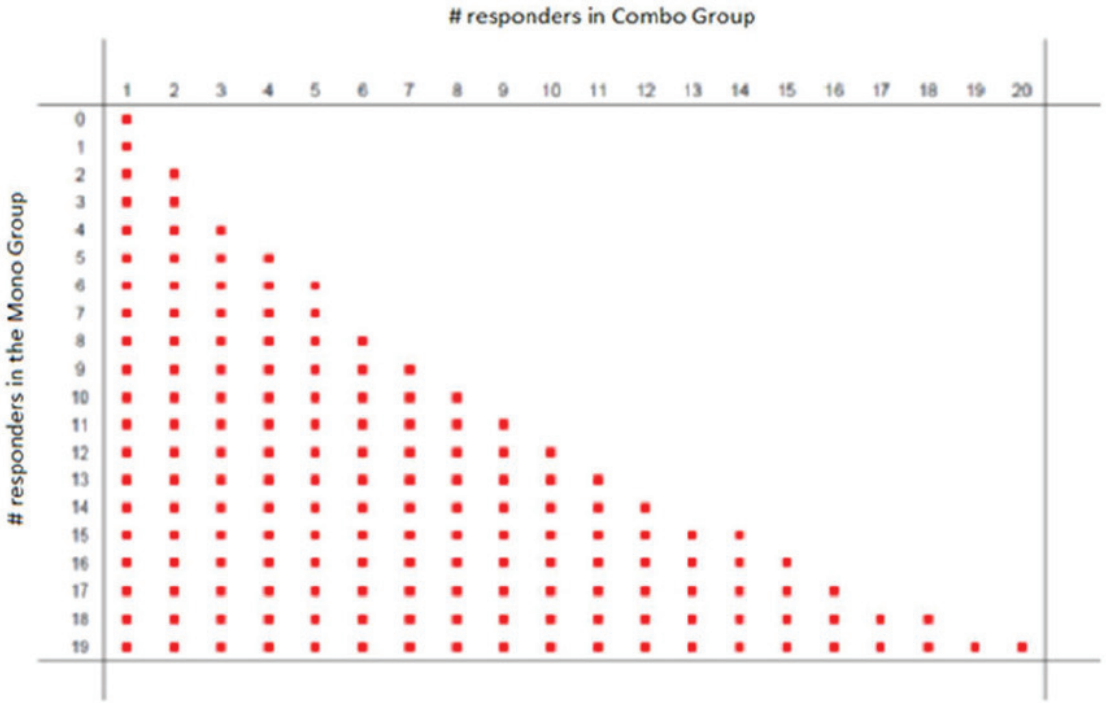
Interim analyses will be conducted during the course of the study to evaluate the clinical activity and safety of any treatment arm. The first planned interim analysis will be initiated once at least 1 treatment arm has enrolled 20 efficacy evaluable subjects (see Section 4.8.1). Across all treatment arms, subject accrual beyond 20 subjects will be determined based on interim data. Bayesian predictive probabilities will be used to evaluate clinical activity (Lee and Liu, 2008). In this study, a target value (TV) of ΔMPR as [redacted]% is assumed, where ΔMPR is the difference in MPR between a combination therapy treatment arm and the durvalumab monotherapy arm.

- A treatment arm will meet the No-Go criteria if the probability that the true ΔMPR are larger than TV is less than [redacted]%, ie, Prob.(True ΔMPR > [redacted]) < [redacted] A No-Go decision will be made at the interim analysis if the predictive probability of meeting the No-Go

criteria given observed data are greater than [redacted]%, ie, Predictive Probability(Prob.[ΔMPR > [redacted]] < [redacted]) > [redacted]

A treatment arm will be considered futile if it meets the futility bar for MPR according to Figure 7. If at least 1 treatment arm has more than 20 efficacy evaluable subjects' data at the interim analysis, slightly different futility bars compared to Figure 7 will be provided on a case-by-case basis. In addition, for any treatment arm, enrollment will be stopped if more than 2 out of the first 20 enrolled subjects failed the feasibility to surgery.

Figure 7 Futility Bar for Major Pathological Response



Combo = durvalumab combination; Mono = monotherapy.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally

associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject 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.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject 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.

5.3 Definition of Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the investigational product(s) and may require close monitoring and rapid communication by the investigator to MedImmune. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product(s).

5.3.1 Adverse Events of Special Interest for Durvalumab-containing Regimens

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or

interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the investigator has any questions determining whether an AE is an imAE, the investigator should promptly contact the study physician. AESIs observed with durvalumab include:

- Diarrhea/colitis and intestinal perforations
- Pneumonitis
- Hepatitis
- Endocrinopathies (ie, events of hypophysitis/hypopituitarism, type 1 diabetes mellitus, adrenal insufficiency, and hyper- and hypothyroidism)
- Rash/dermatitis
- Nephritis
- Pancreatitis
- Myocarditis
- Myositis/polymyositis
- Neuropathy/neuromuscular toxicity (eg, Guillain-Barré and myasthenia gravis)
- Immune complex disease. The immune system can respond to foreign mAbs by producing human-anti-human antibodies, which may result in formation of immune complexes and their deposition in blood vessels, joints, and glomeruli causing symptomatic disease (eg, vasculitis, glomerulonephritis, arthritis, serum sickness). Subjects who experience an AE suspected to be immune-complex related and with confirmed presence of ADAs will discontinue treatment. Immune-complex disease will be managed in accordance with standard of care.
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events.

In addition, IRRs and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs. Infusion of biological products is commonly associated with IRRs. Anaphylaxis and IRRs have some common manifestations and may be difficult to distinguish from each other. IRRs are commonly observed during or shortly after the first time of exposure to therapeutic mAbs delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike IRRs, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most

commonly accompanied by severe systemic, skin and/or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to investigational product, and consider the above-mentioned facts prior to making a final diagnosis. For the investigator's convenience and to facilitate consistency in judgments, a copy of the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in Appendix C.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Toxicity Management Guidelines (Section 3.1.3). 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.

5.3.2 Adverse Events of Special Interest Associated with Oleclumab

Cardiac Chest Pain, Transient Ischemic Attack, and Thromboembolism

AEs of cardiac chest pain, transient ischemic attack, and thromboembolism are of special interest due to oleclumab potential risks of arterial calcifications, arterial ischemic disorder, and thrombosis. Because of this potential risk, potential subjects with a history of myocardial infarction or or any other arterial thrombotic event within 6 months before study entry are not eligible (see Section 4.1.3). These events require urgent medical management, which should be performed according to consensus guidelines developed by the American Heart Association or appropriate local standards of care.

Edema

Edema (eg, pulmonary or peripheral) is regarded as an AESI due to oleclumab potential risks of increased microvascular permeability. For subjects who develop ≥ Grade 2 pulmonary edema or ≥ Grade 3 peripheral edema after treatment with durvalumab plus oleclumab, doses should be omitted (Section 3.1.3), and therapy may be discontinued at the discretion of the investigator.

5.3.3 Adverse Events of Special Interest Associated with Monalizumab

There are no specific AESI for monalizumab, outside of the AESIs associated with durvalumab, as stated Section 5.3.1.

5.3.4 Adverse Events of Special Interest Associated with Danvatirsen

There are currently no AESIs associated with danvatirsen.

5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to MedImmune (see Section 5.5). See Section 5.2 for the definition of SAEs and Appendix B for guidelines on assessment of severity and relationship.

If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

5.4.1 Time Period for Collection of Adverse Events

AEs and SAEs will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period.

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved during the end of study visit or when a subject has withdrawn consent for study participation may be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.4.3 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period must be reported as follows:

- Death clearly the result of disease progression should be reported and documented in the eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to disease progression, the AE causing the death must be reported as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. A post-mortem (autopsy) 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 MedImmune representative(s) within the usual timeframes (refer to Section 5.5 for additional information).

5.4.4 Adverse Events Based on Signs and Symptoms

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

5.4.5 Adverse Events Based on Examination and Tests

The results from the protocol-mandated laboratory tests and vital signs will be summarized in the CSR. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased).

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

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

5.4.6 Potential Hy's Law and Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN will need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

5.4.7 Disease Progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product 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 a new metastasis or progression of existing metastasis related to the primary

cancer under study should not be considered an AE. Death clearly resulting from disease progression should not be reported as an SAE (see reporting guidelines in Section 5.4.3).

The term disease progression should not be reported as an AE or SAE, however, medically significant individual events and/or laboratory abnormalities associated with disease progression (see definition of disease progression above) that fulfill the AE or SAE definition should be reported.

New Cancers

The development of a new cancer should be regarded as an SAE. New cancers are those that are not the primary reason for the administration of the investigational product(s) and have been identified after the subject's inclusion in the study. New metastatic lesion(s) of the subject's known cancer should not be reported as a new cancer.

5.5 Reporting of Serious Adverse Events

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

If any SAE occurs in the course of the study, then investigators or other site personnel must inform the appropriate sponsor representative(s) within 1 day, ie, immediately but no later than 24 hours after becoming aware of the event.

The designated study representative works with the investigator to ensure that all the necessary information is provided to the sponsor's patient safety data entry site within 1 calendar day of initial receipt for fatal and life-threatening events and within 5 calendar days of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day, ie, immediately but no later than 24 hours after becoming aware of the event.

Once the investigators or other site personnel indicate an AE is serious in the electronic data capture (EDC) system, an automated email alert is sent to inform the designated sponsor representative(s).

If the EDC system is not available, then the investigator or other study site personnel reports an SAE to the appropriate sponsor representative by telephone. The sponsor representative will advise the investigator/study site personnel how to proceed.

The reference document for definition of expectedness/listedness are the IBs for the study drugs.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the respective IB, unless otherwise specified in this protocol. For danvatirsen, administration in doses significantly exceeding those specified in the protocol (> 10% of recommended dose) is considered an overdose; overdose in an amount ≤ 10% of the specified dose and not associated with AEs does not need to be reported.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated AEs is only reported on the Overdose eCRF module.

If an overdose on any investigational product occurs during the course of the study, then the investigator or other site personnel should inform appropriate sponsor representatives immediately, but no later than 24 hours after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply; see Section 5.5. For other overdoses (ie, those not associated with an AE or SAE), reporting must occur within 30 days.

5.6.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor except if the pregnancy is discovered before the subject has received any study drug.

Females of childbearing potential must have a negative pregnancy test result at screening to be enrolled in the study and treated with study drug.

5.6.2.1 Maternal Exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/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 subject was discontinued from the study.

If any pregnancy occurs during the course of the study, then the investigator or other site personnel will inform the appropriate sponsor representatives within 1 day, ie, immediately but no later than 24 hours after becoming aware of the event.

The designated study representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

5.6.2.2 Paternal Exposure

Pregnancy of the subject's partners 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 90 days after the last dose should, if possible, be followed up and documented.

5.6.3 Medication Error

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

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

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the subject received the study 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:

- Study drug name confusion (ie, instead of receiving the investigational product, the subject received a drug that has a similar-sounding name)
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Study drug not administered as indicated, eg, wrong route or wrong site of administration
- Study drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet

- Study drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong subject received the medication (excluding IXRS errors)
- Wrong study drug administered to subject (excluding IXRS errors)

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

- Errors related to or resulting from IXRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed study drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication

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 the appropriate MedImmune representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated MedImmune representative works with the investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 5.5) and within 30 days for all other medication errors. Medication errors should be reported using a Medication Error Report Form.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for the location of the source data.

6.2.2 Study Agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this protocol and the Clinical Study Agreement, the terms of this protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the Principal Investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through their last protocol-specified visit/assessment, regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.1.5 and Section 4.1.6).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment for the last subject in the study. This date will be 1 year after the final subject is entered into the study or when the sponsor stops the study, whichever occurs first.

6.4 Data Management

Data management will be performed by MedImmune Data Management staff or other party according to the Data Management Plan.

An EDC system will be used for data collection and query handling. The investigator will ensure that data are recorded in the eCRFs as specified in the study protocol and in accordance with the eCRF instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the Principal Investigator. In addition, each subject will receive a toll-free number intended to provide the subject's physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the Principal Investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

Each subject will be assigned a SID to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the trial, eg, demographic

information, physical or mental health condition, diagnosis, comorbidities, laboratory test results, etc. will only be collected with the subject's informed consent. The informed consent form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that describes how subject data will be collected, used, and distributed in compliance with relevant data protection and privacy legislation. Data (clinical and biological samples) from this study may be used and may be combined with results from other studies for additional scientific-related research, based on agreement from the subject as defined in the informed consent form.

Extra precautions will be taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

7.2 Ethics and Regulatory Review

The IRB/IEC responsible for each site must review and approve the final study protocol, including the final version of the informed consent form and any other written information and/or materials to be provided to the subjects. The IRB/IEC must also approve all advertising used to recruit subjects for the study. The investigator is responsible for submitting these documents to the applicable IRB/IEC, and distributing them to the study site staff.

The opinion of the IRB/IEC must be given in writing. The investigator must provide a copy of the written approval to MedImmune before enrollment of any subject into the study.

MedImmune should approve any substantive modifications to the informed consent form that are needed to meet local requirements.

If required by local regulations, the protocol must be re-approved by the IRB/IEC annually.

Before the study is initiated, MedImmune will ensure that the national regulatory authority in each country has been notified and their approval has been obtained, as required. MedImmune will provide safety updates/reports according to local requirements, including SUSARs where relevant, to regulatory authorities, IRB/IEC, and Principal Investigators.

Each Principal Investigator is responsible for providing reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product to the IRB/IEC. MedImmune will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

7.3 Informed Consent

Informed consent of each subject will be obtained through a written and verbal explanation process that addresses all elements required by ICH/GCP. MedImmune will develop a core

informed consent form for use by all investigators in the clinical study. MedImmune must approve any modifications to the informed consent form that are needed to meet local requirements.

The Principal Investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed informed consent form(s) is/are stored in the investigator's Study File
- Ensure a copy of the signed informed consent form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an IRB/IEC

7.4 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and MedImmune. Any changes must be documented in a study protocol amendment.

For a substantial change to the protocol, MedImmune will distribute amended versions of the protocol to the Principal Investigator(s). Before implementation, amended protocols must be approved by relevant IRB/IEC (see Section 7.2) and reviewed as per local regulatory authority requirements. The IRB/IEC must also approve revisions to the informed consent form, advertising, and any other written information and/or materials resulting from the change to the protocol.

Any non-substantial changes will be communicated to or approved by each IRB/IEC and local regulatory authority per local requirements.

7.5 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the

ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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9 CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 2

The primary reasons for the amendment were alignment of monalizumab information with the new manufacturing process (Process C) and inclusion of subjects with Stage IIIA-N2 disease (1 single nodal station ≤ 3 cm only). No subjects were enrolled in Arm C (durvalumab plus monalizumab) prior to Protocol Amendment 2.

Substantial changes to the protocol are summarized below:

1 Title Page, Section 1 (Introduction), Section 1.5 (Rationale for Conducting the Study), Section 1.6.1 (Potential Benefits), Section 1.7 (Research Hypotheses), Section 3.1.1 (Overview), Figure 1 (Study Flow Diagram), and Section 3.2.2 (Rationale for Study Population): Removed 'N0-1' as the patient population was revised to include subjects with N2 disease (1 single nodal station ≤ 3 cm only), as these subjects may receive clinical benefit from the study treatment.

2 Section 4.1.2 (Inclusion Criteria):
   (a) Added that subjects with N2 disease, specifically only those with 1 single nodal station ≤ 3 cm are eligible, as these subjects may receive clinical benefit from the study treatment.
   (b) Revised FEV1 and D_{LCO} requirements from ≥ 60% to ≥ 50%, as these subjects have adequate lung function and may receive clinical benefit from the study treatment.

3 Section 4.1.3 (Exclusion Criteria): Revised so that subjects who have a curative-treated malignancy with no known active disease for > 2 years (previously ≥ 5 years) before enrollment on the study are eligible to enroll into this study to align with common practice; additionally, these subjects may receive clinical benefit from the study treatment.

4 Section 4.5.1 (Identity of Investigational Product[s]) and Table 6 (Identification of Investigational Product): Updated with new monalizumab manufacturing process information.

5 Section 4.5.1.5 (Monalizumab Dose Preparation and Administration): Updated with new monalizumab manufacturing process information.

Changes to the protocol considered to be non-substantial are summarized below:

1 The synopsis was updated to align with changes in the body of protocol.

2 Section 1.1 (Disease Background): Added rationale for including subjects with Stage IIIA-N2 disease (single nodal station ≤ 3 cm only) in this study.

3 Section 1.4.2 (Clinical Experience – Oleclumab Alone and in Combination with Durvalumab) and Section 1.6.2.2 (Oleclumab Plus Durvalumab): Updated the clinical data as of the DCO date of 05Oct2018.

4 [redacted]

[redacted]

5 Section 3.2.3 (Rationale for Endpoints): [redacted]

6 Table 5 (Schedule of Screening, Treatment, and Follow-up Period Procedures):

(a) Added PET scan to the screening assessments because this is recommended for patients with resectable NSCLC.

(b) [redacted]

(c) Added plasma (previously only serum was stated) for ADA evaluation for clarification.

7 Section 4.3.1.2 (Baseline Disease Assessment by PET): Added a description of PET methodology to align with the addition of a baseline PET scan in the schedule of procedures.

8 Section 4.3.2 (Lung Cancer Surgery): Added general guidelines for the surgical therapy of subjects with resectable NSCLC to provide guidance to the investigators.

9 Section 4.5.1 (Identity of Investigational Product[s]): Added study drug storage information and density of durvalumab for clarity.

10 Section 4.5.1.3 (Durvalumab Dose Preparation and Administration): Revised to align with updated preferred durvalumab language, including removal of requirement that IV administration filter be in-line.

11 Section 4.5.1.4 (Oleclumab Dose Preparation and Administration): Revised to align with updated preferred oleclumab language, including removal of requirement that IV administration filter be in-line.

12 Section 4.5.1.5 (Monalizumab Dose Preparation and Administration): Added that a new dose must be prepared from new vials if preparation time or infusion time exceeds the time limits to align with the guidance provided for the other study drugs.

13 Section 4.5.1.7 (Treatment Administration): Moved the IV flushing instructions to this section (previously, this was stated repetitively in each study drug dose preparation and administration section expect oleclumab [instructions were omitted in error]) to simplify instructions for all treatment arms.

14 Section 4.8.7 (Interim Analysis): Added probability calculations for evaluation of ΔMPR for the purpose of providing clarification on the No-Go criteria.

15 Section 5.4.6 (Potential Hy's Law and Hy's Law): Revised section heading to include potential Hy's Law and added requirement to report these cases as SAEs.

16 Section 7.1 (Subject Data Protection): Revised to align with preferred MedImmune standard language.

17 Appendix D (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law): Updated to align with revised MedImmune requirements.

9.2 Protocol Amendment 1

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. The principal reason for this amendment is to address feedback provided by the US Food and Drug Administration (FDA) after the Investigational New Drug filing.

Substantial changes to the protocol are summarized below.

1 Section 3.1.3 (Management of Study Medication Related Toxicities): Specified that for subjects who develop ≥ Grade 2 pulmonary edema or ≥ Grade 3 peripheral edema after treatment with durvalumab plus oleclumab, doses should be omitted, and therapy may be discontinued at the discretion of the investigator per FDA request.
2 Table 5 (Schedule of Screening, Treatment, and Follow-up Period Procedures):
   (a) Added ECG assessments predose and immediately after the end of danvatirsen infusion on Week 0, Day 1 and Week 3, Day 1, respectively, and as clinically indicated per FDA request.
   (b) Added PK assessments on Week 3, Day 1 to align with the ECG assessments on Week 3, Day 1 to address an FDA request.
3 Section 4.8.4 (Safety): Clarified that the SRC will assess feasibility to surgery for all treatment arms during every meeting and added safety measures in the event that more than 1 subject per treatment arm experiences a delay in receiving the planned surgery (outside of the prespecified exclusionary reasons) to address an FDA request.
4 Section 5.3.2 (Adverse Events of Special Interest Associated with Oleclumab): Revised to state that for subjects who develop ≥ Grade 2 pulmonary edema or ≥ Grade 3 peripheral edema (previously ≥ Grade 3 edema) after treatment with durvalumab and oleclumab, doses should be omitted, and therapy may be discontinued at the discretion of the investigator per FDA request.

Changes to the protocol considered to be non-substantial are summarized below:

1 Figure 1 (Study Flow Diagram): Removed Arm E and Arm F from the study design figure per FDA request.
2 Table 5 (Schedule of Screening, Treatment, and Follow-up Period Procedures):
   (a) Footnote a: Added a dosing window of ± 3 days on Week 2, Day 1 and Week 4, Day 1 of danvatirsen administration to provide greater scheduling flexibility for the subjects.
   (b) Footnote n: Removed text on the timing of performing a brain MRI or CT scan, "This must be performed only after study eligibility is confirmed, to detect intracranial metastasis" to correct an error, as subjects with brain metastasis have late-stage NSCLC and would not be eligible to participate in this study.
   (c) Footnote q: Revised to "treatment" arms (previously "combination" arms) to clarify that ADA samples from all treatment arms (including durvalumab monotherapy) will be collected within 60 minutes prior to administration of the first study drug only.

3 Section 4.3.2 (Medical History, Physical Examination, Electrocardiogram, and Vital Signs): Added assessment of temperature to vital signs for clarification.

4 Section 4.3.5 (Immunogenicity Evaluation and Methods):

(a) Clarified that durvalumab, oleclumab, monalizumab, and danvatirsen are considered biological agents and ADA will be assessed against all study treatments, to address an FDA request.

(b) Revised to "treatment" arms (previously "combination" arms) to clarify that ADA samples from all treatment arms (including durvalumab monotherapy) will be collected within 60 minutes prior to administration of the first study drug only.

5 [redacted]

6 Section 4.8.2 (Sample Size): Added justification for the assumed 30% MPR rate and chosen sample size (40 subjects per treatment arm) per FDA request.

Appendix A Contraception Guidance

Females of Childbearing Potential:

Females of childbearing potential must use at least one of the highly effective methods of contraception described in Table A1 from screening to 180 days after the final dose of investigational product. It is strongly recommended for the male partner of a female subject to also use male condom plus spermicide throughout this period. In addition, female subjects must refrain from egg cell donation and breastfeeding while on study and for 180 days after the final dose of investigational product.

Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or postmenopausal. The definition of postmenopausal status in this study include:

- Women < 50 years of age if they have been amenorrhoeic for ≥ 12 months in the absence of any exogenous hormonal treatment, **and** their levels of luteinizing hormone and follicle-stimulating hormone are in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≥ 50 years are considered post-menopausal if they have been amenorrhoeic for ≥ 12 months in the absence of any exogenous hormonal treatment, **or** underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Non-sterilized Male Subjects

Non-sterilized male subjects must use a male condom with spermicide from screening to 180 days after the final dose of study treatment as an effective method of contraception. It is strongly recommended for the female partner of a male subject to also use a highly effective method of contraception throughout this period, as described in Table A1. In addition, male subjects must refrain from sperm donation while on study and for 180 days after the final dose of investigational product.

Table A1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Intrauterine device • Intrauterine hormone-releasing system (UIS) [a] • Bilateral tubal occlusion • Vasectomized partner [b] • Sexual abstinence [c]	• Combined estrogen and progestogen containing hormonal contraception: oral (combined pill), injectable or transdermal (patch) • Progestogen-only hormonal contraception associated with inhibition of ovulation [d]: injectable, implantable or intravaginal

[a] This is also considered a hormonal method.

[b] With appropriate post-vasectomy documentation of surgical success (absence of sperm in ejaculate).

[c] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of the study and if it is the preferred and usual lifestyle of the subject.

[d] Progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action (eg, minipill), is not accepted as a highly effective method).

Appendix B Additional Safety Guidance

Further Guidance on the Definition of a Serious Adverse Event

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Examples of such events are:

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

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 as provided in below. The determination of severity for all other events not listed in the NCI CTCAE v5.0

should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1	An event of mild intensity 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	An event of moderate intensity that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3	A severe event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4	An event, and/or its immediate sequelae, that is associated with an imminent risk of death.
Grade 5	Death 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 5.2. 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 nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

A guide to Interpreting the Causality Question

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the investigational product.

- Time Course. Exposure to suspect investigational product. Has the subject actually received the suspect investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the suspect investigational product?
- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (pharmacology and toxicology) or products of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect investigational product?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected investigational product was reintroduced after having been stopped? MedImmune would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the investigational product?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). 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/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.
Not protocol related:	The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

Appendix C National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

NIAID and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   (b) Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   (a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   (b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   (c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   (d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3 Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   (a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   (b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

For additional information, please refer to the following reference:

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law cases and Hy's Law cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in the Toxicity Management Guidelines (see Section 3.1.3).

During the course of the study, the investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a subject meets potential Hy's Law criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law events; this includes samples taken at scheduled study visits and other visits including all local laboratory evaluations even if collected outside of the study visits.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

The investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury (DILI) caused by the investigational product.

The investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

D 2.1 Potential Hy's Law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of investigational product irrespective of an increase in ALP.

D 2.2 Hy's Law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the investigational product, can be found to explain the combination of increases; eg, elevated ALP indicating cholestasis, viral hepatitis, or another drug.

For potential Hy's Law and Hy's Law, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

D 3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law, it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The investigator will, without delay, review each new laboratory report and if the identification criteria are met will:

- Notify the sponsor study representative
- Determine whether the subject meets potential Hy's Law criteria (see Section D 2) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria Not Met

If the subject does not meet potential Hy's Law criteria the investigator will:

- Inform the study representative that the subject has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the study protocol.

D 4.2 Potential Hy's Law Criteria Met

If the subject does meet potential Hy's Law criteria the investigator will:

- Notify the sponsor study representative who will then inform the study team
- Within 1 day of potential Hy's Law criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to clinical study protocol process for SAE reporting

The medical monitor contacts the investigator, to provide guidance, discuss and agree on an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data. Subsequent to this contact the investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete the follow-up SAE Form as required.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the medical monitor.
- Complete the relevant CRF Modules as information becomes available

D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this section should be followed for all cases where potential Hy's Law criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the medical monitor will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than DILI caused by the investigational product, to ensure timely analysis and reporting to health authorities per local requirements from the date potential Hy's Law criteria were met. The medical monitor and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE, update the previously submitted potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the sponsor's standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the investigational product:

- Send the updated SAE (report term 'Hy's Law') according to the sponsor's standard processes.

  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned

If, there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of Potential Hy's Law (report term now 'Hy's Law case'), ensuring causality assessment is related to the investigational product and seriousness criteria are medically important, according to the clinical study protocol process for SAE reporting
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following clinical study protocol process for SAE reporting, according to the outcome of the review and amend the reported term if an alternative explanation for the liver biochemistry elevations is determined

D 6 Laboratory Tests

To evaluate the underlying etiology of potential Hy's Law cases, relevant laboratory tests will be performed as outlined in Section 4.3.4. Additional laboratory assessments may be performed as clinically indicated.

Appendix E [redacted]

[redacted]

[redacted]

[redacted]

Appendix F RECIST v1.1 Response Criteria

Evaluation of Target Lesions

- **CR** - Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be "0" if there are target nodes).
- **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 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 PD.)
- **Stable Disease (SD)** - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **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).
- **Non-CR/Non-PD** - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **PD** - Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see Section 4.1.6). In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v1.1. Considering the unique response kinetics that have been observed with immunotherapy, new lesions can nonetheless derive clinical benefit (Borghaei et al, 2015).

Evaluation of Overall Response

Table F1 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table F1 Evaluation of Overall Response Using RECIST v1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response (or no non-target lesion)	No	Complete response
No target lesion [a]	Complete response	No	Complete response
Complete response	Not evaluable [b]	No	Partial response
Complete response	Non-complete response / non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable (or no non-target lesion) [b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable (or no non-target lesion) [b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion [a]	Not all evaluated	No	Not evaluable
No target lesion [a]	Non-complete response / non-progressive disease	No	Non-complete response / non-progressive disease
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion [a]	Unequivocal progressive disease	Yes/No	Progressive disease
No target lesion [a]	Any	Yes	Progressive disease

RECIST v1.1 = Response Evaluated Criteria in Solid Tumors version 1.1.

[a] Defined as no target lesion at baseline.

[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

Reference: (Eisenhauer et al, 2009)

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