A Phase 2, Open-label, Multicenter, Randomized, Multidrug Platform Study of Durvalumab Alone or in Combination with Novel Agents in Subjects with Locally Advanced, Unresectable, Stage III Non-small Cell Lung Cancer (COAST)

Sponsor Protocol Number:	D9108C00001
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Sponsor:	MedImmune, LLC, a wholly owned subsidiary of AstraZeneca PLC One MedImmune Way Gaithersburg, Maryland, 20878, USA
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PROTOCOL SYNOPSIS

TITLE

A Phase 2, Open-label, Multicenter, Randomized, Multidrug Platform Study of Durvalumab Alone or in Combination with Novel Agents in Subjects with Locally Advanced, Unresectable, Stage III Non-small Cell Lung Cancer (COAST)

HYPOTHESES

Durvalumab in combination with novel agents will demonstrate superior antitumor activity than durvalumab alone with an acceptable safety profile in subjects with Stage III non-small cell lung cancer (NSCLC) who have not progressed following definitive concurrent chemoradiotherapy (cCRT).

OBJECTIVES and ENDPOINTS

Type	Objective	Endpoint
Primary		
Clinical activity	To compare the antitumor activity of durvalumab alone vs durvalumab in combination with novel agents	Objective response (OR) per Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST v1.1)
Secondary		
Safety	To evaluate the safety and tolerability of durvalumab alone and durvalumab in combination with novel agents	Presence of adverse events (AEs), serious adverse events (SAEs), and abnormal laboratory parameters and vital signs
Clinical activity	To further compare the efficacy of durvalumab alone vs durvalumab in combination with novel agents	Duration of response (DoR), disease control (DC), progression-free survival (PFS) at 12 months, and PFS per RECIST v1.1 and overall survival (OS)
Pharmacokinetics	(a) To describe the pharmacokinetics (PK) of durvalumab alone and durvalumab in combination with novel agents	Concentration of durvalumab or novel agents in serum
	(b) To describe the PK of novel agents in combination with durvalumab	
Immunogenicity	(a) To assess the immunogenicity of durvalumab alone or in combination with novel agents	Antidrug antibody (ADA) incidence of durvalumab or novel biologic agents
	(b) To assess the immunogenicity of novel biologic agents in combination with durvalumab	

Type	Objective	Endpoint
Exploratory		
CCI	CCI	CCI
	CCI	CCI
CCI	CCI	CCI
	CCI	CCI
	CCI	CCI
	CCI	CCI

STUDY DESIGN

Study D9108C00001 (COAST) is a Phase 2, open-label, multicenter, randomized, multidrug platform study of durvalumab alone or in combination with novel agents. Subjects with unresectable, Stage III NSCLC who have not progressed following definitive cCRT are eligible. Subjects will be randomized into the study and initiate study treatment within 42 days from the last session of cCRT. Subjects may be treated for up to 12 months. Study treatment will be discontinued upon disease progression, unacceptable toxicity, or other reason, eg, subject decision or noncompliance with study procedures. Experimental arms may be closed based on results of planned interim analyses. New durvalumab combination experimental arms may be added based on emerging nonclinical and clinical data via protocol amendment. Initially, the study will examine the experimental arms comprising durvalumab plus oleclumab (experimental Arm A) and durvalumab plus monalizumab (experimental Arm B). Treatment arms may be opened sequentially or in parallel at the discretion of the sponsor.

TARGET SUBJECT POPULATION

Unresectable, Stage III NSCLC without progression following definitive cCRT

TREATMENT GROUPS AND REGIMENS

Control arm (durvalumab monotherapy): durvalumab 1500 mg IV every 4 weeks (Q4W) × 12 months

Experimental Arm A (durvalumab + oleclumab): durvalumab IV 1500 mg Q4W × 12 months plus oleclumab 3000 mg IV every 2 weeks (Q2W) for 2 months then Q4W starting on Cycle 3, Day 1 × 10 months

Experimental Arm B (durvalumab + monalizumab): durvalumab 1500 mg IV Q4W × 12 months plus monalizumab 750 mg IV Q2W × 12 months

STATISTICAL METHODS

Sample size: Up to approximately 60 subjects per experimental treatment arm will be randomized with equal ratios to durvalumab control and each of the open experimental arms. New durvalumab combination experimental arms may be added over time and therefore the total number of subjects randomized to the durvalumab control arm might be higher than 60 subjects.

Statistical analyses:

Efficacy

The final efficacy analyses of antitumor activity will be based on the Intent-to-treat (ITT) Population (defined as all subjects are randomized). The rates of OR based on RECIST v1.1 will be summarized with 95% confidence interval based on the exact binomial distribution. Time-to-event endpoints (DoR, PFS, and OS) will be analyzed using the Kaplan-Meier method.

Safety

Safety data, including AEs, SAEs, laboratory evaluations, vital signs, and electrocardiogram results will be summarized based on the As-treated Population (defined as all subjects who receive any investigational product analyzed according to treatment received). Descriptive statistics will be provided for AEs, SAEs, AE grade (severity), and relationship to study drug(s). AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Descriptive statistics will be provided for the clinical laboratory results and toxicities.

Pharmacokinetics and 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, individual durvalumab concentrations will be tabulated with descriptive statistics. Additionally, for each experimental arm, individual novel agent concentrations will be tabulated with descriptive statistics.

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 experimental arms that include a biologic agent, the immunogenic potential of the combination study drug will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs to the combination study drug.

Interim analyses: Interim analyses will be done for early evaluation of the safety and clinical activity of the experimental arms compared to the control arm. The first interim analysis will be performed once the control arm has 30 ITT subjects who have reached the data cutoff criteria (defined as the opportunity to be followed for at least 16 weeks at the time of data cutoff). Bayesian predictive probabilities will be used to evaluate clinical activity. The disease control rate and objective response rate at Week 16 will be used for decision-making. Enrollment will not be paused for interim analyses.

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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
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BOR	best overall response
CD	cluster of differentiation
CI	confidence interval
COAST	Study D9108C00001
CR	complete response
cCRT	concurrent chemoradiotherapy
CSR	clinical study report
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DC	disease control
DCO	data cutoff
DCR	disease control rate
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOI	end of infusion
GCP	Good Clinical Practice
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus

Abbreviation or Specialized Term	Definition
HIV	human immunodeficiency virus
HLA-E	major histocompatibility complex E
HR	hazard ratio
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
imAE	immune-mediated adverse event
IRB	Institutional Review Board
CCI	CCI
IRR	infusion-related reaction
ITT	Intent-to-treat
IV	intravenous
IXRS	interactive voice/web response system
mAb	monoclonal antibody
MRI	magnetic resonance imaging
NCI CTCAE v5.0	National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
NK	natural killer
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PACIFIC	Study D4191C00001 (NCT02125461)
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PD-L2	programmed cell death ligand-2
PET	positron emission tomography
PFS	progression-free survival
PFS-12	progression-free survival 12-month landmark rate
PI	Package Insert
PK	pharmacokinetic(s)
PP	predictive probability(ies)

Abbreviation or Specialized Term	Definition
PR	partial response
Q2W	every 2 weeks
Q4W	every 4 weeks
RECIST v1.1	Response Evaluation Criteria for Solid Tumors version 1.1
SAE	serious adverse event
SD	stable disease
SID	subject identification
SRC	Safety Review Committee
SUV	standardized uptake value(s)
T3	triiodothyronine
T4	thyroxine
TBL	total bilirubin
TSH	thyroid stimulating hormone
TV	target value
ULN	upper limit of normal
US	United States
w/v	weight per volume

1 INTRODUCTION

Study D9108C00001 (COAST) is a platform study dynamically assessing the efficacy and safety of durvalumab alone vs durvalumab in combination with novel agents in subjects with locally advanced, unresectable, Stage III non-small cell lung cancer (NSCLC). Combination treatment arms will be added via protocol amendment during the course of the study as novel agents of interest become available.

1.1 Disease Background

Lung cancer is the most common and lethal cancer worldwide with an estimated 1.8 million new cases annually resulting in approximately 1.6 million deaths (Torre et al, 2015). NSCLC represents approximately 85% of all lung cancers and 30% of patients present with Stage III disease at diagnosis (American Cancer Society, 2018). For patients with Stage III NSCLC not amenable for surgical resection, the standard treatment is platinum-based doublet chemotherapy given concomitantly with radiotherapy followed by durvalumab consolidation. When administered after completion of concurrent chemoradiotherapy (cCRT) in patients with unresectable NSCLC, durvalumab demonstrated a better clinical response than placebo, with prolonged progression-free survival (PFS; hazard ratio [HR]: 0.51; 95% confidence interval [CI]: 0.41, 0.63) and overall survival (OS; HR: 0.68; 99.73% CI: 0.47, 0.997, p = 0.0025; PACIFIC [Study D4191C00001]; Antonia et al, 2018; Antonia et al, 2017). Durvalumab showed a median PFS of 17.2 months compared to 5.6 months in the placebo group. However, despite chemoradiotherapy and durvalumab consolidation most patients will relapse and eventually die from lung cancer.

1.1.1 Immunotherapy

1.1.1.1 Programmed Cell Death Ligand-1 (PD-L1)

Programmed cell death-1 (PD-1), programmed cell death ligand-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 (Juneja et al, 2017; Keir et al, 2008; Chen and Mellman, 2013; 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 (Zou and Chen, 2008; Zou et al, 2016; Pardoll, 2012). Monoclonal antibodies (mAbs) targeting PD-1 (nivolumab, pembrolizumab) and PD-L1 (durvalumab, atezolizumab) have shown evidence of antitumor activity and a manageable safety profile in patients with NSCLC and have been granted approvals by the United States (US) Food and Drug Administration and/or the European Medicines Agency for the treatment of NSCLC (Opdivo® US PI, 2018; Keytruda® US PI, 2018; Imfinzi® 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 over activation, 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 overall survival 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 a diminished cytotoxic potential (Sheu et al, 2005; Mamessier et al, 2011; Platonova et al, 2011) and has been documented in a variety of solid tumors including NSCLC, colorectal, ovarian, endometrial, pancreatic, and prostate cancers (Aparicio-Pagés et al, 1991; Gooden et al, 2011; Iannone et al, 2015; Pardoll, 2012; 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 (Guo et al, 2015; Emens et al, 2017; Gooden et al, 2011; Versluis et al, 2017).

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 inhibits adenosine production as well as leads to a reduction in CD73 expression through internalization (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.

1.3 Summary of Nonclinical Experience

1.3.1 Nonclinical Experience - Durvalumab

Refer to the current durvalumab IB for a complete summary of nonclinical experience.

1.3.2 Nonclinical Experience - Oleclumab

No oleclumab-related adverse effects were noted in CD-1 mice (5-week, repeat intravenous [IV] bolus dose, once every 4 days, total 9 doses) at doses up to 200 mg/kg or in cynomolgus

monkeys (5-week, repeat IV 30-minute infusion dose, once weekly, total 5 doses) at doses up to 300.7 mg/kg in Good Laboratory Practice toxicity studies. Additionally, no oleclumab-related effects on electrocardiogram (ECG), blood pressure, or behavioral examinations were observed in the 5-week cynomolgus monkey study. The no-observed-adverse-effect-level was 200 mg/kg/dose in CD-1 mice and 300.7 mg/kg/dose in cynomolgus monkeys. Refer to the current oleclumab IB for a complete summary of nonclinical experience.

1.3.3 Nonclinical Experience - Monalizumab

The nonclinical safety profiling of monalizumab has not identified any safety issues. Various human in vitro biological assays testing acute pharmacological effects identified no non-target-related or potentially target-related safety issues. No toxicities were observed in cynomolgus monkeys after 13 weeks of dosing of up to 150 mg/kg weekly. The highest dose (150 mg/kg) resulted in approximately 18 weeks of full CD94/NKG2a receptor saturation. In humans, monalizumab binds selectively to CD94/NKG2aA receptors. In monkeys, monalizumab binds with equal affinity to the activating CD94/NKG2c receptor in addition to the inhibitory CD94/NKG2a receptor. This is most likely the reason why it has been impossible to observe effects comparable to those seen in humans in functional in vitro assays with cynomolgus vs human cells. Further risk assessment of long-term blocking of the CD94/NKG2a receptor was therefore performed with a surrogate anti-mouse NKG2a antibody that has been used to demonstrate in vitro antitumor efficacy with mouse cells. In toxicology studies, mice were dosed subcutaneously every second day for up to 26 weeks at doses up to 50 mg/kg. As with the cynomolgus monkey studies, the toxicity studies in mice did not identify any safety issues. Refer to the current monalizumab IB for a complete summary of nonclinical experience.

1.4 Summary of Clinical Experience

A complete summary of clinical experience, including safety, efficacy, and pharmacokinetics (PK), for durvalumab, oleclumab, and monalizumab can be found in the current IB of each respective agent.

1.4.1 Clinical Experience - Durvalumab

To date, durvalumab has been given to more than 6,000 subjects as part of ongoing studies either as monotherapy or in combination with other anticancer agents. In monotherapy clinical studies, the most common adverse events (AEs; ≥ 20%) included fatigue (32%), cough (23%), decreased appetite, dyspnea (21% each), and nausea (20%). Approximately 9% of subjects discontinued durvalumab due to an AE. The majority of treatment-related AEs were manageable, with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 3.1.3).

In the PACIFIC study, 68% (322/475) of subjects with unresectable, Stage III NSCLC without progression after cCRT treated with durvalumab reported a treatment-related AE, with fatigue (13%), hypothyroidism (11%), diarrhea (10%), pneumonitis (9%), rash (8%), pruritus (7%), hyperthyroidism, asthenia, dyspnea, decreased appetite, nausea (6% each), and cough (5%) being the most common. Grade 3 or 4 AEs were reported in 30% (142/475) of subjects, with pneumonia (4%), pneumonitis or radiation pneumonitis, anemia (3% each), and dyspnea (2%) reported in > 1% of subjects (Antonia et al, 2017).

In PACIFIC, durvalumab treatment for 12 months demonstrated superior PFS and OS in comparison to placebo (Section 1.1; Antonia et al, 2018; Antonia et al, 2017).

1.4.2 Clinical Experience - Oleclumab Alone and in Combination with Durvalumab

As of the data cutoff (DCO) date of 09Jan2018, 116 adult subjects with advanced solid tumors have received oleclumab either as monotherapy (42 subjects) or in combination with durvalumab (74 subjects) during the dose-escalation or dose-expansion phases of the first-time-in-human Phase 1 Study D6070C00001.

Following oleclumab monotherapy, 55% (23/42) of subjects reported a treatment-related AE, with fatigue (17%), nausea, and anemia (10% each) being the most common. Grade 3 or 4 AEs were reported in 45% (19/42) of subjects, with ascites (12%), acute kidney injury, hyperglycemia, hyponatremia, and hypotension (5% each) reported in more than 1 subject. Three deaths occurred in subjects treated with oleclumab monotherapy (1 due to small intestinal obstruction and 2 due to disease under treatment); none were considered related to oleclumab.

Following oleclumab plus durvalumab combination therapy, 47% (35/74) of subjects reported a treatment-related AE, with fatigue (14%), increased aspartate aminotransferase (AST), diarrhea, and pyrexia (8% each), increased blood alkaline phosphatase (ALP; 7%), increased alanine aminotransferase (ALT), decreased appetite, and vomiting (5% each) being the most common. Grade 3 or 4 AEs were reported in 53% (39/74) of subjects, with increased ALP (8%), anemia, increased ALT, increased AST, and increased gamma glutamyl transferase (5% each) reported in at least 5% of subjects. Six deaths occurred in subjects treated with oleclumab plus durvalumab (1 each due to renal failure, vomiting, respiratory failure; 2 due to pneumonia; and 1 due to disease under treatment); none of the deaths were considered related to study treatment.

Efficacy data from 42 response-evaluable subjects treated with oleclumab plus durvalumab in the dose-expansion phase (including subjects with colorectal cancer [n = 21], pancreatic adenocarcinoma [n = 20], and NSCLC [n = 1]) showed an objective response rate (ORR;

confirmed and unconfirmed) of 7.1% (3/42 subjects; 95% CI: 1.5%, 19.5%) and a disease control rate (DCR; 8 weeks) of 16.7% (7/42 subjects; 95% CI: 7.0%, 31.4%).

1.4.3 Clinical Experience - Monalizumab Alone and in Combination with Durvalumab

The safety and tolerability as well as single-dose and multiple-dose PK and pharmacodynamic properties of monalizumab were initially investigated in subjects with active rheumatoid arthritis (Study NN8765-3658). In this first study (completed), 68 subjects received monalizumab monotherapy with maximum tested dose levels of 10 mg/kg during IV infusion (single dose) and 4.0 mg/kg following subcutaneous administrations (in single and multiples doses), with a favorable safety profile.

Monalizumab is now being developed for the treatment of various hematologic and solid malignancies as monotherapy or in combination with other drugs. As of 30Apr2018, a total of 315 subjects have been treated with monalizumab in 7 hematology/oncology studies with multiple doses up to 10 mg/kg or 750 mg IV. Most of the reported AEs were Grade 1 or 2, with no obvious dose relationship. The most common (≥ 10%) AEs considered related to monalizumab monotherapy were headache (23%), nausea (18%), fatigue (16%), vomiting (15%), anorexia (11%), diarrhea, abdominal pain, and sore throat (10% each). There was no death related to study treatment.

In Study D419NC00001, as of 30Apr2018, 154 subjects were exposed to monalizumab and durvalumab combination therapy in a dose-escalation (12 subjects) or dose-expansion (139 subjects) phase. Overall, 62% (95/154) of subjects reported a treatment-related AE, with diarrhea, fatigue (10% each), asthenia, pyrexia (8% each), hypothyroidism, nausea (7% each), decreased appetite (6%), and pruritus (5%) being the most common. Grade 3 or 4 AEs were reported in 43% (66/154) of subjects, with anemia (7%) reported in at least 5% of subjects. Three deaths occurred (2 due to intestinal obstructions and 1 due to bipolar disorder); none of the deaths were considered related to study treatment.

Of 39 evaluable subjects with microsatellite-stable colorectal cancer in the dose-expansion phase of Study D419NC00001, 3 (8%) subjects had a partial response (PR) and 11 (28%) subjects had stable disease (SD; Segal et al, 2018).

1.5 Rationale for Conducting the Study

Current standard of care for patients with unresectable, Stage III NSCLC includes cCRT followed by durvalumab maintenance for 12 months. When administered after completion of cCRT in patients with unresectable NSCLC, durvalumab demonstrated improved PFS (HR: 0.51; 95% CI: 0.41, 0.63) and OS (HR: 0.68; 99.73% CI: 0.47, 0.997, p = 0.0025) vs

placebo (PACIFIC study; Antonia et al, 2018). Durvalumab showed a median PFS of 17.2 months compared to 5.6 months in the placebo group.

Furthermore, ORR might be an appropriate endpoint to assess antitumor activity when subjects are randomized after cCRT. In the PACIFIC study, ORR following cCRT completed prior to study drug treatment was 50.5% in the durvalumab group and 49.8% in the placebo group (Antonia et al, 2017). Following study drug treatment, ORR was higher in the durvalumab than the placebo group (28.5% vs 16.0%, respectively). Previous studies assessing the role of consolidation or maintenance strategies in subjects with NSCLC treated with CRT were consistently negative, and no differences in ORR were seen between the placebo and experimental arms (Ahn et al, 2015; Kelly et al, 2008). Together, these data suggest that ORR is an appropriate endpoint to assess the antitumor activity in a signal finding study where subjects with unresectable Stage III NSCLC are randomized after completing cCRT.

Despite these therapeutic advances, unresectable, Stage III NSCLC remains a condition with a high risk of relapse and morbidity. Further improvement in clinical outcomes in this patient population with a high unmet medical need may be achieved through combination therapy of durvalumab with other immune modulators or anticancer therapies. Several ongoing studies are exploring durvalumab and/or other immunotherapies for the treatment of Stage III NSCLC (CT03519971, NCT02904954, NCT03217071, and NCT03379441).

The platform study design permits a dynamic assessment of durvalumab combination experimental arms. Experimental arms may be closed based on results of planned interim analyses. New experimental arms may be added via protocol amendment (see Section 1.6.3). Potential new candidate study drugs 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 and monalizumab meet these criteria (see Section 1.5.1 and Section 1.5.2, respectively), and will be used in combination with durvalumab in the initial experimental arms of this platform study. Thus, at the outset, the study will examine the clinical activity and safety of durvalumab plus oleclumab, durvalumab plus monalizumab, and durvalumab alone in subjects with unresectable, Stage III NSCLC who have not progressed after cCRT.

Given this platform study uses randomization and a perpetual control arm, it may require adaptions over time as the standard of care in patients with unresectable, Stage III NSCLC evolves in order to safeguard the best interests of the patients participating in this study. Potential protocol modifications may include changes in the definition of curative intent cCRT, inclusion of durvalumab as part of the cCRT treatment plan, or the duration/schedule

of durvalumab maintenance. Rationale and supporting evidence for any changes to the current protocol design will be addressed via protocol amendment.

1.5.1 Rationale for Inclusion of Durvalumab in Combination with Oleclumab Arm

CCI

[redacted]

1.5.2 Rationale for Inclusion of Durvalumab in Combination with Monalizumab Arm

CCI

[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 and 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

Most patients with unresectable, Stage III NSCLC will relapse and die from lung cancer despite aggressive cCRT, with a 5-year survival of approximately 15% (Curran et al, 2011,

Aupérin et al, 2010). Recently, results from the PACIFIC study demonstrated that durvalumab maintenance for 12 months improved PFS and OS in comparison to placebo, with a favorable safety profile (Antonia et al, 2018; Antonia et al, 2017).

This protocol will allow patients with unresectable, Stage III NSCLC without progression after cCRT to receive durvalumab and potentially achieve survival benefit as demonstrated in the PACIFIC study (Antonia et al, 2018; Antonia et al, 2017). Further improvement in clinical outcomes in this patient population with a high unmet medical need may be achieved through combining novel therapies with durvalumab. Selection of the combination novel agents will be 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.

For information on all identified and potential risks with durvalumab alone or in combination with other anticancer therapies refer to the current version of the durvalumab IB.

1.6.2.2 Oleclumab

As of 09Jan2018, a total of 42 subjects with advanced solid tumors have received oleclumab monotherapy during the dose-escalation phase of the first time-in-human Phase 1 Study D6070C00001. No dose-limiting toxicities (DLTs), treatment-related SAEs, or treatment-related deaths were identified. Following oleclumab monotherapy, 55% (23/42) of subjects reported a treatment-related AE, with fatigue, nausea, and anemia being the most common (≥ 10%). Additionally, some potential risks for the abrogation of CD73 activity caused by oleclumab treatment have been suggested from clinical findings in individuals with CD73 deficiency and findings in CD73-deficient mice. Those potential risks include arterial calcifications, arterial ischemic disorder, thrombosis, and increased microvascular permeability, and potential risks include joint calcifications. Other important potential risks associated with the administration of mAbs include IRRs, anaphylaxis, hypersensitivity or 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, and the potential risks for durvalumab, 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. As of 09Jan2018, a total of 74 subjects with advanced solid tumors have received oleclumab in combination with durvalumab in Study D6070C00001. No DLTs or treatment-related deaths were identified. Following oleclumab plus durvalumab combination therapy, 47% (35/74) of subjects reported a treatment-related AE, with fatigue, increased AST, diarrhea, pyrexia, increased blood ALP, increased ALT, decreased appetite, and vomiting being the most common (≥ 5%). Grade 3 or 4 AEs were reported in 53% (39/74) of subjects, with increased ALP, anemia, increased ALT, increased AST, and increased gamma glutamyl transferase reported in at least 5% of subjects.

Overall, durvalumab plus oleclumab and oleclumab alone have been well tolerated to date. See Section 1.4.2 for a detailed description of AEs reported in Study D6070C00001.

For information on safety and potential risks with oleclumab, refer to the current oleclumab IB. See Section 5.3.2 for adverse events of special interest (AESIs) associated with oleclumab.

1.6.2.3 Monalizumab

As of 30Apr2018, a total of 315 subjects have been treated with monalizumab in hematology/oncology studies. Most of the reported AEs were Grade 1 or 2, with no obvious dose relationship. The most frequent (≥ 10%) AEs considered related to monalizumab monotherapy were headache, nausea, fatigue, vomiting, anorexia, diarrhea, abdominal pain, and sore throat. There were no treatment-related deaths in any of the studies.

Given the mode of action of monalizumab, and the potential risks for durvalumab, the theoretical risk associated when monalizumab is combined with durvalumab may be an increased risk of emergence of autoimmune phenomena. However, no such potential risks have been identified during the conduct of the development program. As of 30Apr2018, 154 subjects were exposed to monalizumab and durvalumab combination therapy. Overall, 62% (95/154) of subjects reported a treatment-related AE, with diarrhea, fatigue, asthenia, pyrexia, hypothyroidism, nausea, decreased appetite, and pruritus being the most common (≥ 5%). Grade 3 or 4 AEs were reported in 43% (66/154) of subjects, with anemia reported in at least 5% of subjects. No deaths were considered related to study treatment.

Given the mode of action of monalizumab, however, there are theoretical risks that may arise when monalizumab is used in combination with durvalumab. The theoretical risk associated with inhibiting NKG2a favors increased antitumor immunity when combined with durvalumab as well as the risk of emergence of autoimmune phenomena. These risks include adverse effects on the immune system, 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.

Overall, durvalumab plus monalizumab and monalizumab alone have been well tolerated to date. See Section 1.4.3 for a description of AEs reported in monalizumab monotherapy and durvalumab combination therapy studies.

For information on safety and potential risks with monalizumab, refer to the current monalizumab IB.

1.6.3 Overall Benefit-Risk

While durvalumab administered after completion of cCRT in patients with unresectable NSCLC has demonstrated improved clinical benefit over placebo, further improvement in clinical outcomes may be achieved through combination therapy of durvalumab with novel therapies such as oleclumab or monalizumab. Clinical and nonclinical data to date have shown an acceptable safety profile for oleclumab and monalizumab in combination with durvalumab.

The design of the current study aims to minimize potential risks to subjects and include the protocol inclusion and exclusion criteria, restrictions on concomitant medication during the study, safety monitoring (including review of all safety, PK, and other relevant data by the Safety Review Committee [SRC]), toxicity management guidelines, study stopping criteria, and rules and procedures to add new durvalumab combination treatment 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 for subjects allocated to a durvalumab combination experimental 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/or 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 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 experimental arm.
- Updated informed consent form with relevant information on the new durvalumab combination experimental arm.

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

1.7 Research Hypotheses

1.7.1 Primary Hypothesis

Durvalumab in combination with novel agents will demonstrate superior antitumor activity than durvalumab alone in subjects with unresectable, Stage III NSCLC who have not progressed following definitive cCRT.

1.7.2 Secondary Hypotheses

Durvalumab alone or in combination with novel agents will demonstrate an acceptable safety profile in subjects with Stage III NSCLC who have not progressed following definitive cCRT.

2 OBJECTIVES AND ENDPOINTS

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

Each combination experimental 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
Clinical activity	To compare the antitumor activity of durvalumab alone vs durvalumab in combination with novel agents	OR per RECIST v1.1

OR = objective response; RECIST v1.1 = Response Evaluation Criteria for Solid Tumors version 1.1.

2.1.1 Secondary Objectives and Associated Endpoints

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Safety	To evaluate the safety and tolerability of durvalumab alone and durvalumab in combination with novel agents	Presence of AEs, SAEs, and abnormal laboratory parameters and vital signs
Clinical activity	To further compare the efficacy of durvalumab alone vs durvalumab in combination with novel agents	DoR, DC, PFS-12, and PFS per RECIST v1.1 and OS
Pharmacokinetics	(a) To describe the PK of durvalumab alone and durvalumab in combination with novel agents	Concentration of durvalumab or novel agents in serum
	(b) To describe the PK of novel agents in combination with durvalumab	

Table 2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
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; DC = disease control; DoR = duration of response; OS = overall survival; PFS = progression-free survival; PFS-12 = progression-free survival 12-month landmark rate; PK = pharmacokinetic; RECIST v1.1 = Response Evaluation Criteria for Solid Tumors version 1.1 SAE = serious adverse event.

2.1.2 Exploratory Objectives and Associated Endpoints

Table 3 Exploratory Objectives and Associated Endpoints

Type	Objective	Endpoint
CCI	CCI	CCI
	CCI	CCI
CCI	CCI	CCI
	CCI	CCI
	CCI	CCI
	CCI	CCI

CCI

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

COAST is a Phase 2, open-label, multicenter, randomized, multidrug platform study of durvalumab alone or in combination with novel agents in subjects with locally advanced, unresectable, Stage III NSCLC.

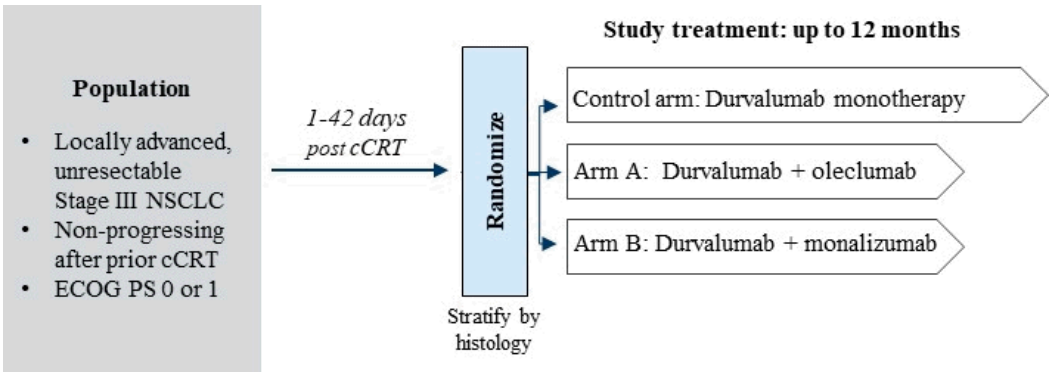
The study will evaluate the clinical activity and safety of durvalumab alone or in combination with novel agents in subjects with Stage III NSCLC who have not progressed following definitive cCRT (Figure 1). Subjects will be randomized into the study and initiate study treatment within 42 days from the last session of cCRT. Information on subject randomization and sample size is provided in Section 4.6.1 and Section 4.8.2, respectively. Up to approximately 80 sites globally will participate in this study.

Subjects may be treated for up to 12 months. Study treatment will be discontinued upon disease progression, unacceptable toxicity, or other reason, eg, subject decision or noncompliance with study procedures. Overall, all subjects continuing in the study must adhere to the study procedures for up to 5 years (from randomization) provided they achieve disease control (DC) and remain disease free. Subjects who have experienced PD will be followed for survival.

All subjects will be followed for survival until the end of the study as per the time points shown in Table 6. After completing the 5-year post-randomization study period, all subjects included into any treatment arm may be contacted annually for survival until 5 years after the final subject is randomized into the study or until the sponsor stops the study, whichever occurs first. The platform nature of the study allows an individual experimental arm to be permanently closed while the overall COAST study remains open.

New durvalumab combination experimental arms may be added based on emerging nonclinical and clinical data via protocol amendment (see Section 1.6.3). Interim futility analyses will be performed using Bayesian predictive probability (PP; see Section 4.8.7).

Figure 1 Study Flow Diagram



cCRT = concurrent chemoradiotherapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; NSCLC = non-small cell lung cancer.

Treatment arms may be opened sequentially or in parallel. Randomization will be stratified by histology (adenocarcinoma vs non-adenocarcinoma).

Enrollment to combination experimental arms may be stopped if planned interim analysis shows safety concerns or lack of efficacy. New combination experimental arms may be added based on emerging nonclinical and clinical data via a protocol amendment.

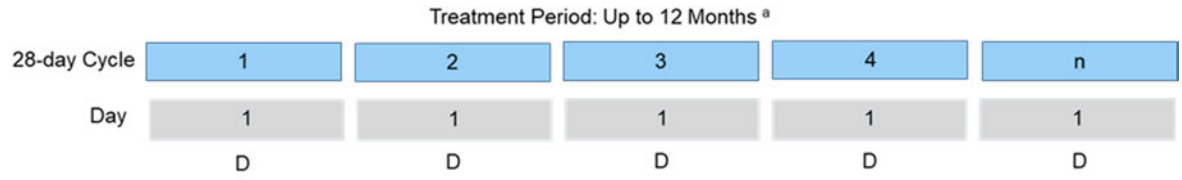
3.1.2 Treatment Regimen

Subjects will be randomized to a treatment arm and may remain on study treatment for up to 12 months. Study treatment will be discontinued upon disease progression, unacceptable toxicity, or other reason. See Section 4.1.6 for information on discontinuation of study drug for individual subjects.

3.1.2.1 Durvalumab Control Arm

Figure 2 presents the treatment regimen for the durvalumab monotherapy control arm.

Figure 2 Treatment Regimen for Control Arm - Durvalumab Monotherapy



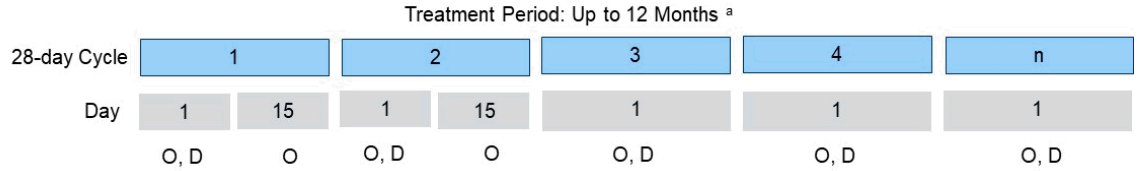
D = durvalumab; IV = intravenous; Q4W = every 4 weeks.

[a] Subjects in the control arm will receive durvalumab 1500 mg IV Q4W on Day 1 of each cycle.

3.1.2.2 Experimental Arm A – Durvalumab Plus Oleclumab

Subjects randomized to Arm A will receive durvalumab in combination with oleclumab as presented in Figure 3.

Figure 3 Treatment Regimen for Arm A - Durvalumab Plus Oleclumab



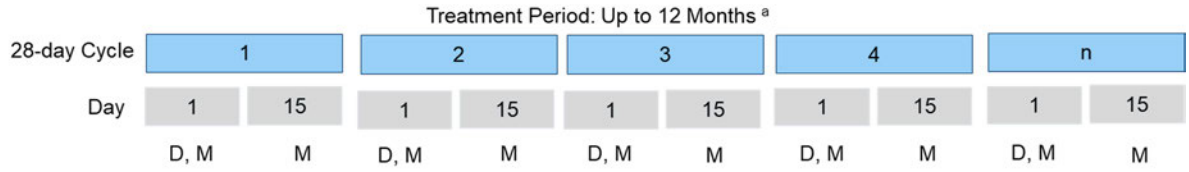
D = durvalumab; IV = intravenous; O = oleclumab; Q2W = every 2 weeks; Q4W = every 4 weeks.

[a] Subjects in Arm A will receive durvalumab 1500 mg IV Q4W on Day 1 of each cycle, and oleclumab 3000 mg IV Q2W (Day 1 and Day 15) for Cycle 1 and Cycle 2 then Q4W starting on Cycle 3, Day 1. On days when both durvalumab and oleclumab are administered, oleclumab will be administered first.

3.1.2.3 Experimental Arm B – Durvalumab Plus Monalizumab

Subjects randomized to Arm B will receive durvalumab in combination with monalizumab as presented in Figure 4.

Figure 4 Treatment Regimen for Arm B – Durvalumab Plus Monalizumab



D = durvalumab; IV = intravenous; M = monalizumab; Q2W = every 2 weeks; Q4W = every 4 weeks.

[a] Subjects in Arm B will receive durvalumab 1500 mg IV Q4W on Day 1 of each cycle, and monalizumab 750 mg IV Q2W on Days 1 and 15 of each cycle.
On days when both durvalumab and monalizumab are administered, durvalumab will be administered first.

3.1.3 Management of Study Medication Related Toxicities

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

1 Next cycle administration can be delayed or discontinued
2 In the absence of clear alternative etiology, all events should be considered potentially immune mediated
3 In the event that an AE is considered related only to durvalumab or the combination novel therapy, both agents must be delayed

If unsure how to manage a subject, please 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, infusion-related reactions, 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 is 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.

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 study 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

Based on available PK and safety data for weight-based doses of durvalumab 10 mg/kg Q2W and 20 mg/kg Q4W and simulated PK data for a fixed dose of durvalumab 1500 mg Q4W, the fixed-dose regimen was predicted to provide comparable exposure to the body weight-based dosing regimens. Durvalumab has a flat exposure-response (efficacy and safety) relationship. Based on all the observed and simulated data, a fixed dosing regimen of 1500 mg Q4W was predicted to provide similar efficacy and safety profiles as the body weight-based dosing regimens. As detailed in the durvalumab IB, a fixed dose of 1500 mg Q4W is being used in

numerous ongoing studies. Therefore, a fixed dosing regimen of 1500 mg Q4W was selected in this study.

For additional details on the nonclinical and clinical data that informed durvalumab dose selection, see the durvalumab IB.

3.2.1.2 Oleclumab

The oleclumab regimen of 3000 mg Q2W × 4 doses and then Q4W was selected based on data from the Phase 1 Study D6070C00001. In that study, oleclumab doses of 5, 10, 20, and 40 mg/kg Q2W were examined both as a monotherapy and in combination with durvalumab 10 mg/kg Q2W. Oleclumab was well tolerated and there were no observed DLTs either as monotherapy or in combination with durvalumab. Additionally, both oleclumab and durvalumab exposures in combination were comparable to monotherapy exposures. The oleclumab 40 mg/kg Q2W dose was selected for evaluation with durvalumab 10 mg/kg Q2W in the dose-expansion phase of that study.

A fixed dose of oleclumab 3000 mg Q2W × 4 doses is currently being explored based on simulations that oleclumab might achieve similar exposures to those observed with the 40 mg/kg Q2W dose schedule. The subsequent Q4W schedule at 3000 mg is predicted to result in adequate long-term exposures with median trough concentration above the estimated CD73 saturating concentration of approximately 40 μg/mL (100-fold of estimated Michaelis-Menten constant from the population PK model) to maintain optimal CD73 saturation at steady state.

3.2.1.3 Monalizumab

The monalizumab dose of 750 mg Q2W was selected based on the available clinical safety, tolerability, efficacy, and PK data from the ongoing Phase 1 Study D419NC00001. In that study, monalizumab doses of 22.5, 75, 225, and 750 mg Q2W and 750 mg Q4W were examined in combination with durvalumab 1500 mg Q4W. Monalizumab was well tolerated in all dose-escalation cohorts, and no DLTs were observed. The monalizumab 750 mg Q2W dose was identified for evaluation with durvalumab 1500 mg Q4W in the dose-expansion phase of the study.

3.2.2 Rationale for Study Population

Patients with unresectable, Stage III NSCLC who have not progressed after cCRT will be considered for enrollment into the study. These characteristics defined the patient population in the Phase 3 PACIFIC study that showed superiority of durvalumab maintenance over placebo (see Section 1.5). Aligning with the PACIFIC target population provides support for use of a durvalumab control arm as the comparator for evaluating novel durvalumab combinations.

3.2.3 Rationale for Endpoints

The primary objective of this platform study is to compare the clinical activity of durvalumab alone vs durvalumab in combination with novel agents. The overall study goal is early identification of novel durvalumab combinations that are more active than durvalumab alone in the treatment of patients with unresectable, Stage III NSCLC who have not progressed after cCRT. The classical efficacy endpoints of PFS and OS require long evaluation periods, eg, the ongoing PACIFIC study showed an interim median PFS of 17.2 months following a 3-year follow-up (Antonia et al, 2018). The current study will use objective response (OR) per Response Evaluation Criteria for Solid Tumors version 1.1 (RECIST v1.1), which is a widespread outcome measure in Phase 1-2 studies, as the primary endpoint to provide an earlier measure of antitumor activity. A difference in ORR between the durvalumab monotherapy arm and the novel combinations arms is believed to be clinically meaningful as responses to immunotherapies can be sustained over time and might relate to the overall PFS benefit. Clinical activity will be further assessed by secondary endpoints routinely used in oncology studies, including duration of response (DoR), DC, PFS-12, and PFS based on RECIST v1.1, and OS.

The safety and tolerability of each study treatment will be assessed by the standard safety endpoints, including AEs, SAEs, laboratory parameters, vital signs, and other standard clinical parameters.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Up to approximately 60 subjects per experimental treatment arm will be randomized with equal ratios to durvalumab control and each of the open experimental arms. New durvalumab combination experimental arms may be added over time following protocol-specific guidelines (see Section 1.6.3) and therefore the total number of subjects randomized to the durvalumab control arm might be higher than 60 subjects. Details regarding the specifics of a new combination arm will be provided via protocol amendment. See also Section 4.6.1 for potential changes to the randomization scheme and changes to overall study enrollment in the control arm and the combination experimental arms during the study.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Written informed consent and any locally required authorization obtained from the subject prior to performing any protocol-related procedures, including screening evaluation
2 Age 18 years or older

3 Body weight ≥ 35 kg

4 Subjects must have histologically or cytologically documented NSCLC who present with locally advanced, unresectable, Stage III disease

5 Subjects must have completed, without progressing, definitive cCRT within 42 days prior to being randomized into the study:
   - Definitive radiotherapy refers to a total dose ≥ 60 Gy at 1.8 Gy per fraction or bioequivalent dose
   - Concurrent chemotherapy refers to a platinum-based doublet
   - The final chemotherapy administration must end prior to, or concurrently with, the final dose of radiation

6 Subjects must have at least one previously irradiated tumor lesion that can be measured by RECIST v1.1 (RECIST v1.1 guidelines permit previously irradiated lesions to be considered measurable if defined in the protocol [see Section 3.1.3 in Eisenhauer et al, 2009])

7 Provision of tumor tissue sample, when available, from original diagnosis obtained before initiation of chemoradiotherapy (tumor tissue block or unstained slides are acceptable; refer to Laboratory Manual for details)

8 Life expectancy ≥ 12 weeks

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

10 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 (1000 per mm^3)
	Platelet count [a]	≥ 100×10^9/L (100,000 per mm^3)
Hepatic	Total bilirubin	≤ 1.5 × ULN in the absence of Gilbert's syndrome
		≤ 3 × ULN if the patient 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 (using actual body weight; Cockcroft and Gault, 1976) or 24-hour urine creatinine clearance.

11 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 (see Appendix A)

4.1.3 Exclusion Criteria

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

1 Involvement in the planning and/or conduct of the study (applies to both sponsor staff and/or staff at the study site)

2 Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

3 Mixed small cell and non-small cell lung cancer histology

4 Current or prior use of immunosuppressive medication within 14 days before the first dose of study drug. The following are exceptions to this criterion:
   - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
   - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
   - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

5 Prior exposure to any anti-PD-1, anti-PD-L1, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody for the treatment of NSCLC

6 Any unresolved toxicity National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) > Grade 2 from the prior chemoradiation therapy

7 Subjects with history of ≥ Grade 2 pneumonitis from prior chemoradiation therapy

8 Subjects with a history of venous thrombosis within the past 3 months.

9 Subjects with history of myocardial infarction, transient ischemic attack, or stroke in the past 6 months.

10 Congestive heart failure ≥ Class 3 based on New York Heart Association Functional Classification

11 Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of study drug

12 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:
   - Subjects with vitiligo or alopecia
   - Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
   - Any chronic skin condition that does not require systemic therapy
   - Subjects with celiac disease controlled by diet alone

13 History of active primary immunodeficiency

14 Active infection including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
15 History of allogenic organ transplantation
16 Known allergy or hypersensitivity to study drug formulation(s)
17 QTcF interval ≥ 470 ms
18 Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent
19 Receipt of live attenuated vaccination within 30 days prior to study entry
20 History of another primary malignancy except for:
   – Malignancy treated with curative intent and with no known active disease ≥ 5 years before the first dose of study drug and of low potential risk for recurrence
   – Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
   – Adequately treated carcinoma in situ without evidence of disease
21 Females who are pregnant, lactating, or intend to become pregnant during their participation in the study

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 (ie, 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. 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 in any of the treatment arms will not receive any further study drug if any of the following occur in the subject in question:

1 Withdrawal of consent
2 Any toxicity/AE that in the opinion of the investigator and/or the sponsor, warrants discontinuation of further dosing
3 Any AE that meets criteria for discontinuation as defined in the Toxicity Management Guidelines (see Section 3.1.3)
4 Pregnancy or intent to become pregnant (Section 5.6.2)
5 Delay of more than 56 days from the last administration of study drug to the next planned dose
6 Confirmation of disease progression (Section 4.3.1)
7 Unconfirmed disease progression and investigator determination that the subject is not eligible for a confirmation scan (Section 4.3.1)
8 Initiation of alternative anticancer therapy
9 Intercurrent illness or medical condition, in the judgment of the investigator and/or the sponsor warrants discontinuation of further dosing

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. All subjects will be followed for survival until the end of the study unless consent is withdrawn from further study participation.

4.1.7 Replacement of Subjects

Subjects 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 (except for the optional tumor biopsy at screening and on-treatment, and optional blood sample at screening for germline DNA) 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 study drug administration that is treatment-arm specific, will be followed for all treatment arms.

The study drug treatment regimens for the control arm and each combination experimental arm are presented in Section 3.1.2.

4.2.1 Enrollment/Screening and Treatment Periods

Table 5 shows all procedures to be conducted during the screening and treatment periods.

Table 5 Schedule of Screening and Treatment Period Procedures

Procedure	Screening	Treatment Period: Up to 12 Months 28-day Cycles				
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5 through Cycle 13
	Day -28 to Day -1	Day 1	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)
Written informed consent	X					
Demographics	X					
Medical history [a]	X					
Verify eligibility criteria	X					
Physical examination	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
ECG [b]	X					
ECOG performance status	X	X	X	X	X	X
Tumor specimen [c]	X					X (optional) [c]
Serum chemistry	X	X [d]	X	X	X	X
Hematology	X	X [d]	X	X	X	X
Urinalysis	X	As clinically indicated				
Thyroid function tests [e]	X	X [d]	X	X	X	X
Pregnancy test [f]	X	X	X	X	X	X
Coagulation parameters	X					
Hepatitis B and C; HIV [g]	X					
Concomitant medications	X	X	X	X	X	X
Assessment of AEs/SAEs	X	X	X	X	X	X
Disease assessment (scans)	X [h]			X (within 7 days)		Cycle 5 then every 2 cycles (within 7 days)

Table 5 Schedule of Screening and Treatment Period Procedures

Procedure	Screening	Treatment Period: Up to 12 Months 28-day Cycles				
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5 through Cycle 13
	Day -28 to Day -1	Day 1	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)
Brain MRI (preferred) or CT	X [h]					
PET scan						Cycle 7 only (within 7 days of Day 1)
CCI [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]			
[redacted]	[redacted]					
Serum for PK		X (predose & EOI) [i]	X (predose) [j]			Cycle 7 and Cycle 11 only (predose) [j]
Serum for ADA		X (predose) [k]	X (predose) [k]			Cycle 7 and Cycle 11 only (predose) [k]
Study drug administration [l]		According to each study drug-specific regimen				

ADA = antidrug antibody; AE = adverse event; β-hCG = beta human chorionic gonadotropin; CT = computed tomography; CCI [redacted] ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; 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; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

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

[a] 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.

[b] 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.

Table 5 Schedule of Screening and Treatment Period Procedures

Procedure	Screening	Treatment Period: Up to 12 Months 28-day Cycles				
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5 through Cycle 13
	Day -28 to Day -1	Day 1	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)

[c] Tumor tissue sample, when available, from the original diagnosis and before initiation of chemoradiotherapy will be collected at screening, per inclusion criterion. Optional fresh tumor tissue specimens may be collected after completion of chemoradiotherapy during screening and on treatment at the time of the PET/CT (Cycle 7). Additional on-treatment fresh tumor tissue specimens may be collected at the investigator's discretion as clinically indicated for correlative biomarker studies. See Section 4.3.7.4.

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

[e] TSH, T3, and T4. If TSH is normal, then T3 or T4 is not required. Free T3/free T4 are preferred over total T3/total T4.

[f] 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 equivocal or positive then serum β-hCG testing should be performed for confirmation.

[g] 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.

[h] Screening disease assessment and brain MRI or CT must be performed after completion of chemoradiotherapy.

[i] In combination arms, PK predose (within 1 hour prior to dosing) and EOI (within 15 minutes 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.

[j] In combination arms, at visits when predose samples only are required, PK samples will be collected within 1 hour prior to administration of the first study drug only. For example: PK predose Agent 1 and Agent 2 collected → Agent 1 administration → Agent 2 administration.

[k] In combination arms, ADA samples will be collected within 1 hour 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.

[l] Treatment regimens are described in Section 3.1.2.

4.2.2 Follow-up Period

Table 6 presents follow-up procedures for subjects who completed study treatment and maintain DC, subjects who discontinued study treatment due to other reason not related to PD (Section 4.1.6), and subjects who experienced unconfirmed PD and are eligible for a confirmation scan. Procedures for subjects who discontinue study treatment due to PD are provided in Section 4.2.3. Overall, all subjects continuing in the study must adhere to the study procedures for up to 5 years (from randomization) provided they achieve DC and remain disease free.

As OS is a late endpoint in this patient population, after the planned 5-year post randomization study period, subjects may be contacted for survival every 12 months.

Table 6 Schedule of Follow-up Procedures: Subjects Who Completed Study Treatment and Maintain DC, Subjects Who Discontinued Study Treatment Due to Other Reason Not Related to PD, and Subjects Who Experienced Unconfirmed PD and are Eligible for a Confirmation Scan

Time since Cycle 1 Day 1	**≤ 12 Months**	**> 12 to ≤ 24 Months**	**> 24 to 60 Months**
Follow-up based on previous scheduled visit	**Every 8 Weeks (± 3 days)**	**Every 12 Weeks (± 7 days)**	**Every 6 Months (± 4 weeks)**
Procedure			
Physical examination	X	X	X
Vital signs	X	X	X
ECOG performance status	X	X	X
Serum chemistry	X	X	X
Thyroid function tests [a]	X	X	X
Hematology	X	X	X
Concomitant medications [b]	X	X (up to Month 15, if applicable)	
Assessment of AEs/SAEs [b]	X	X (up to Month 15, if applicable)	
Disease assessment (scans)	X (within 7 days)	X	X
CCI [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
Serum for PK	10 months post Cycle 1 Day 1 only	Month 15 only	

Table 6 Schedule of Follow-up Procedures: Subjects Who Completed Study Treatment and Maintain DC, Subjects Who Discontinued Study Treatment Due to Other Reason Not Related to PD, and Subjects Who Experienced Unconfirmed PD and are Eligible for a Confirmation Scan

Time since Cycle 1 Day 1	≤ 12 Months	> 12 to ≤ 24 Months	> 24 to 60 Months
Follow-up based on previous scheduled visit	**Every 8 Weeks (± 3 days)**	**Every 12 Weeks (± 7 days)**	**Every 6 Months (± 4 weeks)**
Procedure			
Serum for ADA	10 months post Cycle 1 Day 1 only	Month 15 only	
Survival status (if visits are discontinued, this may be done via telephone contact) [c]	X	X	X

ADA = antidrug antibody; AE = adverse event; CCI [redacted]; DC = disease control; ECOG = Eastern Cooperative Oncology Group; PD = progressive disease; PK = pharmacokinetics; SAE = serious adverse event; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

[a] TSH, T3, and T4. If TSH is normal, then T3 or T4 is not required. Free T3/free T4 are preferred over total T3/total T4.

[b] Concomitant medications and AEs/SAEs will be collected up to 12 months post Cycle 1 Day 1, regardless of whether the subject discontinued treatment. Following the first 12 months, concomitant medications and AEs/SAEs will be collected up to 3 months post last dose of study treatment, if applicable.

[c] Subjects may be contacted for survival status every 12 months beyond 60 months post Cycle 1 Day 1, until the end of the entire study, unless the subject withdraws consent from further participation in the study.

4.2.3 End of Study

Table 7 presents procedures for the end of study visit for all subjects. End of study visit will be performed when a subject discontinues study due to a confirmed PD, or a subject experienced an unconfirmed PD but is not eligible for a confirmation scan, or after 60 months of follow-up for subjects who achieve DC and remain disease free, or at the last study visit for subjects who discontinue study due to reason not related to PD.

Subjects who discontinue treatment due to any reason, including confirmed PD or initiation of alternative anticancer therapy, will be followed for survival according to the timepoints in Table 6 (every 8 weeks up to 12 months post Cycle 1 Day 1, every 12 weeks from > 12 to ≤ 24 months, and every 6 months from > 24 to 60 months post Cycle 1 Day 1) unless the subject withdraws consent from further participation in the study. After 60 months, subjects may be contacted for survival every 12 months until the end of the entire study.

Table 7 Schedule of Procedures for End of Study Visit

Procedure	End of Study Visit (± 4 weeks)
Physical exam	X
Pregnancy test	X
Vital signs	X
ECOG performance status	X
Serum chemistry	X
Thyroid function tests	X
Hematology	X
Urinalysis	X
Concomitant medications [a]	X
Assessment of AEs/SAEs [a]	X
Subsequent anticancer treatment	X
CCI [redacted]	[redacted]
[redacted]	[redacted]

AE = adverse event; CCI [redacted] ECOG = Eastern Cooperative Oncology Group; CCI [redacted]; SAE = serious adverse event.

[a] Concomitant medications and AEs/SAEs will be collected at this visit only.

4.3 Description of Study Procedures

4.3.1 Efficacy

RECIST v1.1 (Eisenhauer et al, 2009; see Appendix E) will be used to assess subject response to treatment and allow calculation of PFS, ORR, and DoR, which will be performed according to the schedules in Section 4.2. Post-radiation changes which affect lesion sizes may occur and there may be high levels of necrosis/fibrosis with little or no active tumor in recently irradiated lesions. However, accepting these limitations in this patient population with prior curative radiation treatment, the prior irradiated lesions may be considered measurable and selected as target lesions providing they fulfill the other criteria for measurability. All images will be collected and stored for possible future central re-analysis. Additional disease assessments may be performed as clinically indicated.

Additionally, disease progression in the absence of clinical deterioration requires confirmation. The confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD. Administration of study drug(s) may continue between the initial assessment of progression and confirmation for progression. Subjects with rapid tumor progression or with symptomatic progression that requires urgent medical intervention (eg, central nervous system metastasis, respiratory failure due to tumor

compression, spinal cord compression) will not be eligible to continue to receive study drug(s) neither will require a confirmatory scan.

CCI CCI

- If progression is not confirmed, then the subject should continue study drug(s) and on treatment assessments.
- If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

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.

4.3.1.1 CCI

CCI

CCI [redacted]

4.3.1.2 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, 2011).

- 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 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, and weight to 0.1 kg; and height (at screening only). Abbreviated symptom-directed physical examinations will be conducted at subsequent visits post dosing.

Vital Signs

Vital signs (blood pressure and pulse rate) 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 at screening and as clinically indicated throughout the study 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.

4.3.3 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 using a serum pregnancy test 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
- Gamma-glutamyl transferase
- 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
- Absolute neutrophil count
- Hemoglobin
- Platelet count
- White blood cell count

Urinalysis

- Blood
- Protein

Pregnancy Test (females of childbearing potential only)

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

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

Other Safety Tests

- Coagulation tests: activated partial thromboplastin time and international normalized ratio. If international normalized ratio is not available the sites may substitute a prothrombin time.
- 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, T3, and T4. If TSH is normal, then T3 or T4 is not required. Free T3/free T4 are preferred over total T3/total T4.

HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone.

4.3.4 Pharmacokinetic Evaluation and Methods

Blood samples will be collected to evaluate PK in serum of durvalumab when administered alone or in combination with novel agents. Additionally, PK in serum of novel agents administered in combination with durvalumab will be evaluated. Novel agents include oleclumab and monalizumab. 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 (EOI) samples are required, PK predose (within 1 hour prior to dosing) and EOI (within 15 minutes 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.

In combination arms, at visits when predose samples only are required, PK samples will be collected within 1 hour prior to administration of the first study drug only. For example: PK predose Agent 1 and Agent 2 collected → Agent 1 administration → Agent 2 administration.

4.3.5 Immunogenicity Evaluation and Methods

Blood samples will be collected to evaluate antidrug antibody (ADA) responses to durvalumab when administered alone or in combination with novel agents. Additionally, ADA responses to novel biologic agents administered in combination with durvalumab will be evaluated. Novel/biologic agents include oleclumab and monalizumab. 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, including possible assessment of neutralizing antibody.

In combination arms, ADA samples will be collected within 1 hour 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.

4.3.6 Genetic Evaluations and Methods

See Appendix E for information regarding genetic research.

4.3.6.1 Collection of Genetic Samples

If the subject agrees to participate in the optional genetic research study, a blood sample will be collected. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

The blood sample for genetic research will be obtained from the subjects at screening. If for any reason the sample is not drawn at screening, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

4.3.6.2 Storage and Destruction of Genetic Samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. 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. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum, or separately in a scientific report or publication.

No personal details identifying the individual will be available to MedImmune or designated organizations working with the DNA.

4.3.7 CCI

CCI

CCI

4.3.7.1 CCI

4.3.7.2 CCI

4.3.7.3 CCI

4.3.7.4 CCI

screening (Day -28 to Day -1) and on treatment at the time of the PET/CT (Cycle 7). Addi-

CCI

[redacted]

4.3.7.5 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 clinical study report (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.

4.3.8 Estimate of Volume of Blood to be Collected

A total of no more than 36.8 mL of blood will be required for all screening tests. No more than 59.0 mL of blood will be drawn at any visit during the treatment period. During the follow-up period, no more than approximately 34.5 mL of blood will be collected at any visit. 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 may include but are not limited to the following:

1 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 any treatment arm based on a planned futility analysis and/or recommendation from SRC (Section 4.8.7 and Section 3.1.4, respectively)

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 Product

4.5.1 Identity of Investigational Product

For all the treatment arms, control arm and each combination experimental arm, MedImmune will provide the investigators with study drug (Table 8) using designated distribution centers.

Table 8 Identification of Investigational Product

Investigational Product	Provider	Concentration and Formulation as Supplied
Durvalumab (MEDI4736)	MedImmune	Supplied as a vialed liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine HCl, 275 mM trehalose dihydrate, and 0.02% (w/v) polysorbate 80, at pH 6.0 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL.
Oleclumab (MEDI9447)	MedImmune	Supplied as a vialed liquid solution containing 500 mg (nominal) oleclumab. The solution contains 50 mg/mL oleclumab, 25 mM histidine/histidine HCl, 240 mM sucrose, 0.03% (w/v) polysorbate 80, at pH 6.0. The nominal fill volume is 10.0 mL.

Table 8 Identification of Investigational Product

Investigational Product	Provider	Concentration and Formulation as Supplied
Monalizumab (IPH2201)	MedImmune	Supplied as a vialed lyophilized powder containing 375 mg (nominal) monalizumab per vial. The powder is to be reconstituted with 7.4 mL WFI. After reconstitution, the vial contains 50 mg/mL monalizumab, 20 mM histidine/histidine hydrochloride, 220 mM sucrose, 0.03% (w/v) polysorbate 80, pH 6.0

DP = drug product; DS = drug substance; HCl = hydrochloride; WFI = Water for Injection; w/v = weight per volume.

Durvalumab is supplied in 10R vials as a sterile, clear to opalescent, colorless to slightly yellow liquid, free from or practically free from visible particles at a concentration of 50 mg/mL.

Oleclumab is supplied in 10R vials as a sterile, clear to opalescent, colorless to yellow liquid, that may contain a few white to off-white translucent particles at a concentration of 50 mg/mL.

Monalizumab is supplied in 20R vials as a vialed lyophilized powder with dried powder visible on the vial wall. The reconstituted drug product is a clear to opalescent and colorless to yellow liquid, that may contain some translucent or white to off-white inherent particles at a concentration of 50 mg/mL.

Durvalumab, oleclumab, and monalizumab vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug products should be kept in original packaging until use to prevent prolonged light exposure.

Each investigational product kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton and vial is labeled with the same unique number.

Commercially available 0.9% (weight per volume [w/v]) saline or 5% (w/v) dextrose will be supplied by each site.

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 4.5.1.8) 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 1500 mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30.0 mL of durvalumab (ie, 1500 mg of durvalumab) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

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 experimental 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.

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.

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

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

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

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

A dose of 3000 mg will be administered using an IV bag containing 0.9% (w/v) saline with a final oleclumab concentration of 1.5 to 30 mg/mL, 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 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 days 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 days 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.

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 IV bags have been observed.

A dose of 750 mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final monalizumab concentration of 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22 µm filter. Add 15.0 mL of monalizumab (ie, 750 mg of monalizumab) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

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 days 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 there are interruptions during infusion for either durvalumab and/or monalizumab on days when both durvalumab and monalizumab are administered, 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.

4.5.1.6 Treatment Administration

The first day of dosing is considered Day 1.

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

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.

4.5.1.7 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 4.2.1.

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.

4.5.1.8 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to AstraZeneca Product Quality Complaints by the site with further notification to the site monitor. All defects will be communicated to AstraZeneca and investigated further with Product Quality Complaints. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

AstraZeneca contact information for reporting product complaints:

E-mail: PPD
Phone: PPD
Website: PPD
Mail: AstraZeneca
Attn: PPD
PPD ,
PPD

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 secondary 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. Randomization will be stratified by histology (adenocarcinoma vs non-adenocarcinoma). The randomization scheme will use an equal ratio to all study treatment arms open for enrollment (eg, if experimental arms are opened sequentially, an experimental arm is added/closed, or enrollment in an experimental arm is suspended). Additionally, the following considerations regarding randomization will apply:

- If there is no experimental arm open for enrollment, then enrollment will be paused. Any subject who had consented previously and was in screening when the experimental arm(s) was closed due to safety concerns may be allowed to enter into the study but must be allocated to the control arm.
- Once the control arm enrolls 60 subjects, a subsequent randomization scheme may be initiated to optimize the number of subjects allocated to control arm.
- At any point during the study, the control arm will have no less than a 33% chance to be randomized in comparison to the active experimental arm that has the lowest randomization ratio in the study.

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 investigational anticancer therapy
- Any concurrent chemotherapy, radiotherapy (except palliative 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 10 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, or topical corticosteroids 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 includes all subjects who are randomized. Subjects will be analyzed according to their randomized treatment group.

The As-treated Population includes all subjects who receive any investigational product. Subjects will be analyzed according to the treatment they actually receive.

The Response-evaluable Population includes subjects from the As-treated Population who have a baseline disease assessment, have the opportunity to be followed for at least 16 weeks at the time of the DCO (ie, dosed at least 16 weeks prior to the time of the DCO), and either has at least one post-baseline disease assessment and/or discontinued treatment due to death or disease progression.

4.8.2 Sample Size

Subjects will be randomized to the durvalumab monotherapy control arm and combination therapy experimental arms. The sample size of 60 subjects per experimental arm is not designed to make explicit power and Type I error considerations for a hypothesis test. It is primarily chosen to obtain a preliminary assessment of antitumor activity with a certain degree of precision.

Table 9 shows estimated differences in ORR between an experimental arm and the control arm along with 2-sided 95% exact CIs with a sample size of 60 subjects each. Sixty subjects per treatment arm provides a 95% CI with reasonable width (approximately ± 18%) for the estimated ORR difference between a durvalumab combination experimental arm and the durvalumab control arm. For a 20% increase in ORR in any durvalumab combination experimental arm over durvalumab control arm (50% vs 30%, respectively), the lower limit of the 95% CI for the difference between these arms is 1%, which is greater than 0%, suggesting that the durvalumab combination experimental arm will have a higher ORR than the durvalumab control arm with 95% confidence.

Table 9 Estimated Differences in ORR Between Experimental and Control Arm of 60 Subjects Each

Number of Responders (ORR)		Difference (%) in ORR (2-sided 95% Exact Confidence Interval)
Experimental Arm (n = 60)	Control Arm (n = 60)	
24 (40%)	18 (30%)	10% (-9%, 28%)
27 (45%)	18 (30%)	15% (-4%, 33%)
30 (50%)	18 (30%)	20% (1%, 38%)
33 (55%)	18 (30%)	25% (6%, 42%)

ORR = objective response rate.

4.8.3 Efficacy

The final efficacy analyses will be based on the ITT Population defined in Section 4.8.1. Response will be summarized and compared between the experimental arm and control arm. Time-to-event data will be summarized using the Kaplan-Meier estimates. The following efficacy endpoints will be analyzed. Each experimental arm will be compared to the control arm. There will be no formal comparisons between any experimental arms. RECIST v1.1 will be used as primary analysis for all endpoints when applicable. Localized post-radiation changes which affect lesion sizes may occur and there may be high levels of necrosis/fibrosis with little or no active tumor in recently irradiated lesions. However, accepting these limitations in this patient population with prior curative radiation, treatment the prior irradiated lesions may be considered measurable and selected as target lesions providing they fulfill the other criteria for measurability. More details will be provided in the statistical analysis plan.

- Best overall response (BOR), defined as the best response (in the order of complete response [CR], PR, SD, PD, and not evaluable) among all overall responses recorded from randomization until progression, or the last evaluable disease assessment in the absence of PD prior to the initiation of subsequent anticancer therapy or discontinuation from the study, whichever occurs first. The BOR of CR or PR must be confirmed, which means a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 28 days (4 weeks) after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.
- OR, defined as BOR of confirmed CR or confirmed PR according to RECIST v1.1.
- DC, defined as BOR of confirmed CR, confirmed PR, or SD based on RECIST v1.1. Disease control rate (DCR) at 16 weeks is defined as a BOR of confirmed CR, confirmed PR or having SD with duration of SD lasting 16 weeks.
- DoR, defined as the time from the first documentation of a subsequently confirmed OR to the first documentation of a disease progression according to RECIST v1.1 or death due to any cause, whichever occurs first. Only subjects who have achieved OR (confirmed CR or confirmed PR) will be evaluated for DoR.

- PFS, defined as the time from randomization until the first documentation of disease progression according to RECIST v1.1 or death due to any cause, whichever occurs first, regardless of whether the subject receives subsequent anticancer therapy prior to progression. Subjects who are alive progression free at the time of DCO will be censored on the date of their last evaluable tumor assessment. PFS-12 will be estimated using the Kaplan-Meier method.

4.8.3.1 Primary Efficacy Analysis

The primary efficacy endpoint is OR per RECIST v1.1. ORR is defined as the proportion of subjects with OR. The 2-sided 95% CI for ORR will be estimated using the exact binomial distribution. In addition, the unconfirmed ORR which is defined as the proportion of subjects who achieved a BOR of confirmed/unconfirmed CR or confirmed/unconfirmed PR will be presented along with its CI. An estimate of the difference in ORR between the experimental arm and the control arm will be reported. Comparison of treatment arms for ORR will be obtained from the Chi-square or Fisher's exact test.

4.8.3.2 Secondary Efficacy Analyses

Secondary efficacy endpoints include DoR, DC, PFS, and OS. Analyses of secondary endpoints will be performed as follows.

- DoR according to RECIST v1.1 will be analyzed using the Kaplan-Meier method for those subjects with OR in the corresponding analysis populations. The median of DoR with 95% CI will be estimated based on the Kaplan-Meier curves.
- The DCR according to RECIST v1.1 is defined as the proportion of subjects with DC. The 2-sided 95% CI of DCR will be provided using an exact probability method. DCR at 16 weeks will be estimated along with the 2-sided 95% CI.
- PFS according to RECIST v1.1 will be analyzed using the Kaplan-Meier method. The median PFS with 95% CI will be estimated based on the Kaplan-Meier curves. PFS-12 will be estimated based on the Kaplan-Meier curves along with their 95% CIs when applicable. An estimate of the difference in PFS-12 between an experimental arm and the control arm will be reported. Comparison of treatment arms for PFS-12 will be performed under complementary log-log transformation of the Kaplan-Meier estimates of PFS-12 (Klein et al, 2007)
- OS will be analyzed using the Kaplan-Meier method. The median OS with 95% CI will be estimated based on the Kaplan-Meier curves. The 1-year OS rates will be estimated based on the Kaplan-Meier curves along with their 2-sided 95% CI when applicable.

4.8.3.3 Exploratory Analyses

CCI [redacted]

CCI [redacted]

4.8.4 Safety

Safety analyses will be based on the As-treated Population defined in Section 4.8.1.

4.8.4.1 Analysis of Adverse Events

Summary statistics will be provided for AEs, SAEs, and AE grade, severity, and relationship to study drug(s). AEs will be graded according to NCI CTCAE v5.0 and coded using system organ class and preferred term using the Medical Dictionary for Regulatory Activities preferred term. Specific AEs will be counted once for each subject when calculating rates, but will be all presented in total in subject listings.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Summary statistics will be provided for clinical laboratory parameters, physical examinations, vital signs, and ECG. Laboratory abnormalities with toxicity grades according to the NCI CTCAE v5.0 will be derived and summarized.

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 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

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 ADAs to durvalumab. For experimental arms that

include a biologic agent, the immunogenic potential of the combination study drug will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs to the combination study drug.

The impact of ADAs on PK and safety will be assessed if data allow. Samples confirmed positive for ADAs may also be evaluated for neutralizing antibody activity.

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 concentrations will be tabulated with descriptive statistics. Additionally, for each experimental arm, individual novel agent concentrations will be tabulated with descriptive statistics.

Non-compartmental PK data analysis will be performed from each treatment arm with scheduled PK sample collection where data allow. Relevant descriptive statistics of non-compartmental PK parameters will be provided and may include: area under the concentration-time curve, observed maximum concentration, clearance, and terminal half-life.

4.8.6 Analyses of Biomarkers

Descriptive statistics will be the primary method for the biomarker analyses (see Section 4.3.7 for a description of the exploratory biomarkers). Depending on the nature of the data, geometric mean and other appropriate statistical summaries might be used as well.

Summaries and analyses for exploratory biomarkers may be reported outside the CSR in a separate report.

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 experimental arm in comparison with the control arm. The results of the interim analyses may be used for internal program decision and/or potential interactions with regulatory agencies on future development. The first interim analysis will be performed once the control arm has 30 ITT subjects who have reached the data cutoff criteria (defined as the opportunity to be followed for at least 16 weeks at the time of data cutoff). The DCR at Week 16 will be used for No-Go decision, and ORR may be used for early Go decision. Enrollment will not be paused for interim analyses.

Bayesian PP will be used to evaluate clinical activity (Lee and Liu, 2008). Table 10 illustrates the sample algorithm to make a No-Go decision based on DCR at 16 weeks at the interim analysis when the control arm and an experimental arm each have 30 subjects. If an early No-Go decision is made, enrollment to the corresponding experimental arm will be stopped. In

this study, we assume a target value (TV) of ΔDCR at 16 weeks as 15%, where ΔDCR is the difference in DCR between an experimental arm and control arm.

- An experimental arm will meet the No-Go criteria if the probability that the true ΔDCR is larger than TV is less than 10%, ie, Prob.(True ΔDCR > 0.15) < 0.10. A No-Go decision will be made at an interim analysis if the PP of meeting the No-Go criteria given observed data is greater than 95%, ie, PP[Prob.(ΔDCR > 0.15) < 0.10)] > 0.95.

Table 10 Criteria of No-Go Decisions Based on DCR at 16 Weeks

Number of Subjects with DCR at 16 weeks in Control Arm	Number of Subjects with DCR at 16 weeks in Experimental Arm
10	≤ 7
11	≤ 8
12	≤ 8
13	≤ 9
14	≤ 10
15	≤ 11
16	≤ 12
17	≤ 13
18	≤ 14
19	≤ 15
20	≤ 16
21	≤ 17
22	≤ 19
23	≤ 20
24	≤ 21
25	≤ 23
26	≤ 24
27	≤ 26
28	≤ 28
29	≤ 29
30	≤ 30

DCR = disease control rate.

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 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.

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 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 mediated diseases
- 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). Subjects who experience an AE suspected to be immune-complex related and with confirmed presence of ADAs will discontinue treatment. 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. 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 allergic mediated 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 adverse reactions observed during or shortly after drug infusion, 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 Disease and Food and Allergy Anaphylaxis Network guidance for anaphylaxis diagnosis is provided in Appendix C.

Further information on all those 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 (see 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 venous thrombosis in the prior 3 months, or myocardial infarction, stroke, or transient ischemic attack in the prior 6 months 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 AESI due to oleclumab potential risks of increased microvascular permeability. For subjects who develop ≥ Grade 3 edema, 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 identified AESIs associated with monalizumab that are not included in the AESIs for durvalumab-containing regimens (see Section 5.3.1).

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 0 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 up to 12 months post Cycle 1 Day 1, regardless of whether the subject discontinued treatment. Following the first 12 months post Cycle 1 Day 1, AEs and SAEs will be collected up to 3 months post last dose of study treatment, if applicable.

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 consented to study participation may be followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. The sponsor 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 following investigator awareness of the event. 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 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 is the IB for the study drug.

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 IB, unless otherwise specified in this protocol.

- 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 study drug 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 drug, but rather a human- or process-related failure while the 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 drug
- Did not occur, but circumstances were recognized that could have led to an error

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

- Drug name confusion (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
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- 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 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 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 location of 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 (including telephone contact) for the last subject in the study. This date will be 5 years 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(s) 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 study, 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 sample) 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.

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 suspected unexpected serious adverse reactions 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(s) 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 the sponsor. 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 4

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. All subjects have completed their treatment period as specified by the protocol and no subjects are currently receiving any study treatment. The primary reason for this amendment is to clarify the frequency and length for collection of overall survival data.

Substantial changes to the protocol are summarized below:

1 Title page: Replaced PPD with PPD as Medical Monitor.
2 Section 3.1.1 (Overview): Clarified that all subjects, including those who have experienced PD, will be followed for survival until the end of the study.
3 Section 4.1.6 (Discontinuation of Investigational Product), Section 4.2.2 (Follow-up Period), Table 6 (Schedule of Follow-up Procedures: Subjects Who Completed Study Treatment and Maintain DC, Subjects Who Discontinued Study Treatment Due to Other Reason Not Related to PD, and Subjects Who Experienced Unconfirmed PD and are Eligible for a Confirmation Scan), and Section 4.2.3 (End of Study): Clarified that survival status will be collected for all subjects until 60 months post Cycle 1 Day 1, at time points detailed in Table 6. Further, subjects may be contacted for survival status every 12 months beyond 60 months post Cycle 1 Day 1, until the end of the entire study, unless consent is withdrawn.

Non-substantial changes to the protocol are as follows:

1 Protocol Synopsis: Updated to align with the body of the protocol.
2 Section 3.1.3 (Management of Study Medication Related Toxicities): A reference to the website hosting the toxicity management guidelines for durvalumab was deleted as the website has been decommissioned.
3 Section 4.1.1 (Number of Subjects) and Section 4.8.2 (Sample Size): Clarified that the recruitment estimate of 60 subjects per experimental treatment arm is approximate.
4 Section 4.2.3 (End of Study), Table 7 (Schedule of Procedures for End of Study Visit): Added a footnote to clarify that concomitant medications, AEs and SAEs will be collected at this visit only.
5 Section 4.5.1.8 (Reporting Product Complaints): Updated the contact information for reporting product complaints.

9.2 Protocol Amendment 3

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. The primary reason for the amendment is to increase the window from the subject's last cCRT to randomization into the study.

Substantial changes to the protocol are summarized below.

1 Protocol synopsis; Section 3.1.1 (Overview), including Figure 1 (Study Flow Diagram); and Section 4.1.2 (Inclusion Criteria), Criterion 5: The window from the subject's last cCRT to randomization was increased from 28 days to 42 days to align with the PACIFIC study design and to provide sites more flexibility in identifying and enrolling subjects.
2 Section 4.1.3 (Exclusion Criteria): Added criterion (new Criterion 5) excluding subjects with prior exposure to any anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibody for the treatment of NSCLC to avoid confounding factors affecting safety and efficacy assessments for this study.

Non-substantial changes to the protocol are summarized below.

1 Table 5 (Schedule of Screening and Treatment Period Procedures):
   (a) Added assessment for ECOG performance status for Cycle 5 through Cycle 13. This assessment was inadvertently omitted in the original protocol. ECOG performance status is to be assessed throughout the study, as noted in Table 6 (Schedule of Follow-up Procedures) throughout the follow-up period and Table 7 (Schedule of Procedures for End of Study Visit).
   (b) Footnote "e" revised to align with changes to required TSH tests described in Section 4.3.3, Other Safety Tests.
2 Table 6 (Schedule of Follow-up Procedures: Subjects Who Completed Study Treatment and Maintain DC, Subjects Who Discontinued Study Treatment Due to Other Reason Not Related to PD, and Subjects Who Experienced Unconfirmed PD and are Eligible for a Confirmation Scan):
   (a) Clarified that disease assessments conducted as part of follow-up procedures ≤ 12 months from Cycle 1 Day 1 can be conducted within 7 days of the visit, in alignment with window for this assessment during the treatment period.
   (b) Footnote "a" revised to align with changes to required TSH tests described in Section 4.3.3, Other Safety Tests.
3 Section 4.3.3 (Clinical Laboratory Tests), Other Safety Tests: Thyroid function tests were revised permitting sites to only conduct T3 or T4 tests when TSH is abnormal for flexibility to accommodate country or institutional guidelines regarding thyroidal abnormality screening. Additionally, it was clarified that free T3/free T4 are preferred over total T3/total T4 tests.
4 Section 4.5.1.8 (Reporting Product Complaints): Updated the telephone information in alignment with current contact.
5 Protocol synopsis and Section 4.8.1 (General Considerations): Modified the definition of the ITT Population to align with the Sponsor's current standard definition.
6 Appendix D (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law): Removed references as not cited in the protocol.

9.3 Protocol Amendment 2

The primary reasons for the amendment were alignment of monalizumab information with the new manufacturing process (Process C), updating the process for identifying and reporting potential Hy's Law and Hy's Law cases, and adding an inclusion criterion to ensure all subjects have at least 1 previously irradiated tumor lesion that can be measured by RECIST v1.1. No subjects were enrolled in experimental Arm B (durvalumab plus monalizumab) prior to Protocol Amendment 2.

All revisions to the protocol are noted below:

1 Section 1.5 (Rationale for Conducting the Study): Included rationale for use of ORR to assess antitumor activity
2 Section 4.1.2 (Inclusion Criterion): Added criterion to clarify that subjects must have at least 1 previously irradiated tumor lesion measurable by RECIST v1.1, consistent with the RECIST v1.1 guidelines
3 Section 4.5.1 (Identity of Investigational Product), Table 8 (Identification of Investigational Product): Updated with new monalizumab manufacturing process information, and added study drug storage information.
4 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.
5 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.
6 Section 4.5.1.5 (Monalizumab Dose Preparation and Administration): Updated with new monalizumab manufacturing process information.
7 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.
8 Section 7.1 (Subject Data Protection): Revised to align with preferred MedImmune standard language.
9 Appendix D (Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law): Updated to align with revised MedImmune requirements.

9.4 Protocol Amendment 1

The protocol was revised to incorporate the following US Food and Drug Administration requests:

1 Figure 1 (Study Flow Diagram): Removed placeholders for new combination experimental arms (A and X) that could be added via a protocol amendment.
2 Table 5 (Schedule of Screening and Treatment Period Procedures): Additional PK and ADA samples will be collected at Cycle 11.

3 Table 6 (Schedule of Follow-up Procedures: Subjects Who Completed Study Treatment and Maintain DC, Subjects Who Discontinued Study Treatment Due to Other Reason Not Related to PD, and Subjects Who Experienced Unconfirmed PD and are Eligible for a Confirmation Scan): PK and ADA samples will be collected at 10 months post Cycle 1 Day 1 (for follow-up during the first 12 months) and on Month 15 (for follow-up > 12 to ≤ 24 months).

4 Section 4.3.4 (Pharmacokinetic Evaluation and Methods): Revised to identify each novel agent to be included in the PK evaluation.

5 Section 4.3.5 (Immunogenicity Evaluation and Methods): Revised to identify each novel/biologic agent to be included in the ADA evaluation.

6 Section 4.3.8 (Estimate of Volume of Blood to be Collected): Updated to align with additional blood samples collected for PK and ADA assessments.

7 Section 4.8.2 (Sample Size): Added detail for sample size determination.

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 while on study and for 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 (ie, 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 an 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 IV 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.

Assessment of Relationship

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?

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

National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network 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: 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 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 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 Case Report Form (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 are related to the investigational product and seriousness criteria is 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 Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a subject meets potential Hy's Law criteria on study treatment and has already met potential Hy's Law criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of potential Hy's Law is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of potential Hy's Law criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of potential Hy's Law criteria being met found to be the disease under study eg, chronic or progressing malignant disease, severe infection, or liver disease?

If **No**: follow the process described in Section D 4.2, for reporting potential Hy's Law as an SAE.

If **Yes**:

Determine if there has been a significant change in the subject's condition compared with when potential Hy's Law criteria were previously met:

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section D 4.2, for reporting potential Hy's Law as an SAE

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the medical monitor if there is any uncertainty.

D 7 Laboratory Tests

To evaluate the underlying etiology of potential Hy's Law cases, relevant laboratory tests will be performed as outlined in Section 4.3.3. Additional laboratory assessments may be performed as clinically indicated.

Appendix E Genetic Research

Rationale and Objectives

MedImmune intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic Research Plan and Procedures

Selection of Genetic Research Population

Study Selection Record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion Criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Discontinuation of Subjects from This Genetic Research

Specific reasons for discontinuing a subject from this genetic research are:

Withdrawal of consent for genetic research: Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for withdrawal of informed consent are outlined in Section 4.1.8 of the protocol.

Collection of Samples for Genetic Research

The blood sample for genetic research will be obtained from the subjects at screening. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an AE, such subjects would be important to include in any genetic analysis. If for any reason the sample is not drawn at screening, it may be taken at any visit until the last study visit. Only one sample should be collected per subject for genetics during the study. Samples will be collected, labelled, stored and shipped as detailed in the Laboratory Manual.

Coding and Storage of DNA Samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years or as per local regulations, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood sample either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable by the second, unique number only. This number is used to identify the sample and corresponding data at the MedImmune genetics laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (MedImmune employee or designated organizations working with the DNA).

The link between the subject enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at MedImmune or designated organizations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 7 of the protocol.

Informed Consent

The genetic component of this study is optional, and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the originals filed at the study center. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the

subject understands that they may freely discontinue from the genetic aspect of the study at any time.

Subject Data Protection

MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, or their general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a MedImmune Physician or an investigator might know a subject's identity and also have access to his or her genetic data. Also, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data Management

Any genotype data generated in this study will be stored at a secure system at MedImmune and/or designated organizations to analyze the samples.

The results from this genetic research may be reported in a separate report from the CSR or published in scientific journals.

MedImmune and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organizations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical Methods and Determination of Sample Size

The number of subjects who will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan will be prepared where appropriate.

Appendix F Response Evaluation Criteria in Solid Tumors Version 1.1

F 1 Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions -** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
  - 10 mm caliper measurement by clinical examination (when superficial).
  - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.
- **Target Lesions -** At baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- **Non-target Lesions -** It is possible to record multiple non-target lesions involving the same organ as a single item (eg, “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).
- **New Lesions** - Though only certain new lesion measurements will be included in the tumor burden, all new lesions that can be accurately measured should be recorded. Up to 5 additional target lesions (maximum of 2 additional lesions per organ) may be added to the tumor burden at each postbaseline assessment to facilitate the exploratory iRECIST analysis. Other new lesions will be included into the non-tumor burden.

F 2 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.
- **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.)
- **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 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.

Evaluation of Overall Response

For the overall response based on RECIST v1.1, confirmation of CR and PR is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. If a subject discontinues the study due to PD and begins another treatment, a confirmatory scan is not required.

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

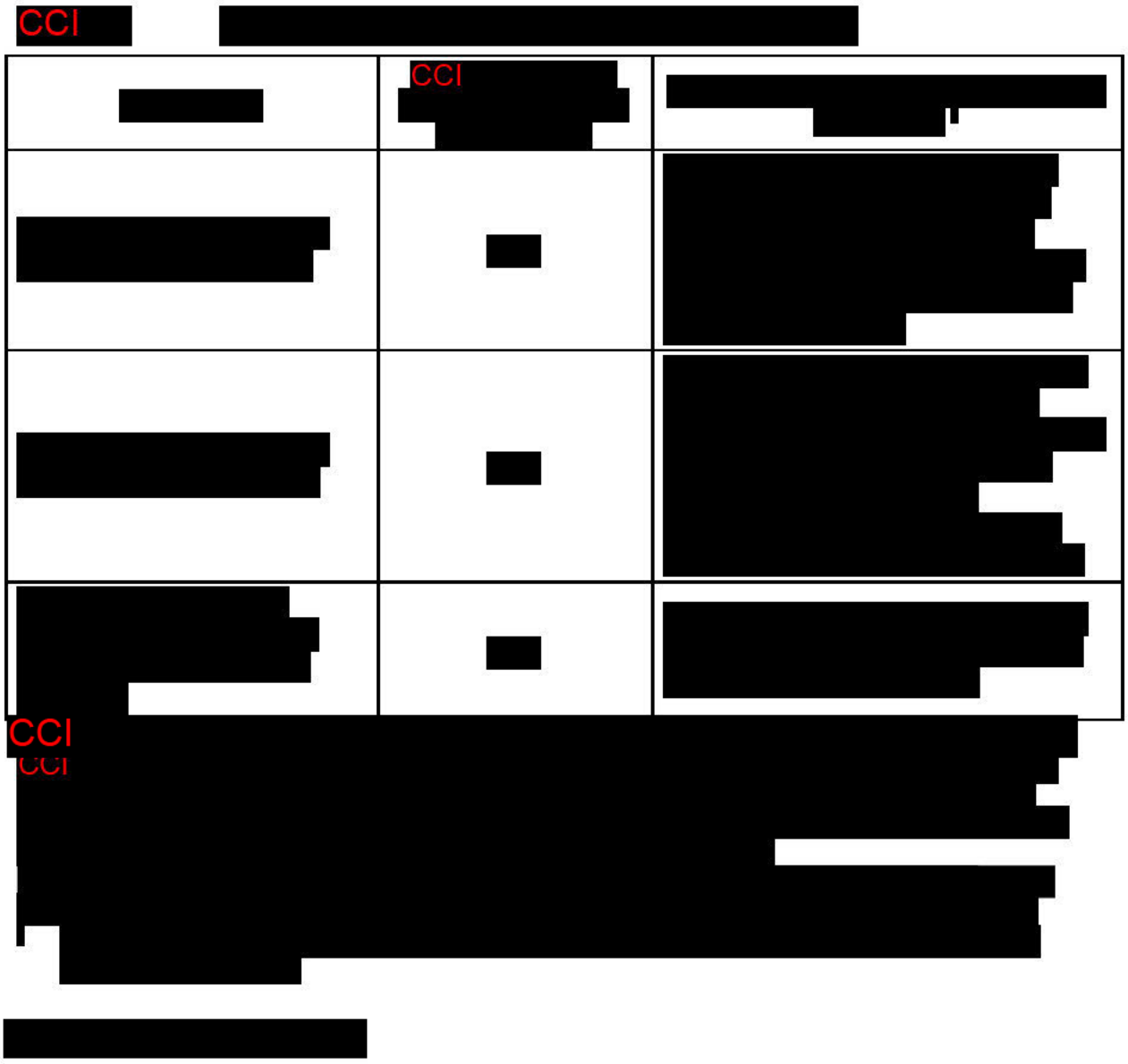
CCI

CCI

CCI .

CCI

	CCI	



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