A Multiarm, Open-label, Multicenter, Phase 1b/2 Study to Evaluate Novel Combination Therapies in Subjects with Previously Treated Advanced EGFRm NSCLC

Sponsor Protocol Number: D6070C00004

Application Number: IND 135539

Investigational Product: Oleclumab (MEDI9447), Osimertinib (Tagrisso®), and AZD4635

Sponsor: MedImmune, LLC, a wholly owned subsidiary of AstraZeneca PLC
One MedImmune Way
Gaithersburg, Maryland 20878
USA

Medical Monitor: PPD
MedImmune
Phone: PPD

Contract Research Organization: ICON Clinical Research Ltd

Protocol History, Date: Original Protocol, 31Aug2017
Amendment 1, 17Oct2017
Amendment 2, 01May2018
Amendment 3, 12Nov2018
Amendment 4, 01Feb2021

PROTOCOL SYNOPSIS

TITLE

A Multiarm, Open-label, Multicenter, Phase 1b/2 Study to Evaluate Novel Combination Therapies in Subjects with Previously Treated Advanced EGFRm NSCLC

HYPOTHESIS

Novel combinations of immunotherapeutics and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) will demonstrate adequate safety, tolerability, and antitumor activity in subjects with previously treated advanced epidermal growth factor receptor mutant (EGFRm) non-small cell lung cancer (NSCLC).

OBJECTIVES

Primary objectives:

Part 1:

- To investigate the safety and tolerability of novel combination therapies administered in subjects with advanced EGFRm NSCLC and confirm the combination dose(s) for further clinical evaluation

Part 2:

- To investigate the antitumor activity of novel combination therapies administered in subjects with advanced EGFRm NSCLC by evaluation of tumor response based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- To investigate the safety and tolerability of novel combination therapies administered in subjects with advanced EGFRm NSCLC

Secondary objectives:

Parts 1 and 2

1. To obtain a preliminary assessment of the antitumor activity of novel combination therapies administered in subjects with advanced EGFRm NSCLC by evaluation of tumor response based on RECIST version 1.1
2. To evaluate the antitumor activity of novel combination therapies administered in subjects with advanced EGFRm NSCLC based upon T790M testing at baseline confirmed by a central lab
3. To determine the pharmacokinetic (PK) profile of individual analytes of novel combination therapies (oleclumab [investigational name MEDI9447], osimertinib, and AZD4635) administered in subjects with advanced EGFRm NSCLC
4. To determine the immunogenicity of oleclumab administered in subjects with advanced EGFRm NSCLC

Exploratory objectives:

CCI

STUDY ENDPOINTS

Primary endpoints:

Part 1

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Dose-limiting toxicities (DLTs)
- Clinically meaningful changes from baseline in laboratory parameters, vital signs, and electrocardiogram (ECG) results

Part 2

- Objective response (OR) according to RECIST version 1.1
- Incidence of AEs and SAEs
- Clinically meaningful changes from baseline in laboratory parameters, vital signs, and ECG results

Secondary endpoints:

Parts 1 and 2:

- Duration of response (DoR), disease control (DC), progression-free survival (PFS), and overall survival (OS). RECIST version 1.1 will be used for assessment of tumor response.
- OR and DC by T790M status at baseline (determined by a central lab) in archival and/or fresh tumor biopsies
- Summary PK for all therapies and/or their metabolites
- Development of detectable antidrug antibodies (ADAs)

Exploratory endpoints:

CCI [redacted]

STUDY DESIGN

This is a multiarm, open-label, multicenter, Phase 1b/2 study to evaluate novel combination therapies in subjects with previously treated advanced EGFRm NSCLC. The study is divided into 2 parts. In Part 1 the safety and tolerability of novel combination therapies will be evaluated and a recommended Phase 2 dose (RP2D) for combination therapy will be identified. In Part 2 the safety, tolerability, and preliminary antitumor activity of novel combination therapies will be evaluated. Subjects will be treated in Arm A (oleclumab and osimertinib combination therapy) or Arm B (oleclumab and AZD4635 combination therapy). The allocation of subjects to treatment arms will be dependent upon the subject's EGFR mutation status and prior therapies.

A total of up to approximately 98 subjects will be enrolled in this study at approximately 15 sites globally: up to approximately 46 subjects in Arm A and up to approximately 52 subjects in Arm B.

Arm A will investigate the safety, tolerability, and antitumor activity of oleclumab given intravenously (IV) every 2 weeks (Q2W) in combination with osimertinib given orally (PO) once daily (QD) in subjects with advanced EGFRm NSCLC who have progressed on an approved first or second generation EGFR TKI therapy and who are T790M mutation negative and who have not received osimertinib.

During Part 1, dose escalation will be performed to determine the maximum tolerated dose (MTD) for oleclumab and osimertinib combination therapy. Dose escalation will begin with enrollment of at least 3 subjects (and up to 6 subjects) at dose level 1 (oleclumab 1500 mg IV Q2W and osimertinib 80 mg PO QD).

Enrollment will be staggered for the first 2 subjects so that the administration of the first dose of investigational product is separated by at least 24 hours. The dose escalation committee (DEC) will monitor subjects for DLTs during the 28-day DLT-evaluation period and will make decisions for enrollment of additional subjects at a dose level, dose escalation to the next dose level, or dose de-escalation.

If no DLTs are observed in a cohort of 3 to 6 evaluable subjects then dose escalation to the next higher dose cohort will be permitted after review of all available safety data. At dose level 1 only, dose escalation to the next higher dose cohort will be permitted after review of all available safety data from a minimum of 3 evaluable subjects in that treatment arm and a minimum of 6 evaluable subjects across both treatment arms (Arms A and B). If 1 subject in a dose-level cohort of 3 or more evaluable subjects experiences a DLT, that dose-level cohort will be expanded to a total of 6 subjects. If no more than 1 of 6 subjects in the dose-level cohort experiences a DLT, dose escalation will continue to the next higher dose-level cohort. If ≥ 2 subjects in a dose-level cohort experience a DLT, the MTD will be exceeded and no further subjects will be enrolled into that dose-level cohort. If this occurs, the preceding dose-level cohort will be evaluated for the MTD and a total of 6 subjects will be treated at the preceding dose level if not already expanded. If ≤ 1 of 6 subjects experiences a DLT at the preceding dose level, then this dose level will be the MTD.

Intra-subject dose escalation will not be allowed. Intra-subject dose de-escalation will not be allowed during the DLT-evaluation period.

If the MTD is exceeded at the starting dose level, then a lower dose level of oleclumab 750 mg Q2W and osimertinib 80 mg PO QD may be evaluated.

Based on emerging safety, efficacy, and PK data from this study as well as other ongoing studies of oleclumab and osimertinib, the sponsor may choose any safe dose for evaluation in Part 2 (Dose Expansion). Once the RP2D has been confirmed, enrollment into the Part 2 dose expansion may proceed. The DEC will continue to monitor the emerging data from the study.

To ensure subject safety, continuous monitoring of interstitial lung disease events that occur in subjects enrolled in Arm A will be performed during the study.

During Part 2 (Dose Expansion) the RP2D confirmed from Part 1 will be administered in approximately 10 to 40 subjects (including subjects dosed at the RP2D in Part 1). Continuous interim monitoring will begin after 10 subjects are response-evaluable (including subjects dosed at the RP2D in Part 1).

Arm B will investigate the safety, tolerability, and antitumor activity of oleclumab given IV Q2W in combination with AZD4635 PO QD in subjects with advanced EGFRm NSCLC who have received 2 to 4 lines of prior therapy and who have progressed on either an approved first or second generation EGFR TKI or osimertinib.

During Part 1, dose escalation will be performed to determine the MTD for oleclumab and AZD4635 combination therapy. Dose escalation will begin with enrollment of at least 3 subjects (and up to 6 subjects) at dose level 1 (oleclumab 1500 mg IV Q2W and AZD4635 75 mg PO QD). Enrollment will be staggered for the first 2 subjects so that the administration of the first dose of investigational product is separated by at least 24 hours. The DEC will monitor subjects for DLTs during the 28-day DLT-evaluation period and will make decisions for enrollment of additional subjects at a dose level, dose escalation to the next dose level, or dose de-escalation.

If no DLTs are observed in a cohort of 3 to 6 evaluable subjects then dose escalation to the next higher dose cohort will be permitted after review of all available safety data. At dose level 1 only, dose escalation to the next higher dose cohort will be permitted after review of all available safety data from a minimum of 3 evaluable subjects in that treatment arm and a minimum of 6 evaluable subjects across both treatment arms (Arms A and B). A minimum of 3 evaluable subjects will be required at subsequent dose levels. If 1 subject in a dose-level cohort of 3 or more evaluable subjects experiences a DLT, that dose-level cohort will be expanded to a total of 6 subjects. If no more than 1 of 6 subjects in the dose-level cohort experiences a DLT, dose escalation will continue to the next higher dose-level cohort. If ≥ 2 subjects in a dose-level cohort experience a DLT, the

MTD will be exceeded and no further subjects will be enrolled into that dose-level cohort. If this occurs, the preceding dose-level cohort will be evaluated for the MTD and a total of 6 subjects will be treated at the preceding dose level if not already expanded. If ≤ 1 of 6 subjects experiences a DLT at the preceding dose level, then this dose level will be the MTD.

Intra-subject dose escalation will not be allowed. Intra-subject dose de-escalation will not be allowed during the DLT-evaluation period.

If the MTD is exceeded at the starting dose level, then lower dose levels will be evaluated (see Treatment Groups and Regimens).

Based on emerging safety, efficacy, and PK data from this study as well as other ongoing studies of oleclumab and AZD4635, the sponsor may choose any safe dose for evaluation in Part 2 (Dose Expansion). Once the RP2D has been confirmed, enrollment into the Part 2 dose expansion may proceed. The DEC will continue to monitor the emerging data from the study.

During Part 2 (Dose Expansion) the RP2D confirmed from Part 1 will be administered in approximately 20 to 40 subjects (including subjects dosed at the RP2D in Part 1). Continuous interim monitoring will begin after 20 subjects are response-evaluable (including subjects dosed at the RP2D in Part 1).

TARGET SUBJECT POPULATION

Male or female subjects ≥ 18 years of age with histologically or cytologically-confirmed locally advanced/metastatic NSCLC with EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q). All subjects must have received and then progressed on at least one approved first or second generation EGFR TKI (eg, erlotinib or gefitinib [first generation] or afatanib [second generation]). Subjects in Arm A must have received 1 prior line of EGFR TKI therapy in the locally advanced/metastatic setting, be T790M mutation negative, and osimertinib naïve. Subjects in Arm B must have received at least 2 but not more than 4 prior lines of therapy in the locally advanced/metastatic setting.

NOTE: For subjects in Arm B who received osimertinib as first-line treatment, then treatment with a first or second generation EGFR TKI is not required, and these subjects may enroll after having received and progressed on osimertinib alone but can still have received no more than 4 prior lines of therapy.

TREATMENT GROUPS AND REGIMENS

For Arm A

- Part 1: Up to approximately 12 subjects will be treated in dose escalation. The planned dose levels are:
  - Dose Level 1 (3 to 6 subjects): Oleclumab 1500 mg IV Q2W and osimertinib 80 mg PO QD
  - Dose Level 2 (6 subjects): Oleclumab 3000 mg IV Q2W and osimertinib 80 mg PO QD
  - Dose Level -1 (3 to 6 subjects): If the MTD is exceeded at the starting dose level (dose level 1), a lower dose level of oleclumab 750 mg IV Q2W and osimertinib 80 mg PO QD may be evaluated.
- Part 2: The RP2D confirmed from Part 1 will be administered in approximately 10 to 40 subjects (including subjects dosed at the RP2D in Part 1).

For Arm B

- Part 1: Up to approximately 18 subjects will be treated in dose escalation. The planned dose levels are:
  - Dose Level 1 (3 to 6 subjects): Oleclumab 1500 mg IV Q2W and AZD4635 75 mg PO QD
  - Dose Level 2 (3 to 6 subjects): Oleclumab 3000 mg IV Q2W and AZD4635 75 mg PO QD
  - Dose Level 3 (6 subjects): Oleclumab 3000 mg IV Q2W and AZD4635 100 mg PO QD
  - If the MTD is exceeded at Dose Level 1:
    Dose Level -1 (3 to 6 subjects): Oleclumab 1500 mg IV Q2W and AZD4635 50 mg PO QD
    Dose Level -1a (6 subjects): Oleclumab 3000 mg IV Q2W and AZD4635 50 mg PO QD
  - If the MTD is exceeded at Dose Level -1:
    Dose Level -2 (3 to 6 subjects): Oleclumab 1500 mg IV Q2W and AZD4635 25 mg PO QD
    Dose Level -2a (6 subjects): Oleclumab 3000 mg IV Q2W and AZD4635 25 mg PO QD

- Part 2: The RP2D confirmed from Part 1 will be administered in approximately 20 to 40 subjects (including subjects dosed at the RP2D in Part 1).

All subjects will remain on their respective treatments until documentation of disease progression, intolerable toxicity, or other reason for subject withdrawal develops. The assigned investigational product may be continued in the setting of progressive disease (PD) as long as the subject does not meet any of the investigational product discontinuation criteria and the treatment criteria in the setting of PD are met. Subjects with PD who are eligible to continue receiving investigational product will be made aware of the potential benefits and risks of continuing treatment in the setting of PD and must provide a separate written informed consent prior to treatment.

STATISTICAL METHODS

Sample size: A total of up to approximately 98 subjects will be enrolled in this study: up to approximately 46 subjects in Arm A and up to approximately 52 subjects in Arm B.

Statistical analyses:

Safety

Safety data, including DLTs, AEs, SAEs, laboratory evaluations, vital signs, cardiac left ventricular function (Arm A only), and ECG results will be summarized based on the As-treated Population, defined as all subjects who receive any investigational product, analyzed according to treatment received. Summary statistics will be provided for AEs, SAEs, AE grade (severity) and relationship to investigational product(s), clinical laboratory parameters, vital signs, cardiac left ventricular function (Arm A only), and ECG. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Efficacy

The efficacy analyses of antitumor activity will be based on the As-treated Population. The rates of OR and DC based on RECIST version 1.1 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. Additional analyses of antitumor activity may be conducted in the Response-evaluable Population, defined as all subjects who receive any investigational product, had measurable disease at baseline and at least 1 post-baseline tumor assessment, or who died from any cause or who discontinued due to clinical PD prior to any post-baseline tumor assessment.

Pharmacokinetics

Individual concentrations will be tabulated by dose cohort along with descriptive statistics. Non-compartmental PK data analysis will be performed from each dose cohort with scheduled PK sample collection where data allow. Relevant descriptive statistics of non-compartmental PK parameters will be provided for individual compounds.

Anti-drug antibodies/immunogenicity

For each arm, the immunogenic potential of oleclumab will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs. CCI [redacted] Samples will be collected for potentially evaluating the neutralizing capacity of ADAs in the future.
CCI [redacted]
CCI [redacted]

Interim analysis: Bayesian predictive probabilities will be used for continuous interim monitoring by estimating the probability of observing a targeted treatment effect or futility of the treatment if the trial were to continue to its predefined maximum sample size.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
A_1R	adenosine 1 receptor
$A_{2A}R$	adenosine2A receptor
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AMP	adenosine monophosphate
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	Area under the concentration-time curve
BID	twice daily
BP	blood pressure
CD	cluster of differentiation
CI	confidence interval
CL	clearance
CL/F	Apparent plasma clearance
C_{max}	maximum observed concentration
CT	computed tomography
C_{trough}	trough plasma concentration
CNS	central nervous system
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
CCI	CCI
CV	coefficient of variation
CYP	cytochrome P
DC	disease control
DCR	disease control rate
DEC	Dose Escalation Committee
DHEA	dehydroepiandrosterone
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram

Abbreviation or Specialized Term	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EGFR	epidermal growth factor receptor
EGFRm	epidermal growth factor receptor mutant
FTIH	first-time-in-human
GCP	good clinical practice
GI	gastrointestinal
GLP	Good Laboratory Practice
HRCT	high resolution computed tomography
IC_{50}	concentration giving half-maximal inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
Ig	immunoglobulin
ILD	interstitial lung disease
imAE	immune-mediated adverse event
IO	immuno-oncology
IRB	Institutional Review Board
CCI	CCI [redacted]
CCI	CCI [redacted]
CCI	CCI [redacted]
IRR	infusion-related reaction
iRECIST	Immune Response Evaluation Criteria in Solid Tumors
IV	intravenous(ly)
IXRS	interactive voice response system/interactive web response system
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MDSC	myeloid-derived suppressor cell
MRI	magnetic resonance imaging
MSS-CRC	microsatellite stable colorectal cancer
MTD	maximum tolerated dose
MUGA	multigated acquisition scan

Abbreviation or Specialized Term	Definition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PART	Post Analysis and Reporting Team
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	per os (orally)
PR	partial response
Q2W	every 2 weeks
Q4W	every 4 weeks
QD	once daily
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia's formula
RP2D	recommended Phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SID	subject identification
TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal half-life
TBL	total bilirubin
TKI	tyrosine kinase inhibitor
t_{max}	time to reach C_{max}
Treg	regulatory T cells
ULN	upper limit of normal
V_z/F	apparent volume of distribution
w/v	weight/volume

1 INTRODUCTION

1.1 Disease Background

Lung cancer is the most common and lethal cancer worldwide with an estimated 1.83 million new cases annually resulting in 1.59 million deaths (GLOBOCAN, 2015). The majority (80% to 85%) of these cases are non-small cell lung cancer (NSCLC). Unfortunately, most patients present with advanced or metastatic disease not amenable to curative treatments. Furthermore, many of the patients treated for early stage disease will have recurrence and die as a result of their lung cancer (Pisters and Le Chevalier, 2005).

Patients presenting with advanced NSCLC have a median overall survival (OS) of 10 to 12 months (Bonomi, 2010). However, outcomes can be significantly better for patients whose tumors are found to harbor certain targetable molecular drivers such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase or ROS1 gene rearrangements. Approximately, 10% of Caucasian patients and up to 50% of Asian patients with NSCLC will harbor a targetable activating EGFR mutation, the most common of which are L858R and deletions in exon 19 (Ettinger et al, 2017). For these subjects, EGFR tyrosine kinase inhibitors (TKIs) are now the established first-line therapy and result in an objective response rate (ORR) of approximately 70% (Oxnard and Miller, 2010). Unfortunately, TKI resistance is inevitable and the median progression-free survival (PFS) is only 8 to 13 months (Mok, 2011). The emergence of a secondary T790M mutation in patients treated with a first-generation EGFR TKI agent has been described as a major route of development of resistance (Kobayashi et al, 2005; Pao et al, 2005) in approximately 60% of patients (Yu et al, 2013). Second-line therapy for epidermal growth factor receptor mutant (EGFRm) NSCLC is dependent upon the presence or absence of the T790M mutation. Second-line therapy options include a third generation EGFR TKI such as osimertinib (Tagrisso®) for those with a T790M mutation, or platinum-based chemotherapy for those that lack the T790M mutation. In a Phase 3 trial of patients with an EGFRm T790M mutation comparing osimertinib to platinum-doublet therapy the ORRs were 71% and 31% with a median PFS of 10.1 and 4.4 months, respectively (Mok et al, 2017). Currently, there is no global standard of care for third-line therapy in T790M negative patients or fourth-line therapy in T790M positive patients who have previously received osimertinib, but this may include single-agent chemotherapy, therapy with an alternative EGFR TKI not used during the initial treatment, or anti-programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) monotherapy (Becker et al, 2011; Ettinger et al, 2017; Langer et al, 2013; Novello et al 2016).

1.2 Oleclumab, Osimertinib, and AZD4635 Background

Oleclumab (investigational name MEDI9447), osimertinib, and AZD4635 are briefly described below. Refer to the respective current Investigator's Brochures for details.

1.2.1 Oleclumab Background

Oleclumab is a human immunoglobulin (Ig) G1 lambda monoclonal antibody (mAb) that selectively binds to and inhibits the ectonucleotidase activity of cluster of differentiation (CD)73. The triple mutation, L234F/L235E/P331S (according to European Union numbering convention), is encoded in the heavy chain constant region to significantly reduce IgG effector function. Oleclumab inhibits the catalysis of adenosine monophosphate (AMP) to adenosine and organic phosphate by CD73. Extracellular adenosine contributes to the immunosuppressive effects of both regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), among others (Antonioli et al, 2013). The enzymatic blockade of CD73 caused by binding of oleclumab to CD73 may lead to increased antitumor immunity.

1.2.2 Osimertinib Background

Osimertinib is a potent, selective, central nervous system (CNS)-active, irreversible inhibitor of both the single EGFRm (TKI sensitivity conferring mutation) and dual EGFRm/T790M (TKI resistance conferring mutation) receptor forms of EGFR with a wide margin of selectivity against EGFR wild-type (Ballard et al, 2016; Cross et al, 2014; Goss et al, 2017; Ward et al, 2013; Yang et al, 2017). Therefore, osimertinib has the potential to provide clinical benefit to patients with advanced NSCLC harboring both the single sensitivity mutations and the resistance mutation following prior therapy with an EGFR TKI. Osimertinib is currently approved in 50 countries including the United States and South Korea for the treatment of patients with EGFR T790M mutation who have progressed on prior EGFR TKI therapy.

1.2.3 AZD4635 Background

AZD4635 is a potent, selective adenosine$_{2A}$ receptor ($A_{2A}R$) antagonist. Adenosine, produced by CD73 catalysis of AMP or other extracellular enzymes, binds to $A_{2A}R$ and suppresses an immune response in order to limit tissue injury (Leone et al, 2015). AZD4635 blocks the ability of adenosine to bind $A_{2A}R$ in a dose-dependent manner and clinical trials have demonstrated that $A_{2A}R$ receptor blockade in humans leads to immune activation in the tumor microenvironment (Emens et al, 2017).

1.3 Summary of Nonclinical Experience

The nonclinical experience with oleclumab, osimertinib, and AZD4635 is briefly described below. Refer to the respective current Investigator's Brochures for additional details.

1.3.1 Oleclumab Nonclinical Experience

In nonclinical studies, oleclumab has been shown to:

- CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- CCI [redacted]
- Activate the myeloid compartment of spleens from syngeneic CT26 tumor-bearing mice when administered in combination with anti-PD-1

CCI [redacted] As CD73 is found in most tissues (Colgan et al, 2006; Resta et al, 1998; Zhang B., 2010), the widespread immunoreactivity of oleclumab in this study was anticipated.

The ability of oleclumab (alone or in combination with durvalumab [investigational name MEDI4736; anti-PD-L1 mAb]) to induce cytokine release was evaluated in human in vitro assays using blood or peripheral blood mononuclear cell from healthy donors. Oleclumab alone or in combination with durvalumab, presented in solution or immobilized on plastic wells by dry-coating, did not induce cytokine release.

1.3.2 Osimertinib Nonclinical Experience

Carcinogenicity studies have not been performed with osimertinib. Osimertinib did not cause genetic damage in in vitro and in vivo assays.

CCI

[redacted]

1.3.3 AZD4635 Nonclinical Experience

Key findings from the nonclinical pharmacology testing include:

- AZD4635 is a potent, highly selective inhibitor of $A_{2A}R$.
- AZD4635 blocks cyclic AMP production in a dose-dependent manner.
- AZD4635 decreases adenosine's suppressive effect on T cells as noted by restoration of CD8+ cell proliferation and interferon gamma secretion in in vitro assays.

CCI

[redacted]

- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

CCI

- CCI
- CCI
- CCI
- CCI

- CCI [redacted]
- CCI [redacted]

1.4 Summary of Clinical Experience

The clinical experience with oleclumab, osimertinib, and AZD4635 is briefly described below. Refer to the respective current Investigator's Brochures for details.

1.4.1 Oleclumab Clinical Experience

1.4.1.1 Study D6070C00001

Study D6070C00001 is a first-time-in-human (FTIH), Phase 1, multicenter, open-label, dose-escalation, and dose-expansion study of oleclumab to be administered as a single agent or in combination with durvalumab in adult subjects with selected advanced solid tumors. CCI [redacted]

CCI

[redacted]

CCI

[redacted]

[redacted]

[redacted]

1.4.1.2 Study D6070C00004

Arm A

CCI

[redacted]

Arm B

1.4.2 Osimertinib Clinical Experience

The clinical experience of osimertinib is summarized below. Additional information is available in the Investigator's Brochure and the local Health Authority approved Prescribing Information.

CCI

CCI

CCI

- CCI
  - CCI
  - CCI
  - CCI
  - CCI
  - CCI
  - CCI

CCI

- CCI
- CCI

- CCI
- CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

CCI

1.4.3 AZD4635 Clinical Experience

A FTIH study of AZD4635 (D8730C00001) is currently being conducted.
Study D8730C0001 is a Phase 1, open-label, multicenter study to assess the safety, tolerability, PK, and preliminary antitumor activity of ascending doses of AZD4635 both as

monotherapy and in combination with durvalumab in subjects with advanced solid malignancies.

CCI

- CCI
  - CCI
  - CCI
  - CCI
- CCI
  - CCI
  - CCI

CCI

CCI

CCI

1.5 Rationale for Conducting the Study

This is an open-label, multiarm, multicenter, Phase 1b/2 study to evaluate novel combination therapies in subjects with previously treated advanced EGFRm NSCLC.

Despite therapeutic advances in recent years with both targeted and immunotherapeutic agents, patients who present with metastatic NSCLC still have poor OS. Of the 1.8 million new cases of NSCLC worldwide each year, approximately, 10% of Caucasian patients and up to 50% of Asian patients with NSCLC will harbor an activating EGFR mutation that serves as the molecular driver of their cancer. Notably, these mutations are more likely to be found in younger, never smokers, and females as compared to the overall population afflicted by NSCLC (Ettinger et al, 2017; Novello et al, 2016).

Upon progression after the standard of care EGFR TKI, most patients will receive second-line (T790M negative) or third-line (T790M positive, treated with osimertinib) platinum-based chemotherapy. This generally provides response rates in the range of 25% to 35% with a median PFS of 3 to 6 months (Goldberg et al, 2012; Gridelli et al, 2012; Maemondo et al, 2010; Mok et al, 2014; Mok et al, 2017; Wang et al, 2012b; Wu et al, 2011). However, this therapy is accompanied by the typical toxicities associated with cytotoxic therapies including nausea, vomiting, bone marrow suppression, alopecia, fatigue, and peripheral neuropathy.

Furthermore, there is no global standard of care for later lines of therapy but options include single-agent chemotherapy, therapy with an alternative EGFR TKI not used during the initial treatment, anti-PD-1/PD-L1 monotherapy, or clinical trials. In unselected NSCLC patients who progressed on prior platinum-containing doublet chemotherapy, low response rates (approximately 10%) and short PFS (median PFS, approximately 2 to 3 months) were observed after treatment with single agent chemotherapy such as docetaxel or pemetrexed (Alimita Prescribing Information, 2015; Taxotere Prescribing Information, 2016). Re-treatment with an EGFR TKI (eg, switching to erlotinib following failure of gefitinib, or to afatinib following failure of erlotinib or gefitinib, or re-treatment with the same EGFR TKI after a period off drug) provided low response rates (approximately 10%) and PFS in a similar range to that of single agent chemotherapy (Hata et al, 2011; Lee et al, 2013; Miller et al, 2012). Similarly, anti-PD-1/PD-L1 inhibitors have demonstrated low response rates (approximately 10%) and their role in the treatment of EGFRm NSCLC is still being elucidated (Garassino et al, 2017; Lee et al, 2017). Other novel agents and combinations have tried to overcome the acquired resistance to EGFR TKIs with response rates generally lower than 10% (eg, EGFR TKI plus everolimus: response rate, 0% (Riely et al, 2007); neratinib response rate, 3% (Sequist et al, 2010a), IPI 504 response rate, 4% (Sequist et al, 2010b).

There is a considerable unmet clinical need for well-tolerated, efficacious therapeutic options, with minimal side effects, that build upon the molecular aberrations that are specific for patients with EGFRm NSCLC following progression on EGFR TKI therapy and to delay the initiation of chemotherapy and its long term consequences.

Immunotherapy in EGFRm NSCLC

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to grow and metastasize unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. PD-L1 is one such protein, and is expressed in a broad range of cancers. This inhibits immune activating signals by binding and signaling through PD-1 and CD80 receptors on T cells. The use of mAbs against PD-L1 or PD-1 to block this interaction and the subsequent inhibitory signals has led to significant improvement in the treatment of NSCLC (Brahmer et al, 2015; Fehrenbacher et al, 2016; Herbst et al, 2016). Unfortunately, patients with EGFRm NSCLC have not realized the same benefits from treatment with single-agent anti-PD-1 or PD-L1 therapy as the subset analyses have demonstrated no improvement in survival over chemotherapy (Brahmer et al, 2015; Rittmeyer et al, 2017). This suggests that EGFRm NSCLC has developed different mechanisms of immune escape compared to EGFR wild-type tumors necessitating innovative treatment combinations to restore antitumor immunity.

CD73 Blockade in EGFRm NSCLC

Adenosine is a regulatory autocrine and paracrine factor that accumulates in the tumor microenvironment, influencing immune activity, angiogenesis, and metastasis (Antonioli et al, 2013). 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. In order to prevent an immune reaction stimulated by cell death, tissues express CD39 and CD73 to enzymatically convert ATP to adenosine which induces a localized immunosuppressive response through pleotropic effects upon multiple immune cell types. Elevated levels of extracellular adenosine have been reported within the tumor microenvironment, in part due to up-regulation of CD73 within cancerous tissues (Zhang, 2010).

One mechanism by which EGFRm tumors may have evolved to evade the immune system is via overexpression of CD73. Recent investigations found that CD73 overexpression was more frequent in EGFRm NSCLC as compared to EGFR wild-type NSCLC (Inoue et al, 2017). Furthermore, CD73 overexpression was found to be an independent predictor of poor survival in 642 resected NSCLC specimens (Inoue et al, 2017). CD73 overexpression in EGFRm NSCLC has been further corroborated and confirmed by an independent analysis conducted by MedImmune of The Cancer Genome Atlas database as well as profiling of both messenger RNA and protein expression in previously collected samples (Liu et al, 2012; Streicher et al, 2017; Wu et al, 2012). Of note, the majority of these samples were from resected specimens and thus were TKI-naïve. In addition to the results in NSCLC, tumor overexpression of CD73 has also been associated with poor prognosis in other malignancies including colorectal cancer (Liu et al, 2012; Wu et al, 2012), triple-negative breast cancer (Loi et al, 2013), renal cell carcinoma (Yu et al, 2015), gastric cancer (Lu et al, 2013), high-grade serous ovarian cancer (Turcotte et al, 2015), head and neck squamous cell carcinoma (Ren et al, 2016), or with metastasis in prostate cancer (Yang et al, 2013) and melanoma (Wang et al, 2012a). Thus, there is sufficient data to support the hypothesis of combining anti-CD73 blockade with other treatment modalities for advanced EGFRm NSCLC to restore antitumor immunity.

This study will help to identify a novel therapeutic strategy for EGFRm NSCLC by investigating combinations of both approved and investigational agents (immunotherapy + TKI and immuno-oncology [IO]-IO) to improve clinical outcomes.

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 Conference of Harmonisation (ICH)/Good Clinical Practice (GCP), and applicable regulatory requirements.

Potential benefits

Oleclumab is a human immunoglobulin IgG1 lambda mAb that selectively binds to and inhibits the ectonucleotidase activity of CD73. Oleclumab inhibits the catalysis of AMP to adenosine and organic phosphate by CD73. The enzymatic blockade of CD73 caused by binding of oleclumab to CD73 may lead to increased antitumor immunity. Preliminary data from study D6070C00001 demonstrate that treatment with oleclumab is well tolerated (Section 1.4.1) and leads to a reduction in CD73 expression on circulating immune cells. As CD73 overexpression has been identified as a possible mechanism of immune escape for EGFRm NSCLC, oleclumab is a potential candidate to be combined with other active and novel agents to reduce CD73 expression and block adenosine-mediated immunosuppression thereby enhancing the therapeutic response.

Osimertinib is a potent, selective, CNS-active, irreversible inhibitor of both the single EGFRm and dual EGFRm/T790M receptor forms of EGFR with a significant selectivity margin over wild-type EGFR. Efficacy and safety findings in the AURA3 trial have shown that osimertinib has superior efficacy and a more favorable safety profile compared with platinum-doublet chemotherapy in patients with EGFR T790M mutation positive NSCLC who have progressed on prior EGFR-TKI therapy. These findings for osimertinib were supported by efficacy and safety data in the AURA Extension and AURA2 trials. Additionally, the AURA trial (Phase 1 component) demonstrated that subjects with EGFRm T790M negative NSCLC had an ORR of 24.6% across all osimertinib doses (20 to 240 mg QD) and 20.7% at osimertinib 80 mg QD (Section 1.4.2).

AZD4635 is a novel $A_{2A}R$ antagonist agent that acts against cancer by blocking adenosine-mediated $A_{2A}R$ signaling in tumor infiltrating cells. AZD4635 blockade is hypothesized to modulate the tumor microenvironment so that an active antitumor immune response will be more effective. Therefore, AZD4635 may have the potential to provide benefit in terms of increased efficacy in subjects with advanced EGFRm NSCLC. Additionally, synergistic antitumor activity was demonstrated by the dual blockade of CD73 and $A_{2A}R$ in preclinical studies (Young et al, 2016). There is no standard of care for third-line therapy (T790M negative patients) or fourth-line therapy (T790M positive patients who have previously received osimertinib) for EGFRm NSCLC. The most common treatment is docetaxel with an ORR of approximately 10%, however, this therapy has a significant toxicity profile. In the advanced cancer setting, prolonged survival rates are very low and there is considerable unmet clinical need for novel therapeutic agents and combinations (Section 1.5). The combination of oleclumab and AZD4635 to block the adenosine pathway may lead to antitumor activity in subjects with EGFRm NSCLC.

Potential risks

CCI [redacted]

The study design aims to minimize potential risks to subjects participating in this study based on the protocol inclusion and exclusion criteria (Sections 4.1.2 and 4.1.3), restrictions on concomitant medication during the study (Section 4.8), safety monitoring (including review of all safety, PK, and other relevant data by the Dose Escalation Committee [DEC]) (Sections 3.1.3 and 5), toxicity management guidelines (Section 3.1.4), starting dose selection (Section 3.2.1), dose escalation scheme (Section 3.1.2), and stopping criteria (Section 4.5). Specific intensive safety monitoring is in place (Sections 3.1.4 and 5.3) for those risks deemed to be most likely.

1.7 Research Hypotheses

Novel combinations of immunotherapeutics and EGFR TKIs will demonstrate adequate safety, tolerability, and antitumor activity in subjects with previously treated advanced EGFRm NSCLC.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives and Associated Endpoints

Type	Objective	Endpoint
Part 1		
Safety	To investigate the safety and tolerability of novel combination therapies administered in subjects with advanced EGFRm NSCLC and confirm the combination dose(s) for further clinical evaluation	• Incidence of AEs and SAEs • DLTs • Clinically meaningful changes from baseline in laboratory parameters, vital signs, and ECG results
Part 2		
Efficacy	To investigate the antitumor activity of novel combination therapies administered in subjects with advanced EGFRm NSCLC by evaluation of tumor response based on RECIST version 1.1	• OR, according to RECIST version 1.1
Safety	To investigate the safety and tolerability of novel combination therapies administered in subjects with advanced EGFRm NSCLC	• Incidence of AEs and SAEs • Clinically meaningful changes from baseline in laboratory parameters, vital signs, and ECG results

AE = adverse event; DLT = dose-limiting toxicity; ECG = electrocardiogram; EGFRm = epidermal growth factor receptor mutant; NSCLC = non-small cell lung cancer; OR = objective response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event.

2.2 Secondary Objectives and Associated Endpoints

Type	Objective	Endpoint
Parts 1 and 2		
Efficacy	To obtain a preliminary assessment of the antitumor activity of novel combination therapies administered in subjects with advanced EGFRm NSCLC by evaluation of tumor response based on RECIST version 1.1	• DoR, DC, PFS, and OS. RECIST version 1.1 will be used for assessment of tumor response.
	To evaluate the antitumor activity of novel combination therapies administered in subjects with advanced EGFRm NSCLC based upon T790M testing at baseline confirmed by a central lab	• OR and DC by T790M status at baseline (determined by a central lab) in archival and/or fresh tumor biopsies
Pharmacokinetic	To determine the PK profile of individual analytes of novel combination therapies (oleclumab, osimertinib, and AZD4635) administered in subjects with advanced EGFRm NSCLC	• Summary PK for all therapies and/or their metabolites
Immunogenicity	To determine the immunogenicity of oleclumab administered in subjects with advanced EGFRm NSCLC	• Development of detectable ADAs

ADA = antidrug antibody(ies); DC = disease control; DLT = dose-limiting toxicity; DoR = duration of response; ECG = electrocardiogram; EGFRm = epidermal growth factor receptor mutant; NSCLC = non-small cell lung cancer; OR = objective response; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors.

2.3 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

This is a multiarm, open-label, multicenter, Phase 1b/2 study to evaluate novel combination therapies in subjects with previously treated advanced EGFRm NSCLC. The study is divided into 2 parts. In Part 1 the safety and tolerability of novel combination therapies will be evaluated and a RP2D for combination therapy will be identified. In Part 2 the safety, tolerability, and preliminary antitumor activity of novel combination therapies will be evaluated. Subjects will be treated in Arm A (oleclumab and osimertinib combination

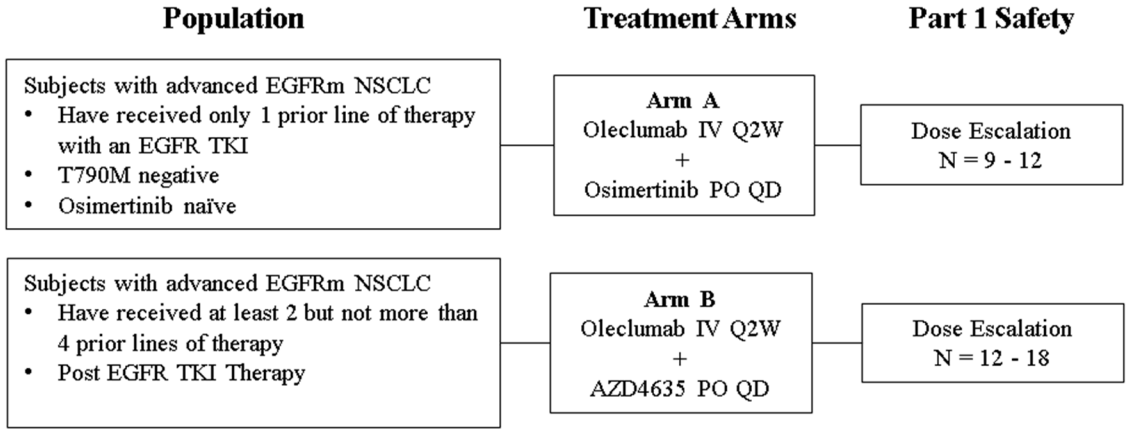
therapy) or Arm B (oleclumab and AZD4635 combination therapy). The allocation of subjects to treatment arms will be dependent upon the subject's EGFR mutation status and prior therapies. Additional treatment arms may be added as part of this multidrug protocol as decisions on the most appropriate combinations to use become available and as the scientific understanding of EGFRm NSCLC develops. A substantial protocol amendment with relevant nonclinical and clinical data will be put in place before starting a new combination treatment arm.

A total of up to approximately 98 subjects will be enrolled in this study at approximately 15 sites globally: up to approximately 46 subjects in Arm A and up to approximately 52 subjects in Arm B.

During Part 2 dose expansion, Bayesian predictive probabilities will be used for continuous interim monitoring analysis for efficacy and safety. Subjects dosed at the RP2D in Part 1 will be included in this analysis (Section 4.9.8).

The study flow is presented in Figure 1 for Part 1 and in Figure 2 for Part 2.

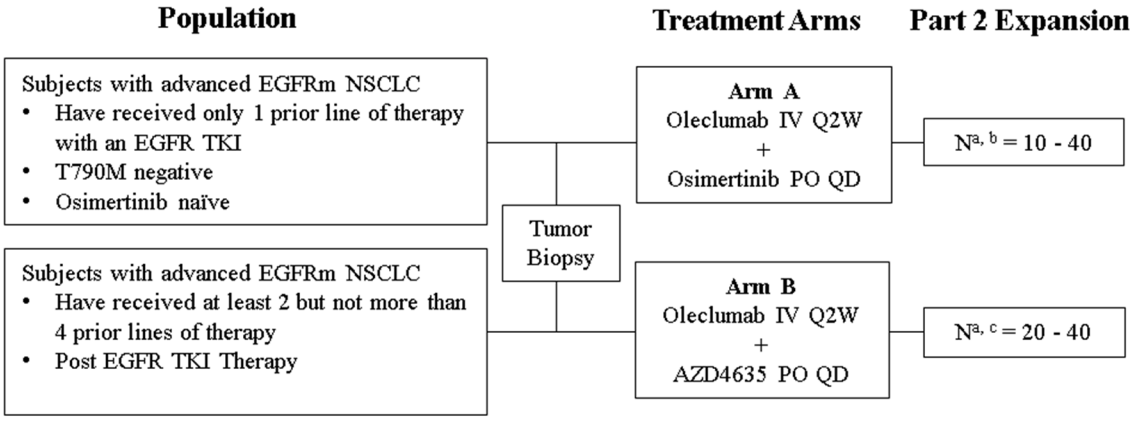
Figure 1 Study Flow Diagram for Part 1: Dose Escalation



EGFRm = epidermal growth factor receptor mutant; EGFR TKI = epidermal growth factor receptor tyrosine kinase inhibitor; IV = intravenously; N = number; NSCLC = non-small cell lung cancer; PO = orally; Q2W = every 2 weeks; QD = once daily.

NOTE: For both Arms A and Arm B, subjects must have received treatment with an approved first or second generation EGFR TKI except for subjects in Arm B who received osimertinib as first-line treatment, in which case, treatment with a first or second generation EGFR TKI is not required, and these subjects may enroll after having received and progressed on osimertinib alone (but can still have received no more than 4 prior lines of therapy).

Figure 2 Study Flow Diagram for Part 2: Dose Expansion



EGFRm = epidermal growth factor receptor mutant; EGFR TKI = epidermal growth factor receptor tyrosine kinase inhibitor; IV = intravenously; N = number; NSCLC = non-small cell lung cancer; PO = orally; Q2W = every 2 weeks; QD = once daily; RP2D = recommended Phase 2 dose.

NOTE: For both Arms A and Arm B, subjects must have received treatment with an approved first or second generation EGFR TKI except for subjects in Arm B who received osimertinib as first-line treatment, in which case, treatment with a first or second generation EGFR TKI is not required, and these subjects may enroll after having received and progressed on osimertinib alone (but can still have received no more than 4 prior lines of therapy).

Response-evaluable subjects are subjects who receive any investigational product, had measurable disease at baseline and at least 1 post-baseline tumor assessment, or who died from any cause or who discontinued due to clinical progressive disease prior to any post-baseline tumor assessment.

[a] Including subjects dosed at the RP2D in Part 1

[b] Arm A: Continuous interim monitoring will begin after 10 subjects are response-evaluable (including subjects dosed at the RP2D in Part 1).

[c] Arm B: Continuous interim monitoring will begin after 20 subjects are response-evaluable (including subjects dosed at the RP2D in Part 1).

The endpoints to be measured in this study are described in Section 2.

3.1.2 Treatment Regimen

The treatment arms are described below. All subjects will remain on their respective treatments until documentation of disease progression, intolerable toxicity, or other reason for subject withdrawal develops (Section 4.1.6).

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive investigational product. Investigational product will be provided via an extension of the study, a rollover study requiring approval by a responsible health authority and ethics committee, or through another mechanism at the discretion of the sponsor. The sponsor reserves the right to terminate access to investigational product if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a

government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.1.2.1 Treatment Regimen: Arm A

Arm A will investigate the safety, tolerability, and antitumor activity of oleclumab IV Q2W in combination with osimertinib PO QD in subjects with advanced EGFRm NSCLC who have progressed on an approved first or second generation EGFR TKI therapy and who are T790M mutation negative and who have not received osimertinib.

During Part 1, dose escalation will be performed to determine the MTD for oleclumab and osimertinib combination therapy. Dose escalation will begin with enrollment of at least 3 subjects (and up to 6 subjects) at dose level 1 (oleclumab 1500 mg IV Q2W and osimertinib 80 mg PO QD) (Table 1). The DEC (Section 3.1.3.1) will monitor subjects for DLTs during the DLT-evaluation period as defined in Section 3.1.3.3. Enrollment of additional subjects at a dose level, dose escalation to the next dose level, or dose de-escalation will progress according to the rules outlined in Section 3.1.3.2. If the MTD is exceeded at the starting dose level, then a lower dose level of oleclumab 750 mg Q2W and osimertinib 80 mg QD may be evaluated (Table 1).

Based on emerging safety, efficacy, and PK data from this study as well as other ongoing studies of oleclumab and osimertinib, the sponsor may choose any safe dose for evaluation in Part 2 (Dose Expansion). Once the RP2D has been confirmed, enrollment into the Part 2 dose expansion may proceed. The DEC will continue to monitor the emerging data from the study.

Table 1 Arm A Combination Therapies and Dose Levels (Part 1: Dose Escalation)

Agents	Dose Level [a]		
	Dose Level -1 N = 3-6 subjects	**Dose Level 1 [b] N = 3-6 subjects**	**Dose Level 2 N = 6 subjects**
Oleclumab	750 mg IV Q2W	1500 mg IV Q2W	3000 mg IV Q2W
Osimertinib	80 mg PO QD	80 mg PO QD	80 mg PO QD

IV = intravenously; PO = orally; QD = once daily; Q2W = every 2 weeks.

[a] Administration of the first dose of investigational product must be staggered by a minimum of 24 hours for the first 2 subjects in each dose level.

[b] Starting dose level

Continuous monitoring of ILD events will be performed as described in Section 4.9.7.

During Part 2 (Dose Expansion), the RP2D confirmed from Part 1 will be administered in approximately 10 to 40 subjects (including subjects dosed at the RP2D in Part 1). Continuous interim monitoring will begin after 10 subjects are response-evaluable (including subjects dosed at the RP2D in Part 1) (Sections 4.9.1 and 4.9.8).

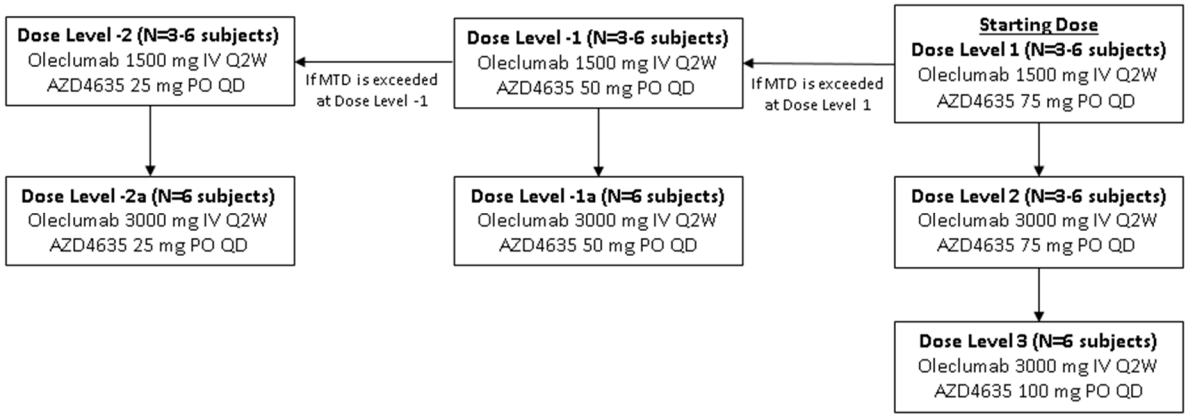
3.1.2.2 Treatment Regimen: Arm B

Arm B will investigate the safety, tolerability, and antitumor activity of oleclumab IV Q2W in combination with AZD4635 PO QD in subjects with advanced EGFRm NSCLC who have received 2 to 4 lines of prior therapy and who have progressed on either an approved first or second generation EGFR TKI or osimertinib.

During Part 1, dose escalation will be performed to determine the MTD for oleclumab and AZD4635 combination therapy. Dose escalation will begin with enrollment of at least 3 subjects (and up to 6 subjects) at dose level 1 (oleclumab 1500 mg IV Q2W and AZD4635 75 mg PO QD) (Figure 3). The DEC (Section 3.1.3.1) will monitor subjects for DLTs during the DLT-evaluation period as defined in Section 3.1.3.3. Enrollment of additional subjects at a dose level, dose escalation to the next dose level, or dose de-escalation will progress according to the rules outlined in Section 3.1.3.2. If the MTD is exceeded at the starting dose level, then lower dose levels will be evaluated as shown in Figure 3.

Based on emerging safety, efficacy, and PK data from this study as well as other ongoing studies of oleclumab and AZD4635, the sponsor may choose any safe dose for evaluation in Part 2 (Dose Expansion). Once the RP2D has been confirmed, enrollment into the Part 2 dose expansion may proceed. The DEC will continue to monitor the emerging data from the study.

Figure 3 Arm B Combination Therapies and Dose Levels (Part 1: Dose Escalation)



IV = intravenous; MTD = maximum tolerated dose; PK = pharmacokinetic; PO = oral; QD = once daily; Q2W = every 2 weeks.

Administration of the first dose of investigational product must be staggered by a minimum of 24 hours for the first 2 subjects in each dose level.

Based on emerging safety, efficacy, and PK data from this study as well as other ongoing studies of oleclumab and AZD4635, the sponsor may choose any safe dose for evaluation in Part 2 (Dose Expansion).

During Part 2 (Dose Expansion) the RP2D confirmed from Part 1 will be administered in approximately 20 to 40 subjects (including subjects dosed at the RP2D in Part 1). Continuous

interim monitoring will begin after 20 subjects are response-evaluable (including subjects dosed at the RP2D in Part 1) (Sections 4.9.1and 4.9.8).

3.1.3 Dose Escalation, Cohort Progression, and Dose-limiting Toxicity

3.1.3.1 Dose Escalation Committee (Arms A and B)

Subjects will be followed for safety throughout the study. A study-specific DEC (including at a minimum the sponsor medical monitor/clinical lead and all participating investigators who have enrolled subjects in that dose level) will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety and other relevant data. This committee may also meet to review data at other time points (eg, in response to AEs assessed as medically relevant by the medical monitor). This committee will be responsible for dose escalation or dose de-escalation decisions and recommendations regarding further conduct of the study. All decisions by this committee will be documented and shared with all participating sites in writing.

3.1.3.2 Rules for Dose Escalation and Cohort Progression (Arms A and B)

In Part 1 of this study novel combination therapies without previously defined dosing schedules will be evaluated. The following rules will be applicable to dose escalation in Arms A and B. The study design and planned dose levels are described in Section 3.1.2.1 (Arm A) and Section 3.1.2.2 (Arm B).

1 The MTD will be determined based on the assessment of DLT during the DLT-evaluation period (Section 3.1.3.3). Subjects who do not meet the criteria for the DLT-evaluable population will be replaced (Sections 4.9.1 and 4.1.8).

2 Administration of the first dose of investigational product must be staggered by a minimum of 24 hours for the first 2 subjects in each cohort. Intra-subject dose escalation will not be allowed. Intra-subject dose de-escalation will not be allowed during the DLT-evaluation period.

3 A minimum of 3 subjects will be enrolled in each dose-level cohort. If no DLTs are observed in a cohort of 3 to 6 evaluable subjects, then dose escalation may occur. At dose level 1 only, dose escalation to the next higher dose cohort will be permitted after review of all available safety data from a minimum of 3 evaluable subjects in that treatment arm and a minimum of 6 evaluable subjects across both treatment arms (Arms A and B). At subsequent dose levels, dose escalation to the next higher dose cohort will be permitted after review of all available safety data from a minimum of 3 evaluable subjects in that treatment arm.

4 If 1 subject in a dose-level cohort of 3 or more evaluable subjects experiences a DLT, that dose-level cohort will be expanded to a total of 6 subjects. If no more than 1 of 6 subjects in the dose-level cohort experiences a DLT, dose escalation will continue to the next higher dose-level cohort.

5 If $\geq$ 2 subjects in a dose-level cohort experience a DLT, the MTD will be exceeded and no further subjects will be enrolled into that dose-level cohort. If this occurs, the preceding dose-level cohort will be evaluated for the MTD and a total of 6 subjects will

be treated at the preceding dose level if not already expanded. If ≤ 1 of 6 subjects experiences a DLT at the preceding dose level, then this dose level will be the MTD.

6 If ≥ 2 subjects in the first dose cohort experience a DLT, then no further subjects will be enrolled into that dose-level cohort. A dose de-escalation (Dose Level -1) will then be evaluated for the MTD in 6 subjects.

7 If the highest protocol-defined dose level is reached and no DLTs are observed in a minimum of 3 evaluable subjects, the sponsor may choose to evaluate the previous dose level in the dose expansion phase or expand the highest protocol-defined dose level to 6 subjects. In the latter case, if ≤ 1 of 6 subjects experiences a DLT, then the highest protocol-defined dose level may be selected for further evaluation in the dose expansion phase.

8 At the discretion of the sponsor, dose escalation may be stopped before an MTD is reached. In this case, an expanded cohort dose may be chosen based on an assessment of PK, CCI [redacted] safety, and antitumor activity data.

9 With the exception of dose level 1 as described in Rule 3, dose escalation proceeds independently between the arms of this study.

3.1.3.3 Dose-Limiting Toxicity (Arms A and B)

Dose-limiting toxicities will be evaluated during the dose-escalation phase of Arms A and B. The period for DLT evaluation will be from the first dose of both investigational products until the planned administration of the third dose of oleclumab (ie, through Day 28 post Dose 1). Subjects who do not complete the DLT-evaluation period for reasons other than DLT, did not receive all planned doses of oleclumab, or did not receive at least 75% of the daily administrations of osimertinib (Arm A) or AZD4635 (Arm B) during this time will be considered nonevaluable for DLT assessment and will be replaced with another subject at the same dose level (Sections 4.1.8 and 4.9.1). Grading of DLTs will be according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

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

- Any Grade 4 immune-mediated adverse event (imAE)
- Any ≥ Grade 3 colitis
- Any ≥ Grade 3 nausea, vomiting, or diarrhea that does not resolve to Grade 2 or less within 3 days of the initiation of maximal supportive care
- Any ≥ Grade 3 pneumonitis or ILD
- Any Grade 2 pneumonitis or ILD that does not resolve to Grade 1 or less within 3 days of the initiation of maximal supportive care
- Any Grade 4 anemia
- Any Grade 4 thrombocytopenia or neutropenia that is present for more than 4 days

- Grade 3 thrombocytopenia with bleeding
- Any grade febrile neutropenia
- Convulsions, seizures, or stroke
- Isolated liver transaminase elevation ≥ 5 × but ≤ 8 × upper limit of normal (ULN) or isolated total bilirubin (TBL) ≥ 3 × but ≤ 5 × ULN that does not downgrade to Grade 2 or less within 14 days after onset with optimal medical management, including systemic corticosteroids. Isolated liver transaminase elevation > 8 × ULN or isolated TBL > 5 × ULN regardless of duration.
- Any increase in AST or ALT > 3 × ULN and concurrent increase in TBL > 2 × ULN (Hy's Law [see Section 10.5.2]) without evidence of cholestasis or alternative explanations (eg, viral hepatitis, disease progression in the liver)
- Confirmed QT interval corrected for heart rate by Fridericia's formula (QTcF) prolongation (≥ 501 msec) on triplicate ECGs within a short period of time (eg, a total of 3 ECGs within 30 minutes). Only if the average QTcF value, manually over-read by a medically qualified person based on 3 ECGs, is ≥ 501 msec would it be declared a DLT.
- Any other toxicity that is greater than that at baseline, is clinically significant and/or unacceptable, and is judged to be a DLT by the DEC

A DLT excludes the following:

- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc) that resolved to Grade 1 or less within 30 days
- Concurrent vitiligo or alopecia of any AE grade
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance that are not defined as a DLT above.

Immune-mediated AEs are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. If late-emerging imAEs (imAEs occurring after the DLT-evaluation period) are observed, these events will be considered by the DEC during data reviews for dose escalation or de-escalation decisions.

3.1.4 Management of Study Medication Related Toxicities

If a subject experiences a CTCAE Grade 3 and/or unacceptable toxicity including a DLT not attributable to the disease or disease-related processes under investigation, dosing will be interrupted and supportive therapy administered.

3.1.4.1 For Toxicity That Occurs While on Oleclumab and Osimertinib (Arm A)

Following the DLT-evaluation period, the treatment modification and toxicity management guidelines for immune-mediated AEs, IRRs, and non-immune-mediated reactions provided in Section 10.6 will be followed. In addition, information for adverse events of special interest (AESIs) is provided in Section 5.3.

Exceptions to the management of non-immune mediated reactions that are allowed for osimertinib are provided in Section 10.7. If a toxicity resolves to ≤ CTCAE Grade 2 or baseline within 3 weeks of onset, treatment with osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg) using the rules for dose modifications (Section 10.7) and with discussion and agreement with the medical monitor as needed. There will be no individual modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption. If the toxicity does not resolve to ≤ CTCAE Grade 2 or baseline after 3 weeks, then the subject should be discontinued from study treatment and observed until resolution of the toxicity. On resolution of toxicity within 3 weeks: If an AE subsequently requires dose interruption, osimertinib may be restarted at the same dose or the reduced dose, on resolution/improvement of the AE at the discretion of the investigator.

Subjects experiencing corneal ulceration, ILD, or QTc prolongation with signs/symptoms of serious arrhythmia will not be permitted to restart study treatment. To ensure subject safety, continuous monitoring of ILD events will be performed as described in Section 4.9.7.

If treatment-related toxicity meeting criteria for discontinuation occurs, both oleclumab and osimertinib must be discontinued.

3.1.4.2 For Toxicity That Occurs While on Oleclumab and AZD4635 (Arm B)

Following the DLT-evaluation period, the treatment modification and toxicity management guidelines for immune-mediated AEs, IRRs, and non-immune-mediated reactions provided in Section 10.6 will be followed. In addition, information for AESIs is provided in Section 5.3.

For non-immunologic toxicities, it may be possible for the investigator to ascribe relationship with AZD4635 dosing, but not related to oleclumab. In such a case, the investigator should follow guidelines for AZD4635 dose modifications in Section 10.8 (Table 17 [hematologic toxicities], Table 18 [non-hematologic toxicities], Table 19 [hypertension], and Table 20 [CNS toxicities]) and may continue to administer oleclumab. If the toxicity resolves to ≤ CTCAE Grade 2 or baseline within 2 weeks of onset and the subject is showing clinical benefit per the investigator, treatment with AZD4635 may be restarted at the same dose or a lower dose using the rules for dose modifications (Section 10.8) and with discussion and agreement with the medical monitor as needed. Anticipated AZD4635 dose levels are 75 and 100 mg QD; dose levels of AZD4635 50 mg QD (dose level -1) and 25 mg QD (dose level -2) are allowed for de-escalation, if needed (Figure 3). There will be no individual

modifications to dosing schedule in response to toxicity, only potential dose reduction or dose interruption. Intra-subject dose re-escalation is not permitted. If the toxicity does not resolve to ≤ CTCAE Grade 2 or baseline within 2 weeks, then the subject should be discontinued from study treatment and observed until resolution of the toxicity. Maximum time allowed for dose interruption is 2 weeks.

If treatment-related toxicity meeting criteria for discontinuation occurs, both oleclumab and AZD4635 must be discontinued.

3.2 Rationale for Dose, Population, and Endpoints

3.2.1 Dose Rationale

Oleclumab (Arms A and B)

The oleclumab starting dose of 1500 mg Q2W (equivalent to 20 mg/kg Q2W in a 75 kg individual) was selected based on the available clinical safety, tolerability, efficacy, and PK data from the ongoing Phase 1 Study D6070C00001. In this study 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 (Section 1.4.1). The oleclumab 40 mg/kg Q2W dose (equivalent to the oleclumab 3000 mg Q2W fixed dose for a 75 kg individual) was identified for evaluation with durvalumab 10 mg/kg Q2W in the dose-expansion phase of this study (Study D6070C00001).

Many published articles have previously reported a similarity of exposures following either fixed or body size-based dosing of mAbs (Narwal et al, 2013; Ng et al, 2006; Wang et al, 2009; Zhang et al, 2012). Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 mAbs (Wang et al, 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamics parameters (Zhang et al, 2012). A fixed dosing approach is also preferred by the prescribing community due to ease of use and reduced dosing errors. Given the expectation of similar PK exposure and variability, it is considered feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, the fixed doses of oleclumab 1500 mg Q2W (equivalent to 20 mg/kg Q2W) and oleclumab 3000 mg Q2W (equivalent to 40 mg/kg Q2W) are included in the current study. Oleclumab 1500 mg Q2W is one dose level below the highest monotherapy and combination weight-based dose that has been tested and declared tolerable in FTIH Study D6070C00001. Therefore, oleclumab 1500 mg Q2W has been selected as the starting dose to be used in combination with osimertinib and AZD4635. Additionally, in Arm A, a fixed dose of oleclumab 750 mg Q2W (equivalent to 10 mg/kg Q2W) is included as dose level -1, if needed.

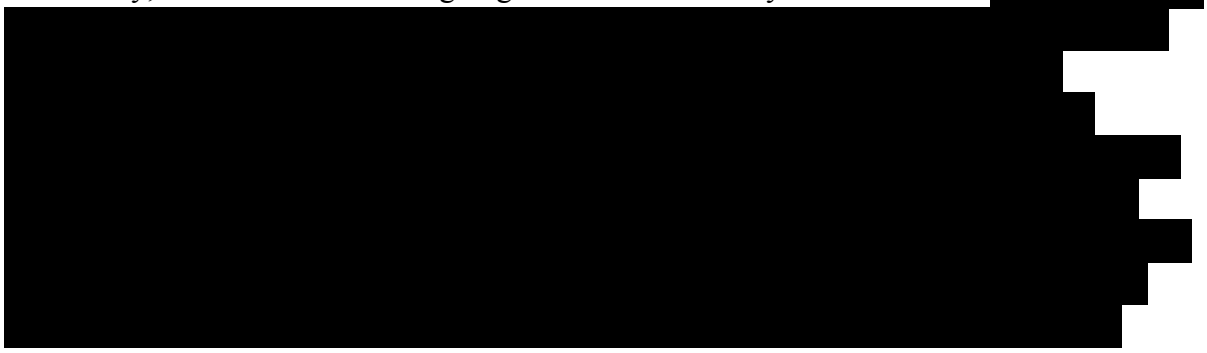
Osimertinib (Arm A)

The osimertinib dose of 80 mg QD is the global Health Authority approved monotherapy dose in patients with advanced EGFRm T790M mutation positive NSCLC. This dose is not the MTD as osimertinib was previously administered up to 240 mg daily with no observed DLTs.

Given the favorable safety profiles of both oleclumab and osimertinib and the non-overlapping mechanisms of action and toxicity, the fixed dose of oleclumab 1500 mg Q2W and the approved dose of osimertinib 80 mg QD are selected as the starting dose level for combination therapy in Arm A of this study.

AZD4635 (Arm B)

The AZD4635 starting dose of 75 mg QD was selected based on the available clinical safety, tolerability, and PK data in the ongoing FTIH Phase 1 Study D8730C00001. CCI



AZD4635 75 mg QD is one dose level below the highest monotherapy dose that has been tested and declared tolerable in FTIH Study D8730C00001 and is the same dose level that has been tested in combination with durvalumab 1500 mg and declared tolerable in the FTIH study. Therefore, AZD4635 75 mg QD has been selected as the starting dose to be used in combination with oleclumab 1500 mg Q2W in this study. Also, AZD4635 50 mg QD (dose level -1) and 25 mg QD (dose level -2) are included, if needed.

3.2.2 Rationale for Study Population

Lung cancer is the most common cause of cancer-related death worldwide and the majority of these cases are NSCLC (Section 1.1). Approximately 10% to 30% of these patients harbor an EGFR mutation that serves as the molecular driver of their cancer. While this has led to improvements in the outcomes from early lines of therapy with targeted EGFR TKIs, upon progression patients have limited therapeutic options and poor survival. Furthermore, recent advances in immunotherapy with anti-PD-1 and anti-PD-L1 antibodies have not been realized to the same extent in this subset of patients. Genetic and immune profiling of these tumors has demonstrated that alternative gene expression such as increased CD73 expression may help to explain the lack of efficacy of currently approved immunotherapy. It has become increasingly clear that long-term therapeutic benefit in metastatic cancers can be achieved by

enhancing the antitumor immune response. As discussed in Section 1.5, oleclumab is a potential candidate to be combined with other active and novel agents to restore antitumor immunity and enhance the therapeutic response.

3.2.2.1 Rationale for Study Population (Arm A)

The combination of a targeted therapy such as osimertinib with an immune-mediated therapy such as oleclumab provides an orthogonal approach of inhibiting tumor growth signals while promoting tumor immune recognition to improve antitumor activity. Currently, osimertinib is only approved for EGFRm NSCLC subjects who have progressed on first-line EGFR TKI therapy and have acquired the T790M mutation. This leaves approximately 50% of patients with limited targeted therapy options and most will proceed to chemotherapy. However, the AURA study (Phase 1 component) for osimertinib demonstrated that T790M negative tumors can also respond to this targeted therapy. In this trial, 69 patients without centrally detectable EGFR T790M received osimertinib at ranges from 20 to 240 mg QD, 29 of whom received osimertinib at the 80 mg dose. The investigator-assessed ORR was 24.6% across all doses and 20.7% in the 80 mg group (Section 1.4.2). Similarly, in the Phase 1 trial of rociletinib, an EGFR TKI also targeting the EGFR T790M mutation, an ORR of 29% in the centrally confirmed T790M negative population was reported (Sequist et al, 2015). In the Phase 1b trial of afatinib plus the anti-EGFR antibody cetuximab, an ORR of 25% in the EGFRm NSCLC T790M negative population was reported. However, this combination of dual anti-EGFR inhibition had a significant safety and tolerability burden (Janjigian et al, 2014). Furthermore, disease progression and acquired resistance to all targeted therapies is inevitable. Unlike targeted therapy, immune-mediated therapies have demonstrated significantly longer DoRs and even long-term disease control (DC) in some instances. Therefore, this novel combination of a targeted therapy and an immune-mediated therapy with strong scientific support has the potential to improve the response rate to osimertinib alone and improve the DoR for subjects with EGFR T790M mutation-negative NSCLC receiving the combination, thus delaying the initiation of cytotoxic therapies.

3.2.2.2 Rationale for Study Population (Arm B)

The combination of AZD4635 with oleclumab, which both target the adenosine pathway, has the potential to restore the antitumor response in subjects with EGFRm NSCLC.

As described in Section 1.5, ATP is rapidly catabolized to adenosine by the enzymatic activity of CD39 and CD73. Once generated, in the tumor microenvironment adenosine is capable of binding to $A_{2A}R$ which is expressed on a variety of immune cell types, including T-effector cells, Tregs, natural killer cells, MDSCs, and tumor associated macrophages. Nonclinical studies have demonstrated pleotropic effects on a multitude of immune cells resulting in an immunosuppressive state with decreases in cytotoxic responses and pro-inflammatory cytokines. By exerting such widespread effects on the immune system,

adenosine signaling through $A_{2A}R$ inhibits antitumor responses and enables immune escape of tumors.

Given the substantial evidence supporting the role of the adenosinergic pathway in tumor immune evasion, investigators evaluated the impact of inhibiting both CD73 and $A_{2A}R$. In murine models of mammary carcinoma and melanoma, investigators found that dual inhibition resulted in a reduced tumor growth, increased immune infiltrates, and improvement in OS as compared to either placebo or each treatment as monotherapy (Young et al, 2016). Given the overexpression of CD73 in EGFRm NSCLC, dual inhibition of this pathway is a potential therapeutic approach.

AZD4635 is a potent, highly selective inhibitor of $A_{2A}R$. The safety and efficacy of AZD4635 are currently being investigated both as a monotherapy and in combination with durvalumab as part of an ongoing Phase 1 study (D8730C00001) (Section 1.4.3). This study will identify the RP2D dose for AZD4635 and oleclumab combination therapy and evaluate its safety and preliminary efficacy.

3.2.3 Rationale for Endpoint(s)

The primary aim of this study is to determine the safety and tolerability of novel therapeutic combinations in subjects with EGFRm NSCLC, identify the MTD or highest protocol defined dose in the absence of establishing an MTD and assess the antitumor activity for all combinations for which a confirmed safe dose is established. The occurrence of DLTs will be used to establish the MTD and thus the standard safety endpoints, such as AEs, SAEs, clinically meaningful changes from baseline in laboratory parameters, vital signs, and ECGs will be included in the evaluation.

The endpoints for assessment of antitumor activity are those routinely included in oncology studies and will include OR and DC (based on RECIST version 1.1), DoR, PFS, and OS. Additionally, OR and DC will be assessed by T790M status. Archival and/or fresh tumor biopsies will be centrally tested to determine T790M status. CCI

The PK parameters that will be determined for the secondary objective will be specific for the study treatments within each arm. These parameters may include C_{max}, AUC, clearance (CL), and $t_{1/2}$ after IV doses and C_{max}, t_{max}, AUC, apparent plasma clearance (CL/F), apparent

volume of distribution (V_z/F) and $t_{1/2}$ after oral doses if the data allow as well as others if deemed important. As oleclumab is administered on a repeating dosing schedule, the development of antidrug antibodies (ADA) CCI [redacted] will also be assessed.

CCI [redacted]

CCI [redacted]

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

A total of up to approximately 98 subjects will be enrolled in this study: up to approximately 46 subjects in Arm A and up to approximately 52 subjects in Arm B.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1 Age ≥ 18 years at the time of screening or age of consent according to local law.
2 Written informed consent and any locally required authorization (eg, data privacy) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
3 ECOG Performance Status of 0 or 1.
4 Weight ≥ 35 kg.
5 Subjects diagnosed with histologically or cytologically confirmed locally advanced/metastatic NSCLC with EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q)
   (a) **For Arm A**: Subjects must have received 1 prior line of therapy with an EGFR TKI in the locally advanced/metastatic setting.
      (i) Must have received and progressed on an approved first or second generation EGFR TKI (eg, erlotinib or gefitinb [first generation] or afatanib [second generation])

(ii) Subjects must be T790M negative by an approved testing assay on tumor biopsy. If plasma testing was performed, they must also be negative by this as well. Negative testing by plasma testing alone will not be considered sufficient for study entry.

(iii) Prior chemotherapy received in the neoadjuvant or adjuvant settings will not be considered a line of therapy.

(b) **For Arm B:** Subjects must have received at least 2 but not more than 4 prior lines of therapy (including investigational therapy) in the locally advanced/metastatic setting.

(i) Must have received and progressed on an approved first or second generation EGFR TKI (eg, erlotinib or gefitinb [first generation] or afatanib [second generation]) for their known mutation status.

(ii) If subjects are known to be T790M positive and subjects had access to an approved third generation EGFR TKI therapy, they should have received and progressed on this therapy as well.

(iii) Maintenance therapy following platinum-doublet is not considered a separate line of therapy.

(iv) Prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease is considered first-line therapy only if recurrent (local or metastatic) disease developed within 6 months of completing therapy.

(v) If subjects received osimertinib as first-line treatment, then treatment with a first or second generation EGFR TKI is not required. In addition, these subjects may enroll after having received and progressed on osimertinib alone but can still have received no more than 4 prior lines of therapy.

6 Subjects must have at least 1 measurable lesion according to RECIST version 1.1.

(a) A previously irradiated lesion can be considered a target lesion if the lesion is well defined, measurable per RECIST, and has clearly progressed.

(b) Subjects must have a non-target lesion that can be biopsied at acceptable risk (if biopsy is required for enrollment) as judged by the investigator or if no other lesion is suitable for biopsy, then an RECIST target lesion used for biopsy must be ≥ 2 cm in longest diameter.

7 CCI [redacted]

8 All subjects in the dose expansion phase of the study (Part 2) must consent to a fresh biopsy unless a biopsy was obtained within 3 months from screening, during or after the most recent line of therapy (with no intervening anticancer therapy). CCI [redacted]

9 **For Arm B:** Normotensive or well-controlled BP (< 140/90), with or without current antihypertensive treatment. If diagnosis or history of hypertension, subject must have adequately controlled BP on a maximum of 2 antihypertensive medications, as demonstrated by 2 BP measurements taken in the clinical setting by a medical professional.

10 Adequate organ and marrow function, as defined below. Criteria "a," "b," and "c" cannot be met with ongoing or recent blood transfusions (within 14 days of starting first dose) or require growth factor support (within 28 days of starting the first dose)

(a) Hemoglobin ≥ 9 g/dL

(b) Absolute neutrophil count ≥ 1,500/μL

(c) Platelet count ≥ 100,000/μL

(d) TBL ≤ 1.5 × ULN if no liver metastases or ≤ 3 × ULN in the presence of documented Gilbert's syndrome or liver metastases

(e) ALT and AST ≤ 2.5 × ULN if no demonstrable liver metastases or ≤ 5 × ULN in the presence of liver metastases

(f) Calculated creatinine clearance ≥ 40 mL/minute as determined by Cockcroft-Gault (using actual body weight) or 24-hour urine creatinine clearance

11 Females of childbearing potential who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception (Section 10.2 for definition of females of childbearing potential and for a description of highly effective methods of contraception) from screening to 180 days after the final dose of concurrent therapy. It is strongly recommended for the male partner of a female subject to also use a male condom plus spermicide throughout this period. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.

12 Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use a male condom with spermicide from screening to 180 days after the final dose of concurrent therapy. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. It is strongly recommended for the female partner of a male subject to also use one highly effective method of contraception throughout this period, as described in Section 10.2. In addition, male subjects must refrain from sperm donation while on study and for 180 days after the final dose of combination therapy.

4.1.3 Exclusion Criteria

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

1 Receipt of an EGFR TKI within 14 days of the first dose of study treatment.

2 Receipt of any conventional or investigational anticancer therapy not otherwise specified within 21 days of the planned first dose.

3 Prior receipt of any investigational immunotherapy. Subjects may have received agents that have local health authority approval for the disease indication.

4 Concurrent enrollment in another therapeutic clinical study. Enrollment in observational studies will be allowed.

5 Any toxicity (excluding alopecia) from prior standard therapy that has not been completely resolved to baseline at the time of consent. Subjects with NCI CTCAE version 4.03 Grade 1 or 2 toxicities that are deemed stable or irreversible can be enrolled on a case-by-case basis with prior consultation and agreement with the medical monitor.

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

7 Subjects with prior history of myocardial infarction, transient ischemic attack, or stroke in the last 6 months.

8 Active or prior documented autoimmune or inflammatory disorders within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
   (a) Subjects with vitiligo or alopecia.
   (b) Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment.

9 Subjects with confirmed HIV (even if viral load is undetectable), chronic or active hepatitis B or C, or active hepatitis A.

10 History of primary immunodeficiency, solid organ transplantation, or active tuberculosis. In settings where there is a clinical or radiographic evidence of tuberculosis, active disease must be excluded prior to enrollment.

11 Other invasive malignancy within 2 years. Noninvasive malignancies (ie, cervical carcinoma in situ, in situ prostate cancer, non-melanomatous carcinoma of the skin, ductal carcinoma in situ of the breast that has been surgically cured) are excluded from this definition.

12 Refractory nausea and vomiting, chronic GI diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib or AZD4635.

13 Known allergy or hypersensitivity to investigational product formulations.

14 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection requiring antibiotic therapy, uncontrolled hypertension, bleeding diatheses, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs, or compromise the ability of the subject to give written informed consent.

15 Untreated CNS metastatic disease, leptomeningeal disease, or cord compression. Note: Subjects previously treated for CNS metastases that are radiographically and neurologically stable for at least 28 days and do not require corticosteroids (of any dose) for symptomatic management for at least 14 days prior to the first dose will be eligible. Contrasted computed tomography (CT) or magnetic resonance imaging (MRI; preferred) scan to assess for CNS metastatic disease will be performed at screening.

16 Current or prior use of immunosuppressive medication within 14 days prior to the first dose. The following are exceptions to this criterion:
   (a) Intranasal, topical, inhaled corticosteroids or local steroid injections (eg, intraarticular injection).

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

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

17 Receipt of live, attenuated vaccine within 28 days prior to the first dose of investigational products (Note: Subjects, if enrolled, should not receive live vaccine during the study and 180 days after the last dose of investigational product[s]). Vaccination with a killed vaccine is permitted at any time.

18 Major surgery (as defined by the investigator) within 28 days prior to first dose or still recovering from prior surgery. Local procedures (eg, placement of a systemic port, core needle biopsy, and prostate biopsy) are allowed if completed at least 24 hours prior to the administration of the first dose of study treatment.

19 Females who are pregnant, lactating, or intend to become pregnant during their participation in the study.

20 Subjects who are involuntarily incarcerated or are unable to willingly provide consent or are unable to comply with the protocol procedures.

21 Any condition that, in the opinion of the investigator or sponsor, would interfere with safe administration or evaluation of the investigational products or interpretation of subject safety or study results.

Additional Exclusion Criteria for Arm A

1 Concurrent treatment (or inability to stop therapy) with medications or herbal supplements known to be potent inducers of CYP3A4 (Table 21). Refer to Sections 4.8.2 and 10.9 for the list of prohibited medications.

2 Any of the following cardiovascular conditions:

(a) Mean resting QTcF > 470 msec when manually over-read by a medically qualified person and based on 3 ECGs

(b) Any current clinically important abnormalities in rhythm, conduction or morphology of resting ECG (eg, complete left bundle branch block, third-degree heart block, second-degree heart block)

(c) Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives or concurrent treatment (or inability to stop therapy) with medications listed in Table 23, which are known to prolong QT interval

(d) Any clinically important abnormalities in cardiac structure or function including left ventricular ejection fraction (LVEF) < 50% measured by echocardiography/ multigated acquisition scan (MUGA), cardiomyopathy, or symptomatic valvular heart disease

3 Subject has a history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD.

4 Subject requires supplemental oxygen for any reason. Note: Intermittent supplemental oxygen required for vigorous activity or sleep is allowed.

5 Subject has a resting SpO2 < 95% on room air.

Additional Exclusion Criteria for Arm B

1 Subject has had prescription or non-prescription drugs or other products known to be sensitive CYP1A2 substrates, or moderate/potent inhibitors/inducers of CYP1A2, or sensitive substrates of BCRP and OAT1, which cannot be discontinued 14 days prior to Day 1 of dosing and withheld throughout the study until 14 days after the last dose of AZD4635. NOTE: the use of warfarin is prohibited during treatment with AZD4635. Refer to Sections 4.8.2 and 10.10 for the list of prohibited medications.

2 Herbal preparations/medications are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Subjects should stop using all herbal medications 14 days prior to the first dose of AZD4635.

3 Concomitant medications with another A_1R antagonist that would increase risk of seizure (eg, theophylline, aminophylline)

4 History of seizures, excluding those that occurred due to previously untreated CNS metastasis

5 Any of the following cardiovascular conditions:

(a) Mean resting QTcF > 470 msec when manually over-read by a medically qualified person and based on 3 ECGs

(b) Any current clinically important abnormalities in rhythm, conduction or morphology of resting ECG (eg, complete left bundle branch block, third-degree heart block, second-degree heart block)

(c) Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in first degree relatives or concurrent treatment (or inability to stop therapy) with medications listed in Table 23 which are known to prolong QT interval

(d) Any clinically important abnormalities in cardiac structure or function including, cardiomyopathy, or symptomatic valvular heart disease

6 Subjects who have received prior immunotherapy are NOT permitted to enroll unless all of the following apply:

(a) Dose of immunotherapy must have been administered at least 28 days prior to planned first dose.

(b) Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy

(c) All AEs while receiving prior immunotherapy must have resolved to ≤ Grade 1 or baseline prior to screening. Must not have experienced a related ≥ Grade 3 AE or neurologic or ocular AE of any grade which was deemed to be related to the prior immunotherapy. Subjects with an endocrine AE of any grade are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.

7 Any subject with an open ulceration(s) should avoid dosing with AZD4635 oral suspension.

4.1.4 Subject Enrollment

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice response system/interactive 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), including the reason(s) for screening failure.

Subjects who do not meet all eligibility requirements within the screening period (ie, screen failures) may be rescreened and receive a new SID number.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments) at any time, without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the subject is willing, the subject will be seen and assessed by the investigator. Adverse events will be followed up and all study medications should be returned by the subject. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

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

1 Withdrawal of consent from the study (Section 4.1.5)
2 Withdrawal of consent from further treatment with investigational product
3 Lost to follow-up
4 Any AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing
5 Any AE that meets criteria for discontinuation from investigational product as defined in the Toxicity Management Guidelines (Section 3.1.4)
6 Subject experienced a DLT during the DLT-evaluation period

7 Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing treatment with investigational product might constitute a safety risk
8 Pregnancy (Section 5.6.4) or intent to become pregnant
9 Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits)
10 Initiation of alternative anticancer therapy including another investigational agent
11 Confirmed or unconfirmed PD and treatment criteria in the setting of PD are not met (Section 4.1.7)
12 Investigator determination that the subject is no longer benefiting from the treatment regimen

Subjects who are permanently discontinued from receiving investigational product 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), the subject is lost to follow-up, the subject starts alternative treatment, the subject is enrolled in another clinical study, or the subject dies.

4.1.7 Treatment Beyond Progression

Subjects in all treatment arms may continue receiving their originally assigned treatment, at the investigator's discretion, after the first overall time point assessment of PD by RECIST version 1.1 until PD is confirmed on a follow-up scan (confirmed radiological PD). A confirmatory scan is required following the initial assessment of PD by RECIST version 1.1, preferably at the next scheduled visit and no earlier than 4 weeks after the immediate previous assessment of PD.

For all subjects who are treated through progression, the investigator should ensure that the subject does not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the subject.

The criteria for continuing treatment despite RECIST version 1.1-defined progression are as follows:

- There is absence of clinical symptoms or signs indicating clinically significant disease progression accompanied by a decline of more than 1 in ECOG performance status.
- There is absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, or spinal cord compression) requiring urgent alternative medical intervention (concurrent radiation treatment is not permitted). NOTE: If a subject requires palliative radiation for isolated progression at an immunologically privileged site (eg, brain) while maintaining disease control outside the CNS, consult MedImmune for an exception to this rule; if

palliative radiation is agreed to by MedImmune in a subject with isolated progression, protocol therapy will need to be held prior to and during the radiation.

Subjects with confirmed radiological PD may continue to receive their assigned treatment at the discretion of the investigator (following consultation with MedImmune) as long as they are gaining clinical benefit; collection of additional scans subsequent to confirmed radiological PD will continue according to the original imaging schedule.

Subjects with PD who are eligible to continue receiving their assigned treatment will be made aware of the potential benefits and risks of continuing treatment in the setting of PD and must provide a separate written informed consent prior to treatment.

Subjects who MedImmune and the investigator determine may not continue treatment after PD will be followed up for survival. Subjects who have discontinued treatment due to toxicity or symptomatic deterioration will be followed up until radiological PD and for survival. Subjects who have commenced subsequent anticancer therapy will be followed up only for survival.

4.1.8 Replacement of Subjects

Subjects who do not complete the DLT-evaluation period as defined in Section 3.1.3.3 for reasons other than DLT, did not receive all planned doses of oleclumab, or did not receive at least 75% of the daily administrations of osimertinib (Arm A) or AZD4635 (Arm B) during this time will be considered nonevaluable for DLT assessment and will be replaced with another subject at the same dose level.

4.1.9 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If a subject withdraws consent to the use of mandatory biological samples, the samples will be disposed of/destroyed if possible and the action documented. If samples have already been analyzed, the sponsor is not required to destroy the results of this research.

CCI [redacted]

CCI [redacted]

CCI

CCI

CCI

4.2 Schedule of Study Procedures

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the blood draws should occur last, if possible. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the proper nominal time.

4.2.1 Enrollment/Screening Period

Table 2 shows all procedures to be conducted at the screening visit.

Table 2 Schedule of Screening Procedures (All Arms)

Procedure	Screening Visit 1 Day -28 to Day -1
Written informed consent/assignment of SID number	X
Demographics (age, race, and ethnicity)	X
Medical history (including smoking, caffeine, prior therapies, and prior imaging [a])	X
Verify eligibility criteria	X
Assessment of AEs/SAEs	X

Table 2 Schedule of Screening Procedures (All Arms)

Procedure	Screening Visit 1 Day -28 to Day -1
Concomitant medications	X
Physical examination (full)	X
Height and weight	X
Vital signs (including pulse oximetry)	X
ECG [b]	X
ECOG performance status	X
LVEF by echocardiogram/MUGA (Arm A only)	X
Ophthalmologic examination (Arm A only)	X
Laboratory Assessments:	
Serum chemistry	X
Hematology	X
TSH and free T_4 (If TSH is normal then free T_4 is not required)	X
Lipid panel	X
Urinalysis	X
Pregnancy test, serum β-HCG [c]	X
Coagulation parameters	X
Hepatitis B, C; HIV-1	X
Disease Evaluation:	
Contrasted CT (preferred) of the chest, abdomen and pelvis [d]	X
MRI (preferred) scan for brain metastases [d]	X
CCI	
CCI	
CCI	
CCI	
CCI	
CCI	

AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CT = computerized tomography; CCI DICOM = Digital Imaging and Communications in Medicine; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV-1= human immunodeficiency virus-1; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition scan; SAE = serious adverse event; SID = subject identification; T_4 = thyroxine; THS = thyroid-stimulating hormone.

[a] If allowed by country: Prior imaging includes raw imaging data (eg DICOM) of a previous disease assessment that has been performed between 4 weeks and 6 months prior to baseline scan obtained during screening.

[b] ECG will be obtained in triplicate within a 5-minute time period.

[c] Females of childbearing potential only

[d] Previous scans for brain metastases and baseline disease that were performed within 28 days of dosing and meet the protocol requirements do not need to be repeated.

CCI

[redacted]

4.2.2 Treatment Period

All procedures to be conducted during the treatment period are shown in Table 3 for Arm A and Table 4 for Arm B.

Table 3 Treatment Period Study Procedures – Arm A (Oleclumab + Osimertinib)

Study Period	**Treatment Period**					
Visit Number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7-Vn**
Procedure/ Study Day	**Day 1**	**Day 15 (± 1 day)**	**Day 29 (± 1 day)**	**Day 43 (± 3 days)**	**Day 57 (± 3 days)**	**Q2W (± 3 days) Starting on D71 (unless otherwise noted)**
Clinical Assessments:						
Verify eligibility criteria	X					
Physical examination (abbreviated, symptom directed)	X[a]	X	X		X	Q4W (± 3D) starting on D85
ECOG	X		X		X	Q4W (± 3D) starting on D85
Weight	X		X		X	Q4W (± 3D) starting on D85
ECG[b]	X	X	X		X	Q12W (± 3D) starting on D113
Vital signs[c]	X	X	X	X	X	X
LVEF by echocardiogram/MUGA						Q12W (± 3D) starting on D85
Assessment of AEs/SAEs	All visits					
Concomitant medications	All visits					
Laboratory Assessments[d]:						
Serum chemistry[d]	X	X	X	X	X	X
Hematology[d]	X	X	X	X	X	X
TSH and free T_4 (If TSH is normal then free T_4 is not required)[d]	X		X		X	Q4W (± 3D) starting on D85
Lipid Panel[d]	X				X	Q8W (± 3D) starting on D113

Table 3 Treatment Period Study Procedures – Arm A (Oleclumab + Osimertinib)

Study Period	**Treatment Period**					
Visit Number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7-Vn**
Procedure/ Study Day	**Day 1**	**Day 15 (± 1 day)**	**Day 29 (± 1 day)**	**Day 43 (± 3 days)**	**Day 57 (± 3 days)**	**Q2W (± 3 days) Starting on D71 (unless otherwise noted)**
Pregnancy test[d, e]	X				X	Q8W (± 3D) starting on D113
Urinalysis[d]	X				X	Q8W (± 3D) starting on D113
Efficacy:						
Disease assessment (scans)[f]					X	Q8W (± 3D) starting on D113 through D393 then Q12W (± 3D)
Study Drug Administration:						
Oleclumab administration[g]	X	X	X	X	X	X
Osimertinib administration[g]	X (daily dosing)					
Pharmacokinetics/CCI **:**						
Plasma for osimertinib PK[h]	X	Pre-dose	X	Pre-dose	Pre-dose	Pre-dose on D113 (± 3D) only
Serum for oleclumab PK[i]	X		X		X	Q12W (± 3D) starting on D141
Serum for oleclumab ADA[d]	X		X		X	Q12W (± 3D) starting on D141
CCI						
CCI						

Table 3 Treatment Period Study Procedures – Arm A (Oleclumab + Osimertinib)

Study Period	Treatment Period					
Visit Number	**V2**	**V3**	**V4**	**V5**	**V6**	**V7-Vn**
Procedure/ Study Day	**Day 1**	**Day 15 (± 1 day)**	**Day 29 (± 1 day)**	**Day 43 (± 3 days)**	**Day 57 (± 3 days)**	**Q2W (± 3 days) Starting on D71 (unless otherwise noted)**
CCI [redacted]						
CCI [redacted]						

ADA = anti-drug antibody; AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CCI [redacted] D = Day(s); ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; PK = pharmacokinetics; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SAE = serious adverse event; T_4 = thyroxine; THS = thyroid-stimulating hormone; V = Visit.

[a] Physical examination can be performed up to 24 hours prior to dosing on Day 1.

[b] All ECGs will be obtained in triplicate (all within a 5-minute time period). ECGs will be recorded prior to the administration of any investigational product and within 30 minutes post end of oleclumab infusion.

[c] On days of oleclumab investigational product administration, vital signs will be measured according to the following schedule: Within 60 minutes prior to start of oleclumab infusion then every 30 minutes (± 5 minutes) during the infusion, the end of infusion (± 5 minutes), and 30 minutes (± 10 minutes) post end of oleclumab infusion. On Day 1, additional vital sign measurements will be taken at 60 minutes (± 10 minutes) and 3 hours (± 15 minutes) post end of oleclumab infusion. On Day 1, subjects should remain at the site for monitoring (with immediate access to medical resuscitation equipment) for at least 3 hours following the end of the oleclumab infusion.

[d] Assessments will be collected prior to administration of any investigational product. If screening assessments have been performed within the 5 days prior to Day 1 (Days -5 to -1), then assessment does not need to be performed on Day 1 pre-dose. All safety laboratory results must be reviewed by the investigator or physician designee prior to administration of any investigational product.

[e] Females of childbearing potential only, if urine test is positive or equivocal then serum β-hCG testing should be performed for confirmation.

[f] Subjects with pelvic disease and/or brain metastases at screening or subjects who develop neurologic or other clinical symptoms that warrant imaging must have pelvic and/or brain imaging with each disease assessment. Disease assessments will be performed during the treatment period or as indicated by signs/symptoms. If radiographic progression is observed in the absence of clinical deterioration, a confirmatory scan should be performed not less than 4 weeks later. If clinical deterioration occurs then a confirmatory scan is not required.

[g] On oleclumab dosing days, the administration of osimertinib should precede the oleclumab infusion.

[h] On Days 1 and 29 plasma samples for osimertinib PK will be collected pre-dose (within 90 minutes prior to dosing osimertinib) and 60 minutes (± 5 minutes), 2 hours (± 10 minutes), and 4 hours (± 15 minutes) post-dose. For all other visits, PK will be collected pre-dose.

[i] Serum samples for oleclumab PK will be collected pre-dose (within 90 minutes prior to start of oleclumab infusion) and 10 minutes (± 5 minutes) post end of oleclumab infusion

Table 4 Treatment Period Study Procedures - Arm B (Oleclumab + AZD4635)

Study Period	**Treatment Period**								
Visit Number	**V2**	**V2a Dose Escalation only**	**V3**	**V4**	**V5**	**V6**	**V7**	**V7a Dose Escalation Only**	**V8-Vn**
Procedure/ Study Day	**Day 1**	**Day 2**	**Day 8**	**Day 15 (± 1 day)**	**Day 29 (± 1 day)**	**Day 43 (± 3 days)**	**Day 57 (± 3 days)**	**Day 58**	**Q2W (± 3 days) Starting on D71 (unless otherwise noted)**
Clinical Assessments:									
Verify eligibility criteria	X								
Physical examination (abbreviated, symptom directed)	X[a]			X	X		X		Q4W (± 3D) starting on D85
ECOG	X				X		X		Q4W (± 3D) starting on D85
Weight	X				X		X		Q4W (± 3D) starting on D85
ECG[b]	X[b]		X	X	X		X[b]		D113 (± 3D) only
Vital signs[c]	X	X	X	X	X	X	X		X
Assessment of AEs/SAEs	All visits								
Concomitant medications	All visits								
Laboratory Assessments[d]:									
Serum chemistry[d]	X		X	X	X	X	X		X
Hematology[d]	X		X	X	X	X	X		X

Table 4 Treatment Period Study Procedures - Arm B (Oleclumab + AZD4635)

Study Period	**Treatment Period**								
Visit Number	**V2**	**V2a Dose Escalation only**	**V3**	**V4**	**V5**	**V6**	**V7**	**V7a Dose Escalation Only**	**V8-Vn**
Procedure/ Study Day	**Day 1**	**Day 2**	**Day 8**	**Day 15 (± 1 day)**	**Day 29 (± 1 day)**	**Day 43 (± 3 days)**	**Day 57 (± 3 days)**	**Day 58**	**Q2W (± 3 days) Starting on D71 (unless otherwise noted)**
TSH and free T_4 (If TSH is normal then free T_4 is not required)[d]	X				X		X		Q4W (± 3D) starting on D85
Lipid Panel[d]	X						X		Q8W (± 3D) starting on D113
Pregnancy test[d, e]	X						X		Q8W (± 3D) starting on D113
Urinalysis[d]	X						X		Q8W (± 3D) starting on D113
Efficacy:									
Disease assessment (scans)[f]							X		Q8W (± 3D) starting on D113 through D393 then Q12W (± 3D)
Study Drug Administration:									
Oleclumab[g]	X			X	X	X	X		X
AZD4635[g, h]	X (daily dosing)								
Pharmacokinetics/CCI :									
Plasma for AZD4635 PK[i]	X	X		Pre-dose	Pre-dose		X	X	D113 (± 3D) only

Table 4 Treatment Period Study Procedures - Arm B (Oleclumab + AZD4635)

Study Period	Treatment Period								
Visit Number	**V2**	**V2a Dose Escalation only**	**V3**	**V4**	**V5**	**V6**	**V7**	**V7a Dose Escalation Only**	**V8-Vn**
Procedure/ Study Day	**Day 1**	**Day 2**	**Day 8**	**Day 15 (± 1 day)**	**Day 29 (± 1 day)**	**Day 43 (± 3 days)**	**Day 57 (± 3 days)**	**Day 58**	**Q2W (± 3 days) Starting on D71 (unless otherwise noted)**
Serum for oleclumab PK[j]	X				X		X		Q12W (± 3D) starting on D141
Serum for oleclumab ADA[d]	X				X		X		Q12W (± 3D) starting on D141
CCI									
CCI									
CCI									
CCI									

ADA = anti-drug antibody; AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CCI ECG = electrocardiogram; D = Day(s); ECOG = Eastern Cooperative Oncology Group; PK = pharmacokinetics; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SAE = serious adverse event; T_4 = thyroxine; THS = thyroid-stimulating hormone; V = Visit.

[a] Physical examination can be performed up to 24 hours prior to dosing on Day 1.

[b] All ECGs will be obtained in triplicate (all within a 5-minute time period). ECGs will be recorded prior to the administration of any investigational product and within 30 minutes post end of oleclumab infusion. For AZD4635, triplicate ECGs will also be performed on the extensive PK sampling days at 1, 2, and 4 hours (±15 minutes) post-dose on Day 1 and Day 57.

[c] On days of oleclumab investigational product administration, vital signs will be measured according to the following schedule: Within 60 minutes prior to start of oleclumab infusion then every 30 minutes (± 5 minutes) during the infusion, the end of infusion (± 5 minutes), and 30 minutes (± 10 minutes) post end of oleclumab infusion. On Day 1, additional vital sign measurements will be taken at 60 minutes (± 10 minutes) and 3 hours (± 15 minutes) post end of oleclumab infusion. On Day 1, subjects should remain at the site for monitoring (with immediate access to medical resuscitation equipment) for at least 3 hours following the end of the oleclumab infusion.

[d] Assessments will be collected prior to administration of any investigational product. If screening assessments have been performed within the 5 days prior to Day 1 (Days -5 to -1), then assessment does not need to be performed on Day 1 pre-dose. All safety laboratory results must be reviewed by the investigator or physician designee prior to administration of any investigational product.

[e] Females of childbearing potential only, if urine test is positive or equivocal then serum β-hCG testing should be performed for confirmation.

[f] Subjects with pelvic disease and/or brain metastases at screening or subjects who develop neurologic or other clinical symptoms that warrant imaging must have brain and/or pelvic imaging with each disease assessment. Disease assessments will be performed during the treatment period or as indicated by signs/symptoms. If radiographic progression is observed in the absence of clinical deterioration, a confirmatory scan should be performed not less than 4 weeks later. If clinical deterioration occurs then a confirmatory scan is not required.

[g] On oleclumab dosing days, the administration of AZD4635 should precede the oleclumab infusion.

[h] All doses of AZD4635 should be taken at approximately the same times each day, in a fasted state (water to drink only) from at least 2 hours prior to the dose to at least 1 hour post-dose.

[i] **For all subjects:** On Day 1 and Day 57, plasma samples for AZD4635 PK will be collected pre-dose (within 90 minutes prior to dosing AZD4635) and 60 minutes (± 5 minutes), 2 hours (± 10 minutes), and 4 hours (± 15 minutes) post-dose. On Day 15 and Day 29, plasma samples for AZD4635 PK will be collected pre-dose (within 90 minutes prior to dosing AZD4635). On Day 113, plasma samples for AZD4635 PK will be collected pre-dose and within 30 minutes (± 10 minutes) post end of oleclumab infusion to coincide with the ECG collection.
For subjects in Dose-Escalation: On Day 1 and Day 57, additional plasma samples for AZD4635 PK will be collected 6 hours (± 15 minutes) and 24 hours (± 120 minutes) post-dose. The 24 hour (± 120 minutes) post-dose plasma sample for the Day 1 and Day 57 visits will be collected at V2a (Day 2) and V7a (Day 58), respectively. Visits 2a and 7a are only required for subjects in dose-escalation.

[j] Serum samples for oleclumab PK will be collected pre-dose (within 90 minutes prior to start of oleclumab infusion) and 10 minutes (± 5 minutes) post end of oleclumab infusion.

4.2.3 Follow-up Period

Table 5 shows all procedures to be conducted during the follow-up period.

Table 5 Schedule of Follow-up Procedures (All Arms)

Study Period	Follow-up Period	
Visit Number	**EOT-1**	**EOT-n**
Procedure/Study Day	**30 Days Post Last Dose (± 7 Days)**	**Q12W (± 7 days) Starting 90 Days Post Last Dose**
Clinical Assessments:		
Physical examination (abbreviated, symptom directed)	X	
Weight	X	
ECOG	X	
ECG[a]	X	
LVEF by echocardiogram/MUGA (Arm A only)[b]	X	
Vital signs	X	
Assessment of AEs/SAEs	X	Only EOT-2
Concomitant medications	X	
Follow-up for survival and subsequent anticancer treatment (telephone contact if visits are discontinued)		X
Laboratory Assessments:		
Serum chemistry	X	
Hematology	X	
TSH and free T_4 (If TSH is normal then free T_4 is not required)	X	
Lipid panel	X	
Pregnancy test[c]	X	
Urinalysis	X	
Efficacy:		
Disease assessment (scans)[d]	X	X
Pharmacokinetics CCI **:**		
Serum for oleclumab PK		Only EOT-2
Serum for oleclumab ADA		Only EOT-2
CCI [redacted]		

ADA = anti-drug antibody; AE = adverse event; β-hCG = beta-human chorionic gonadotropin; CCI [redacted] ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; LVEF = left ventricular ejection fraction; MUGA = multigated acquisition scan; PD = progressive disease; PK = pharmacokineteic; Q12W = every 12 weeks; SAE = serious adverse event; T_4 = thyroxine; THS = thyroid-stimulating hormone.

[a] All ECGs will be obtained in triplicate (all within a 5-minute time period).

[b] Echocardiogram/MUGA are only required for subjects that were enrolled in Arm A. If the subject had an evaluation in the preceding 4 weeks this assessment is not required. However, a follow-up assessment will be required if the on-treatment assessment was abnormal at the time of discontinuation of investigational product, to confirm reversibility of the abnormality.

[c] Females of childbearing potential only, if urine test is positive or equivocal then serum β-hCG testing should be performed for confirmation.

[d] If a subject discontinues treatment, the EOT-1 disease assessment is only required if it has been > 28 days since the last disease assessment. Disease assessment should then continue Q12W starting with EOT-2 date for subjects who discontinued treatment due to reasons other than PD.

4.3 Description of Study Procedures

4.3.1 Efficacy

The primary assessment of tumor response will be based on RECIST version 1.1 (Eisenhauer et al, 2009) and will be performed according to the schedule in Section 4.2. All images will be collected and stored for possible future central re-analysis. The assessment schedule also applies to those subjects who continue to receive study therapy in the setting of PD (Section 4.1.7). For those subjects who discontinue study therapy as a result of confirmed PD, disease evaluation will be performed at the end of treatment visit if clinically appropriate (ie, in the absence of rapidly deteriorating clinical status). After discontinuation of investigational product(s), all subjects will complete the end of treatment visit and enter follow-up; disease evaluation will be performed according to the schedule in Table 5. Additional disease assessments may be performed as clinically indicated. All subjects will be followed for survival until the end of the study (defined as 2 years after the last subject begins treatment with investigational product or when the sponsor stops the study, whichever occurs earlier [Section 6.3]).

Tumor assessments may include the following evaluations: physical examination (with photograph and measurement of skin lesions as applicable); cross-sectional imaging using CT or MRI scan of the chest, abdomen, pelvis; and brain. Computed tomography or MRI scan of the chest and abdomen will be performed with each disease assessment for all subjects. Additionally, CT or MRI scan of the pelvis and brain will be performed at screening for all subjects. Any subjects with pelvic disease and/or brain metastases at screening or any subjects who develop neurologic or other clinical symptoms that warrant imaging must also have pelvic and/or brain imaging with each disease assessment. 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 CNS imaging is MRI; if CT scan is performed,

CT with contrast is required. The same method is preferred for all subsequent tumor assessments.

Physical examination

- Lesions detected by physical examination will only be considered measurable if superficial, eg, skin nodules and palpable lymph nodes. Documentation by color photography including ruler is recommended for estimating the size of skin lesions.

Computed tomography scan

- Computed tomography (contrast preferred) scans of the chest, abdomen, and pelvis 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

- Magnetic resonance imaging scan of the chest, abdomen, and pelvis 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.

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.

RECIST Version 1.1 Response Criteria

Evaluation of Target Lesions

- **Complete Response** - 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).
- **Partial Response** - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease** - 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 progression.)
- **Stable Disease** - 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

- **Complete Response** - 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-complete response/Non-progressive disease** - Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease** - 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 stable disease (SD) or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy (see Section 4.1.7). In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST version 1.1. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive study therapy if investigators consider that subjects continue to benefit from treatment (see Section 4.1.7).

Evaluation of Overall Response

For the overall response based on RECIST version 1.1, confirmation of CR and PR is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. A confirmatory scan will also be required after an initial assessment of PD for the purpose of managing treatment [redacted]. If a subject discontinues the study due to PD and begins another treatment, a confirmatory scan is not required. Treatment of subjects may continue between the initial assessment of PD and confirmation of PD (which is not required by RECIST version 1.1). These subjects may continue to receive study therapy beyond confirmed PD in accordance with Section 4.1.7 and if investigators consider that subjects continue to receive benefit from treatment. In the absence of clinical deterioration, such modifications to the RECIST may discourage the early discontinuation of treatment and provide a more complete evaluation of study therapy antitumor activity than would be seen with conventional response criteria.

Table 6 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 6 Evaluation of Overall Response

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

[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.

4.3.1.1 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted]

Table 7 CCI

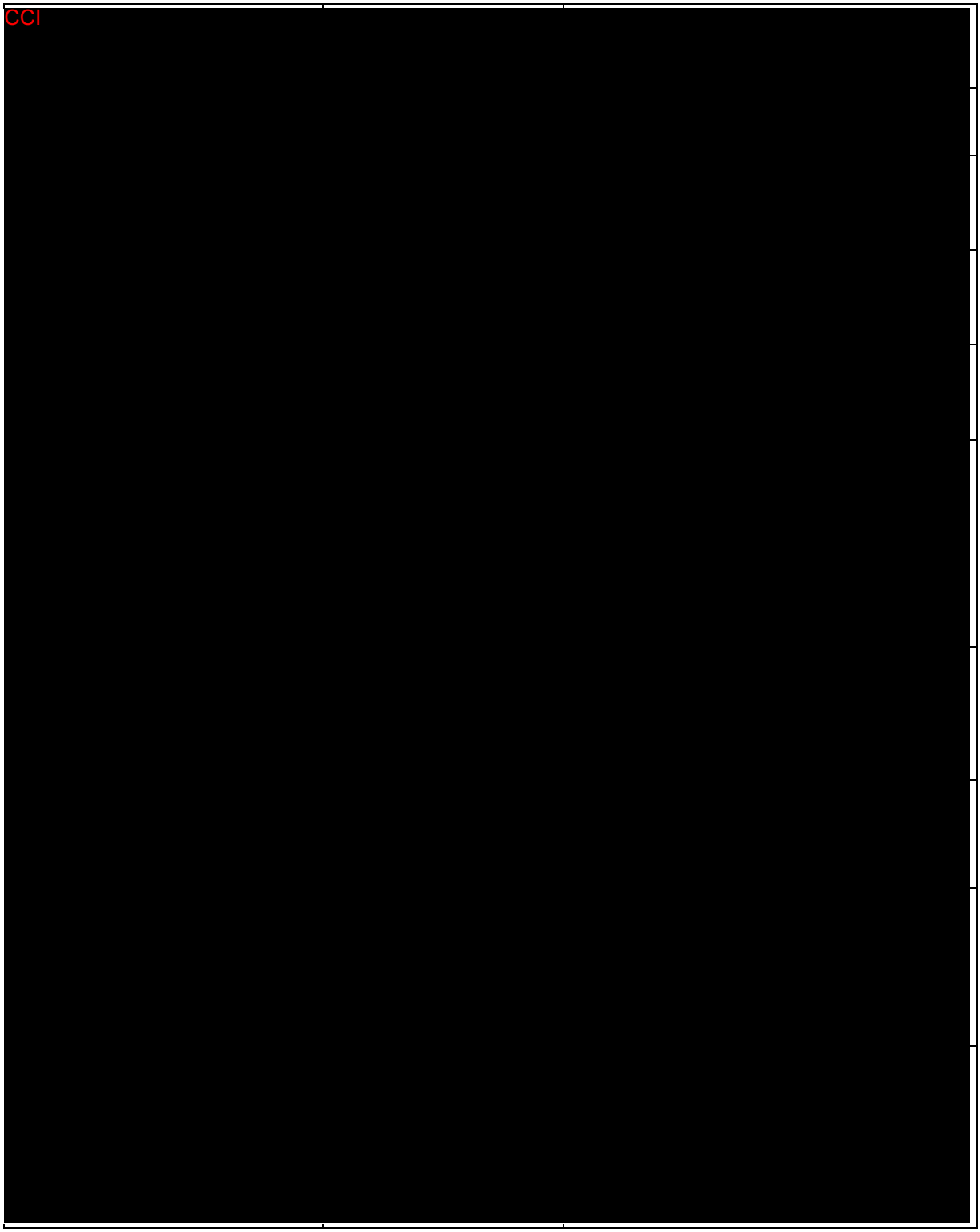


Table 7 CCI [redacted]

CCI [redacted]		

CCI [redacted]

4.3.1.2 CCI [redacted]

CCI [redacted]

4.3.2 Medical History, Physical Examination, Ophthalmologic Examination, Electrocardiogram, Echocardiogram/MUGA, Weight, 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 schedule 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, GI, 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.

Ophthalmologic Examination (Arm A only)

Full ophthalmologic assessment, including slit lamp, testing of visual acuity and ophthalmoscopic examination, should be performed at screening and if a subject experiences any visual symptoms, with additional tests if clinically indicated (Section 4.2).

Ophthalmologic examination results should be collected in the electronic case report form (eCRF).

Vital Signs

Vital signs (temperature, BP, pulse rate, and respiratory rate) will be measured according to the schedule 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. Pulse oximetry will be assessed at screening only (Section 4.2.1). On Day 1, subjects should remain at the site for monitoring (with immediate access to medical resuscitation equipment) for at least 3 hours following the end of the oleclumab infusion.

Electrocardiograms

According to the schedule in Section 4.2, 12-lead ECGs will be obtained by the site in triplicate (all 3 within a 5-minute time period) after the subject has been in supine or semi-recumbent rest for 10 minutes. Electrocardiograms will be recorded prior to the administration of any investigational product and within 30 minutes post end of oleclumab infusion on the day of the visit. In Arm B, triplicate ECGs will also be performed on the extensive AZD4635 PK sampling days at 1, 2, and 4 hours post-dose on Day 1 and Day 57 (Table 4).

In case of clinically significant ECG, abnormalities including an ECG that demonstrates a QTcF value > 500 msec, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation based on the average QTcF value manually over-read by a medically qualified person.

Cardiac Left Ventricular Function Assessed by Echocardiogram/MUGA (Arm A only)

Assessment of cardiac left ventricular function will be performed by echocardiogram/MUGA according to the schedule in Section 4.2. Subjects should have high quality standardized 2-D echocardiographic examinations performed by an experienced sonographer (preferably with the same sonographer performing all studies for a given subject). LVEF determinations should be determined quantitatively based on bi-plane measurements of end diastolic and end systolic left ventricular volumes.

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.

Routine clinical laboratory safety tests (serum chemistry, lipid panel, hematology, urinalysis, thyroid function, coagulation, and pregnancy tests) will be performed in a local clinical

laboratory. Clinically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed at the visits specified in Section 4.2:

Serum Chemistry

• Sodium	• Total bilirubin
• Potassium	• ALP
• Bicarbonate	• Albumin
• Blood urea nitrogen	• Gamma-glutamyl transpeptidase
• Creatinine	• Total protein
• Glucose	• Lactate dehydrogenase
• Calcium	• Uric acid
• Magnesium	• Amylase
• AST	• Lipase
• ALT	

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase.

Note for serum chemistry: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently. If a site is unable to perform serum chemistry testing and all testing is available on plasma samples this alternative method is acceptable.

Lipid Panel

• Total Cholesterol
• Triglycerides

Hematology

• White blood cells count	• Absolute monocyte count
• Absolute neutrophil count	• Hemoglobin
• Absolute lymphocyte count	• Platelet count

Urinalysis

• Protein	• Blood
• Ketones	• If abnormal, then microscopy including WBC/HPF, RBC/HPF

HPF = high power field; RBC = red blood cells; WBC = white blood cells.

Pregnancy Test (females of childbearing potential only)

• Urine hCG
• Serum β-hCG (at screening only and if a urine hCG is equivocal or positive during the remainder of the study)

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

Other Safety Tests

- Coagulation tests: prothrombin time, partial thromboplastin time, fibrinogen. International normalized ratio can be obtained instead of prothrombin time but should remain consistent throughout the study.
- Hepatitis B testing: hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, IgM hepatitis B core antibody. If hepatitis B core (total) antibody testing is unavailable, then the hepatitis B core IgG and IgM should both be obtained instead. If a test is not locally available, then standard local practice for assessing hepatitis B status should be utilized. If screening tests are positive, a hepatitis B virus (HBV)-DNA test should be obtained to assess infection status.
- Hepatitis C antibody. If screening antibody is positive, a hepatitis C virus (HCV)-RNA test should be performed to assess infection status.
- Human immunodeficiency virus-1 antibody
- Thyroid function tests: thyroid stimulating hormone (TSH) and free thyroxine (T4). Note: If TSH is normal then free T_4 is not required.

4.3.4 Pharmacokinetic Evaluation and Methods

Blood will be collected to evaluate PK of oleclumab in serum and PK of osimertinib and AZD4635 in plasma (see Section 4.2 or collection time points). The PK of oleclumab in serum and the PK of osimertinib and AZD4635 in plasma will be measured utilizing a validated assay.

Pharmacokinetic analysis of the plasma data for osimertinib, AZD4635, and their metabolites will be performed. The actual sampling times will be used in the parameter calculations and appropriate PK parameters after single and multiple doses will be derived using standard non-compartmental methods.

Blood samples will be collected for measurement of oleclumab (see Section 4.2 for collection time points). Evaluations will be performed using a validated assay.

4.3.5 Immunogenicity Evaluation and Methods

Blood samples will be collected prior to administration of any investigational product to evaluate ADA responses to oleclumab in serum (see Section 4.2 for collection time points). Evaluations will be performed using a validated assay.

4.3.6 CCI

CCI [redacted]

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

4.3.7 Estimate of Volume of Blood to Be Collected

A total of no more than 57 mL (12 teaspoons) of blood will be required for all screening tests, which may be conducted over 1 or more days during screening. No more than 72 mL (15 teaspoons) of blood will be drawn on any visit day after screening. Up to 120 mL (24 teaspoons) of blood will be collected between Days 1 through 28 after the first dose of oleclumab within any cohort. The total volume to be collected will depend on the number of doses administered and the length of follow-up.

4.4 Expected Start and End of Study

The study started on 08 May 2018 (first subject screening visit). The data entry cut-off in support of final database lock will occur approximately 12 months + 90 days follow up after the last subject is administered the first dose of investigational product. Data analysis will be performed and a CSR will be written based on the final database lock.

Any subject still receiving investigational product at the time of this data entry cut-off will continue to receive investigational product within the current study through a continued treatment period (managed by the sponsor's Post Analysis and Reporting Team [PART] program) as long as, in the Investigator's opinion, the subject is deriving clinical benefit and has not fulfilled any discontinuation criteria. During this continued treatment period, assessments will revert to the standard of care for each individual site. Data will not be entered into the clinical study database after the data entry cut-off date. During this continued treatment period, all SAEs, overdoses, and pregnancies will be reported until 28 days after the last dose of investigational product. Paper based SAE reporting will be used by the study sites

during this period. Reported SAE data will be entered into the sponsor's global safety database. Investigational product dispensation and reconciliation will be handled by the study site at each subject's visit. The investigational product accountability information must still be collected until all subjects have completed treatment. Individual sites will be closed after database lock has occurred and once their final subject completes the 28-day follow-up visit. The continued treatment period will remain available to subjects until the Last Subject Last Visit which is defined as the date of the last subject's 28-day safety follow-up visit.

4.5 Study Suspension or Termination

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

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Non-compliance that might significantly jeopardize the validity or integrity of the study
- Sponsor decision to terminate development of the investigational product for this indication
- Sponsor decision to terminate the study or any treatment arm based on continuous interim monitoring (Sections 4.9.7 and 4.9.8)

If MedImmune determines that temporary suspension or permanent termination of the study or any treatment arm 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 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 or its representatives 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.6 Investigational Products

4.6.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 8) using designated distribution centers.

Table 8 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Oleclumab (MEDI9447)	MedImmune	Supplied as a 200-mg sterile lyophilized product for infusion after reconstitution and dilution. After reconstitution with sterile WFI, the solution contains 50 mg/mL oleclumab (MEDI9447) in 25mM histidine/histidine hydrochloride, 240 mM sucrose, 0.03% (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 4.0 mL.
		Supplied as a 500-mg sterile solution for infusion after dilution. The solution contains 50 mg/mL oleclumab (MEDI9447) in 25mM histidine/histidine hydrochloride, 240 mM sucrose, 0.03% (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL.
Osimertinib	AstraZeneca	Supplied as beige, film-coated tablets containing either 40 or 80 mg of osimertinib expressed as free base (equivalent to 47.7 and 95.4 mg of osimertinib mesylate, respectively). Osimertinib tablets contain osimertinib mesylate, mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose and sodium stearyl fumarate. The tablet film-coat contains polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, yellow iron oxide, red iron oxide and black iron oxide.
AZD4635	AstraZeneca	Supplied as a white powder containing 5.5% w/w AZD4635 drug substance, hydroxypropyl methyl cellulose, docusate sodium, poloxamer 188, and sucrose.

WFI = water for injection; w/v = weight/volume; w/w = weight per weight.

Oleclumab (MEDI9447) is supplied in 10R vials as a sterile, white to off white, lyophilized product or a as a sterile liquid drug product. The lyophilized product, after reconstitution with

4.0 mL sterile water for injection (WFI), and the liquid product are both clear to opalescent, colorless to slightly yellow liquids, free from or practically free from visible particles and contain 50 mg/mL oleclumab (MEDI9447) in 25 mM histidine/histidine hydrochloride, 240 mM sucrose, 0.03% (weight/volume [w/v]) polysorbate 80, at pH 6.0. Oleclumab (MEDI9447) will be diluted into an IV bag containing 0.9% (w/v) saline and administered via IV infusion.

Osimertinib is supplied as beige, film-coated tablets (Table 8) for oral administration. Osimertinib tablets are packed in high-density polyethylene bottles with child-resistant closures. The packaging includes bottles, caps and a label. Each investigational product bottle has a unique number that is printed on the label.

The AZD4635 nano-milled, spray dried powder for oral suspension is presented as a white powder containing 5.5% weight per weight AZD4635 drug substance (Table 8). The bulk drug will be weighed out at a contracted compounding pharmacy into amber polyethylene terephthalate bottles with child-resistant screw caps. A portion of AZD4635 powder for oral suspension will be supplied to sites or by delivery directly to the subject in prefilled bottles with child-resistant screw caps, to support clinical doses from 25 to 100 mg. The drug product will be constituted extemporaneously as an oral suspension by the subject immediately prior to dosing. The aqueous suspending vehicle contains 2 mg/mL simethicone. Further details on the method of constitution will be provided in the Handling Instructions.

4.6.1.1 Investigational Product Inspection

Remove the required number of oleclumab (MEDI9447) vials from storage at 2°C to 8°C (36°F to 46°F).

- 750 mg dose: 4 vials of lyophilized product or 2 vials of liquid product
- 1500 mg dose: 8 vials of lyophilized product or 3 vials of liquid product
- 3000 mg dose: 15 vials of lyophilized product or 6 vials of liquid product

Each vial selected for dose preparation should be inspected.

If any defects are noted with the investigational product(s), the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.6.1.5) for further instructions.

4.6.1.2 Oleclumab (MEDI9447) IV Bag Preparation and Administration

The oleclumab (MEDI9447) dose must be prepared by an investigator or site-designated investigational product manager using aseptic technique.

Total time from needle puncture of the oleclumab (MEDI9447) 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 (MEDI9447) does not contain preservatives, and any unused portion must be discarded.

Reconstitution Procedure for Oleclumab (MEDI9447) Lypholized Product

Oleclumab (MEDI9447) investigational product requires reconstitution with sterile WFI prior to use. Clean the rubber stopper of the oleclumab (MEDI9447) vial with 70% ethanol or equivalent and allow to air dry. Slowly add 4.0 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. Let the vial sit for 60 seconds before swirling the vial. Gently swirl the vial by rotating the vial for 60 seconds and then let it sit for 60 seconds. Repeat this procedure until all the solids are dissolved. DO NOT SHAKE OR VIGOROUSLY AGITATE THE VIAL. At the end of the reconstitution invert the vial to dissolve any product that might be on the cap. Visually inspect the solution to ensure that entire content of 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.

Oleclumab (MEDI9447) IV Bag Preparation and Administration

No incompatibilities between oleclumab (MEDI9447) and polyvinyl chloride or polyolefin IV bags have been observed.

The dose of oleclumab (MEDI9447) will be administered using an IV bag containing 0.9% (w/v) saline, with a final in-bag oleclumab (MEDI9447) concentration ranging from 1.5 to 30 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. The desired dose is prepared by adding the following volume of reconstituted or liquid oleclumab (MEDI9447) product to the IV bag: 15.0 mL for the 750 mg dose; 30.0 mL for the 1500 mg dose; or 60.0 mL for the 3000 mg dose. The IV bag size should be selected such that the final concentration is within 1.5 to 30 mg/mL. Mix the bag gently to ensure homogeneity of the bag.

Oleclumab (MEDI9447) will be administered at room temperature (approximately 20 to 25°C) by controlled infusion into a peripheral or central vein. Standard infusion time for oleclumab (MEDI9447) is one 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.

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 and document if the line was not flushed.

4.6.1.3 Treatment Administration

The first day of dosing is considered Day 1. The administration of osimertinib (Arm A) or AZD4635 (Arm B) will precede the oleclumab (MEDI9447) infusion.

After Day 1, at visits that coincide with oleclumab (MEDI9447) dosing days, the subject should bring the osimertinib or AZD4635 dose for that day to the site. On these visits, after predose assessments, the administration of osimertinib (Arm A) or AZD4635 (Arm B) will also precede the oleclumab (MEDI9447) infusion.

Whenever possible, osimertinib and AZD4635 should be taken at approximately the same time each day. Dosing details will be captured in the subject dosing diary.

Oleclumab (MEDI9447)

Dose preparation and administration instructions are provided in Section 4.6.1.2 for oleclumab (MEDI9447). 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. Investigational product must not be administered via IV push or bolus but as a slow IV infusion. The entire content of each IV bag will be infused using an infusion pump.

Osimertinib

One bottle of osimertinib will be dispensed during select oleclumab (MEDI9447) administration visits. Bottles will be dispensed to subjects in the original packing provided. The packaging includes bottles, caps, and a label. Bottle tampers should not be broken prior to dispensing study drug to a subject.

Osimertinib will be administered PO QD. Osimertinib should be taken at approximately the same time each day and can be taken with or without food.

Should a subject miss a scheduled dose of osimertinib, the subject will be allowed to take the dose up to a maximum of 12 hours after the scheduled dose time. If greater than 12 hours after the scheduled dose time, the missed dose should not be taken and the reason noted in the diary. The subject should take the allotted dose at the next scheduled time.

AZD4635

AZD4635 will be dispensed to subjects at scheduled visits to the clinic or by delivery directly to the subject. Dosing and handling instructions and subject emergency contact details will be provided to subjects in writing.

AZD4635 will be administered orally as a nanosuspension PO QD, unless safety findings indicate that a change to this is required.

Whenever possible, AZD4635 should be taken at approximately the same time each day, in a fasted state (water to drink only) from at least 2 hours prior to the dose to at least 1 hour post-dose. The recommendation is for water only during this time period, but subjects should also be reminded that beverages containing caffeine are to be avoided during this time period. The fasting requirement may be reassessed, modified, or removed based on emerging data if appropriate. If vomiting occurs after AZD4635 dosing, the subject should not re-dose, but should note it in the diary.

Should a subject miss a scheduled dose, the subject will be allowed to take the dose up to a maximum of 4 hours after the scheduled dose time. If greater than 4 hours after the scheduled dose time, the missed dose should not be taken and the reason noted in the diary. The subject should take the allotted dose at the next scheduled time. If a subject needs to take the dose earlier for any reason, the subject can take the dose up to 4 hours earlier than the scheduled dose time. The subject should make every reasonable effort to take the study drugs on time.

4.6.1.4 Monitoring of Dose Administration

Subjects will be monitored during and after infusion of oleclumab (MEDI9447). Vital signs will be measured according to the schedule described in Section 4.2.2.

Management of investigational product-related toxicities are described in Section 3.1.4. Acetaminophen and/or an antihistamine (eg, diphenhydramine) may be administered at the discretion of the investigator. If the IRR is severe or prolonged, methylprednisolone 100 mg (or the equivalent) should be administered as well. Investigators may administer steroids at their discretion as clinically indicated and per their institution's guidelines. The medical monitor should be informed if steroids are utilized for management of an IRR.

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.

4.6.1.5 Reporting Product Complaints

Any defects with the investigational product(s) must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site

monitor. All defects will be communicated to MedImmune and investigated further with the Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

Email: PPD

Phone: PPD
PPD

Fax: PPD

Mail: MedImmune
Attn: Product Complaint Department
One MedImmune Way,
Gaithersburg, MD USA 20878

4.6.2 Additional Study Medications

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

4.6.3 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.

4.6.4 Storage

Oleclumab (MEDI9447) investigational product vials should be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Vials should be kept in secondary packaging to avoid prolonged exposure to light.

The AZD4635 powder for oral suspension should be stored in the pack provided according to the storage conditions on the label.

Osimertinib should be stored below 30°C (86°F) with desiccant.

4.6.5 Treatment Compliance

Oleclumab (MEDI9447) is administered by study site personnel, who will monitor compliance.

Osimertinib and AZD4635 should only be used as directed in this protocol. Subjects should return all unused medication and empty containers to the investigator.

Details of treatment with investigational products for each subject will be recorded in the eCRF.

4.6.6 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 according to investigational site policy.

4.7 Treatment Assignment and Blinding

4.7.1 Methods for Assigning Treatment Groups

Each subject who meets the eligibility criteria will be assigned open-label investigational product.

An IXRS will be used for assignment of unblinded investigational product kit numbers. A subject is considered entered into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of unblinded investigational product kit numbers to the subject.

Oleclumab must be administered within 1 business day after the investigational product is assigned. If there is a delay in the administration of oleclumab such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

4.7.2 Methods to Ensure Blinding

This study is not blinded.

4.8 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 end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

4.8.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 4.8.2. Specifically, subjects should receive full supportive care during the

study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

Specific to Osimertinib (Arm A)

If medically feasible, subjects taking regular medication, with the exception of potent inducers of CYP3A4 (Section 4.8.2), should be maintained on it throughout the study period. Subjects taking concomitant medications whose disposition is dependent upon BCRP and which have a narrow therapeutic index should be closely monitored for signs of changed tolerability as a result of increased exposure of the concomitant medication whilst receiving osimertinib. Guidance on medications to avoid, medications that require close monitoring and on washout periods is provided (see Sections 4.8.2 and 10.9).

Subjects taking rosuvastatin should have creatine phosphokinase levels monitored (due to BCRP-mediated increase in exposure). If the subject experiences any potentially relevant AEs suggestive of muscle toxicity including unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever, rosuvastatin must be stopped and any appropriate further management should be taken.

Specific to AZD4635 (Arm B):

Subjects who are already taking erythropoietin at the time of screening for the study may continue it provided they have been taking it for more than one month at the time investigational product is started. Prophylactic erythropoietin should not be started during the first 3 weeks of any cohort, but may be started thereafter.

Granulocyte colony stimulating factors should not be used prophylactically during the first 3 weeks of any cohort. Use of prophylactic colony stimulating factors may be considered thereafter following discussion with the Medical Monitor.

4.8.2 Prohibited Concomitant Medications

Other than the medications described above, use of concomitant medications including over-the-counter medications, vitamins, etc is discouraged. Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The sponsor must be notified if a subject receives any of these during the study.

- Any investigational anticancer therapy
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of

hormones for non-cancer-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. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal and 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 investigational product
- Herbal supplements or herbal/natural remedies

Specific to Osimertinib (Arm A):

Concomitant use of any medications, herbal supplements and/or ingestion of foods with known inducer effects on CYP3A4 is prohibited (Table 21).

The medications listed in Table 23 are known to prolong QT interval and should not be combined with osimertinib.

Guidance regarding prohibited medications and potential interactions with concomitant medications for osimertinib are presented in Section 10.9.

Specific to AZD4635 (Arm B):

The following treatments and the medications listed in Section 10.10 are prohibited or are to be used with caution while in this study

- Beverages containing caffeine should be avoided for a time period from 2 hours before a dose of AZD4635 through 1 hour post-dose. Moderate use of caffeine-containing beverages at other times is not restricted, but subjects should be advised not to increase their average daily consumption.
- Contribution of CYP1A2 to AZD4635 metabolism appears to be approximately 80% (AZD4635 Investigator's Brochure). Therefore, potent or moderate inhibitors or inducers of CYP1A2 and substrates of CYP1A2 are prohibited during administration of AZD4635. Refer to Section 10.10 for a list of the restricted medications.
- The use of warfarin is prohibited during treatment with AZD4635 (Section 10.10).
- Since AZD4635 is an in vitro inhibitor of BCRP (IC_{50} 6.2 µM) and OAT1 (IC_{50} 6.6 µM), there is a risk of drug-drug interactions with sensitive substrates of BCRP (both in the gut and systemically) and OAT1 (systemically). Modeling has predicted a substantial increase in the exposure (> 2 fold) of certain statins (simvastatin, rosuvastatin, and atorvastatin) when co-administered with AZD4635. Therefore, the use of sensitive substrates of BCRP and OAT1 is prohibited in the current study (Section 10.10). Other drugs for which the

disposition is mediated via BCRP/OAT1 should be administered with caution, considered for dose modification, or substituted with an alternative drug.

- Herbal preparations/medications and certain foods that are reported to be potent inhibitors/inducers of CYP1A2 are not allowed throughout the study. These herbal medications include, but are not limited to: St. John's wort, kava, ephedra (ma huang), gingko biloba, DHEA, yohimbe, saw palmetto, and ginseng. Subjects should stop using all herbal medications 14 days prior to first dose of AZD4635.
- Subjects should avoid medications or drugs that increase risk for seizure (eg, tricyclic antidepressants, pseudoephedrine, anesthetics, amphetamines, cocaine).

4.9 Statistical Evaluation

4.9.1 General Considerations

Tabular summaries will be presented by dose cohort within each 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, including mean, standard deviation, median, minimum, and maximum. Additional details of statistical analyses will be described in the statistical analysis plan.

The As-treated Population is defined as all subjects who receive any investigational product, analyzed according to treatment received. All analyses will be performed on the As-treated Population unless otherwise specified.

The Response-evaluable Population is defined as all subjects who receive any investigational product, had measurable disease at baseline and at least 1 post-baseline tumor assessment, or who died from any cause or who discontinued due to clinical PD prior to any post-baseline tumor assessment.

The DLT-evaluable Population is defined as all subjects who receive all planned doses of oleclumab and at least 75% of the daily administrations of osimertinib (Arm A) or AZD4635 (Arm B) during the DLT-evaluation period (defined in Section 3.1.3.3) and complete the safety follow-up through the DLT-evaluation period or experience any DLT.

4.9.2 Sample Size

A total of up to approximately 98 subjects will be enrolled in this study, up to approximately 46 subjects in Arm A and up to approximately 52 subjects in Arm B.

CCI [redacted]

CCI

CCI

Table 9 CCI

CCI

4.9.3 Safety

4.9.3.1 Analysis of Safety Endpoints

Safety data, including DLTs, AEs, SAEs, laboratory evaluations, vital signs, cardiac left ventricular function (Arm A only), and ECG results will be summarized based on the As-treated Population defined in Section 4.9.1. Summary statistics will be provided for AEs, SAEs, AE grade (severity), and relationship to investigational product(s), clinical laboratory parameters, vital signs, cardiac left ventricular function (Arm A only) and ECG. Adverse events will be graded according to the NCI CTCAE version 4.03.

Summary of safety data will be based on the reporting period for each endpoint (see Section 5.4.1 for AEs and SAEs and Section 4.2 for laboratory parameters, vital signs, cardiac left ventricular function [Arm A only], and ECG results).

4.9.4 Efficacy Analyses

4.9.4.1 Analysis of Efficacy Endpoints

The efficacy analyses of antitumor activity will be based on the As-treated Population (defined in Section 4.9.1). The rates of OR and DC based on RECIST version 1.1 will be summarized with 95% CI based on the exact binomial distribution. Time-to-event endpoints (DoR, PFS, and OS) will be analyzed using the Kaplan-Meier method. Additional analyses of antitumor activity may be conducted in the Response-evaluable Population (defined in

Section 4.9.1). More details will be provided in the statistical analysis plan. The following efficacy endpoints will be analyzed:

- OR is defined as best overall response of confirmed CR or confirmed PR according to RECIST version 1.1. The best overall response is defined as the best response (in the order of CR, PR, SD, PD, and not evaluable) among all overall responses recorded from the start of treatment with investigational product until objective documentation of PD, or the last evaluable disease assessment in the absence of PD prior to the initiation of subsequent anticancer therapy or end of the study, whichever occurs first. The best overall response of CR or PR must be confirmed, which means a response of CR/PR is recorded at a 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. The ORR will be estimated by the proportion of OR, and its 95% CI will be estimated using the exact binomial distribution.
- DoR is defined as the duration from the first documentation of OR to the first documented disease progression or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of data cut-off for analysis, DoR will be censored at the last tumor assessment date. The DoR will only be evaluated for the subgroup of subjects with an OR using the Kaplan-Meier method.
- DC is defined as CR, PR, or SD (if subjects maintain SD for ≥ 8 weeks [± 3 days]). DC will be analyzed by estimating the DCR, defined as the proportion of subjects with DC and its 2-sided 95% CIs using an exact probability method.
- PFS will be measured from the start of treatment with investigational product until the first documentation of disease progression or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of data cut-off for analysis, PFS will be censored at the last tumor assessment date. The Kaplan-Meier method (Kaplan and Meier, 1958) will be used to estimate the PFS curve and the PFS rate at time points of interest.
- The OS will be determined as the time from the start of treatment with investigational product until death due to any cause. For subjects who are alive at the time of data cutoff, OS will be censored on the last date when subjects are known to be alive. The Kaplan-Meier method will be used to estimate the OS curve and the OS rate at time points of interest.

Subjects' tumor samples (archival and/or from fresh biopsies) will be analyzed for T790M mutation that may predict increased frequency of response or longer disease stabilization. The analyses will be performed to determine if there is an association between the presence of the T790M mutation and clinical activity.

4.9.5 Analysis of Immunogenicity/Pharmacokinetics

Individual concentrations will be tabulated by dose cohort along with descriptive statistics. Non-compartmental PK data analysis will be performed from each dose cohort with scheduled PK sample collection where data allow. Relevant descriptive statistics of non-compartmental

PK parameters will be provided and may include: C_{max}, AUC, CL, and $t_{1/2}$ after IV doses and C_{max}, t_{max}, AUC, CL/F, V_z/F and $t_{1/2}$ after oral doses.

For each arm, the immunogenic potential of oleclumab will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs. CCI [redacted] Samples will be collected for potentially evaluating the neutralizing capacity of ADAs in the future.

4.9.6 CCI [redacted]

CCI [redacted]

4.9.7 Continuous Monitoring for Interstitial Lung Disease (Arm A only)

The development of ILD-like events was prospectively identified as a potential safety concern from a review of osimertinib in combination with durvalumab. To ensure subject safety, continuous monitoring of ILD events that occur in subjects enrolled in Arm A will be performed. The study team, including the medical monitor, will review all potential cases of pneumonitis/ILD via the automatic notification system from AESI reporting by the investigators from the start of the trial. As these reports are required within 24 hours, this will facilitate a rapid detection of any potential concerns. In addition, the sponsor will programmatically identify any potential cases of pneumonitis/ILD in the clinical database from the reported AE terms. The programmatic listings will commence with the enrollment of the sixth subject and then occur on a regular basis every 2 months thereafter.

If either of these methods of detection identify potential ILD cases exceeding the predefined threshold where the posterior probability of a true ILD rate of ≥ 10% is more than 90%, then an ILD review meeting will occur to adjudicate the cases and determine if any changes to the trial are necessary (Table 10). In addition, an ad hoc ILD review can be triggered at any time at the request of the study investigators or sponsor based on evolving data.

Table 10 ILD Monitoring Plan - Continuous Monitoring Based on the Potential Number of ILD Cases

Number of Potential ILD Cases Observed	Number of Subjects Enrolled	Observed ILD Rate	Posterior Probability Given True ILD Rate ≥ 10%
2	6 – 8	25.0%	91.1%
3	9- 14	21.4%	91.3%
4	15 - 21	19.0%	90.8%
5	22 - 28	17.9%	91.0%
6	29 - 36	16.7%	90.3%
7	37 - 43	16.3%	90.9%
8	44 - 46	17.4%	94.4%

ILD = interstitial lung disease.

The ILD review meeting will be comprised of all of the investigators at active sites (ie, sites which are IRB/IEC approved to enroll subjects) and the sponsor study team members (including but not limited to the medical monitor, clinical scientist, study safety physician, and study biostatistician). In advance of each ILD review meeting, all available clinical data about the cases from the sponsor and investigators will be summarized as case narratives and an overall summary of all potential pneumonitis/ILD cases will be provided. Investigators will provide a recommendation to continue the study with or without modification, or to halt enrollment for safety concerns. The decision of the review team will be based on a majority vote. All decisions by this committee will be documented and shared with all participating sites in writing.

During the course of the study, ILD risk was assessed and rates were closely monitored. A single patient discontinued treatment due to Grade 2 pneumonitis, which is expected with osimertinib monotherapy in the EGFRm NSCLC population. Special further assessments will not be devoted to ILD but will be monitored as part of overall safety assessments. Once patients transition to PART, safety assessments performed by the sponsor will be performed as outlined in Section 4.4.

4.9.8 Interim Analysis

Bayesian predictive probabilities will be used for continuous interim monitoring by estimating the probability of observing a targeted treatment effect or futility of the treatment if the trial were to continue to its predefined maximum sample size (Lee and Liu, 2008). CCI [redacted]. An efficacy analysis may be performed at

each interim analysis. The results of the efficacy analysis will not impact on the stopping rule but may trigger other planning activities for further development of oleclumab combinations.

For Arms A and B, different ORRs were assumed as the target response rates for decision making. CCI [redacted] The interim analyses will be performed separately for each arm. In Arm A, the first interim analysis will be performed after 10 subjects are response-evaluable (including subjects enrolled in Part 1 who receive the expansion dose) (Figure 4). In Arm B, the first interim analysis will be performed after 20 subjects are response-evaluable (including subjects enrolled in Part 1 who receive the expansion dose) (Figure 5). Enrollment may be paused at the initial interim analysis for each arm to allow full analysis of results. If the No-Go criteria are NOT met, enrollment may continue. After the initial interim analysis, the subsequent interim analyses will be performed after every 5 additional subjects are response-evaluable. The interim analyses will be based on the Response-evaluable Population as defined in Section 4.9.1.

Figure 4 CCI [redacted]

CCI [redacted]

Figure 5 CCI

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The ICH Guideline for GCP E6(R1) defines an AE as:

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

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. 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 below) that fulfill the AE or SAE definition should be reported. 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). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

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

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.

Adverse Events Associated with 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 5.5).

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.

5.2 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. Additional guidance is provided in Section 10.3.

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 the sponsor. 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.

Hepatic function abnormality meeting the definition of Hy's Law is considered an AESI. See Section 5.6.3 for the definition and reporting of AESIs of hepatic function abnormality.

The management of study medication related toxicities is discussed in Section 3.1.4

5.3.1 Adverse Events of Special Interest for Oleclumab

5.3.1.1 Infusion-related Reactions

Intravenous administration of mAbs can cause an acute reaction called an IRR. Acute allergic reactions may also occur during the infusion of investigational product. Manifestations of IRR and acute allergic reactions are similar and they are managed the same way. IRRs predominantly occur at the first exposure to drug, and are uncommon at subsequent exposures. The sponsor requests the study sites to include the signs/symptoms that occur during or after an infusion of oleclumab. Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and IRRs are provided in Section 10.6. A full definition of anaphylaxis is provided in Section 10.4.

5.3.1.2 Cardiac Chest Pain, Transient Ischemic Attack, and Thromboembolism

AEs of cardiac chest pain, transient ischemic attack, and thromboembolic events are of special interest due to oleclumab potential risks of arterial calcifications, arterial ischemic disorder, and thrombosis. Because of this potential risk, subjects with a prior history of myocardial infarction, stroke, or transient ischemic attack in the past 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.

5.3.1.3 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 as per Section 3.1.4, and therapy may be discontinued at the discretion of the investigator.

5.3.1.4 Immune Complex Disease

The immune system can respond to foreign protein, even to humanized mAb by producing human-anti-human antibodies, which may result in formation of immune complexes and their deposition in blood vessels, joints, and glomeruli causing symptomatic disease (eg, vasculitis, glomerulonephritis, arthritis, serum sickness). Subjects will be monitored clinically and for the presence of ADAs. Subjects who experience an AE suspected to be immune-complex related and with confirmed presence of ADAs will discontinue treatment. Immune-complex disease will be managed in accordance with standard of care.

5.3.2 Adverse Events of Special Interest for Osimertinib

5.3.2.1 Interstitial Lung Disease/Pneumonitis

Interstitial lung disease describes a group of disorders characterized by progressive scarring of the lung. It affects the alveolar epithelium, pulmonary capillary endothelium, basement membrane, perivascular and perilymphatic tissues. It may cause progressive lung stiffness, eventually affecting the ability to get enough oxygen into the bloodstream.

The development of ILD-like events was prospectively identified as a potential safety concern from a review of osimertinib in combination with durvalumab and is therefore considered a topic of special interest in the osimertinib clinical development program. If new or worsening pulmonary symptoms (eg, dyspnea, cough, fever) or radiological abnormality suggestive of ILD are observed, an interruption in study treatment dosing is recommended, and the medical monitor should be informed. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. Additionally, it should be considered that NSCLC and its treatment are factors which are known to predispose subjects to the occurrence of ILD. In the presence of confirmatory high resolution computed tomography (HRCT) scans where other causes of respiratory symptoms have been excluded, a diagnosis of ILD should be considered and study treatment permanently discontinued. A questionnaire regarding the results of the full diagnostic workup (including HRCT, blood and sputum culture, hematological parameters) will be sent to investigators (Section 5.4.4). In the absence of a diagnosis of ILD, study treatment may be restarted following consultation with the medical monitor.

ILD/pneumonitis should be reported as an AESI and should be reported within 24 hours of knowledge of the event (Section 5.6.5).

Continuous monitoring of ILD events will be performed as described in Section 4.9.7.

5.3.2.2 QTc Prolongation and Arrhythmias

QTc prolongation is a measure of delayed ventricular repolarization. Excessive QTc prolongation can predispose the myocardium to the development of early after-depolarizations, which in turn can predispose to the development of arrhythmias. An analysis performed on clinical data indicated that osimertinib leads to a small (approximately 15 msec) increase in QTcF at the 80 mg dose level. Subjects with QTcF prolongation to > 500 msec should have study treatment withheld and regular ECGs performed until resolution to < 481 msec and then restarted at a reduced dose of 40 mg. If the toxicity does not resolve to ≤ Grade 1 within 21 days, the subject will be permanently discontinued from study treatment (Table 16). A manual over-read by a medically qualified person should be performed for all QTc values > 500 msec prior to withholding or discontinuing study treatment (Section 4.3.2).

Arrhythmias assessed as related to a QT prolongation should be reported as AESIs.

5.3.2.3 Changes in Cardiac Contractility

Across clinical trials, LVEF decreases ≥ 10% and a drop < 50% occurred in 3.9% (35/908) of subjects treated with osimertinib who had a baseline and at least one follow-up LVEF assessment. Cardiac monitoring for all subjects in Arm A will include LVEF assessments at screening and during treatment according to the schedule in Section 4.2.

Changes in cardiac contractility should be reported as AESIs.

5.4 Recording of Adverse Events

Adverse events will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to the sponsor (Section 5.5). See Section 5.2 for the definition of SAEs and Section 10.3 for guidelines for 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.

Infusion of biological products is commonly associated with IRRs. Anaphylaxis and IRRs have some common manifestations and may be difficult to distinguish from each other. IRRs are commonly observed during or shortly after the first time of exposure to therapeutic mAbs delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike IRRs, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic, skin, and/or mucosal reactions. The investigator is advised to carefully examine symptoms of

adverse reactions observed during or shortly after exposure to oleclumab, and consider the above mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the investigator's convenience and in order 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 Section 10.4.

5.4.1 Time Period for Collection of Adverse Events

Adverse events and SAEs will be collected from time of signature of informed consent through 90 days (± 7 days) after the last dose of investigational product.

For non-TEAEs (ie, AEs that occur during the period from the time informed consent is signed but prior to the subject receiving investigational product), only AEs associated with protocol-related procedures should be reported. After the start of treatment, all TEAEs (Section 5.1) should be reported.

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.4.3 Deaths

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

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

5.4.4 Recording of Interstitial Lung Disease/Pneumonitis

Adverse events of ILD and/or pneumonitis will require the completion of a comprehensive questionnaire to help better assess the etiology. This will include further details about the subject's medical and cancer history, diagnostic workup (including HRCT, blood and sputum culture, hematological parameters), and final outcome to be completed in the eCRF.

5.5 Reporting of Serious Adverse Events

All SAEs must 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 sponsor 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.

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 Investigator's Brochure, 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 symptoms is only reported on the Overdose eCRF module.

If an overdose on a MedImmune investigational product occurs during the course of the study, then the investigator or other site personnel inform appropriate sponsor representatives immediately, or 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, reporting must occur within 30 days.

5.6.2 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate sponsor representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated sponsor representative works with the investigator to ensure that all relevant information is completed within 1 (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 (other serious initial and follow-up) 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.

The definition of a medication error can be found in Section 10.3.

5.6.3 Hepatic Function Abnormality

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 may need to be reported as SAEs. Refer to Section 10.5 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

5.6.4 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor.

5.6.4.1 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 study treatment and completed end of 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 sponsor 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 (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 paper forms are used to report the outcome of the pregnancy.

5.6.4.2 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 180 days after the last dose of investigational product should, if possible, be followed up and documented.

5.6.5 Interstitial Lung Disease/Pneumonitis

Adverse events of ILD/pneumonitis are required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety.

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/the 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 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 (including telephone contact), 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 (Sections 4.1.5 and 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 approximately 2 years after the final subject is entered into the study or when the sponsor stops the study, whichever occurs earlier.

6.4 Data Management

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

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

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

6.5 Medical Monitor Coverage

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

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Subject Data Protection

Each subject will be assigned a SID to ensure that personally identifiable information is kept separate from the study data. Subject data that are relevant to the trial, eg, demographic information, physical or mental health condition, diagnosis, comorbidities, laboratory test results, etc. will only be collected with the subject's informed consent. The informed consent form (ICF) 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. Clinical data from this study may be combined with results from other studies for additional scientific-related research.

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 ICF 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 ICF 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 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 ICF for use by all investigators in the clinical study. MedImmune must approve any modifications to the ICF 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 ICF(s) is/are stored in the Investigator's Study File.
- Ensure a copy of the signed ICF 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 ICF that is approved by an IRB/IEC.

7.4 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and MedImmune.

Substantial changes must be documented in a study protocol amendment. MedImmune will distribute amended versions of the protocol to the Principal Investigator(s). Before implementation, amended protocols must be approved by relevant IRB/IEC (Section 7.2) and according to local requirements, the national regulatory authority approval. The IRB/IEC must also approve revisions to the ICF, advertising, and any other written information and/or materials resulting from the change to the protocol.

If local regulations require, any unsubstantial changes will be communicated to or approved by each IRB/IEC.

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.

8 REFERENCES

Alimita Prescribing Information. ALIMTA premetrexed disodium heptahydrate injection, powder, lyophilized, for sodium. US Approval, 2004. Indianapolis, IN: Eli Lilly and Company; Revised 2/2015. Available at: http://uspl.lilly.com/alimta/alimta.html#pi. Accessed on 21 August 2017. 2015.

Antonioli L, Blandizzi C, Pacher P, Hasko G. Immunity, inflammation and cancer: a leading role for adenosine. Nat Rev Cancer. 2013;13(12):842-57.

Baden LR, Swaminathan S, Angarone M, Blouin G, Camins BC, Casper C et al. Prevention and Treatment of Cancer-Related Infections, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2016;14(7):882-913.

Ballard P, Yates JW, Yang Z, Kim DW, Yang JC, Cantarini M et al. Preclinical Comparison of Osimertinib with Other EGFR-TKIs in EGFR-Mutant NSCLC Brain Metastases Models, and Early Evidence of Clinical Brain Metastases Activity. Clin Cancer Res. 2016;22(20):5130-40.

Becker A, Crombag L, Heideman DA, Thunnissen FB, van Wijk AW, Postmus PE et al. Retreatment with erlotinib: Regain of TKI sensitivity following a drug holiday for patients with NSCLC who initially responded to EGFR-TKI treatment. Eur J Cancer. 2011;47(17):2603-6.

Bonomi PD. Implications of key trials in advanced nonsmall cell lung cancer. Cancer. 2010;116(5):1155-64.

Brahmer JR, Hammers H, Lipson EJ. Nivolumab: targeting PD-1 to bolster antitumor immunity. Future Oncol. 2015;11(9):1307-26.

Colgan SP, Eltzschig HK, Eckle T, Thompson LF. Physiological roles for ecto-5'-nucleotidase (CD73). Purinergic Signal. 2006;2(2):351-60.

Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ et al. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov. 2014;4(9):1046-61.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Emens L, Powderly J, Fong L, Brody J, Forde P, Hellmann M et al. Abstract CT119: CPI-444, an oral adenosine A2a receptor (A2aR) antagonist, demonstrates clinical activity in patients with advanced solid tumors. AACR; 2017.

Ettinger DS, Wood DE, Aisner DL, Akerley W, Bauman J, Chirieac LR et al. Non-Small Cell Lung Cancer, Version 8.2017, NCCN Clinical Practice Guidelines in Oncology. Available at: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed 21 August 2017. 2017;(4).

FDA. US Food and Drug Administration. Drug-induced liver injury: premarketing clinical evaluation. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf. Accessed 21 August 2017. 2009.

Fehrenbacher L, Spira A, Ballinger M, Kowanetz M, Vansteenkiste J, Mazieres J et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. Lancet. 2016;387(10030):1837-46.

Garassino M, Cho B, Gray J, Mazières J, Park K, Soo R et al. Durvalumab in≥ 3rd-line EGFR mutant/ALK+, locally advanced or metastatic NSCLC: Results from the phase 2 ATLANTIC study. Annals of Oncology. 2017;28(suppl_2).

GLOBOCAN. GLOBOCAN Cancer Fact Sheets: Lung Cancer. Available at: http://globocan.iarc.fr/old/FactSheets/cancers/lung-new.asp. Accessed on: 21 Aug 2017 2015.

Goldberg SB, Supko JG, Neal JW, Muzikansky A, Digumarthy S, Fidias P et al. A phase I study of erlotinib and hydroxychloroquine in advanced non-small-cell lung cancer. J Thorac Oncol. 2012;7(10):1602-8.

Goss G, Tsai C-M, Shepherd F, Ahn M-J, Bazhenova L, Crinò L et al. MA16. 11 CNS response to osimertinib in patients with T790M-positive advanced NSCLC: pooled data from two phase II trials. Journal of Thoracic Oncology. 2017;12(1):S440-S1.

Gridelli C, Ciardiello F, Gallo C, Feld R, Butts C, Gebbia V et al. First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: the TORCH randomized trial. J Clin Oncol. 2012;30(24):3002-11.

Hata A, Katakami N, Yoshioka H, Fujita S, Kunimasa K, Nanjo S et al. Erlotinib after gefitinib failure in relapsed non-small cell lung cancer: clinical benefit with optimal patient selection. Lung Cancer. 2011;74(2):268-73.

Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016;387(10027):1540-50.

Inoue Y, Yoshimura K, Kurabe N, Kahyo T, Kawase A, Tanahashi M et al. Prognostic impact of CD73 and A2A adenosine receptor expression in non-small-cell lung cancer. Oncotarget. 2017;8(5):8738-51.

Janjigian YY, Smit EF, Groen HJ, Horn L, Gettinger S, Camidge DR et al. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. Cancer Discov. 2014;4(9):1036-45.

Kobayashi S, Boggon TJ, Dayaram T, Janne PA, Kocher O, Meyerson M et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. N Engl J Med. 2005;352(8):786-92.

Langer CJ, Mok T, Postmus PE. Targeted agents in the third-/fourth-line treatment of patients with advanced (stage III/IV) non-small cell lung cancer (NSCLC). Cancer Treat Rev. 2013;39(3):252-60.

Lee CK, Man J, Lord S, Links M, Gebski V, Mok T et al. Checkpoint Inhibitors in Metastatic EGFR-Mutated Non-Small Cell Lung Cancer-A Meta-Analysis. J Thorac Oncol. 2017;12(2):403-7.

Lee JC, Jang SH, Lee KY, Kim YC. Treatment of Non-small Cell Lung Carcinoma after Failure of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor. Cancer Res Treat. 2013;45(2):79-85.

Leone RD, Lo YC, Powell JD. A2aR antagonists: Next generation checkpoint blockade for cancer immunotherapy. Comput Struct Biotechnol J. 2015;13265-72.

Liu N, Fang XD, Vadis Q. CD73 as a novel prognostic biomarker for human colorectal cancer. J Surg Oncol. 2012;106(7):918-9; author reply 20.

Loi S, Pommey S, Haibe-Kains B, Beavis PA, Darcy PK, Smyth MJ et al. CD73 promotes anthracycline resistance and poor prognosis in triple negative breast cancer. Proc Natl Acad Sci U S A. 2013;110(27):11091-6.

Lu XX, Chen YT, Feng B, Mao XB, Yu B, Chu XY. Expression and clinical significance of CD73 and hypoxia-inducible factor-1alpha in gastric carcinoma. World J Gastroenterol. 2013;19(12):1912-8.

Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362(25):2380-8.

Miller VA, Hirsh V, Cadranel J, Chen YM, Park K, Kim SW et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol. 2012;13(5):528-38.

Mok T, Wu Y, Bakagawa K, editors. Gefitinib/chemotherapy vs chemotherapy in epidermal growth factor receptor mutation-positive non-small-cell lung cancer after progression on first-line gefitinib: the phase III randomised IMPRESS study (abstract LBA2). 2014 European Society of Medical Oncology meeting; 2014.

Mok TS. Personalized medicine in lung cancer: what we need to know. Nat Rev Clin Oncol. 2011;8(11):661-8.

Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017;376(7):629-40.

Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon-alpha monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet. 2013;52(11):1017-27.

Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006;23(6):1275-84.

Novello S, Barlesi F, Califano R, Cufer T, Ekman S, Levra MG et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(suppl 5):v1-v27.

Oxnard GR, Miller VA. Use of erlotinib or gefitinib as initial therapy in advanced NSCLC. Oncology. 2010;24(5):392.

Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med. 2005;2(3):e73.

Pisters KM, Le Chevalier T. Adjuvant chemotherapy in completely resected non-small-cell lung cancer. J Clin Oncol. 2005;23(14):3270-8.

Ren ZH, Lin CZ, Cao W, Yang R, Lu W, Liu ZQ et al. CD73 is associated with poor prognosis in HNSCC. Oncotarget. 2016;7(38):61690-702.

Resta R, Yamashita Y, Thompson LF. Ecto-enzyme and signaling functions of lymphocyte CD73. Immunol Rev. 1998;16195-109.

Riely GJ, Kris MG, Zhao B, Akhurst T, Milton DT, Moore E et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. Clin Cancer Res. 2007;13(17):5150-5.

Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255-65.

Sequist LV, Besse B, Lynch TJ, Miller VA, Wong KK, Gitlitz B et al. Neratinib, an irreversible pan-ErbB receptor tyrosine kinase inhibitor: results of a phase II trial in patients with advanced non-small-cell lung cancer. J Clin Oncol. 2010a;28(18):3076-83.

Sequist LV, Gettinger S, Senzer NN, Martins RG, Janne PA, Lilenbaum R et al. Activity of IPI-504, a novel heat-shock protein 90 inhibitor, in patients with molecularly defined non-small-cell lung cancer. J Clin Oncol. 2010b;28(33):4953-60.

Sequist LV, Soria JC, Goldman JW, Wakelee HA, Gadgeel SM, Varga A et al. Rociletinib in EGFR-mutated non-small-cell lung cancer. N Engl J Med. 2015;372(18):1700-9.

CCI [redacted]

Streicher K, Higgs BW, Wu S, Coffman K, Damera G, Durham N et al. Increased CD73 and reduced IFNG signature expression in relation to response rates to anti-PD-1 (L1) therapies in EGFR-mutant NSCLC. American Society of Clinical Oncology; 2017.

Taxotere Prescribing Information. Taxotere (docetaxel) injection concentrate, IV. US Approval, 1996. Bridgewater, NJ; Sanofi-Aventis U.S. LLC; Revised 10/2016. Available at: http://products.sanofi.us/Docetaxel/Docetaxel.pdf. Accessed on 21 Aug 2017. 2016.

CCI [redacted]

Turcotte M, Spring K, Pommey S, Chouinard G, Cousineau I, George J et al. CD73 is associated with poor prognosis in high-grade serous ovarian cancer. Cancer Res. 2015;75(21):4494-503.

Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012-24.

Wang H, Lee S, Nigro CL, Lattanzio L, Merlano M, Monteverde M et al. NT5E (CD73) is epigenetically regulated in malignant melanoma and associated with metastatic site specificity. Br J Cancer. 2012a;106(8):1446-52.

Wang M, Zhao J, Zhang LM, Li H, Yu JP, Ren XB et al. Combined Erlotinib and Cetuximab overcome the acquired resistance to epidermal growth factor receptors tyrosine kinase inhibitor in non-small-cell lung cancer. J Cancer Res Clin Oncol. 2012b;138(12):2069-77.

Ward RA, Anderton MJ, Ashton S, Bethel PA, Box M, Butterworth S et al. Structure- and reactivity-based development of covalent inhibitors of the activating and gatekeeper mutant forms of the epidermal growth factor receptor (EGFR). J Med Chem. 2013;56(17):7025-48.

Wu JY, Wu SG, Yang CH, Chang YL, Chang YC, Hsu YC et al. Comparison of gefitinib and erlotinib in advanced NSCLC and the effect of EGFR mutations. Lung Cancer. 2011;72(2):205-12.

Wu XR, He XS, Chen YF, Yuan RX, Zeng Y, Lian L et al. High expression of CD73 as a poor prognostic biomarker in human colorectal cancer. J Surg Oncol. 2012;106(2):130-7.

Yang JC, Ahn MJ, Kim DW, Ramalingam SS, Sequist LV, Su WC et al. Osimertinib in Pretreated T790M-Positive Advanced Non-Small-Cell Lung Cancer: AURA Study Phase II Extension Component. J Clin Oncol. 2017;35(12):1288-96.

Yang Q, Du J, Zu L. Overexpression of CD73 in prostate cancer is associated with lymph node metastasis. Pathol Oncol Res. 2013;19(4):811-4.

Young A, Ngiow SF, Barkauskas DS, Sult E, Hay C, Blake SJ et al. Co-inhibition of CD73 and A2AR Adenosine Signaling Improves Anti-tumor Immune Responses. Cancer Cell. 2016;30(3):391-403.

Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res. 2013;19(8):2240-7.

Yu YI, Wang W, Song L, Hu W, Dong C, Pei H et al. Ecto-5'-nucleotidase expression is associated with the progression of renal cell carcinoma. Oncol Lett. 2015;9(6):2485-94.

Zhang B. CD73: a novel target for cancer immunotherapy. Cancer Res. 2010;70(16):6407-11.

Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012;52(1):18-28.

9 CHANGES TO THE PROTOCOL

All changes described below have been incorporated into the current version of the protocol.

9.1 Protocol Amendment 4

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. The primary reason for the Amendment was to add Section 4.4, to allow for the continuation of a subject's treatment after the Last Subject Last Visit for the primary endpoint.

Substantial changes to the protocol are summarized below:

1. Section 1.6 (Benefit-Risk and Ethical Assessment):
    a. Arterial calcifications and arterial ischemic disorder have been removed as important potential risks for oleclumab, and added as potential risks for oleclumab.
    b. Erythema multiforme, Stevens-Johnson syndrome (rare) and cutaneous vasculitis have been added as expected adverse drug reactions for osimertinib.
2. Section 4.4 (Expected Start and End of Study): New section added to provide guidance for the continuation of a subject's treatment after the Last Subject Last Visit for the primary endpoint. In addition, the actual study start and the data cut-off dates for the primary endpoint were added.
3. Section 4.9.7 (Continuous Monitoring for Interstitial Lung Disease [Arm A only]): Updated to include results of ILD monitoring, and to provide guidance for continued ILD monitoring as part of the overall safety assessment.

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

1. Medical monitor updated on the title page
2. Minor formatting changes were made and the table of contents and abbreviation list were updated accordingly

9.2 Protocol Amendment 3

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. The main reason for this Amendment was to add dose levels for Arm B as detailed below. The major changes to the protocol are summarized below.

1 The protocol synopsis was updated to correspond to the body of the document.
2 Section 1.3.3 (AZD4635 Nonclinical Experience): Updated text to reflect that data from in vitro studies suggest the main enzyme involved in the metabolism of AZD4635 is CYP1A2 per AZD4635 Investigator's Brochure edition 4.0.

3 Section 1.4.3 (AZD4635 Clinical Experience): Updated clinical experience for Study D8730C00001 as of the data cut-off of 16 January 2018 per AZD4635 Investigator's Brochure edition 4.0.

4 Section 1.4.1.2 (Study D6070C00004): Added new section with clinical experience for the current study as of the data cut-off of 05 October 2018.

5 Section 1.6 (Benefit-Risk and Ethical Assessment): Revised potential risks of AZD4635 to align with the AZD4635 Investigator's Brochure edition 4.0. Changes include removal of important potential risk of increased risk of seizures, removal of potential risks of tachycardia, increased serum calcium and cholesterol, reduced adenosine diphosphate platelet aggregation, and thyroid hypertrophy, and addition of potential risk of diarrhea.

6 Section 3.1.2.2 (Treatment Regimen: Arm B): Since the starting dose level (dose level 1 [oleclumab 1500 mg Q2W and AZD4635 75 mg QD]) was de-escalated to dose level -1 (oleclumab 1500 mg Q2W and AZD4635 50 mg QD) due to incidence of nausea and vomiting (see updated clinical experience for Study D6070C00004 in Section 1.4.1.2), the dose-escalation scheme was revised to add additional dose levels of -1a, -2, and -2a. Table 2 (Arm B Combination Therapies and Dose Levels [Part 1: Dose Escalation]) was replaced with Figure 3 to reflect the change in study design. The changes included:

- dose escalation to dose level -1a (oleclumab 3000 mg Q2W and AZD4635 50 mg QD) if dose level -1 is safely tolerated
- dose de-escalation to dose level -2 (oleclumab 1500 mg Q2W and AZD4635 25 mg QD) if the MTD is exceeded at dose-level -1
- dose escalation to dose level -2a (oleclumab 3000 mg Q2W and AZD4635 25 mg QD) if dose level -2 is safely tolerated

7 Section 3.1.4.2 (For Toxicity That Occurs While on Oleclumab and AZD4635 [Arm B]): Revised text to reflect that the AZD4635 25 mg QD dose is also allowed for de-escalation, if needed.

8 Section 3.2.1 (Dose Rationale): Under the subheading "AZD4635 (Arm B)", updated text to be consistent with the changes in Section 1.4.3 (AZD4635 Clinical Experience) and to reflect that the AZD4635 25 mg QD dose is also allowed for de-escalation, if needed.

9 Section 4.1.3 (Exclusion Criteria [Additional Exclusion Criteria for Arm B]): The following revisions were made:

- Exclusion criterion 1: Restrictions for concomitant treatment with sensitive substrates of CYP2C9 and CYP2C19 were removed, as data from in vitro studies suggest the main enzyme involved in the metabolism of AZD4635 is CYP1A2 per AZD4635 Investigator's Brochure edition 4.0. Clarified that warfarin is prohibited during treatment with AZD4635.
- Exclusion criterion 4: The restriction to exclude subjects with prior traumatic brain injury, prior stroke, or other predisposing risk of seizure was removed. Increased risk of seizure is not considered a potential risk for AZD4635 per AZD4635 Investigator's Brochure edition 4.0.
- Exclusion criterion 7: Added exclusion criterion that any subject with open ulceration(s) should avoid dosing with AZD4635. The exclusion criterion was added because the healing of ulcers might be affected by the local absorption of the liquid.

10 Section 4.3.2 (Medical History, Physical Examination, Ophthalmologic Examination, Electrocardiogram, Echocardiogram/MUGA, Weight, and Vital Signs): For Arm A echocardiographic examinations, removed requirement for Doppler as high quality standardized 2-D is sufficient to evaluate LVEF.

11 Section 4.5.1 (Identity of Investigational Product[s]) and Table 8 (Identification of Investigational Products): In Table 8, revised concentration and formulation details for AZD4635 to be consistent with the AZD4635 Investigator's Brochure edition 4.0. Removed second sentence concerning primary packaging of AZD4635 as this level of detail is not included in AZD4635 Investigator's Brochure edition 4.0. Revised text to reflect that AZD4635 will be supplied to support clinical doses from 25 to 100 mg (previously 50 to 100 mg).

12 Section 4.5.4 (Storage): Revised storage details for AZD4635 per AZD4635 Investigator's Brochure edition 4.0.

13 Sections 4.7.2 (Prohibited Concomitant Medications [Specific to AZD4635 (Arm A)]) and 10.10 (Appendix 10 - Prohibited Medications for Subjects treated with AZD4635 in Arm B): Data from in vitro studies suggest the main enzyme involved in the metabolism of AZD4635 is CYP1A2 per AZD4635 Investigator's Brochure edition 4.0. In Section 4.7.2, revised second bullet to reflect that contribution of CYP1A2 to AZD4635 metabolism appears to be approximately 80% (previously stated that no formal clinical drug interactions have been performed). Restrictions for concomitant treatment with sensitive substrates of CYP2C9 and CYP2C19 were removed in Sections 4.7.2 and 10.10. Clarified that warfarin is prohibited during treatment with AZD4635.

14 Sections 5.3.3 (Adverse Events of Special Interest for AZD4635) and 5.3.3.1 (Seizures): The AESI of seizures for AZD4635 was removed. The increased risk of seizures was a theoretical risk and is not supported by the available clinical data from the FTIH study and thus is no longer considered to be a risk for AZD4635 per AZD4635 Investigator's Brochure edition 4.0.

15 Section 7.1 (Subject Data Protection): Added statement that clinical data from this study may be combined with results from other studies for additional scientific-related research.

9.3 Protocol Amendment 2

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. The major changes to the protocol are summarized below.

1 The protocol synopsis was updated to correspond to the body of the document.

2 MEDI9447 was revised to oleclumab throughout the protocol.

3 Tables and figures were renumbered sequentially throughout the protocol (previously numbered sequentially by section number).

4 Section 1.4.1 (Oleclumab Clinical Experience): Updated per most recent edition of the oleclumab Investigator's Brochure.

5 Section 1.4.1 (Osimertinib Clinical Experience): Updated per most recent edition of the osimertinib Investigator's Brochure.

6 Sections 1.6 (Benefit-Risk and Ethical Assessment) and 5.3.1.4 (Tuberculosis): In Section 1.6 under the subheading "Potential Risks" (first paragraph), the important potential risk of reactivation of latent tuberculosis for oleclumab was removed. The text, "observation of CD73 expression in human tuberculosis granulomas", was also removed. Additionally, the AESI of tuberculosis (prior Section 5.3.1.4) was removed and the subsequent section renumbered accordingly. Review of the literature determined there is insufficient evidence to support the original inclusion of reactivation of latent tuberculosis as an important potential risk. Please refer to the summary of changes section of Edition 4.0 of the Investigator's Brochure for full details.

7 Section 1.6 (Benefit-Risk and Ethical Assessment): In Section 1.6 under the subheading "Potential Risks" (second paragraph), updated risks for osimertinib per most recent edition of the osimertinib Investigator's Brochure.

8 Sections 2.3 (Exploratory Objectives and Associated Endpoints), 3.2.3 (Rationale for Endpoints), 4.3.1 (Efficacy), 4.3.1.1 CCI [redacted], 4.3.1.2 CCI [redacted]

9 Sections 3.1.1 (Overview; Figures 1 [Study Flow Diagram for Part 1: Dose Escalation] and 2 [Study Flow Diagram for Part 2: Dose Expansion], previously numbered Figures 3.1.1-1 and 3.1.1-2, respectively), 3.1.2.1 (Treatment Regimen: Arm A), and 3.1.2.2 (Treatment Regimen: Arm B): Text and figures were revised to reflect that subjects in Arm B must have received at least 2 but not more than 4 prior lines of therapy (previously 3) and that treatment with a first or second generation EGFR TKI is not required for subjects in Arm B who received osimertinib as first-line treatment and these subjects may enroll after having received and progressed on osimertinib alone (but can still have received no more than 4 prior lines of therapy). The changes were made to be consistent with the changes to the inclusion criteria detailed below.

10 Sections 3.1.2 (Treatment Regimen): Removed text pertaining to treatment beyond progression. Requirements for treatment beyond progression are covered in new section (Section 4.1.7 [Treatment Beyond Progression]).

11 Section 4.1.2 (Inclusion Criteria): The following revisions were made:

(a) Revised inclusion criterion 5b to specify a maximum of 4 prior lines of therapy for Arm B for enrollment purposes.

(b) Added inclusion criteria "v" under 5b that subjects in Arm B who received osimertinib as first–line treatment may be enrolled, as osimertinib is becoming standard of care for first-line treatment of EGFRm NSCLC.

(c) For inclusion criterion 7, clarified that archival tumor samples as core biopsies or larger resection, no fine-needle aspiration samples.

(d) Revised inclusion criterion 10f to require that subjects have creatinine clearance ≥ 40 mL/minute (previously ≥ 50 mL/minute). Further safety and PK data for AZD4635 have reduced the toxicity concern for subjects with mild renal impairment.

12 Section 4.1.3 (Exclusion Criteria): The following revisions were made:

(a) For exclusion criterion 15, clarified that scans for CNS metastatic disease will be performed at screening.

(b) Under the subheading "Additional Exclusion Criteria for Arm A", exclusion criterion 4 was revised to clarify that "intermittent supplemental oxygen required for vigorous activity or sleep is allowed" per investigator feedback.

(c) Revised exclusion criteria 2a under the subheading "Additional Exclusion Criteria for Arm A" and 5a under the subheading"Additional Exclusion Criteria for Arm B" to clarify that QTcF > 470 msec must be over-read by medically qualified person.

13 Section 4.1.7 (Treatment Beyond Progression): Added new section with requirements for treatment beyond progression including treatment after the initial assessment of PD by RECIST version 1.1 until PD is confirmed on a follow-up scan as well as requirements for treatment beyond confirmed PD. The change was made to allow treatment beyond PD if a subject has clinical benefit, so that subjects with a new lesion, including CNS metastases, but decrease in systemic tumor burden do not necessarily have to discontinue. Subsequent sections were renumbered accordingly.

14 Section 4.2.1 (Enrollment/Screening Period): The following revisions were made to Table 3 (Schedule of Screening Procedures), previously numbered Table 4.2.1-1:

(a) Included prior imaging in the assessment for medical history. Added footnote that prior imaging will be collected if allowed by country and includes raw imaging data that has been performed between 4 weeks and 6 months prior to baseline scan. The revision was made to provide additional data for tumor kinetics.

(b) Revised assessment for thyroid function to clarify that free thyroxine is not required if thyroid stimulating hormone is normal.

(c) Added footnote that previous scans for brain metastases and baseline disease performed within 28 days of dosing do not need to be repeated at screening.

15 Sections 4.2.2 (Treatment Period): The following revisions were made to Tables 4 (Treatment Period Study Procedures – Arm A [MEDI9447Oleclumab + Osimertinib]) and 5 (Treatment Period Study Procedures – Arm B [Oleclumab + AZD4635]), previously numbered Tables 4.2.2-1 and 4.2.2-2, respectively:

(a) Added footnote that the physical examination may be performed up to 24 hours prior to dosing on Day 1 to facilitate PK collection.

(b) Revised assessment for thyroid function to clarify that free thyroxine is not required if thyroid stimulating hormone is normal.

(c) In Table 5 (previously numbered 4.2.2-2), removed the 3-day window for the V7a/Day 58 visit as this visit is for 24-hour post-dose PK sample.

16 Section 4.2.3 (Follow-up Period): Revised assessment for thyroid function to clarify that free thyroxine is not required if thyroid stimulating hormone is normal in Table 6 (Schedule of Follow-up Procedures [All Arms]), previously numbered Table 4.2.3-1. Clarified in the footnote for disease assessments that disease assessments continue Q12W for subjects who discontinued treatment due to reasons other than PD.

17 Section 4.3.6 CCI [redacted]

18 Section 4.5 (Investigational Products): This section to be revised to also include oleclumab liquid formulation. Revisions included:
   (a) In Section 4.5.1 (Identity of Investigational Products): The liquid formulation for oleclumab was added to Table 9 (Identification of investigational Products), previously numbered Table 4.5.1-1. Text after the table was added with details for the lypholized product and liquid formulation. Text for AZD4635 and osimertinib was moved to this section (previously located in Section 4.5.1.1).
   (b) Section 4.5.1.1 (Investigational Product Inspection): Revised section title (previously "Investigational Product Dose Preparation"). Added details for the number of oleclumab vials required for lypholized and liquid product by dose.
   (c) Section 4.5.1.2 (Oleclumab [MEDI9447] IV Bag Preparation and Administration): Made new subsection and subsequent sections were renumbered accordingly. The dose preparation and administration instructions were updated and consolidated and instructions for liquid formulation were added. The standard infusion time was reduced from 80 minutes to 1 hour as clinical data demonstrate that oleclumab infusion has been well tolerated at 80 minutes and CMC data support a reduced infusion time which is more patient friendly.
   (d) Section 4.5.1.3 (Treatment Administration [previously numbered 4.5.1.2]): Under subheading for MEDI9447, added cross references to dose preparation/administration instructions for oleclumab in Section 4.5.1.2 and removed administration instructions as this is located in Section 4.5.1.2.
   (e) Section 4.5.4 (Storage): Added statement for oleclumab that vials should be kept in secondary packaging to avoid prolonged exposure to light.
19 Section 5.3.2.2 (QTc Prolongation and Arrhythmias): For management of subjects with QTc prolongation > 500 msec, removed "or recovery to baseline if baseline QTcF is ≥ 481 msec" as subjects with baseline QTcF > 470 msec are excluded from the study. Clarified that a manual over-read by a medically qualified person should be performed for all QTc values > 500 msec prior to **withholding or** discontinuing study treatment (bold indicates added text) and added cross-reference to Section 4.3.2 (Medical History, Physical Examination, Ophthalmologic Examination, Electrocardiogram, Echocardiogram/MUGA, Weight, and Vital Signs).
20 Section 5.3.2.3 (Changes in Cardiac Contractility): Updated data for LVEF per most recent edition of the osimertinib Investigator's Brochure.
21 Section 5.3.2.4 (Keratitis): Removed keratitis as an AESI for osimertinib per most recent edition of the osimertinib Investigator's Brochure.
22 Section 8 (References): Updated references.
23 Section 10.6 (Appendix 6 - Treatment Modification and Toxicity Management Guidelines for Oleclumab): Updated tables with the most recent toxicity management guidelines.

9.4 Protocol Amendment 1

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. The principal reason for this amendment is to revise the starting dose level for MEDI9447 from 3000 mg Q2W to 1500 mg Q2W in both treatment arms and to stipulate that

dose escalation cannot proceed from the starting dose level of MEDI9447 1500 mg to the MEDI9447 3000 mg dose level in a treatment arm until after a minimum of 3 subjects have been evaluated for DLTs in that treatment arm and a total of at least 6 subjects have been evaluated for DLTs across both treatment arms. The changes were made per request of the Food and Drug Administration. The major changes to the protocol are summarized below.

1 Synopsis: The Synopsis was revised to be consistent with the changes in the body of the protocol.

2 Figure 3.1.1-1 (Study Flow Diagram for Part 1: Dose Escalation): The figure was modified to reflect the changes in the study design. In Arm A, safety run-in was changed to dose escalation. The subject numbers were changed to n = 9 to 12 subjects for Arm A (previously n = 6 to 12 subjects) and n = 12 to 18 subjects for Arm B (previously n = 6 to 18 subjects).

3 Section 3.1.2.1 (Treatment Regiment: Arm A): In Table 3.1.2.1-1(Arm A Combination Therapies and Dose Levels [Part 1: Dose Escalation]), the dose levels and subject numbers were revised to MEDI9447 750 mg/osimertinib 80 mg (dose level -1 [n = 3 to 6 subjects]), MEDI9447 1500 mg/osimertinib 80 mg (dose level 1 [n = 3 to 6 subjects]), and MEDI9447 3000 mg/osimertinib 80 mg (dose level 2 [n = 6 subjects]). The text in Section 3.1.2.1 was revised to reflect the starting dose level of MEDI9447 1500 mg/osimertinib 80 mg and the change in study design from a safety run-in to dose escalation.

4 Section 3.1.2.2 (Treatment Regimen: Arm B): In Table 3.1.2.2-1(Arm B Combination Therapies and Dose Levels [Part 1: Dose Escalation]), the dose levels and subject numbers were revised to MEDI9447 1500 mg/AZD4635 50 mg (dose level -1 [n = 3 to 6 subjects]), MEDI9447 1500 mg/AZD4635 75 mg (dose level 1 [n = 3 to 6 subjects]), MEDI9447 3000 mg/AZD4635 75 mg (dose level 2 [n = 3 to 6 subjects]), and MEDI9447 3000 mg/AZD4635 100 mg (dose level 3 [n = 6 subjects]). The text in Section 3.1.2.2 was revised to reflect the starting dose level of MEDI9447 1500 mg/AZD4635 75 mg. A statement was added in the text and as a footnote in Table 3.1.2.2-1 that if the MTD is exceeded at dose level 2 an intermediate dose level of MEDI9447 3000 mg and AZD4635 50 mg may be evaluated.

5 Section 3.1.3.2 (Rules for Dose Escalation and Cohort Progression [Arms A and B]): The text and section title were revised to state that the dose escalation rules will apply to both Arms A and B. The following rules were revised:

   (a) Rule 3 was modified to state that at dose level 1 only, dose escalation to the next higher dose cohort will be permitted after review of all available safety data from a minimum of 3 evaluable subjects in that treatment arm and a minimum of 6 evaluable subjects across both treatment arms (Arms A and B) and that at subsequent dose levels, dose escalation to the next higher dose cohort will be permitted after review of all available safety data from a minimum of 3 evaluable subjects in that treatment arm.

   (b) Rule 9 was revised to state that “with the exception of dose level 1 as described in Rule 3, dose escalation proceeds independently between the arms of this study”.

6 Section 3.2.1 (Dose Rationale): Under the subheadings for MEDI9447, osimertinib, and AZD4635, the starting dose level of MEDI9447 was changed to 1500 mg Q2W (previously 3000 mg Q2W). Under the subheading for MEDI9447, a statement was added that the MEDI9447 1500 mg Q2W dose is one dose level below the highest monotherapy and combination weight-based dose that has been tested and declared tolerable in FTIH Study D6070C00001. Under the subheading for MEDI9447, text was revised to include a statement that the MEDI9447 750 mg Q2W dose (equivalent to MEDI9447 10 mg/kg Q2W) is included as dose level -1.

7 Section 4.2.2 (Treatment Period), Tables 4.2.2-1 (Treatment Period Study Procedures – Arm A (MEDI9447 + Osimertinib) and 4.2.2-2 (Treatment Period Study Procedures – Arm B (MEDI9447 + AZD4635): In both tables, under the visit column "V7-Vn", the timing for disease assessments CCI was changed to "Q8W (± 3D) starting on D113 through D393" (previously "Q8W (± 3D) starting on D113 through D365") to correct an oversight.

8 Sections 4.5.1.1 (Investigational Product Dose Preparation): Under subheading "Investigational Product Inspection", the number of required vials for the MEDI9447 750 mg dose level was added. Under the subheading "Intravenous Dose Preparation", instructions for the MEDI9447 750 mg dose were added.

9 Section 4.8.7 (Continuous Monitoring for Interstitial Lung Disease [Arm A only]): In Table 4.8.7-1 (ILD Monitoring Plan - Continuous Monitoring, Based on the Potential Number of ILD Cases), "after run-in phase" was removed from the title and the column for phase was removed as continuous interim monitoring begins after the enrollment of the sixth subject regardless of the study phase and safety run-in is no longer applicable for Arm A. The first row of the table was deleted. The number of subjects in the second row was changed to "6 – 8" previously ("7 – 8"). The number of subjects for the last row was changed to "37 – 43" (previously "37 – 40"), and the observed ILD rate and posterior probability were revised accordingly. A row was added for 44 – 46 subjects. The revisions were made as up to 46 subjects may be enrolled in Arm A.

10 Section 10.1 (Appendix 1 – Signatures): The Sponsor signature name and phone number were updated on the Sponsor Signature Page.

10 APPENDICES

10.1 Appendix 1 - Signatures

Sponsor Signature(s)

A Multiarm, Open-label, Multicenter, Phase 1b/2 Study to Evaluate Novel Combination Therapies in Subjects with Previously Treated Advanced EGFRm NSCLC

I agree to the terms of this protocol.

Signature and date: _____

PPD

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: PPD

Signature of Principal Investigator

A Multiarm, Open-label, Multicenter, Phase 1b/2 Study to Evaluate Novel Combination Therapies in Subjects with Previously Treated Advanced EGFRm NSCLC

I, the undersigned, have reviewed this protocol and all amendments, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available) _____

10.2 Appendix 2 – Contraception Guidance

For females of childbearing potential:

- Females of childbearing potential are defined as those who are not surgically sterile (ie, surgical sterilization includes bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or those who are not postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. The methods of contraception are described in Table 11.
- Female subjects must refrain from egg cell donation and breastfeeding while on study and for 180 days after the final dose of investigational product.

Table 11 Methods of Contraception

Barrier Methods	Hormonal Methods
• Male or female condom with or without spermicide[a, b] • Cap, diaphragm, or sponge with spermicide[a, b] • Copper T intrauterine device[d] • Levonorgestrel-releasing intrauterine system (eg. Mirena®)[c, d]	• Implants[d] • Hormone shot or injection[d] • Combined pill[d] • Minipill[a] • Patch[d]

[a] Not highly effective (failure rate of ≥ 1% per year)

[b] A male condom plus cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

[c] Also considered a hormonal method

[d] Highly effective (failure rate of < 1% per year).

10.3 Appendix 3 - Additional Safety Guidance

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

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

Hospitalization

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

Important Medical Event or Medical Intervention

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

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

Examples of such events are:

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

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03 as provided in below.

The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1	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 or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5	Death as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

Relationship to Investigational Product

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

- Time Course. Exposure to suspect investigational product. Has the subject actually received the suspect investigational product? Did the AE occur in a reasonable temporal relationship to the administration of the suspect investigational product?

- Consistency with known investigational product profile. Was the AE consistent with the previous knowledge of the suspect investigational product (pharmacology and toxicology) or products of the same pharmacological class? OR could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect investigational product?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected investigational product was reintroduced after having been stopped? MedImmune would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

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

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

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

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

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

Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

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
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, 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 fridge 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, or standard of care medication in open-label studies, even if an AZ/MedImmune product

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

10.4 Appendix 4 - National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

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.

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

1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING
   (a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow (PEF), hypoxemia)
   (b) Reduced 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 GI 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

10.5 Appendix 5 - Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

10.5.1 Introduction

This appendix describes the process to be followed to identify and appropriately report cases of Hy's Law. 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 Section 10.6 of the protocol.

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.

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.

10.5.2 Definitions

10.5.2.1 Potential Hy's Law

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

10.5.2.2 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.

10.5.3 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 (Section 10.5.2) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

10.5.4 Follow-up

10.5.4.1 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.

10.5.4.2 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

The medical monitor contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up 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
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the medical monitor.
- If at any time (in consultation with the medical monitor) the potential Hy's Law case meets serious criteria, report it as an SAE using standard reporting procedures

10.5.5 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.

No later than 3 weeks 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. 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.

If 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, record the AE /SAE in the CRF accordingly and follow 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:

- Report an 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 3 weeks 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:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- 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 met. Update the SAE report according to the outcome of the review

10.5.6 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 10.5.4.2.

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 10.5.4.2

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.

10.6 Appendix 6 – Treatment Modification and Toxicity Management Guidelines for Oleclumab

Version 01November 2017

Table 12 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events – General Considerations

General Considerations	
Dose Modifications	**Toxicity Management**
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: ° Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen ° Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1 The event stabilizes and is controlled. 2 The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3 Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen. Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: ° It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. ° Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. ° Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. ° For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. ° Some events with high likelihood for morbidity and/or mortality – e.g., myo-carditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. ° If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). ° More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are

Table 12 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events – General Considerations

General Considerations	
Dose Modifications	**Toxicity Management**
Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	not currently noted in the guidelines – when these events are not responding to systemic steroids. ° With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. ° Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

AE = adverse event; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; imAE = immune-mediated adverse event; IV = intravenous; NCI = National Cancer Institute; PJP = *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO = by mouth; TNF = tumor necrosis factor.

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** ° Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. ° Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** ° Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. ° Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. ° If toxicity worsens, then treat as Grade 3 or Grade 4. ° If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** ° Monitor symptoms daily and consider hospitalization. ° Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). ° Reimage as clinically indicated. ° If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started ° If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). **Caution**: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. ° Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			treatment of cancer-related infections [Category 2B recommendation])[a] ° Consider pulmonary and infectious disease consult. ° Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** ° Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. ° Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. ° Hospitalize the patient. ° Supportive care (e.g., oxygen). ° If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. **Caution**: rule out sepsis and refer to infliximab label for general guidance before using infliximab. ° Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade:** ° Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). ° Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			medications, or infections), including testing for clostridium difficile toxin, etc. ° Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. ° Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** ° Monitor closely for worsening symptoms. ° Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 ° If toxicity worsens, then treat as Grade 3 or Grade 4. ° If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** ° Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. ° Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. ° If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. ° If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution**: it is important to rule out bowel

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			perforation and refer to infliximab label for general guidance before using infliximab. ° Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. ° Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indi-cated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** ° Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. ° Monitor stool frequency and volume and maintain hydration. ° Urgent GI consult and imaging and/or colonoscopy as appropriate. ° If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. ° Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs)	**Any Grade**	**General Guidance**	**For Any Grade:** ° Monitor and evaluate liver function test: AST, ALT, ALP, and TB. ° Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Infliximab should not be used for management of immune-related hepatitis.	**Grade 1** (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN)	° No dose modifications. ° If it worsens, then treat as Grade 2 event.	**For Grade 1:** Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN)	° Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. ° If toxicity worsens, then treat as Grade 3 or Grade 4. ° If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** ° Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. ° If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. ° If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. ° If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. ° If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. ° Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN:	**For Grade 3 or 4:** ° Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. ° If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	>3.0×ULN and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	◦ Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline ◦ Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. ◦ Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	(i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used**. ◦ Perform hepatology consult, abdominal workup, and imaging as appropriate. ◦ Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Nephritis or renal dysfunction	**Any Grade**	**General Guidance**	**For Any Grade:** ◦ Consult with nephrologist.

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
(elevated serum creatinine)			° Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). ° Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). ° Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** ° Monitor serum creatinine weekly and any accompanying symptoms. ° If creatinine returns to baseline, resume its regular monitoring per study protocol. ° If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. ° Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. ° If toxicity worsens, then treat as Grade 3 or 4. ° If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** ° Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. ° Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. ° Consult nephrologist and consider renal biopsy if clinically indicated. ° If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. ° If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. ° Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] ° When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** ° Carefully monitor serum creatinine on daily basis. ° Consult nephrologist and consider renal biopsy if clinically indicated. ° Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. ° If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. ° Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** ° Monitor for signs and symptoms of dermatitis (rash and pruritus). ° IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED**.

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 1	No dose modifications.	**For Grade 1:** Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. ° If toxicity worsens, then treat as Grade 3. ° If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** ° Obtain dermatology consult. ° Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). ° Consider moderate-strength topical steroid. ° If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. ° Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4**:	**For Grade 3 or 4:** ° Consult dermatology. ° Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. ° Consider hospitalization. ° Monitor extent of rash [Rule of Nines]. ° Consider skin biopsy (preferably more than 1) as clinically feasible. ° Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		Permanently discontinue study drug/study regimen.	° Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** ° Consider consulting an endocrinologist for endocrine events. ° Consider, as necessary, discussing with study physician. ° Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. ° Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). ° Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). ° For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. ° If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** ° Monitor patient with appropriate endocrine function tests.

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			° For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). ° If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. ° If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1 The event stabilizes and is controlled. 2 The patient is clinically stable as per investigator or treating physician's clinical judgement. 3 Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including those with symptomatic endocrinopathy):** ° Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. ° For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). ° Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. ° Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. ° Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			° For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1 The event stabilizes and is controlled. 2 The patient is clinically stable as per investigator or treating physician's clinical judgement. 3 Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 3 or 4:** ° Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. ° For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). ° For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. ° Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. ° Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. ° Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03	**General Guidance**	**For Any Grade:** ° Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications).

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	for defining the CTC grade/severity)		° Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). ° Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). ° Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** ° Consider, as necessary, discussing with the study physician. ° Obtain neurology consult. ° Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). ° Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. ° If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days.	**For Grade 3 or 4:** ° Consider, as necessary, discussing with study physician. ° Obtain neurology consult. ° Consider hospitalization. ° Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. ° If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG).

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		For Grade 4: Permanently discontinue study drug/study regimen.	° Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** ° The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. ° Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. ° Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. ° It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:**

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			◦ Consider, as necessary, discussing with the study physician. ◦ Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. ◦ Obtain a neurology consult.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** ◦ Consider, as necessary, discussing with the study physician. ◦ Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. ◦ Obtain a neurology consult ◦ Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* ◦ Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. ◦ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. ◦ If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ◦ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			◦ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** ◦ Consider, as necessary, discussing with study physician. ◦ Recommend hospitalization. ◦ Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* ◦ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ◦ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ◦ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ◦ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ◦ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** ◦ The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. ◦ Consider, as necessary, discussing with the study physician. ◦ Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. ◦ Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. ◦ Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** ◦ Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. ◦ Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity	**If Grade 2** -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve,	**For Grade 2-4:** ◦ Monitor symptoms daily, hospitalize. ◦ Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. ◦ Supportive care (e.g., oxygen). ◦ If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	permanently discontinue study drug/study regimen. **If Grade 3-4**, permanently discontinue study drug/study regimen.	immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). **Caution**: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. ° Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** ° Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. ° If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. ° Consider, as necessary, discussing with the study physician.

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			° Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	No dose modifications.	**For Grade 1:** ° Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. ° Consider Neurology consult. ° Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** ° Monitor symptoms daily and consider hospitalization. ° Obtain Neurology consult, and initiate evaluation. ° Consider, as necessary, discussing with the study physician. ° If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant ° If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue

Table 13 Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day ° If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). **Caution**: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. ° Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** ° Monitor symptoms closely; recommend hospitalization. ° Obtain Neurology consult, and complete full evaluation. ° Consider, as necessary, discussing with the study physician. ° Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. ° If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). **Caution**: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. ° Consider whether patient may require IV IG, plasmapheresis. ° Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

AChE = acetylcholine esterase; ACTH = adrenocorticotropic hormone; ADL = activities of daily living; AE = adverse event; ALP = alkaline phosphatase test; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP = B-type natriuretic peptide; BUN = blood urea nitrogen; CT = computed tomography; CTC = Common Terminology Criteria; CTCAE = Common Terminology Criteria for Adverse Events; DM = diabetes mellitus; ECG = electrocardiogram; ECHO = echocardiogram; HgA1C = hemoglobin A1C; ILD = interstitial lung disease; imAE = immune-mediated adverse event; IG = immunoglobulin; INR = international normalized ratio; IV = intravenous; GI = gastrointestinal; LDH = lactate dehydrogenase; LFT = liver function tests; LLN = lower limit of normal; MRI = magnetic resonance imaging; NCI = National Cancer Institute; NCCN = National Comprehensive Cancer Network; PJP = *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO = by mouth; T3 = triiodothyronine; T4 = thyroxine; TB = total bilirubin; TNF = tumor necrosis factor; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

[a] ASCO Educational Book 2015 “Managing Immune Checkpoint Blocking Antibody Side Effects” by Michael Postow MD.

[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

Table 14 Treatment Modification and Toxicity Management Guidelines for Infusion-related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** ° Manage per institutional standard at the discretion of investigator. ° Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2**: The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** ° Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. ° Consider premedication per institutional standard prior to subsequent doses. ° Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

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

Table 15 Treatment Modification and Toxicity Management Guidelines for Non-immune-mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

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

10.7 Appendix 7 – Exceptions to the Management of Non-immune-mediated Reactions for Osimertinib

Table 16 Exceptions to the Management of Non-immune-mediated Reactions for Osimertinib

Target Organ	Adverse Reaction[a]	Dose Modification
Pulmonary	ILD/Pneumonitis	Hold osimertinib while ILD/pneumonitis is being evaluated and if ILD/pneumonitis is confirmed permanently discontinue osimertinib
Cardiac	QTc > 500 msec on at least 2 separate ECGs	Withhold osimertinib until QTc < 481 msec or recovery to baseline if baseline QTc ≥ 481 msec, then restart at a reduced dose (40 mg).
	QTc prolongation with signs/symptoms of life threatening arrhythmia	Permanently discontinue osimertinib.
Other	Grade 3 or higher adverse reaction	Withhold osimertinib for up to 3 weeks.
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of osimertinib for up to 3 weeks	Osimertinib may be restarted at the same dose (80 mg) or a lower dose (40 mg).
	If Grade 3 or higher adverse reaction does not improve to Grade 0-2 after withholding of osimertinib for up to 3 weeks	Permanently discontinue osimertinib.

ECG = electrocardiogram; ILD = Interstitial lung disease; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QTc = QT interval corrected for heart rate.

[a] Adverse reactions graded by NCI CTCAE version 4.03.

10.8 Appendix 8 – Treatment Modification Guidelines for AZD4635

Table 17 AZD4635 Dose Modifications for Hematologic Toxicities

Table 18 AZD4635 Dose Modifications and Discontinuation Criteria for Non-hematologic Toxicities (except Hypertension and CNS Toxicities)

Table 19 AZD4635 Dose Modifications and Discontinuation Criteria for Management of Hypertension

Table 20 AZD4635 Dose Modifications and Discontinuation Criteria for CNS Toxicities (Including Seizure)

Table 17 AZD4635 Dose Modifications for Hematologic Toxicities

Severity/Grade[a]	Action	AZD4635 Dose Modification
Enrolled without bone marrow involvement		
Neutropenia, Grade 3 (ANC 500 to 1000/mm^3)	Hold AZD4635 1 week or until ANC > 1000/mm^3.	Restart at same dose level. If recurrent toxicity then restart with 1 dose level reduction.
Thrombocytopenia (platelets < 25 K/mm^3)	Hold AZD4635 1 week or until platelets resolve to ≥ 75 K/mm^3.	Restart at same dose level. If recurrent toxicity then restart with 1 dose level reduction.
Febrile neutropenia	Hold AZD4635 until infection is resolved, antibiotics no longer required, and ANC > 1000/mm^3.	Restart with 1 dose level reduction.

ANC = absolute neutrophil count; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

[a] NCI CTCAE version 4.03

Table 18 AZD4635 Dose Modifications and Discontinuation Criteria for Non-hematologic Toxicities (except Hypertension and CNS Toxicities)

Severity/Grade [a]	Action
Grade 1 or 2	None required
Grade 3 or 4 and/or clinically significant [b]	Hold AZD4635
Toxicity resolved to Grade 1, Grade 2, or baseline < 14 days	Restart AZD4635 at 1 dose level reduction
Toxicity remains Grade 3 to 4 or is clinically significant [b] > 14 days	Discontinue AZD4635
Recurrence of Grade 3	Reduce one more dose level if available, or if not, discontinue study drug
Recurrence of Grade 3 cardiac event [b]	Discontinue AZD4635
Recurrence of Grade 4	Discontinue AZD4635

bpm = beats per minute; CK = creatine kinase; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QTc = QT interval corrected for heart rate.

[a] NCI CTCAE version 4.03

[b] Includes significant change in CK/CK-mb ratio (relative index > 5%), increases in heart rate of +25 bpm (up to 100 to 125 bpm) for more than 24 hours or increase in heart rate >125 bpm for more than 12 hours), QTc prolongation > 500 ms.

Table 19 AZD4635 Dose Modifications and Discontinuation Criteria for Management of Hypertension

Severity/Grade[a]	Antihypertensive Therapy	BP Monitoring	AZD4635 Dose Modification
Grade 2 Systolic BP 140 to 159 mm Hg or diastolic BP 90 to 99 mmHg; medical intervention indicated; recurrent or persistent (≥ 24 hours); symptomatic increase by > 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits	Initiate/escalate antihypertensive medication as per local guidelines. BP goal and the choice of the antihypertensive drug will be individualized for each subject.	Increase frequency of monitoring until stabilized to BP < 140/90 mmHg	None
Grade 3 (systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated	Initiate or maximize BP therapy as per local guidelines. Consider consult with a BP management specialist	Increase frequency of monitoring until stabilized to BP < 140/90 mmHg	May continue AZD4635 with optimization of antihypertensive management unless persistent BP-related clinical symptoms. Hold AZD4635 if BP is not decreased to Grade 2 within 48 hours after optimum therapy is instituted. If BP is reduced to baseline or Grade 1 within 14 days and considered stable, AZD4635 may be resumed at original dose. Discontinue AZD4635 if BP does not resolve to Grade 1 within 14 days. Discontinue AZD4635 if BP systolic ≥180 mmHg and/or diastolic ≥110 mmHg. Recurrence of Grade 3: Discontinue study drug.

Table 19 AZD4635 Dose Modifications and Discontinuation Criteria for Management of Hypertension

Severity/Grade[a]	Antihypertensive Therapy	BP Monitoring	AZD4635 Dose Modification
Grade 4 Life-threatening consequences (eg, malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Initiate treatment per local guidelines, including hospitalization, ICU management, and IV therapy as necessary		Discontinue AZD4635

BP = blood pressure; ICU = intensive care unit; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

[a] NCI CTCAE version 4.03

Table 20 AZD4635 Dose Modifications and Discontinuation Criteria for CNS Toxicities (Including Seizure)

Severity/Grade [a]	Action
Seizure (any grade) [b]	Hold AZD4635.
Grade 1 or 2 CNS toxicity (other than seizure)	None
Grade 3 or 4 or clinically significant CNS toxicity (other than seizure)	Hold AZD4635.
Toxicity resolved to Grade 1, Grade 2, or baseline < 14 days Toxicity remains Grade 3 to 4 or is clinically significant > 14 days	Restart AZD4635 at 1 dose level reduction. Discontinue AZD4635.
Recurrence of Grade 3 CNS toxicity	Reduce one more dose level if available, or if not discontinue study drug.
Recurrence of seizure	Discontinue AZD4635
Recurrence of Grade 4 CNS toxicity	Discontinue AZD4635

CNS = central nervous system; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

[a] NCI CTCAE version 4.03

[b] Hold drug for safety review. Subsequent decision for restarting AZD4635 to be based on Benefit-Risk ratio as assessed by Principal Investigator in collaboration with the medical monitor

10.9 Appendix 9 - Guidance Regarding Potential Interactions of Osimertinib with Concomitant Medications (Arm A)

The use of any natural/herbal products or other "folk remedies" is prohibited, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

10.9.1 Drugs Inducing CYP3A4 Metabolism that Sponsor Strongly Recommends Are Not Combined with Osimertinib

Osimertinib is metabolised by CYP3A4 and CYP3A5 enzymes.

A drug-drug interaction study of osimertinib evaluated in subjects showed that there is potential for osimertinib being a victim when co-administered with strong inducers of CYP3A4 (osimertinib concentrations are decreased when co-dosed with rifampicin).

The following potent inducers of CYP3A4 must not be used during this study for any subject receiving osimertinib.

Table 21 Drugs Inducing CYP3A4

Contraindicated Drugs	Withdrawal Period Prior to Osimertinib Start
Carbamazepine, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentin St John's Wort	3 weeks
Phenobarbitone	5 weeks

This list is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to strongly modulate CYP3A4 activity. Appropriate medical judgment is required. Please contact the medical monitor with any queries on this issue.

10.9.2 Medicines Whose Exposures May Be Affected by Osimertinib that Sponsor Considers May Be Allowed with Caution

Osimertinib may increase the concentration of sensitive BCRP substrates (concentration of the sensitive BCRP substrate, rosuvastatin, is increased).

Table 22 Exposure, Pharmacological Action, and Toxicity May Be increased by Osimertinib

Warning of Possible Interaction	Advice
Rosuvastatin	Drugs are permitted but caution should be exercised and subjects monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with osimertinib.
Sulfasalazine	
Doxorubicin	
Daunorubicin	
Topotecan	

10.9.3 Drugs That May Prolong QT Interval

The drugs listed in this section are taken from information provided by The Arizona Center for Education and Research on Therapeutics and The Critical Path Institute, Tucson, Arizona and Rockville, Maryland. Ref: https://crediblemeds.org/index.php/drugsearch.

This list shown below is not intended to be exhaustive, and a similar restriction will apply to other agents that are known to prolong or modulate QT interval. Appropriate medical judgment is required. Please contact the medical monitor with any queries on this issue.

10.9.3.1 Drugs Known to Prolong QT Interval

The following drugs are known to prolong QT interval or induce Torsades de Pointes and should not be combined with osimertinib. Recommended withdrawal periods following cessation of treatment with these agents are provided in the table.

Table 23 Drugs Prolonging QT Interval

Contraindicated Drug	Withdrawal Period Prior to Osimertinib Start
Clarithromycin, droperidol, erythromycin, procainamide	2 days
Cisapride, disopyramide, dofetilide, domperidone, ibutilide, quinidine, sotalol, sparfloxacin, thioridazine	7 days
Bepridil, chlorpromazine, halofantrine, haloperidol, mesoridazine	14 days
Levomethadyl, methadone, pimozide	4 days
Arsenic trioxide	6 weeks[a]
Pentamidine	8 weeks
Amiodarone, chloroquine	1 year

[a] Estimated value as pharmacokinetics of arsenic trioxide have not been studied

10.9.3.2 Drugs That May Possibly Prolong QT Interval

The use of the following drugs is permitted (notwithstanding other exclusions and restrictions) provided the subject has been stable on therapy for the periods indicated.

Table 24 Drugs That May Prolong QT Interval

Drug	Minimum Treatment Period on Medication Prior to Osimertinib Start
Alfuzosin, chloral hydrate, ciprofloxacin, dolasetron, foscarnet, galantamine, gemifloxacin, isridipine, ketoconazole, levofloxacin, mexiletine, nicardipine, octreotide, ofloxacin, ondansetron, quetiapine, ranolazine, telithromycin, tizanidine, vardenafil, venlafaxine, ziprasidone	2 days
Amantadine, amitriptyline, amoxapine, clozapine, doxepin, felbamate, flecainide, fluconazole, fosphenytoin, gatifloxacin, granisetron, imipramine, indapamide, lithium, moexipril/HCTZ, moxifloxacin, risperidone, roxithromycin, sertraline, trimethoprin-sulfa, trimipramine, voriconazole	7 days
Azithromycin, citalopram, clomipramine, itraconazole, nortriptyline, paroxetine, solifenacin, tacrolimus	14 days
Fluoxetine	5 weeks
Protriptyline	6 weeks
Tamoxifen	8 weeks

10.10 Appendix 10 - Prohibited Medications for Subjects treated with AZD4635 in Arm B

The use of warfarin is prohibited during treatment with AZD4635.

Use of potent or moderate inhibitors or inducers of CYP1A2 or sensitive substrates of CYP1A2, BCRP, and OAT1 is not permitted from 2 weeks before the first dose of AZD4635 until at least 2 weeks after the last dose of AZD4635.

Examples of potent or moderate CYP1A2 inhibitors/inducers are presented in Table 25. Examples of sensitive substrates of CYP1A2, BCRP, and OAT1 are presented in Table 26.

The lists of medications in Table 25 and Table 26 are not exhaustive and the absence of a drug from these lists does not imply that its combination with AZD4635 is safe. Appropriate medical judgment is required. Please contact the medical monitor with any queries on this issue.

Information on any treatment in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study with reasons for the treatment should be recorded. If medically feasible, subjects taking regular medication, with the exception of potent or moderate inhibitors or inducers of CYP1A2 or sensitive substrates of CYP1A2, BCRP, and OAT1 should be maintained on it throughout the study period.

Table 25 Examples of potent and moderate CYP1A2 enzyme inhibitors and inducers

CYP1A2 Enzyme Category	Examples of drugs in the category
Potent inhibitors	ciprofloxacin, clinafloxacin,enoxacin, fluvoxamine, oltipraz, zafirlukast, rofecoxib, angelica root (Bai Zhi [Angelica dahurica radix])
Moderate inhibitors	methoxsalen, mexiletine ,oral contraceptives,3,4-methylene-dioxymethamphetamine (MDMA), etintidine, genistein, idrocilamide, osilodrostat, phenylpropanolamine, pipemidic acid, propafenone, propranolol, troleandomycin, vemurafenib, grepafloxacin, piperine, zileuton
Moderate inducers	phenytoin, rifampin, ritonavir, smoking, teriflunomide

Table 26 Examples of sensitive substrates of CYP1A2, BCRP, and OAT1

Sensitive substrate category	Examples of drugs in the category
CYP1A2	alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine, pirfenidone, selegiline, tacrine
BCRP	Methotrexate, mitoxantrone, imatinib, lapatinib, sulfasalazine, topotecan, daunorubicin, doxorubicin, SN-38, irinotecan, prazosin, pantoprazole, atorvastatin, fluvastatin, rosuvastatin, and simvastatin.
OAT1	Adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine, ciprofloxacin, cephaloridine, methotrexate, pravastatin

SIGNATURE PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature

Document Name: protocol-d6070c00004-amendment-4		
Document Title:	protocol-d6070c00004-amendment-4	
Document ID:	CCI [redacted]	
Version Label:	3.0 CURRENT LATEST APPROVED	
Server Date (dd-MMM-yyyy HH:mm 'UTC'Z)	**Signed by**	**Meaning of Signature**
08-Feb-2021 11:52 UTC	PPD [redacted]	Management Approval
05-Feb-2021 16:53 UTC	PPD [redacted]	Author Approval
05-Feb-2021 14:00 UTC	PPD [redacted]	Content Approval

CCI [redacted]