Statistical Analysis Plan

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

Protocol Number: D6070C00004

Protocol Version: Amendment 2, 01May2018

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BL	baseline
CI	confidence interval
CR	complete response
CRC	colorectal cancer
DA	disease assessment
DC	disease control
DCR	disease control rate
DLT	dose-limiting toxicity
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
CCI	CCI
CCI	CCI
CCI	CCI
ILD	Interstitial Lung Disease
CCI	CCI
IP	investigational product
CCI	CCI
CCI	CCI
CCI	CCI
CCI	CCI
IV	Intravenous
IXRS	interactive voice/web response system
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic(s)

Abbreviation or Specialized Term	Definition
PR	partial response
RP2D	recommended Phase 2 dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SPP	statistical programming plan
TEAE	treatment-emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal

1 INTRODUCTION

This document describes the statistical analysis methodology for protocol D6070C00004, a multiarm, open-label, multicenter, phase 1b/2 study to evaluate novel combination therapies in subjects with previously treated advanced EGFRm NSCLC. As background information, an overview of the study design is provided. The main portion of this document details the statistical summaries relating to each study objective and describes the general conventions and definitions that will be used. In addition, a set of table templates and specifications will be included in a statistical programming plan (SPP) to complement this document.

2 STUDY OVERVIEW

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

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

2.1.2 Secondary Study 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 with 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

2.1.3 Exploratory Study Objectives

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2.2 Study Design

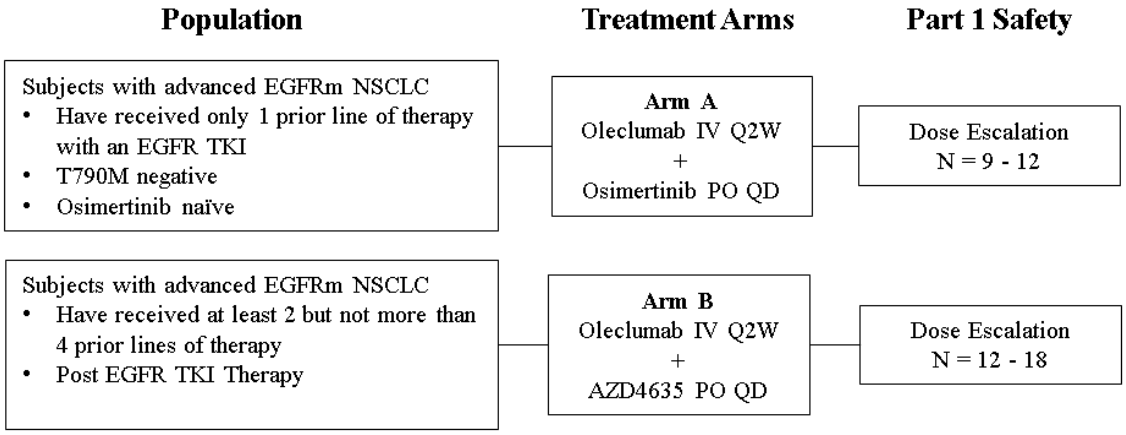
This is a multiarm, open-label, multicenter, Phase 1b/2 study to evaluate novel combination therapies in subjects with previously treated advanced EGFRm NSCLC. The study is divided into 2 parts. In Part 1 the safety and tolerability of novel combination therapies will be evaluated and a RP2D for combination 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 (Protocol Section 4.8.8).

The study flow is presented in Figure 2.1.3-1 for Part 1 and in Figure 2.1.3-2 for Part 2.

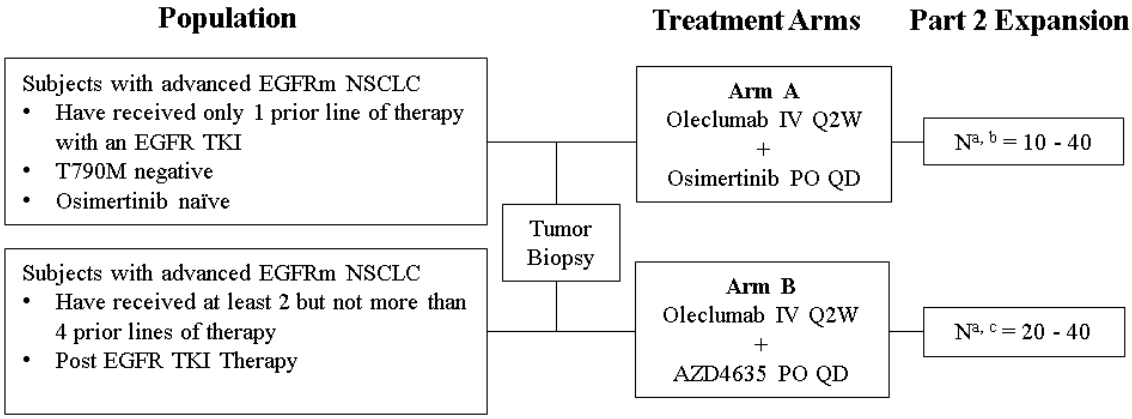
Figure 2.1.3-1 Study Flow Diagram for Part 1: Dose Escalation



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 2.1.3-2 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).

2.3 Treatment Assignment and Blinding

Treatment Assignment

An interactive voice/web response system (IXRS) will be used for assignment of unblinded investigational product kit numbers to each subject who meets the eligibility criteria. 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.

Blinding

The study is not blinded.

2.4 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.

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Table 2.1.3-1 CCI [redacted]

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3 STATISTICAL METHODS

3.1 General Considerations

Tabular summaries will be presented by treatment group. Categorical data will be summarized by frequency distribution (number and percentage of subjects falling within each category). Continuous variables will be summarized by descriptive statistics including N, mean, standard deviation, median, and range (minimum and maximum). All available data will be used and thus missing data will not be imputed. In general, subjects with missing data for a parameter will be excluded from the summary of this parameter. Tables will be supported by data listings showing the original data forming the basis for the summaries. Data listings will be sorted by treatment group, subject number and date collected where applicable.

In general, unless stated otherwise, two-sided confidence intervals will be produced at 95%. Baseline values will be defined as the last valid assessment prior to the first administration of investigational product.

The data analyses will be conducted using the SAS® System (SAS Institute, Inc., Cary, NC, USA) Version 9.3 or above. All analysis outputs will be validated according to MedImmune SAS programming standards and MedImmune validation procedures.

3.2 Analysis Populations

Table 3.2-1 Analysis Populations

Population	Description
As-treated population	The As-treated population includes subjects who receive any study investigational product. Subjects will be analyzed according to the treatment they actually receive. All analyses will be performed on the As-treated Population unless otherwise specified.
Response-evaluable population	The Response-evaluable population includes subjects from the As-treated Population who have a baseline disease assessment (DA), have the opportunity to be followed for at least 8 weeks at the time of the data cutoff (ie, dosed at least 8 weeks prior to the time of the data cutoff), and either has at least one post-baseline DA and/or discontinued treatment due to death or disease progression.
DLT evaluable population	The DLT evaluable Population includes subjects enrolled in the dose-escalation phase 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 as from the first dose of both investigational products until the planned administration of the third dose of oleclumab; this corresponding to Day 28 post Dose 1 of oleclumab) and complete the safety follow-up through the DLT-evaluation period or experience any DLTs.

The number and percent of subjects in each subject population for evaluation will be summarized.

Unless stated otherwise, subject disposition and baseline characteristics, exposure to each investigational product (IP), safety analyses, and efficacy analyses will be based on as-treated population; DLT-evaluable population will be used for the RP2D evaluation.

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

Table 3.3.1-1 presents the summaries that will be prepared for subject disposition.

Table 3.3.1-1 Subject Disposition to be Summarized

Summary	Population
Number of Subjects Entered by Site	All subjects entered
Subject Status at the End of Treatment	As-treated
Subject Status at the End of Study	As-treated
Mortality Summary	As-treated

Summaries of the number and percentage of subjects entered at each site will be provided.

The summary of subject status at the end of study treatment will include the number and percentage of subjects who ended treatment due to any of the following reasons: completed protocol-defined end of treatment, adverse event (AE), progressive disease, death, lost to follow-up, protocol violation, subject decision, investigator decision, or other.

Subject status at the end of study will be summarized in terms of the number and percent of subjects who are classified as the following: completed, lost to follow-up, withdrawal by subject, death, or other. For the subjects who discontinue the study due to withdrawal of consent, the reason for withdrawal (AE or other) will be summarized.

The end of study mortality summary will include subjects who are dead at the end of study, the cause of death (due to disease vs not due to disease) and the relationship to investigational product (related vs. not related).

3.3.2 Demographics and Baseline Characteristics

Summaries of demographics and baseline characteristics will be provided for the As-treated population to describe the subject populations in this study. These summaries will aid in interpretation of the assessment of the primary and secondary objectives and provide an overview of study conduct. The summaries to be provided are listed in Table 3.3.2-1.

Table 3.3.2-1 Summaries of Baseline Characteristics

Summary	Population
Demographics	As-treated
Disease History	As-treated
Prior Cancer Treatment	As-treated
Baseline Disease Status Assessment	As-treated
Baseline Tumor Characteristics	As-treated
Baseline ECOG Performance Status	As-treated
Smoking History	As-treated

ECOG = Eastern Cooperative Oncology Group.

Demographics will be summarized for the following characteristics: age (year), gender, height (cm), weight (kg), ethnicity, and race.

The disease history summary will include frequency distributions for disease stage at initial diagnosis (IA, IB, IIA, IIB, IIIA, IIIB, IV, unknown), tumor stage at initial diagnosis (T0, Tis, T1, T2, T3, T4, TX, unknown), node stage at initial diagnosis (N0, N1, N2, N3, NX, unknown), metastasis stage at initial diagnosis (M0, M1, MX, unknown), histologic type

(carcinoma, adenocarcinoma), and descriptive statistics of time from primary diagnosis to study entry (months). Mutation will be provided in listing and will be summarized by mutation type. (e.g. Exon 18 Gly719#, Exon 20 insertion, etc).

Prior cancer treatment will be summarized by using the number and percentage of subjects who have received each of the following therapy categories: systemic therapy, radiation, cancer related surgery, or other. Previous lines of therapy will be summarized. Best response of prior cancer treatment will be summarized by the following categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable, not applicable and unknown. Descriptive statistics of number of prior treatment regimens will be provided.

Baseline disease status assessment summary will include frequency distributions for disease stage at study entry (IA, IB, IIA, IIB, IIIA, IIIB, IV), tumor stage at study entry (T0, Tis, T1, T2, T3, T4, TX, unknown), node stage at study entry (N0, N1, N2, N3, NX, unknown), metastasis stage at study entry (M0, M1, MX, unknown) and T790M status determined by a central lab (negative, positive) when available.

Baseline tumor characteristics including number and sites of target tumor lesions and number and sites of non-target tumor lesions will be summarized. The size of baseline target lesions will also be summarized in terms of sum of the measurement of measurable target lesions using descriptive statistics.

Baseline Eastern Cooperative Oncology Group (ECOG) performance status will be summarized using frequency distributions for the collected categories.

Smoking history will be summarized.

3.3.3 Study Drug Exposure

The summaries of exposure to each IP to be provided are listed in Table 3.3.3-1.

Table 3.3.3-1 Study Drug Exposure

Summary	Population
Study Treatment Exposure	As-treated
Dosing Delay of Investigational Products	As-treated
Summary of Subsequent Alternative Cancer Treatment	As-treated

Summary of study treatment exposure will include descriptive statistics of the following: total duration of exposure in months, total number of IP doses, total dose received during the study, dose intensity and relative dose intensity. Dose intensity and relative dose intensity to IP(s) will be summarized by descriptive statistics.

The duration of exposure for oleclumab is defined as last dose date + 14 days minus first dose date for subjects on treatment or minimum of (date of death plus 1 day, data cutoff date plus 1 day, or last dose date + 14 days) minus first dose date for subjects who discontinued treatment. The duration of exposure for Osimertinib or AZD4635 is defined as last dose date + 1 days minus first dose date. The relative dose intensity is a percent of total actual dose that a subject received during corresponding study treatment period versus the total intended dose for the same study treatment period according to the study protocol. The details of the dose intensity calculation will be provided in the SPP as part of the standard exposure TFL templates.

Dosing deviations for IP(s) will be summarized with reasons for deviations for the following categories: delays, omissions, reductions, and interruptions. Dosing delays will be derived based on the scheduled dosing dates. The number of subjects with dosing delays and total dose delays will be summarized.

3.3.4 Concomitant Medications

The number and percentage of subjects who took at least 1 dose of medication other than investigational product during the study (concurrent medications) will be summarized by the generic name coded by World Health Organization (WHO) dictionary. The summary table of concomitant medications will include all concomitant medications taken on or after the date of first dose of investigational product or any concomitant medication started prior to first dose of study treatment that continued beyond the date of first dose of investigational product.

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint(s) and Analyses

3.4.1.1 Primary Efficacy Endpoint(s) and Analysis

The primary efficacy endpoint is objective response per RECIST 1.1 by investigator assessment. Objective response rate (ORR) is defined as the proportion of subjects with a best overall response of confirmed CR or confirmed PR that occur prior to the initiation of

subsequent anticancer treatment. The rules for confirmation of CR or PR are the same as described in Section 3.4.2.1. The primary analysis of ORR will be based on the as-treated population in Part 2 (including subjects dosed at the RP2D in Part 1). ORR will be estimated with a 95% CI using the exact binomial distribution. Subjects that have missing best overall response assessments will be considered non-responders, and will therefore be counted in the denominator, but not in the numerator of ORR. In addition, above analysis may also be performed based on the response -evaluable population in Part 2 (including subjects dosed at the RP2D in Part 1).

3.4.2 Secondary Efficacy Endpoint(s) and Analyses

The secondary efficacy endpoints include best overall response (BOR); duration of response (DOR); progression-free survival (PFS); overall survival (OS); disease control (DC). The efficacy endpoints will be summarized based on the as-treated population. Additional summaries based on the response--evaluable population may be presented.

Efficacy analyses, except for OS, will be based on an application of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (Eisenhauer et al, 2009) to investigator assessed tumor measurements.

The Investigator assessed Response per RECIST 1.1 will be programmatically derived based on the investigator reported target, non-target, and new lesions assessments. Appendix 7.1 provides the derivation rules.

3.4.2.1 Best Overall Response

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. Best overall response (BOR) will be programmatically derived based on all post-baseline disease assessments that occur prior to the initiation of subsequent anticancer treatment. BOR will be summarized with the number and percentage of subjects for the following categories: CR; PR; SD; PD; and non-evaluable (NE). At least 8 weeks [-3 days] from the first dose of investigational product must elapse without a subsequent radiological disease progression in order to assign a best overall response of SD. The definition of 54 days will allow for the protocol-defined disease assessment window of 8 weeks (57 ± 3 days) for the first post dose disease assessment.

Confirmation of CR and PR is required and must occur no fewer than 4 weeks after initial documentation of CR or PR. If CR is pending confirmation and is designated at an assessment followed by 1 or more NE assessments, and/or PR assessments such that a) the Target Lesion Response is CR and the Non-Target Lesion Response is NE, or b) the Target Lesion Response is PR due solely to an increase in one or more lymph nodes to a size ≥ 10 mm and the Non-Target Lesion Response is either CR or NE, CR may be confirmed thereafter. Similarly, if a PR is pending confirmation and is designated at an assessment followed by 1 or more NE and/or SD assessments, PR may be confirmed thereafter.

In general, subjects not classifiable under the RECIST 1.1 response categories due to insufficient data or early death will be classified as non-evaluable for BOR, but will be counted in the denominator of all response rate calculations. This generalization includes if a subject has missing lesion data at baseline. In this scenario, the subject will be classified as non-evaluable for BOR. If a subject is missing lesion data at a disease assessment and yet progressive disease criteria is met despite the missing data, the subject will be classified as PD.

3.4.2.2 Disease Control

Disease control rate (DCR) is defined as the proportion of subjects with a BOR of confirmed CR, confirmed PR, or SD (maintained for ≥ 8 weeks [-3 days]). Duration of SD is defined as the time from the first dose of investigational product until the first documentation of disease progression or death due to any cause, whichever occurs first, and will allow for the protocol-defined disease assessment window of 57 ± 3 days for first post dose disease assessment. DCR will be estimated with a 95% CI using the exact binomial distribution. DCR will also be summarized by T790M status based on tumor biopsies and plasma T790M status at baseline (determined by a central lab) with a 95% CI estimated using the exact binomial distribution.

3.4.2.3 Duration of Response

Duration of response (DOR) is defined as the time from the first documentation of a subsequently confirmed objective response until the first documentation of disease progression or death due to any cause, whichever occurs first regardless of whether the subject receives subsequent anticancer therapy prior to progression. 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. Only subjects who have achieved objective response (confirmed CR or confirmed PR) will be evaluated for DOR. DOR is defined in months as follows:

DOR (months) = (Date of PD/death or censoring – Date of first confirmed disease response + 1) / (365.25/12),

The date of PD/death or censoring is the same as defined for PFS. The median DOR and its 95% CI will be estimated using the Kaplan-Meier method.

3.4.2.4 Progression-free Survival

Progression-free survival (PFS) is defined as the time from the first dose of investigational product until the first documentation of a disease progression or death due to any cause, whichever occurs first, regardless of whether the subject receives subsequent anticancer treatment prior to progression. Patients who have no documented progression and are still alive at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. PFS is defined in months as follows:

PFS (months) = (Date of PD/death or censoring – Date of the first dose of investigational product + 1) / (365.25/12),

The censoring guidance and the date of PD/death or censoring are given in the table below. The number and percentage of patients experiencing a PFS event and Kaplan-Meier plots of PFS will be presented by treatment group. The median PFS and its 95% CI will be estimated using the Kaplan-Meier method. The proportion of subjects progression free and alive at time points of interest months (such as 3 months and 6 months) and associated 95% CI will be estimated using the Kaplan-Meier method.

Table 3.4.2-1 Summary of Censoring Guidelines for PFS

Situation	Date of PD/Death or Censoring	PFS Outcome
Documented Progressive Disease (PD) or death	Date of earliest sign of PD or death, whichever comes first	Event (unless the censoring rule specified below)
Death or PD immediately after ≥ 2 consecutive missed or non-evaluable disease assessments as per the protocol specified assessment schedule	Date of last progression-free disease assessment prior to missed or non-evaluable assessments, or the first dose of investigational product, whichever occurred last	Censored
No PD or death at time of analysis or lost to follow-up	Date of last adequate progression-free disease assessment	Censored
No tumor assessment at baseline and no evidence of PD at first post-baseline disease assessment OR No tumor assessment post-first dose, and no death prior to second scheduled post-baseline disease assessment	Date of the first dose of investigational product	Censored

PD = progressive disease; PFS = progression-free survival

Subjects having missing lesion data at baseline or no disease assessments post-first dose of investigational product will have PFS censored at the date of the first dose of investigational product unless the subject dies prior to the second scheduled post-baseline disease assessment in which case the death date will qualify as a PFS event.

If a subject has two or more consecutive completely missed or non-evaluable assessments followed immediately by death or an assessment showing radiologic disease progression, then the subject will be censored for PFS. PFS will be censored at the date of the first dose of investigational product or the last progression-free disease assessment prior to the missed or non-evaluable assessments, whichever occurred last.

If a subject has two or more consecutive missed or non-evaluable assessments followed by an assessment showing no radiologic disease progression, then the assumption will be that the subject did not progress during the missed or non-evaluable assessments. Two or more consecutive assessments is defined as ≥16 weeks plus 6 days (two disease assessments as per protocol plus a 6 days visit window to allow for a late assessment) after the last evaluable post-baseline disease assessment.

Subjects remaining on study without radiologic disease progression or death at the time of analysis will be censored for PFS at the date of their last adequate disease assessment. An adequate assessment is one that has recorded measurements for all target lesions defined at

baseline and a non-NE non-target lesion response (ie, the last non-missing or non-evaluable disease assessment).

3.4.2.5 Overall Survival

Overall survival (OS) is defined as the time from the first dose of investigational product until death due to any cause. For patients who are alive at the time of analysis, OS will be censored on the last date when patients are known to be alive. The last date for each individual subject is defined as the latest among the following dates recorded on the case report forms (CRFs):

- AE start, stop, and change dates
- Admission and discharge dates of hospitalization
- Study treatment date
- Date of last contact, withdrawal consent, refuse to be followed up, or last known alive on end of treatment, end of study, and survival status/follow-up CRFs
- Laboratory test dates including (but not limited to) hematology, chemistry, urinalysis, coagulation, tumor biopsy, immunoglobin, pharmacokinetics CCI [redacted] CCI [redacted].
- Disease assessment dates on RECIST CRF
- Date of visit, vital signs, ECOG, ECG, and physical examination
- Start and stop dates of alternative anticancer treatment
- Dates on quality of life questionnaire CRFs
- Start and end date of concomitant medication and surgical/medical procedure

OS is defined in months as follows:

OS (months) = (Date of death or censoring – Date of the first dose of investigational product + 1) / (365.25/12).

The number and percentage of patients experiencing a OS event and Kaplan-Meier plots of OS will be presented by treatment group. The median OS and its 95% CI will be estimated using the Kaplan-Meier method. The proportion of subjects alive at time points of interest (such as 3 months and 6 months) and associated 95% CI will be estimated using the Kaplan-Meier method.

3.4.3 Handling of Dropouts and Missing Data

In general, missing data are not imputed for statistical analysis. Guidance regarding the handling of dropouts and missing data and censoring will apply uniformly to all efficacy analyses resulting from an application of RECIST 1.1 to investigator assessed tumor measurements (details are specified in the corresponding endpoint section and Appendix 7.1). For investigator reported outcomes, analyses will present outcomes reported by the investigator without consideration of missing data or censoring rules.

3.4.4 Subgroup Analyses

When appropriate (e.g. sufficient sample size in each subgroup), the analysis of OR and DC may be performed by T790M status (gene mutation vs. no gene mutation) at baseline (determined by a central lab) in archival and/or fresh tumor biopsies.

3.4.5 Exploratory CCI Analyses

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3.4.6 Other Efficacy Analyses

3.4.6.1 Change from Baseline in Tumor Sizes

The percent change from baseline in target lesion sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) will be calculated at each adequate post-baseline disease assessment. The percent change from baseline in target lesion sum of diameters is defined as follows:

100 * (Σ Diameters at DA X - Σ Diameters at BL) / (Σ Diameters at BL).

DA = Disease Assessment; BL = Baseline.

The percent change from baseline in target lesion sum of diameters will be presented by subject using spider plots. The best percent change from baseline in target lesion sum of diameters is defined as the largest reduction or smallest increase (in the case where a

reduction does not occur) from baseline observed over all post-baseline disease assessments prior to the initiation of subsequent anticancer treatment. The best percent change from baseline will be presented using waterfall plots. Target lesion measurements and sum of diameters will be listed by disease assessment and subject.

3.5 CCI

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3.6 Safety Analyses

All safety analyses will be performed based on as-treated population, unless otherwise specified.

3.6.1 RP2D Evaluation

The Recommended Phase 2 dose (RP2D) evaluation will be based on the DLT Evaluable Population. The number and percentage of subjects with DLTs will be presented by dose level. The RP2D level will be indicated in the summary.

3.6.2 Adverse Events and Serious Adverse Events

Treatment-emergent adverse event (TEAE) is defined as events present at baseline that worsen in intensity after administration of study investigational product or events absent at baseline that emerge after administration of study investigational product. All TEAEs that occurred on and after first dose to 28 days after last dose of IP will be listed and summarized.

TEAEs will be summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, severity graded according to National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE, v4.03) (Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5), and relationship to study drug.

Subjects will be counted only once for each preferred term, once for each system organ class, and by the highest severity, regardless of how many events the subject experienced. TEAEs that result in permanent discontinuation of investigational product(s) or death will be summarized descriptively and listed.

The TEAE summaries to be provided are listed in Table 3.6.2-1

Table 3.6.2-1 Treatment-emergent Adverse Events and Serious Adverse Events to be Summarized

Summary	Population
Rate summary of all Treatment Emergent Adverse Events	As-treated
Treatment Emergent Adverse Events / Related TEAEs	As-treated
Treatment Emergent Adverse Events by Highest Severity / Related TEAEs by Highest Severity	As-treated
Treatment Emergent Adverse Events Sorted by Frequency / Related Treatment Emergent Adverse Events Sorted by Frequency	As-treated
Grade 3 or Grade 4 TEAEs / Related Grade 3 or Grade 4 TEAEs	As-treated
Serious TEAEs / Related Serious TEAEs	As-treated
Serious TEAEs by Serious Adverse Criteria	As-treated
Treatment Emergent Adverse Events Resulting in Permanent Discontinuation of Study Drug /Related TEAEs Resulting in Permanent Discontinuation of Study Drug	As-treated
Treatment Emergent Adverse Events Resulting in Dose Delay or Omission or Dose Interruption / Related TEAEs Resulting in Dose Delay or Omission or Dose Interruption	As-treated
Treatment Emergent Adverse Events Resulting in Death / Related TEAEs Resulting in Death	As-treated

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The AEs occurring from the signing of the informed consent and prior to the initiation of study investigational product will be listed.

3.6.3 Adverse Events of Special Interest

Per protocol section 5.3, Adverse Events of Special Interest for oleclumab include the following:

- Infusion-related Reactions
- Cardiac Chest Pain, Transient Ischemic Attack, and Thromboembolism
- Edema
- Immune Complex Disease

Adverse Events of Special Interest for Osimertinib include:

- Interstitial Lung Disease/Pneumonitis
- QTc prolongation and Arrhythmias
- Changes in cardiac contractility

Adverse Events of Special Interest for AZD4635 include:

- Seizures

Other categories may be added or existing terms may be modified as necessary. Preferred terms used to identify each AESI group will be listed before data base lock. AESI grouping summary tables will be produced and may also show the individual preferred terms within each AESI grouping.

AESI summaries to be provided are listed below. For patients on Arm A, two sets of AESI summaries will be prepared: one for oleclumab and the other for osimertinib; for patients on Arm B, two sets of AESI summaries will be prepared: one for oleclumab and the other for AZD4635;

- All AESI
- All AESI by highest severity
- Treatment related AESI
- Treatment related AESI by highest severity

3.6.4 AEs During Which Systemic Steroids, Endocrine Therapy, or Other Immunosuppressants Were Administered

AEs during which systemic steroids, endocrine therapy, or other immunosuppressants were administered will be programmatically identified by searching for dates of initiation of these agents and comparing to the onset dates and resolution dates of AEs for individual subjects. The concomitant medications administered to subjects will be identified by searching the clinical database for select ATC codes to identify systemic steroids, endocrine therapy and other immunosuppressants. See a list of select ATC codes in the durvalumab imAE Charter. The last version of the imAE charter before the DCO (Data Cut Off) date for analysis will be used.

Summaries of AESIs during which systemic steroids, endocrine therapy, or other immunosuppressants were administered as listed in the imAE charter will be provided.

3.6.5 Immune-mediated Adverse Events (imAE)

To fully characterize the AEs during which systemic steroids, endocrine therapy, or other immunosuppressants were administered, the Sponsor will perform medical review of those AEs and classify them as immune-mediated AEs (imAEs) or not imAEs. See further details in the durvalumab imAE Charter.

Immune-mediated AEs will be defined as are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology.

imAEs will be derived by first programmatically identifying AEs during which systemic steroids, endocrine therapy, or other immunosuppressants were administered as outlined above in Section 3.6.4. A further clinical evaluation of all such events will be made to ensure there was no clear alternate etiology before classifying them as imAEs for the purpose of analysis and reporting.

The imAEs will be summarized in the same manner as for the summaries for AESI described above in Section 3.6.3 and Section 3.6.4.

In addition, analyses of time to first onset imAE, time to resolution of imAE, and systemic steroid use for imAE may be provided by imAE group. See further details in the imAE Charter with respect to derivation rules associated with these endpoints and their analyses.

3.6.6 Deaths and Treatment Discontinuations due to Adverse Events

Refer to Section 3.6.2.

3.6.7 Clinical Laboratory Evaluation

Laboratory tests will be grouped according to hematology, serum chemistry, urinalysis, and thyroid function tests (TSH, free thyroxine T4). For all continuous laboratory assessments, absolute value and change from baseline will be summarized for each scheduled assessment, "worst-case" (nadir and/or zenith) on treatment, and the last assessment on-treatment using descriptive statistics. Laboratory abnormalities with toxicity grades according to the NCI CTCAE 4.03 will be derived according to laboratory values. Shift tables from baseline to worst toxicity grade on treatment will be presented. Separate summaries indicating hyper- and hypo- directionality of change will be produced, where appropriate. In addition, the number and percentage of subjects experiencing at least 2-Grade shift, and any shift to a worst post-baseline toxicity Grade of 3 to 4 from baseline will be summarized. For each lab test condition, percentages are calculated based on the number of treated subjects who have a baseline and at least one post-baseline assessment. In the shift table analysis, for a given subject, if a subject has both missing and non-missing CTCAE grades for one laboratory test, the missing CTCAE grade of that laboratory test will be treated as the lowest grade.

Laboratory abnormalities with toxicity grades according to the NCI CTCAE 4.03 will be derived for the following parameters:

Hematology: Anemia (Hemoglobin decreased), White Blood Cell decreased, Neutrophils decreased, Platelets decreased, Lymphocytes decreased

Serum chemistry: Alanine Amino Transferase (ALT) increased, Aspartate Amino Transferase (AST) increased, Alkaline Phosphatase (ALP) increased, Total bilirubin increased, Creatinine increased, Magnesium hypo and hyper, Sodium hypo and hyper, Potassium hypo and hyper, Corrected calcium hypo and hyper, Glucose hypo and hyper, Cholesterol high, GGT increased, Lipase increased, Amylase increased.

For thyroid function tests (TSH, free thyroxine T4) with no CTCAE grading, summary table of shifts from baseline relative to the normal range in thyroid function will be provided. Number of subjects will be summarized for those with normal baseline and at least one post-baseline TSH value below LLN and a concurrent free Thyroxine above the ULN and those with normal baseline and at least one post-baseline TSH value above ULN and a concurrent free Thyroxine below the LLN.

Liver Function Parameters

Subjects with elevated post-baseline ALT, AST or Total Bilirubin that fall into the following categories will be identified. Number and percentage of these subjects will be tabulated.

Liver Function Parameters	Category
ALT	• >=3 × – <=5 × ULN • >5 × – <=8 × ULN • >8 × – <=10 × ULN • >10 × – <=20 × ULN • >20 × ULN
AST	• >=3 × – <=5 × ULN • >5 × – <=8 × ULN • >8 × – <=10 × ULN, • >10 × – <=20 × ULN • >20 × ULN
Total bilirubin	• >=2 × – <=3 × ULN • >3 × – <=5 × ULN • >5 × ULN
ALT or AST	• >=3 × – <=5 × ULN • >5 × – <=8 × ULN • >8 × – <=10 × ULN, • >10 × – <=20 × ULN • >20 × ULN
Potential Hy's law	• (AST >= 3 × ULN or ALT >= 3 × ULN) and (Total Bilirubin >= 2×ULN)[a]

Liver Function Parameters	Category

ULN: upper limit of normal range.

[a]: Total Bilirubin >= 2×ULN is defined as at least one case of post-dose TBL >= 2 x ULN occurred at the same day or after the first incidence date of ALT or AST >= 3 x ULN post treatment.

Individual subject data where elevated ALT or AST plus total bilirubin fall into the "Potential Hy's law" will be listed.

Assessment of Nephrotoxicity

Creatinine clearance rate will be calculated using serum creatinine and the Cockcroft-Gault formula to estimate glomerular filtration rate (GFR). The Cockcroft and Gault formula (1973) is as follows:

- Male: $C_{Cr}=\{((140–age) \times weight)/(72 \times S_{Cr})\}$
- Female: $C_{Cr}=\{((140–age) \times weight)/(72 \times S_{Cr})\} \times 0.85$,

where C_{Cr} denotes Creatinine clearance rate (mL/minute), S_{Cr} denotes serum creatinine (mg/dL), weight (kg) denotes the weight at the current visit or the most recent visit, age in years.

Shift tables from baseline to "worst-case" on treatment C_{Cr} value will be provided. Baseline and "worst-case" on treatment C_{Cr} value will be categorized for the following categories:

- Normal: ≥ 90 mL/min
- Mild Impairment: ≥ 60 − < 90 mL/min
- Moderate Impairment: ≥ 30 − < 60 mL/min
- Severe Impairment: ≥ 15 − < 30 mL/min
- Kidney Failure: < 15 mL/min

3.6.8 Other Safety Evaluations

3.6.8.1 Vital Signs

Vital signs will be assessed at screening, baseline and throughout the study. Descriptive statistics of baseline value, post-baseline value, and change from baseline value for heart rate, blood pressure, temperature, and respiratory rate will be provided for each scheduled time

point with available data in at least 10% of subjects. Table 3.6.8.1-1 presents the summary to be prepared for vital sign parameters.

Table 3.6.8.1-1 Vital Sign Parameters to be Summarized

Summary	Population
Change from Baseline in Vital Sign Parameters	As-treated

3.6.8.2 Electrocardiogram

Electrocardiogram (ECG) parameters will be assessed at baseline as well as throughout the study. Abnormal ECG parameters (PR, QRS, QTcF) will be summarized using descriptive statistics; changes from baseline to scheduled time of evaluation and to the maximum post-baseline values will be summarized. The QTcF will be considered as the primary correction method to assess subject cardiac safety.

The number and percentage of subjects having the following notable ECG interval values on treatment will be summarized:

- Maximum QTcF intervals > 450 milliseconds, > 480 milliseconds, and > 500 milliseconds.
- Maximum changes from baseline in QTcF > 30, >60, and > 90 milliseconds.

3.6.8.3 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be assessed at baseline as well as throughout the study. ECOG will be summarized by study visit and will include descriptive statistics for the value of the parameters and the changes from baseline.

3.6.9 Subgroup Analyses

No subgroup analyses are planned.

3.7 Immunogenicity

Analysis to immunogenicity will be performed by the MedImmune Clinical Pharmacology & DMPK (CPD) group or designee. The details of the analyses and presentation of these data will be included in a separate PK report.

3.8 Pharmacokinetics

Pharmacokinetic data analyses will be performed by the MedImmune Global PK-PD group or designee. The details of the analyses and presentation of these data will be included in a separate PK report.

3.9 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 list of preferred terms used to identify potential cases of pneumonitis/ILD AE is included in Appendix 7.3. 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 3.6.9-1). 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 3.6.9-1 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 of 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.

4 INTERIM ANALYSIS

The interim analyses will be performed separately for each dose-expansion cohort (Arm A and Arm B) starting at 10 response-evaluable subjects for Arm A and 20 response-evaluable subjects for Arm B (including subjects dosed at the RP2D in Part 1). 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. If futility decision is made at an interim analysis, the enrollment will be terminated. An efficacy analysis may also 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.

Continuous monitoring based on Bayesian predictive probability will be used for the interim analyses (Lee and Liu, 2008). In this study, for dose expansion cohorts Arm A and B, different ORRs were assumed as the target response rates for decision making. CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI [redacted] The interim analyses will be based on the Response-evaluable Population as defined in Section 3.2.


CCI

CCI

To assess the operating characteristics of this continuous interim monitoring method, overall go or no-go probabilities, average sample sizes to achieve the decisions, and probabilities of making early decisions were calculated based on 10000 simulations and assumed true response rates (CCI). Decision consistencies (or accordance) between a design using continuously monitoring and a design without interim monitoring were also compared. The results are shown in Table for Arm A and Table for Arm B.

Table 3.6.9-1 CCI

CCI

Table 3.6.9-2 CCI

CCI

For example, when the true response rate is 0.4 for Arm A, there is a low probability (8%) that a no-go decision will be made using this paradigm throughout the study. There is about 3.8% probability that a decision would be made before the end of the study.

5 REFERENCES

J Jack Lee and Diane D Liu. A predictive probability design for phase II cancer clinical trials. Clinical Trials. 2008; 5; 93

6 VERSION HISTORY

Version	Date	Summary of Changes	Reason for Change
1.0	18Jun2018	Initial document	Initial document

7 APPENDIX

7.1 Derivation of Investigator-based RECIST 1.1 Visit Response

Guidance regarding the handling of dropouts and missing data will apply uniformly to all efficacy analyses resulting from an application of RECIST 1.1 to investigator assessed tumor measurements. For investigator reported outcomes, analyses will present outcomes reported by the investigator without consideration of missing data or censoring rules.

7.1.1 Target Lesion Response

Target lesion response will be programmatically derived on the data collection instrument once RECIST 1.1 criteria are applied to the site personnel recorded target lesion measurements.

Possible values include:

- CR – Complete Response
- PR – Partial Response
- SD – Stable Disease
- PD – Progressive Disease
- NE – Non-evaluable
- NA – Not Applicable (*set value for all post-baseline disease assessments only if no target lesions are identified at baseline*)

The derivation for target lesion response is as follows *(please note the order of the algorithm below is important)*:

1. If "Any Target Lesions Present" equals "No" on the *Target Lesions – Baseline* CRF, then all post-baseline "Target Lesion Response" equals "NA".

2. Else, if "Percent Change from Nadir Sum of Diameters" is greater than or equal to 20% and the absolute increase from the nadir (defined as the "Total" for each post-baseline disease assessment minus the "Nadir Sum of Diameters") is greater than or equal to 5 mm, then "Target Lesion Response" equals "PD".

3. Else, if "Not Done" is selected, or "Measurement" is left blank, or "Lesion no longer Measureable" is selected and equal to "NE", or "Lesion Intervention" is selected for any Target Lesion identified at Baseline, then "Target Lesion Response" equals "NE".

4. Else, if "Total Non-Lymph Node" equals "0" and all Lymph Node Target Lesion "Measurements" are less than "10" individually, then "Target Lesion Response" equals "CR".

   Note: This step requires examining "Measurements" separately for Target Lesions with "Lymph Node" equal to "Yes" and "No".

5. Else, if "Percent Change from Baseline Sum of Diameters" is less than or equal to -30%, then "Target Lesion Response" equals "PR".

6. Else, "Target Lesion Response" equals "SD".

If a subject has a missing tumor measurement at a disease assessment for 1 or more target lesions, the sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) will be reported for the remaining target lesions. These data will be used to indicate radiologic disease progression if the sum of diameters for the observed lesions increases at least 20% from the nadir sum of diameters of all target lesions and demonstrates at least a 5 mm absolute increase from the nadir sum of diameters of all target lesions, in spite of the missing data (or if other criteria for PD are met).

7.1.2 Non-Target Lesion Response

Non-target lesion response will be assigned by site personnel following a qualitative overall assessment of all non-target lesions.

Possible values include:

- CR – Complete Response

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

- Non-CR/Non-PD – Non-Complete Response / Non-Progressive Disease
  - Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

- PD – Progressive Disease
  - Unequivocal progression of existing non-target lesions.

- NE – Non-evaluable

- NA – Not Applicable (*set value for all post-baseline disease assessments only if no non-target lesions are identified at baseline*)

Though non-target lesion responses are a subjective decision made by the site personnel, certain responses may be limited depending on the non-target lesion statuses recorded. An algorithm is provided below highlighting appropriate possible non-target lesion responses based on recorded data. Reaching a red box (■) signifies having reached the only allowable non-target lesion responses based on non-target lesion statuses. Reaching a green box (■) signifies having reached the end of the algorithm and more than one possible non-target lesion response is possible from which the Investigator may choose.

1. a) If no non-target lesions are identified at baseline, all post-baseline non-target lesion responses should equal NA. ■
   b) Else, if any non-target lesions are identified at baseline, responses may be limited to CR, Non-CR/Non-PD, PD, NE (ie, responses of NA are not permitted).
   Go to Rule 2.
2. a) If all non-target lesions have a status are "Absent", the responses may be limited to CR. ■
   b) Else, if at least one non-target lesion status is NOT "Absent", the responses may be limited to Non-CR/Non-PD, PD, NE (ie, responses of CR, NA are not permitted).
   Go to Rule 3.
3. a) If all non-target lesions have a status of "Unequivocal Progression", responses may be limited to PD. ■
   b) Else, if no non-target lesions have a status of "Unequivocal Progression", responses may be limited to Non-CR/Non-PD, NE (ie, responses of CR, PD, NA are

not permitted).
Go to Rule 4.

c) Else, if at least one (but not all) non-target lesion has a status of "Unequivocal Progression", the responses may be limited to Non-CR/Non-PD, PD, NE (ie, responses of CR, NA are not permitted). (*Note: No response has been eliminated as an option here.*)
Go to Rule 5.

4. a) If all non-target lesions have a status of "Non-evaluable" and/or "Not Done" is selected, responses may be limited to NE. ■
   b) Else, if no non-target lesions have a status of "Non-evaluable" and "Not Done" is not selected, responses may be limited to Non-CR/Non-PD (ie, responses of CR, PD, NE, NA are not permitted). ■
   c) Else, if at least one (but not all) non-target lesion has a status of "Non-evaluable" and/or "Not Done" is selected, the responses may be limited to Non-CR/Non-PD, NE (ie, responses of CR, PD, NA are not permitted). ■
   (*Note: No response has been eliminated as an option here.*)
5. a) If all non-target lesions have a status of "Non-evaluable" and/or "Not Done" is selected, responses may be limited to NE. ■
   b) Else, if no non-target lesions have a status of "Non-evaluable" and "Not Done" is not selected, responses may be limited to Non-CR/Non-PD, PD (ie, responses of CR, NE, NA are not permitted). ■
   c) Else, if at least one (but not all) non-target lesion has a status of "Non-evaluable" and/or "Not Done" is selected, the responses may be limited to Non-CR/Non-PD, PD, NE (ie, responses of CR, NA are not permitted). ■
   (*Note: No response has been eliminated as an option here.*)

If a subject has a missing tumor status at a disease assessment for 1 or more non-target lesions, radiologic disease progression will be determined if the remaining non-target lesions qualitatively demonstrate unequivocal progression (or if other criteria for PD are met).

7.1.3 Visit Disease Response per RECIST1.1

Investigator visit disease response will be programmatically derived on the data collection instrument using RECIST 1.1 criteria based upon target lesion response, non-target lesion response, and new lesion data. Missing values in any of target lesion response, non-target lesion response, and new lesion data will result in the disease response not being derived.

Possible values include:

- CR – Complete Response

- PR – Partial Response
- SD – Stable Disease
- PD – Progressive Disease
- NE – Non-evaluable

Target Lesion Response	Non-Target Lesion Response	New Lesion	Derived RECIST Disease Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No (or NE)	PR
PR	CR or Non-CR/Non-PD or NE or NA	No (or NE)	PR
SD	CR or Non-CR/Non-PD or NE or NA	No (or NE)	SD
PD	Any	Any	PD
Any	PD	Any	PD
Any	Any	Yes	PD
NE	CR or Non-CR/Non-PD or NE or NA	No	NE
NA	CR	No	CR
NA	Non-CR/Non-PD	No	SD (Non-CR/Non-PD)[a]
NA	NE or NA	No (or NE)	NE
NA	CR or Non-CR/Non-PD	NE	SD (Non-CR/Non-PD)[a]

[a] Per RECIST 1.1, "SD (Non-CR/Non-PD)" is preferred over "SD" for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

If a subject has a missing tumor measurement at some assessment(s) for 1 or more target lesions and criteria for PD are not otherwise met, an overall response of NE will be assigned for the assessment(s).

7.1.4 Locoregional therapy

Any subject receiving locoregional therapy, including surgery, while on study that directly affects one or more of the target lesions selected at baseline and/or new lesions included in tumor burden will be identified. A subject with a subsequent response or SD/irSD will be considered to be non-evaluable at all disease assessments that occur on or after the date of locoregional therapy. Otherwise, the subject will be assessed ignoring the locoregional therapy.

7.1.5 Assignment of Dates of Disease Progression or Disease Response

For all analyses of endpoints resulting from an application of RECIST 1.1 to investigator assessed tumor measurements, there may be cases in which disease assessments span a series of dates. For establishing the start date of a subsequently confirmed response in which the disease assessment spans multiple days, the date of response assigned will be the latest date of evaluations corresponding to the disease assessment. The date of latest evaluation will also

be assigned for a mid-study assessment showing SD as the date assigned for the purposes of censoring duration of response, TTP and PFS.

The date of PD will be the first date at which any objective diagnostic test provides data indicating PD. Specifically, for RECIST 1.1 the date of PD will be the earliest of the following 3 evaluation dates:

- Date of PD as indicated by target lesions: If PD is triggered by a change in sum of diameters of target lesions, and the dates of evaluation of the target lesions vary for the same assessment, assign the first evaluation date among target lesions.
- Date of PD as indicated by non-target lesions: If the dates of evaluation of the non-target lesions vary for the same assessment, assign the first evaluation date for which any non-target lesion exhibits a status of Unequivocal Progression.
- Date of PD as indicated by new lesions: If multiple new lesions are identified and the dates of evaluation for the new lesions vary for the same assessment, assign the first evaluation date for which any new lesion is detected.

In scenarios where the Investigator disease response is either a response or PD, and differs from that of the application of RECIST 1.1 to investigator assessed tumor measurements separate response and/or progression dates will be required. Determination of the start date of a subsequently confirmed response in which the disease assessment spans multiple days remains the same as described previously. Specifically, the date of response assigned will be the latest date of evaluations corresponding to the disease assessment. The date of PD will be the earliest date of evaluations corresponding to the disease assessment.

7.2 CCI

CCI

CCI

[redacted]

CCI

[redacted]

7.3 Preferred Terms for Pneumonitis/ILD AE

The following list of preferred terms will be used for identifying potential cases of pneumonitis/ILD AE

Interstitial lung disease	CCI [redacted]
Lung disorder	
Pneumonitis	
Diffuse Alveolar Damage	
Pulmonary fibrosis	
Alveolitis	
Idiopathic pulmonary fibrosis	
Acute Interstitial Pneumonitis	
Pulmonary Toxicity	

MedImmune

A member of the AstraZeneca Group

Statistical Analysis Plan Approval

Date: 18Jun2018
To: Study File
From: PPD
Re: Statistical Analysis Plan Approval for Study D6070C00004

The Statistical Analysis Plan, version 1.0, for Study D6070C00004 has been reviewed and approved.

Name:	PPD	Signature:	PPD
Role:	Statistician	Date:	18 June 2018
Name:	PPD	Signature:	PPD
Role:	Statistical Programmer	Date:	
Name:	PPD	Signature:	PPD
Role:	Clinical Development Lead	Date:	18 June 2018
Name:	PPD	Signature:	PPD
Role:	Clinical Biostatistics Therapeutic Area Head	Date:	18 June 2018
Name:	PPD	Signature:	PPD
Role:	Head of Clinical Biostatistics & Data Management	Date:	18 June 2018