# Statistical Analysis Plan

A Phase 1b/2 Study to Evaluate the Safety, Pharmacokinetics, and Clinical Activity of Oleclumab (MEDI9447) with or without Durvalumab in Combination with Chemotherapy in Subjects with Metastatic Pancreatic Ductal Adenocarcinoma

**Protocol Number:** D6070C00005

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## LIST OF ABBREVIATIONS

| Abbreviation or Specialized Term | Definition |
|---|---|
| 1L | First-line |
| 2L | Second-line |
| 5-FU | 5-fluorouracil |
| ADA | Anti-Drug Antibody |
| AE | Adverse vent |
| AESI | Adverse event of special interest |
| ALT | Alanine amino transferase |
| AST | Aspartate amino transferase |
| ATC | Anatomical Therapeutic Chemical |
| AZ | AstraZeneca |
| BICR | Blinded independent central review |
| BL | Baseline |
| CCI [redacted] | [redacted] |
| CD | Cluster of differentiation |
| CI | Confidence interval |
| CR | Complete response |
| CRP | C-reactive protien |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| ctDNA | Circulating tumor DNA |
| CV | Coefficient of Variance |
| DA | Disease assessment |
| DC | Disease control |
| DCO | Data cut-off |
| DLT | Dose-limiting toxicity |
| DoR | Duration of response |
| eCRF | electronic case report form |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| CCI [redacted] | CCI [redacted] |
| CCI [redacted] | CCI [redacted] |

| Abbreviation or Specialized Term | Definition |
|---|---|
| FOLFOX | Leucovorin, 5-fluorouracil, and oxaliplatin |
| GCP | Good clinical practice |
| CCI [redacted] | [redacted] |
| ICF | Informed consent form |
| IHC | Immunohistochemistry |
| imAE | Immune-mediated adverse event |
| IP | Investigational product |
| CCI [redacted] | CCI [redacted] |
| ITT | Intent-to-treat |
| IVRS | Interactive voice response systems |
| LLOQ | Lower limit of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mRNA | Messenger RNA |
| MID | Minimally important difference |
| MTD | Maximum tolerated dose |
| NA | Not applicable |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NE | Not evaluable |
| NLR | Neutrophil to Lymphocyte ratio |
| NQ | Not quantifiable |
| NR | Not reportable |
| NS | No sample |
| OR | Objective response |
| ORR | Objective response rate |
| OS | Overall survival |
| PD | Progressive disease |
| PDAC | Pancreatic ductal adenocarcinoma |
| PD-L1 | Programmed cell death ligand-1 |
| PFS | Progression-free survival |
| PK | Pharmacokinetics |
| PR | Partial response |
| PRO | Patient reported outcome |
| RECIST | Response evaluated criteria in solid tumors |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SD | Stable disease |

| Abbreviation or Specialized Term | Definition |
|---|---|
| SPP | Statistical programming plan |
| TEAE | Treatment-emergent adverse event |
| TFL | Tables, Figures and Listings |
| TTFD | Time to first deterioration |
| TTR | Time to response |
| TV | Target value |
| ULN | Upper limit of normal range |
| v | version |
| WHO | World Health Organization |

## AMENDMENT HISTORY

| Version | Date | Summary of Changes | Reason for Change |
|---|---|---|---|
| 1.0 | 26Jul2018 | Corrected grammar errors and finalized the document. | Final document |
| 2.0 | 18Sep2018 | Updated sample size and power calculation based on protocol amendment 1; added details to analysis of time-to-event endpoints; added interim analysis section based on protocol amendment 1; updated TEAE reporting time window, MedDRA and CTCAE version number | Update in accordance with protocol amendment 1. |
| 2.1 | 01Aug2022 | Updated sample size for Part 2 cohort A based on protocol amendment 2. Addition of analysis by recruitment wave and further subgroup analysis. Defined which objectives may have analysis performed outside of the CSR. CCI [redacted] Clarification of baseline definition and protocol deviation categories. Restriction of formal statistical testing to OR, PFS and OS analyses. Update of landmark timings for PFS and OS and also the subgroup analysis. Added BICR analysis. CCI [redacted]. CCI [redacted]. Addition of Oleclumab related TEAE analyses. Expansion of ECG analysis section to incorporate parameter data. Immunogenicity and PK analyses added. | Update in accordance with Protocol amendment and additional analyses requirements. |

# 1 INTRODUCTION

This document has been written in alignment with amendment 3 of the Clinical Study Protocol (CSP) approved on 24th June 2022 and describes the statistical analysis methodology for protocol D6070C00005. This is a Phase 1b/2 multicenter, open-label, dose-escalation and dose-expansion study to assess the safety, preliminary antitumor activity, immunogenicity, and pharmacokinetic (PK) of oleclumab with or without durvalumab in combination with chemotherapy administered in subjects with metastatic pancreatic ductal adenocarcinoma (PDAC). 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 Objective(s) and Associated Endpoints

**Table 2.1 – 1 Primary Objective(s) and Associated Endpoints**

| Type | Objective | Endpoint |
|---|---|---|
| Safety | Part 1: To assess the safety and tolerability of oleclumab plus durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC. | • DLTs<br>• Incidence of AEs and SAEs<br>• Clinically meaningful changes from baseline in clinical laboratory parameters, vital signs, and ECG results |
| Clinical Activity | Part 2: To evaluate the preliminary antitumor activity of oleclumab with or without durvalumab in combination with gemcitabine and nab-paclitaxel compared to gemcitabine and nab-paclitaxel in subjects with 1L metastatic PDAC. | • OR according to RECIST v1.1 |
| | Part 2: To evaluate the preliminary antitumor activity of oleclumab with or without durvalumab in combination | • OR according to RECIST v1.1 |

| | | |
|---|---|---|
| | with mFOLFOX administered in subjects with 2L metastatic PDAC. | |

1L = first-line; 2L = second-line; AE = adverse event; ECG = electrocardiogram; DLT = dose-limiting toxicity; mFOLFOX = modified regimen of leucovorin, 5-fluorouracil and oxaliplatin; OR = objective response; PDAC = pancreatic ductal adenocarcinoma; RECIST = Response Evaluable Criteria in Solid Tumors; SAE = serious adverse event; v = version
Note: Part 1 is dose escalation and Part 2 is dose expansion.

### 2.1.2 Secondary Objective(s) and Associated Endpoints

**Table 2.1.2 – 1 Secondary Objectives and Associated Endpoints**

| Type | Objective | Endpoint |
|---|---|---|
| Safety | Part 2: To assess the safety and tolerability of oleclumab with or without durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC. | • Incidence of AEs and SAEs<br>• Clinically meaningful changes from baseline in clinical laboratory parameters, vital signs |
| Clinical Activity | Part 1: To evaluate the preliminary antitumor activity of oleclumab plus durvalumab in combination with gemcitabine and nab-paclitaxel administered in subjects with 1L metastatic PDAC. | • OR and DC according to RECIST v1.1 |
| | Part 1: To evaluate the preliminary antitumor activity of oleclumab plus durvalumab in combination with mFOLFOX administered in subjects with 2L metastatic PDAC. | • OR and DC according to RECIST v1.1 |
| | Part 2: To evaluate the preliminary antitumor activity of oleclumab with or without durvalumab in combination with gemcitabine and nab-paclitaxel compared to gemcitabine and nab-paclitaxel administered in subjects with 1L metastatic PDAC. | • OS<br>• PFS, DoR and DC according to RECIST v1.1 |
| | Part 2: To evaluate the preliminary antitumor activity of oleclumab with or without durvalumab in combination with mFOLFOX compared to mFOLFOX administered in subjects with 2L metastatic | • OS<br>• PFS, DoR and DC according to RECIST v1.1 |

| | | |
|---|---|---|
| | PDAC. | |
| | Part 2: To evaluate the preliminary antitumor activity of oleclumab with or without durvalumab in combination with chemotherapy compared to chemotherapy alone in the population defined by CD73 expression. | • OS<br>• OR and PFS according to RECIST v1.1 by CD73 expression at baseline |
| Immunogenicity | To assess the immunogenicity of oleclumab and durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC. | • Development of detectable ADAs following oleclumab and durvalumab |
| Pharmacokinetics | To determine the pharmacokinetic (PK) profile of oleclumab and durvalumab in combination with chemotherapy administered in subjects with metastatic PDAC. | • Summary PK for oleclumab, durvalumab, and selected chemotherapies and/or their metabolites |

1L = first-line; 2L = second-line; ADA = anti-drug antibody; AE = adverse event; CD = cluster of differentiation; DC = disease control; DoR = duration of response; ECG = electrocardiogram; mFOLFOX = modified regimen of leucovorin, 5-fluorouracil, and oxaliplatin; OR = objective response; OS = overall survival; PDAC = pancreatic ductal adenocarcinoma; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; v = version.
Note: Part 1 is dose escalation and Part 2 is dose expansion.

### 2.1.3 Exploratory Objective(s) and Associated Endpoints

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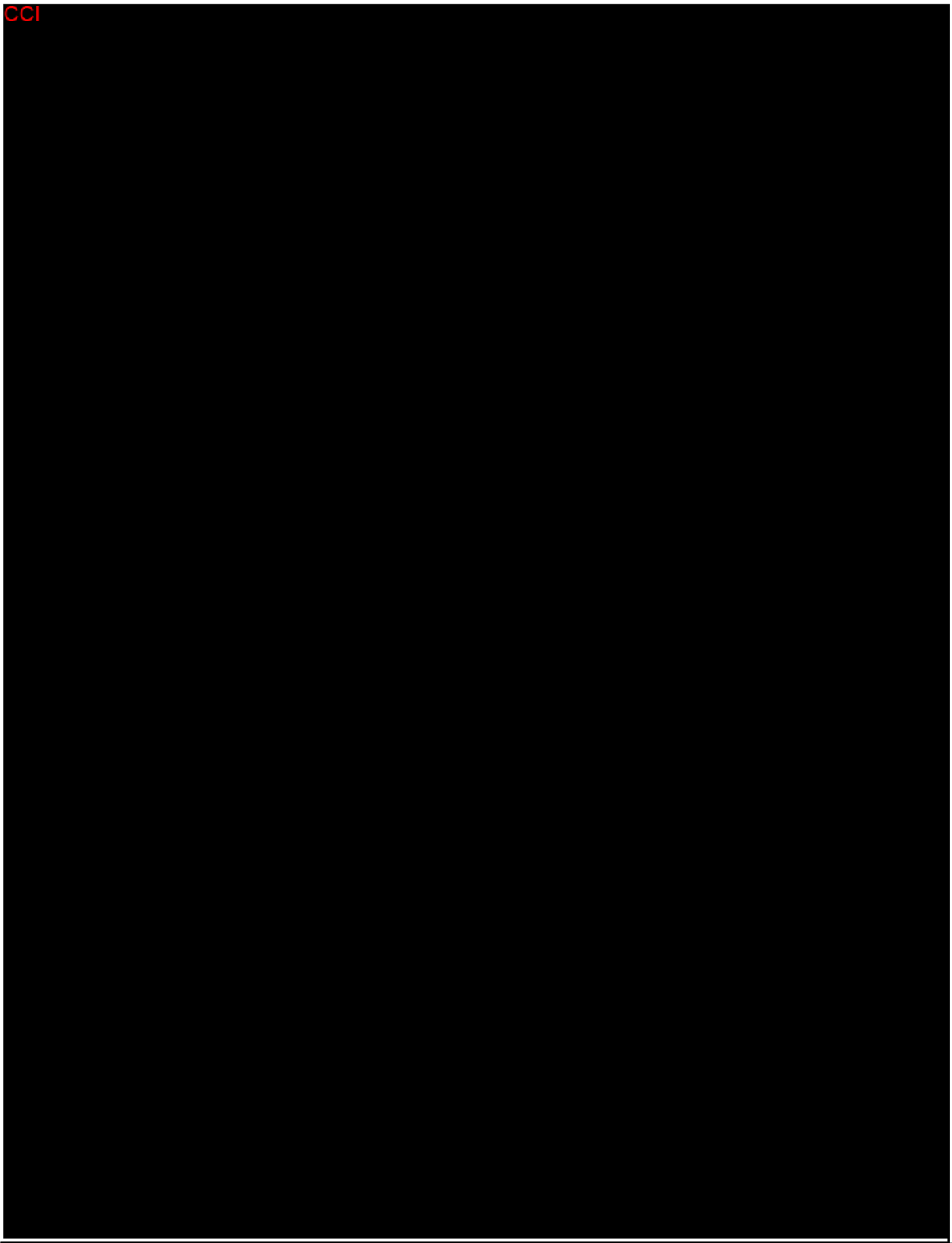

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## 2.2 Study Design

This is a Phase Ib/2, multicenter, open label, dose escalation and dose expansion study to assess the safety, preliminary antitumor activity, immunogenicity and PK of oleclumab with or without durvalumab in chemotherapy administered in subjects with metastatic PDAC. Subjects with previously untreated metastatic PDAC (1L metastatic PDAC) will be enrolled in Cohort A. Subjects with metastatic PDAC previously treated with gemcitabine-based chemotherapy (without exposure to 5-FU, capecitabine , or oxaliplatin; 2L metastatic PDAC) will be enrolled in Cohort B. The study consists of 2 parts, dose escalation (Part 1) and dose expansion (Part 2). All subjects in both cohorts will be treated until disease progression, intolerable toxicity, withdrawal of subject consent, or another discontinuation criterion is met. Refer to Section 3.1 of the Clinical Study Protocol (CSP) for additional details.

For Cohort A, an interim analysis will be performed when approximately 30 evaluable subjects in each treatment arm have been dosed and reached the data cut-off criteria. Refer to Section 4.8.7 of the CSP for additional details.

## 2.3 Treatment Assignment and Blinding

### Treatment Assignment

This is an open-label study. Subjects enrolled in Part 1 who meet the eligibility criteria will be assigned open-label investigational product.

In Part 2 subjects in Cohort A will be randomized using a 1:1:1 ratio to receive either gemcitabine and nab-paclitaxel (Arm A1), oleclumab + gemcitabine and nab-paclitaxel (Arm A2) or oleclumab + durvalumab + gemcitabine and nab-paclitaxel (Arm A3). Subjects in Cohort B will be randomized using a 1:1:1 ratio to receive either mFOLFOX (Arm B1), oleclumab + mFOLFOX (Arm B2) or oleclumab + durvalumab + mFOLFOX (Arm B3). Randomization will be stratified by CD73 expression level. Refer to Section 4.6 of the CSP for additional details.

### Blinding

This study is not blinded.

### 2.4 Sample Size

A total of up to approximately 339 subjects will be enrolled in the study: up to approximately 24 subjects in Part 1, dose escalation and up to approximately 315 subjects in Part 2, dose expansion (approximately 210 subjects in Cohort A and approximately 105 subjects in Cohort B). Refer to Section 4.8.2 of the CSP for additional details.

## 3 STATISTICAL METHODS

### 3.1 General Considerations

Tabular summaries will be presented for the dose escalation and dose expansion phase separately. Unless otherwise stated, in the dose escalation phase data will be summarized by cohort and dose levels and, in the dose expansion phase data will be summarized by cohort, treatment arms and where appropriate by CD73. A total column will be presented for tables related to study subjects, exposure, adverse events, immunogenicity and pharmacokinetics.

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, unless otherwise specified. 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. Unless stated otherwise, two-sided confidence intervals (CIs) will be produced at 95%.

Baseline values are defined as the last valid assessment prior to the first administration of investigational product. For efficacy data this is the last assessment prior to randomization. Baseline is derived by identifying records such that date of collection is prior to treatment start date. In the scenario where the time part is missing, only the date parts will be compared. If no baseline record is present when date of collection is missing but treatment start date is not missing then the data collected at screening will be used as baseline. For laboratory parameters where the clinical safety signal is a Low Abnormality or Bi-directional, the baseline values are identified as the minimum of all pre-dosing values on that particular date. For laboratory parameters where the safety signal is a High Abnormality, the baseline values are identified as the maximum of all pre-dosing values on that particular date.

Data analyses will be conducted using the SAS® System (SAS Institute, Inc., Cary, NC, USA) Version 9.3 or above, unless otherwise specified.

## 3.2 Analysis Populations

The analysis populations are defined in **Error! Reference source not found.**.

**Table 3.2 – 1 Analysis Populations**

| Population | Description |
|---|---|
| All randomized population | The all randomized population is defined as all randomized subjects. |
| Intent-to-treat (ITT) population | The ITT population is defined as all subjects who are randomized and receive any amount of investigational product, analyzed according to randomized treatment assignment. All analyses will be performed on the ITT population unless otherwise specified. |
| As-treated population | The as-treated population is defined as all subjects who receive any investigational product analyzed according to treatment received. |
| 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 16 (for cohort A) or 12 (for cohort B) weeks at the time of the data cutoff (i.e., dosed at least 16 (for cohort A) or 12 (for cohort B) 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 is defined as all subjects enrolled in Part 1 (dose escalation) who receive all planned doses of oleclumab, durvalumab, and chemotherapy during the DLT-evaluation period (from the first dose of all study treatments through Day 28) and complete the safety follow-up through the DLT evaluation period or experience any DLT. |
| PK evaluable population | The PK evaluable population is defined as all subjects who receive at least one dose of IP with at least one reportable PK concentration. If necessary there may instead be as many as four PK evaluable populations (one for each of oleclumab, durvalumab, gemcitabine and nab-paclitaxel). |
| ADA evaluable population | The ADA evaluable population is defined as all subjects in the safety analysis set who have a non-missing baseline ADA result and at least one non-missing post-baseline ADA result. If necessary there may instead be two ADA evaluable populations (one for each of oleclumab and durvalumab). |

ADA= anti-drug antibody; DLT = dose-limiting toxicity; IP = investigational product; PK = pharmacokinetic

The baseline and efficacy analyses of antitumor activity will be based on the intent-to-treat population. The safety parameters will be summarized based on the as-treated population. DLT-evaluable population will be used for the MTD evaluation. The efficacy parameters may be summarized based on response-evaluable population for interim analysis.

## 3.3 Study Subjects

### 3.3.1 Subject Disposition and Completion Status

Subject disposition and completion status will be listed per subject. Disposition of subjects throughout the study and with respect to discontinuation of treatment and end of study and completion status will be summarized by the number and percentage of subjects for the ITT population.

Time on study from time of first dose/randomization will be presented using swimmer plots for the ITT population and where appropriate these may be presented by CD73 levels.

### 3.3.2 Demographics and Baseline Characteristics

Demographics and baseline disease characteristics will be summarized for the ITT population and summaries will include a total column. Demographic and baseline characteristic information related to age, sex, race, ethnicity, weight, height, Eastern Cooperative Oncology Group (ECOG) status will be summarized with summary statistics and may be listed with further information. Information relating to prior anticancer treatment, prior systemic therapy, prior radiation therapy and prior surgical and medical procedures will also be listed for each subject.

Tumor history including histology, stage, and pertinent biomarker results at the time of initial diagnosis and at study entry will be summarized and where appropriate this may also be summarized by CD73 levels. The baseline disease characteristics summary will include descriptive statistics of time from primary diagnosis to study entry (months), baseline CRP and baseline carbohydrate antigen 19-9 (CA19-9). It will also include frequency distributions for disease stage at initial diagnosis (I, II, III, IVa, IVb, IVc, unknown), 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).

Prior anticancer treatment will be summarized and where appropriate may also be summarized by CD73 levels and recruitment wave. The summary will include the number and percent of subjects per treatment category (systemic therapy, radiation, cancer related surgery, other), number of previous systemic regimens for metastatic disease, best response (complete response, partial response, stable disease, progressive disease, not evaluable, not applicable) to the most recent line of therapy, line of therapy, time on prior systemic therapy (≤6 months, >6 months) and time on prior radiation (≤6 months, >6 months).

Baseline tumor characteristics including number and sites of target and non-target tumor lesions as well as sum of target lesions diameter will be summarized. Number of metastatic sites at baseline, defined as the number of organs that have baseline target or nontarget lesions

not at the primary site, will also be listed. Other baseline tumor characteristics, including, PD-L1 tumor cells, PD-L1 immune cells and smoking history, will be summarized. In addition, a listing detailing significant medical history findings will be provided.

### 3.3.3 Study Drug Exposure

Treatment exposure will be summarized for the as-treated population. Duration of exposure to the IPs in weeks, number of doses and relative dose intensity will be summarized by descriptive statistics and by frequency.

Duration of exposure in weeks is defined by last date of actual dosing (i.e., a dose was actually given) in the last cycle plus the number of days in the dosing interval minus the date of first treatment with IP. For subjects who die or if a DCO occurs prior to the last dose date plus the number of days in the dosing interval, duration of exposure in weeks is defined as date of death/DCO (whichever occurs first) minus the date of first treatment plus 1 day.

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 exposure TFL templates.

Dosing deviations for IP(s) will be listed with reasons for deviations for the following categories: delays, omissions, reductions, and interruptions. Dosing delays will be derived based on the scheduled dosing dates using the previous dose given as reference. 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 concomitant medications will be summarized for the ITT population by the generic name, coded by WHO Drug Dictionary. A listing providing information about the route, indication, dose and frequency will also be provided. Concomitant medications will include all concomitant medications taken on or after the date of first dose of IP or any concomitant medication started prior to the first dose of study treatment that continued beyond the date of first dose of IP.

The use of subsequent anticancer treatment after the discontinuation of study treatment will be summarized and where appropriate may also be summarized by CD73 levels by the type of subsequent anticancer treatment for the as-treated population.

### 3.3.5 Protocol Deviations

Incidence of important protocol deviations will be summarized by deviation categories. A protocol deviation is determined to be important if it meets any one of the following criteria:

- Subject entered into the study but does not satisfy inclusion criteria number 5, 6, 8, 9, 10 or exclusion criteria 2, 3, 5, 6, 15, 18.
- Incorrect informed consent procedure (including reconsent) for main ICF such as no ICF, consent not signed, wrong consent version signed, unapproved consent used.
- Serious breach of GCP.
- Subject received the incorrect treatment, overdose or expired treatment.
- A deviation that affects the ability to interpret data with respect to the primary objective for example, missing or incorrectly collected disease assessments or any error that impacts the ability to properly measure the disease response.
- Criteria met during the study but the subject was not withdrawn as per protocol requirements.
- Subject not randomized per protocol or per IVRS procedure (this does not include dispensing or administering study treatment). In some cases unreported SAEs detected in the source data may be defined as important protocol deviations.

Incidence of COVID-19 important protocol deviations will also be summarized by deviation categories.

Further information for important protocol deviations can be found in the Protocol Deviation Criteria Form.

A listing will be provided with protocol deviation details. None of the deviations will lead to subjects being excluded from any analysis populations described in 3.2, unless otherwise specified. If a deviation is serious enough to have a potential impact on the primary analysis, sensitivity analyses may be performed.

## 3.4 Efficacy Analyses

For each of the analyses there will be no formal statistical comparison between dose levels in Part 1.

### 3.4.1 Primary Efficacy Endpoint and Analyses

The primary efficacy endpoint is objective response (OR). OR is defined as best overall response of confirmed response (CR) or partial response (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 objective response rate (ORR) will be estimated by the proportion of OR, and its 95% CI will be estimated using the exact binomial distribution. Subjects that have missing overall response assessments will be considered as non-responders, and will therefore be counted in the denominator, but not in the numerator of ORR. The primary analysis of ORR will be based on the ITT population and will be reported by treatment arm. An estimate of the rate difference and its CI (80% and 95%) of the ORR between the control arm and experimental treatment arms will be reported. Comparison of arms for ORR will be obtained from Cochran-Mantel-Haenszel test, stratified by CD73 level.

In addition, further information describing the response (per programmatic derivation performed by the Sponsor based upon the investigator assessed data) for each of target, non-target and new lesions and the subjects overall response, and additionally an investigator assessment of overall response by RECIST version 1.1 will be listed for each subject by visit.

### 3.4.2 Secondary Efficacy Endpoint(s) and Analyses

The secondary efficacy endpoints include duration of response (DoR), disease control (DC), progression-free survival (PFS) and overall survival (OS). The efficacy endpoints will be summarized based on the ITT Population. The efficacy endpoints will also be listed for each subject.

Efficacy analyses, except for OS, will be based on an application of RECIST version 1.1 (Eisenhauer et al, 2009) to investigator assessed tumor measurements.

Programmatic derivation guidance used for the application of RECIST version 1.1 are provided in Appendix A: Derivation of RECIST 1.1 Disease Assessment Overall Response. RECIST version 1.1 guidelines will be used to determine disease response.

#### 3.4.2.1 Duration of Response

Analysis of duration of response is for Part 2 only.

Duration of response (DoR) is defined as the time from the first documentation of an objective response until the first documentation of a disease progression or death due to any cause, whichever occurs first. 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 in 3.4.2.3. The median DoR and its 95% CI will be estimated using the Kaplan-Meier method.

#### 3.4.2.2 Disease Control

Disease control (DC) is defined as CR, PR, or SD (maintained for ≥ 8 weeks [± 3 days]). DCR will be estimated by the proportion of subjects with DC and its 2-sided 95% CIs will be estimated using an exact probability method. An estimate of the difference in DCR between the control arm and experimental treatment arm will be reported.

#### 3.4.2.3 Progression-free Survival

Analysis of progression-free survival is for Part 2 only.

Progression-free survival (PFS) is defined as the time from randomization 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. Subjects 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 in months is defined in months as follows:

PFS (months) = (Date of PD/death or censoring – randomization + 1) / (365.25/12),

The censoring guidance and the date of PD/death or censoring are given in Table 3.4.2-1. The number and percentage of subjects experiencing a PFS event and Kaplan-Meier plots of PFS will be presented by treatment arm. The median PFS and its 95% CI will be estimated using the Kaplan-Meier method. The proportion of subjects progression free and alive at 4, 6, 8, 12, 15, 18 months (PFS-4, PFS-6, PFS-8, PFS-12, PFS-15, PFS-18) and associated 95% CIs will be estimated using the Kaplan-Meier method.

The difference in PFS between each treatment arm and control arm will be tested for significance by using a stratified log-rank test at the overall 2-sided $\alpha$=0.05 significance level adjusting for CD73 level (CD73 High vs Low). The stratified log-rank test will be carried out with the Breslow method for handling ties. The hazard ratio between each treatment arm and the control arm with two-sided 95% CI will be estimated by stratified Cox regression model with ties handled by the Efron method (Efron et al, 1977).

**Table 4.4.2 – 1 Summary of Censoring Guidelines for PFS**

| Situation | Date of PD/Death or Censoring | PFS Outcome |
|---|---|---|
| Documented confirmed 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 the last progression-free disease assessment prior to missed or non-evaluable assessments, or the randomization (first dose date for Part 1), 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<br>OR<br>No tumor assessment post-first dose, and no death prior to second scheduled post-baseline disease assessment | Date of randomization (first dose date for Part 1) | 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 randomization (first dose date for Part 1) 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 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 follows: for cohort A, ≥ 16+1 weeks for the first 48 weeks or ≥ 24+1 weeks thereafter; for cohort B, ≥ 12+1 weeks for the first 24 weeks or ≥ 16+1 weeks thereafter (two disease assessments as per protocol plus a 1 week visit window to allow for a late assessment) after the last evaluable post-baseline disease assessment.

#### 3.4.2.4 Overall Survival

Analysis of overall survival is for Part 2 only.

Overall survival (OS) is defined as the time from the randomization until death due to any cause. A subject alive at the end of study or lost to follow-up will be censored for OS at the last date when the subject was known to be alive obtained from 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.

For incomplete OS data (e.g. for OS analysis at interim analysis), 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, date AE met the criteria for SAE, date AE met and no longer met criteria for AESI
- 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].
- Disease assessment dates on RECIST CRF
- Date of visit, vital signs, ECOG, ECG, brain scan and physical examination
- Start and stop dates of prior or subsequent anticancer treatment
- Dates on CCI [redacted]
- Start and end date of concomitant medication and surgical/medical procedure
- For women, date of last menstrual period
- Onset and resolution date of infusion related reactions
- Diagnosis date of pancreatic cancer
- Date of screen failure
- Date of collection of data collected externally

OS is defined in months as follows:

OS (months) = (Date of death or censoring – Date of randomization + 1) / (365.25/12).

The number and percentage of subjects experiencing an OS event and Kaplan-Meier plots of OS will be presented by treatment arm. The median OS and its 95% CI will be estimated using the Kaplan-Meier method. The proportion of subjects alive at 4, 6, 8, 12, 15 and 18 months (OS-4, OS-6, OS-8, OS-12, OS-15, OS-18) and associated 95% CI will be estimated using the Kaplan-Meier method.

The difference in OS between groups will be tested for significance by using a stratified log-rank test at the overall 2-sided $\alpha$=0.05 significance level, with CD73 level (CD73 High vs Low) as the stratification variable. The stratified log-rank test will be carried out with the Breslow method for handling ties. The hazard ratio with two-sided 95% CI will be estimated by stratified Cox regression model with ties handled by the Efron method (Efron et al, 1977).

### 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 A: Derivation of RECIST 1.1 Disease Assessment Overall Response). 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

Subgroup analyses (where explored) are applicable to Part 2 only.

#### 3.4.4.1 Analysis by CD73 Levels

When appropriate (e.g. sufficient sample size in each subgroup), analysis of OR, PFS and OS by CD73 expression level at baseline (high vs low) as measured by IHC in archival and/or fresh tumor biopsies will be conducted for Part 2. For the OR analysis within each subgroup category Fishers exact test will be used and for PFS and OS Cox Proportional Hazards will be used. Additional efficacy endpoints may also be explored.

#### 3.4.4.2 Univariate Analyses

Univariate analysis may be performed for the ITT population in Part 2 to compare the efficacy effect of the control arm against the experimental treatment arms. For the univariate analysis the following subgroup factors may be considered:

- Sex (Male, Female)
- Age group (<65 years, ≥ 65 years)
- Tumor stage at study entry (T1 or T2, T3 or T4)
- ECOG at baseline (0, 1)
- CRP at baseline (<4.5mg/L, ≥4.5mg/L)
- Sum of target lesions at baseline (≤100mm, >100mm)
- Liver metastasis present at baseline (Yes, No)
- NLR at baseline (≤5, >5)

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For each treatment arm overall and within each subgroup level the number and percentage of subjects with a confirmed response will be reported. In addition the rate difference and corresponding 95% CI for the comparison of treatment arms will be provided.

For each treatment arm overall and within each subgroup level the number and percentage of patients with an event will be reported. Median PFS (based on application of RECIST version 1.1 to investigator assessments) and OS will be assessed via Kaplan-Meier methods.

Hazard ratios for PFS and OS will be calculated using a Cox proportional hazards model with treatment as the only term and the 95% CI will be calculated using a profile likelihood approach, and ties being handled using Efron method. A hazard ratio of <1 will favor the experimental treatment arm. A 'by' statement will be used to obtain the HR and 95% CI for each subgroup level separately. For a subgroup factor with less than 20 events across both treatment arms, hazard ratios and CI will not be presented.

### 3.4.5 CCI

CCI

#### 3.4.5.1 CCI

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#### 3.4.5.2 CCI

CCI

### 3.4.6 Other Efficacy Analyses

#### 3.4.6.1 Time to Response

Time to response (TTR) is defined as the time from randomization until the first documentation of an objective response. Only subjects who have achieved objective response (confirmed CR or confirmed PR) will be evaluated for TTR. TTR is defined in months as follows:

TTR (months) = (date of first confirmed objective response – date of first dose/randomization +1) / (365.35/12)

The median TTR and its 95% CI will be estimated using the Kaplan-Meier method (without censoring because all subjects have events) for the ITT population.

#### 3.4.6.2 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 (see Appendix A: Derivation of RECIST 1.1 Disease Assessment Overall Response) and presented as summary statistics for the ITT population. It may also be presented by using spider plots. 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).

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. This will be presented as summary statistics and the best percent change from baseline may also be presented alongside duration of treatment (as bars) using waterfall plots for the ITT population and where appropriate these may be presented by CD73 levels.

Target lesion measurements and sum of diameters will be listed by disease assessment and subject.

#### 3.4.6.3 Sensitivity Analysis

Some analysis of efficacy endpoints may be repeated using the all randomized population as a sensitivity analysis.

#### 3.4.6.4 Blinded Independent Central Review (BICR) Analysis

Any analysis of the BICR is for Part 2 only and may be reported separately. The independent data review will provide a RECIST v1.1 response for each visit for each subject. For each

patient, the independent reviewer will provide the first and last dates of imaging data for each time point (i.e. for visits where progression is/is not identified). The independent review RECIST response for each visit will not include any imputation for missing data or scaling rules for total tumor size. The data from the independent review of scans will be programmatically combined with death information by AZ or designee for the calculation of progression and response. Further information can be found in the Independent Review Master Charter.

The derivation and analyses of the BICR best overall response and ORR and PFS is identical to that given in Sections 3.4.1 and 3.4.2. Analyses of disagreements between response and/or progression status between the sponsor (based upon the investigator data) and the BICR may also be performed. A listing of concordance between BICR and investigator data in terms of visit responses may also be provided.

#### 3.4.6.5 Analysis by Recruitment Wave

Some efficacy endpoints in Part 2 for Cohort A may be repeated for analysis by recruitment wave.

Recruitment wave 1 is defined as subjects recruited up to and including 15Nov2019. Recruitment wave 2 is defined as subjects recruited from 08Dec2020.

## 3.5 CCI [redacted]

CCI [redacted]

### 3.5.1 CCI [redacted]

CCI [redacted]

CCI

[redacted]

### 3.5.3 CCI

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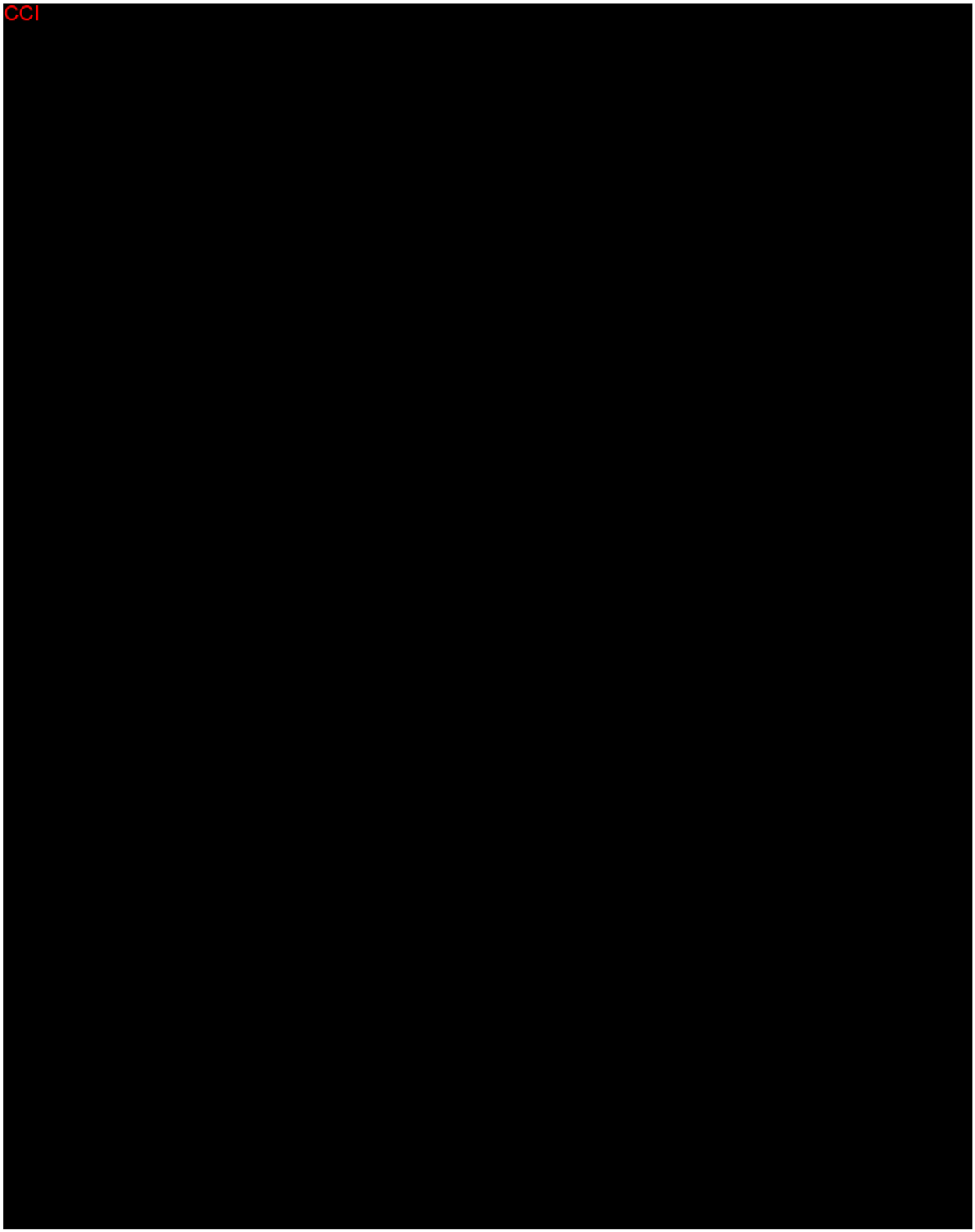

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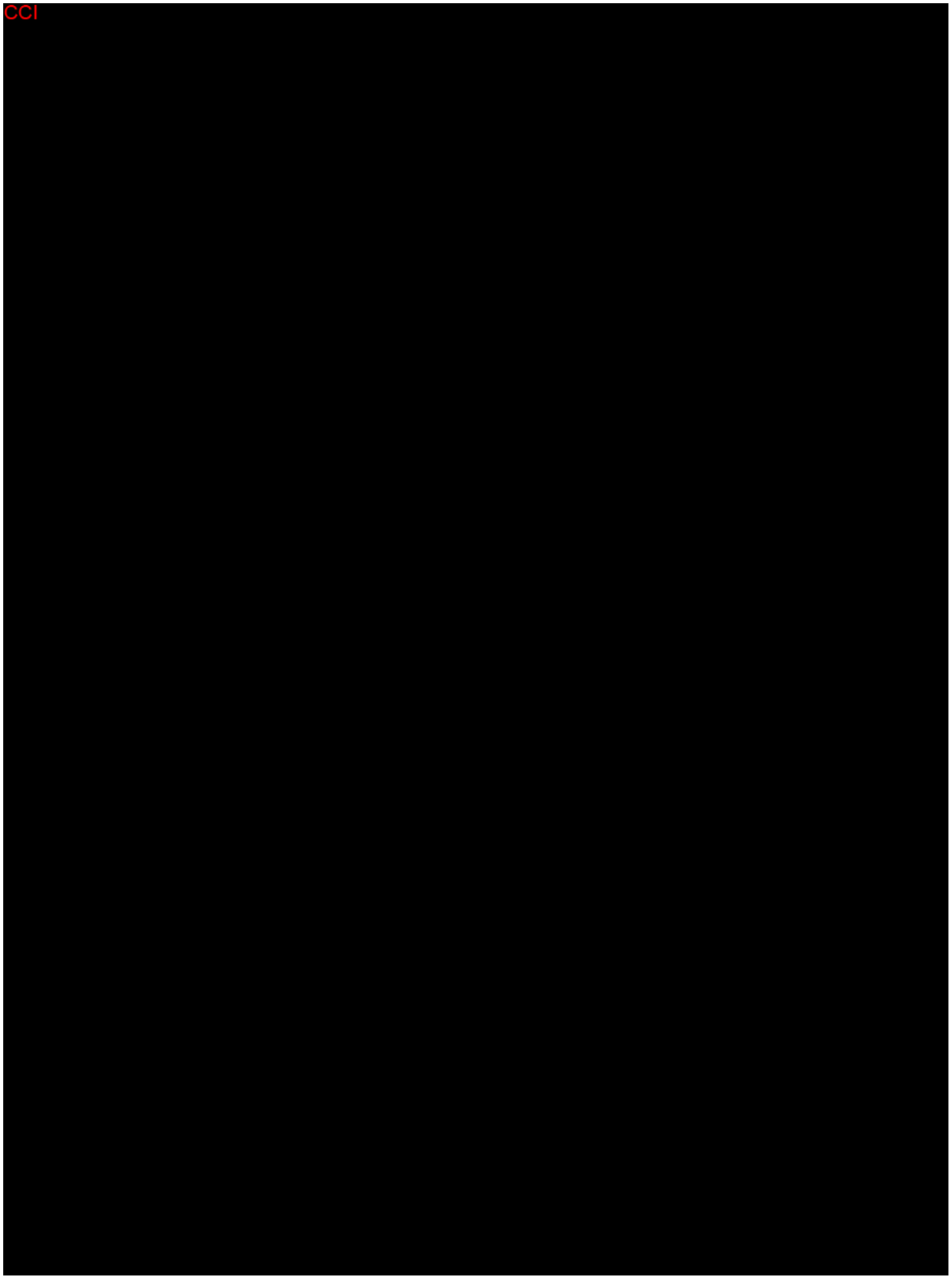

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[redacted]

## 3.6 CCI [redacted]

CCI [redacted].

## 3.7 Safety Analyses

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

### 3.7.1 Maximum Tolerated Dose Evaluation

The Maximum Tolerated Dose (MTD) evaluation will be based on the DLT Evaluable Population. The number and percentage of subjects with DLTs during the dose escalation phase will be presented by dose level.

### 3.7.2 Adverse Events and Serious Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 22 or a more recent version will be used to code the adverse events (AEs).

Treatment-emergent adverse events (TEAEs) are defined as events present at baseline that worsen in intensity after administration of IP or events absent at baseline that emerge after administration of IP. TEAEs will be presented by system organ class and preferred term and reported as frequencies. They may be sorted according to frequency in an experimental treatment arm or total subjects across all dose levels/treatment arms per cohort or, by highest severity. Incidence, severity and relationship to IP will also be listed. Specific TEAEs will be counted once for each subject for calculating percentages. In addition, if the same TEAE occurs multiple times within a particular subject, the highest severity and level of relationship observed will be reported. An overall summary of TEAEs, treatment related TEAEs to at least one study drug, oleclumab related TEAEs high grade (Grade >=3) TEAEs, treatment related high grade TEAEs to at least one study drug and oleclumab related high grade TEAEs will also be presented and, if any associations of interest between TEAEs and baseline characteristics are observed, additional stratified results may be presented.

Treatment emergent serious adverse events (SAEs) will be presented by system organ class and preferred term and reported as frequencies. Treatment related treatment emergent SAEs and oleclumab related treatment emergent SAEs will be presented in the same way.

AEs and SAEs considered to be non-treatment emergent meaning they occurred after the signing of the informed consent and prior to the initiation of IP will be listed.

### 3.7.3 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor.

Per protocol Section 5.3, Adverse Events of Special Interest Group terms for Oleclumab include but are not limited to the following:

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

Per protocol Section 5.3, Adverse Events of Special Interest Group terms for Durvalumab include but are not limited to the following:

- Diarrhea/colitis and intestinal perforations
- Pneumonitis
- Hepatitis
- Endocrinopathy (i.e. events of hypophysitis/hypopituitarism, Type 1 diabetes mellitus, adrenal insufficiency, and hyper- and hypothyroidism, thyroiditis)
- Rash/dermatitis
- Nephritis
- Pancreatitis
- Myocarditis
- Myositis/polymyositis
- Neuropathy / neuromuscular toxicity (e.g., Guillain-Barre syndrome and myasthenia gravis)
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events, vasculitis, non-infectious meningitis, and non-infectious encephalitis.

More information regarding AESIs can be found in protocol. Other categories may be added or existing terms may be modified as necessary. An AZ medically qualified expert after consultation with the Global Patient Safety Physician has reviewed the AEs of interest and identified which higher-level and which preferred terms contribute to each AESI group. Further reviews may take place prior to DBL to ensure any further terms not already included are captured within the categories. Preferred terms used to identify each AESI group will be listed before DBL.

The AESIs for oleclumab and durvalumab will be listed by group and preferred term for each subject. Summaries will include TEAEs of special interest for each of oleclumab and

durvalumab and treatment related TEAEs of special interest, both of which will be presented by group and preferred term and may be ordered by highest severity.

### 3.7.4 AESIs During Which Systemic Steroids, Endocrine Therapy, or Other Immunosuppressants Were Administered

AESIs 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 AESIs 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 durvalumab imAE charter before the DCO (Data Cut Off) date for analysis will be used.

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

### 3.7.5 Immune-mediated Adverse Events (imAE)

To fully characterize the AESI (excluding AESI group Infusion related/ Hypersensitivity/ Anaphylactic reactions) during which systemic steroids, endocrine therapy, or other immunosuppressants were administered (See Section 3.7.4), the Sponsor will perform medical review of those AESIs 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 any AESIs that (1) during which the use of systemic steroids, endocrine therapy, or other immunosuppressants were administered, (2) is consistent with an immune mediated mechanism of action, and (3) for which, there is no clear alternate etiology.

imAEs will be derived by first programmatically identifying AESIs during which systemic steroids, endocrine therapy, or other immunosuppressants were administered as outlined above in Section 3.7.3. 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.

Immune-mediated adverse events will be listed by preferred term for each subject and sorted by treatment arm. Summaries will include treatment emergent imAEs which may also be ordered by highest severity and treatment related treatment emergent imAEs.

### 3.7.6 Deaths and Treatment Discontinuations due to Adverse Events

The mortality summary will summarize subjects whose end of study status is death, as well as cause of death (toxicity related to investigational product or disease under investigation, or other). For those subjects who died due to an AE, the AE contributing to death and the AE's relationship to IP will be summarized.

Summaries will be provided for TEAEs and treatment related TEAEs resulting in permanent discontinuation of treatment Supporting listings will be provided for AEs resulting to death and AEs resulting in permanent discontinuation of treatment. Additionally summaries will be provided for TEAEs and oleclumab related TEAEs resulting in permanent discontinuation of oleclumab.

### 3.7.7 Clinical Laboratory Evaluation

Laboratory tests will be grouped according to chemistry, coagulation, hematology, thyroid function and urinalysis. Listings will be provided for all laboratory results, including urinalysis. Descriptive statistics may be provided for the clinical laboratory results, including the values at baseline and end of treatment visit as well as the maximum and minimum post-baseline values.

Laboratory parameters will be assessed at baseline as well as throughout the study. For chemistry and hematology parameters, laboratory abnormalities with toxicity grades according to the NCI CTCAE version 4.03 will be derived. Laboratory abnormalities occurring from the start of IP administration to the last assessment on study will be presented. Worst toxicity grade, grade shifts of 2 or more from baseline to the maximum grade and change from baseline will be presented. Summaries indicating hyper- and hypo- directionality of change may be produced where appropriate. Laboratory parameters that cannot be graded via NCI CTCAE will be summarized with frequencies of post-baseline laboratory values categorized as low (L), normal (N), or high (H) using laboratory normal ranges compared to baseline.

**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<br>• >5 × – <=8 × ULN<br>• >8 × – <=10 × ULN<br>• >10 × – <=20 × ULN<br>• >20 × ULN |

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

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

### 3.7.8 Other Safety Evaluations

#### 3.7.8.1 Vital Signs

Vital signs will be assessed at baseline and throughout the study. Vital sign data will be listed by subject and may be summarized by study visit which will include descriptive statistics for the value of the parameters and the changes from baseline for the as-treated population. Data will be summarized only when the visit has at least 10% subjects with non-missing values.

#### 3.7.8.2 Electrocardiogram

Electrocardiogram (ECG) results will be assessed at baseline as well as throughout the study. ECG parameters include: ECG mean heart rate, PR, RR, QRS, QT, QTcB, and QTcF. For triplicates, averages will be taken at each time point prior to the calculation of descriptive statistics. Clinically significant ECG results will be reported as AEs. ECG parameter data and results (normal vs. abnormal) will be listed by subject. ECG parameter data will be summarized by study visit which will include descriptive statistics for the value of the parameters and the

changes from baseline for the as-treated population. Data will be summarized only when the visit has at least 10% subjects with non-missing values.

Additionally, a summary will be produced that shows the number and percentage of subjects meeting the criteria for a notable QTc interval. This will be produced for QTcF only; the categories for observed values are > 450, > 480, and> 500 and the categories for change from baseline values are > 30 and > 60.

#### 3.7.8.3 Eastern Cooperative Oncology Group Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be assessed at baseline as well as throughout the study. ECOG will be summarized for the shift from baseline to the "worst" performance post-baseline on treatment period.

## 3.8 Immunogenicity

A summary of immunogenicity results will be provided showing the number and percentage of subjects who develop detectable antidrug antibodies (ADAs) to oleclumab and durvalumab, based on the subjects in the ADA evaluable population. Subjects and/or data excluded from the ADA evaluable population may be presented in separate outputs.

The following categories will be included in the summary table:

- ADA positive at baseline and/or post-baseline visits
- ADA incidence, defined as percentage of subjects with treatment emergent ADA
- Persistent positive, defined as positive at ≥2 post-baseline assessments (with ≥16 weeks between first and last positive) or positive at last post-baseline assessment
- Transient positive, defined as negative at last post-baseline assessment and positive at only one post-baseline assessment or at ≥2 post-baseline assessments (with <16 weeks between first and last positive)
- Treatment-boosted, defined as baseline ADA positive that was boosted to a 4-fold or higher level following drug administration

Subjects with positive ADA results will also be listed.

## 3.9 Pharmacokinetics

Serum concentrations of oleclumab and durvalumab, and plasma concentrations of gemcitabine and nab-paclitaxel for each scheduled time-point will be summarized for each visit/timepoint and dose level or treatment arm (as appropriate) using appropriate descriptive statistics. All serum and plasma concentration data will be listed for each subject, by analyte. The following descriptive statistics are presented for serum and plasma concentrations:

- n
- n below LLOQ
- geometric mean (gmean)
- geometric coefficient of variance (%) (gCV)
- arithmetic mean of non log-transformed data (mean)
- standard deviation of non log-transformed data (Std Dev)
- coefficient of variance (%) (CV)
- median
- minimum (min)
- maximum (max)

The gmean is calculated as exp(μ), where μ is the mean of the data on the natural log scale. The gCV is calculated as 100 x sqrt[exp(s2)-1], where s is the Std Dev of the data on the natural log scale.

**Handling of Non-Quantifiable Concentrations**

Individual concentrations below the LLOQ of the bioanalytical assay are reported as NQ in the listings with the LLOQ defined in the footnotes of the relevant TFLs. Individual plasma concentrations that are Not Reportable are reported as NR and those that are missing are reported as NS (No Sample) in the listings. Plasma concentrations that are NQ, NR or NS are handled as follows for the provision of descriptive statistics:

- Any values reported as NR or NS are excluded from the summary tables and corresponding figures.
- At a time point where less than or equal to 50% of the concentration values are NQ, all NQ values are set to the LLOQ, and all descriptive statistics are calculated accordingly.
- At a time point where more than 50% (but not all) of the values are NQ, the gmean, gSD and gCV% are set to NC. The maximum value is reported from the individual data, and the minimum and median are set to NQ.
- If all concentrations are NQ at a time point, no descriptive statistics are calculated for that time point. The gmean, minimum, median and maximum are reported as NQ and the gCV% and gmean ± gSD as NC.
- The number of values below LLOQ (n < LLOQ) are reported for each time point together with the total number of collected values (n).

Three observations > LLOQ are required as a minimum for a plasma concentration to be summarized.

Two observations > LLOQ are presented as minimum and maximum with the other summary statistics as NC.

**Precision and Rounding Rules for PK concentration data**

PK concentration data listings present to the same number of significant figures as the data received from the bioanalytical laboratory (usually but not always to 3 significant figures) and against the same units as received.

PK concentration descriptive statistics present 4 significant figures with the exception of the min and max which present 3 significant figures and n and n<LLOQ which present as integers.

# 4 INTERIM ANALYSIS

Interim analyses comparing the experimental treatment arm to the control arm will be performed in Part 2 Cohort A using a joint Bayesian predictive probability. Bayesian predictive probability allows for continuous assessments for early Go/No-Go decision making in single arm trials (Lee and Liu, 2008). A joint Bayesian predictive probability approach allows for continuous assessments of the delta (δ), or difference, of the ORRs between the experimental treatment arm and control arm (Pulkstenis et al., 2017).

Futility interim analysis will be performed after approximately 30 subjects in each treatment arm of Part 2 Cohort A have been dosed and reach the data cutoff criteria. The data cutoff criterion is defined as the opportunity to be followed for at least 16 weeks at the time of the data cutoff and have at least one post-baseline disease assessment and/or discontinued treatment due to death or disease progression. The interim analysis will be based on the subset of the ITT Population that have satisfied the data cutoff criteria. Enrollment may be paused during the interim analysis before the decision is made.


**Figure 4.1** CCI

# 5 REFERENCES

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Lee JJ, Liu DD. A predictive probability design for phase II cancer clinical trials. Clin Trials. 2008; 5:93-106.

CCI [redacted]

CCI [redacted]

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CCI

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# APPENDICES

## Appendix A: Derivation of RECIST 1.1 Disease Assessment Overall 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.

### 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 Measurable" 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).

**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 (i.e., 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 (i.e., 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 (i.e., 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 (i.e., 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 (i.e., 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 (i.e., 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 (i.e., 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 (i.e., 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).

**Disease Assessment Overall Response per RECIST 1.1**

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

**Table A1 Assignment of responses using RECIST**

| 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.

*(Note: "(or NE)" values under New Lesion will only be included in confirmation of progression or confirmation of new lesions are required per protocol. The last 4 rows may be eliminated from any study that requires identification of at least one measurable lesion at Baseline. One may choose to allow such cells to remain if an independent central review is included in the trial.)*

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).

**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 will be identified. A subject with a subsequent response or SD 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.

**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.

CCI [redacted]

[redacted]

CCI [redacted]

Unlike RECIST 1.1, CCI [redacted]

**Overall Response at Single Time Point**

Table B1 shows how the disease response will be determined based on the CCI criteria.

**Table B1 Assignment of time-point response using** CCI

CCI


CCI
CCI

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