STATISTICAL ANALYSIS PLAN

Protocol Number: CD-ON-MEDI-573-1030 (Original Protocol)

A Phase 1b/2 Randomized Study of MEDI-573 in Combination with an Aromatase Inhibitor (AI) Versus AI Alone in Women with Metastatic Breast Cancer (MBC)

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	Antidrug Antibody
AE	Adverse Event
AI	Aromatase Inhibitor
[redacted]	[redacted]
CI	Confidence Interval
CTCAE	Common Terminology Criteria For Adverse Events
CR	Complete Response
CT	Computed Tomography
DLT	Dose-Limiting Toxicity
DR	Duration of Response
ECG	Electrocardiogram
[redacted]	[redacted]
HR+	Hormone Receptor Positive
HER2	Human Epidermal Growth Factor Receptor 2
IGF-I/II	Insulin-Like Growth Factor I/II
IM	Immunogenicity
ITT	Intent-to-Treat
KPS	Karnofsky Performance Status
MBC	Metastatic Breast Cancer
SAE	Serious Adverse Event
TEAE	Treatment Emergent Adverse Event
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OS	Overall Survival
OR	Objective Response
ORR	Objective Response Rate
RECIST	Response Evaluation Criteria in Solid Tumors
PD	Progression Disease
PK	Pharmacokinetics

Abbreviation or Specialized Term	Definition
PRO	Patient-Reported Outcome
PFS	Progression-Free Survival
PR	Partial Response
SD	Stable Disease
SPP	Statistical Programming Plan
TTR	Time to Response
TTP	Time to Progression

1 Introduction

This document describes the statistical methodology and summaries for protocol CD-ON-MEDI-573-1030, a study of MEDI-573 in combination with an aromatase inhibitor (AI) versus AI alone in women with metastatic breast cancer (MBC). 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 as well as the general conventions and definitions that will be used.

In addition, a set of table templates and specifications are planned to be created in a statistical programming plan (SPP) to complement this document.

2 Background

2.1 Study Overview

This is a Phase 1b/2, multicenter, open-label study to evaluate the safety, tolerability, antitumor activity, and pharmacology of MEDI-573 in combination with an AI in adult subjects with HR+, HER2-negative MBC. This study has 2 phases: a dose-evaluation phase (Phase 1b) and a randomization phase (Phase 2).

In the Phase 1b portion of the study, 2 cohorts will be examined. In each cohort, 3 to 6 evaluable subjects will each receive MEDI 573 at doses of [redacted] 9 (Cohorts A) or [redacted] (Cohorts B) by IV infusion on Day 1 of each 21-day cycle. An AI of the investigator's choice (anastrozole, letrozole, or exemestane) will be given orally once daily. Enrollment into Cohorts A and B will be initiated sequentially.

Approximately 255 subjects with HR+, HER2-negative MBC will be randomized into the Phase 2 portion of the study in a 1:1:1 ratio to receive MEDI-573 [redacted] and an AI (investigator's choice) (Arm 1), MEDI-573 [redacted] and an AI (Arm 2), or an AI alone (Arm 3). MEDI-573 will be administered via IV infusion on Day 1 of 21-day cycles. An AI will be given orally once daily. Randomization will be stratified by geographic region (North America vs rest of world) and AI type. All subjects will be followed every 9 weeks (three 21-day cycles) until disease progression and then followed for survival every 3 months until the end of the study as defined in Section 4.8 of the study protocol.

Subjects will be treated until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal (see Section 4.2.3 of the study protocol). Approximately 5 investigational sites in North America and Europe will participate in the Phase 1b portion of the study and approximately 70 investigational sites worldwide will participate in the Phase 2 portion of the study. Tumor measurements and assessments will be based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines.

The primary objective of the dose-evaluation phase (Phase 1b) of this study is to evaluate the safety and tolerability of 2 dose levels of MEDI-573 in combination with an AI in subjects with HR+, HER2-negative MBC.

The primary objective of the randomization phase (Phase 2) of this study is to evaluate the PFS of subjects with HR+, HER2-negative MBC treated with MEDI-573 and an AI versus treatment with an AI alone.

The secondary objectives of this study are:

- To describe the safety and tolerability of MEDI-573 when used in combination with an AI
- To evaluate the antitumor activity of MEDI-573 when used in combination with an AI versus treatment with an AI alone
- To evaluate OS in subjects treated with MEDI-573 when used in combination with an AI versus treatment with an AI alone
- To describe the PK of MEDI-573 in combination with an AI
- To determine the pharmacodynamics of MEDI-573 in combination with an AI on circulating levels of IGF-I and IGF-II
- To determine the IM of MEDI-573 in combination with an AI

The exploratory objectives of this study are:

- To evaluate biomarkers related to MEDI-573 treatment
- To investigate the effects of MEDI-573 on patient-reported outcomes (PROs)

2.2 Randomization and Blinding

This is an open-label study. Blinding is not applicable to this study. Details of treatment assignment and randomization are described in Section 4.3 of the study protocol.

2.3 Schedule of Evaluations

The schedule of evaluations is outlined in Section 5.1 of the study protocol.

2.4 Sample Size Considerations

In the Phase 1b portion of the study, a minimum of 6 evaluable subjects (3 each at the MEDI-573 [redacted] dose levels) will be required to determine the safety and tolerability of 2 doses of MEDI-573 in combination with an AI. Up to 12 evaluable subjects (6 subjects each at the MEDI-573 [redacted] dose levels) may be needed if dose-limiting toxicity (DLT) occurs. A subject will be considered evaluable if the subject receives 1 full cycle of MEDI 573 and is followed for safety through the DLT evaluation period (as defined in Section 4.5.8.1 of the study protocol) or if the subject experiences a DLT in the DLT evaluation period. Any nonevaluable subject will be replaced.

In the Phase 2 portion of the study, the primary objective is to compare 2 dose levels of MEDI-573 and an AI to single-agent AI alone in terms of PFS in order to select one dose for potential further development. Assuming that the median PFS for subjects with single-agent AI alone is 9.4 months (Mouridsen et al, 2001), and that the median PFS for subjects receiving the [redacted] doses of MEDI-573 plus an AI will each be 13.4 months, an improvement in PFS of 42.6% would be achieved (corresponding to a hazard ratio of 0.7). Based on these assumptions and simulations, a total of 182 events (subjects with disease progression or death) are required to provide 80% power for two log-rank tests (one for each dose vs control) at an overall 2-sided type I error of 0.2, adjusting for 2 comparisons associated with 2 MEDI-573 arms being compared to the AI alone arm. If the median PFS in 1 of the MEDI-573 plus AI arms is assumed to be 13.4 months and the median PFS in the other arm is 12.4 or 14 months, the power will change to 75% or 85%, respectively. A total sample size of 255 subjects is required given that subjects will be followed until approximately 71% have PFS events at the time of PFS analysis. With a planned accrual period of 18 months, the estimated follow-up period after the last subject is randomized into

the study would be approximately 13 months. The primary analysis (log-rank test) will be performed after 182 PFS events have occurred.

3 Statistical Methods

3.1 General Considerations

All data will be provided in data listings and sorted by treatment group and subject number. All tabular summaries will be presented by treatment group and all subjects combined. Categorical data will be summarized by the number and percentage of subjects falling within each category. In general, continuous variables will be summarized by descriptive statistics including mean, standard deviation, median, minimum, and maximum. All available data will be used and thus, missing data will not be imputed for the primary analysis. Confidence intervals, whenever specified, will be produced at 88% to align with the nominal significance level, 0.12, for this study and, also, at 95% for convenience of comparison with traditional 95% CI in literature.

Subjects with missing data for a parameter will be excluded from the summary of this parameter. This rule is applicable for the summaries of demographics and baseline characteristics, laboratory, electrocardiogram (ECG), and Karnofsky Performance Status (KPS).

The data analyses will be conducted using the SAS® System Version 9.1.3 (SAS Institute Inc., Cary, NC) in a UNIX environment. All SAS programs used to generate analytical results will be developed and validated according to MedImmune SAS programming standards and MedImmune SAS validation procedures.

3.2 Subject Populations

The following subject populations will be used when summarizing data:

- Intent-to-Treat (ITT) Population includes all subjects who are entered into the Phase 1b portion or randomized into the Phase 2 portion of the study. The treatment arm in the Phase 2 portion will be assigned according to the initial randomization, regardless of whether subjects receive any study treatment or receive a study treatment different from that to which they were randomized.

- Evaluable Population for Phase 1b includes all subjects entered in the Phase 1b who receive at least 1 full cycle of MEDI-573 and complete the safety follow-up through the DLT evaluation period, which is defined as Cycle 1, Day 1 through Day 21, or experience any DLT during the DLT evaluation period.

- Safety Population includes all subjects who receive any study treatment.

- Per Protocol Population includes all subjects who are in the randomization phase of the study, receive any study treatment, have at least one post baseline tumor assessment, and have no major protocol violations. The Per Protocol Population will be identified prior to database lock.

For the Evaluable Population for Phase 1b, the Per Protocol Population, and the Safety Population, the treatment arm will be assigned according to the study treatment that is actually received at the first dose.

The number and percent of subjects in each subject population for evaluation will be summarized by treatment arm and all subjects combined.

3.3 Subject Disposition

Table 3.3-1 presents the summaries that will be prepared for subject disposition. Summaries will be prepared by treatment arm and all subjects combined based on the ITT population.

Table 3.3-1 Subject Disposition to be Summarized

Summary	Population
Number of Subjects Enrolled/Randomized by Site	ITT
Subject Status at the End of Study treatment	ITT
Subject Status at the End of Study and Mortality Summary	ITT

Summaries of the number and percentage of subjects enrolled/randomized by site will be provided.

The summary of subject status at the end of study treatment will include a frequency distribution of reason for treatment discontinuation for the following categories: lost to follow-up, withdrawal of consent, death, adverse event, disease progression, investigator discretion, or other.

Subject status at the end of study will be summarized in terms of the number and percentage of subjects who completed the study. For those who did not complete the study, a summary table will be provided with the following reasons: lost to follow-up, withdrawal of consent, death, or other. For subjects who die by the end of the study, the cause of death (due to disease vs not due to disease) and the relationship to study treatment (related vs not related) and MEDI-573 (related vs not related) will be summarized. For those subjects who died on-study, which is defined as a death within 60 days from the last dose date, the cause of death and the relationship to study treatment and MEDI-573 will also be summarized.

3.4 Baseline Characteristics

Summaries of demographics, disease history, sub-groups of interest at baseline, prior cancer treatment, baseline disease status assessment, baseline tumor characteristics, and baseline Karnofsky performance status will be provided to describe the subject population in this study. Parameters that will be summarized for the ITT population by treatment arm for subjects randomized into the Phase 2 portion of the study and all subjects combined are presented in Table 3.4-1.

Table 3.4-1 Baseline Characteristics to be Summarized

Summary	Population
Demographics	ITT
Disease History	ITT
Subgroups of Interest at Baseline	ITT
Prior Cancer Treatment	ITT
Baseline Disease Status Assessment	ITT
Baseline Tumor Characteristics	ITT
Baseline Karnofsky Performance Status	ITT

Demographics will be summarized for the following characteristics: age (year), height (cm), weight (kg), ethnicity, and race. Subjects will be excluded from the summary for each parameter if data are missing.

Disease history summary will include frequency distributions for stage at initial diagnosis (0, I, II, IIIA, IIIB, IV, unknown), tumor stage (T0, Tis, T1, T2, T3, T4, TX), node stage (N0, N1, N2, N3, NX), metastasis stage (M0, M1, MX) and descriptive statistics of time from primary diagnosis to study entry (months).

The sub-groups of interest at baseline are listed in Table 3.4-2. Subgroup analysis of anti-tumor activity will be performed if there are a sufficient number of subjects in a subgroup.

Prior cancer treatment will be summarized by using the number and percentage of subjects who had received each of the following therapy categories: chemotherapy, biologic, hormonal, radiation, surgery, transplant, or other. In addition, treatment type will be summarized for the following categories: neoadjuvant, adjuvant, primary, or recurrence locally advanced or metastatic, and best response of prior cancer treatment will be summarized for the categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), not evaluable and not done.

The baseline disease status assessment summary will include frequency distributions for sites of metastatic disease and stage of disease at study entry.

Baseline tumor characteristics include number and sites of target lesions as well as number and sites of non-target lesions to be summarized using frequency distribution. The size of target lesions will be also summarized in terms of sum of the longest diameter of target lesions using descriptive statistics.

A summary of baseline Karnofsky performance status will be done using frequency distribution for the following categories: <70, 70, 80, 90, and 100.

Table 3.4-2 Subgroups of Interest

Subgroups of Interest	Description
Geographic Region	North America or rest of world
Prior Usage of AI	Yes vs No
Baseline Ki-67 Index	Low vs High
Baseline IGF-I Level	Low vs High
Baseline IGF-II Level	Low vs High
Age Subgroup	< 55, 55 - 64, or >= 65 years

3.5 Study Drug Exposure

Table 3.5-1 presents the summaries of study drug exposure that will be provided for the ITT and/or safety population by treatment arm.

Table 3.5-1 Study Drug Exposure

Summary	Population
Study Treatment Exposure - Overall	ITT and Safety
Study Treatment Exposure - by AI Subgroup	ITT
Dosing Delay and Modifications of MEDI-573	Safety
Summary of Subsequent Alternative Cancer Treatment	ITT

Summary of study treatment exposure will include descriptive statistics of the following: total number of treatment cycles, defined as the number of cycles during which subject received any treatment of MEDI-573 and/or AI, number of MEDI-573 doses and total MEDI-573 dose received during the study, duration of AI treatment (days) during the study. The total number of treatment cycles will also be summarized using frequency distribution. The dose intensity for MEDI-573 or AI (anastrozole, letrozole, or exemestane) is a percent of total actual dose that a subject received during the study treatment period for MEDI-573 or AI (anastrozole, letrozole, or exemestane) respectively, versus total intended dose of MEDI-573 or AI (anastrozole, letrozole, or exemestane) respectively, for the same study treatment period according to the study protocol. It will be summarized using descriptive statistics as part of the study treatment exposure summary. The dose intensity calculation details will be provided in the SPP.

Dosing delays and modifications will be summarized for the following categories: number of subjects with MEDI-573 dose delays, the reasons for MEDI-573 dose delay (adverse events, scheduling conflict, other), the total number of subjects for whom the entire MEDI-573 dose was not administered as scheduled, the reasons the entire MEDI-573 dose was not administered as scheduled (adverse events, other) and the reason the subject did not receive MEDI-573 (adverse events, other).

The use of subsequent alternative cancer treatment after the discontinuation of study treatment will be summarized by type of treatment. Descriptive statistics of time from treatment discontinuation to initiation of subsequent cancer treatment (months) will be provided.

3.6 Summaries to Support the Primary Objectives

The following summaries will be presented to support the primary objectives.

3.6.1 Primary Endpoints of Safety in Phase 1b

The primary safety endpoints are the following:

- Dose-limiting toxicities (defined in the study protocol Section 4.5.8.1) occurring during the DLT period in the Phase 1b portion of this study
- Adverse events and SAEs occurring during the protocol-specified reporting period (as defined in Section 6.4 of the study protocol)

Adverse events, treatment-related AEs and SAEs will be summarized by system organ class and MedDRA preferred term, severity, and relationship to study treatment. The number and percentage of subjects with DLT in the Evaluable Population for Phase 1b of this study will be summarized.

3.6.2 Primary Endpoint of Efficacy in Phase 2

The primary endpoint of the Phase 2 portion of this study is progression-free survival (PFS).

3.6.2.1 Primary Analysis of PFS

Progression-free survival (PFS) is measured from randomization until the first documentation of disease progression or death, whichever occurs first. PFS will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression and are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Subjects having no tumor assessments after randomization will have PFS censored on the date of randomization. The primary definition of PFS variables is presented in Table 3.6.2.1-1 and is calculated (in months) as follows:

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

Table 3.6.2.1-1 Definition and Censoring Information for PFS

Situation	Date of PD/death or Censoring	Outcome
Documented Progressive Disease (PD) as determined by investigator	Date of earliest sign of PD	Progressed
Death before the first post-baseline disease assessment or between adequate tumor assessment visits	Date of death	Death

Table 3.6.2.1-1 Definition and Censoring Information for PFS

Situation	Date of PD/death or Censoring	Outcome
No PD as determined by investigator/death	Date of last progression-free disease assessment	Censored
Death or PD as determined by investigator after ≥ 2 missed consecutive disease assessments	Date of last progression-free disease assessment prior to missed assessments	Censored
Initiation of other anticancer therapy	Date of last progression-free disease assessment prior to initiation of other anticancer therapy	Censored
No tumor assessment at baseline or post-baseline	Date of randomization	Censored

PFS will be evaluated using Kaplan-Meier method in the ITT population and compared with a 2-sided stratified log-rank test at α=0.2 significance level (overall type I error rate) between each of the two MEDI-573 ([redacted] or [redacted]) + AI arms and the AI alone arm. To adjust for multiple comparisons, the nominal significance level based on simulation will be 0.12 for each of the 2 comparisons associated with 2 MEDI-573 arms being compared to the AI alone arm. The stratification factors will be geographic region (North America vs rest of world) and AI type (anastrozole, letrozole, or exemestane). Assessments of disease response by investigators will be the basis for the primary analysis.

As supportive information, median PFS and its 88% and 95% confidence interval (CI) will be estimated using the Kaplan-Meier method. The hazard ratio (MEDI-573+AI vs. AI alone) with two-sided 88% and 95% confidence intervals will be estimated by using the Cox proportional hazard model with treatment group and the 2 stratification factors in the model.

3.6.2.2 Supportive Analysis of PFS

3.6.2.2.1 Sensitivity Analysis of PFS on Analysis Population

PFS will be analyzed based on per-protocol populations in addition to ITT population.

3.6.2.2.2 Sensitivity Analyses of PFS on Variable Definition

Three different definitions of PFS will be explored. First, the assessments by blinded independent central review (BICR) in addition to investigators' assessments will be used, as shown in Table 3.6.2.2.2-1.

Table 3.6.2.2.2-1 Definition and Censoring Information for PFS Based on BICR

Situation	Date of PD/death or Censoring	Outcome
Progressive Disease (PD) as determined by BICR	Date of earliest sign of PD	Progressed
Death before the first post-baseline disease assessment or between adequate tumor assessment visits	Date of death	Death
No PD as determined by BICR/death	Date of last progression-free disease assessment	Censored
Death or PD as determined by BICR after ≥ 2 missed consecutive disease assessments	Date of last progression-free disease assessment prior to missed assessments	Censored
Initiation of other anticancer therapy	Date of last progression-free disease assessment prior to initiation of other anticancer therapy	Censored
No tumor assessment at baseline or post-baseline	Date of randomization	Censored

Second, PFS events are considered as events regardless of missing visits before the events. The corresponding definition of PFS is presented in Table 3.6.2.2.2-2.

Table 3.6.2.2.2-2 Definition and censoring information for PFS (PFS Events Only)

Situation	Date of PD/death or Censoring	Outcome
Documented Progressive Disease (PD) as determined by investigator	Date of earliest sign of PD	Progressed
Death	Date of death	Death
No PD as determined by investigator /death	Date of last progression-free disease assessment	Censored
No tumor assessment at baseline or post-baseline	Date of randomization	Censored

Last, the scheduled tumor visit dates according to the study protocol will be used to assign the dates for censoring and events in order to avoid the potential bias in actual follow-up schedules for tumor assessment. For example, a patient is supposed to have tumor assessment on Day 63 according to the study protocol. However, the patient actually has tumor assessment on Day 60 and has evidence of progressive disease. The dates of Day 63 and Day 60 will be the date of the scheduled visit and the actual date of the earliest sign of PD, respectively. The corresponding PFS variables are summarized in Table 3.6.2.2.2-3.

Table 3.6.2.2.2-3 Definition and Censoring Information for PFS (Uniform Progression and Assessment Dates)

Situation	Date of PD/death or Censoring	Outcome
Documented Progressive Disease (PD) documented between scheduled visits determined by investigator	Date of next scheduled visit	Progressed
Death before the first post-baseline disease assessment or between adequate tumor assessment visits	Date of death	Death
No PD as determined by investigator /death	Date of last progression-free disease assessment	Censored
Death or PD after ≥ 2 missed consecutive disease assessments	Date of last progression-free disease assessment prior to missed assessments	Censored
Initiation of other anticancer therapy	Date of last progression-free disease assessment prior to initiation of other anticancer therapy	Censored
No tumor assessment at baseline or post-baseline	Date of randomization	Censored

3.6.2.2.3 Subgroup Analysis of PFS

Subgroup analyses of PFS will be based on the stratification factors and baseline characteristics specified in Table 3.4-2 in ITT population. The 2-sided log-rank test will be applied for each subgroup if there are enough patients in the subgroup population. The hazard ratio (MEDI-573+AI vs. AI alone) with a two-sided 95% confidence interval for each subgroup will be estimated by using the Cox proportional hazard model.

3.7 Summaries to Support the Secondary Objectives

3.7.1 Secondary Endpoints of Safety and Tolerability

Safety and tolerability will be assessed by summarizing AEs, SAEs, electrocardiogram (ECG) results, significant or important clinical findings in Karnofsky performance status, laboratory assessments, and vital signs during the study. All summaries for toxicity profile evaluation will be done by treatment arm based on the safety population.

Adverse Events and Serious Adverse Events

Only treatment-emergent adverse events (TEAEs), defined as events present at baseline that worsen in intensity after administration of study treatment, or events absent at baseline that emerge after administration of study treatment, for the period extending to 60 days after the last dose of study treatment, will be summarized by system organ class and preferred term using the MedDRA dictionary, severity (graded according to NCI CTCAE v4.0), and relationship to study treatment. The AEs/SAEs occurring from the signing of the informed consent and prior to the initiation of study treatment will be listed. The AEs/SAEs that begin 60 days after last dose will not be summarized or listed.

Subjects will be counted only once for each preferred term, once for each system organ class, and by the highest event severity, regardless of how many events the subject experienced. Table 3.7.1-1 presents the treatment emergent adverse event summaries to be provided.

Table 3.7.1-1 Treatment Emergent Adverse Events and Serious Adverse Events

Summary	Population
Rate Summary of All Treatment Emergent Adverse Events - All Subjects	Safety
Number of Subjects with Treatment Emergent Adverse Events - All Subjects	Safety
Number of Subjects with Treatment Emergent Adverse Events - by AI Subgroup	Safety
Number of Subjects with Treatment Emergent Adverse Events by Highest Severity - All Subjects	Safety
Number of Subjects with Treatment Emergent Adverse Events Sorted by Frequency - All Subjects	Safety
Number of Subjects with Treatment Emergent Adverse Events (Grade >= 3) - All Subjects	Safety
Number of Subjects with Treatment Emergent Adverse Events (Grade >= 3) - by AI Subgroup	Safety
Number of Subjects with Treatment-Related Treatment Emergent Adverse Events - All Subjects	Safety
Number of Subjects with Treatment-Related Treatment Emergent Adverse Events by Highest Severity - All Subjects	Safety
Number of Subjects with MEDI-573 Related Treatment Emergent Adverse Events - All Subjects	Safety
Number of Subjects with Treatment Emergent Serious Adverse Events - All Subjects	Safety
Number of Subjects with Treatment Emergent Serious Adverse Events - by AI Subgroup	Safety
Number of Subjects with Treatment Emergent Serious Adverse Events by Serious Adverse Events Criteria - All Subjects	Safety
Number of Subjects with Treatment-Related Treatment Emergent Serious Adverse Events - All Subjects	Safety
Number of Subjects with Treatment-Related Treatment Emergent Serious Adverse Events by Highest Severity - All Subjects	Safety

Table 3.7.1-1 Treatment Emergent Adverse Events and Serious Adverse Events

Number of Subjects with MEDI-573 Related Treatment Emergent Serious Adverse Events - All Subjects	Safety
Number of Subjects with Treatment Emergent Adverse Events Resulting in Permanent Discontinuation of Study treatment - All Subjects	Safety

DLT-like events

The DLT-like events, defined as an event which meets the definition of DLT but occurs during Cycle 1 in all subjects treated within the study, will be summarized by treatment group.

ECG Parameters

Table 3.7.1-2 presents the summaries to be provided for ECG parameters.

Table 3.7.1-2 ECG Parameters

Summary	Population
Change from Baseline in ECG parameters	Safety

Descriptive statistics for ECG parameters will be provided for each scheduled time point.

Karnofsky performance Parameters

Table 3.7.1-3 presents the summaries to be provided for Karnofsky performance status (KPS).

Table 3.7.1-3 Karnofsky Performance Parameters

Summary	Population
Summary of Karnofsky performance status	Safety

Karnofsky performance status will be summarized using a shift table showing change in KPS from baseline to the worst performance status on-study and to the last assessment on-study.

Laboratory Parameters

The change in each laboratory parameter from baseline to the "worst-case" (nadir and/or zenith) on-study (including any post-baseline assessments that occur through 60 days after

the last dose) and to the last assessment on-study (including any post-baseline assessments that occur through 60 days after the last dose) for hematology/coagulation and blood chemistry will be summarized by descriptive statistics. Baseline values will be defined as the last valid assessment prior to the first administration of study treatment.

Laboratory abnormalities with toxicity grades according to the NCI CTCAE v4.0 will be derived according to laboratory values. Laboratory abnormalities occurring from the start of study treatment administration through 60 days after the last dose of the study treatment will be presented. Shift tables from baseline to the maximum severity grade on-study and to the last assessment on-study will be generated for each of laboratory parameter.

Table 3.7.1-4 presents the summaries for lab parameters to be prepared.

Table 3.7.1-4 Laboratory Parameters to be Summarized

Summary	Population
Change from Baseline in Hematology/Coagulation Parameters	Safety
Change from Baseline in Chemistry Parameters	Safety
Toxicity Grades for Hematology/Coagulation Parameters	Safety
Toxicity Grades for Chemistry Parameters	Safety

Vital Signs

Descriptive statistics of value and change from baseline value for heart rate, blood pressure, temperature, and respiratory rate will be provided for each scheduled time point. Table 3.7.1-5 presents the summary to be prepared for vital sign parameters based on the safety population.

Table 3.7.1-5 Vital Signs

Summary	Population
Change from Baseline in Vital Sign Parameters	Safety

3.7.2 Secondary Efficacy Endpoints

The secondary endpoints for assessing antitumor activity include best disease response, objective response rate (ORR), time to response (TTR), duration of response (DR), time to progression (TTP), overall survival (OS) and change in tumor size. They will be summarized by treatment arm based on the ITT Population in Phase 2.

Best Overall Response

The best overall response will be calculated, based upon the disease assessments recorded during the study visits, and summarized with the number and percentage of subjects for the following categories: complete response (CR) with confirmation, complete response (CR) without confirmation, partial response (PR) with confirmation, partial response (PR) without confirmation, stable disease (SD), progressive disease (PD), and not evaluable (NE). Confirmed CR and PR are those that persist on repeat imaging study ≥ 4 weeks after the initial documentation of response. If the best overall response of a subject can be categorized as both a CR without confirmation and a PR with confirmation, the subject will be summarized under PR with confirmation.

Objective Response Rate

The objective response rate (ORR), which is defined as the proportion of subjects with confirmed CR or confirmed PR, will be estimated with 88% and 95% confidence intervals based on the exact probability method. Subjects that have missing overall response assessments will be considered non-responders, so they will be counted in the denominator, but not in the numerator of ORR. In addition, ORR of the 2 MEDI-573 treatment arms will be compared with the AI arm using the Cochran–Mantel–Haenszel test stratified by geographic region (North America vs rest of world) and AI type (anastrozole, letrozole, or exemestane).

Time to Response

Time to response (TTR) is measured from randomization to the first documentation of disease response and will be evaluated only in subjects who have achieved objective response (confirmed CR or confirmed PR). Time to response is defined in months as follows:

TTR (months) = (Date of first disease response – Date of randomization + 1) / (365.25/12)

The median TTR and its 88% and 95% CIs will be assessed using the Kaplan-Meier method.

Duration of Response

Duration of response (DR) is measured from the first documentation of disease response to the first documented progressive disease and will be evaluated only in subjects that have

achieved objective response (confirmed CR or confirmed PR). Duration of response is defined in months as follows:

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

where date of PD or censoring is given in Table 3.7.2-1. The median time of DR and its 88% and 95% CIs will be assessed using the Kaplan-Meier method.

Table 3.7.2-1 Definition and Censoring Information for DR

Situation	Date of PD or Censoring	Outcome
Documented Progressive Disease (PD) as determined by investigator	Date of earliest sign of PD	Progressed
No PD	Date of last progression-free disease assessment	Censored
PD as determined by investigator after ≥ 2 missed consecutive disease assessments	Date of last progression-free disease assessment prior to missed assessments	Censored
Initiation of other anticancer therapy	Date of last progression-free disease assessment prior to initiation of other anticancer therapy	Censored

Time to Progression

Time to progression (TTP) is measured from randomization until the first documentation of disease progression. Time to progression is defined in months as follows:

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

where date of PD or censoring is given in Table 3.7.2-2. The median TTP will be estimated using the Kaplan-Meier method with 88% and 95% CIs.

Table 3.7.2-2 Definition and censoring information for TTP

Situation	Date of PD or Censoring	Outcome
Documented Progressive Disease (PD) as determined by investigator	Date of earliest sign of PD	Progressed
No PD	Date of last progression-free disease assessment	Censored
PD as determined by investigator	Date of last progression-free	Censored

Table 3.7.2-2 Definition and censoring information for TTP

Situation	Date of PD or Censoring	Outcome
after ≥ 2 missed consecutive disease assessments	disease assessment prior to missed assessments	
Initiation of other anticancer therapy	Date of last progression-free disease assessment prior to initiation of other anticancer therapy	Censored
No tumor assessment at baseline or post-baseline	Date of randomization	Censored

Overall Survival

Overall survival (OS) is measured from randomization until death. For subjects who are alive at the end of study or lost to follow-up, OS will be censored on the last date when subjects were known to be alive. Overall survival is defined in months as follows:

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

The median OS will be estimated using the Kaplan-Meier method with 88% and 95% CIs.

Change in Tumor Size

The change in tumor size will be summarized in terms of percent change in tumor size, defined as the sum of longest diameters of the measurable target tumor lesions, from baseline to each scheduled visit as well as nadir and zenith. At each visit, the change in tumor size will be analyzed using a mixed model with treatment arm and time as factors and geographic region (North America vs rest of world) and AI type (anastrozole, letrozole, or exemestane) as covariates. In addition, the change in tumor size at nadir and zenith, at 18 weeks and 27 weeks will be analyzed using analysis of covariance (ANCOVA) with treatment arm as factor and geographic region (North America vs rest of world) and AI type (anastrozole, letrozole, or exemestane) as covariates.

Subgroup Analysis of Antitumor Activity

A subgroup analysis of best overall response, objective response, and OS will be performed for the sub-populations defined in Section 3.3.

3.7.3 Immunogenicity of MEDI-573

Analysis of IM results will be assessed by summarizing the number and percentage of subjects who develop detectable anti-MEDI-573 antibodies for all subjects entered in Phase 1b and Phase 2 (Arm 1 and Arm 2). The ADA titer will be reported for samples confirmed positive for the presence of anti-MEDI-573 antibodies. The effect of ADA on PK, pharmacodynamics, and safety will be evaluated by the MedImmune Global PK-PD & Bioanalysis group or designee.

3.7.4 Pharmacology and Pharmacodynamics of MEDI-573

Other secondary endpoints are the pharmacokinetics and pharmacodynamics endpoints. The Analyses will be preformed by the MedImmune Global PK-PD & Bioanalysis group or designee.

3.8 Exploratory Summaries

3.8.1 Exploratory Analyses of Biomarkers

Exploratory analyses of biomarkers will be performed by the MedImmune Translational Sciences group or designee.

3.8.2 Exploratory Analysis [redacted]

[redacted]

3.8.2.1 [redacted]

[redacted]

[redacted]

[redacted]

3.8.2.2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

4 Interim Analyses

No formal interim analysis is planned.

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STATISTICAL ANALYSIS PLAN

Protocol Number: CD-ON-MEDI-573-1030 Amendment 2

A Phase 1b/2 Randomized Study of MEDI-573 in Combination with an Aromatase Inhibitor (AI) Versus AI Alone in Women with Metastatic Breast Cancer (MBC)

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	antidrug antibody
AE	adverse event
AI	aromatase inhibitor
ANCOVA	analysis of covariance
[redacted]	[redacted]
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria For Adverse Events
DLT	dose-limiting toxicity
DR	duration of response
ECG	electrocardiogram
[redacted]	[redacted]
HER2	human epidermal growth factor receptor 2
HR+	hormone receptor positive
IGF-I/II	insulin-like growth factor I/II
IM	immunogenicity
ITT	intent-to-treat
KPS	Karnofsky Performance Status
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
NE	not evaluable
NCI	National Cancer Institute
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetics

Abbreviation or Specialized Term	Definition
PR	partial response
PRO	patient-reported outcome
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	stable disease
SPP	statistical programming plan
TEAE	treatment emergent adverse event
TTR	time to response
TTP	time to progression

1 Introduction

This document describes the statistical methodology and summaries for protocol CD-ON-MEDI-573-1030 amendment 2, a study of MEDI-573 in combination with an aromatase inhibitor (AI) versus AI alone in women with metastatic breast cancer (MBC). 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 as well as the general conventions and definitions that will be used.

In addition, a set of table templates and specifications are planned to be created in a statistical programming plan (SPP) to complement this document.

2 Study Overview

This is a Phase 1b/2, multicenter, open-label study to evaluate the safety, tolerability, antitumor activity, and pharmacology of MEDI-573 in combination with an AI in adult subjects with HR+, HER2-negative MBC. This study has 2 phases: a dose-evaluation phase (Phase 1b) and a randomization phase (Phase 2).

In the Phase 1b portion of the study, 3 cohorts (Cohorts A, B, and C) will be examined. In each cohort, 3 to 6 evaluable subjects will receive MEDI-573 at doses of [redacted] (Cohort A), [redacted] (Cohort B), or [redacted] (Cohort C) by IV infusion on Day 1 of each 21-day cycle. As a combination therapy, an AI of the investigator's choice (anastrozole, letrozole, or exemestane) will also be given orally once daily. Enrollment into Cohorts A, B and C will be initiated sequentially. Approximately 9-18 evaluable subjects will be required for this portion of the study. Non-evaluable subjects will be replaced in the same dose cohort.

Following evaluation of the safety of MEDI-573 at the [redacted] dose level in combination with an AI in Phase 1b, approximately 178 subjects with HR+, HER2-negative MBC will be randomized into the Phase 2 portion of the study in a 1:1 ratio to receive MEDI-573 at [redacted] and an AI (Arm 1), or an AI alone (Arm 2). MEDI-573 will be administered via IV infusion on Day 1 of 21-day cycles. An AI will be given orally once daily. The MEDI-573 treatment regimens and the overall study design are illustrated in Figure 2.1-1.

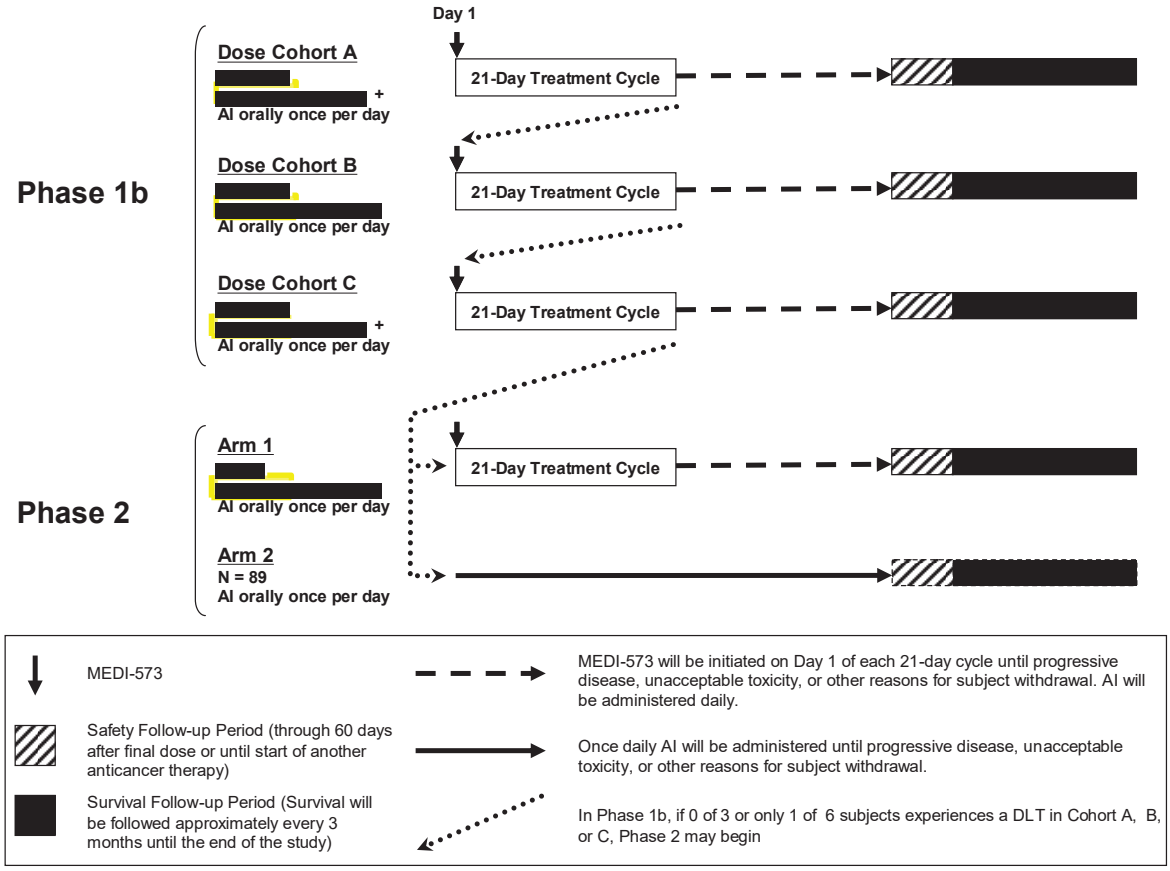

Figure 2.1-1 Study Design

AI = aromatase inhibitor; DLT = dose-limiting toxicity.

Randomization will be stratified by geographic region (North America vs rest of world) and AI type. All subjects will be followed every 9 weeks (three 21-day cycles) until disease progression and then followed for survival every 3 months until the end of the study as defined in Section 4.8 of the study protocol.

Subjects will be treated until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal (see Section 4.2.3 of the study protocol). Up to 20 investigational sites in North America will participate in the Phase 1b portion of the study and approximately 100 investigational sites worldwide will participate in the Phase 2 portion of the study. The schedule of evaluations is outlined in Section 5.1 of the study protocol.

Tumor measurements and assessments will be based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al, 2009). Details are described in Section 5.2.6.1 of the study protocol.

2.1 Study Objectives

2.1.1 Primary Study Objectives

The primary objective of the dose-evaluation phase (Phase 1b) of this study is to evaluate the safety and tolerability of 3 dose levels of MEDI-573 in combination with an AI in subjects with HR+, HER2-negative MBC.

The primary objective of the randomization phase (Phase 2) of this study is to evaluate the progression-free survival (PFS) of subjects with HR+, HER2-negative MBC treated with MEDI-573 and an AI versus treatment with an AI alone.

2.1.2 Secondary Study Objectives

The secondary objectives of this study are:

- To describe the safety and tolerability of MEDI-573 when used in combination with an AI
- To evaluate the antitumor activity of MEDI-573 when used in combination with an AI versus treatment with an AI alone
- To evaluate overall survival (OS) in subjects treated with MEDI-573 when used in combination with an AI versus treatment with an AI alone
- To describe the PK of MEDI-573 in combination with an AI
- To determine the pharmacodynamics of MEDI-573 in combination with an AI on circulating levels of IGF-I and IGF-II
- To determine the IM of MEDI-573 in combination with an AI

2.1.3 Exploratory Study Objectives

The exploratory objectives of this study are:

- To evaluate biomarkers related to MEDI-573 treatment
- To investigate the effects of MEDI-573 on patient-reported outcomes (PROs)

2.2 Treatment Assignment and Blinding

This is an open-label study. Blinding is not applicable to this study. Details of treatment assignment and randomization are described in Section 4.3 to 4.5 of the study protocol.

2.3 Sample Size

In the Phase 1b portion of the study, a minimum of 9 evaluable subjects (3 each at the MEDI-573 [redacted] dose levels) will be required to determine the safety and tolerability of 3 doses of MEDI-573 in combination with an AI. Up to 18 evaluable subjects (6 subjects each at the 3 MEDI-573 dose levels) may be needed if dose-limiting toxicity (DLT) occurs. A subject will be considered evaluable if the subject receives 1 full cycle of MEDI-573 and is followed for safety through the DLT evaluation period (as defined in Section 4.5.8.1 of the study protocol) or if the subject experiences a DLT in the DLT evaluation period. Any non-evaluable subject will be replaced.

In the Phase 2 portion of the study, the primary objective is to compare PFS among subjects treated at [redacted] MEDI-573 and an AI versus subjects treated with single-agent AI alone. Assuming that the median PFS for subjects with single-agent AI alone is 9.4 months (Mouridsen et al, 2001), and that the expected median PFS for subjects receiving the [redacted] doses of MEDI-573 plus an AI is 13.4 months, an improvement in PFS of 42.6% would be achieved (corresponding to a hazard ratio of 0.7). Based on these assumptions and simulations, a total of 122 events (i.e. subjects with disease progression or death) are required to provide 75% power for a log-rank test at a two-sided significance level of 0.2. With a planned accrual period of 12 months and a minimum follow-up period of 14 months, it is estimated that a total of approximately 178 subjects are needed to observe 122 PFS events by the end of the minimum follow-up period. The primary analysis (log-rank test) will be performed after 122 PFS events have occurred. If the expected median PFS in the MEDI-573 group is 13.8 months (corresponding to HR of 0.68), the power will change to 80% with 122 PFS events. Subjects will not be replaced in this phase of the study.

3 Statistical Methods

3.1 General Considerations

All data will be provided in data listings and sorted by treatment group, subject number, and date collected where appropriate. All tabular summaries will be presented by treatment group and all subjects combined. Categorical data will be summarized by the number and percentage of subjects within each category. In general, continuous variables will be summarized by descriptive statistics including mean, standard deviation, median, minimum, and maximum. Confidence intervals, whenever specified, will be produced at 80% to align with the nominal significance level, 0.2, for this study and, also, at 95% for convenience of comparison with traditional 95% CI in literature.

All available data will be used and thus, missing data will not be imputed for the primary analysis. Subjects with missing data for a parameter will be excluded from the summary of that parameter. This rule is applicable for the summaries of demographics and baseline characteristics, laboratory, electrocardiogram (ECG), and KPS.

The data analyses will be conducted using the SAS® System Version 9.1.3 (SAS Institute Inc., Cary, NC) in a UNIX environment. All SAS programs used to generate analytical results will be developed and validated according to MedImmune SAS programming standards and MedImmune SAS validation procedures.

3.2 Analysis Populations

The following subject populations will be used when summarizing data:

- Intent-to-Treat (ITT) Population: Subjects who receive any study investigational product will be included in the ITT population and subjects will be analyzed according to their randomized treatment group. Evaluable Population for Phase 1b includes all subjects entered in the Phase 1b who receive at least 1 full cycle of MEDI-573 and complete the safety follow-up through the DLT evaluation period, which is defined as Cycle 1, Day 1 through Day 21, or experience any DLT during the DLT evaluation period.
- Safety Population: Subjects who receive any study investigational product will be included in the safety population and subjects will be analyzed according to the treatment they actually receive. AI will be defined as the first AI Type to which the subject was exposed.

Unless stated otherwise, analyses performed on the efficacy, baseline and demographics, disposition, concomitant medications, and exposure data will be based on the ITT population. Analyses performed on the safety [redacted] data will be based on the safety population. For the evaluable population, Phase 1b and the safety population, the treatment group will be assigned according to the study treatment that is actually received at the first dose.

The number and percent of subjects in each subject population for evaluation will be summarized by treatment group and all subjects combined.

3.3 Study Subjects

3.3.1 Subject Disposition

Summaries will be prepared by treatment group and all subjects combined based on the ITT population.

The number and percentage of subjects enrolled/randomized by site will be provided.

The summary of subject status at the end of study treatment will include a frequency distribution of reason for treatment discontinuation.

Subject status at the end of study will be summarized in terms of the number and percentage of subjects who completed the study. For those who did not complete the study, a summary table of reasons will be provided.

For subjects who die on study, the cause of death (due to disease vs not due to disease) and the relationship to study treatment (related vs not related) and MEDI-573 (related vs not related) will be summarized. For those subjects who died within 60 days from the last dose date, the adverse event resulting in death and the adverse event relationship to MEDI-573 will also be summarized.

3.3.2 Demographics and Baseline Characteristics

Summaries of demographics, disease history, subgroups of interest at baseline, prior cancer treatment, baseline disease status assessment, baseline tumor characteristics, and baseline Karnofsky performance status will be provided to describe the subject population in this study. Parameters will be summarized for the ITT population by treatment group for subjects randomized into the Phase 2 portion of the study and all subjects combined.

Subjects will be excluded from the summary for each parameter if data are missing.

Disease history summary will include frequency distributions for stage at initial diagnosis, tumor stage, node stage, metastasis stage, and descriptive statistics of time from primary diagnosis to study entry (months).

The subgroups of interest at baseline are listed in Table 3.3-1. Subgroup analysis of anti-tumor activity will be performed if there are a sufficient number of subjects in a subgroup.

Prior cancer treatment, treatment type, and best response of prior cancer treatment will be summarized by frequency distributions.

The baseline disease status assessment summary will include frequency distributions for sites of metastatic disease and stage of disease at study entry.

Baseline tumor characteristics include number and sites of target lesions as well as number and sites of non-target lesions to be summarized using a frequency distribution. The size of target lesions will be also summarized in terms of sum of the longest diameter of target lesions using descriptive statistics.

A summary of baseline KPS will be provided using frequency distributions.

3.3-1 Subgroups of Interest

Subgroups of Interest	Description
Geographic Region	North America or rest of world
AI type	Anastrozole, Letrozole, or Exemestane
Baseline Ki-67 Index	Low vs High
Baseline IGF-I Level	Low vs High
Baseline IGF-II Level	Low vs High

3.3.3 Study Drug Exposure

Summaries of study drug exposure will be provided for the ITT and/or safety population by treatment group.

Summary of study treatment exposure will include descriptive statistics of the following: total number of treatment cycles, defined as the number of cycles during which subject received any treatment of MEDI-573 and/or AI, number of MEDI-573 doses and total MEDI-573 dose received during the study, duration of AI treatment (days) during the study. The total number of treatment cycles will also be summarized using frequency distribution. The dose intensity for MEDI-573 or AI is a percent of total actual dose that a subject received during the study treatment period for MEDI-573 or AI respectively, versus total intended dose of MEDI-573 or AI respectively, for the same study treatment period according to the study protocol. It will be summarized using descriptive statistics as part of the study treatment exposure summary. The dose intensity calculation details will be provided in the SPP.

Dosing delays and modifications will be summarized for the following categories: number of subjects with MEDI-573 dose delays, the reasons for MEDI-573 dose delay, the total number of subjects for whom the entire MEDI-573 dose was not administered as scheduled, the reasons the entire MEDI-573 dose was not administered as scheduled and the reason the subject did not receive MEDI-573.

The use of subsequent alternative cancer treatment after the discontinuation of study treatment will be summarized by type of treatment. Descriptive statistics of time from treatment discontinuation to initiation of subsequent cancer treatment (months) will be provided.

3.4 Efficacy Analyses

3.4.1 Primary Efficacy Endpoint and Analyses in Phase 2

3.4.1.1 Primary Efficacy Endpoints

The primary endpoint of the Phase 2 portion of this study is progression-free survival (PFS) defined as the time from randomization until the first documentation of disease progression or death, whichever occurs first:

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

Refer to Table 3.4-1 for date of PD/death or censoring.

3.4.1.2 Primary Efficacy Analysis

Progression-free survival (PFS) will be evaluated using the Kaplan-Meier method in the ITT population and compared with a two-sided stratified log-rank test at α=0.2 significance level (overall type I error rate) between MEDI-573 [redacted] + AI group and the AI alone group. The stratification factors will be geographic region (North America vs rest of world) and AI type (anastrozole, letrozole, or exemestane). Assessments of disease response by investigators will be the basis for the primary analysis.

As supportive information, median PFS and its 80% and 95% confidence interval (CI) will be estimated using the Kaplan-Meier method. The PFS rate will be presented at 6 and 12 months. The p-value from the two-sided stratified log-rank test will be used for the primary assessment of efficacy. The stratification factors will be region (NA versus rest of world) and AI type (anastrozole, letrozole, or exemestane). The hazard ratio (MEDI-573 [redacted]+AI vs. AI alone) with two-sided 80% and 95% confidence intervals will be estimated using a Cox proportional hazard model with treatment and the stratification factors as explanatory variables in the model.

Subgroup analyses of PFS by subgroups defined in Table 3.3-1 will also be performed in the ITT population. Hazard ratios (MEDI-573 [redacted]+AI vs. AI alone) with a two-sided 80% and 95% confidence intervals will be estimated by a non-stratified Cox proportional hazard model using the subgroups defined in Table 3.3-1.

3.4.2 Secondary Efficacy Endpoints and Analyses in Phase 2

3.4.2.1 Secondary Efficacy Endpoints

The secondary endpoints for assessing antitumor activity include best overall disease response, objective response rate (ORR), time to response (TTR), duration of response (DR), time to progression (TTP), overall survival (OS) and change in tumor size. They will be summarized by treatment group based on the ITT population in Phase 2.

3.4.2.2 Secondary Efficacy Analyses

3.4.2.2.1 Best Overall Response

The best overall response will be calculated, based upon the disease assessments recorded during the study visits, and summarized with the number and percentage of subjects for the following categories: complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). At least 6 weeks from the baseline disease assessment must elapse without progressive disease (PD) in order to assign a best overall response of SD. Confirmation of PR and CR is required and must occur at least 4 weeks after initial documentation of PR or CR. If PR or CR is pending confirmation at an assessment followed by 1 or more non-evaluable assessments or assessments of SD, response may be confirmed thereafter.

3.4.2.2.2 Objective Response Rate

The objective response rate (ORR), defined as proportion of subjects with confirmed CR or confirmed PR, will be estimated with 80% and 95% confidence intervals based on the exact probability method. Subjects that have missing overall response assessments will be considered non-responders, so they will be counted in the denominator, but not in the numerator of ORR. In addition, ORR of the MEDI-573 [redacted] + AI treatment group will be compared with that of the AI alone group using the Cochran–Mantel–Haenszel (CMH) test stratified by geographic region (North America vs rest of world) and AI type (anastrozole, letrozole, or exemestane).

3.4.2.2.3 Time to Response

Time to response (TTR) is measured from randomization to the first documentation of disease response and will be evaluated only in subjects who have achieved objective response (confirmed CR or confirmed PR). Time to response is defined in months as follows:

TTR (months) = (Date of first disease response – Date of randomization + 1) / (365.25/12)

The median TTR and its 80% and 95% CIs will be assessed using the Kaplan-Meier method.

3.4.2.2.4 Duration of Response

Duration of response (DR) is measured from the first documentation of disease response to the first documented progressive disease and will be evaluated only in subjects that have achieved objective response (confirmed CR or confirmed PR). Duration of response is defined in months as follows:

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

where date of PD or censoring is given in Table 3.4-1. The median time of DR and its 80% and 95% CIs will be assessed using the Kaplan-Meier method.

3.4.2.2.5 Time to Progression

Time to progression (TTP) is measured from randomization until the first documentation of disease progression. Time to progression is defined in months as follows:

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

where date of PD or censoring is given in Table 3.4-1. The median TTP will be estimated using the Kaplan-Meier method with 80% and 95% CIs.

The hazard ratio (MEDI-573 [redacted]+AI vs. AI alone) with two-sided 80% and 95% confidence intervals will be estimated by a Cox proportional hazard model with treatment and the 2 stratification factors as explanatory variables in the model.

3.4.2.2.6 Overall Survival

Overall survival (OS) is measured from randomization until death. Overall survival is defined in months as follows:

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

The median OS will be estimated using the Kaplan-Meier method with 80% and 95% CIs.

The hazard ratio (MEDI-573 [redacted]+AI vs. AI alone) with two-sided 80% and 95% confidence intervals will be estimated by a Cox proportional hazard model with treatment and the 2 stratification factors as explanatory variables in the model.

Time to Disease Assessments

Time to Disease Assessments (TDA) is measured from randomization until each disease assessment. Estimates of median time to disease assessments in each group will be calculated using Kaplan Meier methods. The median time to disease assessment for the first six disease assessments on study will be reported with 95% confidence intervals. Subjects lost to follow-up or that reach the survival endpoint prior to the planned disease assessment will be censored at the date of their last disease assessment. For disease assessments that span multiple days, the disease assessment date assigned will be the date when the first imaging scan from the disease assessment was performed.

Time to Disease Assessments is defined in days as follows:

TDA (days) = (Date of disease assessment or censoring – Date of randomization + 1).

3.4.2.2.7 Best Percent Change in Target Lesion Sizes

For each subject, target lesion diameters will be listed by visit. In addition, best percent change in the sum of the target lesion sizes identified at baseline will be listed and presented by subject in a waterfall graph. Descriptive statistics will be used to summarize the best percent change in the sum of the target lesion sizes. In addition, percent change in the sum of the target lesion sizes identified at baseline will be listed per visit.

3.4.2.3 Subgroup Analyses

Subgroup analyses of best overall response, ORR, TTP, and OS by subgroups defined in Table 3.3-1 will also be performed in the ITT Phase 2 population. Hazard ratios (MEDI-573 [redacted] AI vs. AI alone) with a two-sided 80% and 95% confidence intervals will be estimated by a non-stratified Cox proportional hazard model using the subgroups defined in Table 3.3-1.

3.4.3 Handling of Dropouts and Missing Data in Phase 2

These rules will apply uniformly to all efficacy analyses resulting from investigator assessed tumor measurements using RECIST 1.1. 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 objective response, but will be counted in the denominator of all response rate calculations.

3.4.3.1 Handling of Missing Data

3.4.3.1.1 Missing Data at Baseline

If a subject has missing lesion data at baseline, the subject will be assigned PD if criteria for PD is exhibited at the first disease assessment. Otherwise, the subject will be classified as non-evaluable for objective response and censored at date of randomization for TTP. For PFS the subject will be censored at date of randomization unless the subject dies within the first scheduled disease assessment period post-baseline in which case this date will qualify as a PFS event.

3.4.3.1.2 Missing Data at a Disease Assessment

If a subject has missing tumor measurements at some assessment for 1 or more target lesions, the sum of the longest diameters (SLD) will be reported for the remaining target lesions. These data will be used to indicate radiologic disease progression if the SLD for the observed lesions increases at least 20% from the nadir SLD of all lesions and demonstrates at least a 5 mm absolute increase from the nadir SLD of all lesions, in spite of the missing data (or if other criteria for PD are met). If a subject has missing tumor assessments at some 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). If a subject has missing tumor measurements at some assessment(s) for 1 or more target or missing recorded status at some assessment(s) for 1 or more non-target lesions and criteria for PD are not met, an overall response of non-evaluable will be assigned for the assessment(s).

3.4.3.1.3 Missing Disease Assessment(s)

If a subject has more than two consecutive completely missed or non-evaluable assessments followed by death or an assessment showing radiologic disease progression, then the subject will be censored at the date of the last progression-free disease assessment prior to the missed or non-evaluable assessments. If a subject has more than two consecutive missed or non-evaluable assessments followed by an assessment showing no radiologic disease progression, then the assumption will be that the subject remained stable during the missed or non-evaluable assessments.

3.4.3.2 Other Censoring Rules

Subjects having no tumor assessments after randomization will have PFS and TTP censored at the date of randomization. Subjects who reach the survival endpoint due to any reason

prior to experiencing a radiologic disease progression will be censored for TTP at the date of their last complete disease assessment. Subjects remaining on study without radiologic disease progression or death at the time of analysis will be censored for TTP and PFS at the date of their last complete disease assessment. Subjects lost to follow-up prior to experiencing a radiologic disease progression or death will be censored for TTP and PFS at the date of their last complete disease assessment. Additionally, a sensitivity analysis may be performed censoring PFS on the date of last progression-free assessment prior to initiation of alternate anticancer therapy. Subjects who are alive at the end of study or lost to follow-up will be censored for OS on the last date when the subjects were known to be alive.

Any subject receiving locoregional therapy, including surgery, while on study that directly affects one or more of the target lesions selected at baseline and results in 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.

3.4-1 Summary of Censoring Guidelines for Efficacy Endpoints

Situation	Date of PD/Death or Censoring	PFS/TTP Outcome
Documented Progressive Disease (PD) as determined by investigator	Date of earliest sign of PD	Progressed
Death before the first post-baseline disease assessment or between adequate tumor assessment visits	Date of death (PFS) Date of last progression-free disease assessment (TTP)	Death (PFS) Censored (TTP)
No PD as determined by investigator or death at time of analysis or lost to follow-up	Date of last progression-free disease assessment	Censored
Death or PD as determined by investigator after ≥ 2 missed consecutive disease assessments	Date of last progression-free disease assessment prior to missed assessments	Censored
Initiation of alternative anticancer therapy	Date of last progression-free disease assessment prior to initiation of other anticancer therapy	Censored for Sensitivity Analyses
No tumor assessment at baseline or post-baseline	Date of randomization	Censored

3.4.4 Assignment of Dates of Disease Progression or Disease Response

For all analyses of endpoints analyses resulting from investigator assessed tumor measurements using RECIST 1.1., 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 response date assigned will be the latest date of evaluations corresponding to the disease assessment. The date of latest assessment will

also be assigned for a mid-study assessment showing SD as the date assigned to that SD for the purposes of censoring duration of SD.

The date of PD will be the 1st date at which any objective diagnostic test provides data indicating PD. Specifically, the date of PD will be the earliest of the following 3 dates:

- Date of PD as indicated by target lesions: if PD is triggered by a change in SLD of target lesions, and all evaluations occurred on the same day, assign that date. If 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: the 1st date for which any non-target lesion exhibits a response of PD.
- Date of PD as indicated by new lesions: the 1st date for which any new lesion is detected.

3.5 Safety Analyses

3.5.1 Primary Endpoints of Safety in Phase 1b

The primary safety endpoints are the following:

- Adverse events and SAEs occurring during the protocol-specified reporting period (as defined in Section 6.4 of the study protocol)
- Dose-limiting toxicities (defined in the study protocol Section 4.5.8.1) occurring during the DLT period in the Phase 1b portion of this study

Adverse events, treatment emergent AEs and SAEs will be summarized by system organ class and MedDRA preferred term, severity, and relationship to study treatment. The number and percentage of subjects with DLT in the evaluable population for Phase 1b of this study will be summarized.

3.5.2 Secondary Endpoints of Safety and Tolerability in Phase 2

Safety and tolerability will be assessed by summarizing AEs, SAEs, electrocardiogram (ECG) results, significant or important clinical findings in Karnofsky performance status, laboratory assessments, and vital signs during the study. All summaries for toxicity profile evaluation will be done by treatment group based on the safety population.

3.5.2.1 Adverse Events and Serious Adverse Events

Only treatment-emergent adverse events (TEAEs), defined as events present at baseline that worsen in intensity after administration of study treatment, or events absent at baseline that emerge after administration of study treatment, for the period extending to 60 days after the last dose of study treatment, will be summarized by system organ class and preferred term using the MedDRA dictionary, severity (graded according to NCI CTCAE v4.3), and relationship to study treatment. The AEs/SAEs occurring from the signing of the informed consent and prior to the initiation of study treatment will be listed. The AEs/SAEs that begin 60 days after last dose will not be summarized or listed.

Subjects will be counted only once for each preferred term, once for each system organ class, and by the highest event severity, regardless of how many events the subject experienced.

Summaries will be provided for TEAEs resulting in permanent discontinuation of study drug and TEAEs resulting to death. Supporting listings will be provided for AEs resulting in permanent discontinuation of study drug and AEs resulting to death.

3.5.2.2 DLT-like events

The DLT-like events, defined as an event which meets the definition of DLT but occurs during Cycle 1 in all subjects treated within the study, will be summarized by treatment group.

3.5.2.3 Clinical Laboratory Evaluation

The change in each laboratory parameter from baseline to the “worst-case” (nadir and/or zenith) on-study (including any post-baseline assessments that occur through 60 days after the last dose) and to the last assessment on-study (including any post-baseline assessments that occur through 60 days after the last dose) for hematology/coagulation and blood chemistry will be summarized by descriptive statistics. Baseline values will be defined as the last valid assessment prior to the first administration of study treatment.

Laboratory abnormalities with toxicity grades according to the NCI CTCAE v4.3 will be derived according to laboratory values. Laboratory abnormalities occurring from the start of study treatment administration through 60 days after the last dose of the study treatment will be presented. Shift tables from baseline to the maximum severity grade on-study and to the last assessment on-study will be generated for each of laboratory parameter.

3.5.2.4 Vital Signs

Descriptive statistics of value and change from baseline value for heart rate, blood pressure, body temperature, and respiratory rate will be provided for each scheduled time point.

3.5.2.5 Electrocardiogram

Descriptive statistics for electrocardiogram (ECG) parameters will be provided for each scheduled time point.

3.5.2.6 Karnofsky Performance Status

Karnofsky performance status will be summarized using a shift table showing change in KPS from baseline to the worst performance status on-study and to the last assessment on-study.

3.5.3 Immunogenicity

Analysis of immunogenicity (IM) results will be assessed by summarizing the number and percentage of subjects who develop detectable anti-MEDI-573 antibodies for all subjects entered in Phase 1b and Phase 2 (Group 1 and Group 2). The ADA titer will be reported for samples confirmed positive for the presence of anti-MEDI-573 antibodies. The effect of ADA on PK, pharmacodynamics, and safety will be evaluated by the MedImmune Global PK-PD & Bioanalysis group or designee.

3.5.4 Pharmacology and Pharmacodynamics of MEDI-573

Other secondary endpoints are the pharmacokinetics and pharmacodynamics endpoints. The analyses will be performed by the MedImmune Global PK-PD & Bioanalysis group or designee.

3.6 Exploratory Summaries

3.6.1 Exploratory Analyses [redacted]

[redacted]

3.6.2 Exploratory Analysis [redacted]

[redacted]

[redacted]

3.6.2.1 [redacted]

[redacted]

3.6.2.2 [redacted]

[redacted]

[redacted]

4 Interim Analyses

No formal interim analysis is planned.

5 References

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