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
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
βhCG	beta human chorionic gonadotropin
[redacted]	[redacted]
C_{max}	maximum observed concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CT	computed tomography
CTC	circulating tumor cell
CXR	chest x-ray
DLT	dose-limiting toxicity
DMC	data monitoring committee
DR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
[redacted]	[redacted]
ER	estrogen receptor
EU	European Union
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Hb	hemoglobin
HbA1c	hemoglobin A1c
HEENT	head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
HER-2	human epidermal growth factor receptor 2
HR	hormone receptor
HR+	hormone receptor positive
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGF	insulin-like growth factor
IGF-I	insulin-like growth factor I
IGF-II	insulin-like growth factor II

Abbreviation or Specialized Term	Definition
IGF-1R	insulin-like growth factor 1 receptor
IGF-2R	insulin-like growth factor 2 receptor
IM	immunogenicity
IR	insulin receptor
IR-A	insulin receptor isoform A
IR-B	insulin receptor isoform B
IRB	Institutional Review Board
IRS	insulin receptor substrate
IV	intravenous
IXRS	interactive web or voice response system
KLH	Keyhole Limpet Hemocyanin
KPS	Karnofsky Performance Status
MAb	monoclonal antibody
MBC	metastatic breast cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEDI	MedImmune
MEDI-573	human immunoglobulin G2 lambda MAb directed against human IGF-I and IGF-II
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PgR	progesterone receptor
PgR+	progesterone receptor positive
PK	pharmacokinetics
PR	partial response
PRO	patient-reported outcome
Q3W	once every 3 weeks
RECIST	Response Evaluation Criteria In Solid Tumors
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SD	stable disease
SID	subject identification
SMC	Safety Monitoring Committee
TTP	time to progression
ULN	upper limit of normal
VEGF	vascular endothelial growth factor

Study Abstract

TITLE

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)

OBJECTIVES

Primary Objective

Phase 1b (Dose-evaluation Phase)

The primary objective of the dose-evaluation phase is to evaluate the safety and tolerability of 3 dose levels of MEDI-573 in combination with an AI in subjects with hormone receptor positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative MBC.

Phase 2 (Randomization Phase)

The primary objective of the randomization phase 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.

Secondary Objectives

- To describe the safety and tolerability of MEDI-573 when used in combination with an AI
- To evaluate the anti-tumor 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 pharmacokinetics (PK) of MEDI-573 when used in combination with an AI
- To evaluate the pharmacodynamics of MEDI-573 when used in combination with an AI on circulating levels of insulin-like growth factor I (IGF-I) and insulin-like growth factor II (IGF-II)
- To evaluate the immunogenicity (IM) of MEDI-573 when used in combination with an AI

Exploratory Objectives

- [redacted]
- [redacted]

STUDY DESIGN

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).

Phase 1b (Dose-evaluation Phase)

In the Phase 1b portion of the study, 3 cohorts (Cohorts A, B, and C) will be examined. In Cohorts A, B, and C, 3 to 6 evaluable subjects will receive [redacted] or [redacted] MEDI-573, respectively, by IV infusion on Day 1 of each 21-day cycle. Subjects in each of the 3 cohorts will also be given an AI of the investigator's choice (letrozole, anastrozole, or exemestane) orally once daily. Subjects will be treated until unacceptable toxicity, documentation of disease progression, or subject withdrawal for other reasons. Eligible subjects are considered evaluable if they receive 1 full cycle of MEDI-573 and are followed for safety through the dose-limiting toxicity (DLT) evaluation period (defined as 21 days following the first dose of MEDI-573) or if the subject experiences a DLT. Enrollment into Cohorts A, B, and C will be initiated sequentially. Approximately 9-18 evaluable subjects will be required for the Phase 1b portion of this study. Nonevaluable subjects will be replaced in the same dose cohort. Up to 20 investigational sites in North America may participate in the Phase 1b portion of the study.

Phase 2 (Randomization Phase)

Following evaluation of the safety of MEDI-573 at the [redacted] dose level in combination with an AI, 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). A limit of approximately 30 subjects with metastases to bone-only will be randomized to reflect the proportion of subjects with bone-only metastases in the target population. MEDI-573 will be administered via IV infusion on Day 1 of each 21-day cycle. An AI of the investigator's choice will be given orally once daily. Subjects will be treated until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal. Approximately 100 investigational sites worldwide will participate in the Phase 2 portion of the study.

Randomization will be stratified by geographic region (North America vs rest of world) and AI type (letrozole, anastrozole, or exemestane). 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 (up to 36 months from the date the last subject is entered into the trial or when the sponsor stops the study). As of 10Jul2016, this milestone will have been met. All follow-up for any subjects that have discontinued treatment by 10Jul2016 (whether or not they have progressed), will end, as per the original protocol. However, as of Amendment 3, subjects still on treatment at that time will be allowed to continue treatment until they meet one of the criteria for treatment discontinuation. The end of the study will therefore be when the last subject still on treatment as of 10Jul2016 finishes the 60-day (+/- 3 days) safety follow-up following treatment discontinuation.

SUBJECT POPULATION

Adult (age ≥ 18 years [≥ 20 years for subjects enrolled in Japan]) postmenopausal females with HR+, HER2-negative MBC

TREATMENT

Phase 1b (Dose-evaluation Phase)

In Phase 1b, all subjects will be treated with MEDI-573 at doses of [redacted] mg/kg (as a 60-minute IV infusion [+ 20 minutes for potential overfill]), [redacted] mg/kg, or [redacted] mg/kg (as a 90-minute IV infusion [+ 20 minutes for potential overfill]) on Day 1 of each 21-day cycle in combination with an AI of the investigator's choice orally once daily. Subjects will be treated until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal.

Phase 2 (Randomization Phase)

Following Phase 1b, approximately 178 subjects with MBC will be randomly assigned in a 1:1 ratio in Phase 2 to receive 1 of the following regimens, depending on treatment assignment:

Arm 1: MEDI-573 [redacted] IV infusion on Day 1 of each 21-day cycle plus an AI (investigator's choice) orally once daily

Arm 2: AI (investigator's choice) orally once daily

Subjects will be treated with the assigned regimen until documentation of progressive disease, initiation of alternative anticancer therapy, unacceptable toxicity, or another reason for treatment discontinuation is observed.

ASSESSMENT OF ENDPOINTS

Primary Endpoints

Phase 1b (Dose-evaluation Phase)

The primary endpoints for safety are the number of subjects with a DLT as well as the adverse events (AEs) and serious adverse events (SAEs) occurring during the protocol-specified period. The number and percentage of subjects with DLT in the Evaluable Population for Phase 1b will be summarized. Adverse events, treatment-related AEs and SAEs will be summarized by system organ class and Medical Dictionary for Regulatory Activities preferred term, severity, and relationship to investigational product. Safety analysis will be descriptive in nature and no formal statistical comparison will be made.

Phase 2 (Randomization Phase)

The primary endpoint is PFS, measured from randomization until the documentation of disease progression

(according to Response Evaluation Criteria in Solid Tumors, Version 1.1) or death due to any cause, whichever occurs first.

Progression-free survival will be evaluated using the Kaplan-Meier method and comparisons among the treatment groups will be performed using a log-rank test. Progression-free survival will be summarized based on the Intent-to-Treat Population in the Randomization Phase of the study as the primary analysis. Several sensitivity analyses may be conducted based on different analysis populations, tumor response determined by different reviewers, different methods of handling missing data, or other statistical analysis methods. The details of the sensitivity analyses will be described in the statistical analysis plan.

Secondary Endpoints

Efficacy

Endpoints include objective response rate, time to response, duration of response, time to progression, OS, and change in tumor size. Response Evaluation Criteria in Solid Tumors (version 1.1) guidelines will be used to evaluate tumor response. The time to event data, including time to response, duration of response, time to progression, and OS, will be evaluated using Kaplan-Meier methods. The objective response rate and the change in tumor size will be analyzed using appropriate statistical methods.

Safety

The safety endpoints include AEs, SAEs, and changes in clinical laboratory evaluations from baseline. Safety analysis will be descriptive in nature and no formal statistical comparison will be made.

Other

MEDI-573 PK: Individual MEDI-573 concentrations will be tabulated by dose cohort along with descriptive statistics. Noncompartmental PK data analysis will be performed for data obtained from each dose cohort with scheduled PK sample collection. Descriptive statistics will be used to assess noncompartmental PK parameters (area under the concentration-time curve, maximum observed concentration, systemic clearance, and concentration half-life).

MEDI-573 pharmacodynamics: Circulating IGF-I and IGF-II levels will be summarized by dose cohort and summarized using descriptive statistics. The time-course of circulating IGF will be graphed based on dose group.

MEDI-573 IM: 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). The impact of anti-MEDI-573 antibodies on PK will be assessed.

Exploratory Endpoints

The variables to be included in the exploratory analyses may include:

- Evaluation of biomarkers related to MEDI-573 treatment
- Evaluation of patient-reported outcomes

Descriptive statistics will be used to describe the exploratory analyses. Depending on the nature of the data, geometric mean and other appropriate statistical summaries might be used as well.

PLANNED ANALYSIS

Two formal analyses are planned for the study. The primary analysis of PFS and safety will be performed after 122 PFS events have occurred. The final analysis of OS and safety will be performed at the end of study.

SAMPLE SIZE AND POWER CALCULATIONS

In the Phase 1b portion of the study, a minimum of 9 evaluable subjects (3 subjects each for the MEDI-573 dose of [redacted] and [redacted] mg/kg) will be required to determine the safety and tolerability of 3 dose levels of MEDI-573 in combination with an AI. Up to 18 evaluable subjects (6 subjects each at [redacted] mg/kg and [redacted] mg/kg doses) may be needed if a 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 (defined as 21 days following the first dose of MEDI-573) or if the subject experiences a DLT. Any nonevaluable subject will be replaced.

In the Phase 2 portion of the study, the primary objective is to compare PFS among subjects treated with [redacted] mg/kg MEDI-573 when co-administered with an AI. The assumed median PFS for subjects with single-agent AI alone is 9.4 months (Mouridsen et al, 2001), and the expected median PFS for subjects receiving the [redacted] mg/kg dose of MEDI-573 plus an AI is 13.4 months, which represents an improvement in PFS of 42.6% and corresponds to a hazard ratio of 0.7. Based on these assumptions, a total of 122 events (ie, subjects with disease progression or death) are required to provide 75% power for the log-rank test at a 2-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 MEDI-573 arm is 13.8 or 14.4 months (corresponding to hazard ratio of 0.68 or 0.653), the power will change to 80% or 85%, respectively, with 122 PFS events.

1 INTRODUCTION

1.1 Disease Background

Breast cancer represents a heterogeneous group of diseases with distinct biological features and clinical course, and the optimal management requires an individual strategy on the basis of tumor biology. Metastatic breast cancer (MBC) provides one of the greatest treatment challenges as the optimal approach to treatment is evolving, and also because development of drug resistance can render available options ineffective. The incidence of MBC appears to be decreasing and patients with MBC are living longer (Martin et al, 2006; Chia et al, 2007; Jemal et al, 2010). These observations seem to be linked to the introduction of agents, such as the third-generation aromatase inhibitors (AI) and targeted therapies, and to a lesser extent, to improvements in palliative care, cancer prevention, and screening techniques (Chia et al, 2007). Despite these advances, most women with MBC have a limited survival time of 18-24 months, and only 20% of them will be alive 5 years after the initial diagnosis of distant metastasis has been made (Gligorov and Lotz, 2008; Gueth et al, 2009). Since treatment of metastatic disease is not likely to be curative, the main goals are to prolong progression-free survival (PFS) and overall survival (OS), reduce disease symptoms, and achieve the best possible quality of life for the patient (Smith, 2006).

Approximately two-thirds of breast cancer patients have hormone receptor-positive (HR+) tumors. Endocrine manipulation is the cornerstone of therapy in HR+ tumors. Tamoxifen was for many years the most widely used first-line hormonal therapy for postmenopausal patients with hormone-sensitive advanced or MBC. Aromatase inhibitors, which have shown superior efficacy in advanced disease compared with tamoxifen, have now largely replaced tamoxifen as first-line therapy in postmenopausal women (Gibson et al, 2007). Their long-term efficacy, however, is limited by relapse of disease and development of resistance following adjuvant endocrine therapy. Despite documented levels of estrogen receptor (ER) at relapse in either locally recurrent or secondary metastatic tumors, up to 50% of patients with HR+/ER-positive (ER+) primary breast cancer who develop metastatic disease do not respond to first-line endocrine treatment (de novo resistance), and the remainder will eventually relapse despite an initial response (acquired resistance) (Ring and Dowsett, 2004). Several preclinical models have been proposed to explain the mechanisms of hormone resistance, including estrogen hypersensitivity and aberrant growth signaling pathways. A greater understanding of the biology of resistance may aid to define regimens combining AIs and novel targeted agents to enhance the efficacy of ER+ breast cancer treatment.

1.1.1 Insulin-like Growth Factor Signaling / Insulin Receptor Isoform A

Insulin-like growth factors (IGFs), IGF-I and IGF-II, are small polypeptides involved in regulating cell proliferation, survival, differentiation and transformation. Both ligands are expressed ubiquitously and act as endocrine, paracrine, and autocrine growth factors (Pollak, 2008; De Meyts, 2004; Tao et al, 2007; Ryan and Goss, 2008). Insulin-like growth factor I and IGF-II exert their various actions through binding to the IGF-I receptor tyrosine kinase (IGF-1R) and insulin receptor isoform A (IR-A) activating multiple intracellular signaling cascades, including the insulin receptor substrate (IRS) proteins, Akt, and mitogen-activated protein kinase pathways (Sciacca et al, 1999; Chitnis et al, 2008; Belfiore et al, 2009; Baserga, 2009). Both IR-A and IGF-1R are involved in IGF signaling and play significant roles in cancer development and progression (Frasca et al, 2008).The overexpression of IR-A and IGF-II has also been proposed as a potential mechanism that may lead to the resistance to IGF-1R-directed therapies (Hendrickson and Haluska, 2009; Zhang et al, 2007).

Numerous preclinical studies have reported that down regulation of IGF-1R expression or inhibition of signaling leads to the inhibition of tumor growth, both in vitro and in vivo (Ryan and Goss, 2008; Sachdev and Yee, 2007; Baserga, 2005). Inhibition of IGF signaling has also been shown to increase the susceptibility of tumor cells to chemotherapeutic agents in vivo (Tao et al, 2007; Chitnis et al, 2008; Ryan and Goss, 2008; Yuen and Macaulay, 2008). Dual inhibition of both the IR-A and IGF-1R receptors may enhance therapeutic efficacy against IGF-driven cancers (Sachdev and Yee, 2007).

1.2 Description of MEDI-573

MEDI-573 is briefly described below. Refer to the current Investigator's Brochure for details.

1.2.1 Product Derivation

MEDI-573 is a human immunoglobulin G2 lambda monoclonal antibody (MAb) generated with Xenomouse® technology that selectively binds to human IGF-I and IGF-II. The antibody was isolated from mice immunized alternately with soluble recombinant human IGF-II (hIGF-II) and hIGF-I coupled to keyhole limpet hemocyanin (KLH).

1.2.2 Summary of Nonclinical Experience with MEDI-573

MEDI-573 inhibited both IGF-I- and IGF-II-stimulated phosphorylation of IGF-1R and downstream signaling proteins including protein kinase B (Akt) and mitogen-activated

protein kinase in a number of engineered NIH3T3 and human tumor cell lines. Further, MEDI-573 inhibited autocrine phosphorylation of these signaling molecules. Functionally, MEDI-573 effectively inhibited the growth of a number of engineered NIH3T3 and human tumor cell lines. In vivo, MEDI-573 significantly inhibited the growth of implanted Clone 32 and P12 tumors, which overexpress human IGF-1R and either human IGF-II or IGF-I, respectively.

Using mRNA expression profiles, ER+ breast cancers can be further classified by hierarchical cluster analysis into luminal-A and luminal-B subtypes. Luminal-A cancers are histologically low grade and sensitive to neoadjuvant endocrine therapy. In contrast, luminal-B cancers are often high grade, less sensitive to neoadjuvant endocrine therapy, and have more cancer proliferation markers and poorer prognosis. In the MedImmune mRNA expression studies in ER+, progesterone receptor-positive (PgR+) and human epidermal growth factor receptor 2 (HER2)-negative primary tumor tissues, a positive correlation was found between mRNA ratios of IR-A and IR-B (insulin receptor isoform B) and the expression of multiple proliferation genes, as well as a more prominent IR-A:IR-B expression differential (ΔCt) in luminal-B breast cancers classified according to conventional methods. Therefore, these findings support the assertion that the significant increase of IR-A: IR-B ratio in patients with luminal-B tumors may be related to the high rate of tumor cell proliferation and poor prognosis observed in patients with this tumor subtype. The association of increased IR-A:IR-B ratio with the luminal-B subtype suggests the luminal-B patients could benefit more by co-targeting IGF-1R and IR-A therapy and it emphasizes the potential importance of targeting IR-A in this subgroup.

Based on the results of a single dose, non-Good Laboratory Practice (GLP), intravenous (IV) infusion, toxicity, pharmacokinetics (PK), and pharmacodynamics study in cynomolgus monkeys (the relevant toxicology species) with MEDI-573 at doses of [redacted]g, MEDI-573 was well tolerated and there was no evidence of test article-related local or systemic toxicity. MEDI-573 at doses of [redacted], administered once weekly for a total of 13 doses showed no evidence of test article-related local or systemic toxicity in a GLP, 13-week, repeat dose, 30-minute continuous IV infusion, toxicity study in cynomolgus monkeys. There were no test article-related effects on behavior or on heart rate, respiration rate, body temperature, blood pressure, or electrocardiography measurements taken in anesthetized monkeys. In the GLP tissue cross-reactivity study, no tissue cross-reactivity was observed in the brain, heart, or lung of the human or cynomolgus monkey tissues examined. There were no clinical observations of adverse findings at the injection site. There were also no macroscopic or microscopic observations of adverse findings at the injection site 7 days after the final dose. In summary, MEDI-573 was well tolerated in cynomolgus monkeys

following administration of up to 13 once-weekly doses, by 30-minute continuous IV infusion; the no observed adverse effect level was [redacted], the highest dose tested, which resulted in a dose-normalized area under the concentration-time curve (AUC/dose) of [redacted]

1.2.3 Clinical Experience with MEDI-573

The first clinical study of MEDI-573 in humans (Study MI-CP184) was designed as a Phase 1, multicenter, open-label, single-arm, dose-escalation and dose-expansion study to evaluate the safety, tolerability, maximum tolerated dose (MTD), and optimal biologically effective dose of MEDI-573 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. Secondary objectives include PK, pharmacodynamics, immunogenicity (IM), and antitumor activity. MEDI-573 has been administered at doses of 0.5, 1.5, 5, 10 or 15 mg/kg given once every 7 days and at a dose of 30 or 45 mg/kg once every 21 days.

A total of 43 patients, including 23 in the dose-escalation phase and 20 in the dose-expansion phase with urothelial (bladder) cancer, received MEDI-573. The MTD was not reached after enrolling patients through the highest dose level on the weekly (15 mg/kg) or every 3 week (45 mg/kg) schedules. No dose-limiting toxicities (DLTs) (≥ Grade 3 adverse event (AE) during the first cycle) were observed at any dose level. Overall, the most common AEs were decreased appetite (46.5%), fatigue (41.9%), nausea (32.6%), diarrhea (25.6%), vomiting (23.3%), and abdominal pain (20.9%). The most common treatment-related AEs were fatigue (27.9%), decreased appetite (23.2%), nausea (18.6%), diarrhea (16.3%), and anemia (11.6%). Of all the treatment-related AEs, most were ≤ Grade 2, with 1 report each of Grade ≥ 3 fatigue and hypoglycemia. Overall, 34 serious adverse events (SAEs) occurred in 17 subjects; 1 subject treated with 15.0 mg/kg experienced 2 treatment-related SAEs. Five of 43 patients (11.6%) in the dose-escalation phase and 1 of 20 patients (5.0%) in the dose-expansion phase discontinued treatment because of AEs. Three deaths occurred during the study, all because of progressive disease and none considered related to MEDI-573 treatment. Clinically, significant changes in serum glucose related to study treatment were rare, observed in 1 of 43 patients. No clinically significant changes to insulin or somatotropin levels, to hematologic parameters, or in ECGs were observed.

Following the first dose in Study CP184, MEDI-573 exhibited nonlinear PK. Serum exposure of free MEDI-573 increased more than dose-proportionally from 0.5 m/kg to 1.5 mg/kg.

After weekly and once every 3 weeks (Q3W) repeated doses, serum trough concentration increased with each dose and reached steady state in approximately 3-4 weeks. Free IGF-I and free IGF-II concentrations in plasma were fully suppressed following administration of MEDI-573. At doses above 5 mg/kg weekly and 30 or 45 mg/kg Q3W, MEDI-573 produced sustained suppression of both IGF-I and IGF-II throughout the dosing interval. None of the subjects in Study CP184 tested positive for antidrug antibodies (ADA) against MEDI-573 throughout the study. [redacted]-573 Q3W dose cohort tested borderline-positive for ADA with titer of ≤ 1:39 on Study Day 273 and 294. Serum exposure of free MEDI-573 in this ADA positive subject was slightly lower compared to others in the same cohort, suggesting a possible impact of ADA on MEDI-573 PK. No suppression of free IGF-I and IGF-II in plasma was observed in AI alone cohort. Following IV administration of MEDI-573 at [redacted] in combination of an AI, free IGF-II in plasma was fully suppressed through all dosing intervals, except 1 subject in [redacted] dose cohort with detectable free IGF-II from Day 273 through Day 399 and other 3 subjects in the same cohort with a detectable free IGF-II at a single time-point. Free IGF-I was not fully suppressed at the 2 low dose levels of [redacted]. At the high dose level of [redacted], free IGF-I in plasma was fully suppressed in 66 subjects (79%).

Between June 2011 and June 2013, a total of 185 patients (safety population) were enrolled into Study CD-ON-MEDI-573-1030. The Phase 1b portion of the study treated a total of 9 subjects, 3 subjects each received MEDI-573 at [redacted] in combination with an AI. In Phase 2, a total of 176 patients were enrolled in the intent-to-treat population, with 90 subjects receiving MEDI-573 and AI and 86 subjects receiving AI-only.

One hundred and four (104) total progression events (radiologic progression and/or death), 55 (61%) in the MEDI-573 and AI arm, and 49 (60%) in the AI-only arm, had occurred by data cut-off for this analysis (15Oct2014). A median (PFS) of 12.6 months was observed in the MEDI573 and AI cohort compared with 11.0 months in the AI-only cohort. The adjusted HR (stratified for Region and AI Type) was 0.95 (95% CI: 0.642, 1.408; P = 0.795).

The objective response rate (ORR) for patients with measurable disease was 25.6 % (n = 23) for MEDI-573 and AI vs. 25.6 % (n = 22) for AI-only. The overall survival data were not mature at this time.

No DLTs were observed in the Phase 1b portion of the study. The most common AEs in patients who received MEDI-573 and AI were fatigue (47%), nausea (38%), arthralgia (31%), and back pain (30%), whereas the most common AEs in patients in the AI-alone arm were arthralgia (38%), hot flashes (34%), nausea (31%), and fatigue (30%).

Patients who received MEDI-573 and AI experienced a higher incidence of ≥ Grade 3 AEs (n = 36 [36%] vs. n = 28 [32.6%]), serious AEs [SAEs] (n = 23 [23%] vs. n = 13 [15%]) and AEs leading to discontinuation of MEDI-573 and AI (n = 10 [10%] vs. n = 4 [4.7%]) compared with patients who received AI-only. The most common SAE in the MEDI-573 and AI arm was vomiting, reported by three (3%) patients. None led to discontinuation and all three patients recovered. All other SAEs in the MEDI-573 and AI arm were reported by no more than one patient. SAEs of supraventricular tachycardia and pleural effusion were reported by 2 patients each in the AI-only arm and remainder of the SAEs were reported by no more than 1 patient. There were 18 (18%) deaths reported in the MEDI-573 and AI arm and 18 (21%) deaths in the AI-alone arm. Majority of the deaths were due to disease progression (16 of 18 [89%] deaths in the MEDI-573 and AI arm and 17/18 (94%) deaths in the AI-only arm) and none of the deaths were attributable to study treatment in either arm.

Refer to the Investigator's Brochure for further details.

1.3 Research Hypothesis

This study has 2 phases: a dose-evaluation phase (Phase 1b) and a randomization phase (Phase 2). The primary objective of the dose-evaluation phase is to evaluate the safety and tolerability of 3 doses of MEDI-573 in combination with an AI in subjects with HR+, HER2-negative MBC. The primary objective of the randomization phase 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. Secondary objectives of the study include MEDI-573 safety and tolerability, antitumor activity, PK/pharmacodynamics, and IM.

The research hypothesis is that MEDI-573 will be able to be safely administered in combination with an AI and that MEDI-573 administered in combination with an AI will result in improved PFS in subjects with HR+, HER2-negative MBC compared to AI treatment alone.

1.4 Rationale for Study Conduct

Aberrant estrogen-receptor expression/functioning has been implicated in the development of over 70% of breast cancers (Riemsma et al, 2010). Many of these cancers respond to hormonal therapy, but a large number will ultimately develop resistance with long-term

treatment. There is evidence that peptide growth factors and their downstream effectors may interact with ER signaling to influence the sensitivity of breast cancer cells to endocrine therapy, and thus may be important targets for novel treatments (Leary and Dowsett, 2006; Johnston, 2010). Combining the most effective estrogen-deprivation therapies, including third-generation AIs, with new therapies that target estrogen-independent signaling pathways may increase the efficacy of breast cancer treatment. Expression of ER and associated genes characterizes the luminal breast cancers with luminal B having worse outcomes than luminal A. The association of increased IR-A:IR-B ratio with the luminal-B subtype suggests a rationale for targeting IR-A and suggests that these patients may benefit from treatment that targets both IGF-1R and IR-A. As the distinction between luminal A and luminal B tumors is somewhat difficult to achieve, Cheang et al have suggested that the Ki-67 index, which is a widely applicable, easily assessed marker of cell proliferation, can be used to identify the luminal B breast cancer subtype (Cheang et al, 2009).

1.5 Benefit-risk and Ethical Assessment

MEDI-573 has been shown to inhibit tumor growth in a wide range of human cancer models as a single agent. Nonclinical studies suggest that MEDI-573 has the potential to achieve broad anti-tumor efficacy owing to its ability to inhibit both IGF-1R and IR-A pathways. Furthermore, MEDI-573 has potential to achieve this without perturbing glucose homeostasis, which has been an endocrine liability of other investigational agents that target IGF-1R (Gao et al, 2011). In nonclinical safety studies, MEDI-573 was well tolerated with no evidence of test-article related toxicity. In all trials testing MEDI-573 to date, the AEs observed were consistent with the underlying diseases and associated therapies in the study populations, with the most common AEs being decreased appetite, fatigue, and gastrointestinal events such as nausea and diarrhea. No DLTs have been observed to date. Across the ongoing clinical studies, 3 subjects to date have experienced increased liver function test results that led to discontinuation of MEDI-573, with 1 subject experiencing increased ALT and increased AST considered to be related to MEDI-573.

Three major classes of therapeutic compounds that target the IGF axis are currently in development: (1) small molecule tyrosine kinase inhibitors (TKIs) that inhibit kinase activities of IGF-1R and IR, (2) antibodies that target IGF-1R, and (3) antibodies that target IGF ligands. Due to the high degree of homology among the kinase domains, the majority of IGF-1R-targeting TKIs inhibit not only IGF-1R but also IR-A and IR-B, thus impairing glucose homeostasis and contributing to the transient hyperglycemia observed in clinical trials (Weroha and Haluska, 2008). Antibodies that target IGF-1R inhibit the binding of IGF to IGF-1R and are furthest along in clinical development. Many of these MAbs induce

IGF-1R internalization and degradation upon binding to the receptor. Although they do not bind to IR-A or IR-B, many of these MAbs partially modulate the activity of IGF-1R/IR-A or IGF-1R/IR-B hybrid receptors, which may contribute to the transient, treatment-related hyperglycemia observed in as many as 10-20% of subjects (Atzori et al, 2008). Although typically mild in nature, hyperglycemia has occasionally been dose-limiting and has resulted in Grade 3-4 adverse events in various studies (Atzori et al, 2009; Gualberto and Pollak, 2009, Weroha and Haluska, 2008).

If toxicities reported in studies of other investigational agents (mAbs as well as small molecules) that target the IGF axis are based on activity against IGF-1R, it is possible that hyperglycemia, anorexia, nausea, diarrhea, weight loss, elevated transaminases, anemia, thrombocytopenia, pruritus, rash, arthralgia, paresthesia, fatigue, autoantibody production, and infusion reactions might occur on Study CD-ON-MEDI-573-1030 (Weroha and Haluska, 2008). Based on published literature with similar therapies (ie, MAbs targeting the IGF signaling pathway), observed AEs were generally mild (Grade 1 or 2) and included hyperglycemia, gastrointestinal disturbances, hypersensitivity reactions, pruritus, asthenia, and anemia (Haluska et al, 2007; Atzori et al, 2008). Other toxicities included Grade 3/4 thrombocytopenia (Tolcher et al, 2008; Hidalgo et al, 2008), Grade 3 hyperglycemia (Higano et al, 2007), Grade 3 purpura (Atzori et al, 2008), Grade 4 uric acid increase, and Grade 3 bilateral deep venous thrombosis (Olmos et al, 2008).

Limited data have been published from breast cancer studies testing MAbs that target the IGF axis in combination with AIs. The largest study published to date randomized 156 postmenopausal women with HR+, metastatic or locally advanced breast cancer to AMG 479 (ganitumab) an IGF-1R targeting MAb plus exemestane or fulvestrant versus exemestane or fulvestrant alone. No unanticipated safety findings or improvement in PFS were reported for the combination of AMG 479 plus exemestane or fulvestrant versus exemestane or fulvestrant alone (Kaufman et al, 2010). Three other studies are currently testing IGF-targeting MAbs together with 1 of several different AIs (including anastrazole, letrozole, and/or exemestane) in the second-line breast cancer setting.

The proposed Phase 1b/2 study will characterize the safety and tolerability of MEDI-573, as well as evaluate the anti-tumor activity of MEDI-573 in combination with an AI, an approved treatment for patients with HR+ MBC, with the goal of more fully elucidating the benefit-risk profile of the combination. The proposed exclusion criteria, safety monitoring, starting dose, dose-escalation scheme, and stopping criteria are designed to minimize the potential risks for subjects participating in this clinical trial. Subjects will be carefully monitored for abnormal liver function test results given that elevated LFT results have led to

treatment discontinuation across the MEDI-573 studies. Based on the tolerability of MEDI-573, the benefit-risk profile is considered acceptable for the proposed clinical study.

2 STUDY OBJECTIVES

2.1 Primary Objective

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 PFS of subjects with HR+, HER2-negative MBC treated with MEDI-573 and an AI versus treatment with an AI alone.

2.2 Secondary 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 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 evaluate the pharmacodynamics of MEDI-573 in combination with an AI on circulating levels of IGF-I and IGF-II
- To evaluate the IM of MEDI-573 in combination with an AI

2.3 Exploratory Objectives

[redacted]

3 STUDY DESIGN

3.1 Overview of Study Design

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).

3.1.1 Phase 1b (Dose-evaluation Phase)

In the Phase 1b portion of the study, 3 cohorts (Cohorts A, B, and C) will be examined. In Cohorts A, B, and C, 3 to 6 evaluable subjects will receive [redacted] MEDI 573, respectively, by IV infusion on Day 1 of each 21-day cycle. Subjects in each of the 3 cohorts will also be given an AI of the investigator's choice (letrozole, anastrozole, or exemestane) orally once daily. Subjects will be treated until unacceptable toxicity, documentation of disease progression, or subject withdrawal for other reasons (see Section 4.2.3). Enrollment into Cohorts A, B, and C will be initiated sequentially.

Modifications of the MEDI-573 dosing schedule for toxicities other than DLTs are described in Section 4.5.8. Eligible subjects are considered evaluable if they receive 1 full cycle of MEDI-573 and are followed for safety through the DLT evaluation period (defined as 21 days following the first dose of MEDI-573) or if the subject experiences a DLT, as defined in Section 4.5.8.1. Nonevaluable subjects will be replaced in the same dose cohort. Approximately 9 to 18 evaluable subjects will be required for the Phase 1b portion of this study. A study flow diagram for Phases 1b and 2 is shown in Figure 3.1.2-1. Up to 20 investigational sites in North America may participate in the Phase 1b portion of the study.

3.1.2 Phase 2 (Randomization Phase)

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] mg/kg and an AI (investigator's choice of anastrozole, letrozole, or exemestane) (Arm 1) or an AI alone (Arm 2). A limit of approximately 30 subjects with metastases to bone-only will be randomized to reflect the proportion of subjects with bone-only metastases in the target population. MEDI-573 will be administered via IV infusion on Day 1 of 21-day cycles. An AI will be given orally once daily. Subjects will be treated until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal (see

Section 4.2.3). Approximately 100 investigational sites worldwide will participate in the Phase 2 portion of the study. A study flow diagram for Phases 1b and 2 is shown in Figure 3.1.2-1.

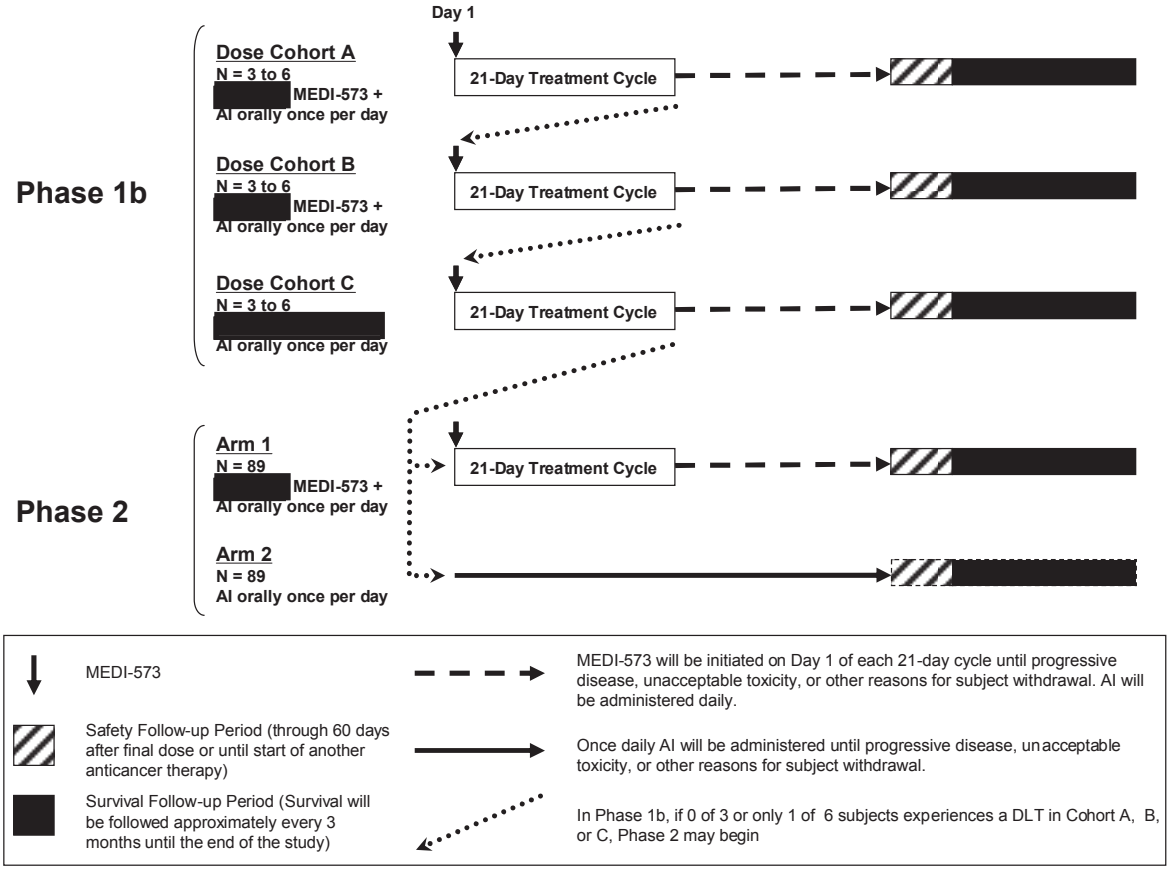

Figure 3.1.2-1 Study Flow Diagram

AI = aromatase inhibitor; DLT = dose-limiting toxicity

Randomization will be stratified by geographic region (North America vs rest of world) and AI type (letrozole, anastrozole, or exemestane). The endpoints to be measured in this study are described in Section 7.3. 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.

3.2 Estimated Duration of Subject Participation

In both the Phase 1b and 2 portions of the study, subjects will be treated either with the combination of MEDI-573 and an AI or single-agent AI until PD, initiation of alternative anticancer treatment, unacceptable toxicity, or another reason to discontinue therapy, and will also be followed for survival until the end of the study as defined in Section 4.8.

3.3 Study-stopping Criteria

If any of the following occur, administration of investigational product may be stopped and no additional subjects will be entered or randomized into the study:

1. Death in any subject in which the cause of death is assessed as related to investigational product
2. Anaphylactic reaction to investigational product in any subject
3. A cumulative rate of 30% or greater for DLT-like events that occur within the first cycle in all subjects treated within the study. A DLT-like event is one that otherwise meets the definition of DLT but occurs during Cycle 1 of the Phase 2 portion of the study, which does not have a formal DLT period
4. Other events that, in the judgment of the medical monitor, are deemed serious enough to warrant immediate review by the Safety Monitoring Committee (SMC) and/or Data Monitoring Committee (DMC)

If any of the above-listed events occur, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted (see Section 6.5) to determine whether dosing and study entry/randomization should be stopped, remain stopped, or resumed (depending on the initial response to any of the above-listed events); whether the protocol will be modified; or whether the study will be discontinued permanently. Review and approval by the MedImmune SMC are required for resumption of the study in the event the study is interrupted because of one of the above-listed events. Where applicable, regulatory authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be notified of any actions taken with the study.

Any subjects who have already received investigational product and are currently in the study at the time study stopping criteria are met will continue to be followed by the investigator for safety. Decisions regarding ongoing treatment for other already enrolled subjects will be made on a case-by-case basis after discussion with the subject, investigator, sponsor, and the health authority.

Withdrawal criteria for individual subjects are provided in Section 4.2.3.

3.4 Rationale for Study Design, Doses, and Control Groups

A study design that constitutes an open-label dose-evaluation phase (Phase 1b) followed by a randomization phase (Phase 2) is common in early-phase oncology trials. Because some breast cancers respond to estrogen, lowering the estrogen level in postmenopausal women using AIs has been proven to be effective in breast cancer treatment. Aromatase inhibitors

are an approved standard of care for postmenopausal women with endocrine-responsive MBC and will be administered to all subjects in the study with or without MEDI-573.

In Amendment 2, the inclusion criterion for patients with MBC is being revised to limit the enrollment of subjects with bone-only metastases to approximately 30 subjects. This change is being made to ensure that the study population remains representative of the overall target population. The prevalence of bone-only metastases in studies reported by Paridaens and Nabholtz ranged from 12% to 20% (Paridaens et al, 2008; Nabholtz et al, 2000). To date, the current study has been enrolling a higher percentage of subjects with bone-only disease. This may bias the study results because subjects with bone-only disease generally have a better prognosis (Niikura et al, 2011). Accordingly, to limit enrollment to a more representative proportion of bone-only subjects and better predict efficacy in later-stage trials, enrollment will be capped at approximately 30 subjects.

The primary objective for the dose-evaluation phase is to assess the safety of MEDI-573 when used in combination with an AI. Outcome measures include DLT identification and descriptions of AEs. As a result, the doses of MEDI-573 to be investigated in the Phase 1b clinical study will enable assessments on the safety, tolerability, PK, immunogenicity, and pharmacodynamics of the combination of MEDI-573 and an AI for proceeding to Phase 2. The primary endpoint for the randomization phase is PFS, which provides a direct measure of the effect of MEDI-573 on antitumor activity when used in combination with an AI. Progression-free survival has been used to assess potential clinical benefit in patients with MBC, and unlike OS, measurement of PFS is not confounded by subsequent antitumor therapies. Overall survival and ORR will both be collected as secondary endpoints to help in the evaluation of MEDI-573 as an antitumor therapy. Response and progression will be determined according to Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) guidelines (Eisenhauer et al, 2009).

No unacceptable toxicities are anticipated based on the mechanisms of action and safety profiles of MEDI-573 and AIs. At present, evidence for quantitative translation of IGF-I and IGF-II suppression levels to clinical improvement in cancer patients is limited. Therefore, full suppression (> 90%) of IGF-I and IGF-II in the periphery is used to guide clinical dose selection. Dose selection for the Phase 2 portion of this study is based on the pharmacokinetic and pharmacodynamic profiles of MEDI-573 obtained from Phase 1 (Study MI-CP184) and Phase 1b (Study CD-ON-MEDI-573-1030) studies. In these two trials, a wide range of MEDI-573 doses ([redacted] once every week and [redacted] - [redacted] mg/kg Q3W) has been tested. No DLT has been observed to date at any dose level or schedule of MEDI-573 tested (either as monotherapy or in combination with an AI). Following weekly

dosing, MEDI-573 at dose levels greater than [redacted] resulted in complete and sustained suppression of plasma IGF-I and IGF-II over the entire dosing interval. In the case of [redacted] Q3Wk dosing, MEDI-573 was administered in conjunction with an AI on Study CD-ON-MEDI-573-1030. Following this 3-week dosing interval, [redacted] Q3Wk produced complete suppression of IGF-II in the plasma over the entire 3 weeks, while IGF-I in the plasma was only fully suppressed for about 7 days. MEDI-573 monotherapy administered at [redacted] and [redacted] mg/kg Q3Wk has yielded complete suppression of IGF-I and II throughout the entire 3 week dosing interval. Given that the doses of [redacted] and [redacted] mg/kg Q3Wk were well tolerated with no DLT, and in order to maximize tumor penetration of MEDI-573, the highest MEDI-573 dose tested [redacted] mg/kg Q3Wk) has been selected for administration in the Phase 2 portion of the study. This Phase 2 dose will facilitate an evaluation of the relationship between MEDI-573 exposure and clinical efficacy as well as safety endpoints.

4 STUDY PROCEDURES

4.1 Subject Participation and Identification

Study participation begins once written informed consent is obtained (see Section 10.3 for details). Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive web or voice response system [IXRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria and/or are not randomized), including the reason(s) for screening failure [see Section 9.1 for details]).

4.2 Subject Selection and Withdrawal

The subjects in this study will be postmenopausal women with HR+, HER2-negative MBC.

The investigator (physician) or qualified designee will discuss the study with a subject/the legal representative of a subject who is considered a potential candidate for the study and provide the subject/legal representative with the study-specific informed consent form(s) approved by the IRB/IEC. The investigator or designee will address any questions and/or concerns that the subject/legal representative may have and, if there is continued interest, will secure written informed consent for participation in the study. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act

[HIPAA] authorization in the US, European Union [EU] Data Privacy Directive authorization in the EU) will be obtained prior to conducting any protocol-specific procedures, including screening evaluations or medication washouts. See Section 10.3 for additional details concerning informed consent.

4.2.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1. Subjects must have histologically-confirmed MBC not deemed amenable to curative surgery or curative radiation therapy
   - Subjects with metastases to bone only are eligible (enrollment of subjects with metastases to bone will be capped at approximately 30 subjects)
   - Subjects must be evaluated based on RECIST 1.1 guidelines
2. Tumors are positive for ER, PgR, or both (ie, 10% or more of infiltrating cancer cells exhibit nuclear staining for ER and/or PgR; positive biochemical test results are also acceptable). Expression can be ascertained on either primary or metastatic site. For subjects who have had the hormonal status of their tumor(s) assessed more than once over the course of their disease, the most recent assessment will determine eligibility.
3. Tumors must be negative for HER2 by fluorescence in situ hybridization (FISH), chromogenic in situ hybridization (CISH), immunohistochemistry (IHC) used per local guidelines or manufacturer's scoring criteria and instructions.
4. Female gender and age ≥ 18 years (≥ 20 years for subjects enrolled in Japan) at time of study entry
5. Women must be postmenopausal as defined by 1 of the following:
   a. Bilateral oophorectomy
   b. ≥ 55 years old with cessation of menses
   c. < 55 years old with:
      - Spontaneous amenorrhea > 1 year duration prior to randomization, except for patients having both ovaries removed, OR
      - Spontaneous menses within 1 year before randomization, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy) and with postmenopausal gonadotropin levels (luteinizing hormone [LH] and follicle stimulating hormone [FSH] levels > 40 IU/L) or post-menopausal estradiol levels (< 5 ng/dL) within the postmenopausal range according to local guidelines OR
      - Radiation-induced menopause (≥ 3 months prior to randomization) OR
      - FSH levels in the postmenopausal range according to local guidelines prior to receipt of neo-adjuvant or adjuvant chemotherapy or radiation therapy OR
      - Women rendered amenorrheic by neoadjuvant or adjuvant chemotherapy who were premenopausal or perimenopausal prior to chemotherapy must be amenorrheic for at least 12 months prior to randomization and must have FSH levels in the postmenopausal range, with postmenopausal gonadotropin levels within the postmenopausal range, according to local guidelines.

6. Karnofsky Performance Status (KPS) ≥ 70 (Appendix 2)
7. Life expectancy of ≥ 6 months
8. Subjects must have adequate organ and marrow function as defined below:
   - Hemoglobin (Hb) ≥ 9 g/dL
   - Absolute neutrophil count ≥ 1000/mm^3
   - Platelet count ≥ 75,000/mm^3
   - Aspartate aminotransferase and ALT ≤ 2.5 × institutional upper limit of normal (ULN) in subjects without liver metastasis or ≤ 5 × ULN in subjects with liver metastasis
   - Bilirubin ≤ 1.5 × ULN
   - Creatinine ≤ 1.5 × ULN
9. Ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures
10. Suitable candidate for AI therapy, including the ability to swallow and absorb oral agents
11. Subjects must consent to allow collection of available paraffin-embedded tumor tissue from either the primary or metastatic tumor site
12. Written informed consent and any locally-required authorization (eg, HIPAA in the US, EU Data Privacy Directive in the EU) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations

4.2.2 Exclusion Criteria

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

1. Subjects who received prior chemotherapy, hormonal therapy, immunotherapy or biologic therapy for advanced or metastatic disease with the following exceptions:
   - Prior adjuvant therapy with an AI and/or tamoxifen is allowed, provided treatment ended at least 2 weeks prior to the first dose of MEDI-573
   - Prior neoadjuvant and/or adjuvant chemotherapy for breast cancer is allowed
2. Subject for whom endocrine therapy of breast cancer is not appropriate (ie, life-threatening or rapidly progressing metastatic disease)
   - Subjects with extensive symptomatic visceral disease including hepatic involvement and pulmonary lymphangitic spread of tumor, or disease that is considered by the investigator to be rapidly progressing or life threatening (eg, subjects who are intended for chemotherapy).
3. Active brain metastases.
   - Known brain metastases are only acceptable if they have been treated and subjects are asymptomatic, and there has been no evidence of central nervous system (CNS) progression for at least 4 weeks before starting trial medication. If on dexamethasone, the subject must be on a stable or tapering dose for at least 4 weeks prior to starting trial medication. If on anti-epileptic therapy, the subject must be on a stable dose for at least 4 weeks prior to starting trial medication

4. Evidence of ongoing spinal cord compression or leptomeningeal carcinomatosis
    - Subjects with evidence (CT, MRI, or x-ray) of spinal canal involvement who are asymptomatic are allowed
5. Unresolved toxicities from prior therapy with the exception of alopecia that have not resolved to ≤ Grade 1 (by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] version 4.0) at the time of starting study treatment
    - An exception may be made in the case of a persistent, stable ≤ Grade 2 AE that, in the opinion of the investigator, would not interfere with evaluation of the investigational product, the interpretation of subject safety, or study results
6. Receipt of any investigational therapy within 30 days or 5 half-lives, whichever is longer, prior to receiving the first dose of study treatment
7. Previous treatment with an agent that targets IGF-1 or IGF-2 ligands or the IGF receptor
8. History of allergy or reaction attributed to compounds of chemical or biologic composition similar to those of MEDI-573 or AI
9. Use of immunosuppressive medication other than steroids within 7 days before the first dose of MEDI-573
10. History of another invasive malignancy within 5 years prior to starting study treatment except for curatively resected nonmelanoma skin cancer or carcinoma in situ of the cervix
11. Poorly controlled diabetes mellitus as defined by investigator assessment
12. History of cardiac disease including, but not limited to, congestive heart failure > Class II New York Heart Association (see Appendix 1); active coronary artery disease (eg, unstable angina pectoris), new onset angina pectoris, myocardial infarction within the past 6 months, ventricular arrhythmias requiring antiarrhythmic therapy, or uncontrolled hypertension within the last 6 months
13. Current active hepatic or biliary disease (with exception of subjects with Gilbert's syndrome, asymptomatic gallstones, liver metastases or stable chronic liver disease per investigator assessment)
14. Known human immunodeficiency virus or hepatitis B or C virus infection (either active, previously treated or both)
15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring parenteral antibiotics, or a psychiatric illness/social situations that would limit compliance with study requirement
16. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results
17. Concurrent enrollment in another clinical study testing an investigational agent or intervention for cancer treatment or prevention
18. Subject directly involved with the conduct of the study or an immediate family member of any such individual
19. Any condition that compromises the subject's ability to give informed consent

4.2.3 Withdrawal Criteria

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

1. Withdrawal of consent or lost to follow-up
2. Subject has met at least one exclusion criterion for study participation
3. Grade 3 or greater allergic or infusion reactions. Any allergic or infusion reaction that necessitates the use of systemic pressor agents will cause dose discontinuation in that subject
4. Infusion reactions ≥ Grade 2 that do not respond to medical therapy or slowing the infusion rate and are not of limited duration
5. Dose-limiting toxicity (see Section 4.5.8.1 for rules relating to dose escalation and DLTs), except for those DLTs that are considered to be controllable and allow for retreatment (see Section 4.5.8.1)
6. Grade 2 or higher toxicities that cause a cumulative delay of ≥ 21 days in 3 consecutive cycles
7. Delay of cycle for > 21 days
8. Documentation of disease progression
9. Adverse event that in the opinion of the investigator contraindicates further dosing
10. Significant subject noncompliance
11. Treatment with another investigational agent
12. Initiation of alternative anticancer therapy
13. Pregnancy or intent to become pregnant

Withdrawal of consent: If consent is withdrawn, the subject will not receive any further investigational product or further study observation. Note that the subject may need to undergo additional tests or tapering of treatment to withdraw safely.

Lost to follow-up: Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the subject's status through 30 days after the last dose of MEDI-573.

- Note: Subjects refusing to return to the site or to continue participation in the study should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost-to-follow-up and any evaluations should resume according to the protocol.

Permanent discontinuation of investigational product: Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment. Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study (see Section 4.7).

Subjects who are permanently discontinued from receiving investigational product will be followed for safety for 60 days after the last administration of investigational product, including the collection of any protocol-specified blood or urine specimens, unless consent is withdrawn, subject is lost to follow-up, subject has enrolled in another clinical study, or has initiated an alternative anticancer therapy. In addition, subjects will be followed for disease evaluation every 9 weeks until disease progression and then followed for survival every 3 months until the end of the study, as defined in Section 4.8.

4.2.4 Replacement of Subjects

Nonevaluable subjects will be replaced in the same dose cohort in Phase 1b. Subjects will not be replaced in the Phase 2 portion of the study.

4.3 Treatment Assignment

For Phase 1b, each subject who meets the eligibility criteria will be assigned open-label investigational product and an AI. In Phase 2, each subject who meets the eligibility criteria will be assigned either open-label investigational product and an AI (investigator's choice of anastrozole, letrozole, or exemestane) or an AI alone. Additional details on dosing are provided in Section 4.5.6.

An IXRS will be used for entry (Phase 1b)/randomization to a treatment arm (Phase 2) and assignment of unblinded investigational product and/or an AI (see Section 4.1). A subject is considered entered/randomized into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of unblinded investigational product and/or AI to the subject.

In Phase 2 of the study, subjects will be randomized at a 1:1 ratio to receive either MEDI-573 at [redacted] mg/kg and an AI or an AI alone. Please refer to Section 3.1.2 for randomization stratification factors.

The procedure for using IXRS is as follows:

- The investigator or designee contacts the IXRS and provides the SID number and subject's baseline characteristic(s) used to verify that it is the same subject
- The IXRS assigns a cohort (Phase 1b) or treatment arm (Phase 2) and investigational product to the subject
- Confirmation of this information is sent to the investigator/designee who dispenses the investigational product to the subject per the communication and records the appropriate information in the subject's medical records and investigational product accountability log

Investigational product (MEDI-573) must be administered within 24 hours of investigational product assignment. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified immediately.

4.4 Blinding

This study is not blinded.

4.5 Study Treatment

4.5.1 Investigational Products

Investigational product will be distributed to clinical sites using designated distribution centers. MedImmune will provide the investigator(s) with adequate quantities of investigational product. MEDI-573 must be stored at 2°C to 8°C (36°F to 46°F) in the original container and must not be frozen.

MEDI-573: [redacted]

Diluent: [redacted]

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

4.5.2 Other Study Medications

Subjects will receive an AI during this study. The AI will be purchased locally from a supplier chosen by the site, with reimbursement by MedImmune as appropriate. If reimbursement is required, MedImmune will reimburse up to the end of study as defined in Section 4.8. Labeling information for the AI should be kept on file. The 3 AIs (anastrozole, letrozole, and exemestane) that will serve as standard background therapy options are commercially available and are supplied as oral formulations. The AIs are supplied in tablet form for oral administration. Standard practice and local prescribing information should be followed. Subjects will be provided with a diary in which to record their intake of AI (an example of the diary is provided in Appendix 3). This information will be recorded in the case report form.

4.5.3 Treatment Regimens

4.5.3.1 Phase 1b

In Phase 1b, all subjects will be treated with MEDI-573 at doses of [redacted] (as a 60-minute IV infusion), [redacted] or [redacted] (as a 90 minute IV infusion) on Day 1 in combination with an AI of the investigator's choice orally once daily. MEDI-573 will be administered at an every 21-day treatment cycle along with daily AI until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal (see Section 4.2.3). Rules for dose evaluation are described in Section 4.5.6. Dose modification for toxicities will be allowed as described in Section 4.5.8. Nonevaluable subjects, as defined in Section 4.5.8.1, will be replaced in the same dose cohort. A summary of dose cohorts is provided in Table 4.5.3.1-1.

Table 4.5.3.1-1 Summary of Dose Cohorts

Dose Cohort	Number of Subjects	MEDI-573 Dose
A	3-6	[redacted] as a 60-minute (+ 20-minute) IV infusion on Day 1
B	3-6	[redacted] as a 90-minute (+ 20-minute) IV infusion on Day 1
C	3-6	[redacted] as a 90-minute (+ 20-minute) IV infusion on Day 1

4.5.3.2 Phase 2

Following Phase 1b as described in Section 4.5.6, approximately 178 subjects with MBC will be randomly assigned to receive either MEDI-573 and an AI or single-agent AI. Subjects in

Phase 2 will be treated with one of the following regimens, depending on treatment assignment (see Section 4.5.6 for dose evaluation rules):

Arm 1: MEDI-573 [redacted] mg/kg IV infusion on Day 1 of each 21-day cycle

AI (investigator's choice) orally once daily

Arm 2: AI (investigator's choice) orally once daily

Subjects will be treated with the assigned regimen until documentation of PD, initiation of alternative anticancer therapy, unacceptable toxicity, or another reason for treatment discontinuation (see Section 4.5.8) is observed.

Each new cycle will begin 21 days after the first day of the previous cycle. Subjects who do not receive the required dose of MEDI-573 (Arm 1) within a cycle will not advance to the next cycle of MEDI-573 and will be removed from treatment with MEDI-573. In Phases 1b and 2 of the study, all visits during Cycle 2 and subsequent visits may occur in a ± 2-day window to accommodate schedule changes, but doses of MEDI-573 must not occur more frequently than every 21 days.

4.5.3.3 Investigational Product Preparation

The dose of investigational product for administration must be prepared by the Investigator's or site's designated investigational product manager using aseptic technique. The [redacted] drug product within each MEDI-573 vial will be reconstituted [redacted] for injection. To reconstitute the [redacted], slowly add [redacted] for injection to the vial. The vial should be tilted slightly and gently rotated or swirled for 30 seconds or until dissolution is complete. Do not shake or vigorously agitate the vial. This is a critical step to avoid prolonged foaming. Reconstituted MEDI-573 should stand undisturbed at room temperature for a minimum of 2 minutes until the solution clarifies. Total in-use storage time from reconstitution of MEDI-573 to the start of administration should not exceed 4 hours at room temperature. If in-use storage time exceeds this limit, a new dose must be prepared from a new vial or vials. MEDI-573 does not contain any preservatives, so any unused portion must be discarded.

MEDI-573 is compatible with an IV bag composed of polyolefin (ethylene and propylene) that is polyvinyl chloride (PVC)-free and di(2-ethylhexyl)phthalate (DEHP)-free; IV tubing composed of PVC that is DEHP-free; and a 0.2-µm in-line filter composed of polyethersulfone.

The dose of investigational product for IV administration must be prepared using aseptic technique. The volume (dose) of MEDI-573 will be calculated based on the subject's body weight (kg) (obtained prior to the administration of MEDI-573 on Day 1 of each treatment cycle) and the subject's dose level (mg). The dose volume of MEDI-573 will be calculated using the following formula:

Dose Volume (mL) = Dose Level (mg/kg) × Subject Weight (kg) ÷ Concentration (mg/mL)

[redacted]

MEDI-573 is prepared for administration by dilution into the appropriate volume of normal saline to a final volume of [redacted] depending on the dose level. To prepare the IV bag, the volume of normal saline equivalent to the calculated dose volume of MEDI-573 is removed from the IV bag, and then the calculated MEDI-573 dose volume is added to the IV bag containing the remaining saline.

4.5.4 Treatment Administration

The day of receipt of the first dose of investigational product is considered Day 1.

MEDI-573: MEDI-573 should be administered as a 60-minute (+ 20-minutes for potential overfill; for [redacted]) or 90-minute (+ 20-minutes for potential overfill; for [redacted] and [redacted] mg/kg doses) IV infusion. After the contents of the IV bag are fully administered, the IV line should be flushed with a volume of normal saline equal to the priming volume of the infusion set used. Subjects will be monitored during and after infusion with assessment of vital signs at the beginning of the infusion, at every 30 minutes (± 5 minutes) during the MEDI-573 infusion, at the end of infusion (± 10 minutes) and 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) after the end of infusion.

Since the compatibility of MEDI-573 with other IV medications and solutions, [redacted], is not known, the MEDI-573 solution should not be infused through an IV line in which other solutions or medications are being administered. The date, start time, and completion time of MEDI-573 administration must be recorded in the source documents.

Aromatase Inhibitor of Investigator's Choice: Letrozole, anastrozole, or exemestane will be dispensed per investigator's choice. Standard practice and local prescribing information should be followed. Letrozole, anastrozole, and exemestane are commercially available and are supplied in tablet form for oral administration.

4.5.5 Monitoring of Dose Administration

All subjects in Phases 1b and 2 will be monitored during and after infusion with assessment of vital signs (temperature, respiratory rate, pulse, and blood pressure) at the start of MEDI-573 infusion, at every 30 minutes (± 5 minutes) during the MEDI-573 infusion, at the completion of the infusion (± 10 minutes), and 30 and 60 minutes (± 5 minutes) after completion of the MEDI-573 infusion.

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis.

In the event of an infusion-related reaction, the infusion of MEDI-573 may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. Acetaminophen 650 mg and/or an antihistamine (eg, diphenhydramine 50 mg) or equivalent medications per institutional standard may be administered. Alternatively, or in addition, the rate of infusion of MEDI-573 may be diminished at the discretion of the investigator. Any such activities must be recorded appropriately. If the infusion reaction is severe or prolonged, methylprednisolone 100 mg (or the equivalent) should be administered as well.

For subsequent infusions in subjects who experience an infusion reaction and do not require discontinuation of MEDI-573, acetaminophen 650 mg and/or an antihistamine (eg, diphenhydramine 50 mg) or equivalent medications per institutional standard will be administered prior to all subsequent infusions with MEDI-573. If the infusion reaction is severe or prolonged, glucocorticoids (methylprednisolone 100 mg [or the equivalent]) should be administered 30 minutes prior to the initiation of MEDI-573 infusion, or by standard institutional practice.

At the discretion of the investigator, appropriate medical therapy may also be administered per institutional standard for management of allergic or infusion reactions.

4.5.6 Phase 1b (Dose-evaluation Phase)

Three dose levels of MEDI-573 will be evaluated in combination with AI during Phase 1b. Rules for dose evaluation are as follows:

1. Dosing will be administered according to the standard 3 + 3 design, beginning with the [redacted] group (Cohort A) and followed by the [redacted]g (Cohort B) and [redacted] (Cohort C) groups sequentially. Dosing in each group will occur every 21 days. If no DLTs are observed in the initial 3 evaluable subjects, dose evaluation will continue with the next cohort.
2. If 1 of 3 subjects within a cohort experiences a DLT, that cohort will be expanded to a total of 6 subjects. If no additional subjects in a cohort experience a DLT through the first 21 days of administration of MEDI-573 and an AI, dose evaluation will continue with the next cohort.
3. If ≥ 2 subjects within a specific dose cohort experience a DLT during the DLT evaluation period, the MTD will be exceeded and study enrollment will temporarily stop. Pharmacokinetic and response data of subjects treated at representative dose levels will be analyzed to determine if a lower MEDI-573 dose may achieve target serum concentrations and/or if a weekly dosing schedule would be appropriate. Three to 6 additional subjects may be enrolled to explore this alternate dose and/or schedule.
4. If 0 of 3 or no more than 1 of 6 subjects in any cohort experiences a DLT through the first 21 days of administration of MEDI-573 and an AI, enrollment into Phase 2 may begin. Dosing in Phase 2 will begin simultaneously in both treatment arms.

A study-specific safety committee will provide ongoing safety surveillance throughout the study, with regularly scheduled reviews of safety and other relevant data. This committee will be responsible for decisions regarding the initiation of the randomization phase and making recommendations regarding further conduct of the study. This committee will also review data at other time points in response to AEs assessed as medically relevant by the medical monitor, and will communicate outcomes and decisions to the MedImmune SMC. Safety outcomes will be evaluated on a quarterly basis by the SMC to identify any nascent safety concerns.

4.5.7 Phase 2 (Randomization Phase)

Following Phase 1b, 178 subjects with HR+, HER2-negative MBC will be randomized to one of 2 arms to receive either the combination of MEDI-573 at [redacted] mg/kg with an AI, or an AI alone, in order to evaluate in more detail the safety profile and antitumor activity of the combination.

4.5.8 Management of Toxicities, Dose Reductions and Dose Delays

No dose modification is allowed for MEDI-573. Following the DLT period (Phase 1b) and starting with Cycle 2 in Phase 2, dosing of MEDI-573 may be delayed or discontinued based on hematologic and nonhematologic toxicities observed during each subsequent cycle of treatment as described in Table 4.5.8-1. Both hematologic and nonhematologic toxicities will be graded according to the NCI CTCAE v4.0. Standard practice and local prescribing information should be followed to manage AI-related toxicities.

Adverse events for which a cause other than MEDI-573 or the AI can be clearly attributed (such as an accident) will not require a dose delay.

Subjects with allergic or infusion reactions of Grade 3 or higher will permanently discontinue MEDI-573. Allergic or infusion reactions at or below Grade 2 that respond to medical therapy or slowing the infusion rate and are of limited duration will not necessitate dose interruption or discontinuation; however, any such events that necessitate the use of systemic pressor agents will result in dose discontinuation. Dosing will not be interrupted or discontinued for a Grade 2 laboratory toxicity that does not represent deterioration since study entry.

Table 4.5.8-1 MEDI-573 Dose Delays or Discontinuation for Toxicity

Hematologic or Nonhematologic Toxicity	Schedule Adjustment
Grade 1	• No change (resume MEDI-573 at the current dose level)
Grade 2 [a]	• If resolution to ≤ Grade 1 or baseline occurs within 21 days of the previous dose, resume MEDI-573 at the current dose level. • If resolution to ≤ Grade 1 or baseline does not occur within 21 days of previous dose, MEDI-573 will be discontinued unless toxicity is clearly attributable to another cause. • Grade 2 laboratory toxicities that do not have clinical significance may not require dose delay. The medical monitor should be consulted in the event of Grade 2 laboratory toxicities that are deemed clinically insignificant to determine if dosing may continue. • If toxicities cause a cumulative delay of ≥ 21 days in 3 consecutive cycles, MEDI-573 will be discontinued.

Table 4.5.8-1 MEDI-573 Dose Delays or Discontinuation for Toxicity

Hematologic or Nonhematologic Toxicity	Schedule Adjustment
Grade 3 or 4 [b]	• If resolution to ≤ Grade 1 or baseline occurs within 21 days of the previous dose, resume MEDI-573 at the current dose level. • If resolution to ≤ Grade 1 or baseline does not occur within 21 days of the previous dose, MEDI-573 will be discontinued. • If resolution to ≤ Grade 1 or baseline occurs within 21 days of the previous dose and the subject has not achieved some degree of clinical benefit while on MEDI-573 therapy, MEDI-573 will be discontinued.

[a] Allergic or infusion reactions at or below Grade 2 that respond to medical therapy or slowing the infusion rate and are of limited duration will not necessitate dose interruption or discontinuation; however, any such events that necessitate the use of systemic pressor agents will result in dose discontinuation. Dosing will not be interrupted or discontinued for a Grade 2 laboratory toxicity that does not represent deterioration since study entry.

[b] Subjects with allergic or infusion reactions of Grade 3 or higher will permanently discontinue MEDI-573.

4.5.8.1 Dose-limiting Toxicity

The period for evaluating DLTs in Phase 1b will be defined as Cycle 1, Day 1 through Day 21. Subjects who do not receive 1 full cycle of MEDI-573 for reasons other than DLT will be replaced at the same dose level. Grading of DLTs will be according to the NCI CTCAE v4.0 (Appendix 5).

All AEs that are suspected of having a causal relationship to MEDI-573 and are ≥ Grade 3 in severity are considered DLTs. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT. Any such events occurring during Cycle 1 of Phase 2 will be considered to be DLT-like events and will contribute to the study-stopping rule described in Section 3.3.

4.5.9 Treatment Compliance

Investigational product (MEDI-573) is administered by study site personnel who will monitor compliance.

4.6 Concomitant Medications

4.6.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care.

Bisphosphonate, denosumab or calcitonin treatment established 2 weeks or more prior to randomization is allowed for the management of hypercalcemia, bone pain and/or

osteoporosis. After Cycle 1, Day 21, such therapy may be initiated for the management of hypercalcemia, bone pain and/or osteoporosis, but not for the prevention of bone metastasis. Palliative radiotherapy for bone pain is acceptable, provided that the radiated area does not overlap with that of the target lesions.

Ongoing ovarian suppression with a depot luteinizing hormone-releasing hormone agonist is allowed if initiated 2 weeks prior to entry into the study. Subjects who have been treated previously with depot luteinizing hormone-releasing hormone analogues must have received their last dose ≥ 12 months prior to randomization.

All concomitant medications given to the subject from the time the subject signs the informed consent form through 60 days after the last study treatment will be recorded on the source document. The sponsor must be notified if any subject receives any prohibited concomitant medications as outlined above or in Section 4.2.2.

4.6.2 Excluded Concomitant Medications

Subjects may receive medications as supportive care or to treat AEs as deemed necessary by the investigator or the subject's physician.

4.7 Subject Completion

An individual subject will be considered to have completed the study if the subject was followed until the end of the study as defined in Section 4.8, regardless of the number of doses of investigational product received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.2.3).

4.8 End of the Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study. Per the original protocol, this date was to be up to 36 months from the date the last subject was entered into the trial or earlier at the discretion of the sponsor. As of 10Jul2016, this milestone will have been met. All follow-up for any subjects that have discontinued treatment by 10Jul2016 (whether or not they have progressed), will end, as per the original protocol, 36 months after the last subject was entered into the study. However, as of Amendment 3, subjects still on treatment at that time will be allowed to continue treatment until they meet one of the criteria for treatment discontinuation. Once treatment discontinues,

the subject will be followed for 60 days as described in Section 5.1.4. The end of the study will therefore be when the last subject still on treatment as of 10Jul2016 finishes the 60-day (+/- 3 days) safety follow-up following treatment discontinuation.

All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon study completion, as directed by the site monitor. The investigator will notify the IRB/IEC when the study has been completed.

5 STUDY PROCEDURES

5.1 Schedule of Study Procedures

All subjects who are assigned an SID number and receive any investigational product will be followed according to the protocol regardless of the number of doses received, unless consent is withdrawn. The investigator must notify the sponsor or designee of deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule. Protocol deviations will be recorded on the source document with an explanation for the deviation. The investigator must comply with the applicable requirements related to the reporting of protocol deviations to the IRB/IEC.

Subjects/legal representatives will be instructed to call study personnel to report any abnormalities during the intervals between study visits and to come or to bring the subject to the study site if medical evaluation is needed and the urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator and made available to the sponsor or designee during monitoring visits.

The schedules of study procedures for the screening and treatment periods are provided in Table 5.1-1 and Table 5.1-2, and those for the follow-up period are provided in Table 5.1-3 and Table 5.1-4. A description of the study procedures is provided in Section 5.2.

Table 5.1-1 Schedule of Subject Evaluations: Screening and Treatment Periods - All Subjects Unless Otherwise Specified (not applicable for subjects continuing on treatment under Amendment 3)

Evaluation	Screening	Cycle 1				Cycle 2 and Every Cycle Thereafter	Every 9 Weeks (-7 days) through 24 months post study entry	Every 6 months (± 7 Days) > 24 months post study entry	End of Treatment
	Day -30 through Day -1	Day 1	Day 2 (Phase 1b only)	Day 8	Day 15 (± 2 days)	Day 1 (± 2 days)			
Written Informed Consent and HIPAA (where applicable)	X								
Assignment of SID number	X								
Medical History	X								
[redacted]	X								
Protocol/Safety Evaluations									
[redacted]	X	X				X			X
Serum βHCG	X								
Urine or Serum pregnancy test		X				X			X
Physical Examination	X	X				X			X
Height	X								
Weight (-2 days is acceptable)	X	X				X			X
Vital Signs	X	X				X			X
12-lead ECG	X	X				X			X
AE/SAE Assessment	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X

Table 5.1-1 Schedule of Subject Evaluations: Screening and Treatment Periods - All Subjects Unless Otherwise Specified (not applicable for subjects continuing on treatment under Amendment 3)

Evaluation	Screening	Cycle 1				Cycle 2 and Every Cycle Thereafter	Every 9 Weeks (-7 days) through 24 months post study entry	Every 6 months (± 7 Days) > 24 months post study entry	End of Treatment
	Day -30 through Day -1	Day 1	Day 2 (Phase 1b only)	Day 8	Day 15 (± 2 days)	Day 1 (± 2 days)			
Karnofsky Performance Status	X	X				X			X
[redacted]	X	X				X			X
Study Entry (Phase 1b)/Randomization (Phase 2) and Treatment									
Verify Eligibility Criteria	X	X							
Study Entry (Phase 1b)/ Randomization (Phase 2)		X							
MEDI-573 Administration (Phase 1b and Phase 2; Arm 1. Dose interval no shorter than 21 days)		X				X			
AI Administration (Once daily throughout treatment period)		X	X	X	X	X	X	X	
Laboratory Evaluations									
Hematology	X	X		X	X	X			X
Hemoglobin A1c	X								X
Serum Chemistry	X	X		X	X	X			X
Urinalysis	X	X		X		X			X
MEDI-573 serum concentration (Phase 1b and Phase 2; Arm 1)		X	X	X	X	X			X

Table 5.1-1 Schedule of Subject Evaluations: Screening and Treatment Periods - All Subjects Unless Otherwise Specified (not applicable for subjects continuing on treatment under Amendment 3)

Evaluation	Screening	Cycle 1				Cycle 2 and Every Cycle Thereafter	Every 9 Weeks (-7 days) through 24 months post study entry	Every 6 months (± 7 Days) > 24 months post study entry	End of Treatment
	Day -30 through Day -1	Day 1	Day 2 (Phase 1b only)	Day 8	Day 15 (± 2 days)	Day 1 (± 2 days)			
Anti-MEDI-573 Antibodies (Phase 1b and Phase 2; Arm 1)		X				X			X
[redacted]	X	X		X		X			X
[redacted]		X		X	X	X			X
[redacted]	X	X		X		X			X
[redacted]	X			X		X			X
DNA Sample (optional)		X							
Archived Tumor Sample, if available (consent required)	X								
Tumor Measurements									
CXR, CT or MRI Scans (see Section 5.2.6.1 for detailed evaluation schedule)	X						X	X	X

AE = adverse event; AI = aromatase inhibitor; βhCG = beta human chorionic gonadotropin; CT = computed tomography; CXR = chest x-ray; ECG = electrocardiogram; [redacted]; HIPAA = Health Insurance Portability and Accountability Act; IGF = insulin-like growth factor; MRI = magnetic resonance imaging; SAE= serious adverse event; SID = subject identification

Table 5.1-2 Schedule of Subject Evaluations: Screening and Treatment (Subjects continuing treatment under Amendment 3 only)

Evaluation	Screening	Cycle 1				Cycle 2 and Every Cycle Thereafter	Every 9 Weeks (± 7 days) post study entry	Every 6 months (± 7 Days) > 24 months post study entry	End of Treatment
	Day -30 through Day -1	Day 1	Day 2 (Phase 1b only)	Day 8	Day 15 (± 2 days)	Day 1 (± 5 days)			
Written Informed Consent and HIPAA (where applicable)	X								
Assignment of SID number	X								
Medical History	X								
[redacted]	X								
Protocol/Safety Evaluations									
[redacted]	X	X							
Serum βHCG	X								
Urine or Serum pregnancy test		X					X		X
Physical Examination	X	X				X			X
Height	X								
Weight (-2 days is acceptable)	X	X				X			X
Vital Signs	X	X				X	`		X
12-lead ECG	X	X							X

Table 5.1-2 Schedule of Subject Evaluations: Screening and Treatment (Subjects continuing treatment under Amendment 3 only)

Evaluation	Screening	Cycle 1				Cycle 2 and Every Cycle Thereafter	Every 9 Weeks (± 7 days) post study entry	Every 6 months (± 7 Days) > 24 months post study entry	End of Treatment
	Day -30 through Day -1	Day 1	Day 2 (Phase 1b only)	Day 8	Day 15 (± 2 days)	Day 1 (± 5 days)			
AE/SAE Assessment	X	X	X	X	X	X			X
Concomitant Medications	X	X	X	X	X	X			X
Karnofsky Performance Status	X	X				X			X
[redacted]	X	X							
Study Entry (Phase 1b)/Randomization (Phase 2) and Treatment									
Verify Eligibility Criteria	X	X							
Study Entry (Phase 1b)/ Randomization (Phase 2)		X							
MEDI-573 Administration (Phase 1b and Phase 2; Arm 1. Dose interval no shorter than 21 days)		X				X			
AI Administration (Once daily throughout treatment period)		X	X	X	X	X			
Laboratory Evaluations									
Hematology	X	X		X	X		X		X
Hemoglobin A1c	X								
Serum Chemistry	X	X		X	X		X		X
Urinalysis	X	X		X			X		X

Table 5.1-2 Schedule of Subject Evaluations: Screening and Treatment (Subjects continuing treatment under Amendment 3 only)

Evaluation	Screening	Cycle 1				Cycle 2 and Every Cycle Thereafter	Every 9 Weeks (± 7 days) post study entry	Every 6 months (± 7 Days) > 24 months post study entry	End of Treatment
	Day -30 through Day -1	Day 1	Day 2 (Phase 1b only)	Day 8	Day 15 (± 2 days)	Day 1 (± 5 days)			
MEDI-573 serum concentration (Phase 1b and Phase 2; Arm 1)		X	X	X	X				
Anti-MEDI-573 Antibodies (Phase 1b and Phase 2; Arm 1)		X							
[redacted]	X	X		X					
[redacted]		X		X	X				
[redacted]	X	X		X					
[redacted]s	X			X					
DNA Sample (optional)		X							
Archived Tumor Sample, if available (consent required)	X								
Tumor Measurements									
CXR, CT or MRI Scans (see Section 5.2.6.1 for detailed evaluation schedule)	X							X	X

Table 5.1-2 Schedule of Subject Evaluations: Screening and Treatment (Subjects continuing treatment under Amendment 3 only)

Evaluation	Screening	Cycle 1				Cycle 2 and Every Cycle Thereafter	Every 9 Weeks (± 7 days) post study entry	Every 6 months (± 7 Days) > 24 months post study entry	End of Treatment
	Day -30 through Day -1	Day 1	Day 2 (Phase 1b only)	Day 8	Day 15 (± 2 days)	Day 1 (± 5 days)			

AE = adverse event; AI = aromatase inhibitor; βhCG = beta human chorionic gonadotropin; CT = computed tomography; CXR = chest x-ray; ECG = electrocardiogram; [redacted] HIPAA = Health Insurance Portability and Accountability Act; IGF = insulin-like growth factor; MRI = magnetic resonance imaging; SAE= serious adverse event; SID = subject identification

Table 5.1-3 Schedule of Study Procedures: Follow-up Period- All Subjects Unless Otherwise Specified (not applicable for subjects continuing on treatment under Amendment 3)

All Treatment Arms	Follow-up/Posttherapy			
	30 Days Post Last Dose (± 3 days)and 60 Days Post Last Dose (± 5 days)	Every 9 weeks (± 7 Days) Post Last Dose for Subjects Without PD through 24 months posttreatment	Every 3 months Post Last Dose(± 7 Days)	Every 6 months Post Last Dose (± 7 Days) > 24 months posttreatment for Subjects Without PD
Physical examination	X	X		
Vital signs	X			
12-lead ECG	X (30 days post visit only)			
Weight	X			
Hematology	X			
Serum chemistry	X			
Urinalysis	X			
AE/SAE assessment	X			
Concomitant medications	X			

Table 5.1-3 Schedule of Study Procedures: Follow-up Period- All Subjects Unless Otherwise Specified (not applicable for subjects continuing on treatment under Amendment 3)

All Treatment Arms	Follow-up/Posttherapy			
	30 Days Post Last Dose (± 3 days)and 60 Days Post Last Dose (± 5 days)	**Every 9 weeks (± 7 Days) Post Last Dose for Subjects Without PD through 24 months posttreatment**	**Every 3 months Post Last Dose(± 7 Days)**	**Every 6 months Post Last Dose (± 7 Days) > 24 months posttreatment for Subjects Without PD**
Subsequent anticancer therapy		X	X	
Karnofsky Performance Status	X	X		
Survival status		X	X	
MEDI-573 Serum Concentration (Phase 1b and Phase 2; Arm 1)	X		X (first 3-month visit only)	
Anti-MEDI-573 antibodies (Phase 1b and Phase 2; Arm 1)	X		X (first 3-month visit only)	
[redacted]	X			
[redacted]	X			
CXR, CT or MRI Scans (see Section 5.2.6.1 for detailed long term follow up schedule)		X		X

AE = adverse event; CT = computed tomography; CXR = chest x-ray; ECG = electrocardiogram; IGF = insulin-like growth factor; MRI = magnetic resonance imaging; PD = progressive disease

Table 5.1-4 Schedule of Study Procedures: Follow-up Period (Subjects continuing treatment under Amendment 3 only)

All Treatment Arms	Follow-up/Posttherapy
	30 Days Post Last Dose (± 3 days)and 60 Days Post Last Dose (± 5 days)
Physical examination	X
Vital signs	X
12-lead ECG	X (30 days post visit only)
Weight	X
Hematology	X
Serum chemistry	X
Urinalysis	X (30 days post visit only)
AE/SAE assessment	X
Concomitant medications	X
Subsequent anticancer therapy	X
Karnofsky Performance Status	X
Survival status	
MEDI-573 Serum Concentration (Phase 1b and Phase 2; Arm 1)	X
Anti-MEDI-573 antibodies (Phase 1b and Phase 2; Arm 1)	X
[redacted]	
[redacted] (see Section 7.3.3)	
CXR, CT or MRI Scans (see Section 5.2.6.1 for detailed long term follow up schedule)	

AE = adverse event; CT = computed tomography; CXR = chest x-ray; ECG = electrocardiogram; IGF = insulin-like growth factor; MRI = magnetic resonance imaging; PD = progressive disease

5.1.1 Screening (All Subjects Unless Otherwise Specified)

All screening procedures must be performed within 30 days before study entry/randomization, unless otherwise specified. The screening evaluations may be carried out over more than one visit. Written informed consent and any locally required authorization (eg, HIPAA in the US, EU Data Privacy Directive authorization in the EU) must be obtained prior to performing any protocol-specific procedures, including screening evaluations.

1. Obtain written informed consent and appropriate privacy act document authorization
2. Assign an SID number via IXRS
3. Verify eligibility criteria, including review of lab results
4. [redacted]

b. [redacted]

5. Obtain medical history
6. Perform a complete physical examination
7. Record height
8. Record weight
9. Record vital signs
10. Assess KPS
11. Obtain 12-lead electrocardiogram (ECG) as described in Section 5.2.1.
12. Collect blood for screening samples:
    - Serum chemistry
    - Hematology
    - Hemoglobin A1c
    - Beta human chorionic gonadotropin (βhCG) serum pregnancy test (women of childbearing potential)
    - [redacted]
    - [redacted]
    - [redacted]
13. Collect urinalysis sample
14. Collect archive tumor sample, where available
15. [redacted]
16. Perform chest x-ray (CXR), computed tomography (CT), or magnetic resonance imaging (MRI) scan
17. Assess for AEs and serious adverse events (SAEs)
18. Record concomitant medications

5.1.2 Treatment Period

5.1.2.1 Cycle 1, Day 1 (All Subjects Unless Otherwise Specified)

Note that any assessments performed within 24 hours prior to dosing may be used for Cycle 1, Day 1 assessments.

1. Verify eligibility criteria, including review of lab results
2. Study entry (Phase 1b)/randomization (Phase 2) in IXRS
3. [redacted]
   a. [redacted]
   b. [redacted]
4. Perform directed physical examination
5. Record weight

6. Record pretreatment vital signs
7. Assess KPS
8. Update concomitant medications
9. Collect urine or serum for pregnancy test (women of childbearing potential); ensure result is negative pretreatment
10. Collect urinalysis sample
11. Collect blood for baseline samples prior to treatment:
    - Serum chemistry
    - Hematology
    - MEDI-573 serum concentration (Phase 1b and Phase 2; Arm 1)
    - Anti-drug antibodies (Phase 1b and Phase 2; Arm 1)
    - [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
12. Perform 12-lead ECG prior to treatment as described in Section 5.2.1 (Phase 1b and Phase 2, Arm 1)
13. Infuse MEDI-573 (Phase 1b and Phase 2; Arm 1)
14. Collect blood after infusion of MEDI-573 (Phase 1b and Phase 2; Arm 1)
    - MEDI-573 serum concentration (immediately postinfusion [± 5 minutes])
    - [redacted]
15. Record posttreatment vital signs (Phase 1b and Phase 2; Arm 1)
    - 30 minutes [± 5 minutes] after the start of MEDI-573 infusion
    - 60 minutes [± 5 minutes] after the start of MEDI-573 infusion
    - At the end of infusion [±10 minutes]
    - 30 minutes [± 5 minutes] postinfusion
    - 60 minutes [± 5 minutes] postinfusion
16. Perform 12-lead posttreatment ECG (Phase 1b and Phase 2, Arm 1) as described in Section 5.2.1
17. Start daily AI treatment, continued throughout the treatment period.
18. Assess for AEs and SAEs throughout the treatment period
19. Update concomitant medications, as needed

5.1.2.2 Cycle 1, Day 2 (For Phase 1b only)

1. Continue daily AI administration throughout treatment period
2. Collect blood
    - MEDI-573 serum concentration (24 ± 2 hours post-Day 1 infusion)
3. Assess for AEs and SAEs

4. Update concomitant medications

5.1.2.3 Cycle 1, Day 8 (All Subjects Unless Otherwise Specified)

1. Collect urinalysis sample
2. Collect blood
   - Serum chemistry
   - Hematology
   - MEDI-573 serum concentration (Phase 1b and Phase 2; Arm 1)
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
3. Assess for AEs and SAEs
4. Update concomitant medications
5. Continue daily AI administration throughout treatment period

5.1.2.4 Cycle 1, Day 15 (Plus/Minus 2 Days, All Subjects Unless Otherwise Specified)

1. Assess for AEs and SAEs
2. Update concomitant medications
3. Collect blood
   - Serum chemistry
   - Hematology
   - MEDI-573 serum concentration (Phase 1b and Phase 2 Arm 1)
   - [redacted] (see Section 7.3.3)
4. Continue daily AI administration throughout the treatment period

5.1.2.5 Cycle 2 and Every Cycle Thereafter, Day 1 (Plus/Minus 2 Days, All Subjects Unless Otherwise Specified)

For subjects continuing on treatment under Amendment 3, please refer to Section 5.1.2.5.1 for applicable study related procedures.

Note that any assessments performed within 24 hours prior to dosing may be used for Cycle 1, Day 1 assessments.

1. [redacted]
   a. [redacted]
   b. [redacted]

2. Perform directed physical examination
3. Record weight
4. Record pretreatment vital signs
5. Assess KPS
6. Collect urine or serum for pregnancy test (women of childbearing potential); ensure result is negative pretreatment
7. Collect urinalysis sample
8. Perform 12-lead ECG prior to treatment (Phase 1b and Phase 2, Arm 1) as described in Section 5.2.1
9. Collect pretreatment blood samples:
    - Serum chemistry
    - Hematology
    - MEDI-573 serum concentration (Phase 1b and Phase 2 Arm 1)
    - Anti-drug antibodies (Phase 1b and Phase 2 Arm 1)
    - [redacted]
    - [redacted] (see Section 7.3.3)
    - [redacted]
    - [redacted]
10. Infuse MEDI-573 (Phase 1b and Phase 2 Arm 1)
11. Collect blood after infusion of MEDI-573 (Phase 1b and Phase 2; Arm 1)
    - MEDI-573 serum concentration (immediately postinfusion [± 5 minutes])
    - [redacted]
12. Record posttreatment vital signs (Phase 1b and Phase 2: Arm 1)
    - 30 minutes [± 5 minutes] after the start of MEDI-573 infusion
    - 60 minutes [± 5 minutes] after the start of MEDI-573 infusion
    - At the end of infusion [± 10 minutes]
    - 30 minutes [± 5 minutes] postinfusion
    - 60 minutes [± 5 minutes] postinfusion
13. Perform 12-lead ECG post-dose (Phase 1b and Phase 2, Arm 1)
14. Continue daily AI treatment
15. Assess for AEs and SAEs
16. Update concomitant medications, as needed

5.1.2.5.1 Every Cycle, Day 1 (± 5 Days) (For subjects continuing on treatment under Amendment 3 only)

1. Perform symptom-directed physical examination
2. Record weight
3. Record pretreatment vital signs
4. Infuse MEDI-573 (Phase 1b and Phase 2 Arm 1) every cycle (Q21D)

5. Record posttreatment vital signs (Phase 1b and Phase 2: Arm 1)
   a. 30 minutes [± 5 minutes] after the start of MEDI-573 infusion
   b. 60 minutes [± 5 minutes] after the start of MEDI-573 infusion
   c. At the end of infusion [± 10 minutes]
   d. 30 minutes [± 5 minutes] postinfusion
   e. 60 minutes [± 5 minutes] postinfusion
6. Continue daily AI treatment
7. Assess for AEs and SAEs
8. Update concomitant medications, as needed
9. Assess KPS

5.1.2.6 Every 9 Weeks Minus 7 Days (All Subjects) Through 24 Months Post Study Entry

For subjects continuing on treatment under Amendment 3, please refer to Section 5.1.2.6.1 for applicable study related procedures.

1. Assess for AEs and SAEs
2. Update concomitant medications
3. Perform CXR, CT, or MRI scan (complete within 7 days prior to start of next cycle, see Section 5.2.6.1 for detailed schedule)
4. Continue daily AI treatment

5.1.2.6.1 Every 9 Weeks (± 7 Days) Post Study Entry unless otherwise specified (For subjects continuing on treatment under Amendment 3 only)

1. Collect pretreatment blood samples (continue until End of Treatment):
   a. Serum chemistry
   b. Hematology
2. Collect urine or serum for pregnancy test (women of childbearing potential); ensure result is negative pretreatment (continue until End of Treatment)
3. Collect urinalysis sample

5.1.2.7 Every 6 Months Plus/Minus 7 Days, Beginning > 24 Months Post Study Entry (All Subjects)

For subjects continuing on treatment under Amendment 3, please refer to Section 5.1.2.7.1 for applicable study related procedures.

1. Assess for AEs and SAEs
2. Update concomitant medications

3. Perform CXR, CT, or MRI scan (complete within 7 days prior to start of next cycle, see Section 5.2.6.1 for detailed schedule)
4. Continue daily AI treatment

5.1.2.7.1 Every 6 Months (± 7 Days), Beginning > 24 Months Post Study Entry (For subjects continuing on treatment under Amendment 3 only)

1. Perform CXR, CT, or MRI scan (complete within 7 days prior to start of next cycle, see Section 5.2.6.1 for detailed schedule)

5.1.3 End-of-Treatment Visit (All Subjects Unless Otherwise Specified)

For subjects continuing on treatment under Amendment 3, please refer to Section 5.1.3.1 for applicable study related procedures.

1. [redacted]
   a. [redacted]
   b. [redacted]
2. Perform a complete physical exam
3. Record weight
4. Record vital signs
5. Assess KPS
6. Obtain 12-lead ECG as described in Section 5.2.1
7. Collect blood
   - Serum chemistry
   - Hematology
   - Hemoglobin A1c
   - MEDI-573 serum concentration (Phase 1b and Phase 2 Arm 1)
   - Anti-drug antibodies (Phase 1b and Phase 2 Arm 1)
   - [redacted]
   - [redacted]
   - [redacted]
   - [redacted]
8. Collect urine or serum for pregnancy test (women of childbearing potential)
9. Collect urinalysis sample
10. Assess for AEs and SAEs
11. Update concomitant medications
12. Perform CXR, CT, or MRI scan (unless it has been performed within 14 days of treatment discontinuation)

5.1.3.1 End-of-Treatment Visit (For subjects continuing on treatment under Amendment 3 only)

1. Perform a symptom-directed physical exam
2. Record weight
3. Record vital signs
4. Obtain 12-lead ECG as described in Section 5.2.1
5. Collect blood
   a. Serum chemistry
   b. Hematology
6. Collect urine or serum for pregnancy test (women of childbearing potential)
7. Collect urinalysis sample
8. Assess for AEs and SAEs
9. Update concomitant medications
10. Assess KPS
11. Perform CXR, CT, or MRI scan (complete within 7 days prior to start of next cycle, see Section 5.2.6.1 for detailed schedule)

5.1.4 Posttreatment Follow-up Period

The reporting period for AEs/SAEs is the period immediately following the time that written informed consent is obtained through 60 days after the last dose of MEDI-573 or until the subject begins another anticancer therapy, whichever occurs first. New (nonserious) AEs that start after the reporting period will not be collected. All AEs/SAEs will be followed to resolution through the end of subject participation in the study, even if the date extends beyond the reporting period.

5.1.4.1 30 Days (Plus/Minus 3 Days) and 60 Days (Plus/Minus 5 Days) Posttreatment (All Subjects Unless Otherwise Specified)

For subjects continuing on treatment under Amendment 3, please refer to Section for 5.1.4.1.1 applicable study related procedures.

1. Perform directed physical exam
2. Record weight
3. Record vital signs
4. Assess KPS
5. Perform 12-lead ECG (at 30 days after visit only) as described in Section 5.2.1
6. Collect blood
   - Serum chemistry
   - Hematology

- MEDI-573 serum concentration (Phase 1b and Phase 2 Arm 1)
- Anti-MEDI-573 antibodies (Phase 1b and Phase 2 Arm 1)
- [redacted]
- [redacted]

7. Collect urinalysis sample
8. Assess for AEs and SAEs
9. Update concomitant medications

5.1.4.1.1 30 Days (± 3 Days) and 60 Days (± 5 Days) Posttreatment (For subjects continuing on treatment under Amendment 3 only)

1. Perform directed physical exam
2. Record weight
3. Record vital signs
4. Collect blood
   a. Serum chemistry
   b. Hematology
   c. MEDI-573 serum concentration (Phase 1b and Phase 2, Arm 1)
5. Collect urinalysis sample (at 30 Days Post Last Dose visit only)
6. Obtain 12-lead ECG as described in Section 5.2.1 (30 day posttreatment visit only)
7. Record any subsequent anticancer therapy
8. Anti-MEDI-573 antibodies (Phase 1b and Phase 2, Arm 1)
9. Assess for AEs and SAEs
10. Assess KPS
11. Update concomitant medications

5.1.4.2 Every 9 Weeks (Plus/Minus 7 Days) Posttreatment for Subjects Without Progressive Disease Through 24 Months Posttreatment

For subjects continuing on treatment under Amendment 3, there will be no additional assessments beyond those indicated at the 60 days posttreatment visit.

1. Perform directed physical exam
2. Assess KPS
3. Record subsequent anticancer therapy
4. Record survival status
5. Perform CXR, CT, or MRI scan (see Section 5.2.6.1 for detailed schedule)

5.1.4.3 Every 3 Months (Plus/Minus 7 Days) Posttreatment

For subjects continuing on treatment under Amendment 3, there will be no additional assessments beyond those indicated at the 60 days posttreatment visit.

1. Record subsequent anticancer therapy
2. Record survival status
3. Collect blood (first 3-month posttreatment visit only)
   - MEDI-573 serum concentration (performed only at first 3-month posttreatment visit; Phase 1b and Phase 2 Arm 1)
   - Anti-MEDI-573 antibodies (performed only at first 3-month posttreatment visit; Phase 1b and Phase 2 Arm 1)

5.1.4.4 Every 6 Months (Plus/Minus 7 Days) Posttreatment Beginning > 24 Months Post Study Entry For Subjects Without PD

For subjects continuing on treatment under Amendment 3, there will be no additional assessments beyond those indicated at the 60 days posttreatment visit.

1. Perform CXR, CT, or MRI scan (see Section 5.2.6.1 for detailed schedule)

5.2 Description of Study Procedures

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information.

5.2.1 Medical History, Physical Examination, Electrocardiogram, Weight and Vital Signs

A medical history will be recorded at Screening.

Complete physical examinations will be performed by a licensed independent healthcare provider (ie, physician, physician's assistant, or licensed nurse practitioner) as described in Table 5.1-1, Table 5.1-2, Table 5.1-3 and Table 5.1-4. Physical examinations will include an assessment of head, eyes, ears, nose and throat (HEENT), respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, and endocrine systems; and height (screening only). A directed physical exam will include assessment of only specific organ systems as appropriate based on the subject's complaints/symptoms and should be performed at the time points specified in Section 5.1.2.

Findings from medical history and physical exam shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to or below the pre-study grade (baseline).

A 12-lead ECG will be obtained for all subjects at screening, end of treatment, and 30 days posttreatment and for subjects enrolled in Phase 1b and Phase 2, Arm 1 only on Day 1 of each cycle (see Table 5.1-1, Table 5.1-2, Table 5.1-3 and Table 5.1-4). Prior to Amendment 3, the specific ECG collection times on Day 1 of each cycle for subjects enrolled in Phase 1b and Phase 2, Arm 1 are as follows: prior to infusion, at the time of completion of infusion (± 10 minutes), and 2 hours (± 15 minutes) post completion of infusion. For all subjects continuing treatment under Amendment 3, ECGs will no longer be collected during treatment but will still be collected at end of treatment and 30 days posttreatment. All ECGs should be done prior to PK draw for the corresponding time point. Electrocardiogram equipment, with instant print-out and electronic transmission capabilities, and training will be provided to all study sites. All ECGs performed during the study will be obtained in triplicate (ie, 3 ECGs should be obtained within a 5 minute time period). The ECGs will be transmitted and interpreted by a central vendor selected by the sponsor.

Vital signs will be collected as described in Table 5.1-1, Table 5.1-2, Table 5.1-3 and Table 5.1-4. Vital signs include temperature, blood pressure (seated), pulse rate, respiratory rate, and weight (where indicated). For subjects enrolled in Phase 1b and Phase 2, Arm 1, vital sign collection times are specified in Sections 5.1.1 and 5.1.2.

5.2.2 Clinical Laboratory Tests

Clinical laboratory safety tests for all study visits will be performed in a licensed clinical laboratory. Urine or serum pregnancy tests on Day 1 of each dosing period prior to MEDI-573 administration will be performed in the clinic using a licensed test for females of childbearing potential. Abnormal laboratory results that are deemed clinically significant by the investigator should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed (see Table 5.1-1 and Table 5.1-2 for the schedule of assessment for the Screening and Treatment Phases, Table 5.1-3 and Table 5.1-4 for the Follow-up Phase):

Serum Chemistry

• Calcium	• Blood urea nitrogen
• Chloride	• Uric acid
• Magnesium	• Creatinine
• Potassium	• Total bilirubin
• Sodium	• Glucose
• Aspartate transaminase	• Albumin
• Alanine transaminase	• Total protein
• Alkaline phosphatase	• Triglycerides
• Gamma glutamyl transferase	• Cholesterol
• Lactate dehydrogenase	

Hematology

• White blood cell count with differential	• Platelet count
• Red blood cell count	• Mean corpuscular volume
• Hematocrit	• Mean corpuscular Hb concentration
• Hemoglobin	• Hemoglobin A1c - performed only at Screening and End-of-Treatment visits

Urinalysis

• Color	• Glucose
• Appearance	• Ketones
• Specific gravity	• Blood
• pH	• Bilirubin
• Protein	• Microscopy including white blood cell/high-power field, red blood cell/high-power field

Pregnancy Test

• Urine human chorionic gonadotropin
• Serum βhCG (required at screening visit only. Serum βhCG or urine pregnancy test permitted at postscreening visits)

5.2.3 Pharmacokinetic Evaluation and Methods

An electrochemiluminescence (ECL) assay using a Meso Scale Discovery® (MSD) platform will be used for the quantitative determination of MEDI-573 in human serum. Blood samples for assessment of MEDI-573 serum concentrations will be collected as described in Section 5.1.

5.2.4 Immunogenicity Evaluation and Methods

[redacted]. Confirmed positive samples will be evaluated for the titer of ADA and will be archived for future testing in a neutralizing ADA assay. For all subjects receiving MEDI-573, the presence of anti-MEDI-573 antibodies will be assessed at the intervals specified in Section 5.1.

5.2.5 Biomarker Evaluation and Methods

[redacted]

[redacted]

[redacted]

5.2.6 Disease Evaluation and Methods

5.2.6.1 Tumor Assessments and Response Criteria

Tumor measurements and assessments will be based on RECIST 1.1 and will be performed as specified in Section 5.1. Additional tumor measurements may be performed at the discretion of the investigator or according to institutional practice. In subjects who achieve a complete response (CR) or partial response (PR) to treatment, tumor measurements will be repeated for confirmation at least 4 weeks later using the same imaging tests. The confirmatory scan may be conducted at least 4 weeks later or at the regularly scheduled response assessments that occur every 9 weeks for subjects on treatment, or at 9 weeks after the last dose for subjects without PD. The same tumor assessment method should be used throughout the study.

Tumor measurements must be recorded in metric notation by use of a ruler or calipers, and the same method/technique of tumor assessment must be used throughout the study. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of the treatment. All scans will be reviewed locally. Decisions regarding management of individual subjects will be based on local interpretation of the imaging data. All scans will be collected and stored for possible future central analysis by a third party vendor.

Tumor assessments may include the following evaluations: physical examination, CXR, CT, or MRI scan of the chest, abdomen, and pelvis, and CT or MRI scan of the brain. Computed tomography or MRI scan of the brain will be performed if the subject is neurologically symptomatic. The same method must be used for all subsequent tumor assessments. Imaging will be completed every 9 weeks, per the schedule of subject evaluations, through 24 months post study entry. Imaging will then be completed every 6 months beginning after 24 months post study entry through the End of Study.

- **Physical examination**. Lesions detected by physical examination will only be considered measurable if superficial, eg, skin nodules and palpable lymph nodes. Documentation by color photography including ruler is recommended for estimating the size of skin lesions.
- **Chest x-ray.** Lesions considered acceptable for measurement on CXR should be clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Computed tomography scans of the chest, abdomen, and pelvis**. Computed tomography scans should be performed with contiguous cuts in slice thickness of 10 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.
- **Magnetic resonance imaging scans**. Magnetic resonance imaging is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast enhanced T1-weighted images. However, there are no specific sequence recommendations.

Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions -** Must be accurately measured by at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (irrespective of scanner type) or MRI (no less than double the slice thickness and a minimum of 10 mm)
  - 10 mm caliper measurement by clinical exam (when superficial)
  - 20 mm by CXR (if clearly defined and surrounded by aerated lung)
  - Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
- **Target Lesions -** All lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

- **Nontarget Lesions -** It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases")

Response Criteria

Evaluation of Target Lesions

- **Complete Response -** Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm (the sum may not be "0" if there are target nodes).
- **Partial Response -** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease-** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease -** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Nontarget Lesions

- **Complete Response -** Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (< 10 mm short axis).
- **Non-CR/Non-PD** - Persistence of 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease -** Unequivocal progression of existing nontarget lesions will be defined as the overall level of substantial worsening in nontarget disease such that, even in the presence of stable disease (SD) or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in nonmeasurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread.

Evaluation of Overall Response

Table 5.2.6.1-1 provides overall responses for all possible combinations of tumor responses in target and nontarget lesions with or without the appearance of new lesions.

Table 5.2.6.1-1 Evaluation of Overall Response

Target Lesions (T)	Nontarget Lesions (NT)	New Lesions	Overall Response
CR	CR	No	CR
No-T [b]	CR	No	CR
CR	NE [a]	No	PR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD and NE [a]	No	PR
SD	Non-PD and NE [a]	No	SD
Not all evaluated	Non-PD	No	NE
No-T [b]	Not all evaluated	No	NE
No-T [b]	Non-CR/Non-PD	No	Non-CR/Non-PD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
No-T [b]	Unequivocal PD	Yes or No	PD
No-T [b]	Any	Yes	PD

CR = complete response; NE = not evaluable; PR = partial response; SD = stable disease; PD = progressive disease

[a] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

[b] No-T is defined as no target lesions at baseline.

Overall Survival Outcomes

Survival will be followed approximately every 3 months by clinic visit or telephone until the end of the study.

5.2.6.2 [redacted]

[redacted]

[redacted]

5.2.7 Estimate of Volume of Blood to Be Collected

In Phase 1b, the estimated volume of blood to be collected for screening for each subject is 40 mL. The estimated volume of blood to be collected during the first treatment cycle is 130 mL and during every other cycle is 60 mL. In Phase 2, the estimated volume of blood to be collected during the first treatment cycle is 125 mL and during every other cycle is 60 mL. The total volume of blood to be collected for all subjects will depend on the number of cycles administered and the length of follow-up.

6 ASSESSMENT OF SAFETY

6.1 Safety Parameters

6.1.1 Adverse Events

The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

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

An AE includes, but is not limited to, any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

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

Elective or preplanned (ie, scheduled prior to the subject being enrolled into the study) treatments or surgeries for documented pre-existing conditions are not considered AEs (serious or nonserious) if deemed unrelated to MEDI-573.

6.1.2 Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening. This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that may have led to death.
- Requires inpatient hospitalization or prolongation of existing hospitalization. In general, hospitalization signifies that the subject has been detained (usually involving at least an

overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting.

- Results in persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above. Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

6.2 Assessment of Safety Parameters

6.2.1 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.0 as provided in Appendix 5. The determination of severity for all other events not listed in the NCI CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eg, eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

6.2.2 Assessment of Relationship

6.2.2.1 Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered "not related" to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before or too long after administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Associated with the use of the drug" means that there is a "reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

6.2.2.2 Relationship to Protocol Procedures

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

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

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

6.3 Recording of Safety Parameters

6.3.1 Recording of Adverse Events and Serious Adverse Events

Adverse events will be recorded on the CRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets the criteria of an SAE and therefore requires immediate notification to MedImmune Patient Safety. See Section 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 for guidelines for assessment of severity and relationship, respectively. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

6.4 Reporting Requirements for Safety Parameters

6.4.1 Study Reporting Period and Follow-up for Adverse Events

The reporting period for AEs is the period immediately following the time that written informed consent is obtained through 60 days after the subject's last dose of MEDI-573 or until the subject begins another anticancer therapy, whichever occurs first. New (nonserious) AEs that start after the reporting period will not be collected. All AEs will be followed to resolution through the end of subject participation in the study, even if the date extends beyond the reporting period.

6.4.2 Reporting of Serious Adverse Events

6.4.2.1 Study Reporting Period and Follow-up for Serious Adverse Events

The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 60 days after the subject's last dose of treatment or until the subject begins another anticancer therapy, whichever occurs first. The reporting period for protocol-related SAEs (see Section 6.1.2) is the period immediately following the time that written informed consent is obtained through the end of subject participation in the

study. After submitting an initial SAE report for a subject (to MedImmune Patient Safety), the investigator is required to follow the subject proactively and provide further information on the subject's condition to MedImmune Patient Safety.

At any time after completion of the study, if an investigator or qualified designee becomes aware of an SAE that is suspected by the investigator or qualified designee to be related to investigational product, the event must be reported to MedImmune Patient Safety.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

6.4.2.2 Notifying the Sponsor of Serious Adverse Events

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and fax it to MedImmune Patient Safety.

MedImmune contact information:

Patient Safety
MedImmune
One MedImmune Way
Gaithersburg, MD 20878
Fax: +1 301 398 4205

Note: Sites outside of North America should use the international fax number indicated on the SAE form.

The sponsor is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements (see Section 6.4.2.3). The sponsor may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor as soon as it becomes available.

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form

(separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

6.4.2.3 Safety Reporting to Investigators, Institutional Review Boards or Independent Ethics Committees, and Regulatory Authorities

The sponsor is responsible for reporting all applicable SAEs to regulatory authorities, investigators, and IRBs/IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational product or that would be sufficient to consider changes in the administration of the investigational product or in the overall conduct of the study.

For all investigators located in the European Economic Area, the sponsor will be responsible for reporting suspected unexpected serious adverse reactions and any other applicable SAEs to regulatory authorities including the European Medicines Agency, investigators, and IRBs/IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Suspected unexpected serious adverse reactions will be submitted within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations.

For all other investigators, the sponsor will prepare an expedited report for all SAEs that are unexpected and potentially related to the investigational product, and copies will be distributed to all concerned regulatory authorities, investigator(s), and IRBs/IECs according to applicable laws and regulations. The investigational site also will forward a copy of all expedited reports to the site's applicable IRB/IEC. Investigators must also submit safety information provided by the sponsor to the IRB/IEC as detailed in Section 10.1 and Section 10.2.

6.4.3 Other Events Requiring Immediate Reporting

6.4.3.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety using the Fax Notification Form (see Section 6.4.2.2 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE CRF

(see Section 6.3.1). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, eg, death or hospitalization, the event is serious and must be reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.4.3.2 Pregnancy

Pregnancy in a female subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Fax Notification Form (see Section 6.4.2.2 for contact information).

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. After obtaining the subject's consent, the pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to MedImmune Patient Safety after outcome.

6.4.3.3 Events Meeting Study Stopping Criteria

Events that meet any of the study stopping criteria (Section 3.3), with or without associated AEs or SAEs, are required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information). The occurrence of these events does not automatically make an AE serious, but if the consequences of the event are serious, eg, death or hospitalization, the event is serious and must be reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.5 Safety Management During the Study

The medical monitor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes review of SAEs and timely review of AEs and "other events" reported during the study. MedImmune Patient Safety is responsible for the receipt, immediate medical/clinical review, investigation, and follow-up of SAEs and other immediately reportable events (eg, overdose and pregnancies) from the clinical study sites.

The MedImmune SMC will regularly review safety data and the decisions of the medical monitor regarding dose escalation throughout the study and make recommendations regarding further conduct of the study if required. At any time during the study, the MedImmune SMC will also review safety data assessed by the medical monitor as medically relevant.

A study-specific safety committee will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety and other relevant data. This committee will be

responsible for dose-escalation decisions and recommendations regarding further conduct of the study. This committee will also review data at other time points in response to AEs assessed as medically relevant by the medical monitor and will communicate outcomes and decisions to the MedImmune SMC.

A formal data monitoring committee (DMC) consisting of a biostatistician and multiple clinicians who have appropriate expertise will be established to monitor the safety of subjects in this study. The DMC will consist of external advisory members, who are not MedImmune employees, must be independent of study sites, and must have no financial or other conflict of interest in accordance with the DMC Charter. The DMC, in accordance with its Charter, will review data in response to AEs felt to be medically significant by the medical monitor, or in accordance with Section 3.3 and Section 4.5.8.1. The DMC will also review safety data on a periodic basis throughout the study. The DMC is advisory to the MedImmune SMC.

7 STATISTICAL CONSIDERATIONS

7.1 General Considerations

Data will be provided in data listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals will be 2-sided, unless otherwise stated. Details of endpoint analyses will be described in the statistical analysis plan.

7.2 Analysis Populations

The Intent-to-Treat Population includes all subjects who are enrolled in 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 investigational product or receive an investigational product different from that to which they were randomized.

The Evaluable Population for Phase 1b includes all subjects enrolled 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 (defined in Section 4.5.8.1) or experience any DLT during the DLT evaluation period.

The Per-Protocol Population includes all subjects who are in the randomization phase of the study, receive any investigational product, have at least one postbaseline tumor assessment,

and have no major protocol violations. The Per-Protocol Population will be identified prior to database lock.

The Safety Population includes all subjects who receive any investigational product.

For the Evaluable Population for Phase 1b, the Safety Population, and the Per-Protocol Population, treatment arm will be assigned according to the investigational product that is actually received.

7.3 Endpoints

7.3.1 Primary Endpoints

The endpoints related to the primary objectives are described in the sections below.

7.3.1.1 Primary Safety Endpoint

The primary safety endpoints are the following:

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

Adverse events, treatment-related AEs and SAEs will be summarized by system organ class and MedDRA preferred term, severity, and relationship to investigational product. The safety analysis will be descriptive with no formal statistical comparisons.

The number and percentage of subjects with DLT in the Evaluable Population for Phase 1b of this study will be summarized.

7.3.1.2 Primary Efficacy Endpoint

Progression-free survival is the primary endpoint for assessing antitumor activity and will be measured from randomization until the documentation of disease progression or death due to any cause, whichever occurs first. Disease progression is defined according to RECIST 1.1 guidelines. Progression-free survival will be censored on the date of the 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.

Progression-free survival will be evaluated using the Kaplan-Meier method and comparisons among the treatment groups will be performed using the log-rank test. Progression-free survival will be summarized based on the Intent-to-Treat Population in the randomization phase of the study as the primary analysis. Several sensitivity analyses may be conducted based on different analysis populations, tumor response determined by different reviewers, different methods of handling of missing data, or other statistical analysis methods. The details of the sensitivity analyses will be described in the statistical analysis plan.

7.3.2 Secondary Endpoints

The secondary endpoints related to safety and tolerability of MEDI-573 when used in combination with an AI, PK/pharmacodynamic assessments, IM of MEDI-573, and antitumor activities are presented below.

7.3.2.1 Safety and Tolerability of MEDI-573 in Phase 2

The safety endpoints include AEs, SAEs, and changes in clinical laboratory evaluations from baseline. These will be summarized using the same method as stated in Section 7.3.1.1.

7.3.2.2 Pharmacokinetic Endpoint

Individual MEDI-573 concentrations will be tabulated by dose cohort along with descriptive statistics. Noncompartmental PK data analysis will be performed for data obtained from each dose cohort with scheduled PK sample collection. Descriptive statistics of noncompartmental PK parameters (AUC, C_{max}, systemic clearance, half-life) will be provided.

7.3.2.3 Pharmacodynamic Endpoints

Circulating IGF-I and IGF-II levels will be summarized by dose cohort and descriptive statistics will be used. The time course of circulating IGF will be graphed based on dose group. Exposure-response analysis will be conducted to explore the relationship between MEDI-573 exposure and circulating biomarkers (such as IGF-I and IGF-II).

7.3.2.4 Immunogenicity of MEDI-573

Immunogenicity 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.

7.3.2.5 Secondary Efficacy Endpoints

The secondary endpoints for assessing antitumor activity include ORR, time to response, duration of response (DR), time to progression (TTP), and OS and change in tumor size. Response Evaluation Criteria in Solid Tumors v1.1 guidelines will be used to evaluate tumor response.

- Objective response rate is defined as the proportion of subjects with confirmed CR or confirmed PR according to RECIST 1.1 guidelines. Confirmed responses are those that persist on repeat imaging study ≥ 4 weeks after the initial documentation of response.
- Time to response will be measured from randomization to the first documentation of objective response and will only be assessed in subjects who have achieved objective response.
- Duration of response will be defined as the duration from the first documentation of objective response to the first documented disease progression. The DR will be censored on the date of last tumor assessment documenting absence of disease progression for subjects who have no documented progression prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. The DR will only be evaluated for the subgroup of subjects with an objective response.
- Time to progression will be measured from randomization until the documentation of disease progression. Disease progression is defined according to RECIST 1.1 guidelines. The TTP will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Subjects having no tumor assessments after randomization will have TTP censored on the date of randomization.
- Overall survival will be determined as the time from randomization until death due to any cause. 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 are known to be alive.
- Change in tumor size will be summarized by the percent change of the sum of the longest diameters for target tumor(s) from baseline.

The time-to-event data, including time to response, DR, TTP, and OS, will be evaluated using Kaplan-Meier methods. The ORR will be summarized by study arm and compared using Fisher's exact test between three study arms. The 95% confidence interval of the ORR for each study arm will be calculated based on an exact probability method. The change in tumor size will be analyzed using appropriate statistical methods.

7.3.3 Exploratory Endpoints

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

7.4 Planned Analysis

Two formal analyses are planned for the study. The primary analysis of PFS and safety will be performed after 122 PFS events have occurred. The final analysis of OS and safety will be performed at the end of study as defined in Section 4.8.

7.5 Sample Size and Power Calculations

In the Phase 1b portion of the study, a minimum of 9 evaluable subjects (3 each at the MEDI-573 [redacted] mg/kg dose levels) will be required to evaluate the safety and tolerability of 3 doses of MEDI-573 in combination with an AI. Up to 18 evaluable subjects

(6 subjects each at 3 dose levels) may be needed if 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) 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 PFS among subjects treated at [redacted] mg/kg MEDI-573 and an AI versus subjects treated with single-agent AI alone. The assumed median PFS for subjects with single-agent AI alone is 9.4 months (Mouridsen et al, 2001) and the expected median PFS for subjects receiving the [redacted] mg/kg dose of MEDI-573 plus an AI is 13.4 months, which represents an improvement in PFS of 42.6% and corresponds to a hazard ratio (HR) of 0.7. Based on these assumptions, a total of 122 events (ie, subjects with disease progression or death) are required to provide 75% power for the log-rank test at a 2-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 MEDI-573 arm is 13.8 or 14.4 months (corresponding to HR of 0.68 or 0.653), the power will change to 80% or 85%, respectively, with 122 PFS events.

8 DIRECT ACCESS TO SOURCE DOCUMENTS

The study will be monitored by the sponsor on a regular basis throughout the study period. During monitoring visits, the investigator will provide direct access to all source documentation relevant to the subject's participation in the study. Source documentation includes, but is not limited to, the subject's clinic and/or office chart, hospital chart, informed consent forms, treatment notes, laboratory reports, pharmacy records, radiographs, recorded data from automated instruments, and any other records maintained to conduct and evaluate the clinical study. The investigator must also ensure that direct access to study documents be made available for study-related audits, IRB/IEC review, or regulatory inspection.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Data Collection

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol. Case histories include CRFs and supporting data including, but not limited to, signed and

dated informed consent forms, progress notes, hospital charts, nurse's notes, diary cards, laboratory reports, ECG strips, etc.

Subject demographics and key/essential disease baseline characteristics thought to affect outcome, ie, stratification variables and other prognostic factors, will be collected, as available, for all subjects who provide written informed consent. For subjects who provide informed consent and were not entered/randomized into the study, the reason the subject was not entered/randomized, ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn), will also be collected.

9.2 Study Monitoring

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the investigator(s), both the medical record and the research records will be monitored/audited for the purposes of the study.

The investigator and institutions involved in the study will permit study-related monitoring and provide direct access to all study records and facilities. Adequate time and space for monitoring visits should be made by the investigator or other investigator site staff.

The monitor will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter. The monitor will assess subject enrollment and informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto validated data collection instruments (paper CRF or electronic data screen) against original source documents; and the occurrence of AEs/SAEs. All aspects of the study will be carefully monitored for compliance with the protocol, applicable regulatory requirements, GCP, and the site's standard operating procedures.

The monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the monitor to ensure that corrective action is taken to resolve any problems noted in the course of the monitoring, and that the preventative measures are put into place to prevent recurrence of issues. In cases where compliance is not achieved, shipment(s) of investigational product to the investigator will be discontinued and study participation by that investigator will be terminated.

9.3 Audit and Inspection of the Study

During the conduct of the study, the sponsor or its representative may conduct audits of any data and any facility participating in the study. The investigator and institutions involved in

the study will permit such study-related audits and provide direct access to all study records and facilities. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also perform inspections either during or after the study. In the event of an inspection by any regulatory authority, the investigator should promptly notify the sponsor. The investigator agrees to cooperate fully with inspections conducted by regulatory authorities and to allow representatives of the regulatory authority access to all study records. The investigator will forward to the sponsor a copy of any inspection records received.

10 ETHICS

10.1 Regulatory Considerations

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC that approves this study to be conducted in its territory. Good clinical practice is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study subjects are protected.

Per GCP, the protocol will be reviewed and approved by the IRB or IEC of each participating center prior to study initiation. Serious adverse events, regardless of causality, will be reported to MedImmune Patient Safety, and the investigator will keep the IRB/IEC informed as to the progress of the study.

The investigator will explain the nature of the study and will inform the subject/legal representative that participation is voluntary and that the subject can withdraw or be withdrawn from the study at any time. Written informed consent will be obtained from each subject/legal representative prior to the screening procedures to determine if study eligibility criteria are met. A copy of the signed consent form will be given to every subject/legal representative, and the original will be maintained with the subject’s records.

10.2 Institutional Review Board or Independent Ethics Committee

A list of IRB/IEC members or a Statement of GCP Compliance should be obtained by the investigator and provided to the sponsor.

Any documents that the IRB/IEC may need to fulfill its responsibilities, such as protocol amendments, and information concerning subject recruitment, payment, or compensation procedures, or information from the sponsor will be submitted to the IRB/IEC. The IRB/IEC's written unconditional approval of the study protocol, the informed consent form(s), and any other written materials to be provided to subjects will be in the possession of the investigator and the sponsor before the study is initiated. The IRB/IEC's unconditional approval statement will be transmitted by the investigator to the sponsor prior to shipment of investigational product supplies to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

Protocol modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted should be obtained.

The IRB/IEC must be informed by the investigator of informed consent form changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

10.3 Informed Consent

Freely given informed consent will be obtained and documented for all subjects under this protocol (or a subject's legal representative, if the subject is unable to provide informed consent) in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC.

Information should be given in both oral and written form, and subjects or their legal representatives must be given ample opportunity to inquire about details of the study.

The consent form(s) generated by the investigator must be approved by the IRB/IEC and be acceptable to the sponsor. Consent forms must be written so as to be understood by the prospective subject/legal representative. Informed consent will be documented by the use of a written consent form(s) approved by the IRB/IEC and signed and dated by the subject or the subject's legal representative, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form(s) must be kept on file by the investigator for possible inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The subject or the subject's legal representative should receive a copy of the signed and dated written informed consent form(s) and any other written information provided to the subject, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

10.4 Withdrawal of Consent for Continued Study Participation

Data and Samples Obtained for the Main Study

Study data are protected by the use of a SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any data collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

Samples Obtained for Genetic Research or Future Research

Samples obtained for genetic research or future research will be labeled with a sample identification number but will not be labeled with personal identifiers such as the subject's name. A file linking this sample identification number with the SID number will be kept in a secure place at the sponsor with restricted access. If the subject withdraws consent for participating in the genetic research or future research, this link will allow the sponsor to locate the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject consents to have his/her samples used for genetic research or future research, this additional research may not start immediately and may start at any time during the

storage period. The subject's sample(s) including any specimens of extracted DNA will be stored by the sponsor with similar samples from other subjects at MedImmune. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be used for genetic research or future research, the samples will be destroyed by the sponsor at the conclusion of the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for genetic research or future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for genetic research or future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's samples have already been used for research, the sponsor is not required to destroy results of this research. In this case, only the remaining sample(s) will be destroyed.

11 DATA HANDLING AND RECORD KEEPING

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a SID or coded number. All study records, source medical records, and code sheets or logs linking a subject's name to an SID number will be kept in a secure location. Study records such as CRFs may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject/legal representative, except as specified in the informed consent form(s) (eg, necessary for monitoring by regulatory authorities or the sponsor of the clinical study). The investigator must also comply with all applicable privacy regulations (eg, HIPAA 1996, EU Data Protection Directive 95/46/EC).

Study documents (including subject records, copies of data submitted to the sponsor, study notebook, and pharmacy records) must be kept secured in accordance with the specific data retention periods that are described in the clinical study site agreement and based upon local requirements. Study documents must not be destroyed without prior written approval of the sponsor.

12 FINANCING AND INSURANCE

Financing and insurance are addressed in the individual site contracts.

13 PUBLICATION POLICY

Publication by the site of any data from this study must be carried out in accordance with the clinical study site agreement.

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15 SUMMARY OF PROTOCOL AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

Protocol Amendment 1, 07Feb2012

The following changes were made:

1. **Cover Page:** The name of the CRO for the study was added.
2. **Study Abstract:** Updated to be consistent with the changes made to the body of the protocol.
3. **Section 1.2.1 Product Derivation:** the word "fully" was removed from the description of MEDI-573's human derivation.
4. Section 1.2.3 Clinical Experience with MEDI-573:
   - The text was updated to specify that MEDI-573 has been administered at the [redacted] mg/kg dose level once every 21 days.
   - The text was updated to include current information on subject exposure to MEDI-573.
   - The text was updated to include current safety findings in MI-CP184.
5. Section 1.3 Research Hypothesis:
   - The number of dose levels to be tested in the current study was changed from 2 to 3.
   - Last sentence of section, added "with HR+, HER2-negative MBC" for consistency.
6. Section 1.5: Benefit-risk and Ethical Assessment:
   - The text was modified to account for the fact that MEDI-573 has been administered to subjects in more than one clinical trial.
   - Discussion of potential adverse reactions based on sequestering IGF ligands in contrast to current knowledge of adverse reactions resulting from inhibition of other molecular targets within the IGF signaling pathway was added.
7. **Section 2.1: Primary Objective:** The number of dose levels to be tested in the current study was changed from 2 to 3.
8. Section 3.1.1 Phase 1b (Dose-evaluation Phase):
   - The text was modified to account for the addition of a [redacted] mg/kg plus AI treatment arm.
   - The text referring to the number of subjects to be evaluated in the study was changed to state: "Approximately 9 to 18" and the number of investigational sites was changed to 20 in North America.
9. **Section 3.1.2: Phase 2 (Randomization Phase):** Phase 2 was changed to a 2-arm structure to test [redacted] mg/kg MEDI-573 plus AI versus AI alone. The text and study flow diagram were updated to account for the change.
10. Section 3.3 Study-stopping Criteria: added DMC to bullet 4.
11. **Section 3.4: Rationale for Study Design, Doses, and Control Groups:** Rationale for the dosing schedule was provided, including the addition of a [redacted] mg/kg arm in Phase 1b and Phase 2, based on PK and pharmacodynamic experience.

12. Section 4.2.1 Inclusion Criteria:
    - Inclusion Criterion 1 added "Subjects with metastases to bone only are eligible
    - Inclusion Criterion 3 was clarified to specify that HER2 negativity will be assessed by FISH or CISH assay will be used according to local guidelines or manufacturer's scoring criteria.
    - Text was added to Inclusion Criterion 4 indicating that subjects enrolled in Japan must be ≥ 20 years of age at study entry.
    - Text was added to Inclusion Criterion 5 to clarify the definition of postmenopausal.
13. Section 4.2.2 Exclusion Criteria:
    - The required washout period following tamoxifen or an AI prior to receiving the first dose of MEDI-573 was changed to 2 weeks.
    - Eligibility was extended to subjects with bone-only metastases.
    - Text was added to clarify the exclusion of subjects with active brain metastases.
    - The text regarding the exclusion of subjects with known CNS metastases and leptomeningeal carcinomatosis was edited to exclude subjects with spinal cord compression or leptomeningeal carcinomatosis.
    - Text was added to exclude subjects with a history of allergy or reaction attributed to compounds of chemical or biologic composition similar to those of MEDI-573 or AI.
    - The text referring to the exclusion of subjects with a history of another primary malignancy within 5 years prior to starting study treatment was modified to exclude subjects with a history of another invasive malignancy.
    - The text referring to exclusion of subjects with poorly controlled diabetes mellitus was edited to remove the hemoglobin test requirement.
14. Section 4.3 Treatment Assignment:
    - The text was modified to specify that an IXRS will be used for entry (Phase 1b)/randomization to a treatment arm (Phase 2) and assignment of unblinded investigational product and/**or** an AI.
    - The text was modified to specify that in Phase 2 of the study, subjects will be randomized at a 1:1 ratio to receive either MEDI-573 at [redacted] mg/kg and an AI or an AI alone.
15. **Section 4.5.1 Investigational Products:** Reference to the Investigational Product Manual was removed.
16. Section 4.5.2 Other Study Medications:
    - The text stating that manufacturer and batch numbers should be recorded in the drug accountability log was deleted.
    - The following text was added: "Subjects will be provided with a diary in which to record their intake of AI (an example of the diary is provided in Appendix 3). This information will be recorded in the case report form". A new appendix containing the subject diary of AI usage was added.
17. **Section 4.5.3.1 Phase 1b:** The text was modified to account for the addition of a [redacted] mg/kg MEDI-573 dose cohort.

18. **Section 4.5.3.2 Phase 2:** The text was modified to account for the change in the Phase 2 dose structure to [redacted] mg/kg MEDI-573 plus AI versus AI alone.
19. Section 4.5.3.3 Investigational Product Preparation:
    - Reference to the Investigational Product Manual was deleted.
    - Information of the compatibility of MEDI-573 with IV bags and tubing was updated.
20. Section 4.5.4 Treatment Administration:
    - The text was modified to clarify that the infusion time for [redacted] MEDI-573 recipients will be 60 minutes whereas that for the [redacted] and [redacted] MEDI-573 recipients will be 90 minutes.
    - Removed "Subjects are to continue with an AI initially assigned to them for the duration of their treatment on the study" in response to investigator feedback.
21. **Section 4.5.6 Dose Evaluation Phase:** The text was modified to account for the addition of a [redacted] MEDI-573 dose cohort.
22. **Section 4.5.7 Phase 2 (Randomization Phase):** The text was modified to account for the addition of a [redacted] MEDI-573 arm and the number of subjects to be randomized into Phase 2 was changed to 178.
23. **Section 4.5.8 Management of Toxicities, Dose Reductions and Dose Delays:** Text was added to specify that dosing will not be interrupted or discontinued for a Grade 2 laboratory toxicity that does not represent deterioration since study entry.
24. **Section 4.6.1 Permitted Concomitant Medications:** Text on the permitted use of concomitant bisphosphonate or denosumab treatment was added.
25. Section 5.1 Schedule of Study Procedures:
    - Text was added to the schedule of assessments to specify that the Cycle 1, Day 2 assessments are only required for Phase 1b.
    - A -2 day window for weight determination prior to dosing was added to the schedule of assessments.
    - Text was added in the schedule of assessments table to specify that the dose interval for the Cycle 2 (and subsequent cycles), Day 1 infusion should be no shorter than 21 days.
    - The row header text in the schedules of study procedures was modified where appropriate to account for the change in structure of Phase 2 to include a [redacted] mg/kg MEDI-573 plus AI arm and an AI alone arm.
    - The visit descriptions in Section 5.1.1 through Section 5.1.4.3 were modified according to the changes described above.
    - Text was added in the schedule of assessment table to reference Section 5.2.6.1 for detailed schedule for CXR, CT, or MRI scans.
26. **Section 5.2.1 Medical History and Physical Examination:** Additional physical examination details were added and the title was edited to include ECG, weight, and vital signs.
27. **Section 5.2.2 Clinical Laboratory Tests:** Text was added to clarify that only abnormal laboratory tests that are deemed clinically significant by the investigator will be repeated.
28. Section 5.2.5 Biomarker Evaluation and Methods:

- [redacted]
- The corresponding changes were made to **Section 7.3.3 Exploratory Endpoints**.

29. Section 5.2.6.1 Tumor Assessments and Response Criteria:
    - Text added to define plans for archived images.
    - Text added to clarify the imaging requirements throughout the study.
30. **Section 6.5 Safety Management During the Study:** Text describing the DMC and its role in safety management was added.
31. Section 7.3.1.2 Primary Efficacy Endpoint:
    - The text stating that blinded central independent imaging review of response and disease progression will be the basis for the primary analysis was removed because the primary endpoint will be based on investigator assessment.
    - The text was modified to specify that sensitivity analyses may be conducted based on different analysis populations, tumor response determined by reviewers' different handling of missing data, or other statistical analysis methods.
32. **Section 7.4 Planned Analyses:** The text was changed to specify that the primary analysis of PFS and safety would be performed after 122 PFS events have occurred.
33. Section 7.5 Sample Size and Power Calculations:
    - The required number of evaluable subjects to determine the safety and tolerability of MEDI-573 was changed to 9 and the text was modified to state that up to 18 evaluable subjects may be needed if DLT occurs.
    - The primary objective of the Phase 2 portion of the study is now to compare PFS among subjects treated at [redacted] MEDI-573 and an AI versus subjects treated with single-agent AI alone; the text was modified accordingly.
    - Additional edits were made to the text describing the number of subjects required to observe an adequate number of PFS events for study powering based on the changes in study design as described above.
34. Other minor text edits and corrections were incorporated into the document.
35. Corresponding edits based on the above changes were made in the study synopsis.

Protocol Amendment 2, 05Dec2012

The protocol was updated to incorporate changes described in Administrative Change 1 and Administrative Change 2, and to make other changes where possible to streamline study conduct and decrease subject burden. In addition, a limit of approximately 30 subjects with bone metastases only was added to reflect the proportion of subjects with bone-only metastases in the target population. The following changes were made:

1. **Cover page:** The medical monitor was updated.
2. **Study Abstract:** The abstract was updated to be consistent with changes made in the body of the protocol.
3. **Section 3.1.2, Phase 2 (Randomization Phase):** A statement was added to indicate that a limit of approximately 30 subjects with bone-only disease will be randomized to reflect the proportion of subjects with bone-only metastases in the target population.
4. **Section 3.4, Rationale for Study Design, Doses, and Control Groups:** The rationale for the limit of 30 subjects with bone-only metastases was added.
5. Section 4.2.1, Inclusion Criteria:
   a. It was clarified that subjects with metastases to bone only will be capped at approximately 30 subjects, and that subjects must be evaluated for inclusion based on RECIST criterion 1.1.
   b. Immunohistochemistry was added as a method of determining HER2 status because some locations do not have access to FISH or CISH.
6. Section 4.2.2, Exclusion Criteria:
   a. It was clarified that prior adjuvant therapy with an AI and/or tamoxifen is allowed.
   b. It was clarified that subjects with evidence of spinal canal involvement who are asymptomatic of spinal cord compression or leptomeningeal carcinomatosis are allowed to enroll.
7. **Section 4.5.3.1, Phase 1b; and Section 4.5.4, Treatment Administration:** A window of + 20 minutes was added to infusion times to account for potential overfill.
8. **Section 4.5.4, Treatment Administration:** Windows for collection of vital signs during and after MEDI-573 infusion were added.
9. **Section 4.6.1, Permitted Concomitant Medications:** It was clarified that bisphosphonate, denosumab, or calcitonin treatment may be initiated after Cycle 1, Day 21 for the management of hypercalcemia, bone pain, and/or osteoporosis.
10. **Section 4.6.2, Excluded Concomitant Medications:** The statement regarding recording of concomitant medications was deleted for redundancy with the prior section.
11. Section 5.1, Schedule of Study Procedures:
    - Table 5.1-1: A urine or serum pregnancy test was added at Cycle 2 (and every cycle thereafter), Day 1.
    - Table 5.1-1: It was clarified that the column for evaluations to be conducted every 9 weeks is to be followed until 24 months post study entry.

- Table 5.1-1: A column was added for evaluations to be conducted every 6 months beginning > 24 months post-randomization, primarily to reduce the radiation exposure that would result in continued tumor evaluations every 9 weeks.
- Table 5.1-1: The archival tumor biopsy was changed from mandatory to "if available", as per Administrative Change 1.
- Table 5.1-2: It was clarified that the column for evaluations to be conducted every 9 weeks is to be followed until 24 months post study entry.
- Table 5.1-2: A column was added for evaluations to be conducted every 6 months beginning > 24 months post-randomization to reduce the radiation exposure that would result in continued tumor evaluations every 9 weeks.

12. **Section 5.1.1, Screening (All Subjects Unless Otherwise Specified):** Text was added to Item #3 to clarify that verification of eligibility criteria should include review of laboratory results. Item #12 was clarified to indicate that pregnancy tests are required for women of childbearing potential only. Item #14 was modified to indicate that archival tumor samples are not mandatory, but will be collected if available, as outlined in Administrative Change 1.
13. **Section 5.1.2.1, Cycle 1, Day 1 (All Subjects Unless Otherwise Specified):** A statement was added to indicate that any assessments performed within 24 hours prior to dosing may be used for Cycle 1, Day 1 assessments. Text was added to Item #1 to clarify that verification of eligibility criteria should include review of laboratory results. The window for the end of infusion vital signs was increased to 10 minutes to allow sufficient time for completion of all end of infusion assessments. It was clarified that the 12-lead posttreatment ECG is required only for subjects enrolled in Phase 1b and Phase 2, Arm 1. Item #9 was clarified to indicate that pregnancy tests are required for women of childbearing potential only.
14. **Section 5.1.2.5, Cycle 2 and Every Cycle Thereafter, Day 1 (Plus/Minus 2 Days, All Subjects Unless Otherwise Specified):** A urine or serum pregnancy test and post-dose 12-lead ECG were added to this visit. These were inadvertently omitted from the previous version of the protocol.
15. **Section 5.1.2.6, Every 9 Weeks Minus 7 Days, Starting with Cycle 4 (All Subjects) Through 24 Months Post Study Entry:** The title of this section was edited to indicate that these evaluations are conducted through 24 months post study entry.
16. **Section 5.1.2.7, Every 6 Months Plus/Minus 7 Days, beginning > 24 Months Post Study Entry:** This section was added to describe the assessments required after 2 years on study for subjects who remain on study drug. This change was made to decrease radiation exposure, as tumor assessments will decrease from every 9 weeks to every 6 months after 2 years on study.
17. **Section 5.1.3, End-of-Treatment Visit (All Subjects Unless Otherwise Specified):** It was clarified that the pregnancy test is to be conducted in women of childbearing potential only.
18. **Section 5.1.4.2, Every 9 Weeks (Plus/Minus 7 Days)** Posttreatment for Subjects Without Progressive Disease Through 24 Months Post Study Entry: The title of this section was changed to indicate that the assessments should be done only through 24 months post study entry.

19. **Section 5.1.4.4, Every 6 Months (Plus/Minus 7 Days) Beginning > 24 Months Post Study Entry:** This section was added to describe the assessments required after 2 years on study for subjects who have discontinued study drug. This change was made to decrease radiation exposure, as tumor assessments will decrease from every 9 weeks to every 6 months after 2 years on study.
20. **Section 5.2.1, Medical History, Physical Examination, Electrocardiogram, Weight and Vital Signs:** Language was added to clarify which subjects receive ECGs at each timepoint. The window for completion of the ECG at the end of infusion was increased to 10 minutes. The ECG at 6 hours post-infusion was deleted as per Administrative Change 1. Language was added to clarify the times at which vital signs are collected for subjects enrolled in Phase 1b and Phase 2, Arm 1.
21. **Section 5.2.5, Biomarker Evaluation and Methods:** Language was changed to indicate that IGF-1R signaling proteins will be evaluated for their expression levels on archived tissue samples where available, as outlined in Administrative Change 1.
22. **Section 5.2.6.1, Tumor Assessments and Response Criteria:** Clarification that the scan to confirm CR or PR may be completed at the regularly scheduled response assessments that occur every 9 weeks was added as described in Administrative Change 2.
23. Other minor text edits and corrections were incorporated into the document.

Protocol Amendment 3, 25Jul2016

The following changes were made:

1. **Cover page:** The name and contact information of the medical monitor was updated.
2. **Study Abstract:** The study abstract was updated to be consistent with changes made in the body of the protocol.
3. **Section 1.2.3 Clinical Experience with MEDI-573:** Language has been updated to include the results from the completed FTIH study (CP-184) and the primary analysis of CD-ON-MEDI-573-1030 study.
4. **Section 4.8 End of Study:** The language was updated to clarify the follow-up procedures for patients that have discontinued treatment. Additionally, text was added to specify that patients still on treatment at the end of 36 months will be allowed to continue treatment until they meet the criteria for treatment discontinuation.
5. **Section 5.1 Schedule of Study Procedures:** Language was updated to clarify and simplify required procedures for subjects continuing treatment with Amendment 3 approval, given primary analysis of the study is completed.
    - Table 5.1-2, Schedule of Subject Evaluations: Screening and Treatment Periods – All subjects unless otherwise specified (Subjects continuing treatment under Amendment 3 only) and Table 5.1-4, Schedule of Study Procedures: Follow-up Period (Subjects continuing treatment under Amendment 3 only): Tables were added to include subjects continuing treatment under Amendment 3 only.
    - Table 5.1.3, Schedule of Study Procedures: Follow-up Period (All Subjects Unless Otherwise Specified): The table number and title were updated.

6. **Section 5.1.2.5.1 Cycle 2 and Every cycle Thereafter, Day 1 (Plus/Minus 5 days):** Section was added to clarify follow-up evaluations for the subjects on treatment at the time of Amendment 3.
7. **Section 5.1.2.6.1 Every 9 Weeks (± 7 Days) Post Study Entry unless otherwise specified (For subjects continuing on treatment under Amendment 3 only):** Section was added to clarify evaluations for the subjects on treatment at the time of Amendment 3.
8. **Section 5.1.2.7.1 Every 6 Months (± 7 Days), Beginning > 24 Months Post Study Entry (For subjects continuing on treatment under Amendment 3 only):** Section was added to clarify evaluations for the subjects on treatment at the time of Amendment 3.
9. **Section 5.1.3.1 End-of-Treatment Visit (For subjects continuing on treatment under Amendment 3 only):** Section was added to clarify evaluations for the subjects on treatment at the time of Amendment 3.
10. **Section 5.1.4.1.1 30 Days (± 3 Days) and 60 Days (± 5 Days) Posttreatment (For subjects continuing on treatment under Amendment 3 only):** Section was added to clarify follow-up evaluations for the subjects on treatment at the time of Amendment 3.
11. **Section 5.2.1 Medical History, Physical Examination, Electrocardiogram, Weight and Vital Signs:** Language was updated to be consistent with the Schedule of Study Procedures.
12. **Section 5.2.6.1 Tumor Assessments and Response Criteria:** Language was added to clarify the management of subject imaging data.

Appendix 1 Signatures

Sponsor Signature(s)

[redacted]

[redacted]

Appendix 2 Karnofsky Performance Status Scale

Karnofsky Performance Status Scale	
Score	**Description**
100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of his needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death not imminent
20	Very sick; hospitalization necessary; active support treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Source: Adapted from Karnofsky D, Abelman W, Craver L, Burchenal J. The use of nitrogen mustards in the palliative treatment of carcinoma. Cancer. 1948;1:634-56.

Appendix 3 Aromatase Inhibitor Subject Diary

MedImmune

MEDI-573-1030 Study Diary

Subject ID: ___________________

Medication Name: ___________________ **Dose & Unit:** ____________ **Frequency:** _______________

Start Date: ____________________
dd/mmm/yyyy

Stop Date: ____________________
dd/mmm/yyyy

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken
Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken
Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken
Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken
Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken	Date: ☐ AI Taken

****Please enter the date on the calendar and check AI dose taken for that day.****

Page _____ of _____

Appendix 4 New York Heart Association Cardiac Performance Status Assessment Function Scale

New York Heart Association Cardiac Performance Status Assessment Function Scale	
Class	**Description**
I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

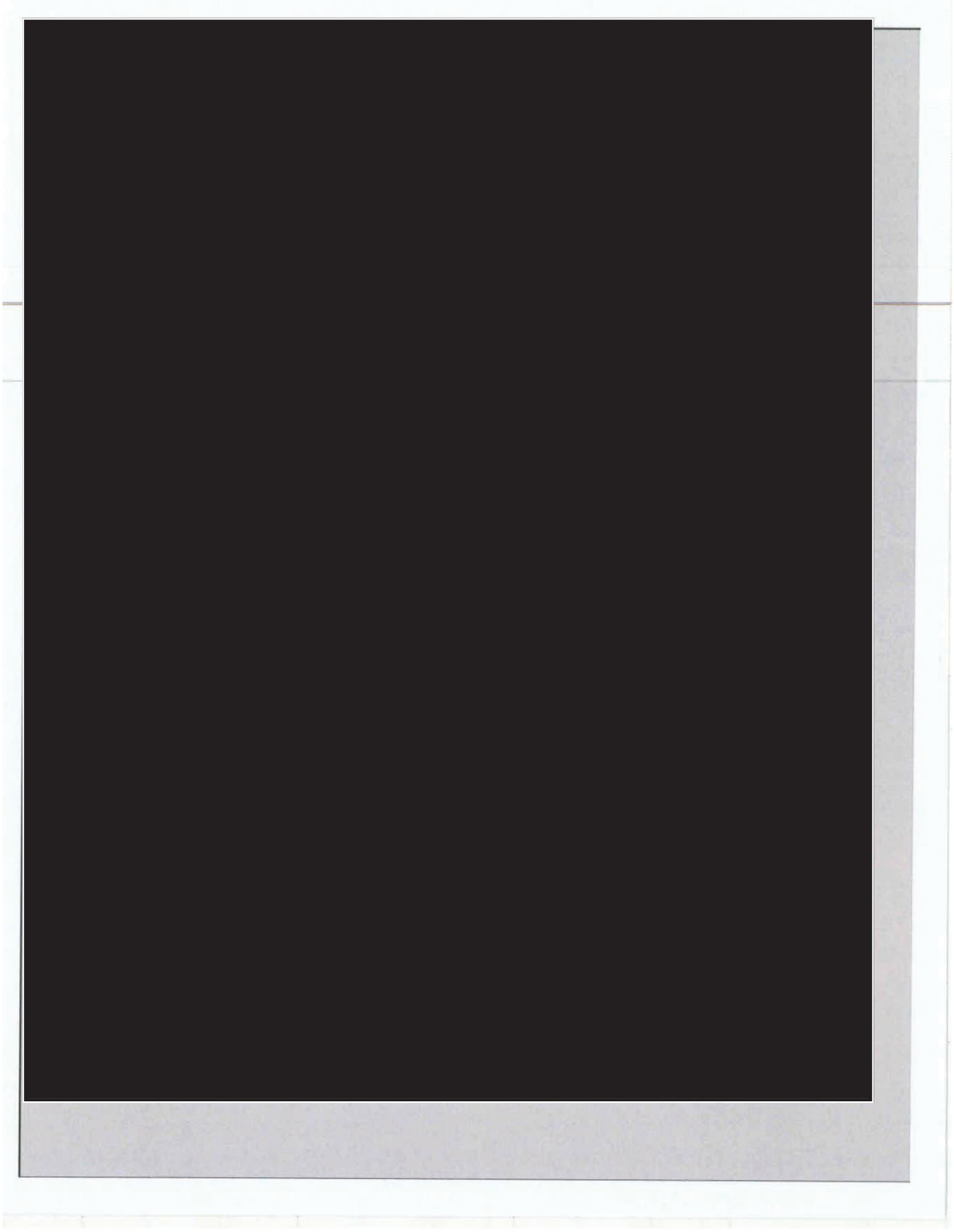
Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-6.

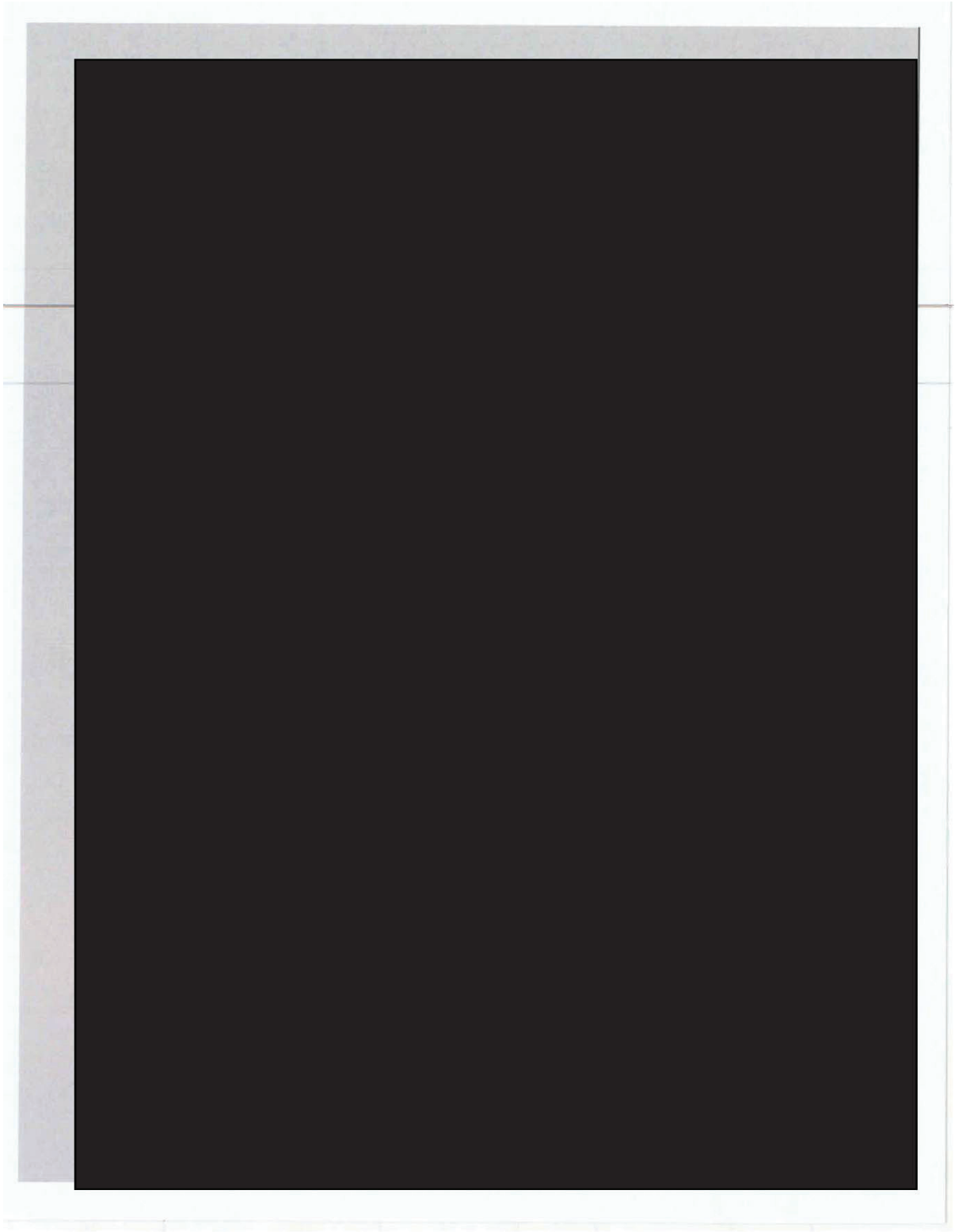
Appendix 5 National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE V4.0)

The NCI CTCAE V4.0 can be downloaded from the Cancer Therapy Evaluation Program homepage (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

[redacted]

[redacted]





Appendix 7 [redacted]

ENGLISH

ENGLISH

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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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