# A Phase 1, Open-label Study to Evaluate the Safety and Tolerability of MEDI-565 in Adults with Gastrointestinal Adenocarcinomas

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# Table of Contents

# List of In-text Tables

# List of In-text Figures

# List of Appendices

# List of Abbreviations

| Abbreviation or Specialized Term | Definition |
|---|---|
| ADA | anti-drug antibodies |
| AE | adverse event |
| ALL | acute lymphocytic leukemia |
| ALP | alkaline phosphatase |
| ALT | alanine transaminase |
| ANC | absolute neutrophil count |
| ARDS | adult respiratory distress syndrome |
| AST | aspartate aminotransferase |
| $AUC_{inf}$ | area under the concentration-time curve to infinity |
| $AUC_{0-1h}$ | area under the concentration-time curve from time zero to 1 hour |
| $AUC_{0-4h}$ | area under the concentration-time curve from time zero to 4 hours |
| Beta-hCG | beta-human chorionic gonadotropin |
| BiTE® | bispecific T-cell engager |
| BUN | blood urea nitrogen |
| CEA | carcinoembryonic antigen |
| CEACAM5 | carcinoembryonic antigen-related cell adhesion molecule 5 |
| CI | confidence interval |
| CL | clearance |
| $C_{max}$ | peak concentration |
| CNS | central nervous system |
| CR | complete response |
| CRC | colorectal cancer |
| CRF | case report form |
| CT | computed tomography |
| CTC | circulating tumor cells |
| CXR | chest x-ray |
| dL | deciliter |
| DLT | dose-limiting toxicity |
| DNA | deoxyribonucleic acid |

| Abbreviation or Specialized Term | Definition |
|---|---|
| DR | duration of response |
| $EC_{20}$ | effective concentration that induced 20% of the maximum effect |
| $EC_{50}$ | effective concentration that induced 50% of the maximum effect |
| ECLA | electrochemiluminescent assay |
| EGFR | epidermal growth factor receptor |
| ECG | electrocardiogram |
| ELISA | enzyme-linked immunosorbent assay |
| EOI | end of infusion |
| EpCAM | tumor cell epithelial cell adhesion molecule |
| Erbitux® | cetuximab |
| E:T | effector-to-target |
| EU | European Union |
| FACS | fluorescence-activated cell sorting |
| FDA | Food and Drug Administration |
| FTIH | first-time-in-human |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transpeptidase |
| GI | gastrointestinal |
| GLP | Good Laboratory Practice |
| HAMA | human anti-murine antibodies |
| hCG | human chorionic gonadotropin |
| HEENT | head, eyes, ears, nose, and throat |
| HER2 | human epidermal growth factor receptor-2 |
| Herceptin® | trastuzumab |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | human immunodeficiency virus |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IgE | immunoglobulin E |
| IM | immunogenicity |
| INR | international normalized ratio |

| Abbreviation or Specialized Term | Definition |
|---|---|
| IRB | Institutional Review Board |
| IV | intravenous |
| IXRS | Interactive (voice, web, etc) response system |
| $K_D$ | dissociation constant |
| KPS Scale | Karnofsky Performance Status Scale |
| LDH | lactic dehydrogenase |
| LFT | liver function test |
| MABEL | minimum anticipated biological effect level |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MEDI-565 | bispecific single-chain antibody of the bispecific T-cell engager that targets human CEA |
| MMSE | Mini-Mental State Examination |
| MRI | magnetic resonance imaging |
| MRSD | maximum recommended starting dose |
| MTD | maximum tolerated dose |
| NCI CTCAE | National Cancer Institute Common Toxicity Criteria for Adverse Events |
| ng | nanogram |
| NHL | non-Hodgkin lymphoma |
| NK | natural killer |
| nM | nanomolar |
| NYHA | New York Heart Association |
| OBD | optimum biologic dose |
| ORR | objective response rate |
| OS | overall survival |
| ORTHOCLONE OKT3 | muromonab-CD3 |
| PBMC | peripheral blood mononuclear cell |
| PD | progressive disease |
| PFS | progression-free survival |
| PK | pharmacokinetics |
| PKPD | pharmacokinetics/pharmacodynamics |
| PR | partial response |
| PT | prothrombin time |

| Abbreviation or Specialized Term | Definition |
|---|---|
| PTT | partial thromboplastin time |
| QTc | corrected QT interval |
| RECIST | Response Evaluation Criteria in Solid Tumor |
| SC | subcutaneous |
| SAE | serious adverse event |
| SCID | severe combined immunodeficient |
| SD | stable disease |
| SID | subject identification |
| SIRS | systemic inflammatory response syndrome |
| SMC | Safety Monitoring Committee |
| TGI | tumor growth inhibition |
| Treg | regulatory T cells |
| $T_{max}$ | time to maximum concentration |
| TTP | time to progression |
| TTR | time to response |
| $t_{1/2}$ | half-life |
| ULN | upper limit of normal |
| $V_d$ | volume of distribution |
| $V_{ss}$ | volume of distribution at steady state |
| WBC | white blood cell |

# Study Abstract

**TITLE**

A Phase 1, Open-label Study to Evaluate the Safety and Tolerability of MEDI-565 in Adults with Gastrointestinal Adenocarcinomas

**OBJECTIVES**

The primary objective of the study is to determine the maximum tolerated dose (MTD) and/or optimum biologic dose (OBD) of MEDI-565 in adult subjects and evaluate the safety profile in adult subjects with advanced gastrointestinal (GI) adenocarcinomas who have no available standard or curative treatments.

The secondary objectives of the study are:

1) To describe the pharmacokinetics (PK) of MEDI-565
2) To determine the immunogenicity (IM) of MEDI-565
3) To evaluate the antitumor activity of MEDI-565

The exploratory objectives of the study are:

1) To evaluate protein, nucleic acid, and cellular biomarkers in blood following MEDI-565 treatment
2) To assess potential central nervous system (CNS)-related events using the Mini-Mental State Examination (MMSE) and the Timed Get-Up and Go Test
3) To assess multiple aspects of the tumor and tumor microenvironment before and following MEDI-565 treatment which may include: CEA expression, markers of necrosis or apoptosis, and potential changes in the nature and number of tumor infiltrating lymphocytes

**STUDY DESIGN**

This is a first-time-in-human (FTIH), dose-escalation and expansion Phase 1 study. The first part is a multicenter, open-label, single-arm, dose-escalation study of MEDI-565 to determine the MTD or OBD and evaluate the safety, tolerability, PK, IM, and antitumor activity of MEDI-565 in adult subjects who have GI adenocarcinomas for which no standard or curative treatments are available. The second part is a dose-expansion study at the MTD or OBD in subjects with refractory colorectal cancer (CRC), refractory pancreatic cancer, or refractory gastroesophageal cancer. Approximately 4 to 10 investigational sites throughout the United States of America (USA) will participate in this study.

Dose escalation began with single subject cohorts (Cohorts 1 through 4) and continued with standard 3+3 dose-escalation cohorts from Cohort 5 through 10. Ten cohorts have been enrolled to date. The starting dose of

0.75 μg was chosen based on the $EC_{20}$ (effective concentration that induced 20% of the maximum effect) obtained using a sensitive in vitro tumor cell lysis assay. The initial 4 cohorts were single-subject cohorts with approximately 200% increases in dose up to the fifth cohort. The first subject enrolled in Cohort 5 (initially a single-subject cohort) experienced Grade 2 adverse events (AEs) of vomiting and infusion reaction, and 2 additional subjects were enrolled per the original protocol. One of these additional subjects in Cohort 5 experienced a Grade 2 AE of abdominal pain, triggering implementation of standard 3+3 enrollment in Cohort 5. As described in previous versions of the protocol, the dose in Cohort 6 was increased by 100% (from 60 to 120 μg) instead of 200%. Doses in Cohorts 6 through 10 were increased by approximately 100% to 150% according to the protocol dose-escalation rules. Two subjects in Cohort 10 experienced dose-limiting hypoxia events after their first infusion of MEDI-565. Under previous versions of the protocol, the occurrence of these events would have indicated that the MTD has been exceeded at the 3 mg dose. However, available data suggest that the observed DLTs were reversible and potential future cases of hypoxia temporally associated with MEDI-565 administration should be manageable with the implementation of additional risk mitigation measures including prophylactic dexamethasone administration prior to MEDI-565 administration and additional blood pressure, heart rate, and pulse oximetry monitoring during and following administration of MEDI-565. Thus,

under Amendment 4 of the protocol, dosing will re-start at the next previously lower dose of 1.5 mg (Cohort 11) with additional risk mitigation measures outlined above for all new subjects. Provided no more than 1 out of 6 subjects experience DLTs, dose escalation will continue in sequential fashion with re-evaluation of the 3 mg dose (Cohort 12), followed by 5 mg (Cohort 13), 7.5 mg (Cohort 14), and 10 mg (Cohort 15) doses.

MEDI-565 will be administered by IV infusion over 3 hours per day for 5 consecutive days (ie, Days 1 through 5) every 28 days (defined as 1 cycle). Subjects in the dose-escalation phase are considered evaluable if they receive at least 1 full cycle of MEDI-565 and complete the safety follow-up through the DLT evaluation period of 28 days after the first dose of MEDI-565, or experience any DLT. Subsequent cycles may be delayed for up to 7 days for management of some types of toxicity or to accommodate scheduling issues. Nonevaluable subjects will be replaced in the same dose cohort. No intra-subject dose escalation will be allowed.

Dose escalation will continue until the MTD or a maximum dose of 10 mg is reached. In the event that no DLTs are observed during dose escalation and significant antitumor activity is observed, the Sponsor may halt dose escalation prior to determining the MTD provided that PK, pharmacology, safety and preliminary antitumor activity data support the use of an OBD below the MTD.

Once the MTD or OBD is determined, a total of 60 additional subjects (20 subjects each with refractory pancreatic adenocarcinoma, refractory CRC, or refractory gastroesophageal cancer) may be enrolled at the MTD or OBD in a dose-expansion phase. Commencement of the dose-expansion phase and the selection of any tumor types will be based on any previously observed signal of antitumor activity and the safety profile of MEDI-565 emerging from the dose-escalation phase. Subjects in the expansion phase will receive MEDI-565 at the MTD or OBD as a 3-hour IV infusion per day for 5 consecutive days every 28 days (defined as 1 cycle). Subjects in the dose-expansion phase are considered evaluable for antitumor activity if they receive at least 2 full cycles of MEDI-565 or discontinue due to progressive disease or toxicity. Nonevaluable subjects in the dose-expansion phase will be replaced. All subjects who receive any amount of MEDI-565 will be considered evaluable for safety.

In both the dose-escalation and dose-expansion phases, subjects will be treated with MEDI-565 until confirmed progressive disease (PD), initiation of alternative anticancer therapy, unacceptable toxicity, or other reasons to discontinue treatment. Subjects will be followed until the end of the study, which is defined as 1 year after the last subject begins treatment with MEDI-565 or the date the study is closed by the sponsor, whichever occurs first.

**SUBJECT POPULATION**

The subjects in this study will include adults with GI adenocarcinomas with no available standard or curative treatments.

**TREATMENT**

MEDI-565 will be administered by IV infusion over 3 hours per day for 5 consecutive days every 28 days (1 cycle). The starting dose was 0.75 µg.

The proposed dose levels for MI-CP216 are 0.75µg, 2.25 µg, 6.75µg, 20 µg, 60 µg, 120 µg, 300 µg, 750 µg, 1.5mg, 3 mg, 5 mg, 7.5 mg, and 10 mg.

Treatment may be continued in subjects who have a response of stable disease (SD) or better until documentation of disease progression, initiation of alternative anticancer therapy, unacceptable toxicity, or other reasons for treatment withdrawal.

Beginning with Amendment 4, subjects will receive inpatient administration of MEDI-565 starting with Cycle 1, Day 1 until completion of the infusion on Cycle 1, Day 2 and again beginning with the infusion on Cycle 1, Day 4 until completion of the infusion on Cycle 1 Day 5. Subsequent infusions of MEDI-565 will be administered to subjects on an outpatient basis.

In the dose-expansion phase, 3 treatment arms of approximately 20 subjects with refractory pancreatic adenocarcinoma, 20 subjects with refractory CRC, and 20 subjects with refractory gastroesophageal cancer may be enrolled and receive MEDI-565 at the MTD/OBD dose by IV infusion over 3 hours per day for 5 consecutive

days every 28 days. Commencement of the dose-expansion phase and the selection of any tumor types will be based on any previously observed signal of antitumor activity and the safety profile of MEDI-565 emerging from the dose-escalation phase.

**ASSESSMENT OF ENDPOINTS**

Primary Endpoints

The number (percentage) of subjects with a DLT will be summarized by dose level and overall. The MTD evaluation will be based on the evaluable population for DLT and is defined as the highest dose, up to 10 mg, where the DLT frequency is less than 33%.

The OBD will be determined based upon analysis of all available subject data including safety, PK, pharmacodynamic, biomarker, and antitumor activity data.

The number (percentage) of subjects with AEs and SAEs reported through 30 days after the last dose of MEDI-565 will be summarized for all subjects who received at least one dose of study drug (Safety Population). Adverse events and SAEs will be graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) v4.03 and described by system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severity, and relationship to MEDI-565. Frequency rates will be calculated for each system organ class and MedDRA preferred term.

The number (percentage) of subjects with significant or important clinical findings on electrocardiogram (ECG) will be summarized by dose cohort.

The number (percentage) of subjects who had clinically significant laboratory changes recorded as AEs will be summarized. Laboratory hematology and chemistry values will be summarized with the worst value during the study by dose cohort. Clinically significant coagulation profile and urinalysis results will be described.

Secondary Endpoints

The secondary objectives of this study are to describe the PK, IM, and antitumor activity of MEDI-565. The endpoints associated with these objectives are described below.

Pharmacokinetic Assessment

Individual MEDI-565 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. If the data allow, descriptive statistics of noncompartmental PK parameters (AUC, $C_{max}$, $T_{max}$, CL, $V_d$, $t_{½}$) will be provided.

Immunogenicity Assessment

The immunogenic potential of MEDI-565 will be assessed by summarizing the number and percentage of subjects who develop detectable anti-drug antibodies. Immunogenicity results will be listed for each subject. The impact of anti-drug antibodies on PK, PD, antitumor activity and safety will be assessed if data allow.

Efficacy Assessments

The efficacy profile will be assessed using objective response rate (ORR), time to response (TTR), duration of response (DR), time to progression (TTP), progression-free survival (PFS) and overall survival (OS). The objective response rate is defined as the proportion of subjects with confirmed CR or confirmed PR according to RECIST guidelines; 95% confidence intervals of ORR will be estimated using the exact probability method. Time-to-event endpoints will be evaluated using the Kaplan-Meier method.

Exploratory Endpoints

Descriptive statistics will be the primary methods used for the exploratory analyses. Depending on the nature of the data, geometric mean and other appropriate statistical summaries might be used as well. The variables to be included in the exploratory analyses include:

Serum CEA levels before and after treatment with MEDI-565 to evaluate the association with response to treatment with MEDI-565 and clinical outcome

Peripheral blood populations before and after treatment, including absolute numbers of T cells, T-cell subsets, NK cells, and B cells as well as their cellular phenotypes, to evaluate the association with MEDI-565 dose and subject responses to MEDI-565 treatment

Cytokine response to explore its association with MEDI-565 treatment, clinical outcome, and infusion-related reactions

Circulating DNA, M30, and/or M65 as markers of tumor apoptosis to evaluate their association with MEDI-565 treatment

Circulating tumor cell numbers and the CEA-expression CTC subset to explore their relationship to treatment effects with MEDI-565

Drug target expression, tumor markers of response and T-cell infiltration and phenotype based on the archived and/or fresh tumor tissues, when available, to explore their relationship to treatment effects with MEDI-565

Percentage of subjects with potential CNS-related events using the Mini-Mental State Examination (MMSE) and the Timed Get-Up and Go Test

**INTERIM ANALYSIS**

No interim analyses are planned.

**SAMPLE SIZE**

The number of subjects who may be enrolled ranges from approximately 99 to 114, depending upon how many subjects are required per cohort based on occurrence of DLTs and also depending on how many subjects are enrolled in the dose-expansion phase.

For the dose-escalation phase, as of Amendment 4, approximately 39 evaluable subjects will be required if no DLTs are observed in any of the 15 cohorts. Of the 15 cohorts, Cohorts 1-4 each require a minimum of 1 subject. Cohorts 5-15 follow a 3+3 design and each requires a minimum of 3 subjects. Up to approximately 54 evaluable subjects (1 subject per cohort in Cohorts 1-4, 3 subjects in Cohort 5 through 9, 5 subjects in Cohort 10, and up to 6 evaluable subjects per cohort in Cohorts 11-15) will be required during the dose-escalation phase. At the discretion of the sponsor, more subjects may be enrolled for situations which might prompt selection of an intermediate dose and nonevaluable subjects for DLT determination, defined as any subject discontinued during the DLT evaluation period for reasons other than study drug-related toxicity, will be replaced in the same dose cohort.

For the dose-expansion phase, approximately 60 subjects (20 subjects each) may be entered into 3 disease arms, refractory CRC, refractory pancreatic adenocarcinoma, and refractory gastroesophageal cancer. Commencement of the dose-expansion phase and the selection of any tumor types will be based on any previously observed signal of antitumor activity and the safety profile of MEDI-565 emerging from the dose-escalation phase. An equal number of subjects in each arm will be treated to evaluate the safety and antitumor activity profile of MEDI-565. This projected sample size was chosen to obtain a preliminary safety and antitumor activity profile.

# 1 Introduction

AstraZeneca AB, a company incorporated in Sweden with offices at SE-151 85 Södertälje, Sweden ("AstraZeneca"), is the global sponsor of this study. MedImmune, LLC, with offices at One MedImmune Way, Gaithersburg, Maryland 20878, USA ("MedImmune") is an affiliate of AstraZeneca.

Refractory adenocarcinomas comprise a range of neoplasms including the most prevalent types of cancer, such as breast and colorectal, and malignancies with the worst prognoses, such as pancreatic and gastroesophageal cancers. Monoclonal-based therapies, such as trastuzumab (Herceptin®) for human epidermal growth factor receptor-2 (HER2) or cetuximab (Erbitux®) for epidermal growth factor receptor (EGFR), that target tumor-expressed cell surface proteins have demonstrated significant clinical benefit for patients with cancers of the breast and gastrointestinal (GI) system (Cunningham et al, 2004; Piccart-Gebhart et al, 2005). Despite these available treatments, there is still a significant unmet medical need for patients with refractory adenocarcinomas. The development of new therapies that target tumor-expressed cell surface proteins has become a well-established strategy that may address existing unmet medical needs for patients with advanced malignancies.

Carcinoembryonic antigen (CEA), more specifically described as carcinoembryonic antigen cell adhesion molecule 5 (CEACAM5), represents a significant potential target for adenocarcinomas. Carcinoembryonic antigen is an oncofetal glycoprotein of the immunoglobulin superfamily which is normally expressed during fetal gut development and in adult tissues, with expression of CEA limited to columnar epithelial and goblet cells in the colon; mucous neck cells and pyloric mucous cells of the stomach; squamous epithelial cells of the tongue, esophagus, and cervix; and secretory epithelia and duct cells of the prostate (Hammarström, 1999). Carcinoembryonic antigen is expressed on tumor cells in adenocarcinomas, including colorectal, pancreatic, gastroesophageal, lung, breast, ovary, uterus, and a subset of melanomas (Sanders et al, 1994). Tumor expression of CEA is particularly prevalent in adenocarcinomas of the GI system, with greater than 90% of cases demonstrating expression in colorectal, pancreatic, and gastric cancers (Allum et al, 1986).

Carcinoembryonic antigen has been widely used as a target for both tumor imaging and various antibody-based therapeutic approaches for cancer treatment (Granowska et al, 1990; Granowska et al, 1993; Mayer et al, 2000). Carcinoembryonic antigen can also be released from the cell surface by phospholipases, which produces a soluble form of the protein in

circulation (Graham et al, 1998). Elevated serum levels of soluble CEA are found in many cancer patients, and increases in CEA levels correlate with disease progression, making serum CEA a potentially useful marker for disease monitoring of CEA-positive cancers (Mujagić et al, 2004). Conventional CEA-specific antibodies tested in radioimmunoscintigraphy human trials can bind with high sensitivity and selectivity to CEA-positive tumors in vivo while they do not bind as well to soluble CEA or CEA expressed on the luminal side of several normal epithelial tissues (Granowska et al 1993; Mayer et al, 2000).

## 1.1 Description of MEDI-565

MEDI-565 is a novel, bispecific single-chain antibody of the bispecific T-cell engager (BiTE®) class that targets human CEA on tumor cells and the CD3 epsilon (ε) subunit of the human T-cell receptor complex present on T cells. The pharmacological action of BiTE antibodies is based on their ability to mediate T-cell lysis of target-expressing tumor cells. Nonclinical in vitro studies of human tumor cell lines expressing CEA and in vivo studies using animal tumor models have demonstrated that MEDI-565 has potent antitumor cell activity and growth inhibition, and antitumor activity is not inhibited by soluble CEA (Lutterbuese et al, 2009). MEDI-565 is proposed for the treatment of GI adenocarcinoma.

## 1.2 Experience with MEDI-565

### 1.2.1 Nonclinical Pharmacology

MEDI-565 specifically and selectively bound to a nonlinear, conformational epitope in human CEA with a high binding affinity ($K_D$ of 8.4 nM); it cross-reacted with chimpanzee and cynomolgus monkey CEA. In addition, MEDI-565 specifically bound to human CD3 with a low binding affinity ($K_D$ of 310 nM), and cross-reacted with chimpanzee CD3, but did not cross-react with cynomolgus monkey and or mouse CD3. Concomitant binding of MEDI-565 to CEA and CD3 over a wide range of E:T (effector-to-target) ratios led to the activation of primarily CD8+ T cells and the subsequent killing of cells expressing CEA. In vitro cytotoxicity assays revealed that activation of T cells by MEDI-565 was specific and selective. At the same time, T cells expanded, increased cell surface expression of activation markers, and released proinflammatory cytokines, perforin, and granzyme B. Importantly, MEDI-565 did not activate T cells in the presence of cells lacking expression of CEA.

MEDI-565 was tested in nonclinical models of cancer employing human tumor cell lines mixed with human T cells and grown in mice. MEDI-565 inhibited the growth of CEA-expressing cancer cell lines following IV treatment in cancer models of colonic, pancreatic, lung and stomach origins, and following SC treatment in cancer models of colonic origins. MEDI-565 did not inhibit the growth of cancer cells in the absence of human T cells or in the absence of CEA expression on cancer cells. These results demonstrated that the expression of CEA on cancer cells and the presence of CD3+ T cells are essential for the activity of MEDI-565.

Other than the chimpanzee, no pharmacologically relevant animal species exist for toxicology testing of MEDI-565. Two hybrid surrogate BiTE molecules, cyS111 and hyS111, were generated to develop a pharmacologically relevant animal species model for predicting the human toxicity of MEDI-565. The in vitro and in vivo pharmacodynamic activity of hyS111 and the in vitro pharmacodynamic activity of cyS111 were compared to that of MEDI-565; nonspecific activity and different functional characteristics than those of MEDI-565 were revealed. These findings suggested that hyS111 and cyS111 would not represent the specific activity and effects of MEDI-565 in humans, and thereby limit their utility in nonclinical safety studies. Thus, no safety pharmacology studies were conducted with MEDI-565.

### 1.2.2 Pharmacokinetics

The PK of MEDI-565 was studied in mice and cynomolgus monkeys. Following single dose IV administration in mice and cynomolgus monkeys, serum concentrations of MEDI-565 declined with a rapid initial distribution/elimination phase followed by a slower terminal elimination phase. In CD-1 mice (using a CD3 PK assay), although the terminal phase $t_{1/2z}$ was 5 hours, the $AUC_{0\text{-}4h}$ was approximately 90% of the $AUC_{inf,}$ representing a significant decrease in serum concentrations of MEDI-565 by 4 hours postdose, and thus indicating that the elimination of MEDI-565 may be better reflected by the initial $t_{1/2\alpha}$ of 0.2 hours. In C57BL/6 mice (using a whole-molecule PK assay), the $AUC_{0\text{-}1h}$ was approximately 90% of the value of the $AUC_{inf,}$ representing a significant decrease in serum concentrations of MEDI-565 by 1 hour postdose. The $t_{1/2\alpha}$ was 0.12 hours in wild-type mice and 0.13 hours in mice transgenic for human CEA. In cynomolgus monkeys (using a CD3 PK assay), the $AUC_{0\text{-}4h}$ was 90% of the value of $AUC_{inf,}$ representing a significant decrease in serum concentrations of MEDI-565 by 4 hours postdose. The $t_{1/2\alpha}$ was 0.37 hour. The subcutaneous $t_{max}$ was 6 to 7.3 hours and SC bioavailability was 73% to 82%.

A 3-compartment model was fit to serum MEDI-565 concentration versus time data in cynomolgus monkeys to estimate the PK parameters. Based on allometric scaling of PK parameters from cynomolgus monkeys, the predicted human clearance was 2068 mL/hr; the central volume was 2958 mL; the peripheral volume was 9485 mL and 1195 mL for compartments 2 and 3, respectively; and intercompartmental clearance was 187 mL/hr and 183 mL/hr for compartments 2 and 3, respectively. The lowest $EC_{20}$ value obtained from an in vitro tumor cell lysis assay in response to treatment with MEDI-565 was 0.097 ng/mL. This concentration was selected as the minimum anticipated biological effect level (MABEL). The maximum recommended starting dose (MRSD) of MEDI-565 is 0.75 μg administered as a 3-hour IV infusion once daily for 5 consecutive days. Based on the nonclinical information, the target efficacious dose of MEDI-565 in cancer patients is 1.5 mg administered as a 3-hour IV infusion once daily for 5 consecutive days.

Following IV infusion in subjects enrolled in Cohorts 1 through 10, peak serum concentrations of MEDI-565 increased approximately dose-proportionally from 0.48 ng/mL at the 0.75 μg dose level to 321 ng/mL at the 3 mg dose level. MEDI-565 concentrations decreased rapidly after the end of infusion with a short terminal elimination half-life of 3 hours. At the highest dose tested to date (3 mg), mean $C_{max}$ at the end of infusion was 321 ng/mL, which decreased to 2.7 ng/mL within 24 hours. There was no notable accumulation between doses within a cycle and the PK was similar across cycles for a given dose.

### 1.2.3 Toxicology

Formal in vivo toxicity studies of MEDI-565 were not performed given the lack of a suitable pharmacologically relevant animal model to assess toxicity. The nonclinical strategy for MEDI-565 to support selection of the first dose in human and the Phase 1 clinical study is based on data from detailed in vitro cytotoxicity studies, human peripheral T-cell cytokine release assays, T-cell activation and proliferation assays, and PK modeling in cynomolgus monkeys. This strategy was chosen because there is no pharmacologically relevant animal model for in vivo toxicity studies of MEDI-565. The human PK profile for MEDI-565 was predicted based on its PK parameters in cynomolgus monkeys. Data from these in vitro and in vivo studies were collectively used to estimate the MABEL of MEDI-565, and to select a starting dose for the Phase 1 clinical study.

Results from in vitro studies on human cells, using the most sensitive test systems and assay conditions, were utilized to identify the effective concentrations of MEDI-565 that induced 20% of the maximum effect ($EC_{20}$ values). T-cell mediated lysis of cancer cells was the most sensitive measure for determining MABEL. Based on these results, the MABEL of MEDI-565 was calculated to be 0.097 ng/mL. Additional in vitro studies demonstrated that the ability of MEDI-565 to induce cytokine release and T-cell proliferation required simultaneous engagement of both CD3 on T cells and CEA on target cells. Thus, the in vivo activation of T cells in the absence of expression of CEA on target cells is not likely. Results from a PK and bioavailability study in male cynomolgus monkeys demonstrated only treatment-related, reversible erythema and bruising at the administration site following IV injection. There were no changes in clinical observations, body weight, serum chemistry, hematology, coagulation, or urinalysis parameters. Results from a GLP-compliant tissue cross-reactivity study on a full panel of human tissues showed expected staining of epithelial cells, consistent with known tissue expression of CEA (Hammarström, 1999).

### 1.2.4 Clinical

This is the first clinical study using MEDI-565. As of 01Mar2013, 24 subjects were enrolled across 10 dose levels ranging from 0.75 μg to 3 mg. Adverse events (AEs) were most frequently reported in the system organ class of Gastrointestinal Disorders (17 subjects, 70.8%). The most common AEs were nausea (45.8%), abdominal pain (37.5%), vomiting and chills (25.0% each), anemia, dyspnea, fatigue, headache, and pyrexia (20.8% each).

Two subjects in the 3 mg cohort experienced DLTs of hypoxia as summarized below:

A 53-year-old female with a history of colon cancer was enrolled in the 3 mg dose group of Study MI-CP216. Beginning 1.5 hours after the end of the Cycle 1, Day 1 infusion, she developed rigors, nausea, vomiting, and fever > 102°F. The fever was treated and it decreased to approximately 99°F. Prior to starting the Cycle 1, Day 2 infusion, the subject had decreased oxygen saturation of 79% to 81% with respiratory rate of 30 breaths per minute. Supplemental oxygen improved oxygen saturation to 94%. The subject's temperature increased to 101°F and her white blood cell count increased from $7.6 \times 10^9$ cells per liter prior to infusion to $14.5 \times 10^9$ cells per liter. Furosemide and clindamycin were administered. Blood and urine cultures were negative. After limited diuresis, the subject continued to be hypoxic as confirmed by arterial blood gas. The event resolved 3 days after receiving the

Cycle 1, Day 1 infusion and the subject was permanently discontinued from MEDI-565 treatment due to this event.

A 66-year-old male with a history of pancreatic cancer was enrolled in the 3 mg dose group of Study MI-CP216. Beginning 4.5 hours after the end of infusion the Cycle 1, Day 1 infusion, the subject experienced abdominal pain and bloating, nausea, and chills. Approximately 10 hours after the end of infusion, the subject's oxygen saturation was noted to be 80% on room air and temperature was increased to 102.6°F. Supplemental oxygen improved oxygen saturation to 92%. The subject complained of a headache and was noted to have labored breathing, lung crackles, and wheezing. Acetaminophen and Solu-Medrol® were administered. His white blood cell count was noted to be elevated following administration of the steroid and was assessed to be related to Solu-Medrol. Chest and abdominal x-rays did not reveal alternative etiology for the subject's symptoms. The Grade 3 hypoxia resolved 1 day after receiving the Cycle 1, Day 1 infusion. The subject was permanently discontinued from MEDI-565 treatment due to this event.

## 1.3 Rationale for Study Conduct

The antitumor activity of MEDI-565 has been investigated using both in vitro and in vivo models for CEA-expressing human tumor cell lines and human T cells and PBMCs, either in cell culture or reconstituted in vivo using immunocompromised murine models. MEDI-565 treatment demonstrated significant in vivo antitumor activity specific to CEA-expressing tumors following either daily IV or SC dosing for 5 days in murine models. The ability of MEDI-565 to inhibit the growth of established human tumors in murine models was dependent on the presence of transferred human T cells and required the expression of CEA on the tumor cells. In vitro studies of MEDI-565 demonstrated significant and specific tumor cell cytotoxicity after a minimum of 24 hours of co-culture of MEDI-565 with CEA-expressing human tumor cells and T cells. These nonclinical studies suggest that MEDI-565 has potential antitumor activity against CEA-expressing malignancies and support a study design in which MEDI-565 is administered by either IV or SC administration daily for 5 days per cycle to subjects with CEA-expressing malignancies.

Study MI-CP216 will evaluate the safety, tolerability, immunogenicity (IM), pharmacology (PK and biomarkers), and preliminary antitumor activity of MEDI-565 given by IV infusion over 3 hours per day for 5 consecutive days of a 28-day cycle in adult subjects who have refractory GI adenocarcinomas for which no standard or curative therapies are available. The

study will consist of an initial dose-escalation phase to determine the maximum tolerated dose (MTD) or optimum biologic dose (OBD). Approximately 39 to 54 subjects will be evaluated.

Once the dose-escalation phase has been completed and an MTD/OBD has been achieved an additional 60 subjects may be enrolled. This expansion may include 20 subjects with refractory pancreatic adenocarcinoma, 20 subjects with refractory colorectal cancer (CRC), and 20 subjects with refractory gastroesophageal cancer. These tumor types were chosen based on high prevalence of CEA expression, poor outcomes following standard therapy, and differing levels of T-cell infiltration in the absence of specific immunotherapy. Commencement of the dose-expansion phase and selection of any tumor types will be based on any previously observed signal of antitumor activity and the safety profile of MEDI-565 emerging from the dose-escalation phase. Other study endpoints include PK, IM, and biomarkers of MEDI-565.

## 1.4 Benefit-risk and Ethical Assessment

MEDI-565 may offer a benefit to subjects with CEA-expressing malignancies and who have failed standard therapies. Nonclinical data support the antitumor activity of MEDI-565 in a variety of tumor cell lines. Specifically, MEDI-565 showed potent in vitro activity against multiple cell lines that express CEA. Subjects with relapsed or refractory GI adenocarcinoma have no available therapies after their disease has progressed while on treatment with approved or standard of care chemotherapies. Therefore, MEDI-565 has the potential to address an unmet medical need.

MEDI-565 is human species-specific, interacting with human CEA-expressing cells and human CD3-expressing T cells, and not with commonly accepted animal model systems used for toxicology and pharmacology studies. Efforts to develop suitable surrogate animal models have not been successful. Therefore, no suitable pharmacologically relevant animal models exist for predicting human safety or estimating the starting dose in the first-time-in-human (FTIH) study with MEDI-565. For this reason, the starting dose for Protocol MI-CP216 was determined based on in vitro experiments (T-cell mediated cytotoxicity of CEA-expressing cells) conducted with MEDI-565 to determine the MABEL, in conjunction with PK data from cynomolgus monkeys administered MEDI-565. While there are currently no identified risks for MEDI-565, because of limited clinical experience with this product, potential risks, based on the nature of the molecule, the mechanism of action, and the safety profile of other molecules that may be relevant include hypersensitivity, central nervous system toxicity,

hepatotoxicity, infection/viral re-activation, immune-related reactions, reproductive toxicity, hematologic toxicity, and infusion-related reactions, including cytokine release syndrome.

Two of 5 subjects in Cohort 10 (3 mg) experienced hypoxia within several hours after completion of the Cycle 1, Day 1 infusion that met the protocol definition of DLT. Under previous versions of the protocol, the occurrence of dose-limiting hypoxia in two subjects in Cohort 10 (3 mg dose) would have indicated that the MTD has been exceeded at the 3 mg dose. However, available data suggest that the observed DLTs were reversible and potential future cases of hypoxia temporally associated with MEDI-565 administration should be manageable with the implementation of additional risk mitigation measures including prophylactic dexamethasone administration prior to MEDI-565 administration and additional blood pressure, heart rate, and pulse oximetry monitoring during and following administration of MEDI-565. Thus, under Amendment 4 of the protocol, dosing will re-start at the next previously lower dose of 1.5 mg (Cohort 11) with implementation of the additional risk mitigation measures outlined above for all new subjects. Provided no more than 1 out of 6 subjects experience DLTs in the preceding cohort, dose escalation will continue in sequential fashion and re-evaluate the 3-mg dose (Cohort 12), followed by 5 mg (Cohort 13), 7.5 mg (Cohort 14), and 10 mg (Cohort 15) doses.

Currently, there are no anticancer agents approved by the United States Food and Drug Administration (FDA) with a CD3 effector mechanism to comparatively assess the potential safety and tolerability of MEDI-565, although one such agent is approved in the EU. A monoclonal antibody directed against CD3, muromonab-CD3 (Orthoclone OKT3) is approved by the FDA for use in acute transplant rejection. The most frequent adverse events (AEs) associated with muromonab-CD3 use are symptoms related to cytokine release syndrome, associated most strongly with the first few doses, which range from self-limited flu-like symptoms to more severe shock-like reactions. Cardiorespiratory findings included dyspnea, chest pain, bronchospasm, tachypnea, cardiovascular collapse, hypotension and adult respiratory distress syndrome (ARDS). Central nervous system events include seizures, encephalopathy, cerebral edema and aseptic meningitis, some resulting in permanent impairment. Other serious and occasionally fatal hypersensitivity reactions include cardiovascular collapse, hypotension, shock, tachycardia, angioedema, bronchospasm, urticaria and pruritus (Orthoclone OKT3 package insert, 2004).

There is experience with at least one molecule which targets CEA as a mechanism of action. $^{131}$I-labetuzumab is a radio-iodinated anti-CEA antibody that is in clinical development as a radioimmunotherapy treatment of metastatic CRC. The primary toxicities associated with

this molecule were related to reversible myelosuppression, likely related to radiation exposure, and have not involved off-target normal epithelial tissues where CEA might be expressed at low levels, or other unexpected toxicities (Liersch et al, 2005).

Potential risks based on the mechanism of action for MEDI-565 have also been identified from safety data reported from clinical studies with other BiTE or similar multifunctional antibodies that have a known or postulated mechanism of action similar to MEDI-565. Catumaxomab (Removab®) is a monoclonal bispecific, trifunctional antibody, approved in the European Union in 2009 for the intraperitoneal treatment of patients with malignant ascites. The antibody binds tumor cell epithelial cell adhesion molecule (EpCAM) and also T cell CD3 antigen (Burges et al, 2007). In addition, the Fc region provides a functional binding site to FcRγ positive accessory immune cells. Adverse effects have been primarily related to cytokine release symptoms and both IL-6 and TNFα have been found elevated in the majority of treated patients. Fever, chills, nausea and vomiting were frequently reported, while systemic inflammatory response syndrome (SIRS) occurred in 0.8% of patients (Removab® Assessment Report, 2009). Catumaxomab has also been studied in a single-dose, Phase 1 trial of non-small cell lung cancer patients, where the dose-limiting toxicity (DLT) consisted of transient Grade 3 and 4 elevations of AST/ALT/GGT (Sebastian et al, 2007). Unlike catumaxomab, MEDI-565 does not possess any FcRγ binding sites.

Blinatumomab (MT103, previously known also as MEDI-538) is a BiTE with specificity for the B cell antigen CD19 and CD3, in clinical development for the treatment of acute lymphocytic leukemia (ALL) and non-Hodgkin lymphoma (NHL). The majority of AEs from a Phase 1 trial in subjects with ALL consisted of flu-like symptoms, transient leukopenia/lymphopenia, and transient elevation of LFTs during the initial days of treatment. Central nervous system (CNS) symptoms (disorientation, confusion, speech disorders, tremor and convulsions), Grades 2 and 3, have been observed in approximately 17% of lymphoma patients (Nagorsen et al, 2009).

MT110 is a BiTE with specificity for EpCAM and CD3 currently in development in the EU for use in solid tumors. EpCAM is expressed on most solid tumors of epithelial origin. In a Phase 1 trial, MT110 has been administered at doses of up to 24 micrograms/day by continuous IV infusion in cycles of 28 days. Common Grade 1 or 2 related events included pyrexia, nausea, vomiting, diarrhea, and fatigue. There was one Grade 3 event of diarrhea. Transient elevations in transaminases were observed at all dose cohorts, which resulted in DLT in 3 subjects. One subject had a DLT of elevated bilirubin (Fiedler et al, 2010). EpCAM is known to be expressed on the biliary tract epithelium.

The experience with other therapies with similar mechanisms of action indicates that there is no consistent type or pattern of toxicities that can be predicted based on available data. While T-cell activation has been observed with some CD3-targeting agents, it is not uniform. Elevation in liver enzymes with EpCAM-specific multifunctional agents may be due to specific expression on biliary tract epithelium and is not necessarily predictive of toxicity with MEDI-565.

Given the promising activity of MEDI-565 in nonclinical models, the lack of available curative or life-prolonging therapies for subjects with refractory disease, and the additional risk mitigation measures being implemented with Amendment 4 to address potential future cases of hypoxia temporally associated with MEDI-565 administration, treatment with MEDI-565 represents a reasonable risk in this population.

# 2 Study Objectives

## 2.1 Primary Objective

The primary objective of this study is to determine the MTD and/or OBD of MEDI-565 in adult subjects and evaluate the safety profile in adult subjects with advanced GI adenocarcinomas who have no available standard or curative treatments.

## 2.2 Secondary Objectives

The secondary objectives of this study are:

1) To describe the PK of MEDI-565
2) To determine the IM of MEDI-565
3) To evaluate the antitumor activity of MEDI-565

## 2.3 Exploratory Objectives

The exploratory objectives of this study are:

1) To evaluate protein, nucleic acid, and cellular biomarkers in blood for MEDI-565 treatment
2) To assess potential CNS-related events using the Mini-Mental State Examination (MMSE) and the Timed Get-Up and Go Test

3) To assess multiple aspects of the tumor and tumor microenvironment before and following MEDI-565 treatment which may include: CEA expression, markers of necrosis or apoptosis, and potential changes in the nature and number of tumor-infiltrating lymphocytes

# 3 Study Design

## 3.1 Overview of Study Design

This is a FTIH, dose-escalation and expansion Phase 1 study. The first part is a multicenter, open-label, single-arm, dose-escalation study of MEDI-565 to determine the MTD or OBD and evaluate the safety, tolerability, PK, IM, and antitumor activity of MEDI-565 in adult subjects who have GI adenocarcinomas for which no standard or curative treatments are available. The second part is a dose-expansion study at the MTD or OBD in subjects with refractory CRC, refractory pancreatic cancer, or refractory gastroesophageal cancer. Approximately 4 to 10 investigational sites throughout the United States of America (USA) will participate in this study.

Dose escalation began with single-subject cohorts (Cohorts 1 through 4; see Figure 3.1-1 and Table 4.5.2-1) and continued with standard 3+3 dose-escalation cohorts from Cohort 5 through 10. Ten cohorts have been enrolled to date. The starting dose of 0.75 μg was chosen based on the $EC_{20}$ (effective concentration that induced 20% of the maximum effect) obtained using a sensitive in vitro tumor cell lysis assay (Section 1.2.3). The initial 4 cohorts were single-subject cohorts with approximately 200% increases in dose up to the fifth cohort. The first subject enrolled in Cohort 5 (initially a single-subject cohort) experienced treatment-related Grade 2 AEs of vomiting and infusion reaction, and 2 additional subjects were enrolled per the original protocol. One of these additional subjects in Cohort 5 experienced a treatment-related Grade 2 AE of abdominal pain, triggering implementation of standard 3+3 enrollment in Cohort 5 and for all subsequent cohorts. As described in previous versions of this protocol, the dose in Cohort 6 was increased by 100% from Cohort 5 (from 60 to 120 μg) rather than by 200%. Doses in cohorts 6 through 10 were increased by approximately 100% to 150% following the dose-escalation rules described in Section 4.5.4.2. Under Amendments 1-3 of the protocol, the occurrence of dose-limiting hypoxia in 2 subjects in Cohort 10 (3-mg dose), indicates that the MTD has been exceeded at the 3-mg dose. However, available data suggest that the observed DLTs were reversible and potential future cases of hypoxia temporally associated with MEDI-565 administration should be manageable with the implementation of additional risk mitigation measures including prophylactic dexamethasone

administration prior to MEDI-565 administration and additional blood pressure, heart rate, and pulse oximetry monitoring during and following administration of MEDI-565. To minimize risk to subjects, Amendment 4 of Study MI-CP216 will re-start dosing at the next previously lower dose of 1.5 mg (ie, 1 dose level below the level at which the hypoxia events were observed) with implementation of the additional risk mitigation measures outlined above for all new subjects. A dose of 1.5 mg was chosen to re-start the study because it was judged to be more conservative from a safety standpoint and consistent with standard practice to de-escalate one dose level below the dose level (ie, 3 mg) at which the DLTs of hypoxia were observed. Provided no more than 1 out of 6 subjects experience DLTs in the preceding cohort, dose escalation is planned to continue in sequential fashion and re-evaluate the 3 mg dose (Cohort 12) followed by 5 mg (Cohort 13), 7.5 mg (Cohort 14), and 10 mg (Cohort 15) doses.

MEDI-565 will be administered by IV infusion over 3 hours per day for 5 consecutive days (ie, Days 1 through 5) every 28 days (defined as 1 cycle). Subjects in the dose-escalation phase are considered evaluable if they receive at least 1 full cycle of MEDI-565 and complete the safety follow-up through the DLT evaluation period of 28 days after the first dose of MEDI-565, or experience any DLT as defined in Section 4.5.4.5. Subsequent cycles may be delayed for up to 7 days for management of some types of toxicity (Section 4.5.4.4) or to accommodate scheduling issues. Nonevaluable subjects, defined as any subject discontinued during the DLT evaluation period for reasons other than a DLT, will be replaced in the same dose cohort. No intra-subject dose escalation will be allowed.

Dose escalation will continue until the MTD or a maximum dose of 10 mg is reached. In the event that no DLTs are observed during dose escalation and significant antitumor activity is observed, the Sponsor may halt dose escalation prior to determining the MTD provided that PK, pharmacology, safety and preliminary antitumor activity data support the use of an OBD below the MTD. On determination of the MTD or OBD, additional subjects will be enrolled so that a total of 6 subjects receive the MTD/OBD during the dose-escalation phase.

Once the MTD or OBD is determined, a total of 60 additional subjects (20 each with refractory pancreatic adenocarcinoma, refractory CRC, or refractory gastroesophageal cancer) may be enrolled at MTD or OBD in a dose-expansion phase. Commencement of the dose-expansion phase and the selection of any tumor types will be based on any previously observed signal of antitumor activity and the safety profile of MEDI-565 emerging from the dose-escalation phase. Subjects in the dose-expansion phase will receive MEDI-565 at the MTD or OBD as a 3-hour IV infusion per day for 5 consecutive days every 28 days (defined

as 1 cycle). Subjects in the dose-expansion phase are considered evaluable for antitumor activity if they receive at least 2 full cycles of MEDI-565 or discontinue due to progressive disease or toxicity. Nonevaluable subjects in the dose-expansion phase will be replaced. All subjects who receive any amount of MEDI-565 will be considered evaluable for safety.

A study flow diagram is shown in Figure 3.1-1.

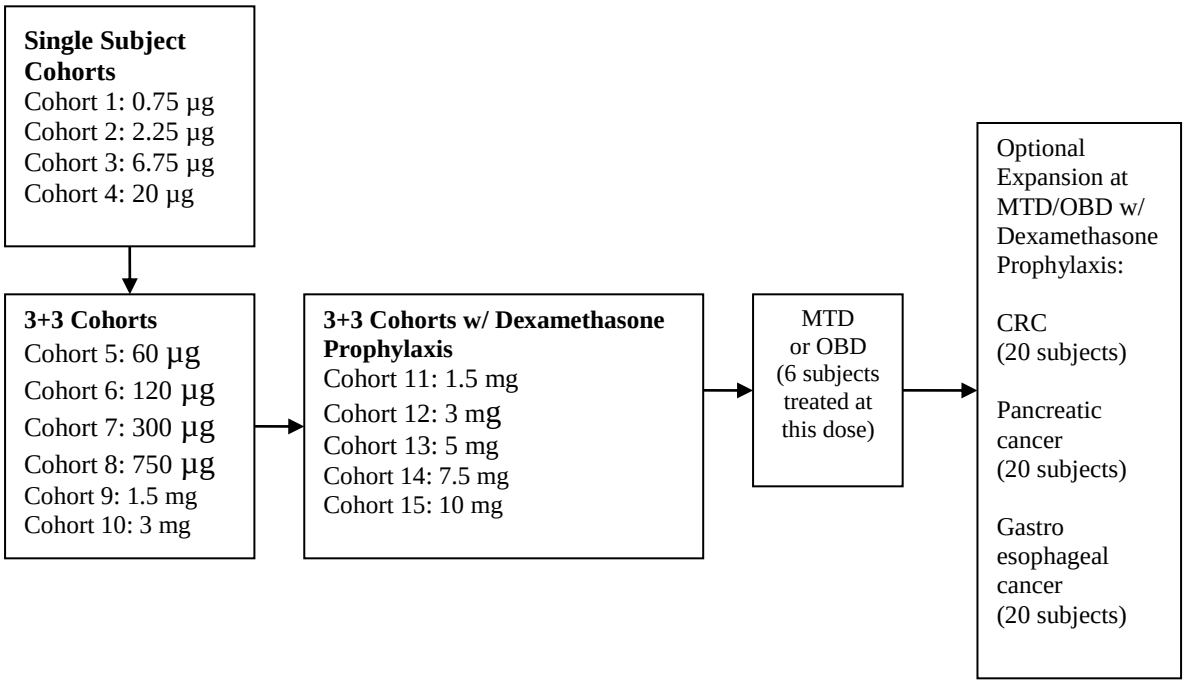


**Figure 3.1-1 Study Flow Diagram**

CRC = colorectal cancer; MTD = maximum tolerated dose; OBD = optimum biologic dose

The endpoints to be measured in this study are described in Section 7.3.

Standard 3+3 design for study enrollment is shown in Figure 3.1-2.

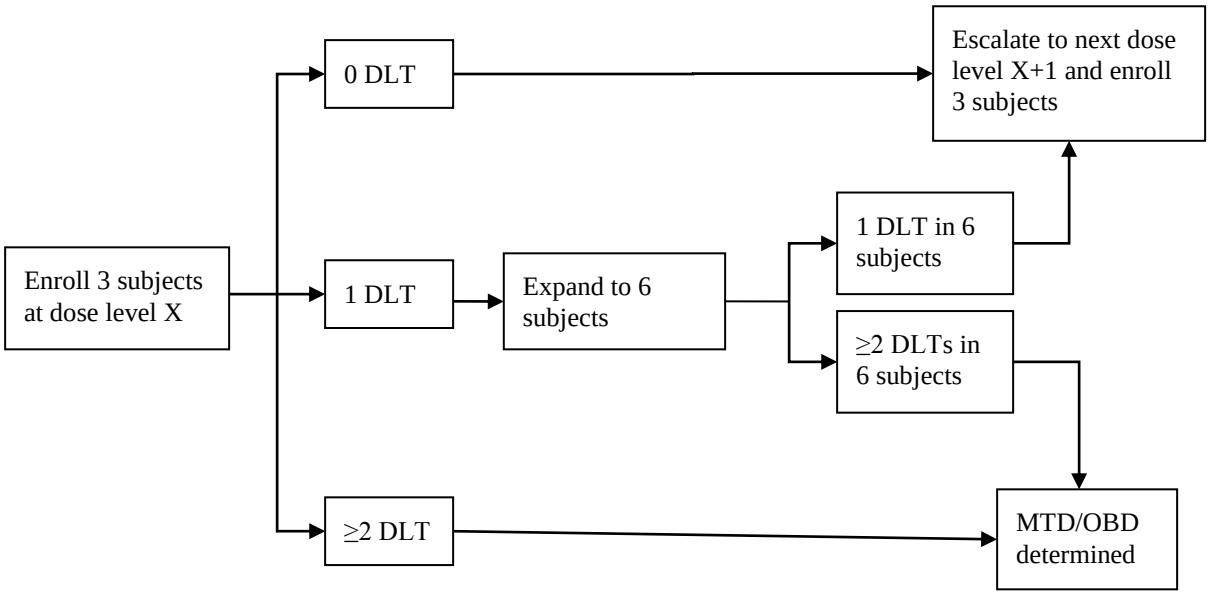


**Figure 3.1-2 Standard 3+3 Flow Diagram**

DLT = dose-limiting toxicity; MTD = maximum tolerated dose; OBD = optimum biologic dose

The diagram above shows the work flow of a standard "3+3" design. A dose-escalation trial enrolls a group of 3 subjects at dose level X. If no subject experiences a DLT, escalate to the next higher dose level, X+1. If 2 or more subjects experience a DLT, stop dose escalation. If 1 subject experiences a DLT, expand dose level X to a total of 6 evaluable subjects. If 1 of 6 experiences DLT, escalate to dose level X+1. If 2 or more of 6 experience DLT, stop dose escalation. If the study stops at dose level X, then the MTD is estimated as the prior dose level (X-1).

## 3.2 Estimated Duration of Subject Participation

In both the dose-escalation and dose-expansion phases, subjects will be treated with MEDI-565 until confirmed progressive disease (PD), initiation of alternative anticancer therapy, unacceptable toxicity, or other reasons to discontinue treatment. Subjects will be followed until the end of the study, which is defined as 1 year after the last subject begins treatment with MEDI-565 or the date the study is closed by the sponsor, whichever occurs first.

## 3.3 Study-stopping Criteria

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

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to subjects in the current study, determined after review of relevant information through internal MedImmune safety data review procedures.
- Subject enrollment is unsatisfactory.
- Non-compliance that might significantly jeopardize the validity or integrity of the study.
- Sponsor decision to terminate development.

In the case that a safety event requiring enrollment suspension occurs, 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 should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. The US FDA, relevant competent health authorities in participating countries, and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be notified of any event that triggers suspension of enrollment in this study. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

Decisions regarding ongoing treatment for any subjects who have already received investigational product and are currently in the study at the time study-stopping criteria are met will be made on a case-by-case basis after discussion with the subject, principal investigator, and the sponsor. In the case that a safety event requiring enrollment suspension occurs, all subjects on treatment will be re-consented. Regardless of whether dosing is continued or not, all subjects who were on treatment at the time of study-stopping criteria were met will continue to be followed by the investigator for safety.

Withdrawal criteria for individual subjects are provided in Section 4.2.3.

## 3.4 Rationale for Study Design, Doses, and Control Groups

An open-label, dose-escalation study with an expansion arm is a common study design in early-phase oncology trials and is considered appropriate for a FTIH study.

The purpose of this study is to determine the MTD or OBD of MEDI-565 in subjects with advanced adenocarcinomas of the GI tract. The study population, subjects with advanced adenocarcinomas with no available standard or curative therapies, is an appropriate population for testing a FTIH compound with potential for significant toxicities. This patient population has no available therapies that are likely to prolong survival and thus these patients have a significant unmet medical need. Subjects with less advanced disease still have options for life prolonging therapy, and administration of an agent without proven benefit would be inappropriate.

The dose-escalation scheme employed in this study is designed to rapidly achieve dose levels at which clinical activity may be observed while maintaining an adequate safety margin. The starting dose, 0.75 μg, was chosen based on the MABEL which was calculated from an $EC_{20}$ value derived from a sensitive in vitro assay (T-cell-mediated cytotoxicity). The administration schedule is based on nonclinical xenograft studies using exogenous human T cells which showed significant in vivo antitumor efficacy following daily IV or SC dosing with MEDI-565 for 5 days in mice. The same in vitro cytotoxicity assays predict that a 1.5 mg dose of MEDI-565 in humans will achieve blood concentrations equivalent to the $EC_{50}$ (effective concentration that induced 50% of the maximum effect) value, at which it is predicted that clinical activity may be observed. In order to achieve these serum concentrations as quickly as possible, while maintaining a sufficient safety margin, dose escalation under the original protocol was to proceed using 200% increases up to a dose of 1.5 mg after which subsequent increases in dose of 100%, 67%, 50%, and 33% would occur until the MTD or OBD was reached.

Cohorts 1 through 4 were successfully enrolled as single-subject cohorts to minimize the number of subjects with advanced, incurable cancers who are exposed to what are likely to be ineffective doses. Following the observation of a Grade 2 treatment-related AE that occurred in the first subject enrolled into Cohort 5, this cohort was expanded to 3 subjects to further evaluate the safety of the 60 μg dose level. A second subject in Cohort 5 experienced a Grade 2 treatment-related AE. Under the rules of the previous versions of the protocol, dose escalation was to then follow a modified Fibonacci sequence. However, given that no ≥ Grade 3 toxicities or DLTs were observed, dose-escalation continued at approximately

150% increases from 120 μg (starting with Cohort 6) up to 1.5 mg, followed by a 100% dose increase to 3 mg (Cohort 10).

Two of 5 subjects in Cohort 10 experienced DLTs of hypoxia. The hypoxia events could be indicative of pharmacodynamic changes induced by MEDI-565 exposure. Cytokine release may have been a contributing factor, and would be consistent with the mechanism of action and the overall clinical presentation. Under the previous version of the protocol, these 2 DLTs would have indicated that the MTD has been exceeded at the 3 mg dose. Available data suggest, however, that the observed DLTs were reversible and potential cases of hypxia temporally associated with MEDI-565 administration should be manageable with implementation of additional risk mitigation measures including prophylactic dexamethasone administration prior to MEDI-565 administration and additional blood pressure, heart rate, and pulse oximetry monitoring during and following administration of MEDI-565. Under Amendment 4, it is proposed that dosing can resume at the next previously lower dose of 1.5 mg (Cohort 11) with implementation of specific risk mitigation measures, and provided no more than 1 out of 6 subjects experience DLTs in a given cohort, dose escalation may continue in sequential fashion and re-evaluate higher doses including the 3 mg dose without undue risk, based on the following points:

- The observed hypoxia events occurred within hours after completion of the first MEDI-565 infusion and resolved without sequelae.
- In one case, the hypoxia was successfully managed with corticosteroids which appear to have shortened the time to resolution.
- Close monitoring for early identification of symptoms followed by rapid intervention could prevent any future hypoxia events from progressing.
- Subjects who had milder (Grade 1 or 2) symptoms on Cycle 1, Day 1 that were consistent with infusion-related reactions and went on to receive a second cycle of treatment, did not have recurrence of their initial symptoms.

Accordingly, Amendment 4 of the protocol will implement prophylactic measures and additional monitoring for hypoxia as described above. Unscheduled sampling for pharmacokinetic (PK) and cytokine release analysis will be collected from subjects who exhibit symptoms consistent with infusion-related reactions (see Section 4.5.4.1). Dosing will resume at a lower dose of 1.5 mg, followed by 3 mg, after which subsequent increases in dose will follow consist of relative dose escalations of 67% (ie, 5 mg), 50% (ie, 7.5 mg), and 33% (ie, 10 mg). This scheme will provide an opportunity to appropriately identify an MTD or OBD, while minimizing risk to subjects from potential infusion-associated hypoxia.

The second part of the trial (dose-expansion phase) may be initiated in any of the proposed tumor types (refractory pancreatic adenocarcinoma, refractory CRC, or refractory gastroesophageal cancer), and is designed to further examine the antitumor activity of MEDI-565 in these populations. However, commencement of the dose-expansion phase and the selection of any tumor types will be based on any previously observed signal of antitumor activity and the safety profile of MEDI-565 emerging from the dose-escalation phase.

Pancreatic cancer, CRC, and gastroesophageal cancer are being proposed based on a high prevalence of CEA expression on the tumor cells (> 90%) and differences in T-cell infiltration in these tumor types. Colorectal cancer patients have relatively high levels of infiltration with favorable prognosis associated with this feature independent of tumor stage (Galon et al, 2006), and patients with pancreatic cancer demonstrate reduced levels of circulating lymphocytes compared to healthy controls (Fogar et al, 2006) and lower levels of infiltration in a highly immunosuppressive environment (von Bernstorff et al, 2001). In gastric cancer, Maruyama et al demonstrated that the accumulation of Th17 cells as well as regulatory T cells (Treg) in the tumor microenvironment occurred at an early stage of the disease and then the infiltration of Th17 cells gradually decreased according to disease progression, in contrast to increased Treg (Maruyama et al, 2010). This may be important because T-cell infiltration may play a role in the activity of MEDI-565. As defined in the inclusion/exclusion criteria, these patient populations do not have therapies that are known to be life-prolonging or curative, and the observation of tumor shrinkage in even one or two subjects may suggest that further clinical evaluation should be undertaken. The dose-expansion phase is not intended to replace a randomized controlled Phase 2 study, but rather to explore the possibility of antitumor activity in advanced GI tract tumors that are not responsive to currently available therapies.

# 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 voice response system [IVRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

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

## 4.2 Subject Selection and Withdrawal

The subjects in this study will be adults with GI adenocarcinomas with no available standard or curative treatments.

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 Institutional Review Board (IRB). 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 USA), 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) Age ≥ 18 years of age at the time of screening
2) Written informed consent and any locally required authorization (eg, HIPAA in the USA) obtained from the subject or where allowed a legal representative prior to performing any protocol-related procedures, including screening evaluations
3) Females of childbearing potential, unless surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy), has a sterile male partner, or at least 2 years postmenopausal, or practices abstinence, must use 2 effective methods of avoiding pregnancy (including oral, transdermal, or implanted contraceptives, intrauterine device, female condom with spermicide, diaphragm with spermicide, cervical cap, or use of a condom with spermicide by the sexual partner) from screening, and must agree to continue using such precautions for 30 days after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician
4) Males, unless surgically sterile, must use 2 effective methods of birth control with a female partner of childbearing potential (as defined above) and must agree to continue

using such contraceptive precautions from Day 1 through 30 days after the last dose of MEDI-565

5) For the dose-escalation phase, subjects with GI adenocarcinomas with no available standard or curative treatments, including but not limited to, esophageal, gastric, small intestine, colorectal, biliary tract or pancreatic cancers confirmed by prior pathological assessment

6) For the dose-expansion phase, subjects must have CRC, pancreatic cancer, or gastroesophageal adenocarcinoma confirmed by prior pathological assessment with no available standard or curative treatments. Subjects must have measurable disease as defined by Response Evaluation Criteria in Solid Tumor (RECIST) criteria (Eisenhauer et al, 2009)

7) Adequate hematological function as defined by:

   a) Hemoglobin ≥ 8.0 g/dL

   b) Absolute neutrophil count (ANC) > $1.0 \times 10^9$/L

   c) Platelet count ≥ $75.0 \times 10^9$/L

   d) Lymphocyte count ≥ $0.8 \times 10^9$/L

   e) Prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR) within 1.5 times ULN or if receiving anticoagulant therapy an INR of ≤ 3.0 is allowed with concomitant increase in PT or an aPTT ≤ 2.5 × control

8) Adequate organ function as defined by:

   a) Total bilirubin ≤ 1.5 × upper limit of normal (ULN)

   b) Aspartate transaminase (AST), alanine transaminase (ALT), amylase, and lipase ≤ 2 × ULN

   c) Creatinine clearance greater than 50 mL/min as determined by Cockcroft -Gault equation (Cockcroft and Gault, 1976) or 24 hour urine creatinine determination.

9) For subjects who had prior treatment with chemotherapy, biological therapy, radiotherapy, or had prior surgery: eligible for study entry if at least 30 days have passed since their treatment/surgery, provided that all toxicities related to prior treatment have resolved to ≤ Grade 1 severity by the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.03 (NCI CTCAE v4.03) and all surgical wounds have healed

10) Life expectancy of at least 3 months

11) Karnofsky performance status ≥ 70%

12) Body weight ≥ 45 kg

### 4.2.2 Exclusion Criteria

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

1) 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
2) Concurrent enrollment in another clinical study
3) Employees of the clinical study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals
4) Prior treatment with MEDI-565
5) History of allergy or reaction to any component of the MEDI-565 formulation
6) History of malignancy other than GI adenocarcinoma, within 5 years prior to study entry, with the exception of ductal carcinoma in situ of the breast, basal cell carcinoma of the skin or carcinoma in situ of the cervix successfully treated with curative therapy
7) Diagnosis of hepatocellular carcinoma
8) Clinical history of significant CNS pathology, (including but not limited to history of brain metastasis, multiple occurrences of confusion, dementia, previous CNS infarcts, migraine headaches [within 6 months prior to starting therapy with MEDI-565], seizure disorder, or major brain surgery)
9) Active bacterial infection or known bacteremia. Subjects with documented evidence of culture positive sepsis or active infection requiring IV antibiotic therapy must complete a full course of antibiotic treatment with no clinical or laboratory evidence of bacterial infection at least 2 weeks prior to starting therapy with MEDI-565
10) Vaccination (either preventive or therapeutic for infectious disease or cancer) within 2 weeks prior to initiation of MEDI-565
11) Infection with HIV-1 or HIV-2; chronic infection with hepatitis B or C
12) History of primary immunodeficiency
13) History of chronic autoimmune disease, eg, rheumatoid arthritis, systemic lupus erythematosus, or multiple sclerosis
14) Elective surgery planned during the study period through 30 days after discontinuation of MEDI-565. Minor surgery such as removal or placement of a central venous access device or stent placement will be allowed.
15) Treatment with any chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment within 30 days prior to study entry and not recovered from treatment
16) Treatment with any investigational agent within 30 days prior to initiation of MEDI-565

17) Chronic use of systemic corticosteroids or other systemic immunosuppressive therapy during the 30 days prior to initiation of MEDI-565

18) Contraindication to any protocol-specified concomitant medications (including acetaminophen, antacids, antihistamines) administered during this study

19) Pregnancy or lactation

20) Evidence of any uncontrolled systemic disease (other than GI adenocarcinoma)

21) Recent history of cardiac disease, including myocardial infarction, unstable angina pectoris or uncontrolled arrhythmia within 6 months, or evidence of severe congestive heart failure with severity New York Heart Association (NYHA) classification > Class 1 within 12 weeks prior to screening

22) A marked baseline prolongation of corrected QT interval (QTc) interval (ie. demonstration of QTc interval ≥ 500 milliseconds)

23) Contraindications to the use of dexamethasone or equivalent prophylaxis

### 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) Any AE, that, in the opinion of the investigator or the sponsor, contraindicates further dosing

3) Subject is determined to have met one or more of the exclusion criteria for study participation (such subjects will be replaced if identified during the DLT period in the dose-escalation phase or at any point in the expansion phase)

4) Pregnancy or intent to become pregnant (see Section 6.4.3.3)

5) Documentation of PD

   If radiographic changes are believed by the investigator to be secondary to drug induced inflammation and not tumor progression, the investigator may postpone a diagnosis of PD until the next scheduled radiographic evaluation in the study (Wolchok et al, 2009).

6) Subject noncompliance

7) Initiation of alternative anti-cancer treatment

8) Treatment with another investigational agent

9) Dose-limiting toxicity (see Section 4.5.4.5 for definition of DLTs)

10) After Cycle 1 (protocol-defined DLT period), any events of unacceptable toxicity (as defined by DLT criteria). Exceptions to this may be granted on a case-by-case basis

for subjects who are receiving clinical benefit and whose unacceptable toxicity resolves within 7 days, and must be agreed to in conjunction with the FDA (see Section 4.5.4.4)

11) After Cycle 1 (protocol-defined DLT period), any events where MEDI-565 treatment is interrupted and a cycle is delayed more than 7 days for reasons of toxicity, or treatment is delayed more than once during the study (see Section 4.5.4.4)

12) Occurrence of an acute infusion reaction or cytokine release syndrome resulting in pyrexia, chills, or NCI CTCAE v4.03 Grade 2 hypotension that does not allow for the completion of the infusion within 6 hours from the start of the infusion despite a slowing of the infusion rate or treatment with fluids, antihistamines, or steroids

13) Occurrence of a Grade 3 or greater event as a component of the cytokine release syndrome

14) Occurrence of a suspected immunoglobulin E (IgE)-mediated allergic reaction (ie. presence of urticaria or bronchospasm)

15) Significant medical events that in the opinion of the medical monitor or investigator warrant subject discontinuation.

**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 end of study (defined as 1 year after the final subject is entered into the study or the date the study is closed by the sponsor).

- 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 4.6).

Subjects who are permanently discontinued from receiving investigational product will be followed for safety through the full study period through 30 days after the last administration

of MEDI-565, including the collection of any protocol-specified blood or urine specimens, unless consent is withdrawn, lost to follow-up, or enrolled in another clinical study. In addition, subjects will be followed for disease evaluations every 3 months (± 2 weeks) until disease progression, death, initiation of alternative anticancer treatment, withdrawal of consent, or end of study (defined as 1 year after the last subject begins treatment or the date the study is closed by the sponsor), and for survival every 3 months until death, withdrawal of consent, or end of study.

### 4.2.4 Replacement of Subjects

In the dose-escalation phase, nonevaluable subjects, defined as any subject discontinued during the DLT evaluation period for reasons other than a DLT, will be replaced in the same dose cohort.

In the dose-expansion phase, subjects who do not complete at least 2 cycles of MEDI-565 for reasons other than disease progression or toxicity will be replaced.

## 4.3 Treatment Assignment

An Interactive Voice/Web Response System (IXRS) will be used to both document participation and to assign a dose cohort (dose-escalation phase), a dose level (tumor regression escalation), or a treatment arm (dose-expansion phase) to the subject. A subject is considered entered into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and the IXRS provides the assignment of investigational product.

The procedure for using IXRS is as follows:

- Once the subject has signed the informed consent form, the investigator or designee contacts the IXRS and the SID number will be provided. The subject will keep this SID number throughout the study.
- After confirmation of eligibility, 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 dose cohort or treatment arm 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, site's subject screening log, and investigational product accountability log

Details for using the IXRS will be provided in the IXRS manual.

Investigational product (MEDI-565) must be administered after the dose cohort or treatment arm is assigned. 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 (see Section 4.5.3).

## 4.4 Blinding

This study is not blinded.

## 4.5 Study Treatment

### 4.5.1 Investigational Product Supplies and Accountability

Investigational product will be distributed to clinical sites using designated distribution centers. MedImmune will provide the investigator(s) with adequate quantities of investigational product. All MEDI-565 materials must be stored at 2°C to 8°C (36°F to 46°F).

**MEDI-565:** MEDI-565 is supplied in 3 mL vials. MEDI-565 is a sterile lyophilized formulation (0.25 mg MEDI-565 per vial, 0.5 mL nominal after reconstitution). The formulation after reconstitution is 0.5 mg/mL in 30 mM sodium citrate/citric acid, 75 mM L-lysine hydrochloride, 172 mM (6.5% w/v) trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0.

**MEDI-565 IV Bag Protectant:** MEDI-565 IV Bag Protectant is supplied in 20 mm vials as a sterile liquid formulation. The formulation is 25 mM citric acid, 1.25 M L-lysine hydrochloride and 0.1% (w/v) polysorbate 80, pH 7.0.

The compatibility of reconstituted MEDI-565 Drug Product was demonstrated for the preparation and administration procedures described below. The results showed that administration of MEDI-565 requires the use of an IV Bag Protectant to minimize adsorption of active material to IV bag and administration set components. MEDI-565 is compatible with properly treated standard IV infusion components composed of polyethylene or polyolefin that are DEHP-free and latex-free. IV bags containing a 0.9% sodium chloride (normal saline) solution using a representative administration set with a 0.2 μm in-line filter were tested.

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 or its designee.

### 4.5.2 Treatment Regimen

MEDI-565 will be administered by IV infusion over 3 hours per day for 5 consecutive days every 28 days (1 cycle). The starting dose will be 0.75 μg.

The proposed dose levels for MI-CP216 are detailed in Table 4.5.2-1.

Criteria for stopping and restarting the infusion are described in Section 4.5.4.4. Treatment may be continued in subjects who have a response of SD or better, until documentation of disease progression, initiation of alternative anticancer therapy, unacceptable toxicity, or other reasons for treatment withdrawal. Cycles may be delayed for up to 7 days for management of toxicity as described in Section 4.5.4.4 or to accommodate scheduling issues.

Beginning with Amendment 4 and as part of the overall risk mitigation plan, subjects will be admitted for inpatient infusion of MEDI-565 starting with Cycle 1, Day 1 until completion of the infusion on Cycle 1, Day 2 and again beginning with the infusion on Cycle 1, Day 4 until completion of the infusion on Cycle 1, Day 5. Subjects may be discharged after all protocol-mandated procedures and monitoring for the given visit are complete and the subject is clinically stable. Subsequent infusions of MEDI-565 will be administered to subjects on an outpatient basis.

**Table 4.5.2-1 MEDI-565 Dose Levels for Dose-escalation Cohorts and Expansion Arm**

| Dose Cohort | No. of Subjects | MEDI-565 Dose |
|---|---|---|
| 1 | 1 | 0.75 µg by IV infusion over 3 hours per day for 5 days |
| 2 | 1 | 2.25 µg by IV infusion over 3 hours per day for 5 days |
| 3 | 1 | 6.75 µg by IV infusion over 3 hours per day for 5 days |
| 4 | 1 | 20 µg by IV infusion over 3 hours per day for 5 days |
| 5 | 3 | 60 µg by IV infusion over 3 hours per day for 5 days |
| 6 | 3 | 120 µg by IV infusion over 3 hours per day for 5 days |
| 7 | 3 | 300 µg by IV infusion over 3 hours per day for 5 days |
| 8 | 3 | 750 µg by IV infusion over 3 hours per day for 5 days |
| 9 | 3 | 1.5 mg by IV infusion over 3 hours per day for 5 days |
| 10 | 5 | 3 mg by IV infusion over 3 hours per day for 5 days |
| 11 [a] | 3-6 | 1.5 mg by IV infusion over 3 hours per day for 5 days |
| 12 [a] | 3-6 | 3 mg by IV infusion over 3 hours per day for 5 days |
| 13 [a] | 3 - 6 | 5 mg by IV infusion over 3 hours per day for 5 days |
| 14 [a] | 3 - 6 | 7.5 mg by IV infusion over 3 hours per day for 5 days |
| 15 [a] | 3 - 6 | 10 mg by IV infusion over 3 hours per day for 5 days |
| Pancreatic cancer expansion | Up to 20 | MTD/OBD by IV infusion over 3 hours per day for 5 days |
| CRC expansion | Up to 20 | MTD/OBD by IV infusion over 3 hours per day for 5 days |
| Gastroesophageal cancer expansion | Up to 20 | MTD/OBD by IV infusion over 3 hours per day for 5 days |

CRC = colorectal cancer; IV = intravenous; MTD = maximum tolerated dose; OBD = optimum biologic dose.
[a] All subjects enrolled in Cohort 11 or higher or in an expansion cohort will receive dexamethasone prophylaxis.

In the dose escalation phase, the minimum number of subjects (1 or 3) will enroll according to DLT rules. The maximum number of subjects includes up to 6 evaluable subjects enrolled in each cohort.

In the dose-expansion phase, 3 treatment arms of approximately 20 subjects with refractory pancreatic adenocarcinoma, 20 subjects with refractory CRC, and 20 subjects with refractory gastroesophageal cancer will receive MEDI-565 at the MTD/OBD dose by IV infusion over 3 hours per day for 5 consecutive days every 28 days.

### 4.5.3 Investigational Product Preparation

MEDI-565 is supplied as a lyophilized Drug Product requiring reconstitution prior to use. The reconstitution should be performed with 0.7 mL sterile water for injection (WFI) for each vial with the liquid added gently to the side of the vial to minimize product foaming. The vial should be gently rotated or swirled for 30 seconds or until dissolution is complete. Do not shake or vigorously agitate the vial. Reconstituted MEDI-565 should stand undisturbed at room temperature for a minimum of 5 minutes or until the solution clarifies. The reconstituted solution should appear clear or slightly opalescent. A thin layer of bubbles on the liquid surface is considered normal. MEDI-565 IV Bag Protectant is supplied as a ready-to-use liquid that should appear as a clear to slightly opalescent, colorless to slightly yellow liquid. Allow the vials selected for administration to come to room temperature. The volumes of reconstituted MEDI-565 Drug Product and MEDI-565 IV Bag Protectant to be added to the IV bag are calculated as described below.

#### Calculations:

The volume of MEDI-565 IV Bag Protectant to be added to the IV bag is equal to 5% of the nominal volume of the IV bag:

Volume of IV Bag Protectant (mL) = IV bag nominal volume × 0.05

For example, in preparing a 100 mL IV bag the following amount of MEDI-565 IV Bag Protectant will be required:

100 mL IV bag × 0.05 = 5.0 mL MEDI-565 IV Bag Protectant

The volume of reconstituted MEDI-565 Drug Product (dose volume) for IV infusion is calculated based on the dose using the following formula:

Dose Volume (mL) = Dose Level (mg/day) ÷ Concentration (0.5 mg/mL).

For example, a subject scheduled to receive a dose of MEDI-565 at 0.6 mg/day will require the following amount:

0.6 mg/day ÷ 0.5 mg/mL = 1.2 mL dose volume.

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 volume of

0.9% sodium chloride solution equivalent to the calculated MEDI-565 dose volume plus the volume of IV Bag Protectant must first be removed. This step is then followed, in order, by the addition of the calculated volume of the IV Bag Protectant and then the MEDI-565 dose volume. The bag should be gently and thoroughly mixed after addition of the IV Bag Protectant and again after addition of MEDI-565.

MEDI-565 and IV Bag Protectant do not contain preservatives and any unused portion must be discarded. Total in-use storage time from reconstitution of MEDI-565 to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C. If in-use storage time exceeds these limits, a new dose must be prepared from new vials.

The entire volume of the 100 mL IV bag should be administered over 3 hours and followed by a 20 mL flush of normal saline. The end of the infusion is the time after the flush has been administered.

The MEDI-565 Dose Preparation Table will be utilized to ensure correct dose preparation. For doses less than or equal to 120 μg/day, MEDI-565 must be prepared in two dilution steps. For doses greater than 120 μg/day, MEDI-565 must be prepared in one dilution step (see Appendix 5).

### 4.5.4 Investigational Product Administration

The day of receipt of the first dose of investigational product is considered Day 1. For each treatment cycle, MEDI-565 will be administered by IV infusion over 3 hours per day for 5 consecutive days.

Under Amendment 4 of the protocol and as part of the overall risk mitigation plan for infusion-associated hypoxia, prophylactic dexamethasone (8 mg) or equivalent will be administered at the following 4 time points during Cycle 1, Day 1:

- 8 hours (± 15 minutes) and within 30 minutes PRIOR to the start of MEDI-565 infusion, and
- 8 hours (± 15 minutes) and 16 hours (± 15 minutes) AFTER the start of MEDI-565 infusion.

This regimen or equivalent may be followed during subsequent MEDI-565 infusions per the investigator's clinical judgment.

#### 4.5.4.1 Monitoring of Dose Administration

Subjects will be monitored with assessment of vital signs and pulse oximetry at the following time points: within 15 minutes prior to the start of infusion, every 0.5 hours (± 5 minutes) during infusion, immediately post end of infusion (EOI) (± 5 minutes), and 0.5 hours (± 5 minutes), 1 hour (± 5 minutes), and 2 hours (± 15 minutes) after the EOI.

Specifically on Cycle 1, Day 1, monitoring of vital signs and pulse oximetry will continue beyond the 2 hour post EOI time point until the start of infusion on Cycle 1, Day 2 as follows:

- 4 hours (± 15 minutes), 6 hours (± 15 minutes), and 8 hours (± 15 minutes) post EOI
- 12 hours (± 15 minutes), 16 hours (± 15 minutes), 20 hours (± 15 minutes), and 24 hours (± 15 minutes) post EOI

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.

With MEDI-565, the most frequent acute signs/symptoms observed with study drug infusions and assessed as drug-related included: fever, shaking chills, nausea, vomiting, abdominal pain, headache and hypoxia. In the event that such adverse events are noted and are clinically significant, in the absence of a clear alternative etiology, consider steroid treatment (8 mg dexamethasone every 8 hours, or equivalent) until evidence of resolution. If a subject experiences any symptoms such as those listed above, further dosing should be delayed until the subject is clinically stable and the symptoms are resolved. If steroids are clinically indicated to manage any Grade 3 or higher infusion-related signs/symptoms, all remaining doses in the current cycle should be aborted. If steroids are clinically indicated to manage any Grade 2 or lower infusion-related signs/symptoms, the infusion rate should be decreased for the current dose and all remaining doses in the cycle.

In the event of an infusion-related reaction, the infusion of MEDI-565 may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and reinitiated at 50% of the initial rate until completion of the infusion. Acetaminophen and/or an antihistamine (eg. diphenhydramine) may be administered at the discretion of the investigator as long as liver function tests (LFTs) are within normal limits. If the infusion reaction is severe or prolonged, glucocorticoids (dexamethasone 8 mg every 8 hours, or equivalent, or by standard

institutional practice) should be administered as well following best medical practice. For subsequent infusions in subjects who experience an infusion reaction and do not require discontinuation of MEDI-565 (see Table 4.5.4.4-1), acetaminophen and an antihistamine may be administered prior to initiation of the MEDI-565 infusion.

### 4.5.4.2 Dose Escalation

Rules for dose escalation are as follows:

1) The MTD will be determined based on the assessment of a DLT (refer to Section 4.5.4.5) during the DLT period, which is defined as the time from the first dose of MEDI-565 to 28 days after the first dose of MEDI-565 (Cycle 1). Subjects are considered evaluable for assessment of DLT if they receive at least 1 full cycle of MEDI-565 (Days 1-5, Cycle 1) and complete the safety follow-up (Days 6-28, Cycle 1) through the DLT evaluation period or experience any DLT. Nonevaluable subjects will be replaced.
2) If a Grade 3 or greater AE or toxicity corresponding to a DLT occurs in any cohort, that cohort will be expanded to 6 evaluable subjects. If 1 of 6 subjects experiences a DLT in the expanded cohort, dose escalation will proceed to the next dose level. If ≥ 2 subjects experience a DLT in a given cohort, the MTD will have been exceeded and the next lower dose will be evaluated as the MTD. The MTD will be defined as the highest dose, up to 10 mg, at which no more than 1 out of 6 subjects experience a DLT.
3) If the MTD is exceeded during dose escalation (≥ 2 out of 6 subjects experience a DLT in a given cohort), and the prior lower dose level is demonstrated to be safe (≤ 1 out of 6 subjects with DLTs), an intermediate dose may be evaluated if appropriate based on available PK, pharmacodynamics, safety, and clinical data. Dose escalation must stop prior to reaching the dose and exposure for the cohort that exceeded the MTD.
4) If significant antitumor activity is observed during dose escalation prior to identifying an MTD and before reaching the 10 mg dose, the Sponsor may halt dose escalation without determining the MTD. In this case, an OBD below the MTD may be chosen for the dose-expansion phase of the study, provided this is supported by the safety, antitumor activity, PK, pharmacodynamic, and biomarker data.

A study-specific Dose Escalation 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 making recommendations regarding further conduct of the study. The sponsor will notify sites when enrollment into each dose cohort has been completed and when enrollment into the next dose cohort is permitted. In addition, MedImmune's internal safety monitoring committee (ie, SMC or equivalent), provides safety

surveillance, guidance, and oversight for all clinical development trials in which MedImmune has sponsor accountabilities. Details of the composition and role of the Dose Escalation Committee and the SMC (or equivalent) are presented in Section 6.5.

At the discretion of the sponsor, an intermediate dose may be chosen for dose escalation. Situations that might prompt selection of an intermediate dose include unexpected toxicities that do not meet the definition of DLT or multiple similar toxicities in a cohort that do not meet definition of a DLT. If an intermediate dose is chosen, dose escalation will be to the next listed dose, provided all the criteria for dose escalation above are met. Further escalation will be based on toxicities observed at each dose level, and may proceed on the original schedule or include additional intermediate steps based on accumulated safety data.

#### 4.5.4.3 Dose Expansion

During the dose-escalation phase, the MTD will be determined as described in Section 4.5.4.2 or an OBD will be selected as determined by available PK, IM, biomarkers, safety, and available antitumor activity data. The selected dose for the dose-expansion phase will not exceed the MTD nor the highest dose tested in the dose-escalation phase.

#### 4.5.4.4 Dose Modification for Toxicity Management

**Management of Dose Interruption During Infusion**

The MEDI-565 infusion will be stopped immediately for the following events:

- The subject experiences a DLT as defined in Section 4.5.4.5
- The subject meets criteria for temporary or permanent discontinuation of MEDI-565 as described in Section 4.2.3
- The investigational product is incorrectly prepared or administered (eg, overdose)
- There is a technical problem with the infusion pump

The MEDI-565 infusion may be restarted according to the criteria listed below:

- If the MEDI-565 infusion is interrupted for reasons other than toxicity, it can be restarted at the same dose with no additional measures required
- If the MEDI-565 infusion is interrupted for management of toxicity, it may be restarted according to the guidelines in Table 4.5.4.4-1

## Dose Modification Following the DLT Period

Following the DLT period, any unacceptable toxicity (as defined by the DLT criteria) will result in the discontinuation of MEDI-565; subjects who have DLT-like events after the DLT period will not be retreated with MEDI-565. Exceptions to this may occur on a case-by-case basis for subjects who have experienced clinical benefit and whose unacceptable toxicity resolves within 7 days. Decisions to retreat such subjects will be made in conjunction with the FDA.

For other toxicities observed following completion of the DLT period, subsequent cycles of MEDI-565 may be delayed or modified as described in Table 4.5.4.4-1. Both hematologic and nonhematologic toxicities will be graded according to NCI CTCAE v4.03.

**Table 4.5.4.4-1 MEDI-565 Dose Modification Table (Cycle 2 and Greater)**

| Hematologic or Nonhematologic Toxicity | Dose Modification of MEDI-565 |
|---|---|
| ≤ Grade 1 | None |
| Grade 2 | For AEs occurring during treatment with MEDI-565, do not stop infusion. The infusion may be slowed but must be completed within 6 hours. Grade 2 hypotension, pyrexia or chills that do not respond to medical therapy and do not allow completion of the infusion within 6 hours will result in permanent discontinuation of MEDI-565.<br><br>For AEs present at the end of the treatment cycle, delay next cycle of MEDI-565 for up to 7 days until resolution to ≤ Grade 1 or baseline, and resume at current dose level.<br><br>If AE does not resolve to ≤ Grade 1 or baseline within 7 days of the end of the cycle, initiate next cycle at 50% of current dose level. |

**Table 4.5.4.4-1 MEDI-565 Dose Modification Table (Cycle 2 and Greater)**

| Hematologic or Nonhematologic Toxicity | Dose Modification of MEDI-565 |
|---|---|
| Grade 3 or 4 | **First Occurrence** [a] **:**<br>Discontinue MEDI-565 if toxicity meets the criteria for DLT as defined for the first cycle of treatment (see Section, 4.5.4.5) including Grade 3 or 4 cytokine release syndrome or allergic reactions. Subjects who experience a Grade 3 or 4 toxicity that meets DLT criteria that resolves within 7 days (except cytokine release syndrome or allergic reaction) and who are demonstrating clinical benefit may be allowed to continue receiving MEDI-565 following consultation with FDA.<br>For Grade 3 or 4 toxicities that do not meet DLT criteria and resolve to Grade 1 or baseline within 7 days MEDI-565 may be continued at 50% of current dose level.<br>For acute infusion reactions, AEs will be treated symptomatically and the rate of infusion may be slowed. If infusion is completed within 6 hours, subsequent doses of MEDI-565 may resume at 50% of current dose level. If infusion is not completed within 6 hours, discontinue MEDI-565.<br>**Second Occurrence** [a]**:**<br>Discontinue MEDI-565. |

[a] Refers to the first or second occurrence of a Grade 3 or 4 toxicity in a given subject, at any dose level, for any cycle after Cycle 1

### 4.5.4.5 Dose-limiting Toxicity

The period for evaluating DLTs will be from the time of first administration of MEDI-565 through the first 28-day cycle. Subjects who do not receive 1 full cycle of MEDI-565 for reasons other than a DLT will be replaced with another subject in the same dose level. Grading of DLTs will be according to the NCI CTCAE v4.03.

Dose-limiting toxicities include any Grade 3 or greater nonhematological toxicity or laboratory abnormality that cannot be reasonably ascribed to another cause (such as disease progression or accident) with the following exceptions:

1) Grade 3 or 4 elevations in liver transaminases (either AST, ALT or both) that resolve to ≤ 2 × ULN or baseline within 14 days after cessation of MEDI-565 infusion

2) Grade 3 changes in serum electrolytes in subjects with previously identified electrolyte abnormalities that resolve within 48 hours of initiation of repletion or cessation of MEDI-565

3) Grade 3 elevations in temperature that do not result in an SAE and resolve with or without medical therapy, unless associated with other symptoms of cytokine release syndrome

4) Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)

5) Grade 3 infusion-related event that resolves with appropriate supportive care within 12 hours, with no associated sequelae

For hematological toxicities, any related Grade 3 or greater hematological toxicities or laboratory abnormalities will be considered to be DLTs with the following exceptions:

- Grade 3 or greater lymphopenia
- Grade 3 neutropenia that resolves prior to the next cycle of MEDI-565

### 4.5.5 Concomitant Medications

Subjects may receive medications as supportive care or to treat AEs as deemed necessary by the investigator or the subject's physician. Chronic use of corticosteroids or other immunosuppressives is not permitted during treatment with MEDI-565; however, use as a primary prophylaxis, and when medically indicated as treatment for an acute illness or as pretreatment before CT scans (for contrast allergies) is allowed. Permitted uses of corticosteroids as treatment for infusion reactions or pretreatment before infusions are described in Section 4.5.4.1. No other concomitant medications are limited or excluded other than monoclonal antibodies and investigational therapies.

All concomitant medications given to the subject from the time the subject signs the informed consent form through 30 days after the last dose of MEDI-565 will be recorded on the source document. The sponsor must be notified if any subject receives immunosuppressive therapy including corticosteroids in excess of 40 mg/day of prednisone or the equivalent, except if given in the management of an acute infusion reaction.

### 4.5.6 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

### 4.6 Subject Completion

An individual subject will be considered to have completed the study if the subject was followed until the end of the study (defined as 1 year after the last subject entered the study or the date the study is closed by the sponsor), regardless of the number of doses of investigational product that was received.

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

### 4.7 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. This date will be 1 year after the final subject is entered into the study or the date the study is closed by the sponsor, whichever occurs first. 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 Assessment of Efficacy and Clinical Pharmacology

### 5.1 Efficacy and Clinical Pharmacology Parameters

#### 5.1.1 Efficacy and Clinical Pharmacology Parameters

The PK parameters for MEDI-565 to be assessed include $C_{max}$, $T_{max}$, AUC, CL, $V_d$, and, $t_{1/2.}$

Immunogenicity of MEDI-565 will be evaluated by examining the presence of anti-MEDI-565 antibodies in blood samples.

The antitumor activity of MED-565 will be assessed using objective response rate (ORR), time to response (TTR), duration of response (DR), time to progression (TTP), progression-free survival (PFS), and overall survival (OS) using RECIST guidelines (Eisenhauer et al, 2009).

If radiographic changes are believed by the investigator to be secondary to drug induced inflammation and not tumor progression, the investigator may postpone a diagnosis of PD until the next scheduled radiographic evaluation in the study (Wolchok et al, 2009).

Biomarkers that will be evaluated in this study include, but are not limited to, flow cytometric analysis of whole blood for T cell, B cell and natural killer (NK) cell counts and subsets, circulating cytokines, circulating soluble protein markers (eg, CEA, nucleosomal DNA, M30/M65), circulating tumor cells, expression level of CEA protein and T-cell numbers in archival tumor tissue samples (if samples and assays are available).

## 5.2 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 and 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 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.

For cycle 2 or greater, the start of the cycle may be delayed for up to 7 days to accommodate scheduling.

A schedule of study procedures is presented in Table 5.2-1 and Table 5.2-2 followed by a description of each visit. A description of the study procedures is included in Section 5.3.

**Table 5.2-1 Schedule of Subject Evaluations: Screening and Treatment Periods**

| Procedure | Screening | Cycle 1 | | | | | | | | Cycle 2 and Every Cycle Thereafter | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Evaluation** | **Day -30 to Day -1** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 8** | **Day 15** | **Day 22** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 8** | **Day 15** | **Day 22** |
| Written informed consent & HIPAA/ assignment of SID | X | | | | | | | | | | | | | | | | |
| Verify eligibility criteria | X | X | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | |
| Hepatitis B, C | X | | | | | | | | | | | | | | | | |
| HIV-1, HIV-2 | X | | | | | | | | | | | | | | | | |
| Serum βHCG | X | | | | | | | | | | | | | | | | |
| Urine or Serum βHCG | | X | | | | | | | | X | | | | | | | |
| Mini-Mental State Exam and gait assessment | X | X | X | X | X | X | X | X | X | X | | | | | X | X | X |
| MEDI-565 administration | | X | X | X | X | X | | | | X | X | X | X | X | | | |
| Dexamethasone prophylaxis | | X | | | | | | | | | | | | | | | |
| Toxicity monitoring | | X | X | X | X | X | | | | X | X | X | X | X | | | |
| Physical examination | X | X | | | | | | | | X | | | | | | | |
| Height | X | | | | | | | | | | | | | | | | |

**Table 5.2-1 Schedule of Subject Evaluations: Screening and Treatment Periods**

| Procedure | Screening | Cycle 1 | | | | | | | | Cycle 2 and Every Cycle Thereafter | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Evaluation** | **Day -30 to Day -1** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 8** | **Day 15** | **Day 22** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 8** | **Day 15** | **Day 22** |
| Weight | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Vital signs and pulse oximetry | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| ECG | X | X | | | | X | | | | X | | | | | | | |
| AE/SAE assessment | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Karnofsky Performance Status | X | X | | | | | X | X | X | X | | | | | X | X | X |
| Hematology | X | X | | | | X | X | X | X | X | | | | | X | X | X |
| Serum chemistry | X | X | | | | X | X | X | X | X | | | | | X | X | X |
| Urinalysis | X | X | | | | X | X | X | X | X | | | | | X | X | X |
| Coagulation parameters | X | X | | | | X | X | X | X | X | | | | | X | X | X |
| MEDI-565 serum concentration | | X | X | X | X | X | X | | | X | X | | | X | X | | |
| Anti-MEDI-565 antibodies | | X | | | | | X | | | X | | | | | X | | |
| Circulating tumor cells | X | | | | | | | | | | | | | | | | |
| Flow cytometric analysis | | X | X | X | X | X | X | X | X | X | X | | | X | X | X | X |

## Table 5.2-1 Schedule of Subject Evaluations: Screening and Treatment Periods

| Procedure | Screening | Cycle 1 | | | | | | | | Cycle 2 and Every Cycle Thereafter | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Evaluation** | **Day -30 to Day -1** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 8** | **Day 15** | **Day 22** | **Day 1** | **Day 2** | **Day 3** | **Day 4** | **Day 5** | **Day 8** | **Day 15** | **Day 22** |
| Circulating cytokines | | X | X | X | | | X | | X | X | | | | X | | | |
| Circulating soluble protein biomarkers | X | X | X | | X | | X | | X | X | | X | | | | | |
| Core-needle tumor biopsy (optional) | X | | | | X | | | | | | | | | | | | |
| Archival tumor tissue (optional) | X | | | | | | | | | | | | | | | | |
| CXR, CT, or MRI scans | X | | | | | | | | | | | | | | | | |

AE = adverse event; βHCG = beta-human chorionic gonadotropin; CT = computed tomography; CXR = chest x-ray; ECG = electrocardiogram; HIPAA = Health Insurance Portability and Accountability Act; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging SAE serious adverse event; SID = subject identification

Note: Dexamethasone prophylaxis is required at Cycle 1, Day 1 and may be administered at other time points according to the investigator's clinical judgment.

Note: In addition to the time points noted above, MEDI-565 serum concentration levels and circulating cytokines should be collected as an unscheduled sample collection at any visit if symptoms consistent with infusion-related reactions are present.

**Table 5.2-2 Schedule of Subject Evaluations: After Every 2 Cycles, End of Treatment, and Follow-up Periods**

| Procedure | After Every 2 Cycles | End of Treatment | Post Treatment | |
|---|---|---|---|---|
| **Evaluation** | | | **D30 Post** | **Q3 months** |
| Mini Mental State Exam and gait assessment | | X | X | |
| Physical examination | | X | X | X |
| Weight | | X | X | |
| Vital signs and pulse oximetry | | X | X | |
| ECG | | X | X | |
| AE/SAE assessment | X | X | X | |
| Concomitant medications | X | X | X | |
| Karnofsky Performance Status | | X | X | |
| Hematology | | X | X | X |
| Serum chemistry | | X | X | |
| Urinalysis | | X | X | |
| Coagulation parameters | | X | X | |
| MEDI-565 serum concentration | | X | X | |
| Anti-MEDI-565 antibodies | | X | X | |
| Circulating tumor cells | | X | X | |
| Flow cytometric analysis | | X | X | X |
| Circulating cytokines | | X | X | |
| Circulating soluble protein | | X | X | |

**Table 5.2-2 Schedule of Subject Evaluations: After Every 2 Cycles, End of Treatment, and Follow-up Periods**

| Procedure | After Every 2 Cycles | End of Treatment | Post Treatment | |
|---|---|---|---|---|
| **Evaluation** | | | **D30 Post** | **Q3 months** |
| biomarkers | | | | |
| CXR, CT, or MRI scans | X | X | X | X |
| Subsequent anticancer therapy | | | | X |
| Survival status | | | | X |

AE = adverse event; CT = computed tomography; CXR = chest x-ray; ECG = electrocardiogram; MRI = magnetic resonance imaging SAE = serious adverse event

Note: In addition to the time points noted above, MEDI-565 serum concentration levels and circulating cytokines may be collected at any visit if symptoms consistent with infusion-related reactions are present.

### 5.2.1 Screening

All screening procedures must be performed within 30 days before first dose of investigational product (Day -30 to Day -1), 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 USA) must be obtained prior to performing any protocol-specific procedures, including screening evaluations. However, if evaluations performed for other purposes prior to obtaining informed consent are suitable for screening, those evaluations do not need to be repeated if the subject consents to their use.

1) Obtain written informed consent and appropriate privacy act document authorization
2) Assign an SID number by using IXRS
3) Verify eligibility criteria
4) Perform medical history
5) Perform physical examination
6) Record height
7) Record weight
8) Record vital signs and pulse oximetry
9) Record ECG
10) Assess Karnofsky Performance Status
11) Perform Mini Mental State Exam and gait assessment
12) Collect blood for screening samples:
    - Serum chemistry (including soluble CEA)
    - Hematology
    - Coagulation parameters
    - Hepatitis B, C; HIV-1, HIV-2
    - Beta human chorionic gonadotropin (βHCG) serum pregnancy test
    - Circulating tumor cells
    - Circulating soluble protein biomarkers
13) Collect urine for screening sample
14) Collect fresh core-needle tumor biopsy (optional)
15) Collect archival tumor sample (optional)

16) Perform chest x-ray (CXR), computerized tomography (CT) or magnetic resonance imaging (MRI) scan

17) Assess for AEs and SAEs

18) Record concomitant medications

### 5.2.2 Treatment Period

#### 5.2.2.1 Cycle 1, Day 1: First Infusion

Screening laboratory evaluations collected prior to infusion (serum chemistry, hematology, coagulation parameters, and urinalysis) and physical exam do not need to be repeated if these evaluations occur within 72 hours prior to infusion on Cycle 1, Day 1. Blood collected on Days 1 through 5 will be drawn from a peripheral line away from the IV Infusion site for the following samples: concentrations of MEDI-565, anti-MEDI-565 antibodies, flow cytometric analysis, circulating cytokines, and circulating soluble protein biomarkers.

1) Verify eligibility criteria

2) Begin dexamethasone prophylaxis regimen (8 mg) or equivalent, 8 hours (± 15 minutes) and within 0.5 hours PRIOR to start of infusion, and 8 hours (± 15 minutes) and 16 hours (± 15 minutes) AFTER start of infusion

3) Perform physical examination

4) Record weight (prior to start of infusion)

5) Record vital signs and pulse oximetry (within 0.5 hours prior to start of infusion)

6) Record ECG (within 0.5 hours prior to start of infusion)

7) Assess Karnofsky Performance Status

8) Perform Mini Mental State Exam and Gait Assessment

9) Assess for AEs and SAEs (prior to start of infusion)

10) Update concomitant medications

11) Collect blood prior to MEDI-565 infusion for baseline samples:

- Serum chemistry (including soluble CEA)
- Hematology
- Coagulation parameters
- Concentration of MEDI-565
- Anti-MEDI-565 antibodies
- Flow cytometric analysis

- Circulating cytokines
- Circulating soluble protein biomarkers

12) Collect urine or serum for pregnancy test; ensure result is negative

13) Collect urinalysis sample

14) Administer MEDI-565

15) Measure blood pressure, heart rate, and pulse oximetry during the infusion every 0.5 hours (± 5 minutes); immediately post EOI (± 5 minutes); 0.5 hours (± 5 minutes) and 1 hour (± 5 minutes) after the EOI; at 2 hours, 4 hours, 6 hours, and 8 hours (each ± 15 minutes) after the EOI. NOTE: Continue assessments every 4 hours until the start of infusion on Day 2.

16) Collect blood post-infusion with MEDI-565

- Concentrations of MEDI-565
  - 1 hour [± 5 minutes] after the start of infusion
  - Immediately at the EOI [± 5 minutes]
  - 1 hour [± 15 minutes] after the EOI
  - 2 hours [± 15 minutes] after the EOI
  - 5 hours [± 15 minutes] after the EOI
  - 10 hours [± 15 minutes] after the EOI
  - 15 hours [± 15 minutes] after the EOI
- Flow cytometric analysis (2 hours [± 15 minutes] after the EOI)
- Circulating cytokines (2 hours [± 15 minutes] after the EOI)

17) Record ECGs (immediately at the EOI and 2 hours [± 15 minutes] after the EOI)

18) Assess for AEs and SAEs (after start of infusion)

19) Monitor for early signs/symptoms of toxicity. Blood samples for unscheduled PK and circulating cytokine analyses should be collected if symptoms consistent with infusion-related reactions are present (see Section 4.5.4.1) and the planned time for the next scheduled PK and circulating cytokine samples is more than 4 hours away.

#### 5.2.2.2 Cycle 1, Day 2

1) Record vital signs and pulse oximetry (within 0.5 hours prior to start of infusion)

2) Perform Mini Mental State Exam and gait assessment

3) Assess for AEs and SAEs (prior to start of infusion)

4) Record weight (prior to start of infusion)

5) Update concomitant medications

6) Collect blood prior to MEDI-565 infusion:
   - Concentration of MEDI-565
   - Flow cytometric analysis
   - Circulating cytokines
   - Circulating soluble protein biomarkers
7) Administer MEDI-565
8) Collect blood after end of infusion with MEDI-565
   - Concentrations of MEDI-565 (immediately at the EOI [± 5 minutes])
9) Record vital signs and pulse oximetry (every 0.5 hours [± 5 minutes] during MEDI-565 administration, at the end of infusion [± 5 minutes] and 0.5 hours [± 5 minutes], 1 hour [± 5 minutes], and 2 hours [± 5 minutes] after the EOI)
10) Assess for AEs and SAEs (after the start of infusion)
11) Monitor for early signs/symptoms of toxicity. Blood samples for unscheduled PK and circulating cytokine analyses should be collected if symptoms consistent with infusion-related reactions are present (see Section 4.5.4.1) and the planned time for the next scheduled PK and circulating cytokine samples is more than 4 hours away.

#### 5.2.2.3 Cycle 1, Day 3

1) Record vital signs and pulse oximetry (within 0.5 hours prior to start of infusion)
2) Perform Mini Mental State Exam and gait assessment
3) Assess for AEs and SAEs (prior to start of infusion)
4) Record weight (prior to start of infusion)
5) Update concomitant medications
6) Collect blood prior to start of MEDI-565 infusion:
   - Concentration of MEDI-565
   - Circulating cytokines
   - Flow cytometric analysis
7) Administer MEDI-565
8) Collect blood after the EOI with MEDI-565
   - Concentrations of MEDI-565 (immediately at the EOI [± 5 minutes])
9) Record vital signs and pulse oximetry (every 0.5 hours [± 5 minutes] during MEDI-565 administration, at the EOI [± 5 minutes] and 0.5 hours [± 5 minutes],1 hour [± 5 minutes], and 2 hours [± 5 minutes] after the EOI)
10) Assess for AEs and SAEs (after the start of infusion)

11) Monitor for early signs/symptoms of toxicity. Blood samples for unscheduled PK and circulating cytokine analyses should be collected if symptoms consistent with infusion-related reactions are present (see Section 4.5.4.1) and the planned time for the next scheduled PK and circulating cytokine samples is more than 4 hours away.

#### 5.2.2.4 Cycle 1, Day 4

1) Record vital signs and pulse oximetry (within 0.5 hours prior to start of infusion)
2) Perform Mini Mental State Exam and gait assessment
3) Assess for AEs and SAEs (prior to start of infusion)
4) Record weight (prior to start of infusion)
5) Update concomitant medications
6) Collect blood prior to start of MEDI-565 infusion:
   - Concentration of MEDI-565
   - Flow cytometric analysis
   - Circulating soluble protein biomarkers
7) Administer MEDI-565
8) Collect fresh core-needle tumor biopsy (optional; collect between 2 hours post EOI on Cycle 1, Day 4 and start of Cycle 1, Day 5 infusion from the same lesion biopsied at Screening visit if possible)
9) Collect blood after the EOI with MEDI-565
   - Concentrations of MEDI-565
     – 1 hour [± 5 minutes] after the start of infusion
     – Immediately at the EOI [± 5 minutes]
     – 1 hour [± 15 minutes] after the EOI
     – 2 hours [± 15 minutes] after the EOI
     – 5 hours [± 15 minutes] after the EOI
     – 10 hours [± 15 minutes] after the EOI
     – 15 hours [± 15 minutes] after the EOI
10) Record vital signs and pulse oximetry (every 0.5 hours [± 5 minutes] during MEDI-565 administration, at the EOI [± 5 minutes] and 0.5 hours [± 5 minutes], 1 hour [± 5 minutes], and 2 hours [± 5 minutes] after the EOI)
11) Assess for AEs and SAEs (after the start of infusion)
12) Monitor for early signs/symptoms of toxicity. Blood samples for unscheduled PK and circulating cytokine analyses should be collected if symptoms consistent with

infusion-related reactions are present (see Section 4.5.4.1) and the planned time for the next scheduled PK and circulating cytokine samples is more than 4 hours away.

#### 5.2.2.5 Cycle 1, Day 5

1) Record vital signs and pulse oximetry (within 0.5 hours prior to start of infusion)
2) Record ECG (within 0.5 hours prior to start of infusion)
3) Perform Mini Mental State Exam and gait assessment
4) Assess for AEs and SAEs (prior to start of infusion)
5) Record weight (prior to start of infusion)
6) Update concomitant medications
7) Collect blood prior to start of MEDI-565 infusion:
   - Serum chemistry (including soluble CEA)
   - Hematology
   - Coagulation parameters
   - Concentration of MEDI-565
   - Flow cytometric analysis
8) Collect urinalysis sample
9) Administer MEDI-565
10) Collect blood after EOI with MEDI-565
   - Concentrations of MEDI-565 (immediately at the EOI [± 5 minutes]).
11) Record ECGs (immediately at the EOI and 2 hours [± 15 minutes] after the EOI
12) Record vital signs and pulse oximetry (every 0.5 hours [± 5 minutes] during MEDI-565 administration, at the EOI [± 5 minutes], and 0.5 hours [± 5 minutes],1 hour [± 5 minutes], and 2 hours [± 5 minutes] after the EOI)
13) Assess for AEs and SAEs (after the start of infusion)
14) Monitor for early signs/symptoms of toxicity. Blood samples for unscheduled PK and circulating cytokine analyses should be collected if symptoms consistent with infusion-related reactions are present (see Section 4.5.4.1) and the planned time for the scheduled PK and circulating cytokine samples is more than 4 hours away.

#### 5.2.2.6 Cycle 1, Day 8

1) Record vital signs and pulse oximetry
2) Assess Karnofsky Performance Status
3) Perform Mini Mental State Exam and gait assessment

4) Assess for AEs and SAEs
5) Record weight
6) Update concomitant medications
7) Collect blood samples:
   - Serum chemistry (including soluble CEA)
   - Hematology
   - Coagulation parameters
   - Concentration of MEDI-565
   - Anti-MEDI-565 antibodies
   - Flow cytometric analysis
   - Circulating cytokines
   - Circulating soluble protein biomarkers
8) Collect urinalysis sample

#### 5.2.2.7 Cycle 1, Day 15

1) Record vital signs and pulse oximetry
2) Assess Karnofsky Performance Status
3) Perform Mini Mental State Exam and gait assessment
4) Assess for AEs and SAEs
5) Record weight
6) Update concomitant medications
7) Collect blood samples:
   - Serum chemistry (including soluble CEA)
   - Hematology
   - Coagulation parameters
   - Flow cytometric analysis
8) Collect urinalysis sample

#### 5.2.2.8 Cycle 1, Day 22

1) Record vital signs and pulse oximetry
2) Assess Karnofsky Performance Status
3) Perform Mini Mental State Exam and gait assessment

4) Assess for AEs and SAEs
5) Record weight
6) Update concomitant medications
7) Collect blood samples:
   - Serum chemistry (including soluble CEA)
   - Hematology
   - Coagulation parameters
   - Flow cytometric analysis
   - Circulating cytokines
   - Circulating soluble protein biomarkers
8) Collect urinalysis sample

#### 5.2.2.9 Cycle 2 (and every cycle thereafter), Day 1

1) Perform physical examination
2) Record weight (prior to start of infusion)
3) Record vital signs and pulse oximetry (within 0.5 hours prior to start of infusion)
4) Record ECG (within 0.5 hours prior to start of infusion)
5) Assess Karnofsky Performance Status
6) Perform Mini Mental State Exam and gait assessment
7) Assess for AEs and SAEs (prior to start of infusion)
8) Update concomitant medications
9) Collect blood prior to start of MEDI-565 infusion:
   - Serum chemistry (including soluble CEA)
   - Hematology
   - Coagulation parameters
   - Concentration of MEDI-565
   - Anti-MEDI-565 antibodies
   - Flow cytometric analysis
   - Circulating cytokines
   - Circulating soluble protein biomarkers
10) Collect urine or serum for pregnancy test; ensure result is negative
11) Collect urinalysis sample

12) Administer MEDI-565

13) Record vital signs and pulse oximetry (every 0.5 hours [± 5 minutes] during MEDI-565 administration, at the EOI [± 5 minutes], and 0.5 hours [± 5 minutes], 1 hour [± 5 minutes], and 2 hours [± 5 minutes] after the EOI)

14) Collect blood after the EOI with MEDI-565

- Concentrations of MEDI-565 (immediately at the EOI [± 5 minutes])
- Flow cytometric analysis (2 hours [± 15 minutes] after the EOI)
- Circulating cytokines (2 hours [± 15 minutes] after the EOI)

15) Record ECGs (immediately after EOI and 2 hours [± 15 minutes] after the EOI)

16) Record vital signs and pulse oximetry (every 0.5 hours [± 5 minutes] during MEDI-565 administration, at the EOI [± 5 minutes], 1 hour [± 5 minutes], and 2 hours [± 5 minutes] after the EOI)

17) Assess for AEs and SAEs (after the start of infusion)

18) Monitor for early signs/symptoms of toxicity. Blood samples for unscheduled PK and circulating cytokine analyses should be collected if symptoms consistent with infusion-related reactions are present (see Section 4.5.4.1) and the planned time for the next scheduled PK and circulating cytokine samples is more than 4 hours away.

#### 5.2.2.10 Cycle 2 (and every cycle thereafter), Day 2

1) Record vital signs and pulse oximetry (within 0.5 hours prior to start of infusion)

2) Assess for AEs and SAEs (prior to start of infusion)

3) Record weight (prior to start of infusion)

4) Update concomitant medications

5) Collect blood prior to MEDI-565 infusion:

- Concentration of MEDI-565
- Flow cytometric analysis

6) Administer MEDI-565

7) Record vital signs and pulse oximetry (every 0.5 hours [± 5 minutes] during MEDI-565 administration, at the EOI [± 5 minutes] and 0.5 hours [± 5 minutes], 1 hour [± 5 minutes], and 2 hours [± 5 minutes] after the EOI)

8) Assess for AEs and SAEs (after the start of infusion)

9) Monitor for early signs/symptoms of toxicity. Blood samples for unscheduled PK and circulating cytokine analyses should be collected if symptoms consistent with infusion-related reactions are present (see Section 4.5.4.1) and the planned time for the next scheduled PK and circulating cytokine samples is more than 4 hours away.

#### 5.2.2.11 Cycle 2 (and every cycle thereafter), Day 3

1) Record vital signs and pulse oximetry (within 0.5 hours prior to start of infusion)
2) Assess for AEs and SAEs (prior to start of infusion)
3) Record weight (prior to start of infusion)
4) Update concomitant medications
5) Collect blood prior to start of MEDI-565 infusion:
   - Circulating soluble protein biomarkers
6) Administer MEDI-565
7) Record vital signs and pulse oximetry (every 0.5 hours [± 5 minutes] during MEDI-565 administration, at the EOI [± 5 minutes] and 0.5 hours [± 5 minutes], 1 hour [± 5 minutes], and 2 hours [± 5 minutes] after the EOI)
8) Assess for AEs and SAEs (after the start of infusion)
9) Monitor for early signs/symptoms of toxicity. Blood samples for unscheduled PK and circulating cytokine analyses should be collected if symptoms consistent with infusion-related reactions are present (see Section 4.5.4.1) and the planned time for the next scheduled PK and circulating cytokine samples is more than 4 hours away.

#### 5.2.2.12 Cycle 2 (and every cycle thereafter), Day 4

1) Record vital signs and pulse oximetry (within 0.5 hours prior to start of infusion)
2) Assess for AEs and SAEs (prior to start of infusion)
3) Record weight (prior to start of infusion)
4) Update concomitant medications
5) Administer MEDI-565
6) Record vital signs and pulse oximetry (every 0.5 hours [± 5 minutes] during MEDI-565 administration, at the EOI [± 5 minutes] and 0.5 hours [± 5 minutes], 1 hour [± 5 minutes] , and 2 hours [± 5 minutes] after the EOI)
7) Assess for AEs and SAEs (after the start of infusion)
8) Monitor for early signs/symptoms of toxicity. Blood samples for unscheduled PK and circulating cytokine analyses should be collected if symptoms consistent with infusion-related reactions are present (see Section 4.5.4.1) and the planned time for the next scheduled PK and circulating cytokine samples is more than 4 hours away.

#### 5.2.2.13 Cycle 2 (and every cycle thereafter), Day 5

1) Record vital signs and pulse oximetry (within 0.5 hours prior to start of infusion)
2) Assess for AEs and SAEs (prior to start of infusion)

3) Record weight (prior to start of infusion)

4) Update concomitant medications

5) Collect blood prior to start of MEDI-565 infusion:

- Concentration of MEDI-565
- Flow cytometric analysis
- Circulating cytokines

6) Administer MEDI-565

7) Collect blood after EOI with MEDI-565

- Concentrations of MEDI-565 (immediately at the EOI [± 5 minutes])

8) Record vital signs and pulse oximetry (every 0.5 hours [± 5 minutes] during MEDI-565 administration, at the EOI [± 5 minutes] and 0.5 hours [± 5 minutes], 1 hour [± 5 minutes] , and 2 hours [± 5 minutes] after the EOI)

9) Assess for AEs and SAEs (after the start of infusion)

10) Monitor for early signs/symptoms of toxicity. Blood samples for unscheduled PK and circulating cytokine analyses should be collected if symptoms consistent with infusion-related reactions are present (see Section 4.5.4.1) and the planned time for the next scheduled PK and circulating cytokine samples is more than 4 hours away.

#### 5.2.2.14 Cycle 2 (and every cycle thereafter), Day 8 (plus or minus 1 Day)

1) Record vital signs and pulse oximetry

2) Assess Karnofsky Performance Status

3) Perform Mini Mental State Exam and gait assessment

4) Assess for AEs and SAEs

5) Record weight

6) Update concomitant medications

7) Collect blood samples:

- Serum chemistry (including soluble CEA)
- Hematology
- Coagulation parameters
- Concentration of MEDI-565
- Anti-MEDI-565 antibodies
- Flow cytometric analysis

8) Collect urinalysis sample

#### 5.2.2.15 Cycle 2 (and every cycle thereafter), Day 15 (plus or minus 1 Day)

1) Record vital signs and pulse oximetry
2) Assess Karnofsky Performance Status
3) Perform Mini Mental State Exam and gait assessment
4) Assess for AEs and SAEs
5) Record weight
6) Update concomitant medications
7) Collect blood samples:
   - Serum chemistry (including soluble CEA)
   - Hematology
   - Coagulation parameters
   - Flow cytometric analysis
8) Collect urinalysis sample

#### 5.2.2.16 Cycle 2 (and every cycle thereafter), Day 22 (plus or minus 1 Day)

1) Record vital signs and pulse oximetry
2) Assess Karnofsky Performance Status
3) Perform Mini Mental State Exam and gait assessment
4) Assess for AEs and SAEs
5) Record weight
6) Update concomitant medications
7) Collect blood samples:
   - Serum chemistry (including soluble CEA)
   - Hematology
   - Coagulation parameters
   - Flow cytometric analysis
8) Collect urinalysis sample

#### 5.2.2.17 After Every 2 Cycles

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

3) Perform CXR, CT or MRI scan (disease assessments must be performed within 7 days prior to the planned start of the next cycle)

#### 5.2.2.18 End of Treatment Visit

This visit is to be conducted at the time a decision is made for a subject to discontinue MEDI-565 treatment due to PD, initiation of alternative anticancer therapy, unacceptable toxicity, or other reasons.

1) Perform physical examination
2) Record weight
3) Record vital signs and pulse oximetry
4) Record ECG
5) Assess Karnofsky Performance Status
6) Perform Mini Mental State Exam and gait assessment
7) Assess for AEs and SAEs
8) Update concomitant medications
9) Collect blood samples for end of treatment (EOT):
    - Serum chemistry (including soluble CEA)
    - Hematology
    - Coagulation parameters
    - Concentrations of MEDI-565
    - Anti-MEDI-565 antibodies
    - Circulating tumor cells
    - Flow cytometric analysis
    - Circulating cytokines
    - Circulating soluble protein biomarkers
10) Collect urinalysis sample
11) Perform CXR, CT or MRI scan (unless it has been performed within 14 days of treatment discontinuation)

Note: If the End of Treatment visit occurs on the same day as another treatment visit or a post treatment visit, only perform one of the same evaluations and avoid duplication of evaluations.

### 5.2.3 Post-Treatment Follow-up Period

#### 5.2.3.1 30 Days (plus or minus 3 Days) Post-treatment

This visit is only required for subjects who discontinue treatment for a reason other than disease progression.

1) Perform physical examination
2) Record weight
3) Record vital signs and pulse oximetry
4) Record ECG
5) Assess Karnofsky Performance Status
6) Perform Mini Mental State Exam and gait assessment
7) Assess for AEs and SAEs
8) Update concomitant medications
9) Collect blood samples for post-treatment follow-up:
    - Serum chemistry (including soluble CEA)
    - Hematology
    - Coagulation parameters
    - Concentrations of MEDI-565
    - Anti-MEDI-565 antibodies
    - Circulating tumor cells
    - Flow cytometric analysis
    - Circulating cytokines
    - Circulating soluble protein biomarkers
10) Collect urinalysis sample
11) Perform CXR, CT or MRI scan (only required for subjects who discontinued treatment without progressive disease and who have not initiated alternative anticancer therapy)

#### 5.2.3.2 3 Months Post End of Treatment

1) Perform physical examination (only for subjects who discontinued treatment without progressive disease and who have not initiated an alternative anticancer therapy)
2) Record subsequent anticancer therapy

3) Record survival status

4) Collect blood samples for post-treatment follow-up

- Complete blood count (CBC) (performed only at 3 months post-treatment)
- Flow cytometric analysis (performed only at 3 months post-treatment)

5) Perform CXR, CT, or MRI scan (only for subjects who discontinued treatment without progressive disease and who have not initiated an alternative anticancer therapy)

#### 5.2.3.3 6 Months and Every 3 Months (plus or minus 7 Days) Post-treatment

This visit may be conducted by telephone if CXR, CT, or MRI scan is not completed. Visits every 3 months post-treatment should be continued until disease progression is documented.

1) Record subsequent anticancer therapy

2) Record survival status

3) Perform CXR, CT, or MRI scan (only for subjects who discontinued treatment without progressive disease and who have not initiated an alternative anticancer therapy)

## 5.3 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.

### 5.3.1 Medical History, Physical Examination, Toxicity Monitoring, Dexamethasone Prophylaxis Regimen, ECG, Weight, and Vital Signs

Physical examinations will be performed at time points as described in Table 5.2-1 and Table 5.2-2 (screening, treatment, and post-treatment visits) and will include assessments of the head, eyes, ears, nose, and throat (HEENT), respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, and endocrine systems; and height (at screening only).

Following the Day 1 infusion of each cycle and continuing through Day 5, subjects should be closely monitored for early symptoms of toxicity (see Section 4.5.4.1). In the event that such AEs are noted and are clinically significant, and in the absence of clear alternative etiology, continued dexamethasone treatment (8 mg, every 8 hours) or equivalent should be considered until evidence of resolution is observed. If a subject experiences any symptoms such as those

described in Section 4.5.4.1, further dosing should be delayed until the symptoms are completely resolved.

Body weight will be recorded at Screening, on Days 1 to 5 prior to MEDI-565 infusion, Days 8, 15, and 22 of each cycle, at the end of treatment, and 30 days post-treatment.

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) and pulse oximetry will be measured at Screening, on Days 1 through 5 of each cycle prior to MEDI-565 administration, every 0.5 hours (± 5 minutes) during MEDI-565 administration, at the EOI (± 5 minutes) and 0.5 hours (± 5 minutes), 1 hour (± 5 minutes), and 2 hours (± 5 minutes) post EOI.

Specifically on Cycle 1, Day 1, monitoring of vital signs and pulse oximetry will continue beyond the 2-hour post EOI time point until the start of infusion on Cycle 1, Day 2, as follows: 4 hours, 6 hours, 8 hours, 12 hours, 16 hours, 20 hours, and 24 hours (each ± 15 minutes) after the EOI until the start of infusion on Cycle 1, Day 2.

Vital signs will also be performed on Days 8, 15, and 22 of each cycle, at the end of treatment, and 30 days post-treatment.

A 12-lead ECG will be obtained for all subjects during Screening, Cycle 1, Days 1 and 5 (within 15 minutes prior to the start of infusion, immediately post EOI, and 2 hours [± 15 minutes] post EOI), Day 1 of every cycle (within 15 minutes prior to the start of infusion, immediately post EOI, and 2 hours [± 15 minutes] post EOI), at the end of treatment, and 30 days post-treatment. All ECGs performed during the study will be obtained in triplicate. This means that the 3 ECG readings should all be obtained within 5 minutes at each designated time period.

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 prestudy baseline.

### 5.3.2 Mental Status, Speech, and Gait

Mental status, speech, and gait will be assessed as described in Table 5.2-1 and Table 5.2-2 using the Mini-Mental State Exam (MMSE) and the Timed Get-Up and Go Test (Appendix 4).

The Mini-Mental State Exam is a brief, quantitative, practical measure of cognitive status in adults (Folstein, 1975; Appendix 4). The test is used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time, to follow the course of cognitive changes in an individual over time, and to document an individual's response to treatment. The MMSE also performs as a screen for aphasia.

Gait will be assessed using the timed "Get-Up and Go Test" in order to screen for ataxia (Mathias, 1986; Podsiadlo and Richardson, 1991). For this test subjects are asked to rise from a chair, walk 10 feet, turn, walk back, and sit down. Non-ambulatory subjects will be screened for upper extremity ataxia during administration of the MMSE.

### 5.3.3 Clinical Laboratory Tests

Clinical laboratory safety tests including serum pregnancy tests will be performed in a licensed clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours or prior to MEDI-565 infusion when indicated).

The following clinical laboratory tests will be performed (see Table 5.2-1 and Table 5.2-2 for the schedule of tests):

#### Serum Chemistry

- Calcium
- Chloride
- Magnesium
- Potassium
- Sodium
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Alkaline phosphatase (ALP)
- Total bilirubin
- Gamma glutamyl transferase (GGT)
- Lactic dehydrogenase (LDH)
- Blood urea nitrogen (BUN)
- Uric acid
- Creatinine
- Glucose
- Albumin
- Total protein
- Triglycerides
- Cholesterol
- Lipase
- Soluble CEA*

Note for serum chemistry: tests for AST, ALT, ALP and total bilirubin must be conducted concurrently and assessed concurrently.

*****Soluble CEA will be tested locally at each visit serum chemistry is performed

#### Hematology

- Complete blood count (CBC) with differential and Platelet count

### Urinalysis

- Glucose
- Ketones
- Blood
- Bilirubin
- Protein

### Pregnancy Test (females of childbearing potential only)

- Serum beta-hCG (Screening only)
- Urine human chorionic gonadotropin (hCG) or serum beta-hCG (Day 1 of cycle)

### Other Safety Tests

- Coagulation parameters: prothrombin time (PT), partial thromboplastin time (PTT), international normalized ratio (INR)
- Hepatitis B surface antigen, hepatitis C antibody (Screening only)
- HIV-1 and HIV-2 antibody (Screening only)

## 5.3.4 Pharmacokinetic Evaluation and Methods

Serum samples will be collected at various study visits for the determination of MEDI-565 concentration using an electrochemiluminescent assay (ECLA). Specific time points are indicated in the Subject Evaluation Schedules (Table 5.2-1 and Table 5.2-2) and described in Section 5.2. In addition to the timepoints noted in the Subject Evaluation Schedules, unscheduled blood samples for PK analysis should be drawn if a subject develops clinically significant signs or symptoms that are consistent with an infusion-related adverse event (see Section 4.5.4.1) within 24 hours after a MEDI-565 infusion and that occur with more than a 4 hour interval from the next scheduled collection for these assays. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to sites.

## 5.3.5 Immunogenicity Evaluation and Methods

Serum samples will be collected at various study visits to monitor anti-MEDI-565 antibodies using an ECLA. Specific time points are indicated in the Subject Evaluation Schedules (Table 5.2-1 and Table 5.2-2) and described in Section 5.2. Instructions for sample collection, processing, storage, and shipment can be found in a separate Laboratory Manual provided to the sites.

Anti-MEDI-565 antibodies in serum will be evaluated using screening and confirmatory assays. Samples that are confirmed positive for anti-drug antibodies (ADA) will be titered to determine the relative levels of ADA in the samples.

### 5.3.6 Biomarker Evaluation and Methods

Blood samples will be collected and analyzed to evaluate protein, nucleic acid and cellular biomarkers that relate to MEDI-565 treatment.

Whole blood samples will be analyzed for the numbers of the total circulating tumor cells and the CEA-expressing circulating tumor cell (CTC) subset using CellSearch® to evaluate their association with response to MEDI-565 treatment and clinical outcome. Whole blood samples will be collected at screening, at the end of treatment, and 30 days post treatment.

The numbers of T cells, B cells, and NK cells as well as the subsets of T cells will be evaluated in whole blood by flow cytometric analysis. The activation status of T cells will also be assessed in the same study. Whole blood samples will be collected at Day 1 pre-infusion and 2 hours after the end of infusion, Day 2, Day 3, Day 4, Day 5, Day 8, Day 15, and Day 22. For Cycle 2 and every cycle thereafter, whole blood samples will be collected at Day 1 (pre-infusion and 2 hours after the end of infusion), Day 2, Day 5, Day 8, Day 15, and Day 22, as well as at the end of treatment, 30 days post-treatment, and at the first 3 month post-treatment visit.

Blood samples will be collected for analysis of circulating levels of cytokines and chemokines in relation to T-cell activities. They include but are not limited to IFN-γ, TNF-α, IL-2, IL-6, IL-10, IL-8, and IL-12 and will be assessed by multiplex protein analyses and enzyme-linked immunosorbent assays (ELISA). Blood samples will be collected on each cycle at Day 1 pre-infusion and 2 hours after the end of infusion as well as at the end of treatment. For cycle 1, blood samples will also be collected at Day 2, Day 3, Day 8, Day 22 and for cycle 2 and every cycle thereafter, samples will be collected at Day 5. In addition to these timepoints, unscheduled blood samples for circulating cytokine analysis should be drawn if a subject develops clinically significant signs or symptoms that are consistent with an infusion-related reaction within 24 hours after a MEDI-565 infusion and that occur more than 4 hours from the next scheduled collection for these assays.

Blood samples will be used to analyze circulating levels of soluble protein markers of apoptosis such as nucleosomal DNA, M30, and M65 by immunoassays and explore their association with MEDI-565 treatment and clinical outcome. Samples will be collected at screening, at the end of the treatment, and 30 days post treatment. For Cycle 1, samples will also be collected at Day 1 pre-infusion, Day 2, Day 4, Day 8, Day 22, and for Cycle 2 and every cycle thereafter, samples will be collected at Day 1 pre-infusion and Day 3.

Optional core-needle tumor biopsies taken at screening and after the Cycle 1, Day 4 infusion will be assessed using immunohistochemical staining techniques to examine multiple aspects of the tumor and microenvironment before and following MEDI-565 treatment which may include CEA expression, markers of necrosis or apoptosis, and potential changes in the nature and number of tumor infiltrating lymphocytes. If a subject agrees to complete the biopsies, they must agree to complete them at both the screening and Cycle 1, Day 4 timepoints; if a subject declines the screening biopsy, the Cycle 1, Day 4 biopsy is not necessary. The screening biopsy should be taken with enough time prior to study entry to ensure there is no residual inflammation caused by the biopsy. It is preferred to biopsy the primary tumor, although metastatic lesions are acceptable. The on-treatment biopsy, taken at least 2 hours after completion of the Cycle 1, Day 4 infusion and before initiation of the Day 5 infusion, should be taken from the same lesion that was biopsied at baseline if possible.

When archival tissue samples are available, tumor biomarkers including but not limited to the expression level of CEA protein on tumor cells (by immunohistochemistry analysis) and the T-cell number and phenotype in tumor tissues (if the assays are available) will be evaluated for any relationship with subject response to treatment with MEDI-565.

Other biomarkers may be evaluated as determined by additional data. Details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

### 5.3.7 Disease Evaluation and Methods

Survival will be followed approximately every 3 months beginning at 3 months post-treatment by clinic visit or telephone (beginning at 6 months post-treatment) until the end of the study.

Tumor measurements and assessments will be based on RECIST v 1.1 (Eisenhauer et al, 2009) and will be performed at time points as specified in Table 5.2-1 and Table 5.2-2. Additional tumor measurements may be performed at the discretion of the investigator or according to institutional practice. In subjects who achieve a complete or partial response to treatment, tumor measurements will be repeated for confirmation at least 4 weeks later using the same imaging tests. 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. The analysis for tumor response will be based on the investigator's assessment during the conduct of the study.

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. CT 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.

- **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 chest radiograph should be clearly defined and surrounded by aerated lung. However, CT is preferable.
- **CT scans of the chest, abdomen, and pelvis**. CT 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.
- **MRI scans**. MRI 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 in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm)
  - 10 mm caliper measurement by clinical exam (when superficial)
  - 20 mm by chest X-ray (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 2 lesions per organ) representative of all involved organs should be identified as target lesions. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- **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 (CR) -** 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 (PR) -** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD) -** 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 (SD) -** 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 (CR) -** 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 one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD) -** Unequivocal progression of existing nontarget lesions will be defined as the overall level of substantial worsening in nontarget disease such that, even in presence of 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 5.3.7-1 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

**Table 5.3.7-1 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; PD = progressive disease; PR = partial response, SD = stable disease,

[a] NE (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.

### 5.3.8 Estimate of Volume of Blood to Be Collected

No more than 47 mL of blood will be drawn on a per-day basis across all tests combined on days in which blood is collected. An additional 5 mL may be drawn any time unscheduled samples for circulating cytokine analysis are required. The estimated volume of blood to be collected during screening and the first treatment cycle is 182 mL and during every other cycle is 76 mL. The total volume to be collected 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 ICH Guideline for Good Clinical Practice E6 (R1) defines an AE as:

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

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including electrocardiogram [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 treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious).

### 6.1.2 Serious Adverse Events

A serious adverse event (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.

### 6.1.3 Other Events of Special Interest

#### 6.1.3.1 Hepatic Function Abnormality

A 'hepatic function abnormality' of special interest to the sponsor is defined as any increase in ALT or AST to greater than 3 × ULN **and concurrent** increase in bilirubin to greater than

2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality, where the etiology is unknown, follow-up investigations and inquiries should be initiated promptly by the investigational site based on medical judgment to make an informed decision regarding the etiology of the event.

## 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 v4.03. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

| | |
|---|---|
| Grade 1 (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 (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 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.

### 6.3.2 Recording of Other Events of Special Interest

#### 6.3.2.1 Hepatic Function Abnormality

Events of hepatic function abnormality (as defined in Section 6.1.3.1) should be recorded according to the definitions of AE and SAE (Section 6.1.1 and Section 6.1.2, respectively):

- If an event of hepatic function abnormality is a pre-existing condition, the event does not meet the definition of an AE and does not need to be recorded as such.

- If the etiology of the hepatic function abnormality is known (including progression of primary or metastatic malignancy) and/or not a pre-existing condition, the diagnosis should be recorded as an AE/SAE per Section 6.3.1.
- If the hepatic function abnormality remains unexplained, the term "hepatic function abnormal" should be used to report the AE/SAE per Section 6.4.2.

## 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 30 days after the last dose of MEDI-565. 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 30 days post the subject's last dose of treatment or until the subject begins another anticancer therapy. 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

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.

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, for example 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 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 6.1.3.1) in a study subject, with or without associated clinical manifestations, where the etiology is unknown, is required to be reported as "hepatic function abnormal" ***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 investigator shall review the data with the medical monitor. The investigator should use clinical judgement to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated. If, after appropriate workup, in the opinion of the investigator, the underlying diagnosis for the abnormality remains unexplained, discontinuation of dosing for this subject should be considered.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor. If the etiology of the event remains unconfirmed and/or is considered related to investigational product (see Section 6.2.2.1), a prompt cumulative

review of safety data and the circumstances of the event in question will be conducted and assessed by the MedImmune Safety Monitoring Committee (SMC) (see Section 6.5) to determine whether continued dosing of current study subjects and/or study entry should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the SMC is required for resumption of subject dosing or study entry in the event that the study is interrupted. Where applicable, regulatory authorities and IRBs/IECs will be notified of any actions taken with the study.

#### 6.4.3.3 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.

### 6.4.4 Study Reporting Period for Other Events of Special Interest

The following events are considered immediately reportable events and must be reported ***within 24 hours of knowledge of the event*** to MedImmune Product Safety using the Fax Notification Form:

- Any withdrawal of consent during the study
- Any treatment-related event resulting in discontinuation of investigational product, interruption of dosing, or delay in completion of a study treatment cycle

## 6.5 Safety Management During the Study

The MedImmune 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 review, investigation, and follow-up of SAEs and other immediately reportable events (eg, overdose and pregnancies) reported from the clinical study sites.

A study-specific Dose Escalation 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 making recommendations regarding further conduct of the study. The Dose Escalation Committee includes the MedImmune medical monitor for the study, the MedImmune Patient Safety physician for the study, and the principal investigator from each actively enrolling study site. This committee will review data, including all AEs, laboratory parameters, pharmacokinetics, and pharmacodynamic data, following the full enrollment of any dose-escalation cohort and completion of the DLT evaluation period. This committee will also review data at other time points in response to AEs assessed as medically relevant by the medical monitor. Dose-escalation decisions and outcomes of reviews of safety and other relevant data will be communicated in writing to all participating sites and principal investigators. The sponsor will notify sites when enrollment into each dose cohort has been completed and when enrollment into the next dose cohort is permitted.

The MedImmune SMC (or equivalent) provides safety surveillance, guidance, and oversight for all clinical development trials in which MedImmune has sponsor accountabilities. The SMC (or equivalent) reviews protocol-specific safety data at regularly scheduled meetings and ad hoc meetings, and provides oversight for individual study protocol safety committees, such as those specified for early-phase dose-escalation trials. Based on review of safety data, the SMC (or equivalent) may suspend enrollment or subject dosing in clinical studies, request modification of study documents, or take other actions as deemed necessary.

# 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 (CIs) will be 2-sided, unless otherwise stated. Details of endpoint analyses will be described in the statistical analysis plan.

## 7.2 Analysis Populations

The Evaluable Population for DLT includes all subjects enrolled in the dose-escalation phase who received at least one full cycle of MEDI-565 and completed safety follow-up through the DLT evaluation period (defined in Section 4.5.4.5) or experience any DLT. The Evaluable Population for DLT will be used for the MTD evaluation.

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

The Per-Protocol Population will include all subjects who complete 2 cycles of treatment or discontinue treatment due to disease progression or toxicity.

## 7.3 Endpoints

### 7.3.1 Primary Endpoints

The primary endpoints are as follows:

- The number (percentage) of subjects with a DLT will be summarized by dose level and overall. The MTD evaluation will be based on the evaluable population for DLT.
- The OBD will be determined based upon analysis of all available subject data including safety, PK, pharmacodynamic, biomarker, and antitumor activity data.
- The number (percentage) of subjects with AEs and SAEs reported through 30 days after the last dose of MEDI-565 will be summarized for all subjects who received at least one dose of study drug (Safety Population). Adverse events and SAEs will be graded according to the NCI CTCAE v4.03 and described by system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severity, and relationship to MEDI-565. Frequency rates will be calculated for each system organ class and MedDRA preferred term.
- The number (percentage) of subjects with significant or important clinical findings in ECG will be summarized by dose cohort.
- The number (percentage) of subjects who had clinically significant laboratory changes recorded as AEs will be summarized. Laboratory hematology and chemistry values will be summarized with the worst value during the study by dose cohort. Clinically significant coagulation profile and urinalysis results will be described.

### 7.3.2 Secondary Endpoints

#### 7.3.2.1 Pharmacokinetic Assessment

Individual MEDI-565 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. If the data allow, descriptive statistics of noncompartmental PK parameters (AUC, $C_{max}$, $T_{max}$, CL, $V_d$, $t_{½}$) will be provided.

#### 7.3.2.2 Immunogenicity Assessment

The immunogenic potential of MEDI-565 will be assessed by summarizing the number and percentage of subjects who develop detectable anti-drug antibodies. Immunogenicity results will be listed for each subject. The impact of anti-drug antibodies on PKPD, antitumor activity, and safety will be assessed if data allow.

#### 7.3.2.3 Efficacy Assessments

Assessments of antitumor activity of MEDI-565 include ORR, TTR, DR, TTP, PFS, and OS. RECIST guidelines (v1.1; Eisenhauer et al, 2009) will be used to determine tumor response.

**Objective Response Rate**

Objective response rate is defined as the proportion of subjects with confirmed CR or confirmed PR according to RECIST guidelines. Confirmed responses are those that persist on repeat imaging study ≥ 4 weeks after the initial documentation of response. The 95% confidence interval of ORR will be estimated using the exact probability method.

**Time to Response**

Time to response will be measured from the start of MEDI-565 administration to the first documentation of response (CR or PR) and will only be assessed in subjects who have achieved objective response.

**Duration of 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. Duration of response will only be evaluated for the subgroup of subjects with an objective response using the Kaplan-Meier method (Kaplan and Meier, 1958).

**Time to Progression**

Time to progression will be measured from the start of treatment with MEDI-565 until the documentation of disease progression. Disease progression is defined according to RECIST guidelines v1.1 (Eisenhauer et al, 2009). 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 the start of treatment with MEDI-565 will have TTP censored on the first date of treatment with MEDI-565. The TTP will be evaluated using the Kaplan-Meier method (Kaplan and Meier, 1958).

**Progression-free Survival**

Progression-free survival will be measured from the start of treatment with MEDI-565 until the documentation of disease progression or death due to any cause, whichever occurs first. Disease progression is defined according to RECIST guidelines. Progression-free survival will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression and are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Subjects having no tumor assessments after the start of treatment with MEDI-565 will have PFS censored on the first date of treatment with MEDI-565. PFS will be evaluated using the Kaplan-Meier method (Kaplan and Meier, 1958).

**Overall Survival**

Overall survival will be determined as the time from the start of treatment with MEDI-565 until death. For subjects who are alive at the end of study or lost to follow-up, OS will be censored on the last date when subjects are known to be alive. The OS will be evaluated using the Kaplan-Meier method (Kaplan and Meier, 1958).

### 7.3.3 Exploratory Endpoints

Descriptive statistics will be the primary methods used for the exploratory analyses. Depending on the nature of the data, geometric mean and other appropriate statistical

summaries might be used as well. The variables to be included in the exploratory analyses include:

- Serum CEA levels before and after treatment with MEDI-565 to evaluate the association with response to treatment with MEDI-565 and clinical outcome
- Peripheral blood populations before and after treatment, including absolute numbers of T cells, T-cell subsets, NK cells, and B cells as well as their cellular phenotypes, to evaluate the association with MEDI-565 dose and subject responses to MEDI-565 treatment
- Cytokine response to explore its association with MEDI-565 treatment and clinical outcome
- Circulating DNA, M30, and/or M65 as markers of tumor apoptosis to evaluate their association with MEDI-565 treatment
- Circulating tumor cell numbers and the CEA-expression CTC subset to explore their relationship to treatment effects with MEDI-565
- Drug target expression, tumor markers of response and T-cell infiltration and phenotype based on the archived and/or fresh core-needle tumor tissues, when available, to explore their relationship to treatment effects with MEDI-565
- Percentage of subjects with potential CNS-related events using the Mini-Mental State Examination (MMSE) and the Timed Get-Up and Go Test
- Endpoints related to multiple aspects of the tumor and microenvironment before and following MEDI-565 treatment which may include: CEA expression, markers of necrosis or apoptosis, and potential changes in the nature and number of tumor infiltrating lymphocytes, from pre- and post-treatment biopsies examined using immunohistochemical staining techniques.

## 7.4 Interim Analysis

No interim analyses are planned.

## 7.5 Sample Size

As of Amendment 4, the number of subjects who may be enrolled ranges from approximately 99 to 114, depending upon how many subjects are required per cohort based on occurrence of DLTs. The protocol specifies the exact circumstances guiding the number of subjects enrolled per cohort.

For the dose-escalation phase as of Amendment 4, approximately 39 evaluable subjects will be required if DLTs do not occur, for a total of 15 cohorts. Of the 15 cohorts, Cohorts 1-4

each require a minimum of 1 subject. Cohorts 5-15 follow a 3+3 design and each requires a minimum of 3 subjects (see Table 4.5.2-1). Up to approximately 54 evaluable subjects (1 subject each in Cohorts 1 through 4, 3 subjects in Cohort 5 through 9, 5 subjects in Cohort 10, and up to 6 subjects each in Cohorts 11 through 15 will be required during the dose-escalation phase.

At the discretion of the sponsor, more subjects may be enrolled for situations which might prompt selection of an intermediate dose and nonevaluable subjects will be replaced in the same dose cohort as described in Section 4.5.4.2.

Table 7.5-1 provides the probability of dose escalation to the next higher lever for each underlying true DLT rate at the dose levels with 3+3 design. For example, for a common toxicity that occurs in 10% of subjects, there is a greater than 90% probability of escalating to the next higher dose level. Conversely, for a toxicity that occurs with a rate of 60%, the probability of escalating to the next higher dose level is less than 10%.

**Table 7.5-1 True Underlying DLT Rate at a Given Dose Level**

| True underlying DLT rate | 10% | 20% | 30% | 40% | 50% | 60% | 70% | 80% | 90% |
|---|---|---|---|---|---|---|---|---|---|
| Probability of escalating dose | 0.91 | 0.71 | 0.49 | 0.31 | 0.17 | 0.08 | 0.03 | 0.009 | 0.001 |

For the dose-expansion phase, approximately 60 subjects (20 subjects each) will be entered into 3 disease arms: refractory CRC, refractory pancreatic adenocarcinoma, and refractory gastroesophageal cancer. An equal number of subjects in each arm will be treated to evaluate the antitumor activity profile of MEDI-565. This projected sample size was chosen to obtain a preliminary safety and antitumor activity profile. A total of 20 subjects will provide approximately 80% power for testing the following hypotheses at 1-sided significance level of 0.1.

- Null hypothesis: undesirable ORR rate = 5%
- Alternative hypothesis: desirable ORR rate = 20%

# 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 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 reapproval; 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. Written informed consent will additionally be obtained for the conduct of certain protocol-specified procedures for genetic testing and future specimen use testing using separate consent forms.

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.

# 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 subject's 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

**Amendment 1, 05May2011**

The original protocol was amended due to plans to add additional subjects in the dose escalation phase of the study. Major changes to the protocol are listed below:

1) The Medical Monitor has been updated to reflect the new Medical Monitor, [redacted], assigned to the protocol

2) Study Abstract: Updated to be consistent with the changes made to the body of the protocol

3) Section 1.2.1 Nonclinical Pharmacology: "Preclinical" has been replaced with "nonclinical" for consistency throughout protocol

4) Section 1.3 Rationale for Study Conduct: This has been updated to reflect the rationale for adding the additional subjects in the specified tumor types

5) Section 1.4 Benefit-Risk and Ethical Assessment: Updated to include the most recent package insert for Orthoclone OKT3 (2004)

6) Section 3.1 Overview of Study Design: 10 investigational sites throughout the United States of America will participate in this study, instead of 5. This section was also updated to reflect the disease specific tumor regression groups that have been added during the escalation phase of this study, as well as to update the numbers of subjects to participate in the trial

7) Figure 3.1-1: Study Flow Diagram: Updated to add the tumor regression group as well as correction of errors regarding toxicities

8) Figure 3.1-2 Standard 3+3 Design Flow: Has been added to the protocol to enhance understanding of the escalation arm and rules for expansion of a cohort

9) Section 1.4 Benefit-Risk and Ethical Assessment: Updated binding site from Fcγ to FcRγ

10) Section 4.2.1 Inclusion Criteria: Updated criteria #7 to allow INR within 1.5 times ULN, as well as INR of ≤3 for those on anticoagulant therapy. Updated CTCAE from version 4.0 to 4.03

11) Section 4.2.3 Withdrawal Criteria: Updated to include the postponement of PD diagnosis.

12) Section 4.3 Treatment Assignment Updated to reflect IXRS instead of IVRS, as well as dose level assignment

13) Section 4.5.2 Treatment Regimen Table 4.5.2-1: Number of subjects updated to reflect possible addition of subjects in the specified tumor regression group with text added below table to explain the number of subjects

14) Section 4.5.4.2 Dose Escalation: Updated section with addition of rules required for the tumor regression group

15) Section 4.5.4.5 Dose-Limiting Toxicity: Updated to allow for transient elevated LFTs that resolve within specified time period as well as removal of GGT which is not a transaminase

16) Section 5.1.1 Efficacy and Clinical Pharmacology Parameters: Updated language to be consistent with section 4.2.3 and diagnosis of disease progression

17) Table 5.2-1 Schedule of Subject Evaluations: Allow urine or serum pregnancy test to be performed at all specified visits. This change was also made throughout protocol for consistency

18) Section 5.3.3 Clinical Laboratory Tests: Updated for consistency with previous language in protocol, as well as protocol template language requiring liver enzymes to be conducted and assessed concurrently

19) Section 5.3.4 Pharmacokinetics Evaluation and Methods: Updated ECL to ECLA for consistency

20) Section 5.3.6 Biomarker Evaluation and Methods: Updated for consistency

21) Section 6.1.3 Other Events of Special Interest and 6.1.3.1 Hepatic Function Abnormality: Sections added due to new protocol requirements

22) Section 6.3.2 Recording of Other Events of Special Interest and 6.3.2.1 Hepatic Function Abnormality: Sections added due to new protocol requirements

23) Section 6.4.3.2 Hepatic Function Abnormality: Section added due to new protocol requirements

24) Table 7.5-2 Objective Response Rate and Its 80% Confidence Interval: Table was added to illustrate confidence rates dependent on number of subjects noted with response. Text also added to explain calculations

25) References: Updated for consistency with body of protocol

**Amendment 2, 08Sep2011**

Protocol Version 2.0 dated 05May2011 was amended to Protocol Version 3.0 dated 08Sep2011 due to plans to add additional PK time points in addition to several clarifications. Major changes to the protocol are listed below:

1) Section 1.2.4 Clinical: Updated to reflect this is the first clinical study using MEDI-565

2) Section 4.2.1, Inclusion Criteria #7.e: Language adjusted to clarify criteria

3) Section 4.2.1 Inclusion Criteria #8.b: Removal of GGT as inclusion criteria due to a decision not to group GGT with liver enzymes listed

4) Section 4.3 Treatment Assignment: Clarification of how SID is assigned as well as where to document the information. All relevant sections were updated for consistency

5) Section 4.5.3 Investigational Product Preparation: Language modified to include sterility guidance

6) Section 4.5.4.2 Dose Escalation #3 and #8: Clarification of language for tumor regression group as well as first 3-subject cohort rules

7) Section 4.5.5 Concomitant Medications: Removed language regarding acetaminophen administration as this is an investigator/physician decision

8) Section 5.2 Schedule of Study Procedures: Updated to clarify when soluble CEA is being collected and tested locally, all relevant sections updated for consistency

9) Section 5.2.2.1 Cycle 1, Day 1: Language added to clarify where blood should be drawn for various tests, as well as additional time points added to PK testing for further evaluation. Reformatted for easier viewing

10) Section 5.2.2.3 Cycle 1, Day 3 and Section 5.2.2.4 Cycle 1, Day 4: Flow cytometric analysis added to pre-dose blood collection for further biomarker testing on Days 3 and 4

11) Section 5.2.2.4 Cycle 1, Day 4: Additional time points added to PK testing for further evaluation

12) Section 5.2.2.5 Cycle 1, Day 5: PK time points were removed from Day 5 and moved to Day 4

13) Section 5.3.6 Biomarker Evaluation and Methods: Updated this section with additional flow cytometric collection time points for Cycle 1 and clarified the remaining samples to be collected for Cycle 2 and thereafter

14) Section 5.3.8 Estimate of Volume of Blood to be Collected: Updated for consistency with the new PK and flow cytometric collections

**Amendment 3, 14Feb2012**

Protocol Version 3.0 dated 08Sep2011 was amended to Protocol Version 4.0 dated 14Feb2012 to introduce a revised dose-escalation scheme and make other modifications to the protocol. Major changes to the protocol are listed below:

1) Title Page: The Medical Monitor assigned to this study was changed from Ramy Ibrahim, MD to [redacted].

2) Study Abstract: Updated to be consistent with the changes made to the body of the protocol.

3) Section 1.3 (Rationale for Study Conduct), Section 3.1 (Overview of Study Design), Section 3.4 (Rationale for Study Design, Doses, and Control Groups), Section 4.5.2 (Treatment Regimen), Section 4.5.4.1 (Monitoring of Dose Administration), and Section 4.5.4.2 (Dose Escalation) were revised to reflect a revised dose-escalation plan for cohorts following Cohort 6, removal of the tumor response cohorts, and the addition of a 20-subject cohort of refractory gastroesophageal cancer subjects in the expansion phase.

4) Modification of Dose-escalation Scheme: The dose-escalation scheme was modified to allow doses for Cohorts 7 and 8 to increase 150% to 300 μg and 750 μg, respectively. The Cohort 9 dose would be a 100% increase, to 1.5 mg. Doses for remaining cohorts would follow the modified Fibonacci dosing scheme, with increases of 100%, 67%, 50%, and 33% to 3 mg, 5 mg, 7.5 mg, and 10 mg.

5) Removal of Tumor Response Cohorts: The tumor regression cohorts were removed from the protocol to simplify dose escalation. Additional subjects outside of the dose-escalation portion of the study with gastroesophageal, pancreatic, and colorectal cancer will be enrolled in the expansion phase of the study once a MTD/OBD is identified.

6) Addition of Expansion Phase cohort of gastroesophageal cancer subjects.

7) Section 4.2 (Subject Selection and Withdrawal) and Section 4.5.5 (Concomitant Medications): Revised to clarify exclusion of subjects receiving chronic corticosteroid treatment and acceptable uses of corticosteroids during the study.

8) Section 4.5.3 (Investigational Product Preparation): Revised to reflect updated instructions on the handling and storage requirements for MEDI-565.

9) Section 7.5 (Sample Size): Revised to reflect the addition of Cohort 13 in the dose-escalation phase and the removal of the response cohorts.

10) Appendices (Appendix 1): The reference to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 was moved from the Appendices to the References section. Other appendices were renumbered.

**Amendment 4, 31May2013**

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. The protocol was amended to provide initial safety data, reflect a revised dose-escalation scheme, and add risk mitigation measures to the protocol. Major changes to the protocol are listed below:

1) The medical monitor was changed.

2) The study abstract was updated to be consistent with changes made to the body of the protocol.

3) Section 1.2.2 (Pharmacokinetics): Updated with a brief summary of the PK results to date in Study MI-CP216.

4) Section 1.2.4 (Clinical): Updated with a brief overview of initial safety data from Study MI-CP216.

5) Section 1.3 (Rationale for Study Conduct): The planned number of subjects to be enrolled was updated. Language was added to indicate that the expansion phase of the study may be initiated at the sponsor's discretion based on signal of antitumor activity and safety profile of MEDI-565.

6) Section 1.4 (Benefit-risk and Ethical Assessment): Updated to reflect potential risks based on initial data from Study MI-CP216.

7) Section 2.3 (Exploratory Objectives): An additional objective to assess multiple aspects of the tumor and tumor microenvironment was added to enable examination of the pharmacodynamic effect of MEDI-565.

8) Section 3.1 (Study Design): Updated to describe study activity through Cohort 10 and the addition of 2 new cohorts to be dosed at 1.5 mg and 3 mg. In addition, a statement was added to indicate that the expansion phase of the study will commence based on signal of antitumor activity and the safety profile of MEDI-565. Figure 3.1-1 was updated with the revised study design.

9) Section 3.2 (Estimated Duration of Subject Participation): Complete response was deleted from the possible reasons for discontinuation of treatment because subjects who are benefiting from treatment should continue to receive MEDI0639.

10) Section 3.3 (Study-stopping Criteria): Reasons for temporarily suspending or terminating the study were revised, and the criterion that review and approval by the MedImmune SMC are required before resumption of the study was removed.

11) Section 3.4 (Rationale for Study Design, Doses, and Control Groups: A brief description of 2 events of hypoxia that occurred in subjects in Cohort 10 was added; data indicating that the events are manageable were added as rationale for the study design changes in the current amendment. Language was added to indicate that the expansion phase may be initiated based on antitumor activity and safety profile of MEDI-565.

12) Section 4.2.2 (Exclusion Criteria): Contraindication to dexamethasone or equivalent prophylaxis was added.

13) Section 4.2.4 (Replacement of Subjects): Language was added to define nonevaluable subjects and to indicate that subjects in the dose-expansion phase who do not complete at least 2 cycles of MEDI-565 for reasons other than disease progression or toxicity will be replaced.

14) Section 4.5.2 (Treatment Regimen): A statement was added to indicate that subjects will receive Cycle 1, Days 1-2 and 4-5 on an inpatient basis. Complete response was deleted as a reason to discontinue treatment. Table 4.5.2-1 was updated to indicate the number of subjects enrolled through Cohort 10 and to add 2 new cohorts.

15) Section 4.5.3 (Investigational Product Preparation): Procedures for preparing doses less than or equal to 120 μg were clarified.

16) Section 4.5.4 (Investigational Product Administration): Text describing dexamethasone prophylaxis was added.

17) Section 4.5.4.1 (Monitoring of Dose Administration): A description of additional monitoring procedures, including blood pressure, heart rate, and pulse oximetry, as well as monitoring for early signs/symptoms of toxicity, was added. If toxicity signs/symptoms are noted without clear alternative etiology, dexamethasone treatment is recommended and further dosing should be delayed until resolution of symptoms. A description of the most frequent acute signs/symptoms observed with MEDI-565 infusion to date was added.

18) Section 4.5.4.4 (Dose Modification for Toxicity Management): A statement was added to indicate that subjects receiving dexamethasone prophylaxis who have MEDI-565 infusion interrupted for 4 hours or more must restart dexamethasone upon resuming infusion to ensure that sufficient prophylaxis is provided. Text surrounding neurological AEs that must resolve to baseline within 48 hours or they will be considered DLTs was deleted from Table 4.5.4.4-1. No important neurological events have been observed to date; neurological events of Grade 3 or higher will be treated as other AEs in evaluating DLTs.

19) Section 4.5.4.5 (Dose-limiting Toxicity): The exception of Grade 3 or 4 elevations in liver transaminases that resolve to ≤ 2 × ULN or baseline within 14 days after cessation of MEDI-565 infusion was modified to delete the allowance for cessation of elevated liver transaminases that resolve to ≤ 2 × ULN or baseline by the next cycle. Grade 3 hypoxia that resolves in less than 12 hours with maximal supportive care was added as an exception to the DLT criteria because these events have been manageable and of short duration. The list of neurological events that will be considered DLTs was deleted. The exceptions to hematological toxicities that are considered to be DLTs was clarified to indicate that these exceptions are in cases considered to be related to MEDI-565.

20) Section 5.2 (Schedule of Study Procedures): Table 5.2-1 was modified to add dexamethasone prophylaxis on Cycle 1, Day 1; toxicity monitoring on Days 1 through 5 of each cycle; pulse oximetry monitoring at each visit; additional timepoints for weight measurement; and tumor biopsy during screening and Cycle 1, Day 4.

21) Section 5.2.1 (Screening): A statement was added to indicate that screening evaluations that have been obtained for other purposes before a subject provides informed consent may be used if suitable for screening purposes, if the subject consents to their use. Fresh biopsy collection and pulse oximetry were added.

22) Section 5.2.2.1 (Cycle 1, Day 1: First Infusion): Dexamethasone prophylaxis was added; additional timepoints for vital signs and pulse oximetry monitoring were added; and additional monitoring for toxicity was added.

23) Section 5.2.2.2 (Cycle 1, Day 2): Pre-infusion weight was added; additional timepoints for vital signs and pulse oximetry monitoring were added; additional monitoring for toxicity and unscheduled PK and cytokine blood samples were added.

24) Section 5.2.2.3 (Cycle 1, Day 3): Pre-infusion weight, additional timepoints for vital signs and pulse oximetry monitoring, and additional monitoring for toxicity and unscheduled PK and cytokine blood samples were added.

25) Section 5.2.2.4 (Cycle 1, Day 4): Pre-infusion weight, biopsy collection, additional timepoints for vital signs and pulse oximetry monitoring, additional monitoring for toxicity, and unscheduled PK and cytokine blood samples were added.

26) Section 5.2.2.5 (Cycle 1, Day 5): Pre-infusion weight, additional timepoints for vital signs and pulse oximetry monitoring, additional monitoring for toxicity, and unscheduled PK and cytokine blood samples were added.

27) Section 5.2.2.6 (Cycle 1, Day 8): Weight and pulse oximetry were added.

28) Section 5.2.2.7 (Cycle 1, Day 15): Weight and pulse oximetry were added.

29) Section 5.2.2.8 (Cycle 1, Day 22): Weight and pulse oximetry were added.

30) Section 5.2.2.9 (Cycle 2 [and every cycle thereafter], Day 1): Dexamethasone prophylaxis was added; additional timepoints for vital signs and pulse oximetry monitoring were added; and additional monitoring for toxicity, and unscheduled PK and cytokine blood samples were added.

31) Section 5.2.2.10 (Cycle 2 [and every cycle thereafter], Day 2: Pre-infusion weight was added; additional timepoints for vital signs and pulse oximetry monitoring were added; additional monitoring for toxicity and unscheduled PK and cytokine blood samples were added.

32) Section 5.2.2.11 (Cycle 2 [and every cycle thereafter], Day 3): Pre-infusion weight, 2 hour post-infusion vital signs and pulse oximetry, additional monitoring for toxicity and additional monitoring for toxicity were added.

33) Section 5.2.2.12 (Cycle 2 [and every cycle thereafter], Day 4): Pre-infusion weight, 2 hour post-infusion vital signs and pulse oximetry, additional monitoring for toxicity and additional monitoring for toxicity were added.

34) Section 5.2.2.13 (Cycle 2 [and every cycle thereafter], Day 5): Pre-infusion weight, 2 hour post-infusion vital signs and pulse oximetry, additional monitoring for toxicity and unscheduled PK and cytokine blood samples were added.

35) Section 5.2.2.14 (Cycle 2 [and every cycle thereafter], Day 8): Pre-infusion weight and pulse oximetry were added.

36) Section 5.2.2.15 (Cycle 2 [and every cycle thereafter], Day 15): Pre-infusion weight and pulse oximetry were added.

37) Section 5.2.2.16 (Cycle 2 [and every cycle thereafter], Day 22): Pre-infusion weight and pulse oximetry were added.

38) Section 5.2.2.18 (End of Treatment Visit): Pulse oximetry was added.

39) Section 5.2.3.1 (30 Days [plus or minus 3 Days] Post-treatment [if not done as part of End-of-Treatment Visit]): Pulse oximetry was added.

40) Section 5.2.3.2 (Every 3 Months [plus or minus 7 Days] Post-treatment): Clarification was added that physical examination and CXR, CT, or MRI scan are only required for subjects who discontinued treatment without progressive disease and who have not initiated an alternative anticancer therapy.

41) Section 5.3.1 (Medical History, Physical Examination, Toxicity Monitoring, Dexamethasone Prophylaxis Regimen, ECG, Weight, and Vital Signs): Procedures for toxicity monitoring, dexamethasone prophylaxis, additional weight measurements, additional timepoints for vital signs and pulse oximetry monitoring were added.

42) Section 5.3 4 (Pharmacokinetic Evaluation and Methods): Unscheduled PK blood samples were added.

43) Section 5.3.6 (Biomarker Evaluation and Methods): Details regarding the optional tumor biopsies at screening and Cycle 1, Day 4 and unscheduled samples for circulating cytokines were added.

44) Section 7.3.3 (Exploratory Endpoints): Endpoints related to multiple aspects of the tumor and microenvironment were added.

45) Section 7.5 (Sample Size): Updated information on sample size was added.

# Appendix 1 Signatures

## Sponsor Signature(s)

A Phase 1, Open-label Study to Evaluate the Safety and Tolerability of MEDI-565 in Adults with Gastrointestinal Adenocarcinomas

I agree to the terms of this protocol and all amendments/administrative changes.

[redacted]

## Sponsor Signature(s)

A Phase 1, Open-label Study to Evaluate the Safety and Tolerability of MEDI-565 in Adults with Gastrointestinal Adenocarcinomas

I agree to the terms of this protocol and all amendments/administrative changes.

[redacted]

## Sponsor Signature(s)

A Phase 1, Open-label Study to Evaluate the Safety and Tolerability of MEDI-565 in Adults with Gastrointestinal Adenocarcinomas

I agree to the terms of this protocol and all amendments/administrative changes.

[redacted]

## Signature of Coordinating Investigator

A Phase 1, Open-label Study to Evaluate the Safety and Tolerability of MEDI-565 in Adults with Gastrointestinal Adenocarcinomas

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

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

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available or applicable) _____

## Signature of Principal Investigator

A Phase 1, Open-label Study to Evaluate the Safety and Tolerability of MEDI-565 in Adults with Gastrointestinal Adenocarcinomas

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

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

Signature and date: _____

Name and title: _____

Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available) _____

## Appendix 2 Karnofsky Performance Status and Definitions

Performance Status: Subjects will be graded according to the Karnofsky Performance Status Scale.

| Karnofsky Performance Status (KPS) 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 of 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 |

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 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; 1994:253-256

## Appendix 4 Mini-Mental State Examination and Timed Get-Up and Go Test

1) Mini-Mental State Examination (MMSE)

The MMSE comprises 11 different tasks, each with a maximum total score.

| Task | Possible Score Range |
|---|---|
| Orientation to Time | 0-5 |
| Orientation to Place | 0-5 |
| Registration | 0-3 |
| Attention and Calculation | 0-5 |
| Recall | 0-3 |
| Naming | 0-2 |
| Repetition | 0-1 |
| Comprehension | 0-3 |
| Reading | 0-1 |
| Writing | 0-1 |
| Drawing | 0-1 |

The maximum total score is 30 points. Total scores that decrease by ≥ 3 points from the baseline (screening examination, pretreatment) examination scores should immediately be reported to the subject's physician. Subjects with total score decreases of ≥ 3 points from baseline will be evaluated for neurological toxicity at the discretion of the subject's physician. Patients with ≥ Grade 2 neurological toxicity (except headache in the absence of other neurological symptoms) must immediately be reported to the Sponsor.

2) Gait Assessment - Timed Get-Up and Go Test

The subject is seated. Ask the subject to:

- Get up from the chair
- Walk 10 feet
- Turn
- Walk back to the chair and sit

Time the examination and note any abnormalities in gait such as difficulty with balance or foot placement, or swaying gait.

Any change ≥ 15 seconds from the subject's baseline time and/or gait abnormalities (difficulty with balance or foot placement, swaying gait) should be reported to the subject's physician immediately. Care should be taken to compare assessments to the appropriate baseline examination. Subjects who experience a change from baseline or who are noted to have gait abnormalities will be evaluated for neurological toxicity at the discretion of the patient's physician. Subjects with ≥ Grade 2 neurological toxicity (except headache in the absence of other neurological symptoms) must immediately be reported to the Sponsor.

Non-ambulatory subjects will be evaluated for upper extremity ataxia using the MMSE.

## Appendix 5 MEDI-565 Dose Preparation Table

To ensure accurate dose preparation for MEDI-565 doses less than or equal to 120 μg/day, the dose must be prepared in two dilution steps. The reconstituted MEDI-565 at 0.5 mg/mL must first be diluted according to Table 1, and a second dilution must be prepared for administration from the diluted Drug Product according to Table 2.

MEDI-565 doses greater than 120 μg/day must be prepared in one dilution step (final dilution only). Table 3. provides detailed information for dose preparation for doses equal to or greater than 300 μg/day.

**Table 1. Initial Dose Preparation for MEDI-565 Less Than or Equal to 120 µg/day**

| Dose per Day (µg) | Number of Vials Bag Protectant | Number of Vials DP | Dose Preparation | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | First Dilution | | | | | | |
| | | | Start IV Bag Volume (mL) | Final IV Bag Volume (mL) | Volume of Saline to **Remove (mL)** | Volume of Protectant to **Add** (mL) | Volume of MEDI-565 to **Add** (mL) | Mass MEDI-565 to **Add** (µg) | Target concentration (µg/mL) |
| 0.75 | 3 | 1 | 500 | 333 | 183 | 16.7 | 0.10 | 50 | 0.150 |
| 2.25 | 2 | 1 | 250 | 111 | 145 | 5.6 | 0.10 | 50 | 0.450 |
| 6.75 | 2 | 1 | 250 | 111 | 145 | 5.6 | 0.30 | 150 | 1.350 |
| 20 | 2 | 1 | 100 | 63 | 41 | 3.1 | 0.50 | 250 | 4.000 |
| 60 | 2 | 1 | 100 | 21 | 81 | 1.0 | 0.50 | 250 | 12.000 |
| 120 | 2 | 2 | 100 | 21 | 81 | 1.0 | 1.00 | 500 | 24.000 |
| 300 | 1 | 2 | NA | | | | | | |
| 750 | 1 | 3 | | | | | | | |
| 1500 | 1 | 6 | | | | | | | |
| 3000 | 1 | 12 | | | | | | | |
| 5000 | 1 | 20 | | | | | | | |
| 7500 | 1 | 30 | | | | | | | |
| 10000 | 1 | 40 | | | | | | | |

**Table 2. Dose Preparation of MEDI-565 (All Doses)**

| Dose per Day (µg) | Number of Vials Bag Protectant | Number of Vials DP | Dose Preparation | | | | |
|---|---|---|---|---|---|---|---|
| | | | Final Dilution | | | | |
| | | | IV Bag Volume (mL) | Volume of Saline to **Remove (mL)** | Volume of Protectant to **Add** (mL) | Volume of MEDI-565 to **Add** (mL) | Target concentration (µg/mL) |
| 0.75 | 3 | 1 | 100 | 10.0 | 5.0 | 5.0 | 0.0075 |
| 2.25 | 2 | 1 | 100 | 10.0 | 5.0 | 5.0 | 0.0225 |
| 6.75 | 2 | 1 | 100 | 10.0 | 5.0 | 5.0 | 0.0675 |
| 20 | 2 | 1 | 100 | 10.0 | 5.0 | 5.0 | 0.2 |
| 60 | 2 | 1 | 100 | 10.0 | 5.0 | 5.0 | 0.6 |
| 120 | 2 | 2 | 100 | 10.0 | 5.0 | 5.0 | 1.2 |
| 300 | 1 | 2 | 100 | 5.6 | 5.0 | 0.6 | 3 |
| 750 | 1 | 3 | 100 | 6.5 | 5.0 | 1.5 | 7.5 |
| 1500 | 1 | 6 | 100 | 8.0 | 5.0 | 3.0 | 15 |
| 3000 | 1 | 12 | 100 | 11.0 | 5.0 | 6.0 | 30 |
| 5000 | 1 | 20 | 100 | 15.0 | 5.0 | 10.0 | 50 |
| 7500 | 1 | 30 | 100 | 20.0 | 5.0 | 15.0 | 75 |
| 10000 | 1 | 40 | 100 | 25.0 | 5.0 | 20.0 | 100 |

Note: For doses up to and including 120 µg, initial dilution must be completed as described in Table 1. For doses of 300 µg and above, the volume of MEDI-565 added is directly from the reconstituted vial(s).