A Phase 1, Multicenter, Open-label, Single-arm, Dose-escalation Study to Evaluate the Safety, Tolerability, and Antitumor Activity of MEDI-575, a Fully Human Monoclonal Antibody Directed Against Platelet-derived Growth Factor Receptor Alpha (PDGFRα), in Subjects with Advanced Solid Tumors Refractory to Standard Therapy or for Which No Standard Therapy Exists

Investigational Product:	MEDI-575
MedImmune Protocol Number:	MI-CP187
IND Number:	IND 103255
Manufacturer:	MedImmune [redacted]
Sponsor:	MedImmune
Medical Monitor:	[redacted] Director, Clinical Development MedImmune [redacted]
Study Monitor:	MedImmune
Protocol Date:	[redacted]

Principal Investigator Agreement:

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), the ethical principles set forth in the Declaration of Helsinki and with the USA Code of Federal Regulations governing the protection of human subjects (21 CFR Part 50), Financial Disclosure by Clinical Investigators (21 CFR Part 54), Institutional Review Boards (21 CFR Part 56) and the obligations of clinical investigators (21 CFR Part 312).

Signature_____ Date_____

Printed Name_____

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
bFGF	Basic fibroblast growth factor
βhCG	β human chorionic gonadotropin
CA-125	Cancer antigen 125
CBC	Complete blood count
CEL	Chronic eosinophilic leukemia
CIS	Carcinoma in situ
CL	Total body clearance
C_{max}	Maximum concentration
CR	Complete response
CrCl	Creatinine clearance
CT	Computed tomography
DCIS	Ductal carcinoma in situ
DR	Duration of response
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
FIP1L1	Human gene coding for a subunit of the cleavage and polyadenylation specificity factor complex
FIP1L1-PDGFRα	Oncogenic mutation resulting in a constitutively activated PDGFRα and cell proliferation
Flt-1	VEGF receptor
GBM	Glioblastoma multiforme
GCP	Good clinical practice
GIST	Gastrointestinal stromal tumors
HCC	Hepatocellular carcinoma
HED	Human equivalent dose
HEENT	Head, eyes, ears, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation

IEC	Independent Ethics Committee
IM	Immunogenicity
IND	Investigational new drug application
IRB	Institutional Review Board
IRE	Immediately reportable event
IV	Intravenous
Ki67	Antigen identified by mAb Ki-67; a cellular marker for proliferation
KPS	Karnofsky Performance Status
LD	Longest diameter
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MAPK	Mitogen-activated protein kinase
MEDI-575	Fully human mAb directed against PDGFRα
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTD	Maximum tolerated dose
NCI CTCAE V3.0	National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0
NOAEL	No observable adverse effect level
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
P1GF	Placenta growth factor
p-Akt	Activated (phosphorylated)-serine/threonine kinase
PD	Progressive disease
PDGF	Platelet-derived growth factor
PDGF-AA, PDGF-BB	A- and B-chain homodimers, respectively, of PDGF
PDGFRα	Platelet-derived growth factor receptor alpha
PDGFRβ	Platelet-derived growth factor receptor beta
PFS	Progression-free survival
PK	Pharmacokinetics
p-MAPK	Phosphorylated mitogen-activated protein kinase
p-PDGFRα	Phosphorylated PDGFRα
PR	Partial response

PSA	Prostate-specific antigen
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
SID	Subject identification number
SMC	Safety monitoring committee
$t_{½}$	Half-life
T_{max}	Time to maximum concentration
TTP	Time to progression
TTR	Time to response
TUNEL	Terminal deoxynucleotidyl transferase dUTP nick end labeling; DNA fragmentation assay
ULN	Upper limit of normal
USA	United States of America
VEGF	Vascular endothelial growth factor

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Study Abstract

Title:

A Phase 1, Multicenter, Open-label, Single-arm, Dose-escalation Study to Evaluate the Safety, Tolerability, and Antitumor Activity of MEDI-575, a Fully Human Monoclonal Antibody Directed Against Platelet-derived Growth Factor Receptor Alpha (PDGFRα), in Subjects with Advanced Solid Tumors Refractory to Standard Therapy or for Which No Standard Therapy Exists

Objectives:

The primary objectives of this study are:

1) To evaluate the safety and tolerability of MEDI-575 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists; and
2) To determine the maximum tolerated dose (MTD) and/or optimal biologic dose of MEDI-575 in adult subjects with advanced solid tumors.

The secondary objectives of this study are:

1) To describe the pharmacokinetics of MEDI-575 and establish the serum exposures that result in saturation of antigen (PDGFRα) sink in this subject population;
2) To evaluate the immunogenicity of MEDI-575; and
3) To evaluate any antitumor activity of MEDI-575 in adult subjects with advanced solid tumors.

The exploratory objectives of this study are:

1) To determine levels of selected circulating soluble proteins, including PDGF-AA, PDGF-AB/BB, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), soluble VEGF receptor (Flt-1), and placenta growth factor (PlGF), and to explore their association with treatment with MEDI-575 and clinical outcome;
2) To evaluate the effects of genetic variation and PDGF signaling protein expression levels including PDGFRα, p-PDGFRα, phosphorylated serine/threonine kinase (p-Akt), and phosphorylated mitogen-activated protein kinase (p-MAPK) on subject response to treatment with MEDI-575, when fresh and/or archival tumor samples are available; and
3) To evaluate the effects of genetic variation and PDGFRα and expression levels of related signaling proteins on subject response to treatment with MEDI-575, when circulating tumor cells are available.

Study Design:

This is a Phase 1, multicenter, open-label, single-arm, dose-escalation and dose-expansion study to evaluate the safety, tolerability, and antitumor activity of MEDI-575 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. Approximately 3 to 6 investigational sites in the United States of America (USA) will participate in this study, with cohorts of 3 to 6 evaluable subjects each receiving 1 of 5 doses of MEDI-575 (3.0, 6.0, 9.0, 12, or 15 mg/kg) every 7 days. Subjects enrolled in Dose Cohort 1 (3.0 mg/kg) only will receive as a 60-minute intravenous (IV) infusion a single lead-in dose of MEDI-575 at 0.5 mg/kg administered 7 days prior to receipt of the first dose of MEDI-575 at the 3.0 mg/kg dose level. Subjects are considered evaluable if they receive 3 doses of MEDI-575 at the 3.0 mg/kg (Dose Cohort 1) or higher (Dose Cohorts 2 through 5) dose level and are followed 21 days after the first administration of MEDI-575 at 3.0 mg/kg or higher or they discontinue MEDI-575 at any dose due to dose-limiting toxicities (DLTs). Non-evaluable subjects will be replaced in the same dose cohort.

During the dose-escalation phase (through Cohort 5), MEDI-575 will be administered once every 7 days (on Study Days 1, 8, and 15 of each 21-day cycle of treatment) as a 60-minute IV infusion until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal (see Section 4.7). Intrasubject dose escalation will not be allowed, except in the first dose cohort (Dose Cohort 1) which will receive a single lead-in dose of 0.5 mg/kg 7 days prior to the receipt of the first dose at 3.0 mg/kg. This single lead-in dose at 0.5 mg/kg in the first dose cohort of 3 subjects (3.0 mg/kg dose level) will be used to obtain pharmacokinetic (PK) and pharmacodynamic data under conditions in which the available sites for MEDI-575 binding would not be expected to be saturated, and has no therapeutic intent. The duration of Cycle 1 for Dose Cohort 1 will be 28 days; the duration of all subsequent cycles for Dose Cohort 1 and all cycles for all other dose cohorts will be 21 days. Dose reduction for toxicities other than DLTs will be allowed as described in Section 3.5.5.

Two additional cohorts will be added to the dose-escalation phase to evaluate alternate treatment schedules: 25 mg/kg (Dose Cohort 6) and 35 mg/kg (Dose Cohort 7) administered as a 90-minute IV infusion once every 21 days on Study Day 1 will be explored (every 3-week schedule). The infusion time will be increased for the 25 or 35 mg/kg doses (every 3-week schedule) due to the larger protein load. These subjects will be evaluated identically to other subjects during the dose escalation phase since the cycle length and DLT period will be 21 days. Subjects in Cohorts 6 and 7 will be considered evaluable if they receive a single

dose of MEDI-575 and complete the 21-day DLT period or discontinue due to a DLT. The doses and schedule were chosen based on PK and pharmacodynamic modeling and data obtained in the first 3 treated cohorts, and are predicted to provide target saturation of PDGFRα receptors for the duration of the dosing interval. A minimum of 21 evaluable subjects or up to approximately 42 evaluable subjects will be required during the dose-escalation phase.

Dose escalation will follow a standard 3+3 study design. Rules for dose escalation are described in Section 4.9.

For the dose-expansion phase, approximately 12 subjects may be enrolled. All 12 subjects to be enrolled in the dose-expansion phase must have one of the following advanced solid tumors: non-small cell lung cancer (NSCLC), glioblastoma multiforme (GBM), ovarian cancer, or synovial sarcoma. These subjects will be evaluated identically to the other subjects during the dose-escalation phase. Of the 12 subjects in the dose-expansion phase, 6 subjects will be treated once every 7 days of a 21-day cycle (weekly schedule) at a dose to be determined based on an analysis of PK, pharmacodynamic markers, and safety from Cohorts 1 through 5. Another 6 subjects in the dose-expansion phase will be treated at a dose of either 25 or 35 mg/kg once every 21 days on Study Day 1 (every 3-week schedule) based on an analysis of PK, pharmacodynamic markers, and safety from Cohorts 6 and 7. The 25 or 35 mg/kg dose will be pursued pending no significant safety findings at these doses during the dose escalation phase (Cohorts 6 and 7). Enrollment in the weekly dose-expansion schedule can occur simultaneously with Cohorts 6 and 7. Subjects will be enrolled in the every 3-week dose-expansion schedule once Cohorts 6 and 7 are completed and a choice of dose is made as described above.

Subject Population:

The subjects in this study will be adults with advanced solid tumors refractory to standard therapy or for which no standard therapy exists.

Treatment:

In the dose-escalation phase (through Cohort 5), subjects will be treated with 1 of 5 doses of MEDI-575 (3.0, 6.0, 9.0, 12, or 15 mg/kg) once every 7 days (Table 3.5.2-1). Subjects enrolled in Dose Cohort 1 (3.0 mg/kg) only will receive as a 60-minute IV infusion a single lead-in dose of MEDI-575 at 0.5 mg/kg administered 7 days prior to receipt of the first dose of MEDI-575 at the 3.0 mg/kg dose level. The single lead-in dose at 0.5 mg/kg will be used

to assess PK and pharmacodynamic parameters. The day of administration of the 0.5 mg/kg dose will be considered the day of initiation of treatment (Study Day 1). The DLT period for this dose cohort only will begin with the single administration of MEDI-575 at the dose level of 0.5 mg/kg and continue until 21 days after administration of the first dose at 3.0 mg/kg (Study Day 28) for a total of 28 days. Thereafter MEDI-575 will be administered as a 60-minute IV infusion on Study Days 1, 8, and 15 of each 21-day treatment cycle until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal (see Section 4.7). In Cycle 2 and beyond, a dose can be delayed up to 7 days based on hematologic and nonhematologic toxicities, according to the conditions described in Section 3.5.5 (Dose Modifications and Toxicity Management), but all 3 planned doses (if a subject is enrolled on the weekly dosing schedule) must be completed within the cycle. Subjects enrolled on the weekly dosing schedule who do not receive all 3 doses within a cycle will not advance to the next cycle and will be removed from treatment; therefore, each cycle after the first cycle of the weekly dosing schedule will be considered complete after administration of 3 doses. For the weekly dosing schedule, each new cycle will begin no fewer than 7 days after the last dose of the previous cycle; and for the every 3-week dosing schedule, each new cycle will begin no fewer than 21 days after the last dose of the previous cycle. Rules for dose escalation are described in Section 4.9. Intrasubject dose escalation, except for the first cohort as described above, will not be allowed. Dose reduction for toxicities other than DLTs (see Section 4.10 for definition of DLTs) will be allowed as described in Section 3.5.5.

For Dose Cohorts 6 and 7 in the dose-escalation phase and 6 subjects in the dose-expansion phase, the dose and schedule of MEDI-575 will be 25 or 35 mg/kg administered as a 90-minute IV infusion once every 21 days (on Study Day 1 of a 21-day cycle). Another 6 subjects in the dose-expansion phase will be treated once every 7 days of a 21-day cycle (weekly schedule, 60 minute infusion) at a dose to be determined based on an analysis of PK, pharmacodynamic markers, and safety from Cohorts 1 through 5.

Subject Evaluation and Follow-up:

Subject evaluations are described in Table 3.6-1 and Table 3.6-2, and a schedule of follow-up visit procedures is presented in Table 3.6-3.

After informed consent has been obtained, screening evaluations will occur within 28 days prior to study entry and include the following evaluations: eligibility verification, medical history; serum β human chorionic gonadotropin (βhCG) for women (unless surgically sterile

or >1 year post menopause); complete physical examination (including height and weight); 12-lead electrocardiogram (ECG); routine laboratory evaluations (hematology, serum chemistry, and urinalysis); vital signs; assessment of protocol-related adverse events (AEs) and serious adverse events (SAEs); notation of concomitant medications; disease evaluations (including computed tomography [CT] or magnetic resonance imaging [MRI] scans, and Karnofsky performance status); and pharmacodynamic evaluations (including serum tumor biomarkers [as relevant to tumor type], circulating tumor cells, RNA analysis, DNA analysis [optional], and collection of archived tumor samples when available [optional]).

The following evaluations will be performed during the treatment period: urine βhCG at Study Day 1 of each treatment cycle only for women (unless surgically sterile or >1 year post menopause); physical examination (for disease evaluation); weight; vital signs; ECG; routine laboratory evaluations (hematology, serum chemistry, and urinalysis); notation of concomitant medications; PK and immunologic (IM) evaluations (MEDI-575 serum concentrations and anti-MEDI-575 antibodies, respectively); and pharmacodynamic evaluations (including circulating tumor cells, plasma biomarker analysis, serum tumor biomarkers [as relevant to tumor type], and RNA analysis).

Treatment-emergent AEs and SAEs will be assessed from the time the subject receives the first dose of MEDI-575 through 30 days after the last dose of MEDI-575. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE V3.0). In addition, disease evaluations (including CT or MRI scan, complete physical examination, and Karnofsky performance status) will be performed after every 2 cycles of treatment until documentation of disease progression or initiation of alternative anticancer therapy. For subjects who discontinue treatment due to reasons other than disease progression or initiation of alternative anticancer therapy, disease evaluations will be performed every 3 months until documentation of disease progression, initiation of alternative anticancer therapy, or the end of study (defined as 1 year after the last subject entered the study). Subjects will be evaluated for disease response using Response Evaluation Criteria in Solid Tumors (RECIST; Therasse et al, 2000). Survival will be followed every 3 months by clinic visit or telephone contact until the end of the study.

Sample Size:

For the dose-escalation phase, a minimum of 21 evaluable subjects (3 subjects in Dose Cohorts 1 through 7) or up to approximately 42 evaluable subjects (3+3 subjects per dose cohort) will be required to determine the MTD. A subject will be considered evaluable if the

subject receives at least 1 full cycle of MEDI-575 and completes the safety follow-up through the DLT evaluation period, or the subject experiences a DLT. Any non-evaluable subject will be replaced in the same dose cohort.

For the dose-expansion phase, approximately 12 subjects may be entered.

Assessment of Endpoints:

The primary objectives of this study are to evaluate the safety and tolerability of MEDI-575 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists and to determine the MTD and/or optimal biological dose of MEDI-575 in this subject population. All safety endpoints will be summarized descriptively. Adverse events and SAEs will be summarized by dose cohort, system organ class, severity, and relationship to MEDI-575 through 30 days after the last dose of MEDI-575.

Determination of the MTD is described in Section 4.9 and descriptive statistics will be provided to summarize the occurrence of DLTs by dose cohort.

Secondary endpoints include assessments of PK, IM, and antitumor activity of MEDI-575.

The PK of MEDI-575 will be assessed using the variables of area under the concentration-time curve (AUC), which will be calculated by the trapezoidal rule, maximum concentration (C_{max}), time to maximum concentration (T_{max}), half-life ($t_{½}$), and total body clearance (CL). These parameters will be obtained by non-compartmental methods. Linearity in the PK of MEDI-575 will be assessed from $t_{½}$ and dose-normalized AUC and C_{max}. Descriptive statistics will be provided by dose cohort.

Immunogenicity of MEDI-575 will be assessed and summarized descriptively by dose cohort.

The antitumor activity of MEDI-575 will be assessed based on objective response rate (ORR), time to response (TTR), duration of response (DR), time to progression (TTP), progression-free survival (PFS), and overall survival (OS).

Objective response rate (ORR) is defined as the proportion of subjects with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST guidelines. Confirmed responses are those that persist on repeat imaging study ≥ 4 weeks after the initial documentation of response.

Time to response (TTR) will be measured from the start of treatment with MEDI-575 to the first documentation of objective response and will only be assessed in subjects who have achieved objective response.

Duration of response (DR) 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 therapy. Duration of response will only be calculated for the subgroup of subjects with an objective response.

Time to progression (TTP) will be measured from the start of treatment with MEDI-575 until the documentation of disease progression. Disease progression is defined according to RECIST guidelines. The TTP will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression prior to data cutoff, dropout, or the initiation of alternate anticancer therapy. Subjects having no tumor assessments after the start of treatment with MEDI-575 will have TTP censored on the first date of treatment with MEDI-575.

Progression-free survival (PFS) will be measured from the start of treatment with MEDI-575 until the documentation of disease progression or death due to any cause, whichever occurs first. Disease progression is defined according to RECIST guidelines. The PFS will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression and are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer therapy. Subjects having no tumor assessments after the start of treatment with MEDI-575 will have PFS censored on the first date of treatment with MEDI-575.

Overall survival (OS) will be determined as the time from the start of treatment with MEDI-575 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 time to event data including TTR, DR, TTP, PFS, and OS will be evaluated using Kaplan-Meier methods.

A select panel of biomarkers will be employed which may include evaluation of the effects of MEDI-575 on serum tumor biomarkers including prostate-specific antigen (PSA) and cancer

antigen125 (CA-125) or other tumor markers as determined by tumor type. Descriptive statistics will also be provided.

Interim Analysis:

Not applicable.

1 Introduction

1.1 Background

Platelet-derived growth factors (PDGFs) are peptide growth factors that stimulate cellular growth, proliferation, and differentiation (Fredriksson et al, 2004). The PDGFs exert their cellular effects through transmembrane receptor tyrosine kinases, PDGF receptor alpha (PDGFRα) and PDGF receptor beta (PDGFRβ). PDGFRα plays an important role in human carcinogenesis, both as a direct target on tumor cells and also as a mediator of stromal support for cancer cell growth. Genetic modifications leading to overexpression or activation of PDGFRα have been demonstrated in at least 3 different malignancies. In glioblastoma multiforme (GBM), an internal deletion leads to ligand-independent signaling in malignant cells (Shih and Holland, 2006); in gastrointestinal stromal tumors (GIST), small deletions and point mutants lead to independent activation (Corless et al, 2004); and in chronic eosinophilic leukemia (CEL), a fusion of FIP1L1 and PDGFRα leads to aberrant activation of PDGFRα in eosinophil and other hematopoietic precursors, leading to excessive proliferation (Buitenhuis et al, 2007).

Inhibition of PDGFRα signaling has been used as an effective therapeutic strategy in those diseases where such signaling is known to be important for tumor progression. For example, in patients with CEL who have the FIP1L1-PDGFR fusion (between the genes for PDGFRα and FIP1L1 in chromosome 4 coding for a constitutively activated PDGFRα tyrosine kinase), treatment with imatinib, a tyrosine kinase inhibitor with activity against PDGFRα led to 100% response whereas, when the receptor was not expressed, the response rate was only 14% (Baccarani et al, 2007). PDGFRα inhibitors have also been shown to be useful in GIST (Sleijfer et al, 2008). The use of currently available small molecule PDGFR inhibitors is limited in part by toxicities related to inhibition of PDGFRβ, which is thought to mediate the extravascular fluid accumulation that is observed with agents such as imatinib and dasatinib (Jayson et al, 2005; Quintás-Cardama et al, 2007). Targeting PDGFRα specifically with a

small molecule inhibitor has not yet been accomplished clinically, and may be difficult due to the high degree of structural similarity between the 2 isoforms of the receptor.

Expression of PDGFRα has also been observed in multiple solid tumors, including lung (Bauman et al, 2007), breast (Carvalho et al, 2005), prostate, ovarian, and hepatocellular carcinomas (Alvarez et al, 2006). In non-small cell lung cancer (NSCLC), PDGFRα expression has been noted in up to 100% of tumors studied (Zhang et al, 2003), and expression in tumor stroma is high. In breast cancer, tumors that expressed high levels of PDGFRα were more likely to metastasize as determined by the presence of malignant cells in lymph nodes (Carvalho et al, 2005). Expression of PDGFRα is widespread in ovarian cancer, with 58% of tumors expressing the receptor in one study (Wilczynski et al, 2005). High percentages of expression in human tumors and a paracrine-activating loop were also observed in another study (Matei et al, 2006). In monophasic and biphasic histologic subtypes of pediatric synovial sarcoma, activation of epidermal growth factor receptor, PDGFRα, and PDGFRβ was observed with concomitant activation of Akt. Consistently, Akt activation was completely abolished in a synovial sarcoma cell line assay when stimulated by PDGF-AA and treated with the phosphatidylinositol 3-kinase inhibitor LY294002 (Bozzi et al, 2008). PDGF signaling has been shown to be a key regulator of glioma development. The concurrent expression of PDGFA and PDGFRA in different subtypes of gliomas, reinforces the recognized significance of this signaling pathway in gliomas (Martinho et al, 2009). The role of PDGFRα in regulating the growth of hepatocellular carcinoma (HCC) is more complex. PDGFRα is necessary for epithelial-mesenchymal transformation, a prerequisite for carcinogenesis, induced by transforming growth factor beta (Gotzmann et al, 2006). PDGFRα expression was seen to be widespread in HCC tumors (Stock et al, 2007). These data suggest that PDGFRα may have an important and relatively underemphasized role in the development and progression of multiple cancer types.

Inhibition of PDGFRα may serve to inhibit tumor growth by another mechanism as well. PDGFRα is widely expressed in tumor stromal cells that support malignant cell growth and contribute to such processes as angiogenesis (Östman, 2004). This has best been studied in NSCLC, where expression of PDGFRα is essentially uniform in stromal cells of the tumor, and the ligand PDGF-AA (A-chain homodimer of PDGF) is expressed in malignant cells (Shikada et al, 2005). Studies in mice demonstrate that PDGFRα signaling is critical for normal lung development, and overexpression of the ligand PDGF-AA, which can only signal through the activation of PDGFRα, by lung epithelial cells leads to hyperproliferation of alveolar epithelium with an immature phenotype (Betsholtz, 2004). In vivo xenograft

NSCLC models demonstrated that disruption of PDGFRα signaling in the stromal cells can lead to an inhibition of tumor growth (Tejada et al, 2006). Thus, targeting PDGFRα in the stromal compartment, particularly in the lung, may be a useful mechanism to promote epithelial differentiation and inhibition of tumor growth.

1.2 Description of MEDI-575

MEDI-575 is a fully human IgG2 kappa monoclonal antibody (mAb) directed against PDGFRα. It binds to PDGFRα with a high degree of specificity and avidity, and does not cross-react with PDGFRβ. MEDI-575 blocks PDGF binding to receptor and inhibits signaling at low nanomolar concentrations. It cross-reacts with monkey PDGFRα but does not recognize mouse PDGFRα. Treatment with MEDI-575 is expected to block signaling through PDGFRα/α homodimers, but have no effect on PDGFRβ/β homodimers. This has the theoretical advantage of potentially limiting toxicity related to extravascular fluid accumulation, which is thought to be mediated via PDGFRβ, while retaining significant antitumor activity.

1.3 Nonclinical Experience with MEDI-575

Pharmacokinetic (PK) studies in cynomolgus monkeys indicated that, following administration of a single intravenous (IV) infusion of the mAb at 0.6, 6.0, and 60 mg/kg on Day 1, anti-PDGFRα antibody exhibited dose-dependent and nonlinear PK. The clearance (CL) was decreased by approximately 2-fold over the dose range examined. The nonlinear CL following administration of MEDI-575 in cynomolgus monkeys is consistent with PDGFRα-mediated clearance of the mAb. Administration of single doses of the mAb up to 60 mg/kg was well tolerated in this study with no apparent toxicities observed in any of the safety endpoints measured. A 13-week, repeat-dose toxicology study examined the PK, pharmacodynamics, and toxicology of MEDI-575 administered to cynomolgus monkeys at doses of 3, 30, and 100 mg/kg once every 7 days. The 13-week treatment period was followed by an 8-week treatment-free period to follow recovery from any potential toxic effects. All animals survived to scheduled euthanasia on Day 87 (terminal animals) or Day 141 (recovery animals). No significant adverse effects were observed at doses up to 100 mg/kg/week. Similar nonlinear (dose-dependent) PK parameters were observed for MEDI-575 following administration of 13 weekly doses of the mAb in monkeys. Additionally, consistent with dose-dependent inhibition of PDGF-AA binding to PDGFRα,

dose-related increases in serum concentrations of PDGF-AA were observed following administration of MEDI-575 in monkeys.

1.4 Clinical Experience with MEDI-575

As of [redacted], there is 1 on-going clinical study (MI-CP187). Subjects have been enrolled through Cohort 5 (0.5/3.0, 6.0, 9.0, 12, and 15 mg/kg once every 7 days) and no dose-limiting toxicities (DLTs) have been identified to date.

A different mAb to PDGFRα has been tested in a Phase 1 study in patients with advanced cancers and the results recently reported (Chiorian et al, 2008). In this study, subjects were administered 1 of 3 doses of antibody (4.0, 8.0, or 16.0 mg/kg) weekly or 15 or 20 mg/kg once every 2 weeks. No DLTs were observed. No adverse events (AEs) ≥ Grade 3 were observed. The longest duration of treatment for any subject was > 52 weeks. Pharmacokinetic analyses suggested that target saturation was reached or approached at the highest dose. No definitive tumor responses were observed. This study demonstrates an acceptable safety profile for administration of a mAb to PDGFRα at the doses tested.

1.5 Rationale for Study

The PDGF pathway plays important roles in cancer development. Briefly, PDGFs and their related receptors are associated with the development or propagation of lung, ovarian, hepatocellular, and other solid tumors. Mutations in PDGFRα have been identified as key components in CEL and GIST, where it has been targeted by small molecule inhibitors of the receptor. Antibody targeting of this receptor will allow specific inhibition of the PDGFRα pathway without affecting PDGFRβ signaling, which may lead to an improved toxicity profile compared to less specific small molecule inhibitors.

MEDI-575 is being developed for the treatment of solid tumors. The first-in-human study proposed here will treat patients with advanced solid tumors that are refractory to standard therapies, or for which no standard therapies exist. Patients in this population have no treatment options that are known to be of benefit, and may derive clinical benefit from an experimental therapy such as this one. No additional studies are proposed for the first year.

The starting dose of MEDI-575 proposed for this study is based on nonclinical PK and toxicological studies in cynomolgus monkeys. The cynomolgus monkey is the relevant species for toxicological studies based on a high degree of sequence identity between human

and cynomolgus monkey PDGFRα, binding of MEDI-575 to human and monkey PDGFRα with similar affinity, demonstration of inhibition of PDGFRα phosphorylation in human and monkey cells treated with MEDI-575 with similar potency, and an increase in circulating PDGF-AA, a ligand for PDGFRα, in monkeys administered MEDI-575. In contrast, rodents are not a relevant species due to the lack of binding of MEDI-575 to mouse PDGFRα. Monkeys administered MEDI-575 as a once-weekly 30-minute IV infusion over 13 weeks exhibited no adverse effects at doses up to 100 mg/kg/week, the highest dose tested. Because only a single toxicological species is relevant, the human equivalent dose (HED) based on a scaling factor of 3.1 of the no observable adverse effect level (NOAEL) in monkeys is 32 mg/kg. Allowing for a safety margin of 10-fold, a starting dose of 3.0 mg/kg once every 7 days was chosen. A single lead-in dose at 0.5 mg/kg in the first dose cohort of 3 subjects (3.0 mg/kg dose level) will be used to obtain PK and pharmacodynamic data under conditions in which the available sites for MEDI-575 binding would not be expected to be saturated, and has no therapeutic intent. Pharmacokinetic modeling based on data obtained in preclinical studies in cynomolgus monkeys predicts that following administration of single doses in man the half-life (t½) of MEDI-575 is expected to be very short at the simulated dose of 0.5 mg/kg, with the predicted average receptor occupancy at steady state of around 60% over the weekly dosing interval. The PK simulations also predict that the initial dose of 0.5 mg/kg followed by weekly dosing of 3.0 mg/kg should provide greater than 99% receptor occupancy at steady state. Evaluation of PK and pharmacodynamic markers during the dose escalation portion of the proposed clinical study will determine if steady state levels that saturate > 99% of available receptors can be maintained using a weekly dosing schedule. The model does not account for a possible sink of available receptors in tumors. MEDI-575, like other mAbs, is only bioavailable as a parenterally administered agent. Intravenous administration is the safest and most consistent method of administration.

Based on nonclinical studies, no potential toxicities have been identified to date. Inhibitors that target both PDGFRα and PDGFRβ can lead to extravascular fluid accumulation, but this is likely to be primarily an effect of inhibition of PDGFRβ (Östman, 2004; Jayson et al, 2005). Subjects will be monitored regularly throughout the course of treatment and in follow-up while enrolled in the proposed study.

This Phase 1 study will evaluate the safety and tolerability of MEDI-575, a fully human mAb directed against PDGFRα, in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. In this study, for the dose-escalation phase, MEDI-575 will be administered once every 7 days as a 60-minute IV infusion at doses of 0.5/3.0, 6.0, 9.0, 12, and 15 mg/kg (Dose Cohorts 1 through 5, respectively) until

unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal. For Dose Cohorts 6 and 7 (25 and 35 mg/kg, respectively) of the dose-escalation phase, the dose and schedule of MEDI-575 will be 25 or 35 mg/kg administered as a 90-minute IV infusion once every 21 days on Study Day 1 (every 3-week schedule). In the dose-expansion phase, 6 subjects will be treated once every 7 days of a 21-day cycle (weekly schedule) at a dose to be determined based on an analysis of PK, pharmacodynamic markers, and safety from Cohorts 1 through 5. Another 6 subjects in the dose-expansion phase will be treated at a dose of either 25 or 35 mg/kg once every 21 days on Study Day 1 (every 3-week schedule) as a 90-minute IV infusion based on an analysis of PK, pharmacodynamic markers, and safety from Cohorts 6 and 7. Additional endpoints include PK, immunogenicity (IM), pharmacodynamic markers, and antitumor activity.

2 Study Objectives and Overview

2.1 Primary Objectives

The primary objectives of this study are:

1) To evaluate the safety and tolerability of MEDI-575 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists; and
2) To determine the maximum tolerated dose (MTD) and/or optimal biologic dose of MEDI-575 in adult subjects with advanced solid tumors.

2.2 Secondary Objectives

The secondary objectives of this study are:

1) To describe the PK of MEDI-575 and establish the serum exposures that result in saturation of antigen (PDGFRα) sink in this subject population;
2) To evaluate the IM of MEDI-575; and
3) To evaluate any antitumor activity of MEDI-575 in adult subjects with advanced solid tumors.

2.3 Exploratory Objectives

The exploratory objectives of this study are:

1) To determine levels of selected circulating soluble proteins, including PDGF-AA, PDGF-AB/BB, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), soluble VEGF receptor (Flt-1), and placenta growth factor (PlGF), and to explore their association with treatment with MEDI-575 and clinical outcome;
2) To evaluate the effects of genetic variation and PDGF signaling protein expression levels including PDGFRα, p-PDGFRα, phosphorylated serine/threonine kinase (p-Akt), and phosphorylated mitogen-activated protein kinase (p-MAPK) on subject response to treatment with MEDI-575, when fresh and/or archival tumor samples are available; and
3) To evaluate the effects of genetic variation and PDGFRα and expression levels of related signaling proteins on subject response to treatment with MEDI-575, when circulating tumor cells are available.

2.4 Overview

Study Design

This is a Phase 1, multicenter, open-label, single-arm, dose-escalation and dose-expansion study to evaluate the safety, tolerability, and antitumor activity of MEDI-575 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. Approximately 3 to 6 investigational sites in the United States of America (USA) will participate in this study, with cohorts of 3 to 6 evaluable subjects each receiving 1 of 5 doses of MEDI-575 (3.0, 6.0, 9.0, 12, or 15 mg/kg) every 7 days. Subjects enrolled in Dose Cohort 1 (3.0 mg/kg) only will receive as a 60-minute IV infusion a single lead-in dose of MEDI-575 at 0.5 mg/kg administered 7 days prior to receipt of the first dose of MEDI-575 at the 3.0 mg/kg dose level. Subjects are considered evaluable if they receive 3 doses of MEDI-575 at the 3.0 mg/kg (Dose Cohort 1) or higher (Dose Cohorts 2 through 5) dose level and are followed 21 days after the first administration of MEDI-575 at 3.0 mg/kg or higher or they discontinue MEDI-575 at any dose due to DLTs. Non-evaluable subjects will be replaced in the same dose cohort.

During the dose-escalation phase (through Cohort 5), MEDI-575 will be administered once every 7 days (on Study Days 1, 8, and 15 of each 21-day cycle of treatment) as a 60-minute IV infusion until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal (see Section 4.7). Intrasubject dose escalation will not be

allowed, except in the first dose cohort (Dose Cohort 1) which will receive a single lead-in dose of 0.5 mg/kg 7 days prior to the receipt of the first dose at 3.0 mg/kg. This single lead-in dose at 0.5 mg/kg in the first dose cohort of 3 subjects (3.0 mg/kg dose level) will be used to obtain PK and pharmacodynamic data under conditions in which the available sites for MEDI-575 binding would not be expected to be saturated, and has no therapeutic intent. The duration of Cycle 1 for Dose Cohort 1 will be 28 days; the duration of all subsequent cycles for Dose Cohort 1 and all cycles for all other dose cohorts will be 21 days. Dose reduction for toxicities other than DLTs will be allowed as described in Section 3.5.5.

Two additional cohorts will be added to the dose-escalation phase to evaluate 25 mg/kg (Dose Cohort 6) and 35 mg/kg (Dose Cohort 7) administered as a 90-minute IV infusion once every 21 days on Study Day 1 of each cycle. The infusion time is increased for the 25 or 35 mg/kg doses (every 3-week schedule) due to the larger protein load. These subjects will be evaluated identically to other subjects during dose escalation, since the cycle length and DLT period will be 21 days. Subjects in Cohorts 6 and 7 will be considered evaluable if they receive a single dose of MEDI-575 and complete the 21-day DLT period or discontinue due to DLTs. The doses and schedule were chosen based on PK and pharmacodynamic modeling and data obtained in the first 3 treated cohorts, and are predicted to provide target saturation of PDGFRα receptors for the duration of the dosing interval. A minimum of 21 evaluable subjects or up to approximately 42 evaluable subjects will be required during the dose-escalation phase.

Pharmacokinetic/pharmacodynamic modeling was performed based on data generated in cynomolgus monkey PK studies and the first 2 cohorts (3 and 6 mg/kg) from this protocol. The PK/pharmacodynamic model accurately predicted the serum concentrations obtained in humans following the 3, 6, and 9 mg/kg dose of MEDI-575 in this study. Based on the PK/pharmacodynamic modeling, preclinical xenograft efficacy data, and the human data obtained to date, including the measurement of PDGF-AA in the serum, a predicted target average concentration of 250 µg/mL and trough levels above 150 µg/mL were identified. These concentrations ensure consistent saturation of PDGFRα receptor over the entire dosing interval and are predicted to provide maximum antitumor activity based on animal models. This effect is predicted to be achieved with a dosing schedule of 25 mg/kg or greater administered every 3 weeks. In the current study, no DLTs have been observed in the first 5 cohorts. The increase in dosing interval is under investigation in order to evaluate the feasibility of administration in conjunction with standard chemotherapeutic regimens. This dose regimen will be compared to the once-weekly dosing regimen in the dose-expansion

phase. The prolonged schedule should still allow for adequate blood concentrations as described above to achieve potential antitumor effects.

Dose escalation will follow a standard 3+3 study design. Rules for dose escalation are described in Section 4.9.

For the dose-expansion phase, approximately 12 subjects may be enrolled. All 12 subjects enrolled in the dose-expansion phase must have one of the following advanced solid tumors: NSCLC, GBM, ovarian cancer, or synovial sarcoma. The subjects in the dose-expansion phase will be evaluated identically to the other subjects during the dose-escalation phase. In the dose-expansion phase, 6 subjects will be treated once every 7 days of a 21-day cycle (weekly schedule) as a 60-minute IV infusion at a dose to be determined based on an analysis of PK, pharmacodynamic markers, and safety from Cohorts 1 through 5. Another 6 subjects will be treated at a dose of either 25 or 35 mg/kg once every 21 days beginning on Study Day 1 (every 3-week schedule) as a 90-minute IV infusion based on an analysis of PK, pharmacodynamic markers, and safety from Cohorts 6 and 7. The 25 or 35 mg/kg dose will be pursued pending no significant safety findings at these doses during the dose-escalation phase (Cohorts 6 and 7). Enrollment in the weekly dose-expansion schedule can occur simultaneously with Cohorts 6 and 7. Subjects will be enrolled in the every 3-week dose-expansion schedule once Cohorts 6 and 7 are complete and a choice of dose is made as described above.

Subject Evaluation/Follow-up

Subject evaluations are described in Table 3.6-1 and Table 3.6-2, and a schedule of follow-up visit procedures is presented in Table 3.6-3.

After informed consent has been obtained, screening evaluations will occur within 28 days prior to study entry and include the following evaluations: medical history; serum β human chorionic gonadotropin (βhCG) for women (unless surgically sterile or > 1 year post menopause); complete physical examination (including height and weight); 12-lead electrocardiogram(ECG); routine laboratory evaluations (hematology, serum chemistry, and urinalysis); vital signs; assessment of protocol-related AEs and serious adverse events (SAEs); notation of concomitant medications; disease evaluations (including CT or MRI scans, and Karnofsky performance status); and pharmacodynamic evaluations (including serum tumor biomarkers [as relevant to tumor type], circulating tumor cells, RNA analysis, DNA analysis [optional], and collection of archived tumor samples when available [optional]).

The following evaluations will be performed during the treatment period: urine βhCG at Study Day 1 of each treatment cycle only for women (unless surgically sterile or > 1 year post menopause); physical examination (for disease evaluation); weight; vital signs; ECG; routine laboratory evaluations (hematology, serum chemistry, and urinalysis); notation of concomitant medications; PK and IM evaluations (MEDI-575 serum concentrations and anti-MEDI-575 antibodies, respectively); and pharmacodynamic evaluations (including circulating tumor cells, plasma biomarker analysis, serum tumor biomarkers [as relevant to tumor type], and RNA analysis).

Treatment-emergent AEs and SAEs will be assessed from the time the subject receives the first dose of MEDI-575 through 30 days after the last dose of MEDI-575. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE V3.0). In addition, disease evaluations (including CT or MRI scans, complete physical examination, and Karnofsky performance status) will be performed after every 2 cycles of treatment until documentation of disease progression or initiation of alternative anticancer therapy. For subjects who discontinue treatment due to reasons other than disease progression or initiation of alternative anticancer therapy, disease evaluations will be performed every 3 months until documentation of disease progression, initiation of alternative anticancer therapy, or the end of study (defined as 1 year after the last subject entered the study). Subjects will be evaluated for disease response using Response Evaluation Criteria in Solid Tumors (RECIST; Therasse et al, 2000). Survival will be followed every 3 months by clinic visit or telephone contact until the end of the study.

A study flow diagram of the dose-escalation phase (Cohorts 1 through 7) is presented in Figure 2.4-1.

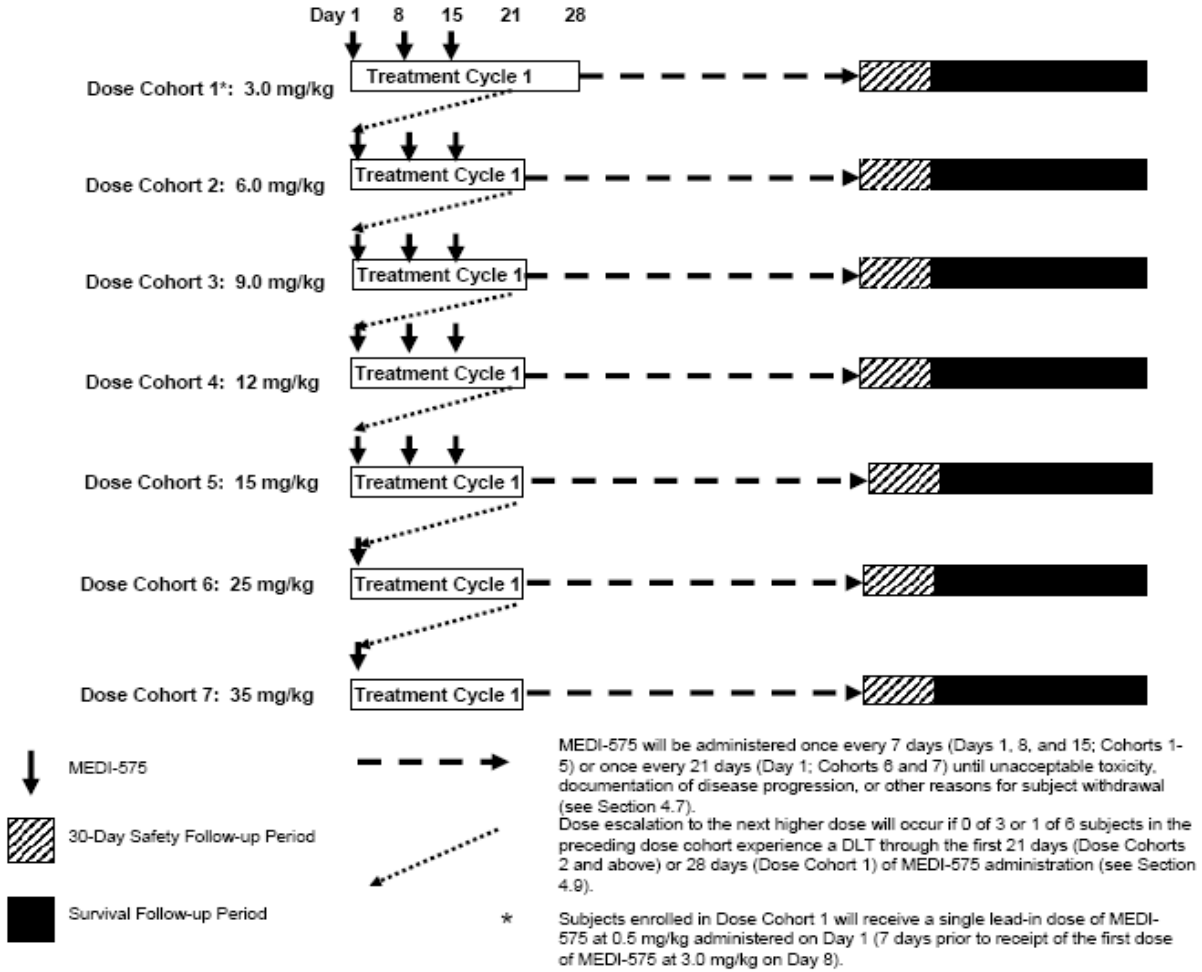

Figure 2.4-1 Study Flow Diagram of the Dose-escalation Phase (Cohorts 1-7)

3 Study Procedures

3.1 Subject Selection

The subjects in this study will be adults with advanced solid tumors refractory to standard therapy or for which no standard therapy exists.

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. If there is interest in participating in the study, the subject/legal representative will be provided with the informed consent form. 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 Health Insurance Portability and Accountability Act (HIPAA) authorization (applies to covered entities in the USA only) will be obtained prior to conducting any protocol-related procedures, including screening evaluations or medication washouts. See Section 7.3 for additional details concerning the informed consent.

3.1.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1) Men or women at least 18 years of age or older at time of study entry
2) Written informed consent and HIPAA authorization (applies to covered entities in the USA only) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations
3) Women of child-bearing potential, unless surgically sterile (including tubal ligation) or at least 1 year post menopause, must have used 2 effective methods of avoiding pregnancy (including oral, transdermal, or implanted contraceptives, intrauterine device, female condom with spermicide, diaphragm with spermicide, cervical cap, abstinence, use of a condom with spermicide by the sexual partner, or sterile sexual partner) from the time of signing the informed consent, 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) Men, unless surgically sterile, with their female partners (unless surgically sterile or 1 year post menopause) must use 2 effective methods of birth control as described in item 3 and must agree to continue using such contraceptive precautions from Cycle 1, Study Day 1 through 30 days after the final dose of investigational product

5) Histologically confirmed advanced solid tumor for which no curative or standard therapies exist

- The 12 additional subjects treated in the dose-expansion phase must have measurable disease (as defined in Section 3.7.5), and a histologically-confirmed diagnosis of NSCLC, GBM, ovarian cancer, or synovial sarcoma.

6) Karnofsky performance status of ≥ 60 (see Appendix 1)

7) Life expectancy of ≥ 12 weeks

8) Prior radiation therapy is allowed provided exposure does not exceed an area of 25% of marrow space

9) Toxicities from previous cancer therapies must have recovered to < Grade 2

10) Prothrombin time elevation ≤ Grade 2 is acceptable for subjects on anticoagulant therapy

11) Adequate hematologic function defined as:

- Hemoglobin ≥ 10 g/dL
- Absolute neutrophil count ≥ 1500/mm^3
- Platelet count ≥ 100,000/mm^3

12) Adequate organ function defined as follows:

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2 × institutional upper limit of normal (ULN)
- Bilirubin ≤ 1.5 × ULN except in the case of subjects with documented or suspected Gilbert's disease ≤ 5 × ULN
- Creatinine clearance (CrCl) ≥ 60 mL/min as determined by the Cockcroft-Gault equation (Cockcroft and Gault, 1976) or by 24-hour urine collection for determination of CrCl

13) Negative serum βhCG test (women only)

14) Subjects in the expansion cohorts must have at least 1 lesion that is measurable using RECIST. Other non-measurable lesions are allowed.

3.1.2 Exclusion Criteria

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

1) Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for treatment of cancer
2) Previous mAb treatment specifically directed against PDGF or PDGF receptors
3) History of allergy or reaction to any component of the MEDI-575 formulation
4) Receipt of any chemotherapy regimens within 4 weeks prior to the first dose of MEDI-575
5) Receipt of any biological or immunological based therapies (including, but not limited to, mAb therapy such as bevacizumab or cancer vaccine therapies) within 6 weeks prior to the first dose of MEDI-575
6) Receipt of any investigational anticancer therapy within 4 weeks prior to the first dose of MEDI-575
7) Major surgery (defined as invasive abdominal, pelvic, cardiothoracic, neurological, orthopedic or vascular surgery) within 4 weeks of receipt of MEDI-575 or minor surgery (superficial surgery with minimal invasiveness) within 2 weeks prior to receipt of MEDI-575. All surgical wounds must be without healing complications such as infection or dehiscence
8) New York Heart Association ≥ Grade 2 congestive heart failure
9) History of myocardial infarction, unstable angina, transient ischemic attack or stroke within the previous 6 months prior to the first dose of MEDI-575
10) History of other invasive malignancy within 5 years except for cervical carcinoma in situ (CIS), non-melanomatous carcinoma of the skin or ductal carcinoma in situ (DCIS) of the breast that have been surgically cured
11) Evidence of significant active infection requiring antimicrobial, antifungal, antiparasitic, or antiviral therapy or for which other supportive care is given
12) Use of immunosuppressive medication (inhaled and topical corticosteroids are permitted) within 7 days prior to the first dose of MEDI-575
13) Systemic immunosuppressive steroid therapy. Subjects may take replacement doses of steroids (defined as ≤ 30 mg day hydrocortisone or the equivalent) if on a stable dose for at least 2 weeks prior to receipt of MEDI-575
14) Known brain metastases
15) Pregnancy or lactation
16) Previous medical history or evidence of an intercurrent illness that may, in the opinion of the investigator, compromise the safety of the subject in the study
17) Clinically significant abnormality on ECG

18) Any physical, social, or psychiatric condition which would prevent effective cooperation or participation in the study

3.2 Enrollment into the Study

A subject is considered enrolled into the study once written informed consent is obtained. Once informed consent is obtained, a subject identification number (SID) will be assigned by the sponsor and the screening evaluations may begin. This number will be used to identify the subject during the screening process and throughout study participation, if applicable.

Subjects for whom written informed consent has been obtained will be screened by investigators to assess eligibility for entry into the study. A record of all consented subjects, including all screening failures (ie, subjects who are consented but not entered) and the reason for screening failure, will be collected in the database.

Subjects who fail to meet all eligibility criteria, who decline further participation, or who are lost to follow-up will not proceed to entry.

Notification of planned dosing should be remitted to the sponsor within 48 hours of the first dosing.

3.3 Assignment of Treatment Group (Study Entry)

The procedure for study entry is as follows:

- The investigator or designee confirms that written informed consent and HIPAA authorization has been obtained and that the subject meets all eligibility criteria.
- The investigator or designee faxes the sponsor and provides the SID (previously assigned by the sponsor) and subject's baseline characteristic(s) used to verify that it is the same subject.
- The sponsor assigns the subject to a dose cohort. When both a dose-escalation cohort and a dose-expansion cohort are available, subjects will be assigned to the dose-escalation cohort unless they have one of the targeted tumor types (NSCLC, GBM, ovarian cancer, or synovial sarcoma), in which case they will be assigned to the dose-expansion cohort. When two dose-expansion cohorts are available, subjects will be assigned in an alternating pattern.
- A confirmatory fax with this information is sent to the investigator/designee.

A subject is considered entered into the study at the time of the first administration of investigational product (Cycle 1, Study Day 1).

3.4 Blinding

This study is not blinded.

3.5 Investigational Product (MEDI-575)

3.5.1 Investigational Product Supplies and Accountability

Investigational product will be distributed to clinical sites using designated distribution centers. The sponsor will provide the investigator(s) with adequate quantities of investigational product. MEDI-575 is supplied as a 10 mg/mL solution, 100 mg/vial, and must be stored in the refrigerator at 2°C to 8°C. The 10 mg/mL solution will be diluted into a saline bag for IV infusion.

MEDI-575: MEDI-575 is supplied in vials as a 10 mg/mL solution, 100 mg/vial. The solution also contains 50 mM sodium acetate, 100 mM sodium chloride, and 0.01% (w/v) polysorbate 80, pH 5.5.

Diluent: Normal saline, 250 mL bag

Normal saline, 500 mL bag (for doses ≥ 25 mg/kg)

Specific details regarding investigational product supplies, dose preparation, and accountability will be provided in the Investigational Product Manual supplied to the sites.

The Investigational Product Manager/site pharmacist is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of all investigational product accountability records will be returned to the sponsor. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune (refer to the Investigational Product Manual or other written instructions provided by MedImmune or its designee for contact information and specific shipping instructions).

3.5.2 Treatment Regimen

In the weekly schedule of the dose-escalation phase (Cohorts 1 through 5), subjects will be treated with 1 of 5 doses of MEDI-575 (3.0, 6.0, 9.0, 12, or 15 mg/kg) once every 7 days (Table 3.5.2-1). Subjects enrolled in Dose Cohort 1 (3.0 mg/kg) only will receive as a

60-minute IV infusion a single lead-in dose of MEDI-575 at 0.5 mg/kg administered 7 days prior to receipt of the first dose of MEDI-575 at the 3.0 mg/kg dose level. The single lead-in dose at 0.5 mg/kg will be used to assess PK and pharmacodynamic parameters. The day of administration of the 0.5 mg/kg dose will be considered the day of initiation of treatment (Study Day 1). The DLT period for this dose cohort only will begin with the single administration of MEDI-575 at the dose level of 0.5 mg/kg and continue until 21 days after administration of the first dose at 3.0 mg/kg (Study Day 28) for a total of 28 days. Thereafter MEDI-575 will be administered as a 60-minute IV infusion on Study Days 1, 8, and 15 of each 21-day treatment cycle until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal (see Section 4.7). In Cycle 2 and beyond, a dose can be delayed up to 7 days based on hematologic and nonhematologic toxicities, according to the conditions described in Section 3.5.5 (Dose Modifications and Toxicity Management), but all 3 planned doses (if a subject is enrolled in the weekly dosing schedule) must be completed within the cycle. Subjects enrolled in the weekly dosing schedule who do not receive all 3 doses within a cycle will not advance to the next cycle and will be removed from treatment; therefore, each cycle after the first cycle of the weekly dosing schedule will be considered complete after administration of 3 doses. For the weekly dosing schedule, each new cycle will begin no fewer than 7 days after the last dose of the previous cycle. For the every 3-week schedule (Dose Cohorts 6 and 7, 25 mg/kg and 35 mg/kg, respectively) of the dose-escalation phase, MEDI-575 will be administered as a 90-minute IV infusion once every 21 days (on Study Day 1 of a 21-day cycle). Each new cycle will begin no fewer than 21 days after the last dose of the previous cycle. Rules for dose escalation are described in Section 4.9. Intrasubject dose escalation, except for the first cohort as described above, will not be allowed. Dose reduction for toxicities other than DLTs (see Section 4.10 for definition of DLTs) will be allowed as described in Section 3.5.5.

In the dose-expansion phase, 6 subjects will be treated once every 7 days of a 21-day cycle (weekly schedule) as a 60-minute IV infusion at a dose to be determined based on an analysis of PK, pharmacodynamic markers, and safety from Cohorts 1 through 5. Another 6 subjects in the dose-expansion phase will be treated at a dose of either 25 or 35 mg/kg once every 21 days beginning on Study Day 1 (every 3-week schedule) as a 90-minute IV infusion based on an analysis of PK, pharmacodynamic markers, and safety from Cohorts 6 and 7.

Table 3.5.2-1 Summary of Dose Cohorts

Dose Cohort	Number of Subjects	MEDI-575 Dose
1	3 to 6	Single lead-in dose at 0.5 mg/kg as a 60-minute IV infusion administered 7 days prior to first dose at 3.0 mg/kg; 3.0 mg/kg as a 60-minute IV infusion once every 7 days
2	3 to 6	6.0 mg/kg as a 60-minute IV infusion once every 7 days
3	3 to 6	9.0 mg/kg as a 60-minute IV infusion once every 7 days
4	3 to 6	12 mg/kg as a 60-minute IV infusion once every 7 days
5	3 to 6	15 mg/kg as a 60-minute IV infusion once every 7 days
6	3 to 6	25 mg/kg as a 90-minute IV infusion once every 21 days
7	3 to 6	35 mg/kg as a 90-minute IV infusion once every 21 days
Expansion	Up to 12	Doses to be determined based on an analysis of PK, pharmacodynamic markers, and safety as a 60-minute IV infusion once every 7 days; and 25 mg/kg or 35 mg/kg as a 90-minute IV infusion once every 21 days

Note: For the dose-expansion phase, approximately 12 subjects may be enrolled. All 12 subjects must have one of the following advanced solid tumors: NSCLC, GBM, ovarian cancer, or synovial sarcoma.

3.5.3 Investigational Product Preparation

The dose of investigational product for administration must be prepared by the Investigational Product Manager/site pharmacist using aseptic technique. Detailed instructions regarding investigational product preparation can be found in the Investigational Product Manual that will be provided to the Investigational Product Manager/site pharmacist.

The dose of investigational product will be calculated by the Investigational Product Manager/site pharmacist on the basis of the subject's body weight (obtained prior to the first administration of MEDI-575 in each treatment cycle) and the subject's dose level. The dose volume of MEDI-575 will be calculated using the following formula:

Dose Volume (mL) = Dose Level (mg/kg) × Subject Weight (kg) ÷ Concentration (10 mg/mL)

MEDI-575 is prepared for administration by dilution into the appropriate volume of normal saline to a final volume of 250 mL. The final volume will be 500 mL for subjects enrolled in the every 3-week dosing schedule.

Prior to dilution into normal saline, the required number of vials for each dose of MEDI-575 must equilibrate separately at room temperature (23°C to 27°C; 73°F to 81°F) for 90 minutes.

To prepare the IV bag, the volume of normal saline equivalent to the calculated dose volume of MEDI-575 is removed from the IV bag, and then the calculated dose volume of MEDI-575 is added to the IV bag containing the remaining saline.

MEDI-575 should be administered immediately as a 60-minute (Cohorts 1 through 5 and weekly dosing schedule of the dose-expansion phase) or 90-minute (Cohorts 6 and 7 and every 3-week dosing schedule of the dose-expansion phase) IV infusion.

3.5.4 Administration of Investigational Product

The investigational product must be administered within 6 hours after IV bag preparation. If the dose is not administered within 6 hours, a new dose must be prepared using a new vial or vials as the investigational product contains no bacteriostatic agents.

The investigational product should be dispensed by the Investigational Product Manager/site pharmacist or qualified designee and administered as an IV infusion. The infusion should be administered over a period of 60 or 90 minutes using a protein-sparing/low in-line filter, as specified in the Investigational Product Manual.

Vital signs will be monitored prior to and 15, 30, and 45 minutes (± 5 minutes) post initiation of infusion, at the end of infusion (± 5 minutes), and 30 and 60 minutes (± 5 minutes) post completion of infusion.

If a subject experiences an infusion reaction during infusion of MEDI-575, diphenhydramine (Benadryl®) 50 mg and acetaminophen (Tylenol®) 650 mg, or the institutional equivalents, may be administered. Alternatively, or in addition, the rate of infusion of MEDI-575 may be decreased. Any such activities must be recorded appropriately. In subjects who experience an infusion reaction, prophylactic administration of acetaminophen and/or diphenhydramine (or equivalents) may be considered for subsequent administration of MEDI-575.

3.5.5 Dose Modifications and Toxicity Management

Dose modifications of MEDI-575 will be based on hematologic and nonhematologic toxicities that cannot be attributed to another cause, such as disease progression or accident, following the first cycle of treatment (Table 3.5.5-1). Both hematologic and nonhematologic

toxicities will be graded according to NCI CTCAE V3.0. All DLTs must be documented as an AE on the source document. If enrolled in the weekly schedule, a cycle will be considered complete after administration of 3 doses for all cycles after the first cycle. If enrolled in the every 3-week schedule, a cycle will be considered complete after the administration of 1 dose.

Table 3.5.5-1 MEDI-575 Dose Modification Table

Hematologic or Nonhematologic Toxicity	Dose Modification of MEDI-575
≤ Grade 1	None
Grade 2	Withhold MEDI-575 for up to 7 days until resolution to ≤ Grade 1 or baseline and resume at current dose level. Grade 2 laboratory toxicities that do not have clinical significance may not require dose delay. The Medical Monitor should be consulted in the event of Grade 2 laboratory toxicities that are deemed clinically insignificant to determine if dosing may continue. Discontinue MEDI-575 if MEDI-575 is withheld for > 7 days without resolution of toxicity to ≤ Grade 1 or baseline unless clearly attributable to another cause such as disease progression or accident.
Grade 3 or 4	**First Occurrence:** Withhold MEDI-575 for up to 7 days until resolution to ≤ Grade 1 or baseline. Discontinue MEDI-575 if no clinical benefit has been documented. For subjects who experience Grade 3 or Grade 4 toxicity that resolves as above, and who have achieved some degree of clinical benefit while on MEDI-575 therapy, the United States Food and Drug Administration (FDA) will be consulted regarding the possibility of continued administration of MEDI-575. MEDI-575 therapy should not be continued without agreement from the FDA. Discontinue MEDI-575 if MEDI-575 is withheld for > 7 days without resolution of toxicity to ≤ Grade 1 or baseline regardless of clinical benefit. **Second Occurrence:** Discontinue MEDI-575.

If toxicity ≥ Grade 3 that is at least possibly attributable to MEDI-575 is observed in a subject or subjects during the second or subsequent treatment cycle, dose escalation will be temporarily suspended to review the cumulative safety data. Such an event may prompt cessation of dose escalation or modification of the dose escalation scheme, including a decrease of subsequent doses from the first cycle dose, if appropriate. Subjects may continue to receive MEDI-575 during this review and subjects may continue to be enrolled into an open cohort until a determination of necessary action, if any, is made.

3.5.6 Concomitant Medications

Use of concomitant medications from the first day of administration of MEDI-575 through 30 days after the last dose of MEDI-575 is discouraged; however, subjects may receive medications to treat AEs as deemed necessary by the investigator or the subject's physician.

All concomitant medications used by the subject from the time of signing of the informed consent form through 30 days after the last dose of MEDI-575 will be recorded on the source document.

3.6 Schedule of Evaluations

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

A schedule of screening and on-study visit procedures is presented in Table 3.6-1 and Table 3.6-2, and a schedule of follow-up visit procedures is presented in Table 3.6-3, followed by a detailed description of each visit. All visits during Cycle 2 and subsequent visits may occur in a ± 2-day window to accommodate schedule changes, but doses of MEDI-575 must not occur more frequently than every 6 days if in the weekly schedule or every 19 days if in the every 3-week schedule.

For Cohorts 6 and 7, and subjects enrolled in the every 3-week schedule of the dose-expansion phase, visits and study procedures on Study Days 8 and 15 are required only

during the first cycle. For Cycle 2 and subsequent cycles, no Study Day 8 or Study Day 15 visits are required.

Table 3.6-1 Schedule of Evaluations (Cohorts 1-5 and Dose-Expansion Weekly Schedule): Screening and Treatment Periods

Evaluations	Screening[a]	Cycle 1					Cycle 2 and Every Cycle Thereafter			Every 2 Cycles, Beginning With Cycle 3	End of Treatment
Cohort 1		Days 1, 8	Days 2, 9	Days 3, 10	Day 15	Day 22	Day 1	Day 8	Day 15		
Cohorts 2 through 5 and dose-expansion weekly schedule		Day 1	Day 2	Day 3	Day 8	Day 15					
Written Informed Consent and HIPAA	X										
Verify Eligibility Criteria	X	X[b]									
Medical History	X										
Serum βhCG	X										
Urine βhCG		X[b]					X				
MEDI-575 Administration		X			X	X	X	X	X		
Physical Examination [c]	X	X[b]					X			X	X[d]
Height	X										
Weight	X	X[b]					X				X
Vital Signs	X	X[e]		X	X[e]	X[e]	X[e]	X[e]	X[e]		X
12-lead ECG [f]	X	X [g]					X [h]				X
Hematology [q]	X	X[i]		X	X[i]	X[i]	X[i]	X[i]	X[i]		X
Serum Chemistry [j]	X	X[i]		X	X[i]	X[i]	X[i]	X[i]	X[i]		X

Table 3.6-1 Schedule of Evaluations (Cohorts 1-5 and Dose-Expansion Weekly Schedule): Screening and Treatment Periods

Evaluations	Screening[a]	Cycle 1					Cycle 2 and Every Cycle Thereafter			Every 2 Cycles, Beginning With Cycle 3	End of Treatment
Cohort 1		Days 1, 8	Days 2, 9	Days 3, 10	Day 15	Day 22	Day 1	Day 8	Day 15		
Cohorts 2 through 5 and dose-expansion weekly schedule		Day 1	Day 2	Day 3	Day 8	Day 15					
Routine Urinalysis	X	X			X	X	X	X	X		X
AE/SAE Assessment	X[k]	X		X	X	X	X	X	X	X	X
Concomitant Medications	X	X		X	X	X	X	X	X	X	X
CT or MRI Scans	X									X	X[d]
Karnofsky Performance Status	X	X[b]					X				X[d]
MEDI-575 Serum Concentration		X[l]	X[m]	X[n]	X[o]	X[o]	X[o]	X[o]	X[o]		X
Anti-MEDI-575 Antibodies		X[b, h]					X[h]				X
Serum Tumor Biomarkers (as relevant to tumor type)	X						X				
Circulating Plasma Biomarker Analysis		X[l]	X[m]	X[n]	X[o]	X[o]	X[o]	X[o]	X[o]		X
Circulating Tumor Cells	X						X[h]				X[r]
RNA Analysis	X						X[h]				X
DNA Analysis (Optional)	X										

Table 3.6-1 Schedule of Evaluations (Cohorts 1-5 and Dose-Expansion Weekly Schedule): Screening and Treatment Periods

Evaluations	Screening[a]	Cycle 1					Cycle 2 and Every Cycle Thereafter			Every 2 Cycles, Beginning With Cycle 3	End of Treatment
Cohort 1		**Days 1, 8**	**Days 2, 9**	**Days 3, 10**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**		
Cohorts 2 through 5 and dose-expansion weekly schedule		**Day 1**	**Day 2**	**Day 3**	**Day 8**	**Day 15**					
Archived Tumor Sample (Optional)	X[p]										

[a] To occur within 28 days prior to the first dose of MEDI-575.

[b] Study Day 1 only.

[c] Complete physical examination at screening, after every 2 cycles, and at the end of treatment; a focused examination at the start of each cycle.

[d] These procedures do not need to be repeated if they have been performed within 14 days of disease progression or treatment discontinuation.

[e] Monitor vital signs prior to infusion, at 15, 30, and 60 minutes (±5 minutes) post initiation of infusion, at the completion of infusion (±5 minutes), and 30 and 60 minutes (±5 minutes) post completion of infusion.

[f] ECG equipment (with instant print-out and electronic transmission capabilities) and training will be provided to all study sites. All ECGs performed during the study will be obtained in triplicate, ie, 3 ECGs are to be obtained within a 5-minute time interval.

[g] Prior to infusion, at the time of completion of infusion (± 5 minutes), 2 hours post completion of infusion (± 15 minutes), and 6 hours (± 15 minutes) post completion of infusion. All ECGs should be done prior to PK draw for corresponding time points.

[h] Prior to the initiation of infusion.

[i] Prior to infusion on day indicated.

[j] Includes AST/ALT, total bilirubin, creatinine (and creatinine clearance at screening), alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and LDH.

[k] Only those AEs assessed by the investigator as protocol/procedure related. All SAEs are to be reported.

[l] Prior to infusion, immediately post completion of infusion (± 5 minutes), and 2 hours (± 15 minutes) and 6 hours (± 15 minutes) post completion of infusion.

Table 3.6-1 Schedule of Evaluations (Cohorts 1-5 and Dose-Expansion Weekly Schedule): Screening and Treatment Periods

Evaluations	Screening[a]	Cycle 1					Cycle 2 and Every Cycle Thereafter			Every 2 Cycles, Beginning With Cycle 3	End of Treatment
Cohort 1		Days 1, 8	Days 2, 9	Days 3, 10	Day 15	Day 22	Day 1	Day 8	Day 15		
Cohorts 2 through 5 and dose-expansion weekly schedule		Day 1	Day 2	Day 3	Day 8	Day 15					

[m] 24 hours (± 2 hours) post completion of infusion on Study Day 1, Cycle 1 (all dose cohorts), and Study Day 9, Cycle 1 (Dose Cohort 1, only).

[n] 48 hours (± 2 hours) post completion of infusion on Study Day 1, Cycle 1 (all dose cohorts), and Study Day 10, Cycle 1 (Dose Cohort 1, only).

[o] Prior to and immediately (±5 minutes) post completion of infusion.

[p] If archived tumor sample is available and subject provides consent, collect and ship per instructions in Specimen Collection Manual.

[q] Includes complete blood count (CBC), differential, and platelet count.

[r] Only for dose-expansion weekly schedule.

Table 3.6-2 Schedule of Evaluations (Cohorts 6 and 7, and Dose-Expansion Every 3-Week Schedule): Screening and Treatment Periods

Evaluations	Screening[a]	Cycle 1					Cycle 2 and Every Cycle Thereafter	Every 2 Cycles, Beginning With Cycle 3	End of Treatment
		Day 1	Day 2	Day 3	Day 8	Day 15	Day 1		
Written Informed Consent and HIPAA	X								
Verify Eligibility Criteria	X	X[b]							
Medical History	X								
Serum βhCG	X								
Urine βhCG		X[b]					X		
MEDI-575 Administration		X					X		
Physical Examination [c]	X	X[b]					X	X	X[d]
Height	X								
Weight	X	X[b]					X		X
Vital Signs	X	X[e]		X	X	X	X[e]		X
12-lead ECG [f]	X	X[g]					X[h]		X
Hematology [q]	X	X[i]		X	X	X	X[i]		X
Serum Chemistry [j]	X	X[i]		X	X	X	X[i]		X
Routine Urinalysis	X	X			X	X	X		X
AE/SAE Assessment	X[k]	X		X	X	X	X	X	X

Table 3.6-2 Schedule of Evaluations (Cohorts 6 and 7, and Dose-Expansion Every 3-Week Schedule): Screening and Treatment Periods

Evaluations	Screening[a]	Cycle 1					Cycle 2 and Every Cycle Thereafter	Every 2 Cycles, Beginning With Cycle 3	End of Treatment
		Day 1	Day 2	Day 3	Day 8	Day 15	Day 1		
Concomitant Medications	X	X		X	X	X	X	X	X
CT or MRI Scans	X							X	X[d]
Karnofsky Performance Status	X	X[b]					X		X[d]
MEDI-575 Serum Concentration		X[l]	X[m]	X[n]	X	X	X[o]		X
Anti-MEDI-575 Antibodies		X[b, h]					X[h]		X
Serum Tumor Biomarkers (as relevant to tumor type)	X						X		
Circulating Plasma Biomarker Analysis		X[l]	X[m]	X[n]	X	X	X[o]		X
Circulating Tumor Cells	X						X[h]		X
RNA Analysis	X						X[h]		X
DNA Analysis (Optional)	X								
Archived Tumor Sample (Optional)	X[p]								

Table 3.6-2 Schedule of Evaluations (Cohorts 6 and 7, and Dose-Expansion Every 3-Week Schedule): Screening and Treatment Periods

Evaluations	Screening[a]	Cycle 1					Cycle 2 and Every Cycle Thereafter	Every 2 Cycles, Beginning With Cycle 3	End of Treatment
		Day 1	Day 2	Day 3	Day 8	Day 15	Day 1		

[a] To occur within 28 days prior to he first dose of MEDI-575

[b] Study Day 1 only.

[c] Complete physical examination at screening, after every 2 cycles, and at the end of treatment; a focused examination at the start of each cycle.

[d] These procedures do not need to be repeated if they have been performed within 14 days of disease progression or treatment discontinuation.

[e] Monitor vital signs prior to infusion, at 15, 30, and 60 minutes (±5 minutes) post initiation of infusion, at the completion of infusion (±5 minutes), and 30 and 60 minutes (±5 minutes) post completion of infusion.

[f] ECG equipment (with instant print-out and electronic transmission capabilities) and training will be provided to all study sites. All ECGs performed during the study will be obtained in triplicate, ie, 3 ECGs are to be obtained within a 5-minute time interval.

[g] Prior to infusion, at the time of completion of infusion (± 5 minutes), 2 hours post completion of infusion (± 15 minutes), and 6 hours (± 15 minutes) post completion of infusion. All ECGs should be done prior to PK draw for corresponding time points.

[h] Prior to the initiation of infusion.

[i] Prior to infusion on day indicated.

[j] Includes AST/ALT, total bilirubin, creatinine (and creatinine clearance at screening), alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and LDH.

[k] Only those AEs assessed by the investigator as protocol/procedure related. All SAEs are to be reported.

[l] Prior to infusion, immediately post completion of infusion (± 5 minutes), 2 hrs (± 15 minutes) and 6 hrs (± 15 minutes) post completion of infusion.

[m] 24 hours (± 2 hours) post completion of infusion on Study Day 1, Cycle 1 (all dose cohorts).

[n] 48 hours (± 2 hours) post completion of infusion on Study Day 1, Cycle 1 (all dose cohorts).

[o] Prior to and immediately (±5 minutes) post completion of infusion.

[p] If archived tumor sample is available and subject provides consent, collect and ship per instructions in Specimen Collection Manual.

[q] Includes complete blood count (CBC), differential, and platelet count.

Table 3.6-3 Schedule of Evaluations: Follow-up Period

All Cohorts and Dose Expansion	Follow-up/Post-therapy	
	30 Days	Every 3 Months
Physical Examination	X	
Weight	X	
12-lead ECG	X	
Vital Signs	X	
Hematology	X	
Serum Chemistry	X	
Routine Urinalysis	X	
Urine βhCG	X	
AE/SAE Assessment	X	
Concomitant Medications	X	
CT or MRI Scans		X[a]
Focused Physical Examination		X[a]
Karnofsky Performance Status	X	X[a]
Subsequent Anticancer Therapy	X	X
Survival Status		X
MEDI-575 Serum Concentration	X	
Anti-MEDI-575 Antibodies	X	X[b]
Circulating Plasma Biomarker Analysis	X	

[a] For subjects who discontinue treatment due to reasons other than disease progression or initiation of alternative anticancer therapy, disease evaluations will be performed every 3 months until documentation of disease progression, initiation of alternative anticancer therapy, or the end of study (defined as 1 year after the last subject enters the study).

[b] This test will be performed at 3 months post dose only.

Screening

Note: All screening procedures must be performed within 28 days before the first dose of investigational product (Study Day 1), unless otherwise specified. The screening evaluations may be carried out over more than 1 visit. Written informed consent and HIPAA (applies to covered entities in the USA only) must be obtained prior to performing any study-related procedure, including screening evaluations. However, if evaluations that have been performed for other purposes prior to informed consent are otherwise suitable for use as screening evaluations, those studies need not be repeated if the subject/legal representative consents to allow use.

1) Written informed consent and HIPAA
2) Obtain SID from sponsor
3) Verify eligibility criteria
4) Perform medical history
5) Perform complete physical examination, including height and weight
   Note: Items 4 and 5 above are designed to collect information on the subject once written informed consent has been obtained to start the screening process. Any new physical examination finding, symptom, disease, or untoward medical event that begins after written informed consent has been obtained, but before receipt of investigational product, that is not related to a protocol requirement must be added to the baseline medical history or physical examination records.
6) Perform 12-lead ECG. All ECGs performed will be obtained in triplicate (ie, 3 ECGs should be obtained within approximately a 5-minute time interval).
7) Routine urinalysis
8) Vital signs
9) Evaluation of disease
   - CT or MRI scans
   - Karnofsky performance status
10) Blood collection for screening
   - Chemistry panel (AST/ALT, total bilirubin, creatinine, creatinine clearance, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and lactate dehydrogenase [LDH])
   - Hematology (complete blood count [CBC], differential, and platelet count)
   - Serum βhCG
   - Serum tumor biomarker analysis (as relevant to tumor type)

- DNA analysis (optional)
- Circulating tumor cell analysis
- RNA analysis

11) Assess for SAEs and protocol-related AEs

12) Record concomitant medications

13) If archived tumor tissue is available and subject provides consent to release, ship block to sponsor per instructions in Specimen Collection Manual.

14) Complete enrollment paperwork and fax to sponsor within 48 hours of the anticipated time of first dosing with MEDI-575.

Cycle 1, Study Day 1 (and Study Day 8 for Dose Cohort 1 only)

1) Verify eligibility criteria (Study Day 1 only, for all dose cohorts and dose-expansion phase)

2) Update screening history and physical examination findings (any new findings since screening; Study Day 1, only, for all dose cohorts and dose-expansion phase)

3) Assess for SAEs and protocol-related AEs

4) Update concomitant medications

5) Obtain body weight for dosing calculations (Study Day 1, only, for all dose cohorts and dose-expansion phase)

6) Blood collection prior to infusion of MEDI-575

- Chemistry panel (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and LDH)
- Hematology (CBC, differential, and platelet count)
- Serum concentration of MEDI-575
- Circulating plasma biomarker analysis
- Anti-MEDI-575 antibodies (Study Day 1, only, for all dose cohorts and dose-expansion phase)

7) Routine urinalysis

8) Urine βhCG (Study Day 1, only, for all dose cohorts and dose-expansion phase)

9) Karnofsky performance status (Study Day 1, only, for all dose cohorts and dose-expansion phase)

10) Focused physical examination (Study Day 1, only, for all dose cohorts and dose-expansion phase)

11) 12-lead ECG (prior to infusion), at the time of completion of infusion (± 5 minutes), 2 hours (± 15 minutes) post completion of infusion, and 6 hours (± 15 minutes) post completion of infusion. All ECGs performed will be obtained in triplicate (ie, 3 ECGs should be obtained within approximately a 5-minute time interval). All ECGs should be done prior to PK draw for the corresponding time point.

12) Vital signs prior to infusion of MEDI-575 (temperature, blood pressure, pulse rate, respiratory rate)

13) Administration of MEDI-575

14) Monitor for AEs and SAEs

15) Monitor vital signs at 15, 30, and 45 minutes (± 5 minutes) post initiation of infusion, at the completion of infusion (± 5 minutes), and 30 and 60 minutes (± 5 minutes) post completion of infusion

16) Blood collection immediately after and 2 and 6 hours (± 15 minutes) post completion of infusion

- Serum concentration of MEDI-575
- Circulating plasma biomarker analysis

Cycle 1, Study Day 2 (and Study Day 9 for Cohort 1, Only)

1) Blood collection 24 hours (± 2 hours) post completion of infusion

- Serum concentration of MEDI-575
- Circulating plasma biomarker analysis

Cycle 1, Study Day 3 (and Study Day 10 for Cohort 1, Only)

1) Vital signs

2) Assessment of AEs and SAEs

3) Update concomitant medications

4) Blood collection 48 hours (± 2 hours) post completion of infusion

- Chemistry panel (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and LDH)
- Hematology (CBC, differential, and platelet count)
- Serum concentration of MEDI-575
- Circulating plasma biomarker analysis

Cycle 1, Study Day 8 (and Study Day 15 for Cohort 1 only)

1) Update concomitant medications
2) Blood collection (prior to infusion of MEDI-575 for weekly dosing schedule)
   - Chemistry panel (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and LDH)
   - Hematology (CBC, differential, and platelet count)
   - Serum concentration of MEDI-575
   - Circulating plasma biomarker analysis
3) Routine urinalysis
4) Vital signs (prior to infusion of MEDI-575 for weekly dosing schedule) (temperature, blood pressure, pulse rate, respiratory rate)
5) Administration of MEDI-575 **(weekly dosing schedule)**
6) Assessment of AEs and SAEs
7) Monitor vital signs (at 15, 30, and 45 minutes [± 5 minutes] post initiation of infusion, at the completion of infusion [± 5 minutes], and 30 and 60 minutes [± 5 minutes] post completion of infusion for weekly dosing schedule)
8) Blood collection (immediately after [± 5 minutes] completion of infusion with MEDI-575 for weekly dosing schedule)
   - Serum concentration of MEDI-575
   - Circulating plasma biomarker analysis

Cycle 1, Study Day 15 (Cohorts 2 and Above) and 22 (Cohort 1 only)

1) Update concomitant medications
2) Blood collection (prior to infusion of MEDI-575 for weekly dosing schedule)
   - Chemistry panel (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and LDH)
   - Hematology (CBC, differential, and platelet count)
   - Serum concentration of MEDI-575
   - Circulating plasma biomarker analysis
3) Routine urinalysis
4) Vital signs (prior to infusion of MEDI-575 for weekly dosing schedule) (temperature, blood pressure, pulse rate, respiratory rate)

5) Administration of MEDI-575 **(weekly dosing schedule)**

6) Assessment of AEs and SAEs

7) Monitor vital signs (at 15, 30, and 45 minutes [± 5 minutes] post initiation of infusion, at the completion of infusion [± 5 minutes], and 30 and 60 minutes [± 5 minutes] post completion of infusion for weekly dosing schedule)

8) Blood collection (immediately [± 5 minutes] after completion of infusion with MEDI-575 for weekly dosing schedule)

- Serum concentration of MEDI-575
- Circulating plasma biomarker analysis

Cycle 2 and All Subsequent Cycles, Study Day 1 (All Dose Cohorts and Dose Expansion Phase)

1) Update concomitant medications

2) Obtain body weight for dosing calculations

3) Blood collection prior to infusion of MEDI-575

- Chemistry panel (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and LDH)
- Hematology (CBC, differential, and platelet count)
- Serum concentration of MEDI-575
- Circulating plasma biomarker analysis
- Serum tumor biomarkers analysis (as relevant to tumor type)
- Circulating tumor cell analysis
- RNA analysis
- Anti-MEDI-575 antibodies

4) Routine urinalysis

5) Urine βhCG

6) Karnofsky performance status

7) Focused physical examination

8) 12-lead ECG prior to dosing, only. All ECGs performed will be obtained in triplicate (ie, 3 ECGs should be obtained within approximately a 5-minute time interval).

9) Vital signs prior to infusion of MEDI-575 (temperature, blood pressure, pulse rate, respiratory rate)

10) Administration of MEDI-575

11) Assessment of AEs and SAEs

12) Monitor vital signs at 15, 30, and 45 minutes (± 5 minutes) post initiation of infusion, at the completion of infusion (± 5 minutes), and 30 and 60 minutes (± 5 minutes) post completion of infusion

13) Blood collection immediately after (± 5 minutes) completion of infusion with MEDI-575

- Serum concentration of MEDI-575
- Circulating plasma biomarker analysis

Cycle 2 and All Subsequent Cycles, Study Day 8 (Cohorts 1 through 5 and Weekly Dose-Expansion)

1) Update concomitant medications

2) Blood collection prior to infusion of MEDI-575

- Chemistry panel (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and LDH)
- Hematology (CBC, differential, and platelet count)
- Serum concentration of MEDI-575
- Circulating plasma biomarker analysis

3) Routine urinalysis

4) Vital signs prior to infusion of MEDI-575 (temperature, blood pressure, pulse rate, respiratory rate)

5) Administration of MEDI-575

6) Assessment of AEs and SAEs

7) Monitor vital signs at 15, 30, and 45 minutes (± 5 minutes) post initiation of infusion, at the completion of infusion (± 5 minutes), and 30 and 60 minutes (± 5 minutes) post completion of infusion

8) Blood collection immediately after (± 5 minutes) completion of infusion with MEDI-575

- Serum concentration of MEDI-575
- Circulating plasma biomarker analysis

Cycle 2 and All Subsequent Cycles, Study Day 15 (Cohorts 1 through 5 and Weekly Dose-Expansion)

1) Update concomitant medications

2) Blood collection prior to infusion of MEDI-575

- Chemistry panel (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and LDH)
- Hematology (CBC, differential, and platelet count)
- Serum concentration of MEDI-575
- Circulating plasma biomarker analysis

3) Routine urinalysis

4) Vital signs prior to infusion of MEDI-575 (temperature, blood pressure, pulse rate, respiratory rate)

5) Administration of MEDI-575

6) Assessment of AEs and SAEs

7) Monitor vital signs at 15, 30, and 45 minutes (± 5 minutes) post initiation of infusion, at the completion of infusion (± 5 minutes), and 30 and 60 minutes (± 5 minutes) post completion of infusion

8) Blood collection immediately after (± 5 minutes) completion of infusion of MEDI-575

- Serum concentration of MEDI-575
- Circulating plasma biomarker analysis

Every 2 Cycles (Within 3 Days Prior to Subsequent Cycle, Beginning With Cycle 3; All Dose Cohorts and Dose-Expansion Phase)

The following evaluations will be performed every 2 cycles (ie, every 6 weeks) unless otherwise indicated, beginning at Cycle 3 (eg, Cycle 3, Cycle 5, etc)

1) Complete physical examination

2) Update concomitant medications

3) Assess for AEs and SAEs

4) Evaluation of disease

- CT or MRI scans
- Focused physical examination

End of Treatment (All Dose Cohorts and Dose-Expansion Phase)

The following evaluations will be performed at the time the subject completes therapy or is withdrawn /discontinued from the study therapy, or at the time of the first objective disease

progression, whichever comes first. These procedures do not need to be repeated if completed within 14 days of discontinuation of participation.

1) Complete physical examination
2) Obtain body weight
3) Update concomitant medications
4) Assess for AEs and SAEs
5) Vital signs (temperature, respiration rate, pulse, blood pressure)
6) Evaluation of disease
   - CT or MRI scans
   - Focused physical examination
   - Karnofsky performance status
7) Blood collection
   - Chemistry panel (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and LDH)
   - Hematology (CBC, differential, and platelet count)
   - Serum concentration of MEDI-575
   - Circulating plasma biomarker analysis
   - Circulating tumor cell analysis (for Cohorts 6 and 7 and all of the dose-expansion phase)
   - RNA analysis
   - Anti-MEDI-575 antibodies
8) Routine urinalysis
9) 12-lead ECG. All ECGs performed will be obtained in triplicate (ie, 3 ECGs should be obtained within approximately a 5-minute time interval).

30 Days Post Therapy (+ 3 Days; All Dose Cohorts and Dose-Expansion Phase)

The following evaluations will be performed at 30 days (+ 3 days) after the last dose of MEDI-575:

1) Complete physical examination
2) Obtain body weight
3) Update concomitant medications

4) Assess for AEs and SAEs

5) Assess for subsequent anticancer therapy

6) Vital signs (temperature, respiration rate, pulse, blood pressure)

7) Evaluation of disease

- Karnofsky performance status

8) Blood collection

- Chemistry panel (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, magnesium, albumin, and LDH)
- Hematology (CBC, differential, and platelet count)
- Serum concentration of MEDI-575
- Anti-MEDI-575 antibodies
- Circulating plasma biomarker analysis

9) Routine urinalysis

10) Urine βhCG (women of child bearing potential only)

11) 12-lead ECG. All ECGs performed will be obtained in triplicate (ie, 3 ECGs should be obtained within approximately a 5-minute time interval).

Every 3 Months Post Therapy (± 2 Weeks; All Dose Cohorts and Dose Expansion Phase)

The following evaluations will be performed every 3 months (±2 weeks) after the last dose of MEDI-575 as specified:

1) Evaluation of disease (subjects who discontinue treatment due to reasons other than disease progression or initiation of alternative anticancer therapy; these evaluations will be performed until documentation of disease progression, initiation of alternative anticancer therapy, or the end of study [defined as 1 year post entrance of the last subject into the study])

- CT or MRI scans
- Focused physical examination
- Karnofsky performance status

2) Blood collection (all subjects)

- Anti-MEDI-575 antibodies (3 months post last dose, only)

3) Survival status and subsequent anticancer therapy by clinic visit or telephone contact until death or the end of the study (all subjects).

3.7 Subject Evaluation Methods

3.7.1 Routine Laboratory Evaluations

Routine laboratory tests (hematology, serum chemistry, and urinalysis) during screening and during the study (see Table 3.6-1, Table 3.6-2, and Table 3.6-3) will be performed in a licensed local clinical laboratory. Urine pregnancy tests during the study will be performed in the clinic using a licensed test. Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Creatinine clearance (CrCl) will be calculated using the Cockcroft-Gault formula (Cockcroft and Gault, 1976) as shown in Table 3.7.1-1.

Table 3.7.1-1 Creatinine Clearance Calculation

For Women	$CrCl = \frac{[140\text{-Age (years)}] \times \text{Mass (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times 0.85$ or $CrCl = \frac{[140\text{-Age (years)}] \times \text{Mass (kg)}}{815 \times \text{serum creatinine (mmol/L)}} \times 0.85$
For Men	$CrCl = \frac{[140\text{-Age (years)}] \times \text{Mass (kg)}}{72 \times \text{serum creatinine (mg/dl)}}$ or $CrCl = \frac{[140\text{-Age (years)}] \times \text{Mass (kg)}}{815 \times \text{serum creatinine (mmol/L)}}$

3.7.2 Physical Examination and Vital Signs

Physical examinations will be performed as described in Table 3.6-1 and Table 3.6-2 (screening and treatment visits), and Table 3.6-3 (follow-up visits) and will include assessments of the head, eyes, ears, nose, and throat (HEENT), respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, and endocrine systems; and height (at screening only).

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be performed as described in Table 3.6-1 and Table 3.6-2. On treatment days vital signs will be performed prior to and 15, 30, and 45 minutes (±5 minutes) post initiation of infusion with MEDI-575,

at the completion of the infusion (±5 minutes), and 30 and 60 minutes (±5 minutes) post completion of the infusion with MEDI-575.

3.7.3 Electrocardiographic Evaluations

Twelve-lead ECGs will be performed as described in Table 3.6-1, Table 3.6-2, and Table 3.6-3. Electrocardiogram equipment, with instant print-out and electronic transmission capabilities, and training will be provided to all study sites. All ECGs performed during the study will be obtained in triplicate (ie, 3 ECGs should be obtained within a 5-minute time period). The ECGs will be collected at screening, Cycle 1, Study Day 1 and Study Day 8 (Dose Cohort 1, only) (prior to infusion, at the time of completion of infusion [± 5 minutes], 2 hours post completion of infusion [± 15 minutes], and 6 hours [± 15 minutes] post completion of infusion), Study Day 1 of all subsequent cycles prior to dosing, at the time of discontinuation of MEDI-575, and at 30 days after the last dose of MEDI-575. All ECGs should be done prior to the PK draw for corresponding time points. Electrocardiograms will be transmitted and interpreted by a central vendor selected by the sponsor.

3.7.4 Pharmacokinetic and Immunologic Evaluations

Blood samples for assessment of PK parameters for MEDI-575 and anti-MEDI-575 antibodies will be collected as described in Table 3.6-1, Table 3.6-2, and Table 3.6-3

Details for collection, aliquoting, storage, and shipment of serum samples for PK and IM evaluations are presented in the Specimen Collection Manual provided by the sponsor.

3.7.5 Disease Evaluations

Tumor measurements and assessments will be based on RECIST guidelines (Therasse et al, 2000) and will be performed as specified in Table 3.6-1 and Table 3.6-2, and a schedule of follow-up visit procedures is presented in Table 3.6-3. 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 at least 4 weeks later using the same imaging tests. The same tumor assessment method should be used throughout the treatment period.

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. Radiographic images may be collected and archived by the sponsor or its designee.

Tumor assessments may include the following evaluations: physical examination; chest radiograph (x-ray); CT or MRI scan of the chest, abdomen, and pelvis; and CT or MRI scan of the brain. A CT scan or MRI 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. The CT 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 at Screening

At screening, tumor lesions will be categorized as follows:

- **Measurable Lesions -** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter [LD] to be recorded) as ≥ 20 mm with conventional techniques (CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters by use of a ruler or calipers.
- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (LD < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Lesions considered truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confined and followed by imaging techniques, and cystic lesions.

- **Target Lesions -** All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded at screening. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
- **Non-Target Lesions -** All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at screening. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the study.

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR) -** Disappearance of all target lesions.
- **Partial Response (PR) -** At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
- **Progressive Disease (PD) -** At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.
- **Stable Disease (SD) -** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

- **Complete Response (CR) -** Disappearance of all non-target lesions and normalization of tumor marker level.
- **Incomplete Response/Stable Disease (SD) -** Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD) -** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression of an existing lesion can only be categorized as such if actual measurement with a ruler or caliper is not required and progression is obvious on visual inspection. For malignant ascites, PD is defined as an increase in abdominal girth (abdominal circumference measured at a fixed point at the level of the iliac crest) greater than 25% over baseline, with a worsening of clinical signs and symptoms. Malignant pleural or pericardial effusions will be considered PD only if there is worsening of associated symptoms.

Evaluation of Overall Response

Table 3.7.5-1 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 3.7.5-1 Evaluation of Overall Response

Target Lesions (T)	Non-target Lesions (NT)	New Lesions	Overall Response
CR	CR	No	CR
CR	No-NT [a]	No	CR
No-T [b]	CR	No	CR
CR	Non-PD and not Unknown	No	PR
PR	Non-PD and not Unknown	No	PR
PR	No-NT	No	PR
SD	No-NT	No	SD
SD	Non-PD and not Unknown	No	SD
No-T	Non-PD and not Unknown	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
Unknown	Non-PD	No	UNK
Non-PD	Unknown	No	UNK

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

Karnofsky Performance Status

Karnofsky performance status (see Appendix 1) will be performed as described in Table 3.6-1, Table 3.6-2, and Table 3.6-3.

3.7.6 Pharmacodynamic Evaluations

3.7.6.1 Biomarker Analysis

Blood collection for assessment of selected soluble proteins and tumor biomarkers and other biological processes will be performed as described in Table 3.6-1, Table 3.6-2, and Table 3.6-3. Biomarkers to be evaluated include specific circulating soluble proteins, ie, PDGF-AA, PDGF-AB/BB, bFGF, VEGF, soluble Flt-1, and/or P1GF, as well as tumor markers when appropriate such as PSA and CA-125. Circulating tumor cells will also be assessed for genetic variations, PDGFRα, and expression levels of related signaling proteins when circulating tumor cells are available. Additionally, evaluation of the effects of genetic variation and PDGFRα expression levels will be performed when fresh and/or archival tumor samples are available. Specific biomarkers may be used to assign subjects to the expansion phase if target saturation and biological efficacy is observed below the MTD or maximum dose (15 mg/kg).

Details regarding blood sample collection for assessment of biomarkers are described in the Specimen Collection Manual provided by the sponsor.

3.7.6.2 RNA Analysis

Whole blood samples will be used to analyze the effects of MEDI-575 on levels of messenger RNA (mRNA) sequences. This analysis is performed using Affymetrix® whole genome expression array and taqMan-based assay on selected panel of genes.

3.7.6.3 DNA Analysis (Optional)

To investigate characteristics associated with subject's clinical response and safety, one blood sample (8.5 mL) will be collected at screening and frozen at –80°C for DNA sample preparation. The sample will be frozen and stored for use in exploratory analyses.

The collection of blood for DNA analysis is optional in this study. The completion of a separate informed consent form (Informed Consent Form for DNA Analysis) is requested but not required for participation in the study. Subjects who do not wish to have the DNA test done will still be eligible for the study. Subjects who elect to have the DNA test done may, at any time, request that the blood collected for DNA analysis be destroyed.

All specimen and subject identifiers will be removed from the DNA blood samples such that under no circumstances can the DNA blood samples be linked back to a specific subject. In most cases, this will require that DNA blood samples have current labeling removed and the tubes relabeled. Special labeling capable of adhering to frozen tubes must be used. If it is not possible to remove the original labeling, then it must be determined whether the DNA blood samples can go through a freeze-thaw cycle and be re-aliquoted to maintain confidentiality. All relabeled DNA blood samples must be cross referenced to the original demographics in a secure database to ensure that only appropriate laboratory personnel have access to these data. These data will be utilized in the event that at any time a subject requests that a sample be destroyed. A special release must be obtained prior to use of specified DNA blood samples.

3.8 Subject Completion of Study and Loss to Follow-up

Subjects will be considered to have completed the study if they were followed until the end of the study (defined as 1 year after the last subject entered the study). It should be specified on the source document whether or not the subject completed the study follow-up procedures through the end of study.

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. Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, follow-up should resume according to the protocol.

4 Safety Assessment

4.1 Adverse Events

4.1.1 Definition of Adverse Events

As defined by the ICH Guideline for Good Clinical Practice (CPMP/ICH/135/95), an AE is:

- Any untoward medical occurrence in a subject or clinical investigations subject administered a pharmaceutical product and which does not necessarily have to 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 pre-existing condition;
- An AE occurring from overdose (ie, a dosage higher than that prescribed by a healthcare professional for clinical reasons, or a dosage higher than that described on the marketed product label) of an investigational or marketed product, whether accidental or intentional;
- An AE occurring from abuse (eg, use for nonclinical reasons) of an investigational or marketed product;
- Any laboratory abnormality that is judged by the investigator to be medically significant (except as noted in Section 4.10);
- An event related to a medical procedure or associated with the discontinuation of the previous use of an investigational or marketed product required by protocol (protocol-related AE).

4.1.2 Study Reporting Period for Adverse Events

All AEs that are not classified as serious (for which an expanded reporting period is used, see Section 4.2 below) and occur after a subject has received the investigational product through 30 days after the last dose of MEDI-575 must be reported by the investigator.

Any new sign or symptom, disease, or other untoward medical event that occurs after the subject/legal representative signs the informed consent form but before the subject has received investigational product, and which may possibly be causally related to the protocol (ie, results from a required procedure or from withdrawal of prior medication), must be reported by the investigator as an adverse event in the same way as adverse events that occur after the subject receives investigational product.

4.1.3 Recording of Adverse Events

Adverse events will be reported 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 as a SAE and, therefore, requires immediate notification of the sponsor. See Section 4.2.1 for the definition of SAEs, and Section 4.3 and Section 4.4 for guidelines for

assessment of severity and relationship, respectively. If the event has not resolved at the end of the study reporting period it will be documented as ongoing. If an AE evolves into a condition that becomes "serious" it will be reported on the SERIOUS ADVERSE EVENT (SAE) REPORT FORM.

4.2 Serious Adverse Events

4.2.1 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death;
- Is immediately life-threatening.

This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

- 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. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity.

The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect in offspring of the subject.

A pregnancy should be reported to MedImmune Patient Safety as an immediately reportable event (IRE). A pregnancy should be followed for outcome and the health status of the mother

and the child. If the child is born with any congenital anomaly or birth defect, this should be reported to Patient Safety as a SAE.

- 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.

A serious event related to a medical procedure required by protocol prior to dosing of the investigational product should also be reported to Patient Safety as an SAE (protocol-related SAE).

4.2.2 Study Reporting Period 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 after the last dose of MEDI-575. After the initial SAE report, the investigator is required to follow each subject proactively and provide further information on the subject's condition to MedImmune Patient Safety.

All SAEs should be followed up to resolution by the investigator, even if this extends beyond the study reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

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 the investigational product, the event should be reported to MedImmune Patient Safety.

4.2.3 Notification of 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 to MedImmune Patient Safety.

MedImmune contact information:

Patient Safety
MedImmune
[redacted]

MedImmune, as sponsor of the study being conducted under an Investigational New Drug Application (IND), is responsible for reporting certain SAEs as IND safety reports to the US Food and Drug Adminstration (FDA), other applicable regulatory authorities, and participating investigators, in accordance with the USA Code of Federal Regulations (21 CFR Parts 312.32 and 312.33) ICH Guidelines, and/or local regulatory requirements. MedImmune 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 MedImmune as soon as it becomes available.

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

4.2.4 Notification of Institutional Review Board or Independent Ethics Committee of Serious Adverse Events

The investigator must comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB or IEC. The IRB or IEC must be informed in a timely manner by the principal investigator of serious AEs occurring at their site during the study. Investigators must also submit safety information provided by MedImmune to the IRB or IEC as detailed in Section 7.2.

4.2.5 Recording of Serious Adverse Events

Serious adverse events will be recorded on the SAE REPORT FORM using a recognized medical term or diagnosis that accurately reflects the event. Each SAE will be assessed by the investigator for severity, relationship to the investigational product, and possible etiologies. See Section 4.2.1 for the definition of SAEs, and Section 4.3 and Section 4.4 regarding guidelines for assessment of severity and relationship, respectively.

For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report to the sponsor the outcome of the event using the SAE REPORT FORM.

4.3 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by a health care professional who is qualified to review AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment and the severity categories of *Grade 1, Grade 2, Grade 3, Grade 4, or Grade 5* using the NCI CTCAE v3.0.

Adverse events not described within the NCI CTCAE v3.0 will be reported using the severity categories as follows:

Grade 1:	Mild AE
Grade 2:	Moderate AE
Grade 3:	Severe AE
Grade 4:	Life-threatening or disabling AE
Grade 5:	Death related to AE

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 4.2.1. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but would be an SAE.

4.4 Assessment of Relationship

An AE is considered "product-related" for the purposes of regulatory reporting if the investigator, the medical monitor, or the Patient Safety physician assesses the AE as possibly, probably, or definitely related to investigational product. This is not a conclusive determination of causal association between the product and the event.

Whenever the investigator's assessment is unknown or unclear, the AE is treated as product-related for the purposes of reporting to regulatory authorities. An AE may be deemed to be not related to the product for purposes of regulatory reporting only if the investigator, medical monitor, and Patient Safety physician, if applicable, agree that the AE is not product-related.

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product. A number of factors should be considered in making this assessment including: 1) the temporal relationship of the event to the administration of investigational product; 2) whether an alternative etiology has been identified; and 3) biological plausibility. The following guidelines should be used by investigators to assess the relationship of an AE to investigational product administration.

Relationship assessments that indicate an **"Unlikely Relationship"** to investigational product:

None: The event is related to an etiology other than the investigational product (the alternative etiology must be documented in the study subject's medical record).

Remote: The event is unlikely to be related to the investigational product and likely to be related to factors other than investigational product.

Relationship assessments that indicate a **"Likely Relationship"** to investigational product:

Possible: There is an association between the event and the administration of the investigational product, and there is a plausible mechanism for the event to be related to investigational product; but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.

Probable: There is an association between the event and the administration of investigational product, a plausible mechanism for the event to be related to the investigational product, and the event could not be reasonably explained by known characteristics of the subject's clinical status or an alternative etiology is not apparent.

Definite: There is an association between the event and the administration of investigational product, a plausible mechanism for the event to be related to the investigational product, and causes other than the investigational product have been ruled out and/or the event re-appeared on re-exposure to the investigational product.

For AEs that occur prior to the administration of investigational product, an assessment of protocol relatedness must be made. Protocol-related AEs may occur as a result of procedures required during the screening process (eg, blood collection, washout of an existing medication) prior to the initial administration of investigational product. For AEs that occur before administration of investigational product, only those that are assessed by the investigator as protocol-related should be reported to the sponsor. The following guidelines should be used by investigators to assess the relationship of an AE to a protocol-required procedure:

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 study procedure (the alternative etiology must be documented in the study subject's medical record).

4.5 Other Events Requiring Immediate Reporting

The following events must be reported ***within 24 hours*** by fax to MedImmune Patient Safety using the fax notification form:

1) Any withdrawal of consent during the study

2) Pregnancy or intent to become pregnant*

* Subjects who become pregnant during the study period must not receive additional doses of investigational product but will be followed for the duration of the study. A pregnancy should be followed for outcome, any premature terminations reported, and the health status of the mother and child, including date of delivery and the child's gender and weight, should be reported to MedImmune Patient Safety after delivery.

4.6 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 immediate review of SAEs and timely review of other AEs reported during the study. The MedImmune Patient Safety Specialist has responsibility for the day-to-day safety monitoring of the study, including the receipt, review, investigation, and follow-up of SAEs reported by the clinical study sites.

The Safety Monitoring Committee (SMC) will independently review cumulative safety surveillance data, as well as the decisions of the medical monitor regarding dose escalation, on a regular basis throughout the study and make recommendations regarding further conduct of the study. The SMC will also review safety data at other time points in response to AEs felt to be medically significant by the medical monitor. The SMC is composed of at least 2 MedImmune physicians who are not directly involved in the day-to-day operations of the study, and at least 2 physicians who are not employees of MedImmune.

4.7 Interruption or Discontinuation of Study Dosing in Individual Subjects

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
2) Allergic reactions ≥ Grade 2. Infusion reactions ≤ Grade 3 that respond to medical therapy or slowing the infusion rate and that are of limited duration will not necessitate dose interruption or discontinuation. Any infusion or allergic reaction that necessitates the use of systemic pressor agents will cause dose discontinuation in that subject.
3) Pregnancy or intent to become pregnant
4) DLT (see Section 4.10 for definition of DLTs)
5) Recurrence of Grade 3 or Grade 4 hematologic or non-hematologic toxicity after the first cycle of treatment
6) ≥ Grade 2 toxicities (after completion of Cycle 1) that do not return to ≤ Grade 1 or baseline within 7 days unless clearly attributable to another cause such as disease progression or an accident
7) Grade ≥ 2 toxicities that cause a cumulative delay of ≥ 21 days in 3 consecutive cycles
8) Documentation of disease progression

9) Event which, in the opinion of the investigator, contraindicates further dosing such as intercurrent illnesses, significant drug toxicities or complications if judged by the investigator to be in the best interest of the subject

10) Subject non-compliance.

11) Treatment with another investigational agent

12) Initiation of alternative anticancer therapy

Subjects who are permanently discontinued from investigational product will be followed for the full study period (through 30 days after the last dose of MEDI-575), including the collection of any protocol-specified blood and skin specimens, unless consent is withdrawn.

4.8 Interruption or Discontinuation of Study Dosing and Entry

If any of the following occur, no further administration of investigational product will take place and no further subjects will be entered into the study:

1) Death in any subject in which the cause of death is assessed as possibly, probably, or definitely related to investigational product;

2) Anaphylactic reaction to investigational product in any subject; or

3) Other events that, in the judgment of the medical monitor, are serious enough to warrant immediate review by the sponsor Safety Monitoring Committee (SMC).

If one of the above-listed events occurs, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted by the medical monitor and the SMC to determine whether dosing and study entry should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the SMC are required for resumption of the study in the event the study is interrupted because of one of the above-listed events.

4.9 Dose Escalation

Rules for dose escalation are as follows:

1) Subjects enrolled in Dose Cohort 1 (3.0 mg/kg) only will receive a single, lead-in dose of MEDI-575 at 0.5 mg/kg administered 7 days prior to receipt of the first dose of MEDI-575 at the 3.0 mg/kg dose level. The DLT period for this dose cohort only will begin with the single administration of MEDI-575 at the dose level of 0.5 mg/kg (Study Day 1) and continue until 21 days after the administration of the first dose of MEDI-575 at the 3.0 mg/kg dose level (Study Day 28). Any DLTs that occur in subjects in this cohort after the administration of the lead-in dose, but prior to

administration of the first dose at the 3.0 mg/kg dose level will be considered related to the 0.5 mg/kg dose. DLTs that occur after MEDI-575 has been administered at a dose of 3.0 mg/kg will be considered related to the 3.0 mg/kg dose. Dose escalation and administration of investigational product for this and all subsequent cohorts will follow the rules outlined below.

2) Dose escalation will begin with a single subject in each dose cohort. If no DLTs (as defined in Section 4.10) are observed in this subject within the first 7 days of administration of MEDI-575, 2 additional subjects will be enrolled into that dose cohort and may be dosed immediately.

3) If no DLTs are observed in the first 3 subjects treated in the dose cohort through the first 28 days (Dose Cohort 1) or 21 days (Dose Cohort 2 and above) of administration of MEDI-575, enrollment into the next higher dose cohort will begin using the same rules described in Item 2.

4) If 1 out of 3 subjects within a dose cohort experiences a DLT, that dose cohort will be expanded to a total of 6 subjects provided no further subjects experience a DLT. If no further subjects experience a DLT through the first 28 days (Dose Cohort 1) or 21 days (Dose Cohort 2 and above) of administration of MEDI-575 in the expanded dose cohort, dose escalation will continue in the next higher dose cohort using the same rules described in Item 2.

5) If 2 or more subjects within a dose cohort experience a DLT within the first 28 days (Dose Cohort 1) or 21 days (Dose Cohort 2 and above) of administration of MEDI-575, then the MTD will be exceeded and no further subjects will be enrolled into that dose cohort. If this happens, the preceding dose cohort will be evaluated as the MTD, with the addition of 3 subjects if this dose cohort has not previously been expanded to 6 subjects. If ≤ 1 of 6 subjects experiences a DLT, this dose will be declared the MTD. Approximately 6 additional subjects will be enrolled into the MTD dose cohort as well as the dose cohort below the MTD dose cohort to evaluate PK and pharmacodynamic parameters and determine tumor response.

6) If the MTD is not reached at a dose of 15 mg/kg/week, a dose will be determined from Cohorts 1 through 5 using a combination of PK, pharmacodynamic markers, safety, and when available, efficacy data. The maximum dose for the weekly schedule will be 15 mg/kg. This weekly dose level will be used in the dose-expansion phase as the weekly dose-expansion dose. Two additional cohorts will also be added at 25 mg/kg (Dose Cohort 6) and 35 mg/kg (Dose Cohort 7) administered as a 90-minute IV infusion once every 21 days (on Study Day 1) to the dose-escalation phase. One of these doses (based on PK, pharmacodynamic markers, safety, and, when available, efficacy data) will be used in the dose-expansion phase as the every 3-week expansion dose. The subjects enrolled in Cohorts 6 and 7 will be evaluated identically to subjects in Cohorts 1 through 5 in the dose-escalation phase. The decision to escalate from 25 mg/kg to 35 mg/kg will be made using the same parameters as those used for the weekly dosing schedule.

7) The dose-expansion phase will consist of approximately 12 subjects. Approximately 6 subjects will be treated once every 7 days of a 21-day cycle (weekly schedule) at a dose identified by the criteria in Item 6 from Cohorts 1 through 5. Another 6 subjects will be treated once every 21 days on Study Day 1 (every 3-week schedule) at a dose identified by the criteria in Item 6 from Cohorts 6 and 7. The subjects in these dose-expansion cohorts must have one of the following advanced solid tumors: NSCLC, GBM, ovarian cancer, or synovial sarcoma.

8) At the discretion of the sponsor, an intermediate dose may be chosen for dose escalation. Situations which 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 the 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 in Items 2 through 4 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.

The decision to enroll the next higher dose cohort or to continue enrollment in the current dose cohort will be based on review of safety data following the proscribed observation period. The decision will be jointly made following a meeting or teleconference attended by all investigators, the medical monitor, a MedImmune Patient Safety physician, and the therapeutic area head (optional). A representative from clinical operations will document the discussion and decision. Treating investigators will provide a verbal or written summary of treatment including description of any AEs. If a treating investigator is unable to attend, a written summary of findings will be submitted. A decision will not be reached unless all treating physicians have attended the meeting or teleconference or submitted a written summary. Dose escalation will not proceed until approved by the sponsor.

At the discretion of the sponsor, the dosing interval may be increased from once every 7 days to once every 14 days or longer at a dose or doses at or below the MTD. This decision will be based on accumulated PK, pharmacodynamic markers, tumor response, and safety data. Administration of investigational product and dose escalation may continue on a weekly schedule concurrently with dose escalation using an increased dosing interval. The maximum dose administered will be 15 mg/kg per dose.

4.10 Definitions of Dose-limiting Toxicities

Dose-limiting toxicities will be graded according to the NCI CTCAE V3.0. The DLT period for Dose Cohort 1 only will begin with the single lead-in administration of MEDI-575 at the dose level of 0.5 mg/kg (Cycle 1, Study Day 1) and continue through the entire first cycle of treatment (Cycle 1, Study Day 28) for a total of 28 days. The DLT period for Dose Cohorts 2

through 7 will begin with the administration of the first dose of MEDI-575 and continue through the entire first cycle of treatment (Cycle 1, Study Day 1 through Cycle 1, Study Day 21).

A DLT is defined as:

1) Any Grade 3 or higher non-hematologic toxicity that occurs during the DLT assessment period where a cause other than the investigational product (such as disease progression or accident) cannot be reasonably justified with the following exceptions:
   - Grade 3 fever (in the absence of neutropenia) defined as > 40.0°C (>104.0°F) that resolves to normal or baseline within 24 hours of treatment and is not considered an SAE; or
   - Grade 3 rigors/chills that respond to optimal therapy.
2) Any Grade 3 or higher hematologic toxicity where a cause other than the investigational product (such as disease progression or accident) cannot be reasonably justified.

5 Statistical Considerations

5.1 General Considerations

The analysis of study data is the responsibility of MedImmune or its designee. A comprehensive statistical analysis plan will be approved prior to the analysis of study data.

All data will be provided in data listings sorted by dose cohort. Continuous variables will be summarized by descriptive statistics including N, mean, standard deviation, median, and range. Descriptive statistics for summarizing categorical variables include frequency and percentage. Missing data will be treated as missing and no data will be imputed.

5.2 Sample Size

For the dose escalation phase, a minimum of 21 evaluable subjects (3 subjects in Dose Cohorts 1 through 7) or up to approximately 42 evaluable subjects (3+3 subjects per dose cohort) will be required to determine the MTD. A subject will be considered evaluable if the subject receives at least 1 full cycle of MEDI-575 and completes the safety follow-up through the DLT evaluation period, or the subject experiences a DLT. Any non-evaluable subject will be replaced in the same dose cohort.

For the dose-expansion phase, approximately 12 subjects may be entered; approximately 6 subjects at a dose to be determined from Dose Cohorts 1 through 5 (weekly schedule) and approximately 6 subjects at a dose to be determined from Dose Cohorts 6 and 7 (every 3-week schedule).

5.3 Analysis Populations

The safety population will include all subjects who receive any MEDI-575.

The evaluable population for MTD is defined as all those subjects who receive at least 1 full cycle of MEDI-575 and complete the safety follow-up through the DLT evaluation period, or who experience a DLT.

5.4 Primary Endpoints

The primary objectives of this study are to evaluate the safety and tolerability of MEDI-575 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists and to determine the MTD and/or optimal biological dose of MEDI-575 in this subject population. All safety endpoints will be summarized descriptively. Adverse events and SAEs will be summarized by dose cohort, system organ class, severity, and relationship to MEDI-575 through 30 days after the last dose of MEDI-575.

Determination of the MTD is described in Section 4.9 and descriptive statistics will be provided to summarize the occurrence of DLTs by dose cohort.

5.5 Secondary Endpoints

Secondary endpoints include assessments of PK, IM, and antitumor activity of MEDI-575.

5.5.1 Pharmacokinetics of MEDI-575

The PK of MEDI-575 will be assessed using the variables of AUC, (which will be calculated by the trapezoidal rule), C_{max}, T_{max}, $t_{½}$, and CL. These parameters will be obtained by non-compartmental methods. Linearity in the PK of MEDI-575 will be assessed from $t_{½}$ and dose-normalized AUC and C_{max}. Descriptive statistics will be provided by dose cohort.

5.5.2 Immunogenicity of MEDI-575

Immunogenicity of MEDI-575 will be assessed and summarized descriptively by dose cohort.

5.5.3 Antitumor Activity of MEDI-575

The antitumor activity of MEDI-575 will be assessed based on ORR, TTR, DR, TTP, PFS, and OS.

The ORR 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 TTR will be measured from the start of treatment with MEDI-575 to the first documentation of objective response and will only be assessed in subjects who have achieved objective response.

The DR 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 therapy. The DR will only be calculated for the subgroup of subjects with an objective response.

The TTP will be measured from the start of treatment with MEDI-575 until the documentation of disease progression. Disease progression is defined according to RECIST guidelines. The TTP will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression prior to data cutoff, dropout, or the initiation of alternate anticancer therapy. Subjects having no tumor assessments after the start of treatment with MEDI-575 will have TTP censored on the first date of treatment with MEDI-575.

The PFS will be measured from the start of treatment with MEDI-575 until the documentation of disease progression or death due to any cause, whichever occurs first. Disease progression is defined according to RECIST guidelines. The PFS will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression and are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer therapy. Subjects having no tumor assessments after the start

of treatment with MEDI-575 will have PFS censored on the first date of treatment with MEDI-575.

The OS will be determined as the time from the start of treatment with MEDI-575 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 time to event data, including TTR, DR, TTP, PFS, and OS, will be evaluated using Kaplan-Meier methods.

A selected panel of biomarkers will be employed which may include evaluation of the effects of MEDI-575 on serum tumor biomarkers including PSA and CA-125, or other tumor markers as determined by tumor type. Descriptive statistics will also be provided.

6 Data Collection and Monitoring

The study will be monitored by MedImmune or its designee 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, 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.

Data recorded on source documents will be transcribed onto a validated data collection instrument (a paper case report form or electronic data screen) provided by MedImmune or its designee. The investigator must ensure the accuracy and completeness of the data reported, and its consistency with the source documentation.

The primary source document for this study will be the subject's medical records. 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.

Study documents (including subject records, copies of collected data, study notebook, and pharmacy records) must be kept secured in accordance with MedImmune policies and applicable regulatory requirements for a period of 2 years following marketing of MEDI-575 or for 2 years after centers have been notified that the study has been closed and the IND has

been discontinued. There may be other circumstances for which MedImmune is required to maintain study records and, therefore, MedImmune should be contacted prior to removing study records for any reason.

7 Human Subjects

7.1 Ethics and Regulatory Considerations

The study will be conducted according to the Declaration of Helsinki, the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), Protection of Human Subjects (21 CFR Part 50), Institutional Review Boards (21 CFR Part 56), and Investigational New Drug Application (21 CFR Part 312).

The protocol will be reviewed and approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to the sponsor and to the IRB/IEC, 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 they can withdraw/can withdraw their child at any time. Written informed consent will be obtained from each subject/legal representative prior to the screening procedures required for entry into the study. 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.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a subject identification number (SID) will be stored separately in another locked file cabinet. Study records 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 necessary for monitoring by regulatory authorities or the sponsor of the clinical study. The principal investigator must also comply with all applicable privacy regulations (eg, HIPAA 1996, EU Data Protection Directive 95/46/EC).

7.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

A list of IRB/IEC members 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, and any other written materials to be provided to subjects will be in the possession of the investigator and the sponsor before the study is initiated. The IRB/IEC's unconditional approval statement will be transmitted by the investigator to the sponsor prior to shipment of investigational product supplies to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

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

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

7.3 Informed Consent

The principles of informed consent in the Declaration of Helsinki should be implemented before any protocol-specified procedures or interventions are carried out. Informed consent will be obtained in accordance with 21 Part CFR 50 and any applicable local regulations.

Information should be given in both oral and written form, and subjects or their legal representatives must be given ample opportunity to inquire about details of the study. The written informed consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations.

Subjects or their legal representatives must be informed that the study involves research. They must be informed about the aims, expected benefits, possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or the fetus of the subject, if the subject should become pregnant) that are currently unforeseeable. They must also be informed of the study procedures to be followed and alternative treatment available to them. Subjects or their legal representatives must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained. They must be informed whom to contact for answers to any questions relating to the research project. The subjects or their legal representatives must be informed that participation is voluntary and that they are free to withdraw or withdraw their child from the study for any reason at any time, without penalty or loss of benefits to which they are otherwise entitled. The extent of the confidentiality of subject records must be defined, and subjects or their legal representatives must be informed that applicable data protection legislation will be complied with. They must be informed that the monitor(s), auditor(s), IRB/IEC members, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

The consent form generated by the investigator must be approved by the IRB/IEC and be acceptable to MedImmune. 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 approved by the IRB/IEC and signed and dated by the subject or the subject's legally authorized 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 must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or MedImmune professional and Regulatory Compliance persons. The subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form 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.

8 Study Completion

Study completion is defined as the date of the last assessment for the last subject in the study.

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

9 Publications

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

10 Changes in the Protocol

The protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory agencies and IRBs/IECs, and must be approved by the IRB/IEC prior to their implementation. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Changes to the protocol are described in Appendix 2.

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Appendix 1 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 2 Summary of Amendments to the Protocol

Protocol Version 3.0, [redacted]

Protocol MI-CP187, Version 2.0, dated [redacted], has been amended to create Version 3.0, dated [redacted]. The protocol is amended primarily to add a urine βhCG test for women of child-bearing potential at the 30 day post-treatment follow-up assessment (Table 3.6-3), to define the duration and criteria for completion of a treatment cycle, to specify that Grade 2 laboratory toxicities that lack clinical significance may not require dose delay, and to note that subjects with Grade ≥ 2 toxicities that cause a cumulative delay of ≥ 21 days in 3 consecutive cycles will not receive any further investigational product. Minor editorial changes such as corrections in spelling and grammar have been incorporated in the protocol.

All text revisions resulting from this amendment are incorporated in the body of protocol Version 3.0. Major changes to the protocol are presented below. Added text is shown bolded and underlined (eg, **text**) and deleted text is shown with strikethrough (eg, ~~**text**~~).

1) Section 3.5.2 (Treatment Regimen), and Study Abstract / Study Design:

Added text:

MEDI-575 will be administered once every 7 days (on Study Days 1, 8, and 15 of each 21-day cycle of treatment) as a 60-minute IV infusion until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal (see Section 4.7). **In Cycle 2 and beyond, a dose can be delayed up to 7 days based on hematologic and nonhematologic toxicities, according to the conditions described in Section 3.5.5 (Dose Modifications and Toxicity Management), but all 3 planned doses must be completed within the cycle. Subjects who do not receive all 3 doses within a cycle will not advance to the next cycle and will be removed from treatment. Therefore, each cycle after the first cycle will be considered complete after administration of 3 doses. Each new cycle will begin no fewer than 7 days after the last dose of the previous cycle.**

Reason for change: This text was added to clarify that in Cycle 2 and beyond, all 3 planned doses of MEDI-575 must be administered in order for the cycle to be considered complete.

2) Section 3.5.5 (Dose Modifications and Toxicity Management) and Table 3.5.5-1 (MEDI-575 Dose Modification Table)

Added text:

Dose modifications of MEDI-575 will be based on hematologic and nonhematologic toxicities **that cannot be attributed to another cause such as disease progression or**

accident following the first cycle of treatment (Table 3.5.5-1). Both hematologic and nonhematologic toxicities will be graded according to NCI CTCAE V3.0. All DLTs must be documented as an AE on the source document. **A cycle will be considered complete after administration of 3 doses for all cycles after the first cycle.**

Table 5.5.3-1 MEDI-575 Dose Modification Table

Hematologic or Nonhematologic Toxicity	Dose Modification of MEDI-575
≤ Grade 1	None
Grade 2	Withhold MEDI-575 for up to 7 days until resolution to ≤ Grade 1 or baseline and resume at current dose level. **Grade 2 laboratory toxicities that do not have clinical significance may not require dose delay. The Medical Monitor should be consulted in the event of Grade 2 laboratory toxicities that are deemed clinically insignificant to determine if dosing may continue.** Discontinue MEDI-575 if MEDI-575 is withheld for > 7 days without resolution of toxicity to ≤ Grade 1 or baseline unless clearly attributable to another cause such as disease progression or accident.

Reason for change: Text was added to the protocol to clarify that laboratory changes of Grade 2 will not lead to a dose delay unless they are considered clinically significant. We have required that if Grade 2 changes are to be considered insignificant, the Medical Monitor must be consulted prior to the administration of MEDI-575.

3) Table 3.6-1 (Schedule of Evaluations: Screening and Treatment Periods, footnote "i" and footnote "o") and throughout Section 3.6 (Schedule of Evaluations) as appropriate

[i] ~~**No more than 2 hours p**~~**P**rior to infusion **on day indicated.**

[o] ~~**Up to 2 hours p**~~**P**rior to and immediately (±5 minutes) post completion of infusion.

Blood collection ~~**up to 2 hours**~~ prior to infusion of MEDI-575

Reason for change: These changes correct an editorial error in the original protocol.

4) Table 3.6-2 (Schedule of Evaluations: Follow-up Period), and Section 3.6 (Schedule of Evaluations)

An assessment for urine βhCG was added to Table 3.6-2 (Schedule of Evaluations) at the 30 days Follow-up / Post-therapy timepoint, and in the text under the heading for the evaluations to be performed at 30 days post therapy.

10) **Urine βhCG (women of child bearing potential only)**

Reason for change: Subjects in the trial are followed for 30 days post therapy for safety monitoring. Urine pregnancy testing was added to monitor for pregnancy during this time period.

5) Section 4.7 (Interruption or Discontinuation of Study Dosing in Individual Subjects)

Added text:

6) ≥ Grade 2 toxicities **(after completion of Cycle 1)** that do not return to ≤ Grade 1 or baseline within 7 days unless clearly attributable to another cause such as disease progression or an accident.

7) Grade ≥ 2 toxicities that cause a cumulative delay of ≥ 21 days in three consecutive cycles.

Reason for change: This was added to clarify that a dosing delay is only allowed in Cycle 2 and beyond, and that cumulative delays of 21 days over 3 or fewer cycles will lead to discontinuation. This insures that cumulative delays will be detected as a potential safety signal and will not allow treatment in subjects who have multiple or sequential Grade 2 toxicities that cause dose delay.

6) Section 5.5.3 (Antitumor Activity of MEDI-575), and Study Abstract / Assessment of Endpoints

Added text:

Disease progression is defined **according to** ~~**as radiographic progression by**~~ RECIST **guidelines**.

Reason for change: We have clarified throughout the protocol that disease progression will be assessed based on RECIST criteria.

Protocol Version 4.0, [redacted]

Protocol MI-CP187, Version 3.0, dated [redacted], has been amended to create Version 4.0, dated [redacted].

Two additional cohorts will be added to the dose-escalation phase to evaluate 25 mg/kg (Dose Cohort 6) and 35 mg/kg (Dose Cohort 7) administered once every 21 days on Day 1. These subjects will be evaluated identically to other subjects during dose escalation since the cycle length and DLT period will be 21 days. The doses and schedule were chosen based on PK and pharmacodynamic modeling and data obtained in the first 3 treated cohorts, and are predicted to provide target saturation of PDGFRα receptors for the duration of the dosing

interval. Pharmacokinetic/pharmacodynamic modeling was performed based on data generated in cynomolgus monkey PK studies and the first 2 cohorts (3 and 6 mg/kg) from this protocol. The PK/pharmacodynamic model accurately predicted the serum concentrations obtained in humans following the 3, 6, and 9 mg/kg dose of MEDI-575 in this study. Based on the PK/pharmacodynamic modeling, preclinical xenograft efficacy data, and the human data obtained to date, including the measurement of PDGF-AA in the serum, a predicted target average concentration of 250 μg/mL and trough levels above 150 μg/mL were identified. These concentrations ensure consistent saturation of PDGFRα receptor over the entire dosing interval and are predicted to provide maximum antitumor activity based on animal models. This effect is predicted to be achieved with a dosing schedule of 25 mg/kg or greater administered every 3 weeks. In the current study, no DLTs have been observed in the first 5 cohorts. The increase in dosing interval is under investigation in order to evaluate the feasibility of administration in conjunction with standard chemotherapeutic regimens. This dose regimen will be compared to the once weekly dosing regimen in the dose-expansion phase. The prolonged schedule should still allow for adequate blood concentrations as described above to achieve potential anti-tumor effects.

Changes in the protocol for this amendment include:

- Minor editorial changes such as corrections in spelling and grammar, changes to the reference section, and consistency in using abbreviations have been incorporated in the protocol.
- Addition of Cohorts 6 and 7 (25 and 35 mg/kg, respectively) to the dose-escalation phase to evaluate the alternative treatment schedule: a 90-minute IV infusion administered every 21 days on Study Day 1.
- Addition of dose-expansion phase details regarding: dosing schedule, targeted tumor types and their supporting references, and treatment/schedule assignment. The dose-expansion phase will include 6 subjects at a weekly dose determined from Cohorts 1 through 5; and 6 subjects at an every 3-week dose determined from Cohorts 6 through 7. Subjects in the dose-expansion phase will have NSCLC, GBM, ovarian cancer, or synovial sarcoma.
- Addition of assessments to support the alternate treatment schedule (dosing every 21 days on Day 1).
- Change in rules for dose-escalation to include Cohorts 6 and 7 and how they relate to the dose-expansion phase.
- Addition of a 500 mL bag of normal saline for the 25 and 35 mg/kg doses.

Attachment 1 **National Cancer Institute's Common Terminology Criteria for Adverse Events Version 3.0**

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf