A Phase 2 Study of MEDI-575 in Adult Subjects with Recurrent Glioblastoma Multiforme

Sponsor Protocol Number: CD-ON-MEDI-575-1042

Application Number: IND 103255

Investigational Product: MEDI-575

Sponsor: MedImmune, LLC, an affiliate of AstraZeneca AB

Medical Monitor: [redacted]

Protocol History, Date: Original Protocol, 13 August 2010

Version 2.0, 19 May 2011

Sponsor Agreement:

I, the undersigned, am authorized to sign the protocol on behalf of the sponsor.

Medical Monitor Signature _____ Date _____

Medical Monitor Name _____
(please print)

Investigator Agreement: CD-ON-MEDI-575-1042

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

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

Investigator Signature _____ Date _____

Investigator Name and Title _____
(please print)

Investigator Affiliation, City, State/Province _____

_____
(please print)

Site/Center Number (if available) _____

Table of Contents

List of In-text Tables

List of In-text Figures

List of Appendices

List of Abbreviations

Abbreviation or Specialized Term	Definition
AE	adverse event
AJCC	American Joint Commission on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate transaminase
AUC	area under the curve
BBB	blood-brain barrier
βHCG	beta human chorionic gonadotropin
CEL	chronic eosinophilic leukemia
CI	Confidence interval
CIS	cervical carcinoma in situ
CR	complete response
CRF	case report form
CSF	cerebrospinal fluid
DCIS	ductal carcinoma in situ
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DR	duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
ECG	Electrocardiogram
ELISA	enzyme-linked immunosorbent assay
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FACT	Functional Assessment of Cancer Therapy
FGF	fibroblast growth factor
GBM	glioblastoma multiforme
GIST	gastrointestinal stromal tumor
HGF	Hepatocyte growth factor
HIPAA	Health Insurance Portability and Accountability Act

Abbreviation or Specialized Term	Definition
HIV	human immunodeficiency virus
IC_{50}	50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGF	insulin-like growth factor
IgG2	immunoglobulin Type G Subclass 2
IM	Immunogenicity
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent to treat
IV	Intravenous
IWRS	Interactive web response system
K_M	Michaelis constant
mAb	monoclonal antibody
MEDI	MedImmune
MEDI-575	fully human IgG2 kappa mAb directed Against PDFGRα
mRNA	Messenger ribonucleic acid
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
ORR	objective response rate
OS	overall survival
PR	partial response
PDGF	platelet-derived growth factor
PDGF-AA	A chain homodimer of PDGF
PDGF-CC	C chain homodimer of PDGF
PDGFRα	platelet-derived growth factor receptor alpha
PDGFRβ	platelet-derived growth factor receptor beta

Abbreviation or Specialized Term	Definition
PFS	progression free survival
PFS-6	progression-free-survival at 6 months
PI3k	Phosphoinositide 3-kinase
PK	Pharmacokinetic
PR	partial response
PRO	patient-reported outcomes
PTEN	phosphatase and tensin homolog
QLQ	quality of life questionnaire
RANO	Response Assessment in Neuro-Oncology
RT	radiation therapy
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SD	stable disease
SID	subject identification
SMC	Safety Monitoring Committee
SCC	squamous cell carcinoma
TGF	transforming growth factor
TKI	tyrosine kinase inhibitor
TLDA	TaqMan low-density array
TMA	tissue microarray
TMZ	Temozolomide
TNM	tumor node metastases
TTR	time to response
TTP	time to progression
ULN	upper limit of normal
USA	United States
VEGF	vascular endothelial growth factor
WHO	World Health Organization

Study Abstract

TITLE

A Phase 2 Study of MEDI-575 in Adult Subjects with Recurrent Glioblastoma Multiforme

OBJECTIVES

Primary Objective:

The primary objective of this study is to evaluate the progression-free survival at 6 months (PFS-6) in adult subjects with a first recurrence of GBM who are treated with MEDI-575

Secondary Objectives:

1) To evaluate other antitumor activities of MEDI-575
2) To describe the safety and tolerability of MEDI-575
3) To determine the expression of PDGFRα in the tumor cells of archived tumor samples

Exploratory Objectives

1) To determine the immunogenicity of MEDI-575
2) To describe the PK of MEDI-575
3) To evaluate the biomarkers associated with MEDI-575 treatment
4) To evaluate intratumoral MEDI-575 levels in GBM following treatment
5) To investigate the effects of MEDI-575 on patient reported outcomes

STUDY DESIGN

This is a Phase 2, multicenter, open-label, single-arm study to evaluate the antitumor activity, safety, and pharmacology of MEDI-575 in adult subjects with first recurrence of GBM.

Approximately 55 subjects will be enrolled to determine the preliminary efficacy profile of MEDI-575 in the treatment of subjects with first recurrence of GBM. Subjects will receive MEDI-575 as a 60-minute IV infusion on Day 1 every 21 days until disease progression, initiation of alternative anticancer therapy, unacceptable toxicity, or other reasons for subject withdrawal. (see Section 4.2.3) (Figure 3.1-1). In Cycle 2 and beyond, a dose can be delayed up to 7 days for unavoidable scheduling issues. MEDI-575 may be withheld for up to 21 days until resolution to ≤ Grade 1 toxicity after agreement with the sponsor. The primary assessment of antitumor activity is PFS-6; tumor response and progression will be determined using *Updated Response Assessment Criteria of High Grade Gliomas- Neuro-Oncology Working Group v.1* (see Appendix 5) (Wen et al, 2010). Approximately 15 investigational sites in the United States (USA) will participate in this study. Subjects who receive any amount of MEDI-575 and proceed to subsequent surgery as therapy for GBM (at second recurrence/disease progression) will be requested to allow use of surgically resected tissue for analysis of intratumoral levels of MEDI-575

Administration of MEDI-575 may be continued based on the criteria described in Section 4.5.2. All subjects will be followed every 3 months for the duration of the trial (defined as 9 months from the date the last subject is entered into the trial or when the sponsor stops the study) until the criteria in Section 4.6 are met.

SUBJECT POPULATION

The subjects in this study will be adults with first recurrence of GBM (Stage IV malignant glioma) following first-line therapy of temozolomide and radiation.

TREATMENT

Subjects will be treated with MEDI-575 at 25 mg/kg on Day 1 every 21 days until documentation of disease

progression, initiation of alternative anticancer therapy, unacceptable toxicity, or another reason for treatment discontinuation (see Section 4.2.3) is observed. In Cycle 2 and beyond, a dose can be delayed up to 7 days for unavoidable scheduling issues. MEDI-575 may be withheld for up to 21 days until resolution to ≤ Grade 1 toxicity after agreement with the sponsor. Subjects who demonstrate stable disease or better may continue to receive MEDI-575 under the criteria above. Each new cycle will begin no fewer than 21 days after the last dose of the previous cycle.

Subjects who receive any number of doses of MEDI-575 and proceed to surgical resection as subsequent therapy for GBM may be asked to allow procurement of resected tissue to determine intratumoral levels of MEDI-575.

ASSESSMENT OF ENDPOINTS

Primary Endpoint

- The primary endpoint for efficacy is PFS-6, the rate will be summarized and its 2 sided 90% CI will be calculated based on the Kaplan-Meier method (Kaplan and Meier, 1958)

Secondary Endpoints

- Antitumor Activity Assessments
- Assessments of other antitumor activities include objective response rate (ORR), time to response (TTR), duration of response (DR), time to progression (TTP), progression-free survival (PFS), and overall survival (OS)
- Safety and Tolerability Assessment
- Endpoints include adverse events (AEs) and serious adverse events (SAEs) occurring from the signing of ICF to 90 days after the last dose or until the subject begins another anticancer therapy, whichever occurs first, and changes in clinical laboratory and electrocardiogram (ECG) evaluations from baseline.
- Expression of PDGFRα
- Archival tissue samples (obtained from subjects prior to trial enrollment) and, when available, fresh tumor biopsy samples (obtained from subjects following discontinuation of MEDI-575) will be evaluated using IHC. Expression of PDGFRα in tumor cells and/or tumor stromal cells will be evaluated for intensity and distribution of staining and relationship with clinical endpoints and circulating soluble factors associated with cancer-associated fibroblasts and/or a PDGF-AA paracrine mechanism of action. The percentage of target positive subjects will be described if there are sufficient data. Descriptive statistics will be used

Exploratory Endpoints

Descriptive statistics will be used to describe the exploratory analyses. The variables in exploratory analyses may include:

- PK Assessment

  Pharmacokinetics of MEDI-575 will be assessed using parameters including peak concentration (C_{max}), time to peak concentration (T_{max}), and area under the concentration-time curve within a dosing interval (AUC_{τ}) after the first dose. MEDI-575 steady state PK parameters including peak concentration ($C_{ss,\ max}$), trough concentration ($C_{ss,\ min}$), time to peak concentration ($T_{ss,\ max}$). A population PK model will be developed using a non-linear mixed-effects modeling approach. A PK compartmental model incorporating both linear and target-mediated clearances will be used to characterize the PK of MEDI-575 in subjects with GBM. Sequential PK-pharmacodynamic modeling will be performed to explore the relationship between MEDI-575 exposure (antibody serum concentration) and biomarkers, such as PDGF-AA ligand in plasma.

- IM Assessment

  The immunogenic potential of MEDI-575 will be analyzed by summarizing the number and percentage of patients who develop detectable anti-MEDI-575 antibodies and summarized descriptively

- Biomarkers Associated with MEDI-575

  PDGF-AA levels at baseline and in response to MEDI-575 treatment

  Selected circulating soluble proteins that may include but are not limited to PDGF, fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), fibronectin, osteopontin, and transforming growth factor (TGF) at baseline and in response to treatment

  mRNA profiling from whole blood samples may be performed and gene expression analysis will examine the potential relationship between inhibition of PDGF-related genes, clinical activity and other circulating factors. The miRNA expression pattern in the periphery of subjects enrolled may also be examined. Circulating apoptotic markers will be measured by determining nucleosomal DNA using either ELISA or RT-PCR to evaluate tumor cell apoptosis in response to treatment.

  When fresh tumor biopsy samples are available (optional), an evaluation of the presence of MEDI-575 in tumor tissue will be performed

- Patient Reported Outcomes

  Patient-reported outcomes as measured by the EORTC QLQ-C30 and the EORTC QLQ-BN20 will be summarized descriptively. Additionally, these endpoints will be summarized individually; with change from baseline for both domain and subscale scores by time point and change from baseline to be explored

INTERIM ANALYSIS

No formal interim analysis will be performed during this trial

SAMPLE SIZE AND POWER CALCULATIONS

The primary objective of this study is to evaluate the PFS-6 in adult subjects with a first recurrence of GBM who are treated with MEDI-575. The sample size estimation is based on the assumption that the historical PFS-6 rate in this population is $\leq$ 16% (null hypothesis). This is because the estimated PFS-6 rate for irinotecan single agent in recurrent GBM from a single arm Phase 2 trial was 15.8% (Prados, 2006). Using a one sample nonparametric test for survival probability (Brookmeyer and Crowley, 1982) and assuming the desired PFS-6 rate for MEDI-575 is 30%, a total of 50 subjects will provide 80% power to have a statistically significant test outcome at the 2-sided significance level of 0.1, accrual period of 12 months and a follow-up period of 6 months. Assuming a drop-out rate of 10%, a total of 55 subjects will be required to enter this study.

1 Introduction

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

1.1 Disease Background

Glioblastoma is the most frequent brain tumor and accounts for approximately 12% to 15% of all brain tumors and 50% to 60% of all astrocytic tumors. The peak incidence occurs between the ages of 45 and 70 years. (National Cancer Institute, 2010). Glioblastoma multiforme occurs in only 3.19 cases per 100,000 people annually in North America. (Central Brain Tumor Registry of the United States, 2011). The standard of care for newly diagnosed GBM is surgery followed by treatment with the alkylating agent temozolomide administered concurrently with adjuvant radiation therapy (RT), followed by continued adjuvant temozolomide. This treatment regimen has demonstrated an increase in overall survival (OS) when compared with RT alone (Stupp et al, 2005). In this study, median OS was 14.6 months with temozolomide verus 12.1 months with RT alone, median progression-free survival (PFS) was 6.9 months versus 5 months, and progression free survival at 6 months (PFS-6) was 53.9% versus 36.4% respectively. Glioblastoma multiforme tumors are extremely aggressive and are characterized by rapid proliferation of undifferentiated cells and extensive infiltration. Nearly all recur despite initial treatment (Chang et al, 2006).

Standard therapies for recurrent GBM include repeated resection, RT, chemotherapy, or supportive care. Repeated resection is the best method of prolonging survival of a select group of patients with recurrent GBM, especially those suffering from mass effect. Surgery is not always possible, however, and prognostic factors such as age, performance status, and presumed maximal extent of resection must also be considered (Pinsker et al, 2002). Patients with recurrent GBM have almost invariably undergone a previous full course of external-beam radiotherapy, making repeated irradiation more difficult and potentially more toxic. Given the difficulty and risk of administering repeated irradiation to the brain, it is offered to a relatively small minority of patients with recurrent GBM (Chang et al, 2006). Nitrosoureas are perhaps the most common salvage agents, followed by carboplatin, etoposide, irinotecan, or a combination of these agents (Brandes et al, 2004; Franceschi et al, 2004;

Reardon et al, 2005; Rosenthal et al, 2004). The prognosis for patients with recurrent GBM is poor. For example, in a recent Phase 2 study, PFS-6 for patients treated with either temozolomide or carmustine was 24% (Van den Bent et al, 2009), which is consistent with data from other studies with other agents (Brandes et al, 2008). Treatment of GBM often fails because the tumors are highly resistant to conventional cytoxic chemotherapy and RT (Reardon et al, 2006).

Antiangiogenic therapies, which include the anti-vascular endothelial growth factor (VEGF) monoclonal antibody (mAb), bevacizumab, and a number of orally administered small molecule agents (eg, cediranib), have been shown to prolong PFS-6 in the recurrent setting. In May 2009, the Federal Drug Administration granted bevacizumab accelerated approval for GBM in the relapsed setting. In the initial Phase 2 study conducted in 35 patients with recurrent GBM, bevacizumab in combination with irinotecan produced a radiographic response rate of 57% (Reardon et al, 2008). In a second Phase 2 study of single-agent bevacizumab in 48 patients previously treated with standard external beam fractionated radiation and temozolomide chemotherapy (Kreisl et al, 2009), the PFS-6 was 29% and OS at 6 months was 57%. The clinical efficacy of bevacizumab for recurrent GBM was confirmed in a larger randomized Phase 2 study (BRAIN trial) that included 167 patients who received bevacizumab with or without irinotecan (Friedman et al, 2009). In this study, the reported PFS-6 was 43% for single-agent bevacizumab and 50% for bevacizumab in combination with irinotecan, objective response rates (ORR) were 28% and 38%; and the median OS was 9.2 months and 8.7 months, respectively. Prior to the advent of antiangiogenic agents for GBM, few treatment options were available for recurrent GBM. Single agent irinotecan (CPT-11), a topoisomerase 1 inhibitor used in the relapsed setting, produces response rates of ≤15% (Friedman et al, 2009). In recurrent GBM, PFS-6 rates typically range from 9% to 21%, and median OS is ≤ 30 weeks (Friedman et al, 2009).

Recent developments in targeted drug therapies are being tested in the clinic as treatment options for patients with GBM. Treatments against specific molecular targets, in particular the epidermal growth factor receptor (EGFR), have been investigated in brain tumor patients. In a Phase 2 gefitinib trial for recurrent GBM, no objective responses were observed (Rich et al, 2004) and the PFS-6 (13%) was similar to that of historical controls (Franceschi et al, 2007). Targeted therapies that have been investigated in the neuro-oncological setting (ie, gefitinib, cediranib, erlotinib, temsirolimus, and cilengitide) have demonstrated PFS-6 rates ranging from 8% to 26% (Franceshi et al, 2007; Batchelor et al, 2007; Van den Bent et al, 2009; Galanis et al, 2005; Reardon et al, 2008).

Development of effective novel therapies is needed for patients with recurrent GBM.

1.2 Description of MEDI-575

MEDI-575 is a fully human immunoglobulin G2 kappa antibody that selectively binds to platelet-derived growth factor receptor alpha (PDGFRα). This fully human mAb was generated using XenoMouse® technology and is manufactured in [redacted] cells.

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, PDGFRα and PDGF receptor beta (PDGFRβ). The transmembrane receptor tyrosine kinase 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: GBM (Shih and Holland, 2006), gastrointestinal stromal tumors (GIST) (Corless et al, 2004), and chronic eosinophilic leukemia (CEL) (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, including CEL (Baccarani et al, 2007) and GIST (Sleijfer et al, 2008). Additionally, expression of PDGFRα has 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).

MEDI-575 binds to PDGFRα with a high degree of specificity and avidity, and does not cross-react with PDGFRβ. MEDI-575 blocks PDGF binding to PDGFRα 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 PDGRFα homo- and heterodimers, but have no effect on PDGFRβ homodimers. This has the potential advantage of limiting toxicity related to extravascular fluid accumulation, which is likely primarily an effect of inhibition of PDGFRβ, while retaining significant antitumor activity (Östman, 2004; Jayson et al, 2005).

1.2.1 Preclinical Activity of MEDI-575 in Glioblastoma Multiforme Models

In GBM, PDGFRα is activated in an autocrine fashion, which is reminiscent of PDGFRα functions during development of tissues derived from mesenchyme. Since GBM is a

malignant tumor derived from the mesenchyme, the hypothesis is that blockade of tumoral PDGFRα will result in antitumor activity. In vivo xenograft GBM models demonstrated that blockade of PDGFRα signaling in the tumor cells inhibited tumor growth (Loizos et al, 2005). Studies with MEDI-575 demonstrated significant antitumor activity in 3 different GBM xenograft mouse models that express PDGFRα on the tumor cells. Furthermore, combination treatment studies demonstrated that treatment of tumor-bearing mice with MEDI-575 and temozolomide is tolerated and results in better antitumor activity than either regimen alone. Thus, strong efficacy of MEDI-575 in GBM xenografts supports further testing of MEDI-575 in clinical settings to develop innovative therapies for GBM.

1.2.2 Preclinical Pharmacokinetic and Safety Evaluation of MEDI-575 in Cynomolgus Monkeys

Pharmacokinetic (PK) studies in cynomolgus monkeys indicated that, following administration of a single intravenous (IV) infusion of MEDI-575 at 0.6, 6.0, and 60 mg/kg on Day 1, anti-PDGFRα antibody exhibited dose-dependent and nonlinear PK. The clearance was decreased by approximately 2-fold over the dose range examined. The nonlinear clearance following administration of MEDI-575 in cynomolgus monkeys is consistent with PDGFRα-mediated clearance of the mAb. Administration of single doses of MEDI-575 up to 60 mg/kg were 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 A-chain homodimer of PDGF (PDGF-AA) binding to PDGFRα, dose-related increases in serum concentrations of PDGF-AA were observed following administration of MEDI-575 in monkeys.

1.2.3 Clinical Experience with MEDI-575

A Phase 1, multicenter, open-label, single-arm, dose-escalation and dose-expansion study (MI-CP187) is ongoing 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. This study has a standard 3+3 dose-escalation design with MEDI-575 administered at doses of 0.5 (lead-in), 3, 6, 9, 12, or 15 mg/kg once every 7 days as a 60-minute IV infusion and at 25 mg/kg and 35 mg/kg once every 21 days as a 90-minute IV infusion. The expansion portion of the study evaluates selected tumor types including non-small cell lung cancer (NSCLC), GBM, ovarian and synovial sarcoma at both weekly and every-3-week schedules. In the expansion phase, 12 subjects were enrolled; 6 at the weekly dose level of 9 mg/kg and 6 at every-3-week dose of 25 mg/kg.

Preliminary safety data as of 25Aug2010 from MI-CP187 showed that the most common (occurring in > 10% of subjects) treatment-related (possibly, probably, or definitely related) adverse events (AEs) were fatigue, nausea, hypokalemia, muscle spasms, anemia, decreased appetite, diarrhea, and hypomagnesemia. Most AEs were Grade 1 or 2 in severity and no dose-limiting toxicities (DLTs) were observed at any dose level. Serious adverse events (SAE) were generally related to the subject's underlying disease and most were assessed as unrelated to MEDI-575. One SAE, pulmonary embolism, was assessed as possibly related to MEDI-575. Preliminary efficacy data from MI-CP187 showed that 33% of subjects achieved a best response of stable disease (SD). The median duration of stable disease was 2.9 months. Based on these data, MEDI-575 appears to have a tolerable safety profile at 15 mg/kg weekly and 25 and 35 mg/kg every 3 weeks.

Based on an interim PK analysis, MEDI-575 exhibited nonlinear (dose-dependent) PK consistent with receptor-mediated clearance of the antibody resulting in a faster rate of MEDI-575 elimination at lower doses compared with high doses. The concentration-time profile of MEDI-575 was best described using a PK model accounting for both linear and non-linear (target-mediated) clearances. The Michaelis constant (K_M) describing saturation of PDGFRα sink was 7.88 µg/mL. The maximum non-linear intrinsic clearance of the PDGFRα sink was 2.22 L/day, suggesting that at non-saturating levels of MEDI-575 (serum concentrations K_M) the PDGFRα sink accounts for greater than 90% of MEDI-575 clearance. A dose-dependent increase in serum concentrations of PDGF-AA ligand was observed following administration at all weekly doses of MEDI-575, consistent with the dose-dependent inhibition of PDGF-AA binding to PDGFRα. The serum concentration of MEDI-575 required for 50% inhibition (IC_{50}) of PDGF-AA elimination was estimated to be approximately 0.9 µg/mL with a between-subject variability of approximately 46%. Based on the mean IC_{50} value, 99% saturation of PDGFRα is expected at about 100 µg/mL of MEDI-575. Considering a variability of approximately 46% on IC_{50}, 99% saturation of

PDGFRα is expected at approximately 150 µg/mL. Additionally, based on PK/pharmacodynamic modeling using tumor xenograft mouse models treated with MEDI-575, an average serum concentration of 250 µg/mL was identified as the target level for efficacy in preclinical models. The dose of 25 mg/kg administered every 3weeks is expected to achieve a trough MEDI-575 concentration of above 150 µg/mL at steady state and is the recommended Phase 2 dose.

1.3 Rationale for Study Conduct

Patients with GBM who have disease recurrence after initial treatment with surgery, RT, and temozolomide (first recurrence) have no curative options for treatment; and few therapies that have been shown to prolong survival. In this patient population, bevacizumab has demonstrated improved PFS-6, however, an OS benefit has not been shown. PDGFRα is known to be expressed in both newly diagnosed and recurrent GBM at consistent and high levels, but whether bevacizumab therapy alters PDGFRα expression is also unknown. Preclinical mouse xenograft studies with GBM cell lines have demonstrated that inhibition of PDGFRα signaling by MEDI-575 as a single agent can cause regression of tumors. This group of patients clearly needs additional therapies that may prolong survival and reduce the burden of disease.

Evaluating MEDI-575 in this patient population represents a rational and ethical approach to determine whether MEDI-575 has clinical activity against GBM. Available therapies either do not significantly prolong PFS or have not clearly demonstrated an improvement in OS. Treatment with MEDI-575 would not prevent subsequent treatment with either bevacizumab or a cytoxic agent such as carmustine or temozolomide. Response rates and PFS-6 for therapies given subsequent to bevacizumab are not well understood and a single-arm trial in such a population would be difficult to size and evaluate. Anecdotal reports from investigators also suggest that patients become refractory to subsequent therapies after treatment with bevacizumab, but the reason for this is not known. Thus, given the choice between evaluation of MEDI-575 at first recurrence or second recurrence following bevacizumab, first recurrence is more likely to identify activity and will not prevent subsequent treatment with bevacizumab, which has been shown to prolong PFS-6. Moreover, there are no clinical or non-clinical data to suggest that treatment with MEDI-575 would prevent subjects from obtaining benefit with other subsequent therapies.

1.4 Benefit-Risk and Ethical Assessment

The Phase 1 study of MEDI-575 (MI-CP187) in subjects with advanced solid tumors did not identify any significant risks. Most toxicities observed in the Phase 1 study were ≤ Grade 2 in severity and SAEs were generally related to the subject's underlying disease and assessed as unrelated to MEDI-575. One SAE, pulmonary embolism (Grade 4), was assessed as possibly related to MEDI-575, although this interpretation is complicated by a previous history of pulmonary embolism prior to treatment with MEDI-575. Prolonged exposure to MEDI-575 has not been identified with any unique risks; however, prolonged exposure at the Phase 2 dose of 25 mg/kg every 3 weeks has not yet been evaluated. Together, these data suggest that MEDI-575 when used as a single agent is safe and does not represent an undue risk in this patient population.

Subjects to be treated in the current protocol have no available curative therapies, and standard therapies only provide a median OS of about 7 months (Franceschi et al, 2009). Even if MEDI-575 should prove to be ineffective, there are no clinical or non-clinical data to suggest that treatment with MEDI-575 would prevent subjects from obtaining benefit with other subsequent therapies. Therefore, evaluation of MEDI-575 at first recurrence of GBM is reasonable given the possibility of activity, the difficulty in evaluating activity in later lines, and the availability of subsequent therapies. Continued therapy in the absence of toxicity or progression should provide the maximum benefit to subjects enrolled in this trial.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to evaluate the PFS-6 in adult subjects with a first recurrence of GBM who are treated with MEDI-575.

2.2 Secondary Objectives

The secondary objectives of this study are:

1) To evaluate other antitumor activities of MEDI-575
2) To describe the safety and tolerability of MEDI-575
3) To determine the expression of PDGFRα in the tumor cells of archived tumor samples

2.3 Exploratory Objectives

The exploratory objectives of this study are:

1) To determine the immunogenicity of MEDI-575
2) To describe the PK of MEDI-575
3) To evaluate the biomarkers associated with MEDI-575 treatment
4) To evaluate intratumoral MEDI-575 levels in GBM following treatment
5) To investigate the effects of MEDI-575 on patient reported outcomes

3 Study Design

3.1 Overview of Study Design

This is a Phase 2, multicenter, open-label, single-arm study to evaluate the antitumor activity, safety, and pharmacology of MEDI-575 in adult subjects with first recurrence of GBM.

Approximately 55 subjects will be enrolled to determine the preliminary efficacy profile of MEDI-575 in the treatment of subjects with first recurrence of GBM. Subjects will receive MEDI-575 as a 60-minute IV infusion on Day 1 every 21 days until disease progression, initiation of alternative anticancer therapy, unacceptable toxicity, or other reasons for subject withdrawal (see Section 4.2.3) (Figure 3.1-1). In Cycle 2 and beyond, a dose can be delayed up to 7 days for unavoidable scheduling issues. MEDI-575 may be withheld for up to 21 days until resolution to ≤ Grade 1 toxicity after agreement with the sponsor. The primary assessment of antitumor activity is PFS-6; progression will be determined using *Updated Response Assessment Criteria of High Grade Gliomas- Neuro-Oncology Working Group v.1* (see Appendix 5) (Wen et al, 2010). Approximately 15 investigational sites in the United States (USA) will participate in this study. Subjects who receive any amount of MEDI-575 and proceed to subsequent surgery as therapy for GBM (at second recurrence/disease progression) will be requested to allow use of surgically resected tissue for analysis of intratumoral levels of MEDI-575.

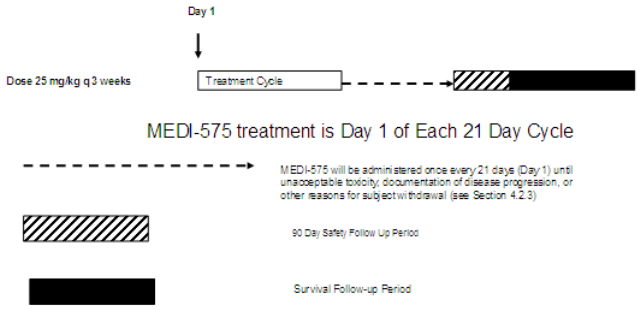

Figure 3.1-1 Study Flow Diagram

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

3.2 Estimated Duration of Subject Participation

Administration of MEDI-575 may be continued based on the criteria described in Section 4.5.2. All subjects will be followed every 3 months for the duration of the trial (defined as 9 months from the date the last subject is entered into the trial or when the sponsor stops the study) until the criteria in Section 4.6 are met.

3.3 Study Stopping Criteria

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

1) Death in any subject in which the cause of death is assessed as related to investigational product
2) Anaphylactic reaction to investigational product in any subject
3) Other events that, in the judgement of the medical monitor, are deemed serious enough to warrant immediate review by the MedImmune Safety Monitoring Committee (SMC)
4) A DLT rate greater than 30% in the first 15 subjects enrolled in the study (see Section 4.5.4.2)

If any of the above-listed events occurs, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted (see Section 6.5) to determine whether dosing and study entry should be resumed, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the MedImmune SMC are required for resumption of the study in the event the study is

interrupted because of 1 of the above-listed events. Where applicable, regulatory authorities and Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) will be notified of any study actions taken.

Any subjects who have already received investigational product and are currently in the study at the time study stopping criteria are met will continue to be followed by the investigator for safety.

Withdrawal criteria for individual subjects are provided in Section 4.2.3.

3.4 Rationale for Study Design, Doses, and Control Groups

This is a multicenter, open-label, single arm, single agent study of MEDI-575 to determine the safety and antitumor efficacy of MEDI-575 in adult subjects with first recurrence of GBM. Progression free survival at 6 months (PFS-6) will be used to determine efficacy, and provides a direct measure of the effect of MEDI-575 on antitumor activity. Progression free survival or PFS-6 may correlate with OS, and prolongation of PFS may in itself be a measure of clinical benefit. Unlike OS, measurement of PFS is not confounded by subsequent therapies. Overall survival and ORR will be secondary endpoints. Response and progression will be measured using proposed criteria developed by the Response Assessment in Neuro-Oncology (RANO) Working Group (see Appendix 4 and Appendix 5), which will be assessed by an independent radiographic analysis.

The choice of a single-arm trial is appropriate given this patient population and the goals of the study. MEDI-575 has not yet been evaluated in GBM. Patients with recurrent GBM have no curative therapies, and there is still a need for additional therapies for this population. A PFS-6 of 15-20% is generally accepted as demonstration of clinical activity in patients with first recurrence of GBM (Ballman et al, 2007; Prados, 2006). In the absence of therapy, all patients who have a recurrence will continue to progress rapidly. A randomized trial would require comparison to another agent, or addition to another agent, and would require a large number of patients from a very limited pool. In this patient population with very limited therapeutic options and no firmly established standard of care, a single-arm trial is an acceptable design to evaluate the single-agent activity.

The Phase 2 dose (25 mg/kg every 21 days) is based on the ongoing Phase 1 first time in human study (MI-CP187), which evaluates the safety, tolerability, and antitumor activity of MEDI-575 in advanced solid tumors refractory to standard therapy. In MI-CP187, a standard

3+3 dose-escalation study, MEDI-575 was evaluated at doses up to 15 mg/kg once every 7 days and 25 and 35 mg/kg every 21 days. No DLTs were identified at any doses, demonstrating that MEDI-575 appears to be tolerable. The Phase 2 dose was chosen based on PK/pharmacodynamic modeling using preclinical pharmacology models, as well as analysis in the Phase 1 study.

In preclinical tumor xenograft studies, using lung cancer models, MEDI-575 demonstrated maximal activity at average intravascular concentrations of approximately 250 µg/mL. Higher concentrations did not result in superior antitumor activity. Glioblastoma multiforme models were the most sensitive to MEDI-575, demonstrating maximal activity at an approximately 10-fold lower dose than other solid tumor models. In the Phase 1 study of MEDI-575, a minimum trough concentration of 150 µg/ml resulted in maximal pharmacodynamic response, as measured by circulating PDGF-AA. Pharmacokinetic analysis demonstrates that at a dose of 9 mg/kg every 7 days or 25 mg/kg every 21 days, the serum trough concentration of MEDI-575 is expected to be above this value of 150 µg/mL throughout the dosing interval and the average concentration is at or above 250 µg/mL.

In general, large molecules such as monoclonal antibodies do not cross the blood brain barrier (BBB), which may pose difficulty in achieving adequate drug levels of MEDI-575 in the treatment of GBM. Despite this, there are preclinical and clinical data suggesting that sufficient drug levels may be achieved in this disease setting. Disruption of the BBB occurs in brain ischemia, malignancies, and neurodegenerative disorders including Alzheimer disease (Morita et al, 1999; Wolburg et al, 2003). Gliomas, particularly GBM, disrupt the BBB and cause brain edema that contributes to morbidity and mortality. Breakdown of the BBB and the formation of edema are well characterized hallmarks of brain tumors and are intrinsic to their pathogenesis and clinical effects (Stummer, 2007). Electronic microscopic studies have revealed that brain tumors induce tight-junction openings that become more pronounced with increasing malignancy (Nir et al, 1989). Tight-junction protein expression is altered *in situ* in anaplastic astrocytomas and GBM and in vitro treatment with GBM-derived factors, resulting in the disruption of the barrier function of brain-derived endothelial cells (Isihara, 2008). In one mouse model of Alzheimer's disease (Banks et al, 2007), a monoclonal immunoglobin M has been shown to cross the BBB to target amyloid. At least two antibodies have been studied in humans for their ability to cross the BBB. In patients with multiple sclerosis, rituximab, which targets CD20 on B-cells, has been shown to be present in the cerebrospinal fluid (CSF) up to 24 weeks following systemic administration (Petereit, 2009). In another study, trastuzumab, which targets human epidermal growth factor 2 present on metastatic breast cancer, was shown to be present in the CSF following

systemic administration, and levels were increased with disruption to the BBB caused by radiotherapy (Stemmler et al, 2007). Although these data are not specific to GBM, they suggest that there is a reasonable likelihood that MEDI-575 will cross the BBB and be able to target tumors expressing PDGFRα, especially in the setting of a disrupted BBB occurring in GBM.

4 Study Procedures

4.1 Subject Participation and Identification

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

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

4.2 Subject Selection and Withdrawal

The subjects in this study will be adults with first recurrence of GBM (Stage IV malignant glioma) following first-line therapy of temozolomide and radiation. The investigator (physician) or qualified designee will discuss the study with a subject/legal representative of a subject who is considered a potential candidate for the study and provide the subject/legal representative with the study-specific informed consent form(s) approved by the IRB/IEC. The investigator or designee will address any questions and/or concerns that the subject/legal representative may have and, if there is continued interest, will secure written informed consent for participation in the study. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] authorization in the USA and European Union [EU] Data Privacy Directive authorization in the EU), will be obtained prior to conducting any protocol-specific procedures, including screening evaluations or medication washouts. See Section 10.3 for additional details concerning informed consent.

4.2.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1) 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

2) Age ≥18 years old at the time of screening

3) Histologically confirmed diagnosis of World Health Organization Grade IV malignant glioma (glioblastoma or gliosarcoma)

4) Previous first line treatment with radiotherapy and temozolomide (treatment prior to radiation and temozolomide permitted, [ie, Gliadel])

5) Documented first recurrence of GBM by diagnostic biopsy or by contrast-enhanced magnetic resonance imaging (MRI) as per *Updated Response Assessment Criteria of High Grade Gliomas- Neuro-Oncology Working Group* (see Appendix 5, Wen et al, 2010)

6) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (see Appendix 1)

7) Life expectancy ≥ 12 weeks

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

9) Adequate hematologic function defined as:

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

10) 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;
   - Calculated creatinine clearance (CrCl) ≥ 50 mL/min as determined by the Cockcroft-Gault equation (Cockcroft and Gault, 1976)

11) Provide consent to allow collection of archived tumor samples

12) Negative serum beta human chorionic gonadotropin (βHCG) test (women only)

13) Women of childbearing 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 contraceptive precautions for 90 days after the final dose of investigational product; cessation of birth control after this point should be discussed with a responsible physician

14) 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 Criterion 13 above and must agree to continue using such contraceptive precautions from Cycle 1, Study Day 1 through 90 days after the final dose of investigational product

4.2.2 Exclusion Criteria

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

1) Treatment with any investigational agent 30 days prior to study entry

2) Concurrent enrollment in another clinical study involving an investigational agent

3) Employees of the clinical study site or any other individuals involved with the conduct of the study, or immediate family members of such individuals

4) Any chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for treatment of cancer within 30 days prior to study entry

5) Previous mAb treatment specifically directed against PDGF or PDGF receptors

6) Previous bevacizumab or other VEGF and anti-angiogenic treatment

7) More than 1 recurrence of GBM

8) Any surgery (not including minor diagnostic procedures) within 2 weeks prior to baseline disease assessments; or not fully recovered from any side effects of previous procedures

9) History of serious allergy or reaction to any component of the MEDI-575 formulation

10) New York Heart Association $\geq$ Grade 2 congestive heart failure within 6 months prior to study entry (see Appendix 3)

11) Uncontrolled or significant cardiovascular disease, including:

- Myocardial infarction and transient ischemic attack or stroke within 6 months prior to enrollment
- Uncontrolled angina within 6 months

- Diagnosed or suspected congenital long QT syndrome
- Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes);
- Clinically significant abnormality on electrocardiogram (ECG)

12) History of other invasive malignancy within 5 years prior to study entry 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

13) Any evidence of active infection requiring the use of systemic antimicrobial treatment within 72 hours prior to initial treatment with MEDI-575

14) History of active human immunodeficiency virus or active hepatitis B or C viral infection will be excluded to eliminate the risk of increased AEs due to immune compromise.

15) Systemic immunosuppressive therapy. Subjects taking corticosteroids must be on a stable dose for 7 days prior to initiation of treatment with MEDI-575

16) Presence of extracranial metastatic or leptomeningeal disease

17) Pregnancy or lactation

18) 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

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

20) Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results

21) Patients who can not safely undergo MRI due to pacemakers, metal implants, infusion catheters or other metal device.

4.2.3 Withdrawal Criteria

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

1) Withdrawal of consent or lost to follow-up

2) Adverse event that, in the opinion of the investigator or medical monitor, contraindicates further dosing

3) Subject is determined to have met 1 or more of the exclusion criteria for study participation

4) Pregnancy

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

Lost to follow-up: Subjects will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status at the end of study (defined as 9 months from the date the last subject is entered into the trial or when the sponsor stops the study).

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

Permanent discontinuation of treatment: Subjects who are permanently discontinued from further receipt of treatment, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment. Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study (see Section 4.6).

Subjects who are permanently discontinued from receiving treatment will be followed for safety through 90 days after the last dose of treatment, including the collection of any protocol-specified blood or urine specimens, unless the subject withdraws consent, is lost to follow-up, or has enrolled in another clinical study.

4.2.4 Replacement of Subjects

Subjects will not be replaced in this study.

4.3 Treatment Assignment

An IWRS will be used for assignment of unblinded investigational product to the subject. A subject is considered entered into the study when the investigator notifies the IWRS that the subject meets eligibility criteria and the IWRS provides the assignment of unblinded investigational product to the subject.

The procedure for using IWRS is as follows:

- The investigator or designee contacts the IWRS and provides the SID number and subject's baseline characteristic(s) used to verify the subject's identification
- Confirmation of this information is sent to the investigator/designee who dispenses the assigned treatment to the subject per the communication and records the appropriate information in the subject's medical records and investigational product accountability log

MEDI-575 must be administered within 48 hours after treatment assignment. If there is a delay in the administration of treatment such that it will not be administered within the specified timeframe, the study monitor must be notified *immediately*.

4.4 Blinding

This is an open-label study.

4.5 Study Treatment

4.5.1 Investigational Product Supplies and Accountability

Investigational product will be supplied to the site in open-label containers. Detailed instructions are provided in the Investigational Product Manual.

Investigational product will be distributed to clinical sites using designated distribution centers. MedImmune will provide the investigator(s) with adequate quantities of investigational product. MEDI-575 must be stored in the refrigerator at 2°C to 8°C (36°F to 46°F).

MEDI-575: MEDI-575 is supplied in vials as a 20-mg/mL solution, 200 mg/vial for dilution. Formulation: [redacted].

Diluent: Normal saline, 250 or 500 mL bag (based on subject weight) for dilution of MEDI-575 to be provided by the clinical site.

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

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

4.5.2 Treatment Regimens

Subjects will be treated with MEDI-575 at 25 mg/kg on Day 1 every 21 days until documentation of disease progression, initiation of alternative anticancer therapy, unacceptable toxicity, or another reason for treatment discontinuation (see Section 4.2.3) is observed. In Cycle 2 and beyond, a dose can be delayed up to 7 days for unavoidable scheduling issues. MEDI-575 may be withheld for up to 21 days until resolution to ≤ Grade 1 toxicity after agreement with the sponsor. Subjects who demonstrate stable disease or better may continue to receive MEDI-575 under the criteria above. Each new cycle will begin no fewer than 21 days after the last dose of the previous cycle.

Subjects who receive any number of doses of MEDI-575 and proceed to surgical resection as subsequent therapy for GBM may be asked to allow procurement of resected tissue to determine intratumoral levels of MEDI-575.

4.5.3 Investigational Product Preparation

The dose of investigational product for administration must be prepared by the investigator's or site's designated investigational product manager using aseptic technique. Detailed instructions regarding investigational product preparation can be found in the Investigational Product Manual that will be provided to the investigator's or site's designated investigational product manager.

The dose of investigational product will be calculated based on the subject's screening body weight (obtained prior to the first administration of MEDI-575) .The weight collected at

screening is considered the baseline weight and will be used to calculate the dose of investigational product unless a change in weight of ± 10% occurs. If there is a ± 10% change in weight, the new weight will be used for dose calculation and will be considered the new baseline weight. The dose volume of MEDI-575 will be calculated using the following formula:

Dose Volume (mL) = 25 (mg/kg) × Subject Weight (kg) ÷ Concentration (20 mg/mL)

For subjects weighing < 140 kg, MEDI-575 is prepared for administration by dilution into the appropriate volume of normal saline to a final volume of 250 mL. For subjects weighing ≥ 140 kg, the final volume will be 500 mL.

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.

4.5.4 Investigational Product Administration

The day of receipt of the first dose of MEDI-575 is considered Day 1.

MEDI-575 administration must be completed within 6 hours after IV bag preparation. If the dose cannot be completely administered within 6 hours, a new dose must be prepared using a new vial or vials as the investigational product contains no bacteriostatic agents.

MEDI-575 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 minutes using a protein-sparing/low in-line filter, as specified in the Investigational Product Manual.

4.5.4.1 Monitoring of Dose Administration

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

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

4.5.4.2 Dose-limiting Toxicities

Dose-limiting toxicity rate will be analyzed after the first 15 subjects have completed the first cycle of treatment. If the DLT rate equals or exceeds 30%, further enrollment will be suspended to evaluate safety. The MedImmune SMC will be consulted prior to resumption of enrollment.

The period for evaluating DLTs will be from the time of first administration of MEDI-575 through the first 21-day cycle. Grading of DLTs will be according to the National Cancer Institute Common Terminology Toxicity Criteria for Adverse Events (Appendix 2).

A DLT is defined as:

1. Any Grade 3 or higher non-hematologic toxicity that occurs during the DLT assessment period and is suspected of a causal relationship to MEDI-575 with the following exceptions:

    a. Grade 3 fever (in the absence of neutropenia) that resolves to normal or baseline within 24 hours of treatment and is not considered an SAE; or

    b. Grade 3 rigors/chills that respond to optimal therapy

2. Any Grade 3 or higher hematologic toxicity suspected of a casual relationship to MEDI-575.

4.5.4.3 Dose Modification for 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 (see Table 4.5.4.3-1). Both hematologic and nonhematologic toxicities will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 (Appendix 2). A cycle will be considered complete after administration of 1 dose of MEDI-575 for all cycles.

Table 4.5.4.3-1 MEDI-575 Dose Modification Table

Hematologic or Nonhematologic Toxicity Attributable to MEDI-575 alone	Dose Modification of MEDI-575
≤ Grade 1	None
Grade 2	MEDI-575 may be withheld for up to 21 days until resolution to ≤ Grade 1 or baseline and resume at current dose level after discussion with the medical monitor. If subjects experience Grade 2 toxicities that are clinically manageable MEDI-575 may be continued at the current dose and schedule following consultation with the medical monitor. Grade 2 electrolyte abnormalities that can be alleviated through electrolyte replacement do not require dose delay or reduction. Discontinue MEDI-575 if withheld for > 21 days without resolution of toxicity to ≤ Grade 1 or baseline unless clearly attributable to another cause such as disease progression, concomitant therapy or accident.
Grade 3 or 4	**First Occurrence:** Withhold MEDI-575 for up to 21 days until resolution to ≤ Grade 1 or baseline. Restart MEDI-575 at 50% of the starting dose. Subjects who experience Grade 3 or Grade 4 laboratory abnormalities or AEs without associated clinical findings that resolve to ≤ Grade 1 or baseline within 21 days will not require dose modification or discontinuation Discontinue MEDI-575 if withheld for > 21 days without resolution of toxicity to ≤ Grade 1 or baseline. **Second Occurrence:** Discontinue MEDI-575.

4.5.5 Concomitant Medications

Use of concomitant medications, including over-the-counter medications, herbal supplements, and vitamins from the first day of administration of MEDI-575 through 30 days after the last dose is discouraged. However, subjects may receive medications as supportive care or to treat AEs as deemed necessary by the investigator or the subject's physician.

All concomitant medications given to the subject from the time of signing of the informed consent form (ICF) through 30 days after the last dose of MEDI-575 will be recorded in the source document.

4.5.6 Treatment Compliance

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

4.6 Subject Completion

An individual subject will be considered to have completed the study if followed through the end of the study (defined as 9 months after the last subject has entered the trial or when the sponsor stops the study), regardless of the number of doses of treatment received. Subjects who demonstrate stable disease or better may continue to receive MEDI-575 after study completion following further consultation with the sponsor. Subjects will be considered to not have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.2.3).

4.7 End of the Study

End of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study. This date will be 9 months after the last subject is entered into the trial or when the sponsor stops the study. All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon study completion as directed by the site monitor. The investigator will notify the IRB/IEC when the study has been completed.

5 Assessment of Efficacy and Clinical Pharmacology

5.1 Efficacy and Clinical Pharmacology Parameters

The efficacy profile for MEDI-575 will be assessed using PFS-6, time to response (TTR), duration of response (DR), time to progression (TTP), PFS, and OS (see Section 7.3.2).

5.2 Schedule of Study Procedures

All subjects who are assigned an SID number and receive any treatment will be followed according to the protocol regardless of the number of doses received, unless consent is withdrawn. The investigator must notify the sponsor or designee of deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original scheduled visit. Protocol deviations will be recorded in the source document with an explanation for the deviation and any study-specific electronic case report forms (eCRFs) or logs designated for capturing protocol deviations, if

applicable for the study. The investigator must comply with the applicable requirements related to reporting of protocol deviations to the IRB/IEC.

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

Schedules of study procedures for the screening and treatment period as well as the follow-up period are presented in Table 5.2-1 and Table 5.2-2 , respectively, followed by a description of each visit. A description of the study procedures is included in Section 5.3

Table 5.2-1 Schedule of Study Procedures: Screening and Treatment Period

Procedure	Screening	Treatment Period Cycle 1			Cycles ≥ 2	Every 2 Cycles, Beginning With Cycle3	Treatment Discontinuation
	Day -28 to Day -1	Day 1	Day 8	Day 15	Day 1 (+7 days)	Day 1 (-7 days)	
Written informed consent and HIPAA/assignment of SID number	X						
Verify eligibility criteria	X						
Medical history	X						
Physical examination	X	X			X		X
Weight (-1 day allowed)	X	X			X		X
Height	X						
Vital signs	X	X			X		X
Serum chemistry (-1 day allowed)	X	X	X	X	X		X
Hematology (-1 day allowed)	X	X	X	X	X		X
Coagulation parameters (-1 day allowed)	X	X			X		X
Routine urinalysis (-1 day allowed)	X	X	X	X	X		X
Serum pregnancy test	X						
Urine pregnancy test		X			X		
12-lead ECG	X						X
12-lead ECG prior to infusion		X			X		
12-lead ECG post infusion (+ 5 minutes)		X					

Table 5.2-1 Schedule of Study Procedures: Screening and Treatment Period

Procedure	Screening	Treatment Period Cycle 1			Cycles ≥ 2	Every 2 Cycles, Beginning With Cycle3	Treatment Discontinuation
	Day -28 to Day -1	Day 1	Day 8	Day 15	Day 1 (+7 days)	Day 1 (-7 days)	
ECOG Performance Status	X	X			X		X
PRO: EORTC QLQ-C30 (-3 days allowed)	X	X			X		X
PRO: EORTC QLQ-BN20 (-3 days allowed)	X	X			X		X
Mandatory archived tumor sample	X						
Anti-MEDI-575 antibodies		X			X		X
MEDI-575 serum concentration		X	X	X	X		X
Circulating soluble proteins	X	X	X	X	X		X
Circulating apoptotic markers	X	X		X	X		X
Circulating mRNA/miRNA	X		X				X
DNA analysis (optional)	X						
MRI scan	X					X	X
Assessment of AEs/SAEs	X	X	X	X	X		X
Concomitant medications	X	X	X	X	X		X

Table 5.2-1 Schedule of Study Procedures: Screening and Treatment Period

Procedure	Screening	Treatment Period Cycle 1			Cycles ≥ 2	Every 2 Cycles, Beginning With Cycle3	Treatment Discontinuation
	Day -28 to Day -1	Day 1	Day 8	Day 15	Day 1 (+7 days)	Day 1 (-7 days)	
MEDI-575 administration		X			X		
Optional tumor tissue sample							X

AE = adverse event; DNA = deoxyribonucleic acid, ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, EORTC = European Organization of Research and Treatment of Cancer, HIPAA = Health Insurance Portability and Accountability Act, mRNA = messenger ribonucleic acid; miRNA = micro ribonucleic acid; MRI = magnetic resonance imaging, PRO = patient reported outcomes, QLQ = quality of life questionnaire; RNA = ribonucleic acid; SAE = serious adverse event ; SID = subject identification

Table 5.2-2 Schedule of Study Procedures: Follow-up Period

Procedure	Follow-up/Post Therapy	
	30-Days After Last Dose (+ 3 days) 60-Days After Last Dose (± 5 days) 90-Days After Last Dose (± 5 days)	**Every 3-Months After Last Dose (±2 weeks)**
Physical examination	X	X (focused physical exam)
12-lead ECG	X (30-day post visit only)	
Vital signs, including weight	X	
Hematology	X	
Serum chemistry	X	
Routine urinalysis	X	
Urine pregnancy test	X (90-day post visit only)	
AE/SAE assessment	X	
Concomitant medications	X (30-day post visit only)	
MRI scan		X
ECOG Performance Status	X	X
Subsequent anticancer therapy	X	X
Survival status	X	X
MEDI-575 serum concentration	X	
Anti-MEDI-575 antibodies	X	X (first 3-month visit only)
Circulating soluble proteins	X	
Circulating apoptotic markers	X	

AE = adverse event; ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group; MRI = magnetic resonance imaging; SAE = serious adverse event

5.2.1 Screening (All Subjects)

All screening procedures must be performed within 28 days prior to the first dose of treatment (Day -28 to Day -1), unless otherwise specified. The screening evaluations may be carried out over more than one visit. Written informed consent and any locally required authorization (eg, HIPAA in the USA, EU Data Privacy Directive authorization in the EU) must be obtained prior to performing any protocol-specified procedures, 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 evaluations need not be repeated if the subject/legal representative consents to allow use. The following evaluations/procedures will be performed during screening:

1) Obtain written informed consent and appropriate privacy act document authorization
2) Assign an SID number via IWRS
3) Verify eligibility criteria
4) Obtain medical history
5) Perform complete physical examination
6) Obtain vital signs, including height and weight (-1 day allowed for weight)
7) Obtain 12-lead ECG
8) Collect blood samples for:
    - Serum chemistry (-1 day allowed)
    - Hematology (-1 day allowed)
    - Coagulation parameters (-1 day allowed)
    - Serum pregnancy test
    - Circulating soluble proteins
    - Circulating apoptotic markers
    - Circulating messenger ribonucleic acid (mRNA)/microRNA (miRNA)
    - DNA analysis (optional)
9) Collect urine for screening sample (-1 day allowed)
10) Collect archive tissue for biomarker screening sample
11) Measure tumors using MRI
12) Assess for AEs and SAEs
13) Record concomitant medications

14) Assess for ECOG performance status

15) Administer Patient Reported Outcome (PRO) questionnaires (-3 days allowed):

- European Organization of Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30
- EORTC QLQ-BN20

16) Enroll subject if all eligibility criteria are met

5.2.2 Treatment Period

5.2.2.1 Cycle 1, Day 1: First Infusion

The following evaluations will be performed on Day 1 of Cycle 1:

1) Perform directed physical examination (if applicable, record new findings as AEs or SAEs)

2) Assess for AEs and SAEs since screening visit

3) Update concomitant medications

4) Obtain vital signs (temperature, blood pressure, pulse, respiratory rate) including weight prior to infusion (-1 day allowed for weight)

5) Assess ECOG performance status

6) Collect blood for baseline samples prior to infusion:

- Serum chemistry (-1 day allowed)
- Hematology (-1 day allowed)
- Coagulation parameters (-1 day allowed)
- Anti-MEDI-575 antibodies
- MEDI-575 serum concentration
- Circulating soluble proteins
- Circulating apoptotic markers

7) Collect urine for routine urinalysis and urine pregnancy test; ensure result is negative (-1 day allowed)

8) Perform 12-lead ECG prior to infusion and post infusion (+ 5 minutes)

9) Administer PRO questionnaires (-3 days allowed)

- EORTC QLQ-C30
- EORTC QLQ-BN20

10) Administer MEDI-575 infusion

11) Obtain vital signs at the end of the infusion (± 5 minutes) and 30 minutes post-completion of infusion (± 5 minutes)

12) Obtain blood for PK analysis:

- MEDI-575 serum concentration: immediately post-completion of infusion (± 5minutes)

5.2.2.2 Cycle 1, Day 8

The following evaluations will be performed on Day 8 of Cycle 1:

1) Collect blood samples for:

- Serum chemistry
- Hematology
- MEDI-575 serum concentration
- Circulating soluble proteins
- Circulating mRNA/miRNA

2) Collect urine for routine urinalysis

3) Assess for AEs and SAEs

4) Update concomitant medications

5.2.2.3 Cycle 1, Day 15

The following evaluations will be performed on Day 15 of Cycle 1:

1) Collect blood samples for:

- Serum chemistry
- Hematology
- MEDI-575 serum concentration
- Circulating soluble proteins
- Circulating apoptotic markers

2) Collect urine for routine urinalysis

3) Assess for AEs and SAEs

4) Update concomitant medications

5.2.3 Cycle 2 and Beyond, Day 1 (+7 Days)

The following evaluations will be performed on Day 1 of Cycle 2 and all subsequent cycles:

1) Perform directed physical examination (if applicable, record new findings as AEs or SAEs)
2) Assess for AEs and SAEs
3) Update concomitant medications
4) Obtain vital signs (temperature, blood pressure, pulse, respiratory rate) including weight prior to infusion (-1 day allowed for weight)
5) Assess ECOG performance status
6) Collect blood for baseline samples prior to infusion:
   - Serum chemistry (-1 day allowed)
   - Hematology (-1 day allowed)
   - Coagulation parameters (-1 day allowed)
   - Anti-MEDI-575 antibodies
   - MEDI-575 serum concentration
   - Circulating soluble proteins
   - Circulating apoptotic markers
7) Collect urine for routine urinalysis and urine pregnancy test (women of childbearing potential only. (-1 day allowed)
8) Perform 12-lead ECG prior to infusion
9) Administer PRO questionnaires (-3 days allowed)
   - EORTC QLQ-C30
   - EORTC QLQ-BN20
10) Administer MEDI-575 infusion
11) Obtain blood for PK analysis:
   - MEDI-575 serum concentrations: Immediately after (± 5 minutes) completion of infusion
12) Assess for AEs/SAEs observed during treatment

5.2.4 Every 2 Cycles, Beginning with Cycle 3

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) Assess for disease response:

- MRI scan (within 7 days prior to start of cycle)

5.2.5 Treatment Discontinuation Visit

The following evaluations will be performed at the time (or up to 5 days after) the subject completes therapy or is withdrawn/discontinued from the study therapy, or at the time of first objective disease progression, whichever comes first. Any procedures conducted within 14 days before treatment discontinuation (eg, procedures conducted on Day 1 of a cycle) do not need to be repeated at the treatment discontinuation visit.

1) Perform complete physical examination (if applicable, record new findings as AEs or SAEs)
2) Assess for AEs and SAEs
3) Update concomitant medications
4) Obtain vital signs (temperature, blood pressure, pulse, respiratory rate) including weight (-1 day allowed for weight)
5) Assess ECOG performance status
6) Collect blood samples for:
   - Serum chemistry (-1 day allowed)
   - Hematology (-1 day allowed)
   - Coagulation parameters (-1 day allowed)
   - Anti-MEDI-575 antibodies
   - MEDI-575 serum concentration
   - Circulating soluble proteins
   - Circulating apoptotic markers
   - Circulating mRNA/miRNA
7) Collect urine for routine urinalysis (-1 day allowed)
8) Perform 12-lead ECG

9) Obtain consent and collect fresh tissue tumor biopsy (optional)

10) Administer PRO questionnaires (-3 days allowed)

- EORTC QLQ-C30
- EORTC QLQ-BN20

11) Disease evaluations:

- MRI scan

5.2.6 Follow-up Period (All Subjects)

5.2.6.1 30-Days (Plus 3 days) After Last Treatment

The following evaluations will be performed 30 days (+ 3 days) after the last treatment as specified:

1) Perform complete physical examination (if applicable, record new findings as AEs or SAEs)

2) Assess survival status and AEs and SAEs since the time of discontinuation until the subject begins another anticancer therapy

3) Obtain vital signs (temperature, blood pressure, pulse, respiratory rate) including weight

4) Assess ECOG performance status

5) Obtain 12-lead ECG

6) Collect blood samples for:

- Serum chemistry
- Hematology
- Anti-MEDI-575 antibodies
- MEDI-575 serum concentration
- Circulating soluble proteins
- Circulating apoptotic markers

7) Collect urine for routine urinalysis

8) Update concomitant medications; ascertain whether subsequent anticancer therapy has been initiated

5.2.6.2 60 and 90 Days (Plus or Minus 5 Days) After Last Treatment

The following evaluations will be performed 60 and 90 days (± 5 days) after the last treatment as specified:

1) Perform complete physical examination (if applicable, record new findings as AEs or SAEs)
2) Assess survival status, AEs, and SAEs since the time of discontinuation until the subject begins another anticancer therapy
3) Obtain vital signs (temperature, blood pressure, pulse, respiratory rate) including weight
4) Assess ECOG performance status
5) Collect blood samples for:
   - Serum chemistry
   - Hematology
   - Anti-MEDI-575 antibodies
   - MEDI-575 serum concentration
   - Circulating soluble proteins
   - Circulating apoptotic markers
6) Collect urine for routine urinalysis and urine pregnancy test (women of childbearing potential only (90-day post visit only).
7) Record subsequent anticancer therapy

5.2.6.3 Every 3 Months (Plus or Minus 14 Days) After Last Treatment

The following evaluations will be performed every 3 months (± 14 days) after the last treatment as specified (for 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 9 months post the date the last subject is entered on the trial or when sponsor stops the study]):

1) Evaluation of disease
   - MRI scan
   - Focused physical examination
   - ECOG performance status

2) Blood collection for anti-MEDI-575 antibodies (3-month post visit only)

3) Survival status and subsequent anticancer therapy must be collected in every subject regardless of the reason for treatment discontinuation. Assessment can be either performed on a clinic visit or telephone contact until death or the end of the study

5.3 Description of Study Procedures

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

5.3.1 Medical History, Physical Examination, ECG, Weight, and Vital Signs

Complete physical examinations will be performed as described in Table 5.2-1 and Table 5.2-2 by a licensed independent healthcare provider (ie, physician, physician's assistant, or licensed nurse practitioner). It will include an assessment of head, eyes, ears, nose and throat, respiratory, cardiovascular, gastrointestinal (GI), urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, and endocrine systems; and height (at screening only).

Vital signs will be collected as described in Table 5.2-1 and Table 5.2-2. Vital signs include temperature, blood pressure (seated), pulse rate, and respiratory rate and weight (when indicated).

Twelve-lead ECGs will be performed as described in Table 5.2-1 and Table 5.2-2. Electrocardiograph 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 electrocardiograms will be transmitted and interpreted by a central vendor selected by the sponsor.

5.3.2 Clinical Laboratory Tests

Clinical laboratory safety tests including serum pregnancy tests will be performed in a licensed clinical laboratory. Clinically significant abnormal laboratory tests should be repeated as soon as possible (preferably within 24 to 48 hours). Clinically significant abnormal labs should be repeated subsequently at the investigator's discretion. These tests can be collected up to 1 day in advance of treatment Day 1 in each cycle.

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

Serum Chemistry

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

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

Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Platelet count
- Hemoglobin

Urinalysis

- pH
- Protein
- Blood
- Glucose
- Ketones
- Bilirubin

Pregnancy Test (women of childbearing potential only)

- Urine human chorionic gonadotropin (hCG)
- Serum βHCG (at screening only)

Other Safety Tests

- Coagulation parameters: prothrombin time (PT), partial thromboplastin time (PTT), and fibrinogen, international normalized ratio (INR)

5.3.3 Pharmacokinetic Evaluation and Methods

The timepoints for PK sampling are described in Table 5.2-1 and Table 5.2-2. A competitive electrochemiluminescence assay using a Meso Scale Discovery® (MSD) platform will be used for the quantitative determination of MEDI-575 in human serum.

Details of PK sample collection are provided in the laboratory manual.

5.3.4 Immunogenicity Evaluation and Methods

Presence of anti-MEDI-575 antibodies will be assessed prior to infusion of MEDI-575 on Day 1 of each cycle as well as at the end of treatment and during follow up. Details for sample collection will be provided in the laboratory manual.

5.3.5 Biomarker Evaluation and Methods

Blood samples will be analyzed to evaluate protein, deoxyribonucleic acid (DNA), and mRNA/miRNA biomarkers that relate to MEDI-575 treatment. For the assessment of MEDI-575 pharmacodynamic activity, plasma levels of PDGF-AA ligand will be measured at baseline and in response to MEDI-575 treatment. In addition to evaluating circulating levels of PDGF-AA, multiplex protein analysis may be utilized to evaluate circulating levels of soluble proteins related to tumor-associated factors, angiogenesis, and growth factors that may include, but are not limited to, PDGF, fibroblast growth factor (FGF), VEGF, fibronectin, osteopontin, transforming growth factor (TGF), and hepatocyte growth factor (HGF), and to explore their association with MEDI-575 treatment and clinical outcome. Circulating apoptotic markers will be evaluated by determining nucleosomal DNA levels at baseline and in response to treatment using either an enzyme linked immunosorbent assay (ELISA) or reverse transcription polymerase chain reaction (RT-PCR) as a biomarker for tumor apoptosis. Messenger RNA profiling from whole blood samples may be performed and gene expression analysis will examine the potential relationship between inhibition of PDGF-related genes, clinical activity, and other circulating factors. Additionally, the miRNA expression pattern in the periphery of subjects enrolled may be examined.

In tissue samples which have been collected prior to study entry (mandatory archival samples), expression of PDGF signaling protein by immunohistochemistry (IHC) analysis may include, but is not limited to, PDGFRα, PDGF ligands, and EGFR. Additionally, for tumor cells that stain intensely for PDGFRα, an analysis of genomic amplification may be

performed. The expression level of PDGFRα in tumor cells and tumor stroma including intensity of staining and distribution of staining will be evaluated for any relationship to treatment with MEDI-575.

If fresh tumor biopsy samples obtained following discontinuation of treatment with MEDI-575 are available (optional), the presence of MEDI-575 in the tumor tissue will be evaluated using IHC, ELISA, or mass spectrometry. If sufficient tissue is collected then the relationship of growth factor receptor pathways and related components at the protein mRNA and miRNA levels may be evaluated from tumor biopsies obtained post-treatment using IHC, proteomic analysis, TaqMan QRTPCR assays, and/or microarray studies. These factors may include but are not limited to, PDGFR, EGFR, insulin-like growth factor-1 receptor (IGF1R), VEGFR2, and associated growth factors (PDGF, HGF, VEGF, FGF, insulin-like growth factor [IGF], and interleukins). These studies serve the purpose of evaluating MEDI-575 drug levels in the tumor and, if possible, molecular characteristics of the tumor and relationship with MEDI-575 treatment. If enough tumor tissue and blood samples are available, a competitive allele-specific TaqMan-based-PCR assay will be used to evaluate potential point mutations in the key genes such as PDGFRα, EGFR, phosphoinositide 3-kinase (PI3k), phosphatase and tensin homolog and their correlations with clinical activity of MEDI-575. Additionally, the TaqMan low density array based assays may be used to evaluate miRNA profile in the tissue, plasma and/or whole blood of patients pre- and post-MEDI-575 dosing.

Other biomarkers may be evaluated as determined by additional data. Details for collection will be provided in the laboratory manual.

5.3.6 Patient-reported Outcomes

The European Organization of Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and the 20-item EORTC QLQ brain cancer module (EORTC QLQ-BN20) are self administered and are to be completed by the subject without the assistance of the investigational site personnel. All questionnaires should be completed if possible before any other study procedures are conducted at the study visit. If a subject anticipates that he/she will be unable to complete the questionnaire on Day 1 of a cycle visit, the questionnaire may be completed within 3 days prior to the schedule Day 1 visit provided there is another reason for the subject to be in the clinic prior to the assessment time point. If the questionnaire cannot be completed within 3 days prior to dosing Day 1, subjects will be allowed to complete the questionnaire following the infusion.

5.3.6.1 EORTC QLQ-C30 and EORTC QLQ-BN20

The EORTC QLQ-C30 is a 30-item self-administered questionnaire that consists of 5 functional scales (physical, role, cognitive, emotional and social functioning), 3 symptom scales (fatigue, pain, and nausea, and vomiting), and a number of single items assessing additional symptoms commonly reported by cancer patients (eg, dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties). In addition, a disease-specific 20-item, self-administered questionnaire for brain cancer (EORTC QLQ-BN20) was developed comprising both multi-item and single-item measures of brain-cancer-associated symptoms (eg. fatigue and sleep disturbance, emotional, physical, role, and social functioning, and global quality of life) (Osoba et al, 1996) to be used in conjunction with the EORTC QLQ-C30.

Subjects will be asked to rate each item on a 4-point scale (eg, for the preceding week, they will be asked, “Have you had pain?” and will then be asked to choose among “Not at all, a little, quite a bit, or very much.”). Each of the multi-item scales includes a different set of items - no item occurs in more than 1 scale. All of the scales and single-item measures range in score from 0 to 100. Scores are then transformed onto a 0-100-point scale. For the 5 functional scales, higher scores represent better level of functioning. For the symptom scales, higher scores represent worse symptoms. (Aaronson et al, 1993).

5.3.7 Disease Evaluation and Methods

Tumor measurements and assessments will be based on *Updated Response Assessment Criteria of High Grade Gliomas- Neuro-Oncology Working Group* (Wen et al, 2010) (see Appendix 4 and Appendix 5) and will be performed as specified in Table 5.2-1 and Table 5.2-2. Tumor assessments include an MRI scan of the brain. Additional tumor assessments 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. It is recommended to use the same MRI scanner or one with same magnet strength throughout the assessments.

Blinded central independent imaging review of response and disease progression will be utilized. Details of study-specific procedures for collection and shipment of images will be provided in a separate manual.

Measurability of Tumor Lesions

Measurable disease is defined as bidimensionally contrast enhancing lesions with clearly defined margins by MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip. In the event the MRI is performed with thicker slices, the size of a measurable lesion at baseline should be two times the slice thickness.10 In the event there are interslice gaps, this also needs to be considered in determining the size of measurable lesions at baseline. Measurement of tumor around a cyst or surgical cavity represents a particularly difficult challenge. In general, such lesions should be considered nonmeasurable unless there is a nodular component measuring 10 mm in diameter. The cystic or surgical cavity should not be measured in determining response. (Wen et al, 2010).

Nonmeasurable disease is defined as either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm. (Wen et al, 2010).

Number of Lesions

If there are multiple contrast-enhancing lesions, a minimum of the two largest lesions should be measured, and the sum of the products of the perpendicular diameters of these lesions should be determined. A maximum of five of the largest lesions may be measured; the largest enlarging lesion(s) should be selected, with emphasis placed on lesions that allow reproducible repeated measurements.

For patients with recurrent disease who have multiple lesions of which only one or two are increasing in size, the enlarging lesions should be considered the target lesions for evaluation of response. The other lesions will be considered nontarget lesions and should also be recorded. Rarely, unequivocal progression of a nontarget lesion requiring discontinuation of therapy or development of a new contrast enhancing lesion may occur, even in the setting of stable disease or partial response in the target lesions. These changes would qualify as progression.

Evaluation of Overall Response

Table 5.3.7-1 provides overall responses for possible combinations of tumor responses.

Table 5.3.7-1 Evaluation of Overall Response

Criterion	Response Category			
	CR	**PR**	**SD**	**PD**
T1 gadolinium enhancing disease	None	≥50% ↓	< 50% ↓but < 25% ↑	≥25% ↑[a]
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑[a]
New lesion	None	None	None	Present[a]
Corticosteroids	None	Stable or ↓	Stable or ↓	NA[†]
Clinical status	Stable or ↑	Stable or ↑	Stable or ↑	↓[a]
Requirement for response	All	All	All	Any[a]

↓ = decreased, ↑ = increased ; CR = complete response, FLAIR = fluid attenuated inversion recovery; NA = not applicable; PD = progressive disease; PR = partial response, SD = stable disease,

[a] Progression occurs when this criterion is present

Source: Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorenson AG, Galanis E, et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group; J Clin Oncol. 2010Apr10;28(11):1963-72.

5.3.8 Estimate of Volume of Blood to Be Collected

No more than 35 mL of blood will be drawn on a per-day basis across all tests combined on days in which blood is collected. The estimated volume of blood to be collected during the first treatment cycle is 115 mL whereas 30 mL will be collected during every subsequent cycle. The total volume to be collected for all subjects will depend on the number of cycles administered and the length of follow-up.

6 Assessment of Safety

6.1 Safety Parameters

6.1.1 Adverse Events

The ICH Guideline for Good Clinical Practice E6(R1) defines an AE as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal

relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

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

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

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious).

6.1.2 Serious Adverse Events

A serious adverse event (SAE) is any AE that:

- Results in death
- Is immediately life-threatening

  This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that may have led to death.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting.

- Results in persistent or significant disability/incapacity

  The term disability means a substantial disruption of a person's ability to conduct normal life functions.

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

- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

  Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

6.1.3 Other Events of Special Interest

6.1.3.1 Hepatic Function Abnormality

A hepatic function abnormality of special interest to the sponsor is defined as any increase in ALT or AST to greater than 3× ULN **and concurrent** increase in bilirubin to greater than 2× ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder or an agent other than the investigational product).

6.1.3.2 Infusion Reaction

Any infusion related reaction resulting in permanent discontinuation of investigational product must be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety or designee using the Fax Notification Form (see Section 6.4.2.2 for contact information)

6.2 Assessment of Safety Parameters

6.2.1 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.03 as provided in Appendix 2. The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

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

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

6.2.2 Assessment of Relationship

6.2.2.1 Relationship to Investigational Product

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

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

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

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

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

6.2.2.2 Relationship to Protocol Procedures

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

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

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

6.3 Recording of Safety Parameters

6.3.1 Recording of Adverse Events and Serious Adverse Events

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

6.3.2 Recording of Other Events of Special Interest

Special interest events will be recorded on the eCRF using recognized medical terms or diagnosis that accurately reflects the event in the same manner all AEs and SAEs are captured as described in Section 6.3.1. See Section 6.1.3 for definitions of events of special interest and Section 6.4.4 for additional reporting requirements.

Hepatic Function Abnormality

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

- If an event of hepatic function abnormality is considered to be related to a pre-existing condition and does not represent a worsening of this condition and/or is considered to be within the range of normal physiological fluctuation for the subject, the event does not meet the definition of an AE and does not need to be recorded as such.
- If a definitive diagnosis for an underlying condition unrelated to the investigational product is established for an event of hepatic function abnormality, the diagnosis should be recorded as an AE/SAE per Section 6.3.1.
- If no definitive diagnosis is determined for an event of hepatic function abnormality, the term "hepatic function abnormal" should be used to report the AE/SAE per Section 6.3.1.

6.4 Reporting Requirements for Safety Parameters

6.4.1 Study Reporting Period and Follow-up for Adverse Events

The reporting period for AEs is the period immediately following the time that written informed consent is obtained through 90 days post the last dose of treatment or until the subject begins another anticancer therapy, whichever occurs first. New (nonserious) AEs that start after the reporting period will not be collected.

All AEs will be followed to resolution through the end of subject participation in the study, even if the date extends beyond the reporting period.

6.4.2 Reporting of Serious Adverse Events

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

The reporting period for nontreatment and treatment-emergent SAEs is the period immediately following the time that written informed consent is obtained through 90 days post the subject's last dose of treatment or until the subject begins another anticancer therapy, whichever occurs first. The reporting period for protocol-related SAEs (see Section 6.2.2.2) is the period immediately following the time that written informed consent is obtained through the end of subject participation in the study. After submitting an initial SAE report for a subject (to MedImmune Patient Safety), the investigator is required to follow the subject proactively and provide further information on the subject's condition to MedImmune Patient Safety or designee.

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

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

6.4.2.2 Notifying the Sponsor of Serious Adverse Events

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

MedImmune or designee

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

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

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

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

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

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

6.4.3 Other Events Requiring Immediate Reporting

6.4.3.1 Overdose

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

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety or designee using the Fax Notification Form (see Section 6.4.2.2 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE CRF (see Section 6.3.1). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.4.3.2 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 6.1.3.1) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information), unless a definitive underlying diagnosis for the abnormality (eg, cholelithiasis and bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor. If the etiology of the event remains unconfirmed and/or is considered related to investigational product (see Section 6.2.2.1), a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by the MedImmune SMC (see Section 6.5) to determine whether continued dosing of current study subjects and/or study entry should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the MedImmune SMC is required for resumption of subject dosing or study entry in the event that the study is interrupted. Where applicable, regulatory authorities and IRBs/IECs will be notified of any actions taken with the study.

6.4.3.3 Pregnancy

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

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

6.4.3.4 Events Meeting Study Stopping Criteria

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

6.4.4 Study Reporting Period for Other Events of Special Interest

Any infusion reaction of a study subject with the investigational product causing permanent discontinuation of dosing with investigational product, with or without associated AEs/SAEs,

is required to be reported within 24 hours of knowledge of the event to MedImmune Patient Safety or designee using the Fax Notification Form (see Section 6.4.2.2 for contact information). An infusion reaction does not automatically make an AE serious, but if the consequences of the reaction are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.5 Safety Management During the Study

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

The MedImmune SMC, chaired by the MedImmune Chief Medical Officer, provides safety surveillance, guidance, and oversight for all clinical development studies in which MedImmune has sponsor accountabilities. In addition to the Chief Medical Officer, SMC members include the heads of Patient Safety, Clinical Development, and Regulatory Affairs, and external physician members with expertise in relevant therapeutic areas. The SMC reviews protocol-specific safety data at regularly scheduled meetings and ad hoc meetings, and provides oversight for individual study protocol safety committees. Based on review of safety data, the SMC may suspend enrollment or subject dosing in clinical studies, request modification of study documents, or take other actions as deemed necessary.

7 Statistical Considerations

7.1 General Considerations

Data will be provided in data listings sorted by SID. Tabular summaries will be presented such that categorical data will be summarized by the number and percentage of subjects in each category and continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals (CIs) will be 2-sided, unless otherwise stated. Details of endpoint analyses will be described in the Statistical Analysis Plan.

7.2 Analysis Populations

The intent-to treat (ITT) population will include all subjects entered into the study. The ITT population is the primary population for the efficacy analyses and the summary of baseline characteristics.

The evaluable population will include all subjects who received at least 1 dose of MEDI-575 and had at least 1 post-baseline disease assessment. The evaluable subject population will be the secondary population for efficacy analysis.

The safety population will include all subjects who receive at least 1 dose of MEDI-575 and will be used to summarize the safety assessments.

7.3 Endpoints

7.3.1 Primary Endpoint

The primary objective of this study is to evaluate the PFS-6 in adult subjects with a first recurrence of GBM who are treated with MEDI-575.

The PFS-6 rate will be summarized and its 2-sided 90% CI will be calculated based on the Kaplan-Meier method (Kaplan and Meier, 1958).

7.3.2 Secondary Endpoints

The secondary objectives of this study are to evaluate other antitumor activities of MEDI-575; describe the safety and tolerability of MEDI-575; and evaluate the expression of PDGFRα in the tumor cells in archival tumor samples in this subject population. Endpoints related to these objectives are described below.

7.3.2.1 Secondary Endpoints of Antitumor Activity of MEDI-575

Assessments of other antitumor activities include ORR, TTR, DR, TTP, PFS, and OS. *The Updated Response Assessment Criteria of High Grade Gliomas - Neuro-Oncology Working Group* (Wen et al, 2010) will be used to determine tumor response.

- Objective response rate is defined as the proportion of subjects with confirmed CR or confirmed PR according to the *Updated Response Assessment Criteria of High*

Grade Gliomas- Neuro-Oncology Working Group (Wen et al, 2010). Confirmed responses are those that persist on repeat imaging studies at least 4 weeks after the initial documentation of response. The 2-sided 90% and 95% CIs of ORR will be estimated using the exact probability method.

- Time to response will be measured from the start of MEDI-575 administration to the first documentation of response (CR or PR) and will only be assessed in subjects who have achieved objective response.
- Duration of response will be defined as the duration from the first documentation of objective response to the first documented disease progression. Duration of response will be censored on the date of last tumor assessment documenting absence of disease progression for subjects who have no documented progression prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Duration of response will only be evaluated for the subgroup of subjects with an objective response and will be assessed using the Kaplan-Meier method.
- Time to progression will be measured from the start of treatment with MEDI-575 until the documentation of disease progression. Time to progression will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Subjects having no tumor assessments after the start of treatment with MEDI-575 will have TTP censored on the first date of treatment with MEDI-575. Time to progression will be evaluated using the Kaplan-Meier method.
- Progression-free survival 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. Progression-free survival will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression and are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Subjects having no tumor assessments after the start of treatment with MEDI-575 will have PFS censored on the first date of treatment with MEDI-575. Progression-free survival will be evaluated using the Kaplan-Meier method.
- Overall survival 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. Overall survival will be evaluated using the Kaplan-Meier method.

7.3.2.2 Secondary Endpoints of Safety and Tolerability of MEDI-575

Secondary safety endpoints of this study include:

- Adverse events and SAEs occurring from the signing of an ICF to 90 days after the last dose or until the subject begins another anticancer therapy, whichever occurs first.

- Changes in clinical laboratory and ECG evaluations from baseline.

7.3.2.3 Expression of PDGFR alpha

Archival tissue samples and, when available, fresh tumor biopsy samples will be evaluated using IHC. Expression of PDGFRα in tumor cells and/or tumor stromal cells will be evaluated for intensity and distribution of staining and relationship with clinical endpoints and circulating soluble factors associated with cancer-associated fibroblasts and/or a PDGF-AA paracrine mechanism of action. The percentage of target positive subjects will be described if there are sufficient data. Descriptive statistics will be used to summarize data.

7.3.3 Exploratory Endpoints

7.3.3.1 Pharmacokinetics and Immunogenicity of MEDI-575

7.3.3.1.1 Non-Compartmental Analysis

The PK of MEDI-575 will be assessed using parameters including peak concentration (C_{max}), time to peak concentration (T_{max}), and area under the concentration-time curve within a dosing interval (AUC_{τ}) after the first dose. MEDI-575 steady state PK parameters including peak concentration ($C_{ss,\ max}$), trough concentration ($C_{ss,\ min}$), and time to peak concentration ($T_{ss,\ max}$) will be estimated. All PK parameters will be estimated by non-compartmental analysis. The highest observed concentration will be recorded as C_{max} and the time to C_{max} will be recorded as T_{max}. Accumulation to steady state will be assessed as the ratio of $C_{ss,max}$:C_{max}.

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable anti-MEDI-575 antibodies.

7.3.3.1.2 Population Pharmacokinetic-Pharmacodynamic Analysis

A population PK model will be developed using a non-linear mixed-effects modeling approach. Pharmacokinetic compartmental model incorporating both linear and target-mediated clearances will be used to characterize the PK of MEDI-575 in subjects with GBM. Sequential PK-pharmacodynamic modeling will be performed to explore the relationship between MEDI-575 exposure (antibody serum concentration) and biomarkers, such as PDGF-AA ligand in plasma. Exposure response modeling will be performed to examine the

relationship between MEDI-575 serum exposure and clinical endpoints. The impact of physiologically-relevant subject characteristics (covariates) and disease on PK, pharmacodynamic parameters (and possibly clinical endpoints) will be tested. The final population PK-pharmacodynamic model will be validated using standard techniques such as visual predictive check or bootstrapping.

7.3.3.2 Exploratory Analysis

Descriptive statistics will be used to describe the exploratory analyses. The following variables may be included in the exploratory analysis:

- PDGF-AA levels at baseline and in response to MEDI-575 treatment
- Selected circulating soluble proteins such as proteins related to cancer-associated fibroblasts, angiogenesis and cytokines using multiplex proteomic analysis that may include but are not limited to PDGF, FGF, VEGF, fibronectin, osteopontin, TGF, HGF; at baseline and in response to treatment
- mRNA profiling from whole blood samples may be performed and gene expression analysis will examine the potential relationship between inhibition of PDGF-related genes, clinical activity and other circulating factors. The miRNA expression pattern in the periphery of subjects enrolled may also be examined. Circulating apoptotic markers will be measured by determining nucleosomal DNA using either ELISA assays or RT-PCR to evaluate tumor cell apoptosis in response to treatment.
- When fresh tumor biopsy samples are available (optional), an evaluation of the presence of MEDI-575 in tumor tissue will be performed
- Patient-reported outcomes as measured by the EORTC QLQ-C30 and the EORTC QLQ-BN20 will be summarized descriptively. Additionally, these endpoints will be summarized individually; with change from baseline for both domain and subscale scores by time point and change from baseline to be explored.

7.4 Interim Analysis

No formal interim analysis will be performed during this trial.

7.5 Sample Size and Power Calculations

The primary objective of this study is to evaluate the PFS-6 in adult subjects with a first recurrence of GBM who are treated with MEDI-575. The sample size estimation is based on the assumption that the historical PFS-6 rate in this population is $\leq 16\%$ (null hypothesis). This is because the estimated PFS-6 rate for irinotecan single agent in recurrent GBM from a

single-arm Phase 2 trial was 15.8% (Prados, 2006). Using a 1-sample nonparametric test for survival probability (Brookmeyer and Crowley, 1982) and assuming the desired PFS-6 rate for MEDI-575 is 30%, a total of 50 subjects will provide 80% power to have a statistically significant test outcome at the 2-sided significance level of 0.1, accrual period of 12 months, and a follow-up period of 6 months. Assuming a drop-out rate of 10%, a total of 55 subjects will be required to enter this study.

Table 7.5-1 presents the power for detecting different PFS-6 rates for MEDI-575 at a 2-sided significance level of 0.1 with 50 subjects assuming a historical PFS-6 rate of 16%.

Table 7.5-1 Power Calculation for Sample Size of 50 Subjects Based on Nonparametric Test for Survival Probability

Sample Size	Historical PFS-6 Rate (Null Hypothesis)	Desirable PFS-6 Rate for MEDI-575	Power (%)
50	16%	25%	55
50	16%	28%	72
50	16%	30%	80
50	16%	32%	86
50	16%	35%	92

PFS-6 - progression-free survival at 6 months

Note: Based on an accrual period of 12 months and a follow-up period of 6 months

The study will be considered positive if the lower bound of the 2-sided 90% CI for PFS-6 rate is $\geq$ 16%.

7.6 Data Safety Monitoring Board

As an open-label study, no formal data safety monitoring board will be employed. Safety monitoring will be performed by the medical monitor who will regularly review rates and types of AEs. Results will be reported to the MedImmune SMC at regular intervals.

8 Direct Access to Source Documents

The study will be monitored by the sponsor on a regular basis throughout the study period. During monitoring visits, the investigator will provide direct access to all source documentation relevant to the subject's participation in the study. Source documentation includes, but is not limited to, the subject's clinic and/or office chart, hospital chart, informed

consent forms, treatment notes, laboratory reports, pharmacy records, radiographs, recorded data from automated instruments, and any other records maintained to conduct and evaluate the clinical study. The investigator must also ensure that direct access to study documents be made available for study-related audits, IRB/IEC review, or regulatory inspection.

9 Quality Control and Quality Assurance

9.1 Data Collection

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol. Case histories include CRFs and supporting data including, but not limited to, signed and dated informed consent forms, progress notes, hospital charts, nurse's notes, diary cards, laboratory reports, ECG strips, etc.

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

9.2 Study Monitoring

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

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

The monitor will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter. The monitor will assess subject enrollment and informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto validated data collection instruments (paper CRF or electronic

data screen) against original source documents; and the occurrence of AEs/SAEs. All aspects of the study will be carefully monitored for compliance with the protocol, applicable regulatory requirements, GCP, and the site's standard operating procedures.

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

9.3 Audit and Inspection of the Study

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

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

10 Ethics

10.1 Regulatory Considerations

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC that approves this study to be conducted in its territory. Good clinical practice is defined as a

standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study subjects are protected.

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

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

10.2 Institutional Review Board or Independent Ethics Committee

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

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

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

will be submitted to the IRB/IEC and written verification that the modification was submitted should be obtained.

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

10.3 Informed Consent

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

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

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

11 Data Handling and Record Keeping

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

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

12 Financing and Insurance

Financing and insurance are addressed in the individual site contracts.

13 Publication Policy

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

14 References

Aaronson NK, Ahmedzai S, Bergman B, et al., for The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

Alvarez RH, Kantarjian HM, Cortes JE. Biology of platelet-derived growth factor and its role in disease. Mayo Clin Proc. 2006 Sep;81(9):1241-57.

Baccarani M, Cilloni D, Rondoni M, Ottaviani E, Messa F, et al. The efficacy of imatinib mesylate in patients with FIP1L1-PDGFRα-positive hypereosinophilic syndrome. Results of a multicenter prospective study. Haematologica 2007 Sep;92:1173-9.

Ballman KV, Buckner JC, Brown PD, Giannini C, Flynn PJ, et al. The relationship between six-month progression-free survival and 12-month overall survival end points for Phase II trials in patients with glioblastoma multiforme. Neuro. Oncol. 2007 Jan;9(1),29-38.

Banks WA, Farr SA, Morley JE, Wolf KM, Geylis V, Steinitz M. Anti-amyloid beta protein antibody passage across the blood-brain barrier in the SAMP8 mouse model of Alzheimer's disease: An age-related selective uptake with reversal of learning impairment, Experimental Neurology. 2007 May 22;206:248-56.

Batchelor TT, Sorensen AG, di Tomaso E et al. AZD2171, a pan-VEGF receptor tyrosin kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer Cell. 2007 Jan;11:83-95.

Bauman JE, Eaton KD, Martins RG. Antagonism of platelet-derived growth factor receptor in non-small cell lung cancer: rationale and investigation. Clin Cancer Res. 2007 Aug01;13(15 Suppl).

Brandes AA, Tosoni A, Basso U, et al. Second-line chemotherapy with irinotecan plus carmustine in glioblastoma recurrent or progressive after first-line temozolomide chemotherapy: a phase II study of the Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). J Clin Oncol. 2004 Dec 01;22(23):4779-86.

Brandes AA, Tosoni A, Franceschi E, Reni M, Gatta G, et al. Glioblastoma in Adults. Crit Rev Oncol Hematol. 2008(67)139-152.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics 1982; 38: 29–41.

Buitenhuis M, Verhagen LP, Cools J, Coffer PJ. Molecular mechanisms underlying FIP1L1-PDGFRA-mediated myeloproliferation. Cancer Res. 2007 Apr 15;67(8):3759-66.

Carvalho I, Milanezi F, Martins A, Reis RM, Schmitt F. Overexpression of platelet-derived growth factor α in breast cancer is associated with tumour progression. Breast Cancer Res. 2005 Aug 01;R788-95.

Central Brain Tumor Registry of the United States. Statistical report: Primary brain tumors in the United States, 2004-2007 (February 2011). . http://www.cbtrus.org/2010-NPCR-SEER/CBTRUS-WEBREPORT-Final-3-2-10.pdf.

Chang SM, Butowski NA, Sneed PK, Garner IV. Standard treatment and experimental targeted drug therapy for recurrent glioblastoma multiforme. Neurosurg Focus. 2006;20(4).

Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol. 2004 Sep15;22:3813-25.

Franceschi E, Cavallo G, Scopece L, et al. Phase II trial of carboplatin and etoposide for patients with recurrent high-grade glioma. Br J Cancer 2004 Aug10;91:1038-44.

Franceschi E, Cavallo G, Lonardi S et al. Gefitinib in patients with progressive high grade-gliomas; a multicentre PhaseII study of Gruppo Italiano Cooperative di Neuro-Oncologia (GICNO). Br J. Cancer. 2007 Mar 13;96(7):1047-51.

Franceschi E, Tosoni A, Bartolini S, Mazzocchi V, Fioravanti A, et al. Treatment Options for Recurrent Glioblastoma: Pitfalls and Future Trends. Expert Rev. Anticancer Ther. 2009,9(5);613-619.

Fredriksson L, Li H, Eriksson U. The PDGF family: four gene products form five dimeric isoforms. Cytokine Growth Factor Rev. 2004 Aug;15(4):197-204.

Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009 Oct 01;27:4733-40.

Galanis E, Bucker JC, Maurer MJ et al. Phase II trial of temsirolimus (CCI-779) in recurrent glioblastoma multiform: A North Central Cancer Treatment Group Study. J. Clin. Oncol. 2005 Aug 10;23(23)5294-304.

Ishihara H, Kubota H, Lindberg RL, Leppert D, Gloor SM, et al. Endothelial cell barrier impairment induced by glioblastomas and transforming growth factor beta2 involves matrix metalloproteinases and tight junction proteins. J Neuropathol Exp Neurol. 2008 May;67(5):435-48.

Jayson GC, Parker GJM, Mullamitha S, Valle JW, Saunders M, et al. Blockade of Platelet-Derived Growth Factor Receptor-Beta by CDP860, a Humanized, PEGlyated di-Fab', Leads to Fluid Accumulation and Is Associated with Increased Tumor Vascularized Volume. J Clin Oncol. 2005 Feb;23(5): 973-981.

Kaplan, EL and Meier, P. Non-parametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53:457-81.

Kreisl TN, Kim L, Moore K, Duic P, Royce C, et al. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol. 2009;27(5):740–745.

Loizos N, Xu Y, Huber J, Liu M, Lu D, Finnerty B, et al. (2005). Targeting the platelet-derived growth factor receptor alpha with a neutralizing human monoclonal antibody inhibits the growth of tumor xenografts: Implications as a potential therapeutic target. Mol. Cancer Ther. 2005;4(3):369-79.

Morita K, Sasaki H, Furuse M, Tsukita, S. Endothelial claudin: claudin-5/TMVCF constitutes tight junction strands in endothelial cells. J Cell Biol. 1999;147:185-94.

National Cancer Institute [Internet]. US National Institutes of Health. Adult Brain Tumors Treatment (PDQ®) [updated 07/08/10; cited 13Aug2010]. Available at: http://www.cancer.gov/cancertopics/pdq/treatment/adultbrain/HealthProfessional.

Nir I, Levanon D, Iosilevsky G. Permeability of blood vessels in experimental gliomas: Uptake of 99mTC-glucoheptonate and alteration in blood-brain barrier as determined by cytochemistry and electron microscopy. Neurosurgery 1989;25:523-31.

Oken MM, Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5:649-55.

Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsu MA, Yung WKA, et al. The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. Quality of Life Research. 1996 Feb;5:139-50.

Östman A. PDGF receptors-mediators of autocrine tumor growth and regulators of tumor vasculature and stroma. Cytokine and Growth Factor Reviews. 2004 Aug;15:275-86.

Petereit HF, Rubbert-Roth A. Rituximab levels in cerebrospinal fluid of patients with neurological autoimmune disorders. Mult Scler. 2009 Feb;15(2):189-92.

Pinsker M, Lumenta C. Experiences with reoperation on recurrent glioblastoma multiforme. Zentralbl Neurochir. 2002;62,43-47.

Prados MD, Lamborn K, Yung WKA, Jaeckle K, Robins HI, et al. A phase 2 trial of irinotecan (CPT-11) in patients with recurrent malignant glioma: A North American Brain Tumor Consortium study. Neuro-Oncology. 2006; 8(2)189-93.

Reardon DA, Fink KL, Mikkelsen T et al. Randomized Phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme. J Clin.Oncol. 2008 Dec 01:26:5610-17.

Reardon DA, Quinn JA, Vredenburgh J, et al: Phase II trial of irinotecan plus celecoxib in adults with recurrent malignant glioma. Cancer. 2005 Jan 15;103:329-38.

Reardon, DA and Wen PY. Therapeutic advances in the treatment of glioblastoma: Rationale and potential role of targeted agents. The Oncologist. 2006 Feb;11:152-64.

Rich JN, Reardon DA, Peery T et al. Phase II trial of gefitinib in recurrent glioblastoma. J Clin Oncol. 2004. Jan 01; 22:133-42.

Rosenthal MA, Ashley DL, Cher L. BCNU as second line therapy for recurrent high-grade glioma previously treated with temozolomide. J Clin Neurosci. 2004 May;11:374-75.

Shih AH, Holland EC. Platelet-derived growth factor (PGDF) and glial tumorigenesis. Cancer Letters. 2006 Feb;232:139-47.

Sleijfer S, Wiemer E, Verweij J. Drug insight: gastrointestinal stromal tumors (GIST)-the solid tumor model for cancer-specific treatment. Nat Clin Pract Oncol. 2008 Feb;5(2):102-11.

Stemmler HJ, Schmitt M, Willems A, Bernhard H, Harbeck N, Heinemann V. Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood-brain barrier. Anticancer Drugs. 2007 Jan;18(1):23-8.

Stupp R, Mason WP, van den Bent MJ et al. Radiotherapy plus concomitant and adjuvant temozolamide for glioblastoma. N Engl. J. Med. 2005 Mar10;352:987-96.

Stummer W. Mechanisms of tumor-related brain edema. Neurosurg Focus 2007;22:1-7.

Van den Bent MJ, Brandes AA, Rampling R et al. Randomized Phase II trial of erlotinib versus temozolomide or carmustine in recurrent glioblastoma: EORTC brain tumor group study 26034. J Clin. Oncol. 2009 Mar 10;27:1268-74.

Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorenson AG, Galanis E, et al. Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group; J Clin Oncol. 2010 Apr 10;28(11):1963-72.

Wolburg H, Wolburg-Buchholz K, Kraus J, Rascher-Eggstein G, Liebner S, et al. Localization of claudin-3 in tight junctions of the blood-brain barrier is selectively lost during experimental autoimmune encephalomyelitis and human glioblastoma multiforme. Acta Neuropathol. 2003;105:586-92.

15 Summary of Protocol Amendments and Administrative Changes to the Protocol

Protocol Amendment 1, 19 May 2011

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Major changes to the protocol are summarized below.

Title Page:

A new medical monitor was assigned to this study. Therefore, the name, title and contact information for the Medical Monitor was updated.

Study Abstract:

Abstract was updated to be consistent with the changes made to the body of the protocol.

Section 1.2.3 (Clinical Experience with MEDI-575):

Preliminary safety data from the ongoing Phase 1 study of MEDI-575 was updated to include the following observed toxicities: nausea, hypokalemia, muscle spasms, decrease appetite and diarrhea.

Preliminary efficacy data from the ongoing Phase 1 study of MEDI-575 was updated to show that 33% of subjects achieved a best response of stable disease and that the median duration of that response was 2.9 months.

Interim PK analysis data was updated.

Section 3.1 (Overview of Study Design):
Section 4.5.2 (Treatment Regimens):

The following text was added to provide additional time for participants to complete their cycle visits, “In Cycle 2 and beyond, a dose can be delayed up to 7 days for unavoidable scheduling issues. MEDI-575 may be withheld for up to 21 days until resolution to ≤ Grade 1 toxicity after agreement with the sponsor”.

Section 3.3 (Study Stopping Criteria):

Text was added to clarify that the study will be stopped and no additional subjects will be enrolled if the DLT rate is greater than 30% in the first 15 subjects enrolled in the study.

Section 4.2.1 (Inclusion Criteria):

Inclusion criterion (10) which describes adequate organ function was revised to clarify the procedure to calculate creatine clearance.

Inclusion criteria (13 and 14) contraceptive precautions were extended to 90 days to mirror safety follow up period

Section 4.2.2 (Exclusion Criteria):

Exclusion criterion (21) was added to exclude patients who can not safely undergo MRI due to pacemakers, metal implants, infusion catheters or other metal device.

Section 4.5.1 (Investigational Product Supplies and Accountability):

[redacted] was added to revised MEDI-575 formulation

Section 4.5.3 (Investigational Product Preparation):

The following text was added to clarify the weight used for dose calculation: “The weight collected at screening is considered the baseline weight and will be used to calculate the dose of investigational product unless a change in weight of ± 10% occurs. If there is a ± 10% change in weight, the new weight will be used for dose calculation and will be considered the new baseline weight.”

Section 4.5.5.1 (Monitoring of Dose Administration):

MedImmune study-specific safety committee paragraph was deleted since is repetitive and describes the role of SMC which is already described in section 6.5.

Section 4.5.4.2 (Dose-limiting Toxicities):

This section was added to describe the Dose limiting toxicity (DLT) analysis that will be performed after the first 15 subjects complete the first cycle of treatment. Section also includes the definition of DLT.

Section 4.6 (Subject Completion):

The following text was added to clarify future treatment options for those subjects who present stable disease or better “Subjects who demonstrate stable disease or better may

continue to receive MEDI-575 after study completion following further consultation with the sponsor".

Section 5 and subsections (Assessments of Efficacy and Clinical Pharmacology):

References to CT scan were removed to ensure consistency with allowable modalities of tumor assessments. For purposes of this protocol only MRI is allowed as required for RANO criteria.

-1 day window was added to allow for laboratory assessments and weight collection for ease of subject scheduling

Review ECG schedule to monitor ECG at baseline and the minimum and maximum concentrations, at steady-state, and at end of study as requested by FDA

The pharmacokinetic schedule was revised on Cycle 1 Day 8 to correct inconsistency between table 5.2.1 and text 5.2.2.2 noted by FDA

Tables 5.2-1 was updated to include windows for dose delays in Cycle 2 and beyond.

Section 4.2.3 (Withdrawal Criteria)

Section 5.2.6.2 (60 and 90 Days (Plus or Minus 5 Days) After Last Treatment):

Section 6.4.1 (Study Reporting Period and Follow-up for Adverse Events)

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

Section 7.3.2.2 (Secondary Endpoints of Safety and Tolerability of MEDI-575)

The safety follow up period is being extended to 90 days to ensure that the MEDI-575 level is lower than the lower limit of quantification

Section 5.2.6.2 60 and 90 Days (Plus or Minus 5 Days) After Last Treatment

Table 5.2-2 Schedule of Study Procedures: Follow-up Period

Pregnancy test was added to 90 day follow up visit. The safety follow up period is being extended to 90 days to ensure that the MEDI-575 level is lower than the lower limit of quantification.

Section 5.2.6.3 (Every 3 Months (Plus or Minus 14 days) After last Assessment:

Section was reviewed to clarify that survival status and subsequent anticancer therapy must be collected in every subject regardless of the reason for treatment discontinuation.

Section 5.3.2 (Clinical Laboratory Tests):

Clarify that clinically significant abnormal results should be repeated as soon as possible

Add Phosphorous and Carbon dioxide/bicarbonate in serum chemistry assessment

Note for serum chemistries for AST, ALT and ALP was added to ensure that they are conducted and assessed concurrently.

Section 5.3.6 (Patient Reported Outcomes):

Review patient reported outcome schedule for ease of subject scheduling

Section 6.1.3.1 (Hepatic function Abnormality):

Section 6.3.2 (Recording of Other Events of Special Interest):

Section 6.4.3 (Other Events Requiring Immediate Reporting):

Sections were added to define hepatic functional abnormality, interpretation, recording and reporting. Sections were added as part of MedImmune new protocol template.

Sections 6.4.3.4 (Events Meeting Study Stopping Criteria)

Section 6.5 (Safety Management During the Study)

Sections were added and revised to comply with the new approved protocol template.

Section 7.5:

Significance level of 0.1 with 50 subjects was revised for consistency

Appendix 6 and 7

Text was updated to note that patient reported outcome questionnaires (EORTC QLQ-C30 and EORTC QLQ-BN20) are currently part of the Study Operations Manual

Appendix 1 ECOG Performance Status and Definitions

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

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Source: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 2 National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.03

http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Appendix 3 New York Heart Association Cardiac Performance Status Assessment Function Scale

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

Source: The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256

Appendix 4 Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
Complete response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial response	Requires all of the following: ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Response	Criteria
Progression	Defined by any of the following: ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids[*]; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy[*] not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

Note: All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.
Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery.
[*] Stable doses of corticosteroids include patients not on corticosteroids.

Appendix 5 Summary of the Proposed RANO Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥50% ↓	< 50%↓ but < 25%↑	≥25% ↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA†
Clinical status	Stable or ↑	Stable or↑	Stable or ↑	↓*
Requirement for response	All	All	All	Any*

RANO, Response Assessment in Neuro-Oncology; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; FLAIR, fluid-attenuated inversion recovery; NA, not applicable.

* Progression occurs when this criterion is present.

† Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Appendix 6 Patient Reported Outcome Questionnaire EORTC QLQ-C30

Final questionnaires are provided as part of the Study Operations ManuaL

Appendix 7 Patient Reported Outcome Questionnaire: EORTC QLQ-BN20

Final questionnaires are provided as part of the Study Operations ManuaL