A Phase 1, Multicenter, Open-label, Single-arm, Dose-escalation Study to Evaluate the Safety, Tolerability, and Antitumor Activity of MEDI-573, a Fully Human Monoclonal Antibody Directed Against Insulin-like Growth Factors I and II, in Subjects with Advanced Solid Tumors Refractory to Standard Therapy or for Which No Standard Therapy Exists

Investigational Product: MEDI-573

MedImmune Protocol Number: MI-CP184

IND Number: IND 103091

Manufacturer: MedImmune
[redacted]
Phone: [redacted]
Fax: [redacted]

Sponsor: MedImmune

Medical Monitor: [redacted]

Study Monitor: MedImmune
[redacted]
Phone: [redacted]

Protocol Date: [redacted]

Principal Investigator Agreement:

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

Signature_____ Date_____

Printed Name_____

Title_____

Phone_____

List of Abbreviations

Abbreviation	Definition
AE	Adverse event
Akt	Protein kinase B
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration curve
βhCG	β human chorionic gonadotropin
BWS	Beckwith-Wiedemann Syndrome
CAST	Competitive allele-specific TaqMan-based PCR
CBC	Complete blood count
CFR	Code of Federal Regulations
CIS	Carcinoma in situ
CL	Clearance
C_{max}	Maximum observed serum concentration
CR	Complete response
CrCl	Creatinine clearance
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	Ductal carcinoma in situ
DLT	Dose-limiting toxicity
DR	Duration of response
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good clinical practice
GH	Growth hormone
HbA1c	Glycosylated hemoglobin
HCC	Hepatocellular carcinoma
HEENT	Head, eyes, ears, nose, and throat
hIGF	Soluble recombinant human IGF
HIPAA	Health Insurance Portability and Accountability Act
IEC	Independent Ethics Committee
IGF	Insulin-like growth factor
IgG2λ	Immunoglobulin G2 lambda

Abbreviation	Definition
IGFBP	IGF-binding protein
IM	Immunogenicity
IND	Investigational New Drug Application
IP	Investigational Product
IR	Insulin receptor
IRB	Institutional Review Board
IRE	Immediate reportable event
IRS	Insulin receptor substrate
IV	Intravenous
KLH	Keyhole Limpet Hemocyanin
KPS	Karnofsky performance status
LD	Longest diameter
LDH	Lactate dehydrogenase
MAPK	Mitogen-activated protein kinase
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
miRNA	Microribonucleic acid
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NMP	Nuclear matrix protein
NOAEL	No observable adverse effect level
NSCLC	Non-small cell lung cancer
OBED	Optimal biologically effective dose
ORR	Objective response rate
OS	Overall survival
PAHA	Primate anti-human antibody response
pAkt	Akt signaling protein
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetics
pMAPK	Phosphorylated mitogen activated protein kinase signaling protein
PR	Partial response
qRT-PCR	Quantitative real-time polymerase chain reaction
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Definition
RNA	Ribonucleic acid
SAE	Serious adverse event
SD	Stable disease
SID	Subject Identification Number
SMC	Safety Monitoring Committee
T_{max}	Time to peak concentration
TLDA	TaqMan Low Density Array
TTR	Time to response
TTP	Time to progression
TUNEL	Deoxyuride-5'-triphosphate biotin nick end labeling
TURBT	Transurethral resection of bladder tumor
ULN	Upper limit of normal
US	United States of America
WFI	Water for injection

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Study Abstract

Title:

A Phase 1, Multicenter, Open-label, Single-arm, Dose-escalation Study to Evaluate the Safety, Tolerability, and Antitumor Activity of MEDI-573, a Fully Human Monoclonal Antibody Directed Against Insulin-like Growth Factors I and II, in Subjects with Advanced Solid Tumors Refractory to Standard Therapy or for Which No Standard Therapy Exists

Objectives:

The primary objectives of this study are to:

1) Evaluate the safety and tolerability of MEDI-573 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists; and
2) Determine the maximum tolerated dose (MTD) or optimal biologically effective dose (OBED) of MEDI-573 in subjects with solid tumors.

The secondary objectives of this study are to:

1) Describe the pharmacokinetics (PK) of MEDI-573;
2) Determine the immunogenicity (IM) of MEDI-573;
3) Determine the pharmacodynamics of MEDI-573 on circulating plasma levels of insulin-like growth factor-1 (IGF-1) and insulin-like growth factor-2 (IGF-2);
4) Observe any antitumor activity of MEDI-573 in subjects with solid tumors

The exploratory objectives of this study are to:

1) Determine levels of circulating soluble proteins that may include but are not limited to growth hormone (GH), IGF-binding proteins (IGFBPs), insulin, and glucose, and explore associations with clinical outcome;
2) Assess levels of phosphorylated and/or unphosphorylated factors in specimens. These factors may include but are not limited to IGF receptor type 1 (IGF-1R), insulin receptor substrate-1 (IRS-1), mitogen-activated protein kinase (MAPK), insulin receptor (IR), antigen identified by monoclonal antibody Ki-67 (Ki67), caspase 3, and/or protein kinase B signaling protein (Akt) in archived tumor biopsies, biopsies obtained during surgical procedures conducted in the course of routine patient care, and/or exfoliated cells collected in voided urine, catheterized urine, and/or bladder washings. Deoxyuride-5'-triphosphate biotin nick end labeling (TUNEL) analysis may also be performed.

3) Evaluate the relationship of IGF pathway-related components at the messenger ribonucleic acid (mRNA) and microribonucleic acid (miRNA) level, including IR-A mRNA level in tumor biopsies obtained pre- and post-MEDI-573 treatment using TaqMan quantitative real-time polymerase chain reaction (qRT-PCR) assays and microarray studies.

4) Evaluate the relationship of IGF pathway-related factors including IR expression levels using whole genome array with subject tumor response to MEDI-573.

5) Perform genomics and proteomics analyses on exfoliated cells collected in bladder washings from selected subjects in the dose-expansion phase

6) For the dose-expansion phase, evaluate the expression level of IGF pathway-related factors such as IGF-1R on subject response to MEDI-573 when circulating tumor cells are available

7) For the dose-expansion phase, evaluate the levels of proteins in urine that may include but are not limited to IGF-1, IGF-2, IGFBPs, and nuclear matrix protein (NMP), and explore their relationship with clinical outcome.

Study Design:

This is a Phase 1, multicenter, open-label, single-arm, dose-escalation and dose-expansion study to evaluate the safety, tolerability, and antitumor activity of MEDI-573 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. Approximately 10 investigational sites in the USA will participate in this study, with cohorts of 3 to 6 evaluable subjects each receiving 1 of 5 dosage levels of MEDI-573 [redacted] every 7 days in the dose-escalation phase of the study (Cohorts 1 through 5). Two additional dose escalation cohorts will evaluate an alternate every-3-week treatment schedule: [redacted] (Cohort 6) and [redacted] (Cohort 7, if applicable) administered as [redacted] intravenous (IV) infusion on Day 1 of each 21-day cycle. [redacted]. Subjects in the dose escalation phase are considered evaluable if they receive 3 doses of MEDI-573 (Cohorts 1 through 5) or 1 dose of MEDI-573 (Cohorts 6 and 7) and are followed for 21 days from the date of first dose (one cycle) or they discontinue MEDI-573 due to dose-limiting toxicities (DLTs). Non-evaluable subjects will be replaced in the same cohort. A total of 21 to 42 evaluable subjects will be evaluated during the dose-escalation phase. The decision to continue enrollment in Cohort 7 [redacted] will be based on the Sponsor's assessment of PK, pharmacodynamic, IM and safety assessments obtained from subjects' exposure to MEDI-573 at [redacted] Cohort 6. The rules for enrolling in the next higher cohort are described in Section 4.9.

The dose-expansion phase will evaluate PK and pharmacodynamic parameters and determine preliminary tumor response in approximately 20 subjects with advanced urothelial carcinoma (eg, bladder cancer). Two cohorts of approximately 10 subjects each will be examined in the dose expansion phase. Based on the available pharmacodynamic, PK, and safety parameters, [redacted] have been selected for further evaluation in the expansion phase of the protocol. Enrollment in the dose-expansion phase can occur simultaneously with Cohorts 6 and 7. Both dose-expansion dose levels were explored in the dose-escalation phase of the study, in which 17 subjects were enrolled. No MTD has been established at doses of MEDI-573 [redacted]

MEDI-573 will be administered once every 7 days (on Days 1, 8, and 15 of each 21-day treatment cycle) as [redacted] IV infusion (Cohorts 1 through 5 and the expansion phase) or once every 21 days (on Day 1 of each 21-day treatment cycle) as [redacted] IV infusion (Cohorts 6 and 7). Subjects will continue to receive treatment until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal. Intra-subject dose escalation will not be allowed. Dose reduction for toxicities other than DLTs will be allowed as described in Section 3.5.5. Rules for interruption or discontinuation of MEDI-573 in individual subjects are described in Section 4.7. Rules for interruption or discontinuation of MEDI-573 and study entry are described in Section 4.8.

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

Subject Population:

The subjects in the dose-escalation phase of this study will be adults with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. Subjects in the dose-expansion phase of this study will be adult subjects with advanced urothelial carcinoma (eg, bladder cancer).

Treatment:

Subjects in the dose-escalation phase will be treated with 1 of 5 dosage levels of MEDI-573 [redacted] once each week, ie, every 7 days (Cohorts 1 through 5). Two additional dose escalation cohorts will evaluate an alternate every-3-week treatment schedule: [redacted] Cohort 6, and [redacted] Cohort 7, if applicable, administered as [redacted] IV infusion on Day 1 of each 21-day cycle. MEDI-573 will be administered once every week as a 60-minute IV infusion (Cohorts 1 through 5) or once every 21 days (on Day 1 of each 21-

day treatment cycle) as [redacted] IV infusion (Cohorts 6 and 7). Treatment will continue until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal.

In the dose-expansion phase, 2 cohorts of approximately 10 subjects each will be examined in the dose-expansion phase at dose levels [redacted] every 7 days. The first 10 subjects enrolled into the dose-expansion phase will receive doses of MEDI-573 [redacted] every 7 days. The decision to continue enrollment of subjects into the lower [redacted] dose-expansion cohort will be based on pharmacodynamic assessments of tissue obtained from subjects pre- and post-exposure to MEDI-573 at the [redacted] level. In the event there is insufficient activity at the tissue level in the higher dose expansion cohort, the sponsor may halt dose-expansion and no additional subjects will be enrolled into the expansion phase. Enrollment in the dose-expansion phase can occur simultaneously with Cohorts 6 and 7.

In both the dose-escalation (Cohorts 1 through 5 only) and the dose-expansion phases of the study, in Cycle 2 and beyond, a dose can be delayed up to 7 days based on hematologic and nonhematologic toxicities, according to the conditions described in Section 3.5.5, but all 3 doses (Cohorts 1 through 5 and the dose expansion phase only) must be completed within the cycle in order for the cycle to be considered complete. Subjects in Cohorts 6 and 7 cannot have dose delays for hematologic or nonhematologic toxicities. Subjects who do not receive all required doses within a cycle will not advance to the next cycle and will be removed from treatment. Each new cycle will begin 7 days after the last dose of the previous cycle (Cohorts 1 through 5 and the dose expansion phase) or 21 days after the first dose of the previous cycle (Cohorts 6 and 7). For Cohorts 1 through 5 and the dose expansion phase, all visits during Cycle 2 and subsequent visits may occur in a ± 2-day window to accommodate schedule changes, but doses of MEDI-573 must not occur more frequently than every 6 days. For Cohorts 6 and 7, all visits during Cycle 2 and subsequent visits may occur in a + 2-day window to accommodate schedule changes, but doses of MEDI-573 must not occur more frequently than every 21 days.

Subject Evaluation and Follow-up:

After informed consent has been obtained, screening evaluations will occur within 28 days prior to study entry and include the following evaluations: medical history; serum β human chorionic gonadotropin (βhCG) for women (unless surgically sterile or >1 year postmenopausal); complete physical examination (including height and weight); vital signs;

electrocardiogram (ECG); routine laboratory evaluations (hematology, serum chemistry, and urinalysis); assessment of protocol-related adverse events (AEs) and serious adverse events (SAEs); notation of concomitant medications; and disease evaluations (including computed tomography [CT] or magnetic resonance imaging [MRI] scans, Karnofsky performance status [KPS]).

For subjects enrolled on the dose-escalation phase of the study, the following specimens will be collected:

- archived tumor biopsies (optional)
- biopsies obtained during procedures conducted in the course of routine patient care (optional)
- circulating tumor cells
- whole blood RNA

For subjects enrolled on the dose-expansion phase of the study, the following specimens will be collected:

- biopsies of bladder cancers and/or bladder cancer metastatic deposits (eg, in patients without bladders using image-guidance as needed) will be required from all subjects before and after treatment with study drug. Samples will be collected at two timepoints: prior to the first treatment of Cycle 1, and after the last dose of Cycle 1 but prior to administration of the first dose of Cycle 2.
- archived tumor biopsies (optional)
- biopsies obtained during procedures conducted in the course of routine patient care (optional)
- exfoliated cells from voided urine or catheterized urine, and when available (in the case of patients with bladders who may be undergoing cystoscopic procedures) from bladder washings
- circulating tumor cells
- whole blood RNA

For subjects enrolled on either the escalation or expansion phase of the study, the following biomarker studies will be performed:

- PK evaluations (MEDI-573 serum concentrations) and IM evaluation (anti-MEDI-573 antibodies)
- pharmacodynamic evaluations, including

  - analysis of circulating levels of IGF-1, IGF-2 and IGFBPs in blood and, for subjects in the dose-expansion phase, urine and
  - analysis of exfoliated cells collected from voided urine, catheterized urine, and/or in the case of patients with bladders who may be undergoing cystoscopic procedures, bladder washings
- blood biomarker analysis
- whole blood RNA analysis

Treatment-emergent AEs and SAEs will be assessed from the time the subject receives the investigational product through 30 days after the last dose of MEDI-573. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE V3.0). In addition, disease evaluations (including CT or MRI scans, physical examination, and KPS) will be performed after every 2 cycles of treatment until documentation of disease progression or initiation of alternative anticancer therapy. For subjects who discontinue treatment due to reasons other than disease progression or initiation of alternative anticancer therapy, disease evaluations will be performed every 3 months until documentation of disease progression, initiation of alternative anticancer therapy, or the end of study (defined as 1 year after the last subject entered the study).

Sample Size:

For the dose-escalation phase, a minimum of 21 evaluable subjects (3 subjects in Cohorts 1 to 7) will be required if no subject experiences a DLT. Up to a total of 21 additional evaluable subjects may be enrolled if DLTs occur. Subjects are considered evaluable if they receive 3 doses of MEDI-573 (Cohorts 1 through 5) or 1 dose of MEDI-573 (Cohorts 6 and 7) and are followed for 21 days from the date of first dose (1 cycle) or they discontinue MEDI-573 due to DLTs. Non-evaluable subjects will be replaced in the same cohort.

Two cohorts of approximately 10 subjects each will be examined in the dose-expansion phase [redacted] every 7 days.

Assessment of Endpoints:

Primary Endpoints:

The primary objectives of this study are to evaluate the safety and tolerability of MEDI-573 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists and to determine the MTD or OBED of MEDI-573 in this subject population. The OBED will be the dose at which all circulating IGF-1 and IGF-2 ligand is

expected to be sequestered by MEDI-573, and will be based on pre-clinical data, PK/pharmacodynamic modeling, and pharmacodynamic analyses of circulating IGFs in representative samples of human blood collected in the dose-escalation phase of the study. All safety endpoints will be summarized descriptively. Adverse events and SAEs will be summarized by cohort, system organ class, severity, and relationship to MEDI-573 through 30 days after the last dose of MEDI-573. For assessment of the MTD, descriptive statistics will be provided to summarize the occurrence of DLTs by cohort.

Secondary Endpoints:

Secondary objectives include assessments of PK, IM, pharmacodynamic markers, and antitumor activity.

The PK of MEDI-573 will be assessed by noncompartmental aproach using a validated computer software package [redacted] The noncompartmental pharmacokinetic parameters to be obtained and reported include, but are not limited to: maximum observed serum concentration of MEDI-573 (C_{max}), time to peak concentration (T_{max}), and area under the concentration-time curve (AUC), if the data allow. Descriptive statistics will be provided by cohort.

Immunogenicity of MEDI-573 will be assessed and summarized descriptively by cohort

For the assessment of pharmacodynamic activity, suppression profiles of both IGF-1 and IGF-2 post administration of MEDI-573 in relation to time course of antibody concentrations in serum will be evaluated during treatment, including a final assessment 21 days after the last dose of MEDI-573.

The antitumor activity of MEDI-573 will be assessed based on objective response rate (ORR), time to response (TTR), duration of response (DR), time to progression (TTP), progression-free survival (PFS), and overall survival (OS).

Objective response rate is defined as the proportion of subjects with confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Confirmed responses are those that persist on repeat imaging study $\geq$ 4 weeks after the initial documentation of response.

Time to response will be measured from the start of treatment with MEDI-573 to the first documentation of objective response and will only be assessed in subjects who have achieved objective response.

Duration of response will be defined as the duration from the first documentation of objective response to the first documented disease progression. 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 calculated for the subgroup of subjects with an objective response.

Time to progression will be measured from the start of treatment with MEDI-573 until the documentation of disease progression. Disease progression is defined according to RECIST guidelines. 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-573 will have TTP censored on the first date of treatment with MEDI-573.

Progression-free survival will be measured from the start of treatment with MEDI-573 until the documentation of disease progression or death due to any cause, whichever occurs first. Disease progression is defined according to RECIST guidelines. Progression-free survival will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression and are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Subjects having no tumor assessments after the start of treatment with MEDI-573 will have PFS censored on the first date of treatment with MEDI-573.

Overall survival will be determined as the time from the start of treatment with MEDI-573 until death. For subjects who are alive at the end of study or lost to follow-up, OS will be censored on the last date when subjects are known to be alive.

The time to event data including TTR, DR, TTP, PFS, and OS will be evaluated using Kaplan-Meier methods.

Exploratory Endpoints:

Additional exploratory objectives of pharmacodynamic activity include an evaluation of MEDI-573 treatment on the levels and/or phosphorylation of IGF pathway protein biomarkers that may include but are not limited to IGF-1R, IRS-1, MAPK, IR, Ki67, caspase 3, and/or pAkt. TUNEL analysis may also be performed; these analyses will include archived tumor biopsies (optional), and biopsies obtained during surgical procedures conducted in the course of routine patient care (optional). In the dose-expansion phase, additional samples will be obtained from subjects who may be undergoing cystoscopic procedures (optional); exfoliated cells collected in voided urine, catheterized urine, and/or bladder washings; and cancers or of bladder cancer metastatic deposits (with image guidance as needed). The biopsies of bladder cancers or bladder cancer metastatic deposits will be required before and after treatment with study drug for all subjects in the dose-expansion phase of the study. Samples will be collected at two timepoints: prior to the first treatment of Cycle 1, and after the last dose of Cycle 1 but prior to administration of the first dose of Cycle 2. Additional exploratory endpoints will include IGF pathway factor analysis such as IR expression levels via whole genome array, and for the dose-expansion phase, levels of proteins in urine that may include but are not limited to IGF-1, IGF-2, IGFBPs and NMP. The relationship of IGF pathway-related components at the mRNA and miRNA level, including IR-A mRNA level in tumor biopsies obtained pre- and post-MEDI-573 treatment will also be evaluated using TaqMan QRTPCR assays and microarray studies. If applicable, a CAST assay will be performed to evaluate potential point mutations in the key genes downstream of IGF signaling pathway to evaluate their correlations with clinical activity of MEDI-573. Circulating tumor cells when available will be analyzed for IGF pathway factor analysis including IGF-1R.

These studies serve the purpose of evaluating target modulation of MEDI-573 and its downstream effect of neutralizing IGF at the tumor level. We will also evaluate whether there is a positive correlation between target modulation in the tumor and clinical response.

For the expansion phase, selected genomics and/or genetics studies described above will be performed in archived tumor biopsies obtained for other reasons prior to and/or during MEDI-573 treatment. For the expansion study, if studies described above were executed, TaqMan low-density array (TLDA)- based assays will be used to evaluate the miRNA profile in the plasma and/or WB of subjects pre- and post MEDI-573 dosing.

1 Introduction

1.1 Background

The insulin-like growth factor (IGF) system consists of ligands (IGF-1 and IGF-2), the cell surface receptors (IGF-1R and IGF-2R), and the IGF-binding proteins (IGFBPs), all of which play a critical role in normal growth and development (Ryan and Goss, 2008; Sachdev and Yee, 2007). IGF-1 and IGF-2 are small polypeptides involved in regulating cell proliferation, survival, differentiation, and transformation. Both are expressed ubiquitously and act as endocrine, paracrine, or autocrine growth factors. IGF-1 and IGF-2 exert their actions through binding to the IGF-1 receptor tyrosine kinase (IGF-1R) and activate various intracellular signaling cascades. Activation of IGF signaling cascades leads to both stimulation of cell growth through activation of mitogen-activated protein kinase (MAPK) pathways as well as inhibition of apoptosis through stimulation of the protein kinase B (Akt) pathway. Insulin-like growth factors can also stimulate signaling through the insulin receptor (IR) pathway. There are two isoforms of the IR, IR-A and IR-B, which differ in the extra 12 amino acid residues present at the C-terminal end of the α-subunit of IR-B. Insulin receptor-B is the isoform that signals metabolic activities of insulin, while IR-A acts as a growth stimulatory signal, and is often overexpressed in tumor tissue compared to normal tissue. IGF-1 and IGF-2 can bind to a heterodimeric IGF-1R/IR receptor, and IGF-2 can bind to homomeric IR receptors with affinities approaching insulin. Thus, IGFs can activate growth stimulatory signals through activating either IGF-1R or IR-A pathways. The binding properties of IGFs also suggest that inhibition of the IGF-1R receptor alone may incompletely inhibit IGF growth stimulatory activity. IGFs circulate in serum mostly bound to IGFBP-1 to 6. The interaction of IGFs with the IGF-1R is regulated by the IGFBPs, and IGFs can only bind to the IGF-1R once released from the IGFBPs. This release occurs mostly by proteolysis of the IGFBPs. Thus inhibition of "free" IGF is likely to result in a reduction of signal flux through the relevant receptors.

Numerous previously published preclinical studies have reported that down-regulation of IGF-1R expression and/or inhibition of signaling lead to inhibition of tumor growth, both in vitro and in vivo (Yuen and Macaulay, 2008). Inhibition of IGF signaling has also been shown to increase the susceptibility of tumor cells to chemotherapeutic agents (Wu et al, 2007). A variety of strategies (antisense oligonucleotides, soluble receptor, inhibitory peptides, dominant negative receptor mutants, small molecules that inhibit the kinase activity, and anti-soluble recombinant human IGF [hIGF]-1R antibodies) have been

developed to inhibit the IGF-1R signaling pathway in tumor cells. Each of these strategies has demonstrated the IGF-1R signaling pathway plays an important role in tumor cell growth and survival (Sachdev and Yee, 2007).

In addition, epidemiologic studies support the assertion that IGFs play an important role in human cancers (Renehan et al, 2004; Wolpin et al, 2007). High levels of circulating IGF-1 are associated with an increased risk for development of several common cancers (Renehan et al, 2004). In particular, the association is strongest for breast, prostate, and colorectal cancer but also present in non-small cell lung cancer (NSCLC), hepatocellular carcinoma (HCC), gastro-esophageal cancer, pancreatic cancer, and others.

In one prospective case-control study of prostate cancer, individuals with the highest quartile of IGF-1 levels had a five-fold greater risk of advanced prostate cancer compared to those in the lowest quartile (Chan et al, 1998). Similarly, levels of the principal binding protein of IGF (IGFBP-3), which acts as a negative regulator of IGF signaling, have a negative predictive value for development of many common cancers (Chan et al, 2002; Lu et al, 2006; Renehan et al, 2004).

IGF signaling likely plays an important role in the development and/or progression of breast cancer. Epidemiologic studies suggest that elevated levels of IGF-1 in serum correlate with a higher risk for developing breast cancer in women over the age of 50 (Rinaldi et al, 2006). The IGF signaling cascade appears to be activated in numerous cancer types as determined by examination of human tumors. For example, IGF-1R levels are elevated in breast cancer cell lines and often in fresh tumor biopsies. Insulin-like growth factor 2 is expressed by both tumor and stromal cells, and IGF-1 by stromal cells (Yee et al, 1989). Insulin receptor is also often overexpressed in breast cancer, and it has recently been demonstrated that IR-A is the predominant IR isoform expressed in breast cancer cells (Sciacca et al, 1999). Cells that overexpress IR-A respond to treatment with IGF-2 by growth stimulation (Sciacca et al, 1999), suggesting a role for IGF-2 in tumor growth through activation of IR signaling pathways. IGF signaling may have particular importance in relationship to the generation of resistance to effective anticancer therapies (Nahta et al, 2006). Specifically, inhibition of IGF signaling has been shown to restore the growth inhibitory activity of trastuzumab in cells that had become resistant to HER2 blockade (Lu et al, 2004a). Similarly, resistance to anti-estrogen therapy such as tamoxifen may be mediated in part by up-regulation of IGF signaling (Milano et al, 2006).

In colon cancer, multiple lines of evidence suggest the importance of IGF signaling. Higher levels of IGF-1 were found in patients with adenomas and advanced adenomas compared to controls without lesions (Schoen et al, 2005). High serum IGF-2 concentrations have also been found in patients with colorectal cancer, with a trend towards higher concentrations in advanced disease (Giovannucci, 2001). Additionally, most primary tumors and transformed cell lines overexpress IGF-2 mRNA and protein. Overexpression of IGF-2 in colon cancer is associated with an aggressive phenotype, and the loss of imprinting (loss of allele-specific expression) of the IGF-2 gene may lead to higher expression and may be important in colorectal carcinogenesis (Woodson et al, 2004). Cancer cells with a strong tendency to metastasize have significantly higher levels of IGF-2 expression than those cells with a low ability to metastasize (Sekharam et al, 2003). Insulin receptor-A is also reported to be expressed more frequently than IR-B in colon cancer (Frasca et al, 1999).

IGF-1, IGF-2, and IGF-1R are also overexpressed in bladder cancer (Zhao et al, 2003; Gallagher et al, 2008; Rochester et al, 2007). In vitro studies of human bladder cell lines demonstrate that IGF-1 induces cell proliferation and blocks apoptosis (Iwamura et al, 1993). Furthermore, neutralization of IGF-1R signaling sensitizes urothelial cells to mitomycin-induced apoptosis (Sun et al, 2001). In vivo studies have shown that caloric restriction markedly reduces carcinogen-induced bladder cancers by lowering circulating IGF-1, an effect that is reversed by the administration of human IGF-1 (Dunn et al, 1997).

In the clinical setting, higher circulating levels of free IGF-1 and IGF-2 bound to its carrier IGFBP-3 have been found in patients with bladder cancer as compared to matched controls. In one study, mean IGF-1 was significantly higher (175.8 versus 153.2 ng/ml, $p < 0.01$) and mean IGFBP-3 was significantly lower (2,632.9 versus 3,056.6 ng/ml, $p < 0.01$) in 154 cases as compared to 154 matched controls (Zhao et al, 2003). This study also found a significant association between the highest quartile plasma levels of IGF-1 and risk of bladder cancer (odds ratio [OR] 3.10, 95% CI 1.43 to 6.70). Conversely, the highest quartile plasma levels of IGFBP-3 were associated with a reduced risk of bladder cancer (OR 0.38, 95% CI 0.19 to 0.78) (Zhao et al, 2003).

IGF-2, a maternally imprinted fetal growth factor gene, regulates cellular proliferation and differentiation. Although the paternal chromosome typically expresses IGF-2 while the imprinted maternal chromosome remains “silent”, in the setting of IGF-2 loss of imprinting (LOI) bi-allelic expression of IGF-2 has been associated with increased IGF-2 protein levels, cellular hyperproliferation, and a broad array of solid, embryonal, and hematologic malignancies (Cui, 2007; Gallagher et al, 2008). Beckwith-Wiedemann Syndrome (BWS), a

genetic model for IGF-2 LOI that is characterized by congenital overgrowth syndrome, is associated with embryonal tumors early in life such as nephroblastoma (also known as Wilms tumor), hepatoblastoma, neuroblastoma, adrenocortical carcinoma, and rhabdomyosarcoma.

1.2 Anti-IGF Receptor Therapy Clinical Experience

Monoclonal antibodies (mAb) directed against IGF-1R have been developed for clinical use and several of them have advanced to Phase 2 and 3 studies. Until recently, toxicity has generally been regarded as mild and manageable. However, a Phase 3 NSCLC study testing an IGF-1R targeting mAb, figitumumab (Pfizer, CP-751,871), in combination with carboplatin and paclitaxel was suspended in October 2009 on the recommendation of an independent safety monitoring board that identified on routine review an increased number of serious adverse events (SAEs) and fatalities on the figitumumab arm of the study. No specific information regarding those events has been released to date and 10 other studies testing figitumumab continue to enroll and treat subjects, including a Phase 3 NSCLC study testing figitumumab in combination with erlotinib. Reported Grade 3 or greater toxicities for monoclonal antibodies targeting the IGF signaling pathway have included Grade 3 thrombocytopenia (Tolcher et al, 2008), Grade 4 thrombocytopenia (Hidalgo et al, 2008), Grade 3 hyperglycemia (Higano et al, 2007), Grade 3 purpura (Atzori et al, 2008), Grade 4 uric acid increase, and Grade 3 bilateral deep venous thrombosis (Olmos et al, 2008). Other toxicities reported in these studies were generally mild (Grade 1 or 2), and included hyperglycemia, gastrointestinal disturbances, hypersensitivity reactions, pruritus, asthenia, and anemia (Haluska et al, 2007). One study reported a 10% rate of Grade 1 or 2 hyperglycemia (Atzori et al, 2008), which was easily treatable with metformin.

With regard to efficacy, in Phase 2 studies, anti-IGF-1R therapy has been shown to have activity against NSCLC (Karp et al, 2008) and Ewing's sarcoma (Olmos et al, 2008). In NSCLC with non-adenocarcinoma histology, the addition of anti-IGF-1R monoclonal therapy to standard first-line carboplatin and paclitaxel chemotherapy led to an overall response rate of 72% compared to 42% for those who received carboplatin and paclitaxel alone (Karp et al, 2008). In a sarcoma study, among 19 subjects treated, 1 PR was seen in a subject with Ewing's sarcoma and 6 subjects with other histologies demonstrated stable disease lasting more than 3 months. These data demonstrate that monoclonal antibody therapy directed against IGF-1R is generally well tolerated and may have activity in several tumor types, thus demonstrating the potential of this pathway as a target for therapy. Based on the mechanism of IGF-1R activation (binding by IGFs), it is possible that toxicities due to inhibition of IGF-1R signaling may be observed with MEDI-573, and therefore appropriate

inclusion and exclusion criteria have been incorporated to account for any possible pathway effects.

1.3 Description of MEDI-573

MEDI-573 is a fully human immunoglobulin G2 lambda (IgG2λ) monoclonal antibody [redacted] that selectively binds to human IGF-2 and IGF-1. The antibody was isolated from mice immunized alternately with soluble recombinant human IGF-2 (hIGF-2) and hIGF-1 coupled to Keyhole Limpet Hemocyanin (KLH). Following comparisons with germ line sequences, no mutations have been identified in the monoclonal antibody.

1.4 Nonclinical Experience with MEDI-573

MEDI-573 inhibited both IGF-1- and IGF-2-stimulated phosphorylation of IGF-1R and downstream signaling proteins including pAkt and pMAPK in a number of engineered NIH3T3 and human tumor cell lines. Further, MEDI-573 inhibited autocrine phosphorylation of these signaling molecules. Functionally, MEDI-573 effectively inhibited the growth of a number of engineered NIH3T3 and human tumor cell lines. In vivo, MEDI-573 significantly inhibited the growth of implanted Clone 32 and P12 tumors, which overexpress hIGF-1, hIGF-2, and hIGF-1R.

Pharmacokinetic (PK) and pharmacodynamic studies performed in cynomolgus monkeys following single-dose (0, 6, or 60 mg/kg) and repeated-dose (two doses of 1, 3, 10, or 30 mg/kg on Days 1 and 8) administration of MEDI-573 demonstrated that free IGF-1 and IGF-2 levels were reduced dose-dependently by greater than 90% at doses higher than 10 mg/kg for 1 week. At doses of 30 mg/kg and greater, both IGF-1 and IGF-2 were suppressed for at least 2 weeks.

A non-GLP single intravenous (IV) infusion dose toxicity, PK, and pharmacodynamic study was conducted in cynomolgus monkeys using MEDI-573 at doses of 6 or 60 mg/kg. Doses of 6 or 60 mg/kg were administered via a 30-minute IV infusion to 2 male and 2 female cynomolgus monkeys on Day 1 and the animals were humanely euthanized and necropsy performed on Day 23. There were no MEDI-573-related adverse changes in mortality, clinical observations, physical examinations (including blood pressure, respiration rate, and body temperature), food consumption, body weights, urinalysis, hematology, coagulation, serum chemistry, insulin and fasted glucose levels, GH levels, organ weights, macroscopic

pathology, or microscopic pathology. Based on these data, single, 30-minute continuous IV infusions of MEDI-573 to naïve cynomolgus monkeys at doses up to 60 mg/kg were well tolerated and there was no evidence of test article-related local or systemic toxicity. The no observable adverse effect level (NOAEL) was 60 mg/kg, which resulted in a dose normalized AUC (AUC∞/Dose) of 0.122 ±0.029 (μg·day/mL)/(μg/kg), a mean clearance (CL) of 8.67 ± 2.49 mL/day/kg, and mean C_{max} value of 1643 ± 278 μg/mL.

A GLP 13-week repeat IV infusion (30-minute, continuous) dose toxicity study was conducted in cynomolgus monkeys using MEDI-573 at doses of 1, 10, or 60 mg/kg/dose, administered once weekly for a total of 13 doses. The main study animals were humanely euthanized and necropsy performed 7 days after the final dose and the recovery animals (vehicle and high dose groups only) were humanely euthanized and necropsy performed following an 8-week recovery period. The high dose of 60 mg/kg is 12-fold higher (mg/kg basis) than the dose (5 mg/kg) that is anticipated to result in 99% suppression of IGF-2 and over 90% suppression of IGF-1 in humans. There were no MEDI-573-related adverse changes in mortality, clinical observations, physical examinations (including heart rate, respiration rate, and body temperature), blood pressure, electrocardiography, ophthalmology, food consumption, body weights, urinalysis, hematology, coagulation, serum chemistry (including fasted glucose), insulin levels, organ weights, macroscopic pathology, and microscopic pathology. One low-dose (1 mg/kg/dose) and one high-dose (60 mg/kg/dose) female had a positive primate anti-human antibody response (PAHA) on Days 50-92 (terminal necropsy) and Day 135, respectively. The concentrations of MEDI-573 were below the limit of quantitation near the time a positive PAHA was detected (Weeks 5-12 and Day 128, respectively), suggesting the PAHA had an effect on PK. Following administration of MEDI-573, dose-dependent decreases in both IGF-1 and IGF-2 serum concentrations were observed. The serum concentrations of MEDI-573 (free antibody) required for 50% suppression (EC50) of free IGF-1 and IGF-2 were 1.2 and 0.99 μg/mL, respectively. Based on these data, once-weekly, 30-minute continuous IV infusions of MEDI-573 to naïve cynomolgus monkeys at doses of 1, 10, and 60 mg/kg were well tolerated and there was no evidence of test article-related local or systemic toxicity. The NOAEL was 60 mg/kg/week, which resulted in a dose normalized AUC (AUC∞/Dose) of 0.085 ± 0.028 (μg·day/mL)/(μg/kg), a mean clearance of 12.6 ±3.15 mL/day/kg, and mean (C_{max}) value of 1343 ±409 μg/mL.

Safety pharmacology parameters including central nervous system/behavior, cardiovascular, and respiratory changes were evaluated following administration of MEDI-573 in the 13-week toxicology study in cynomolgus monkeys. There were no test

article-related effects on behavior or on heart rate, respiration rate, body temperature, blood pressure, or electrocardiography measurements taken in anesthetized monkeys. There was also no tissue cross-reactivity observed in the brain, heart, or lung of the human or cynomolgus monkey tissues examined in the GLP tissue cross-reactivity study.

The local tolerance of MEDI-573 was evaluated in the 13-week GLP monkey toxicity study. Evaluations included standard clinical observations performed twice daily and, gross pathology and histopathology evaluation of the IV injection sites 7 days after the final dose. There were no clinical observations of adverse findings at the injection site. There were also no gross or histopathology observations of adverse findings at the injection site, 7 days after the final dose.

In summary, MEDI-573 was well tolerated following up to 13 once-weekly, 30-minute continuous IV infusion administrations in cynomolgus monkeys, the relevant toxicology species, with a NOAEL of 60 mg/kg, the highest dose tested. MEDI-573 was pharmacologically active with plasma concentrations well above the needed concentration.

1.5 Clinical Experience with MEDI-573

This study is the first time that MEDI-573 has been given to humans. From the time the study started and until 17 February 2010, 17 subjects have been treated with MEDI-573 at doses [redacted] given once every 7 days. To date no dose limiting toxicities (DLTs) have been observed. Treatment emergent AEs observed in at least 2 subjects each (>10% of subjects) have been the following: decreased appetite, fatigue, anemia, diarrhea, abdominal pain, nausea, vomiting, dehydration, pruritis, thrombocytopenia, early satiety, pyrexia, bronchitis, urinary tract infection, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, cough and rash. These events range in severity from Grade 1 to 5, AEs considered to be treatment-related have been Grade 1 or 2.

1.6 Rationale for Study

Early indications of efficacy with mAbs directed against IGF-1R (ie, receptor) suggest the possibility of achieving greater efficacy by inhibiting IGF-mediated signaling through binding and sequestering available IGF-1 and IGF-2 (ie, ligands). The development of an antibody that neutralizes both IGF-1 and IGF-2 offers the opportunity to inhibit IGF-1R as well as IR-A signaling. As a result, a ligand-targeting antibody such as MEDI-573 might be expected to have greater activity than IGF-1R targeting antibodies in tumors that express both

IGF-1R and IR-A (eg, breast, bladder, colon, lung, thyroid), or IR-A alone. Small molecule IGF-1R kinase inhibitors described to date inhibit both IGF-1R and IR-A/IR-B, which have identical kinase domains. These molecules are likely to show greater toxicity than an IGF-1/IGF-2 ligand antibody due to inhibition of IR-B, which is primarily involved in the regulation of glucose metabolism. Thus, an IGF-1/IGF-2 neutralizing antibody with no effect on insulin signaling and metabolism represents a novel mechanism of action against the IGF signaling pathway, which is believed to be important for tumor growth and survival in a wide range of tumor types.

These results suggest that IGF-1 and IGF-2 act as powerful mitogenic and anti-apoptotic signals, and that their overexpression correlates with poor prognosis in a variety of cancers.

Based on simulations using data from the cynomolgus monkey, over a one week dosing interval, on average, approximately 50% suppression of IGF-1 and 70% to 80% suppression of IGF-2 are predicted following administration of 0.5 mg/kg/week. The predicted maximum serum concentrations of MEDI-573 at 0.5 mg/kg every week in man should provide approximately an 80- to a 100-fold safety margin relative to the maximum MEDI-573 concentrations observed following administration of the 60 mg/kg/week dose in the toxicology study in cynomolgus monkeys, a dose at which no adverse effects were observed. At a dose of 10 mg/kg/week, 99% suppression of the targets (IGF-1 and IGF-2) is predicted. Assessment of subjects treated in the 5, 10, or 15 mg/kg cohorts showed complete suppression of circulating IGF-1 and IGF-2. Serum concentrations of MEDI-573 for all 3 cohorts were sustained well above 28 μg/mL, a concentration which has been determined in preclinical in vivo antitumor studies to be the EC_{90} for tumoral IGF-1R pathway suppression. Based on available pharmacodynamic, pharmacokinetic and safety parameters 5 and 15 mg/kg have been selected for further evaluation in the expansion phase. These two doses provide a dose range in which to compare tolerability and biologic effects achieved at the tumor level.

Evaluation of MEDI-573 activity at the tissue level will be performed in the dose-expansion phase by studies of archived human tumor biopsies when available (optional); any biopsies obtained during surgical procedures conducted in the course of routine patient care (optional); and exfoliated cells in urine, bladder washing specimens, and/or circulating tumor cell samples. Biopsies before and after treatment (including biopsy of metastatic deposits) will be required of all subjects in the dose-expansion phase and will be collected at two timepoints; prior to the first treatment of Cycle 1 and after the last dose of Cycle 1 but prior to administration of the first dose of Cycle 2. These samples will be assessed for phosphorylated

and/or unphosphorylated levels of IGF pathway biomarkers that may include but are not limited to IGF receptor type 1 (IGF-1R), insulin receptor substrate-1 (IRS-1), mitogen-activated protein kinase (MAPK), insulin receptor (IR), antigen identified by monoclonal antibody Ki-67 (Ki67), caspase 3, and/or protein kinase B signaling protein (pAkt). Deoxyuride-5'-triphosphate biotin nick end labeling (TUNEL) analysis may also be performed. Evaluation of levels of proteins in the voided urine that may include but are not limited to IGF-1, IGF-2, IGFBPs, nuclear matrix protein (NMP) will be evaluated and their relationship with clinical outcome explored. For the dose-expansion phase, the expression level of IGF pathway-related factors such as IGF-1R on subject response to treatment will be evaluated in circulating tumor cells and tumor cells in urine.

MEDI-573 will be administered once every week as [redacted] IV infusion [redacted] or as a [redacted] IV infusion for doses [redacted] As a monoclonal antibody, IV administration is the only convenient and safe route that will ensure adequate bioavailability. The length of infusion in the clinical protocol is increased compared to the GLP toxicology study in order to minimize the possibility of infusion-related adverse events (AEs).

MEDI-573 is supplied as a sterile lyophilized product in single-use 10 mL vials. The product is reconstituted with sterile water [redacted] prior to clinical use.

2 Study Objectives and Overview

2.1 Primary Objectives

The primary objectives of this study are to:

1) Evaluate the safety and tolerability of MEDI-573 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists;
2) Determine the maximum tolerated dose (MTD) or optimal biologically effective dose (OBED) of MEDI-573 in subjects with solid tumors.

2.2 Secondary Objectives

The secondary objectives of this study are to:

1) Describe the pharmacokinetics of MEDI-573;
2) Determine the immunogenicity of MEDI-573;

3) Determine the pharmacodynamics of MEDI-573 on circulating plasma levels of IGF-1 and IGF-2;

4) Observe any antitumor activity of MEDI-573 in subjects with solid tumors.

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

1) Determine levels of circulating soluble proteins that may include but are not limited to growth hormone (GH), IGF-binding proteins (IGFBPs), insulin, and glucose, and explore associations with clinical outcome;

2) Assess levels of phosphorylated and/or unphosphorylated factors in specimens. These factors may include but are not limited to IGF receptor type 1 (IGF-1R), insulin receptor substrate-1 (IRS-1), mitogen-activated protein kinase (MAPK), insulin receptor (IR), antigen identified by monoclonal antibody Ki-67 (Ki67), caspase 3, and/or protein kinase B signaling protein (Akt) in archived tumor biopsies, biopsies obtained during surgical procedures in the course of routine patient care, and/or exfoliated cells collected in voided urine, catheterized urine and/or bladder washes. Deoxyuride-5'-triphosphate biotin nick end labeling (TUNEL) analysis may also be performed.

3) Evaluate the relationship of IGF pathway-related components at the mRNA and miRNA level, including IR-A mRNA level in tumor biopsies obtained pre- and post-MEDI-573 treatment using TaqMan qRT-PCR assays and microarray studies.

4) Evaluate the relationship of IGF pathway-related factors including IR expression levels using whole genome array and subject tumor response to MEDI-573.

5) Perform genomics and proteomics analyses on exfoliated cells collected in bladder washings from selected subjects in the dose-expansion phase

6) For the dose-expansion phase, evaluate the expression level of IGF pathway-related factors such as IGF-1R on subject response to MEDI-573 when circulating tumor cells are available.

7) For the dose-expansion phase, evaluate the levels of proteins in urine that may include but are not limited to IGF-1, IGF-2, IGFBPs, and nuclear matrix protein (NMP), and explore their relationship with clinical outcome.

2.4 Overview

Study Design

This is a Phase 1, multicenter, open-label, single-arm, dose-escalation, and dose-expansion study to evaluate the safety, tolerability, and antitumor activity of MEDI-573 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy

exists. Approximately 10 investigational sites in the USA will participate in this study, with cohorts of 3 to 6 evaluable subjects each receiving 1 of 5 dosage levels of MEDI-573 [redacted] every 7 days in the dose-escalation phase of the study (Cohorts 1 through 5). Two additional dose escalation cohorts will evaluate an alternate every-3-week treatment schedule: [redacted] Cohort 6 and [redacted] Cohort 7, if applicable, administered as [redacted] IV infusion on Day 1 of each 21-day cycle. [redacted]. Subjects in the dose escalation phase are considered evaluable if they receive 3 doses of MEDI-573 (Cohorts 1 through 5) or 1 dose of MEDI-573 (Cohorts 6 and 7) and are followed for 21 days from the date of first dose (one cycle) or if they discontinue MEDI-573 due to dose-limiting toxicities (DLTs). Non-evaluable subjects will be replaced in the same cohort. A total of 21 to 42 evaluable subjects will be evaluated during the dose-escalation phase. The decision to continue enrollment in Cohort 7 [redacted] will be based on the Sponsor's assessment of PK, pharmacodynamic, IM, and safety assessments obtained from subjects' exposure to MEDI-573 at the [redacted] Cohort 6. The rules for enrolling in the next higher cohort are described in Section 4.9.

The dose-expansion phase will evaluate PK and pharmacodynamic parameters and determine tumor response in approximately 20 subjects with advanced urothelial carcinoma (eg, bladder cancer). Two cohorts of approximately 10 subjects each will be examined in the dose-expansion phase. Based on the available pharmacodynamic, pharmacokinetic, and safety parameters, [redacted] have been selected for further evaluation in the expansion phase of the protocol. Enrollment in the dose-expansion phase can occur simultaneously with Cohorts 6 and 7. Both dose-expansion dose levels were explored in the dose-escalation phase of the study, in which 17 subjects were enrolled. No MTD has been established at doses of MEDI-573 [redacted].

MEDI-573 will be administered once every 7 days (on Days 1, 8, and 15 of each 21-day treatment cycle) as [redacted] intravenous (IV) infusion (Cohorts 1 through 5 and the expansion phase) or once every 21 days (on Day 1 of each 21-day treatment cycle) as [redacted] infusion (Cohorts 6 and 7). Treatment will continue until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal. Intra-subject dose-escalation will not be allowed. Dose reduction for toxicities other than DLTs will be allowed as described in Section 3.5.5. Rules for interruption or discontinuation of MEDI-573 in individual subjects are described in Section 4.7. Rules for interruption or discontinuation of MEDI-573 and study entry are described in Section 4.8.

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

The first 10 subjects enrolled into the dose-expansion phase will receive doses of MEDI-573 [redacted] every 7 days. The decision to continue enrollment in the lower [redacted] dose-expansion cohort will be based on pharmacodynamic assessments of tissue obtained from subjects pre- and post-exposure to MEDI-573 at the [redacted] level. In the event there is insufficient activity at the tissue level in the higher dose-expansion cohort, the sponsor may halt dose expansion and no additional subjects will be enrolled into the expansion phase.

Subject Evaluation/Follow-up

After informed consent has been obtained, screening evaluations will occur within 28 days prior to study entry and include the following evaluations: medical history; serum β human chorionic gonadotropin (βhCG) for women (unless surgically sterile or >1 year postmenopausal); complete physical examination (including height and weight); vital signs; electrocardiogram (ECG); routine laboratory evaluations (hematology, serum chemistry, and urinalysis); assessment of protocol-related adverse events (AEs) and serious adverse events (SAEs); notation of concomitant medications; and disease evaluations (including computed tomography [CT] or magnetic resonance imaging [MRI] scans, Karnofsky performance status [KPS]).

For subjects enrolled on the dose-escalation phase of the study, the following specimens will be collected:

- archived tumor biopsies (optional)
- biopsies obtained during procedures conducted in the course of routine patient care (optional)
- circulating tumor cells
- whole blood RNA

For subjects enrolled on the dose-expansion phase of the study, the following specimens will be collected:

- biopsies of bladder cancers and/or bladder cancer metastatic deposits (eg, in patients without bladders using image-guidance as needed) will be required from all subjects before and after treatment with study drug. Samples will be collected at two timepoints: prior to the first treatment of Cycle 1, and after the last dose of Cycle 1 but prior to administration of the first dose of Cycle 2.
- archived tumor biopsies (optional)
- biopsies obtained during procedures conducted in the course of routine patient care (optional)
- exfoliated cells from voided urine, catheterized urine, and/or (in the case of patients with bladders who may be undergoing cystoscopic procedures) bladder washings
- circulating tumor cells
- whole blood RNA

For subjects enrolled on either the escalation or expansion phase of the study, the following biomarker studies will be performed:

- PK evaluations (MEDI-573 serum concentrations) and IM evaluation (anti-MEDI-573 antibodies)
- pharmacodynamic evaluations (including analysis of circulating levels of IGF-1, IGF-2 and IGFBPs in blood and [for subjects in the dose-expansion phase] urine as well as exfoliated cells collected in voided urine, catheterized urine, or bladder washings)
- blood biomarker analysis
- whole blood RNA analysis

Treatment-emergent AEs and SAEs will be assessed from the time the subject receives the investigational product through 30 days after the last dose of MEDI-573. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE V3.0). In addition, disease evaluations (including CT or MRI scans, physical examination, and KPS) will be performed after every 2 cycles of treatment until documentation of disease progression or initiation of alternative anticancer therapy. For subjects who discontinue treatment due to reasons other than disease progression or initiation of alternative anticancer therapy, disease evaluations will be performed every 3 months until documentation of disease progression, initiation of alternative anticancer therapy, or the end of study (defined as 1 year after the last subject entered the study).

A study flow diagram is presented in Figure 2.4-1.

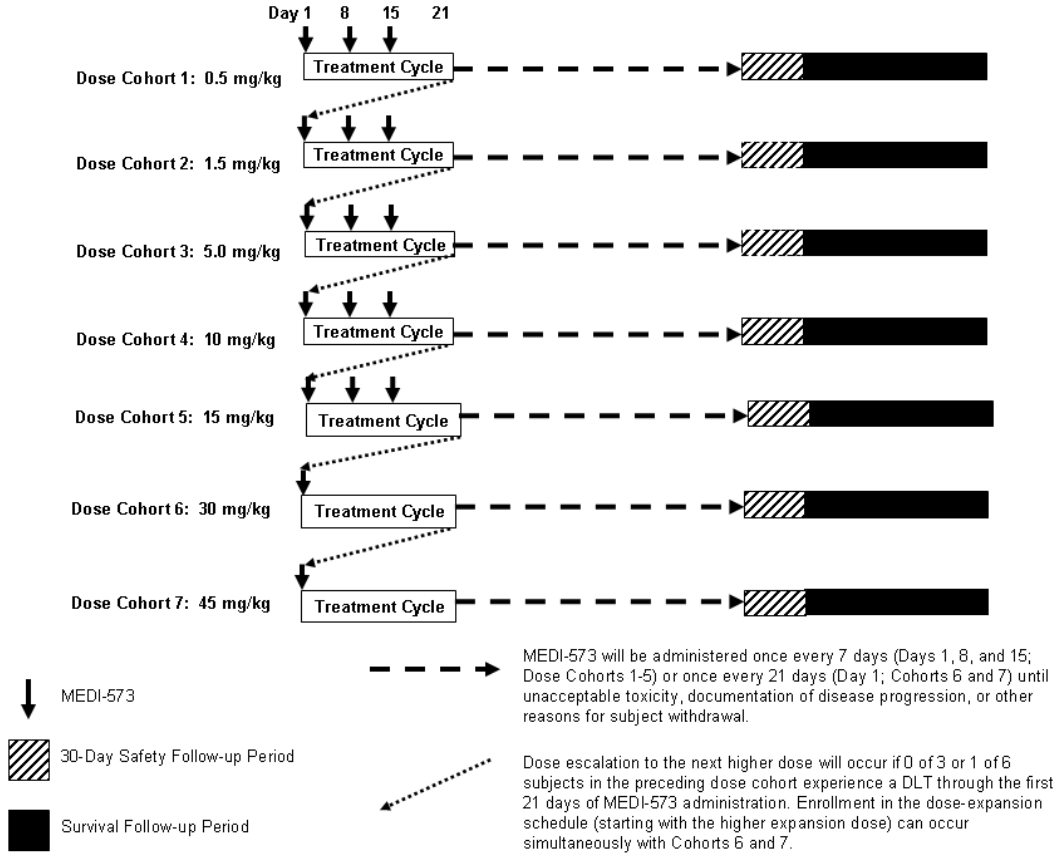

Figure 2.4-1 Study Flow Diagram

3 Study Procedures

3.1 Subject Selection

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

The investigator (physician) or qualified designee will discuss the study with a subject/the legal representative of a subject who is considered a potential candidate for the study. If there is interest in participating in the study, the subject/legal representative will be provided with the informed consent form. The investigator or designee will address any questions and/or concerns that the subject/legal representative may have and, if there is continued interest, will secure written informed consent for participation in the study. Written informed consent and Health Insurance Portability and Accountability Act (HIPAA) authorization (applies to

covered entities in the USA only) will be obtained prior to conducting any protocol-related procedures, including screening evaluations or medication washouts.

3.1.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1) Men or women at least 18 years of age or older at time of study entry
2) Written informed consent and HIPAA authorization (applies to covered entities in the US only) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations
3) Histologically confirmed advanced solid tumor for which no curative or standard therapies exist
    a) Twenty subjects will be treated in the dose-expansion phase. Subjects must have measurable disease (as defined in Section 3.7.4) and a histologically confirmed diagnosis of advanced urothelial carcinoma (ie, pure or mixed histology transitional cell carcinoma of the upper or lower urinary tract).
4) Karnofsky performance status ≥60
5) Life expectancy of ≥ 12 weeks
6) Prior radiation therapy is allowed provided exposure does not exceed an area of 25% of marrow space.
7) Toxicities from previous cancer therapies must have recovered to Grade < 2.
8) Adequate hematological function defined as:
    - Hemoglobin ≥ 10 g/dL
    - Absolute neutrophil count ≥ 1500/mm^3
    - Platelet count ≥100,000/mm^3
9) Adequate organ function defined as follows:
    - AST and ALT ≤ 2 × institutional upper limit of normal (ULN)
    - Bilirubin ≤ 1.5 × ULN except in the case of subjects with documented or suspected Gilbert's disease ≤ 5 × ULN
    - Creatinine clearance ≥ 60 mL/min as determined by the Cockcroft-Gault equation (Cockcroft and Gault, 1976) or by 24-hour urine collection for determination of creatinine clearance (creatinine clearance ≥ 50 mL/min will be acceptable for subjects in the dose-expansion phase of the study).

10) Women of non-child-bearing potential (defined as being >1 year post-menopausal or surgically sterile) or using effective contraception, eg, use of oral contraceptives with an additional barrier method (since the investigational product may impair the effectiveness of oral contraceptives), double barrier methods (diaphragm with spermicidal gel or condoms with contraceptive foam), Depo-Provera, partner vasectomy, or total abstinence, from the time the informed consent is signed through 30 days after the last dose of MEDI-573. Male subjects with partners of child-bearing potential must be surgically sterile or use contraceptive method as described above from the time of the initiation of MEDI-573 through 30 days after the last dose of MEDI-573.

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

3.1.2 Exclusion Criteria

Subjects must have *none* of the following:

1) Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for treatment of cancer

2) History of allergy or reaction to any component of the MEDI-573 formulation

3) Receipt of any chemotherapy or small molecule targeted therapy (such as sorafenib or other tyrosine kinase inhibitors) regimens within 4 weeks prior to the first dose of MEDI-573

4) Receipt of any biological or immunological based therapies (including, but not limited to, monoclonal antibody therapy such as bevacizumab or cancer vaccine therapies) within 6 weeks prior to the first dose of MEDI-573

5) Receipt of any investigational anticancer therapy within 4 weeks prior to the first dose of MEDI-573, or in the case of monoclonal antibodies, 6 weeks prior to the first dose of MEDI-573

6) Previous therapy with monoclonal antibodies directed against IGF-1R

7) Poorly controlled diabetes mellitus as defined by the investigator's assessment and/or glycosylated hemoglobin (HbA1c) reading > 8% within 28 days prior to the first dose of MEDI-573

8) New York Heart Association Grade ≥ 2 congestive heart failure

9) History of myocardial infarction, unstable angina, transient ischemic attack or stroke within the previous 6 months prior to the first dose of MEDI-573

10) History of other invasive malignancy within 5 years except for cervical carcinoma in situ (CIS), non-melanomatous carcinoma of the skin or ductal carcinoma in situ (DCIS) of the breast that have been surgically cured

11) Evidence of significant active infection requiring antimicrobial, antifungal, antiparasitic, or antiviral therapy or for which other supportive care is given

12) Use of immunosuppressive medication other than steroids within 7 days before the first dose of MEDI-573

13) Use of systemic steroids within 7 days before the first dose of MEDI-573 (inhaled and topical corticosteroids are permitted). Subjects may take replacement doses of steroids (defined as ≤ 30 mg/day hydrocortisone or the equivalent) if on a stable dose for at least 2 weeks prior to the first dose of MEDI-573.

14) Documented brain metastasis

15) Pregnancy or lactation

16) Previous medical history, or evidence, of an intercurrent illness that in the view of the principal investigator may compromise the safety of the subject in the study

17) Clinically significant abnormality on ECG

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

19) Refusal to undergo biopsy of bladder cancer or bladder cancer metastasis pre- and post-administration of MEDI-573 (dose-expansion subjects only)

3.2 Enrollment into the Study

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

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

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

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

3.3 Assignment of Treatment Group (Study Entry)

The procedure for study entry is as follows:

- The investigator or designee confirms that written informed consent and HIPAA authorization has been obtained and that the subject meets all eligibility criteria.
- The investigator or designee faxes the eligibility form to the Sponsor with the SID previously assigned by the Sponsor, and the subject's baseline characteristic(s) used to verify that it is the same subject.
- The Sponsor assigns the subject to a cohort.
- A confirmatory fax/email with this information is sent to the investigator/designee.

A subject is considered entered into the study at the time of investigational product administration (Cycle 1, Day 1). Enrollment in the dose-expansion phase can occur simultaneously with Cohorts 6 and 7.

3.4 Blinding

This study is not blinded because only one treatment is used in this study.

3.5 Investigational Product (MEDI-573)

3.5.1 MEDI-573 Supplies and Accountability

MEDI-573 is manufactured by MedImmune, LLC, One MedImmune Way, Gaithersburg, MD 20878. MEDI-573 will be distributed to clinical sites using designated distribution centers. MEDI-573 is supplied as a white to off-white, lyophilized powder. Each vial contains [redacted] nominal [redacted] of active investigational product. MEDI-573 will be reconstituted with 4.0 mL water for injection (WFI) [redacted] The reconstituted solution [redacted] will be further diluted into a saline bag for IV infusion.

The MEDI-573 formulation is described in Table 3.5.1-1. MEDI-573 must be stored at 2°C to 8°C (36°F to 46°F).

Table 3.5.1-1 MEDI-573 Formulation

Ingredient	[redacted]
Active Ingredients: MEDI-573 [a]	[redacted]
Inactive Ingredients: Polysorbate-80 Trehalose Dihydrate L-Histidine L-Histidine Hydrochloride Monohydrate	[redacted]
Vial Size	[redacted]

[a] Lyophilized MEDI-573 powder is to be initially reconstituted with 4 mL of water for injection [redacted] prior to dilution for intravenous infusion.

The Sponsor will provide the investigator with adequate quantities of MEDI-573. The investigator is required to maintain accurate Investigational Product (IP) accountability records of use of the MEDI-573 vials. The investigator-appointed IP Manager/site pharmacist will be responsible for IP accountability and dose preparation. Upon completion of the study, copies of all study IP accountability records will be returned to the Sponsor.

Specific details regarding IP supplies, dose preparation, and accountability will be provided in the IP Manual supplied to the sites.

3.5.2 Treatment Regimens

Subjects will be treated in the dose-escalation phase of the study with 1 of 5 dosage levels of MEDI-573 [redacted] (Table 3.5.2-1) administered as [redacted] IV infusion once every 7 days, on Days 1, 8, and 15 of repeating 21-day cycles (Cohorts 1 through 5). Two additional dose escalation cohorts will evaluate an alternate every-3-week treatment schedule: [redacted] Cohort 6 [redacted] and [redacted] Cohort 7, if applicable [redacted] administered as [redacted] IV infusion on Day 1 of each 21-day cycle. [redacted]. The decision to continue enrollment in Cohort 7 [redacted] will be based on the Sponsor's assessment of PK, pharmacodynamic, IM, and safety assessments obtained from subjects' exposure to MEDI-573 at the [redacted] Cohort 6 [redacted]. The rules for enrolling in the next higher cohort are described in Section 4.9.

The dose-expansion phase will evaluate PK and pharmacodynamic parameters and determine tumor response in approximately 20 subjects with advanced urothelial carcinoma (eg, bladder cancer). Two cohorts of approximately 10 subjects each will be examined in the dose-expansion phase at dose levels [redacted] every 7 days. The first 10 subjects enrolled into the dose expansion phase will receive doses of MEDI-573 [redacted] every 7 days. The decision to continue enrollment of subjects in the lower [redacted] dose-expansion cohort will be based on pharmacodynamic assessments of tissue obtained from subjects pre and post exposure to MEDI-573 at the [redacted] dose level. In the event there is insufficient activity at the tissue level in the higher dose expansion cohort, the sponsor may halt dose expansion and no additional subjects will be enrolled into the expansion phase.

In the dose escalation phase (Cohorts 1 through 5 only) and the dose expansion phase, in Cycle 2 and beyond, a dose can be delayed up to 7 days based on hematologic and nonhematologic toxicities, according to the conditions described in Section 3.5.5, but all 3 doses (Cohorts 1 through 5 and the dose expansion phase) must be completed within the cycle in order for the cycle to be considered complete. Subjects who do not receive all required doses within a cycle will not advance to the next cycle and will be removed from treatment. Each new cycle will begin 7 days after the last dose of the previous cycle (Cohorts 1 through 5 and the dose expansion phase). Subjects in Cohorts 6 and 7 cannot have a delay in treatment due to hematologic or nonhematologic toxicities. For Cohorts 1 through 5 and the expansion phase, all visits during Cycle 2 and subsequent visits may occur in a ± 2-day window to accommodate schedule changes, but doses of MEDI-573 must not occur more frequently than every 6 days. For Cohorts 6 and 7 (if applicable), all visits during Cycle 2 and subsequent visits may occur in a + 2-day window to accommodate schedule changes, but dosing of MEDI-573 must not occur more frequently than every 21 days.

Treatment with MEDI-573 will continue until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal. Rules for dose-escalation are described in Section 4.9. Intra-subject dose-escalation will not be allowed. Dose reduction for toxicities other than DLTs will be allowed as described in Section 3.5.5.

Table 3.5.2-1 Summary of Dose Cohorts

Dose Cohort	Number of Subjects	MEDI-573 Dose
1	3-6	[redacted] IV infusion once every 7 days
2	3-6	[redacted] infusion once every 7 days

Table 3.5.2-1 Summary of Dose Cohorts

Dose Cohort	Number of Subjects	MEDI-573 Dose
3	3-6	[redacted] IV infusion once every 7 days
4	3-6	[redacted] IV infusion once every 7 days
5	3-6	[redacted] IV infusion once every 7 days
6	3-6	[redacted] V infusion once every 21 days
7 (if applicable)	3-6	[redacted] IV infusion once every 21 days
Dose-expansion	Up to 20	[redacted] IV infusion once every 7 days

IV = intravenous
Note: The dose-expansion phase will evaluate PK and pharmacodynamic parameters and determine tumor response in approximately 20 subjects with advanced urothelial carcinoma (eg, bladder cancer).

3.5.3 Investigational Product Preparation

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

The volume (dose) of MEDI-573 will be calculated based on the subject's body weight (kg) (obtained prior to the first administration of MEDI-573 in each treatment cycle) and the subjects dose level (mg).

3.5.3.1 Reconstitution of MEDI-573 Vials

Each MEDI-573 vial will be reconstituted with 4.0 mL of sterile water for injection (WFI) for each vial. To reconstitute the lyophilized product, slowly add 4.0 mL of sterile WFI to the vial. The vial should be tilted slightly and gently rotated or swirled for 30 seconds or until dissolution is complete. Do not shake or vigorously agitate the vial. This is a critical step to avoid prolonged foaming. Reconstituted MEDI-573 should stand undisturbed at room temperature for a minimum of 2 minutes until the solution clarifies. Reconstituted MEDI-573 does not contain a preservative and should be administered promptly (no longer than 6 hours) after reconstitution. MEDI-573 is used as a single-use vial and any unused portion must be discarded.

3.5.4 Administration of Investigational Product

All subjects must be weighed (according to institutional practice) prior to each treatment cycle for calculation of MEDI-573 dosing.

MEDI-573 will be administered to subjects on an outpatient basis as follows:

1) Before the MEDI-573 infusion is started, epinephrine 1:1,000, dexamethasone 10 mg, and diphenhydramine (50 mg), or another functionally equivalent H1 blocker, for IV administration and resuscitation equipment for the emergency management of an anaphylactic reaction will be available.
2) MEDI-573 will be administered as a 60-minute IV infusion once every 7 days (Cohorts 1 through 5 and the dose expansion phase) or as a 90-minute IV infusion once every 21 days (Cohorts 6 and 7).The Investigator or his/her qualified designee will infuse MEDI-573 until the entire dose is delivered over the infusion period. Vital signs (temperature, respiration rate, pulse, and blood pressure) will be measured immediately prior to MEDI-573 infusion, at every 15 minutes (±5 minutes) during the MEDI-573 infusion, at the completion of the infusion (±5 minutes) and 30 and 60 minutes (±5 minutes) after completion of the MEDI-573 infusion and will be captured in the subject's source documents.
3) In the event of an infusion-related reaction, the infusion rate of MEDI-573 may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. Acetaminophen 650 mg and/or an antihistamine (eg, diphenhydramine 50 mg) or equivalent medications per institutional standard may be administered. Alternatively, or in addition, the rate of infusion of MEDI-573 may be diminished at the discretion of the investigator. Any such activities must be recorded appropriately. If the infusion reaction is severe or prolonged, methylprednisolone 100 mg (or the equivalent) should be administered as well. In such subjects who experience an infusion reaction, prophylactic administration of acetaminophen and/or diphenhydramine or the equivalents may be considered for subsequent administration of MEDI-573.
4) Subjects will remain at the study site for at least 60 minutes after the MEDI-573 infusion for medical monitoring.

Since the compatibility of MEDI-573 with other IV medications and solutions, other than 0.9% Sodium Chloride for Injection, is not known, the MEDI-573 solution should not be infused through an IV line in which other solutions or medications are being administered. The date, start time, and completion time of MEDI-573 administration must be recorded in source documents.

3.5.5 Dose Modifications of MEDI-573 Due to Toxicity

Dose modifications of MEDI-573 will be based on hematologic and nonhematologic toxicities that cannot be attributed to another cause such as disease progression or accident following the first cycle of treatment (Table 3.5.5-1). Both hematologic and nonhematologic toxicities will be graded according to NCI CTCAE V3.0. All DLTs must be documented as an AE on the source document.

Table 3.5.5-1 MEDI-573 Dose Modification Table

Hematologic or Nonhematologic Toxicity	Dose Modification of MEDI-573
Grade ≤ 1	None
Grade 2	Cohorts 1 through 5 and the Expansion Phase Withhold MEDI-573 for up to 7 days until resolution to Grade ≤ 1 or baseline and resume at current dose level. Grade 2 laboratory toxicities that do not have clinical significance may not require dose delay. The Medical Monitor should be consulted in the event of Grade 2 laboratory toxicities that are deemed clinically insignificant to determine if dosing may continue. Discontinue MEDI-573 if MEDI-573 is withheld for > 7 days without resolution of toxicity to Grade ≤ 1 or baseline unless clearly attributable to another cause such as disease progression or accident. Cohorts 6 and 7 (if applicable) The Medical Monitor should be consulted in the event of Grade 2 laboratory toxicities that are deemed clinically insignificant to determine if dosing may continue. Discontinue MEDI-573 if the toxicity does not return to Grade ≤ 1 or baseline prior to Day 1 of the subsequent cycle unless clearly attributable to another cause such as disease progression or accident.

Table 3.5.5-1 MEDI-573 Dose Modification Table

Hematologic or Nonhematologic Toxicity	Dose Modification of MEDI-573
Grade 3 or 4	**First Occurrence:** Cohorts 1 through 5 and the Expansion Phase: Withhold MEDI-573 for up to 7 days until resolution to Grade ≤ 1 or baseline. Discontinue MEDI-573 if no clinical benefit has been documented . If MEDI-573 is withheld for > 7 days without resolution of toxicity to Grade ≤ 1 or baseline, discontinue MEDI-573 regardless of clinical benefit Cohorts 6 and 7 (if applicable) Discontinue MEDI-573 if no clinical benefit has been documented and the toxicity does not resolve to Grade ≤1 or baseline by Day 1 of the subsequent cycle. For all subjects who experience a Grade 3 or 4 toxicity that resolves as above, and who have achieved some degree of clinical benefit while on MEDI-573 therapy, the Food and Drug Administration (FDA) will be consulted regarding the possibility of continued administration of MEDI-573. MEDI-573 therapy should not be continued without agreement from the FDA. **Second Occurrence:** Discontinue MEDI-573.

If Grade ≥ 3 toxicity that is at least possibly attributable to MEDI-573 is observed in a subject in the second or greater cycle, dose escalation will be temporarily suspended to review the cumulative safety data. Such an event may prompt cessation of dose escalation or modification of the dose-escalation scheme, including lowering of subsequent doses from the first cycle dose, if appropriate. Subjects may continue to receive MEDI-573 during this review and subjects may continue to be enrolled into an open cohort until a determination of necessary action, if any, is made.

3.5.6 Concomitant Medications

All concomitant medications used by the subject from the time the subject signs the informed consent form through 30 days after the last dose of MEDI-573 will be recorded on source documentation.

The Sponsor must be notified if any subject receives prohibited concomitant medications.

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

3.6 Schedule of Subject Evaluations

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

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

A schedule of screening and treatment visit procedures is presented in Table 3.6-1, and Table 3.6-2. A schedule of follow-up visit procedures is presented in Table 3.6-3. A summary of biopsy collection is provided in Table 3.6-4. For Cohorts 1 through 5 and the expansion phase, all visits during Cycle 2 and subsequent visits may occur in a ± 2-day window to accommodate schedule changes, but dosing of MEDI-573 must not occur more frequently than every 6 days. For Cohorts 6 and 7, all visits during Cycle 2 and subsequent visits may occur in a + 2-day window to accommodate schedule changes, but dosing of MEDI-573 must not occur more frequently than every 21 days.

Table 3.6-1 Schedule of Subject Evaluations: Screening and Treatment Periods (Dose Escalation Cohorts 1 through 5 and the Expansion Phase)

Evaluation	Screen [a]	Cycle 1					End of Cycle 1 and start of Cycle 2	Cycle 2 and Every Cycle Thereafter			Every 2 Cycles	End of Treatment [d]
		Day 1	Day 2	Day 3	Day 8	Day 15	≥Day 15≤Day21	Day 1	Day 8	Day 15		
Written informed consent and HIPAA	X											
Verify eligibility criteria	X	X										
Medical history	X											
Serum βhCG	X											
Urine βhCG		X						X				
MEDI-573 administration [b]		X			X	X		X	X	X		
Physical examination [c]	X	X						X			X	X
Height	X											
Weight	X	X						X				X
Vital signs [e]	X	X		X	X	X		X	X	X		X
ECG [f]	X	X [g]						X				X
Hematology [h]	X	X		X	X	X		X	X	X		X
Serum chemistry [i]	X	X		X	X	X		X	X	X		X

Table 3.6-1 Schedule of Subject Evaluations: Screening and Treatment Periods (Dose Escalation Cohorts 1 through 5 and the Expansion Phase)

Evaluation	Screen [a]	Cycle 1					End of Cycle 1 and start of Cycle 2	Cycle 2 and Every Cycle Thereafter			Every 2 Cycles	End of Treatment [d]
		Day 1	Day 2	Day 3	Day 8	Day 15	≥Day 15≤Day21	Day 1	Day 8	Day 15		
Urinalysis [j]	X	X			X	X		X	X	X		X
AE/SAE assessment	X	X		X	X	X		X	X	X	X	X
Concomitant medications	X	X		X	X	X		X	X	X	X	X
CT or MRI scans	X										X	X
Karnofsky performance status	X	X						X				X
Circulating tumor cells [p]	X							X				X
MEDI-573 serum concentration [k]		X	X	X	X	X		X	X	X		X
Anti-MEDI-573 antibodies [l]		X						X				
Blood biomarker analysis [m]		X	X	X	X	X		X	X	X		X
Whole blood RNA analysis	X						X [q]					X
Archived tumor sample [n]	X											

Table 3.6-1 Schedule of Subject Evaluations: Screening and Treatment Periods (Dose Escalation Cohorts 1 through 5 and the Expansion Phase)

Evaluation	Screen [a]	Cycle 1					End of Cycle 1 and start of Cycle 2	Cycle 2 and Every Cycle Thereafter			Every 2 Cycles	End of Treatment [d]
		Day 1	Day 2	Day 3	Day 8	Day 15	≥Day 15≤Day21	Day 1	Day 8	Day 15		
Tumor biopsies [o]	X [q]						X [q]					
Exfoliated urothelial cells (dose-expansion phase only)[r]	X						X [q]	X				X
Urine for analysis of soluble factors (dose-expansion phase only) [p]	X	X			X	X	X [q]	X		X		X

[a] Screening evaluations must be performed within 28 days prior to first administration of MEDI-573.
[b] MEDI-573 will be administered as a 60-minute IV infusion once every 7 days.
[c] Complete physical examination at Screening, after every 2 cycles, and at the end of treatment, and a physical examination for the purpose of disease evaluation at screening and on Day 1 of each cycle.
[d] This procedure does not need to be repeated if performed within 14 days of disease progression or treatment discontinuation.
[e] On days of MEDI-573 administration, vital signs will be recorded immediately prior to infusion, at every 15 minutes during infusion ±5 minutes, at completion of infusion (±5 minutes) and 30 and 60 minutes after completion of the infusion ±5 minutes.
[f] ECG equipment (with instant print-out and electronic transmission capabilities) and training will be provided to all study sites. All ECGs performed during the study will be obtained in triplicate (ie, 3 ECGS will be obtained within a 5 minute time interval). All ECGs should be done prior to PK draw for corresponding timepoints.
[g] Prior to infusion, at the time of completion of infusion (±5 minutes), 2 hours post completion of infusion (±15 minutes), and 6 hours (±15 minutes) after completion of infusion on Cycle 1 Day 1. All ECGs should be done prior to PK draw for corresponding timepoints.
[h] Hematology laboratory parameters include complete blood count (CBC) with differential and platelet count. HgA1c is measured at screening and end of treatment.

Table 3.6-1 Schedule of Subject Evaluations: Screening and Treatment Periods (Dose Escalation Cohorts 1 through 5 and the Expansion Phase)

Evaluation	Screen [a]	Cycle 1					End of Cycle 1 and start of Cycle 2	Cycle 2 and Every Cycle Thereafter			Every 2 Cycles	End of Treatment [d]
		Day 1	Day 2	Day 3	Day 8	Day 15	≥Day 15≤Day21	Day 1	Day 8	Day 15		

[i] Serum chemistry includes AST/ALT, total bilirubin, creatinine (and creatinine clearance at Screening), alkaline phosphatase, sodium, potassium, chloride, phosphorous, calcium, glucose, albumin, magnesium, LDH; TSH will be measured at Day 1 of each new cycle and at the end of treatment.

[j] Routine with microscopy; collected prior to or 48 hours after any cystoscopic procedures.

[k] PK samples will be collected at the following timepoints: Cycle 1 Day 1, pre-infusion and immediately post completion of infusion (±5 minutes), 2 hours ±15 minutes and 6 hours ±15 minutes post infusion; Day 2 at 24 hours post Day 1 infusion ±2 hours; Day 3 at 48 hours post Day 1 infusion ±2 hours; Day 8 and Day 15 pre- and post-infusion; Subsequent cycles treatment Days 1, 8, and 15 immediately prior to and post-infusion; and at the time of treatment discontinuation and 21 and 30 days after the last dose of MEDI-573.

[l] Sample collection for anti-MEDI-573 antibodies should be done pre dose (prior to MEDI-573 administration).

[m] Timepoints for biomarker collections are listed in Section **3.7.6.1**. Insulin and GH are collected at one timepoint per visit. Tumor markers are collected as clinically indicated.

[n] In the dose-escalation and dose-expansion phases, if an archived tumor sample is available and the subject provides consent, the sample is collected at screening only; Collect and ship per instructions in the Specimen Collection Manual.

[o] In dose-escalation and dose-expansion phases, includes any biopsy tissue from intermediate timepoints as routine clinical management permits (optional).

p Sample collection for circulating tumor cells in blood should be done prior to MEDI-573 administration.

q In the dose-expansion phase only, samples will be collected at two timepoints: prior to the first treatment in Cycle 1, and after the last dose on Cycle 1 but prior to administration of the first dose of Cycle 2 and should be done at the same timepoint for all specimen types.

[r] Sample collection for exfoliated urothelial cells (dose-expansion phase only) should be done prior to MEDI-573 administration.

Table 3.6-2 Schedule of Subject Evaluations: Screening and Treatment Periods (Dose Escalation Cohorts 6 and 7 Only)

Evaluation	Screen [a]	Cycle 1				Cycle 2 and Every Cycle Thereafter		Every 2 Cycles	End of Treatment [b]
		Day 1	Day 2	Day 3	Day 8	Day 1	Day 8		
Written informed consent and HIPAA	X								
Verify eligibility criteria	X	X							
Medical history	X								
Serum βhCG	X								
Urine βhCG		X				X			
MEDI-573 administration [c]		X				X			
Physical examination [d]	X	X				X		X	X
Height	X								
Weight	X	X				X			X
Vital signs [e]	X	X		X	X	X	X		X
ECG [f]	X	X [g]				X			X
Hematology [h]	X	X		X	X	X	X		X
Serum chemistry [i]	X	X		X	X	X	X		X
Urinalysis [j]	X	X				X			X

Table 3.6-2 Schedule of Subject Evaluations: Screening and Treatment Periods (Dose Escalation Cohorts 6 and 7 Only)

Evaluation	Screen [a]	Cycle 1				Cycle 2 and Every Cycle Thereafter		Every 2 Cycles	End of Treatment [b]
		Day 1	Day 2	Day 3	Day 8	Day 1	Day 8		
AE/SAE assessment	X	X		X	X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X	X
CT or MRI scans	X							X	X
Karnofsky performance status	X	X				X			X
MEDI-573 serum concentration [k]		X	X	X	X	X			X
Circulating tumor cells [l]	X					X			X
Anti-MEDI-573 antibodies [m]		X				X			
Blood biomarker analysis [n]		X	X	X	X	X			X
Whole blood RNA analysis	X								X
Archived tumor sample [o]	X								
Tumor biopsies [p]	X								

[a] Screening evaluations must be performed within 28 days prior to first administration of MEDI-573.

[b] This procedure does not need to be repeated if performed within 14 days of disease progression or treatment discontinuation

[c] MEDI-573 will be administered as a 90-minute IV infusion once every 21 days.

[d] Complete physical examination at Screening, after every 2 cycles, and at the end of treatment, and a physical examination for the purpose of disease evaluation at screening and on Day 1 of each cycle.

[e] On days of MEDI-573 administration, vital signs will be recorded immediately prior to infusion, at every 15 minutes during infusion ± 5 minutes, at completion of infusion (± 5 minutes) and 30 and 60 minutes after completion of the infusion ± 5 minutes.

Table 3.6-2 Schedule of Subject Evaluations: Screening and Treatment Periods (Dose Escalation Cohorts 6 and 7 Only)

Evaluation	Screen [a]	Cycle 1				Cycle 2 and Every Cycle Thereafter		Every 2 Cycles	End of Treatment [b]
		Day 1	Day 2	Day 3	Day 8	Day 1	Day 8		

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

[g] Prior to infusion and at completion of infusion (±5 minutes), All ECGs should be done prior to PK draw for corresponding timepoints.

[h] Hematology laboratory parameters include complete blood count (CBC) with differential and platelet count. HgA1c is measured at screening and end of treatment.

[i] Serum chemistry includes AST/ALT, total bilirubin, creatinine (and creatinine clearance at Screening), alkaline phosphatase, sodium, potassium, chloride, phosphorous, calcium, glucose, albumin, magnesium, LDH; TSH will be measured at Day 1 of each new cycle and at the end of treatment.

[j] Routine with microscopy

[k] PK samples will be collected at the following timepoints: Cycle 1 Day 1, pre-infusion and immediately post completion of infusion (± 5 minutes); Day 2 at 24 hours post Day 1 infusion ± 2 hours; Day 3 at 48 hours post Day 1 infusion ± 2 hours; Day 8; at Subsequent cycles Day 1 immediately prior to and post infusion; at the time of treatment discontinuation and 21 and 30 days after the last dose of MEDI-573

[l] Sample collection for circulating tumor cells in blood should be done prior to MEDI-573 administration.

[m] Sample collection for anti-MEDI-573 antibodies should be done pre dose (prior to MEDI-573 administration).

[n] Timepoints for biomarker collections are listed in Section 3.7.6.1. Insulin and GH are collected at one timepoint per visit. Tumor markers are collected as clinically indicated.

[o] If an archived tumor sample is available and the subject provides consent, the sample is collected at screening only; Collect and ship per instructions in the Specimen Collection Manual.

[p] Includes any biopsy tissue from intermediate timepoints as routine clinical management permits (optional).

Table 3.6-3 Schedule of Subject Evaluations: Follow-up Periods for All Subjects (Dose Escalation Cohorts 1 through 7 and the Expansion Phase)

Evaluations	Follow-up/Post-therapy		
	21 Days + 3 Days	30 Days + 3 Days	Every 3 Months ±2 Weeks
Physical examination		X	X [a]
Weight		X	
Vital signs		X	
ECG		X	
Hematology		X	
Serum chemistry (including TSH)		X	
Urinalysis		X	
Urine βhCG (women of childbearing potential only)		X	
AE/SAE assessment		X	
Concomitant medications		X	
CT or MRI scans			X[a]
Karnofsky performance status		X	X[a]
Subsequent anticancer therapy		X	X
Survival status			X
MEDI-573 serum concentration	X	X	X [b]
Anti-MEDI-573 antibodies		X	X [b]

Table 3.6-3 Schedule of Subject Evaluations: Follow-up Periods for All Subjects (Dose Escalation Cohorts 1 through 7 and the Expansion Phase)

Evaluations	Follow-up/Post-therapy		
	21 Days + 3 Days	30 Days + 3 Days	Every 3 Months ±2 Weeks
Blood biomarker analysis	X	X	X [b]

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

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

Table 3.6-4 Summary of Biopsy Collection

Specimen	Dose-Escalation Phase		Dose-Expansion Phase	
	Specimen to be Collected?	**Timing of Collection (relative to treatment)**	**Specimen to be Collected?**	**Timing of collection (relative to treatment)**
Archived tumor biopsy	YES [voluntary]	N/A	YES [voluntary]	N/A
Biopsy in the course of routine clinical care	YES [voluntary]	As clinical care may dictate	YES [voluntary]	As clinical care may dictate
Urothelial cells	NO	N/A	YES [voluntary]	When possible if obtained in the course of urologic procedure; otherwise part of standard urine collection
Biopsy of bladder cancer or bladder cancer metastasis	NO	N/A	YES [required]	Pre-treatment & before C2D1[a]

N/A = not applicable

[a] Samples will be collected at two timepoints: prior to the first treatment of Cycle 1, and after the last dose of Cycle 1 but prior to administration of the first dose of Cycle 2.

Screening (All Subjects Unless Otherwise Specified)

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

1) Written informed consent and HIPAA
2) Obtain SID from Sponsor
3) Verify eligibility criteria
4) Medical history
5) Perform complete physical examination

Note: Items 4 and 5 above are designed to collect information on the subject once enrolled into the study and start the screening process. Any new physical examination finding, symptom, disease, or untoward medical event that begins after written informed consent has been obtained, but before receipt of investigational product, that is not related to a protocol requirement must be added to the baseline medical history or physical examination.

6) Height

7) Weight

8) Vital signs

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

10) Blood and urine collection

- Hematology (complete blood count [CBC] with differential, platelets and HbA1c)
- Serum chemistry (AST/ALT, total bilirubin, creatinine, creatinine clearance, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, albumin, magnesium, and lactate dehydrogenase [LDH])
- Serum βhCG
- Urinalysis (routine urinalysis with microscopy)
- Exfoliated urothelial cells and analysis of soluble factors (from urine or bladder washes; dose-expansion cohort only)
- Whole blood RNA analysis
- Circulating tumor cells

11) Assess for SAEs and protocol related AEs

12) Concomitant medications

13) Evaluation of disease

- CT or MRI scans
- Physical examination
- Karnofsky performance status
- Tumor biopsy (required for expansion phase pre- and post-treatment; and may include tissue from intermediate timepoints as routine clinical management permits)

14) For all enrolled subjects, if archived tumor tissue is available and the subject provides consent to its release, ship block to Sponsor per instructions in the Specimen Collection Manual.

15) For all enrolled subjects, if the subject provides consent, tumor specimens acquired during the course of routine patient care will be shipped per instructions in the Specimen Collection Manual.

16) Complete the enrollment paperwork and fax to MedImmune within 48 hours prior to the first MEDI-573 infusion.

Cycle 1: Day 1 (All Subjects Unless Otherwise Specified)

1) Verify eligibility criteria

2) Update screening history and physical examination for evaluation of disease state

3) Assess for SAEs and protocol related AEs

4) Update concomitant medications

5) Obtain body weight for dosing calculations

6) Baseline blood collection (prior to infusion of MEDI-573)

- Hematology (CBC with differentials, platelets)
- Serum chemistry (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, albumin, magnesium, LDH, and TSH)
- Serum concentration of MEDI-573
- Anti MEDI-573 antibodies
- Blood biomarker analysis

7) Baseline urine collection (prior to infusion of MEDI-573)

- Urine βhCG (women of child bearing potential only)
- Urinalysis (routine urinalysis with microscopy)
- Urine for analysis of soluble factors (dose-expansion cohort only)

8) Karnofsky performance status

9) ECG (12-lead): prior to infusion, at the time of completion of infusion (± 5 minutes), 2 hours (± 15 minutes) post completion of infusion, and 6 hours (± 15 minutes) post completion of infusion (Cohorts 1 through 5 and the expansion phase only). Subjects enrolled in Cohorts 6 and 7 will have ECGs collected at the following timepoints: prior to infusion and at the completion of infusion (± 5 minutes). All ECGS performed will be obtained in triplicate (ie, 3 ECGS should be obtained within approximately a 5-minute time interval). All ECGs should be done prior to PK draw for the corresponding timepoint.

10) Vital signs (temperature, respiration rate, pulse, blood pressure) immediately prior to MEDI-573 infusion; at every 15 minutes during the infusion; at the end of the infusion (±5 minutes); and 30 and 60 minutes (±5 minutes) after completion of the infusion.

11) Administration of MEDI-573

12) Monitor for AEs and SAEs

13) Blood collection immediately after infusion (± 5 minutes) and at 2 hours (± 15 minutes) and 6 hours (± 15 minutes)

- Serum concentration of MEDI-573
- Blood biomarker analysis

Cycle 1: Day 2 (All Subjects)

1) Serum concentration of MEDI-573 (sample collection at 24 hours ± 2 hours post Day 1 infusion)

2) Blood biomarker analysis

Cycle 1: Day 3 (All Subjects)

1) Vital signs

2) Blood collection

- Hematology (CBC with differentials, platelets)
- Serum chemistry (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, albumin, magnesium, and LDH)
- Serum concentration of MEDI-573 (sample collection at 48 hours ± 2 hours post-Day 1 infusion)
- Blood biomarker analysis

3) AE/SAE assessment

4) Concomitant medications (changes since Day 1)

Cycle 1: Day 8 (All Subjects unless otherwise specified)

1) Blood collection prior to administration of MEDI-573

- Hematology (CBC with differentials, platelets)
- Serum chemistry (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, albumin, magnesium, and LDH)
- Serum concentration of MEDI-573

- Blood biomarker analysis

2) Urine collection prior to administration of MEDI-573

- Urinalysis (routine urinalysis with microscopy, Cohorts 1 through 5 and the expansion phase only)
- Urine for analysis of soluble factors (dose-expansion cohort only)

3) Vital signs (temperature, respiration rate, pulse, blood pressure) immediately prior to MEDI-573 infusion; at every 15 minutes (± 5 minutes) during the infusion; at the end of the infusion (± 5 minutes); and 30 and 60 minutes (± 5 minutes) after completion of the infusion.

4) Administration of MEDI-573 (Cohorts 1 through 5 and the expansion phase only)

5) Blood collection immediately post infusion of MEDI-573 (± 5 minutes, Cohorts 1 through 5 and the expansion phase only)

- Serum concentration of MEDI-573
- Blood biomarker analysis

6) AE/SAE assessment

7) Concomitant medications

Cycle 1: Day 15 (Cohorts 1 through 5 and Dose Expansion Phase only)

1) Blood collection prior to administration of MEDI-573

- Hematology (CBC with differentials, platelets)
- Serum chemistry (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, albumin, magnesium, and LDH)
- Serum concentration of MEDI-573
- Blood biomarker analysis

2) Urine collection prior to administration of MEDI-573

- Urinalysis (routine urinalysis with microscopy)
- Urine for analysis of soluble factors (dose-expansion cohort only)

3) Vital signs (temperature, respiration rate, pulse, blood pressure) immediately prior to infusion of MEDI-573; at every 15 minutes (± 5 minutes) during the infusion; at the end of the infusion (± 5 minutes); and 30 and 60 minutes (± 5 minutes) after completion of the infusion.

4) Administration of MEDI-573

5) Blood collection immediately post infusion of MEDI-573 (± 5 minutes)

- Serum concentration of MEDI-573

- Blood biomarker analysis

6) AE/SAE assessment

7) Concomitant medications

Day between ≥ Cycle 1, Day 15 and ≤ Cycle 2, Day1 (exclusive; Dose Expansion Phase only)

The following samples will be collected after the last dose on Cycle 1 but prior to administration of the first dose on Cycle 2:

- Whole blood for RNA analysis
- Tumor biopsies
- Exfoliated urothelial cells and analysis of soluble factors (from urine or bladder washes; dose-expansion cohort only)
- Urothelial cells (from urine, dose-expansion cohort only)

Cycle ≥ 2: Day 1 (All Subjects Unless Otherwise Specified)

The following evaluations will be performed on Day 1 of every cycle (ie, every 3 weeks), unless otherwise indicated, starting at Cycle 2:

1) Physical examination for evaluation of disease state

2) Update concomitant medications

3) Obtain body weight for dosing calculations

4) Blood collection prior to administration of MEDI-573
   - Hematology (CBC with differentials, platelets)
   - Serum chemistry (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, albumin, magnesium, LDH and TSH)
   - Serum concentration of MEDI-573 (blood sample collected immediately prior to MEDI-573 infusion)
   - Blood biomarker analysis
   - Circulating tumor cells
   - Anti-MEDI-573 antibodies

5) Urine collection prior to administration of MEDI-573
   - Urine βhCG (women of childbearing potential only)
   - Urinalysis (routine urinalysis with microscopy)

- Exfoliated urothelial cells and analysis of soluble factors (from urine or bladder washes; dose-expansion cohort only)

6) Administration of MEDI-573

7) Blood collection immediately post infusion of MEDI-573 (± 5 minutes)

- Serum concentration of MEDI-573
- Blood biomarker analysis

8) Vital signs (temperature, respiration rate, pulse, blood pressure) immediately prior to infusion of MEDI-573; every 15 minutes (± 5 minutes) during the infusion; at the end of the infusion (± 5 minutes); and 30 and 60 minutes (± 5 minutes) after completion of the infusion.

9) ECG (12-lead) (immediately prior to infusion of MEDI-573 only) All ECGs will be obtained in triplicate, ie, 3 ECGs should be obtained within approximately a 5-minute time interval.

10) AE/SAE assessment

11) Karnofsky performance status

Cycle ≥ 2: Day 8 (All Subjects Unless Otherwise Specified)

The following evaluations will be performed on Day 8 of every cycle, unless otherwise indicated, starting at Cycle 2:

1) Update concomitant medications

2) Blood collection prior to administration of MEDI-573

- Hematology (CBC with differentials, platelets)
- Serum chemistry (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, albumin, magnesium, and LDH)
- Serum concentration of MEDI-573 (blood sample collected immediately prior to infusion of MEDI-573, Cohorts 1 through 5 and the expansion phase)
- Blood biomarker analysis (Cohorts 1 through 5 and the expansion phase)

3) Urine collection prior to administration of MEDI-573

- Urinalysis (routine urinalysis with microscopy, Cohorts 1 through 5 and the expansion phase)

4) Vital signs (temperature, respiration rate, pulse, blood pressure) immediately prior to infusion of MEDI-573; every 15 minutes (± 5 minutes) during the infusion; at the end of the infusion (± 5 minutes); and 30 and 60 minutes (± 5 minutes) after completion of the infusion (Cohorts 1 through 5 and the expansion phase). Subjects in Cohorts 6 and 7 will have only one vital sign assessment during this visit.

5) Administration of MEDI-573 (Cohorts 1 through 5 and the expansion phase)
6) Blood collection immediately after infusion of MEDI-573 (± 5 minutes, Cohorts 1 through 5 and the expansion phase)
   - Serum concentration of MEDI-573
   - Blood biomarker analysis
7) AE/SAE assessment

Cycle ≥ 2: Day 15 (Cohorts 1 through 5 and Dose Expansion Phase only)

The following evaluations will be performed on Day 15 of every cycle, unless otherwise indicated, starting at Cycle 2:

1) Update concomitant medications
2) Blood collection prior to administration of MEDI-573
   - Hematology (CBC with differentials, platelets)
   - Serum chemistry (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, albumin, magnesium, and LDH)
   - Serum concentration of MEDI-573 (blood sample collected immediately prior to infusion of MEDI-573)
   - Blood biomarker analysis
3) Urine collection prior to administration of MEDI-573
   - Urinalysis (routine urinalysis with microscopy)
   - Urine for analysis of soluble factors (dose-expansion cohort only)
4) Vital signs (temperature, respiration rate, pulse, blood pressure) immediately prior to MEDI-573 infusion; every 15 minutes (± 5 minutes) during the infusion; at the end of the infusion (± 5 minutes); and 30 and 60 minutes (± 5 minutes) after completion of the infusion.
5) Administration of MEDI-573
6) Blood collection immediately after infusion of MEDI-573 (± 5 minutes)
   - Serum concentration of MEDI-573
   - Blood biomarker analysis
7) AE/SAE assessment

Every 2 Cycles (Within 3 Days Prior to Subsequent Cycle Starting at Cycle 3; (All Subjects):

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

1) Complete physical examination
2) AE/SAE assessment
3) Concomitant medications
4) Evaluation of disease
    - CT or MRI scans

End of Treatment (All Subjects Unless Otherwise Specified)

The following evaluations will be performed at the time the subject completes therapy or is withdrawn / discontinued from the study therapy, or at the time of the first objective disease progression, whichever comes first. These procedures do not need to be repeated if completed within 14 days of discontinuation of participation.

1) Complete physical examination
2) Weight
3) Vital signs
4) Blood and tissue collection
    - Hematology (CBC with differentials, platelets, and HgA1c)
    - Serum chemistry (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, albumin, magnesium, LDH, TSH)
    - Serum concentration of MEDI-573
    - Blood biomarker analysis
    - Whole blood RNA analysis
    - Circulating tumor cells
    - Urinalysis (routine urinalysis with microscopy)
    - Exfoliated urothelial cells and analysis of soluble factors (from urine or bladder washes; dose-expansion cohort only)
5) AE/SAE assessment
6) Concomitant medications

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

8) Disease evaluations (these procedures do not need to be repeated if they have been performed within 14 days of disease progression or treatment discontinuation)
   - CT or MRI scans
   - Physical examination
   - Karnofsky performance status

21 Days Post-therapy (+ 3 days; All Subjects)

1) Serum concentration of MEDI-573

2) Blood biomarker analysis

30 Days Post-therapy (+ 3 days; All Subjects)

The following evaluations will be performed at 30 days (+ 3 days) after the last dose of MEDI-573:

1) Complete physical examination
2) Weight
3) Vital signs
4) ECG (12-lead) All ECGs performed will be obtained in triplicate, ie, 3 ECGs should be obtained within approximately a 5-minute time interval.
5) Blood collection
   - Hematology (CBC with differentials, platelets)
   - Serum chemistry (AST/ALT, total bilirubin, creatinine, alkaline phosphatase, sodium, potassium, chloride, phosphorus, calcium, glucose, albumin, magnesium, LDH, and TSH)
   - Serum concentration of MEDI-573
   - Anti-MEDI-573 antibodies
   - Blood biomarker analysis
6) Urinalysis (routine urinalysis with microscopy)
7) Urine βhCG (women of child bearing potential only)
8) AE/SAE assessment
9) Concomitant medications
10) Karnofsky performance status

11) Subsequent anticancer therapy

Survival Follow-up / Every 3 Months Post-Therapy (± 2 weeks; All Subjects)

The following evaluations will be performed every 3 months (± 2 weeks) after the last dose of MEDI-573 as specified:

1) Complete physical examination
2) Evaluation of disease (subjects who discontinue treatment due to reasons other than disease progression or initiation of alternative anticancer therapy; these evaluations will be performed until documentation of disease progression, initiation of alternative anticancer therapy, or the end of study [defined as 1 year post entrance of the last subject into the study])
   - CT or MRI scans
   - Karnofsky performance status
3) Anti-MEDI-573 antibodies (this test will only be performed at 3 months after the last dose of MEDI-573 for all subjects)
4) Serum concentration of MEDI-573 (this test will only be performed at 3 months after the last dose of MEDI-573 for all subjects)
5) Blood biomarker analysis (this test will only be performed at 3 months after the last dose of MEDI-573 for all subjects)
6) Survival status and subsequent anticancer therapy by clinic visit or telephone contact until subject death or end of the study (all subjects).

3.7 Subject Evaluation Methods

3.7.1 Routine Laboratory Evaluations

Routine laboratory tests (hematology, serum chemistry, and urinalysis) during Screening and during the study will be performed in a licensed local clinical laboratory. Serum or urine pregnancy tests during the study will be performed in the clinic using a licensed test. Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Creatinine clearance (CrCl) will be calculated using the Cockcroft-Gault formula (Cockcroft and Gault, 1976) as follows:

For women:

$$CrCl = \frac{[140\text{-Age (years)}] \times \text{Mass (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

OR

$$CrCl = \frac{[140\text{-Age (years)}] \times \text{Mass (kg)}}{815 \times \text{serum creatinine (mmol/L)}} \times 0.85$$

For men:

$$CrCl = \frac{[140\text{-Age (years)}] \times \text{Mass (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

OR

$$CrCl = \frac{[140\text{-Age (years)}] \times \text{Mass (kg)}}{815 \times \text{serum creatinine (mmol/L)}}$$

3.7.2 Physical Examinations

Physical examinations will be performed as described in Table 3.6-1 and Table 3.6-2 (Schedule of Subject Evaluations: Screening and Treatment Periods) and Table 3.6-3 (Schedule of Subject Evaluations: Follow-up Periods) and will include assessments of the of the head, eyes, ears, nose, and throat (HEENT), respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, and endocrine systems; and height (at Screening only).

Vital signs (temperature, respiration rate, pulse, blood pressure) immediately prior to MEDI-573 infusion, at every 15 minutes during the infusion, at the end of the infusion (± 5 minutes) and 30 and 60 minutes (± 5 minutes) after completion of the infusion.

3.7.3 Electrocardiographic Evaluations

Twelve-lead ECGs will be performed as described in Table 3.6-1 and Table 3.6-2. Electrocardiogram equipment, with instant print out and electronic transmission capabilities, and training will be provided to all study sites. All ECGs performed during the study will be

obtained in triplicate, ie, 3 ECGs should be obtained within a 5 minutes time period. ECGs will be collected at Screening, Cycle 1 Day 1 (prior to infusion, at the time of completion of infusion [±5 minutes], 2 and 6 hours post completion of infusion [± 15 minutes, Cohorts 1 through 5 and the expansion phase only]), Day 1 of all subsequent cycles prior to dosing, at the time of discontinuation of MEDI-573 and at 30 days after the last dose of MEDI-573. All ECGs should be done prior to the PK draw for corresponding timepoints. Electrocardiograms will be transmitted and interpreted by a central vendor selected by the Sponsor.

3.7.4 Disease Evaluations

Tumor measurements and assessments will be based on RECIST (Therasse et al, 2000) and will be performed as specified in Table 3.6-1 and Table 3.6-2 (Schedule of Subject Evaluations: Screening and Treatment Periods) and Table 3.6-3 (Schedule of Subject Evaluations: Follow-up Periods). Additional tumor measurements may be performed at the discretion of the investigator or according to institutional practice. In subjects who achieve a complete or PR to treatment, tumor measurements will be repeated at least 4 weeks later using the same imaging tests. The same tumor assessment method should be used throughout the treatment period.

Tumor measurements must be recorded in metric notation by use of a ruler or calipers, and the same method/technique of tumor assessment must be used throughout the study. Whenever possible, tumor measurements will be conducted by the same person for a given subject. Imaging based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of the treatment. The analysis for tumor response will be based on the investigator's assessment during the conduct of the study. Radiographic images may be collected and archived by the Sponsor or its designee.

Tumor assessments may include the following evaluations: physical examination, chest radiograph (x-ray), CT or MRI scan of the chest, abdomen, and pelvis, and CT scan or MRI of the brain. CT scan or MRI of the brain will be performed if the subject is neurologically symptomatic. The same method must be used for all subsequent tumor assessments. Bladder tissue and/or bladder cancer tissue obtained via cystoscopic biopsy, transurethral resection of bladder tumor (TURBT) or other surgical removal may also be acquired in the course of routine subject care, if the subject consents.

- Lesions detected by physical examination will only be considered measurable if superficial, eg, skin nodules and palpable lymph nodes. Documentation by color photography including ruler is recommended for estimating the size of skin lesions.

- Chest x-ray. Lesions considered acceptable for measurement on chest radiograph should be clearly defined and surrounded by aerated lung. However, CT is preferable.
- CT scans of the chest, abdomen, and pelvis. CT should be performed with contiguous cuts in slice thickness of 10 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.
- MRI scans. MRI is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast enhanced T1 weighted images. However, there are no specific sequence recommendations.

Measurability of Tumor Lesions at Screening

At Screening, tumor lesions will be categorized as follows:

- **Measurable Lesions -** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (CT, MRI, x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters by use of a ruler or calipers.
- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan). Lesions considered truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confined and followed by imaging techniques, and cystic lesions.
- **Target Lesions -** All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions and recorded at Screening. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as the reference by which to characterize the objective tumor response.
- **Non-Target Lesions -** All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at Screening. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the study.

Response Criteria

Evaluation of Target Lesions

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

Evaluation of Non-Target Lesions

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

Evaluation of Overall Response

Table 3.7.4-1 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 3.7.4-1 Evaluation of Overall Response

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

Table 3.7.4-1 Evaluation of Overall Response

Target Lesions (T)	Non-target Lesions (NT)	New Lesions	Overall Response
PR	No-NT	No	PR
SD	No-NT	No	SD
SD	Non-PD and not Unknown	No	SD
No-T	Non-PD and not Unknown	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
Unknown	Non-PD	No	Unknown
Non-PD	Unknown	No	Unknown

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease
[a] No-NT is defined as no non-target lesions at baseline.
[b] No-T is defined as no target lesions at baseline.

3.7.5 Pharmacokinetic and Immunologic Evaluations

Blood samples for assessment of PK parameters of MEDI-573 and anti-MEDI-573 antibodies will be collected as described in Table 3.6-1, Table 3.6-2, and Table 3.6-3. At Cycle 1 Day 1, serum for PK analysis will be collected immediately prior to infusion, immediately following infusion, and for subjects in Cohorts 1 through 5 and the expansion phase only, PK samples will also be collected 2 and 6 hours post infusion. Subjects in Cohorts 6 and 7 will not have a 2 or 6-hour post infusion PK collection. Additional PK samples will be collected during Cycle 1 on Day 2 at 24 hours post Day 1 infusion ±2 hours and Day 3 at 48 hours post Day 1 infusion ±2 hours, Day 8 and Day 15 pre-infusion and immediately after the infusion. Subsequently PK samples will be collected pre-infusion and immediately following infusion (± 5 minutes) of MEDI-573 every 7 days (ie, on Days 1, 8, and 15 of each cycle, Cohorts 1 through 5 and dose expansion phase) or every 21 days (ie, on Day 1 of each cycle, Cohorts 6 and 7), at the time of discontinuation of MEDI-573, and at 21 days, 30 days and 3 months post-therapy. Samples for anti-MEDI-573 antibodies will be collected at Screening and subsequently prior to each infusion of MEDI-573.

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

3.7.6 Pharmacodynamic Evaluations

3.7.6.1 Biomarker Analysis

Blood collection for assessment of biomarkers and other biological processes will be performed as described in Table 3.6-1, Table 3.6-2, and Table 3.6-3.

Specific biomarkers may include free and bound IGF-1, IGF-2, and IGFBP levels, which will be evaluated by the Sponsor. Growth hormone, insulin, and tumor markers (when appropriate, such as prostate specific antigen [PSA] and cancer antigen 125 [CA 125]) will be drawn and evaluated at local clinical laboratories.

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

Growth hormone and insulin biomarkers will be collected at one timepoint per visit as described in Table 3.6-1, Table 3.6-2, and Table 3.6-3. Tumor markers will be collected as clinically indicated. Samples for biomarker evaluations to be shipped to the sponsor will be collected at the following timepoints:

- Cycle 1 Day 1: pre-infusion
- Cycle 1 Day 1: end of infusion
- Cycle 1 Day 1: 2 hours post-infusion
- Cycle 1 Day 1; 6 hours post-infusion
- Cycle 1 Day 2: 24 hours post-Day 1 infusion
- Cycle 1 Day 3: 48 hours post-Day 1 infusion
- Cycle 1 Day 8: pre-infusion
- Cycle 1 Day 8: end of infusion
- Cycle 1 Day 15: pre-infusion
- Cycle 1 Day 15: end of infusion
- Cycle 2 and higher Days 1, 8 and 15: pre-infusion and end of infusion (Cohorts 1 through 5 and the expansion phase)
- Cycle 2 and higher Day 1 only (Cohorts 6 and 7)
- End of Treatment
- Day 21 post-therapy

- Day 30 post-therapy
- 3 months post-therapy

The levels of IGF-1 and IGF-2 suppression by MEDI-573 determined during dose-escalation will be used to determine the dose administered to subjects enrolled in the dose-expansion phase of the study. In the dose-expansion phase of the study, exfoliated cells from voided urine, catheterized urine, and/or (in the case of subjects with bladders who may be undergoing cystoscopic procedures) bladder washings will be taken at Screening, on Day 1 of Cycle 2 and every cycle thereafter, and the End of Treatment. Cells and proteins from voided urine will be obtained from urine samples collected at Screening, Days 1, 8, and 15 of Cycle 1, on Days 1 and 15 of Cycle 2 and every cycle thereafter, and the End of Treatment. An additional sample for exfoliated urothelial cells from bladder washes or urine will be collected after the last dose on Cycle 1 but prior to administration of the first dose on Cycle 2.

Circulating tumor cells will be taken at Screening, on Days 1 of Cycle 2 and every cycle thereafter, and the End of Treatment and will be analyzed by the Sponsor.

3.7.6.2 Whole Blood RNA Analysis

Whole blood samples will be used to analyze the effects of MEDI-573 on levels of mRNA genes. This analysis is performed using Affymetrix whole genome expression array and TaqMan-based assay on selected panel of genes. Details regarding blood sample collection for assessment of mRNA expression are described in the Specimen Collection Manual provided by the Sponsor. If applicable, a CAST assay will be performed to evaluate potential point mutations in the key genes downstream of IGF signaling pathway to evaluate their correlations with clinical activity of MEDI-573.

3.8 Completion of Study and Loss to Follow-up

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

Subjects will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status. Investigators should document attempts to re-establish contact with missing

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

4 Safety Assessment

4.1 Adverse Events

4.1.1 Definition of Adverse Events

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

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

An AE includes but is not limited to:

- Any clinically significant worsening of a pre-existing condition;
- An AE occurring from overdose (ie, a dosage higher than that prescribed by a healthcare professional for clinical reasons, or a dosage higher than that described on the marketed product label) of an investigational or marketed product, whether accidental or intentional;
- An AE occurring from abuse (eg, use for nonclinical reasons) of an investigational or marketed product;
- Any laboratory abnormality that is judged by the investigator to be medically significant (except as noted in Section 4.10).
- An event related to a medical procedure or associated with the discontinuation of the previous use of an investigational or marketed product required by protocol (protocol-related AE).

4.1.2 Study Reporting Period for Adverse Events

All AEs that occur after a subject has received the investigational product through 30 days after the last dose of MEDI-573 must be reported by the investigator.

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

4.1.3 Recording of Adverse Events

Adverse events will be reported using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies and whether the event meets criteria as a SAE and therefore requires immediate notification of the Sponsor. See Section 4.2.1 for the definition of SAEs, and Section 4.3 and Section 4.4 for guidelines for assessment of severity and relationship, respectively. If the event has not resolved at the end of the study reporting period it will be documented as ongoing. If an AE evolves into a condition which becomes "serious" it will be reported on the SERIOUS ADVERSE EVENT (SAE) REPORT FORM.

4.2 Serious Adverse Events

4.2.1 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

- Results in persistent or significant disability/incapacity
- The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect in offspring of the subject
- A pregnancy should be reported to MedImmune Patient Safety as an immediately reportable event (IRE). A pregnancy should be followed for outcome and the health status of the mother and the child. If the child is born with any congenital anomaly of birth defect, this should be reported to MedImmune Patient Safety as a SAE.
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above
- Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.
- A serious event related to a medical procedure required by protocol prior to dosing of the study medication should also be reported to MedImmune Patient Safety as an SAE (protocol-related SAE).

4.2.2 Study Reporting Period for Serious Adverse Events

The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 30 days after the last dose of MEDI-573. After the initial SAE report, the investigator is required to follow each subject proactively and provide further information on the subject's condition to MedImmune Patient Safety.

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

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

4.2.3 Notification of Sponsor of Serious Adverse Events

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

MedImmune contact information:

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

MedImmune, as Sponsor of the study being conducted under an Investigational New Drug Application (IND), is responsible for reporting certain SAEs as IND safety reports to the FDA, other applicable regulatory authorities, and participating investigators, in accordance with the U.S. Code of Federal Regulations (21 CFR 312.32 and 312.33) ICH Guidelines, and/or local regulatory requirements. MedImmune may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by MedImmune as soon as it becomes available.

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

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

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

4.2.5 Recording of Serious Adverse Events

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

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

4.3 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by a health care professional who is qualified to review AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment and the severity categories of *Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5*. Severity of toxicity will be graded according to the NCI CTCAE V3.0.

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

AEs not described within the NCI CTC AE V3 will be reported using the severity categories as follows:

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

4.4 Assessment of Relationship

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

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

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

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

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

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

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

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

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

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

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

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

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

4.5 Other Events Requiring Immediate Reporting

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

1) Any withdrawal of consent during the study
2) Pregnancy or intent to become pregnant*

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

4.6 Safety Management During the Study

The MedImmune medical monitor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes immediate review of SAEs and timely review of other AEs reported during the study. The MedImmune Patient Safety Specialist has responsibility for the day-to-day safety monitoring of the study, including the receipt, review, investigation, and follow-up of SAEs reported by the clinical study sites.

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

4.7 Interruption or Discontinuation of Study Dosing in Individual Subjects

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

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

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

10) Subject non-compliance

11) Treatment with another investigational agent

12) Initiation of alternative anticancer therapy

Subjects who are permanently discontinued from investigational product will be followed for the full study period (through 30 days after the last dose of MEDI-573), including the collection of any protocol-specified blood and urine specimens, unless consent is withdrawn.

4.8 Interruption or Discontinuation of Study Dosing and Entry

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

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

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

3) Other events that in the judgment of the Medical Monitor are serious enough to warrant immediate review by the MedImmune Safety Monitoring Committee (SMC).

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

4.9 Dose Escalation and Dose Expansion

Rules for dose-escalation are as follows:

1) Dose-escalation will begin with a single subject in each cohort. If no DLTs (as defined in Section 4.10) are observed in this subject within the first 7 days of administration of MEDI-573, two additional subjects will be enrolled into that cohort and may be dosed immediately.

2) If no DLTs are observed in the first 3 subjects treated in the cohort through the first 21 days of administration of MEDI-573, enrollment in the next higher cohort will begin using the same rules described in Item 1.

Note: The decision to continue enrollment into Cohort 7 [redacted] will be based on the sponsor's assessment of PK, pharmacodynamic, IM, and safety data.

3) If 1 out of 3 subjects within a cohort experiences a DLT during the first 21 days of administration of MEDI-573, that cohort will be expanded to a total of 6 subjects provided no further subject experiences a DLT. If no further subjects experience a DLT through the first 21 days of administration of MEDI-573 in the expanded cohort, dose-escalation will continue in the next higher cohort using the same rules described in Item 1.

4) If 2 or more subjects within a cohort experience a DLT within the first 21 days of administration of MEDI-573, then the MTD will be exceeded and no further subjects will be enrolled into that cohort. If this happens, the preceding cohort will be evaluated as the MTD, with three additional subjects if this cohort has not previously been expanded to six subjects. If $\leq$ 1 of 6 subjects experience a DLT, this cohort shall be declared the MTD.

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

Twenty subjects with bladder cancer will be treated in the dose-expansion phase. Subjects enrolled in the dose-expansion phase of the study who consent will have archived tumor biopsies and/or biopsies obtained during surgical procedures conducted in the course of routine patient care. These subjects will provide cells collected in voided urine, catheterized urine, or bladder washings (optional), in addition to other scheduled evaluations. The dose for the expansion phase will be determined as follows:

1) Two cohorts of approximately 10 subjects each will be examined in the dose-expansion phase [redacted] every 7 days. The first 10 subjects enrolled into the dose-expansion phase will receive doses of MEDI-573 [redacted] every 7 days. The decision to continue enrollment of subjects in the lower [redacted] dose-expansion cohort will be based on pharmacodynamic assessments of tissue obtained from subjects pre- and post-exposure to MEDI-573 at [redacted] dose level. In the event there is insufficient activity at the tissue level in the higher dose-expansion cohort, the sponsor may halt dose-expansion and no additional subjects will be enrolled into the expansion phase

2) At the discretion of the Sponsor, an intermediate dose may be chosen for the dose-expansion phase of the study. Situations that might prompt selection of an intermediate dose include unexpected toxicities that do not meet definition of DLT or multiple similar toxicities in a cohort that do not meet the definition of a DLT.

4.10 Definitions of Dose-limiting Toxicities

Dose-limiting toxicities will be graded according to the NCI CTCAE V3.0 and will be assessed during the first cycle of treatment with MEDI-573 (Cycle 1, Day 1 through Cycle 1, Day 21).

A DLT is defined as:

1) Any Grade 3 or higher non-hematologic toxicity that occurs during the DLT assessment period where a cause other than the investigational product (such as disease progression or accident) cannot be reasonably justified with the following exceptions:
   - Grade < 4 serum-high glucose (fasting) with duration of < 24 hours.
   - Grade 3 fever (in the absence of neutropenia) defined as > 40.0°C (>104.0°F) that resolves to normal or baseline within 24 hours of treatment and is not considered an SAE; or
   - Grade 3 rigors/chills that respond to optimal therapy.
2) Any Grade 3 or higher hematologic toxicity that occurs during the DLT assessment period where a cause other than the investigational product (such as disease progression or accident) cannot be reasonably justified.

5 Statistical Considerations

5.1 Sample Size

For the dose-escalation phase, a minimum of 21 evaluable subjects (3 subjects in Cohorts 1 to 7) will be required if no subject experiences a DLT. Up to a total of 21 additional evaluable subjects may be enrolled if DLTs occur. Subjects are considered evaluable if they receive 3 doses of MEDI-573 (Cohorts 1 through 5) or 1 dose of MEDI-573 (Cohorts 6 and 7) and are followed for 21 days from the date of first dose (1 cycle) or they discontinue MEDI-573 due to dose-limiting toxicities (DLTs). Non-evaluable subjects will be replaced in the same cohort. The decision to continue enrollment in Cohort 7 [redacted] will be based on the Sponsor's assessment of PK, pharmacodynamic, IM, and safety

assessments obtained from subjects' exposure to MEDI-573 at [redacted] Cohort 6. The rules for enrolling in the next higher cohort are described in Section 4.9.

Two cohorts of approximately 10 subjects each will be examined in the dose-expansion phase [redacted] every 7 days. The first 10 subjects enrolled into the dose expansion phase will receive doses of MEDI-573 [redacted] every 7 days. The decision to continue enrollment of subjects in the lower [redacted] dose expansion cohort will be based on pharmacodynamic assessments of tissue obtained from subjects pre- and post-exposure to MEDI-573 at the [redacted] dose level. In the event there is insufficient activity at the tissue level in the higher dose expansion cohort, the sponsor may halt dose expansion and no additional subjects will be enrolled into the expansion phase.

5.2 Analysis Populations

The safety population will include all subjects who receive any MEDI-573.

The evaluable population for MTD will include all subjects who receive at least 1 full cycle of MEDI-573 and complete the safety follow-up through the DLT evaluation period, or experience any DLT.

5.3 Primary Endpoints

The primary objectives of this study are to evaluate the safety and tolerability of MEDI-573 in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists and to determine the MTD or OBED of MEDI-573 in this subject population. The OBED will be the dose at which all circulating IGF-1 and IGF-2 ligand is expected to be sequestered by MEDI-573, and will be based on pre-clinical data, PK/pharmacodynamic modeling, and pharmacodynamic analyses of circulating IGFs in representative samples of human blood collected in the dose-escalation phase of the study. All safety endpoints will be summarized descriptively. Adverse events and SAEs will be summarized by cohort, system organ class, severity, and relationship to MEDI-573 through 30 days after the last dose of MEDI-573. For assessment of the MTD, descriptive statistics will be provided to summarize the occurrence of DLTs by cohort.

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

5.4 Secondary Endpoints

Secondary objectives include assessments of PK, IM, pharmacodynamics, and antitumor activity of MEDI-573.

5.4.1 Pharmacokinetics of MEDI-573

The PK of MEDI-573 will be assessed by noncompartmental aproach using a validated computer software package [redacted] The noncompartmental pharmacokinetic parameters to be obtained and reported include, but are not limited to: C_{max}, T_{max}, and AUC, if the data allow. Descriptive statistics will be provided by cohort.

5.4.2 Immunogenicity of MEDI-573

Immunogenicity of MEDI-573 will be assessed and summarized descriptively by cohort.

5.4.3 Pharmacodynamics of MEDI-573

Suppression profiles of both IGF-1 and IGF-2 post administration of MEDI-573 in relation to time course of antibody concentrations in serum will be evaluated. Pharmacodynamic assessment of MEDI-573 treatment on the levels of circulating soluble protein biomarkers may include but are not limited to IGF receptor type 1 (IGF-1R), insulin receptor substrate-1 (IRS-1), mitogen-activated protein kinase (MAPK), insulin receptor (IR), antigen identified by monoclonal antibody Ki-67 (Ki67), caspase 3, and/or protein kinase B signaling protein (pAkt). TUNEL analyses may also be performed. Tissues to be assayed will include archived tumor biopsies (optional), and biopsies obtained during surgical procedures conducted in the course of routine patient care (optional). In the dose-expansion phase, additional samples will be obtained from subjects who may be undergoing cystoscopic procedures (optional); exfoliated cells collected in voided urine, catheterized urine, and/or bladder washings; and biopsies of bladder cancers or of bladder cancer metastatic deposits (with image guidance as needed). The biopsies of bladder cancers or bladder cancer metastatic deposits will be required before and after treatment with study drug for all subjects in the dose-expansion phase of the study. Samples will be collected at two timepoints; prior to the first treatment of Cycle 1, and after the last dose on Cycle 1 but prior to administration of the first dose of Cycle 2. Evaluation of the relationship of IGF pathway-related factors including IR-A expression levels using whole genome array and subject response to study treatments will be

performed on available fresh and/or archival tumor samples from subjects in the dose-escalation phase of the study and on fresh and archival tumor samples obtained in the dose-expansion phase of the study

In the dose expansion phase of the study, expression of IGF pathway factors including gene expression of IGF-1R, IR-A, IR-B and IGF response and modulation of the IGF-1R pathway in tumor cells. Expansion phase analyses include evaluating the relationship of IGF pathway-related components at the mRNA and miRNA level, as well as IR-A mRNA level in tumor biopsies obtained pre- and post-MEDI-573 treatment [redacted]s [redacted]. Additionally, protein expression levels will be evaluated using immunohistochemistry in tumor biopsies obtained pre- and post-MEDI-573 treatment. These studies serve the purpose of evaluating target expression and modulation in response to treatment with MEDI-573 and the downstream effect of neutralizing IGF in tumor tissue. Correlation between target expression and modulation in tumor tissue and clinical activity will also be evaluated. If applicable, a CAST assay will be performed to evaluate potential point mutations in the key genes downstream of IGF signaling pathway to evaluate their correlations with clinical activity of MEDI-573.

5.4.4 Antitumor Activity of MEDI-573

The antitumor activity of MEDI-573 will be assessed based on ORR, time to response TTR, DR, TTP, PFS, and OS.

Objective response rate is defined as the proportion of subjects with confirmed CR or confirmed PR according to RECIST guidelines. Confirmed responses are those that persist on repeat imaging study $\geq$ 4 weeks after the initial documentation of response.

Time to response will be measured from the start of treatment with MEDI-573 to the first documentation of objective response and will only be assessed in subjects who have achieved objective response.

Duration of response will be defined as the duration from the first documentation of objective response to the first documented disease progression. 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 calculated for the subgroup of subjects with an objective response.

Time to progression (TTP) will be measured from the start of treatment with MEDI-573 until the documentation of disease progression. Disease progression is defined according to RECIST guidelines. 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-573 will have TTP censored on the first date of treatment with MEDI-573.

Progression-free survival will be measured from the start of treatment with MEDI-573 until the documentation of disease progression or death due to any cause, whichever occurs first. Disease progression is defined according to RECIST guidelines. Progression-free survival will be censored on the date of last tumor assessment documenting absence of tumor progression for subjects who have no documented progression and are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Subjects having no tumor assessments after the start of treatment with MEDI-573 will have PFS censored on the first date of treatment with MEDI-573.

Overall survival (OS) will be determined as the time from the start of treatment with MEDI-573 until death. For subjects who are alive at the end of study or lost to follow-up, OS will be censored on the last date when subjects are known to be alive.

The time to event data including TTR, DR, TTP, PFS, and OS will be evaluated using Kaplan-Meier methods.

6 Data Collection and Monitoring

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

Data recorded on source documents will be transcribed onto a validated data collection instrument (a paper case report form or electronic data screen) provided by the Sponsor or

designee. The investigator must ensure the accuracy and completeness of the data reported, and its consistency with the source documentation.

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

Study documents (including subject records, copies of collected data, study notebook, and pharmacy records) must be kept secured in accordance with Sponsor policies and applicable regulatory requirements for a period of 2 years following marketing of MEDI-573 or for 2 years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

7 Human Subjects

7.1 Ethics and Regulatory Considerations

This study will be conducted accordance with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), the GCP's applicable to any region where the study is conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki. GCP 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.

The protocol will be reviewed and approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to the Sponsor and to the IRB/IEC, and the investigator will keep the IRB/IEC informed as to the progress of the study.

The investigator will explain the nature of the study and will inform the subject/legal representative that participation is voluntary and that they can withdraw/can withdraw their child at any time. Written informed consent will be obtained from each subject/legal representative prior to the screening procedures required for entry into the study. A copy of the signed consent form will be given to every subject/legal representative and the original will be maintained with the subject's records.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a subject's name to a subject identification number (SID) will be stored separately in another locked file cabinet. Study records may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject/legal representative, except as necessary for monitoring by regulatory authorities or the Sponsor of the clinical study. The principal investigator must also comply with all applicable privacy regulations (eg, Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

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

A list of IRB/IEC members should be obtained by the investigator and provided to the Sponsor.

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

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

The IRB/IEC must be informed by the principal investigator of informed consent form changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study; new information that may affect

adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

7.3 Informed Consent

Freely given informed consent will be obtained and documented for all subjects under this protocol (or a subject's legally authorized representative, if the subject is unable to provide informed consent) in accordance with the ICH guidelines on Good Clinical Practice (GCP), the GCP's applicable to any region where the study is conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki.

Information should be given in both oral and written form, and subjects or their legal representatives must be given ample opportunity to inquire about details of the study. The written informed consent document will comply with the ICH guidelines on GCP, the GCP's applicable to any region where the study is conducted and in accordance with the ethical principles set forth in the Declaration of Helsinki.

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

The consent form generated by the investigator must be approved by the IRB/IEC and be acceptable to 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 approved by the IRB/IEC and signed and dated by the subject or the subject's legally authorized representative, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities and/or the Sponsor's professional and Regulatory Compliance persons. The subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subject, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

8 Study Completion

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

9 Publications

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

10 Changes in the Protocol

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

11 References

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Appendix 1 Karnofsky Performance Status (KPS) Scale

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

Source: Adapted from D Karnofsky, W Abelman, L Craver, J Burchenal: The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer*. 1948; 1:634-656.

Appendix 2 New York Heart Association Cardiac Performance Status Assessment Function Scale

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

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

Appendix 3 National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0 (NCI CTCAE V3.0)

The NCI CTCAE V3.0 can be downloaded from the CTEP homepage (http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf).

Appendix 4 Summary of Amendments to the Protocol

[redacted] The protocol is amended to removed the provision of prophylactic medications, to clarify that patients in which dose limiting toxicities occur will not be continued on the study, and to indicate that Grade <4 serum high glucose will be an exception to the DLT criteria.

All text revisions resulting from this amendment are incorporated in the body of Protocol Version 2.0. Major changes to the protocol are described below. Added text is shown bolded and underlined (eg, **text**) and deleted text is shown with strikethrough (eg, ~~**text**~~).

1) Section 3.5.4 (Administration of Investigational Product):

MEDI-573 will be administered to subjects on an outpatient basis as follows:

1) ~~**In order to prevent possible infusion-related reactions, patients must receive oral diphenhydramine (Benadryl®) 50 mg and acetaminophen (Tylenol®) 650 mg, 30 minutes prior to their infusion of MEDI-573. Analogous premedications may be used according to institutional practice.**~~ **Before the MEDI-573 infusion is started, epinephrine 1:1,000, dexamethasone 10 mg, and diphenhydramine (50 mg), or another functionally equivalent H1 blocker, for IV administration and resuscitation equipment for the emergency management of an anaphylactic reaction will be available.**

2) ~~**Before the MEDI-573 infusion is started, epinephrine 1:1,000, dexamethasone 10 mg, and diphenhydramine (50 mg), or another functionally equivalent H1 blocker, for IV administration and resuscitation equipment for the emergency management of an anaphylactic reaction will be available.**~~ **MEDI-573 will be administered as a 60-minute intravenous infusion once every 7 days. The Principal Investigator or his/her qualified designee will infuse MEDI-573 until the entire dose is delivered over the 60-minute infusion period. Vital signs (temperature, respiration rate, pulse, and blood pressure) will be measured prior to MEDI-573 infusion, 15, 30 and 45 minutes (± 5 minutes) during the MEDI-573 infusion, at the completion of the infusion (± 5 minutes) and 30 and 60 minutes (± 5 minutes) after completion of the MEDI-573 infusion and will be captured in the patient's source documents.**

3) ~~**MEDI-573 will be administered as a 60-minute intravenous infusion once every 7 days. The Principal Investigator or his/her qualified designee will infuse MEDI-573 until the entire dose is delivered over the 60-minute infusion period. Vital signs (temperature, respiration rate, pulse, and blood pressure) will be measured prior to MEDI-573 infusion, 15, 30 and 45 minutes (± 5 minutes) during the MEDI-573 infusion, at the completion of the infusion (± 5 minutes) and 30 and 60 minutes (± 5 minutes) after completion of the MEDI-573 infusion and will be captured in the patient's source documents.~~ **If a subject experiences an infusion reaction during infusion of MEDI-573, diphenhydramine (Benadryl®) 50 mg and acetaminophen (Tylenol®) 650 mg, or the institutional equivalents, may be administered. Alternatively, or in addition, the rate of infusion of MEDI-573 may be diminished. Any such activities must be recorded appropriately. In such patients who experience an infusion reaction, prophylactic administration of acetaminophen and/or diphenhydramine or the equivalents may be considered for subsequent administration of MEDI-573.**

[redacted]

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

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

5) ~~**Recurrence**~~ **Occurrence** of Grade 3 or Grade 4 hematologic or non-hematologic toxicity after the first cycle of treatment.

[redacted]

3) Section 4.10 (Definitions of Dose-Limiting Toxicities):

- Grade ~~**3 or higher**~~ **≤4** serum-high glucose (fasting) with a duration of < 24 hours.

[redacted]

[redacted]

[redacted]. All text revisions resulting from changes to Protocol Amendment 2 are incorporated in the body of Protocol Amendment 3. These changes to the protocol are described below.

1. The Medical Monitor (and subsequent contact information) was changed from [redacted].
2. Versions of all protocol renditions were added to the Title page.
3. Globally changed the use of "+/-" to "±".
4. Corrected units of measure in Section 1.4 (Nonclinical Experience with MEDI-573) from "µg·day/mL/kg" to "(µg·day/mL)/(µg/kg)".
5. Added the text "and surgically sterile" to Inclusion criterion No. 10 regarding women of non-child-bearing potential.
6. Added footnote "p" to Blood Biomarker Analysis line in Table 3.6-1 (Schedule of Subject Evaluations) to reference timepoints in Section 3.7.6.2.
7. Added albumin and magnesium to the components to be assayed for in Serum Chemistry in Table 3.6-1 and Section 3.6.
8. Section 5.4.4 (Antitumor Activity of MEDI-573) and Study Abstract

Added text:

Disease progression is defined according to RECIST guidelines.

Reason for change:

Wording was added to clarify the use of RECIST guidelines for progression.

9. Section 3.5.2 (Treatment Regimens) and Study Abstract

Added text:

Subjects will be treated with 1 of 5 doses of MEDI-573 (0.5, 1.5, 5, 10, or 15 mg/kg) administered as a 60-minute IV infusion once ~~each week, ie~~,**every 7 days, on Days 1, 8, and 15 of repeating 21-day cycles** ~~every 7 days~~(Table 3.5.2-1). **In Cycle 2 and beyond, a dose can be delayed up to 7 days based on hematologic and nonhematologic toxicities, according to the conditions described in Section 3.5.5, but all 3 doses must be completed within the cycle in order for the cycle to be considered complete. Subjects who do not receive all 3 doses within a cycle will not advance to the next cycle and will be removed from treatment. Each new cycle will begin no fewer than 7 days after the last dose of the previous cycle.**

Treatment with MEDI-573 will ~~be administered as a 60-minute infusion~~ **continue** until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal. ~~Each cycle will be considered complete after administration of 3 doses.~~

Reason for change:

Wording was added/ changed to clarify the treatment regimen, dose delay, and cycle completion.

10. Section 3.5.5 (Dose Modifications of MEDI-573 Due to Toxicity) and Table 3.5.5-1 (MEDI-573 Dose Modification Table)

Added text:

Dose modifications of MEDI-573 will be based on hematologic and nonhematologic toxicities **that cannot be attributed to another cause such as disease progression or accident** following the first cycle of treatment (Table 11-1). Both hematologic and nonhematologic toxicities will be graded according to NCI CTCAE V3.0. All DLTs must be documented as an AE on the source document.

Table 11-1 MEDI-573 Dose Modification Table

Hematologic or Nonhematologic Toxicity	Dose Modification of MEDI-573
≤ Grade 1	None
Grade 2	Withhold MEDI-573 for up to 7 days until resolution to ≤ Grade 1 or baseline and resume at current dose level. **Grade 2 laboratory toxicities that do not have clinical significance may not require dose delay. The Medical Monitor should be consulted in the event of Grade 2 laboratory toxicities that are deemed clinically insignificant to determine if dosing may continue.** Discontinue MEDI-573 if MEDI-573 is withheld for > 7 days without resolution of toxicity to ≤ Grade 1 or baseline **unless clearly attributable to another cause such as disease progression or accident**.

Reason for change:

Language was added to clarify that laboratory changes of Grade 2 will not lead to dose delay unless they are considered clinically significant. It is required that if Grade 2 changes are to be considered insignificant, the medical monitor must be consulted prior to administration of MEDI-573.

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

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

12. Urine βhCG (women of child bearing potential only)

Reason for change:

Subjects in the trial are followed for 30 days post therapy for safety monitoring. Urine pregnancy testing was added to insure no subject became pregnant during this time period.

13. Section 3.7.6.2 (Biomarker Analysis)

Added text:

Blood collection for assessment of biomarkers and other biological processes will be performed as described in Table 3.6-1 and Table 3.6-2. Specific biomarkers will include free and bound IGF-1 and IGF-2, **which will be evaluated by the Sponsor**, growth hormone, insulin**, and** tumor markers (when appropriate, such as prostate specific antigen [PSA] and

cancer antigen 125 [CA 125]). **Blood samples for these specific biomarkers will be drawn and evaluated at local clinical laboratories.**

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

Biomarkers will be collected at the following timepoints:

- **Cycle 1 Day 1: pre-infusion**
- **Cycle 1 Day 1: end of Infusion**
- **Cycle 1 Day 1: 2 hours post-infusion**
- **Cycle 1 Day 1; 6 hours post-infusion**
- **Cycle 1 Day 2: 24 hours post-infusion**
- **Cycle 1 Day 3: 48 hours post-infusion**
- **Cycle 1 Day 8: end of Infusion**
- **Cycle 1 Day 15: end of Infusion**
- **Subsequent Cycles Day 1, 8 and 15: end of Infusion**
- **End of Treatment**

Reason for change:

Wording was added for clarification of blood collection timepoints for biomarkers and where analyses will be drawn and conducted.

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

Added text:

15. ≤ Grade 2 toxicities **(after completion of Cycle 1)** that do not return to ≤ Grade 1 or baseline within 7 days **unless clearly attributable to another cause such as disease progression or an accident.**
16. **Grade ≥2 toxicities that cause a cumulative delay of ≥21 days in three consecutive cycles.**

Reason for change:

This is to clarify that dosing delay is only allowed in Cycle 2 and greater, and that cumulative delays of 21 days over three or fewer cycles will lead to discontinuation. This insures that

cumulative delays will be detected as a potential safety signal and will not allow treatment in subjects who have multiple or sequential Grade 2 toxicities that cause dose delay.

[redacted]

[redacted] All text revisions resulting from changes to Protocol Version 3.0 are incorporated in the body of Protocol Version 4.0. These changes to the protocol are described below.

Study Abstract

Study Objectives (also Sections 2.1, 2.2, and 2.3)

- Primary objective 2 was updated to specify that the MTD or the OBED will be determined.
- Exploratory objective 1 was updated to specify that the levels of the listed biomarkers may be determined. The specific IGFBPs 1-3 were deleted in favor of specifying the more general IGFBPs.
- The list of biomarkers to be analyzed per exploratory objective 2 was modified to include levels of phosphorylated and/or unphosphorylated factors that may include but are not limited to IGF receptor type 1 (IGF-1R), insulin receptor substrate-1 (IRS-1), mitogen-activated protein kinase (MAPK), insulin receptor (IR), antigen identified by monoclonal antibody Ki-67 (Ki67), caspase 3, and/or protein kinase B signaling protein (pAkt). Deoxyuride-5'-triphosphate biotin nick end labeling (TUNEL) analysis may also be performed.
- The following exploratory objectives were added:
  - Evaluate the relationship of IGF pathway-related factors including IR expression levels using whole genome array and subject response to MEDI-573.
  - For the dose-expansion phase, evaluate the levels of proteins in urine that may include but are not limited to IGF-1, IGF-2, IGFBPs, and nuclear matrix protein (NMP), and explore their relationship with clinical outcome.
  - For the dose-expansion phase, evaluate the expression level of IGF pathway-related factors such as IGF-1R on subject response to treatment when circulating tumor cells are available.

Study Design (also Section 2.4 [Overview])

- The number of investigational sites in the USA was changed from 3 to 6 to approximately 10.

- Two dose cohorts were added to the dose-escalation phase of the study. Dose Cohort 6 is to be treated with 20 mg/kg MEDI-573. Dose Cohort 7 is to be treated with a dose > 20 mg/kg andbut ≤ 25 mg/kg MEDI-573.
- The number of subjects to be evaluated in the dose-escalation phase was changed from 15 to 30 to 21 to 42.
- The dose-expansion phase was modified to specify that 20 subjects with advanced urothelial carcinoma (eg, bladder cancer) will be treated. Two cohorts of approximately 10 subjects each will be examined in the dose-expansion phase. One of the dose-expansion cohorts will be treated at the OBED, the dose at which all circulating IGF-1 and IGF-2 ligand is expected to be sequestered by MEDI-573 based on pre-clinical data, PK/pharmacodynamic modeling, and pharmacodynamic analyses of circulating IGFs in representative samples of human blood collected in the dose-escalation phase of the study. The second dose-expansion cohort will be treated at a higher dose that may be the MTD and will not exceed 25 mg/kg. In the event that these two doses do not appear to be sufficiently different (ie, the higher dose is less than 10 mg/kg higher than the lower dose), then all 20 subjects in the expansion phase cohort will be treated at the higher dose level.
- The following text was added: Enrollment in the dose-expansion phase (starting with the lower expansion dose) can occur simultaneously with Cohorts 6 and 7 assuming safety has been established for that dose.

Treatment (also Section 2.4 [Overview])

- This section was modified to specify that subjects in the dose-escalation phase will be treated with 1 of 7 dosage levels of MEDI-573.
- Text was added to allow for an increased infusion time of 90-minute and up to 180 minutes for doses ≥ 20 mg/kg. The increased infusion time is being implemented to reduce the risk of infusion reaction at higher doses.

Subject Evaluation and Follow-Up (also Section 2.4 [Overview])

- Skin punch biopsy was removed from the list of evaluations at Screening and during the treatment period, and replaced with collection of biopsies obtained during surgical procedures conducted in the course of routine patient care; and collection of exfoliated cells from voided urine, catheterized urine, and/or bladder washings.
- Karnofsky performance status was added to the list of evaluations to be conducted after every 2 cycles of treatment until documentation of disease progression or initiation of alternative anticancer therapy.
- Text was added to clarify which biopsy tissues will be acquired, the timing of biopsies, and whether the biopsies are optional.

Sample Size

- The minimum number of evaluable subjects required for the dose-escalation phase was changed from 15 to 21. The maximum number of additional subjects to be enrolled if DLTs occur was also changed from 15 to 21.
- The following text was added to describe dosing in the dose-expansion phase: Two cohorts of approximately 10 subjects each will be examined in the dose-expansion phase. One of the dose-expansion cohorts will be treated at the OBED, the dose at which all circulating IGF-1 and IGF-2 ligand is expected to be sequestered by MEDI-573 based on pre-clinical data, PK/pharmacodynamic modeling, and pharmacodynamic analyses of circulating IGFs in representative samples of human blood collected in the dose-escalation phase of the study. The second dose-expansion cohort will be treated at a higher dose that may be the MTD and will not exceed 25 mg/kg.

Assessment of Endpoints

- The following text was added to define OBED: The OBED will be the dose at which all circulating IGF-1 and IGF-2 ligand is expected to be sequestered by MEDI-573 based on pre-clinical data, PK/pharmacodynamic modeling, and pharmacodynamic analyses of circulating IGFs in representative samples of human blood collected in the dose-escalation phase of the study.
- The exploratory endpoints were modified to specify that IGFBPs in general (rather than IGFBPs1-3 in particular) will be measured. In addition, the following text was added to describe which biopsy tissues will be acquired and when they will be collected: archived tumor biopsies (optional), and biopsies obtained during surgical procedures conducted in the course of routine patient care (optional). In the dose-expansion cohort, additional samples will be obtained from subjects who may be undergoing cystoscopic procedures (optional); exfoliated cells collected in voided urine, catheterized urine, and/or bladder washings; and biopsies of bladder cancers or of bladder cancer metastatic deposits (with image guidance as needed). The biopsies of bladder cancers or bladder cancer metastatic deposits will be required before and after treatment with study drug for all subjects in the dose-expansion phase of the study. Samples will be collected preferentially after the last dose on Cycle 1 and prior to administration of the first dose of Cycle 2. If clinical circumstances require samples to be deferred, collection will take place after the last dose on Cycle 2 and prior to administration of the first dose on Cycle 3. If clinical circumstances require samples to be deferred further, collection may occur prior to the first dose of a subsequent cycle or within 2 weeks of treatment discontinuation.

Section 1.1 (Background)

- A summary of the association of IGF activity and bladder cancer was added.

Section 1.2 (Anti-IGF Receptor Therapy Clinical Experience)

- A brief discussion of the recent Phase 3 NSCLC study of the IGF-1R targeting mAb figitumumab (Pfizer, CP-751,871) in combination with chemotherapy, which was suspended upon recommendation of a safety monitoring board due to toxicity, was added.

Section 1.6 (Rationale for the Study)

- The rationale for the doses to be administered and the molecular assays scheduled for the dose-expansion phase was added.
- Text was added to allow for increased infusion time for subjects receiving >20 mg/kg MEDI-573.
- Text was added to clarify biopsy tissue collection for the dose-expansion cohorts.

Section 2.4 (Overview)

- Figure 2.4-1 was updated to include Dose Cohorts 6 and 7, and the dose-expansion phase cohorts.
- Text was added to clarify dosing in the dose-expansion phase.

Section 3 (Study Procedures)

Section 3.1.1 (Inclusion Criteria)

- Inclusion criterion 3 was updated to specify that 20 subjects will be treated in the dose-expansion phase and that subjects must have measurable disease and a histologically confirmed diagnosis of advanced urothelial carcinoma (ie, pure or mixed histology transitional cell carcinoma of the upper or lower urinary tract).
- Text was added to inclusion criterion 9 to specify that creatinine clearance ≥ 50 mL/min will be acceptable for subjects in the dose-expansion phase.

Section 3.1.2 (Exclusion Criteria)

- Exclusion criterion 16 (refusal to undergo skin punch biopsy) was removed.
- Exclusion criterion 19 (refusal to undergo biopsy of bladder cancer or bladder cancer metastasis pre- and post-administration of MEDI-573 for dose-expansion subjects only) was added.

Section 3.3 (Assignment of Treatment Group [Study Entry])

- Text was added to clarify that when enrollment is possible into an escalation cohort as well as into an expansion cohort, subjects will be assigned to the dose-expansion cohort. When two expansion cohorts are available, subjects will be assigned in alternating fashion to the available cohorts until each expansion cohort is complete.

Section 3.5.2 (Treatment Regimens)

- This section was modified to specify that subjects in the dose-escalation phase will be treated with 1 of *7* dosage levels of MEDI-573.
- Table 3.5.2 was updated to include Cohorts 6 and 7, and the 2 dose-expansion phase cohorts. The option to increase infusion time for higher doses was added.
- The text was modified to specify that in both phases of the study, in Cycle 2 and beyond, a dose can be delayed up to 7 days based on hematologic and nonhematologic toxicities.

Section 3.5.4 (Administration of Investigational Product)

- Text was added to clarify that administration protocols will be identical for the dose-escalation and the dose-expansion phases of the study, excluding the dose level >20 mg/kg.
- The option to increase infusion time for higher doses was added.

Section 3.6 (Schedule of Subject Evaluations)

- Assessments for physical exam, HbA1c, circulating tumor cells, blood biomarker analysis, whole blood RNA analysis, archived tumor sample, tumor biopsy, urothelia from bladder washings, and eurothelia from voided urine were added to Table 3.6-1 and assessments for whole blood RNA analysis, archived tumor sample were changed in the table.
- A MEDI-573 serum concentration evaluation at 21 and 30 days post treatment was added to Table 3.6-2.
- Table 3.6-3 (Summary of Biopsy Collection) was added.

Screening

- Exfoliated urothelial cells (from urine or bladder washes; dose-expansion cohort only), whole blood RNA analysis, and circulating tumor cell count were added to the list of evaluations.
- Skin punch biopsy was removed from the list of evaluations. Tumor biopsy was added.

- Text was added to specify that for the dose-expansion phase, shipment of collected tissue will be per instructions in the Specimen Collection Manual.

Cycle 1, Day 8

- Blood biomarker analysis was added to the list of evaluations to be performed on blood collected prior to administration of MEDI-573.

Cycle 1, Day 15

- Blood biomarker analysis was added to the list of evaluations to be performed on blood collected prior to administration of MEDI-573.

Every Cycle (Starting at Cycle ≥2), Day 1

- Blood biomarker analysis was added to the list of evaluations to be performed on blood collected prior to administration of MEDI-573.

A collection timepoint for whole blood for RNA analysis, tumor biopsies, exfoliated urothelial cells from bladder washes, and urothelial cells from urine were added to the study schedule in the period between Cycle 1 Day 15 and Cycle 2 Day 1. This could be done for the period between Cycle 2 Day 15 and Cycle 3 Day 1 if not done after Cycle 1

Every Cycle (Starting at Cycle 2), Day 8 and Day 15

- Blood biomarker analysis was added to the list of evaluations to be performed on blood collected prior to administration of MEDI-573.

Every Cycle (Starting at Cycle 2), Day 15

- Exfoliated urothelial cell assessment was added

End of Treatment

- Soluble factors in urine, exfoliated urothelial cells (from bladder washes; dose-expansion phase only), circulating tumor cells, and tumor biopsy were added to the list of evaluations.

21 Days Post-therapy (+ 3 Days)

- Blood collection for determination of MEDI-573 serum concentration and for biomarker analysis were added.

30 Days Post-therapy (+ 3 Days)

- TSH was added to the list of evaluations.

Survival Follow-up/Every 3 Months Post-Therapy (± 2 weeks)

- Physical examination was added to the schedule.

Section 3.7.1 (Routine Laboratory Evaluations)

- The text was modified to specify that serum or urine pregnancy tests will be performed.

Section 3.7.4 (Disease Evaluations)

- Text was added to specify that bladder tissue and/or bladder cancer tissue obtained via cystoscopic biopsy, TURBT, or other surgical removal may also be acquired in the course of routine patient care, if the subject consents.

Section 3.7.6.1 (Biomarker Analysis)

- Pre-infusion biomarker assessments for Days 8 and 15 were added to the list of collection timepoints and at Days 21 and 30 post-therapy.
- Additional urine samples were added to obtain exfoliated urothelial cells for biomarker analysis at a timepoint between Day 15 of Cycle 1 and Day 1 of Cycle 2 and another between Day 15 of Cycle 2 and Day 1 of Cycle 3.

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

- Text was added to clarify that subjects who are permanently discontinued from investigational product will be followed for the full study period (through 30 days after the last dose of MEDI-573), including the collection of any protocol-specified blood and urine specimens, unless consent is withdrawn.

Section 4.9 (Dose Escalation and Dose Expansion)

- This section was modified to specify that 20 subjects with bladder cancer will be treated in the dose-expansion phase and that subjects enrolled in the dose-expansion phase of the study who consent will have archived tumor biopsies and/or biopsies obtained during surgical procedures conducted in the course of routine patient care. Subjects enrolled on the dose-expansion phase of the study will provide cells collected in voided urine, catheterized urine, or bladder washings (optional), in addition to other scheduled evaluations.
- Text regarding the use of pharmacodynamic assessments showing proportional increases in serum concentrations of MEDI-573 as a determinant of whether to escalate to successive doses was removed.
- Text describing dose-escalation in the dose-expansion phase was removed.

Section 5.1 (Sample Size)

- This section was modified to specify that a minimum of 21 evaluable subjects (3 subjects in Dose Cohort 1 to 7) will be required for the dose-escalation phase if no subject experiences a DLT, and up to 21 additional subjects may be enrolled if DLTs occur. For the dose-expansion phase, 20 subjects are required (10 per dose-expansion cohort).

Section 5.4.3 (Pharmacodynamics)

- The text was updated to include biomarker assessments on bladder tumor biopsies or metastatic deposits, biopsies obtained during surgical procedures conducted in the course of routine patient care and/or archival tumor samples, as well as through the use of exfoliated cells collected in voided urine, catheterized urine, and/or bladder washings (dose-expansion phase only).

Throughout the document

- MedImmune Product Safety was changed to MedImmune Patient Safety.
- The term patient was changed to subject.
- Roman numerals in protein names were replaced with Arabic numerals.
- Other minor text edits, corrections to acronyms, and wording changes.

[redacted] The protocol was amended to eliminate cohorts from the dose-escalation portion of the trial, clarify the dose-expansion phase of the trial, clarify certain sections, and make minor copy edits. All text revisions resulting from changes to Protocol Version 4.0 are incorporated in the body of Protocol Version 5.0. Major changes to the protocol are described below:

Study Abstract

Study Objectives (also Sections 2.1, 2.2, and 2.3)

Exploratory objectives were modified to increase the clarity of the description and two new exploratory objectives were added:

- Evaluate the relationship of IGF pathway-related components at the mRNA and miRNA level, includeing IR-A mRNA level in tumor biopsies obtained pre- and post-MEDI-573 treatment [redacted].
- Perform genomics and proteomics analyses on exfoliated cells collected in bladder washings from selected subjects.

Study Design (also Section 2.4 [Overview])

- The text was edited to remove Cohorts 6 and 7 from the escalation phase and correct the total sample size as a result. The two MEDI-573 doses to be used in the expansion phase were changed from the (1) OBED and (2) the dose at which

all MEDI-573 is expected to be sequestered based on PK/PD modeling to two discrete dose levels of MEDI-573, 5 and 15 mg/kg. These 2 dose levels were chosen because they showed complete suppression of IGF-1 and IGF-2 in PK analyses of subjects from the 5, 10, and 15 mg/kg dose cohorts, and because this dose range was an appropriate one to compare tolerability and biologic effects at the tumor level.

- The text in the sample size description of evaluable patients was edited for consistency to read "Subjects are considered evaluable if they receive 3 doses of MEDI-573 (1 cycle) and are followed for 21 days from the date of first dose or they discontinue MEDI-573 due to dose-limiting toxicities (DLTs). Non-evaluable subjects will be replaced in the same dose cohort."

Treatment (also Section 2.4 [Overview])

- Infusion times of 90- to 180-minutes for administration of MEDI-573 at doses > 20 mg/kg greater were removed because the maximum dose to be administered in the trial was set to 15 mg/kg. Appropriate modifications to the treatment schedule to reflect 60-minute infusions and include dose levels to the defined expansion cohorts based off available PK data were made.

Subject Evaluation and Follow-Up (also Section 2.4 [Overview])

- Text was added to clarify the schedule for required biopsy collections for the dose expansion phase of the trial.

Sample Size

- The minimum number of evaluable subjects for the dose-escalation phase was changed as a result of the removal of Cohorts 6 and 7. Dose levels were added to defined cohorts in the expansion phase based off of available PK data.
- The text in the sample size description of evaluable patients was edited for consistency to read "Subjects are considered evaluable if they receive 3 doses of MEDI-573 (1 cycle) and are followed for 21 days from the date of first dose or they discontinue MEDI-573 due to dose-limiting toxicities (DLTs). Non-evaluable subjects will be replaced in the same dose cohort."

Assessment of Endpoints

Secondary Endpoints

- The method for PK analysis and the parameters to be assessed was clarified.

Exploratory Endpoints

- Text was added to reflect the addition of the new exploratory objectives and assessments in the expansion phase of the trial.

Section 1.5 (Clinical Experience with MEDI-573)

- A brief discussion of the adverse events observed to date in MI-CP184 was added**.**

Section 1.6 (Rationale for the Study)

- The rationale for the doses to be administered and the molecular assays included in the dose-expansion was clarified.

Section 3.3 (Assignment of Treatment Group [Study Entry])

- Text was removed that addressed concurrent enrollment into escalation and expansion cohorts owing to no further recruitment into the dose-escalation phase of the trial.

Section 3.5.2 (Treatment Regimens)

- This section was modified to remove Cohorts 6 and 7 from the dose-escalation phase and to clarify the intended dose levels for the dose-expansion phase. Clarification was made regarding allowable windows for visits during Cycle 2 and higher.

Section 3.5.4 (Administration of Investigational Product)

- This section was modified to remove longer duration of infusions required for dose levels > 20 mg/kg that are no longer being tested in this study.

Section 3.6 (Schedule of Subject Evaluations)

- Clarification was made to this section regarding allowable windows for visits during Cycle 2 and higher. Text was added to Tables 3.6-1, 3.6-2 and 3.6-3 to clarify required assessment timepoints.
- Additional PK/PD timepoint for 3 months post dosing was added for additional safety follow-up.

Day between > Cycle 1, Day 15 and < Cycle 2, Day 1 (exclusive)

- Clarification was made to samples to be collected.

Day between C2D15 and C3D1 (exclusive)

- Section was removed as timepoint is no longer applicable.

Survival Follow-up / Every 3 Months Post-Therapy (± 2 weeks)

- The following text was added:

- Serum concentration of MEDI-573 (this test will only be performed at 3 months after the last dose of MEDI-573 for all subjects)
- Blood biomarker analysis (this test will only be performed at 3 months after the last dose of MEDI-573 for all subjects)

Section 3.7.5 Pharmacokinetic and Immunologic Evaluations

- Timepoint for PK analysis at 3 months post dose was added for additional safety follow-up

Section 3.7.6.1 Biomarker Analysis

- Required assessment timepoints were modified and/or deleted.

Section 3.7.6.2 Whole Blood RNA Analysis

- Additional text was added for planned analysis of samples.

Section 4.9 Dose Escalation and Dose Expansion

- Text was added to the dose expansion description to indicate planned dose levels.

Section 5.1 Statistical Considerations/Sample Size

- The minimum number of evaluable subjects for the dose-escalation phase was changed as a result of the removal of Cohorts 6 and 7. Dose levels were added to defined cohorts in the expansion phase based off of available PK data.
- The text in the sample size description of evaluable patients was edited for consistency to read "Subjects are considered evaluable if they receive 3 doses of MEDI-573 (1 cycle) and are followed for 21 days from the date of first dose or they discontinue MEDI-573 due to dose-limiting toxicities (DLTs). Non-evaluable subjects will be replaced in the same dose cohort."

Section 5.4.1 Pharmacokinetics of MEDI-573

- The method for PK analysis and the parameters to be assessed was clarified

[redacted]

[redacted] All text revisions resulting from changes to Protocol Amendment 4 are incorporated in the body of Protocol Amendment 5. These changes to the protocol are described below:

Study Abstract

Study Design (also Section 2.4 [Overview])

- Two dose cohorts were added to the dose-escalation phase of the study. Dose Cohort 6 is to be treated with 30 mg/kg MEDI-573 infused over 90 minutes every-3-weeks. Dose Cohort 7 is to be treated with 45 mg/kg infused over 90 minutes every-3-weeks.
- The number of subjects to be evaluated in the dose-escalation phase was changed from 15 to 30 to 21 to 42.
- Enrollment into Cohorts 6 and 7 will be limited to the Barbara Ann Karmanos Cancer Center, Detroit, MI 48201
- The decision to continue enrollment in Cohort 7 (ie, 45 mg/kg dose-escalation cohort) will be based on the Sponsor's assessment of PK, pharmacodynamic, IM and safety assessments obtained from subjects' exposure to MEDI-573 at the 30 mg/kg dose level (Cohort 6).

Treatment (also Section 2.4 [Overview])

- The dose level, treatment schedule and infusion rate for Cohorts 6 and 7 were added.
- This section was modified to specify that delays for toxicity are not allowed in Cohorts 6 and 7.
- A +2 visit window was added for Cohorts 6 and 7

Sample Size

- The minimum number of evaluable subjects required for the dose-escalation phase was changed from 15 to 21. The maximum number of additional subjects to be enrolled if DLTs occur was also changed from 15 to 21.

Section 1.6 (Rationale for the Study)

- Text was added to specify that MEDI-573 will be administered once every week as a 60-minute IV infusion for doses ≤ 15 mg/kg or as a 90-minute IV infusion for doses > 15 mg/kg.

Section 2.4 (Overview)

- Figure 2.4-1 was updated to include Dose Cohorts 6 and 7

Section 3 (Study Procedures)

Section 3.1.2 (Exclusion Criteria)

- Exclusion criterion 7 (diabetes criteria) was revised to state subjects with poorly controlled diabetes mellitus defined as an HbA1c reading > 8% within 28 days prior to the first dose of MEDI-573 are excluded.

Section 3.3 (Assignment of Treatment Group [Study Entry])

- Text was added to clarify that enrollment in the dose-expansion phase can occur simultaneously with Cohorts 6 and 7.
- A confirmatory fax or email with this information is sent to the investigator/designee.

Section 3.5.2 (Treatment Regimens)

- Two additional dose escalation cohorts were added to evaluate an alternate every-3-week treatment schedule: 30 mg/kg (Cohort 6) and 45 mg/kg (Cohort 7, if applicable) administered as a 90-minute IV infusion on Day 1 of each 21-day cycle.
- Enrollment into Cohorts 6 and 7 will be limited to the Barbara Ann Karmanos Cancer Center, Detroit, MI 48201.
- Instructions for handling toxicities in Cohorts 6 and 7 subjects were added.
- Visit windows for Cohorts 6 and 7 were added.

Section 3.5.4 (Administration of Investigational Product

- Instructions for administering MEDI-573 in Cohorts 6 and 7 were added.
- Instructions for handling infusion reactions were modified

Section 3.5.5 (Dose Modifications of MEDI-573 Due to Toxicity)

- The dose modification table was revised to explain how toxicities are managed in Cohorts 6 and 7.

Section 3.6 (Schedule of Subject Evaluations)

- Errors in Table 3.6-1 were corrected
- Table 3.6-2 was added to outline the schedule of assessments for Cohorts 6 and 7. Subsequent tables in this section were renumbered.

Section 3.7 (Interruption or Discontinuation of Study Dosing in Individual Subjects)

- Language was added to clarify that DLTs pertain only to subjects in the dose-escalation phase.

Section 3.7.3 (Electrocardiographic Evaluations)

- ECG collection timepoints for subjects in Cohorts 6 and 7 were added.

Section 3.7.5 (Pharmacokinetic and Immunologic Evaluations)

- PK collection timepoints for Cohorts 6 and 7 were added.

Section 3.7.6.1 (Biomarker Analysis)

- Language was added to clarify the collection timepoints for the biomarker analysis.

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

- Language was added to specify that the DLT period applies only to dose-escalation subjects.

Section 4.9 (Dose Escalation and Dose Expansion)

- A note was added to specify that the decision to continue enrollment into Cohort 7 (45 mg/kg dose) will be based on the sponsor's assessment of PK, pharmacodynamic, IM, and safety data.

Section 5.1 (Sample Size)

- The minimum number of evaluable subjects was increased to 21. The maximum number of evaluable subjects was increased to 21.
- Language was added to specify that the decision to continue enrollment in Cohort 7 (ie, 45 mg/kg dose-escalation cohort) will be based on the Sponsor's assessment of PK, pharmacodynamic, IM, and safety assessments obtained from subjects' exposure to MEDI-573 at the 30 mg/kg dose level (Cohort 6).

Throughout the document

- Other minor text edits, corrections to acronyms, and wording changes.
- Dose cohort was changed to Cohort to ensure consistency throughout the document