Clinical Study Protocol

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

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The following Amendment(s) and Administrative Changes have been made to this protocol since the date of preparation:

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Principal Investigator

The name and address of each investigator are shown in Supplement A.

For contact details of AstraZeneca personnel see Section 8.1.

INTRODUCTION & STUDY FLOW CHART

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

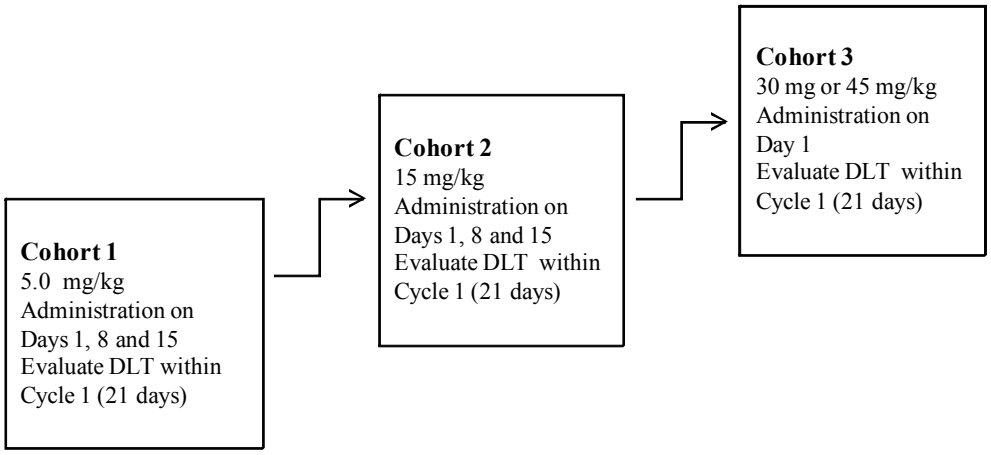
Introduction

MEDI-573 is a fully human IgG2 lambda (IgG2λ) monoclonal antibody that selectively binds to human insulin-like growth factor I and II (IGF-I and IGF-II). When neutralised, it inhibits the IGF-I and IGF-II signalling pathway. Thus, MEDI-573 is expected to have efficacy in treatment of tumours where IGF-I and IGF-II signalling pathway appear to play an important role in tumour cell growth. Once weekly repeat IV infusion of MEDI-573 to cynomolgus monkeys at doses up to 60 mg/kg for 13 weeks was well tolerated and there was no evidence of toxicity. Phase 1 dose escalation study of MEDI-573 (Study MI-CP184) is now on-going in US in advance to this study.

This study is a first phase 1, open-label, dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics of MEDI-573 in Japanese patients with advanced solid tumours refractory to standard therapy or for which no standard therapy exists. The starting dose of this study is 5.0 mg/kg/week.

The safety and tolerability of the starting dose were demonstrated in the first human study conducted in US (Study MI-CP184). Whether to proceed to dose escalation will be determined based on the safety and tolerability data.

Study flow chart



DLT: dose-limiting toxicity
*A dose will be considered non-tolerated and dose escalation will cease if 2 or more of up to 6 evaluable patients experience a DLT at a dose level.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this protocol.

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 6.4.1)
AKT	Protein Kinase B
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{(0-t)}$	Area under the curve up to the last quantifiable sample
CA 125	Cancer antigen 125
CL	Total body clearance
C_{max}	Maximum serum concentration
$C_{max,ss}$	Maximum serum concentration at steady state
C_{min}	Minimum serum concentration
CR	Complete response
CrCl	Creatinine clearance
CRF	Case Report Form (electronic)
CSR	Clinical Study Report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database lock
DEC	Dose escalation committee
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DR	Duration of response
ECG	Electrocardiogram
EC50	50% of maximal suppression concentration
FDA	Food and Drug Administration
GH	Growth Hormone
GLP	Good laboratory practices
HbA1c	Glycosylated haemoglobin

Abbreviation or special term	Explanation
hIGF	Human insulin-like growth factor
HIV	Human immunodeficiency virus
IGF	Insulin-like growth factor
IGFBP	Insulin-like growth factor binding protein
IgG2λ	Immunoglobulin G2 lambda
IM	Immunogenicity /immunologic
IR	Insulin Receptor
IR-A	Insulin receptor A isoform
IRS	Insulin receptor substrate
IV	Intravenous
JDS	Japan Diabetes Society
Ki67	antigen identified by monoclonal antibody Ki-67
KLH	Keyhole limpet hemocyanin
LDH	Lactic dehydrogenase
mAb	Monoclonal antibody
MAPK	Mitogen-activated protein kinase
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MRT	Mean residence time
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
OAE	Other significant adverse events
ORR	Objective response rate
PAHA	Primate anti-human antibody response
pAKT	AKT signaling protein
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetics
pMAPK	MAPK signaling protein
PR	Partial response
qRT-PCR	TaqMan quantitative real-time polymerase chain reaction

Abbreviation or special term	Explanation
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTcF	Resting corrected QT interval
R_{ac}	Accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumours
RNA	Ribonucleic acid
SAE	Serious adverse event (see definition in Section 6.4.2)
SAS	Statistical Analysis System
SD	Stable disease
SID	Subject Identification Number
$t_{1/2}$	Elimination half-life at terminal phase
t_{max}	Time to maximum serum concentration
$t_{max,ss}$	t_{max} at steady state
TSH	Thyroid stimulation hormone
TTP	Time to progression
TTR	Time to response
TUNEL	Triphosphate biotin nick end labeling
ULN	Upper limit of normal
US	United States
V_z	Volume of distribution at terminal phase
WBDC	Web Based Data Capture
WHO	World Health Organization
λz	Terminal elimination rate constant

1. STUDY OBJECTIVES

1.1 Primary objective

The primary objective of this study is to evaluate the safety and tolerability of MEDI-573 in Japanese adult patients with advanced solid tumours refractory to standard therapy or for which no standard therapy exists.

1.2 Secondary objective(s)

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 (IGF)-I and IGF-II

4. Observe any anti-tumour activity of MEDI-573

5. Determine the maximum tolerated dose (MTD) of MEDI-573 in patients with advanced solid tumours, if applicable.

1.3 Exploratory objective(s)

1. Determine levels of circulating soluble proteins including growth hormone (GH), insulin-like growth factor binding protein (IGFBP), insulin, and glucose and explore associations with clinical outcomes.

2. Assess levels of phosphorylated and/or unphosphorylated factors in specimens. These factors may include but are not limited to IGF receptor type I (IGF-IR), 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 tumour biopsies, biopsies obtained during surgical procedures conducted in the course of routine patient care and/or when archival tumour samples are available. Deoxyuride-5'-triphosphate biotin nick end labeling (TUNEL) analysis may also be performed(optional).

3. Evaluate the relationship of IGF pathway-related components at the messenger ribonucleic acid (mRNA) level, including insulin receptor A isoform (IR-A) mRNA level (IGF-I, IGF-II, INSR, IR-B, IR-A, IGF-IR, IGF-IIR, IRS-1, IRS-2, IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, IGFBP-6) in tumour biopsies obtained pre- and post-MEDI-573 treatment using TaqMan quantitative real-time polymerase chain reaction (qRT-PCR) assays or microarray studies, when fresh and /or archival tumour samples are available (optional).

2. BACKGROUND

The IGF system consists of ligands (IGF-I and IGF-II), the cell surface receptors (IGF-IR and IGF-IIR), 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-I and IGF-II 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-I and IGF-II exert their actions through binding to the IGF-I receptor (IGF-IR) tyrosine kinase and activate various intracellular signalling cascades. Activation of IGF signalling 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 signalling through the insulin receptor (IR) pathway. There are two isoforms of the insulin receptor, 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 tumour tissue compared to normal tissue. IGF-I and IGF-II can bind to a heterodimeric IGF-IR/IR receptor, and IGF-II can bind to homomeric IR receptors with affinities approaching insulin. Thus, IGFs can activate growth stimulatory signals through activating either IGF-IR or IR-A pathways. The binding properties of IGFs also suggest that inhibition of the IGF-IR 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-IR is regulated by the IGFBPs, and IGFs can only bind to the IGF-IR 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-IR expression and/or inhibition of signalling lead to inhibition of tumour growth, both *in vitro* and *in vivo* (Yuen and Macaulay 2008). Inhibition of IGF signalling has also been shown to increase the susceptibility of tumour 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 insulin-like growth factor [hIGF]-IR antibodies) have been developed to inhibit the IGF-IR signalling pathway in tumour cells. Each of these strategies has demonstrated that IGF-IR signalling pathway plays an important role in tumour cell growth and survival (Sachdev and Yee 2007).

2.1 Investigational agent

MEDI-573 is a fully human immunoglobulin G2 lambda (IgG2λ) monoclonal antibody (mAb) generated with Xenomouse® technology that selectively binds to human IGF-II and IGF-I. The antibody was isolated from mice immunized alternately with soluble recombinant human IGF-II (hIGF-II) and hIGF-I coupled to keyhole limpet hemocyanin (KLH). Following comparisons with germ line sequences, no mutations have been identified in the mAb.

2.2 Non-clinical and clinical studies

2.2.1 Non-clinical Experience with MEDI-573

MEDI-573 effectively inhibited the growth of a number of engineered NIH3T3 and human tumour cell lines as follows:

- IGF-I- and IGF-II-stimulated phosphorylation of IGF-IR
- downstream signalling proteins including AKT signaling protein (pAKT) and MAPK signaling protein (pMAPK)
- autocrine phosphorylation of the signalling molecules

Moreover, the growth of implanted Clone 32 and P12 tumours, which overexpress hIGF-I, hIGF-II, and hIGF-IR was also found to be inhibited *in vivo*.

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-I and IGF-II 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-I and IGF-II were suppressed for at least 2 weeks.

A non-GLP single intravenous (IV) infusion dose toxicity study was conducted in cynomolgus monkeys using MEDI-573 at doses of 6 or 60 mg/kg. 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 observed adverse effect level (NOAEL) was 60 mg/kg, which resulted in a dose normalized area under the curve (AUC) of 0.122 ± 0.029 (μg•day/mL)/(μg/kg), a mean clearance of 8.67 ± 2.49 mL/day/kg, and mean maximum observed concentration (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. There were no MEDI-573-related adverse changes. 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-I and IGF-II serum concentrations were observed. The serum concentrations of MEDI-573 (free antibody) required for 50% of maximal suppression concentration (EC50) of free IGF-I and IGF-II 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 normalised AUC 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 CNS/behaviour, 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 behaviour 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.

2.2.2 Clinical Experience with MEDI-573

Phase 1 dose escalation study of MEDI-573 (MI-CP184) is now on-going in US in advance to this study. In dose-escalation phase, MEDI-573 is administrated once every 7 days (on Days 1, 8, 15 of each 21-day treatment cycle) as a 60-minute IV infusion in Cohorts 1~5 (0.5, 1.5, 5.0, 10 and 15 mg/kg) and once every 21 days (Day1 of each 21-day treatment cycle) as a 90-minute IV infusion in Cohort 6 (30 mg/kg) and if applicable Cohort 7 (45 mg/kg).Up to Feb. 17, 2011, twenty-five subjects with advanced solid tumours were enrolled in 6 cohorts (4 subjects with 0.5 mg/kg , 3 subjects with 1.5 mg/kg, 4 subjects with 5.0 mg/kg, 3 subjects with 10 mg/kg, 10 subjects with 15 mg/kg, and 1 subject with 30 mg/kg) in dose-escalation phase and dose expansion phase of 15 mg/kg. There has been ever no DLT. The most common AEs (≥3 subjects) were decreased appetite, fatigue, nausea, anaemia, diarrhoea, abdominal pain, vomiting, urinary tract infection, aspartate aminotransferase increased, blood alkaline phosphatase increased, dehydration, pruritus, and rash. Six subjects experienced treatment-emergent serious adverse events (SAEs); cancer pain, malignant neoplasm progression, blood creatinine increased, glomerular filtration rate decreased, dehydration, hypercalcaemia, fatigue, cholangitis, small intestinal obstruction, and haemoptysis, and none of them were considered by the investigator to be treatment-related. A total of 6 subjects discontinued treatment due to an adverse event (hyperbilirubinaemia, malignant neoplasm progression, cholangitis, anaemia, thrombocytopenia, small intestinal obstruction, alanine aminotransferase increased, aspartate aminotransferase increased). The investigator assessed the relationship of events to study drug administration as possible in one case (anaemia and thrombocytopenia), and not related in the other cases.

Further details are provided in the Investigators' Brochure.

3. STUDY DESIGN AND RATIONALE

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

3.1 Overall study design and flow chart

Study Design

This is a Phase 1, open-label, single-arm, dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics of MEDI-573 in Japanese adult patients with advanced solid tumours refractory to standard therapy or for which no standard therapy exists.

The study will be conducted at one site in Japan.

Subjects are considered evaluable if they receive 3 doses of MEDI-573 (Cohorts 1 and 2) or 1 dose of MEDI-573 (Cohort 3) during cycle 1 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). Each cohort will include 3 to 6 evaluable subjects and a total of 9 to 18 evaluable subjects will be evaluated during the study.

MEDI-573 will be administered once every 7 days (on Days 1, 8, and 15 of each 21-day treatment cycle) as a 60-minute IV infusion in Cohorts 1 and 2 and once every 21 days (Day 1 of each 21-day treatment cycle) as a 90-minute IV infusion in Cohort 3 until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal. Intra-subject dose escalation will not be allowed. On 2nd Cycle and beyond, continuation, interruption or permanent discontinuation of treatment will be decided based on the criteria specified in section 5.1.8. Subjects will be considered to have completed a cycle only when they have received all the specified doses at each cycle, and subjects who do not complete a cycle will discontinue the treatment and not move on to the next cycle. Rules for interruption or discontinuation of MEDI-573 in individual subjects are described in Section 5.4.1. Rules for interruption or discontinuation of MEDI-573 and study entry are described in Section 5.4.2.

Dose escalation will follow a standard 3+3 design. Rules for dose escalation are described in Section 5.1.3.

Subject Evaluation/Follow-up

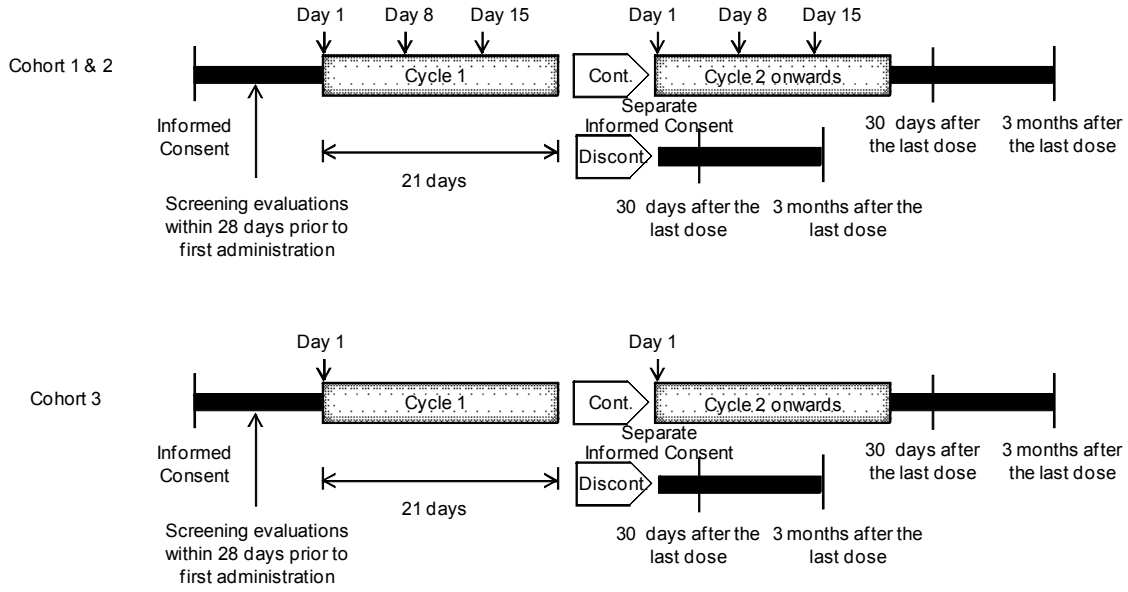
A schedule of screening, treatment visit and follow-up visit procedures are presented in Table 5 (Cohorts 1 and 2) and Table 9 (Cohort 3).

The details of the evaluations are shown in Section 6.1.

AEs and SAEs during the study will be assessed from the time the subject provides the consent through 30 days after the last dose of MEDI-573. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE V4.0). In addition, disease evaluations (including computerised tomography (CT) or magnetic resonance imaging (MRI) scans), focused physical examination, and world health organization (WHO) performance status will be performed after every 2 cycles of treatment until documentation of disease progression or initiation of alternative anticancer therapy. For subjects who discontinue treatment due to reasons other than disease progression or initiation

of alternative anticancer therapy, disease evaluations will be performed at 3 months after the last dose of MEDI-573. Subjects will be evaluated for disease response using Response Evaluation Criteria in Solid Tumours (RECIST ver 1.1; Eisenhauera et al 2009).

Figure 1 Study flow chart



3.2 Rationale for conducting this study and for study design

There were early indications of inhibition of IGF signalling by monoclonal antibodies against anti-IGFI receptor (IGF-IR). On the other hand, blocking IGF-I and IGF-II ligands was expected to create greater inhibition of IGF signalling through inhibition of all IGF signalling. The development of an antibody which neutralises both IGF-I and IGF-II thus offers the opportunity to inhibit both IGF-IR and IR-A signalling. In fact, the antibody was considered to have greater activity than anti-IGF-IR antibodies in tumours that express IR-A alone or both IGF-IR and IR-A (breast, colon, lung, thyroid). On the other hand, small molecule compounds which inhibit IGF-IR kinase are known to inhibit both IGF-IR and IR-A/IR-B, which have identical kinase domains. These kinase inhibitors are likely to show greater toxicity (such as hyperglycaemia) than an anti-IGF-I and IGF-II antibody due to inhibition of IR-B, which is involved in the regulation of glucose metabolism. Compared to these, an IGF-I and IGF-II neutralizing antibody, that will have no effect on insulin signalling and metabolism, are expected to have a growth inhibitory effect in a wide range of tumour types through inhibition of IGF signaling. These results suggest that IGF-I and IGF-II act as powerful mitogenic and anti-apoptotic signals, and that their overexpression correlates with poor prognosis in patients with several types of cancer. Based on all of these results, an antibody directed against IGF-I and IGF-II ligands were considered as a rational anti-tumour drug.

This Phase 1 study will evaluate the safety and tolerability of MEDI-573, a fully human IgG2λ mAb directed against IGF-I and IGF-II, in Japanese adult patients with advanced solid tumours refractory to standard therapy or for which no standard therapy exists. Additional endpoints include immunogenicity (IM), PK, pharmacodynamic, and anti-tumour activity. In this study, MEDI-573 will be administered once every 7 days as a 60-minute IV infusion in Cohorts 1 and 2 at the doses of 5.0 and 15 mg/kg and once every 21 days as a 90-minute IV infusion in Cohort 3 at the dose of 30 or 45 mg/kg until unacceptable toxicity, documentation of disease progression, or other reasons for subject withdrawal. In addition, based on simulations using data from the cynomolgus monkey, the dose (5 mg/kg) that is initial dose of this study is anticipated to result in 99% suppression of IGF-II and over 90% suppression of IGF-I in humans.

As mAb, 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 which there was no evidence of test article-related local toxicity (see Section 2.2.1) (30 minutes) in order to minimize the possibility of infusion-related AEs.

The starting dose, dose escalation, and cohort size are based upon accepted methodology for phase 1 oncology studies (Study MI-CP184) as defined by European and United States regulation (Section 5.2).

As part of the clinical drug development program for MEDI-573 AstraZeneca plans to include investigations into variations in pharmacodynamic and exploratory biomarker profiles and their relationship to drug effect. These biomarkers may be derived from DNA, ribonucleic acids (RNA), proteins and/or metabolites. There are many potential benefits of this exploratory research, including the possibility to identify patients most likely to benefit from treatment, explain outliers or non-responders or explain adverse reactions related to drug exposure. This research may result in an understanding of the impact of variation between individuals and how it can be utilised to bring better drugs to the clinic. The ability to acquire appropriate consent to collect biological samples is of utmost importance in order to establish an archive and allow future meta-analysis of data derived from a number of studies with MEDI-573.

AstraZeneca intends to perform genetic research in the MEDI-573 clinical development programme. Collection of RNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical studies and possibly, to genetically guided treatment strategies. In this study, AstraZeneca performs only the search for the genetic marker that relates to the IGF pathway-related components within the range of a present clinical study protocol before and/or during therapy with MEDI-573. Other research will be not done with the collecting samples.

4. PATIENT SELECTION AND RESTRICTIONS

Investigators should select patients who meet all of the inclusion criteria and none of the exclusion criteria for this study. Investigators should keep a record ie, patient screening log, of patients who entered pre-study screening.

4.1 Inclusion criteria

Patients must meet all of the following criteria:

1. Provision of signed and dated, written informed consent prior to any study specific procedures, assessments, sampling and analyses.
   If a patient declines to participate in any voluntary exploratory research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study

2. Japanese men or women at least 20 years of age

3. Histological or cytological confirmation of a solid, malignant tumour excluding lymphoma that is refractory to standard therapies or for which no standard therapies exist

4. WHO performance status 0-2 with no deterioration over the previous 2 weeks

5. Minimum life expectancy of 16 weeks

6. At least one lesion (measurable and/or non-measurable) that can be accurately assessed at baseline by either CT, magnetic resonance imaging (MRI) or plain X-ray and is suitable for repeated assessment

7. Females should be using adequate contraceptive measures (see Section 4.3), should not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential

   OR

   Females must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:

   - Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following last menses or cessation of all exogenous hormonal treatments

   - Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

8. Male patients should be willing to use barrier contraception ie, condoms for specified period (See Section 4.3)

9. Patients should be willing to remain in hospital for at least 1 week after starting on study treatment

4.2 Exclusion criteria

Patients must have none of the following:

1. Treatment with any of the following:

   - Nitrosourea or mitomycin C within 6 weeks of the first dose of MEDI-573
   - Any investigational agents or investigational products from a previous clinical study within 30 days of the first dose of MEDI-573, or in the case of monoclonal antibodies, within 6 weeks prior to the first dose of MEDI-573
   - Receipt of any systemic chemotherapy, small molecule targeted therapy (eg, sorafenib or other tyrosine kinase inhibitors) or hormonal therapy for cancer related treatment within 4 weeks of the first dose of MEDI-573
   - Receipt of any biological or immunological based therapies (including, but not limited to, mAb therapy such as bevacizumab or cancer vaccine therapies) within 6 weeks prior to the first dose of MEDI-573
   - Use of immunosuppressive medication other than steroids within 7 days before the first dose of MEDI-573
   - Use of systemic steroids within 7 days before the first dose of MEDI-573 (inhaled and topical corticosteroids are permitted). Patients 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
   - Previous therapy with medication against IGF (ie, monoclonal antibodies with IGF-IR or IGF-targeting tyrosine kinase inhibitors)
   - MEDI-573 in the present study (ie, dosing with MEDI-573 previously initiated in this study)
   - Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of MEDI-573
   - Radiotherapy with a wide field of radiation within 4 weeks or radiotherapy with a limited field of radiation for palliation within 2 weeks of the first dose of MEDI-573

2. With the exception of alopecia, any unresolved toxicities from prior to cancer therapy greater than CTCAE grade 1 at the time of starting MEDI-573

3. Spinal cord compression or brain metastases unless asymptomatic, treated and stable and not requiring steroids for at least 4 weeks prior to start of MEDI-573

4. As judged by the investigators, any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diatheses, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus (HIV). Screening for chronic conditions is not required

5. Any of the following cardiac criteria:

   – Clinically significant abnormality on electrocardiogram (ECG) (Mean resting corrected QT interval (QTcF) >470 msec obtained from 3 ECGs)

   – New York Heart Association Grade ≥2 congestive heart failure

   – History of myocardial infarction or unstable angina within 6 months prior to the first dose of MEDI-573

6. History of transient ischemic attack or stroke within 6 months prior to the first dose of MEDI-573

7. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

   – Absolute neutrophil count <1.5 x 10^9/L

   – Platelet count <100 x 10^9/L

   – Haemoglobin <90 g/L (<9 g/dL)

   – Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST) >2.5 times the upper limit of normal (ULN) (if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases)

   – Total bilirubin >1.5 times ULN (if no liver metastases or >3 times ULN in the presence of liver metastases)

   – Creatinine >1.5 times ULN concurrent with creatinine clearance (CrCl) <50 mL/min (measured or calculated by Cockcroft and Gault equation. It gives priority to measured by Cockcroft and Gault more than calculated.)

8. Poorly controlled diabetes mellitus as defined by the investigator's assessment and/or glycosylated haemoglobin (HbA1c) reading >6.5% (JDS scale)within 28 days prior to the first dose of MEDI-573

9. Multiple primary cancers

10. History of other invasive malignancy within 5 years except for cervical carcinoma in situ, non-melanomatous carcinoma of the skin or ductal carcinoma in site of the breast that have been surgically cured, and completely resected intramucosal gastric carcinoma

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

12. History of allergy or reaction to any component of the MEDI-573 formulation or drugs with a similar chemical structure or class to MEDI-573

13. Previous medical history, or evidence, of an intercurrent illness that in the view of the investigators may compromise the safety of the patient in the study

14. Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements

15. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study site)

4.3 Restrictions

The following restrictions apply while the subject is receiving study treatment and for the specified times before and after:

1. Females of child-bearing potential should use reliable methods of contraception from the time of informed consent until 6 months after discontinuing study treatment. Acceptable methods of contraception include the 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 (see Section 8.3.1).

2. Male subjects should use barrier contraception and refrain from donating sperm from the start of dosing until 6 months after discontinuing study treatment. If male subjects wish to father children they should be advised to arrange for freezing of sperm samples prior to the start of MEDI-573 (see Section 8.3.2).

For restrictions relating to concomitant medications see next Section 4.3.1.

4.3.1 Concomitant treatments

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.

Subjects may receive medications to treat AEs as deemed necessary by the investigators.

Any anticancer drug is not allowed during study.

Pre-medication will be allowed after, but not before the first dose of study treatment. This includes management of diarrhoea, nausea and vomiting.

Diphenhydramine and acetaminophen, or the institutional equivalents, may be administered for treatment of an infusion reaction during infusion or prophylactic administration for subjects who experience an infusion reaction. If Grade 2 or Grade 3 infusion reaction occurs and steroid is considered preferable to acetaminoohen and diphenhydramine, staroid may be administered at the investigator's decision.

The routine use of ESAs and colony stimulating factors is not allowed. Use of such agents in the first cycle will require replacement of the subject in that cohort.

5. STUDY TREATMENT AND CONDUCT

5.1 Treatment

MEDI-573 is manufactured by MedImmune. MEDI-573 is supplied as a white to off-white, lyophilized powder in a 10 mL vial. Each vial contains 100 mg (nominal) of active investigational product.

The MEDI-573 formulation is described in Table 1. MEDI-573 must be stored at 2°C to 8°C and must not be frozen.

Table 1 MEDI-573 Formulation

Investigational Product	Dosage form and strength	Manufacturer
MEDI-573	Contains 100 mg of MEDI-573	MedImmune

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into local language.

Each vial of MEDI-573 will have a label indicating 'For clinical study use'.

Detailed instructions regarding investigational product preparation can be found in 'Procedures for drug storage'.

5.1.1 Investigational Product Preparation

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

MEDI-573 will be reconstituted with 4.0 mL sterile water for injection which gives a final concentration of 25 mg/mL. The reconstituted solution at 25 mg/mL will be further diluted into a saline bag for IV infusion.

To reconstitute the lyophilized product, slowly add 4.0 mL of sterile water for injection to the vial. The vial should be tilted slightly and gently rotated or swirled for 30 seconds or until dissolution is complete. Do not shake or vigorously agitate the vial. This is a critical step to avoid prolonged foaming. Reconstituted MEDI-573 should stand undisturbed at room temperature for a minimum of 2 minutes until the solution clarifies. 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 returned to AstraZeneca.

5.1.2 Administration of Investigational Product

All subjects must be weighed (according to institutional practice) prior to a dose on Day 1 of infusion 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, dexamethasone, and diphenhydramine, or another functionally equivalent H1 blocker, should be prepared for IV administration and resuscitation equipment, because the emergency management of an anaphylactic reaction might be needed.

2. MEDI-573 will be administered once every 7 days as a 60-minute IV infusion in Cohorts 1 and 2 and once every 21 days as a 90-minute IV infusion in Cohort 3. Vital signs (body temperature, respiration rate, pulse, and blood pressure) will be measured according to Section 6.3.3 and will be captured in the subject's source documents.

3. If a subject experiences an infusion reaction during infusion of MEDI-573, diphenhydramine 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 subjects who experience an infusion reaction, prophylactic administration of diphenhydramine or the equivalents may be considered for subsequent administration of MEDI-573.

4. In the case of an outpatient , 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.

5.1.3 Starting dose, dose escalation scheme and stopping criteria

The starting MEDI-573 dose is 5.0 mg/kg once per week. The tolerability of this dose was confirmed in the preceding US Phase 1 study (MI-CP 184). The following table presents the dose escalation scheme including dose cohorts and the (maximum) number of evaluable subjects. In addition , the MEDI-573 dose of Cohort 3 will be determined by the result of MI-CP184 study.

Table 2 Summary of Dose Cohorts

Dose Cohort	Number of Subjects	MEDI-573 Dose
1	3-6	5.0 mg/kg as a 60-minute IV infusion once every 7 days
2	3-6	15 mg/kg as a 60-minute IV infusion once every 7 days
3	3-6	30 or 45 mg/kg as a 90-minute IV infusion once every 21 days

Subjects will be enrolled to ensure a minimum of 3 and a maximum of 6 evaluable subjects per cohort. Dose escalation will follow the scheme below, according to the following logic:

If no DLT is observed (for definition see Section 5.1.4) in a cohort of 3 evaluable subjects, then dose escalation may occur. Dose increases will be permitted after review of data from a minimum of 3 evaluable subjects has been performed.

If one subject of the 3 evaluable subjects experiences a DLT, then 3 more evaluable subjects will be enrolled to have 6 evaluable subjects. If only one DLT is observed in the complete cohort of 6 evaluable subjects, then dose escalation may occur.

If 2 or more subjects experience a DLT in a group of up to 6 subjects, irrespective of the number of subjects enrolled, the dose will be considered not tolerated and recruitment to the cohort and dose escalation will cease. If the next lower dose level has 3 evaluable subjects, 3 more evaluable subjects will be enrolled to have 6 evaluable subjects.

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

and may proceed according to the original dosing schedule or may include additional intermediate dosing steps based on accumulated safety data.

There will be no intra-subject dose escalations.

The dose for subsequent cohorts or a decision to stop recruitment will be agreed by the dose escalation committee (DEC) after review of the data from each cohort (see Section **Error! Reference source not found.**).

5.1.4 Definition of dose-limiting toxicity

DLT will be graded according to the NCI CTCAE V4.0 and will be assessed from Cycle 1, Day 1 through Cycle 1, Day 21.

A DLT is defined as:

1. Any Grade 3 or higher non-haematologic toxicity that occurs during the DLT assessment period where a cause other than the investigational product cannot be reasonably justified with the following exceptions:

   - Grade <4 high glucose (fasting) with a duration of <24 hours after administration of MEDI-573
   - Grade 3 fever (in the absence of neutropenia) defined as >40.0°C (39.5°C in the axilla) that resolves to normal or baseline within 24 hours of treatment and is not considered an SAE
   - Grade 3 rigors/chills that respond to optimal therapy
   - Any isolated or transient laboratory changes without associated clinical signs or symptoms.

2. Any Grade 3 or higher haematologic toxicity that occurs during the DLT assessment period where a cause other than the investigational product cannot be reasonably justified.

5.1.5 Definition of maximum tolerated dose

A dose will be considered non-tolerated and dose escalation will cease if 2 or more of up to 6 evaluable subjects experience a DLT at a dose level. Once the non-tolerated dose is defined the MTD will be confirmed at the previous dose-level below the non-tolerated dose.

5.1.6 Definition of evaluable subject

Subjects are considered evaluable if they receive MEDI-573 and either:

- have received 3 doses of MEDI-573 (Cohorts 1 or 2) or 1 dose of MEDI-573 (Cohort 3) during the cycle and are followed for 21 days from the date of first dose (one cycle)

- have experienced a DLT during the cycle 1

Subjects who have a delay in drug administration during the DLT evaluation period are considered as unevaluable.

5.1.7 Dose escalation committee

The DEC will evaluate the safety and tolerability of MEDI-573 collected in the cohort and decide on whether to proceed to dose escalation for the next cohort.

The DEC will consist of:

- Study Team Physician, who will chair the committee, or delegate

- Principal Investigator or representative(s) of the study sites

Sub Investigator from investigational sites, the Study Pharmacokineticist, Study Statistician, Patient Safety Scientist and Study Delivery Team Leader may also be invited as appropriate. The DEC remit document for this study will define the exact membership and who should be present for decisions to be made.

Once there are at least 3 evaluable subjects at a dose level, the DEC will review and assess all available safety data documented by the investigators, if possible, together with available PK data, such as demography, AEs of CTCAE grade ≥2 observed in the DLT assessment period (Days 1 to 21 in Cycle 1), and whether the beginning of Cycle 2 for MEDI-573 has to be postponed or not, to make a decision on for the next cohort of subjects. Any dose interruptions will be taken into account.

The decision may be to:

1. Proceed with dose escalation – refer to Section 5.1.3

2. Expand the cohort to a maximum of 6 evaluable subjects

3. Stop the dose escalation part of the study

Any subject started on treatment in error, as he/she failed to comply with all of the selection criteria but meets the criteria of an evaluable subject, will be reviewed on a case by case basis by the DEC to determine if the subject should be included or excluded in the decision for dose escalation.

The decisions and decision-making of the DEC on the next dose level will be documented and give a notice to the principal investigators prior to dosing any new subjects.

5.1.8 Guidelines for administration of MEDI-573 (after cycle 2)

It is not allowed to delay or modify during Cycle 1.

Dose interruption or discontinuation of MEDI-573, following the first cycle of treatment, will be determined based on AE (see Table 3 and Table 4). In addition, MEDI-573 be able to continue if events occurred is those clearly attributable to another cause such as disease progression or accident, not clinical significant lab abnormality, and not clinically significant and can be controlled by medication. . In Cycle 2 or greater, dosing interval should be 6 days or longer in Cohorts 1and 2, and 20 days or longer in Cohort 3.

Table 3 MEDI-573 does guideline (Cohorts 1 and 2)

AE	Action	Guidance for dosing of MEDI-573
Grade ≤1	Continue	None
Grade 2	Continue	1) Withhold MEDI-573 for other than above up to 7 days until the toxicity resolves or reverts to ≤Grade 1 or baseline and resume at current dose level. 2) Any infusion reaction that responds to medical therapy or slowing the infusion rate.
	Discontinue	1) Discontinue MEDI-573 if MEDI-573 is withheld for >7 days without resolution of toxicity to ≤Grade 1 or baseline. 2) Toxicity that causes a cumulative delay of ≥21 days in 3 consecutive cycles. 3) Any infusion reaction that does not respond to medical therapy or slowing the infusion rate. 4) Any allergic reaction or infusion reaction that necessitates the use of systemic pressor agents.
Grade 3 or 4	Continue	**First Occurrence:** Treatment at the current dose level may be resumed only after recovery of the toxicity is confirmed to be ≤Grade 1 or baseline level during 7 days (at the longest) of cessation of the drug, and clinical benefit has been documented. However, treatment should be discontinued if an AE corresponding to DLT occurs.
	Discontinue	**First Occurrence:** 1) Discontinue MEDI-573 if no clinical benefit has been documented. 2) Discontinue MEDI-573 if MEDI-573 is withheld for >7 days without resolution of toxicity to ≤Grade 1 or baseline, even if clinical benefit has been documented. 3) Grade 3 or greater allergic or infusion reactions. **Second Occurrence:** Discontinue MEDI-573.

Table 4 MEDI-573 does guideline (Cohort 3)

AE	Action	Guidance for dosing of MEDI-573
Grade ≤1	Continue	None
Grade 2	Continue	1) If the toxicity resolve to ≤Grade 1 or baseline level by Day 1 of the subsequent cycle, treatment at the current dose level may be resumed. 2) Any infusion reaction that respond to medical therapy or slowing the infusion rate
	Discontinue	1) Discontinue MEDI-573 if the toxicity does not resolve to ≤Grade 1 or baseline level by Day 1 of the subsequent cycle. 2) Toxicity that causes a cumulative delay of ≥21 days in 3 consecutive cycles 3) Any infusion reaction that does not respond to medical therapy or slowing the infusion rate. 4) Any allergic reaction or infusion reaction that necessitates the use of systemic pressor agents
Grade 3 or 4	Continue	**First Occurrence:** If the toxicity resolve to ≤Grade 1 or baseline level by Day 1 of the subsequent cycle and clinical benefit has been documented, treatment at the current dose level may be resumed. However, treatment should be discontinued if an AE corresponding to DLT occurs
	Discontinue	**First Occurrence:** 1) Discontinue MEDI-573 if no clinical benefit has been documented. 2) Discontinue MEDI-573 if the toxicity does not resolve to ≤Grade 1 or baseline level by Day 1 of the subsequent cycle, even if clinical benefit has been documented. 3) Grade 3 or greater allergic or infusion reactions. **Second Occurrence:** Discontinue MEDI-573.

5.1.9 Duration of therapy

Subjects may continue to receive MEDI-573 as long as they are continuing to show clinical benefit, as judged by the investigator or sub-investigator, no safety concerns, and in the absence of discontinuation criteria (ie, confirmation of disease progression) provided that separate written consent on continuous participation in the study is obtained from the subjects upon proceeding from Cycle 1 to Cycle 2.

Subjects may repeat this schedule, until no clinical benefit is apparent (ie, subject has progressive disease), or the subjects withdraw their consent.

5.1.10 Treatment compliance and accountability

Investigational product will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca. The investigational product should only be used as directed in this protocol. The Investigational Product Storage Manager is responsible for managing the investigational product from receipt by the institution until the return of all unused investigational product to AstraZeneca. AstraZeneca will provide the study documents 'Procedures for drug accountability' and 'Procedures for drug storage' which describes the specific requirements.

Record on investigational product distribution and records on use, destruction and return should be available for verification at the time of study completion. Record on use should include subject identification information, amount and date of prescription, and amount of unused investigational products returned to the investigator(s). Explanation should be provided using the specified form for any inconsistency. The head of the study site or the Investigational Product Storage Manager will sign the certificates of delivery and collection. Empty vials will be disposed of by the medical site.

Details of treatment with investigational product for each subject will be recorded in the Case Record Form.

5.2 Rationale for dose regimen

In a preclinical study, MEDI-573 was administered to cynomolgus monkeys repeatedly as an IV infusion at doses up to 60 mg/kg weekly for 13 weeks, and there was no evidence of toxicity. This result indicated that the no observable adverse effect level (NOAEL in cynomolgus monkeys is higher than 60 mg/kg, which is estimated to be equivalent to higher than 19 mg/kg in human on the basis of body surface area of monkey and human (conversion factor 3.1).

In the US study MI-CP184, up to Feb. 17, 2011, twenty-five subjects with advanced solid tumours were enrolled in 6 cohorts in dose-escalation phase and dose expansion phase of 15 mg/kg. There has been ever no DLTs. (See Section 2.2.2). These results demonstrated the safety and tolerability of MEDI-573 administered weekly at doses up to 15 mg/kg. Thus the safety and tolerability of the starting dose of the scheduled Japanese study (5.0 mg/kg) have been demonstrated in Study MI-CP184.

Consequently, since the above results showed the NOAEL in cynomolgus monkeys is estimated to be equivalent to higher than 19 mg/kg in human and the safety of MEDI-573 up to 15 mg/kg was demonstrated in Study MI-CP184. In addition, the regimen (Cohort 3) that is administration of every 21 days is one of the dose regimens is plan to examine in the development program in the future. As for this regimen, it is plan to execute it in the MI-CP184 study.

Whether to proceed and the dose for the next cohort will be determined based on the safety, tolerability and PK data (if available) of MEDI-573 collected in the cohort in reference to the results of Study MI-CP184.

5.3 Benefit/risk and ethical assessment

MEDI-573 is a fully human mAb directed against IGF-I and IGF-II. IGF-I and IGF-II bind to receptors (IGF-IR and IR-A) as ligands activating the downstream signaling and thus are involved in regulating cell survival, proliferation, and differentiation. On the other hand, excessive activation of IGF signals has been reported in various tumours, and IGF-I and IGF-II are drawing attentions as signalling pathway deeply involved in tumour development, growth and progression through the powerful mitogenic and anti-apoptotic activity. MEDI-573 directly captures and neutralises the IGF-I and IGF-II ligands inhibiting the IGF signalling pathway. MEDI-573 has been shown to inhibit tumour growth in a wide range of human cancer models as a single agent and in combination with chemotherapy. Nonclinical studies suggest that MEDI-573 has the potential to achieve broad anti-tumour efficacy owing to its ability to inhibit both IGF-IR and IR-A pathways.

Antibody drugs against IGF-IR have no effect on IR-A, and so no effect on tumours which highly express IR-A leading to increased mitogenic signalling through IR-A. Also IGF-IR kinase inhibitors inhibit both IGF-IR and IR-A/IR-B, which have identical kinase domains. IR-B plays an important role in insulin signalling and glucose metabolism, and as a result, is strongly associated with glucose metabolism abnormal such as hyperglycaemia as adverse drugs reactions. Furthermore, MEDI-573 has potential to achieve this without perturbing glucose homeostasis, which has been an endocrine liability of other investigational agents that target IGF-IR (Gao et al, 2011).

In non-clinical safety studies, MEDI-573 was well tolerated with no evidence of test-article related toxicity. In the ongoing Phase 1 study (MI-CP184) of MEDI-573 in solid tumours, MEDI-573 has been well tolerated until 15 mg/kg. In this study, adverse events observed to date have been consistent with established conditions in the study population, with the most common AEs being decreased appetite, fatigue, and gastrointestinal events such as nausea and diarrhea. No DLTs have been observed to date. If toxicities reported in studies of other investigational agents that target the IGF axis are based on activity against IGF-IR, it is possible that the following AEs may be observed, such as hyperglycemia, anorexia, nausea, diarrhea, weight loss, elevated transaminases, anemia, thrombocytopenia, pruritus, rash, arthralgia, paresthesia, fatigue, autoantibody production and infusion reactions (Weroha and Haluska, 2008).

Based on published literature with similar therapies (ie, monoclonal antibodies targeting IGF signaling pathway), observed AEs were generally mild (Grade 1 or 2) and included hyperglycemia, gastrointestinal disturbances, hypersensitivity reactions, pruritus, asthenia, and anemia (Haluska et al, 2007; Atzori et al, 2008). Other toxicities included Grade 3/4 thrombocytopenia (Tolcher et al, 2008; Hidalgo et al, 2008), Grade 3 hyperglycemia (Higano et al, 2007), Grade 3 purpura (Atzori et al, 2008), Grade 4 uric acid increase, and Grade 3 bilateral deep venous thrombosis (Olmos et al, 2008).

Since MEDI-573 is an antibody drug, subjects may experience an infusion reaction during infusion of MEDI-573, so all subjects in this study will be closely monitored during the treatment period and throughout the study period.

The potential risk for pain and local irritation at the infusion site is likely to be clinically predictable and be treatable symptomatically. Finally, collection of blood samples for PK sampling will be collected from a vein other than that used to infuse MEDI-573.

No reproductive toxicology nor teratogenic studies have been conducted with MEDI-573 to date, and it is unknown whether the drug is excreted in human milk. Therefore, women of childbearing potential and men should agree to use adequate contraception prior to study entry and for the duration of study participation and women who are breast feeeding are excluded from the study. Both women and men should be fully informed of the lack of reproductive toxicity testing, and women must have a negative pregnancy test prior to enrolment for inclusion in this study.

As described, the study design aims to evaluate safety and tolerability while minimizing potential risks and although the potential benefits in patients are unknown at this time, non-clinical data demonstrate evidence of anti-tumour activity. Thus the benefit/risk assessment for this first time in patient phase 1 study appears acceptable for Japanese patients with advanced solid tumours for whom there is no alternative standard therapy.

5.4 Discontinuation of investigational product and withdrawal from study

5.4.1 Interruption or Discontinuation of Study Dosing in Individual Subjects

Subjects may be discontinued from investigational product in the following situations:

- Subject decision. The subject is at any time free to withdraw his/her participation in the study, without prejudice
- AEs requiring discontinuation of investigational product
- Severe non-compliance to this protocol as judged by the investigator and/or AstraZeneca
- Confirmed disease progression
- Subjects incorrectly initiated on investigational product (Section 5.4.3)
- Lost to follow up
- Pregnancy or intent to become pregnant
- DLT (see Section 5.1.4 for definition of DLTs)
- Treatment with another investigational agent
- Initiation of alternative anticancer therapy

- Infusion reactions ≥Grade 2 that do not respond to medical therapy or slowing the infusion rate and are not of limited duration

- Grade 3 or greater allergic or infusion reactions. Any allergic or infusion reaction that necessitates the use of systemic pressor agents will cause dose discontinuation in that subject

In Cycle 2 or later, in addition to the above, refer to Table 3 and Table 4.

Subjects who are permanently discontinued from investigational product will discontinue the study (see Section 5.4.4).

Subjects that are withdrawn from the study but are evaluable per the definition in Section 5.1.6 will not be replaced. Any subject that is withdrawn and is not evaluable will be replaced to ensure a minimum number of evaluable subjects.

Subjects may withdraw from any aspects of the voluntary exploratory research (see Section 6.7) at any time, without prejudice to further treatment and independent of any decision concerning participation in other aspects of the main study. Procedures for withdrawal from the exploratory research are outlined in Section 6.8.5.

5.4.2 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 related to investigational product

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

3. Other events that in the judgment of the study team physician are serious enough to warrant immediate review by the DEC

If one of the above-listed events occurs, a prompt review of safety data and the circumstances of the event in question will be conducted by the study team physician and the DEC 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 DEC are required for resumption of the study in the event the study is interrupted because of one of the above-listed events.

5.4.3 Procedures for handling subjects incorrectly initiated on investigational product

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be initiated on investigational product.

Where subjects that do not meet the inclusion criteria are enrolled in error or incorrectly started on treatment, or where subjects subsequently fail to meet the study criteria

postinitiation, the investigator should inform the AstraZeneca Study Delivery Team Physician immediately. The Astrazeneca Study Delivery Team Physician is to ensure all such contacts are appropriately documented.

5.4.4 Procedures for withdrawal from study

A subject that discontinues will always be asked about the reason(s) for discontinuation and the presence of any AEs. The Principal Investigator or Sub-Investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal. AEs will be followed up (see Sections 6.4.3 and 6.4.4).

5.5 Study timetable and end of study

Planned duration of the study:

Study period:

Registration period:

There will be an interim data cut-off defined as the earlier of 6 months after the last subject recruited starts investigational product or 3 months after the final subject discontinues investigational product. Data analysis will be performed and a Clinical Study Report written based on this data set.

Any subjects still receiving investigational product at the time of this data cut-off will be able to continue to receive MEDI-573 while deriving clinical benefit. Such subjects will continue to be monitored and all safety assessments performed until the investigational product is discontinued. In addition, these subjects should be followed up for 3 months after the last dose for any new reports of AEs. A Clinical Study Report Addendum may be prepared to summarise the additional safety data collected between the interim data cut-off and the end of the study.

6. STUDY PLAN AND COLLECTION OF STUDY VARIABLES

6.1 Study Plan

A schedule of screening, treatment visit, and follow-up visit procedures is presented in Table 5 (Cohorts 1 and 2) and Table 9 (Cohort 3).

Table 5 Study plan (Cohorts 1 and 2)

Assessment	Screen	Cycle 1					Cycle 2 and Beyond			End of Treatment [d]	Follow-up		Details in
		Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15		30 days after the last dose	3 months after the last dose	
Allowance (days)	**- 28 - 1**	**—**	**—**	**—**	**—**	**—**	**±2**	**±2**	**±2**		**+3**	**±14**	
Written Informed Consent	X						X[a]						Appendix D
Verify Eligibility Criteria	X	X											4.1, 4.2
Medical History	X												6.3
Pregnancy test[b]	X	X					X				X		6.3.5
WHO Performance Status	X	X					X			X	X	X[e]	6.3.2
Physical Examination	X	X					X			X	X	X[e]	6.3.2
Height	X												6.3.2
Weight	X	X					X			X	X		5.1.2
Vital Signs	X	X		X	X	X	X	X	X	X	X		6.3.3
ECG	X	X					X			X	X		6.3.4
Haematology/ Clinical Chemistry	X	X		X	X	X	X	X	X	X	X		6.3.5
Urinalysis	X	X			X	X	X	X	X	X	X		6.3.5
Tumour assessment (CT or MRI Scans)	X						X[c]			X		X[e]	6.9.1
Tumour marker	X						X[c]			X		X[e]	6.9.2
PK [f]		X	X	X	X	X	X	X[g]	X[g]	X	X		6.5
Anti-MEDI-573 Antibodies		X					X				X	X	6.5.3
Blood Biomarker Analysis		X	X	X	X	X	X	X	X	X	X		6.7

Table 5 Study plan (Cohorts 1 and 2)

Assessment	Screen	Cycle 1					Cycle 2 and Beyond			End of Treatment [d]	Follow-up		Details in
		Day 1	Day 2	Day 3	Day 8	Day 15	Day 1	Day 8	Day 15		30 days after the last dose	3 months after the last dose	
Allowance (days)	**- 28 - 1**	**—**	**—**	**—**	**—**	**—**	**±2**	**±2**	**±2**		**+3**	**±14**	
Insulin/GH		X	X	X	X	X	X	X	X	X	X		6.7
Archived Tumour Sample (Optional) [h]	X												6.7
Tumour Biopsy (Optional) [i]	X												6.7
MEDI-573 Administration		X			X	X	X	X	X				5
AE Assessment	X	X	X	X	X	X	X	X	X	X	X		6.4
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X		4.3.1

a Only cycle 2, if subject would like to continue the study.
b All female subjects of child-bearing must be tested. Serum samples will be used at screening only and urine samples will be used at other visits.
c Tumour assessments will be done at odd cycles only and be required before odd treatment starts.
d All possible measures will be performed at end of treatment.
e Subjects who discontinue the study treatment for reasons other than disease progression or initiation of alternative anticancer therapy will undergo Tumour assessment 3 months after the last dose of MEDI-573.
f PK samples will be collected according to Table 13.
g Only cycle 2.
h If an archived tumour sample is available and the subject provides consent for its use; collect and ship per instructions in the Laboratory Manual.
i If the subject provides consent for its use and the samples are collected in a clinical routine at pre- and post (form day 15 to day 21 in cycle 1)- MEDI-573 treatment , the samples will be shipped per instructions in the Laboratory Manual.

Table 6 Time window for vital signs (body temperature, respiratory rate, blood pressure and pulse) (Cycle 1, Cohorts 1 and 2)

Time point	Screen	Day 1							Day 3	Day 8	Day 15
		Pre-dose [a]	15 min post initiation of infusion	30 min post initiation of infusion	45 min post initiation of infusion	End of infusion	30 min post infusion	60 min post infusion			
Allowance	-	-	±5 min	±5 min	±5 min	±5 min	±5 min	±5 min	-	b	b

a Measurement should be done on the day of the first infusion of MEDI-573.
b Measurement should be done at the same time points as Day 1.

Table 7 Time window for vital signs (body temperature, respiratory rate, blood pressure and pulse) (Cycle 2 and Beyond, Cohorts 1 and 2)

Time point	Day 1							Day 8	Day 15	End of Treatment	30 days after the last dose
	Pre-dose [a]	15 min post initiation of infusion	30 min post initiation of infusion	45 min post initiation of infusion	End of infusion	30 min post infusion	60 min post infusion				
Allowance	-	±5 min	±5 min	±5 min	±5 min	±5 min	±5 min	b	b	-	-

a Measurement should be done on the day of the first infusion of MEDI-573.
b Measurement should be done at the same time points as Day 1.

Table 8 Time window for ECG (Cohorts 1 and 2)

Time point [a]	Screen	Cycle 1				Cycle 2 and Beyond	End of Treatment	30 days after the last dose
		Day 1				Day 1		
		Pre-dose	End of infusion	2 h post infusion	6 h post infusion	Pre-dose		
Allowance	-	-	±5 min	±15 min	±15 min	-	-	-

a All ECGs should be done prior to the PK sampling for corresponding time points. Measurement should be done on the day of the first infusion of MEDI-573.

Table 9 Study plan (Cohort 3)

Assessment	Screen	Cycle 1				Cycle 2 and Beyond		End of Treatment [d]	Follow-up		Details in
		Day 1	Day 2	Day 3	Day 8	Day 1	Day 8		30 days after the last dose	3 months after the last dose	
Allowance (days)	**- 28 - 1**	**—**	**—**	**—**	**—**	**+2**	**±2**		**+3**	**±14**	
Written Informed Consent	X					X[a]					Appendix D
Verify Eligibility Criteria	X	X									4.1, 4.2
Medical History	X										6.3
Pregnancy test [b]	X	X				X			X		6.3.5
WHO Performance Status	X	X				X		X	X	X [e]	6.3.2
Physical Examination	X	X				X		X	X	X [e]	6.3.2
Height	X										6.3.2
Weight	X	X				X		X	X		5.1.2
Vital Signs	X	X		X	X	X	X	X	X		6.3.3
ECG	X	X				X		X	X		6.3.4

Table 9 Study plan (Cohort 3)

Assessment	Screen	Cycle 1				Cycle 2 and Beyond		End of Treatment [d]	Follow-up		Details in
		Day 1	Day 2	Day 3	Day 8	Day 1	Day 8		30 days after the last dose	3 months after the last dose	
Allowance (days)	**- 28 - 1**	**—**	**—**	**—**	**—**	**+2**	**±2**		**+3**	**±14**	
Haematology/ Clinical Chemistry	X	X		X	X	X	X	X	X		6.3.5
Urinalysis	X	X				X		X	X		6.3.5
Tumour assessment (CT or MRI Scans)	X					X[c]		X		X[e]	6.9.1
Tumour marker	X					X[c]		X		X[e]	6.9.2
PK [f]		X	X	X	X	X		X	X		6.5
Anti-MEDI-573 Antibodies		X				X			X	X	6.5.3
Blood Biomarker Analysis		X	X	X	X	X		X	X		6.7
Insulin/GH		X	X	X	X	X		X	X		6.7
Archived Tumour Sample (Optional) [g]	X										6.7
Tumour Biopsy (Optional)[h]	X										6.7
MEDI-573 Administration		X				X					5
AE Assessment	X	X	X	X	X	X	X	X	X		6.4
Concomitant Medications	X	X	X	X	X	X	X	X	X		4.3.1

a Only cycle 2, if subject would like to continue the study.
b All female subjects of child-bearing must be tested. Serum samples will be used at screening only and urine samples will be used at other visits.
c Tumour assessments will be done at odd cycles only and be required before odd treatment starts.
d All possible measures will be performed at end of treatment.
e Subjects who discontinue the study treatment for reasons other than disease progression or initiation of alternative anticancer therapy will undergo Tumour assessment 3 months after the last dose of MEDI-573.
f PK samples will be collected according to Table 14.

g If an archived tumour sample is available and the subject provides consent for its use; collect and ship per instructions in the Laboratory Manual.
h If the subject provides consent for its use and the samples are collected in a clinical routine at pre- and post (form day 15 to day 21 in cycle 1)- MEDI-573 treatment , the samples will be shipped per instructions in the Laboratory Manual.

Table 10 Time window for vital signs (body temperature, respiratory rate, blood pressure and pulse) (Cycle 1, Cohort 3)

Time point	Screen	Day 1									Day 3	Day 8
		Pre-dose [a]	15 min post initiation of infusion	30 min post initiation of infusion	45 min post initiation of infusion	60 min post initiation of infusion	75 min post initiation of infusion	End of infusion	30 min post infusion	60 min post infusion		
Allowance	-	-	±5 min	±5 min	±5 min	±5 min	±5 min	±5 min	±5 min	±5 min	-	-

a Measurement should be done on the day of the first infusion of MEDI-573.

Table 11 Time window for vital signs (body temperature, respiratory rate, blood pressure and pulse) (Cycle 2 and Beyond, Cohort 3)

Time point	Day 1									Day 8	End of Treatment	30 days after the last dose
	Pre-dose [a]	15 min post initiation of infusion	30 min post initiation of infusion	45 min post initiation of infusion	60 min post initiation of infusion	75 min post initiation of infusion	End of infusion	30 min post infusion	60 min post infusion			
Allowance	-	±5 min	±5 min	±5 min	±5 min	±5 min	±5 min	±5 min	±5 min	-	-	-

a Measurement should be done on the day of the first infusion of MEDI-573.

Table 12 Time window for ECG (Cohort 3)

Time point [a]	Screen	Cycle 1				Cycle 2 and Beyond	End of Treatment	30 days after the last dose
		Day 1				Day 1		
		Pre-dose	End of infusion	2 h post infusion	6 h post infusion	Pre-dose		
Allowance	-	-	±5 min	±15 min	±15 min	-	-	-

a All ECGs should be done prior to the PK sampling for corresponding time points. Measurement should be done on the day of the first infusion of MEDI-573.

6.2 Recording of data

Web Based Data Capture (WBDC) will be used for data collection and query handling. The investigator will ensure that data are recorded on the Case Report Forms (CRFs) as specified in the protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded on the CRF and for the provision of answers to data queries according to applicable information.

For details of data and study management see Appendix E of this Clinical Study Protocol.

The Principal Investigators will record data on the observations, tests and assessments specified in the protocol on the electronic CRFs provided by AstraZeneca. These instructions provide guidance for the recording of study data in the CRF including how to change data incorrectly recorded.

6.3 Safety procedures

6.3.1 Enrolment and screening

At enrolment, each potential subject will provide informed consent prior to starting any study specific procedures (see Appendix D of this Clinical Study Protocol for Ethics and Regulatory Requirements).

Each potential subject is assigned a subject identification number (SID). The SID (XXXXXXXYYY) consists of a 7-degit centre number (XXXXXXX) and a 3-digit serial number (YYY, starting with 001) issued by each study centre in order of informed consent taken. If a subject withdraws from the study, then the SID cannot be reused.

Demographic data and other characteristics will be recorded and will include date of birth, gender, race, alcohol consumption, smoking history and others. A standard medical, medication and surgical history will be obtained with review of the selection criteria with the patient.

Each subject will undergo screening (see Table 5 and Table 9) during the 28 days prior to the first dose to confirm eligibility (see Sections 4.1 and 4.2). Tumour assessments and other clinical data obtained as standard of care prior to consent may be used for the study provided the assessments prior to the first dose of study treatment. However, no invasive or study-specific screening assessments will be performed until consent is obtained.

6.3.2 Physical examination

Physical examinations and Performance status assessment will be performed as described in Table 5 and Table 9. The physical examinations will include assessments of the head, eyes, ears, nose, and throat, respiratory, cardiovascular, GI, musculoskeletal, neurological, psychiatric, dermatological, haematologic/lymphatic, and endocrine systems; and height (at screening only).

Performance status will be assessed according to WHO criteria (Appendix F).

6.3.3 Vital signs

Body temperature, respiratory rate, and blood pressure/pulse

Supine blood pressure and pulse will be measured after 10 minutes rest. Assessments will be performed at the time points as shown in the study schedule (see Table 5 Table 6, Table 7, Table 9, Table 10 and Table 11). If axillary temperature is taken, CTCAE grade will be determined using 'measured values – 0.5°C'.

6.3.4 ECG

Resting 12-lead ECG

A 12-lead ECG will be performed at the time points according to the study schedule (Table 5, Table 8, Table 9 and Table 12). All ECGs should be performed prior to PK sampling for corresponding time points.

The timing and number of ECGs may be altered depending on the emerging PK and safety profile.

Twelve-lead ECGs will be obtained after the subject has been resting semi-supine for at least 10 minutes prior to times indicated. All ECGs should be recorded with the subject in the same physical position. For each time point three ECG recordings should be taken at not more than 5-minute intervals. A standardised ECG machine should be used and the subject should be examined using the same machine throughout the study if possible.

After paper ECGs have been recorded, the investigator or sub-investigators will review each of the ECGs and may refer to a local cardiologist if appropriate. A paper copy should be filed in the subject's medical records.

If an abnormal ECG finding at screening or baseline is considered to be clinically significant by the investigator, it should be reported as a concurrent condition, and the eligibility of the subject should be evaluated. The investigator or sub-investigator should assess the ECG records for abnormality and record the result.

6.3.5 Laboratory safety assessment

Blood and urine samples for determination of haematology, clinical chemistry, and urinalysis will be taken at the visits as indicated in the study schedule (see Table 5 and Table 9). All assessment timepoints are based on Day 1 as first dose of MEDI-573 and are to be taken with this baseline. Laboratory tests are done on treatment day, it should be done prior to infusion. Laboratory tests do not need to be repeated at baseline if the baseline visit is within 3 days of the screening sample.

The date of each collection will be recorded in the appropriate CRF.

Following review of data from a group of subjects the timing of blood samples may be adjusted for subsequent groups of subject. Laboratory values that meet the criteria for CTCAE grade 3 or have changed significantly from baseline and are considered to be of clinical concern will be repeated/confirmed within 7 days and followed up as appropriate.

The following laboratory variables will be measured:

Clinical chemistry

Albumin	Bilirubin, total
ALT	Calcium, total
AST	Creatinine
Alkaline phosphatase	LDH
Magnesium	Chloride
Phosphorus	Glucose
Potassium	BUN
Sodium	TSH (at Day 1 of every cycle and end of treatment only)
	HbA1c (at Screening and end of treatment only)

Haematology

Haemoglobin	Absolute leukocyte differential count:
Leukocyte Esterase	Neutrophils
Platelet count	Lymphocytes
	Monocytes
	Basophils
	Eosinophils

Urinalysis

PH	Glucose
Protein	Ketones
Bilirubin	Blood

Additionally a serum sample will be collected from all female subjects of child-bearing potential at screening, a urine sample will be collected on Day 1 of every cycle and 30 days after the last dose of MEDI-573 for a pregnancy test.

For blood volume see Section 6.8.1.

6.3.6 Follow-up

A post study assessment will be performed at the time investigational product is permanently discontinued (see Table 5 and Table 9).

In addition subjects should be followed up at 30 days after the last dose of study treatment for any new reports of AEs. Subjects should also be asked about concomitant medications at this follow-up. IM and preliminary anti-tumour activity will be evaluated at the follow-up, which occurs 3 months after the last dose (see Table 5 and Table 9).

6.4 Adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In this clinical study, an AE can include an undesirable medical condition occurring at any time from the time of informed consent until 30 days after the last infusion of MEDI-573, even if no study treatment has been administered.

For cases where it could be suspected that a tissue-derived medicine has been contaminated by a pathogen, information about any of the above conditions (including infection) should be collected.

Any deterioration of the disease under study and associated symptoms or findings should not be regarded as an AE as far as the deterioration can be anticipated.

The term AE is used generally to include any AE whether serious or non-serious.

6.4.2 Definitions of serious adverse events

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to AEs), except hospitalisation that has been planned before enrolment

- Results in persistent or significant disability or incapacity
- Is or results in a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B of this Clinical Study Protocol.

For definition of other significant adverse events (OAE) see Section 7.3.1.

6.4.3 Recording of adverse events

Time period for collection of AEs

All AEs will be collected throughout the study, from informed consent until the end of the follow-up period. The follow-up period is defined as 30 days after the end of study treatment.

Follow-up of unresolved AEs

Any AEs that are unresolved at 30 days after the last study treatment are followed up and written in the medical record by the investigators for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s) at the end of the study, if judged necessary.

If an investigator learns of any SAEs, including death, at any time after a subject has completed the study and he/she considers there is a reasonable possibility that the event is related to MEDI-573, the investigator should notify AstraZeneca.

Variables

The following variables will be collected in the CRF for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the MEDI-573 (yes or no)
- Action taken with regard to MEDI-573
- Outcome

For SAEs additional variables will be collected including treatment given for the event.

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 6.4.2. 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 a 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 a SAE.

The grading scales found in the revised NCI CTCAE version 4.0 will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used.

Causality collection

The investigator will assess causal relationship between MEDI-573 and each AE, and answer "yes" or "no" to the question: "Do you consider that there is a reasonable possibility that the event may have been caused by the MEDI-573?"

For SAEs, a causal relationship will also be assessed for any other medication and study procedure. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix B of this Clinical Study Protocol.

Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarised in the Clinical Study Report. Deterioration as compared to baseline in these parameters will therefore only be reported as AEs if they fulfil any of the criteria for a SAE or DLT, or are the reason for discontinuation of treatment with the investigational product unless clearly due to progression of disease under study (see Disease progression).

If deterioration in a laboratory value, vital sign, ECG or other safety assessment is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or other finding will be considered as additional information.

Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value).

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Disease progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as AEs during the study.

New cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria. New cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the subject's inclusion in this study. They do not include metastases of the original cancer.

Handling of deaths

All deaths that occur during the study, or until 30 days after the last dose of MEDI-573, should be reported as follows:

- Death, which is unequivocally due to disease progression, should be communicated to the study monitor at the next monitoring visit and should be documented in the CRF module, but should not be reported as a SAE during the study

- Where death is not clearly due to disease progression of the disease under study the AE causing the death should be reported to the study monitor as an SAE within 1 day. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign a single primary cause of death together with any contributory causes

- Deaths with an unknown cause should always be reported as a SAE but every effort should be made to establish a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results (with translation of important parts into English) should be reported in an expedited fashion to an AstraZeneca representative within the usual timeframes.

6.4.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs occurred after informed consent will be recorded in the CRF.

Investigators and other site personnel should inform (emergency report) appropriate AstraZeneca representatives of any SAE that occurs at his or her site in the course of the study within 1 day (in this section, within 1 day is defined as "immediately but no later than the end of the next business day") of when he or she becomes aware of it (initial SAE report). This should apply whether or not the SAE is considered causally related to the study treatment or to the study procedure(s). The Principal Investigator should provide detailed information to AstraZeneca in writing **within 4 calendar days** of the initial report. The Principal Investigator should notify the SAEs in writing to the head of the study site immediately.

Follow-up information on SAEs should also be reported to AstraZeneca by the investigator(s) within the same time frames. If a non-serious AE becomes serious, this and other relevant follow-up information should also be provided to AstraZeneca within 1 day as described above.

The following information is required in the initial SAE report to AstraZeneca from the investigator(s): study code, site number, SID, AE, seriousness, start date.

The following detailed information should be sent to AstraZeneca as soon as it becomes available: severity, outcome (including stop date, if available), causality (investigational product and if applicable any other concomitant drug), date when a non-serious AE became serious, withdrawal of study treatment, treatment of AE, concurrent therapy (except for treatment of AE), concurrent medication (including pre-study medication if the causality of the AE cannot be assessed), date of birth, sex, other current illnesses, relevant medical history and if applicable, date and course of death.

The Head of the study site should submit a written report to the Institutional Review Board providing the details of all AE case(s) reported by AstraZeneca.

6.5 Pharmacokinetics

6.5.1 Collection of pharmacokinetic samples

Blood samples for assessment of PK parameters of MEDI-573 and for immunogenicity of anti-MEDI-573 antibodies will be collected as described in Table 5, Table 9 Table 13, and Table 14.

Table 13 Pharmacokinetic and Pharmacodynamics (Cohorts 1 and 2)

Time for blood samples			**PK**		**Biomarkers**
			573	**antibodies**	
Cycle 1	Day 1	Pre-dose	X	X	X
		End of infusion (+5 min)	X		X
		2 h after dose (±15 min)	X		X
		6 h after dose (±15 min)	X		X
	Day 2	24 h after dose of Day 1 (±2 h)	X		X
	Day 3	48 h after dose of Day 1 (±2 h)	X		X
	Day 8	Pre-dose	X		X
		End of infusion (+5 min)	X		X
	Day 15	Pre-dose	X		X
		End of infusion (+5 min)	X		X
Cycle 2	Day 1	Pre-dose	X	X	X
		End of infusion (+5 min)	X		X
	Day 8	Pre-dose	X		X
		End of infusion (+5 min)	X		X
	Day 15	Pre-dose	X		X
		End of infusion (+5 min)	X		X
Cycle 3 and beyond	Day 1	Pre-dose	X	X	X
		End of infusion (+5 min)	X		X
End of treatment			X		X
30 days after the last dose			X	X	X
3 months after the last dose				X	

Table 14 Pharmacokinetic and Pharmacodynamics (Cohort 3)

Time for blood samples			PK		Biomarkers
			573	antibodies	
Cycle 1	Day 1	Pre-dose	X	X	X
		End of infusion (+5 min)	X		X
		2 h after dose (±15 min)	X		X
		6 h after dose (±15 min)	X		X
	Day 2	24 h after dose of Day 1 (±2 h)	X		X
	Day 3	48 h after dose of Day 1 (±2 h)	X		X
	Day 8	168 h after dose of Day 1 (±2 h)	X		X
Cycle 2 and beyond	Day 1	Pre-dose	X	X	X
		End of infusion(+5 min)	X		X
End of treatment			X		X
30 days after the last dose			X	X	X
3 months after the last dose				X	

The timing of the PK samples may be adjusted during the study, dependent on emerging data, in order to ensure appropriate characterisation of the plasma concentration-time profiles. The total number of samples and the total volume of blood taken from each subject will not exceed that presented in Section 6.8.1.

Collection, labelling, storage and shipment of the samples will be done in accordance with the Laboratory Manual.

6.5.2 Determination of drug concentration in pharmacokinetic samples

Samples for determination of MEDI-573 concentrations in serum will be analysed by the central laboratory of AstraZeneca, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

All samples still within the known stability of the analytes of interest (ie, *MEDI-573*) at the time of receipt by the bioanalytical laboratory will be analysed.

6.5.3 Immunogenicity

Anti-MEDI-573 antibodies will be measured at the visits indicated in the Study Plan (Table 5 and Table 9). If sample of anti-MEDI-573 antibodies is collected on treatment day, it should be collected prior to infusion. The date and time of collection of each sample will be recorded. Samples will be analysed by the central laboratory of AstraZeneca.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

6.6 Pharmacodynamics

Samples for biomarker analysis and other biological process evaluation will be collected as indicated in the Study Plan (Table 5 and Table 9). Specific biomarkers will include free and bound IGF-I and IGF-II. See Table 15 for institutions responsible for each measurement.

6.7 Exploratory research

6.7.1 Exploratory biomarker research

If a subject agrees to participate in the exploratory biomarker research component of the study biological samples (eg, plasma, serum, archived and study-obtained tumour, etc) will be collected and may be analysed for exploratory biomarkers to assess correlations with disease activity, effects of investigational product and clinical outcomes.

The results of this exploratory biomarker research will be reported separately and will not form part of the Clinical Study Report.

The results of this exploratory biomarker research may be pooled with biomarker data from other studies with the investigational product to generate hypotheses to be tested in future studies.

6.7.1.1 Collection of archival tumour samples

The effects of genetic variation and expression levels of IGF-IR, IRS-1, MAPK, IR, antigen identified by monoclonal antibody Ki67, caspase 3, and/or AKT will be investigated and their association with treatment with MEDI-573 and clinical outcome will be evaluated when tumour samples are available. And, cell mortality will be assessed by TUNEL. All subjects will be asked to provide consent to supply a sample of their archival tumour blocks if a sample taken at the time of diagnosis is available. No further biopsy procedures are required.

Further details on sample processing, handling and shipment are provided in the Laboratory Manual.

6.7.1.2 Collection of exploratory blood-borne biomarkers

Exploratory biomarker research samples

Blood collection for assessment of biomarkers and other biological processes will be performed as described in Table 5 and Table 9. See Table 15 for specific biomarkers and institutions responsible for each measurement.

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual.

Table 15 Specific biomarkers

Institution	Specific biomarker
central laboratory of Sponsor	free IGF-I and IGF-II
	bound IGF-I and IGF-II
	IGFBPs
clinical laboratory	GH
	insulin
	glucose
	Underlying disease-specific tumour marker (when appropriate, such as prostate specific antigen [PSA] and cancer antigen 125 [CA 125])

6.7.2 Pharmacogenetics

Fresh and /or archival tumour samples will be collected, provided that separate written consent on pharmacogenetics. Tumour samples will be used to analyze the effects of MEDI-573 on levels of mRNA genes. The relationship of IGF pathway-related components at the mRNA level, including IR-A mRNA level (IGF-I, IGF-II, INSR, IR-B, IR-A, IGF-IR, IGF-IIR, IRS-1, IRS-2, IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, IGFBP-6) in tumour biopsies obtained pre- and post-MEDI-573 treatment will be evaluated with qRT-PCR assays or microarray studies. The results of this pharmacogenetic research will be reported separately and will not form part of the Clinical Study Report.

6.7.2.1 Collection of pharmacogenetic samples

Samples will be analysed by the central laboratory of AstraZeneca.

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual.

6.8 Biological sampling procedures

6.8.1 Volume of blood

The total volume of blood that will be drawn from each subject at screening and during Cycle 1 in this study is shown in Table 16.

Table 16 Volume of blood to be drawn from each subject during Cycle 1 (including screening period)

		Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical Chemistry	5	5 (4 [a])	25 (20 [a])
	Haematology	2.6	5 (4 [a])	13 (10.4 [a])
PK	MEDI-573	4	10 (7[a])	40 (28[a])
IM	Anti-MEDI-573 antibodies	8.5	1	8.5
Exploratory biomarker research	Central laboratory of Sponsor	16	10 (7 [a])	160 (112 [a])
Soluble protein	Clinical laboratory	5	10 (7 [a])	50 (35 [a])
Tumour markers[b]		3.5	1	3.5
TOTAL				300 (217.4[a])

a Cohort 3
b Depend on target tumours

The total volume of blood that will be drawn from each subject at cycle 2 in this study is shown in Table 17.

Table 17 Volume of blood to be drawn from each subject during Cycle 2

		Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical Chemistry	5	3 (2 [a])	15 (10 [a])
	Haematology	2.6	3 (2 [a])	7.8 (5.2 [a])
PK	MEDI-573	4	6 (2 [a])	24 (8[a])
IM	Anti-MEDI-573 antibodies	8.5	1	8.5
Exploratory biomarker research	Central laboratory of Sponsor	16	6 (2 [a])	96 (32 [a])
Soluble protein	Clinical laboratory	5	6 (2 [a])	30 (10 [a])
TOTAL				181.3 (73.7 [a])

a Cohort 3
b Depend on target tumours

The total volume of blood that will be drawn from each subject at Cycle 3 and beyond in this study is shown in Table 18.

Table 18 Volume of blood to be drawn from each subject during Cycle 3 and beyond

		Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical Chemistry	5	3 (2 [a])	15 (10 [a])
	Haematology	2.6	3 (2 [a])	7.8 (5.2 [a])
PK	MEDI-573	4	2	8
IM	Anti-MEDI-573 antibodies	8.5	1	8.5
Exploratory biomarker research	Central laboratory of Sponsor	16	2	32
Soluble protein	Clinical laboratory	5	2	10
Tumour markers[b]		3.5	1	3.5
TOTAL				84.8 (77.2 [a])

a Cohort 3
b Depend on target tumours and only on Day 1 of odd cycles (pre-dose)

The total volume of blood that will be drawn from each subject at treatment discontinuation and during the follow-up in this study is shown in Table 19.

Table 19 Volume of blood to be drawn from each subject at the end of treatment, 30 days and 3 months follow-up

		Sample volume (mL)	Number of samples	Total volume (mL)
Safety	Clinical Chemistry	5	2	10
	Haematology	2.6	2	5.2
PK	MEDI-573	4	2	8
IM	Anti-MEDI-573 antibodies	8.5	2	17
Exploratory biomarker research	Central laboratory of Sponsor	16	2	32
Soluble protein	Clinical laboratory	5	2	10
Tumour markers[a]		3.5	2	7
TOTAL				89.2

a Depend on target tumours

6.8.2 Handling, storage and destruction of biological samples

The samples will be used up, or disposed of after analyses or retained for further use as described below.

Biological samples for future research will be retained at the central laboratory of AstraZeneca for a maximum of 15 years following the last subject's last visit in the study.

The results from future analysis will not be reported in the Clinical Study Report but separately in a Clinical Study Report Addendum /Scientific Report or Scientific Publication.

6.8.2.1 Pharmacokinetic samples

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples and reported in a separate bioanalytical report.

6.8.2.2 Samples for exploratory research

Details on sample processing, handling, shipment and storage are provided in the Laboratory Manual.

For exploratory analyses, all collected specimens are identified on the sample itself by study number and alphanumeric number. Collection kits are supplied for each subjects visit and sample type. Alphanumeric numbers are pre-assigned to those kits. There are no personal identifiers associated with the sample tube. Samples are stored in this manner.

Should a withdrawal of consent occur, the participant is to notify the collection personnel which in turn would notify the proper individuals in Japan and then the information is passed to MedImmune. The samples are then destroyed. It is important to note that if data has been obtained prior to the request, that data can still be used. Chain of custody is maintained via inventory during the shipping process and upon receipt at MedImmune where the samples are verified and entered into a relational database and all movements are tracked. All of our samples are stored within an access restricted area.

6.8.3 Labelling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C of this Clinical Study Protocol 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples taken from the subject unless agreed with AstraZeneca and appropriate labelling, shipment and containment provisions are approved.

All archival tumour samples should be shipped at ambient temperature as per the Laboratory Manual to the central laboratory of AstraZeneca.

6.8.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate) and keeps documentation.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

6.8.5 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of voluntarily donated biological samples, then the samples will be disposed of/destroyed, and the action will be documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

If collection of biological samples is a voluntary part of the study include:

As collection of these biological samples is a voluntary part of the study then the subject may continue in the study.

If collection of any biological samples is a mandatory part of the study include:

As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further participation in the study.

The Principal Investigator:

- Ensures AstraZeneca is notified immediately of the subject's withdrawal of informed consent to the use of donated biological samples
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of/destroyed, and the action is documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action is documented and the signed document is returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action is documented and the document is returned to the study site.

6.9 Anti-tumour activity

6.9.1 Tumour assessments

Tumour response will be assessed in all subjects with measurable and/or non-measurable disease at baseline.

RECIST ver1.1 will be used for measurable, non-measurable, target lesions and non-target lesions and the objective tumour response criteria in this study.

The preferred methods of assessment are CT or MRI performed on anatomical coverage to adequately define all areas of disease at baseline.

Baseline tumour assessments should be performed no more than 28 days before the start of study treatment. Following the baseline assessment, tumour burden will be assessed for all subjects by RECIST ver1.1 after start of study treatment (see Table 5 and Table 9) until discontinuation of study treatment (subjects who discontinue the study treatment for reasons other than disease progression or initiation of alternative anticancer therapy will undergo Tumour assessment 3 months after the last dose of MEDI-573) or withdrawal of consent. The same methods of assessment and the same anatomical coverage should be used as per baseline at each subsequent follow-up assessment. Any other sites at which new disease is suspected should also be imaged appropriately.

If the investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesions or the appearance of a new lesion, it is advisable to continue treatment and reassess the subject's status at the next scheduled assessment or sooner if clinically required.

6.9.2 Tumour Marker

For subjects with an abnormal tumour marker strongly related to their tumours, the tumour marker will be measured. Sampling for tumour marker measurements will be performed according to Table 5 and Table 9.

Tumour markers will be measured at the study site or external laboratory in accordance with the standard procedure of each study site. The type of tumour markers and the dates of each measurement and collection will be recorded in the appropriate sections of CRF.

7. EVALUATION AND CALCULATION OF VARIABLES AND STATISTICAL METHODS

7.1 Definition of study endpoints

To meet the objectives for this study, data for the following endpoints will be collected:

- Safety and Tolerability (Primary)
- MTD and/or optimal biologic dose, if possible (Secondary)
- MEDI-573 PK (Secondary)
- IM (Secondary)
- Pharmacodynamics (Secondary)
- MEDI-573 Tumour response (Secondary)
- Exploratory biomarkers (levels of circulating soluble protein biomarkers including GH, IGFBP, insulin and glucose, and levels of phosphorylated and/or factors biomarkers in specimens including IGF-IR, IRS-1, MAPK, IR, Ki67, caspase 3, and/or AKT) (Exploratory)
- Pharmacogenetics (Exploratory)

Safety endpoints are defined in Sections 6.3 and 6.4. Calculations and analysis plans for each of these endpoints are presented below.

7.2 Determination of sample size

The primary objective of this study is to investigate the safety and tolerability and thereby identify the MTD of MEDI-573. Hence the number of subjects has been based on the desire to obtain adequate tolerability, safety and pharmacokinetic and PK data while exposing as few patients as possible to the investigational product and procedures.

For each cohort, cohorts of 3-6 evaluable subjects will be required. The total number of subjects will depend upon the number of dose escalations necessary.

7.3 Calculation or derivation of safety variables

Safety and tolerability will be assessed in terms of AEs, laboratory data, vital signs and ECG changes. These will be collected for all subjects. .

Creatinine Clearance

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

For Women:

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

OR

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

For Men:

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

OR

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

7.3.1 Other significant adverse events

During the evaluation of the AE data, a medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation of investigational product. Based on the expert's judgement, AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the Clinical Study Report. A similar review of laboratory values, vital signs, ECGs and other safety assessments will be performed for identification of OAEs.

Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

7.4 Calculation or derivation of pharmacokinetic variables

PK analysis of the serum concentration data for MEDI-573 will be performed by AstraZeneca K.K. The actual sampling times will be used in the parameter calculations and PK of MEDI-573 will be assessed by noncompartmental approach using a validated computer software package WinNonlin®. Descriptive statistics will be provided by dose cohort.

C_{max}, C_{max} at steady state ($C_{max, ss}$), time to maximum concentration (t_{max}) and the t_{max} at steady state ($t_{max, ss}$) will be determined by inspection of the concentration-time profiles. Where possible the terminal elimination rate constant (λ_z) after first dose will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data and the elimination half-life at terminal phase ($t_{1/2\lambda}$) will be calculated as $\ln 2/\lambda_z$.

The area under the curve up to the last quantifiable sample ($AUC_{(0-t)}$) will be calculated using the linear trapezoidal rule. Where appropriate, the $AUC_{(0-t)}$ will be extrapolated to infinity using λ_z to obtain AUC. Total clearance (CL; following the first dosing) will be determined from the ratio of dose/AUC. The volume of distribution at terminal phase (V_z) will be determined from the mean residence time (MRT) x CL and/or the accumulation ratio (R_{ac}) will be calculated as the ratio of the C_{max} and C_{min} on last dosing interval and first dosing interval.

7.5 Calculation or derivation of immunogenic variables

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

7.6 Calculation or derivation of exploratory research variables

Eploratory biomarkers may include evaluation of MEDI-573 on levels of circulating soluble protein biomarkers including GH, IGFBP, insulin and glucose. Additionally, we will assess levels of phosphorylated and/or unphosphorylated factors in specimens. These factors may include but are not limited to IGF-IR, IRS-1, MAPK, IR, Ki67, caspase 3, and/or AKT in archived tumour biopsies, biopsies obtained during surgical procedures conducted in the course of routine patient care and/or when archival tumour samples are available. The evaluation of cell morarity by TUNEL analysis may also be performed. And, we evaluate the relationship of IGF pathway-related components at mRNA level, including IR-A mRNA level (IGF-I, IGF-II, INSR, IR-B, IR-A, IGF-IR, IGF-IIR, IRS-1, IRS-2, IGFBP-1, IGFBP-2, IGFBP-3,IGFBP-4, IGFBP-5, IGFBP-6) in tumour biopsies obtained pre- and post-MEDI-573 treatment using qRT-PCR assays or microarray studies.

Results from the exploratory biomarker and pharmacogenetic research will be reported separately from the Clinical Study Report for the main study.

7.7 Calculation or derivation of tumour response variables

The preliminary anti-tumour activity of MEDI-573 will be assessed based on the following variables: objective response rate (ORR), time to response (TTR), duration of response (DR), time to progression (TTP), and progression-free survival (PFS).

Categorisation of overall objective tumour response assessment will be based on the RECIST ver1.1: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) for all subjects with measurable disease at entry.

Response will be calculated in comparison to the baseline tumour measurements obtained before starting study treatment. Progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded since starting the study).

For patients that have measurable disease at entry, overall response at entry will be determined programmatically by the measurement of the target lesion, the response of the non-target

lesion and the presence of new lesion according to the RECIST ver1.1. The subject's best overall response is the best response recorded from the start of the study treatment.

In the case of SD, measurements should have met the SD criteria at least once after the study start. To be assigned a status of partial response or complete response, changes in tumour assessments should be confirmed no less than 4 weeks after the criteria for response were first met.

For subjects that only have non-measurable disease at study entry, RECIST will be used. Visit response will be assigned programmatically and summarised separately.

Percentage change in tumour size will be determined by the percentage change in the sum of the longest diameters of target lesions.

7.7.1 Objective response and disease control

ORR is defined as the proportion of subjects with confirmed CR or confirmed PR according to RECIST ver1.1. Confirmed responses are those that persist on repeat imaging study ≥4 weeks after the initial documentation of response.

TTR 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.

DR will be defined as the duration from the first documentation of objective response to the first documented disease progression. DR will only be calculated for the subgroup of subjects with an objective response during the study period (until 3 months after the last dose).

TTP will be measured from the start of treatment with MEDI-573 until the documentation of disease progression during the study period (until 3 months after the last dose).

PFS 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 during the study period (until 3 months after the last dose).

7.8 Description of analysis sets

The analysis of data will be based on different subsets according to the purpose of the analysis. Throughout the safety results sections, erroneously treated subjects (eg, those assigned to receive dose A who actually received dose B, those who failed to meet the selection criteria) will be accounted for in the actual dose group received.

Analysis sets are presented in Table 20.

The classification of subjects into analysis sets will be done at the clean file meeting prior to the database lock.

Table 20 Analysis sets

Analysis Set	Definition
Safety	All subjects who received at least 1 dose of MEDI-573.
MTD	All subjects who have received at least 1 full cycle of MEDI-573 and completed the safety follow-up through the DLT evaluation period, or who experienced a DLT.
PK	All subjects who received at least 1 dose of MEDI-573 and for whom an adequate PK profile has been obtained.
Pharmacodynamics	All subjects who received at least 1 dose of MEDI-573 with any post-pharmacodynamics data
Tumour response	All subjects who have received at least 1 dose of MEDI-573 and at least one tumour assessment after the initiation of MEDI-573.
Exploratory biomarkers	All subjects who received at least 1 dose of MEDI-573 and have biomarkers data.

7.9 Methods of statistical analysis

The statistical analyses will be performed using SAS under the direction of the Biostatistics group, AstraZeneca. Other tools may be used for exploratory summaries and graphical presentations. A comprehensive statistical analysis plan will be finalized prior to the clean file meeting if necessary.

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

7.10 Timing of the analysis

7.10.1 Main analysis

There will be an interim data cut-off defined as the earlier of 6 months after the last subject recruited starts investigational product or 3 months after the final subject discontinues investigational product. These data will be used for the statistical analysis and detailed in the Clinical Study Report (CSR). The main conclusions on the primary, secondary, and exploratory objectives of this study will be made on the basis of these data.

7.10.2 Treatment completion analysis

The data collection may continue following the main analysis database lock (DBL), until all subjects are off the study treatment. These data will provide supplementary information towards the primary objective of this study (to describe safety and tolerability of MEDI-573)

as well as the exploratory objectives. Any data not included in the main analysis DBL, will be reported as an addendum to the CSR.

8. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

8.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator(s) is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. A medical emergency usually constitutes a SAE and is to be reported as such, see Section 6.4.4.

In the case of a medical emergency the investigator may contact monitors (please refer to Supplement A). If the Monitor is not available, contact the Study Delivery Team Leader, and if the Study Delivery Team Leader is also not available, contact the Study Team Physician**.**

Name	**Role in the study**	**Address & telephone number**
	Study Team Physician	
	Study Delivery Team Leader	

8.2 Overdose

Investigators should be advised that any subject who receives a higher dose than that intended should be monitored closely, managed with appropriate supportive care and followed up expectantly.

Such overdoses should be recorded as follows:

- An overdose with associated AEs/SAEs is recorded as the AE diagnosis/symptoms on the relevant AE/SAE modules in the CRF and on the overdose CRF module.
- An overdose with no associated symptoms is only reported on the overdose CRF module.

If an overdose occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day, ie, immediately but no later than the end of the next business day of when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, standard reporting timelines apply (see Section 6.4.4).

8.3 Pregnancy

All pregnancies and their subsequent outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be reported to AstraZeneca using the appropriate forms.

8.3.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of a pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was withdrawn from the study.

If a pregnancy occurs during exposure to investigational product or in the 30 days after discontinuing investigational product, then investigators or other site personnel inform appropriate AstraZeneca representatives within one day ie, immediately but no later than the end of the next business day of when he or she becomes aware of it.

The same timelines apply when outcome information is available.

8.3.2 Paternal exposure

Pregnancy of a subject's partner is not considered to be an AE. However, any conception occurring from the date of dosing until 6 months after dosing should be reported to AstraZeneca and followed up for its outcome.

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