AstraZeneca

Clinical Study Report Synopsis

Drug Substance	MEDI-575
Study Code	D2840C00001
Edition Number	1
Date	27 February 2014

A Phase I, Open-Label Study to Assess the Safety, Tolerability and Pharmacokinetics of Ascending Doses of MEDI-575 in Patients with Advanced Solid Malignancies

Study dates: First subject enrolled: 25 March 2010
Last subject last visit: 14 November 2012

Phase of development: Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

This study was conducted at 5 centres in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate the safety and tolerability of MEDI-575 in adult Japanese patients with advanced solid tumors refractory to standard therapy or for which no standard therapy existed	AEs, physical examination, vital signs, ECG, clinical chemistry, haematology, urinalysis	Safety
Secondary	**Secondary**	
To determine the maximum tolerated dose (MTD) and/or optimal biologic dose of MEDI-575, if possible	AE	Safety
To describe the pharmacokinetics (PK) of MEDI-575	On first dosing at Cycle 1; Maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal rate constant (λ_z), terminal half life ($t_{½\lambda z}$), area under the plasma concentration-time curve from zero to the time of the last measurable concentration ($AUC_{(0-t)}$) and from zero to infinity (AUC), apparent plasma clearance (CL/F). On Day 8 and Day15 and Cycle 2 (on Day1, Day8 and Day15, if appricable); Maximum plasma concentration at steady state ($C_{ss\ max}$), minimum plasma concentration at steady state ($C_{ss\ min}$).	Pharmacokinetic
To evaluate the immunogenicity of MEDI-575 by measuring anti-MEDI-575 antibodies	Anti-MEDI-575 antibodies	Immunogenicity
To obtain a preliminary assessment of the anti-tumor activity of MEDI-575 in patients with advanced solid tumors by evaluation of tumor response using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1	Tumor response	Efficacy
Exploratory	**Exploratory**	
To determine levels of selected circulating soluble proteins, e.g. PDGF-AA and bFGF, and to explore their association with treatment with MEDI-575 and clinical outcome	The levels of specific circulating soluble proteins, ie, PDGF-AA, PDGF-AB/BB, bFGF, VEGF, soluble Flt-1, and/or P1GF	Exploratory biomarker research
To determine if expression levels of RNA on peripheral blood monounclear cell (PBMC) predicted either response or safety outcomes	Expression levels of RNA on peripheral blood monounclear cell (PBMC)	Exploratory biomarker research
To evaluate the effects of genetic variation and platelet-derived growth factor (PDGF) signalling protein expression levels on subject response to treatment with MEDI-575, when fresh and/or archival tumor samples are available (optional)	Genetic variation and platelet-derived growth factor (PDGF) signalling protein expression levels	Exploratory biomarker research

Objectives	Outcome variables	Type
To investigate characteristics associated with subject's clinical response and safety by DNA analysis (optional)	DNA analysis	Pharmacogenetics
To measure ligands/cytokines expression levels, which are relevant to tumor growth and angiogenesis, and to explore their association with treatment with MEDI-575 (optional)	Ligands/cytokines expression levels, ie, plasma concentration of Angiopoietin-2, Follistatin, HGF, IL-8, PDGF-BB, VEGF, Leptin, PECAM-1 and G-CSF	Exploratory biomarker research

Study design

This was a phase I, open-label, multicenter, dose-escalation followed by dose expansion involving adult Japanese subjects with advanced solid malignancies refractory to standard therapy or for which no standard therapy existed.

Target subject population and sample size

Adult Japanese subjects with advanced solid malignancies refractory to standard therapy or for which no standard therapy existed.

For the dose escalation phase of the study, in case of 3 Cohorts, up to 18 subjects were to be required for planned 3 cohorts with 3-6 subjects each cohort. For the dose expansion phase of the study, approximately 12 subjects were to be enrolled.

Investigational product and comparator(s): dosage, mode of administration

MEDI-575 was supplied as 10 mg/mL solution, 100 mg/vial and 20 mg/mL solution, 200 mg/vial. The solution was diluted into a saline bag for intravenous (IV) infusion.

The starting dose of MEDI-575 in this study was 9.0 mg/kg weekly dose. Dose escalation to the next Cohort and dose escalation magnitude was determined based on the data of the current Cohort and in reference to the data from Study MI-CP187 (see Section 5.1.8 of the CSP). One dose was selected for the dose expansion based on safety, tolerability and PK data from dose escalation, and/or target saturation and biomarker data if available.

The starting dose of MEDI-575 in this study was 9.0 mg/kg weekly dose. Dose escalation to the next Cohort and dose escalation magnitude were determined based on the data of the current Cohort and in reference to the data from Study MI-CP187 (see Section 5.1.8 of the CSP). Thus, 15 mg/kg/week and 35 mg/kg/3 week were selected for Cohorts 2 and 3, respectively. One dose (25 mg/kg/3 week) was selected for the dose expansion based on safety, tolerability and PK data from dose escalation, and/or target saturation and biomarker data.

Duration of treatment

Subjects could continue to receive MEDI-575 as long as they were continuing to show clinical benefit, as judged by the investigator, and in the absence of discontinuation criteria.

Statistical methods

The statistical analyses were performed using SAS under the direction of the Statistics & programming department, AstraZeneca.K.K. A comprehensive statistical analysis plan was finalized prior to the database lock.

All data was provided in data listings sorted by dose cohort. Continuous variables were summarized by descriptive statistics including N, mean, standard deviation, median, and range. Descriptive statistics for summarizing categorical variables included frequency and percentage.

Missing data was treated as missing and no data was imputed.

Subject population

(a) Part A

In total, 10 patients were enrolled into the study. All of the 10 patients received MEDI-575 treatments (9 mg/kg/week group: n=4, 15 mg/kg/week group: n=3, 35 mg/kg/3 weeks group: n=3). Eight (8) patients (9 mg/kg/week group: n=4, 15 mg/kg/week group: n=1, 35 mg/kg/3 weeks group: n=3) completed the study and 2 patients (15 mg/kg group/week: n=2) discontinued the study due to lost to follow-up (n=1) and death caused by disease progression (n=1).

All 10 patients registered were Japanese. The mean age of the patients in the safety analysis set was 62.7 years (range: 39 to 71). There were 6 males and 4 females with a mean body weight of 60.40 kg (range: 42.6 to 78.7).

(b) Part B

In total, 13 patients were enrolled into the study. Of those 12 patients received MEDI-575 treatments (25 mg/kg/3 weeks). Six (6) patients completed the study and 6 patients discontinued the study due to lost to follow-up (n=2), withdrawal of consent (n=2) and death caused by disease progression (n=2).

All 12 patients registered were Japanese. The mean age of the patients in the safety analysis set was 64.4 years (range: 46 to 75). There were 10 males and 2 females with a mean body weight of 61.90 kg (range: 53.2 to 71.3).

Summary of pharmacokinetic results

Following the first IV dose, both AUC_{τ} (Day 0-7) and C_{max} increased in a less than dose proportional manner. Following the first IV dose of 25 and 35 mg/kg Q3W, mean AUC_{τ} (Day 1-21) and C_{max} increased in an approximately dose proportional manner.

At steady state, $C_{max.ss}$ and $C_{trough.ss}$ increased in a less than dose proportional manner, over the dose range of 9 to 15 mg/kg QW. Mean accumulation ratio ranged from 1.92 to 1.83 for C_{max} and 3.21 to 3.58 for C_{trough} following 9 to 15 mg/kg QW. The accumulation ratio for C_{trough} was 1.42 and 2.29 for 25 and 35 mg/kg Q3W, respectively.

Summary of pharmacodynamic results

A dose-dependent increase in plasma PDGF-AA level was observed following both QW and Q3W dose of MEDI-575. The increase in plasma PDGF-AA ligand plateaued at approximately 8 ng/mL within 2 days following QW and 4-5 ng/mL within 2 days following Q3W dosing. PDGF-AA levels ranged from 1.7 to 9.79 ng/mL and 0.83 to 8.36 ng/mL throughout the treatment period following QW and Q3W dosing regimens, respectively.

Summary of efficacy results

(a) Part A

None of the 10 patients treated in Part A experienced complete or partial response. Two (2) patients (35 mg/kg/3 weeks group) had a best overall response of "stable disease" ≥6 weeks.

(b) Part B

None of the 10 patients treated in Part B experienced complete or partial response. Three (3) patients had a best overall response of "stable disease" ≥6 weeks.

Summary of immunogenicity results

ADA was detected in 3 subjects prior to the administration of MEDI-575 on Day 1. No obvious impact of immunogenicity was observed on the PK and pharmacodynamics of MEDI-575.

Summary of safety results

(a) Part A

A summary of AEs in each category in Part A is presented in Table S2.

In total, 65 AEs were reported in 9 patients. Fourty-two (42) AEs were reported in 4 patients in 9 mg/kg/week group, 19 AEs were reported in 3 patients in 15 mg/kg/week group, and 4 AEs were reported in 2 patients in 35 mg/kg/3 week group. The AEs with CTCAE grade 3 or higher were reported in 2 patients in 9 mg/kg/week group, no patients in 15 mg/kg/week group or 35 mg/kg/3 week group. There were no AEs leading to death, AEs leading to discontinuation of investigational product (DAEs) and other significant AEs (OAEs). Four (4) SAEs was reported in 1 patient in 9 mg/kg/week group. Twenty (20) causally related AEs were reported for 7 of 10 patients, of those, no AEs with CTCAE grade 3 or higher was reported.

Table S2 Number (%) of patients who had at least 1 AE in any category and number of AEs in any category, Part A (Safety analysis set)

AE category	MEDI-575 9 mg/kg/week (n=4)	MEDI-575 15 mg/kg/week (n=3)	MEDI-575 35 mg/kg/3weeks (n=3)	Total (n=10)
Number (%) of patients who had at least 1 AE in any category [a]				
Any AE	4 (100.0)	3 (100.0)	2 (66.7)	9 (90.0)
Any AE of CTC grade 3 or higher	2 (50.0)	0	0	2 (20.0)
Any AE with outcome = death	0	0	0	0
Any SAE (including events with outcome = death)	1 (25.0)	0	0	1 (10.0)
Any AE leading to discontinuation of IP	0	0	0	0
Any causally related AE [b]	3 (75.0)	3 (100.0)	1 (33.3)	7 (70.0)
Number of AEs in any category (episode level) [c]				
All AEs	42	19	4	65
All AEs of CTC grade 3 or higher	3	0	0	3
All AEs with outcome = death	0	0	0	0
All SAEs (including events with outcome = death)	4	0	0	4
All AEs leading to discontinuation of IP	0	0	0	0
All causally related AEs [b]	11	8	1	20

IP Investigational product
a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
b As assessed by the investigator.
c Multiple events in the same category are counted multiple times in that category. Multiple events belonging to more than one category are counted multiple times in each of those of those categories.

The most commonly reported SOCs were “gastrointestinal disorders” (80.0%) and “general disorders and administration site conditions” (60.0%). The most commonly reported AEs were fatigue (40.0%), diarrhoea (30.0%), nausea (30.0%), and decreased appetite (30.0%).

(b) Part B

A summary of AEs in each category in Part B is presented in Table S3.

Thirty-four (34) AEs were reported in 11 patients. The AEs with CTCAE grade 3 or higher were reported in 2 patients. There were no AEs leading to death, AEs leading to discontinuation of investigational product (DAEs) and other significant AEs (OAEs). One (1) SAE was reported in 1 patient. Eighteen (18) causally related AEs were reported for 9 of 12 patients, of those, no AEs with CTCAE grade 3 or higher was reported.

Table S3 Number (%) of patients who had at least 1 AE in any category and number of AEs in any category, Part B (Safety analysis set)

AE category	MEDI-575 25 mg/kg/3weeks (n=12)
Number (%) of patients who had at least 1 AE in any category [a]	
Any AE	11 (91.7)
Any AE of CTC grade 3 or higher	2 (16.7)
Any AE with outcome = death	0
Any SAE (including events with outcome = death)	1 (8.3)
Any AE leading to discontinuation of IP	0
Any causally related AE [b]	9 (75.0)
Number of AEs in any category (episode level) [c]	
All AEs	34
All AEs of CTC grade 3 or higher	3
All AEs with outcome = death	0
All SAEs (including events with outcome = death)	1
All AEs leading to discontinuation of IP	0
All causally related AEs [b]	18

IP Investigational product
a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
b As assessed by the investigator.
c Multiple events in the same category are counted multiple times in that category. Multiple events belonging to more than one category are counted multiple times in each of those of those categories.

The most commonly reported SOCs were “general disorders and administration site conditions” (50.0%) and “gastrointestinal disorders” (41.7%). The most commonly reported AEs were decreased appetite (33.3%) and neutropenia (25.0%).

None of the patients experienced a DLT. The MTD was not determined in this study.

There were no clinically important changes in any clinical laboratory, vital signs and electrocardiogram at doses of 9 and 15 mg/kg IV infusion once weekly or 25 and 35 mg/kg IV infusion once every 3 weeks.