Drug Substance	Cediranib (AZD2171)	**SYNOPSIS**	(For national authority use only)
Study Code	D8480C00008		
Date	24 November 2008		

A Phase I, Open-Label Study To Assess the Safety, Tolerability, and Pharmacokinetics of AZD2171 (RECENTIN™) and Selected Chemotherapy Regimens When Given in Combination to Patients with Advanced Solid Tumours

Study dates		**Phase of development**
First patient enrolled	05 January 2005	Clinical pharmacology (I)
Last patient enrolled	21 May 2007	

Publications

Lorusso PM, Heath E, Valdivieso M, Pilat M, Wozniak A, Gadgeel S, et al. Phase I evaluation of AZD2171, a highly potent and selective inhibitor of VEGFR signaling, in combination with selected chemotherapy regimens in patients with advanced solid tumors. J Clin Oncol, 2006 ASCO Annual Meeting Proc Part I. Vol 24, No 18S (June 20 Suppl):3034.

LoRusso P, Heath E, Valdivieso M, Pilat MJ, Wozniak A, Gadgeel S, et al. Phase I evaluation of AZD2171, a highly potent and selective inhibitor of VEGF signalling, in combination with selected chemotherapy regimens in patients with advanced solid tumours. Ann Oncol 2006;17(Suppl 9):405P.

Lorusso P, Deluca P, Malburg L, Pilat M, Heath E, Wozniak A, et al. AZD2171 in combination with selected chemotherapy regimens: Results of an ongoing phase I multi-cohort study. 2007 ASCO Gastrointestinal Cancers Symposium, Abstract 361.

Shields AF, Heath E, DeLuca P, Pilat M, Wozniak A, Gadgeel S, et al. AZD2171 in combination with various anticancer regimens: follow-up results of a phase I multi-cohort

study. J Clin Oncol, 2007 ASCO Annual Meeting Proc Part 1. Vol 25, No 18S (June 20 Suppl):3544.

Study design and objectives

Phase I, open-label, multi-centre study conducted in 2 parts. **Part 1:** dose escalation phase to establish safety and tolerability of once-daily oral dosing with cediranib when given to patients with metastatic/advanced cancer in combination with the standard chemotherapy regimens listed in Table S1. The first cediranib dose to be explored in each arm was 30 mg, with dose escalations or reductions as appropriate depending on the dose-limiting toxicities (DLTs) observed in the first 2 cycles. Each patient was allocated to one of the chemotherapy treatment arms according to the standard clinical management of their cancer. Recruitment into the treatment arms could occur simultaneously, except for the cediranib + irinotecan + cetuximab combination, which could be explored once 3 patients had received cediranib 30 mg in combination with irinotecan and there were no DLTs after 2 cycles. DLT was defined as hypertension ≥CTCAE grade 3; or any other ≥CTCAE grade 3 non-haematological or grade 4 haematological toxicity duration >5 days. Blood samples were taken for PK analysis on Day 1 (in the absence of cediranib) and Day 8 (in the presence of cediranib). **Part 2:** cohort expansion phase for treatment with cediranib and mFOLFOX6 to gain additional safety information on this combination.

Table S1 Study objectives and associated variables

Objectives	Variables
Primary	**Primary**
To determine the safety and tolerability of once-daily oral doses with AZD2171 (cediranib; RECENTIN™) when administered in combination with the following anticancer regimens to patients with cancer: **mFOLFOX6** (oxaliplatin, 5-fluorouracil, and leucovorin); or **pemetrexed;** or **irinotecan** (administered with and without cetuximab); or **docetaxel.**	AEs; blood pressure and heart rate; ECG; haematology; clinical chemistry; urinalysis; and physical examination.
Secondary	**Secondary**
To examine the PK interaction when AZD2171 is given in combination with 4 different chemotherapeutic regimens.	**Cediranib:** $C_{ss,max}$, $C_{ss,min}$, t_{max}, AUC_{ss}. **Oxaliplatin:** C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, $t_{½λz}$, MRT. **5-fluorouracil (5-FU):** C_{max}, t_{max}. **Irinotecan, SN-38 and SN-38 glucoronide:** C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, CL (irinotecan only), $t_{½λz}$, MRT. **Pemetrexed:** C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, CL, $t_{½λz}$, MRT. **Docetaxel:** C_{max}, t_{max}, AUC, $AUC_{(0-t)}$, CL, $t_{½λz}$, MRT.
To make a preliminary evaluation of clinical response as measured by objective response rate.	Clinical response at the end of every 2 cycles of chemotherapy, according to RECIST.

AUC Area under plasma concentration-time curve from 0 to infinity; AUC_{ss} Area under plasma concentration-time curve at steady state; $AUC_{(0-t)}$ Area under plasma concentration-time curve from 0 to time t; CL Total body clearance of drug from plasma; $C_{ss,max}$ Maximum steady-state concentration in plasma during dosing interval; $C_{ss,min}$ Minimum steady-state concentration in plasma during dosing interval; MRT Mean residence time; t_{max} Time to reach peak or maximum plasma concentration following drug administration; $t_{½λz}$ Half-life associated with terminal slope ($λ_z$) of a semi-logarithmic concentration-time curve.

Target patient population and sample size

Male and female patients with histologically confirmed metastatic cancer, not amenable to surgery or radiation therapy with curative intent; measurable lesion by CT or other techniques according to Response Evaluation Criteria In Solid Tumours (RECIST); WHO Performance Status 0 – 2; life expectancy >12 weeks.

All treatment arms in Part 1 were initially to enrol 3 patients, except at the cediranib 20 mg dose level, where 6 patients were to be enrolled. In the event that cediranib 30 mg in combination with chemotherapy was considered not tolerated, 6 patients were to be recruited straight into the 20 mg cohort. The cohort expansion (Part 2) was designed to allow up to a further 45 patients to be enrolled, starting with up to 12 evaluable less heavily pre-treated patients, who were to receive cediranib 30 mg in combination with mFOLFOX6. 'Evaluable' defined as: completed ≥2 cycles of chemotherapy at registered approved dose, with cediranib dose intensity ≥75% during first 2 chemotherapy cycles, OR experienced DLT prior to fulfilling these criteria.

Investigational product and comparators: dosage, administration, and batch numbers

The chemotherapy agents were administered as standard regimens. Cediranib doses were made up from 10 mg and 15 mg tablets, to be taken with 240 mL of water, no less than 1 h before, or more than 2 h after a meal. Batch numbers are provided in the main study report.

Duration of treatment

Each cycle of mFOLFOX6 lasted 14 days. Cediranib was to be taken continuously, once daily, from Day 3 of mFOLFOX6 Cycle 1. In Part 2 (mFOLFOX6 cohort expansion), dosing with both cediranib and mFOLFOX6 started on Day 1. Each cycle of pemetrexed, irinotecan, or docetaxel lasted 21 days. Cetuximab was given as a loading dose followed by weekly maintenance doses. Cediranib was to be taken continuously, once daily, from Day 3 of Cycle 1. Daily administration of cediranib was to continue until the end of Cycle 2, assuming patients did not meet a withdrawal criterion. However, patients could continue beyond Cycle 2 with cediranib in combination with chemotherapy if, in the investigator's opinion, they were receiving benefit from the therapy, were free from intolerable toxicity, and did not meet a withdrawal criterion.

Statistical methods

Analyses were descriptive. Where data were available, for each treatment arm (and metabolite of irinotecan), $\log_e$-transformed AUC or C_{max} were to be analysed by analysis of variance (ANOVA), fitting patient and regimen (chemotherapy alone or chemotherapy + cediranib) as factors. Point estimates and corresponding 90% confidence intervals (CIs) were provided for the difference between the PK of the chemotherapy in combination with cediranib compared with the PK of the chemotherapy alone, for the treatment arm and PK parameter of interest. The point and interval estimates from the fitted model were then exponentially back-transformed to provide a point estimate and corresponding 90% CI for the ratio of cediranib + chemotherapy vs chemotherapy alone for the treatment arm and PK parameter of interest.

Patient population, Part 1

Sixty patients with advanced solid tumours were enrolled, of which 59 received cediranib in combination with standard chemotherapy. All patients except one had stopped receiving study treatment by the time of data cut-off (15 August 2007).

There was a broad range of primary tumour types, though the most common primary tumour in the mFOLFOX6 arm was colorectal, as expected. Most of the patients had been heavily pre-treated with prior chemotherapy; only 2 patients had not received prior chemotherapy for advanced disease. Overall, the number of prior chemotherapy regimens ranged from 0 to 11.

Patient population, Part 2

Forty-nine patients with advanced solid tumours were enrolled, of which 47 received cediranib 30 mg in combination with mFOLFOX6. All patients except 2 had stopped receiving study treatment by the time of data cut-off (30 November 2007).

There was a range of primary tumour types; the most common types were from the gastrointestinal tract, including colorectal, pancreas, and biliary tract. Forty-five patients had received prior chemotherapy; the number of prior regimens ranged from 1 to 7, with 37 (78.7%) patients having received 1 or 2 prior regimens.

Summary of pharmacokinetic results

Chemotherapy pharmacokinetics

Cediranib did not appear to have a major effect on the PK profile of the standard chemotherapy regimens evaluated; ie, no PK interactions were observed that appear to necessitate changes in the standard dosages of the tested chemotherapeutic agents when given in combination with cediranib.

A small increase was seen in oxaliplatin exposure when given in combination with cediranib (ratio of lsmeans for $AUC_{(0-t)}$ = 1.25, 90% CI: 1.121, 1.396); this was considered most likely a consequence of accumulation of platinum following repeated dosing, due to the prolonged terminal phase half-life of platinum in plasma.

Small increases in irinotecan AUC or C_{max} were observed when given in combination with cediranib (AUC: ratio of lsmeans = 1.14, 90% CI: 1.013, 1.287; C_{max} ratio of lsmeans = 1.19, 90% CI: 1.007, 1.404), but for the active metabolite SN-38, AUC or C_{max} were similar when alone and in combination with cediranib (AUC: ratio of lsmeans = 0.90, 90% CI: 0.623, 1.292; C_{max} ratio of lsmeans = 1.03, 90% CI: 0.851, 1.246).

Cediranib pharmacokinetics:

The steady-state PK parameters of cediranib when given in combination with each of the chemotherapy regimens were similar to (ie, gmean values within 50% of each other) the single agent steady-state PK parameter values for the same dose level from previous studies.

Summary of efficacy results

There was preliminary evidence of anti-tumour activity, in this broad population of patients with resistant malignancies. Best overall objective tumour response is shown below. Patients who were evaluable for RECIST, but who did not meet the criteria for CR, PR, SD, or PD, were assigned to the overall response category of 'not evaluable' (NE).

Efficacy results: Part 1:

- cediranib + mFOLFOX6: 7 SD, 3 PD, 1 NE
- cediranib + docetaxel: 1 PR, 5 SD, 4 NE
- cediranib + irinotecan: 1 PR, 6 SD, 2 PD, 2 NE
- cediranib + irinotecan + cetuximab: 1 PR, 2 SD, 1 NE
- cediranib + pemetrexed: 1 PR, 6 SD, 3 NE

Efficacy results, Part 2

In Part 2, 44 of the 47 patients had RECIST assessments post Cycle 1. Best objective response was as follows: 5 patients had PR, 23 patients had SD, 5 patients had PD, and 11 patients were NE. Response rate: 10.6% (95% CI: 3.55%, 23.1%).

Summary of safety results, Part 1

There were no observed differences in the known safety profiles of cediranib or the chemotherapy agents when they were given in combination, and no new toxicities were identified. All patients had ≥1 AE. Ten patients died; the causes of death were consistent with the advanced cancer population enrolled and none were considered by the investigator to be study treatment-related. Three patients had AEs of CTCAE grade 3 hypertension. Three patients had SAEs of hypertension: 2 patients who received cediranib 30 mg + docetaxel, and 1 who received cediranib 45 mg + pemetrexed. Hypertension was managed successfully with anti-hypertensive medication; there were no hypertension AEs leading to discontinuation of study treatment (DAEs), and none fulfilled the criteria for DLT. Increased blood TSH >upper limit of normal (ULN) was observed for 30 patients overall, but in the majority of cases, free T4 and T3 remained within normal limits. Two patients had AEs of CTCAE grade 1 hypothyroidism. Seven patients had AEs of proteinuria (all CTCAE grade 1 or 2), reported in all treatment arms except for cediranib + pemetrexed. Fourteen patients had neutrophils $<1 \times 10^9$/L on at least 1 occasion, and 27 patients had platelets below the lower limit of reference range on at least 1 occasion, but there were no DAEs of neutropenia, febrile neutropenia, or thrombocytopenia. There were no clinically important results related to liver or kidney function, ECG, physical findings, or other safety observations.

AEs: cediranib + mFOLFOX6: most common AEs were fatigue (12 patients), diarrhoea (11 patients), and neutropenia (10 patients). Ten of 14 patients had an SAE; most common SAE was neutropenia (6 patients). One patient had an AE with outcome of death (respiratory

failure). Four patients had a DAE. Two patients had DLT: fatigue and diarrhoea (1 patient each at cediranib 30 mg). The MTD of cediranib was 20 mg.

AEs: cediranib + docetaxel: most common AEs were diarrhoea (11 patients), fatigue (10 patients), and anorexia (8 patients). Ten of 12 patients had an SAE; most common SAE was leukopenia (4 patients). One patient had a DAE. Two patients had DLT: neutropenia (at 30 mg) and fatigue and dehydration (at 45 mg). The MTD of cediranib was 30 mg; however, this should be interpreted with caution, as only 5 patients had cediranib dose intensity ≥75%.

AEs: cediranib + irinotecan: most common AEs were diarrhoea (15 patients), fatigue (15 patients), and vomiting (12 patients). Thirteen of 16 patients had an SAE; most common SAEs were fatigue (6 patients) and neutropenia (5 patients). One patient had an AE with outcome of death (pneumonia). Four patients had a DAE. Three patients had DLT: 1 had increased fatigue, febrile neutropenia, and leukopenia (at 30 mg); 1 had hand-foot syndrome (at 30 mg); and 1 had small intestinal obstruction (at 45 mg). The MTD of cediranib was considered to be 20 mg; however, there were only 4 evaluable patients in this cohort.

AEs: cediranib 20 mg + irinotecan + cetuximab: most common AEs were diarrhoea, fatigue, and nausea (reported by all 5 patients). All 5 patients had SAEs; most common SAE was diarrhoea (3 patients). One patient had a DAE. One patient had DLTs of nausea and vomiting. Cediranib 20 mg was only evaluated in 5 patients with this treatment combination, and appeared to be tolerated in the first 2 cycles, but all 5 patients developed grade 3 diarrhoea in later cycles.

AEs: cediranib + pemetrexed: most common AEs were diarrhoea (10 patients), fatigue (10 patients), and hypertension (9 patients). Eight of the 12 patients had an SAE; most common SAE was neutropenia (3 patients). Two patients had a DAE. Three patients had DLT: 1 had fatigue and blood TSH increased (at 30 mg); 1 had thrombocytopenia and neutropenia (at 30 mg), and 1 had fatigue (at 45 mg). The MTD of cediranib was declared as 30 mg, as the 2 DLTs were based on 9 patients.

Summary of safety results, Part 2

All 47 patients had ≥1 AE. Eight (17%) patients died; none of the deaths were considered to be study treatment-related. Hypertension was reported as an AE by 26 (55.3%) patients; 11 patients had grade 3 hypertension, but no grade 4 hypertension was reported. There were no SAEs of hypertension, and no patients had a DAE of hypertension. Thirty-two (68%) patients had increased TSH >ULN on at least 1 occasion, but there were no cases of grade 3 or 4 increased TSH. Fourteen (30%) patients had neutrophils $<1 \times 10^9$/L on at least 1 occasion, and 41 (87%) had platelets <lower limit of reference range on at least 1 occasion; however, there were no discontinuations from study treatment as a result of neutropenia or febrile neutropenia. One patient had a DAE of thrombocytopenia. There were no clinically important results related to liver or kidney function, ECG, physical findings, or other safety observations.

Most common AEs were fatigue (35 [74.5%] patients), diarrhoea (33 [70.2%]) patients), nausea (32 [68.1%] patients), and peripheral neuropathy (31 [66.0%] patients). SAEs were reported by 22 (46.8%) patients; only 5 preferred terms for SAEs were reported by >1 patient: febrile neutropenia, pneumonia, sepsis, dehydration, and pulmonary embolism (each 2 patients). Two (4.3%) patients had an AE with outcome of death: 1 had gastrointestinal haemorrhage, 1 had sepsis. Twelve (25.5%) patients had a DAE.

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