AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Cediranib (AZD2171)
Study Code	D8480C00007
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A Phase II, Double-Blind, Placebo-Controlled, Randomised Study to Assess the Efficacy and Safety of Cediranib in Combination with Fulvestrant vs Fulvestrant alone in Hormone-Sensitive (ER+ve or PgR+ve) Post-Menopausal Metastatic Breast Cancer Patients Who Progressed on Prior Hormonal Therapy

Study dates: First patient enrolled: 29 March 2007
Last patient enrolled: 14 April 2008

Phase of development: Therapeutic exploratory (II)

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

Study centres

This study was conducted at a total of 19 centres in Australia, Brazil, and US.

Publications

None at the time this study report was completed.

Study objectives

Table S1 Primary and secondary study objectives and outcome variables

Objectives	Outcome variables
Primary: To determine the efficacy of cediranib in combination with fulvestrant, compared to the efficacy of fulvestrant alone, by assessment of PFS.	**Primary**: Progression-free survival
Secondary:	**Secondary:**
To determine the efficacy of cediranib in combination with fulvestrant compared to the efficacy of fulvestrant alone	- Objective response rate and duration of response - Clinical benefit rate and duration of clinical benefit
To assess the safety and tolerability of cediranib in combination with fulvestrant in this patient population.	AEs, clinical chemistry, haematology, urinalysis, vital signs including BP, physical examination, ECG, echocardiogram/Multiple Gated Acquisition scan.
To examine the steady-state PK of cediranib and fulvestrant when given in combination.	Minimum (trough) steady-state cediranib concentration in plasma during the dosing interval ($C_{ss,min}$) for fulvestrant and $C_{ss,min}$ for cediranib.

Study design

Double-blind, placebo-controlled, randomised study designed to evaluate the efficacy and safety of cediranib in combination with fulvestrant versus fulvestrant alone in post-menopausal patients with hormone-sensitive metastatic breast cancer. Patients were randomised in a 1:1 ratio to receive cediranib + fulvestrant or cediranib placebo + fulvestrant.

Target patient population and sample size

Key inclusion criteria: post-menopausal female patients aged ≥18 years; histological/ cytological confirmation of ER- and/or PgR-positive breast cancer, with evidence of metastatic disease; evaluable disease (confirmed bone lesion) or ≥1 measurable lesion according to RECIST. **Key exclusion criteria:** prior hormonal therapy with fulvestrant; >1 prior systemic cytotoxic chemotherapy; prior biological therapy (except Herceptin). Patients who had not received any prior hormonal therapy were not eligible.

A study with ≥80% power to detect a true Hazard Ratio (HR) of 0.50 at the 1-sided 10% significance level would require approximately 38 progression events. Assuming a median PFS of 5.5 months for fulvestrant alone, recruitment of 64 patients in 8 months would be expected to yield approximately 38 progression events after 8 months minimum follow-up.

Investigational product, comparator, and placebo: dosage and mode of administration

Cediranib 45 mg was administered as a 30-mg tablet and a 15-mg tablet combination. Batch numbers are provided in the main study report. Cediranib and matching placebo were to be taken orally, once daily, no less than 1 h before, or 2 h after a meal. Dose pauses and dose reductions were permitted for management of toxicity. Fulvestrant was supplied in 5 mL pre-loaded syringes. The 500 mg loading dose was given as 2 x 5 mL im injections of 250 mg, to be administered in each side of the gluteus maximus. Subsequent doses were given as a single 5 mL im injection. Injections after Day 29 were given monthly.

Study treatment was planned to continue until disease progression, death, withdrawal of consent, or unacceptable toxicity.

Statistical methods

The statistical analysis was planned to be performed after 38 progression events had occurred. This number of progression events was expected to have occurred approximately 16 months after the first patient had entered the study. If the true HR for (fulvestrant + cediranib): (fulvestrant + matched placebo) was equal to 0.5, this analysis would have 80% power to demonstrate a statistically significant difference at an 1-sided 10% level.

PFS was defined as the time from randomisation to the earlier date of objective progression or death. Patients who were still alive at the time of the analysis, without a progression event, were censored at the date of their last evaluable objective tumour assessment. Assessment of tumour response was based on RECIST. PFS was analysed using a Cox Proportional Hazards Model, adjusting for performance status and bone metastasis.

Subject population

75 post-menopausal patients with advanced breast cancer were enrolled, of which 62 were randomised to study treatment: 31 to each arm. Five patients on cediranib + fulvestrant, and 8 on placebo + fulvestrant were ongoing at the time of data cut-off (12 December 2008). Most common reasons for discontinuation from the study were disease progression (16/31 patients on cediranib + fulvestrant, 19/31 on placebo + fulvestrant) and voluntary discontinuation (9/31 patients cediranib + fulvestrant; 2/31 on placebo + fulvestrant).

The treatment groups were generally well balanced with respect to demographic and baseline characteristics. There was a numerical imbalance in the proportion of patients with non-measurable versus measurable disease between the 2 arms; exploratory analyses were undertaken to investigate this. Patients with prior hormonal therapy in the adjuvant and metastatic settings were allowed to enter the study; consequently, the population was very heterogeneous in terms of prior anti-cancer therapy.

Summary of efficacy results

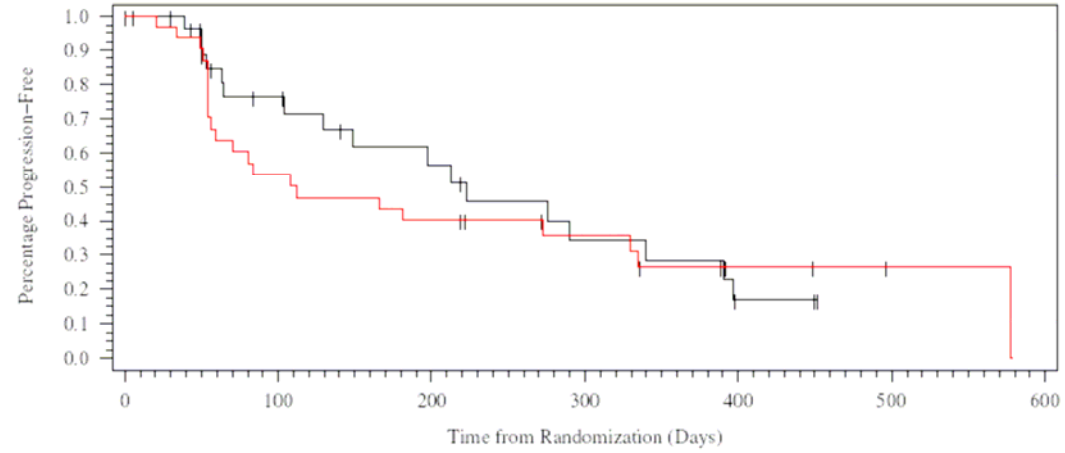
37 progression events had occurred by the time of data cut-off. The difference in PFS between the 2 randomised treatment arms was numerically in favour of cediranib, although it was not statistically significant (Table S2).

Table S2 Progression-free survival (Full analysis set - ITT)

Model	Treatment comparison	Hazard ratio [a]	95% confidence interval	P-value
Adjusted for prognostic factors [b]	Cediranib vs placebo	0.867	0.450 to 1.669	0.669
Unadjusted	Cediranib vs placebo	0.853	0.450 to 1.619	0.627

Progression-free survival defined as the number of days from randomisation until first objective progression event.
[a] Hazard ratio <1 favours cediranib.
[b] Covariates: Performance status (0 or 1/2) and bone metastasis (yes or no).

Figure F1 Kaplan-Meier comparison of PFS between cediranib and placebo in combination with fulvestrant (Full analysis set - ITT)



Of the patients with measurable disease, 4/18 in the cediranib + fulvestrant arm, and 1/12 in the placebo + fulvestrant arm had a confirmed partial response. There was evidence of a greater decrease in tumour size from baseline in the cediranib + fulvestrant arm compared with the placebo + fulvestrant arm (Table S3). Decrease in tumour size was evident at the first post-baseline scan ('Week 8').

Table S3 Best change (%) from baseline in tumour size (Full analysis set – Patients with measurable disease)

Time point	Treatment	N	% change from baseline Mean (SD)	From ANCOVA		
				lsmean	Standard error	95% CI
Week 8	Cediranib	13	-14.08 (28.9)	-16.02	9.28	-35.32, 3.29
	Placebo	11	9.40 (34.2)	10.18	10.18	-9.47, 32.856
Maximum change	Cediranib	16	-17.33 (33.9)	-17.99	9.08	-36.73, 0.75
	Placebo	11	-0.63 (35.3)	0.33	11.11	-22.59, 23.25

Summary of pharmacokinetic results

The range of $C_{ss,min}$ values obtained for fulvestrant was similar both between the cediranib + fulvestrant and placebo + fulvestrant arms and across days (Table S4), indicating that there was no evidence to suggest a clinically significant effect of cediranib on the PK of fulvestrant. Reliable interpretation of the cediranib PK in this study was not possible, owing to the limited data available.

Table S4 $C_{ss,min}$ values (ng/mL) of fulvestrant at steady state (fulvestrant PK set)

Day of study	Summary statistic	Cediranib 45 mg [a] + fulvestrant 250 mg	Placebo + fulvestrant 250 mg
Day 15	N	20	25
	Geometric mean (CV%)	10.3 (46.5)	8.47 (39.1)
	Min, max	4.72, 23.6	4.68, 20.3
Day 29	N	18	22
	Geometric mean (CV%)	8.91 (44.2)	8.66 (34.2)
	Min, max	3.55, 16.7	3.68, 14.5
Day 57	N	13	19
	Geometric mean (CV%)	8.73 (37.6)	6.53 (32.5)
	Min, max	4.06, 13.2	3.54, 12.1
Day 85	N	12	15
	Geometric mean (CV%)	8.04 (36.4)	6.60 (30.3)
	Min, max	4.23, 15.5	4.68, 12.7
Day 113	N	6	13
	Geometric mean (CV%)	8.54 (62.2)	6.92 (25.7)
	Min, max	4.29, 15.0	4.26, 10.5

[a] Nominal dose of was 45 mg, but this may not have been the actual dose received as some patients had dose reductions.

Summary of safety results

23/31 (74.2%) of patients on cediranib + fulvestrant required a dose reduction or pause in their cediranib/placebo tablets compared with 10/31 (32.3%) on fulvestrant + placebo. Median time to first dose reduction or pause was 28 days, and the mean daily dose of cediranib over the study period was estimated as 32 mg.

Most common AEs on fulvestrant + cediranib were diarrhoea, fatigue, and hypertension, reported by 21/31 (68%), 19/31 (61%), and 17/31 (55%) patients, respectively. Most common AEs on fulvestrant + placebo were hot flush, back pain, fatigue, and nausea, reported by 11/31 (36%), 9/31 (29%), 8/31 (26%), and 8/31 (26%) patients, respectively.

Most common grade 3 AEs on cediranib + fulvestrant were hypertension (8/31 [26%] patients) and diarrhoea, (6/31 [19%] patients). When the preferred terms of fatigue, asthenia, and lethargy are considered together, 5/31 patients (16%) reported ≥1 of these terms. Three patients had a grade 4 AE: intracardiac thrombus (1 patient, cediranib + fulvestrant), fatigue (1 patient, placebo + fulvestrant), and back pain (1 patient, placebo + fulvestrant).

SAEs were reported for 15/31 patients on cediranib + fulvestrant and 4/31 patients on placebo + fulvestrant. The most common SAEs on cediranib + fulvestrant were hypertension (4 [13%] patients) and convulsion (3 [10%] patients). None of the SAEs in the placebo + fulvestrant arm were reported by >1 patient. Two patients (both on placebo + fulvestrant) died by the time of data cut-off; both had an SAE with outcome of death (respiratory failure; multi-organ failure). One patient on cediranib + fulvestrant had a SAE that led to discontinuation.

Discontinuations due to AEs (DAEs) were reported by 12/31 patients on cediranib + fulvestrant, and 3/31 on placebo + fulvestrant. Most common DAEs on cediranib + fulvestrant: diarrhoea (6 [31%] patients) and hypertension (4 [13%] patients).

There were no new findings compared with previous cediranib studies relating to haematology, clinical chemistry, blood pressure, or ECG findings. Changes in LVEF during the study appeared to be mild, asymptomatic, and seen mainly in patients who had received prior anthracyclines.