Cediranib in combination with fulvestrant in hormone-sensitive metastatic breast cancer: a randomized Phase II study

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Conflicts of interest

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Summary

Hormone receptor-positive breast cancer is treated with estrogen inhibitors. Fulvestrant (FASLODEX™), an estrogen receptor (ER) antagonist with no known agonist effects, competitively binds, blocks and degrades the ER. Vascular endothelial growth factor (VEGF) may mediate resistance to ER antagonists. Cediranib is a highly potent VEGF signaling inhibitor with activity against all three VEGF receptors. This randomized Phase II study evaluated cediranib plus fulvestrant. Postmenopausal women with hormone-sensitive metastatic breast cancer were eligible. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), duration of response, clinical benefit rate (CBR), safety/tolerability and pharmacokinetics (PK). Patients received cediranib 45mg/day (n=31) or placebo (n=31) both plus fulvestrant. Demographic/baseline characteristics were well balanced. Patients treated with cediranib had a numerical advantage in PFS (hazard ratio=0.867, *P*=0.669; median 223 vs. 112 days, respectively) and ORR (22 vs. 8%, respectively) vs. placebo, although not statistically significant. CBR was 42% in both arms. The most common adverse events (AEs) in the cediranib arm were diarrhea (68%), fatigue (61%) and hypertension (55%). The incidence of grade ≥3 AEs (68% vs. 32%), serious AEs (48% vs. 13%), discontinuation AEs (39% vs. 10%), and cediranib dose reductions/interruptions (74% vs. 32%) were higher in the cediranib arm. There was no evidence of a clinically relevant effect of cediranib on fulvestrant PK. Cediranib plus fulvestrant may demonstrate clinical activity in this population, but cediranib 45mg was not sufficiently well tolerated. Investigation of lower doses of cediranib plus hormonal/chemotherapy could be considered.

Key words: hormone-sensitive; breast cancer; cediranib; fulvestrant

Introduction

Breast cancer is the most common cancer in women. In 2008, there were 1,383,523 cases of breast cancer and 458,367 deaths were attributed to this disease worldwide [1]. Despite many advances in the treatment of this disease ~30-40% of patients develop metastatic disease, which remains incurable and has a reported median survival of just 26 months [2]. With only 13% of trials conducted in metastatic breast cancer (MBC) between 2000 and 2007 reporting an overall survival advantage between different chemotherapy options [3], more effective treatments are needed.

Approximately 75% of all invasive breast cancers are hormone receptor-positive [4]. Patients with hormone receptor-positive disease typically receive treatment with agents that inhibit the activity of estrogen, either through blocking the action of the aromatase enzyme or through blockade of the estrogen receptor (ER) [4]. Fulvestrant (FASLODEX™), an ER antagonist that competitively binds to ER, blocks ER signaling and induces degradation of the ER with no known agonist effects [5]. The complex formed by the binding of fulvestrant with the ER is highly labile; therefore, rapid degradation and marked loss of cellular ER occurs [6]. Fulvestrant was first approved by the FDA in 2004 at a dose of 250mg/month for the treatment of postmenopausal women with advanced breast cancer after recurrence or first progression following anti-estrogen therapy [7, 8]. The pharmacokinetics (PK) of fulvestrant 250mg/month suggest that, typically, 4-6 months is required to achieve steady-state serum concentrations. To help address this, a regimen of fulvestrant 500mg on days 1, 15, 29 and every 28 days thereafter has been approved in the EU and USA. However, based on data available at the time the current study was initiated, a fulvestrant 250mg loading-dose (LD) regimen - consisting of 500mg on day 1, and 250mg on days 15, 29 and every 28 days thereafter - was selected for combination with cediranib, with the aim of achieving steady-state peak drug levels within the first month of treatment.

Resistance to ER antagonists is well documented [9]. Several studies have demonstrated that high tumor expression of vascular endothelial growth factor (VEGF) or VEGFR-2 is associated with shorter survival in breast cancer patients who have received adjuvant tamoxifen [10-13]. Furthermore, inhibition of VEGF-induced angiogenesis has been shown to be a promising treatment in this patient population [14]. Cediranib is a highly potent VEGF signaling inhibitor with activity against all three VEGF receptors and is suitable for once-daily oral dosing [15]. Early clinical data have shown that cediranib has encouraging antitumor activity across a range of tumors at doses of 20, 30 and 45mg/day, both as monotherapy [16-21] and in combination with certain chemotherapy regimens [22-25]. Preclinical data suggest that increased VEGF production in breast cancer could contribute to tumor growth associated with anti-hormone resistance [26]. The addition of a once-daily, oral VEGF signaling inhibitor may offer potential for improved therapeutic outcomes for patients with hormone receptor-positive breast cancers who receive treatment with hormone receptor antagonists. The cediranib dose chosen for this study (45mg) was based on results of the large Phase I study by Drevs and colleagues [16], which demonstrated that cediranib monotherapy was well tolerated up to a dose of 45mg.

This randomized Phase II screening study (ClinicalTrials.gov identifier NCT00454805; AstraZeneca study code D8480C00007) evaluated cediranib 45mg/day in combination with fulvestrant LD in postmenopausal patients with hormone-sensitive MBC whose disease had progressed on prior hormonal therapy.

Methods

Study objectives

The primary objective was to determine whether treatment with cediranib 45mg/day + fulvestrant LD prolonged progression-free survival (PFS) compared with placebo + fulvestrant LD. Secondary assessments included objective response rate (ORR; complete response + partial response), duration of response, clinical benefit rate (CBR; complete response + partial response + stable disease ≥6 months), duration of clinical benefit, safety/tolerability and steady-state PK of cediranib and fulvestrant when given in combination. An exploratory objective was to investigate the relationship between the effect of cediranib on angiogenesis biomarkers (VEGF, soluble [s]VEGFR-2, basic fibroblast growth factor [bFGF]) and clinical efficacy.

Patients

Eligible patients were postmenopausal women (aged ≥18 years) with histologically/cytologically confirmed hormone-sensitive breast cancer with evidence of metastatic disease. Patients were required to have evaluable disease; either ≥1 measurable lesion(s) (≥10mm in longest diameter by spiral computed tomography or 20mm by Response Evaluation Criteria In Solid Tumors; RECIST v1.0) or non-measurable, but evaluable disease (confirmed bone lesion), World Health Organization (WHO) performance status 0-2 and life expectancy ≥12 weeks. Key exclusion criteria included prior biological therapy (except trastuzumab), fulvestrant treatment, >1 course of prior systemic cytotoxic chemotherapy for MBC, radiation therapy within 4 weeks prior to provision of consent and current or history of Class III/IV heart failure as defined by the New York Heart Association (NYHA) functional classification.

Study design

Patients were randomized 1:1 to receive cediranib (oral, 45mg/day) or placebo (oral, daily), in combination with fulvestrant LD (500mg intramuscularly [im] day 1; 250mg im days 15, 29 and every 28 days thereafter). Patients continued study treatment until discontinuation due to disease progression, death, toxicity or withdrawal of informed consent. Adverse events (AEs) were treated with supportive care. If symptoms resolved promptly with supportive care, and if continued treatment with study therapy was considered to provide ongoing patient benefit, the same dose of study medication in addition to supportive care was continued. Up to two dose reductions were permitted for cediranib-related adverse effects.

Efficacy assessments

Assessments of PFS and the secondary efficacy parameters (ORR, duration of response and CBR) were based on investigator-assessed objective tumor response (RECIST v1.0) performed at baseline and every 8 weeks until progression/death. PFS was defined as the time from randomization to the earliest date of objective progression or death. Patients still alive at the time of analysis, without a progression event, were censored at the date of their last evaluable objective tumor assessment.

Safety and tolerability

The safety population included all patients who received ≥1 dose of study treatment. AEs recorded throughout the study were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v3.0.

Pharmacokinetic assessments

PK analyses were based on patients who had ≥1 evaluable PK measurement during the study. Samples were collected from patients in both arms. Fulvestrant PK samples were planned as follows: pre-dose on days 1, 15, 29 and at each monthly visit thereafter for three additional cycles. Cediranib PK samples were planned as follows: pre-dose on day 29 and at each monthly visit thereafter for three additional cycles. To ensure steady-state was attained, only patients who had received cediranib at the same dose for 7 days before sampling were included in the PK analysis.

Pharmacodynamic assessments

Biomarker analyses were based on patients in the safety analysis set who had both baseline and ≥1 post-baseline biomarker value. Mean and median values for the levels of the angiogenesis biomarkers VEGF, sVEGFR-2 and bFGF were determined from samples taken at baseline, during the study (at days 1, 15 and 29, then monthly for three further cycles), and at treatment discontinuation.

Statistical analysis

The statistical analysis was planned to be performed after 38 progression events had occurred (with ≥80% power to detect a true hazard ratio [HR] of 0.50 at a one-sided 10% significance level). Assuming a median PFS of 5.5 months for fulvestrant therapy alone, recruitment of 64 patients in 8 months was expected to yield ~38 progression events after a minimum of 8 months' follow-up. The efficacy analysis was performed on an intention-to-treat (ITT) basis and the safety analysis on actual study treatment received for all patients who received ≥1 dose of study treatment. Analysis of PFS was performed using a Cox proportional hazards regression model, and ORR and CBR were analyzed using logistic regression; these analyses included treatment as a factor and WHO

performance status and bone metastasis as prognostic factors. The effect of treatment on percentage change in tumor size was analyzed using an ANCOVA model, adjusting for the fixed factor of treatment and the covariate of baseline tumor size.

Results

Patients

Between March 2007 and April 2008, 75 female patients from 19 centers in Australia, Brazil and the USA were enrolled into the study. Thirteen patients were not randomized: six did not meet eligibility criteria, four withdrew consent and three were excluded for other reasons. Sixty-two patients were randomized to receive cediranib 45mg/day + fulvestrant LD (n=31) or placebo + fulvestrant LD (n=31). Data cut-off for this analysis was 12 December 2008. In the cediranib + fulvestrant arm, 26 patients discontinued before data cut-off (16 because of disease progression; nine because of voluntary discontinuation and one patient who stopped to begin radiotherapy). In the placebo + fulvestrant arm, 23 patients discontinued before data cut-off (19 because of disease progression; two because of voluntary discontinuation, and two patients who died).

The two randomized treatment groups were generally well balanced with respect to demographic and baseline characteristics, which were consistent with the patient population likely to be treated with fulvestrant (Table 1). There was a numerical imbalance in the proportion of patients with measurable vs. non-measurable disease between the two arms; 41.9% in the cediranib 45mg/day + fulvestrant LD arm had non-measurable disease compared with 61.3% in the placebo + fulvestrant LD arm. The number of prior chemotherapies/hormonal regimens ranged from 1 to 7. Although patients in both arms had received a median of two prior hormonal therapies, this represents a heterogeneous population since the study entry criteria permitted prior hormonal therapies in both the adjuvant and metastatic settings. The most commonly received prior hormonal therapy was tamoxifen and the most commonly received prior chemotherapy was cyclophosphamide. Prior anthracycline treatment was similar in both arms. There were no notable differences in the numbers of patients who received anti-hypertensive medication at baseline.

Efficacy

PFS was analyzed using WHO performance status and bone metastasis as prognostic factors. Thirty-seven progression events (n=17 [54.8%] in the cediranib 45mg/day + fulvestrant LD arm; n=20 [64.5%] in the placebo + fulvestrant LD arm) had occurred by data cut-off (12 December 2008) for this analysis. Patients treated with cediranib + fulvestrant had a numerical advantage in PFS versus placebo + fulvestrant, although the difference was not statistically significant. The adjusted HR was 0.867 (95%CI 0.450-1.669; *P*=0.669; Fig. 1). Median PFS time in the cediranib 45mg/day + fulvestrant LD arm was 223 days (31.9 weeks), vs. 112 days (16.0 weeks) in the placebo + fulvestrant LD arm.

There was an imbalance between the cediranib 45mg/day + fulvestrant LD and placebo + fulvestrant LD arms in the number of patients (10 vs. 1, respectively) who were censored early (<200 days). Assessment of the demographic and baseline characteristics of patients who were censored <200 days after initiation of study treatment revealed that outcomes were in line with the overall study population, suggesting that these patients would not have progressed earlier than those in the placebo + fulvestrant arm. Indeed, the PFS HR was consistent with the expected finding had follow-up been continued. In the cediranib 45mg/day + fulvestrant LD arm, 18 patients had measurable disease and 13 had non-measurable disease. The corresponding numbers for the placebo + fulvestrant LD arm were 12 and 19 patients (Table 2). The ORR for patients with measurable disease was 22% (n=4) for cediranib + fulvestrant vs. 8% (n=1) for placebo + fulvestrant (Table 2). None of the patients had a complete response.

The durations of response for the four patients who received cediranib 45mg/day + fulvestrant LD were 82 (ongoing at data cut-off), 166, 249 (ongoing at data cut-off) and 396 days. For the patient who received placebo + fulvestrant LD, the duration of

response was 224 days. The CBR was 42% (n=13) in both arms (Table 2). There was evidence of a decrease in tumor size from baseline in the cediranib + fulvestrant arm that was not seen in patients in the placebo + fulvestrant arm (Table 3). The decrease in tumor size was evident at the first post-baseline scan (week 8).

Safety and tolerability

Over the study period, the mean daily dose of cediranib was 32mg. The number of patients who had dose interruptions or reductions was higher in the cediranib 45mg/day + fulvestrant LD arm (23/31 patients; 74.2%) than in the placebo + fulvestrant LD arm (10/31 patients; 32.3%). The median time to the first dose reduction or interruption of cediranib 45mg was 28 days. The median tablet dose intensity was lower in the cediranib + fulvestrant arm compared with placebo + fulvestrant (69% vs. 100%, respectively), relating to the greater proportion of dose reductions or dose interruptions with cediranib. Cediranib 45mg/day did not appear to have a significant effect on the dose intensity of fulvestrant (mean [and median] overall dose intensity was 96.8% [100%] and 99.4% [100%] in the cediranib and placebo arms, respectively). No new unexpected toxicities or clinical laboratory findings were observed in patients treated with cediranib 45mg/day + fulvestrant LD and the AE profile (Table 4) was consistent with previous studies of cediranib 45mg/day. The most common AEs in patients who received cediranib 45mg/day + fulvestrant LD were diarrhea (68%), fatigue (61%) and hypertension (55%), whereas the most common AEs in patients in the placebo + fulvestrant LD arm were hot flashes (36%), back pain, fatigue and nausea (all 26%). The most common grade 3 AEs in the cediranib 45mg/day + fulvestrant LD arm were hypertension and diarrhea, reported by 26% and 19% of patients, respectively. Three patients had a grade 4 AE: intracardiac thrombus in one patient in the cediranib 45mg/day + fulvestrant LD arm; fatigue (n=1) and back pain (n=1) in patients in the

placebo + fulvestrant LD arm. Patients who received cediranib 45mg/day + fulvestrant LD experienced a higher incidence of grade ≥3 AEs (n=21 vs. n=10), serious AEs [SAEs] (n=15 vs. n=4) and AEs leading to discontinuation of cediranib or placebo (n=12 vs. n=3) compared with patients who received placebo + fulvestrant LD. The most common SAEs in the cediranib 45mg/day + fulvestrant LD arm were hypertension and convulsion, reported by four (13%) and three (10%) patients, respectively. All three cases of convulsion were experienced within 14 days of beginning cediranib treatment, but none led to discontinuation and all three patients recovered. All other SAEs in the cediranib 45mg/day + fulvestrant LD arm were reported by one or two patients. None of the SAEs in the placebo + fulvestrant LD arm were reported by more than one patient. There were two deaths in the placebo + fulvestrant LD arm during the study; sepsis secondary to a leg ulcer leading to multi-organ failure (considered to be related to the study drug) and respiratory failure in a patient with pulmonary metastases, emphysema and pleural effusion. There were no deaths in the cediranib 45mg/day + fulvestrant LD arm.

There was a mean increase in blood pressure from baseline to day 15 in the cediranib 45mg/day + fulvestrant LD arm (mean diastolic change +10.84mmHg; mean systolic change +17.84mmHg), which subsequently normalized. In the cediranib 45mg/day + fulvestrant LD arm, 17/31 (55%) patients required new antihypertensive therapy compared with 9/31 (29%) in the placebo + fulvestrant LD arm. Changes in left ventricular ejection fraction (LVEF) during the study appeared to be mild and did not result in clinical symptoms. Eleven patients in the cediranib 45mg/day + fulvestrant LD arm and two patients in the placebo + fulvestrant LD arm had grade 1 left ventricular dysfunction (LVEF: 50-59%); 10/13 (77%) cases occurred in patients who had received prior anthracyclines. Three patients in the cediranib 45mg/day + fulvestrant LD arm and

one patient in the placebo + fulvestrant LD arm had grade 2 left ventricular dysfunction (LVEF: 40-49%).

Pharmacokinetics

The range of $C_{ss,min}$ values was similar for fulvestrant LD in both arms (Fig. 2); there was no evidence of a clinically relevant effect of cediranib on the PK of fulvestrant LD. No conclusions could be drawn on the PK of cediranib, as there were limited data available.

Biomarkers

In the cediranib 45mg/day + fulvestrant LD arm, an initial increase in mean VEGF level (391%) was observed at day 15; VEGF levels subsequently decreased, although they remained above baseline during the 4 months of measurement. There was no change from baseline in mean VEGF levels over time in the placebo + fulvestrant LD arm. At day 15, the mean sVEGFR-2 level had decreased by 37.6% below baseline in the cediranib 45mg/day + fulvestrant LD arm; levels remained low during the remainder of the study. By comparison, in the placebo + fulvestrant LD arm, sVEGFR-2 levels remained close to baseline throughout the whole 4-month measurement period. Median bFGF levels increased in both arms during the first 2 months, by 136% and 168% at day 15, and by 158% and 146% at month 1, in the cediranib + fulvestrant arm and placebo + fulvestrant arms, respectively. There was no difference in mean bFGF levels between the arms, although levels in the placebo + fulvestrant LD arm remained below those in the cediranib 45mg/day + fulvestrant LD arm. It was not possible to draw conclusions on any relationship between the change in biomarker levels at week 8 and percentage change in tumor size from baseline at 8 weeks, as too few patients had data available for both variables to allow interpretation.

Discussion

Cediranib 45mg/day + fulvestrant LD demonstrated clinical activity in patients with hormone receptor-positive MBC. Compared with those who received placebo + fulvestrant LD, patients who received cediranib 45mg/day + fulvestrant LD experienced numerical but not statistically significant improvements in PFS, tumor size and ORR. The PFS for the placebo + fulvestrant LD arm (112 days) was in line with outcomes previously observed in two randomized, double-blind Phase III trials of fulvestrant in postmenopausal women with hormone receptor-positive, advanced breast cancer who had received prior hormonal therapy [27, 28]. In the Evaluation of FASLODEX vs. Exemestane Clinical Trial (EFECT), which compared the efficacy of fulvestrant LD to exemestane after prior nonsteroidal aromatase inhibitor therapy, patients who received fulvestrant after other hormonal therapies had a median time to progression (TTP) of 3.7 months [27]. The other Phase III study by Osborne et al [28] reported a longer median TTP (5.4 months) in patients who received fulvestrant 250mg/month after tamoxifen. It is notable that enrollment to the study by Osborne et al [28] was strictly confined to patients who had received only one prior hormonal therapy and therefore were relatively fitter than patients in the current study. As such, the near doubling of median PFS that occurred with the addition of cediranib (7.9 months vs. 4.0 months) is suggestive of a meaningful impact of cediranib on hormonal treatment administered to patients with hormone-sensitive MBC.

The observed AE profile of cediranib 45mg/day in combination with fulvestrant LD in this study appeared to be consistent with that observed in previous studies of cediranib 45mg/kg in other tumor types [16, 18], including an increased incidence of fatigue, diarrhea and hypertension compared with the fulvestrant arm. Although there were no unexpected safety findings with this treatment combination, 45mg was not considered to be a long-term, sustainable dose of cediranib for use in combination with

fulvestrant in this patient population. Of the patients in the cediranib 45mg/day + fulvestrant LD arm, 74% required a cediranib dose reduction or interruption and 39% experienced an AE leading to discontinuation. This sub-optimal tolerability profile may have limited the potential clinical benefit of adding cediranib, at a dose of 45mg/day, to fulvestrant.

Since this trial started, the growing body of data from other cediranib studies has suggested that the 30mg dose, rather than 45mg, would be the most sustainable dose for monotherapy or non-cytotoxic drug combinations. The average dose of 32mg observed in this study suggests that a 30mg initial dosing target would be appropriate for use in future trials of cediranib + fulvestrant LD. A higher dose of fulvestrant (for example, 500mg on days 1, 15, 29 and monthly thereafter) may also be considered for this combination. The COmparisoN of Faslodex In Recurrent or Metastatic breast cancer (CONFIRM) study showed that treatment with fulvestrant 500mg monotherapy reduced the risk of disease progression (assessed as TTP) by 20% (HR=0.80; 95%CI 0.68-0.94, *P*=0.006) compared with the 250mg dose in postmenopausal women with ER-positive advanced breast cancer who had failed on a previous endocrine treatment [29]. More recently, this study reported a 19% reduction in the risk of death for fulvestrant 500mg vs 250mg (median OS [75% maturity], 26.4 months vs. 22.3 months; HR=0.81; 95%CI 0.69-0.96, nominal *P*=0.016) [30]. This regimen has received EU and US approval to replace the 250mg/month dosing schedule. There was no evidence to suggest a clinically relevant effect of cediranib on the PK of fulvestrant LD at the doses administered. No conclusions could be drawn on cediranib PK in this study, owing to the limited data available.

The observed trends in biomarker levels in patients who received cediranib 45mg/day + fulvestrant LD were similar to those seen in previous cediranib studies [16, 20, 31]. These data suggest that there may be a compensatory increase in VEGF

production by tumors seeking to overcome effective VEGFR inactivation. The similar increase of bFGF in both treatment groups is indicative of the important role of pro-angiogenic tumor biology in disease progression in patients with hormonally-sensitive MBC who are undergoing treatment with ER-targeted agents. Although it was not possible to draw conclusions on any relationship between the change in biomarker levels and efficacy, the results of this study highlight the importance of better understanding of this mechanism when considering anti-VEGF treatment strategies.

In summary, the results of this study indicate a potential clinical efficacy of cediranib + fulvestrant LD and suggest that consideration be given to further evaluation of cediranib in combination with hormonal agents or chemotherapy in patients with breast cancer. Such studies should use the lower dose of 30mg cediranib to investigate the potential contribution of tumor angiogenesis to disease progression in this setting.

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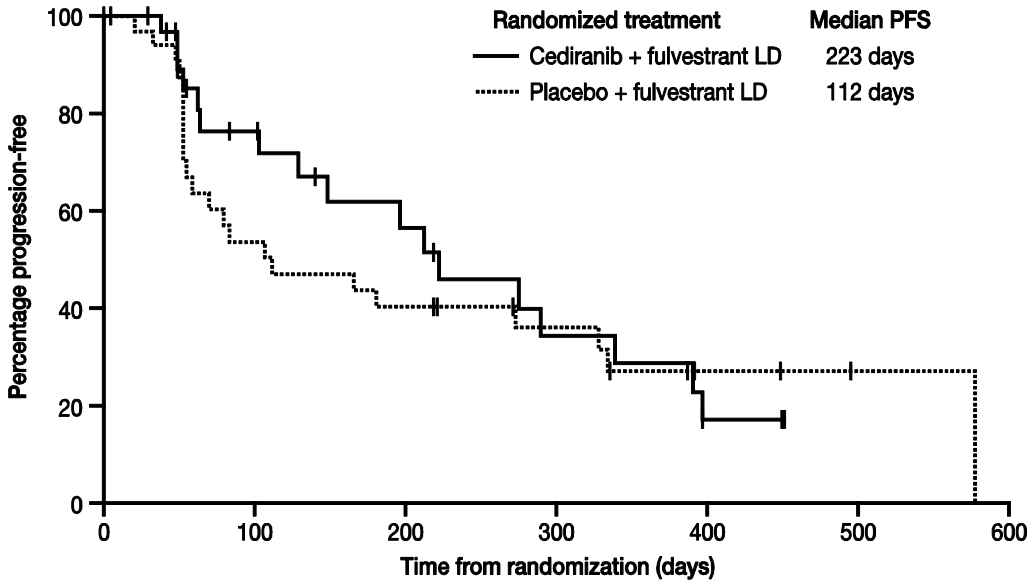
Figure legends

Fig. 1 Progression-free survival

Fig. 2 Geometric mean (± SD) $C_{ss,min}$ values of fulvestrant LD at steady-state

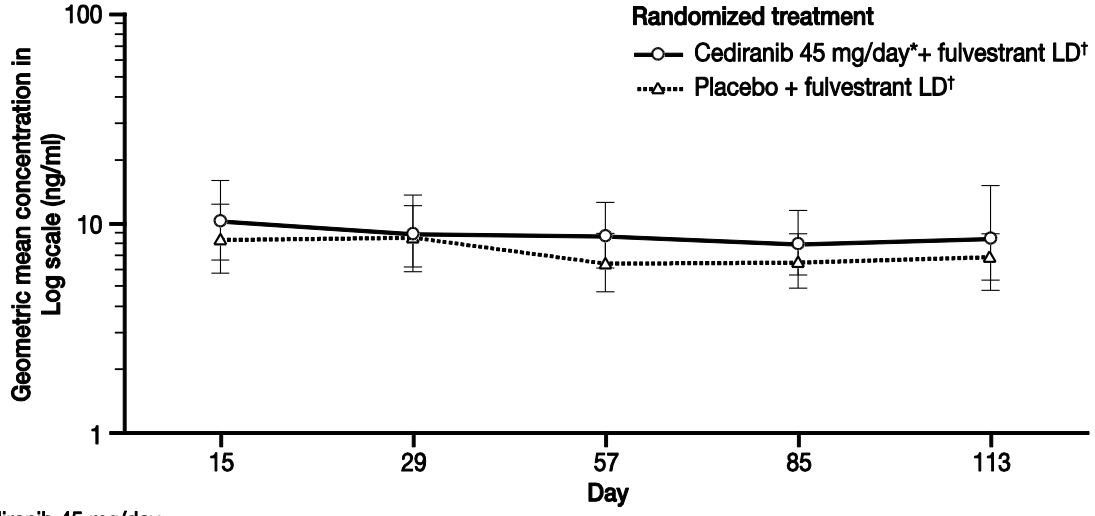
Fig. 1



Days	0	50	100	150	200	250	300	350	400	450	500
Cediranib at risk	31	25	17	12	11	8	6	5	2	2	0
Placebo at risk	31	28	16	14	12	10	8	5	3	2	1

Tick marks indicate censored observations

Fig. 2



Cediranib 45 mg/day + fulvestrant LD, n	20	16	13	12	6
Placebo + fulvestrant LD, n	25	22	19	15	13

*Not all patients received 45 mg cediranib; some patients had dose reductions
†Fulvestrant LD = 500 mg im day 1; 250 mg im days 15, 29 and every 28 days thereafter

Table 1 Patient characteristics

Characteristic, n (%)	Cediranib 45mg/day + fulvestrant LD (n=31)	Placebo + fulvestrant LD (n=31)
Age group		
≥18 to 65 years	19 (61)	24 (77)
>65 years	12 (39)	7 (23)
Race		
Caucasian	25 (81)	26 (84)
Black	2 (6)	1 (3)
Oriental	0 (–)	1 (3)
Other	4 (13)	3 (10)
WHO performance status[a]		
0	22 (71)	25 (81)
1	8 (26)	4 (13)
2	1 (3)	1 (3)
Measurable disease	18 (58)	12 (39)
Non-measurable disease	13 (42)	19 (61)
Previous chemotherapy (cut off >12% in either group)		
Cyclophosphamide	19 (61)	20 (65)
Fluorouracil	14 (45)	14 (45)
Anthracyclines:	16 (52)	21 (68)[b]
Doxorubicin	11 (35)	13 (42)

Epirubicin	5 (16)	9 (29)
Methotrexate	9 (29)	4 (13)
Paclitaxel	4 (13)	7 (23)
Docetaxel	5 (16)	3 (10)
Capecitabine	4 (13)	3 (10)
Previous hormonal therapy (cut off >12% in either group)		
Tamoxifen	24 (77)	24 (77)
Letrozole	11 (35)	15 (48)
Anastrozole	12 (39)	10 (32)
Exemestane	7 (23)	6 (19)
Patients who had surgery for primary breast tumor	30 (97)	28 (90)
Patients who had previous radiotherapy	26 (84)	25 (81)

[a]WHO PS was not available for one patient in the placebo + fulvestrant LD arm

[b]One patient received both doxorubicin and epirubicin

WHO PS, World Health Organization performance status

Table 2 Best overall response rate and clinical benefit rate

Patients with measurable disease		
Best overall response, n (%)	**Cediranib 45mg/day + fulvestrant LD (n=18)**	**Placebo + fulvestrant LD (n=12)**
ORR	4 (22)	1 (8)
Partial response	4 (22)	1 (8)
Stable disease (≥6 weeks)	7 (39)	5 (42)
Progressive disease	5 (28)	5 (42)
Not evaluable	2 (11)	1 (8)

All patients		
Clinical benefit, n (%)[a]	**Cediranib 45mg/day + fulvestrant LD (n=31)**	**Placebo + fulvestrant (n=31)**
Yes		
Total	13 (42)	13 (42)
Measurable disease (partial response/stable disease (≥6 months)	8 (26)	4 (13)
Non-measurable (stable disease ≥6 months)	5 (16)	9 (29)
No	18 (58)	18 (58)

[a]Clinical benefit was defined as having a best overall tumor response of complete response, partial response or stable disease for ≥6 months (includes patients with non-measurable disease)

Table 3 Best percentage change from baseline in size of target lesions (patients with measurable disease)

Time point	Treatment	n	Percentage change from baseline, mean (SD)	LS mean[a] (SE)	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, 32.86
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

[a]Least squares mean, derived from ANCOVA

The duration of follow-up ranged from 30–451 days (one patient was still ongoing at time of data cut off), CI, confidence interval

Table 4 Most common adverse events (frequency >20% in either arm)

Adverse event, n (%)	Cediranib 45mg/day + fulvestrant LD (n=31)	Placebo + fulvestrant LD (n=31)
Fatigue	19 (61)	8 (26)
Diarrhea	21 (68)	4 (13)
Hypertension	17 (55)	6 (19)
Nausea	11 (35)	8 (26)
Headache	11 (35)	7 (23)
Constipation	11 (35)	4 (13)
Vomiting	12 (39)	3 (10)
Anorexia	12 (39)	2 (6)
Arthralgia	7 (23)	7 (23)
Hot flush	3 (10)	11 (36)
Pain in extremity	8 (26)	6 (19)
Stomatitis	11 (35)	3 (10)
Back pain	5 (16)	8 (26)
Dysphonia	11 (35)	0 (–)
Weight decreased	7 (23)	0 (–)