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ORIGINAL ARTICLE

A randomized, phase II, dose-finding study of the pan-ErbB receptor tyrosine-kinase inhibitor CI-1033 in patients with pretreated metastatic breast cancer

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Abstract
Purpose To evaluate the efficacy and safety of the pan-ErbB receptor tyrosine-kinase inhibitor CI-1033 in metastatic breast cancer (MBC).
Experimental design Patients with measurable, progressive, or recurrent MBC whose primary tumor expressed ≥1 ErbB receptor were randomized to the following CI-1033 regimens: 50 mg (arm A) or 150 mg (arm B) daily without rest period, or 450 mg/day × 14 days every 21 days (arm C). The primary endpoint was 1-year progression-free survival (PFS).
Results Overall, 194 patients were treated. One-year PFS estimates were 3.8, 2.0, and 4.6%; median PFS was 61, 56, and 58 days; and investigator-assessed overall response rates were 1.5, 1.5, and 7.3%, in arms A, B, and C, respectively. Response duration was 110–419 days. In arm C, response (18.8 vs. 2.6%) and 1-year overall survival rates (86.7 vs. 47.5%) were greater in patients with HER2-positive versus HER2-negative tumors. The incidence of grade 3/4 adverse events (AEs) was dose-dependent, affecting 10.3, 48.6, and 80.4% of patients in arms A, B and C, respectively. The most common grade 3/4, treatment-related AEs were diarrhea, asthenia, and stomatitis. Arm C enrollment was prematurely discontinued due to a high frequency of grade 3/4 AEs.
Conclusion Single-agent CI-1033 did not show clinically meaningful activity in heavily pretreated patients with MBC expressing ≥1 ErbB receptor. Antitumor activity was observed in arm C patients with HER2-positive tumors. However, only the 50 mg dose was well tolerated, and the highest dose reached unacceptable levels of toxicity.

Keywords CI-1033 · Pan-ErbB receptor tyrosine-kinase inhibitor · Metastatic breast cancer · Efficacy · Safety

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Introduction

The ErbB family of proto-oncogenes comprises the transmembrane receptors ErbB-1 (epidermal growth factor receptor, EGFR), HER2 (ErbB-2/*neu*), ErbB-3, and ErbB-4. Ligand binding to ErbB-1, -3, or -4 leads to homodimerization or heterodimerization with another ErbB receptor.

This phenomenon triggers tyrosine-kinase (TK) activation in ErbB-1, HER2, and/or ErbB-4, leading eventually to cell proliferation, differentiation, or migration [1]. Overexpression of one or more ErbB receptors occurs with high frequency in human solid tumors and is a negative prognostic factor for tumors including breast cancer [2–4].

CI-1033 (canertinib) is a 4-anilinoquinazoline that interacts with and irreversibly inhibits the adenosine triphosphate (ATP) binding site of ErbB-1, HER2, and ErbB-4 receptors, suppressing their downstream signaling pathways [5, 6]. CI-1033 completely inhibited EGF-stimulated autophosphorylation of ErbB-1 in A431 human epidermoid carcinoma cells and heregulin-stimulated autophosphorylation of HER2, ErbB-3, and ErbB-4 in MDA-MB-453 human breast cancer cells [6]. Oral administration of CI-1033 significantly delayed the growth of several human tumor xenografts in mice, including breast cancer [5, 6]. In patients, CI-1033 has a bioavailability of 31% following oral administration [7], and several dosing schedules have been investigated in phase I studies [5, 8–10]. The highest maximum tolerated dose (MTD) given intermittently was 450 mg/day for 14 days every 21 days [9], while 150 mg/day was the MTD when CI-1033 was administered without scheduled off-treatment days [11]. The most common adverse events (AEs) were mild-to-moderate diarrhea, rash, nausea, vomiting, and stomatitis [5, 8–10]. Clinical activity, generally manifested as disease stabilization, was observed from the dose level of 50 mg/day [5, 8–10, 12] (Pfizer Inc., data on file 2008).

We report here findings from a phase II study investigating CI-1033 in patients with metastatic breast cancer (MBC) overexpressing at least one member of the ErbB receptor family.

Materials and methods

Study design and treatment

This open-label, randomized, phase II study was conducted at 47 centers throughout USA, Canada, and Europe. The study was performed in accordance with the Declaration of Helsinki (2,000 amendment) and all applicable local regulatory requirements and laws, and was approved by each center's institutional review board or independent ethics committee.

After giving written consent, patients were stratified according to estrogen receptor (ER) status (ER positive or unknown vs. negative) and disease-free interval (DFI) from initial diagnosis to relapse ($\leq$2 years vs. >2 years), and were then randomized (using an interactive voice response system) to one of three 21-day cycle, open-label, oral treatment arms: continuous daily dosing of CI-1033 at 50 mg (arm A) or 150 mg (arm B), or CI-1033 450 mg/day given for 14 consecutive days followed by 7 off-treatment days (arm C). Each day treatment was scheduled, patients were instructed to take medication once-daily without regard to meals. CI-1033 (Pfizer Inc., Ann Arbor, MI) was provided as 5 and 50 mg capsules. Treatment was continued until disease progression, unacceptable toxicity, or consent withdrawal. Any missed doses or vomited capsules were not replaced. In cases of grade 4 hematological toxicity, grade $\geq$3 neutropenia associated with fever, infection or grade $\geq$3 non-hematological toxicity persisting despite treatment, dosing was interrupted until recovery to grade $\leq$1 or baseline value. Treatment was then resumed, with the dose reduced by 10 or 25 mg in arms A or B, respectively. In arm C, the dose was reduced by 100 mg for the first three reductions, 50 mg for the next two reductions, and by 10 mg thereafter. No cross-over between treatment arms was permitted. An interim analysis of 1-year survival results was conducted for administrative/planning purposes after all patients had been enrolled and begun treatment.

Intent-to-treat (ITT) patients were defined as those who were randomized and received at least one dose of CI-1033. All ITT patients were included in the safety analysis.

Patients

Female patients, aged $\geq$18 years, with histologically proven breast cancer and progressive or recurrent metastatic disease following their most recent therapy were eligible. Other key eligibility criteria included $\leq$2 previous chemotherapy regimens for advanced disease; $\geq$1 measurable target lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) [13] that had not been irradiated; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; and adequate organ and hematological function. Breast tumors had to express $\geq$1 ErbB receptor identified by centralized immunohistochemistry (IHC). A washout period of $\geq$3 weeks for chemotherapy and $\geq$4 weeks for hormone therapy or prior investigational therapy was required, with full recovery from toxicities. Exclusion criteria included prior exposure to CI-1033 or another ErbB-targeted agent (including trastuzumab and lapatinib); hypersensitivity to TK inhibitors; history of another cancer within 5 years (except non-melanoma skin cancers and in situ carcinoma of the cervix); and symptomatic untreated brain metastases.

Study objectives/endpoints

The primary endpoint was the 1-year progression-free survival (PFS) rate (the proportion of patients progression-free and alive 1 year after randomization). Secondary efficacy endpoints included overall objective response/disease

control rates (ORR; defined by RECIST), duration of objective response, 26-week PFS, median PFS, median overall survival (OS), and 1-year OS. Safety evaluations were conducted via clinical laboratory tests, physical examinations, and adverse event (AE) monitoring.

Assessments

A pretreatment tumor sample was required before study entry for IHC phenotyping of ErbB receptor expression. Tumor samples (formalin-fixed tissue, paraffin-embedded tissue blocks or unstained slides) were assessed by Genzyme Analytical Services, Los Angeles, CA. Receptors were detected as follows: ErbB-1 with the DAKO EGFr pharmDx™ kit (DakoCytomation, Carpinteria, CA); HER2 using the HercepTest™ (DakoCytomation); ErbB-3 with anti-c-erbB3 (Neomarkers, Inc., Fremont, CA); and ErbB-4 with anti-c-erbB4 (Sigma-Aldrich, St Louis, MO). Receptor staining intensity was graded from 0 to 3+. To be eligible, samples were required to show $\geq$10% of uniform, intense membrane tumor cells staining for at least one ErbB receptor.

Tumor responses were assessed by CT scan or MRI at baseline, then after every 2 cycles. Physical examination, PS assessment, biochemistry, and coagulation tests were performed at baseline, then after every 21-day cycle. Complete blood cell counts and differential were performed weekly. Electrocardiogram and MUGA scan or echocardiogram were performed at baseline and end of study. AEs were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. If study treatment was discontinued for any reason other than tumor progression, patients were followed until disease progression.

Statistical analyses

The statistical hypothesis was to eliminate a compound that would not double an estimated 15% historical 1-year PFS. Fifty-three patients per treatment arm were needed to detect a difference between a 30% and a 15% 1-year PFS, with 90% power and assuming an α of 10%. Assuming a 30% 1-year PFS, 53 patients per treatment group were expected to yield a 95% confidence interval (CI) of approximately $\pm$12%. Taking into account non-evaluable patients, 168 patients (56 per arm) were planned. PFS and OS estimates were calculated according to Kaplan–Meier's method. The 95% asymptotic CI was based on Collett's complementary log–log transform method for survival probabilities at various time points, and on the method of Brookmeyer and Crowley for medians.

Results

Recruitment commenced in December 2002. Overall, 198 patients were randomized, with 194 treated (68, 70, and 56 in arms A, B, and C, respectively) from January 2003 to April 2005 (Fig. 1). Follow-up was completed in May 2005. Baseline characteristics are summarized in Table 1 and were similar among the three groups. Median overall age was 55.5 years, and most patients were Caucasian and postmenopausal. Median baseline ECOG PS in all three groups was 0 and the most common primary tumor histopathology was ductal (arm A: 77.1%, arm B: 79.2%, and arm C: 89.3%). The majority of patients in each group had previously undergone surgery, systemic therapy, or radiotherapy with a similar number of patients exhibiting metastases to the liver, lung, and lymph tissues. ErbB expression profiles were similar, with ErbB-3 and ErbB-4 showing more dominant expression in all groups.

Patient randomization into arm C was prematurely discontinued in December 2003 due to interim data indicating a high frequency of serious AEs and a relative frequency of grade 3/4 AEs that was expected to exceed 50% in the high-dose arm by study end. Patients already randomized in arm C could continue at the discretion of the investigator based on individual tolerance. Patient disposition is outlined in Fig. 1.

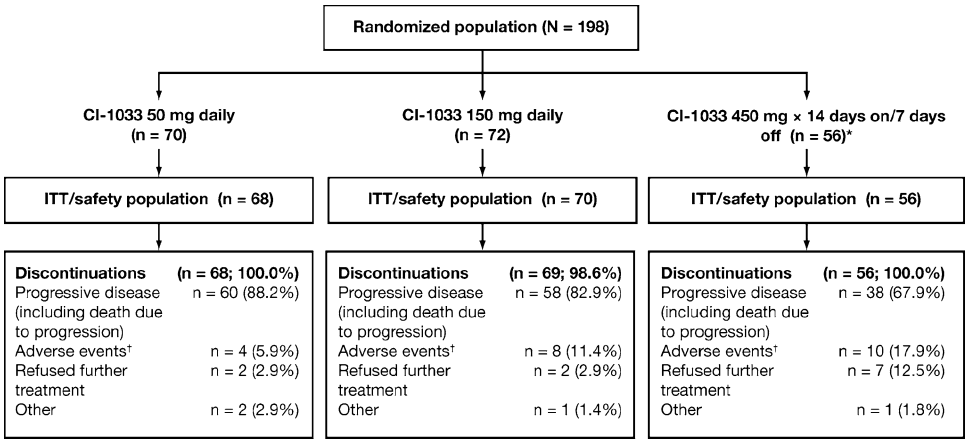

Fig. 1 Patient disposition. *Asterisk* prematurely discontinued in December 2003 because of drug dose safety concerns. Subjects already randomized in arm C could continue at the discretion of the investigator based on individual tolerance. *Dragger* treatment-related adverse events resulting in discontinuation of >2 patients per treatment arm were asthenia, mucous membrane disorder, pulmonary embolus, syncope, and diarrhea

Table 1 Patient characteristics (randomized patients)

	Arm A: 50 mg (continuous) $n = 70$	Arm B: 150 mg (continuous) $n = 72$	Arm C: 450 mg (14 day on/7 day off) $n = 56$[a]
Median age, years (range)	57 (29–87)	54 (29–80)	55 (31–79)
Postmenopausal, n (%)	57 (81.4)	60 (83.3)	50 (89.3)
ECOG PS[b], n (%)			
0	43 (61.4)	37 (51.4)	29 (51.8)
1	24 (34.3)	33 (45.8)	25 (44.6)
ER-positive or unknown, *n* (%)	40 (57.1)	41 (56.9)	31 (55.4)
DFI >2 years, *n* (%)	30 (42.9)	31 (43.1)	21 (37.5)
Stratification categories, *n* (%)			
ER positive/unknown and DFI ≤2 years	21 (30.0)	21 (29.2)	18 (32.1)
ER positive/unknown and DFI >2 years	19 (27.1)	20 (27.8)	13 (23.2)
ER negative and DFI ≤2 years	19 (27.1)	20 (27.8)	17 (30.4)
ER negative and DFI >2 years	11 (15.7)	11 (15.3)	8 (14.3)
Ductal histology, *n* (%)	54 (77.1)	57 (79.2)	50 (89.3)
Previous therapy, *n* (%)			
Surgery	65 (92.9)	69 (95.8)	52 (92.9)
Systemic therapy	66 (94.3)	71 (98.6)	55 (98.2)
Radiotherapy	50 (71.4)	53 (73.6)	40 (71.4)
Metastatic sites, *n* (%)			
Liver	36 (51.4)	32 (44.4)	23 (41.1)
Lung	15 (21.4)	14 (19.4)	15 (26.8)
Lymph	12 (17.1)	18 (25.0)	13 (23.2)
Other	34 (48.6)	38 (52.8)	31 (55.4)
ErbB receptor expression, n (%)			
ErbB1	18 (25.7)	25 (34.7)	21 (37.5)
HER2	23 (32.9)	20 (27.8)	16 (28.6)
ErbB3	65 (92.9)	68 (94.4)	49 (87.5)
ErbB4	57 (81.4)	54 (75.0)	40 (71.4)
Time from end of last regimen to study start, days[c]			
Mean (±SD)	125 (±173)	184 (±445)	200 (±430)
Range	(0–999)[d]	(0–2,913)	(0–2,155)

[a] Arm prematurely closed

[b] Unknown in 7 patients

[c] $n = 66$, 69 and 55 for arms A, B, and C, respectively (sample sizes are less than enrolled due to missing data)

[d] 0 indicates previous therapy date ongoing at study start date

DFI disease-free interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ER* estrogen receptor

The median cumulative dose for the 50, 150, and 450 mg dose groups was 3,100.0, 6,375.0, and 10,187.5 mg, respectively, and the majority of patients started two (16.2, 31.4, and 30.4% of patients in each dose group, respectively) or three (32.4, 24.3, and 19.6%, respectively) 21-day cycles of treatment. The median number of treatment cycles in arms A, B, and C was three (range 1–24), three (range 1–22), and two (range 1–18), respectively. The percentage of patients requiring dose reductions increased with increasing planned dose (2.9, 11.4, and 39.3%, in arms A, B, and C, respectively).

Efficacy

One-year PFS estimates were 3.8% (95% CI, 0.7–11.6), 2.0% (95% CI, 0.2–9.3), and 4.6% (95% CI, 0.8–13.7) for arms A, B, and C, respectively, and therefore did not meet the statistical hypothesis of 30 ± 12% (Table 2A). The number of patients surviving progression-free at 1 year was deemed insufficient to support a stratified analysis. A Kaplan–Meier plot of 1-year PFS is shown in Fig. 2.

Median and 26-week PFS and median and 1-year OS were similar between the three treatment arms (Table 2A). The number of patients surviving progression-free for 26 weeks and the median OS were both deemed insufficient to support a stratified analysis. Stratified analyses for median PFS and 1-year OS are shown in Table 3. Analysis of HER2 status only in arm C demonstrated a near doubling of the median PFS and 1-year OS in patients with HER2-positive tumors, compared with HER2-negative tumors (PFS: 107.0 vs. 57.0 days, 1-year OS 86.7 vs. 47.5%; Table 3B). However, the significance of these findings and

Table 2 Clinical response: (A) primary (1-year PFS) and secondary efficacy endpoints, (B) ErbB receptor status and response magnitude and duration in individual patients experiencing objective partial responses

	Arm A: 50 mg (continuous)	Arm B: 150 mg (continuous)	Arm C: 450 mg (14 day on/7 day off)
(A)			
Progression-free survival			
ITT patients, *n*[a]	68	68	55
1-year PFS, % (95% CI)	3.8 (0.7–11.6)	2.0 (0.2–9.3)	4.6 (0.8–13.7)
26-week PFS, % (95% CI)	13.4 (6.2–23.6)	4.0 (0.8–12.1)	9.2 (2.9–19.8)
Median PFS, days (95% CI)	61 (57–69)	56 (48–59)	58 (54–68)
Overall survival			
ITT patients, *n*	68	70	56
1-year OS, % (95% CI)	54.4 (41.9–65.3)	49.0 (36.8–60.2)	57.6 (43.4–69.4)
Median OS, days (95% CI)	395 (273–474)	364 (210–NA)	483 (327–692)
Best objective response			
ITT patients, *n*[a]	68	68	55
Partial response, *n* (%)	1 (1.5)	1 (1.5)	4 (7.3)
Stable disease, *n* (%)	20 (29.4)	13 (19.1)	6 (10.9)
Progressive disease, *n* (%)	44 (64.7)	44 (64.7)	34 (61.8)

Patient number	Treatment arm	ErbB receptor status	Reduction in tumor size (%)	Duration of response (days)
(B)				
63004	Arm A: 50 mg	ErbB-1−, HER2−, ErbB-3+, ErbB-4+	100	419
63007	Arm B: 150 mg	ErbB-1−, HER2−, ErbB-3+, ErbB-4+	51.9	384
39003	Arm C: 450 mg	ErbB-1+, HER2+, ErbB-3+, ErbB-4+	72.0	334
41001	Arm C: 450 mg	ErbB-1−, HER2+, ErbB-3+, ErbB-4−	47.3	134
41013	Arm C: 450 mg	ErbB-1+, HER2−, ErbB-3+, ErbB-4+	56.4	176[b]
52001	Arm C: 450 mg	ErbB-1−, HER2+, ErbB-3+, ErbB-4+	48.1	110

[a] 3 patients were not evaluable (inadvertently enrolled and then determined to be ineligible based on assessments made prior to enrollment)

[b] Progression not observed

ITT intent-to-treat, *PFS* progression-free survival, *CI* confidence interval, *OS* overall survival, *NA* not available

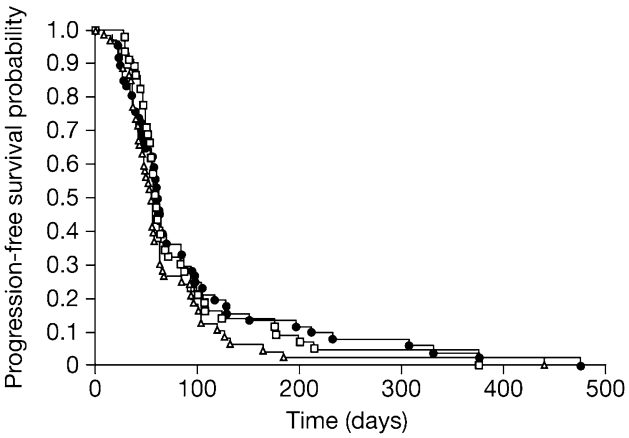

Fig. 2 Kaplan–Meier estimates of 1-year progression free survival (intent-to-treat population). Treatment groups: CI-1033, 50 mg daily ($n = 68$; *circle*), CI-1033, 450 mg × 14 days on/7 days off ($n = 55$; *square*), CI-1033, 150 mg daily ($n = 68$; *triangle*)

others from the stratified analyses is uncertain owing to the small sample size and in most cases, the overlapping 95% CI.

One patient in both arms A and B, and four patients in arm C achieved a partial response (PR); however, no complete responses (CRs) were observed. Accordingly, the estimated ORR was 1.5% (1/68; 95% CI, 0.04–7.92) for arm A, 1.5% (1/68; 95% CI, 0.04–7.92) for arm B and 7.3% (4/55; 95% CI, 2.02–17.59) for arm C (Table 2A). These six PRs ranged from 110 to 419 days, with three responses (one from each arm) lasting over 300 days (Table 2B). In arm C, the ORR was 18.8% (3/16; 95% CI, 4.05–45.6) for patients with HER2-positive tumors, compared with 2.6% (1/39; 95% CI, 0.06–13.5) for HER2-negative disease. Interestingly, three out of six objective responses were in patients with HER2-positive tumors. Stable disease (SD) as a best response to treatment was reported for 29.4% (20/68), 19.1% (13/68) and 10.9% (6/55) of patients in arms A, B, and C, respectively. The disease control rate (response plus SD) was estimated as 30.9% (21/68; 95% CI, 20.24–43.26), 20.6% (14/68; 95% CI, 11.74–32.12), and 18.2% (10/55; 95% CI, 9.08– 30.90), for arms A, B, and C, respectively. The number of responders (six PR/CR) was deemed insufficient to support a stratified analysis.

Table 3 Stratified response analyses: (A) estrogen receptor (ER) status (positive or unknown vs. negative) and disease-free interval (DFI) from initial diagnosis to relapse (≤2 years vs. >2 years), (B) HER2 status (positive or unknown vs. negative)

	Arm A: 50 mg (continuous)	Arm B: 150 mg (continuous)	Arm C: 450 mg (14 day on/7 day off)
(A)			
ER-positive/unknown, DFI ≤2 years[a]			
Patients, *n*	19	18	17
Median PFS, days (95% CI)	44.0 (27.0–57.0)	57.0 (45.0–59.0)	57.5 (44.0–124.0)
1-year OS, % (95% CI)	15.8 (3.9–34.9)	23.7 (7.4–45.2)	56.7 (30.0–76.6)
ER-positive/unknown, DFI >2 years[b]			
Patients, n	11	11	8
Median PFS, days (95% CI)	64.0 (57.0–212.0)	85.0 (27.0–165.0)	50.0 (47.0–106.0)
1-year OS, % (95% CI)	72.7 (37.1–90.3)	71.6 (35.0–89.9)	62.5 (22.9–86.1)
ER-negative, DFI ≤2 years[c]			
Patients, n	20	20	17
Median PFS, days (95% CI)	66.0 (61.0–98.0)	55.0 (42.0–64.0)	62.0 (54.0–71.0)
1-year OS, % (95% CI)	55.0 (31.3–43.5)	52.4 (29.8–70.9)	55.6 (30.5–74.8)
ER-negative, DFI >2 years[c]			
Patients, *n*	18	19	13
Median PFS, days (95% CI)	65.0 (56.0–84.0)	52.0 (37.0–64.0)	58.0 (50.0–93.0)
1-year OS, % (95% CI)	83.3 (56.8–94.3)	55.0 (31.3–73.5)	58.3 (27.0–80.1)
	Arm A: 50 mg (continuous)	Arm B: 150 mg (continuous)	Arm C: 450 mg (14 day on/7 day off)
(B)			
HER2-positive/unknown			
Patients, *n*	23	20	16
Median PFS, days (95% CI)	63.5 (46.0–98.0)	57.0 (47.0–67.0)	107.0 (51.0–177.0)
1-year OS, % (95% CI)	56.5 (36.3–76.8)	40.0 (18.5–61.5)	86.7 (69.4–100)
HER2-negative			
Patients, *n*	45	47	39
Median PFS, days (95% CI)	60.0 (49.0–69.0)	52.0 (42.0–57.0)	57.0 (52.0–62.0)
1-year OS, % (95% CI)	53.3 (38.8–67.9)	49.7 (35.1–64.3)	47.5 (31.6–63.4)

Median PFS data, *n* = 18, 19, and 13; 1-year OS, *n* = 18, 20, 13 in arms A, B, and C, respectively

[a] Median PFS and 1-year OS data, n = 19, 18, and 17 in arms A, B, and C, respectively

[b] Median PFS and 1-year OS data, n = 11, 11, and 8 in arms A, B, and C, respectively

[c] Median PFS data, n = 20, 20, and 17; 1-year OS, n = 20, 21, 18 in arms A, B, and C, respectively

CI confidence interval, *OS* overall survival, *PFS* progression-free survival

Safety

Most frequently reported treatment-related, non-hematological AEs were gastrointestinal (diarrhea, nausea, anorexia, and stomatitis), skin disorders (rash and acne), and general symptoms (asthenia and weight loss, Table 4A). Grade 3/4, treatment-related, hematological AEs included thrombocytopenia and anemia (Table 4B). The incidence and severity of the AEs were clearly dose-related. Few grade 3/4 toxicities occurred at 50 mg/day (arm A), whilst this level of toxicity was common at 150 mg/day (arm B) and reached a level considered unacceptable at 450 mg/day (arm C). In arm C, up to 80% of patients experienced at least one grade 3/4 toxicity and enrollment into this study arm was consequently prematurely discontinued. Likewise, the rate of study treatment discontinuation due to toxicity (mainly diarrhea, asthenia, and mucositis) increased with increasing dose from 5.9 to 11.4% and 17.9% in arms A, B, and C, respectively (Fig. 1).

A small number of patients experienced treatment-related, grade 3/4 pulmonary embolisms (PEs, *n* = 3) and deep venous thrombosis (DVT, *n* = 2). The DVT cases occurred early in the study (days 10 and 16) in arms A and B. The three PEs were in arms A and C and occurred with similar timing (days 11–14). One PE resulted in a fatality in a 59-year-old patient receiving 50 mg/day. An additional

Table 4 Safety findings (intent-to-treat population): (A) non-hematological, treatment-related adverse events (AEs) reported by at least 5% of patients or of clinical interest, (B) grade 3/4 hematological toxicities

	Number of patients (%)					
	Arm A: 50 mg (continuous) $n = 68$		Arm B: 150 mg (continuous) $n = 70$		Arm C: 450 mg (14 day on/7 day off) $n = 56$	
	All	Grade 3–4	All	Grade 3–4	All	Grade 3–4
(A)						
Any AE	60 (88.2)	7 (10.3)	69 (98.6)	34 (48.6)	54 (96.4)	45 (80.4)
Diarrhea	29 (42.6)	0	52 (74.3)	14 (20.0)	48 (85.7)	24 (42.9)
Nausea	21 (30.9)	0	34 (48.6)	3 (4.3)	31 (55.4)	2 (3.6)
Rash	17 (25.0)	0	34 (48.6)	3 (4.3)	35 (62.5)	5 (8.9)
Asthenia	17 (25.0)	0	29 (41.4)	9 (12.9)	26 (46.4)	12 (21.4)
Anorexia	13 (19.1)	0	23 (32.9)	3 (4.3)	22 (39.3)	2 (3.6)
Stomatitis	12 (17.6)	0	21 (30.0)	2 (2.9)	25 (44.6)	9 (16.1)
Vomiting	9 (13.2)	0	21 (30.0)	2 (2.9)	25 (44.6)	5 (8.9)
Acne	9 (13.2)	0	17 (24.3)	1 (1.4)	16 (28.6)	2 (3.6)
Epistaxis	8 (11.8)	0	14 (20.0)	1 (1.4)	19 (33.9)	0
Mucositis	7 (10.3)	0	15 (21.4)	4 (5.7)	17 (30.4)	4 (7.1)
Pruritus	5 (7.4)	0	13 (18.6)	0	13 (23.2)	1 (1.8)
Weight loss	5 (7.4)	0	10 (14.3)	0	13 (23.2)	0
Headache	8 (11.8)	0	7 (10.0)	1 (1.4)	4 (7.1)	0
Rhinitis	3 (4.4)	0	8 (11.4)	0	6 (10.7)	0
Alopecia	2 (2.9)	NA	5 (7.1)	NA	9 (16.1)	NA
Fever	1 (1.5)	0	6 (8.6)	0	7 (12.5)	0
Myalgia	3 (4.4)	0	3 (4.3)	0	7 (12.5)	2 (3.6)
Taste loss	1 (1.5)	0	2 (2.9)	0	6 (10.7)	0
Infection	1 (1.5)	0	1 (1.4)	0	6 (10.7)	1 (1.8)
Conjunctivitis	4 (5.9)	1 (1.5)	4 (5.7)	0	4 (7.1)	1 (1.8)
Hypokalemia	2 (2.9)	1 (1.5)	2 (2.9)	1 (1.4)	3 (5.4)	0
Dehydration	0	0	2 (2.9)	2 (2.9)	3 (5.4)	1 (1.8)
Allergic reaction	0	0	1 (1.4)	0	5 (8.9)	3 (5.4)
Pulmonary embolism[a]	2 (2.9)	2 (2.9)	0	0	1 (1.8)	1 (1.8)
Deep venous thrombosis	1 (1.5)	1 (1.5)	3 (4.3)	3 (4.3)	0	0

	Number of patients[b] (%)					
	Arm A: 50 mg (continuous) $n = 68$		Arm B: 150 mg (continuous) $n = 70$		Arm C: 450 mg (14 day on/7 day off) n = 56	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
(B)						
Anemia	2/66 (3.0)	2/66 (3.0)	1/67 (1.5)	2/67 (3.0)	1/53 (1.9)	0/53 (0)
Neutropenia	0/60 (0)	1/60 (1.7)	1/62 (1.6)	0/62 (0)	0/49 (0)	0/49 (0)
Thrombocytopenia	2/66 (3.0)	2/66 (3.0)	3/67 (4.5)	0/67 (0)	4/52 (7.7)	1/52 (1.9)
Prothrombin time	4/41 (9.8)	0/47 (0)	2/45 (4.4)	0/47 (0)	3/31 (9.7)	0/33 (0)
Activated partial thromboplastin time	3/55 (5.5)	0/58 (0)	0/55 (0)	0/58 (0)	2/39 (5.1)	0/40 (0)
International normalized ratio	0/47 (0)	0/53 (0)	1/51 (2.0)	0/56 (0)	3/40 (7.5)	0/44 (0)

No grade 3 or 4 events were reported for decreased or increased hematocrit

[a] One patient died following a pulmonary embolism (grade 5) considered treatment-related in arm A

[b] Includes only patients with both a baseline value and at least one post-baseline value who are eligible to appear in each column (e.g. only patients with a baseline value < grade 3 are included in the grade 3 column)

NA not available

death due to a cerebral hemorrhage was classified as possibly treatment-related and occurred in a 61-year-old patient receiving 150 mg/day.

Baseline measurements of left ventricular ejection fraction (LVEF) were recorded for 191 patients, with 85 (44.5%) having at least one further measurement. Of these patients, 7.1% (6/85) had an absolute decrease in LVEF of >20 and 8.2% (7/85) had an absolute increase of >20%. All changes in LVEF were asymptomatic.

There was no correlation between toxicity and response. For example, the incidence of diarrhea, the most frequently observed AE, was similar in patients experiencing clinical benefit (PR, CR, or SD) and non-responders (66.7 vs. 54.1%; $P = 0.1368$; Spearman correlation −0.1077). Similarly, acne was observed in 28.9% of patients experiencing clinical benefit and 16.4% of non-responders ($P = 0.0646$; Spearman correlation −0.1337).

Discussion

This randomized, phase II study assessed the clinical antitumor activity of CI-1033 in patients with pretreated advanced or MBC overexpressing at least one ErbB receptor. Since targeted agents may induce clinically relevant tumor growth delay in the absence of significant tumor shrinkage, 1-year PFS was chosen as the primary endpoint, rather than tumor response rate, with a statistical hypothesis for excluding an inactive agent of 30 ± 12%. Consistent with this hypothesis, a recent study conducted in MBC has demonstrated, in the control arm, a 1-year PFS of 15% in a more advanced population (third-line treatment after anthracycline and taxane failure) [14]. In our study, the 1-year survival rate was <5% in all treatment arms, with the upper limit of the 95% CI below the lower limit (18%) of the hypothesized interval. Median PFS was approximately 2 months in all three arms and ORR was 1.5% in arms A and B, and 7.3% in arm C. Based on these parameters, CI-1033 is not active as a single agent in this patient population, with the dosing schedules used. This lack of clinically meaningful activity is consistent with findings for ovarian cancer [15]. Nevertheless, objective responses were long lasting (110–419 days) and provide a proof of concept for single-agent activity. Additionally, 26-week PFS and SD rates (13.4 and 20% in arm A, respectively) suggest clinical activity, and it may be that 26-week PFS would have been a more appropriate endpoint than 1-year PFS.

In our study, the selection of patient ErbB receptor status was arbitrarily chosen. Our hypothesis was to try to demonstrate CI-1033 activity in a broad population beyond the HER2-positive MBC population, rather than focusing on a priori selected population. The cut-off level of ErbB expression required for positive staining can be criticized, as it was not restricted to the highest level of expression. Furthermore, our HER2-positive population definition differs from that described in recent guidelines for determining ErbB overexpression or gene amplification [16]. However, within the limits of the method we used for the HER2-status definition (which overestimates the number of HER2-positive patients), outcomes in arm C suggest that CI-1033 may have greater antitumor activity in HER2-positive tumors with this schedule, as the ORR in these tumors was 18.8% (3/16) versus 2.6% (1/39) for HER2-negative disease. One-year OS rates (86.7 vs. 47.5%) were also greater in HER2-positive versus HER2-negative disease in arm C, suggesting that further study of CI-1033 restricted to HER2 3+ (or amplified) disease may be warranted. Trastuzumab-cross resistance cannot be analyzed in this study, as patients with prior trastuzumab (and lapatinib) treatment were not included in this trial.

This trial was a dose-finding study and had a sixfold variation in planned dose-intensity, from 350 to 2,100 mg/week. Additional, unplanned variations in dose-intensity occurred due to differences in the number of treatment cycles completed (ranging from 1 to 24 cycles in arm A) and due to dose reductions experienced by 2.9–39.3% of patients in each cohort. There is a trend to support a dose–effect relationship, as both ORR (four out of six PRs were observed in arm C) and PFS (in the HER2-positive population) were increased at the highest dose.

Toxicity was also strongly dose-dependent. The incidence and severity of AEs increased considerably with dose and were considered unacceptable at the highest dose level. Thus, insufficient efficacy cannot be accounted for by suboptimal dose. Two treatment-related deaths were reported: one due to thromboembolism and the other due to cerebral hemorrhage. However, these fatalities did not seem to be dose-dependent and their relationship to CI-1033 is uncertain. Thrombocytopenia was observed in this study and has been reported in others with CI-1033. It was generally grade 1/2 and did not require medical intervention [5, 7, 9]. Four cases of treatment-related DVT and three PEs were reported in this trial, producing a greater frequency of these events than that observed in previous studies [15, 17] (Pfizer Inc., data on file 2008). No relationship between ErbB modifiers and thrombosis has previously been reported.

Other clinical studies in MBC after failure of anthracycline and taxane-based therapy have been reported. Capecitabine in unselected patients [18, 19], or single-agent trastuzumab in patients with HER-2 positive tumors [20], resulted in a median survival of approximately 13 months and response rates of 15–26%. These agents were approved in pretreated patients based on these results. Lower

responses rates (1.5–7.3%) and shorter median PFS (56–61 days/approximately 1.9–2.0 months), but a similar median OS (approximately 12.0–15.9 months), were observed with CI-1033.

Reasons for lack of efficacy in this study may include: lack of selection for HER2-positive tumors, insufficient inhibition of HER2, and/or an absence of antitumor activity from ErbB-1-related inhibition. Trastuzumab has demonstrated clear efficacy in HER2-positive breast cancer, and lapatinib, a reversible ErbB-1 and HER2 TK inhibitor, has shown significant single-agent activity in HER2-positive MBC, with preliminary data suggesting an 8.3% ORR [21]. In the present study, 27.8–32.8% of patients had HER2-positive cancers. Nevertheless, an ORR of 7.3% was observed in arm C, which is clinically interesting, although tolerability was poor. The ORR among patients with HER2-positive disease in this arm was 18.8% and compares favorably with other HER2 modulators [20, 21]. Additionally, HER-1 inhibition may not contribute to efficacy in breast cancer, as both erlotinib and gefitinib have had disappointing phase II results [22, 23]. Combined with the lack of patient selection for HER2 positivity, this may explain, in large part, the failure of CI-1033 to demonstrate efficacy in the current study. Additionally, both trastuzumab and lapatinib show improved efficacy combined with chemotherapy versus chemotherapy alone [24, 25], and it is possible that CI-1033 may also enhance the activity of chemotherapeutic agents, particularly in patients with HER2-positive tumors.

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