

Overview



The official journal of the Society for Translational Oncology

First Published Online March 27, 2014

DOI: 10.1634/theoncologist.2014-0022

Title: Bosutinib in Combination With the Aromatase Inhibitor Exemestane: A Phase II Trial in Postmenopausal Women With Previously Treated Locally Advanced or Metastatic Hormone Receptor-Positive/HER2-Negative Breast Cancer

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ClinicalTrials.gov Identifier: NCT00793546

Sponsor(s): Wyeth Research (acquired by Pfizer in October 2009)

Principal Investigator: Beverly Moy

IRB Approved: Yes

Disclosures

Charles Zacharchuk: Pfizer (E), (OI); **Eric Leip:** Pfizer (E), (OI); **Kathleen Turnbull:** Pfizer (E); **Nathalie Bardy-Bouxin:** Pfizer, Bosutinib Asset (E). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Author Summary: Abstract and Brief Discussion

Background

Bosutinib is an oral, selective Src/Abl tyrosine kinase inhibitor with activity in breast cancer (BC). We evaluated bosutinib plus exemestane as second-line therapy in previously treated hormone receptor-positive (HR+) locally advanced or metastatic BC.

Methods

This was a phase II study with patients enrolled in a single-arm safety lead-in phase. Patients receiving bosutinib at 400 mg or 300 mg/day (based on toxicity) plus exemestane at 25 mg/day were monitored for adverse events (AEs) and dose-limiting toxicities for 28 days, and initial efficacy was assessed. After the lead-in and dose-determination phase, randomized evaluation of combination therapy versus exemestane was planned.

Results

Thirty-nine of 42 patients (93%) experienced treatment-related AEs including diarrhea in 28 (67%) and hepatotoxicity in 11 (26%); overall serious treatment-related AEs were recorded in 4 (10%). No liver toxicity met Hy's law criteria. Dose-limiting toxicities occurred in 5 of 13 patients receiving 400 mg (38%) and 3 of 26 patients receiving 300 mg (12%) of bosutinib; all resolved on treatment discontinuation. One patient (300 mg/day) achieved confirmed partial response; three (400 mg/day,

$n = 2$; 300 mg/day, $n = 1$) maintained stable disease for >24 weeks; a best response of progressive disease occurred in 15 of 42 patients (36%). Median progression-free survival was 12.3 weeks (80% confidence interval: 11.0–15.6).

Conclusion

The risk-benefit profile of bosutinib at 300 mg/day plus exemestane resulted in early study termination before the randomized portion. Alternative bosutinib regimens merit investigation in BC.

Discussion

This phase II study was designed to evaluate the safety and efficacy of exemestane with or without bosutinib in previously treated postmenopausal women with HR+ /HER2– locally advanced or metastatic breast cancer (BC). In the safety lead-in phase (part 1), 39 of 42 patients (93%) experienced treatment-related adverse events (AEs), and 8 of 39 evaluable patients (21%) experienced dose-limiting toxicities (DLTs), with a higher incidence of DLTs in the group given bosutinib at 400 mg/day plus exemestane (5 of 13, 38%) than in the group given the recommended phase II dose of bosutinib at 300 mg/day plus exemestane (3 of 26, 12%). No case met Hy's law criteria for drug-induced hepatic injury [1]. One patient in the bosutinib 300 mg/day group achieved a confirmed partial response. The median progression-free survival (PFS) was 12.3 weeks (80% confidence interval [CI]: 8.1–23.7) for bosutinib 400 mg/day plus exemestane and 12.3 weeks (80% CI: 11.0–15.6) for bosutinib 300 mg/day plus exemestane. For bosutinib 300 mg/day plus exemestane, the 80% CI upper boundary for PFS was below the benchmark of 16 weeks for the median PFS for exemestane alone.

Bosutinib at 300 mg/day plus exemestane had a generally acceptable safety profile based on the DLT rate (12%); however, the rate of treatment-related hepatotoxicity (25%) prohibited further evaluation of this combination, given the lower-than-expected antitumor activity. Consequently, the study was terminated early, before initiation of the randomized portion of the study (part 2). Early termination was supported by the results of another phase II trial with the same design of bosutinib at 400 mg/day plus letrozole at 25 mg/day as first-line endocrine therapy in locally advanced or metastatic HR+ /HER2– BC patients (ClinicalTrials.gov identifier NCT00880009) [2]. Bosutinib plus letrozole was associated with DLTs in 4 of 15 evaluable patients (27%). Six of 16 patients experienced treatment-related hepatotoxicity. In that study, one patient with hepatotoxicity met Hy's law criteria for drug-induced liver injury, which also led to early study termination.

Bosutinib has demonstrated antitumor activity in BC cells in vitro and in mammary tumors in vivo [3–5]. The efficacy of single-agent bosutinib at 400 mg/day was demonstrated in a phase II trial in pretreated BC patients, with clinical benefit observed in 27% of patients (the four patients whose tumors responded had HR+ tumors) and a PFS rate of 40% [6]. The most common AEs were gastrointestinal (diarrhea, nausea, vomiting), and grade 3/4 alanine aminotransferase or aspartate aminotransferase elevations also occurred; these AEs were manageable and not life-threatening [6]. A phase I study of bosutinib in advanced solid tumors indicated a similar safety profile [7].

In conclusion, the initial findings from the present study indicate an unfavorable risk-benefit profile of the combination of bosutinib and exemestane in pretreated postmenopausal women with HR+ /HER2– BC and resulted in early termination of this study. However, the efficacy of single-agent bosutinib underscores the potential clinical benefits of Src/Abl inhibition in BC [6] and suggests that studies of other combination regimens with bosutinib may be warranted.

Trial Information

Disease:	Breast cancer
Stage of disease / treatment:	Metastatic / Advanced
Prior Therapy:	No designated number of regimens
Type of study - 1:	Phase II
Type of study - 2:	Randomized
Additional Details of Endpoints or Study Design:	This phase II study in postmenopausal women with HR+ /HER2- BC consisted of a safety lead-in phase, with an initial cohort of 10 patients who received oral bosutinib 400 mg (taken once daily, preferably in the morning) plus exemestane 25 mg (taken once daily, preferably after a meal in the morning 30 minutes to 1 hour after bosutinib intake) and were monitored for AEs and DLTs. Sample size was dependent on the observed DLT rate. If no safety concerns arose and the upper boundary of the 80% confidence interval (CI) for the observed DLT rate was $\leq 34\%$, all subsequent patients were to be enrolled into the randomized portion of the study. However, if safety criteria, defined as calculated DLT rate, were not met in the

lead-in phase, 10 additional patients were to be enrolled at the same dose if the lower and upper boundary of the 80% CI were $\leq 18\%$ and $>34\%$, or at a reduced bosutinib dose of 300 mg if the lower boundary of the 80% CI was $>18\%$, with the possibility of up to 60 patients enrolled in the lead-in phase (30 at each dose). Pending no safety concerns, approximately 164 patients (125 PFS events) were to be randomized 1:1 to receive exemestane 25 mg/day alone or combined with bosutinib at the tolerable dose defined during the lead-in. The randomized portion of the study was sized based on a targeted median PFS of 24 weeks for combination therapy and 16 weeks for exemestane alone.

Investigator's Analysis:

Poorly Tolerated/Not Feasible

Drug Information

Drug 1:

Generic/Working name:

bosutinib

Trade name:

Bosulif

Company name:

Pfizer

Drug type:

Small molecule

Drug class:

Other

Dose:

Approved dose: 500 mg/d; doses evaluated here: 300 mg/d and 400 mg/d milligrams (mg) per flat dose

Route:

oral (po)

Schedule of Administration:

An initial cohort of 10 patients were administered oral bosutinib 400 mg (taken once daily, preferably in the morning) plus exemestane 25 mg (taken once daily, preferably after a meal in the morning 30 minutes to 1 hour after bosutinib intake). If safety criteria, defined as calculated DLT rate, were not met in the lead-in phase, 10 additional patients were to be enrolled at the same dose if the lower and upper boundary of the 80% CI were $\leq 18\%$ and $>34\%$, or at a reduced bosutinib dose of 300 mg if the lower boundary of the 80% CI was $>18\%$, with the possibility of up to 60 patients enrolled in the lead-in phase (30 at each dose).

Drug 2:

Generic/Working name:

exemestane

Trade Name:

Aromasin

Company name:

Pfizer

Drug type:

Other

Drug class:

Other

Dose:

25 mg (mg) per flat dose

Route:

oral (po)

Schedule of Administration:

Exemestane 25 mg taken once daily, preferably after a meal in the morning 30 minutes to 1 hour after bosutinib intake

Patient Characteristics

Number of patients, male:

0

Number of patients, female:

42

Stage:

Ninety-eight percent of patients had stage IV breast cancer; 2% had Stage IIIB breast cancer.

Age:

Median (range): 60.5 years (40-79 years)

Number of prior systemic therapies:

Median (range): Not Collected

Performance Status:

ECOG

0 — 64%

1 — 33%

2 — 2%

	3 — 0%
	Unknown— 0%
Other:	Not Collected

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients screened:	60
Number of patients enrolled:	42
Number of patients evaluable for toxicity:	42
Number of patients evaluated for efficacy:	42
Evaluation method:	Other
Response assessment CR:	0%
Response assessment PR:	2.4%
(Median) duration assessments PFS	12.3 weeks, CI: 11.0-15.6

Serious Adverse Events

Name	Grade	Attribution
Diarrhea	4	Definite
Diarrhea	3	Definite
Fluid overload	3	Definite
Diabetes mellitus	3	Definite
Dyspnea	3	Definite
Pleural effusion	3	Unrelated
Pleural effusion	3	Unrelated
Pleural effusion	2	Unrelated
Renal failure	3	Unrelated
Electrolyte imbalance	3	Unrelated
Pneumonia	3	Unrelated
General physical health deterioration	3	Unrelated
Cardiac arrest	4	Unrelated
Cardiac failure	5	Unrelated
Febrile neutropenia	3	Unrelated

Assessment, Analysis, and Discussion

Completion:	Study terminated before completion
Terminated reason:	Toxicity
Pharmacokinetics / Pharmacodynamics:	Not Collected
Investigator's Assessment:	Poorly Tolerated/Not Feasible

Discussion

This phase II study was designed to evaluate the safety and efficacy of exemestane with or without bosutinib in previously treated postmenopausal women with HR+/HER2- locally advanced or metastatic BC. In the safety lead-in phase (part 1), 39 of 42 patients (93%) experienced treatment-related AEs, and 8 of 39 evaluable patients (21%) experienced DLTs, with a higher incidence of DLTs in the group given bosutinib at 400 mg/day plus exemestane (5 of 13, 38%) than in the group given the recommended phase II dose of bosutinib at 300 mg/day plus exemestane (3 of 26, 12%). No case met Hy's law criteria for

drug-induced hepatic injury [1]. One patient in the bosutinib 300 mg/day group achieved a confirmed partial response. The median PFS was 12.3 weeks (80% CI: 8.1–23.7) for bosutinib at 400 mg/day plus exemestane and 12.3 weeks (80% CI: 11.0–15.6) for bosutinib at 300 mg/day plus exemestane. For bosutinib at 300 mg/day plus exemestane, the 80% CI upper boundary for PFS was below the benchmark of 16 weeks for the median PFS for exemestane alone.

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In conclusion, the initial findings from the present study indicate an unfavorable risk-benefit profile of the combination of bosutinib and exemestane in pretreated postmenopausal women with HR+/HER2– BC and resulted in early termination of this study. However, the efficacy of single-agent bosutinib underscores the potential clinical benefits of Src/Abl inhibition in BC [6] and suggests that studies of other combination regimens with bosutinib may be warranted.

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Figures and Tables

Table. Treatment summary (safety population)

Parameter	Bosutinib 400 mg + exemestane 25 mg (<i>n</i> = 14)	Bosutinib 300 mg + exemestane 25 mg (<i>n</i> = 28)	Total (<i>n</i> = 42)
Duration of treatment, week, median (range)	9.7 (1.1–56.1)	9.2 (1.3–32.1)	9.2 (1.1–56.1)
Dose delay due to AE, <i>n</i> (%)			
Bosutinib	6 (43)	10 (36)	16 (38)
Exemestane	5 (36)	5 (18)	10 (24)
Dose reduction due to AE, <i>n</i> (%)			
Bosutinib	3 (21)	1 (4)	4 (10)
Exemestane	0	0	0
Dose-limiting toxicities, <i>n</i> (%) [80% CI] ^a	5 (38 [20–60])	3 (12 [4–24])	8 (21 [12–31])
ALT increased	3 (23)	1 (4)	4 (10)
Diarrhea and AST/ALT increased	1 (8)	0	1 (3)
Diarrhea	0	1 (4)	1 (3)
Diarrhea/vomiting/nausea	0	1 (4)	1 (3)
Vomiting	1 (8)	0	1 (3)
Discontinued treatment, <i>n</i> (%)	14 (100)	28 (100)	42 (100)
Reason for treatment discontinuation, <i>n</i> (%)			
AE	3 (21)	2 (7)	5 (12)
Death	1 (7)	0	1 (2)
Disease progression	9 (64)	13 (46)	22 (52)
Terminated by sponsor	1 (7)	13 (46)	14 (33)
Withdrawal by patient	0	0	0
Protocol violation	0	0	0

^a*n* = 13 evaluable patients received bosutinib 400 mg; *n* = 26 evaluable patients received bosutinib 300 mg.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval.

Table 1. Patient demographic and baseline clinical characteristics (safety population)

Characteristic, <i>n</i> (%)	Bosutinib 400 mg + exemestane 25 mg (<i>n</i> = 14)	Bosutinib 300 mg + exemestane 25 mg (<i>n</i> = 28)	Total (<i>n</i> = 42)
Age, yr, mean (SD)	64.1 (8.2)	58.2 (10.0)	60.2 (9.8)
Age, yr, median (range)	62.0 (49–76)	58.0 (40–79)	60.5 (40–79)
Age <65 yr, <i>n</i> (%)	8 (57)	20 (71)	28 (67)
Age ≥65 yr, <i>n</i> (%)	6 (43)	8 (29)	14 (33)
Race, <i>n</i> (%)			
White	10 (71)	21 (75)	31 (74)
Asian	2 (14)	6 (21)	8 (19)
Black	1 (7)	0	1 (2)
Other	1 (7)	1 (4)	2 (5)
Stage of disease at screening, <i>n</i> (%)			
IIIB	1 (7)	0	1 (2)
IIIC	0	0	0
IV	13 (93)	28 (100)	41 (98)

ECOG performance status, <i>n</i> (%)			
0	11 (79)	16 (57)	27 (64)
1	2 (14)	12 (43)	14 (33)
2	1 (7)	0	1 (2)
Visceral disease at baseline, <i>n</i> (%)	10 (71)	25 (89)	35 (83)
Number of prior cytotoxic chemotherapy (any setting), <i>n</i> (%)			
0	5 (36)	10 (36)	15 (36)
1	8 (57)	15 (54)	23 (55)
2	0	3 (11)	3 (7)
3	1 (7)	0	1 (2)
Number of prior cytotoxic chemotherapy (metastatic setting), <i>n</i> (%)			
0	10 (71)	21 (75)	31 (74)
1	4 (29)	7 (25)	11 (26)
Prior taxanes and anthracyclines, <i>n</i> (%)	3 (21)	6 (21)	9 (21)
Number of prior endocrine regimens, <i>n</i> (%)			
0	0	0	0
1	7 (50)	17 (61)	24 (57)
2	5 (36)	9 (32)	14 (33)
3	2 (14)	2 (7)	4 (10)
Prior surgical therapy, <i>n</i> (%)	14 (100)	27 (96)	41 (98)
Prior radiotherapy, <i>n</i> (%)	9 (64)	16 (57)	25 (60)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

Table 2. Treatment-emergent adverse events occurring in $\geq 10\%$ of patients (safety population)

Preferred term, <i>n</i> (%)	Bosutinib 400 mg + exemestane 25 mg (<i>n</i> = 14)		Bosutinib 300 mg + exemestane 25 mg (<i>n</i> = 28)		Total (<i>n</i> = 42)	
	All grades	Grades 3/4	All grades	Grades 3/4	All grades	Grades 3/4
Diarrhea	13 (93)	1 (7)	15 (54)	3 (11)	28 (67)	4 (10)
Nausea	11 (79)	1 (7)	15 (54)	2 (7)	26 (62)	3 (7)
Vomiting	8 (57)	1 (7)	12 (43)	1 (4)	20 (48)	2 (5)
Increased ALT	4 (29)	4 (29)	7 (25)	2 (7)	11 (26)	6 (14)
Constipation	1 (7)	0	9 (32)	0	10 (24)	0
Fatigue	4 (29)	0	6 (21)	0	10 (24)	0
Decreased appetite	1 (7)	0	8 (29)	0	9 (21)	0
Rash	4 (29)	0	4 (14)	0	8 (19)	0
Increased AST	3 (21)	1 (7)	4 (14)	0	7 (17)	1 (2)
Headache	3 (21)	0	4 (14)	0	7 (17)	0
Dyspepsia	1 (7)	0	5 (18)	0	6 (14)	0
Asthenia	3 (21)	1 (7)	3 (11)	0	6 (14)	1 (2)
Pyrexia	2 (14)	0	4 (14)	0	6 (14)	0
Cough	3 (21)	0	3 (11)	1 (4)	6 (14)	1 (2)
Upper abdominal pain	2 (14)	0	3 (11)	0	5 (12)	0
Dyspnea	2 (14)	1 (7)	3 (11)	2 (7)	5 (12)	3 (7)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 3. Serious adverse events

Individual SAE ^a	Bosutinib 400 mg + exemestane 25 mg (<i>n</i> = 14)		Bosutinib 300 mg + exemestane 25 mg (<i>n</i> = 28)	
	Grade	Attribution	Grade	Attribution
Diarrhea	4	Related	3	Related
Fluid overload	3	Related	N/A	N/A
Diabetes mellitus	N/A	N/A	3	Related
Dyspnea	3	Related	N/A	N/A
Pleural effusion	3	Unrelated	3	Unrelated
			2	Unrelated
Renal failure	N/A	N/A	3	Unrelated
Electrolyte imbalance	3	Unrelated	N/A	N/A
Pneumonia	N/A	N/A	3	Unrelated
General physical health deterioration	N/A	N/A	3	Unrelated
Cardiac arrest	4	Unrelated	N/A	N/A
Cardiac failure	5	Unrelated	N/A	N/A
Febrile neutropenia	3	Unrelated	N/A	N/A

^aSAEs were not mutually exclusive and could have occurred in the same patient; eight SAEs occurred in four patients receiving bosutinib 400 mg plus exemestane 25 mg and seven SAEs occurred in five patients receiving bosutinib 300 mg plus exemestane 25 mg.
Abbreviations: N/A, not available; SAE, serious adverse event.

Table 4. Investigator-assessed PFS (intent-to-treat population)

PFS	Bosutinib 400 mg + exemestane 25 mg (<i>n</i> = 14)	Bosutinib 300 mg + exemestane 25 mg (<i>n</i> = 28)	Total (<i>n</i> = 42)
Patients with postbaseline tumor assessment, <i>n</i> (%)	12 (86)	25 (89)	37 (88)
PFS, week, median (80% CI)	12.3 (8.1–23.7)	12.3 (11.0–15.6)	12.3 (11.0–15.6)
Patients with PD or who died, <i>n</i> (%)	10 (71)	14 (50)	24 (57)
Patients with PD, <i>n</i> (%)	9 (64)	14 (50)	23 (55)
Censored patients, <i>n</i> (%)	4 (29)	14 (50)	18 (43)

Abbreviations: CI, confidence interval; PD, progressive disease; PFS, progression-free survival.

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