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CLINICAL TRIAL

A randomized phase II study of lapatinib + pazopanib versus lapatinib in patients with HER2+ inflammatory breast cancer

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Abstract This multi-center Phase II study evaluated lapatinib, pazopanib, and the combination in patients with relapsed HER2+ inflammatory breast cancer. In Cohort 1, 76 patients were randomized 1:1 to receive lapatinib 1,500 mg + placebo or lapatinib 1,500 mg + pazopanib 800 mg (double-blind) once daily until disease progression, unacceptable toxicity, or death. Due to high-grade diarrhea observed with this dose combination in another study (VEG20007), Cohort 1 was closed. The protocol was amended such that an additional 88 patients (Cohort 2) were randomized in a 5:5:2 ratio to receive daily monotherapy lapatinib 1,500 mg, lapatinib 1,000 mg + pazopanib 400 mg, or monotherapy pazopanib 800 mg, respectively. The primary endpoint was overall response rate (ORR). Secondary endpoints included duration of response, progression-free survival (PFS), overall survival, and safety. In Cohort 1, ORR for the lapatinib ($n = 38$) and combination ($n = 38$) arms was 29 and 45 %, respectively; median PFS was 16.1 and 14.3 weeks, respectively. Grade $\geq$3 adverse events (AEs) were more frequent in the combination arm (71 %) than in the lapatinib arm (24 %). Dose reductions and interruptions due to AEs were also more frequent in the combination arm (45 and 53 %, respectively) than in the lapatinib monotherapy arm (0 and 11 %, respectively). In Cohort 2, ORR for patients treated with lapatinib ($n = 36$), lapatinib + pazopanib ($n = 38$), and pazopanib ($n = 13$) was 47, 58, and 31 %, respectively; median PFS was 16.0, 16.0, and 11.4 weeks, respectively. In the lapatinib, combination, and pazopanib therapy arms, grade $\geq$3 AEs were reported for 17, 50, and 46 % of patients, respectively, and the incidence of discontinuations

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This study is reported on behalf of VEG108838 Study Investigators. A complete list of the members of the VEG108838 Study Investigators appears in the "Appendix".

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due to AEs was 0, 24, and 23 %, respectively. The lapatinib–pazopanib combination was associated with a numerically higher ORR but no increase in PFS compared to lapatinib alone. The combination also had increased toxicity resulting in more dose reductions, modifications, and treatment delays. Activity with single-agent lapatinib was confirmed in this population.

Keywords Lapatinib · Pazopanib · Inflammatory breast cancer · HER2-positive breast cancer

Introduction

Inflammatory breast cancer (IBC) is a rare, aggressive form of breast cancer that is defined by a rapid onset of distinct features such as diffuse skin erythema, edema involving more than two-thirds of the breast resulting in a pitted appearance (peau d'orange), as well as tenderness, induration, and warmth of the involved breast [1, 2]. IBC tumors are primarily estrogen-receptor-negative, have a high mitotic index (MIB1 > 20), and are characterized by overexpression of e-cadherin, cytoplasmic mucin 1, and human epidermal growth factor receptor 2 (HER2) [3–5]. Standard treatment approaches integrate systemic chemotherapy, surgery, and radiotherapy [1]. In the first-line setting, trastuzumab-containing multi-chemotherapy regimens have shown efficacy in patients with IBC [6, 7]. Although the use of combined treatment modalities has led to improvement in survival in patients with IBC, the prognosis remains poor for patients who experience less than a pathological complete response to induction chemotherapy or who subsequently relapse [8, 9]. Limited data are available regarding second-line treatments for patients with advanced IBC.

Lapatinib is an oral tyrosine kinase inhibitor that targets both epidermal growth factor receptor (EGFR; ErbB1) and HER2 (ErbB2) receptors [10]. Administration of single-agent lapatinib (1,500 mg per day) in patients ($n = 126$) with HER2-positive (HER2+) IBC with disease progression after prior treatment resulted in an overall response rate (ORR) of 39 % [all partial responses by combined clinically evaluable skin disease criteria and Response Evaluation Criteria in Solid Tumors (RECIST)] and median duration of response of 20.9 weeks [11]. Lapatinib's activity in IBC has also been demonstrated in the neoadjuvant setting in which lapatinib monotherapy for 14 days followed by lapatinib + paclitaxel for 12 weeks was associated with a combined clinical response rate of 78.6 % (33 of 42), based on RECIST and clinically evaluable skin disease criteria in treatment-naïve IBC patients [12].

Angiogenesis is thought to play a role in IBC tumorigenesis [13]. Preclinical and early clinical evidence suggests that the combination of anti-angiogenic and anti-HER2 therapies may have a role in the treatment of HER2+ breast cancer [14, 15]; and vascular endothelial growth factor (VEGF)-targeted therapy with bevacizumab in combination with chemotherapy demonstrated anti-tumor activity in previously untreated IBC patients [16]. Pazopanib is an oral angiogenesis inhibitor targeting VEGF receptors-1/-2/-3, platelet-derived growth factor receptors-α/-β, and mast/stem-cell growth factor receptor [17, 18]. Results of a small, single-arm Phase II study provided early evidence that pazopanib alone may have cytostatic activity in patients with advanced, non-inflammatory breast cancer [19]. In a Phase II first-line study (VEG20007) in patients with locally advanced or metastatic HER2+ breast cancer [20, 21], there was a numerical increase in the objective response rate with the combination of pazopanib and lapatinib compared to lapatinib alone; however, the rates of disease progression at Week 12, the primary study endpoint, were statistically similar [Johnston, manuscript submitted].

These considerations provided the rationale for a randomized study evaluating the efficacy and safety of the combination of pazopanib and lapatinib in patients with relapsed HER2 overexpressing or amplified IBC.

Patients and methods

Study population

Women aged ≥18 years with histologically or cytologically confirmed relapsed or refractory HER2 overexpressing or amplified IBC were enrolled in two cohorts. Eligible patients had received prior chemotherapy including prior trastuzumab where available. Patients in Cohort 1 were required to have a previous history of IBC and documented recurrence in the skin and/or other disease sites by radiologic assessments. All patients in Cohort 2 were required to have cutaneous disease documented with photographs at screening. HER2+ status was defined as 3+ staining by immunohistochemistry (IHC), or 2+ staining by IHC in conjunction with HER2 gene amplification by fluorescence in situ hybridization (FISH) or chromogenic in situ hybridization (CISH), or ErbB2 gene amplification by FISH/CISH alone. Eligible patients were also required to have Eastern Cooperative Oncology Group performance status 0–2; adequate hematologic, hepatic, and renal function; and cardiac ejection fraction within the institutional range of normal.

Patients were excluded if they had received prior lapatinib therapy or other HER2/ErbB2-targeted therapy (except trastuzumab), or prior VEGF/VEGFR-targeted therapy. Patients were also excluded for poorly controlled hypertension, QTc interval >480 ms, prior history of cardiovascular abnormalities, any history of cerebrovascular

accident, current active hepatic or biliary disease, or clinically significant gastrointestinal abnormalities.

All patients provided signed informed consent. The study was conducted in accordance with the Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol, amendments, and consent forms were approved by health authorities and local Independent Ethics Committees or Institutional Review Boards. The study was registered at clinicaltrials.gov as NCT00558103.

Study design and treatment

This study enrolled patients into two sequential cohorts. In Cohort 1, patients were stratified by prior trastuzumab therapy versus no prior trastuzumab therapy and location of recurrence, i.e., cutaneous disease only versus radiographically assessed disease with or without cutaneous disease. Patients were randomized 1:1 to receive 1,500 mg lapatinib + placebo or 1,500 mg lapatinib + 800 mg pazopanib daily. Based on a high incidence of grade $\geq$3 diarrhea observed with this dose combination of lapatinib and pazopanib in another study (VEG20007), enrollment was closed after 76 of 320 planned patients had been randomized. Following amendment of the protocol, eligible patients in Cohort 2 were required to have cutaneous disease at study entry, were stratified by prior trastuzumab therapy versus no prior trastuzumab therapy, and were randomized in a 5:5:2 ratio to receive daily monotherapy lapatinib 1,500 mg, lapatinib 1,000 mg + pazopanib 400 mg, or monotherapy pazopanib 800 mg, respectively.

The lapatinib monotherapy and lapatinib + pazopanib treatment arms were double-blinded in both cohorts. The pazopanib monotherapy arm was not blinded for logistic reasons. Patients received continuous daily dosing until disease progression, unacceptable toxicity, or death. Dose reductions and dose delays up to 2 weeks were permitted to manage drug-related toxicities. Patients randomized to the pazopanib monotherapy arm in Cohort 2 who experienced unequivocal evidence of disease progression were given the option to receive monotherapy lapatinib in an open-label extension phase.

Safety assessments including physical examination and laboratory tests were performed at 4-week intervals while patients received study treatment and at the time of permanent discontinuation of treatment. Additional liver function tests (LFTs) were obtained at Weeks 2 and 6. Additional blood pressure measurements were obtained at Day 8 and Week 2. Echocardiography or multiple-gated acquisition scans were obtained at screening and every 8 weeks during study treatment. Radiographic efficacy assessments were performed at baseline, Weeks 4 and 8, and every 8 weeks thereafter until disease progression. Assessments of cutaneous disease were performed at baseline and every 4 weeks thereafter until disease progression. Patients who discontinued study treatment without disease progression continued to be evaluated for efficacy until progression or until receiving the first subsequent anti-cancer therapy. After documentation of progression, patients were followed for survival at approximately 3-month intervals until death or until completion of the study.

Efficacy evaluations

Radiographically measurable disease was assessed by investigators according to RECIST 1.0. In Cohort 1, investigator assessments of cutaneous disease were recorded using a skin assessment tool that included both a quantitative scale for measurable skin disease and assessment of non-measurable cutaneous disease by evaluation of chest wall and skin changes including diffuse erythema, edema, peau d'orange, induration, ulceration, and other clinical symptoms such as tenderness and warmth [11]. In Cohort 2, investigators assessed cutaneous disease using the skin assessment tool for IBC shown in Table 1 [22]. The primary efficacy endpoint was ORR defined as complete response + partial response based on combined RECIST and cutaneous disease assessments, neither of which was required to be confirmed at a timepoint later than the initial response. Secondary efficacy endpoints included duration of response, progression-free survival (PFS), and overall survival (OS).

Safety evaluations

The incidence, severity, and causality of adverse events (AEs), serious AEs (SAEs), and other safety parameters were assessed throughout the study. The severity of AEs was graded by investigators according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Statistical methods

The population analyzed for all efficacy and safety endpoints was the modified intent-to-treat population, which comprised all randomized patients who received at least one dose of study treatment. For Cohort 1, response rates were summarized descriptively; no hypothesis testing was conducted due to premature termination of enrollment. For Cohort 2, which was the population assessed for the primary analysis, the planned sample size was selected to provide 90 % power with a one-sided alpha of 0.05 to detect an increase of at least 20 % in ORR for the lapatinib monotherapy and lapatinib + pazopanib arms compared separately to a null hypothesis response rate of 10 %; H_0: ORR = 0.10, H_1: ORR = 0.30. It is important to note that

Table 1 Inflammatory breast cancer skin assessment tool (IBSAT)

Disease manifestation	Grade	Area of skin involved (%)[a]			Area of measurable plaques and nodules[b]	Cutaneous disease response
		Chest wall	Breast(s)			
			Left	Right		
Plaque(s)	☐ 0 Absent	____%	____%	____%	____mm^2	___
	☐ 1 Present				(Total area of lesions 1001–1005)	(CR/PR/SD)
Nodule(s)	☐ 0 Absent	(0–100 %)	(0–100 %)	(0–100 %)	Lesion 1001 location:_____	
	☐ 1 Present				Perpendicular diameters (mm × mm)___ × ___area (mm^2)____	
Ery thema	☐ 0 Absent				Lesion 1002 location:_____	
	☐ 1 Mild (barely perceptible)				Perpendicular diameters (mm × mm)___ × ___area (mm^2)____	
	☐ 2 Moderate (clearly present)				Lesion 1003 location:_____	
	☐ 3 Severe (intense)				Perpendicular diameters (mm × mm)___ × ___area (mm^2)____	
Induration/	☐ 0 Absent				Lesion 1004 location:_____	
Peau d'orange	☐ 1 Mild (perceptible)				Perpendicular diameters (mm × mm)___ × __area (mm^2)____	
	☐ 2 Moderate				Lesion 1005 location:_____	
	☐ 3 Severe (woody or rocklike)				Perpendicular diameters (mm × mm)___ × ___area (mm^2)____	
Ulceration	☐ 0 Absent					
	☐ 1 Mild (superficial, dry)					
	☐ 2 Moderate (superficial, moist)					
	☐ 3 Severe (deep, weeping/bleeding)					

Complete either chest wall or breast(s) column(s) but not both

If cutaneous disease is not confined to breast(s) or patient underwent mastectomy, complete "area of skin involved (%) chest wall" column

If cutaneous disease is confined to breast(s) and no prior mastectomy, complete "area of skin involved (%) breast(s)" column

CR complete response, *PR* partial response, *SD* stable disease

[a] The "area of skin involved" should include all categories of "disease manifestation" including the area of any measurable plaque or nodule on the anterior chest wall or breast(s). Skin disease outside of the anterior chest wall should be assessed for disease response and progression but not included in the column "area of skin involved."

[b] If present, the sum of bidimensional areas of measurable plaques and nodules (up to 5 plaques and nodules) is to be recorded. These lesions may be located on any cutaneous side of the body. The bidimensional area of a measurable plaque is the product of its largest perpendicular diameters

the study was not designed for comparisons between treatment arms and hence, reported comparisons are solely descriptive. Response rates were summarized as a proportion including approximate 90 % confidence intervals (CI) and compared to the null hypothesis response rate using a binomial exact test. Duration of response, PFS, and OS were estimated using Kaplan–Meier analyses.

Results

Patient characteristics and treatment delivery

Between December 2007 and November 2010, 164 patients were enrolled at 53 centers in 21 countries. Patient disposition is shown in Fig. 1. One hundred sixty-three (163) of the randomized patients received at least one dose of study treatment and were included in the analysis of all efficacy and safety endpoints. In both cohorts, median duration of treatment was longer in the lapatinib monotherapy arm (approximately 16 weeks) than in the lapatinib + pazopanib arm (12–13 weeks; Table 2). Combination therapy resulted in a higher incidence of dose reductions and dose interruptions compared with lapatinib monotherapy; however, during the period of treatment, mean daily doses approached the planned dose across treatment arms. The primary reason for discontinuation of treatment was progression of disease: 83 % of patients in Cohort 1 and 77 % of patients in Cohort 2.

Baseline characteristics were generally balanced across treatment arms (Table 3). Across both cohorts, at least

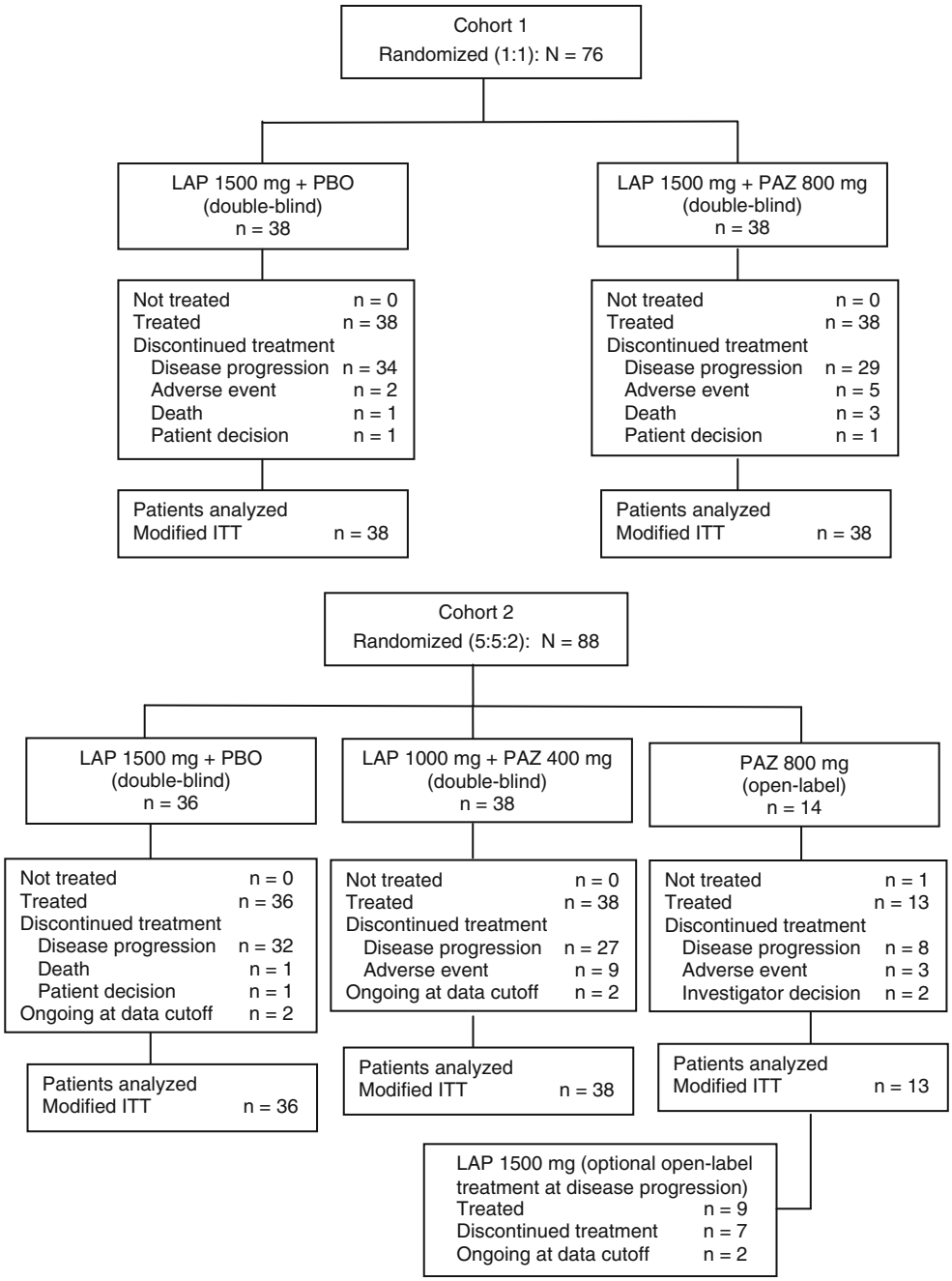

Fig. 1 CONSORT diagrams for Cohorts 1 and 2. *LAP* lapatinib, *PBO* placebo, *PAZ* pazopanib, *ITT* intent-to-treat

74 % of patients in each treatment arm had radiographically measurable disease. In Cohort 1, 84 % of patients in the lapatinib arm and 92 % of patients in the lapatinib + pazopanib arm had evidence of cutaneous disease (Table 3); two (5 %) patients in the lapatinib arm and five (13 %) patients in the lapatinib + pazopanib arm had cutaneous disease only. Prior chemotherapy regimens included anthracyclines for 83 % of patients in Cohort 1 and 85 % of patients in Cohort 2. In both cohorts, at least 50 % of patients in each treatment arm had received prior trastuzumab therapy.

Efficacy

Investigator-assessed best ORR was numerically higher for the lapatinib + pazopanib arm than for the lapatinib monotherapy arm in Cohort 1 [45 % (90 % CI: 30.9, 59.3) vs. 29 % (90 % CI: 17.2, 43.3)] and in Cohort 2 [58 % (90 % CI: 43.3,

Table 2 Exposure to study treatment

	Cohort 1		Cohort 2		
	Lapatinib 1,500 mg + placebo ($N = 38$)	Lapatinib 1,500 mg + pazopanib 800 mg ($N = 38$)	Lapatinib 1,500 mg + placebo ($N = 36$)	Lapatinib 1,000 mg + Pazopanib 400 mg ($N = 38$)	Pazopanib 800 mg ($N = 13$)
Median time on study treatment, weeks					
Lapatinib	16.4	11.9	16.1	12.9	–
Pazopanib	–	12.1	–	12.7	7.4
Dose modifications due to AEs, *n* (%)					
Dose reduction	0	17 (45)	2 (6)	13 (34)	2 (15)
Dose interruption/delay	4 (11)	20 (53)	5 (14)	17 (45)	3 (23)
Mean (SD) daily dose, mg					
Lapatinib	1,500.0 (0)	1,453.8 (103.3)	1,496.5 (17.8)	967.8 (69.5)	–
Pazopanib	–	712.5 (134.6)	–	359.8 (68.3)	780.0 (50.4)

AE adverse event, *SD* standard deviation

Table 3 Patient demographics and baseline disease and treatment characteristics

	Cohort 1		Cohort 2		
	Lapatinib 1,500 mg + placebo	Lapatinib 1,500 mg + pazopanib 800 mg	Lapatinib 1,500 mg + placebo	Lapatinib 1,000 mg + pazopanib 400 mg	Pazopanib 800 mg
Modified intent-to-treat population, *n*	38	38	36	38	13
Mean age, years (SD)	52 (9.0)	52 (12.8)	53 (10.4)	54 (12.7)	55 (12.3)
White, *n* (%)	24 (63)	27 (71)	21 (58)	19 (50)	6 (46)
Asian, *n* (%)	11 (29)	7 (18)	13 (36)	16 (42)	6 (46)
Radiologically measurable disease, *n* (%)[a]	33 (87)	28 (74)	31 (86)	31 (82)	10 (77)
Cutaneous disease, *n* (%)[b]	32 (84)	35 (92)	36 (100)	38 (100)	13 (100)
Stage, *n* (%)					
III	6 (16)	6 (16)	7 (19)	13 (34)	2 (15)
IV	32 (84)	32 (84)	27 (75)[c]	24 (63)[d]	11 (85)
Prior trastuzumab therapy, *n* (%)	21 (55)	22 (58)	18 (50)	19 (50)	7 (54)
Prior chemotherapy, *n* (%)	38 (100)	37 (97)	36 (100)	37 (97)	13 (100)
Prior biologic therapy, *n* (%)	21 (55)	22 (58)	12 (33)	16 (42)	3 (23)
Prior radiotherapy, *n* (%)	17 (45)	18 (47)	23 (64)	23 (61)	11 (85)
Prior hormonal therapy, *n* (%)	6 (16)	5 (13)	5 (14)	5 (13)	2 (15)

SD standard deviation

[a] Based on RECIST criteria

[b] Based on protocol-defined criteria (Cohort 1) or IBSAT criteria (Cohort 2)

[c] Stage not reported for two patients

[d] Stage not reported for one patient

71.5) vs. 47 % (90 % CI: 32.8, 62.1); Table 4]. The response rate for both the lapatinib monotherapy and the lapatinib + pazopanib arms in Cohort 2 exceeded the null hypothesis response rate of 10 % ($P < 0.001$; binomial exact test). There was no consistent effect of prior trastuzumab therapy on response rate in the lapatinib-containing treatment arms in either cohort (Table 4). The duration of response was similar for the lapatinib and combination treatment arms in Cohort 1, with medians of 16.9 weeks (90 % CI: 12.4, 21.0) and 13.0 weeks (90 % CI: 9.1, 28.1), respectively; and in Cohort 2, with medians of 13.6 weeks (90 % CI: 10.0, 19.9) and 12.7 weeks (90 % CI: 8.0, 16.1), respectively. In the pazopanib monotherapy arm, median duration of response was 31.2 weeks; however, these results were based on only

Table 4 Best overall response per patient from combined RECIST-based response and cutaneous disease response

	Cohort 1		Cohort 2		
	Lapatinib 1,500 mg + placebo ($N = 38$)	Lapatinib 1,500 mg + pazopanib 800 mg ($N = 38$)	Lapatinib 1,500 mg + placebo ($N = 36$)	Lapatinib 1,000 mg + pazopanib 400 mg ($N = 38$)	Pazopanib 800 mg ($N = 13$)
Best response, *n* (%)					
Complete response	1 (3)	4 (11)	1 (3)	0	0
Partial response	10 (26)	13 (34)	16 (44)	22 (58)	4 (31)
Stable disease[a]	14 (37)	6 (16)	12 (33)	10 (26)	1 (8)
Progressive disease	11 (29)	11 (29)	6 (17)	5 (13)	5 (38)
Unknown	2 (5)	4 (11)	1 (3)	1 (3)	3 (23)
Response rate (complete response + partial response), *n* (%)	11 (29)	17 (45)	17 (47)	22 (58)	4 (31)
(90 % CI)	(17.2, 43.3)	(30.9, 59.3)	(32.8, 62.1)	(43.3, 71.5)	(11.3, 57.3)
Prior trastuzumab therapy	4 (19)	9 (41)	8 (44)	12 (63)	1 (14)
No prior trastuzumab therapy	7 (41)	8 (50)	9 (50)	10 (53)	3 (50)
P value (one-sided)[b]	NA	NA	<0.001	<0.001	NA

CI confidence interval, *NA* not applicable

[a] Observed for a minimum of 8 weeks

[b] Compared to null hypothesis response rate of 10 % using binomial exact test

four patients with an overall response and a corresponding wide confidence interval (90 % CI: 3.4, 33.1).

There were no differences in PFS among treatment arms in Cohort 1 (Fig. 2) or Cohort 2 (Fig. 3). In Cohort 1, median PFS was 16.1 weeks (90 % CI: 12.0, 21.1) in the lapatinib arm and 14.3 weeks (90 % CI: 8.6, 20.1) in the lapatinib + pazopanib arm. In Cohort 2, median PFS was 16.0 weeks (90 % CI: 12.4, 16.3) in the lapatinib arm, 16.0 weeks (90 % CI: 12.4, 17.9) in the lapatinib + pazopanib arm, and 11.4 weeks (90 % CI: 6.6, 33.6) in the pazopanib arm. Overall survival was similar for the lapatinib-alone and combination arms in Cohort 1 with median OS of 14.7 months (90 % CI: 12.1, 16.5) and 16.2 months (90 % CI: 12.7, 21.1), respectively (Table 5). In Cohort 2, median OS was 15.9 months (90 % CI: 13.4, not estimable) in the lapatinib arm, while median OS could not be estimated for the combination therapy arm or for the pazopanib arm because of an insufficient number of events (Table 5).

Safety

In Cohort 1, diarrhea, nausea, vomiting, fatigue, aminotransferase (ALT/AST) increase, and hypertension were the most frequently reported AEs, and were more common with combination therapy than with lapatinib monotherapy (Table 6). Two patients (5 %) in the lapatinib arm and five (13 %) patients in the lapatinib + pazopanib arm discontinued treatment due to AEs (Fig. 1), including four patients withdrawn due to grade 3 increases in ALT and AST (1, lapatinib arm; 3, combination therapy). These four patients had ALT values that met the protocol stopping criteria of >8 × ULN; ALT values returned to baseline after discontinuation of study treatment. The overall incidence of grade ≥3 AEs was higher in the combination therapy arm than in the lapatinib arm (71 and 24 %, respectively; Table 6), as was the incidence of SAEs (37 and 16 %, respectively). Fatal SAEs were reported for two patients in the lapatinib arm (one, cholestatic liver injury; one, sudden death); and four patients in the lapatinib + pazopanib arm (one, pulmonary embolism; one, sepsis; one, respiratory failure/acute cardiovascular insufficiency; one, sudden death). Cardiac dysfunction events were reported in three patients in the combination therapy arm: one patient with diffuse pulmonary metastases and pneumonia died due to respiratory failure/acute cardiovascular insufficiency (noted above) and two patients had grade 1 reductions in left ventricular ejection fraction (LVEF) during treatment.

In Cohort 2, the most frequently reported AE in all 3 treatment arms was diarrhea (Table 7). In the pazopanib monotherapy arm, one patient each was withdrawn due to AEs of diarrhea, arthralgia, and pneumonia. Nine (24 %) patients in the lapatinib + pazopanib arm were withdrawn due to AEs, including six patients withdrawn due to grade 3 increases in ALT or ALT and AST values. Four of these six patients had ALT elevations that met the protocol stopping criteria of >8 × ULN; values in these patients decreased to normal (three patients) or to <2 × ULN (one patient) after

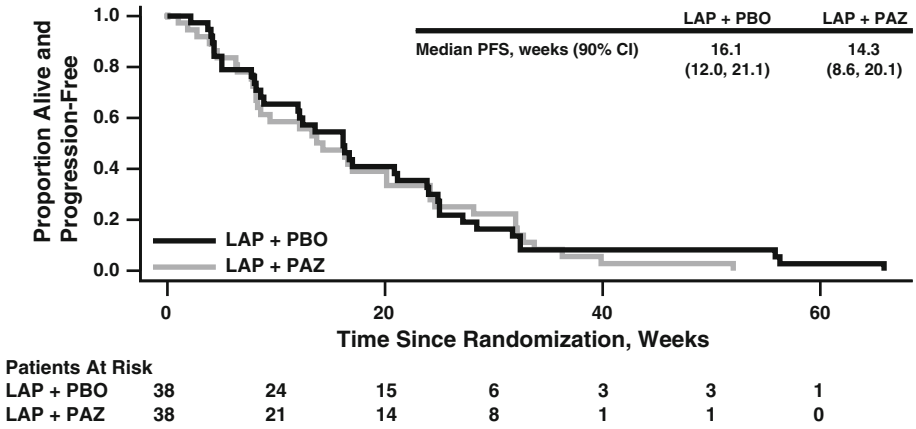

Fig. 2 Kaplan–Meier curves for progression-free survival in Cohort 1

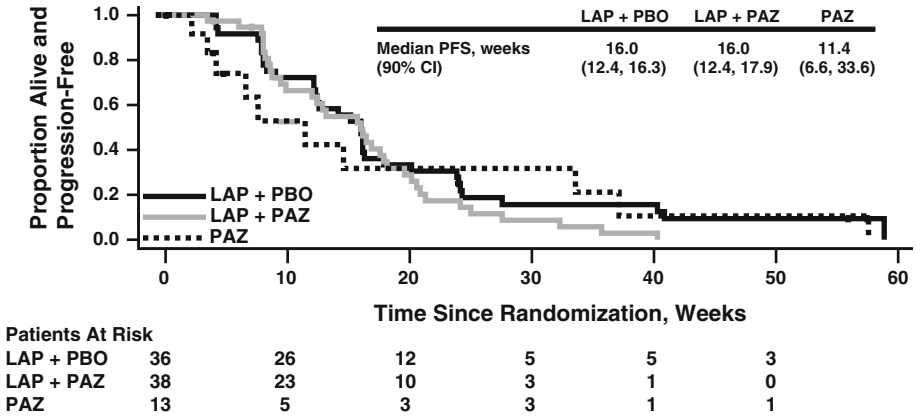

Fig. 3 Kaplan–Meier curves for progression-free survival in Cohort 2

Table 5 Overall survival

	Cohort 1		Cohort 2		
	Lapatinib 1,500 mg + placebo ($N = 38$)	Lapatinib 1,500 mg + pazopanib 800 mg ($N = 38$)	Lapatinib 1,500 mg + placebo ($N = 36$)	Lapatinib 1,000 mg + pazopanib 400 mg ($N = 38$)	Pazopanib 800 mg ($N = 13$)
Deaths, *n* (%)	28 (74)	29 (76)	12 (33)	11 (29)	4 (31)
Median overall survival, months	14.7	16.2	15.9	NE	NE
90 % CI	12.1, 16.5	12.7, 21.1	13.4, NE	12.4, NE	9.8, NE

CI confidence interval, *NE* not estimable due to insufficient number of events

discontinuation of study treatment. The overall incidence of grade ≥3 AEs was 17, 50, and 46 %, respectively, for the lapatinib, lapatinib + pazopanib, and pazopanib arms; the incidence of SAEs was 11, 24, and 31 %, respectively. Fatal SAEs were reported for one patient in the lapatinib monotherapy arm (severe dyspnea and orthopnea); one patient in the combination therapy arm (subarachnoid hemorrhage); and one patient in the pazopanib monotherapy arm (pulmonary edema, pneumonia, cardiopulmonary failure). Cardiac dysfunction events were reported for one patient in the lapatinib arm (grade 1 LVEF decrease); three patients in the combination therapy arm (one patient with grade 2 LVEF decrease and two patients with grade 1 LVEF decrease); and two patients in the pazopanib arm [fatal SAE of cardiopulmonary failure (noted above) and grade 1 LVEF decrease].

Discussion

IBC is a rare disease accounting for 1–2 % of all breast cancers in the US [23, 24], with higher incidence (5–7 %)

Table 6 Treatment-emergent adverse events reported in ≥15 % of patients in the combination arm in Cohort 1; adverse events reported as NCI CTCAE grades

	Lapatinib 1,500 mg + placebo ($N = 38$)		Lapatinib 1,500 mg + pazopanib 800 mg ($N = 38$)	
	n (%)		*n* (%)	
	All grades	≥Grade 3	All grades	≥Grade 3
Any adverse event	33 (87)	9 (24)	38 (100)	27 (71)
Diarrhea	15 (39)	0	33 (87)	7 (18)
Nausea	5 (13)	0	17 (45)	0
Vomiting	6 (16)	0	15 (39)	3 (8)
Fatigue	4 (11)	0	14 (37)	1 (3)
ALT increased	4 (11)	1 (3)	13 (34)	3 (8)
AST increased	5 (13)	1 (3)	13 (34)	2 (5)
Hypertension	1 (3)	0	12 (32)	1 (3)
Decreased appetite	4 (11)	0	9 (24)	1 (3)
Rash	5 (13)	0	9 (24)	1 (3)
Asthenia	4 (11)	0	8 (21)	0
Headache	4 (11)	0	8 (21)	1 (3)
Hyperbilirubinemia	2 (5)	0	7 (18)	0
Mucosal inflammation	0	0	6 (16)	0
Myalgia	1 (3)	0	6 (16)	0
Neutropenia	1 (3)	1 (3)	6 (16)	5 (13)

ALT alanine aminotransferase, *AST* aspartate aminotransferase

Table 7 Treatment-emergent adverse events reported in ≥15 % of patients in the combination arm in Cohort 2; adverse events reported as NCI CTCAE grades

	Lapatinib 1,500 mg + placebo ($N = 36$)		Lapatinib 1,000 mg + pazopanib 400 mg ($N = 38$)		Pazopanib 800 mg ($N = 13$)	
	n (%)		*n* (%)		*n* (%)	
	All grades	≥Grade 3	All grades	≥Grade 3	All grades	≥Grade 3
Any adverse event	35 (97)	6 (17)	36 (95)	19 (50)	13 (100)	6 (46)
Diarrhea	20 (56)	1 (3)	22 (58)	3 (8)	6 (46)	1 (8)
Rash	11 (31)	0	12 (32)	1 (3)	0	0
ALT increased	8 (22)	0	11 (29)	8 (21)	2 (15)	0
AST increased	8 (22)	0	10 (26)	7 (18)	3 (23)	0
Fatigue	6 (17)	1 (3)	9 (24)	3 (8)	4 (31)	1 (8)
Hypertension	1 (3)	1 (3)	9 (24)	0	3 (23)	0
Abdominal pain	2 (6)	0	8 (21)	0	3 (23)	1 (8)
Leukopenia	2 (6)	0	8 (21)	1 (3)	1 (8)	0
Nausea	6 (17)	0	8 (21)	0	2 (15)	0
Serum bilirubin increased	5 (14)	0	7 (18)	0	1 (8)	0
Decreased appetite	3 (8)	0	7 (18)	1 (3)	2 (15)	0
Neutropenia	0	0	7 (18)	1 (3)	4 (31)	0
Dizziness	1 (3)	0	6 (16)	0	1 (8)	0
Hair color changes	1 (3)	0	6 (16)	0	1 (8)	0

ALT alanine aminotransferase, *AST* aspartate aminotransferase

reported in North Africa [25]. Due to this low incidence, few prospective studies have been conducted in this patient population. Multi-modal approaches have become standard for the primary treatment of IBC; however, there is currently no standard of care in relapsed or refractory disease. Current literature suggests that targeted therapies based on known biological characteristics offer the most promise to improve the outcome of patients affected by IBC [2]. The current study evaluating the combination of two targeted agents represents the first prospective randomized trial to be conducted in metastatic IBC.

The current study was designed to evaluate the combination of lapatinib and pazopanib at doses that previously proved effective in single-agent studies. Following the initiation of the trial, results of an ongoing study in HER2+ locally advanced or metastatic breast cancer (VEG20007) indicated that this dose combination was associated with 40 % incidence of grade 3/4 diarrhea as compared to 9 % observed with a lower dose combination of 1,000 mg lapatinib + 400 mg pazopanib [Johnston, manuscript submitted]. Therefore, the current study design was modified to specify the lower dose combination. Additionally, a third treatment arm of single-agent pazopanib was added to better isolate the additive anti-tumor activity of each targeted agent. The Inflammatory Breast Cancer Skin Assessment Tool (IBSAT) was used to assess skin disease in Cohort 2. As IBC is designated as non-measurable according to RECIST and there are no standardized skin assessment tools, the IBSAT was developed as a tool for the objective assessment of skin disease in IBC. Prior to use in this study, the IBSAT was retrospectively applied to a previous study in IBC (EGF103009) by three investigators who independently assessed patient photographs over time. There was a high degree of concordance among all three investigators, and between each of the investigators and the independent reviewer who initially assessed skin disease in EGF103009 [22].

The response rates in the current study (29 % in Cohort 1 and 47 % in Cohort 2) support the reported activity of single-agent lapatinib in a previous study in which 49 of 126 (39 %) patients with HER2+ relapsed or refractory IBC had a partial response [11], although comparisons between studies are confounded by differences in patient populations and study methodologies. The favorable response to lapatinib in IBC has been postulated to result from the presence of phosphorylated (p) HER2 and pHER3 coexpression in tumors [26]. As previously observed [11, 26], the response to lapatinib did not appear to be markedly affected by prior trastuzumab therapy.

Compelling rationale had existed to evaluate the combination of an anti-angiogenic agent with an inhibitor of HER2 signaling in patients with HER2+ IBC. Upregulation of signalling pathways associated with angiogenesis and lymphangiogenesis is thought to contribute to IBC's aggressive phenotype [13, 27, 28], and preclinical and preliminary clinical data suggested that there may be an enhanced effect when these targeted therapies are combined. Administration of the anti-VEGF monoclonal antibody bevacizumab for one cycle in patients with previously untreated IBC ($n = 20$) or locally advanced breast cancer ($n = 1$) with the addition of cytotoxic chemotherapy in subsequent cycles had yielded an objective response rate of 67 % [16]. The combination of bevacizumab and trastuzumab demonstrated activity in a Phase II trial in metastatic breast cancer, with partial clinical response documented in 13 of 28 (46 %) evaluable patients [15]. In the current study, however, the combination of pazopanib with lapatinib did not produce a clinically significant improvement in ORR compared to lapatinib alone. Likewise, there was no difference in PFS for the combination arm versus the lapatinib monotherapy arm in either cohort. Recently reported results in non-inflammatory breast cancer also indicate equivocal results for regimens containing a combination of VEGF and EGFR/HER2 inhibitors. In a randomized, double-blind trial ($n = 96$), the addition of bevacizumab to chemotherapy (paclitaxel ± carboplatin) plus trastuzumab as first-line treatment of HER2+ metastatic breast cancer did not result in an improvement in best overall response or PFS [29]. Similarly, in a randomized Phase III trial (AVEREL) evaluating bevacizumab in combination with trastuzumab + docetaxel ($n = 216$) compared to trastuzumab + docetaxel ($n = 208$) as first-line therapy for HER2+ locally recurrent/metastatic breast cancer, there was no statistically significant difference between the treatment arms for the predefined primary endpoint of PFS by the investigator assessment, although ad-hoc results by independent assessment were significant [30]. Thus, it is unclear if the combination of HER2 and VEGF inhibition has improved efficacy in the treatment of HER2+ breast cancer.

The types of AEs reported in the current study generally reflect the safety profiles of lapatinib and pazopanib established in other studies. The higher dose combination of the two agents administered in Cohort 1 was associated with a higher incidence of gastrointestinal toxicity, as well as LFT abnormalities, hypertension, and rash compared with lapatinib monotherapy. With the lower dose combination administered in Cohort 2, the incidence of gastrointestinal events was substantially lower and showed feasibility of the treatment, but still with significantly higher toxicity and related dose reductions, interruptions, and treatment discontinuation for the combination. The impact of these deviations from the planned treatment schedule upon efficacy results is uncertain.

Hepatotoxicity has been associated with both single-agent lapatinib and pazopanib, and this was the most

common toxicity leading to permanent discontinuation of study drug in the combination arm in both cohorts. Furthermore, elevations in liver enzymes were more frequent in the combination arms than in the single-agent arms even with the lower dose combination in Cohort 2.

Both lapatinib and pazopanib have been associated with cardiac dysfunction, particularly in patients previously exposed to prior anthracycline chemotherapy. In the present study, 137 (84 %) patients had received prior anthracycline therapy. Inhibition of HER2 signaling with agents such as lapatinib and trastuzumab and, in the case of pazopanib, an increase in blood pressure and cardiac afterload are mechanisms thought to be responsible for the precipitation of cardiac dysfunction. Nine patients experienced cardiac dysfunction, 6 of these cases in the combination arm, although the majority of these cases were grade 1. There were 2 fatal AEs associated with cardiac dysfunction: respiratory failure/acute cardiovascular insufficiency in the combination arm of Cohort 1, and cardiopulmonary failure in the pazopanib arm of Cohort 2. The nature of fatal AEs was varied in the treatment arms of both cohorts and, in some cases, was confounded by the underlying disease and pneumonia.

Conclusion

Despite preclinical and early clinical evidence of enhanced activity when an anti-angiogenic agent was added to an anti-HER2 agent, the combination of lapatinib and pazopanib in the present study was associated with a numerically higher response rate but no increase in PFS compared to lapatinib alone. The combination also had increased toxicity resulting in more dose reductions, modifications, and treatment delays. Results of the current study are consistent with other studies showing that inhibitors of VEGF signaling added to inhibitors of HER2 fail to provide a clinically meaningful improvement in efficacy in patients with HER2+ breast cancer, particularly when considering the added toxicity of combination therapy. Future studies should consider inhibition of other critical pathways in IBC to improve efficacy of lapatinib and other inhibitors of HER2 in this aggressive disease.

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Conflict of interest Authors Rubin, Ranganathan, and Redhu are employees and stockholders of GlaxoSmithKline. Authors Johnston and Blackwell report consultant/advisory roles with GlaxoSmithKline. Author Cristofanilli reports consultant/advisory roles with Dompé Farmaceutici SpA and Alere. All other authors report no potential conflicts of interest.

Ethical standards This study was in compliance with the laws of the countries in which it was performed.

Appendix

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