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Academia–Pharma Intersect: Breast Cancer

Phase II Study of Bevacizumab in Combination with Trastuzumab and Capecitabine as First-Line Treatment for HER-2-positive Locally Recurrent or Metastatic Breast Cancer

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ABSTRACT

We report the first results from a phase II, open-label study designed to evaluate the efficacy and safety of bevacizumab in combination with trastuzumab and capecitabine as first-line therapy for human epidermal growth factor receptor (HER)-2-positive locally recurrent (LR) or metastatic breast cancer (MBC). Patients were aged ≥18 years with confirmed breast adenocarcinoma, measurable LR/MBC and documented HER-2-positive disease. Patients received bevacizumab (15 mg/kg on day 1) plus trastuzumab (8 mg/kg on day 1 of cycle 1, 6 mg/kg on day 1 of each subsequent cycle) plus capecitabine (1,000 mg/m^2 twice daily, days 1–14) every 3 weeks until disease progression, unacceptable toxicity, or consent withdrawal. Eighty-eight patients were enrolled; 40 (46%) are still on study treatment. The median follow-up was 8.8 months (range, 0.9–17.1 months). The overall response rate, the primary endpoint, was 73% (95% confidence interval [CI], 62%–82%), comprising 7% complete and 66% partial responses. The median progression-free survival interval was 14.4 months (95% CI, 10.4 months to not reached [NR]), with 35 events. The median time to progression was 14.5 months (95% CI, 10.5 months to NR), with 33 events. Treatment was well tolerated; main side effects were grade 3 hand–foot syndrome (22%), grade ≥3 diarrhea (9%), and grade ≥3 hypertension (7%). Overall, 44% of patients experienced grade ≥3 treatment-related adverse events and 13 patients discontinued capecitabine because of toxicity, but continued with bevacizumab and trastuzumab. Heart failure was seen in two patients. The combination of bevacizumab, trastuzumab, and capecitabine was clinically active as first-line therapy for patients with HER-2-positive MBC, with an acceptable safety profile and no unexpected toxicities. ***The Oncologist*** 2012;17:469–475

INTRODUCTION

Patients with human epidermal growth factor receptor (HER)-2–overexpressing metastatic breast cancer (MBC) present with an aggressive course of disease that requires effective first-line treatment. The humanized monoclonal anti–HER-2 antibody trastuzumab, in combination with ei-

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ther docetaxel or paclitaxel, is the standard of care in this setting [1, 2]. Novel agents and combination regimens are continually sought that offer better efficacy and tolerability than existing therapies.

Vascular endothelial growth factor (VEGF) plays a key role in tumor-mediated angiogenesis [3]. Findings from preclinical studies have provided the rationale for combining agents that target both the HER-2 and VEGF receptor signaling pathways [4–7]. Overexpression of HER-2 is associated with greater VEGF expression in human breast cancer xenografts and greater angiogenic potential [5, 6]. Furthermore, a significant association between HER-2 and VEGF expression ($p < .001$) was demonstrated in patients with early breast cancer, which was shown to predict outcome with therapy [8]. Recent findings on the classification of breast cancer subtypes also indicate the importance of VEGF pathways in patients with HER-2–enriched tumors [9]. Bevacizumab is a humanized monoclonal antibody that recognizes and binds to all isoforms of VEGF [10]. Capecitabine has shown modest activity in patients with chemotherapy- and trastuzumab-resistant HER-2-positive MBC [11, 12].

In preclinical human breast cancer models, the in vivo antitumor activity of combined trastuzumab and capecitabine was at least additive in terms of tumor growth inhibition and tumor growth delay, compared with either agent alone [13]. Greater in vivo antitumor activity was also shown with the combination of bevacizumab and trastuzumab versus the individual agents in a human breast cancer xenograft model [7]. Similarly, synergistic effects were seen with capecitabine and bevacizumab in a breast cancer xenograft model—longer tumor growth inhibition and a longer life span were observed with the combination regimen than with either agent alone ($p < .05$) [14]. Several clinical trials in patients with MBC have also demonstrated efficacy with doublet combinations of trastuzumab, bevacizumab, and capecitabine, with acceptable and manageable safety profiles, both in the first-line setting and in later lines [11, 15–17].

We conducted the current study to investigate a nontaxane-containing, triple-combination regimen of bevacizumab plus trastuzumab and capecitabine as first-line therapy for patients with HER-2-positive locally recurrent (LR) or MBC in a phase II setting. Here, we report first efficacy and safety results from the study.

Methods

Patients

The study (ClinicalTrials.gov identifier, NCT00811135) was carried out in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The protocol and subsequent amendments were approved by the institutional review board or ethics committee of each investigational site. Written informed consent was obtained from each patient prior to any study-related procedure.

Eligible patients were aged ≥18 years with confirmed breast adenocarcinoma and measurable, LR, or metastatic lesions (according to the Response Evaluation Criteria in Solid Tumors [RECIST]). Patients were required to have central laboratory documented HER-2-positive disease (immunohistochemistry 3+ and/or fluorescence in situ hybridization positive and/or chromogenic in situ hybridization positive) and known estrogen receptor and progesterone receptor status. An Eastern Cooperative Oncology Group performance status score ≤2 and adequate bone marrow reserve and liver and renal function were also required. All patients were candidates for chemotherapy.

Previous chemotherapy for LR/MBC was not permitted, but prior neoadjuvant or adjuvant chemotherapy, hormone therapy, or trastuzumab was allowed. Previous anthracycline treatment must not have reached a maximum cumulative dose >360 mg/m^2 of doxorubicin or >720 mg/m^2 of epirubicin and must have been completed ≥6 months before study enrolment. Patients were excluded in the event of another primary tumor ≤5 years prior to enrolment (except adequately treated cervical cancer in situ, squamous cell skin cancer, or adequately controlled basal cell cancer), central nervous system metastases, uncontrolled hypertension, or clinically significant cardiovascular disease.

Study Design

In this single-arm, open-label, multicenter, phase II study, patients received bevacizumab plus trastuzumab plus capecitabine in 21-day cycles until disease progression, unacceptable toxicity, or withdrawal of consent. Trastuzumab was given as a loading dose of 8 mg/kg on day 1 of the first cycle, followed by a maintenance dose of 6 mg/kg on day 1 of each subsequent cycle. Bevacizumab was administered at a dose of 15 mg/kg on day 1, and capecitabine was administered at a dose of 1,000 mg/m^2 twice daily, days 1–14. Doses were selected based on common clinical practice and results of previous clinical trials with these agents [18, 19]. Dose modification (interruptions, adjustments, or discontinuations) of capecitabine was permitted for toxicity; dose administration of trastuzumab or bevacizumab could be delayed but no dose modifications for toxicity were allowed.

The primary objective of the study was to assess the best overall response rate (ORR) (according to investigator-reported RECIST), defined as the percentage of patients with a complete or partial response. Secondary objectives were to assess progression-free survival (PFS), overall survival (OS), time to progression (TTP), and safety (according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0) outcomes. Post-treatment follow-up occurs every 3 months until disease progression (tumor and adverse event [AE] assessments) and for at least 24 months for survival follow-up.

Statistical Analysis

The primary efficacy analysis was conducted in the intent-to-treat (ITT) population (all enrolled patients who received at least one dose of any study medication) and was repeated in the per-protocol (PP) population (all eligible patients who received at least one cycle of study treatment, had at least one postbaseline tumor assessment, and did not have any major protocol violation). Only results for the ITT population are pre-

sented in this manuscript. Safety analyses were conducted in all patients who received at least one dose of any study medication. The primary analysis was performed using a data cutoff date of July 31, 2010 after a median follow-up 8.8 months (range, 0.9–17.1 months). The study will end, and the final analysis will be performed, when the death rate in the ITT population is >80%. Updated PFS analyses and final OS analyses will be performed at the end of the study.

Responders were defined as patients with a best overall response of either a complete response or a partial response. The number and percentage of patients with a best overall response was summarized, and corresponding exact Clopper Pearson 95% confidence intervals (CIs) were calculated. Time-to-event endpoints, that is, OS, TTP, and PFS, were analyzed using Kaplan–Meier methods. The median time to event with its corresponding 95% CI, upper and lower quartiles, and event-free rates were estimated from the Kaplan–Meier approach.

To test the null hypothesis that the study treatment conferred a response proportion ≤0.550 versus the alternative hypothesis that the study treatment conferred a response proportion ≥0.700 at a 5% significance level, 70 evaluable patients were required to achieve a power of 80%. Assuming a 20% dropout rate, ~88 patients were to be enrolled.

Results

Patients

From December 29, 2008 to January 11, 2010, 88 patients were enrolled (ITT population). Forty patients (46%) were still on study treatment at the time of this primary analysis. Two patients were excluded from the PP population, one as a result of major protocol violations (failure of two inclusion criteria) and the other because of missing postbaseline tumor assessments (that patient died shortly after entering the study and was classed as a study failure). The median patient age was 53.0 years (range, 32.0–82.0 years) and the majority of patients had MBC (84.1%) and visceral disease (69.3%) (Table 1). Overall, 51 patients (58.0%) had received chemotherapy in the (neo)adjuvant setting and 22 patients (25.0%) had received (neo)adjuvant trastuzumab and/or lapatinib.

Table 1. Baseline demographic and disease characteristics (intent-to-treat population)

Characteristic	Total (n = 88)
Sex, n (%)	
Male	1 (1.1)
Female	87 (98.9)
Median (range) age, yrs	53.0 (32.0–82.0)
Age category, n (%)	
<60 yrs	61 (69.3)
≥60 yrs	27 (30.7)
Metastatic breast cancer,[a] n (%)	74 (84.1)
Locally recurrent disease,[a] n (%)	13 (14.8)
Visceral,[b] n (%)	61 (69.3)
Nonvisceral, n (%)	27 (30.7)
Estrogen receptor or progesterone receptor, n (%)	
Positive	37 (42.0)
Other	51 (58.0)
Pretreated in the (neo)adjuvant setting, n (%)	
With chemotherapy	51 (58.0)
With a taxane	28 (31.8)
With trastuzumab and/or lapatinib	22 (25.0)
With radiotherapy	40 (45.5)

[a]One patient had neither metastatic breast cancer nor locally recurrent disease and was not included in the per-protocol population.
[b]Of 61 patients, 34 had lung/liver organ site recorded as target or nontarget, but not as both.

Treatment Exposure

The median duration of trastuzumab therapy was 8.4 months (range, 0.7–16.6 months). Treatment exposure was slightly shorter for bevacizumab and capecitabine, at 7.7 months (range, 0.7–16.6 months) and 7.6 months (range, 0.5–16.4 months), respectively. Two thirds of the patients completed more than eight cycles of trastuzumab (69%), bevacizumab (67%), or capecitabine (64%) therapy. Thirteen patients stopped capecitabine therapy but continued with bevacizumab and trastuzumab.

Efficacy Outcomes

The median follow-up time was 8.8 months (range, 0.9–17.1 months). The primary endpoint, best ORR, was 73% in the ITT population (95% CI, 62%–82%), comprising 7% of patients with complete responses and 66% of patients with partial responses. A further 16% of patients achieved stable disease as their best response. Subgroup analyses of the ORR are shown in Table 2.

The median PFS interval was 14.4 months (95% CI, 10.4 months to not reached [NR]), with 35 events (Fig. 1). The median TTP was 14.5 months (95% CI, 10.5 months to NR), with 33 events. The median OS time had not been reached, with a 12-month survival rate of 95.1% with four events to date. Patients previously treated with trastuzumab and/or lapatinib in the (neo)adjuvant setting showed efficacy comparable with that of the ITT population, with an ORR of 68% (95% CI, 45%–86%) and a median PFS interval and TTP of 14.8 months each (Table 3).

Safety

Treatment-related AEs were reported by 92% of patients (n = 81); treatment-related grade ≥3 AEs occurred in 44% of patients (n = 39) (Table 4). Hand–foot syndrome (HFS) was the most frequently reported grade 3 treatment-related AE, in 22% of patients. Grade ≥3 treatment-related diarrhea and hypertension were reported in 9% and 7% of patients, respectively. Overall, 22% of patients (n = 19) experienced a serious AE

Table 2. Subgroup analyses of ORR

Subgroup	*n* of patients	ORR, %	Complete response, %	Partial response, %	ORR 95% confidence interval
Aged >60 yrs	25	68.0	8.0	60.0	47–85
Metastatic breast cancer	74	73.0	6.8	66.2	61–83
Locally recurrent disease	13	76.9	7.7	69.2	46–95
ER positive or PgR positive	37	70.3	5.4	64.9	53–84
ER negative or PgR negative	51	74.5	7.8	66.7	60–86
Visceral	61	70.5	3.3	67.2	57–81
Nonvisceral	27	77.8	14.8	63.0	58–91
Chemotherapy naïve[a]	37	78.4	5.4	73.0	62–90
Chemotherapy pretreated[a]	51	68.6	7.8	60.8	54–81

[a]In the (neo)adjuvant setting.
Abbreviations: ER, estrogen receptor; ORR, overall response rate; PgR, progesterone receptor.

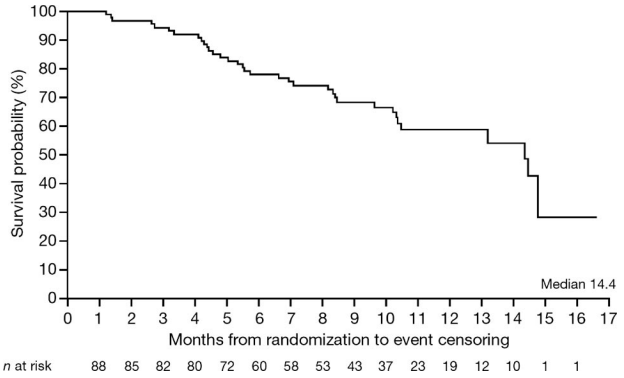

Figure 1. Kaplan–Meier curve of progression-free survival (intent-to-treat population).

Table 3. Efficacy outcomes in patients pretreated with (neo)adjuvant trastuzumab and/or lapatinib and in ITT patients

Outcome	Patients pretreated with trastuzumab and/or lapatinib (*n* = 22)	ITT population (*n* = 88)
Overall response, % (95% CI)	68.2 (45–86)	72.7 (62–82)
Complete response	9.1	6.8
Partial response	59.1	65.9
Progression-free survival events, *n*	9	35
Median, mos (95% CI)	14.8 (8.2–14.8)	14.4 (10.4-NR)
Time to progression events, *n*	8	33
Median, mos (95% CI)	14.8 (8.2–14.8)	14.5 (10.5-NR)

Abbreviations: CI, confidence interval; ITT, intent-to-treat; NR, not reached.

(Table 5), with diarrhea and cardiac failure each occurring in two patients. Serious treatment-related AEs were coded for 15% of patients ($n = 13$); diarrhea occurred in two patients, hematologic events and alopecia were rare.

Grade 3 cardiac failure was reported in a 50-year-old female and was considered probably related to study treatment. That patient received 12 cycles each of bevacizumab, capecitabine, and trastuzumab, but no prior chemotherapy, radiotherapy, or antineoplastic agents for breast cancer. Her pretreatment visit left ventricular ejection fraction was 60% and no cardiac abnormalities were detected by electrocardiogram. She withdrew from the study as a result of the cardiac failure. A 53-year-old female died as a result of treatment-unrelated renal failure, and also experienced treatment-unrelated cardiac failure.

In total, 19 patients (22%) withdrew prematurely from the study. Eight patients (9%) discontinued for administrative or other reasons, including mastectomy ($n = 5$), patient and investigator decision ($n = 2$), and withdrawal of consent ($n = 1$). Five patients (6%) withdrew as a result of AEs or intercurrent illness, three patients (3%) died, and one patient withdrew as a result of disease progression (1%). A further two patients discontinued prematurely (one violation of selection criteria and one protocol violation). At the time of this primary analysis, 84 patients were still alive. Four treatment-unrelated deaths occurred; these were recorded as disease progression ($n = 2$), respiratory failure ($n = 1$), and cause unknown ($n = 1$).

Discussion

This single-arm, phase II study evaluated the efficacy and safety of bevacizumab in combination with trastuzumab and capecitabine as first-line therapy for HER-2-positive LR/MBC. First results from the study showed the regimen to be clinically active, with an ORR of 72.7% and a median PFS time and TTP of 14.4 months and 14.5 months, respectively. The median OS time had not yet been reached. Efficacy com-

Table 4. Treatment-related AEs occurring in ≥2% of patients

AE	Total $n = 88$ (%)	Grade ≥3 $n = 88$ (%)
Patients with at least one AE	81 (92)	39 (44)
Cardiac disorders	5 (6)	2 (2)
Gastrointestinal disorders	49 (56)	10 (11)
Diarrhea	33 (38)	8 (9)
General disorders, administration site conditions	40 (46)	3 (3)
Infections and infestations	11 (13)	2 (2)
Respiratory, thoracic, and mediastinal disorders	33 (38)	2 (2)
Skin and s.c. tissue disorders	66 (75)	19 (22)
Hand–foot syndrome	62 (71)	19 (22)
Vascular disorders	31 (35)	7 (8)
Hypertension	28 (32)	6 (7)

Abbreviation: AE, adverse event.

Table 5. Serious AEs and serious treatment-related AEs

	Total ($n = 88$)	
Serious AE	Total, n (%)	Treatment-related, n (%)
Patients with at least one serious AE	19 (22)	13 (15)
Diarrhea	2 (2)	2 (2)
Cardiac failure (or cardiac failure acute)	2 (2)	1 (1)
Intracardiac thrombus	1 (1)	1 (1)
Abdominal pain	1 (1)	1 (1)
Enteritis	1 (1)	1 (1)
Mesentric artery embolism	1 (1)	1 (1)
Peritonitis	1 (1)	0
Chest pain	1 (1)	1 (1)
Death	1 (1)	0
Erysipelas	1 (1)	1 (1)
Pneumonia	1 (1)	0
Abdominal wound dehiscence	1 (1)	0
Fall	1 (1)	0
Cerebral ischemia	1 (1)	1 (1)
Presyncope	1 (1)	1 (1)
Abortion, spontaneous	1 (1)	0
Hematuria	1 (1)	1 (1)
Renal failure	1 (1)	0
Dyspnea	1 (1)	0
Pulmonary embolism	1 (1)	1 (1)
Respiratory failure	1 (1)	0

Abbreviation: AE, adverse event.

parable with that of the ITT population was observed in patients previously treated with (neo)adjuvant trastuzumab and/or lapatinib, who comprised 25% of the study population. This confirms the benefit of continued treatment with trastuzumab in patients who have previously progressed while receiving this agent and supports the use of trastuzumab in multiple lines [20]. In light of the low number of events, the median PFS interval and median TTP cannot be robustly estimated. The safety profile of the regimen was consistent with prior clinical trials of the individual drugs, with HFS (22%) and diarrhea (9%) being the most frequently reported grade ≥3 treatment-related AEs. There was a relatively high rate of discontinuation from capecitabine treatment ($n = 13$); however, the triple-combination regimen was well tolerated overall. Compared with other triple regimens investigated for HER-2-positive MBC, patients in our study experienced considerably less febrile neutropenia, neutropenia, and alopecia, whereas the incidences of HFS and diarrhea were similar across the studies [21, 22].

The combination of trastuzumab and capecitabine with an antiangiogenic agent represents a novel therapeutic approach for the first-line treatment of HER-2-positive MBC. Trastuzumab has exhibited clinical activity for both adjuvant [23] and first-line metastatic [1, 2] HER-2-positive breast cancer, as well as in subsequent lines [11, 20, 24]. In two randomized, phase II trials, first-line trastuzumab plus paclitaxel or docetaxel led to a significantly longer OS time, higher ORR, and longer TTP than with a taxane alone [1, 2]. Extensive clinical experience with trastuzumab shows it to be generally well tolerated, with mild-to-moderate infusion-related reactions reported most frequently [25]. Capecitabine offers the convenience of oral dosing and has a well-established safety profile that lacks myelosuppression and alopecia, with AEs readily managed by dose modification [26].

A number of studies have demonstrated the high clinical activity of capecitabine in combination with anti–HER-2 agents in MBC patients. The German Breast Group 26/Breast International Group 03–05 phase III trial randomized patients with HER-2-positive MBC that had progressed during prior trastuzumab therapy to receive trastuzumab with or without capecitabine ($n = 156$) [11]. A significantly greater ORR (48.1% versus 27.0%, respectively; odds ratio [OR], 2.50; $p = .0115$) and TTP (median, 8.2 months versus 5.6 months, respectively; hazard ratio [HR], 0.69; $p = .0338$) were observed in patients who continued trastuzumab in combination with capecitabine than in those receiving capecitabine alone. The incidence and severity of AEs were comparable between the treatment arms, with the exception of grade 1–4 anemia, which was more frequent in the trastuzumab arm (64%, versus 44% with capecitabine alone; $p = .021$). Geyer et al. [12] compared the combination of lapatinib and capecitabine with capecitabine alone in a randomized, phase III trial in patients with HER-2-positive MBC previously treated with an anthracycline, a taxane, and trastuzumab ($n = 399$). A significantly lon-

ger TTP (median, 6.2 months versus 4.3 months, respectively; HR, 0.57; 95% CI, 0.43–0.77; $p < .001$) and a higher ORR (23.7% versus 13.9%, respectively; OR, 1.90; $p = .017$) were achieved in patients receiving the combination regimen than in those receiving single-agent capecitabine [27]. Diarrhea, HFS, and nausea were the most common AEs across both treatment groups. The high clinical activity of trastuzumab plus capecitabine combination therapy was also reported in three single-arm, phase II studies as first-line ($n = 63$) and later lines of treatment ($n = 74$) in HER-2-positive MBC patients [16, 17, 28]. In the first-line setting, ORRs were >60%, with a median TTP of 9.2 months and median OS time of 25.6 months [16, 17].

A number of clinical trials have demonstrated the efficacy of doublet combinations of trastuzumab, bevacizumab, and capecitabine in patients with MBC [11, 15–17]. Pegram et al. [15] assessed the combination of trastuzumab and bevacizumab as first-line therapy for HER-2-positive MBC and found clinical benefit in 31 of 37 patients, with complete responses in one of 37 patients and partial responses in 19 of 37 patients. Definitive data on the combination of trastuzumab plus bevacizumab in the first-line setting will be provided by the phase III AVastin in combination with hERceptin/docetaxEL in HER-2-positive MBC (AVEREL) trial; final results are expected at the end of 2011.

Because anthracyclines and taxanes are increasingly used in the (neo)adjuvant setting, an increasing proportion of patients are presenting with MBC who require a nonanthracycline- and nontaxane-containing first-line regimen. First efficacy and safety data from our study indicate that the combination of bevacizumab with trastuzumab and capecitabine is feasible as first-line therapy for patients with HER-2-positive MBC and warrants further investigation. The final analysis is expected in 2012. Although the recent decision by the U.S. Food and Drug Administration to revoke its approval for bevacizumab for the treatment of MBC may reduce interest in this drug, or in this triple combination, new trials in breast cancer are ongoing and the results are eagerly awaited.

Conclusions

The triple-combination regimen of trastuzumab, bevacizumab, and capecitabine appears to be clinically active as first-line therapy for patients with HER-2-positive MBC, with an acceptable safety profile and no unexpected toxicities. Patients previously treated with (neo)adjuvant trastuzumab and/or lapatinib also showed favorable efficacy and safety outcomes. This regimen merits further evaluation in a randomized, phase II trial versus a taxane plus trastuzumab standard combination.

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