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Bevacizumab Combined with Docetaxel or Paclitaxel as First-line Treatment of HER2-negative Metastatic Breast Cancer

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Abstract. *Aim: The study evaluated the efficacy of bevacizumab combined with a taxane-based treatment for advanced breast cancer. Patients and Methods: In this non-randomized phase II study 65 patients received 10 mg/kg bevacizumab i.v. (days 1 and 15, q4w) plus either 50 mg/m^2 docetaxel (days 1 and 15, q4w) or 90 mg/m^2 paclitaxel (days 1,8 and 15, q4w) i.v. until disease progression, maximal response, unacceptable toxicity or the withdrawal of consent. Patients without progression continued bevacizumab at 15 mg/kg i.v. (q3w) alone, or with endocrine therapy. (NCT00979641). Results: Progression-free survival was 11.3 months (95% confidence interval=9.7-16.0 months) and overall survival was 35.1 months (95% confidence interval=22.2-50.3 months). More than half of the patients (62%) responded at least partially. Bevacizumab-related serious adverse events occurred in 10.8% patients and one patient died because of gastrointestinal perforation. Conclusion: Treating advanced breast cancer with a bevacizumab-containing regimen as the first-line cytotoxic treatment resulted in excellent response rates and long survival.*

Metastatic breast cancer remains an incurable disease (1, 2). In Finland, nearly 5,000 patients are diagnosed with invasive breast cancer every year, and the incidence has increased steadily over the past decades. The Finnish cancer registry data from 2014 shows that 815 women died of metastatic breast cancer, which was the most common cause of cancer death in women (3). In the CONCORD-2 study, a central analysis of population-based registry data worldwide for cancer survival was conducted, and the results were published in The Lancet in November 2014. The study reported that the treatment results of breast cancer in Finland are among the best in the world. The 5-year-survival rate of patients with breast cancer in Finland was 86.8% [95% confidence interval (CI)=85.9-87.7%) from 2005-2009, and was the highest in Northern Europe (4). However, new treatment options for advanced human epidermal growth factor receptor 2 (HER2)-negative disease are rare, and the overall survival benefit observed in these patients is modest (5, 6). For this reason, advanced HER2-negative breast cancer is a treatment challenge worldwide.

Bevacizumab is a recombinant humanized monoclonal antibody that inhibits vascular endothelial cell proliferation by blocking the binding of vascular endothelial growth factor A (VEGFA) to its receptor, therefore inhibiting tumor angiogenesis (7). Bevacizumab improves the outcomes of cytotoxic treatment in many metastatic malignancies, including colorectal, kidney, lung and ovarian cancer (8-11). There has been much debate about the status of bevacizumab treatment in metastatic breast cancer. Currently, the European Medicines Agency has only approved bevacizumab when combined with paclitaxel or capecitabine in a first or second-line setting (http://www.ema.europa.eu/ema/). In 2011, the US Food and Drug Administration revoked its accelerated approval of a breast cancer indication for bevacizumab due to the lack of a benefit in breast cancer overall survival and, in addition, due to the potentially life-threatening side-effects (http://www.fda.gov/).

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In locally advanced and metastatic breast cancer, taxane-based treatment (docetaxel or paclitaxel), either in combination with another agent or as single-agent, therapy is considered one of the most effective choices for first-line treatment (5, 12), when cytotoxic treatment is needed. Combining bevacizumab with chemotherapy has been studied in certain phase III studies (13-18). Most of these studies investigated the benefit of bevacizumab combined with a taxane. Furthermore, other chemotherapy regimens have been explored, including capecitabine, anthracycline, vinorelbine and gemcitabine. Adding bevacizumab has led to higher response rates and longer progression-free survival (PFS) throughout the trials, but no significant differences in overall survival (OS) have yet been observed.

In addition to chemotherapy options, bevacizumab can also be combined with endocrine therapy, and the effect may be synergistic. Intracellular VEGF and estrogen signaling pathways cross at several points, and it can be hypothesized that adding bevacizumab to hormonal treatment might delay the development of endocrine therapy resistance (19, 20). In hormone receptor-positive advanced breast cancer, endocrine treatment with either an anti-estrogen or an aromatase inhibitor is a keystone of the treatment (5). It is used in metastatic breast cancer in biologically non-aggressive forms of the disease and in more aggressive forms after a maximal chemotherapy response has been achieved (5). For the first-line therapy of advanced breast cancer, an aromatase inhibitor combined with bevacizumab was investigated in a phase III LEA trial (21). Similarly, as reported in chemotherapy trials, the endocrine therapy–bevacizumab combination resulted in higher response rates but failed to demonstrate statistically significant improvements in both PFS and OS compared to endocrine-therapy alone.

This study aimed to investigate whether bevacizumab combined with either docetaxel or paclitaxel is a feasible choice for first-line therapy in metastatic breast cancer. The study also evaluated if using bevacizumab maintenance therapy with an endocrine therapy would have synergistic effects.

Patients and Methods

Patients. We screened and treated 65 patients at three study centers in Finland: Tampere, Oulu and Turku University hospitals. The study was initiated in May 2009 and data closure took place in April 2015. The median follow-up time was 24.1 months (range=1.6-66.3 months). Pre- and postmenopausal women were eligible if they had histologically or cytologically confirmed HER2-negative metastatic adenocarcinoma of the breast and were considered as candidates for taxane treatment. Patients were not allowed any prior chemotherapy for advanced disease but could have been treated with (neo)adjuvant chemotherapy if the disease-free interval was at least 6 months. Previous endocrine therapy for advanced disease was allowed. Both measurable and non-measurable (bone-only) diseases were eligible. Good performance status was required [Eastern Cooperative Oncology Group (ECOG) performance status 0-2]. Additional inclusion criteria included adequate hematological, renal and hepatic functions.

Patients were excluded if they had history of central nervous system metastases or pre-existing peripheral neuropathy at least grade 2 by National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 3.0 (22). Additionally, circumstances that could increase the serious adverse events associated with bevacizumab were excluded, such as major surgery within the previous month, minor surgery within the last 24 hours prior to bevacizumab initiation, the use of anticoagulants or thrombolytic agents, a history of bleeding diathesis or coagulopathy, uncontrolled hypertension, clinically significant cardiovascular disease, a non-healing wound, an active peptic ulcer or bone fracture, a history of abdominal fistula, and a gastrointestinal perforation or intra-abdominal abscess within 6 months of enrollment. Furthermore, patients with a history of other malignancies were excluded.

The study protocol was approved by the Ethics Committee of Tampere University Hospital (R08142M) and the trial identifier is NCT00979641. Written informed consent was obtained from all patients included in the study.

Treatment. In part I of the treatment, the patients received taxane therapy intravenously (*i.v.*; 50 mg/m^2 docetaxel on days 1 and 15 or 90 mg/m^2 paclitaxel on days 1, 8 and 15) and 10 mg/kg bevacizumab *i.v.* on days 1 and 15 on a treatment cycle of 28 days. Treatment was continued until the maximal response, progressive disease, unacceptable toxicities necessitating the termination of taxane treatment or the patient's refusal. The maximal response was defined as an achieved response (a complete response (CR) or a partial response PR) that was the same between two response evaluations, or stable disease (SD) for more than 6 months. The study was initiated with the docetaxel-bevacizumab combination. After the negative results from the AVADO trial (14) were published, an amendment to the study protocol was made and the following enrolled patients were treated with a combination of paclitaxel and bevacizumab. In part II of treatment, after taxane treatment was discontinued, the responding patients continued to receive 15 mg/kg bevacizumab intravenously on day 1 q 21 days. In hormone receptor-positive patients, an endocrine therapy according to the investigator's choice was added to bevacizumab. This second part of the treatment was given until disease progression, unacceptable treatment-related toxicities or the withdrawal of the patient's consent. The study scheme is presented in Figure 1.

After disease progression, the continuation of bevacizumab with a second-line therapy was optional. The preferred chemotherapy option was capecitabine or the investigator's choice. Capecitabine was administered at a dose 1000 mg/m^2 twice-daily per os given on days 1-14 of a 3-week cycle.

Dose modifications, toxicity and response evaluations. The dosing of bevacizumab was not modified during the study. In case of grade 3-4 bevacizumab-related toxicity, bevacizumab was either temporarily or permanently suspended. If bevacizumab was permanently discontinued but chemotherapy not interrupted, the patient entered the follow-up phase of the study. The bevacizumab-related toxicities were monitored closely and specific treatment algorithms were made for hypertension, proteinuria, thromboembolic events, hemorrhage, gastrointestinal perforations and impaired wound-healing. The dose of the taxane was allowed to be reduced according to each clinic's standards of care in the case of taxane-related toxicity. Toxic effects

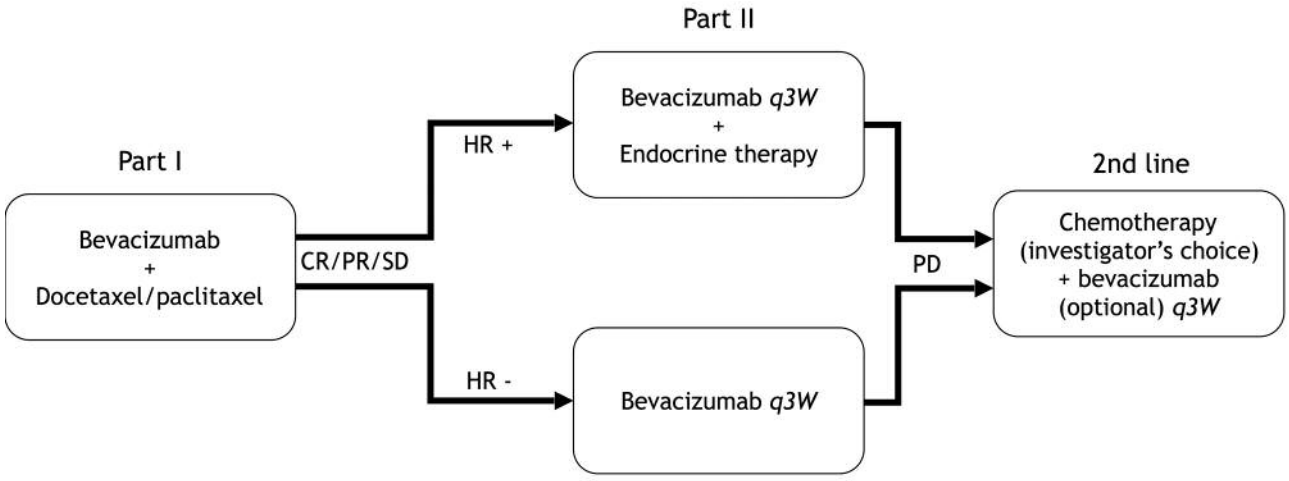

Figure 1. *Study scheme. CR: Complete response, PR: partial response, SD: stable disease, HR: hormone receptor, q3W: every 3 weeks, PD: progressive disease.*

were graded according to the NCI-CTC, version 3.0 (22). For second-line capecitabine, dose modifications were made according to the investigator's assessment. In patients with moderate renal impairment, the dose of capecitabine was reduced by 25%.

Tumor assessment was performed every 12 weeks until progression, according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (23). All patients were followed-up every 6 months for an evaluation of their status and for survival by following the patient records.

Statistical analysis. The primary endpoint of the study was PFS in the first-line treatment setting and it was calculated from the date of treatment initiation to the date of investigator-assessed disease progression according to the RECIST criteria (23) or to the date of patient death. Secondary end-points were safety, the response rate and OS. Adverse events are displayed in standard frequency tables. The proportions of patients with CR, PR, SD and progressive disease (PD) as the best response were tabulated for each part of the treatment. OS was calculated from the date of treatment initiation to the date of death due to any cause. The median PFS and OS were calculated according to the Kaplan–Meier method. The analysis of PFS and OS included the stratification variable taxane choice (docetaxel–bevacizumab or paclitaxel–bevacizumab) and hormone receptor status. The Kaplan–Meier estimates obtained from the model were compared with the historical control group (14).

A total of 65 patients were expected to enter the study. This number would provide a probability of 80% for detecting a difference corresponding to a ratio of 1.34 between this study group and historical control group (equal to PFS of 10.7 months *versus* 8 months). The basis of the assumptions was that the accrual period was 18 months, the follow-up period was 36 months and the median PFS of the historical control group was 8.2 months in a series of 241 patients (14).

Results

Patient baseline characteristics. Between May 2009 and October 2013, 65 patients were enrolled. The baseline characteristics are shown in Table I. The majority of patients were post-menopausal with hormone receptor-positive disease. Additionally, most patients had received different combinations of adjuvant therapy and the vast majority of patients had received adjuvant chemotherapy. Furthermore, 34% of the patients with either estrogen or progesterone receptor-positive disease had received endocrine therapy for advanced disease.

Most patients had a heavy disease burden: visceral disease was common (82%) and liver metastases occurred in 51% of patients. Two-fifths of the patients had more than three metastatic sites. In addition, bone-only disease was observed only in five patients (Table I).

Efficacy. All 65 patients were evaluated for treatment efficacy and the PFS and OS results are shown in Figures 2 and 3. In part I of treatment, 32 patients were treated with docetaxel and 33 patients with paclitaxel. A total of 38 patients (58%) entered part II of treatment. Of these patients, the majority had hormone receptor-positive disease (87%) and only five patients had hormone receptor-negative disease. All hormone receptor-positive patients received endocrine therapy in part II in addition to bevacizumab according to the physician's choice, with letrozole being the most common drug (n=19). Other hormonal drugs that were used included anastrozole (n=4), exemestane (n=4), tamoxifen (n=3) and fulvestrant (n=3).

The median PFS for the first-line treatment was 11.3 months (95% CI=9.7-16.0, Figure 2) and the median OS was 35.1 months (95% CI=22.2-50.3; Figure 3). The overall response rate was high. One patient (1.5%) had a CR and 39 had PR (60.0%) in part I. SD was observed in 15 patients (23.1%). Thus, the clinical benefit rate (CR+PR+SD) for part I was 84.6%. Only three patients (4.6%) had PD as the best response

Table I. *Demographic and baseline characteristics of patients (n=65).*

Characteristic	Value
Median age (range), years	57 (32-75)
Menopausal status, n (%)	
Pre-menopausal	10 (15.4)
Post-menopausal	55 (84.6)
History of early-stage disease, n (%)	
Total	57 (87.7)
Disease-free interval, n (%)	
≤24 Months	11 (16.9)
>24 Months	46 (70.8)
Hormone receptor status, n (%)	
ER+PR+/ER+PR−	53 (81.5)
ER−PR−	12 (18.5)
Estrogen receptor status, n (%)	
Positive	51 (78.5)
Negative	14 (21.5)
Progesterone receptor status, n (%)	
Positive	46 (70.8)
Negative	19 (29.2)
Prior adjuvant chemotherapy, n (%)	
Total	46 (70.8)
Taxane	26 (40.0)
Anthracycline	38 (58.5)
Prior hormonal therapy, n (%)	
Total	44 (67.7)
(Neo)adjuvant	38 (58.5)
Metastatic/advanced disease	18 (27.7)
Current stage of disease, n (%)	
IV	65 (100.0)
Hormonal therapies used in metastatic setting, n (%)	
Anastrozole	4 (10.5)
Exemestane	7 (18.4)
Fulvestrant	5 (13.2)
Letrozole	12 (31.6)
GnRH analogs	3 (7.9)
Tamoxifen	4 (10.5)
Number of metastatic lesions, n (%)	
≤3	14 (21.5)
>3	51 (78.5)
Extent of disease	
<3 Sites	39 (60.0)
≥ 3 Sites	26 (40.0)
Site of metastatic disease, n (%)	
Visceral	53 (81.5)
Non-visceral	12 (18.5)

ER: Estrogen receptor; PR: progesterone receptor; GnRH: gonadotrophin-releasing hormone.

in part I. Docetaxel- and paclitaxel-based regimens led to similar median survival values: median PFS 11.3 months (95% CI=9.1-16.8) for docetaxel *vs*. 11.3 months (95% CI 7.4-30.7, p=0.47) for paclitaxel, median OS 38 months (95% CI=19.8-50.4) *vs*. 34.2 months (95% CI=18.1-not reached, p=0.77) respectively. The median OS for patients with hormone receptor-positive disease was 45.0 months (95% CI=30.2-51.3) and for patients with triple-negative disease, it was 17.9 months (95% CI=8.5-26.9, p=0.011).

Subsequent therapy. Patients were allowed to receive bevacizumab together with a second-line chemotherapy according to investigators' choice. A total of 17 patients began second-line bevacizumab–chemotherapy combination. The preferred chemotherapy in the protocol was capecitabine (n=15) but patients also received paclitaxel and vinorelbine. The median PFS for second-line therapy was 5.1 months (95% CI=4.4-16.1 months) and the OS was 33.8 months (95% CI=24.7 months-NR). With the second-line bevacizumab–chemotherapy, seven patients responded partially (41%) and six patients had SD as the best response to the treatment (35%). No CRs were observed. Disease progression occurred in three patients (18%). For one patient, the response could not be defined because at data closure, the first response evaluation had not yet been performed.

Safety. During part I of the treatment, the bevacizumab–chemotherapy combination was generally well tolerated and most toxicity was mild (grade 1-2). The worst grade of a side-effect per patient is presented. The adverse events of all grades (1-4) that were most frequently reported were neutropenia (n=45, 69%), musculoskeletal pain (n=45, 69%), alopecia (n=44, 68%), leukocytopenia (n=41, 63%), fatigue (n=35, 54%), mucositis (n=35, 54%), anemia (n=35, 54%), epistaxis (n=34, 52%), constipation (n=27, 42%), nail disorders (n=23, 35%), proteinuria (n=22, 34%), diarrhea (n=22, 34%), elevated liver enzymes (n=20, 31%), nausea (n=20, 31%) and peripheral neuropathy (n=18, 28%). Serious adverse events during part I chemotherapy treatment are presented in Table II. The most common serious adverse event was neutropenia but febrile neutropenia was rare. One patient had a grade 5 toxicity due to the treatment and died during part I of the study. This patient had pre-existing diverticulosis and then developed diverticulitis, which resulted in gastrointestinal perforation and peritonitis. During bevacizumab maintenance, grade 3-4 adverse events were rare. The serious adverse events from part II treatment are presented in Table III.

Bevacizumab treatment-related adverse events according to the investigators' judgment are summarized in Table IV. The gastrointestinal perforation, mentioned above, was suspected to be related to bevacizumab. Hypertension and proteinuria were frequently reported but were usually of low grade. However, one patient suffered from grade 4 proteinuria and renal failure. In addition, over half of the patients had low-grade epistaxis.

In the second-line setting, the expected side-effects for capecitabine occurred in 17 patients treated in this part of the trial. The serious adverse events reported were grade 3 hand and foot syndrome (n=3) and a single case of grade 4 diarrhea.

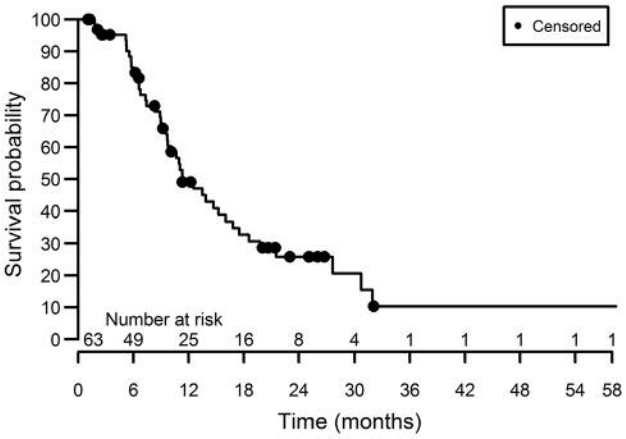

Figure 2. *Progression-free survival for the whole patient cohort.*

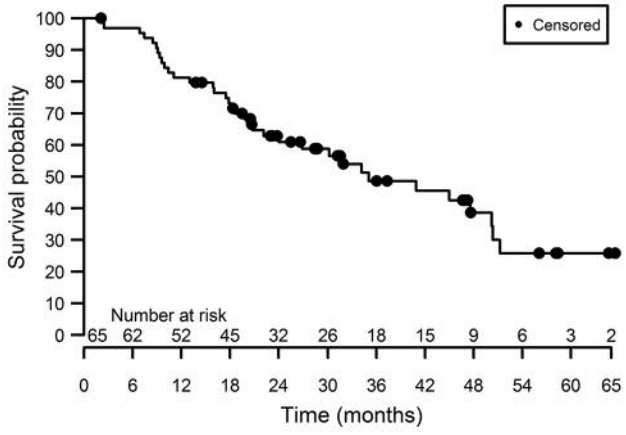

Figure 3. *Overall survival for the whole patient cohort.*

Discussion

This study resulted in excellent OS of almost 3 years (35.1 months) in patients with advanced breast cancer with poor prognostic features at the beginning of the trial. Visceral metastases were common (80%), and most patients had multiple metastases. Prior taxane treatment as adjuvant chemotherapy was given to 40% of these patients. The most favorable results towards a benefit from adding bevacizumab to chemotherapy are reported in the E2100 trial (13). In that study, the number of patients with visceral disease was similar to that observed in our study (79.5-87.1% depending on the treatment arm). Additionally, the extent of disease (42.0-46.3% of patients had more than three metastatic sites) was quite similar in both studies. Only approximately 15% of E2100 patients were pre-treated with taxanes in an adjuvant setting compared to 40% of our patients. PFS was reported

Table II. *Grade 3-4 adverse events experienced by patients in part I of the treatment.*

	Patients (n=65)	
Adverse event	Grade 3	Grade 4
Fatigue	2	
Neutropenia	9	16
Leukocytopenia	11	2
Elevated liver enzymes	1	1
Infection	9	
Febrile neutropenia or neutropenic sepsis	3	1
Peripheral neuropathy	1	
Pain	3	1
Diarrhea	1	
Nausea	1	
Cardiac disorders	1*	
Osteonecrosis of the jaw	1	
Drug hypersensitivity	1	
Gastrointestinal perforation		1**

*Supraventricular tachycardia; **patient died, grade 5 adverse event.

Table III. *Grade 3-4 adverse events experienced by patients in part II of the treatment.*

	Grade 3-4/patients	
Adverse event	HR+ (n=33)	HR− (n=5)
Infection	2	
Leukocytopenia	1	
Elevated liver enzymes	2	
Peripheral neuropathy	1	
Anorexia	1	
Cardiac disorders	2*	
Hyponatremia	1	1

HR+: Hormone receptor-positive (estrogen receptor+ or progesterone receptor+); HR−: hormone receptor-negative. *Congestive heart failure, coronary artery thrombosis.

Table IV. *Bevacizumab-related events experienced by patients in this study.*

	Patients (n=65)			
Adverse event	Grade 1-2	Grade 3	Grade 4	Grade 5
Hypertension	16	2		
Proteinuria	18	3	1	
Bleeding/hemorrhage	9			
Epistaxis	34			
Gastrointestinal fistula/abscess	2			
Gastrointestinal perforation				1

to be very similar between the E2100 study and our study (11.8 months in E2100 and 11.3 months in our trial). Nevertheless, the OS was remarkably longer in our trial: 35.1 months compared to 26.7 months observed in the E2100 trial.

There are some possible explanations for the long OS observed in this study. The main difference in our study when compared to other studies of first-line chemotherapy combining bevacizumab with taxanes (13, 14, 16, 18) is that after a maximal response was reached in our study, bevacizumab was continued as a maintenance treatment with endocrine therapy in patients with hormone receptor-positive disease. Bevacizumab maintenance was given to 38 patients (58%) and the majority of these patients (87%) had hormone receptor-positive disease and received endocrine therapy with bevacizumab. Intracellular estrogen signaling pathways and VEGF pathways have several interactions (19, 20, 24, 25); therefore, endocrine treatment may add a substantial benefit to bevacizumab monotherapy, as also recently shown with androgen signaling pathways and VEGF in prostate cancer (26). In addition, using biweekly instead of triweekly docetaxel infusions might have led to lower treatment toxicity and, therefore, to prolonged survival. This was previously demonstrated in our randomized phase III Prosty trial where triweekly and biweekly docetaxel dosing were compared in advanced castration-resistant prostate cancer (27). Weekly paclitaxel compared to triweekly infusions has also demonstrated survival benefit in advanced breast cancer (28).

This trial has many differences compared to the LEA trial (21). In the LEA trial, patients with advanced disease were endocrine treatment-naïve. In our study, one-third of the patients with hormone receptor-positive disease had received hormonal therapies for advanced disease, meaning that the patients seemed to have less hormone treatment-sensitive disease. Half of the patients in our trial also had liver metastasis compared to only 20% in the LEA trial. Thus, our patients had less favorable prognoses. The OS for this patient population is, as expected, shorter with less favorable prognostic features. In the LEA trial, the OS was 52.1 months in patients treated with the first-line bevacizumab-endocrine therapy combination. This exceeds that of the patients with hormone receptor-positive disease of our study by only 7.1 months, which is less than expected considering the poor prognostic features of the disease at the beginning of our patients' treatments. Both these studies favor the hypothesis of an interaction between hormonal and angiogenetic cellular pathways in breast cancer.

In preclinical studies, it has been reported that tumor progression may be accelerated after short-term angiogenesis inhibition (29). On the other hand, treating colorectal cancer with second-line bevacizumab-chemotherapy combination after disease progression with first-line therapy including bevacizumab was shown to have survival benefits (30). Therefore, some patients with metastatic adenocarcinoma may benefit from prolonged VEGF inhibition in terms of survival. This is one possible explanation for the long OS seen in our study.

High response rates have been reported in all of the trials with bevacizumab combined with a first-line chemotherapeutic. The response rates previously reported with the bevacizumab–taxane combination range from 36.9% to 64.1% compared to 21.2-46.4% with single taxane therapy (13, 14, 31). Similarly, good responses were achieved in this study. The clinical benefit rate was 84.6% and 62% of patients responded at least with PR according to the RECIST criteria, which is in line with previously published data.

In this small series of patients, no difference in PFS or OS was observed between the two taxane-treated groups. Half of the patients in the study were treated with paclitaxel and the other half with docetaxel. Thus, there is an indication that docetaxel and paclitaxel are similarly effective with bevacizumab.

Bevacizumab adds treatment toxicity compared to single taxane chemotherapy. In this study, bevacizumab-related serious events were rare (10.8%). However, one patient died because of bevacizumab-related toxicity, which in this case was a fatal peritonitis. The contributing factor was underlying diverticulosis in our patient. Additionally, high-grade proteinuria and hypertension were observed, which are known side-effects of bevacizumab (13-17, 31). Caution should be exercised when treating patients with known risk factors for the use of bevacizumab, namely a history of thromboembolic events, cardiovascular disease or risk factors for abdominal infection and fistula, among others. The other grade 3-4 toxicities observed were related to chemotherapy or to the metastatic disease itself and were reported at the anticipated rates. In the AVADO trial, 75-78% of the patients, depending on the treatment arm, treated with a bevacizumab–docetaxel combination had at least one grade 3 toxicity due to the treatment (14), whereas a minimum of grade 3 toxicity was observed in 71% of our patients. Only 24% of the patients had grade 3-4 toxicity during bevacizumab–capecitabine treatment in our study. No unexpected new side-effects were reported in our study. In conclusion, combining bevacizumab with paclitaxel or docetaxel or to second-line capecitabine has an acceptable side-effect profile.

The small sample size does not allow us to draw any conclusions about the efficacy of second-line chemotherapy.

Although our patients presented many poor prognostic features at baseline, the OS achieved of nearly 3 years is remarkable. This study intended to determine whether bevacizumab adds an advantage to taxane treatment followed by a bevacizumab maintenance therapy with an endocrine therapy. With an OS of 17.9 months in patients with triple-negative disease and 45.0 months in a hormone receptor-positive study population, it can be concluded that combining bevacizumab with a conventional taxane

treatment is a treatment option. This is especially true in patients with a heavy disease burden and needing rapid tumor shrinkage. We have gathered a comprehensive serum, plasma and tumor biopsy collection from the study population and we aim to explore markers predictive for the long response to bevacizumab combination therapies.

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