Factors Associated with the Selection of First-line Bevacizumab plus Chemotherapy and Clinical Response in HER2-negative Metastatic Breast Cancer: ONCOSUR AVALOX Study

LUÍS MANSO[1], ANDRÉS GARCÍA PALOMO[2], RAMÓN PÉREZ CARRIÓN[3], JAVIER CASSINELLO[4], ISABEL GALLEGOS SANCHO[5], IGNACIO CHACÓN LÓPEZ-MUÑIZ[6], CLARA OLIER[7], ANTONIO FERNÁNDEZ-ARAMBURO[8], CRISTINA LLORCA[9], XAVIER GONZÁLEZ[10], ROSA LLORENTE[11], DOLORES TORREGROSA[12], IÑAKI ÁLVAREZ[13], ELENA GÁLVE[14], CORALIA BUENO[15], ISABEL GARAU[16], MARÍA JOSÉ GARCÍA[17], SANTIAGO GONZÁLEZ-SANTIAGO[18], ANA ISABEL BALLESTEROS[19], ESPERANZA BLANCO[20], ANTONIO GALÁN[21], SONIA GONZÁLEZ[22], ANTONIA PERELLÓ[23], HERNÁN CORTÉS-FUNES[1] and CRISTINA GRÁVALOS[1]

[1]Hospital 12 de Octubre, ONCOSUR, Madrid, Spain; [2]Hospital de León, León, Spain; [3]Clínica Quirón Madrid, Madrid, Spain; [4]Hospital de Guadalajara, ONCOSUR, Guadalajara, Spain; [5]Hospital General de Segovia, ONCOSUR, Segovia, Spain; [6]Hospital Virgen de la Salud, ONCOSUR, Toledo, Spain; [7]Hospital de Alcorcón, ONCOSUR, Madrid, Spain; [8]Complejo Hospitalario Universitario de Albacete, Albacete, Spain; [9]Hospital de Elda, Alicante, Spain; [10]Hospital Clinic i Provincial, Barcelona, Spain; [11]Hospital Dr. Peset, Valencia, Spain; [12]Hospital de Luis Alcanyis, Xátiva, Valencia, Spain; [13]Hospital General San Jorge, Huesca, Spain; [14]Hospital de Basurto, Vizcaya, Spain; [15]Hospital Infanta Cristina, ONCOSUR, Madrid, Spain; [16]Hospital Son Llatzer, Palma de Mallorca, Spain; [17]Hospital General de Ciudad Real, ONCOSUR, Ciudad Real, Spain; [18]Hospital San Pedro de Alcántara, ONCOSUR, Cáceres, Spain; [19]Hospital Universitario La Princesa, Madrid, Spain; [20]Hospital Infanta Cristina, ONCOSUR, Badajoz, Spain; [21]Hospital de Sagunto, Valencia, Spain; [22]Hospital Mutua de Terrassa, Barcelona, Spain; [23]Hospital Son Dureta, Palma de Mallorca, Spain

Abstract. *Aim: To evaluate factors associated with the selection of first-line bevacizumab plus chemotherapy and clinical response in HER2-negative metastatic breast cancer (MBC) in clinical practice in Spain. Patients and Methods: All consecutive adult female patients with HER2-negative MBC who had received first-line bevacizumab plus chemotherapy for at least 3 months were enrolled in the present study. Results: A total of 292 evaluable patients were included; 25% had triple-negative breast cancer (TNBC) and 75% had hormone receptor-positive breast cancer (HRPBC). Nearly 40% of patients had ≥3 metastatic sites, mainly located in the bone (48%) and liver (40%). Bevacizumab was mostly combined with paclitaxel (67.1%). ER-positive tumors were only identified as an independent factor associated with the choice of treatment (odds ratio (OR): 0.538; p=0.02). The overall response rate (ORR) was 63.7% (TNBC: 57.5%; HRPBC: 65.9%). Patients aged 36-50 years (OR: 3.03; p=0.028) and those with metastases at sites other than the bone (OR: 0.38; p=0.001) and ≥3 metastatic sites (OR: 1.41; p=0.018) were more likely to achieve objective responses. Conclusion: First-line bevacizumab plus chemotherapy, mainly paclitaxel, is an effective and well-tolerated treatment option for HER2-negative MBC, particularly in more aggressive disease.*

Correspondence to: Luis Manso, Medical Oncology Department, Hospital 12 de Octubre, Avda. de Córdoba, s/n, 28041 Madrid, Spain. Tel: +34 913908000, e-mail: lmanso@salud.madrid.org

Key Words: Bevacizumab, breast cancer, epidermal growth factor receptor (HER2)-negative, metastatic disease, predictive factors.

The development of targeted-biological agents has led to notable advances in the treatment of human epidermal growth factor receptor (HER2)-negative metastatic breast cancer (MBC). Vascular endothelial growth factor (VEGF) and its receptors play a pivotal role in tumor angiogenesis.

The anti-VEGF humanized monoclonal antibody bevacizumab has been shown to be effective in first-line treatment of HER2-negative MBC (1-4). This is particularly interesting for the triple-negative (TN) patient sub-group, that is associated with a poor prognosis and for whom there was no biological therapy previously available. The efficacy of first-line chemotherapy can be significantly improved when combined with bevacizumab in patients with HER2-negative MBC, as demonstrated in several randomized trials (3-5). Pre-clinical evidence has shown that taxanes exert anti-angiogenic and cytotoxic effects that pointed to synergies with anti-VEGF targeted-agents (6, 7). The E2100 phase III trial demonstrated a significant improvement in progression-free survival (PFS) for the addition of bevacizumab to paclitaxel in the first-line setting when compared to paclitaxel alone in patients with HER2-negative MBC (5). Subsequent first-line trials such as AVADO and RIBBON-1 showed a more modest, but nevertheless significant improved PFS than the E2100 trial (3, 4). None of the trials evaluating bevacizumab and chemotherapy combinations demonstrated an improvement in overall survival (OS), probably due to the confounding effect of subsequent therapy or treatment crossover. Only the recent IMELDA study reported an improved OS in patients treated with first-line bevacizumab and taxane followed by bevacizumab and capecitabine (8). Moreover, despite a notably prolonged PFS when bevacizumab is added to chemotherapy, the absolute improvement varied with the type of chemotherapy, with the greatest benefit derived when combined with paclitaxel (9). The TURANDOT trial supported the efficacy of bevacizumab-paclitaxel combination observed in the E2100 trial (10). More recently, the open-label international ATHENA study supported the efficacy data of the AVADO, E2100 and RIBBON-1 clinical trials and reinforced the safety profile of first-line bevacizumab combined with standard single-agent taxane chemotherapy in routine oncology practice (11). In addition, the prognostic factor index developed in the ATHENA study also showed that a large metastatic tumor burden (≥3 metastatic sites) was associated with a poorer prognosis.

Considering the biological variability of breast cancer, individualization of treatment based on each patient's characteristics is particularly important. There is no standard chemotherapy regimen for HER-negative MBC, and current guidelines and the international consensus statement recommend selecting chemotherapy according to each individual scenario. The treatment decision-making process is therefore complex and influenced by multiple biological and clinical factors. Hence, there exists a need to identify predictive and prognostic factors that may provide physicians with a useful tool to guide clinical management of HER2-negative MBC. Although various studies have evaluated the prognostic factors in MBC patients receiving anthracycline-taxane-based first-line therapy (12-15), there exist limited data available on predictive and prognostic factors in HER2-negative MBC in the context of bevacizumab and chemotherapy treatment in the first-line setting (16), particularly in Spain (17). Hence, patient selection remains a challenging issue in clinical practice. Considering the lack of biomarkers of response, identifying clinical risk factors of response to the addition of bevacizumab to paclitaxel in HER2-negative MBC setting is of paramount importance.

On the basis of this background, we conducted a study to evaluate the factors involved in the selection of first-line bevacizumab plus chemotherapy and the clinical response of patients with HER2-negative MBC in clinical practice in Spain.

Patients and Methods

Study design and patient population. AVALOX (Oncosur Trial ONC-BEV-2010-01) was a national, multi-center, cross-sectional, observational study conducted in the oncology departments of 43 Spanish Hospitals. The study was carried-out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and their amendments. Approval of the protocol was obtained from the Ethics Committee of 12 de Octubre Hospital. Written informed consent was obtained from all patients to retrospectively collect data from medical charts.

Adult (aged ≥18 years) female patients with HER2-negative MBC who had received first-line bevacizumab combined with chemotherapy during at least 3 months under routine clinical practice conditions were eligible for the study after providing informed consent.

The primary study end-point was the identification of potential factors that may be involved in the selection of bevacizumab and chemotherapy combination as first-line treatment for HER2-negative MBC. Secondary end-points included the disease-free interval (DFI), defined as the time from the end of adjuvant treatment or surgery (if adjuvant chemotherapy was not received) to relapse, stratified in <12 months and ≥12 months, and the proportion of patients with DFI <12 or ≥12 months according to prior adjuvant treatment received; the potential relationship between baseline risk factors (age and Eastern Cooperative Oncology Group (ECOG) performance status (PS) at diagnosis of metastatic disease, hormonal receptor (HR) status, number of metastatic sites and location of metastases and the role of patient in treatment decision-making) and the achievement of objective responses (complete response (CR) or partial response (PR)); and safety profile of bevacizumab and health-related quality of life (HRQL) assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) during first-line treatment.

Statistical analysis. A descriptive statistical analysis was performed on the socio-demographic and clinical variables collected from the medical records of patients. To evaluate the potential association between the selection of first-line treatment with bevacizumab plus chemotherapy and age, ECOG PS, HR status and the number of sites and location of metastases a bivariate analysis was carried out using the Chi-square test or the Fisher exact test. Similarly, a bivariate analysis of sociodemographic and clinical variables associated with the selection of first-line treatment was conducted according to HR status in the subgroups of patients with HR-positive breast cancer

Table I. *Patient demographic and clinicopathological characteristics (N=292)*

Characteristic	N (%)
Age at diagnosis of metastatic disease (years)	
<35	18 (6.2)
36-50	118 (40.4)
51-70	130 (44.5)
>70	26 (8.9)
ECOG PS[a]	
0	155 (53.1)
1	125 (42.8)
2	11 (3.8)
Missing	1 (0.3)
Menopausal status[a]	
Pre-menopausal	102 (34.9)
Post-menopausal	190 (65.1)
Hormone receptor status	
Estrogen receptor positive (ER+)[b]	211 (72.5)
Progesterone receptor positive (PR+)[b]	168 (57.5)
HR-positive (RE+or PR+)	217 (74.8)
Triple-negative disease	73 (25.3)
Prior surgery[b]	241 (82.8)
Prior neo (adjuvant) chemotherapy	220 (75.3)
Anthracycline and taxane	132 (60.0)
Anthracycline, no taxane	65 (29.5)
Taxane, no anthracycline	7 (3.2)
Neither anthracycline nor taxane	16 (7.3)
Prior endocrine therapy	167 (74.9)
Disease-free interval	
<12 months	48 (16.4)
≥12 months	193 (66.1)
Missing	51 (17.5)
Extent of disease	
<3 sites	176 (60.3)
≥3 sites	108 (37.0)
Missing	8 (2.8)
Metastatic sites[c]	
Bone	140 (47.9)
Bone with no other metastases	29 (20.7)
Visceral	
Liver	117 (40.1)
Lung	95 (32.5)
Skin and soft tissue	56 (19.2)

ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hormone receptor. Percentages may not add-up to 100% due to the rounding error; [a]At diagnosis of metastatic breast cancer; [b]Missing data: n=1; [c]Patients could have more than one metastasic site.

(HRPBC) and TN breast cancer (TNBC). Variables with statistical significance or with $p<0.20$ in the bivariate model were analyzed in a multivariate logistic regression model. Odds ratios (OR) and 95% confidence interval (95% CI) were calculated for the independent predictive factors of the selection of bevacizumab and paclitaxel as first-line treatment in the overall population and in the sub-groups of patients with TNBC and HRPBC. The clinical profile of patients (age, ECOG PS, HR status and the number of sites and location of metastases) achieving an objective response was also assessed using a multivariate logistic regression model.

The mean scores of the items included in the FACT-B questionnaire (physical, functional, emotional, social well-being and breast-cancer-specific concerns) were calculated. In addition, one item was selected from the Breast Cancer Subscale (BCS) ("I have pain") for individual item analysis. For all questionnaire end-points, including the individual item analysis, a higher score indicates better quality of life.

In order to assess toxicity per patient, the maximum grade for each of toxicity recorded during the cycles of treatment was considered for evaluation. Toxicities were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) (version 3.0). Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients. Between November 2010 and December 2013, a total of 314 patients with HER2-negative MBC were enrolled in the study. Twenty-two patients were excluded from the analysis due to eligibility violations (first-line treatment with bevacizumab and chemotherapy during at least 3 months at the time of study entry). Therefore, a total of 292 patients were evaluable for the study.

The main baseline clinicopathological characteristics of patients are shown in Table I. Briefly, the majority of patients (96%) had ECOG PS of 0 or 1. More than half of patients had at least one comorbid condition (53.3%); hypertension was the most frequent comorbidity (45%). Half of patients were post-menopausal at the time of tumor diagnosis. Infiltrating ductal carcinoma was present in most patients (83.2%); the remaining patients had lobular carcinoma (12.4%) and other histological types (unspecified) (4.4%). Histological grade II and III tumors were found in 39.2% and 43.3% of patients, respectively; 7.2% had grade I tumors (unknown histological grade in 10.3% of patients). One quarter of patients had TNBC and nearly 75% of patients had HRPBC. Prior neo (adjuvant)-chemotherapy was received by 75% of patients, anthracycline plus taxane-based therapy being the most common approach used (60%). Nearly 40% of patients had ≥3 metastatic sites, and metastases were mostly located in bone (47.9%) (bone-only metastases in 20.7%), liver (40.1%) and lung (32.5%). Among patients with bone metastases, 58 (52.3%) also had metastases in the liver and 43 (39%) patients in the lung. The median time (range) interval from diagnosis of primary breast cancer to first-line treatment initiation was 2.9 (1.2-6.2) years. A DFI ≥12 months had been achieved by 66% of patients from the overall population and 69.1% and 83.2% of TNBC and HRPBC patients, respectively.

First-line treatment. Bevacizumab was mostly combined with single-agent taxane (78%), mainly paclitaxel (67.1%), in the overall patient population. The median number of cycles administered was 6 (5-8), and the mean dose received was 13.2±3.8 mg/kg. In the remaining patients, bevacizumab was mainly combined with docetaxel (10.6%) and capecitabine

(8.2%). Bevacizumab plus paclitaxel was also the most common regimen used in patients with TNBC (57.5%) and HRPBC (70.5%). First-line treatment received by patients in the overall population and according to the hormonal receptor status (TNBC or HRPBC) is summarized in Table II.

Factors associated with first-line treatment selection. The potential factors associated with the selection of first-line treatment with bevacizumab plus paclitaxel were analyzed as it was the most common combination used in our series. The estrogen receptor (ER) status and number of metastatic sites (<3 *vs*. ≥3 sites) were factors significantly associated with the selection of first-line treatment with bevacizumab plus paclitaxel in the overall population ($p<0.05$) (Table III). However, ER-positive tumor (OR: 0.538; 95% CI=0.315-0.920; $p=0.02$) was identified as the only independent factor associated with the choice of this combination. Patients with ECOG PS 0 were more likely to receive bevacizumab plus paclitaxel as first-line treatment than those with ECOG 1 in TNBC patients (OR: 0.340; 95% CI=.126-0.916; $p=0.033$). The selection of first-line bevacizumab plus paclitaxel was only significantly influenced by patient's role in treatment decision-making in HRPBC ($p=0.05$). Treatment decision on first-line therapy was more likely to be made by physicians after considering the patient's opinion (*vs*. leaving the final decision to the attending physician (referral category); OR: 2.893; 95% CI=1.157-7.236; $p=0.023$).

Efficacy and factors associated with clinical outcome. The overall response rate (ORR) was 63.7% (95% CI=57.9-69.2%) and a clinical benefit of 86.6% (95% CI=82.2-90.3%) was attained. The data on tumor response to therapy in the overall population and according to subgroup of patients with TNBC and HRPBC is displayed in Table IV.

An age between 36-50 years *vs*. ≤35 years (OR: 3.03; 95% CI=1.04-8.85; $p=0.028$), metastases at other sites than bone (OR: 0.38; 95% CI=0.22-0.67; $p=0.001$) and the presence of ≥3 metastatic sites (*vs*. <3 sites; OR: 1.41; 95% CI=1.06-1.88; $p=0.018$) were identified as independent factors associated with the achievement of objective responses in the overall population.

The multivariate analysis showed an age between 36 and 50 years old (*vs*. ≤35 years; OR: 5.03; 95% CI=1.19-21.30; $p=0.028$) as the only independent factor associated with the attainment of objectives responses in HRPBC. The presence of metastases at other sites than bone was only identified as an independent clinical factor significantly associated with objective responses (OR: 0.293; 95% CI=0.108-0.797; $p=0.016$) in those patients with TNBC.

DFI <12 months (*vs*. ≥12 months) ($p=0.078$), prior therapy with (neo) adjuvant taxanes ($p=0.352$), ≥3 metastatic sites (*vs*. <3 sites) ($p=0.140$) and TNBC (*vs*. non-TN disease) ($p=0.182$) were not identified as factors associated with the attainment of objective responses to bevacizumab plus chemotherapy, mainly based on single-agent taxane, in the overall study population (data not shown).

Table II. *First-line bevacizumab plus chemotherapy combinations in the overall population and according to hormonal receptor status (TNBC and HRPBC)*

First-line therapy	Total (N=292)	TNBC (N=73)	HRPBC (N=217)
Radiotherapy, N (%)	49 (16.8)	13 (17.8)	35 (16.1)
Hormonal therapy, N (%)[a]	71 (24.4)	3 (4.1)[b]	67 (31)
Letrozol	29 (40.8)	--	29 (43.3)
Fulvestrant	18 (25.4)	--	18 (26.9)
Exemestane	11 (15.5)	--	10 (14.9)
Tamoxifen	11 (15.5)	--	9 (13.4)
Median time (range), months	0.6 (0.3-1.3)	--	--
Chemotherapy, N (%)[c]			
Paclitaxel	196 (67.1)	42 (57.5)	153 (70.5)
Docetaxel	31 (10.6)	--	28 (12.9)
Capecitabine	24 (8.2)	--	15 (6.9)
Paclitaxel and carboplatin	18 (6.2)	13 (17.8)	5 (2.3)
Docetaxel and carboplatin	6 (2.1)	3 (4.1)	3 (1.4)
Albumin-bound paclitaxel	--	1 (1.4)	--

HRPBC: Hormone receptor-positive breast cancer; TNBC: triple-negative breast cancer [a]Hormonal therapies received by >10% of patients; [b]Exemestane, tamoxifen and other hormonal therapy in one patient each; [c]Chemotherapy agents administered to >1% of patients.

Among patients with HRPBC, there were 87 (47%) patients presenting with at least two factors associated with poor prognosis defined in this study as DFI <12 months, prior (neo) adjuvant taxanes, ≥3 metastatic sites, or liver metastases. The ORR of these patients defined as high-risk HRPBC was 72.4%.

Receiving hormonal therapy was significantly associated with a DFI ≥12 months in the overall study population ($p<0.005$) and in those patients with HRPBC ($p<0.01$), while adjuvant radiotherapy seemed to be related to the achievement of a DFI ≥12 months ($p<0.05$) in patients with TNBC (data not shown).

Subsequent treatment. First-line bevacizumab plus chemotherapy treatment was switched before disease progression in 96 (40.3%) patients primarily due to toxicity (56.3%) and physician's decision (39.6%). At the time of analysis, 57 (41.6%) patients had received a second-line treatment after disease progression (out of 137 evaluable patients). Bevacizumab combined with capecitabine (57%) was the most common regimen used as second-line treatment followed by bevacizumab plus vinorelbine (19%). Subsequent treatment to first-line therapy is detailed in Table V.

Table III. *Bivariate analysis of baseline factors (age and ECOG PS at diagnosis of metastatic disease, ER status, metastases location and number of metastatic sites and patient's role in treatment decision-making) associated with the selection of bevacizumab plus paclitaxel in the overall population and according to hormonal receptor status (TNBC and HRPBC)*

	Overall population			TNBC			HRPBC		
	Bevacizumab+Paclitaxel			Bevacizumab+Paclitaxel			Bevacizumab+Paclitaxel		
Baseline factors	Yes N=196	No N=96	*p*-Value	Yes N=42	No N=31	*p*-Value	Yes N=153	No N=64	*p*-Value
Age[a], N (%)									
≤35	11 (61.1)	7 (38.9)	0,206	5 (55.6)	4 (44.4)	0.853	6 (66.7)	3 (33.3)	0.171
36-50	72 (61.0)	46 (39.9)		12 (52.2)	11 (47.8)		60 (63.2)	35 (36.8)	
51-70	93 (71.5)	37 (28.5)		23 (62.2)	14 (37.8)		70 (76.1)	22 (23.9)	
>70	20 (76.9)	6 (23.1)		2 (50.0)	2 (50.0)		17 (81.0)	4 (19.0)	
ECOG PS[a], N (%)									
0	101 (65.2)	54 (34.8)	0.434	27 (69.2)	12 (30.8)	0.052	74 (64.3)	41 (35.7)	0.067
1	88 (70.4)	37 (29.6)		13 (43.3)	17 (56.7)		74 (78.7)	20 (21.3)	
2	6 (54.5)	5 (45.5)		1 (33.3)	2 (66.7)		5 (62.5)	3 (37.5)	
ER status, N (%)									
Positive	150 (71.1)	61 (28.9)	<0.05	--	--		--	--	
Negative	45 (57.0)	34 (43.0)		--	--		--	--	
Metastases location, N (%)									
Bone									
Yes	95 (67.9)	45 (32.1)	0.798	14 (53.8)	12 (46.2)	0.635	80 (71.4)	32 (28.6)	0,758
No	101 (66.4)	51 (33.6)		28 (59.6)	19 (40.4)		73 (69.5)	32 (30.5)	
Liver									
Yes	82 (70.1)	35 (29.9)	0.378	12 (70.6)	5 (29.4)	0.214	69 (69.7)	30 (30.3)	0.758
No	114 (65.1)	61 (34.9)		30 (53.6)	26 (46.4)		84 (71.2)	34 (28.8)	
Lung									
Yes	59 (62.1)	36 (37.9)	0.205	12 (46.2)	14 (53.8)	0.143	46 (67.6)	22 (32.4)	0.533
No	137 (69.5)	60 (30.5)		30 (63.8)	17 (36.2)		107 (71.8)	42 (28.2)	
Skin/soft tissue									
Yes	156 (66.1)	16 (28.6)	0.446	9 (56.3)	7 (43.8)	0.906	31 (77.5)	9 (22.5)	0.283
No	40 (71.4)	80 (33.9)		33 (57.9)	24 (42.1)		122 (68.9)	55 (31.1)	
Metastatic sites, N (%)									
<3	109 (61.9)	67 (38.1)	<0.05	28 (51.9)	41 (33.6)	0.131	81 (66.4)	41 (33.6)	0.179
≥3	80 (74.1)	28 (25.9)		13 (72.2)	5 (27.8)		66 (75.0)	22 (25.0)	
Patient's role in treatment decision-making, N (%)									
Patients left the final decision to their attending physician	72 (63.7)	41 (36.3)	0.162	11 (44.0)	14 (56.0)	<0.05	60 (69.0)	27 (31.0)	<0.005
Physicians make the final decision after considering patient's opinion	52 (76.5)	16 (23.5)		7 (43.8)	9 (56.3)		45 (86.5)	7 (13.5)	
Shared decision making	53 (65.4)	28 (34.6)		18 (78.3)	5 (21.7)		35 (61.4)	22 (38.6)	
Patients make treatment decision after considering physician's opinion	6 (50.0)	6 (50.0)		2 (100.0)	--		4 (40.0)	6 (60.0)	

ECOG PS: Eastern Cooperative Oncology Group performance status; ER: estrogen receptor; HRPBC: hormone receptor-positive breast cancer; TNBC: triple-negative breast cancer; [a]At diagnosis of metastatic breast cancer.

Safety. All patients included in the study were considered evaluable for safety analyses (n=292). Among them, 231 (72.9%) patients experienced at least one toxicity during the study. The most common grade 1 or 2 toxicities were asthenia (19.2%) and hypertension (15.8%) followed by hand-foot syndrome and hemorrhage (11%). Grade 3 toxicities were detected in less than 17% of patients (each grade 3 toxicity in <4%). The only grade 4 toxicity reported was neutropenia in one patient. None of the patients died as a result of treatment toxicity. A total of 111 (38%) patients experienced at least one

Table IV. *Summary of efficacy data for first-line bevacizumab plus chemotherapy in the overall population and according to hormonal receptor status (TNBC and HRPBC)*

Efficacy	Total (N=292)	TNBC (N=73)	HRPBC (N=217)
Overall response rate, N (%)	186 (63.7)	42 (57.5)	143 (65.9)
95% CI	57.9-69.2	45.4-69.0	59.2-72.2
Best response, N (%)			
Complete response	27 (9.2)	4 (5.5)	23 (10.6)
Partial response	159 (54.5)	38 (52.1)	120 (55.3)
Stable disease	67 (22.9)	15 (20.5)	51 (23.5)
Disease progression	20 (6.8)	8 (11.0)	12 (5.5)
Not assessable or unknown	19 (6.5)	8 (11.0)	11 (5.1)
Clinical benefit, N (%)	253 (86.6)	57 (78.1)	194 (89.4)
95% CI	82.2-90.3	66.9-86.9	84.5-93.2

CI: Confidence interval; HRPBC: hormone receptor-positive breast cancer; TNBC: triple-negative breast cancer.

Table V. *Subsequent anticancer treatment after disease progression (N=57)*

Type of therapy	N (%)
Any subsequent therapy	57 (41.6)[a]
Bevacizumab and/or chemotherapy, N (%)[b]	21 (36.8)
Bevacizumab/capecitabine	12 (57.1)
Bevacizumab/vinorelbine	4 (19.0)
Bevacizumab/anthracycline/cyclophosphamide	2 (9.6)
Bevacizumab/nab-paclitaxel	1 (4.8)
Bevacizumab/cisplatin	1 (4.8)
Capecitabine	1 (4.8)
Hormonal therapy, N (%)	12 (21.1)
Radiotherapy, N (%)	2 (3.5)

[a]The percentage has been calculated over the total of patients who have progressed and have available data on second line chemotherapy and/or bevacizumab (n=137); [b]Percentages have been calculated over the total of patients who received second line chemotherapy and/or bevacizumab (N=57).

toxicity related to bevacizumab. No grade 4 toxicities were reported. Only six (2%) patients experienced grade 3 toxicities; hypertension in three patients and proteinuria and venous thromboembolism in two patients and one patient each, respectively. The most frequent grade 1 or 2 toxicities were hypertension (15.0%) and hemorrhage (10.6%) (Table VI).

Quality of life. Quality of life questionnaires were available from 265 patients. The data from the questionnaire items were not evaluable in 11 patients; therefore, the questionnaire data of 254 patients were finally analyzed. The mean FACT-G score was 70.2±15.3 and the mean score for the FACT-B was 90.5±19.0 in the overall population. The individual item analysis showed that 91 (35.8%) patients reported "some pain". The mean FACT-G and FACT-B scores for patients with HRPBC were similar to those shown in the overall population (70.8±14.5 and 91.3±17.9 respectively). Among patients with TNBC, the mean FACT-G and FACT-B scores were 68.7±17.6 and 88.5±22.1, respectively, and 23 (38.3%) patients reported "some pain" at certain sites of the body.

Discussion

The AVALOX study showed that bevacizumab was mostly combined with single-agent taxane-based chemotherapy, mainly paclitaxel, in patients with HER2-negative MBC, including those with TNBC and HRPBC. Hence, we identified factors involved in the selection of bevacizumab plus paclitaxel, as the most frequent first-line regimen used in clinical practice in Spain. The findings of this analysis suggest that the number of metastatic sites (<3 *vs.* ≥3 sites) and ER status were factors significantly associated with the choice of first-line treatment with bevacizumab plus paclitaxel, although ER-positive status was only identified as an independent factor associated with the selection of this approach. However, the statistical significance of differences may be explained by the large number of patients with ER-positive MBC included in this series.

Thus, bevacizumab plus paclitaxel seems to be used regardless of other clinical risk factors in HER2-negative MBC, such as location of metastases and ECOG PS (16), and this regimen seems more likely to be used in patients with multiple metastases (≥3 sites), although this clinical factor did not reach statistical significance in the multivariate model.

Of note, bevacizumab plus paclitaxel was the most common regimen used among patients with TNBC, with more than half of this sub-group receiving this regimen, which seems to reflect an increasing use of bevacizumab and single-agent taxane in this sub-group of patients with few treatment options and typically associated with a more aggressive disease and a poor prognosis.

Our findings also suggest that bevacizumab plus chemotherapy treatment, mainly based on single-agent paclitaxel, is an effective treatment option in patients with HER2-negative MBC. As a descriptive comparison only, the efficacy figures in terms of ORR (63.7%) are within the range reported in the phase III clinical trials with bevacizumab and taxane-based chemotherapy (3, 4) where an ORR ranging from 37% to 64% has been shown. In addition, the bevacizumab plus chemotherapy strategy was also effective in TNBC. It is noteworthy that the benefit obtained in patients with TNBC seems to be similar to that observed in patients with HRPBC disease. Similarly, a recent analysis of the ATHENA trial also showed comparable OS between patients with HRPBC and TNBC when adjusted for prognostic factors (16). The AVAREG

Table VI. *Toxicity (N=292).*

Adverse event	Most common toxicities			Bevacizumab-related toxicities		
	Any grade[a] N (%)	Grade 1/2 N (%)	Grade 3 N (%)	Any grade N (%)	Grade 1/2 N (%)	Grade 3 N (%)
Asthenia	60 (20.5)	55 (19.2)	4 (1.4)	6 (2.0)	6 (2.0)	0 (0.0)
Hypertension	49 (16.8)	46 (15.8)	3 (1.0)	47 (16.1)	44 (15.0)	3 (1.0)
Hand-foot syndrome	42 (14.4)	32 (11.0)	10 (3.4)	3 (1.0)	3 (1.0)	0 (0.0)
Hemorrhage	32 (11.0)	32 (11.0)	0 (0.0)	31 (10.6)	31 (10.6)	0 (0.0)
Mucositis	32 (11.0)	30 (10.3)	2 (0.7)	5 (1.7)	5 (1.7)	0 (0.0)
Neutropenia[b]	32 (11.0)	22 (7.5)	9 (3.1)	1 (0.3)	1 (0.3)	0 (0.0)
Neurotoxicity	27 (9.2)	27 (9.2)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)
Diarrhea	25 (8.6)	25 (8.6)	0 (0.0)	--	--	--
Epistaxis	23 (7-9)	23 (7.8)	0 (0.0)	21 (7.2)	21 (7.2)	0 (0.0)
Neuropathy	20 (6.8)	16 (5.5)	4 (1.4)	1 (0.3)	1 (0.3)	0 (0.0)
Proteinuria	17 (5.8)	14 (4.8)	3 (1.0)	15 (5.1)	13 (4.5)	2 (0.7)
Alopecia	16 (5.5)	15 (5.2)	1 (0.3)	--	--	--
Paresthesia	14 (4.8)	13 (4.5)	1 (0.3)	3 (1.0)	3 (1.0)	0 (0.0)
Nausea-vomiting	13 (4.5)	12 (4.1)	1 (0.3)	--	--	--
Onycholysis	12 (4.1)	11 (3.8)	1 (0.3)	1 (0.3)	1 (0.3)	0 (0.0)
Anemia	9 (3.1)	9 (3.1)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)

[a]Toxicities reported in >3% of patients; [b]The only grade 4 toxicity reported was neutropenia in one patient.

study, where half of patients had TNBC, has recently confirmed that first-line bevacizumab plus paclitaxel is an effective and well-tolerated treatment option for patients with HER2-negative MBC (18).

In our series, an age between 36-50 years, metastases at other sites than bone and the presence of multiple metastases (≥3 sites) were identified as independent factors significantly associated with the achievement of objective responses to bevacizumab plus chemotherapy, mainly based on paclitaxel, in the overall study population. Similarly, patients aged 36-50 years were also more likely to achieve an objective response in the HRPBC subgroup, while metastases at other sites than bone was the only factor associated with response in patients with TNBC patients.

The potential prognostic value of age remains uncertain but evidence from the literature points to a worse survival at older ages. Thus, a previous Spanish series reported significant differences in survival at two years according to age in patients with HER2-negative MBC, showing a significantly higher proportion of patients alive at 2 years among the younger population (<35 years and 36-50 years) (14). In our series, we identified an age between 36-50 years old as a predictive factor of clinical response. However, it is noteworthy that age at diagnosis does not seem to influence first-line treatment selection and the majority of patients older than 70 years (77%) received bevacizumab and paclitaxel combination therapy in our series.

Concerning the predictive and prognostic role of metastatic location, when disease is confined to bone and soft tissue, there is generally a more indolent course and survival is longer, while patients with brain, liver and lung metastases usually have a more aggressive condition and a worse outcome. In addition to metastasis location, the number of metastasis sites has been identified as an important prognostic factor in patients receiving first-line bevacizumab plus chemotherapy for HER-2 negative MBC, with ≥3 involved organs associated with a worse outcome (16). Our results suggest that patients with metastases at other sites than bone are more likely to achieve objective responses than those carrying bone metastases, who also had metastases in the liver (52%) and/or lung (39%), typically associated with a worse outcome. Accordingly, a previous study of patients with MBC showed that the median OS dropped from 2.6 years when bone was the only location of disease to one year if other organs were involved (19).

All findings together suggest that patients harboring clinical factors typically associated with more aggressive disease, such as multiple metastatic sites, with ≥3 organs involved, and metastases at other sites than bone, respond well to bevacizumab plus chemotherapy, mainly single-agent taxane. Therefore, this combination may offer an active first-line treatment option for patients usually associated with a clinically defined aggressive disease and poor outcome. Accordingly, a Spanish group of oncology experts has

recently recommended the addition of bevacizumab to standard chemotherapy as first-line treatment for those patients with clinically aggressive disease (20).

In addition, other factors previously associated with a poor prognosis in HER2-negative MBC, such as a DFI <12 months, prior therapy with neo (adjuvant) taxanes and TNBC (16), do not seem to influence the achievement of objective responses in our series. Accordingly, a meta-analysis of the E2100, AVADO and RIBBON-1 trials showed that the benefit of adding bevacizumab to chemotherapy was maintained across all patient subgroups regardless of DFI, prior adjuvant taxane use, the number of metastatic sites or visceral metastases (21). In addition, we found that patients with high-risk HRPBC, defined as those presenting with at least two risk factors (DFI <12 months, prior (neo) adjuvant taxanes and/or ≥3 metastatic sites or liver metastases), had a high response rate (>70%). The ATHENA study, which defined similar factors of poor prognosis, showed that patients with HRPBC and two or more risk factors had a particularly poor prognosis in terms of OS, even shorter than those patients with TNBC (16).

The findings from our analyses also suggest that bevacizumab plus chemotherapy treatment, mainly containing paclitaxel, is well-tolerated in patients with HER2-negative MBC. Bevacizumab-related toxicity was generally mild and manageable in our series. Only 2% of patients experienced grade 3 toxicities and no grade 4 toxicities were detected. In addition, no bevacizumab-related deaths were reported. Safety findings were consistent with phase III trials with bevacizumab and taxanes, with no new or unexpected signals detected (22).

The addition of bevacizumab to paclitaxel has shown no significant adverse effects that interfere with HRQL (23). The results from the E2100 study found that the addition of bevacizumab to paclitaxel was not associated with additional side effect burden from the patient perspective and was related with a greater reduction in breast cancer-specific concerns (24). Our series seems to reflect this trend, and it is interesting to note that FACT-B scores were similar between the overall population, where three-quarters of patients had HRPBC, and the subgroup of patients with TNBC. This finding may suggest that first-line treatment with bevacizumab and taxane-based chemotherapy may be adequate from the patient's perception and its impact on quality of life even in those patients with TNBC, usually associated with an adverse outcome.

In addition to the obvious limitations arising from the observational nature of this study, other limitations should be considered. Firstly, the cross-sectional design of the study does not allow a follow-up period to collect long-term survival data. Therefore, the prognostic value of the clinical factors related to the achievement of response could not be confirmed. Nevertheless, this was not the objective of the study but to reflect the factors that may influence treatment decision-making and identify clinical predictive factors of response. Finally, considering the lack of a follow-up period, the authors acknowledge that a certain degree of underreporting of mild adverse events could have occurred.

Despite the above limitations, to our knowledge, our series of nearly 300 patients with HER2-negative MBC is the largest series where the factors involved in the selection of bevacixumab and paclitaxel and clinical predictive factors for response have been identified in the context of routine oncology practice in Spain. Moreover, our findings, although modest, might provide a welcome addition to the scarce data on predictive factors for efficacy, and given the lack of response biomarkers, help identify patients with HER2-negative MBC who would derive most benefit from the addition of bevacizumab to single-agent taxane-based chemotherapy in clinical practice.

In summary, an ER-positive status appears to be the only independent factor associated with choosing this approach in HER2-negative MBC, although this finding may be influenced by the high proportion of patients with ER-positive MBC in this series. Therefore, we have not found a clear clinical profile for patients with MBC in using bevacizumab and single-agent taxane in clinical practice in Spain. However, our findings suggest that aggressiveness of disease rather than age and other biological factors seem to influence the selection of bevacizumab and paclitaxel in HER2-negative MBC. In addition, first-line bevacizumab plus chemotherapy, mainly based on paclitaxel, seem to be notably more effective in patients who harbor more aggressive disease, defined by large metastatic burden (≥3 sites) and metastases at other sites than the bone. Further studies are required to assess the prognostic implications of these clinical factors that may allow for identification of patients who could derive most benefit from first-line bevacizumab and single-agent taxane-based chemotherapy in patients with HER2-negative MBC in routine oncology practice.

Acknowledgements

The Authors would like to acknowledge the ONCOSUR Group for its contribution to the study and for sponsoring the study. We also would like to thank Roche Farma S.A. for supporting the study. Editorial and medical writing assistance was provided by Cristina Vidal and Antonio Torres, from Solutions S.L., and it was funded by Roche Farma S.A. We also would like to acknowledge the investigators and collaborators of AVALOX Study Group: Perezagua C., Hospital del Henares, Madrid, Spain; Echarri M.J., Hospital Severo Ochoa, Madrid, Spain; Enrech S., Hospital Universitario de Getafe, Madrid, Spain; Illaramendi J.J., Hospital de Navarra, Pamplona, Spain; Lara M.A., Hospital Infanta Leonor, Madrid; Méndez M., Hospital Universitario de Mostoles, Madrid; Murillo L., Hospital Universitario Lozano Blesa, Zaragoza, Spain; Bohn U., Hospital Dr. Negrin, Las Palmas de Gran Canaria, Spain; Díaz N., Hospital Universitario San Juan de Alicante, Alicante, Spain; Espinosa R., Hospital General de La Mancha, Ciudad

Real, Spain; García A., Clínica Quiron, Barcelona, Spain; Gómez Raposo C., Hospital Infanta Sofía, San Sebastián de los Reyes, Madrid; Hernando B., Hospital General Yagüe, Burgos, Spain; Jaén A., Complejo Hospitalario de Jaén, Jaén, Spain; Lobo F., Fundación Jimenez Díaz, Madrid, Spain; Ponce J.J., Hospital General de Alicante, Alicante, Spain; Puertas Álvarez J., Hospital Rio Hortega, Valladolid, Spain; Salinas P., Hospital Sanitas La Zarzuela, Madrid; Valero M., Hospital Infanta Luisa, Sevilla, Spain.

References

1 Brufsky AM, Hurvitz S, Perez E, Swamy R, Valero V, O'Neill V and Rugo HS: RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol *29*: 4286-4293, 2011.

2 Gray R, Bhattacharya S, Bowden C, Miller K and Comis RL: Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel *versus* paclitaxel in women with metastatic breast cancer. J Clin Oncol *27*: 4966-4972, 2009.

3 Miles DW, Chan A, Dirix LY, Cortes J, Pivot X, Tomczak P, Delozier T, Sohn JH, Provencher L, Puglisi F, Harbeck N, Steger GG, Schneeweiss A, Wardley AM, Chlistalla A and Romieu G: Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. J Clin Oncol *28*: 3239-3247, 2010.

4 Robert NJ, Dieras V, Glaspy J, Brufsky AM, Bondarenko I, Lipatov ON, Perez EA, Yardley DA, Chan SY, Zhou X, Phan SC and O'Shaughnessy J: RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol *29*: 1252-1260, 2011.

5 Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D and Davidson NE: Paclitaxel plus bevacizumab *versus* paclitaxel alone for metastatic breast cancer. N Engl J Med *357*: 2666-2676, 2007.

6 Belotti D, Vergani V, Drudis T, Borsotti P, Pitelli MR, Viale G, Giavazzi R and Taraboletti G: The microtubule-affecting drug paclitaxel has antiangiogenic activity. Clin Cancer Res *2*: 1843-1849, 1996.

7 Sweeney CJ, Miller KD, Sissons SE, Nozaki S, Heilman DK, Shen J and Sledge GW, Jr.: The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. Cancer Res *61*: 3369-3372, 2001.

8 Gligorov J, Doval D, Bines J, Alba E, Cortes P, Pierga JY, Gupta V, Costa R, Srock S, de DS, Freudensprung U and Mustacchi G: Maintenance capecitabine and bevacizumab *versus* bevacizumab alone after initial first-line bevacizumab and docetaxel for patients with HER2-negative metastatic breast cancer (IMELDA): a randomised, open-label, phase 3 trial. Lancet Oncol *15*: 1351-1360, 2014.

9 Burstein HJ: Bevacizumab for advanced breast cancer: all tied up with a RIBBON? J Clin Oncol *29*: 1232-1235, 2011.

10 Lang I, Brodowicz T, Ryvo L, Kahan Z, Greil R, Beslija S, Stemmer SM, Kaufman B, Zvirbule Z, Steger GG, Melichar B, Pienkowski T, Sirbu D, Messinger D and Zielinski C: Bevacizumab plus paclitaxel *versus* bevacizumab plus capecitabine as first-line treatment for HER2-negative metastatic breast cancer: interim efficacy results of the randomised, open-label, non-inferiority, phase 3 TURANDOT trial. Lancet Oncol *14*: 125-133, 2013.

11 Smith I, Pierga JY, Biganzoli L, Cortes-Funes H, Thomssen C, Saracchini S, Nisenbaum B, Pelaez I, Duenne AA and Pritchard KI: Final overall survival results and effect of prolonged (>/=1 year) first-line bevacizumab-containing therapy for metastatic breast cancer in the ATHENA trial. Breast Cancer Res Treat *130*: 133-143, 2011.

12 Dafni U, Grimani I, Xyrafas A, Eleftheraki AG and Fountzilas G: Fifteen-year trends in metastatic breast cancer survival in Greece. Breast Cancer Res Treat *119*: 621-631, 2010.

13 Largillier R, Ferrero JM, Doyen J, Barriere J, Namer M, Mari V, Courdi A, Hannoun-Levi JM, Ettore F, Birtwisle-Peyrottes I, Balu-Maestro C, Marcy PY, Raoust I, Lallement M and Chamorey E: Prognostic factors in 1,038 women with metastatic breast cancer. Ann Oncol *19*: 2012-2019, 2008.

14 Puente J, Lopez-Tarruella S, Ruiz A, Lluch A, Pastor M, Alba E, de la Haba J, Ramos M, Cirera L, Anton A, Llombart A, Plazaola A, Fernandez-Aramburo A, Sastre J, Diaz-Rubio E and Martin M: Practical prognostic index for patients with metastatic recurrent breast cancer: retrospective analysis of 2,322 patients from the GEICAM Spanish El Alamo Register. Breast Cancer Res Treat *122*: 591-600, 2010.

15 Regierer AC, Wolters R, Ufen MP, Weigel A, Novopashenny I, Kohne CH, Samonigg H, Eucker J, Possinger K and Wischnewsky MB: An internally and externally validated prognostic score for metastatic breast cancer: analysis of 2269 patients. Ann Oncol *25*: 633-638, 2014.

16 Llombart-Cussac A, Pivot X, Biganzoli L, Cortes-Funes H, Pritchard KI, Pierga JY, Smith I, Thomssen C, Srock S, Sampayo M and Cortes J: A prognostic factor index for overall survival in patients receiving first-line chemotherapy for HER2-negative advanced breast cancer: an analysis of the ATHENA trial. Breast *23*: 656-662, 2014.

17 Redondo A, Martinez V, Zamora P, Castelo B, Pinto A, Cruz P, Higuera O, Mendiola M, Hardisson D and Espinosa E: Continuation of bevacizumab and addition of hormone therapy following weekly paclitaxel therapy in HER2-negative metastatic breast cancer. Onco Targets Ther *7*: 2175-2181, 2014.

18 Dank M, Budi L, Piko B, Mangel L, Erfan J, Cseh J, Ruzsa A and Landherr L: First-line bevacizumab-paclitaxel in 220 patients with metastatic breast cancer: results from the AVAREG study. Anticancer Res *34*: 1275-1280, 2014.

19 James JJ, Evans AJ, Pinder SE, Gutteridge E, Cheung KL, Chan S and Robertson JF: Bone metastases from breast carcinoma: histopathological-radiological correlations and prognostic features. Br J Cancer *89*: 660-665, 2003.

20 Manso L, Moreno F, Márquez R, castelo B, Arcediano A, Arroyo M, Ballesteros A.I, Calvo I, Echarri M.J, Enrech S, Gómez A, González del Val R, López-MIranda E, Martín-Angulo M, Martínez-Jañez N, Olier C, and Zamora P. Use of bevacizumab as first-line treatment for metastatic breast cancer. Curr Oncol *22*: e51-60, 2015.

21 Miles DW, Dieras V, Cortes J, Duenne AA, Yi J and O'Shaughnessy J: First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Ann Oncol *24*: 2773-2780, 2013.

22 Cortes J, Calvo V, Ramirez-Merino N, O'Shaughnessy J, Brufsky A, Robert N, Vidal M, Munoz E, Perez J, Dawood S, Saura C, Di CS, Gonzalez-Martin A, Bellet M, Silva OE, Miles D, Llombart A and Baselga J: Adverse events risk associated with bevacizumab addition to breast cancer chemotherapy: a meta-analysis. Ann Oncol *23*: 1130-1137, 2012.

23 Croom KF and Dhillon S: Bevacizumab: a review of its use in combination with paclitaxel or capecitabine as first-line therapy for HER2-negative metastatic breast cancer. Drugs *71*: 2213-2229, 2011.

24 Cella D, Wang M, Wagner L and Miller K: Survival-adjusted health-related quality of life (HRQL) among patients with metastatic breast cancer receiving paclitaxel plus bevacizumab *versus* paclitaxel alone: results from Eastern Cooperative Oncology Group Study 2100 (E2100). Breast Cancer Res Treat *130*: 855-861, 2011.

Received August 7, 2015
Revised September 16, 2015
Accepted September 23, 2015