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ORIGINAL RESEARCH

Eribulin in combination with bevacizumab as second-line treatment for HER2-negative metastatic breast cancer progressing after first-line therapy with paclitaxel and bevacizumab: a multicenter, phase II, single arm trial (GIM11-BERGI)

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Background: We evaluated the efficacy and safety of the nontaxane microtubule dynamics inhibitor eribulin plus the humanized anti-VEGF monoclonal antibody bevacizumab in a novel second-line chemotherapy scheme in HER2-negative metastatic breast cancer (MBC) patients progressing after first-line paclitaxel and bevacizumab.

Patients and methods: This is a multicenter, single-arm, Simon's two-stage, phase II study. The primary endpoint was the overall response rate, considered as the sum of partial and complete response based on the best overall response rate (BORR). The secondary endpoints were progression-free survival (PFS), overall survival (OS), and clinical benefit rate.

Results: A total of 58 of the 61 patients enrolled in the study were evaluable for efficacy. The BORR was 24.6% (95% CI 14.5-37.3). The clinical benefit rate was 32.8% (95% CI 21.3-46.0). The median PFS was 6.2 months (95% CI 4.0-7.8), and median OS was 14.8 months (95% CI 12.6-22.8). Overall, adverse events (AEs) were clinically manageable and the most common AEs were fatigue, paresthesia, and neutropenia. Quality of life was well preserved in most patients.

Conclusions: The results of this study suggest that second-line therapy with bevacizumab in combination with eribulin has a meaningful clinical activity and may represent a potential therapeutic option for patients with HER2-negative MBC.

Key words: eribulin, bevacizumab, HER2-negative, metastatic breast cancer

BACKGROUND

Metastatic breast cancer (MBC) continues to be incurable. However, the development of novel therapeutic agents have considerably improved patient outcome[1] and have posed novel significant clinical challenges on the most effective long-term management for MBC. Systemic chemotherapy is appropriate for women whose disease is refractory to endocrine therapy, is hormone receptor negative (HR−), or is rapidly progressive with visceral involvement and severe organ dysfunction.[2] In the latter setting, combination chemotherapy is associated with a rapid response but greater toxicity and similar survival outcomes as the sequential use of single cytotoxic drugs.[2]

The humanized monoclonal antibody bevacizumab, which targets all isoforms of vascular endothelial growth factor A (VEGF-A), significantly improves progression-free survival (PFS) when combined with first- or second-line chemotherapy for HER2-negative locally recurrent breast cancer or MBC.[3-11] Interestingly, recent data from the phase III TANIA trial[3,4] show that in patients with HER2-negative breast cancer progressing on a first-line bevacizumab-containing therapy, further bevacizumab with second-line chemotherapy may still be an effective option as it

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significantly improved PFS versus chemotherapy alone. To date, bevacizumab is approved by different regulatory agencies across several countries as a standard anti-angiogenic drug for the treatment of first-line advanced breast cancer.

Eribulin, a synthetic analog of the marine macrolide halichondrin B, is a microtubule inhibitor with a unique mechanism of action. Indeed, eribulin inhibits microtubule stability by blocking microtubule growth without affecting microtubule shortening, thereby sequestering β-tubulin into nonfunctional aggregates and leading to the formation of abnormal mitotic spindles and ultimately apoptosis.[12,13] In the phase III EMBRACE trial, eribulin significantly improved overall survival (OS) versus the physician's treatment choice in patients with anthracycline- and taxane-pretreated locally recurrent breast cancer or MBC[14] and it is currently approved for clinical use in many countries worldwide.

Preclinical studies have also shown that, in addition to the primary anticancer mechanism associated with classical antimitotic effects, eribulin triggers a shift from mesenchymal to epithelial phenotypes via reversal of the epithelial—mesenchymal transition state to the mesenchymal—epithelial transition state[15,16] and exerts antivascular activity inducing tumor vascular remodeling and tumor phenotypic changes that reduce the abnormality of the tumor microenvironment, thereby reducing drug resistance and metastasis-promoting activity.[16] These findings may provide a plausible scientific basis for the relevant clinical benefits observed in patients treated with eribulin.

Considering the clinical efficacy of eribulin and its peculiar mechanism of action we hypothesized that combining this drug with bevacizumab may further improve its activity in patients receiving second-line treatment for MBC. The Gruppo Italiano Mammella (GIM) 11-BERGI is a phase II, multicenter, single-arm trial designed to evaluate the activity and safety of eribulin in combination with bevacizumab as second-line treatment for HER2-negative MBC progressing after first-line therapy with bevacizumab and paclitaxel.

METHODS

Study design and patients

GIM11-BERGI is a phase II, multicenter, single-arm study following a Simon's two-stage optimal design.[17] All patients enrolled in the study received eribulin 1.23 mg/m^2 on days 1 and 8 every 3 weeks intravenously combined with bevacizumab 15 mg/kg every 3 weeks or 10 mg/kg every 2 weeks intravenously, depending on the patient's or physician's preference (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2021.100054). Study treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal. If patients discontinued bevacizumab or eribulin for any reason before disease progression, the other treatment was continued as monotherapy until disease progression, unacceptable toxicity, or patient withdrawal. In the event of toxicity, neither dose reduction nor modification of bevacizumab was allowed, but bevacizumab was to be interrupted or permanently discontinued in case of hypertension, proteinuria, thrombosis, embolism, hemorrhage, congestive heart failure, or wound-healing complications.

Eligible women were those aged 18 years or older who had an HER2-negative breast cancer with documented progression of disease after or during first-line chemotherapy-based treatment with paclitaxel combined with bevacizumab for metastatic disease. Patients must have had a measurable disease as per RECIST version 1.1 criteria[18] according to investigator assessment. Patients with HR+ disease may have been treated with one or more lines of endocrine-based therapy before receiving paclitaxel or bevacizumab. In addition, as part of their first-line maintenance treatment, patients may have received bevacizumab monotherapy, bevacizumab plus endocrine treatment, or no treatment (for $\leq$6 weeks from the last bevacizumab administration).

All eligible patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and an estimated life expectancy of $\geq$12 weeks. Patients were ineligible if they had previously received (i) first-line anti-angiogenic therapy (e.g. tyrosine kinase inhibitors or anti-VEGFs) other than bevacizumab for the first-line treatment of MBC; (ii) if they had exclusively received endocrine therapy combined with bevacizumab for the first-line treatment of MBC; (iii) positive or unknown HER2 status; (iv) inadequately controlled hypertension (defined as systolic blood pressure $>$150 mmHg and/or diastolic blood pressure $>$100 mmHg) while receiving antihypertensive medication; (v) a serious nonhealing wound, active ulcer, or untreated bone fracture; (vi) New York Heart Association Class II or greater congestive heart failure; (vii) pulmonary lymphangitis or pulmonary dysfunction requiring active treatment, including the use of oxygen; (viii) pre-existing grade $\geq$2 neuropathy; (ix) serious active infection requiring intravenous antibiotics and/or hospitalization at study entry; (x) history of hypertensive crisis, hypertensive encephalopathy, nephrotic syndrome, bleeding diathesis, clinically relevant coagulopathy, or grade 3 or 4 venous thromboembolism; and lastly (xi) a history of myocardial infarction, unstable angina, stroke or transient ischemic attack, significant vascular disease, gastrointestinal perforation, abdominal fistula, intra-abdominal abscess, or active gastrointestinal bleeding within 6 months preceding study treatment. Patients were also ineligible if they had inadequate hematological function, coagulation parameters, hepatic function, or renal function.

Statistical analyses

A Simon's two-stage optimal design[17] was adopted to define the total number of patients required for this phase II study. An overall clinical response rate of 25% as the target activity level and 12% as the lowest response rate of interest were considered. The study was designed to have 80% power to accept the hypothesis and a 5% significance to reject the hypothesis. Therefore, the probability of

accepting a therapy with a real response rate below 12% and the risk of rejecting a treatment with a response rate 25% would be, in both cases, <5%.

At the first stage, and in order to proceed to stage II, 19 patients were monitored for a minimum of 18 weeks (corresponding to six cycles of study treatment). If there were fewer than three responses in the initial 19 patients, the study would have been stopped. Otherwise, 42 additional patients were planned to be accrued for a total of 61 patients. At the second stage, at least 12 objective responses in the 61 patients enrolled were required for this regimen to be deemed worthy of further investigation. At the second stage, patients were followed-up for a minimum of 18 weeks (corresponding to six cycles of study treatment).

Outcomes

The primary study endpoint was the overall response rate (ORR) based on the best overall response as defined by RECIST criteria version 1.1 (without confirmation). The best overall response rate (BORR) was estimated by the ratio of patients who had a complete response (CR) or partial response (PR) and the number of individuals in the intention-to-treat (ITT) population. The number of individuals with at least one postbaseline activity assessment was used as denominator in the per-protocol (PP) analysis in supportive analysis. The secondary efficacy variables were second-line PFS, defined as the time from study enrollment to disease progression or death while on second-line treatment, and OS from enrollment to death from any cause; clinical benefit rate estimated by the ratio of patients who had a CR, PR, or stable disease (SD) for ≥24 weeks; the number of individuals in the ITT population; duration of response; safety and tolerability; and quality of life (QoL). Second-line PFS and OS were estimated using the Kaplan—Meier method. QoL was analyzed using a linear mixed model (random intercept only with time in months treated as continuous predictor) using all the available QoL assessments for each patient in the ITT population.

Clinical examinations were performed as clinically indicated before starting each cycle. Safety was assessed using the Common Terminology Criteria for Adverse Events (CTCAE; version 4.0). All grade 3-5 adverse events (AEs) and serious AEs (any grade) were recorded at every study visit. All laboratory assessments were performed locally according to local standards. All patients remained in the study with continued follow-up for OS, except those who withdrew consent, were lost to follow-up, or were removed from the study by the investigator (e.g. because of another illness, an AE, treatment failure after a prescribed procedure, protocol violation, cure, or due to administrative reasons). Patient-reported outcomes were assessed with the Functional Assessment of Cancer Therapy—Breast questionnaire (FACT-B).

The study was registered 26 June 2014 at ClinicalTrials.gov NCT02175446; https://clinicaltrials.gov/ct2/show/NCT02175446. This research has been conducted in accordance with the Declaration of Helsinki. The study protocol and all modifications were approved by independent ethics committees at each participating site. All patients signed the informed consent form.

RESULTS

Between November 2014 and May 2016, eligible patients were enrolled at 16 sites in Italy. Of the 67 patients screened, 61 (91.0%) were enrolled in the study (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2021.100054). A total of 57 patients had discontinued therapy early (43 due to disease progression, 9 due to AEs, 1 due to investigator's decision, and 4 had withdrawn consent). The remaining four patients continued to undergo the study treatment. All patients of the ITT population were considered for the safety analysis. Three patients (4.5%) were excluded from the per-protocol population because they had no postbaseline efficacy assessment (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2021.100054). The patients' baseline characteristics are reported in Table 1. Median age was 56.1 years; 50 patients (83.3%) had hormonal receptor [estrogen receptor (ER) and/or progesterone receptor] positive disease, and 10 patients (16.7%) had triple-negative breast cancer. All patients had previously received treatment with bevacizumab plus paclitaxel for a median duration of treatment of 9.77 months (range 2.43-34.20 months).

Activity

In the first stage, 3 patients of the 19 originally enrolled achieved an objective response. The threshold for the first

Table 1. Patients' characteristics

Characteristics	ITT population ($N = 61$)
Age, mean ± SD (range)	56.1 ± 11 (34.1-78)
Hormonal receptor status, *n* (%)	
ER+ and/or PR+	50 (83.3)
ER− and PR−	10 (16.7)
Missing	1 (1.6)
ECOG performance status, *n* (%)	
0	56 (91.8)
1	5 (8.2)
2	0 (0)
Number of metastatic sites, *n* (%)	
<3	32 (52.5)
≥3	29 (47.5)
Metastatic sites, *n* (%)	
Liver	43 (70.5)
Lung	19 (31.1)
Brain	3 (4.9)
Bone	32 (52.5)
Skin	3 (4.9)
Other	34 (55.7)
Site of disease, *n* (%)	
Visceral	51 (83.6)
Nonvisceral	10 (16.4)
Prior endocrine therapy for advanced disease, *n* (%)	
Yes	26 (42.6)
No	35 (57.4)

ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ITT, intention to treat; PR, progesterone receptor.

Table 2. Summary of treatment best responses

Outcome	ITT population ($N = 61$), n (%)	PP population[a,b] ($N = 58$), n (%)	ER+ ($N = 44$), n (%)	ER− ($N = 13$), n (%)	ER+ versus ER− P value
Best overall response rate	15 (24.6)	15 (25.9)	11 (25.0)	4 (30.8)	0.727
Complete response	1 (1.6)	1 (1.7)	0 (0)	1 (7.7)	0.443
Partial response	14 (23.0)	14 (17.2)	11 (25)	3 (23.1)	
Stable disease	26 (42.6)	26 (44.8)	20 (45.5)	6 (46.2)	
Progressive disease	17 (27.9)	17 (29.3)	13 (29.5)	3 (23.1)	

ER, estrogen receptor; ITT, intention-to-treat; PP, per-protocol.
[a] Three patients without postbaseline efficacy assessments were excluded.
[b] 95% CI 15.3% to 39.0%.

stage of Simon's two-stage design was reached and the trial continued to full accrual. Overall, the median duration of eribulin and bevacizumab treatment was 9.8 months (range 2.3-34.2 months). Objective responses were recorded in 58 of the 61 patients with measurable disease and at least one postbaseline tumor assessment. Among the 61 patients of the ITT population, 1 patient (1.6%) had a CR, 14 patients (23.0%) had a PR, and 26 patients (42.6%) had best response of SD (Table 2). The BORR was 24.6% (95% CI 14.5% to 37.3%). Patients with ER+ and ER− MBC achieved a similar rate of objective responses (Table 2). Twenty patients had a CR, PR, or SD response that persisted for >24 weeks. The clinical benefit rate was 32.8% (95% CI 21.3% to 46.0%). In the subset of patients with objective responses ($n = 15$), the median duration of response was 6.2 months (range 2.2 to 29.4 months).

The median PFS was 6.2 months (95% CI 4.0-7.8; Figure 1A). No differences in median PFS between the ER+ and ER− subgroups were observed (Figure 1B). During a median follow-up of 42.5 months (range 2-62), a total of 43 deaths were observed. Median OS was equal to 14.8 months (95% CI 12.6-22.8). Figure 2 shows the Kaplan–Meier estimate of the survival function. QoL was well preserved in most patients. In the efficacy analysis population, based on the longitudinal trajectories of FACT-B total score, linear mixed model analysis showed a statistically significant, but clinically irrelevant, reduction of QoL, with a 0.2-point reduction for every month of follow-up (95% CI −0.28 to −0.06, $P = 0.004$).

Safety

Overall, 59% of patients experienced a treatment-related AE. The most common AEs were fatigue, paresthesia, mucositis oral, and fever (Table 3). Grade 3 or worse AEs were observed in 23 of 61 patients (37.8%), mainly owing to grade 3 hypertension (7%), neutropenia (7%), and febrile neutropenia (7%). AEs resulted in the death of two patients (3.3%) during treatment. In one case, death was not associated with any CTCAE term and was not related to the study drugs. In the other patient, death was associated with three concomitant serious AEs: (i) hepatic failure, (ii) hypertransaminasemia, and (iii) thrombocytopenia. All these concomitant serious AEs were probably related to eribulin and were observed 177 days after treatment onset. Almost 50% of drug-related AEs were related to eribulin, 7.7% to bevacizumab, and 11.8% to both the study drugs. Treatment for AEs led to dose reductions in 15 patients (24.6%), and were most often due to neutropenia and peripheral neuropathy. Four patients (6.6%) discontinued eribulin treatment due to oral mucositis (2 patients), proteinuria (1 patient), and a thromboembolic event (1 patient).

DISCUSSION

The GIM11-BERGI trial was designed to explore the activity of second-line bevacizumab in combination with a novel and effective chemotherapy agent, eribulin, in patients with HER2-negative MBC progressing after a first-line treatment with bevacizumab and paclitaxel. The results of our 'two-step' Simon phase II trial show that the combination of eribulin and bevacizumab is a safe and active second-line treatment and that continuing bevacizumab may be a reasonable therapeutic option, further confirming and expanding the results of the TANIA[3,4] and RIBBON-2[10] trials in which the combination of bevacizumab with second-line chemotherapy improved PFS and ORR.

The concept of treatment beyond progression is not novel in locoregional or metastatic cancer.[19-21] However, recent updated results from the TANIA study failed to show a significant improvement in third-line PFS or OS (secondary endpoints) with longer continuation of bevacizumab.[3] Different study design and tumor biology, crossover effects, and type and number of further line of therapies received may account for the divergent outcomes observed among the studies.

Eribulin is currently a standard chemotherapy regimen for anthracycline- and taxane-pretreated MBC. In the phase III EMBRACE trial, eribulin induced a significant and clinically meaningful improvement in OS compared with the physician's choice of treatment in women with heavily MBC (hazard ratio 0.81; 95% CI 0.66-0.99; $P = 0.041$).[14] Eribulin also induced a numerical but not significant survival benefit compared with capecitabine in an earlier phase III trial.[22] Despite these positive results, the response rate and median PFS observed in patients treated with eribulin in these two trials were modest (11%-12% and 3.7-4.1 months, respectively).

Our trial is the first to evaluate the efficacy and safety of the combination of eribulin and bevacizumab. Indeed, in the TANIA and RIBBON-2 studies, bevacizumab was

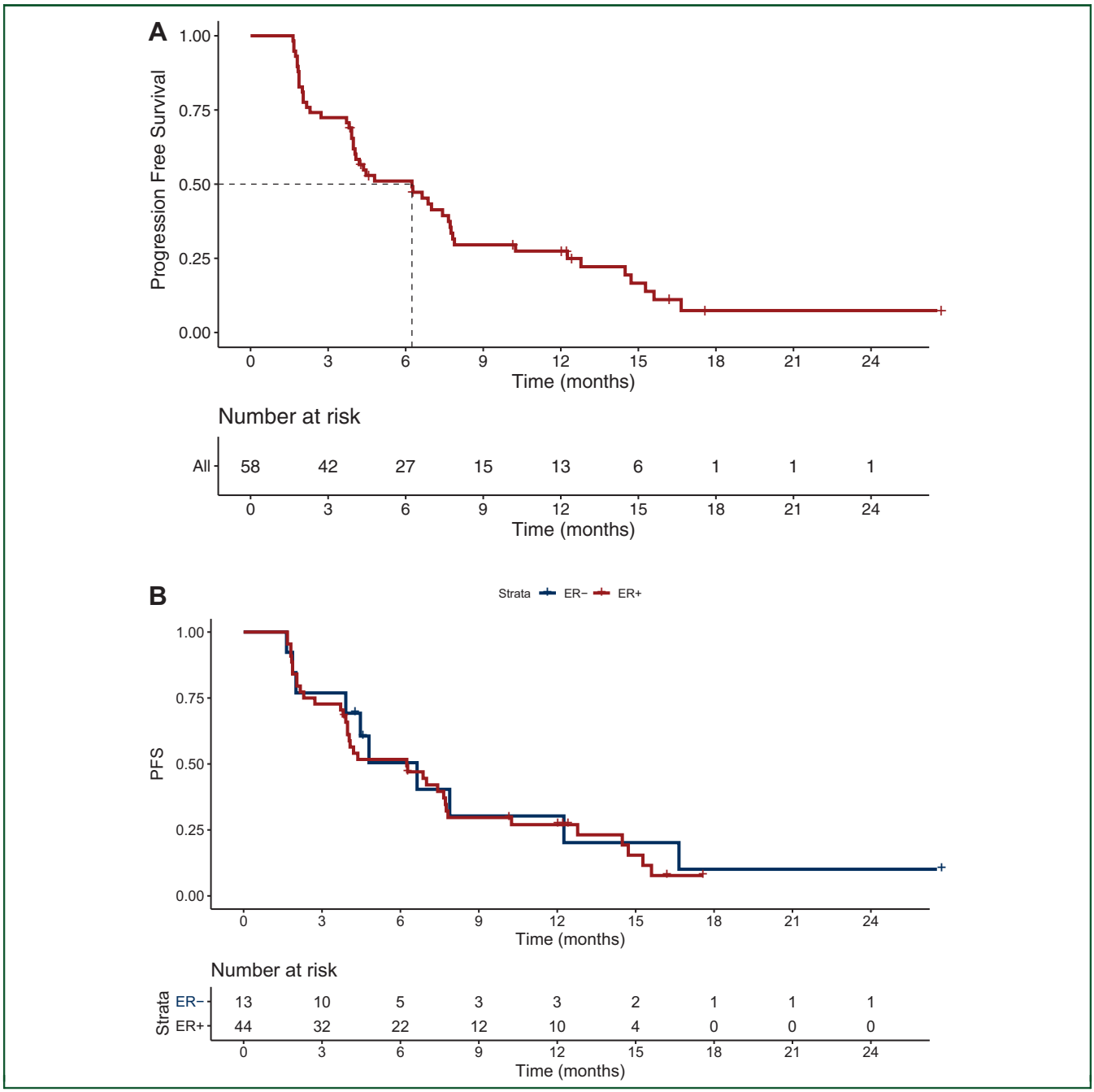

Figure 1. Kaplan–Meier curves for progression-free survival (PFS) (A) in all patients with at least one postbaseline efficacy assessment and (B) in the ER+ and ER− subgroups.
ER, estrogen receptor.

administered in combination with capecitabine, taxanes, and anthracyclines, but not eribulin.[3,4,10] Results from our study show that bevacizumab further improves eribulin activity and, with a median PFS of 6.3 months (95% CI 4.1-7.8 months) and ORR of 24.6%, are in line with the median PFS of 6.3 months (95% CI 0.61-0.93) and an ORR of 21% reported in the TANIA trial, and are similar to those observed in the RIBBON-2 trial [median PFS 7.2 months (95% CI 0.64-0.93) and ORR 39.5%], albeit with the caveat of cross-trial comparisons.

The combination of bevacizumab with eribulin did not modify the safety profiles of either agent and did not cause fatal toxicities. The safety profile of bevacizumab is coherent with that observed in previous studies: hypertension was reported in 17% of patients (9/55) and proteinuria in 17% of cases (9/55), while there was only one case of grade IV pulmonary arterial thromboembolism. No new side-effects were observed with long-term bevacizumab treatment. Finally, in line with this favorable toxicity profile, the overall QoL was well preserved in most patients enrolled in the study.

The lack of OS advantage in both first- and second-line setting and the high cost have contributed to a cost-effectiveness controversy on bevacizumab and brought

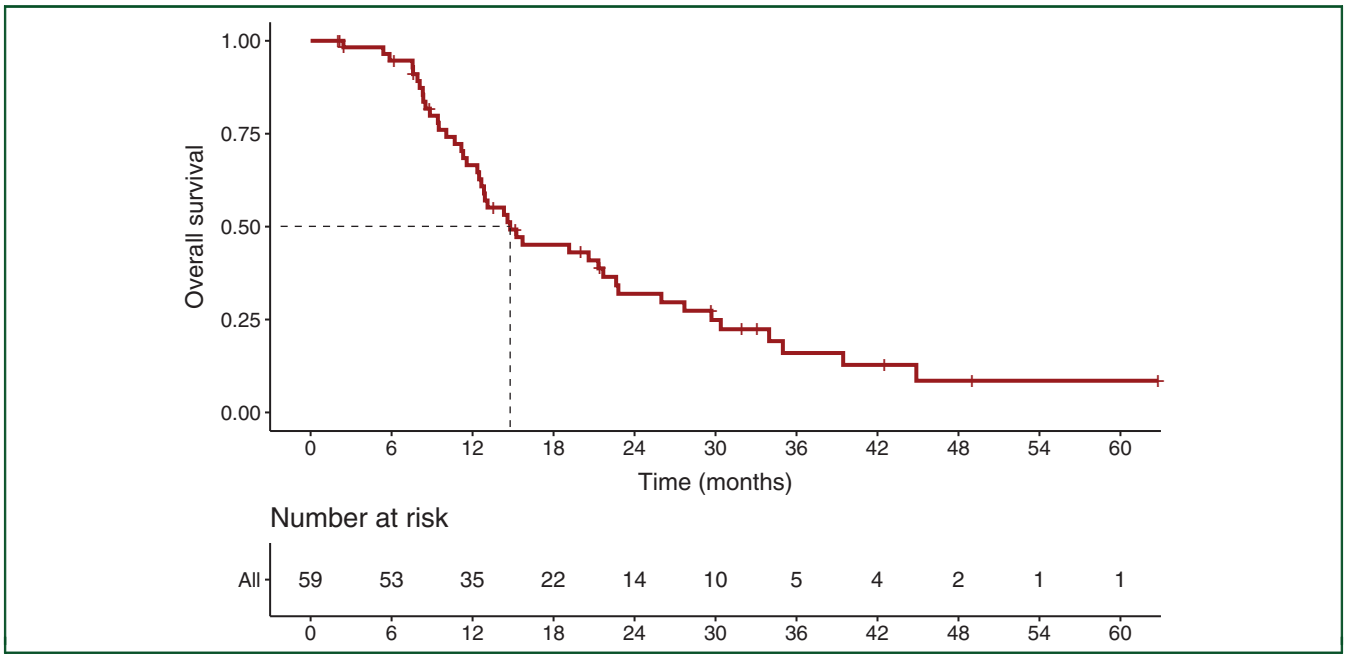

Figure 2. **Kaplan–Meier curves for overall survival (OS).**

Table 3. **List of adverse events occurring at any grade in >5% of patients or grade ≥3 in >2% of patients**

Adverse events	All grades, *n* (%)	Grade 1-2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Grade 5, *n* (%)
Fatigue	32 (52)	29 (46)	3 (5)	0 (0)	0 (0)
Paresthesia	21 (34)	18 (29)	3 (5)	0 (0)	0 (0)
Mucositis oral	18 (29)	15 (25)	3 (5)	0 (0)	0 (0)
Fever	17 (28)	16 (26)	1 (2)	0 (0)	0 (0)
Alopecia	10 (16)	8 (13)	2 (3)	0 (0)	0 (0)
Nausea	17 (28)	17 (28)	0 (0)	0 (0)	0 (0)
Neutropenia	20 (32)	16 (26)	4 (7)	0 (0)	0 (0)
Constipation	10 (16)	9 (15)	1 (2)	0 (0)	0 (0)
Increased alanine aminotransferase/aspartate aminotransferase	10 (16)	9 (15)	0 (0)	1 (2)	0 (0)
Hypertension	9 (15)	5 (8)	4 (7)	0 (0)	0 (0)
Diarrhea	6 (10)	6 (10)	0 (0)	0 (0)	0 (0)
Headache	8 (13)	7 (11)	1 (2)	0 (0)	0 (0)
Peripheral sensory neuropathy	9 (15)	9 (15)	0 (0)	0 (0)	0 (0)
Febrile neutropenia	5 (8)	1 (2)	4 (7)	0 (0)	0 (0)
Cough	4 (7)	4 (7)	0 (0)	0 (0)	0 (0)
Proteinuria	8 (13)	8 (13)	0 (0)	0 (0)	0 (0)
Thrombocytopenia	7 (11)	6 (10)	0 (0)	0 (0)	1 (2)
Abdominal pain	6 (10)	4 (7)	2 (3)	0 (0)	0 (0)
Thromboembolic event	3 (5)	1 (2)	0 (0)	2 (3)	0 (0)

into question its use in MBC. In November 2011, the United States Food and Drug Administration revoked its indication for bevacizumab for breast cancer patients. By contrast, European Medicines Association confirmed the combination of bevacizumab and paclitaxel as a first-line treatment option for patients with HER2-negative MBC. Notably, the recent introduction into clinical practice of less costly bevacizumab biosimilars may result in a wider use of this agent, eventually in different lines of therapy.

We acknowledge that, similar to the TANIA trial, our study may have a selection bias, because we enrolled patients known to well tolerate bevacizumab. However, hypertension and proteinuria have also been reported in patients after long-term treatment (>1 year) with bevacizumab, despite the absence of these toxicities in earlier administrations.[23] In our experience, monitoring and management of these side-effects could prevent treatment discontinuation or delay, and their progression. We also acknowledge that in our study patients with hormonal receptor-positive breast cancer did not receive CDK4/6 inhibitors in combination with endocrine therapy before study enrollment. Nowadays, CDK4/6 inhibitors are standard first- and second-line treatments for HR+/HER2− MBC[2]; however, these agents were not available in clinical practice at the time of trial enrollment. Despite this limitation, our findings may still be clinically relevant, especially for patients with HR+/HER2− MBC who are candidates for chemotherapy.

The encouraging results of our trial suggest that the combination of bevacizumab and eribulin may provide a valid treatment option after failure of first-line chemotherapy and extend the finding that continuing bevacizumab beyond disease progression in association with eribulin could be a valid and well-tolerated treatment choice for HER2− MBC patients progressing after first-line bevacizumab with chemotherapy. Further comparative studies to verify the clinical benefit of this combination are needed.

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DISCLOSURE

CDA is a consultant/advisory board member for Novartis, Eli Lilly, and Pfizer. FP has received travel, accommodations, expenses supported by Takeda, Ely Lilly, and received honoraria from Merck Sharp & Dohme, Ely Lilly, and Novartis outside the submitted work. AM is a consultant/advisory board member for EISAI, Novartis, Astra Zeneca, Teva, Pfizer, Celgene; has received travel accommodations supported by Eisai, Celgene, Novartis, and Ipsen. LDM is a consultant/advisory board member for Roche, Novartis, Celgene, Pfizer, MSD, Genomic Health, Ipsen, Takeda, Eli Lilly, Seattle Genetics, Pierre Fabre, and Eisai. MG, GA, and SDP have declared honoraria from Roche, Pfizer, Astra-Zeneca, Novartis, Celgene, Eli Lilly, Amgen, and Eisai. MDL has declared consulting fees from Pfizer, Novartis, Eli Lilly, Roche, Eisai, and Celgene. The remaining authors have declared no conflicts of interest.

DATA SHARING

The data sets obtained and/or analyzed during this study are available from the corresponding author on reasonable request.

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