HHS Public Access

Author manuscript

*Eur J Cancer*. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:

*Eur J Cancer*. 2019 August ; 117: 91–98. doi:10.1016/j.ejca.2019.06.002.

# Evaluating the Addition of Bevacizumab to Endocrine Therapy as first-line treatment for Hormone-receptor positive metastatic breast cancer: A Pooled-analysis from the LEA (GEICAM/2006-11_GBG51) and CALGB 40503 (Alliance) trials.

**M. Martín**[1], **S. Loibl**[2], **T. Hyslop**[3], **J. De la Haba-Rodríguez**[4], **B. Aktas**[5], **C. T. Cirrincione**[3], **K. Mehta**[2], **W. T. Barry**[6], **S. Morales**[7], **L. A. Carey**[8], **J. A. Garcia-Saenz**[9], **A. Partridge**[10], **N. Martinez-Jañez**[11], **O. Hahn**[12], **E. Winer**[10], **A. Guerrero-Zotano**[13], **C. Hudis**[14], **M. Casas**[15], **C. Rodriguez-Martin**[15], **J. Furlanetto**[2], **E. Carrasco**[15], **M. N. Dickler**[16] **GEICAM Spanish Breast Cancer Group GBG (German Breast Group) Alliance for Clinical Trials in Oncology (Alliance)**

[1]Medical Oncology. Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense, Madrid. Centro de Investigación Biomédica en Red de Oncología, CIBERONC-ISCIII. GEICAM Spanish Breast Cancer Group, Spain;

[2]GBG (German Breast Group), Neu-Isenburg, Germany;

[3]Alliance Statistics and Data Center, Duke University, Durham, NC, USA;

[4]Oncology Department and Research Unit, Instituto Maimónides de Investigación Biomédica de Córdoba, Hospital Reina Sofía, Universidad de Córdoba, Spain. Centro de Investigación Biomédica en Red de Oncología. CIBERONC-ISCIII. GEICAM Spanish Breast Cancer Group;

[5]University Women`s Hospital Leipzig, Leipzig, Germany;

[6]Alliance Statistics and Data Center, Dana-Farber/Partners Cancer Care, Boston, MA, USA;

[7]Medical Oncology. Hospital Arnau de Vilanova de Lérida, Spain. GEICAM Spanish Breast Cancer Group;

[8]University of North Carolina, Chapel Hill, NC, USA;

**CORRESPONDENCE:** Miguel Martín, M.D., Ph.D., Medical Oncology Department, Instituto de Investigación Sanitaria Gregorio Marañon, CIBERONC, GEICAM Spanish Breast Cancer Group, Madrid, Spain, Universidad Complutense de Madrid, C/ Dr. Esquerdo 46, Madrid 28009, Spain. mmartín@geicam.org, Telephone: +34 91 586 8115.



Conflict of interest statement

All remaining authors have declared no conflicts of interest.

I confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us. I further confirm that any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies. Me, as the Corresponding Author I am the sole contact for the Editorial process and the responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

**Trials registration**: ClinicalTrial.Gov and .

[9]Medical Oncology. Instituto de Investigación Sanitaria del Hospital Clinico San Carlos (IdISSC), Madrid. Centro de Investigación Biomédica en Red de Oncología, CIBERONC-ISCIII. GEICAM Spanish Breast Cancer Group;

[10]Dana-Farber/Partners CancerCare, Boston, MA, USA;

[11]Medical Oncology. Universitary Hospital Ramon y Cajal, Madrid, Spain. GEICAM, Spanish Breast Cancer Group;

[12]Alliance Protocol Operations Office, University of Chicago, Chicago, IL, USA;

[13]Medical Oncology. Valencian Institute of Oncology, Valencia, Spain. GEICAM Spanish Breast Cancer Group;

[14]American Society of Clinical Oncology (ASCO), Alexandria, VA, USA;

[15]GEICAM Spanish Breast Cancer Group, Madrid, Spain;

[16]Eli Lilly and Co. Indianapolis, IN, USA;

## Abstract

**Background:** Randomized trials comparing the efficacy of standard endocrine therapy (ET) versus experimental ET+bevacizumab (Bev) in 1st line hormone-receptor positive metastatic breast cancer (MBC) patients have thus far shown conflicting results.

**Patients and Methods:** We pooled data from two similar Phase III randomized trials of ET +/− Bev (LEA and CALGB 40503) to increase precision in estimating treatment effect. Primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS), objective response rate (ORR), clinical benefit rate (CBR) and safety. Exploratory analyses were performed within subgroups defined by patients with recurrent disease, *de novo* disease, prior endocrine sensitivity or resistance, and reported grades 3–4 hypertension and proteinuria.

**Results:** The pooled sample consisted of 749 patients randomized to ET or ET+Bev. Median PFS was 14.3 months for ET versus 19 months for ET+Bev (unadjusted HR 0.77; 95% CI 0.66–0.91; p<0.01). ORR and CBR with ET and ET+Bev were 40 versus 61% (p<0.01) and 64 versus 77% (p<0.01), respectively. There was no difference in OS (HR 0.96; 95% CI 0.77–1.18; p=0.68). PFS was superior for ET+Bev for endocrine-sensitive patients (HR 0.68; 95% CI 0.53–0.89; p=0.004). Grade 3–4 hypertension (2.2 versus 20.1%), proteinuria (0 versus 9.3%), cardiovascular (0.5 versus 4.2%) and liver events (0 versus 2.9%) were significantly higher for ET+Bev (all p<0.01). Hypertension and proteinuria were not predictors of efficacy (interaction test p=0.33).

**Conclusion:** The addition of Bev to ET increased PFS overall and in endocrine-sensitive patients but not OS at the expense of significant additional toxicity.

### Keywords

advanced breast cancer; endocrine therapy; bevacizumab; pooled-analysis

## INTRODUCTION

Several preclinical and clinical studies have suggested that neoangiogenesis in general and high levels of VEGF in particular are linked to the development of resistance to hormonal therapy in breast cancer[1, 2]. These studies provide a rationale for the combination of endocrine therapy (ET) and antiangiogenic drugs in Metastatic Breast Cancer (MBC).

Two phase III randomized trials (LEA and Cancer and Leukemia Group B [CALGB] 40503) have compared standard ET with ET plus Bevacizumab (Bev)[3, 4], with conflicting results. We performed a pooled analysis with the aim to further understand the role of Bev in combination with ET in MBC and to identify subpopulations of patients that might benefit from this treatment strategy.

## MATERIAL AND METHODS

### Study design

This is a post-hoc analysis of individual data pooled from two randomized, multicenter, open-label, similarly designed phase III studies (LEA: GEICAM/2006–11_GBG_51 and CALGB 40503)[3, 4]. Each study was designed independently to compare the efficacy, in terms of progression-free survival (PFS), of ET alone versus ET+Bev as first line treatment for postmenopausal (or ovarian suppressed) MBC patients who were candidates for ET. Randomization was equally weighted and stratified as follows: in the LEA study by previous adjuvant ET with aromatase inhibitors [AI] (yes/no), number of involved sites (single/multiple), presence of measurable disease (yes/no) and participating country (Spain/Germany); and in the CALBG study by presence of measurable disease (yes/no) and disease-free interval from diagnosis to first recurrence/progression (<24 months/>24 months).

Both studies were conducted in compliance with the International Conference on Harmonization Good Clinical Consolidated Guideline and were approved by independent ethics committees and Health Authorities. All patients provided written informed consent to participate.

In our pooled analysis, the primary objective was to compare PFS between the two arms in the total sample. Secondary objectives included comparing overall survival (OS), time to treatment failure (TTF), overall response rate (ORR), clinical benefit rate (CBR), response duration (RD), and safety. Exploratory objectives included testing for a treatment effect on all the efficacy endpoints above within the following subgroups: recurrent disease, *de novo* disease, endocrine-sensitivity and endocrine-resistance (defined as +/− 24 months without recurrence under ET in the adjuvant setting). We also wanted to determine whether grade 3–4 hypertension and/or proteinuria correlated with PFS, OS and ORR in the total sample and by treatment arm.

### Patients

Eligible patients were women at least 18 years old, postmenopausal (plus premenopausal with ovarian suppression in the CALGB study), with diagnosis of unresectable, locally

advanced or metastatic breast cancer, hormone-receptor positive (estrogen-receptor and/or progesterone-receptor >1%) and human epidermal growth factor receptor 2 (HER2) negative (or any HER2 status in the CALGB study). Eastern Cooperative Oncology Group performance status (ECOG PS) < 2 was required.

Exclusion criteria included prior therapy for metastatic disease (LEA study), ET or more than one line of prior chemotherapy for metastatic disease (CALGB study); rapid progressive disease requiring chemotherapy; central nervous system metastasis; uncontrolled arterial hypertension or clinically significant cardiovascular disease; history or evidence of hemorrhagic diathesis or coagulopathy with bleeding risk; major surgery within 28 days or minor surgery within 7 days of randomization; non-healing wounds; inadequate bone marrow, hepatic or renal functions; any other serious concomitant disorder; history of malignancy other than cervical or non-melanoma skin cancer adequately treated, or other cancers treated less than five years before study entry (LEA study) or with more than 30% risk of relapse (CALGB study).

## Treatment

Standard ET was study-dependent and could be letrozole (2.5 mg/day) in both trials, fulvestrant (250 mg every 4 weeks) only in the LEA study or tamoxifen (20 mg/day) only in the CALGB study. Bev was administered as 15 mg/kg body weight every 3 weeks. Treatment continued until disease progression, unacceptable toxicity or withdrawn consent. Premenopausal patients had to undergo ovarian suppression either using luteinizing hormone-releasing hormone agonists or by oophorectomy.

## Study procedures

Baseline assessments were performed within 28 days before study entry. These included chest and abdominal computed tomography (CT-scan), magnetic resonance or PET/CT-scan with intravenous contrast. Bone assessment (with bone-scan or PET/CT-scan) was mandatory in the CALGB study but was performed only if clinical suspicion in the LEA study. Hematology, biochemistry and urinalysis with proteinuria assessment (dip stick) were performed within 14 days before study inclusion.

Tumor assessments were performed, with the same method used at baseline, every 12 weeks until disease progression in the LEA study, and every 3 cycles until cycle 18 and then every 4 cycles in the CALGB study. After confirmed disease progression, patients were followed for survival.

Adverse events were collected during the study treatment until 30 days of last dose of study drug. Serious adverse events related to study therapies were followed until resolution.

## Statistical Analysis

Efficacy and safety analyses included all randomized patients who received at least one dose of study medication.

Kaplan-Meier method was used to estimate PFS, OS, TTF, and RD. The comparison of those endpoints between arms was performed using the logrank test. Cox regression models

were used to estimate unadjusted and adjusted hazard ratios and their 95% confidence intervals.

Multivariate analysis was carried out to assess the influence of the selected covariables (treatment arm, age, ECOG PS, disease-free interval, prior chemotherapy, prior ET, prior endocrine-sensitivity, type of ET, number of involved sites, sites of metastasis and disease measurability) on PFS. Robust sandwich level estimates based on a marginal model approach were utilized to correct standard errors in the Cox model, based on the methods of Lei, Win, and Weissfeld[5].

Logistic regression models were used to test the association of the above covariables with ORR and CBR, and to estimate odds ratios and their 95% confidence intervals.

Pearson $\chi^2$ or Fisher exact tests were used to assess the comparability of the two treatment arms in the incidence of relevant adverse events.

In order to ascertain whether the effect of grade 3–4 hypertension, proteinuria or both on efficacy differed by arm, we constructed Cox regression (for PFS and OS) and logistic regression (for ORR) models; these included an interaction term defined as the cross-product of the occurrence of the toxicity in question (yes/no) and arm (ET/ET+Bev). Additionally, models were constructed to test the toxicity effect within the ET+Bev arm. To adjust for bias that the probability of toxicity is associated with length of Bev treatment, we included a time-dependent covariable defined as less than versus greater than 4 cycles of therapy.

All statistical tests used in the analysis are two-sided. Data were analyzed using SAS Enterprise Guide (version 5.1) and R (version 3.1.2).

## RESULTS

Seven hundred forty-nine patients comprised the pooled sample with 371 on the ET arm and 378 on the ET+Bev arm. All these were evaluable for efficacy and safety (See Consort study flowchart).

Baseline characteristics were similar between arms (Table 1). Forty percent of patients had *de novo* advanced breast cancer and 59% recurrent disease, of whom 88% had disease that recurred more than 2 years after initial diagnosis. Half the sample had visceral metastases and 66.4% had measurable disease at baseline. Regarding prior treatments, 43.3% received prior chemotherapy and 50.7% prior adjuvant ET (21.8% with aromatase inhibitors).

Among patients with recurrent disease who received previous ET, 84% (N=146) in the ET arm and 82% (N=139) in the ET+Bev arm were endocrine-sensitive while, 11.5% (N=20) in the ET arm and 20.6% (N=36) in the ET+Bev arm were endocrine-resistant.

### Adverse events

There was an increased incidence of related adverse events in the ET+Bev arm in comparison to the ET arm (44.2% vs 12.9%, $p<0.0001$), but without any additional unexpected event (supplementary material-SM1). The incidence of commonly related grade

3–5 adverse events in the ET+Bev versus ET arm was: hypertension (20.1% vs 2.2%, p<0.0001), proteinuria (9.3% vs 0.0%, p<0.0001), cardiovascular events (4.2% vs 0.5%, p=0.0006) and liver events (2.9 vs 0%, p=0.0005). Nine patients died while on study, 8 of them on the ET+Bev arm (1 due to pulmonary embolism, 3 of myocardial infarction, 1 of stroke, 2 due to cerebrovascular ischemia and one of liver failure), and one on the ET arm, whose cause was unknown.

## Efficacy analysis

**PFS—**With a median follow-up of 34 months, a statistically significant difference in PFS was observed favoring the addition of Bev (HR for ET+Bev versus ET of 0.77; 95%CI: 0.66–0.91; p= 0.0016). We made a comparison of restricted mean PFS times showing similar results (p=0.0043). Median **PFS** was 19 months (95% CI: 17.2–22.9 months) for ET +Bev arm, and 14.3 months (95% CI: 12.6–17.0) for ET arm (Figure 1). After adjusting for baseline covariables, multivariate analysis maintained the statistically significant benefit of Bev in PFS (HR 0.76; 95% CI 0.64 – 0.89; p=0.0010) (SM2).

Subgroup analyses (Figure 2) found that the ET+Bev arm showed a significant improvement in PFS in the recurrent population (19.3 months in ET+Bev arm vs 12.3 months in ET arm; HR: 0.74, 95% CI 0.60–0.92; p=0.0059) and in patients with prior endocrine-sensitivity (18.5 months in ET+Bev arm vs 14.1 months in ET arm; HR: 0.68, 95%CI: 0.53–0.89; p=0.0042). The improvement in PFS in either de novo MBC patients or the endocrine-resistant patients was not statistically significant (19.3 months in ET+Bev arm vs 14.6 months in ET arm; HR 0.82; 95 % CI 0.63–1.06; p=0.1264 and 24.0 months in ET+Bev arm vs 14.4 months in ET arm; HR 0.73; 95% CI 0.40–1.32; p=0.2931, respectively).

**Secondary Endpoints—ORR** in patients with measurable disease and **CBR** in the total sample were significantly better in patients treated with ET+Bev (61% [n=250] and 77% [n=378]) than those with ET only (40% [n=247] and 64% [n=371]) with p values of <0.01 and 0.01, respectively. *De novo*, recurrent and endocrine-sensitive patients obtained benefit in ORR and CBR with the addition of Bev but not the endocrine-resistant population. The addition of Bev to ET did not show a statistically significant benefit neither in **TTF** (HR 0.90; 95% CI 0.77–1.04; p=0.1583) nor in **RD** (HR 0.82; 95% CI 0.62–1.08; p=0.1512); only patients with prior endocrine-sensitivity did slightly better with ET+Bev (HR 0.54; 95% CI 0.33–0.89; p=0.0152). **OS** (SM3) did not show any difference with the addition of Bev to ET neither in the total sample (HR 0.96; 95% CI 0.77–1.18; p=0.6816; 47.2 months in ET arm vs 47.2 months in ET+Bev), nor in any of the subgroups analyzed.

See Table 2 for treatment effect on all efficacy endpoints in the total sample and the four subgroups of interest.

Table 3 shows the correlation of grade 3–4 hypertension and proteinuria with PFS, OS and ORR. In the ET+Bev arm, the occurrence of grade 3–4 hypertension was significantly asociated with better PFS (HR 0.66; 95% CI 0.48–0.89; p<0.01) and ORR (p=0.02), grade 3–4 proteinuria with better PFS (HR 0.47; 95% CI 0.30–0.73; p<0.01), and grade 3–4 hypertension/proteinuria with better PFS (HR 0.63; 95% CI 0.48–0.83; p<0.01), OS (p=0.02) and ORR (p<0.01) (SM4 Figure a, b and c). An interaction test to evaluate the

statistical validity of the relationship between the magnitud of Bev benefit and those toxicities in PFS was not statistically significant neither with hypertension nor with proteinuria or hypertension/proteinuria (p=0.33, p=na, p=0.35, respectively).

Considering these toxicities were infrequent in the ET arm and although the tests for interaction were not statistically significant, an analysis adjusted by their time of occurrence (within the first 4 cycles or after more than 4 cycles) were performed in the ET+Bev arm. They showed no correlation with PFS when they were occurring within the first 4 cycles (SM4 Figure d and e and f). We performed a landmark analysis at 4 months showing the same results (SM5 Figures a and b).

## DISCUSSION

This pooled analysis demonstrates that the addition of Bev to ET as first-line therapy of hormone-receptor positive MBC significantly improves PFS. This difference is maintained when adjusting for other significant covariates and, therefore, seems to be a real finding. ORR and CBR were also significantly superior in patients treated with Bev. The addition of Bev, however, did not improve OS and was associated with a significant increase in relevant toxicities (hypertension, proteinuria, and cardiovascular events) and led to deaths due to toxicity. These results are very similar to those found in phase III trials in which chemotherapy plus bevacizumab was compared with chemotherapy alone in first-line MBC. The addition of bevacizumab to chemotherapy was associated with an increase in ORR and PFS, at the expense of significant toxicity[6]. The initial enthusiasm for antiangiogenic therapy in MBC following the results of the ECOG 2100 trial[7] was later tempered by the more modest results of other first and second-line bevacizumab-chemotherapy trials[8–10]. Furthermore, other oral antiangiogenic drugs[11–14] have also failed to improve the antitumor activity of chemotherapy in MBC.

Angiogenesis is one of the hallmarks of cancer and probably plays a significant role in the biology of MBC[15]. The reasons why bevacizumab therapy has not, then, succeeded in improving OS in MBC in spite of a clear improvement in PFS are still unknown. Many explanations have been suggested, including a rapid rebound of angiogenesis after discontinuation of therapy with selection of a resistant and more aggressive disease phenotype, and the implication of pro-angiogenic factors other than VEGF[16]. The inability of bevacizumab MBC studies to translate the PFS benefit into an OS benefit due to an inadequate power of the trials is unlikely, since a meta-analysis including thousands of patients has failed to show any signal of OS improvement[6].

Interestingly, GEICAM/2006–11_GBG51 and CALGB 40503 (Alliance) trials have shown a better than initially anticipated outcome of the control arm patients treated with endocrine therapy alone (median of around 14 months), data that should be taken into consideration for reference in modern endocrine therapy trials. The statistical assumption of these trials was a median PFS of 6–9 months, based on historical series that included HER2-positive patients. The increased PFS found in our trials is probably due to patient selection, (i.e: high proportion of patients with *de novo* metastatic disease and mainly hormone-receptor positive/HER2 negative tumors). An improved understanding of patient characteristics and

tumor biology in this selected first-line population could be of help for the design of future endocrine therapy trials.

Unfortunately, all the efforts aimed to find biological or clinical predictors of response to bevacizumab and other antiangiogenic drugs have been unsuccessful to date, as they have been in our pooled analysis. Our attempt to correlate bevacizumab-specific grade 3–4 toxicities (i.e., hypertension and proteinuria) with efficacy was also unsuccessful. The apparent correlation between these toxicities and outcome found in our analysis was simply a reflection of the fact that patients with longer PFS have more probability to develop such toxicities due to longer exposure to bevacizumab. As a matter of fact, when we adjust the analysis by the time of occurrence of these toxicities, we see that an early onset of grade 3–4 hypertension or proteinuria was not correlated with better PFS.

The two bevacizumab studies discussed here were designed when the data from the modern CDK 4–6 inhibitors were not available. The bevacizumab data are today of less relevance in practical terms, since endocrine therapy plus a CDK 4/6 inhibitors rather than endocrine therapy alone is considered the standard of care firt-line therapy for these patients.

## CONCLUSIONS

In summary, our pooled analysis found that adding bevacizumab to first-line endocrine therapy of MBC significantly improves PFS and ORR/CBR without any significant impact on OS and at the cost of significant toxicity. On the basis of this analysis, and unless strong biological predictors of response are found, the combination of endocrine therapy plus bevacizumab should not be recommended in the treatment of hormone-receptor positive/HER2 negative advanced breast cancer.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

We thank the investigators, patients and local research staff involved in the GEICAM 2006-11/GBG51 and CALGB 40503 studies.

Funding

This work was supported by the National Cancer Institute of the National Institutes of Health under Award Numbers U10CA180821 and U10CA180882 (to the Alliance for Clinical Trials in Oncology), P30 CA008748, U10CA180838, and U10CA180867. Partial support was also provided by funds from The Breast Cancer Research Foundation, Genentech, and Roche although they were not involved in study design, data analyses or interpretation, or writing of this report. The corresponding author had full access to all the data and had the final responsibility for the decision to submit this publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Miguel Martin has received speakers honoraria from Pfizer and Lilly, honoraria for participation in Advisory Boards from AstraZeneca, Novartis, Roche-Genentech, Pfizer, Glaxo, Pharmamar, Taiho Oncology and Lilly, and research grants from Novartis and Roche. William T. Barry has research funding from Pfizer and other relationships with ARMO BioSciences. Maura N. Dickler is a full time employee of Eli Lilly and Company. Eva Carrasco has stock and other ownership interests from Lilly, has received travel and accommodations support from Roche and her husband has participated in consulting and advisory board activities with Bristol-Myers Squibb, Novartis, Celgene, Roche Pharma, Janssen, Amgen, Incyte, Abbvie and Pfizer, has received travel and accommodations

support from Celgene, Novartis and Bristol-Myers Squibb. His institution has received research funding from Celgene, Janssen, Bristol-Myers Squibb, Novartis, Celgene, Roche/ Genentech, Amgen, Pfizer and Abbvie. GEICAM has received research funding from Roche/Genentech, Bristol-Myers Squibb, Novartis, Pfizer, Celgene, AstraZeneca, Merck Sharp & Dohme, Pierre Fabre and Takeda.

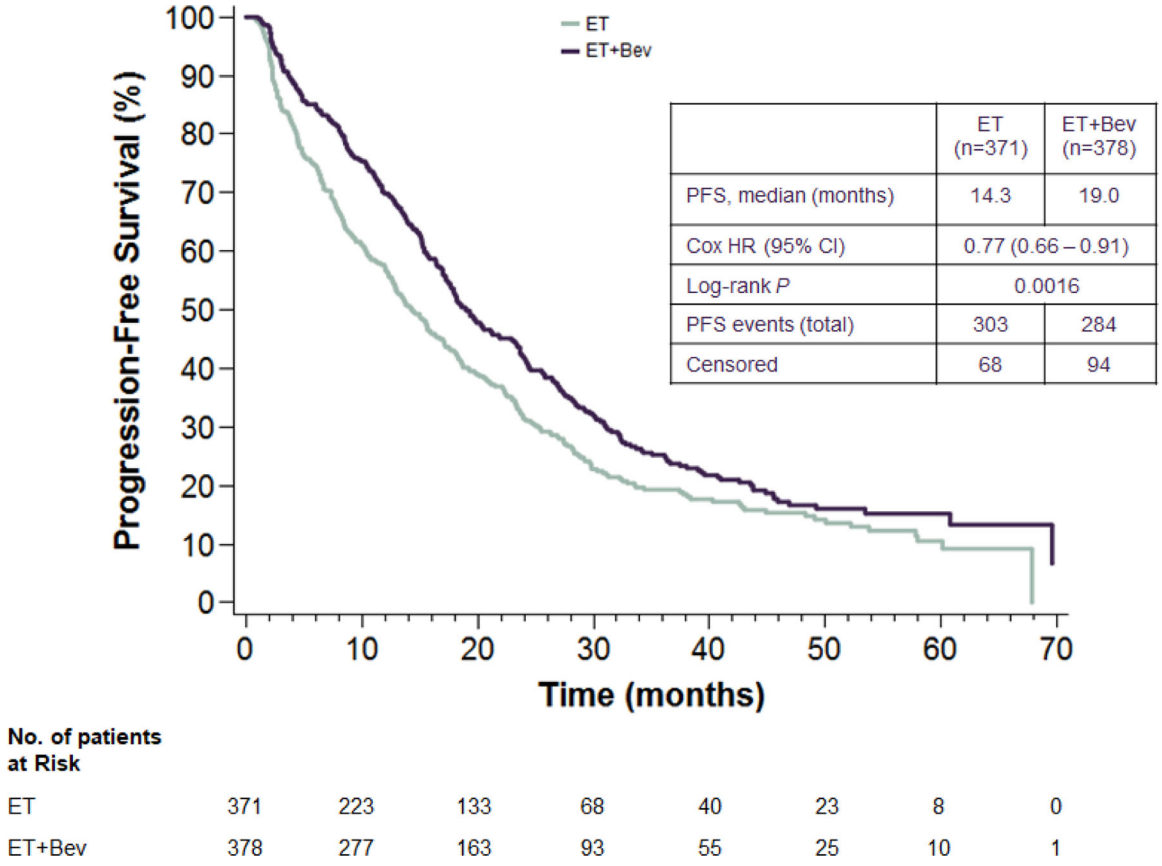
## REFERENCES

1. Qu Z, Van Ginkel S, Roy AM et al. Vascular endothelial growth factor reduces tamoxifen efficacy and promotes metastatic colonization and desmoplasia in breast tumors. Cancer Res 2008; 68: 6232–6240. [PubMed: 18676847]
2. Foekens JA, Peters HA, Grebenchtchikov N et al. High tumor levels of vascular endothelial growth factor predict poor response to systemic therapy in advanced breast cancer. Cancer Res 2001; 61: 5407–5414. [PubMed: 11454684]
3. Martin M, Loibl S, von Minckwitz G et al. Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer: the letrozole/fulvestrant and avastin (LEA) study. J Clin Oncol 2015; 33: 1045–1052. [PubMed: 25691671]
4. Dickler MN, Barry WT, Cirrincione CT et al. Phase III Trial Evaluating Letrozole As First-Line Endocrine Therapy With or Without Bevacizumab for the Treatment of Postmenopausal Women With Hormone Receptor-Positive Advanced-Stage Breast Cancer: CALGB 40503 (Alliance). J Clin Oncol 2016; 34: 2602–2609. [PubMed: 27138575]
5. Lin DYW LJ The Robust Inference for the Proportional Hazards Model. Journal of the American Statistical Association 1989; 84: 1074–1078.
6. Miles DW, Dieras V, Cortes J et al. First-line bevacizumab in combination with chemotherapy for HER2-negative metastatic breast cancer: pooled and subgroup analyses of data from 2447 patients. Ann Oncol 2013; 24: 2773–2780. [PubMed: 23894038]
7. Miller K, Wang M, Gralow J et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357: 2666–2676. [PubMed: 18160686]
8. Miles DW, Chan A, Dirix LY et al. 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 2010; 28: 3239–3247. [PubMed: 20498403]
9. Robert NJ, Dieras V, Glaspy J et al. 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 2011; 29: 1252–1260. [PubMed: 21383283]
10. Brufsky AM, Hurvitz S, Perez E et al. 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 2011; 29: 4286–4293. [PubMed: 21990397]
11. Bergh J, Bondarenko IM, Lichinitser MR et al. First-line treatment of advanced breast cancer with sunitinib in combination with docetaxel versus docetaxel alone: results of a prospective, randomized phase III study. J Clin Oncol 2012; 30: 921–929. [PubMed: 22331954]
12. Baselga J, Zamagni C, Gomez P et al. RESILIENCE: Phase III Randomized, Double-Blind Trial Comparing Sorafenib With Capecitabine Versus Placebo With Capecitabine in Locally Advanced or Metastatic HER2-Negative Breast Cancer. Clin Breast Cancer 2017; 17: 585–594 e584. [PubMed: 28830796]
13. Rugo HS, Stopeck AT, Joy AA et al. Randomized, placebo-controlled, double-blind, phase II study of axitinib plus docetaxel versus docetaxel plus placebo in patients with metastatic breast cancer. J Clin Oncol 2011; 29: 2459–2465. [PubMed: 21555686]
14. Martin M, Roche H, Pinter T et al. Motesanib, or open-label bevacizumab, in combination with paclitaxel, as first-line treatment for HER2-negative locally recurrent or metastatic breast cancer: a phase 2, randomised, double-blind, placebo-controlled study. Lancet Oncol 2011; 12: 369–376. [PubMed: 21429799]
15. Toi M, Hoshina S, Takayanagi T, Tominaga T. Association of vascular endothelial growth factor expression with tumor angiogenesis and with early relapse in primary breast cancer. Jpn J Cancer Res 1994; 85: 1045–1049. [PubMed: 7525523]

16. Mackey JR, Kerbel RS, Gelmon KA et al. Controlling angiogenesis in breast cancer: a systematic review of anti-angiogenic trials. Cancer Treat Rev 2012; 38: 673–688. [PubMed: 22365657]

## HIGHLIGHTS

- Bevacizumab plus endocrine therapy increased progression-free survival overall.
- Bevacizumab plus endocrine therapy does not increased overall survival.
- This combination adds significant toxicity.
- This should not be recommended for 1st line HR+ /HER2- advanced breast cancer.
- Hypertension and proteinuria are not predictive of bevacizumab efficacy.




| | ET (n=371) | ET+Bev (n=378) |
|---|---|---|
| PFS, median (months) | 14.3 | 19.0 |
| Cox HR (95% CI) | 0.77 (0.66 – 0.91) | |
| Log-rank *P* | 0.0016 | |
| PFS events (total) | 303 | 284 |
| Censored | 68 | 94 |

**Figure 1. Progression-free Survival**

Abbreviations: ET, Endocrine Therapy; ET+Bev, Endocrine Therapy + bevacizumab; PFS, progression-free survival.

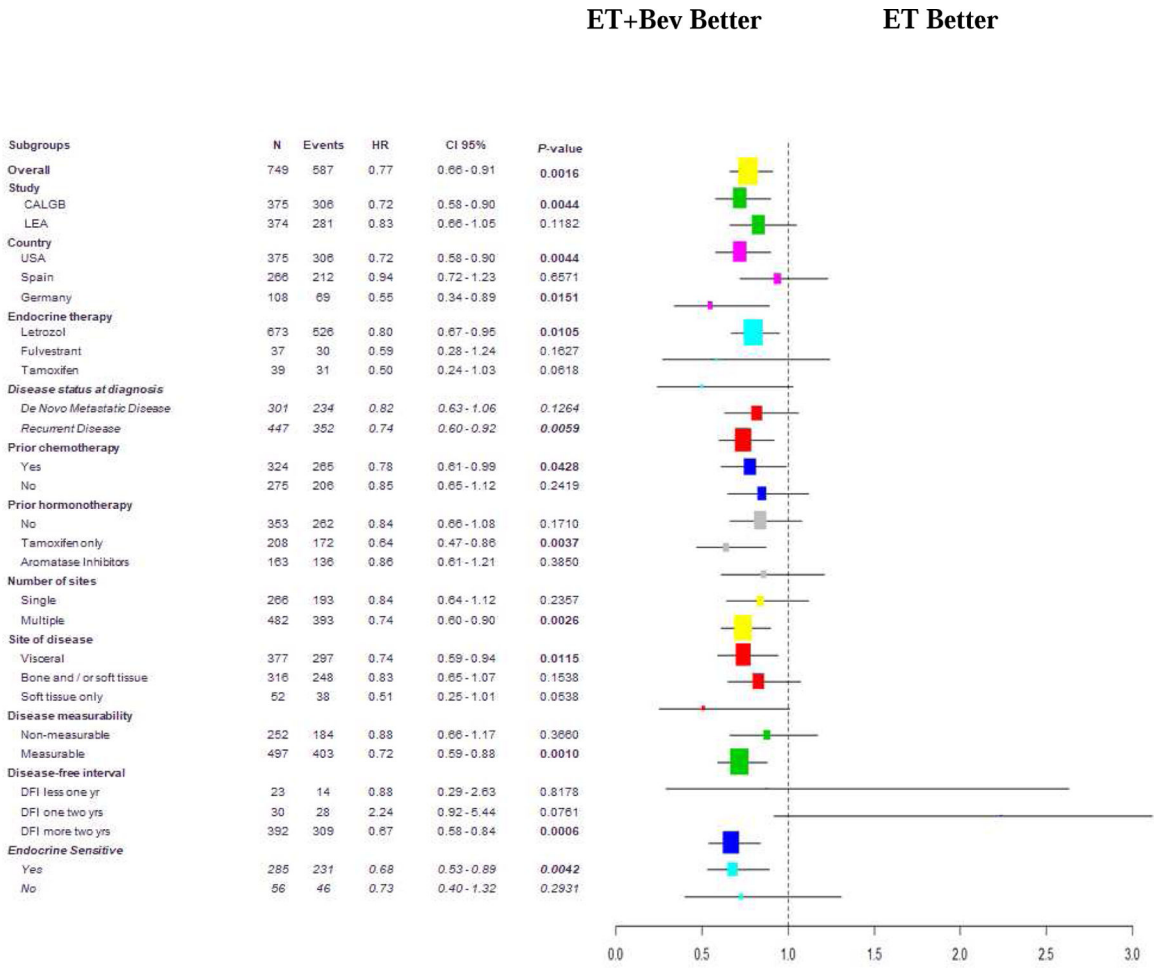



**Figure 2. Forest plot of subgroup analysis for progression-free survival**

Abbreviations: ET, Endocrine Therapy; ET+Bev, Endocrine Therapy + bevacizumab; HR, hazard ratio; DFI, disease-free interval.

**Table 1.**

Patient and baseline tumor characteristics

| Characteristic | Control ET | Experimental ET+Bev |
|---|---|---|
| | n=371 | n=378 |
| **Age** | | |
| Median (range) | 62 (29–87) | 60.5 (25–85) |
| **ECOG PS** | | |
| 0 | 66.3% | 68.5% |
| 1 | 32.9% | 30.9% |
| 2 | 0.5% | 0.3% |
| Not Available | 0.3% | 0.3% |
| **Disease status at diagnosis** | | |
| *De novo* advanced disease | 40.7% | 39.7% |
| Recurrent disease | 59.0% | 60.3% |
| ≤1 year | 2.2% | 4.0% |
| (1–2) years | 3.0% | 5.0% |
| >2 years | 53.3% | 51.3% |
| Not Available | *0.5%* | *0.0%* |
| Not Available | 0.3% | 0.0% |
| **Prior chemotherapy** | | |
| No | 36.1% | 37.3% |
| Yes | 43.1% | 43.4% |
| Not Available | 20.8% | 19.3% |
| **Prior adjuvant ET** | | |
| No | 48.5% | 45.8% |
| Yes | 49.6% | 51.1% |
| Not Available | 1.9% | 3.1% |
| **Type of prior ET** | | |
| No prior ET | 48.5% | 45.8% |
| Tamoxifen only | 25.9% | 29.6% |
| AI (+/−Tamoxifen) | 23.2% | 20.4% |
| Other | 0.5% | 1.1% |
| Not Available | 1.9% | 3.1% |
| **Number involved sites** | | |
| Single | 34.2% | 36.8% |
| Multiple | 65.5% | 63.2% |
| Not Available | 0.3% | 0.0% |
| **Site of metastasis** | | |
| Soft tissue only | 8.1% | 5.8% |
| Bone+/−Soft tissue | 41.0% | 43.4% |

| Characteristic | Control ET | Experimental ET+Bev |
|---|---|---|
| | n=371 | n=378 |
| Visceral | 50.4% | 50.3% |
| Not Available | 0.5% | 0.5% |
| **Disease measurability** | | |
| Non-measurable | 33.4% | 33.9% |
| Measurable | 66.6% | 66.1% |

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ET, Endocrine Therapy; ET+Bev, Endocrine Therapy + bevacizumab; AI, Aromatase Inhibitor.

**Table 2.**

Observed treatment effect on efficacy endpoints in total sample and selected subgroups of interest.

| | | Total sample (N=749) | De novo disease (N=301) | Recurren t disease (N=447) | ET sensitive (N=285) | ET resistant (N=56) |
|---|---|---|---|---|---|---|
| **PFS** | HR (95% CI) | 0.77 (0.66–0.91) | 0.82 (0.63–1.06) | 0.74 (0.60–0.92) | 0.68 (0.53– 0.89) | 0.73 (0.40–1.32) |
| | p-value | **<0.01** | 0.13 | **<0.01** | **<0.01** | 0.29 |
| **OS** | HR (95% CI) | 0.96 (0.77–1.18) | 0.93 (0.68–1.28) | 0.98 (0.73–1.30) | 0.85 (0.59–1.23) | 1.17 (0.56–2.45) |
| | p-value | 0.68 | 0.66 | 0.87 | 0.40 | 0.67 |
| **TTF** | HR (95% CI) | 0.90 (0.77–1.04) | 0.90 (0.71–1.14) | 0.89 (0.73–1.09) | 0.85 (0.67–1.08) | 0.66 (0.37–1.17) |
| | p-value | 0.16 | 0.38 | 0.26 | 0.19 | 0.16 |
| **RD** | HR (95% CI) | 0.82 (0.62–1.08) | 0.85 (0.57–1.26) | 0.76 (0.52–1.12) | 0.54 (0.33–0.89) | 1.16 (0.28–4.78) |
| | p-value | 0.15 | 0.41 | 0.17 | **0.02** | 0.83 |
| **ORR** | OR (95% CI) | 2.70 (1.86–3.93) | 2.36 (1.36–4.11) | 3.03 (1.82–5.05) | 3.32 (1.75–6.31) | 1.79 (0.35–9.13) |
| | p-value | **<0.01** | **<0.01** | **<0.01** | **<0.01** | 0.49 |
| **CBR** | OR (95% CI) | 2.10 (1.48–2.97) | 2.37 (1.33–4.24) | 1.93 (1.25–2.99) | 2.08 (1.21–3.56) | 1.45 (0.44–4.72) |
| | p-value | **<0.01** | **<0.01** | **<0.01** | **<0.01** | 0.54 |

Note: HR < 1.0 indicates ET+Bev benefit; OR > 1.0 indicates ET+Bev benefit.

Abbreviations: ET, endocrine therapy; PFS, progression-free survival; OS, overall survival; TTF, time to treatment failure; RD, response duration; ORR, overall response rate; CBR, clinical benefit rate; HR, hazard ratio.

**Table 3.**

Observed effects of grade 3–4 hypertension and proteinuria on PFS, ORR and OS

| Endpoint | | ET N=371 | | | ET+Bev N=378 | | | Total sample N=749 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **G3–4 HT** | **G3–4 Prot** | **G3–4 HT/Prot** | **G3–4 HT** | **G3–4 Prot** | **G3–4 HT/Prot** | **G3–4 HT** | **G3–4 Prot** | **G3–4 HT/Prot** |
| **PFS** | HR (95% CI) | 0.43 (0.18–1.04) | Na | 0.43 (0.18–1.04) | 0.66 (0.48–0.89) | 0.47 (0.30–0.73) | 0.63 (0.48–0.83) | 0.58 (0.44–0.76) | 0.44 (0.28–0.68) | 0.57 (0.45–0.74) |
| | p-value | 0.06 | Na | 0.06 | **<0.01** | **<0.01** | **<0.01** | **<0.01** | **<0.01** | **<0.01** |
| | $p_{int}$-value | | | | | | | 0.33 | na | 0.35 |
| **OS** | HR (95% CI) | 0.17 (0.02–1.19) | Na | 0.17(0.02–1.19) | 0.69 (0.47–1.02) | 0.55 (0.31–1.00) | 0.65 (0.46–0.94) | 0.63 (0.44–0.91) | 0.56 (0.31–0.99) | 0.62 (0.44–0.86) |
| | p-value | 0.07 | Na | 0.07 | 0.07 | 0.05 | **0.02** | **0.01** | 0.05 | **<0.01** |
| | $p_{int}$-value | | | | | | | 0.16 | na | 0.17 |
| **ORR** | OR (95% CI) | 4.34 (0.44–42.3) | Na | 4.34 (0.44–42.3) | 2.52 (1.15–5.52) | 4.24 (0.94–19.0) | 3.20 (1.52–6.74) | 3.96 (1.93–8.13) | 6.90 (1.56–30.5) | 4.82 (2.44–9.51) |
| | p-value | 0.21 | Na | 0.21 | **0.02** | 0.06 | **<0.01** | **<0.01** | **0.01** | **<0.01** |
| | $p_{int}$-value | | | | | | | 0.66 | na | 0.80 |

Note: Na = zero toxicity events in the ET arm.

Abbreviations: ET, Endocrine Therapy; ET+Bev, Endocrine Therapy + bevacizumab; HT: hypertension; Prot: proteinuria; na: not available; $p_{int}$-value: p-value of interaction test between HT/Prot and treatment arm. PFS, progression-free survival; OS, overall survival; ORR, overall response rate.