2016

Ramucirumab with eribulin versus eribulin in locally recurrent or metastatic breast cancer previously treated with anthracycline and taxane therapy: A multicenter, randomized, phase II study

Foluso Ademuyiwa
Washington University School of Medicine in St. Louis

et al

Ramucirumab With Eribulin Versus Eribulin in Locally Recurrent or Metastatic Breast Cancer Previously Treated With Anthracycline and Taxane Therapy: A Multicenter, Randomized, Phase II Study

Denise A. Yardley,[1] James Reeves,[2] E. Claire Dees,[3] Cynthia Osborne,[4] Devchand Paul,[5] Foluso Ademuyiwa,[6] Hatem Soliman,[7] Troy Guthrie,[8] Jay Andersen,[9] Lea Krekow,[10] Janak Choksi,[11] Brooke Daniel,[12] Michael Danso,[13] Anne Favret,[14] Sanjay Oommen,[15] Adam Brufsky,[16] Jane L. Bromund,[17] Yong Lin,[17] Ayman B. Ibrahim,[18] Paul D. Richards[19]

Abstract

We describe the efficacy and safety of ramucirumab with eribulin versus eribulin monotherapy as third- to fifth-line therapy in women with advanced breast cancer. The primary end point of progression-free survival was not met. Screening for brain metastases upon trial entry showed an unanticipated prevalence of asymptomatic brain disease, raising new considerations for screening in late-stage metastatic breast cancer irrespective of HER2 or hormone receptor status.

Background: Use of antiangiogenic agents in treatment of metastatic breast cancer (MBC) remains controversial. We evaluated the efficacy and safety of ramucirumab and eribulin versus eribulin alone as third- to fifth-line therapy in women with advanced breast cancer. **Patients and Methods:** In this randomized (1:1), open-label, phase II study, US women aged 18 years or older with 2 to 4 previous chemotherapy regimens for locally recurrent or MBC, previous anthracycline and taxane treatment, and Eastern Cooperative Oncology Group performance status of 0 or 1 received ramucirumab with eribulin or eribulin alone in 21-day cycles (eribulin 1.4 mg/m^2 intravenously on days 1 and 8; ramucirumab 10 mg/kg intravenously on day 1). Randomization was stratified according to previous antiangiogenic therapy and triple-negative status. The primary end point was progression-free survival (PFS) in the intention to treat population. **Results:** One hundred forty-one women were randomized to ramucirumab with eribulin (n = 71) or eribulin alone (n = 70). Median PFS for ramucirumab with eribulin was 4.4 months (95% confidence interval [CI], 3.1-6.7) compared with 4.1 months (95% CI, 3.2-5.6) for eribulin (hazard ratio [HR], 0.83; 95% CI, 0.56-1.23; $P = .35$). Median overall survival in patients who received ramucirumab with eribulin was 13.5 months (95% CI, 10.4-17.9) compared

ClinicalTrials.gov: NCT01427933.

[1]Sarah Cannon Research Institute, Tennessee Oncology PLLC, Nashville, TN
[2]Florida Cancer Specialists and Research Institute, Fort Myers, FL
[3]University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, NC
[4]Baylor Charles A. Sammons Cancer Center, US Oncology Research, Dallas, TX
[5]Rocky Mountain Cancer Centers, US Oncology Research, Denver, CO
[6]Division of Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO
[7]Department of Breast Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL
[8]Baptist Cancer Institute, Jacksonville, FL
[9]Northwest Cancer Specialists, PC, US Oncology Research, Portland, OR
[10]Texas Oncology-Bedford, US Oncology Research, Bedford, TX
[11]Medical Oncologist, Alamance Regional Medical Center, Burlington, NC
[12]Tennessee Oncology, Chattanooga, TN
[13]Virginia Oncology Associates, US Oncology Research, Norfolk, VA
[14]Virginia Cancer Specialists, PC, US Oncology Research, Fairfax, VA
[15]Texas Oncology-Fort Worth, US Oncology Research, Fort Worth, TX
[16]Division of Hematology/Oncology, Department of Medicine, University of Pittsburgh School of Medicine, Magee-Women's Hospital of University of Pittsburgh Medical Center, Pittsburgh, PA
[17]Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN
[18]Eli Lilly and Company, Bridgewater, NJ
[19]Oncology and Hematology Associates of Southwest Virginia, US Oncology Research, Salem, VA

Submitted: Feb 27, 2016; Revised: Jul 18, 2016; Accepted: Jul 21, 2016; Epub: Jul 29, 2016

Address for correspondence: Denise A. Yardley, MD, Sarah Cannon Research Institute, Tennessee Oncology PLLC, Nashville, TN 37203
E-mail contact: dyardley@tnonc.com

http://dx.doi.org/10.1016/j.clbc.2016.07.005

with 11.5 months (95% CI, 9.0-17.3) in patients who received eribulin alone (HR, 0.91; 95% CI, 0.59-1.41; $P = .68$); objective response rate was 21% (13 of 62 patients) for the combination and 28% (17 of 60 patients) for eribulin alone. No unexpected toxicity was identified for the combination. **Conclusion:** Ramucirumab combined with eribulin did not significantly improve PFS in advanced MBC.

Clinical Breast Cancer, Vol. 16, No. 6, 471-9

Keywords: Antiangiogenic therapy, Brain metastasis, Targeted agents, Triple-negative status, VEGFR-2

Introduction

In 2016, in the United States, more than 240,000 women will be diagnosed with breast cancer and approximately 40,000 deaths will occur from metastatic breast cancer, with a 25% 5-year survival estimated for women of all races.[1] The pursuit of beneficial therapeutic regimens for metastatic breast cancer has been a compelling campaign in the oncology community. In human breast cancer, intensive neovascularizations and tumor angiogenesis correlate with metastases and poor prognosis.[2,3]

Strong preclinical and clinical evidence suggests vascular endothelial growth factor (VEGF) and angiogenesis play key roles in breast cancer growth, invasion, and metastasis; this evidence paired with strategies of VEGF inhibition showed improved outcomes in early preclinical models.[4,5] However, antiangiogenesis strategy success in other tumor types, including lung, cervical, colorectal, glioblastoma, and renal cancers,[6-10] has yet to be clearly replicated in metastatic breast cancer. After more than a decade of unsuccessful attempts to show an overall survival advantage,[11-15] there is currently no approved US indication for bevacizumab in breast cancer, despite evidence of improved disease control, measured according to response and progression-free survival, when combined with single-agent chemotherapy.

Ramucirumab is a US Food and Drug Administration (FDA)-approved, recombinant human monoclonal antibody that binds the extracellular domain of VEGF receptor (VEGFR)-2, where it blocks receptor interaction with activating ligands (VEGF-a, VEGF-C, and VEGF-D), preventing downstream signaling involved in the formation and maintenance of aberrant blood vessels that supply tumors and maintain endothelial cell proliferation.[16] Its selectivity for VEGFR-2 sets it apart from the ligand-binding function of bevacizumab. Global phase III trials in breast, gastric, lung, hepatocellular, and colorectal cancers were undertaken, leading to ramucirumab's first FDA approval in 2014 as a single-agent treatment, or in combination with paclitaxel, for patients with advanced or metastatic gastric cancer or gastroesophageal junction adenocarcinoma with disease progression during or after fluoropyrimidine- or platinum-containing chemotherapy.[17,18] Despite the efficacy of ramucirumab in gastric cancer, the recently reported Ramucirumab Overall Survival Evaluation/Translational Research In Oncology-12 (ROSE/TRIO-12) study, a randomized, placebo-controlled, phase III trial of first-line docetaxel with ramucirumab versus docetaxel in metastatic breast cancer, did not meet its primary end point of progression-free survival.[19]

Eribulin is a nontaxane microtubule polymerization inhibitor with clinical efficacy and an acceptable toxicity profile that is FDA-approved as a single agent in patients with metastatic breast cancer previously treated with an anthracycline and a taxane.[20,21] Considering the observed efficacy of eribulin in late-stage breast cancer as well as in taxane- and anthracycline-pretreated metastatic breast cancer coupled with the potential contribution of VEGFR−2-mediated pathways in breast cancer pathogenesis,[12-15] the combination of ramucirumab with eribulin was hypothesized to improve clinical outcomes in advanced metastatic breast cancer. Because of the published efficacy of bevacizumab in metastatic breast cancer studies,[22,23] including use in combination with paclitaxel, the ramucirumab with eribulin combination was hypothesized to be active in metastatic breast cancer.

The primary objective of this randomized, open-label, phase II study was to identify whether the combination of ramucirumab with eribulin would increase progression-free survival compared with eribulin alone, as third- to fifth-line therapy in patients with advanced breast cancer.

Patients and Methods

Study Design and Participants

This was a multicenter, randomized, open-label, phase II trial conducted at 44 centers in the United States. Female patients aged 18 years or older with stage III locally recurrent not amenable to curative therapy or stage IV metastatic breast cancer and 2 to 4 previous chemotherapy regimens in the advanced setting were eligible for enrollment. Previous anthracycline and taxane treatment, previous HER2-directed treatment in HER2-positive disease (unless contraindicated), normal left ventricular ejection fraction, and Eastern Cooperative Oncology Group performance status of 0 or 1 were required. Patients were eligible for inclusion if they had measurable and/or nonmeasurable disease defined using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST). Key exclusion criteria included uncontrolled hypertension, bevacizumab administration within 6 weeks, or a Grade ≥ 3 bleeding or venous thromboembolic event within 3 months before randomization. Patients with untreated and unstable central nervous system metastases within 3 months were also excluded; baseline brain imaging was required for all patients and treated brain lesions had to show no progression for ≥ 3 months.

The US study was approved by ethics review boards for each center, and study conduct was guided by the Guideline for Good Clinical Practice and the Declaration of Helsinki. Patients provided written informed consent before initiation of treatments.

Randomization and Masking

Patients were randomized (1:1) via a call-in interactive voice response system. Randomization was stratified according to

previous antiangiogenic therapy and triple-negative status (estrogen receptor-negative, progesterone receptor-negative, and HER2-negative). This was an open-label study; therefore, patients, medical staff, investigators, and funders were unmasked to the treatment assignment.

Study Treatment and Assessments

Female patients received ramucirumab 10 mg/kg intravenously on day 1 with eribulin 1.4 mg/m^2 intravenously on days 1 and 8, or eribulin alone (1.4 mg/m^2 on days 1 and 8). The cycle was repeated every 3 weeks (21 days) until disease progression, development of disease progression, development of unacceptable toxicity, withdrawal of consent, or other withdrawal criteria were met. Dose modifications were permitted, but not required, for ramucirumab in the setting of non–life-threatening, reversible Grade 3-4 adverse events that resolved to Grade $\leq$ 1 within 1 cycle. A second dose reduction to 6 mg/kg every 3 weeks was permitted for Grade 3-4 events. Ramucirumab was to be discontinued for Grade 3-4 events of hemorrhage, thromboembolism, or infusion-related reaction, and Grade 4 hypertension. Eribulin dose modifications were made according to the manufacturer's package insert.[21] Ramucirumab and/or eribulin was allowed to continue if toxicity was considered by the investigator to not be related to that drug in the combination group.

The changes in tumor size in post-treatment tumor assessments were analyzed every 6 weeks. Imaging studies were undertaken every 6 weeks after the first dose until documented disease progression.

Safety was analyzed for all patients who received at least 1 dose of study treatment. A Safety Assessment Committee monitored the study, including review of the safety cohort data for the first 6 and then 12 patients who received 2 cycles of combination therapy. The safety and tolerability of ramucirumab and eribulin were determined by reported adverse events, physical examinations, and laboratory tests. Safety data were graded using the National Cancer Institute - Common Terminology Criteria for Adverse Events version 4.0. Causality relationship to study drug was separately summarized.

Outcomes

The primary outcome was to compare the antitumor activity between ramucirumab and eribulin or eribulin alone, measured according to progression-free survival and defined as the time from the date of randomization until the date of objective progression defined according to RECIST, or death from any cause, whichever occurred first. Secondary efficacy outcomes included overall survival, defined as time from randomization to date of death from any cause; objective response rate, defined as the proportion of patients achieving a best overall response of partial or complete response, determined for patients with measurable disease according to RECIST; duration of response, measured from the time measurement criteria were first met for complete response/partial response (whichever was first recorded) until the first date at which the criteria for progressive disease were met (taking as a reference for progressive disease the smallest measurement recorded since the treatment started), or until death; and change in tumor size in patients with measurable disease at 6-week assessments; as well as to assess the safety and tolerability of ramucirumab with eribulin.

Statistical Analyses

The intention to treat population consisted of all eligible randomized patients, regardless of study drug administration. Assuming an increase in median progression-free survival from 3.7 months in the control group[20] to 5.6 months in the experimental group, with 1:1 randomization, 110 progression-free survival events (objective progression or deaths) conferred 80% power to detect a hazard ratio (HR) experimental/control of 0.667 with a 2-sided significance level of 0.2. For the primary analysis, we compared progression-free survival between the 2 treatment groups using a stratified log rank test at a 2-sided significance level of 0.2, with triple-negative breast cancer status and previous antiangiogenic therapy as stratification factors. Progression-free and overall survival were estimated using the Kaplan–Meier method. For overall survival and duration of response, we used the same model as for the primary analysis. The objective response rate in patients with measurable disease in the experimental group was measured and compared with the control group using the Cochran–Mantel–Haenszel test, adjusted for stratification variables. A 2-sided 95% confidence interval (CI) for the objective response rate of each arm was calculated using Fisher exact test. The percentage of patients in each group with duration of response $>$ 12 weeks was presented with a 2-sided 95% CI.

Changes in tumor size were analyzed by calculating the log ratio of tumor size at time of assessment to tumor size at baseline for each patient. This measure was compared between treatment groups by using an analysis of covariance using previous antiangiogenic therapy and triple-negative status as factors.

We used SAS version 8.2 or later (SAS Institute, Inc, Cary, NC). This study was registered with ClinicalTrials.gov; NCT01427933.

Results

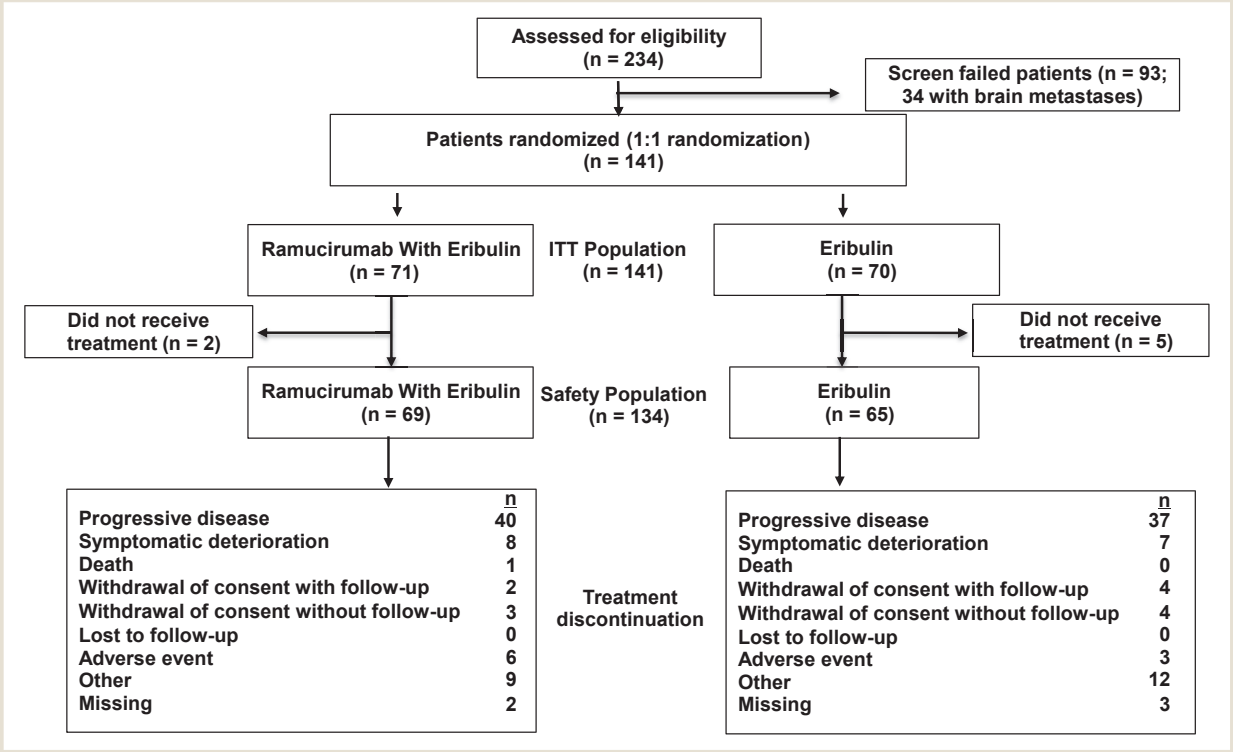
Patients

Patient enrollment began on November 11, 2011; the primary data cutoff for efficacy (progression-free survival, response) and safety was September 11, 2013, and the final data cutoff for overall survival was July 31, 2014. Seventy-one patients in the ramucirumab with eribulin group and 70 patients in the eribulin group were in the intention to treat population (Figure 1). Patients' baseline characteristics were well balanced between the 2 groups (Table 1). There was an unanticipated rate of asymptomatic brain metastases discovered with required brain imaging at screening (20%; 47 patients with brain metastasis of 234 screened), resulting in a screen failure rate of 15% (34 of 234) for this criterion (Figure 1; Table 2). In total, for the 47 patients with asymptomatic brain lesions, 27 of 47 (57%) were in the estrogen receptor- and/or progesterone receptor-positive group and 20 of 47 (43%) were in the triple-negative breast cancer group, with only 2 patients also in the HER2-positive group. Receptor status for the 13 randomized patients was also summarized.

Efficacy

Median progression-free survival was 4.4 months (95% CI, 3.1-6.7) in the ramucirumab with eribulin group versus 4.1 months (95% CI, 3.2-5.6) in the eribulin group, resulting in a nonsignificant HR of 0.83 (95% CI, 0.56-1.23; $P = .35$; Table 3). The HRs were consistent across 4 subgroups analyzed (triple-negative status,

Figure 1 Trial Profile and Study Design. Female Patients With Locally Recurrent or Metastatic Breast Cancer After 2, but No More Than 4, Previous Chemotherapeutic Regimens in the Relapsed/Metastatic Setting Were Stratified According to Previous Antiangiogenic Treatment and Triple Negative Receptor Breast Cancer Status, and Randomly Assigned at a 1:1 Ratio to Ramucirumab With Eribulin or Eribulin Monotherapy and Assessed for Progression-Free Survival and Overall Survival



previous antiangiogenic therapy, visceral vs. nonvisceral sites of metastasis, and number of metastatic sites), including the prespecified stratification factors of triple-negative breast cancer status and previous antiangiogenic therapy status (Figure 2), noting that the study was not powered for subgroup survival analysis. The reported subgroup results numerically favored the ramucirumab combination, with the triple-negative subgroup showing a large benefit. The median overall survival for the ramucirumab with eribulin group was 13.5 months (95% CI, 10.4-17.9) versus 11.5 months (95% CI, 9.0-17.3) in the eribulin group; the HR was 0.91 (95% CI, 0.59-1.41; $P = .68$; Table 3).

Thirteen of 62 patients with measurable disease in the ramucirumab with eribulin group versus 17 of 60 patients in the eribulin group had a partial response, resulting in an objective response rate of 21% (95% CI, 11.7-33.2) versus 28% (95% CI, 17.5-41.4; $P = .39$; Table 4). The median duration of response in the intention to treat population was 5.5 months (95% CI, 3.1-7.1) in the ramucirumab with eribulin group and 3.0 months (95% CI, 1.4-4.4) in the eribulin group; the 6-month rate for patients with response was 39.0% versus 7.1%, with a treatment effect difference of 31.8% (95% CI, 2.1-61.6). An overall reduction in tumor size in both treatment arms was seen after the 6-week tumor assessment (ramucirumab with eribulin: 61% [43 of 71]; eribulin 56% [39 of 70]). The reduction in tumor size up to 36 weeks was similar.

Safety

All-cause treatment-emergent adverse events in $\geq$ 20% of patients and Grade $\geq$ 3 (in $\geq$ 5% of patients) events are listed in Table 5. Overall, there were more events reported in the ramucirumab with eribulin group than in the eribulin group. Treatment-emergent adverse events (any grade) reported more frequently ($P < .05$) in the ramucirumab with eribulin group (n = 69) than in the eribulin group (n = 65) were headache (27 [39%] vs. 10 [15%]) and pyrexia (14 [20%] vs. 5 [8%]). Other than neutropenia and fatigue (known adverse events for eribulin and ramucirumab), most were low-grade events.

Data on treatment-emergent adverse events of special interest were collected, for safety monitoring purposes, on the basis of previously reported adverse events associated with antiangiogenic agents and other therapeutic monoclonal antibodies. Events of special interest of any grade were reported more frequently in the ramucirumab with eribulin group than in the eribulin group (see Supplemental Table 1 in the online version). Hypertension and bleeding were the most frequently reported ($P < .05$) events of special interest in patients who received ramucirumab (9 of 69 [13%] vs. 1 of 65 [2%] and 13 of 69 [19%] vs. 3 of 65 [5%], respectively). Bleeding events in patients treated with ramucirumab with eribulin included 7 Grade 1 epistaxis events and 1 Grade 3 gastrointestinal hemorrhage.

Table 1 Baseline Demographic and Clinical Characteristics in the Intention to Treat Population

Characteristic	Ramucirumab With Eribulin (n = 71)	Eribulin (n = 70)
Age, Years		
Median (range)	57 (32-78)	56 (32-84)
18-64	62 (87)	53 (76)
≥65	9 (13)	17 (24)
Race		
White	54 (76)	58 (83)
Black or African American	11 (15)	8 (11)
Other	5 (7)	2 (3)
Asian	1 (1)	1 (1)
American Indian or Alaska Native	0	1 (1)
ECOG PS		
0	36 (51)	37 (53)
1	35 (49)	32 (46)
≥2	0	1 (1)
Previous Chemotherapy in Relapsed/Metastatic Setting		
Patients with ≥1 line	71 (100)	66 (94)
Patients with ≥2 lines	69 (97)	63 (90)
Patients with ≥3 lines	33 (46)	29 (41)
Patients with ≥4 lines	10 (14)	7 (10)
Randomization Stratum		
Triple negative receptor status		
Yes	21 (30)	22 (31)
No	50 (70)	48 (69)
Previous antiangiogenic therapy		
Yes	24 (34)	26 (37)
No	47 (66)	44 (63)
Receptor status		
ER^+/PR^+	34 (48)	34 (49)
ER^+/PR^-	12 (17)	10 (14)
ER^-/PR^+	2 (3)	1 (1)
ER^-/PR^-	23 (32)	25 (36)
$HER2^+$	6 (8)	6 (9)
Mean Duration of Disease (SD), Months	79.6 (55.4)	85.4 (64.0)

Data are presented as n (%) except where otherwise noted.
Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; ER = estrogen receptor; PR = progesterone receptor.

For the ramucirumab with eribulin group, 69 patients received at least 1 dose of ramucirumab with a median of 4 infusions (interquartile range [IQR], 2-7), median dose intensity of 3.3 mg/kg/wk (IQR, 3.0-3.3), and median relative dose intensity of 99.1% (IQR, 91.2%-100.5%); with eribulin, there was a median of 9 infusions (IQR, 4-15), median dose intensity of 0.8 mg/m^2/wk (IQR, 0.7-0.8), and median relative dose intensity of 83.5% (IQR, 72.9%-90.8%). In the eribulin group, 65 patients received at least 1 dose of eribulin, with a median of 10 infusions (IQR, 4-15), median dose intensity of 0.8 mg/m^2/wk (IQR, 0.6-0.8), and median relative dose intensity of 81.6% (IQR, 69.2%-90.0%). The overall extent of eribulin exposure was similar in both treatment groups.

Table 2 Tumor Receptor Status Characteristics for Patients With Baseline or History of Brain Metastases

Receptor Status	Screen Failure (n = 93), n	Enrolled (n = 141), n
Patients With Brain Metastases	34	13[a]
ER^+ and/or PR^+	21	6
$HER2^+$	2[b]	0
TNBC	13	7

Abbreviations: ER = estrogen receptor; PR = progesterone receptor; TNBC = triple-negative breast cancer.
[a]Early in the conduct of the study, 13 patients were randomized having either treated and stable brain lesions, or protocol violations. Many were discovered randomized for whom baseline brain imaging was not completed. When these errors were found, usually within the first cycle, the patients immediately underwent "delayed" brain imaging and, at times, a brain lesion was found. The study reported on the intention to treat population and patients with protocol violations were still included in the analysis.
[b]The 2 patients with $HER2^+$ tumors also were ER^+ and PR^+.

Treatment-emergent adverse events resulting in at least 1 dose delay or modification occurred in 38 of 69 patients (55%) treated with ramucirumab with eribulin and in 30 of 65 patients (46%) treated with eribulin. Across both treatment groups, the most frequently reported events leading to delay/modification of any study drug were fatigue, neutropenia, and neuropathy. Ramucirumab-related adverse events in 8 of 69 patients (12%) and eribulin-related adverse events in 7 of 69 patients (10%) caused dose discontinuations in the ramucirumab with eribulin group; 6 of 65 patients (9%) had dose discontinuations because of adverse events in the eribulin monotherapy group.

Discussion

In this randomized, phase II study, ramucirumab 10 mg/kg every 3 weeks combined with eribulin did not significantly improve progression-free survival, overall survival, or objective response rate as a third- to fifth-line therapy in patients with metastatic breast cancer. Not surprisingly, higher rates of fatigue, headache, hypertension, diarrhea, pyrexia, and bleeding were observed in the ramucirumab with eribulin group; however, no unexpected toxicities were observed and the safety data were consistent with those reported for ramucirumab in other trials.[17,18,24-26]

When this trial was designed, it was believed that ramucirumab would particularly benefit breast cancer patients, especially if biomarkers could be identified that would delineate those most likely to benefit from antiangiogenic therapies. Antiangiogenic agents in the treatment of metastatic breast cancer remain controversial, with conflicting results regarding their overall effect on survival and the inability to predict which patient subpopulation might derive meaningful benefit. Similar to the results seen with the lower dose in the docetaxel/bevacizumab-based AVADO (Avastin And Docetaxel) trial,[12] a statistically nonsignificant numerical improvement in progression-free survival was seen in the ramucirumab/docetaxel group, whereas a significant improvement in objective response rate, disease control rate, and time to progression was seen in the ROSE trial.[19] A companion analysis of potential predictive biomarkers in the ROSE study and the present metastatic breast cancer phase II study is pending that might potentially identify a patient subpopulation for whom a ramucirumab treatment strategy in breast cancer is beneficial.

Table 3 Progression-Free and Overall Survival in the Intention to Treat Population

	Ramucirumab With Eribulin (n = 71)	Eribulin (n = 70)	HR (95% CI)	*P* (Stratified Log Rank)
Median Progression-Free Survival, Months (95% CI)	4.4 (3.1-6.7)	4.1 (3.2-5.6)	0.83 (0.56-1.23)	.35
Median Overall Survival, Months (95% CI)	13.5 (10.4-17.9)	11.5 (9.0-17.3)	0.91 (0.59-1.41)	.68
Disposition				
Deaths	47 (66)	42 (60)		
Censored	24 (34)	28 (40)		
Alive	18 (25)	20 (29)		
Withdrawal of consent	6 (8)	8 (11)		

Data are presented as median (95% CI) or n (%), except where otherwise noted.
Abbreviation: HR = hazard ratio.

Despite the lack of significant improvements in progression-free survival with the combination of ramucirumab in the recent metastatic breast cancer studies, other solid tumor trials highlight the efficacy and safety of ramucirumab.[17,18,24-26] The phase III REVEL (ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy) trial, using the same dose and schedule of ramucirumab combined with docetaxel as in the ROSE trial, significantly prolonged survival in patients with stage IV non–small-cell lung cancer, compared with those treated with docetaxel alone, and led to FDA approval in the United States.[25] In addition, the placebo-controlled, phase III REGARD (ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma) and RAINBOW

Figure 2 Forest Plot for Subgroup Analyses of Progression-Free Survival. Hazard Ratio (HR) and 95% CI Were Estimated From Unstratified Cox Model. Horizontal Bars Represent 95% CI

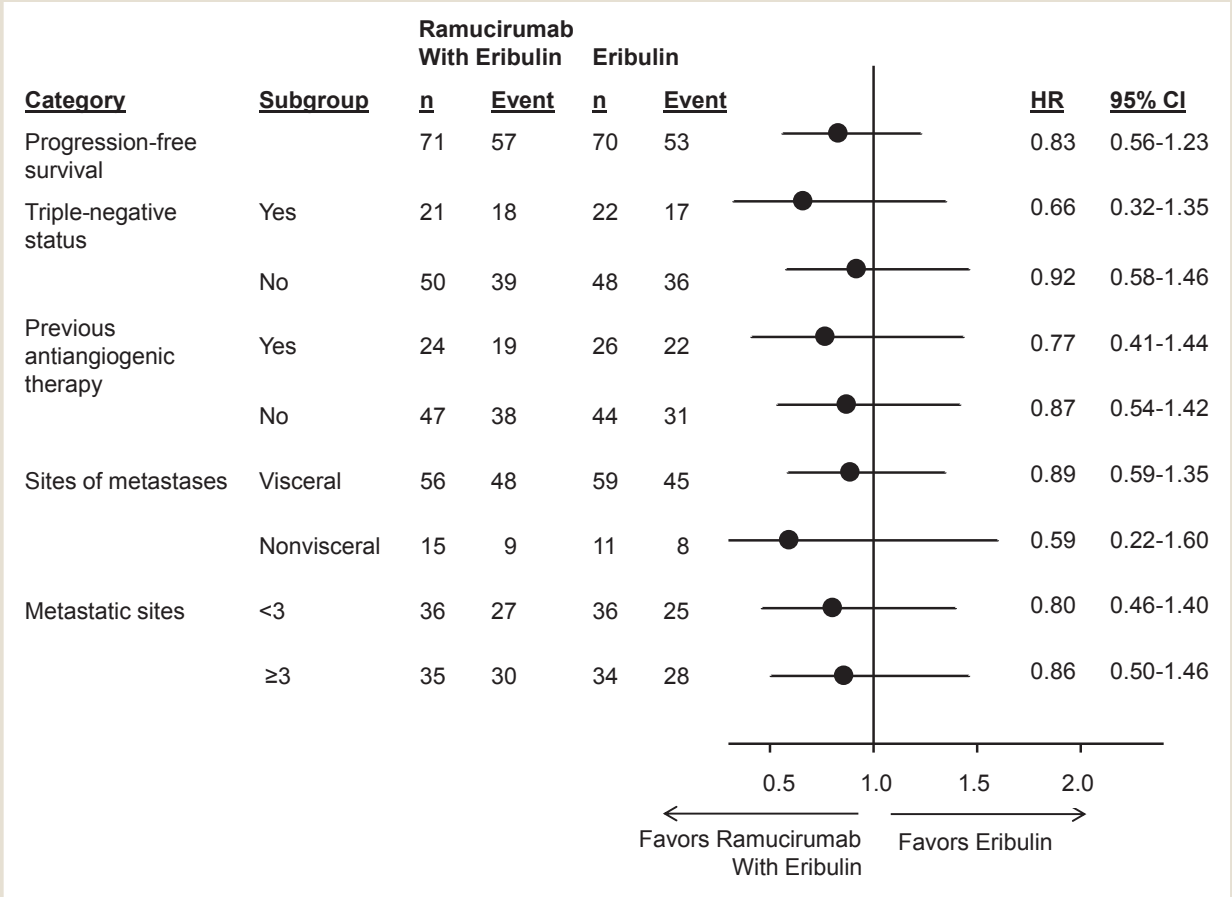


Table 4 Overall Tumor Response in Patients With Measurable Disease

Response	Ramucirumab With Eribulin (n = 62)	Eribulin (n = 60)
Best Overall Response, n (%)[a]		
CR	0	0
PR	13 (21)	17 (28)
SD	27 (44)	21 (35)
PD	13 (21)	14 (23)
Not evaluable	1 (2)	0 (0)
CR + PR + SD ≥12 Weeks, n (%) (95% CI)	30 (48) (35.5-61.4)	25 (42) (29.1-55.1)
Objective Response Rate (CR + PR), n (%) (95% CI)	13 (21) (11.7-33.2)	17 (28) (17.5-41.4)

[a]Response data were not available for 8 patients who received ramucirumab with eribulin (13%) and 8 patients who received eribulin (13%).

(ramucirumab as a single agent, or in combination with paclitaxel, in patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy) studies led to the FDA approval of ramucirumab either as a single agent at 8 mg/kg every 2 weeks or in combination with paclitaxel in patients with advanced gastric or gastroesophageal junction adenocarcinoma whose disease had progressed despite fluoropyrimidine- or platinum-containing chemotherapy.[17,18] Also, a significant overall survival and progression-free survival advantage was noted with the combination of ramucirumab with FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) in the RAISE (ramucirumab in combination with FOLFIRI in patients with metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine) trial, which evaluated ramucirumab as second-line therapy for patients with metastatic colorectal carcinoma in whom first-line oxaliplatin-based chemotherapy with bevacizumab had failed.[26] In all patient populations, including those in the current study, ramucirumab resulted in predictable and manageable toxicities.[17,18,24-26]

Table 5 All-Cause TEAEs ≥ 20% or Grade ≥ 3 (≥ 5%)

TEAE	Selected Safety			
	Ramucirumab With Eribulin (n = 69)		Eribulin (n = 65)	
	Any Grade (≥20%)	Grade ≥3[a] (≥5%)	Any Grade (≥20%)	Grade ≥3[a] (≥5%)
Fatigue	44 (64)	11 (16)	37 (57)	4 (6)
Neutropenia	29 (42)	27 (39)	29 (45)	24 (37)
Nausea	28 (41)	2 (3)	27 (42)	0 (0)
Headache	27 (39)[b]	1 (1)	10 (15)	0 (0)
Constipation	20 (29)	0 (0)	19 (29)	0 (0)
Decreased Appetite	20 (29)	1 (1)	12 (18)	0 (0)
Alopecia	20 (29)	0 (0)	15 (23)	0 (0)
Vomiting	19 (28)	2 (3)	17 (26)	0 (0)
Diarrhea	17 (25)	1 (1)	10 (15)	1 (2)
Dyspnea	15 (22)	3 (4)	14 (22)	0 (0)
Peripheral Sensory Neuropathy	15 (22)	4 (6)	16 (25)	3 (5)
Anemia	14 (20)	3 (4)	16 (25)	3 (5)
Pyrexia	14 (20)[b]	0 (0)	5 (8)	0 (0)
Dehydration	12 (17)	6 (9)	7 (11)	1 (2)
Neutrophil Count Decreased	6 (9)	4 (6)	8 (12)	5 (8)
Leukopenia	4 (6)	2 (3)	8 (12)	7 (11)

Data are presented as n (%).
Abbreviation: TEAE = treatment-emergent adverse event.
[a]There were 2 Grade 5 events (1 septic shock and 1 acute renal failure) in the ramucirumab group and 1 subdural hematoma in the eribulin group.
[b]$P < .05$ for between treatment group comparison, on the basis of Fisher exact test.

Cancer biology remains complex, with different tumor types showing varied responses. Ultimately, it is critical to understand the tumor biology and, perhaps, individual patient characteristics that will allow determination and prediction of clinical benefit with a VEGF strategy, which currently remains elusive. This randomized, phase II trial had several inherent limitations. The study population in this trial was a heterogenous group, with heavily pretreated patients. Therapy tested in patients who receive later lines of therapy might be less effective because of the activation of a variety of resistance mechanisms, which are poorly understood and might contribute to cancer progression. Although there are numerous mechanisms of resistance, preclinical models of eribulin activity have shown that CD31, which facilitates vascularization of capillary beds, and carbonic anhydrase 9 (CA9), a hypoxia marker, both play roles in capillary proliferation in hypoxic, poorly vascularized areas, particularly tumor cores.[27] However, although a decrease in CA9 was seen in preclinical studies with eribulin exposure, an advantage for eribulin with ramucirumab was not evident in this study. Thus a clearer understanding of the biology of this combination might provide further insight into this observed lack of benefit.

Drugs that seemingly demonstrate no overall benefit might benefit subgroups of patients, but identifying these subsets remains challenging. In this trial, all subgroup results were numerically in favor of the ramucirumab combination (Figure 2). Thus, the ability to select patients who might benefit from antiangiogenic therapy might be the key. Identification of reliable biomarkers to assist in the selection and evaluation of the activity of these agents remains elusive, but might lead to the determination of reliable end points.

In this trial, ramucirumab treatment was assessed in an unselected patient population, which might have obscured its potential benefit in a subset population. Despite an extensive search for biomarkers, no convincing candidates have been identified. In lung and colon cancers, bevacizumab is more effective with select chemotherapy pairing.[7,28,29] Similarly, eribulin might not be the optimal chemotherapeutic partner for ramucirumab.

Interestingly, our study had an unanticipated number of women with asymptomatic brain metastases at screening, irrespective of the underlying HER2 or hormone receptor status. Current National Comprehensive Cancer Network guidelines specify brain magnetic resonance imaging for suspicious central nervous system symptoms

during a recurrent or stage IV workup.[30] The prevalence of incidental asymptomatic brain disease in this study might prompt considerations for future studies in metastatic breast cancer on the role of screening and therapy for asymptomatic brain metastases in late-stage metastatic breast cancer, regardless of tumor receptor status.

Conclusion

Metastatic breast cancer clinical trial results to date do not support the combination of ramucirumab at 10 mg/kg every 3 weeks with chemotherapy. Questions remain as to whether the VEGF pathway is a valid target in metastatic breast cancer and whether a single-targeted agent is optimal to effectively inhibit VEGF-mediated signaling. Furthermore, the VEGF pathway likely is not unilaterally essential for cell proliferation, because of the existence of parallel and escape pathways in tumors. Thus, it is imperative to evaluate quantitative biomarkers of response to anti-VEGF strategies, as well as to develop an understanding of the molecular mechanisms of activity and resistance. Perhaps insight might be gained into an understanding of the chemosensitization effects at the cellular and molecular levels and the likelihood that combinations of targeted agents will or will not be necessary to optimize therapeutic efficacy and to sufficiently affect these mechanisms. Serial tumor biopsies to more comprehensively understand the natural history spectrum of tumor biology at baseline and throughout treatment are critical to advancing therapies for metastatic breast cancer. Only then might we expand and improve our understanding of VEGF pathway inhibitors and refine the use of this targeted therapy in breast tumors.

Clinical Practice Points

- Evidence suggests that angiogenesis plays a key role in breast cancer, and intensive neovascularizations and tumor angiogenesis correlate with metastases and poor prognosis.
- Ramucirumab is a human monoclonal antibody that inhibits ligand activation of the VEGFR-2, and is currently approved by the FDA for the treatment of advanced gastric or gastroesophageal junction adenocarcinoma, metastatic colorectal cancer, and metastatic non−small-cell lung cancer.
- Eribulin is approved by the FDA as a single agent in patients with metastatic breast cancer who were previously treated with an anthracycline and a taxane.
- The published efficacy of bevacizumab in combination with paclitaxel in metastatic breast cancer formed the rationale to explore the ramucirumab with eribulin combination as third- to fifth-line therapy in women with advanced breast cancer.
- In our multicenter, randomized, open-label, phase II trial of ramucirumab with eribulin versus eribulin alone, the combination showed acceptable toxicity but failed to meet the primary end point of improved progression-free survival.
- Our study had an unanticipated number of women with asymptomatic brain metastases at screening, irrespective of the underlying hormone or HER2 receptor status.
- Further research into the role of quantitative biomarkers of response to anti-VEGF strategies, as well as developing an understanding of the molecular mechanisms of activity and resistance are required.

Acknowledgments

The authors thank the patients, their caregivers, investigators, and study site personnel for their generous support. Funding for this study was provided by Eli Lilly and Company. Eli Lilly and Company contracted with inVentiv Health Clinical for writing support, provided by Emily Cullinan, and editorial support by Teri Tucker and Noelle Gasco.

Disclosure

D.A.Y. reports institutional grants from Eli Lilly during the course of the study. J.R. reports speaker and advisory board participance for Celgene. E.C.D. reports research funding from GlaxoSmithKline, Genentech, Novartis, Pfizer, Merck, and Bayer outside of the submitted work, and has an immediate family member in an advisory role at Novartis. F.A. reports research funding from Polyphor, AbbVie, and Novartis outside of the submitted work. H.S. reports grants from Genentech, and personal fees from Celgene and Eisai outside the submitted work. T.G. reports speaker and advisory board participance for Bristol-Myers Squibb and Boehringer Ingelheim. J.A. reports speaker and advisory board participance for Genentech, advisory roles at Genentech and Pfizer, and personal fees from Genentech and Genomic Health outside of the submitted work. J.L.B. and Y.L. were employees and stockholders of Eli Lilly and Company (Indianapolis, IN) during the conduct of the study. A.B.I. was an employee and stockholder of Eli Lilly and Company (Bridgewater, NJ) during the conduct of the study. P.D.R. reports research funding from Blue Ridge Cancer Care outside the submitted work. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

The supplemental table accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clbc.2016.07.005.

References

1. American Cancer Society. Cancer Facts and Figures 2016, Available at: http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf. Accessed: February 10, 2016.
2. Weidner N, Semple JP, Welch WR, Folkman J. Tumor angiogenesis and metastasis—correlation in invasive breast carcinoma. *N Engl J Med* 1991; 324:1-8.
3. Weidner N, Folkman J, Pozza F, et al. Tumor angiogenesis: a significant and independent prognostic indicator in early-stage breast carcinoma. *J Natl Cancer Inst* 1992; 84:1875-87.
4. Gasparini G. Prognostic value of vascular endothelial growth factor in breast cancer. *Oncologist* 2000; 5(suppl 1):37-44.
5. Folkman J. What is the evidence that tumors are angiogenesis dependent? *J Natl Cancer Inst* 1990; 82:4-6.
6. Escudier B, Pluzanska A, Koralewski P, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. *Lancet* 2007; 370:2103-11.
7. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; 350:2335-42.
8. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non−small-cell lung cancer. *N Engl J Med* 2006; 355:2542-50.
9. Taal W, Oosterkamp HM, Walenkamp AM, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. *Lancet Oncol* 2014; 15:943-53.
10. Tewari KS, Sill MW, Long HJ 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med* 2014; 370:734-43.

11. US Food and Drug Administration. *FDA commissioner removes breast cancer indication from Avastin label* Nov 18, 2011, Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm279485.htm. Accessed February 10, 2016.
12. 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; 28:3239-47.
13. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007; 357:2666-76.
14. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol* 2005; 23:792-9.
15. Robert NJ, Diéras 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; 29:1252-60.
16. *Cyramza (ramucirumab) Injection [prescribing information]*. Indianapolis, IN: Eli Lilly and Company; 2015.
17. Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2014; 383:31-9.
18. Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. *Lancet Oncol* 2014; 15:1224-35.
19. Mackey JR, Ramos-Vazquez M, Lipatov O, et al. Primary results of ROSE/TRIO-12, a randomized placebo-controlled phase III trial evaluating the addition of ramucirumab to first-line docetaxel chemotherapy in metastatic breast cancer. *J Clin Oncol* 2015; 33:141-8.
20. Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 2011; 377:914-23.
21. *Halaven (eribulin mesylate) Injection [prescribing information]*. Woodcliff Lake, NJ: Eisai Inc; 2014.
22. Gligorov J, Doval D, Bines J, et al. 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* 2014; 15:1351-60.
23. von Minckwitz G, Puglisi F, Cortes J, et al. Bevacizumab plus chemotherapy versus chemotherapy alone as second-line treatment for patients with HER2-negative locally recurrent or metastatic breast cancer after first-line treatment with bevacizumab plus chemotherapy (TANIA): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014; 15:1269-78.
24. Garcia-Carbonero R, Rivera F, Maurel J, et al. An open-label phase II study evaluating the safety and efficacy of ramucirumab combined with mFOLFOX-6 as first-line therapy for metastatic colorectal cancer. *Oncologist* 2014; 19:350-1.
25. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non—small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 2014; 384:665-73.
26. Tabernero J, Yoshino T, Cohn AL, et al. Ramucirumab versus placebo in combination with second-line FOLFIRI in patients with metastatic colorectal carcinoma that progressed during or after first-line therapy with bevacizumab, oxaliplatin, and a fluorpyrimidine (RAISE): a randomised, double-blind, multicentre, phase 3 study [erratum in 2015; 16:e262]. *Lancet Oncol* 2015; 16:499-508.
27. Funahashi Y, Okamoto K, Adachi Y, et al. Eribulin mesylate reduces tumor microenvironment abnormality by vascular remodeling in preclinical human breast cancer models. *Cancer Sci* 2014; 105:1334-42.
28. Reck M, von Pawel J, Zatloukal P, et al. Overall survival with cisplatin-gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non—small-cell lung cancer: results from a randomised phase III trial (AVAiL). *Ann Oncol* 2010; 21:1804-9.
29. Bendell JC, Bekaii-Saab TS, Cohn AL, et al. Treatment patterns and clinical outcomes in patients with metastatic colorectal cancer initially treated with FOLFOX-bevacizumab or FOLFIRI-bevacizumab: results from ARIES, a bevacizumab observational cohort study. *Oncologist* 2012; 17:1486-95.
30. National Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines)® Breast Cancer Version 2.2016, Available at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf, Accessed: August 15, 2016.

Supplemental Table 1 Treatment-Emergent Adverse Events of Special Interest

Event of Special Interest	Ramucirumab With Eribulin (n = 69)		Eribulin (n = 65)	
	Any Grade, n (%)	Grade ≥3, n (%)	Any Grade, n (%)	Grade ≥3, n (%)
Arterial Thromboembolic Event	1 (1)	1 (1)	0 (0)	0 (0)
Bleeding[a]	13 (19)[b]	1 (1)	3 (5)	1 (2)
Congestive Heart Failure	1 (1)	1 (1)	0 (0)	0 (0)
GI Hemorrhage Event	3 (4)	1 (1)	0 (0)	0 (0)
Healing Complication	1 (1)	1 (1)	0 (0)	0 (0)
Hypertension	9 (13)[b]	3 (4)	1 (2)	1 (2)
Infusion-Related Reaction	1 (1)	0 (0)	0 (0)	0 (0)
Proteinuria	4 (6)	0 (0)	3 (5)	0 (0)
Renal Failure	2 (3)	2 (3)	1 (2)	0 (0)
Venous Thromboembolic Event	3 (4)	2 (3)[c]	2 (3)	1 (2)[c]

Abbreviation: GI = gastrointestinal.
[a]Values for ramucirumab with eribulin bleeding included 7 patients with epistaxis.
[b]$P < .05$ for between treatment group comparison of any grade events on the basis of Fisher exact test.
[c]Events were pulmonary emboli.