Subgroup Analyses from a Phase 3, Open-Label, Randomized Study of Eribulin Mesylate Versus Capecitabine in Pretreated Patients with Advanced or Metastatic Breast Cancer

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ABSTRACT

PURPOSE AND METHODS: Our secondary analyses compared survival with eribulin versus capecitabine in various patient subgroups from a phase 3, open-label, randomized study. Eligible women aged ≥18 years with advanced/metastatic breast cancer and ≤3 prior chemotherapies (≤2 for advanced/metastatic disease), including an anthracycline and taxane, were randomized 1:1 to intravenous eribulin mesylate 1.4 mg/m^2 on days 1 and 8 or twice-daily oral capecitabine 1250 mg/m^2 on days 1–14 (21-day cycles).

RESULTS: In the intent-to-treat population (eribulin 554 and capecitabine 548), overall survival appeared longer with eribulin than capecitabine in various subgroups, including patients with human epidermal growth factor receptor 2-negative (15.9 versus 13.5 months, respectively), estrogen receptor-negative (14.4 versus 10.5 months, respectively), and triple-negative (14.4 versus 9.4 months, respectively) disease. Progression-free survival was similar between the treatment arms.

CONCLUSIONS: Patients with advanced/metastatic breast cancer and human epidermal growth factor receptor 2-, estrogen receptor-, or triple-negative disease may gain particular benefit from eribulin as first-, second-, and third-line chemotherapies.

TRIAL REGISTRATION (PRIMARY STUDY): This study reports the subgroup analyses of eribulin versus capecitabine from a phase 3, open-label, randomized study (www.clinicaltrials.gov; ClinicalTrials.gov identifier: NCT00337103).

KEYWORDS: subgroup analyses, eribulin, capecitabine, advanced/metastatic breast cancer, survival, human epidermal growth factor receptor 2

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Introduction

Chemotherapy is an integral part of management of patients with breast cancer, either alone or in combination with other agents. While many chemotherapy options are available for patients with pretreated metastatic breast cancer (MBC), their optimal sequence is unclear with hitherto limited data from randomized trials.[1,2] Despite recent advances, the five-year survival rate in patients with advanced/MBC is around 25%, with over 40,000 patients expected to die from the disease in the United States (US) alone in 2015.[3] There remains, therefore, a major unmet need for effective, well-tolerated therapeutic options with a robust evidence base for the treatment of advanced/MBC.

Eribulin mesylate is a microtubule dynamics inhibitor belonging to the halichondrin class of antineoplastic agents.[4,5] Recent preclinical data suggest that eribulin may also have effects on vascular remodeling, the reversal of epithelial–mesenchymal transition, and suppression of cell migration and invasion.[6,7] Eribulin is approved for the treatment of advanced or MBC in patients who have received at least one (European Union [EU]) or two (US) prior chemotherapy regimens for metastatic disease, including an anthracycline and a taxane

in either the adjuvant or the metastatic setting.[8,9] Approval is based primarily on results from Study 305/EMBRACE, a phase 3, randomized study in which eribulin was associated with a significant improvement in overall survival (OS) compared to the treatment of physician's choice (13.2 versus 10.5 months, respectively; hazard ratio [HR]: 0.81 [95% confidence interval (CI): 0.67, 0.96]; $P = 0.01$) in patients who had received two to five prior chemotherapies.[10]

More recently, Study 301 compared the efficacy and safety of eribulin versus capecitabine as first-, second-, or third-line treatment in 1102 women (eribulin 554 and capecitabine 548) with locally advanced or MBC who had received prior anthracycline- and taxane-based chemotherapies.[11] In this study, eribulin achieved a numerically longer OS than capecitabine (15.9 versus 14.5 months, respectively; HR: 0.88 [95% CI: 0.77, 1.00]; $P = 0.056$), but this did not reach the prespecified criteria for statistical significance ($P = 0.037$). There was no difference in progression-free survival (PFS) between eribulin and capecitabine (4.1 versus 4.2 months, respectively; HR: 1.08 [95% CI: 0.93, 1.25]; $P = 0.30$). The safety profiles of both drugs were manageable and consistent with their known side effects.[11]

Given these findings, practicing oncologists and their patients may want to understand whether specific patient subgroups could derive greater benefit from eribulin. Here, we assess the efficacy of eribulin compared to capecitabine in Study 301 across a range of subgroups, including those with human epidermal growth factor receptor 2 (HER2)- and triple-negative disease status.

Methods and Statistics

Patients. Patient eligibility criteria have been reported previously.[11] Briefly, these included females (aged ≥18 years) with histologically or cytologically confirmed locally advanced or MBC, ≤3 prior chemotherapy regimens (including ≤2 for advanced and/or metastatic disease), including an anthracycline and a taxane. HER2-targeted therapy was not allowed during study treatment.

As part of the original study (Kaufman et al, 2015[11]), all patients provided written informed consent and the primary study protocol was approved by all relevant review bodies. Because these analyses use existing data from the Kaufman primary study, additional consent was not sought for these analyses. The study was conducted in accordance with the Declaration of Helsinki, guidelines of the International Conference for Harmonization/Good Clinical Practice, and local requirements.

Study design. This was an international, phase 3, open-label trial (study number E7389-G000-301; clinicalTrials.gov identifier: NCT00337103). Patients were stratified by geographic region (Latin America, Western Europe/Australia, Eastern Europe, North America, Asia, or South Africa) and HER2 status (positive, negative, or unknown).[11] Patients were randomized (1:1) to receive eribulin mesylate 1.4 mg/m^2 (equivalent to 1.23 mg/m^2 eribulin [expressed as free base]) intravenously over two to five minutes on days 1 and 8 or capecitabine 1.25 g/m^2 orally twice daily on days 1–14, both in 21-day cycles, until disease progression, unacceptable toxicity, or patient/investigator request to discontinue.

Study objectives and subgroup analyses. The coprimary endpoints were OS and PFS; the secondary endpoints were objective response rate, duration of response, one-, two-, and three-year survival, and quality of life. These have been reported previously.[11]

Prespecified analyses were performed based on (i) patient demographics, (ii) receptor status, and (iii) disease status.

(i) Patient demographics included analyses based on age groups (≤40, >40 to <65, and ≥65 years) and geographic region of treatment.
(ii) Receptor status analyses were based on the status of HER2 (positive, negative, or unknown), estrogen receptor (ER; positive, negative, or unknown), hormone receptor (positive [ER-positive and/or progesterone receptor (PR)-positive], negative [both ER-negative and PR-negative], or unknown), and triple-negative (ER-negative, PR-negative, and HER2-negative) disease.
(iii) Analyses by disease status involved the number of prior chemotherapy regimens for advanced/metastatic disease (0 and ≥1); sites of disease (visceral or nonvisceral only); number of organs involved (≤2 and >2); setting of prior anthracycline and taxane therapy (both received as adjuvant therapy versus at least one received as treatment for metastatic disease); and patients whose disease was taxane resistant having progressed within 60 days after the last dose of the taxane.

A nonprespecified sensitivity analysis was previously requested by the EU health technology assessment authority based on the ER status and number of organs involved. In view of subsequent approval by the European Medicines Agency for eribulin in women who have received at least one prior line of chemotherapy for advanced/metastatic disease, further nonprespecified post hoc analyses were carried out in patients treated in this setting. These included analyses by HER2 status, ER status, triple-negative breast cancer, number of organs involved (≤2 and >2), presence of visceral disease, and disease progression within 60 days of the last dose of taxane.

Statistical analyses. Subgroup analyses were carried out using the same general approach (ie, statistical model, missing data handling, and censoring rules) as the primary analysis.[11] The HRs of eribulin versus capecitabine for OS and PFS were estimated in stratified Cox regression models with HER2 status and region as stratification factors. Stratified log-rank tests were used to obtain *P*-values of treatment difference. Kaplan–Meier estimates and distribution curves were determined within each arm. In the Study 301 primary analyses, alphas of 0.04 and 0.01 were used for testing the coprimary endpoints of OS and PFS, respectively. Results of the subgroup analyses are presented with HR and 95% CI with *P*-values shown for descriptive purposes only. No adjustment was made for multiple testing. To assess

whether OS and PFS results were consistent across subgroups, forest plots of HR with 95% CIs are provided.

Results

Patients. Overall, 1102 patients in the intent-to-treat (ITT) population (see Supplementary Fig. 1) were randomly assigned to eribulin ($n = 554$) or capecitabine ($n = 548$). Baseline patient demographics and disease characteristics were generally well balanced,[11] with only modest differences in the proportion of patients with ER-positive (46.8% versus 50.7%) and triple-negative (27.1% versus 24.5%) disease for those randomized to eribulin and capecitabine, respectively. Overall, 68.5% of patients had HER2-negative disease (see Supplementary Table 1).

Prespecified efficacy analyses.

Patient demographics. OS and PFS between the two treatment arms were similar across the age groups studied (Fig. 1). Comparison by geographic region found similar OS in both treatment arms, with the exception of patients treated in Latin America who appeared to have longer OS with eribulin than capecitabine (15.9 versus 12.0 months; $P = 0.03$; Fig. 1A); patients treated in Latin America received a similar relative dose intensity of eribulin and capecitabine (median: 99.1% versus 96.7%, respectively), and there were no imbalances in HER2-, ER-, or triple-negative status.

PFS was similar between the treatment arms, with the exception of apparently greater benefit from capecitabine

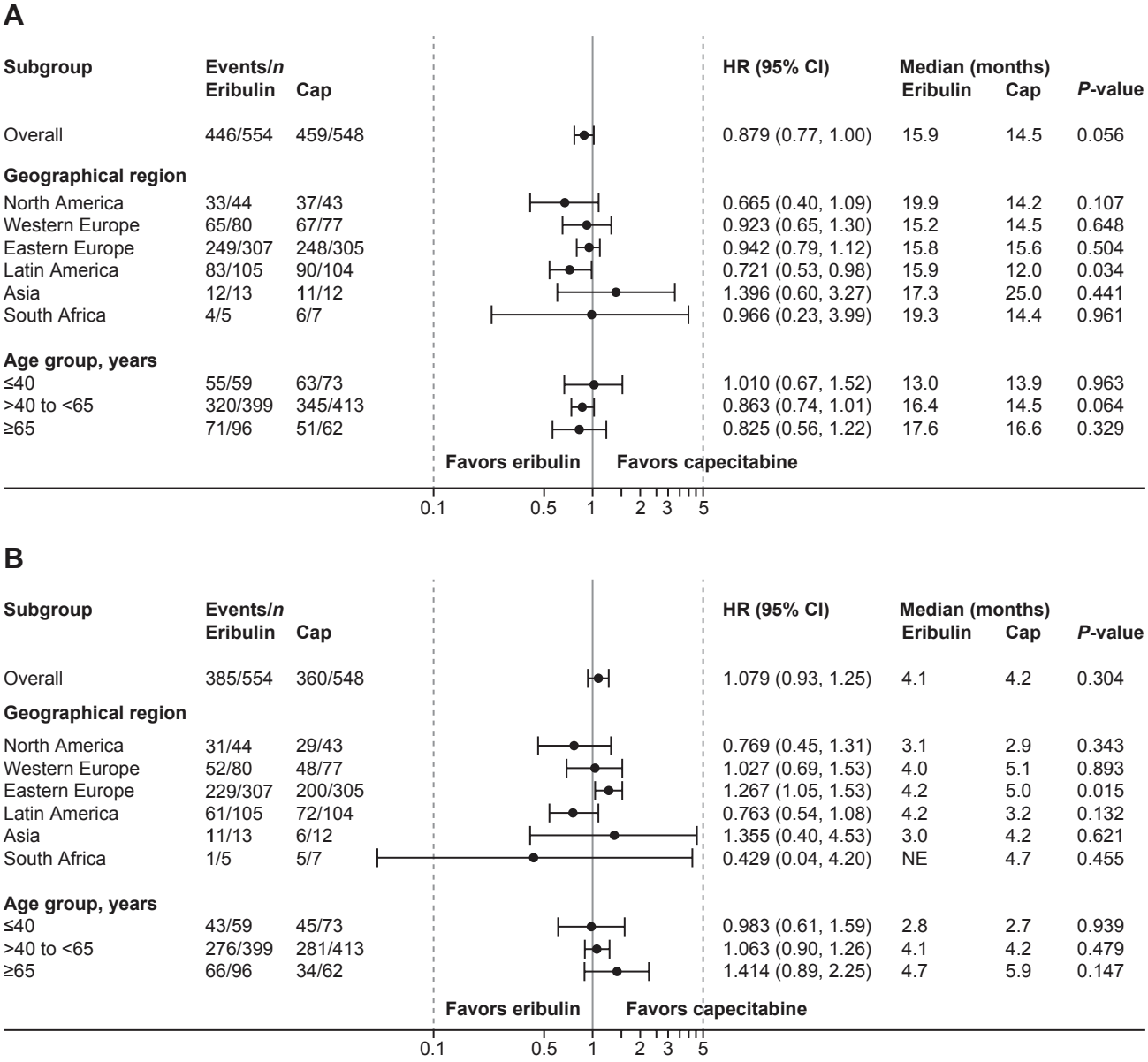


Figure 1. Forest plots of (**A**) OS and (**B**) PFS by patient demographics.
Note: Data based on independent review in the intent-to-treat population.
Abbreviations: Cap, capecitabine; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS; overall survival; PFS, progression-free survival.

than eribulin in patients treated in Eastern Europe (5.0 versus 4.2 months; $P = 0.02$; Fig. 1B), which was not observed for OS analysis.

Receptor status. OS was longer with eribulin compared to capecitabine in patients with HER2-negative (15.9 versus 13.5 months, respectively; HR: 0.84 [95% CI: 0.71, 0.98]; $P = 0.03$; Fig. 2A and Supplementary Fig. 2), ER-negative (14.4 versus 10.5 months, respectively; HR: 0.78 [95% CI: 0.63, 0.96]; $P = 0.02$; Fig. 2A) and triple-negative (14.4 versus 9.4 months, respectively; HR: 0.70 [95% CI: 0.54, 0.91]; $P = 0.01$; Fig. 2A and Supplementary Fig. 3) disease. PFS was similar in these subgroups (Fig. 2B).

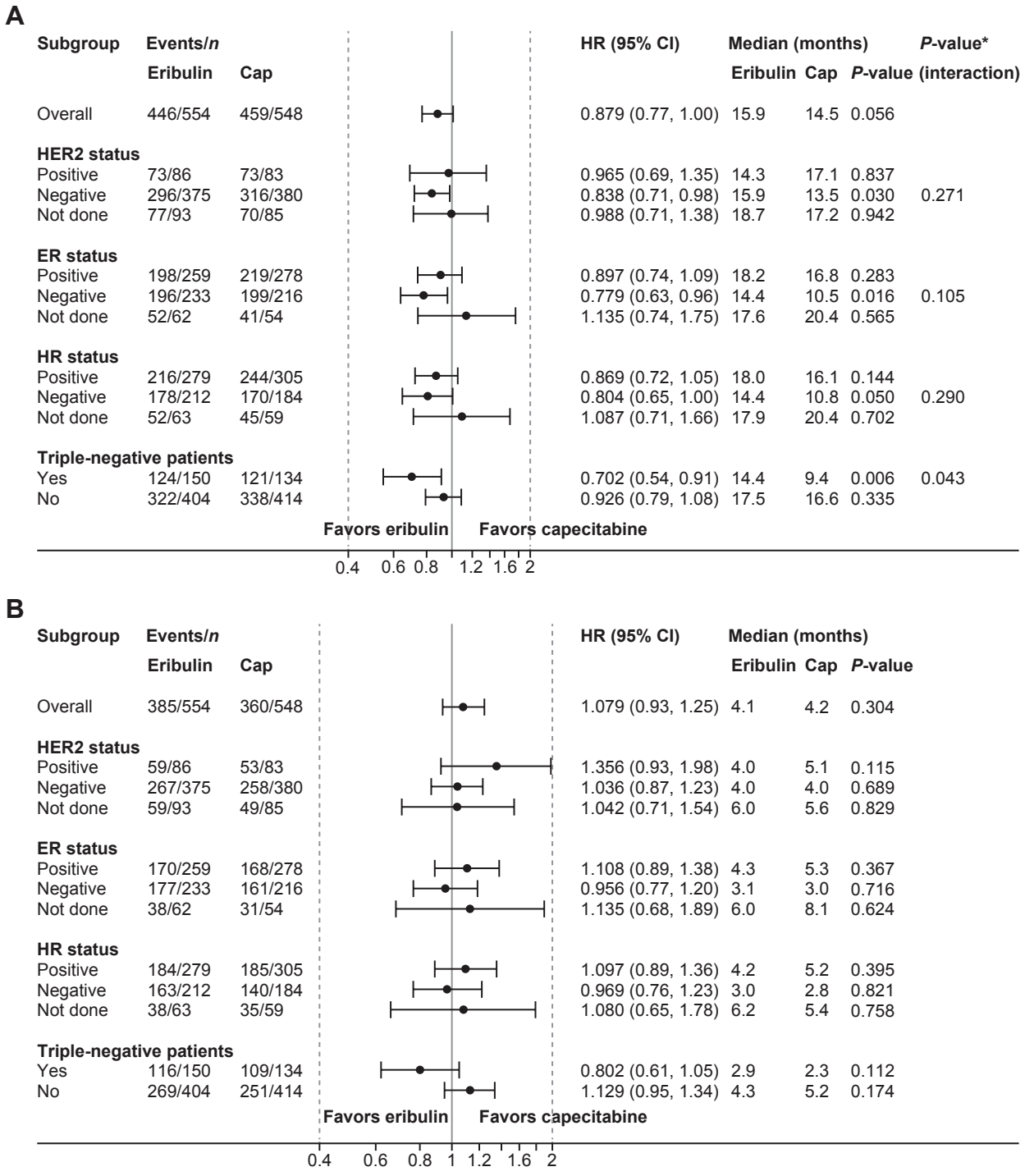


Figure 2. Forest plots of (**A**) OS and (**B**) PFS by receptor status.

Notes: *This *P*-value used values of 'Negative vs Others' for each receptor status. Data based on independent review in the intent-to-treat population.

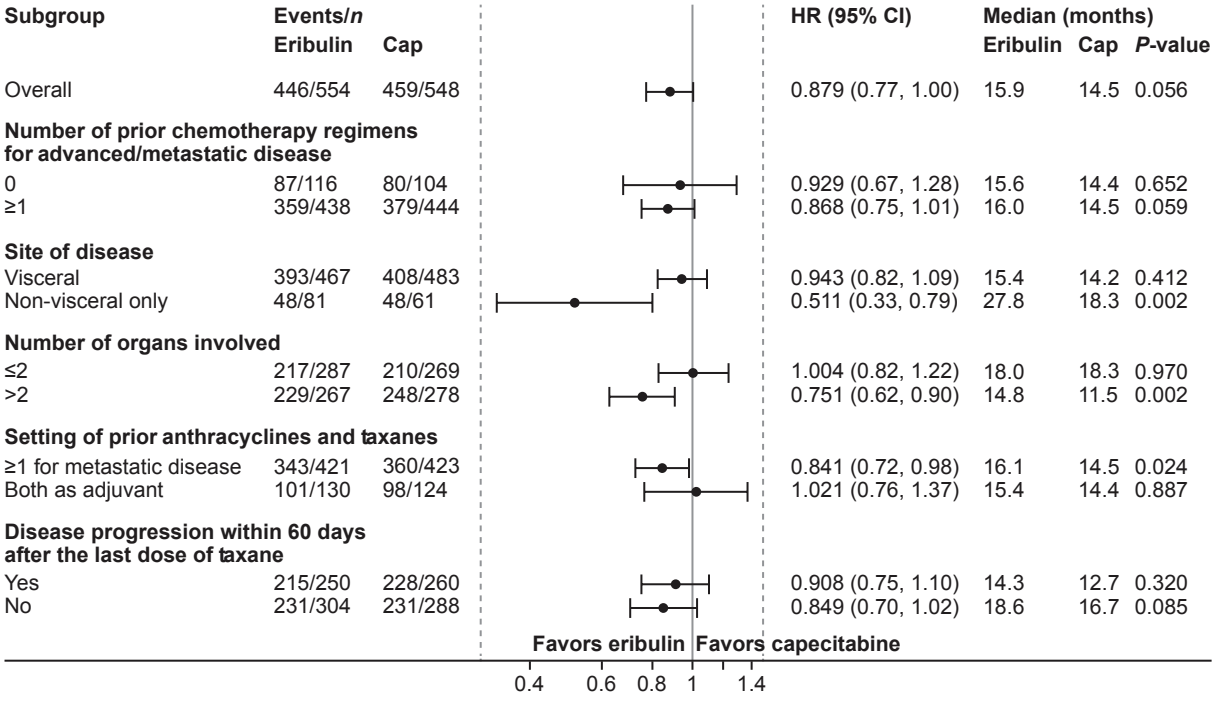
Abbreviations: Cap, capecitabine; CI, confidence interval; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio or hormone receptor; ITT, intent-to-treat; OS; overall survival; PFS, progression-free survival.

Disease status. In total, 882 of 1102 (80.0%) patients in the ITT population (eribulin, $n = 438/554$ [79.1%]; capecitabine, $n = 444/548$ [81.0%]) had received ≥1 prior chemotherapy regimen for advanced disease. OS (HR: 0.87 [95% CI: 0.75, 1.01]) and PFS (HR: 1.07 [95% CI: 0.91, 1.26]) between the two treatment arms were similar in patients who had received no prior chemotherapy for advanced/metastatic disease compared to those who had received ≥1 prior chemotherapy regimens (Fig. 3).

In the overall patient population, longer OS ($P < 0.05$) was also observed with eribulin than capecitabine in patients with only nonvisceral disease (27.8 versus 18.3 months),

A

Subgroup	Events/*n* Eribulin	Cap	HR (95% CI)	Median (months) Eribulin	Cap	*P*-value
Overall	446/554	459/548	0.879 (0.77, 1.00)	15.9	14.5	0.056
Number of prior chemotherapy regimens for advanced/metastatic disease						
0	87/116	80/104	0.929 (0.67, 1.28)	15.6	14.4	0.652
≥1	359/438	379/444	0.868 (0.75, 1.01)	16.0	14.5	0.059
Site of disease						
Visceral	393/467	408/483	0.943 (0.82, 1.09)	15.4	14.2	0.412
Non-visceral only	48/81	48/61	0.511 (0.33, 0.79)	27.8	18.3	0.002
Number of organs involved						
≤2	217/287	210/269	1.004 (0.82, 1.22)	18.0	18.3	0.970
>2	229/267	248/278	0.751 (0.62, 0.90)	14.8	11.5	0.002
Setting of prior anthracyclines and taxanes						
≥1 for metastatic disease	343/421	360/423	0.841 (0.72, 0.98)	16.1	14.5	0.024
Both as adjuvant	101/130	98/124	1.021 (0.76, 1.37)	15.4	14.4	0.887
Disease progression within 60 days after the last dose of taxane						
Yes	215/250	228/260	0.908 (0.75, 1.10)	14.3	12.7	0.320
No	231/304	231/288	0.849 (0.70, 1.02)	18.6	16.7	0.085



B

Subgroup	Events/*n* Eribulin	Cap	HR (95% CI)	Median (months) Eribulin	Cap	*P*-value
Overall	385/554	360/548	1.079 (0.93, 1.25)	4.1	4.2	0.304
Number of prior chemotherapy regimens for advanced/metastatic disease						
0	74/116	68/104	1.037 (0.73, 1.46)	4.2	4.5	0.841
≥1	311/438	292/444	1.073 (0.91, 1.26)	4.1	4.2	0.394
Site of disease						
Visceral	336/467	329/483	1.153 (0.99, 1.35)	4.0	4.2	0.075
Non-visceral only	49/81	31/61	0.835 (0.52, 1.35)	7.0	5.5	0.460
Number of organs involved						
≤2	188/287	162/269	1.126 (0.90, 1.40)	4.3	5.5	0.285
>2	197/267	197/278	1.014 (0.82, 1.25)	4.0	3.1	0.876
Setting of prior anthracyclines and taxanes						
≥1 for metastatic disease	300/421	279/423	1.057 (0.89, 1.25)	4.1	4.2	0.511
Both as adjuvant	84/130	81/124	1.050 (0.76, 1.45)	4.1	4.3	0.769
Disease progression within 60 days after the last dose of taxane						
Yes	190/250	179/260	1.168 (0.94, 1.45)	3.0	3.4	0.157
No	195/304	181/288	1.029 (0.83, 1.27)	4.8	5.0	0.789

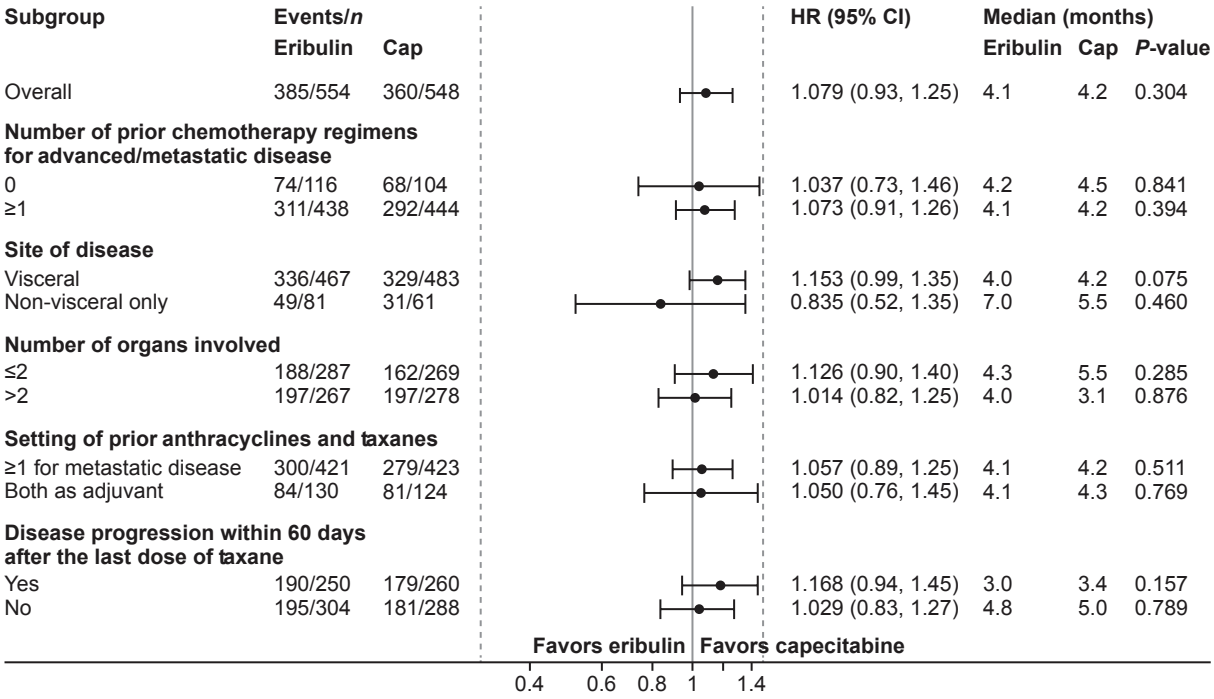


Figure 3. Forest plots of (**A**) OS and (**B**) PFS by disease status.

Note: Data based on independent review in the intent-to-treat population.

Abbreviations: Cap, capecitabine; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS; overall survival; PFS, progression-free survival.

patients with >2 organs involved (14.8 versus 11.5 months), and those who had previously received an anthracycline and/or a taxane in the metastatic setting (16.1 versus 14.5 months; Fig. 3A). No major differences in PFS were observed in these subgroups (Fig. 3B).

Nonprespecified efficacy analyses.

ITT population. The potential benefit of eribulin versus capecitabine is supported by the sensitivity analysis requested by EU regulators using the Cox model adjusted for the number of organs involved and ER status (15.9 versus 13.5 months, respectively; HR: 0.81 [95% CI: 0.69, 0.95]; $P = 0.03$).

Sensitivity analyses in patients with ≥1 prior chemotherapy regimens in the metastatic setting. Within this group of patients, the majority had received eribulin or capecitabine as second-line therapy (63.9% and 66.0%, respectively), the remainder receiving them in the third-line or later setting. OS was similar with eribulin and capecitabine in patients who had received ≥1 prior chemotherapy regimen (16.0 versus 14.5 months, respectively; HR: 0.87 [95% CI: 0.75, 1.01]; $P = 0.06$; Fig. 4). A sensitivity analysis specifically in these patients showed that OS was apparently longer with eribulin compared to capecitabine in several subgroups, including those with HER2-negative (15.9 versus 13.4 months; HR: 0.84 [95% CI: 0.70, 1.00]; $P < 0.05$), ER-negative (15.2 versus 10.3 months; HR: 0.64 [95% CI: 0.51, 0.82]; $P < 0.001$), and triple-negative (15.2 versus 9.2 months; HR: 0.62 [95% CI: 0.46, 0.83]; $P < 0.01$; Fig. 4) disease. With the exception of patients with ER-negative and triple-negative disease, PFS was similar between the treatment arms for most subgroups (see Supplementary Table 2).

To allow for the impact on OS of the large treatment effects in patients with ER-negative disease and those with >2 organs involved, a further sensitivity analysis was conducted, adjusting the statistical model for these effects. In these analyses, median OS in the overall population was in favor of eribulin compared to capecitabine (16.0 versus

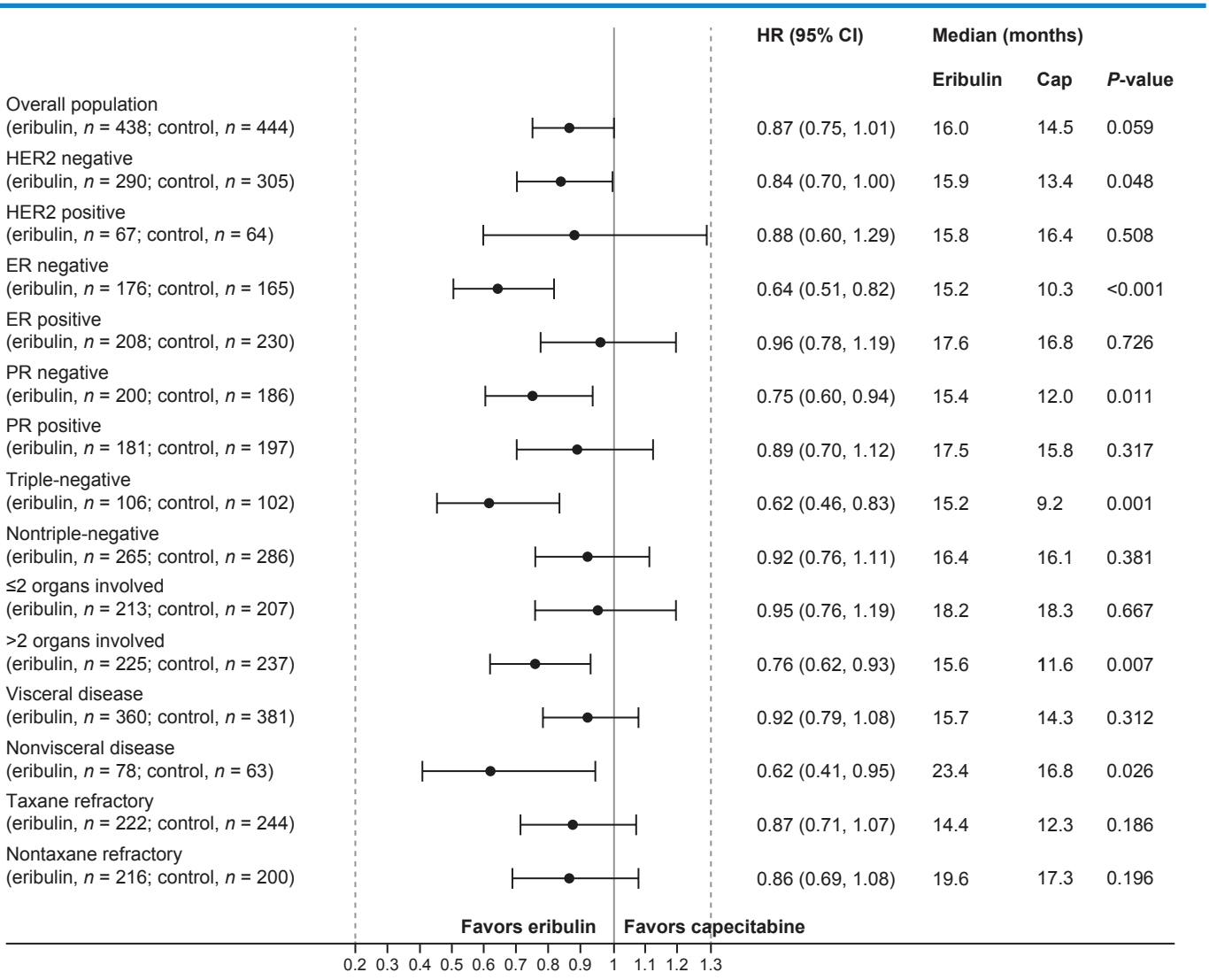


Figure 4. Forest plot of OS in patients who received eribulin after one or more prior chemotherapy regimens for advanced disease.
Abbreviations: Cap, capecitabine; CI, confidence interval; HR, hazard ratio; OS, overall survival.

14.5 months; HR: 0.82 [95% CI: 0.71, 0.95]; $P < 0.01$; see Supplementary Fig. 4). Consistent with above findings, eribulin appeared to prolong OS than capecitabine in this additional sensitivity analysis in several subgroups, including those with HER2-, ER-, and triple-negative disease (see Supplementary Fig. 4).

Discussion

In light of the observed survival benefit seen in Study 305/EMBRACE,[10] eribulin is recommended by all major guidelines for the treatment of patients with advanced/MBC.[1,2,12] As reported previously, eribulin was not statistically superior to capecitabine in Study 301 in terms of OS or PFS, although a numerical improvement in OS was seen with eribulin compared to capecitabine ($P = 0.056$).[11] The current analyses provide important information on the efficacy of eribulin compared to capecitabine in a number of patient subgroups, especially those with HER2-, ER-, and triple-negative disease.

In prespecified analyses of well-known prognostic factors, improvement in OS appeared to be seen in some subgroups with eribulin compared to capecitabine. In particular, median OS was longer in patients with HER2-, ER-, and triple-negative disease receiving eribulin versus capecitabine (by 2.4, 3.9, and 5.0 months, respectively; all $P < 0.05$). These results are clinically relevant because HER2-negative disease is the largest subgroup, comprising almost 85% of women with breast cancer;[13] in addition, systemic treatment options for triple-negative disease are limited to chemotherapy.[14,15] Although capecitabine is active in patients with triple-negative breast cancer, eribulin appears to represent a more effective treatment option for these women, who represented a large subgroup of the Study 301 population, and those treated in routine clinical practice; further studies are, however, warranted to confirm this finding.

A potential survival advantage was suggested in patients with nonvisceral disease and those with >2 organs involved receiving eribulin compared to capecitabine (9.5 and 3.3 months longer OS, respectively; $P < 0.05$). Both findings, especially the subgroup of patients with nonvisceral disease where a greater survival advantage was implied, merit further investigation in larger trials. Patients from Latin America receiving eribulin also appeared to derive greater OS benefit compared to capecitabine treatment. Further exploration of this subgroup indicated no major differences between the treatment arms in terms of receptor status or dose intensity of study drug; this may, therefore, represent a chance finding, together with the apparent benefit in PFS in patients from Eastern Europe receiving capecitabine.

A small increase in OS (1.5 months) with eribulin versus capecitabine was observed in patients who had received ≥1 prior chemotherapy regimen for advanced/metastatic disease. Additional analyses suggested that eribulin prolonged OS compared to capecitabine in several subgroups, including those with HER2-, ER-, and triple-negative disease. These findings provide clinicians and patients with additional evidence specific to the patient population now approved in the EU and elsewhere (but not in the US) for treatment with eribulin.

Similar to the primary analysis of this study[11] and the EMBRACE study,[10] eribulin consistently had a greater impact on OS than PFS. This may, at least in part, be attributable to the phenotypic changes and/or eribulin-induced changes in tumor phenotype and vasculature observed in preclinical models, which may enhance the efficacy of subsequent therapies[6,7] and improve outcomes. Further translational studies are needed to confirm these preclinical findings.

A limitation of these analyses is that all *P* values must be interpreted in the context of the primary analysis for Study 301 not achieving statistical significance. All subsequent secondary and subgroup analyses are, therefore, essentially exploratory. Accordingly, no adjustment was made for multiple testing in the current analyses, and the *P* values are presented for descriptive purposes only; further studies would be needed to confirm these results. While the majority of subgroup analyses were prespecified, some were not, including the additional sensitivity analyses in patients who had received ≥1 prior chemotherapy for advanced/metastatic disease and the use of an adjusted Cox model with added covariates. These analyses resulted, however, from interaction with the EU regulatory authorities. They are important in the absence of data from prospective studies in patient populations that match the approved indication for eribulin in the EU, namely the second-line or later treatment of MBC. In that context, these exploratory and retrospective analyses may provide clinicians and patients with valuable additional data for eribulin relative to capecitabine, especially in women with HER2-, hormone receptor-, and triple-negative breast cancer.

Conclusions

In this subgroup analysis, eribulin was an effective therapeutic option for the treatment of patients with advanced/MBC and may especially benefit those with HER2-negative, ER-negative and triple-negative disease. These data in patients treated in the first-, second-, and third-line settings support eribulin as an active single agent for patients with advanced/MBC who have received prior chemotherapy, including an anthracycline and a taxane.

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Author Contributions

Contributed to the study conception and design: CT, JC, CED, and PAK. Contributed to the collection of data: CT, AA, JC,

LY, CED, MSO, GV, and PAK. Had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis: GV, JS. All authors contributed to the writing and development of the article. All authors reviewed and approved of the final manuscript.

Supplementary Materials

Supplementary figure 1. CONSORT diagram for Study 301 (NCT00337103).

Supplementary figure 2. Kaplan–Meier curve for OS in HER2-negative patients (ITT population).

Supplementary figure 3. Kaplan–Meier curve for OS in patients with triple negative breast cancer (ITT population).

Supplementary figure 4. Forest plot of OS in patients who received eribulin after one or more prior chemotherapy regimens for advanced disease: additional analysis model.

Supplementary table 1. Patient demographics and baseline characteristics (ITT population).

Supplementary table 2. PFS for Study 301 in patients who received eribulin after one or more prior chemotherapy regimens for advanced disease.

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