Phase III Open-Label Randomized Study of Eribulin Mesylate Versus Capecitabine in Patients With Locally Advanced or Metastatic Breast Cancer Previously Treated With an Anthracycline and a Taxane

Purpose
This phase III randomized trial (ClinicalTrials.gov identifier: NCT00337103) compared eribulin with capecitabine in patients with locally advanced or metastatic breast cancer (MBC).

Patients and Methods
Women with MBC who had received prior anthracycline- and taxane-based therapy were randomly assigned to receive eribulin or capecitabine as their first-, second-, or third-line chemotherapy for advanced/metastatic disease. Stratification factors were human epidermal growth factor receptor-2 (HER2) status and geographic region. Coprimary end points were overall survival (OS) and progression-free survival (PFS).

Results
Median OS times for eribulin (n = 554) and capecitabine (n = 548) were 15.9 and 14.5 months, respectively (hazard ratio [HR], 0.88; 95% CI, 0.77 to 1.00; P = .056). Median PFS times for eribulin and capecitabine were 4.1 and 4.2 months, respectively (HR, 1.08; 95% CI, 0.93 to 1.25; P = .30). Objective response rates were 11.0% for eribulin and 11.5% for capecitabine. Global health status and overall quality-of-life scores over time were similar in the treatment arms. Both treatments had manageable safety profiles consistent with their known adverse effects; most adverse events were grade 1 or 2.

Conclusion
In this phase III study, eribulin was not shown to be superior to capecitabine with regard to OS or PFS.
The first phase III trial of eribulin (Eisai Metastatic Breast Cancer Study Assessing Physician’s Choice Versus Eribulin [EMBRACE]) compared eribulin with treatment of physician’s choice (TPC) in patients with MBC who had received at least two prior chemotherapy regimens for advanced disease but no more than five cytotoxic regimens in total. In this trial, there was a significant improvement in OS for eribulin compared with TPC; this was confirmed in the updated analysis requested by European and US regulatory authorities. The median OS was 13.2 months for eribulin versus 10.5 months for TPC (hazard ratio [HR], 0.81; 95% CI, 0.67 to 0.96; nominal [analysis not prespecified] \( P < .01 \)). Furthermore, eribulin had a manageable safety profile, with the most common adverse events (AEs) being asthenia or fatigue, and neutropenia.\(^{18,19}\)

As a result, eribulin has been approved in more than 50 countries as monotherapy for patients with advanced breast cancer or MBC who have previously received at least two chemotherapeutic regimens for advanced/metastatic disease, with prior therapy having included an anthracycline and a taxane in the adjuvant or metastatic setting.\(^{20}\) We report results from a second phase III study comparing eribulin with capecitabine as first-, second-, or third-line therapy for advanced breast cancer or MBC. Detailed QoL and pharmacokinetic/pharmacodynamic results will be reported separately.

**Patients**

Inclusion criteria included: female sex; age ≥ 18 years; histologically or cytologically confirmed breast cancer; up to three prior chemotherapy regimens and up to two prior chemotherapy regimens for advanced and/or metastatic disease; prior therapy with an anthracycline and a taxane; resolution of all chemotherapy- or radiation-related toxicities to grade 1 (except for stable sensory neuropathy ≤ grade 2 and alopecia); Eastern Cooperative Oncology Group performance status of 0 to 2; and adequate renal, bone marrow, and liver function. Measurable or nonmeasurable disease was allowed. Exclusion criteria included prior capecitabine treatment and radiation therapy encompassing more than 30% of marrow. Patients with human epidermal growth factor receptor 2 (HER2)–positive disease could have received HER2-targeted therapy before or after study treatment but not while on study treatment.

![CONSORT diagram](Fig 1. CONSORT diagram.)
### Table 1. Patient Demographic and Baseline Clinical Characteristics (intent-to-treat population)

| Characteristic | Eribulin (n = 554) | Capecitabine (n = 548) |
|----------------|-------------------|-----------------------|
| No. of patients | %                  | %                     |
| **Age, years**  |                   |                       |
| Median          | 54.0              | 53.0                  |
| Range           | 24-80             | 26-80                 |
| **Race**        |                   |                       |
| White           | 496               | 496                   |
| Asian/Pacific Islander | 18   | 18                    |
| Black or African American | 15  | 16                    |
| Other           | 25                | 19                    |
| **ECOG performance status** |     |                       |
| 0               | 250               | 230                   |
| 1               | 293               | 301                   |
| 2               | 11                | 16                    |
| 3               | 0                 | 1                     |
| **No. of prior chemotherapy regimens** |     |                       |
| 0               | 1                 | 0                     |
| 1               | 147               | 153                   |
| 2               | 319               | 314                   |
| 3               | 84                | 152                   |
| 4               | 3                 | 0.5                   |
| 5               | 0                 | 0.2                   |
| **No. of organs involved** |     |                       |
| 0               | 250               | 230                   |
| 1               | 293               | 301                   |
| 2               | 11                | 16                    |
| 3               | 0                 | 1                     |
| **Site of disease** |     |                       |
| 0               | 250               | 230                   |
| 1               | 293               | 301                   |
| 2               | 11                | 16                    |
| 3               | 0                 | 1                     |
| **Most common metastatic sites** |     |                       |
| Bone            | 299               | 308                   |
| Lung            | 279               | 280                   |
| Lymph nodes     | 268               | 274                   |
| Liver           | 247               | 271                   |

(continued in next column)

### Table 1. Patient Demographic and Baseline Clinical Characteristics (intent-to-treat population) (continued)

| Characteristic | Eribulin (n = 554) | Capecitabine (n = 548) |
|----------------|-------------------|-----------------------|
| No. of patients | %                  | %                     |
| **No. of organs involved** |     |                       |
| 1               | 113               | 92                    |
| 2               | 174               | 177                   |
| 3               | 153               | 149                   |
| 4               | 114               | 129                   |
| **Site of disease** |     |                       |
| 0               | 0                 | 1                     |
| **Visceral only** |     |                       |
| 0               | 81                | 61                    |
| **Missing**     | 6                 | 4                     |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor.

*Refractory was defined as progression within 60 days after taking the last dose.
†Reported by at least 20% of the total population.
‡Visceral/nonvisceral was determined by independent assessment.

All patients provided written informed consent. Approval was obtained from independent ethics committees and regulatory authorities in participating countries. The study was conducted in accordance with the World Medical Association Declaration of Helsinki, guidelines of the International Conference for Harmonisation/Good Clinical Practice, and local ethical and legal requirements.

### Study Design

This phase III, open-label, parallel, two-arm, multicenter trial (study No. E7389-G000-301; ClinicalTrials.gov identifier: NCT00337103) stratified patients by geographic region (Latin America, Western Europe/Australia, Eastern Europe, North America, Asia, or South Africa) and the HER2 status of their cancer (positive, negative, or unknown). Patients were randomly assigned (1:1) using a central interactive voice-response system to receive eribulin mesylate 1.25 g/m² intravenously over 2 to 5 minutes on days 1 and 8, or capecitabine 2.0 g/m² orally twice per day on days 1 to 14, both in 21-day cycles. Patients were sequentially randomized before two or more missed scheduled tumor assessments, and confirmed by a second assessment at least 4 weeks after first observation of response. An objective response rate (ORR), defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) by investigator assessment, was the primary end point; OS was the coprimary end point, as used in other clinical trials, were OS and progression-free survival (PFS). Secondary end points included objective response rate (ORR); duration of response; 1-, 2-, and 3-year survival; safety; QoL; and population pharmacokinetic/pharmacodynamic relationships.

### Study Objectives

Coprimary end points, as used in other clinical trials, were OS and progression-free survival (PFS). Secondary end points included objective response rate (ORR); duration of response; 1-, 2-, and 3-year survival; safety; QoL; and population pharmacokinetic/pharmacodynamic relationships.

### Study Assessments

OS was measured from date of random assignment until date of death from any cause or last date known alive/data cutoff (censored). PFS was measured from date of random assignment to date of recorded disease progression or death from any cause.

Tumor response was determined according to RECIST (version 1.0), censored at last tumor assessment before subsequent anticancer therapy or before two or more missed scheduled tumor assessments, and confirmed by a second assessment at least 4 weeks after first observation of response.
interim analyses and final analysis were spending function\(^2\); the nominal significance levels of the first and second of OS was based on Lan-DeMets implementation of the O'Brien-Fleming radiology review (secondary analysis). Tumor assessments were obtained from any cause, or censoring at date of last tumor assessment. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3).

**QoL Analyses**

QoL was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (version 3.0) and breast module Quality of Life Questionnaire BR23 (version 1.0) at baseline, at 6 weeks, and at 3, 6, 12, 18, and 24 months or until disease progression or initiation of other antitumor treatment. The principal prespecified outcome was overall QoL, expressed as change from baseline in Global Health Status (GHS)/QoL measured on a 0 (worst) to 100 (best) scale.

**Statistical Analyses**

Because there were coprimary end points, the total type I error was split, 0.04 for OS and 0.01 for PFS. Sample size was based on a superiority test of OS; when 905 events (deaths) were observed, the two-sided log-rank test had 90% power to detect a 3-month increase in median survival over a 12-month median survival for capecitabine (HR, 0.80). Planned enrollment was 1,100 patients with a maximum of 55 patients per study site.

Primary efficacy analysis used the intent-to-treat population comprising all randomly assigned patients. The safety population included all patients who received at least one dose of treatment. Tumor assessments were obtained from an independent radiology review (primary analysis) and an investigator radiology review (secondary analysis).

The coprimary end points, OS and PFS, were compared between treatment groups using two-sided, stratified (geographic region and HER2 status) log-rank tests. Interim planned OS analyses were performed after 453 and 603 deaths. To maintain an overall level of 0.04, spending for sequential analyses was overall QoL, expressed as change from baseline in Global Health Status (GHS)/QoL measured on a 0 (worst) to 100 (best) scale.

**RESULTS**

**Patients**

From September 2006 to September 2009, 1,102 patients were randomly assigned, 545 to eribulin and 648 to capecitabine (Fig 1). Baseline patient demographics and disease characteristics were generally well balanced (Table 1); there were small differences in the percentages of patients who had estrogen receptor–positive and triple-negative disease (46.8% vs 50.7%, and 27.1% vs 24.5% for eribulin and capecitabine, respectively). Overall, 68.5% of patients had HER2-negative disease. Twenty percent, 52.0%, and 27.2% of patients received study therapy as first-line, second-line, and third-line treatment, respectively, for advanced disease.

**Efficacy**

Median OS was 15.9 months (95% CI, 15.2 to 17.6 months) for eribulin compared with 14.5 months (95% CI, 13.1 to 16.0 months) for capecitabine (Fig 2A), resulting in an HR of 0.88 (95% CI, 0.77 to 1.00; \(P = .056\)). Median PFS was 4.1 months (95% CI, 3.5 to 4.3 months) for eribulin and 4.2 months (95% CI, 3.9 to 4.8 months) for capecitabine (HR, 1.08; 95% CI, 0.93 to 1.25; \(P = .30\); Fig 2B). By investigator review, median PFS times were 4.2 months (95% CI, 3.9 to 4.3 months) and 4.1 months (95% CI, 3.7 to 4.5 months) for eribulin and capecitabine, respectively (HR, 0.98; 95% CI, 0.86 to 1.11; \(P = .74\)).

ORRs by independent review were 11.0% (95% CI, 8.5% to 13.9%) and 11.5% (95% CI, 8.9% to 14.5%; \(P = .85\)) for eribulin and capecitabine, respectively (Table 2). ORRs by investigator review were
16.1% (95% CI, 13.1% to 19.4%) and 19.9% (95% CI, 16.6% to 23.5%; P = .10) for eribulin and capecitabine, respectively.

Analyses by stratification factors. Prespecified exploratory analyses were conducted to assess an effect of eribulin according to HER2 status. Although a possible benefit according to HER2 status was suggested for OS, an interaction test showed no benefit for eribulin when comparing patients with HER2-negative disease and all other patients (HER2-positive and unknown HER2 status).

Safety

For eribulin, the median number of treatment cycles was six (range, one to 65 cycles), and the median duration of treatment was 4.1 months (range, 0.7 to 45.1 months). For capecitabine, the median number of treatment cycles was five (range, one to 61 cycles), and the median duration of treatment was 3.9 months (range, 0.7 to 47.4 months). Relative dose-intensity was 87% for eribulin and 86% for capecitabine.

AEs were reported in 94.1% and 90.5% of patients treated with eribulin and capecitabine, respectively. Serious AEs were reported in 17.5% of those receiving eribulin and 21.1% of those receiving capecitabine; these were life-threatening AEs in 2.2% and 3.5% of patients, respectively, and required or prolonged hospitalization in 13.4% and 17.0% of patients, respectively. AEs leading to discontinuation, reduction, or delay in treatment occurred in 7.9%, 32.0%, and 31.8% of patients receiving eribulin and in 10.4%, 31.9%, and 35.7% of those receiving capecitabine. These were reported as treatment-related AEs for five patients treated with eribulin (sepsis, pericardial effusion, sudden death, toxic hepatitis, and renal failure) and four...
patients treated with capcitabine (sepsis, pneumonia, cardiogenic shock, and pancytopenia).

The most common AEs with eribulin were neutropenia, alopecia, leukopenia, global peripheral neuropathy, and nausea. The most common AEs with capcitabine were hand-foot syndrome, diarrhea, anemia, leukopenia, global peripheral neuropathy, and nausea. The most common AEs leading to discontinuation (occurring in >1% of patients) were neutropenia (1.7%) with eribulin and hand-foot syndrome (2.2%) and dyspnea (1.1%) with capcitabine. Colony-stimulating factors were received by 14.6% and 3.6% of patients in the eribulin and capcitabine arms, respectively.

Table 3. Most Common Adverse Events (incidence of > 10% for all grades or > 2% for ≥ grade 3 in either arm; safety population)

| Adverse Event                  | Eribulin (n = 544) | Capecitabine (n = 546) |
|--------------------------------|--------------------|------------------------|
|                                | All Grades         | Grade 3                | Grade 4                |
|                                | No. of Patients %  | No. of Patients %      | No. of Patients %      |
| Neutropenia                    | 295 54.2           | 134 24.6               | 115 21.1               |
| Leukopenia                     | 171 31.4           | 73 13.4                | 9 1.7                 |
| Anemia                         | 104 19.1           | 11 2.0                 | 0 0                   |
| Hand-foot syndrome             | 11 2.0             | 8 1.5                  | 3 0.6                 |
| Neutropenia                    | 295 54.2           | 134 24.6               | 115 21.1               |
| Leukopenia                     | 171 31.4           | 73 13.4                | 9 1.7                 |
| Anemia                         | 104 19.1           | 11 2.0                 | 0 0                   |
| Hand-foot syndrome             | 11 2.0             | 8 1.5                  | 3 0.6                 |

Nonhematologic

| Adverse Event                  | Eribulin (n = 544) | Capecitabine (n = 546) |
|--------------------------------|--------------------|------------------------|
|                                | All Grades         | Grade 3                | Grade 4                |
|                                | No. of Patients %  | No. of Patients %      | No. of Patients %      |
| Alopecia                       | 188 34.6           | 22 4.0                 |                        |
| Global peripheral neuropathy*  | 149 27.4           | 35 6.4                 | 3 0.6                 |
| Nausea                         | 121 22.2           | 1 0.2                  | 0 0                   |
| Fatigue                        | 91 16.7            | 11 2.0                 | 0 0                   |
| Anemia                         | 83 15.3            | 22 4.0                 | 1 0.2                 |
| Diarrhea                       | 78 14.3            | 6 1.1                  | 0 0                   |
| Pyrexia                        | 70 12.9            | 2 0.4                  | 0 0                   |
| Headache                       | 69 12.7            | 4 0.7                  | 0 0                   |
| Decreased appetite             | 68 12.5            | 3 0.6                  | 0 0                   |
| Vomiting                       | 65 11.9            | 1 0.2                  | 1 0.2                 |
| Dyspnea                        | 56 10.3            | 10 1.8                 | 2 0.4†                |
| Back pain                      | 56 10.3            | 8 1.5                  | 0 0                   |
| Bone pain                      | 50 9.2             | 10 1.8                 | 1 0.2                 |
| ALT increased                  | 46 8.5             | 18 3.3                 | 0 0                   |
| Hypokalemia                    | 19 3.5             | 5 0.9                  | 0 0                   |
| Hand-foot syndrome             | 1 0.2              | 0 0                    | 0 0                   |

**Note:** If a patient had two adverse events in the same system organ class or with the same preferred term with different Common Terminology Criteria for Adverse Events grades, the event with the highest grade was used for that patient.

*Defined as Standardized Medical Dictionary for Regulatory Activities Queries narrow and broad terms.
†Grade 5 events also occurred in four patients (0.7%).
‡Grade 5 events also occurred in three patients (0.5%).

QoL Analyses

Almost all (> 95%) QoL data were available at baseline for both arms; completion rates over time decreased similarly in both arms (Data Supplement). GHS/QoL scores were low at baseline in both the eribulin and capcitabine arms (mean ± standard deviation, 56.3 ± 22.2 and 54.7 ± 21.7, respectively). Over time, average GHS/QoL scores improved in both arms, but the linear mixed model and pattern-mixture model showed no significant difference between the groups (linear mixed model: estimated treatment effect, −0.068; P = .958; pattern-mixture model: estimated treatment effect, 0.082; P = .949).

Although eribulin is an active single agent in patients with MBC, it was not superior to capcitabine with regard to either OS or PFS. Our results contrast with those of EMBRACE, in which a statistically significant improvement in OS was seen with eribulin compared with TPC.18 The reasons for this apparent difference are unclear. It is possible that treatment earlier in the course of MBC is less likely to impact OS, as a consequence of such patients typically receiving further lines of cytotoxic or other therapy. Even if therapeutically more active, a first- or second-line regimen may not impact on OS when multiple subsequent lines of effective treatment are administered.

The influence of postprogression therapies on OS is often discussed in studies of MBC, particularly when cross over is imbalanced, and usually in the context of differences in PFS being more apparent than those in OS (which did not occur in our study). In this trial, more
patients went on to receive further anticancer treatment after study treatment in the eribulin arm (70.4%) than in the capecitabine arm (62.0%). Specifically, patients in the eribulin arm could cross over and receive capecitabine (49.6%), whereas cross over from capecitabine to eribulin (0.4%) was limited by eribulin only being approved toward the end of the study. Nevertheless, no differences in OS were seen in this study.

The OS data in patients with HER2-negative disease were similar to those reported in EMBRACE, and there was no significant difference in PFS between treatment groups in the HER2 subgroups. Although PFS and OS are similar to other studies in this setting, ORRs in this study are low. This may be explained, at least in part, by only 88% of patients having disease available for response; the remainder had no baseline scan per independent review (1%), a baseline scan of any type only (7%), or a RECIST response but no confirmatory bone scan (3%).

Eribulin had a manageable tolerability profile, consistent with previous studies; neutropenia, alopecia, leukopenia, and peripheral neuropathy were the most common AEs.19,24-27 For patients receiving eribulin, the incidences of hematologic and grade 3 or 4 AEs were similar to those in EMBRACE, except for febrile neutropenia. The total incidence of febrile neutropenia with eribulin was lower in this trial (2% with eribulin vs 0.9% with capcitabine) than in EMBRACE (5%), in which patients had received more prior lines of chemotherapy.18 Neutropenia was managed with dose delays, reductions, and growth factors according to local practice. The use of colony-stimulating factors was higher in the eribulin group than in the capecitabine group (14.6% vs 3.6%, respectively), consistent with the greater incidence of neutropenia. There were, however, no deaths as a result of neutropenia in either treatment group. AEs experienced with capecitabine, particularly hand-foot syndrome and diarrhea, were also consistent with known AEs.10,8,28 Even though this study used the approved dose of capecitabine (1.25 g/m2 twice per day), these AEs were generally within the range observed for capecitabine administered at 1.0 g/m2 twice per day, 29-35 a dose commonly used in clinical practice.36 Furthermore, dose-intensity was high for both eribulin and capecitabine in this study. Although incidences of alopecia and peripheral neuropathy were higher for eribulin compared with capecitabine, incidences of diarrhea and vomiting were lower. In summary, the AE profiles of both treatments in this phase III trial were predictable, manageable, and, overall, clinically acceptable. From the patients’ perspective, average GHS/QoL scores generally improved in both treatment arms with no evidence of a difference between treatments.

In conclusion, this trial did not demonstrate superiority of eribulin versus capecitabine for either OS or PFS. The effects on QoL in this population of patients with MBC and the AE profiles of eribulin and capecitabine were consistent with their known AEs.

### AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author’s immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** Martin S. Olivo, Eisai (C); Corina E. Dutuc, Eisai (C) Consultant or Advisory Role: Peter A. Kaufman, Eisai (C); Ahmad Awada, Eisai (C); Chris Twelves, Eisai (C); Galina Velikova, Eisai (U); Javier Cortes, Roche, Novartis, Celgene (C) Stock Ownership: None Honoraria: Peter A. Kaufman, Eisai; Chris Twelves, Eisai; Galina Velikova, Eisai; Javier Cortes, Roche, Novartis, Celgene, Eisai Research Funding: Peter A. Kaufman, Eisai; Louise Yelle, Eisai

**Expert Testimony:** None Patents, Royalties, and Licenses: None Other Remuneration: Galina Velikova, Eisai

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Eribulin v Capecitabine in Metastatic Breast Cancer

HER2/neu (human epidermal growth factor receptor 2): also called ErbB2. HER2/neu belongs to the epidermal growth factor receptor (EGFR) family and is overexpressed in several solid tumors. Like EGFR, it is a tyrosine kinase receptor whose activation leads to proliferative signals within the cells. On activation, the human epidermal growth factor family of receptors are known to form homodimers and heterodimers, each with a distinct signaling activity. Because HER2 is the preferred dimerization partner when heterodimers are formed, it is important for signaling through ligands specific for any members of the family. It is typically overexpressed in several epithelial tumors.

overall survival: the duration between random assignment and death.

progression-free survival: time from random assignment until death or first documented relapse, categorized as either locoregional (primary site or regional nodes) failure or distant metastasis or death.
Acknowledgment

We thank all of the patients and investigators who participated in this study. We also thank Jantien Wanders for contributions to the development of the article and input into the study. In addition, we thank Stacie Hudgens from Clinical Outcomes Solutions for conducting the quality-of-life analyses. Editorial support was provided by Annette Smith, PhD, of Complete Medical Communications. Additional editorial support during article revisions was provided by Oxford PharmaGenesis, United Kingdom. Funding for all editorial support was provided by Eisai.