2. SYNOPSIS

Name of Sponsor Company: Eisai Limited **Name of Finished Product:** Not Applicable **Name of Active Ingredient:** Eribulin mesylate	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Title of Study: The 'EMBRACE' Trial: Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389. A Phase 3 Open Label, Randomized Parallel Two-Arm Multi-Center Study of E7389 versus 'Treatment of Physician's Choice' in Patients with Locally Recurrent or Metastatic Breast Cancer, Previously Treated with at Least Two and a Maximum of Five Prior Chemotherapy Regimens, Including an Anthracycline and a Taxane.		
Study Number: E7389-G000-305		
Principal Investigators: Prof Chris Twelves and Dr Linda Vahdat.		
Study centers: This was a multi-center study conducted in a total of 135 centers in 19 countries (Argentina, Australia, Belgium, Brazil, Canada, Croatia, Czech Republic, France, Germany, Hungary, Italy, Poland, Russia, South Africa, Spain, Switzerland, Turkey, United Kingdom, and the United States).		
Study Period: The study began on 16 November 2006 (first patient entered) and the data cut-off was 12 May 2009. The last date of enrollment was in November 2008.		**Clinical Phase:** Phase 3
Objectives: **Primary**: To compare the overall survival (OS) of patients treated with E7389 versus the Treatment of Physician's Choice (TPC) (including anti-tumor treatment of the Investigator's choice and palliative treatment) in patients with locally recurrent or metastatic breast cancer, who had received 2 to 5 prior chemotherapy regimens, which must have included an anthracycline and a taxane as prior therapy and at least 2 of which must have been given for locally recurrent or metastatic disease. Patients must also have been refractory to their latest chemotherapy regimen, documented by progression on or within six (6) months of therapy. Human epidermal growth factor receptor 2 (HER2/*neu*) positive patients could have been treated with trastuzumab in centers where this treatment was available, and estrogen receptor-positive tumors could have been treated with anti-hormonal therapy. **Secondary:** To compare Progression Free Survival (PFS) between the two treatment groups. Objective Tumor Response Rate (ORR) as measured using Response Evaluation Criteria in Solid Tumors (RECIST) criteria and Duration of Response in each treatment group. Furthermore, safety parameters (adverse events [AEs], laboratory parameters, concomitant medication, and study drug exposure) for all patients.		
Methodology: This was a multi-center, Phase 3, open-label, randomized, study in advanced breast cancer patients who had received two to five prior chemotherapy regimens, which had to include an anthracycline and a taxane as prior therapy unless contraindicated. At least two regimens had to have been given for locally recurrent or metastatic disease. Patients were randomized in a 2:1 ratio to receive either eribulin or the TPC. The TPC was defined as any single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer; or palliative treatment or radiotherapy, administered according to local practice. Treatment with another investigational agent in the TPC group was not allowed. Tumor assessments were performed for all patients at 8-weekly intervals (+/- 1 week) irrespective of the treatment group. Follow-up for survival was assessed every three months after discontinuation of treatment. All AE and concomitant medication data were collected for all patients throughout the study, irrespective of the treatment arm. All other assessments, specified in the study protocol flowchart, applied to patients in the eribulin group only. Patients randomized to receive TPC were assessed according to standard practice for the chosen treatment.		

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Number of Patients:

- Number of patients planned: Up to approximately 1000.
- Number of patients randomized: 762 (508 eribulin, 254 TPC)
- Number of patients analyzed for efficacy (Intent-to-Treat [ITT] population): 762 (508 eribulin, 254 TPC)
- Number of patients analyzed for safety (patients that received treatment) : 750 (503 eribulin, 247 TPC)

Diagnosis and Criteria for Inclusion: Female patients, aged ≥18 years, with locally recurrent or metastatic breast cancer who had received two to five prior chemotherapy regimens, which had to contain an anthracycline and a taxane component, at least two of which had to be given for locally recurrent or metastatic disease. Patients had to prove refractory to the most recent chemotherapy, documented by progression on or within six months of that therapy. In addition, patients with known HER2/*neu* positive tumors might have been previously treated with trastuzumab in centers where this treatment was available, and patients with known estrogen receptor (ER) positive disease might have been treated with anti-hormonal therapy. Patients for whom HER2/*neu* status, ER, and progesterone receptor status were unknown were accepted into the study.
Previous chemotherapy, radiation, trastuzumab or hormonal therapy must have been discontinued three weeks before administration of eribulin or TPC.

Test Product: Eribulin mesylate was provided as a 0.5 mg/mL solution in ethanol/water (5:95).
Dose and Mode of Administration: 1.4 mg/m^2 IV bolus administration was given over 2 to 5 minutes on Days 1 and 8 every 21 days.

Reference Product: TPC
Dose and Mode of Administration: According to local practice

Duration of Treatment: Patients remained on study until one or more of the following occurred: Disease progression as assessed by clinical evaluation or as documented by RECIST, lost clinical benefit because of undue toxicity, patient withdrawal of consent, Investigator concluded that further therapy was not in the best interest of the patient, the presence of other medical conditions that prohibited continuation with therapy, pregnancy, the failure of the patient to comply with study procedures compromising safety, a delay of more than 14 days in starting the next cycle due to toxicities, or the presence of residual toxicities that in the opinion of the Investigator prohibited further administration of treatment, the presence of new medical information that warranted the termination of the study, or termination of the study by the Sponsor.

Criteria for Evaluation:
Efficacy Assessments: OS, PFS, ORR, and duration of response according to RECIST.
Safety Assessments: AEs, serious adverse events (SAEs), concomitant medications, laboratory assessments (chemistry, hematology, and urinalysis), vital signs, physical examination, Eastern Cooperative Oncology Group Performance Status, and electrocardiograms.

Statistical Methods:
The primary analysis of OS was compared between eribulin and the TPC group in the ITT Population using a two-sided stratified log-rank test at a nominal significance level of 0.049 (adjusted for the interim analysis). Patients were stratified by HER2/*neu* status, prior capecitabine treatment, and geographical region. The secondary efficacy endpoints analyzed were PFS, ORR, and duration of response. Kaplan-Meier plots and the Kaplan-Meier estimates of the medians, and first and third quartiles were presented with the 95% confidence intervals for OS, PFS, and duration of response. Tumor response was evaluated according to the RECIST guidelines, modified as per the protocol (Appendix 8 of the protocol). ORR was analyzed using exact Pearson Clopper 2-sided 95% confidence limits for the tumor response rates in each group. The efficacy endpoints of PFS, ORR, and duration of response were assessed according to Investigator and Independent assessment. Sensitivity analyses of these assessments were also performed.
Exploratory subgroup analyses could have been performed for OS, PFS, and ORR, in subgroups of patients depending on whether there were sufficient numbers of patients within each subgroup at the end of the study.
Summary statistics for AEs, laboratory parameters, and other safety parameters were provided for the safety population.

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The primary analysis was planned to occur when 411 events (deaths) had been recorded. An interim analysis (blind to Investigators and the sponsor) was performed after 50% of the deaths had been observed.

RESULTS

Key efficacy results are summarized in the Table below. Subgroup analyses showed a consistent trend in favor of eribulin across a wide variety of patient subpopulations.

Efficacy Parameter	**Eribulin**	**TPC**
Overall Survival (ITT Population)	**(n = 508)**	**(n = 254)**
Number of Events	274	148
Median (95% confidence interval [CI]) days	399 (360, 434)	324 (282, 380)
Hazard Ratio, eribulin: TPC (95% CI) (stratified Cox proportional hazards)	0.809 (0.660, 0.991)	
p-value (stratified log-rank)[a]	0.041	
Progression-free Survival[b] (ITT Population)	**(n = 508)**	**(n = 254)**
Median (95% CI), days	113 (101, 118)	68 (63, 103)
Overall Response Rate[b] (Response Evaluable Population)	**(n=468)**	**(n=214)**
% (95% CI)	12.2 (9.4, 15.5)	4.7 (2.3, 8.4)

a: Stratified by geographic region, HER2/*neu* status, and prior capecitabine therapy.
b: Based upon Independent radiographic review.

Safety

- The AE profile of eribulin in this study was consistent with previous studies with eribulin. The most common AE reported was neutropenia, and the most common AE leading to discontinuation of treatment was peripheral neuropathy. The majority of AEs were Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2, with the exception of neutropenia.
- A lower percentage of patients in the eribulin group (4.0%) than the TPC group (7.7%) died during study treatment, or within 30 days of their last study treatment (this includes patients who died because of disease progression). Similarly, the percentage of patients with AEs with an outcome of death (including patients who died >30 days after the last dose) was also lower in the eribulin group (4.0%) than TPC group (7.3%).
- SAEs were reported for 25.0% of eribulin-treated patients and 25.9% of patients in the TPC group. The most frequently reported SAEs in the eribulin group were febrile neutropenia (4.2%) and neutropenia (1.8%).
- AEs leading to discontinuation were reported for 13.3% of eribulin-treated patients and for 15.4% of patients in the TPC group. The most common AE that led to discontinuation of eribulin was peripheral neuropathy (4.8% of patients).
- In the eribulin group, development of Grade 3 and Grade 4 neutropenia occurred in 28.4% of patients and 28.6% of patients, respectively (AEs of Grade 3 and Grade 4 neutropenia were reported for 21.1% and 24.1% of patients, respectively). Overall, 57.1% of patients in the eribulin arm had a nadir ANC during the treatment period, and the median time to nadir was 78 days. The majority of patients recovered from the nadir (93.7%), with a median time to recovery of eight days. Neutropenia rarely led to febrile neutropenia (4.6%).
- In the eribulin group, AEs of peripheral neuropathy were reported for 34.6% of patients, 7.8% at Grade 3 and 0.4% at Grade 4. Eribulin treatment was discontinued because of peripheral neuropathy for 4.8% patients. More than half of the patients with Grade 3/4 peripheral neuropathy continued eribulin treatment. The 1 year estimate for the rate of development/progression of peripheral neuropathy was 21.4% and 9.5% with eribulin and TPC respectively, based on a Kaplan-Meier analysis.
- The safety pattern for the TPC groups in this patient population appeared to be similar to that expected for

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the use of these drugs.

CONCLUSIONS:

Treatment with eribulin significantly prolonged OS in patients with late-stage breast cancer when compared with TPC (p=0.041). Thus, the study met its primary endpoint. The secondary endpoints of PFS and ORR were consistent with the primary endpoint; PFS was longer for the eribulin group and ORR was greater.

The observed safety profile of eribulin was acceptable for a chemotherapeutic agent in late line settings and the drug was generally well-tolerated. This safety profile was consistent with that observed in Phase 2 studies.

Date of the Report: 19 March 2010