

2. STUDY SYNOPSIS

Name of Company: Eisai	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: Halaven [®]	Referring to Part IV of the Dossier	
Name of Active Ingredient: eribulin mesylate	Volume: Page:	

<p>Study Title</p> <p>A Phase III Open Label, Randomized Two-parallel-arm Multicenter Study of E7389 Versus Capecitabine in Patients With Locally Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes</p>
<p>Investigator/ Sites</p> <p>Peter A. Kaufman, MD; Prof. Christopher Twelves, MD</p> <p>Multicenter: At 210 sites across geographic regions (6 regions: North America, Western Europe, Eastern Europe, Latin America, South Africa and Asia) (refer to Appendix 16.1.4 for the list of investigators and sites)</p>
<p>Publication (Reference) TBD</p>
<p>Study Period</p> <p>Start date 01 Apr 2006; at the date of data cutoff (12 Mar 2012), 10 subjects (5 subjects [0.9%] each in the E7389 and capecitabine groups) were still on treatment.</p>
<p>Phase of Development</p> <p>Phase 3</p>
<p>Objective(s)</p> <p>The primary objective of the study was to compare the efficacy of E7389 versus capecitabine monotherapy in terms of Overall Survival (OS) and Progression-Free Survival (PFS) in subjects with locally advanced or metastatic breast cancer.</p> <p>Secondary objectives were to assess:</p> <ul style="list-style-type: none"> • Quality of life measured using the European Organisation for Research on the Treatment of Cancer (EORTC) questionnaire (QLQ-C30) plus breast module BR23 • Objective tumor response rate as measured using Response Evaluation Criteria in Solid Tumors (RECIST) • Duration of response (DOR) • One, two, and three year survival • Tumor related symptom assessments measured by pain intensity, using a visual analog scale (VAS), and analgesic consumption • Safety parameters (adverse events, laboratory parameters, concomitant medication, and study drug exposure), and • Pharmacokinetic (PK)/pharmacodynamic relationships in a population PK investigation in a minimum of 200 subjects in the E7389 treatment group

Methodology

This was a Phase 3, multicenter, open-label, randomized, two-parallel-group study in breast cancer subjects who had received up to three prior chemotherapy regimens, and no more than two prior regimens for advanced and/or metastatic disease. The chemotherapy regimens must have included an anthracycline and a taxane, either in the (neo) adjuvant setting or for locally advanced or metastatic disease. Subjects enrolled into the study had documented evidence of disease progression during or after their most recent anticancer therapy.

In addition, subjects with known human epidermal growth factor receptor 2 *HER2/neu* overexpressing tumors could have been previously treated with trastuzumab in study centers where this treatment was available, and subjects with known estrogen receptor (ER) and/or progesterone receptor (PR) positive disease may have been treated with hormonal therapy, but not required per protocol. Subjects for whom *HER2/neu* status, estrogen receptor (ER), and progesterone receptor (PR) status were unknown were also accepted into the study.

Subjects were randomized in a ratio of 1:1 to receive either E7389 as an intravenous (IV) infusion of 1.4 mg/m² over 2-5 minutes on Days 1 and 8 every 21 days or capecitabine as an oral administration of 2.5 g/m²/day administered twice daily in two equal doses on Days 1 to 14 each 21-day cycle.

Tumor assessments were performed for all subjects prior to starting study treatment and at every second cycle (starting at Cycle 2) for the first 12 cycles, then every third cycle (starting at Cycle 15) between Days 15 and 21, or sooner if evidence of disease progression was noted by an independent reviewer. OS and PFS were measured from randomization until the date of death due to any cause. Postscreening bone scans were performed every six cycles starting at the end of Cycle 6 and for confirmation of response.

European Organization for Research and Treatment of Cancer (EORTC) Quality of Life (QoL) questionnaires (QLQ-C30 BR23) were completed at Baseline (within seven days of Day 1, Cycle 1), at 6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months after initiation of treatment, before drug administration and before any tumor assessments.

Data regarding subject assessment of pain intensity, consumption of analgesic medications, Eastern Cooperative Oncology Group (ECOG) performance scale, and quality of life assessments were assessed throughout the study.

Safety assessments included monitoring the incidence and severity of adverse events (AEs), clinical laboratory test results, vital signs measurements, physical examination findings, electrocardiogram (ECG) readings, and concomitant medication use.

Subjects continued on treatment until unacceptable toxicity, progression of disease, or until in the opinion of the investigator, discontinuation of therapy was in the best interest of the subject or the subject withdrew consent. Subjects who demonstrated clinical benefit were allowed to continue treatment for as long as clinical benefit was sustained.

Number of Subjects (Planned and Enrolled)

Planned: A total of 1100 subjects (550 per treatment group) were planned for enrollment.

Enrolled: 1102 subjects were enrolled:
E7389: 554; capecitabine: 548

Diagnosis and Main Criteria for Inclusion

Subjects with locally advanced or metastatic breast cancer who had received up to three prior chemotherapy regimens, where no more than two of the prior regimens were as treatment for advanced disease, were enrolled. The regimens had to contain an anthracycline and a taxane component, either in the (neo) adjuvant setting or for locally advanced or metastatic disease. Subjects had to have documented evidence of progression during or after their most recent anticancer therapy. Subjects with a known *HER2/neu* overexpressing status and hormone positive could also have been treated with trastuzumab in centers where this treatment was available. Subjects with ER and/or PR positive tumors could have been treated with hormonal therapy. Measurable lesions were not a requirement.

Test Treatment, Dose, Mode of Administration, and Batch Number(s)

E7389 1.4 mg/m² IV infusion given over 2 to 5 minutes on Days 1 and 8 every 21 days
Due to the duration of the study, many batches were used. A complete list of batches used in the study is provided in [Section 9.4.2.3](#).

Reference Therapy, Dose, Mode of Administration, and Batch Number(s)

Capecitabine 2.5g/m²/day administered orally twice daily in two equal doses on Days 1 to 14 every 21 days.
Due to the duration of the study, many batches were used. A complete list of batches used in the study is provided in [Appendix 16.1.6](#).

Duration of Treatment

Subjects were treated until disease progression or withdrawal from the study due to unacceptable toxicity. As the period of treatment for any subject was dependent on efficacy and toxicity, the duration of treatment varied between subjects.

Assessments**Efficacy**

Efficacy was assessed using OS, PFS, objective tumor response according to RECIST, and duration of response. Baseline tumor assessments, consisting of computed tomography (CT) or magnetic resonance imaging (MRI) scans of areas of suspected disease, as well as photographs of skin lesions, were performed within 28 days prior to starting study treatment and every second cycle (starting at Cycle 2) for the first 12 cycles, then every third cycle (starting at Cycle 15) between Days 15 and 21, or sooner if there was evidence of disease progression.

Quality of Life

Subjects assessment of QoL was evaluated using the EORTC questionnaire ([QLQ-C30] plus breast module BR23) at Baseline and at 6 weeks, 3 months, and then at 6-month intervals after the start of study treatment.

Tumor-related symptom assessments, based on the change from Baseline in pain intensity, were recorded by the subject at Baseline (within 7 days of Day 1 Cycle 1) and weekly during the study using a VAS, and consumption of analgesic medications were recorded at Baseline and throughout the study.

Eastern Cooperative Oncology Group (ECOG) performance status was assessed at Baseline, Day 1 of every cycle, and at Study Termination.

Pharmacokinetics

Population analysis with sparse sampling collection schedule was used to characterize the PK profile of E7389 and covariates that affect drug behavior, or those that explain variability in a heterogeneous subject population were to be identified. Appropriate nonparametric and/or parametric methods were used to examine the PK/pharmacodynamic relationships of E7389.

The PK of E7389 was assessed during the first cycle of treatment only. A total of four samples were taken from each participating subject at specified times on Day 1 (5 min – 24 h), Day 3 (48 ±1 h), Day 4 (72 ±1 h), and Days 5 through 6 (96-120 h) after the start of infusion.

Pharmacodynamics

The pharmacodynamic/PK relationship, as it relates to safety and efficacy, was to be analyzed using a population approach (nonlinear mixed effect modeling), and possibly combined with data from other studies as appropriate and detailed in a separate analysis plan and reported in a separate report.

Safety

Safety assessments included monitoring the incidence and severity of AEs, clinical laboratory test results, vital signs measurements, physical examination findings, ECG readings, and concomitant medication use.

Bioanalytical Methods

Plasma concentration of E7389 was determined using a fully validated liquid chromatography/mass spectrometry/mass spectrometry method (LC/MS/MS) of analysis. Assay sensitivity, specificity, linearity, and reproducibility were documented prior to the analysis of subject plasma samples.

Statistical Methods

The study was to be declared positive after achievement of any of the following outcomes:

1. First interim analysis after 453 deaths: OS of E7389 was statistically significantly better compared to capecitabine ($P \leq 0.002$).
2. Second interim analysis after 603 deaths: OS of E7389 was statistically significantly better compared to capecitabine ($P \leq 0.0081$).
3. Final analysis after 905 deaths: OS of E7389 was statistically significantly better compared to capecitabine ($P \leq 0.0372$).
4. Final analysis after 905 deaths: OS hazard ratio (E7389/capecitabine) was < 1 **and** PFS of E7389 was statistically significantly better compared to capecitabine ($P \leq 0.01$).

Decisions were based on two-sided, stratified log-rank tests with HER2/*neu* status and geographic region as strata. The overall significance level alpha of 0.05 was adjusted for the co-primary endpoints: 0.04 was used for testing OS, and 0.01 was used for testing PFS.

OS was measured from the date of randomization until the date of death from any cause. Subjects who were lost to follow-up or who were alive at the date of data cutoff were censored. To maintain an overall level of 0.04, alpha spending for sequential analyses of OS was based on the Lan–DeMets implementation of the O’Brien–Fleming spending function. The P value boundaries of 0.002, 0.0081, and 0.0372 are examples when the observed number of deaths at the times of interim analyses (453, 603, and 905 deaths, respectively). Hypotheses tested included:

$$H_a: S_{E7389} = S_{Capecitabine}$$
$$H_a: S_{E7389} \neq S_{Capecitabine}$$

where S is the survival distribution of OS.

The P value from a two-sided stratified log-rank test was presented. In subsequent analyses, treatment effect estimates were summarized using 95% confidence intervals (CI). Median and 95% CI were provided for each treatment group. Kaplan–Meier plots were provided for OS. Hazard ratios (E7389/capecitabine) were computed together with the two-sided 95% CI using stratified Cox regression model with treatment as a factor and HER2/*neu* status and geographic region as strata in the model for the Intent-to-Treat (ITT) population. PFS was compared between the two treatment groups using a two-sided 0.01 level stratified log-rank test.

QoL was assessed using the EORTC quality of life questionnaire. Analyses of the QoL data consist of establishing content validity and descriptive comparisons by treatment and time (i.e., visit). Content validity of the instrument is demonstrated with its responsiveness to tumor response. For content validity, a weighted generalized estimating equation (WGEE) statistical method assessed the association of each domain and sign/symptom with tumor response (CR + PR).

Objective response rate (ORR) was compared between the two groups using a Fisher’s exact test. For the duration of response, Kaplan–Meier plots were provided along with the median and the 95% CI. Tumor response data utilized for primary analysis of PFS, ORR, and duration of response were obtained from an independent review of the imaging scans. In addition, these analyses were performed using the investigators’ determination of response. Response was assessed according to RECIST. Complete description of the independent review assessment was detailed in an Independent Imaging Review Charter.

Tumor-related Symptom Assessments were based on change from Baseline in pain intensity and analgesic use. Descriptive statistics were provided at each assessment. Subjects were classified as improved, no change, or worsened. A subject was considered a responder if that subject improved in both parameters (intensity and analgesic use). Responders in the two groups were compared using a chi-square test. Summary statistics for

AEs, laboratory parameters, and other safety parameters were provided for the Safety population. Two interim analyses were performed: one analysis after half of all deaths and a second after two-thirds of all deaths were observed.

Results

Efficacy:

In this study, all 1102 enrolled subjects were included in the efficacy analysis. The following conclusions are based on the results of the primary efficacy endpoints, OS and PFS; secondary efficacy endpoints, ORR and DOR; exploratory efficacy endpoints 1-, 2-, and 3-year survival rates, QOL-C30, and VAS pain scale responses; and an ad hoc analysis of the PFS/OS discordance:

- Although not statistically significant, a positive trend in OS was observed with a 1.4 month longer duration in OS in the E7389 group when compared with the capecitabine group. Median OS was 15.9 months for the E7389 group and 14.5 months for the capecitabine group with a HR (95% CI) of 0.879 (0.770, 1.003) and P value = 0.0560.
- OS adjusted by baseline ER and triple negative status demonstrated improved OS benefit when compared to capecitabine (HR: 0.864, CI: 0.755, 0.990; $P=0.0350$).
- Nominally significant findings in OS for subjects in the E7389 group were observed for the following pre-specified subgroup analyses:
 - HER2/*neu* negative subjects had an increase of 2.4 months (median OS for the E7389 group was 15.9 months and 13.5 months for the capecitabine group) with a HR (95% CI) of 0.838 (0.715, 0.983) and a nominal $P = 0.0299$.
 - Triple negative (ER, PR, and HER2/*neu* negative) subjects had an increase of 5 months (median OS for the E7389 group was 14.4 months and 9.4 months for the capecitabine group) with a HR (95% CI) of 0.702 (0.545, 0.906) and nominal $P = 0.0062$.
 - ER negative subjects had an increase of 3.9 months (median OS for the E7389 group was 14.4 and was 10.5 for the capecitabine group) with a HR (95% CI) of 0.779 (0.635, 0.955) and nominal $P = 0.0162$.
 - Subjects with more than two sites of disease had an increase of 3.3 months (median OS for the E7389 group was 14.8 months and was 11.5 months for the capecitabine group) with a HR (95% CI) of 0.751 (0.624, 0.904) and nominal $P = 0.0023$.
- No statistically significant difference or trend in PFS was observed between the treatment groups.
- Poststudy anticancer therapy did not account for the OS benefit observed in the primary analyses
 - Subjects who received capecitabine following E7389 treatment did not benefit from capecitabine when compared to other anticancer therapies (median OS 18.3 vs 19.9 months). OS sensitivity analysis censoring following poststudy capecitabine was consistent with the primary analysis (HR: 0.731 CI: 0.620, 0.862).
 - OS difference in the primary analysis was not likely due to poststudy anti-HER2 therapy (HR: 0.883, CI: 0.771, 1.010), poststudy hormone therapy (HR: 0.869, CI: 0.752, 1.004), or poststudy anticancer therapy (HR: 0.820, CI: 0.653, 1.030) according to the OS sensitivity analyses.

- There is a discordance between PFS and OS data results
 - Progression is heterogeneous with some subjects showing first progression due to new metastasis or by enlargements of pre-existing lesions.
 - Subjects who progress due to a new metastasis are at a higher risk for death (HR=2.1, $P < 0.0001$).
 - E7389 numerically improves new metastasis-free survival (nMFS) (HR=0.897, $P=0.1657$).
 - E7389 improves OS in subjects with new metastases
 - In this study, nMFS correlates with OS while PFS did not. This phenomenon should be studied prospectively to understand the relationship between PFS and OS.
- ORR and CBR results were comparable between the E7389 and the capecitabine treatment groups.
- Tumor response improved subjects' functionality, especially physical, and appetite while significantly reducing pain for the E7389 and capecitabine groups.
- Subjects in this trial were analogous in functionality and symptomology to those subjects in the EORTC reference group. Consistent with the correlation to tumor response, subjects in both groups had sustained and continual improvements in physical, emotional and social functioning and less pain. Consistent with the adverse event profiles, capecitabine subjects had deteriorating QoL due to nausea and vomiting and diarrhea while E7389 subjects' had deteriorating QoL associated with alopecia, measured in systemic therapy side effects, upset by hair loss, and body image.
- E7389 showed advantages in terms of gastrointestinal effects of nausea and vomiting (-1.9; $P=0.0448$) and diarrhea (-3.8; $P=0.0007$) while capecitabine had advantages in relation to upset by hair loss, systemic side effects (5.2; $P<0.0001$) and upset by hair loss (9.4; $P=0.0221$).

In addition, PK and PK/PD analyses provided the following findings:

- Eribulin PK was well described by a three compartment model with allometric relationship for body weight and was dose-independent.
 - Liver function markers (ALB, ALP, BILI) were found to significantly influence eribulin PK.
 - No significant effect of gender, age, race, ECOG status and renal function (creatinine clearance) on eribulin PK was identified.
 - Reduction in tumor size (the sum of the longest diameter for target lesions) was correlated to E7389 exposure, with higher exposure resulting in a larger shrinkage in tumor size.
 - None of the patient factors (weight, ECOG status, age, year since first diagnosis, HER2/*neu*, ER, PR, and HORM receptor status) or disease factors (tumor stage, visceral disease, previous cancer therapy) were significant predictors of eribulin effect on tumor size.
 - OS was indirectly related to E7389 exposure. The probability of longer survival was increased with a decrease in tumor size, years since first diagnosis, subjects of older age and

better ECOG status.

- Graphical exploration of PK/PD relationship for liver function markers (ALP, BILI, ALT, AST, ALB) and hematology (hemoglobin, platelet count, hematocrit) showed no obvious relationship between the change from baseline in any of these variables and eribulin exposure
- Graphical exploration between E7389 exposure and PFS showed no obvious relationship. Similarly, no relationship could be detected between BOR of partial response, progressive disease, stable disease, and E7389 exposure.

Safety:

- Duration of exposure to study drug was comparable between the E7389 and capecitabine treatment groups. Approximately half the subjects in the E7389 and capecitabine groups received five or more cycles of study drug, with a median of six cycles for the E7389 and five cycles for the capecitabine treatment groups.
- Overall, the incidences of TEAEs were similar for the E7389 and capecitabine treatment groups. The most frequently reported TEAE was neutropenia for subjects in the E7389 group and palmar-plantar erythrodysesthesia for subjects in the capecitabine group.
- The most common AEs reported for subjects in the E7389 and capecitabine treatment groups are consistent with the known safety profile for each drug.
- The number of deaths that occurred within 30 days of the last dose of study drug was slightly lower in the E7389 group (4.8%) than in the capecitabine group (6.6%) and the primary reasons for death during the study was due to disease progression. A total of 9 deaths were reported treatment-related during the study; five subjects in the E7389 group and four subjects in the capecitabine group.
- Overall, the incidence of nonfatal treatment-related serious TEAEs was comparable between the E7389 (7.7%) and capecitabine (8.1%) treatment groups. The most frequently reported treatment-related serious TEAEs were neutropenia (1.8% of subjects) in the E7389 group and diarrhea (2.6% of subjects) in the capecitabine group.
- The most frequently reported serious TEAE in the E7389 and capecitabine groups was dyspnea.
- The most common TEAE leading to discontinuation of study drug was neutropenia (1.7%) in the E7389 group and palmar-plantar erythrodysesthesia (2.2%) in the capecitabine group.
- Overall, a higher percentage of subjects in the E7389 group experienced a severe (CTCAE Grade 3 or 4) TEAE compared with the capecitabine group. The most frequently reported severe nonfatal TEAEs among subjects in the E7389 and capecitabine treatment groups were neutropenia (45.8%) and palmar-plantar erythrodysesthesia (14.5%), respectively.
- Overall, the incidence of TEAEs at Grade 3 or higher and reported as treatment-related was higher in the E7389 group (57.2%) than in the capecitabine group (31.9%). The most frequently reported Grade 3 or 4 treatment-related TEAEs in the E7389 group were neutropenia (45.0%) and leukopenia (14.9%) while the most frequently reported in the capecitabine group were palmar-plantar erythrodysesthesia (14.3%), diarrhea (4.8%), and neutropenia (4.8%).
- Small changes in the mean change from baseline were observed for all laboratory parameters, and no obvious trends in changes in laboratory test results over time were apparent.
- In the E7389 group, development of Grade 3 and Grade 4 neutropenia was reported for 24.6% and 21.1%, respectively.

Conclusions

E7389 is an approved and known effective drug in the treatment of late line metastatic breast cancer. This study, a direct comparison to an approved drug, establishes the activity of E7389 in an earlier line metastatic

breast cancer. This is based on the trend to improved OS relative to capecitabine. For other measures of efficacy the drugs appeared similar. The trend to improved OS cannot be explained by baseline disease factors or poststudy medication therapy. The discordance between PFS and OS observed in this study appears to be due to the composite nature of the PFS endpoint and also does not affect the validity of the OS observation. The safety profile of E7389 is acceptable for subjects with metastatic breast cancer and is comparable to that of capecitabine. Key safety measures such as deaths on treatment (or within 30 days of last treatment), SAEs, and discontinuations due to AEs are similar between the treatment arms and show a small, numerical advantage for the E7389 arm. Overall, the combination of the trend to improved survival and the acceptable safety profile indicate a positive benefit-risk ratio for E7389 in this stage of the disease. Differences from capecitabine in the specific AE profiles and the QoL results suggest that E7389 could be an important option for subjects as the preference for specific risks will vary from subject to subject.

Date of Report

21 Feb 2013