

2. STUDY SYNOPSIS

Name of Company: Eisai Co., Ltd	INDIVIDUAL STUDY TABLE	(For National Authority Use Only)
Name of Finished Product: HALAVEN	Referring to Part IV of the Dossier	
Name of Active Ingredient: E7389 / eribulin mesilate	Volume:	Page:

Study Title A Phase 2 Extension Study of E7389 in Patients with Advanced or Relapsed Breast Cancer
Investigator(s)/ Site(s) Yasuhiro Fujiwara, MD, National Cancer Center Hospital, et al (5 investigators in total) Multicenter: 5 sites in Japan (refer to Appendix 16.1.4 for the list of investigators and sites)
Publication (Reference) None
Study Period 29 Jul 2009 to 14 Jan 2011
Phase of Development Phase 2
Objective(s) <u>Primary objective:</u> To evaluate the safety of E7389 in patients who continued receiving E7389 after completing the Phase 2 clinical study of E7389 for advanced or relapsed breast cancer (E7389-J081-221; hereafter referred to as Study 221). <u>Secondary objective:</u> To evaluate the objective tumor response rate of E7389 based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and the duration of response in patients who responded to E7389. This study (E7389-J081-224; hereafter referred to as Study 224) was conducted in patients who continued receiving E7389 after completing Study 221. The objectives of Study 221 were to investigate the efficacy (objective response rate) and safety of intravenous administration of E7389 in patients with advanced or relapsed breast cancer (primary objective) and to evaluate the duration of overall response (secondary objective).
Methodology <u>Study 221 (the preceding study):</u> Patients with advanced or relapsed breast cancer who received prior therapy with an anthracycline and a taxane were included in Study 221. Study 221 was an open-label, single-arm, multi-center study and E7389 was administered intravenously over 2 to 5 minutes, on Days 1 and 8 of 21-day cycle. Patients could remain on study treatment until they met any of the criteria for study discontinuation. The last observation was to be made on Day 22 of the last cycle. If a subject was confirmed her best overall response and did not fall under any of the criteria for study discontinuation, the subject was to be able to continue receiving E7389 therapy under Study 224. <u>Study 224:</u> This open-label, single-arm, multi-center, Phase 2 extension study of E7389 (Study 224) was conducted in breast cancer patients in whom E7389 was confirmed to be useful in Study 221. In Study 224, the initial dose was administered within 14 days after Day 22 of the last cycle in Study 221. As in Study 221, one cycle consisted of 21 days, and E7389 was administered on Days 1 and 8 in each cycle. Patients could remain on study treatment until they met any of the criteria for study discontinuation. The last observation was to be made on Day 22 of the last cycle.

Number of Subjects (Planned and Enrolled)Study 221 (the preceding study):

Planned: 78 to 82 subjects

Enrolled (i.e., enrolled into the study after eligibility was confirmed): 84 subjects

Treated: 81 subjects

Study 224:

Planned: 14 subjects at a maximum

Enrolled (i.e., enrolled into the study after eligibility was confirmed): 6 subjects

Treated: 6 subjects

Diagnosis and Main Criteria for InclusionStudy 221 (the preceding study):

Female patients aged at least 20 and below 75 years with histologically or cytologically confirmed advanced or relapsed breast cancer. Patients were to have had measurable disease by RECIST and received not more than 3 prior chemotherapy regimens for advanced or relapsed breast cancer including an anthracycline and a taxane. Patients who had a relapse of breast cancer during or within 1 year after neoadjuvant or postoperative adjuvant chemotherapy immediately before the study, or had progressive disease of breast cancer during or within 6 months of last chemotherapy in the metastatic setting. Patients were to have had a life expectancy of at least 3 months, adequate renal, liver, lung and bone marrow function, and no clinically significant therapy-related toxicity at study entry. Patients were to have been an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

Study 224:

Female patients in whom continued administration of E7389 following Study 221 was considered to be useful, and who met the criteria for starting the next cycle in the end of Study 221 were included in Study 224.

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

E7389 2-mL vial

E7389 is a clear, colorless solution for intravenous administration. Each vial contained 1 mg of eribulin mesilate as a 0.5 mg/mL solution in ethanol : water (5:95)

Initial dose for Study 221 was 1.4 mg/m², and initial dose for Study 224 was determined based on the last dose and the criteria for dose reduction for the next cycle in Study 221. When a treatment-related treatment-emergent adverse event (TEAE) which fell under any one of the dose-reduction criteria was noted in a cycle, the dose in the next cycle could be reduced to one level lower than the dose in the previous cycle. Dose reduction was made in the order of 1.4, 1.2, 1.0, and 0.7 mg/m².

E7389 was administered intravenously over 2 to 5 minutes on Days 1 and 8 of 21-day cycle.

Lot Numbers: P5Y008ZZA (Study 221) and P6Z005ZZA (Study 224)

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

None

Duration of Treatment:

Patients could remain on study treatment until they met any of the criteria for study discontinuation.

Assessments**Efficacy**

Best overall response, objective response rate, disease control rate, and clinical benefit rate of E7389 (based on the RECIST), duration of response and time to response in patients who responded to E7389, progression-free survival, overall survival, overall survival from treatment discontinuation, tumor markers, and sum of the longest diameter of target lesions.

Safety

TEAEs based on CTCAE v3.0 (Japanese version), treatment-related TEAEs, clinical laboratory parameters, chest x-ray findings, electrocardiogram (ECG), general findings (vital signs and ECOG performance status), and body weight.

Other

Not applicable.

Statistical Methods

Statistical analyses were performed using SAS Version 9.1.3, SAS Drug Development Version 3.0, and Excel 2003.

Study 224 was designed to evaluate the safety and efficacy of E7389 continuously by collecting data from subjects who continued receiving E7389. Thus, efficacy and safety analyses performed in Study 221 were updated and reported with the additional data collected in Study 224 and the follow-up survey for outcome of survival.

EfficacyObjective response rate

Best overall responses (assessed by the independent review and the investigators) were analyzed for the full analysis set (FAS) and the per protocol set (PPS) by calculating the numbers and percentages of subjects assigned to complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and not evaluable (NE). Number and percentage of subjects with CR or PR (objective response rate), number and percentage of subjects with CR, PR, or SD (disease control rate), and number and percentage of subjects with CR, PR, or SD of at least 6 months (clinical benefit rate), and their exact 90% and 95% confidence intervals (CIs) based on binominal distribution were calculated.

Duration of response

Summary statistics for duration of response and 95% CI of median were calculated by the Kaplan-Meier method. Kaplan-Meier plots for duration of response were presented together with the number of subjects at risk.

Bayesian analysis of objective response rate

For objective response rates, posterior probabilities that true objective response rates were lower than 10%, 15%, and 20% were calculated based on the Bayesian posterior distribution (beta distribution) using Jeffreys non-informative prior distribution in the FAS and PPS. In addition, the posterior mode, 95% equal tail credible interval and 95% highest posterior density credible interval of the posterior distribution for objective response rate were calculated.

Progression-free survival

Summary statistics for progression-free survival and 95% CI of the median were calculated by the Kaplan-Meier method. Progression-free survival rates at 3, 6, 9, and 12 months (the rate at 15 months was added after database lock) and their 95% CIs were calculated using the Kaplan-Meier method. Kaplan-Meier plots of progression-free survival were presented together with number of subjects at risk.

Overall survival and overall survival from treatment discontinuation

Summary statistics for overall survival and 95% CI of the median were calculated by the Kaplan-Meier method. Overall survival rates at 6 and 12 months (the rates at 18 and 24 months were added after database lock) and their 95% CIs were calculated using the Kaplan-Meier method. Kaplan-Meier plots of overall survival were presented together with number of subjects at risk. Same analyses for overall survival from treatment discontinuation were also performed.

Time to response

Summary statistics for time to response and 95% CI of the median were calculated by the Kaplan-Meier method. Kaplan-Meier plots of time to response were presented together with number of subjects at risk.

Tumor markers and sum of the longest diameter of target lesions

For subjects with clinical benefit, figures showing percent changes from baseline by subject in sum of the longest diameters of target lesions over the study period on the vertical axis and assessment timing (days from Day 1 of the first cycle in Study 221) on the horizontal axis were presented. In addition, figures showing changes by subject in each tumor marker over the study period on the vertical axis and measurement timing on the horizontal axis were presented. Waterfall plots showing percent changes from baseline to post-baseline nadir in sum of the longest diameters of target lesions were presented.

Safety**Treatment-emergent adverse events**

Number of TEAEs, number of subjects with TEAEs and incidences of TEAEs were summarized for the safety analysis set. Incidences were calculated as percentages of subjects with at least one TEAE and subjects with TEAEs by system organ class (SOC) and preferred term (PT) for the safety analysis set. TEAEs were also summarized by causal relationship with the study drug and by severity (CTCAE v3.0 [Japanese version]). For TEAEs that are considered to be significant, time to onset and time to recovery were also provided.

Laboratory test values, vital signs and body weight

For continuous variables, summary statistics were calculated, and for categorical variables, frequencies and percentages were calculated for the safety analysis set. The number (percentage) of subjects with Treatment Emergent Abnormal Laboratory Values (TEAVs) was calculated for each test item specified in the CTCAE v3.0 (Japanese version).

Results**Subject Disposition/Analysis Sets**

- Eighty-four subjects were enrolled in the preceding study (Study 221), and 81 subjects were treated with E7389 in the study. In this report of Study 224, efficacy and safety analyses were conducted on the integrated dataset of Studies 221 and 224; therefore, the number of subjects for the FAS, the PPS, and the safety analysis set in Study 224 were identical to those in Study 221 (i.e., 80, 79, and 81 subjects, respectively).
- Six subjects were enrolled and treated with E7389 in Study 224. As to the 6 subjects enrolled in Study 224, safety and efficacy data collected in Studies 221 and 224 were used for the analyses, while those data collected in Study 221 were used for the analyses on the other subjects.

Efficacy

- Of 80 subjects, 17 subjects had PR as a best overall response, and no subjects had a CR in the FAS based on the independent review by the Assessment Committee. As a result, the objective response rate (primary efficacy endpoint) was 21.3% (95% CI: 12.9, 31.8), disease control rate was 58.8% (95% CI: 47.2, 69.6), and clinical benefit rate was 28.8% (95% CI: 19.2, 40.0).
- For objective response rates based on the independent review, the mode of the Bayesian posterior distribution calculated with Jeffreys non-informative prior distribution (Beta distribution Beta [0.5, 0.5]) was 20.9%, the posterior probabilities that true objective response rates were lower than 10%, 15%, and 20% were 0.1%, 6.4%, and 38.0% respectively, and 95% credible intervals of equal tail and highest posterior density on true objective response rates were (13.4%, 31.1%) and (13.0%, 30.6%), respectively.
- The median duration of response for the 17 subjects with PR based on the independent review was 119.5 days (95% CI: 85.0, 148.0), ranging from 29+ to 431 days (+ shows censored observation).
- The median time to response for the 17 subjects with PR based on the independent review was 54.0 days (95% CI: 49.0, 85.0), ranging from 42 to 135 days, or 3.0 cycles (95% CI: 3.0, 5.0), ranging from 2 to 6 cycles.
- The median progression-free survival for the FAS based on the independent review was 112.0 days (95% CI: 61.0, 133.0), ranging from 8 to 863+ days. The 3-, 6-, 9-, 12-, and 15-month progression-free survival rates were 54.2%, 21.0%, 10.5%, 3.5%, and 3.5%, respectively.
- The median overall survival was 337.0 days (95% CI: 240.0, 481.0), ranging from 31 to 913+ days. The 6-, 12-, 18-, and 24-month overall survival rates were 72.5%, 44.5%, 33.6%, and 19.3%, respectively.
- The median overall survival from treatment discontinuation was 217.0 days (95% CI: 149.0, 281.0), ranging from 15+ to 738+ days. The 6-, 12-, 18-, and 24-month overall survival from treatment discontinuation rates were 56.8%, 33.7%, 16.4%, and 16.4%, respectively.
- E7389 exhibited efficacy on metastatic lesions, as demonstrated by tumor shrinkage in the liver, lymph nodes, and lung.
- Subgroup analysis for the FAS did not reveal any factor that affected the efficacy of E7389.

Safety

- The incidence of TEAEs for the safety analysis set was 100% (81/81 subjects). The most frequently reported TEAEs were leukopenia (98.8%, 80/81 subjects), neutropenia (98.8%, 80/81 subjects), alopecia (58.0%, 47/81 subjects), and lymphopenia (54.3%, 44/81 subjects). The incidence of treatment-related TEAEs was 100% (81/81 subjects). The most frequently observed treatment-related TEAEs were leukopenia (98.8%, 80/81 subjects), neutropenia (98.8%, 80/81 subjects), alopecia (58.0%, 47/81 subjects), and lymphopenia (54.3%, 44/81 subjects).
- Grade 4 TEAEs including neutropenia (70.4%, 57/81 subjects), leukopenia (11.1%, 9/81 subjects), and interstitial lung disease (1.2%, 1/81 subjects) occurred. All of them were judged as treatment-related.
- Death during the treatment period or within 30 days after the final administration occurred in one subject in Study 221. The cause of the death was acute aggravation of the primary disease. Treatment-emergent serious adverse events (SAEs) were reported in 14 of 81 subjects (22 events in total) for the safety analysis set and causal relationship to E7389 could not be denied for 13 events in 9 subjects. Among these SAEs, one subject experienced cataract in Study 224. Treatment-related SAEs unexpected from the Investigator's Brochure were gastritis haemorrhagic, oedema and cataract (one event each).
- TEAEs leading to discontinuation of study drug administration and Grade 3 or 4 TEAEs were defined as significant AEs in this study. Six subjects discontinued administration of study drug due to TEAEs. The incidence of Grade 3 or 4 TEAEs was 96.3% (78/81 subjects). Most frequently reported Grade 3 or 4 TEAEs were neutropenia (95.1%, 77/81 subjects), leukopenia (74.1%, 60/81 subjects), febrile neutropenia (14.8%, 12/81 subjects), lymphopenia (13.6%, 11/81 subjects), and gamma-glutamyltransferase increased (12.3%, 10/81 subjects). Most frequently reported Grade 3 or 4 treatment-related TEAEs were neutropenia (95.1%, 77/81 subjects), leukopenia (74.1%, 60/81 subjects), febrile neutropenia (14.8%, 12/81 subjects), lymphopenia (13.6%, 11/81 subjects), and gamma-glutamyltransferase increased (6.2%, 5/81 subjects).
- CTCAE grades of white blood cell count and neutrophil count deteriorated at post-baseline visits in most subjects. As to white blood cell count, the median time to nadir with Grade 3 or 4 was 15.0 days, and the median time to recovery from nadir with Grade 3 or 4 to Grade 0 or 1 was 8.0 days. As to neutrophil count, the median time to nadir with Grade 3 or 4 was 15.0 days, and the median time to recovery from nadir with Grade 3 or 4 to Grade 0 or 1 was 8.0 days.
- Overall incidence of TEAVs was 95.1% (77/81 subjects). Frequently observed TEAVs in decreasing order were neutrophil count (95.1%, 77/81 subjects), white blood cell count (74.1%, 60/81 subjects), gamma-glutamyltransferase (18.5%, 15/81 subjects), and lymphocyte count (14.8%, 12/81 subjects).
- There were no frequently-observed abnormalities in vital signs, ECG, or chest x-ray.

Conclusions

The intravenous administrations of E7389 at a dose of 1.4 mg/m² over 2 to 5 minutes on Days 1 and 8 of 3-week cycle had an acceptable tolerability profile, with leukopenia, neutropenia, and alopecia being the most common treatment-related TEAEs.

E7389 had anti-tumor activity in heavily pretreated Japanese patients who had received a median of 3 prior chemotherapy regimens including an anthracycline and a taxane. The objective response rate for FAS based on the independent review was 21.3% (95% CI: 12.9, 31.8).

These findings demonstrate that the safety profile of E7389 is predictable and manageable, similar to previous Phase 2 studies, and acceptable for an efficacious cytotoxic agent.

Date of Report

02 Feb 2012