CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201532

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	201532/0
Drug Name:	Eribulin Mesylate Injection
Indication(s):	(b) (4) or Metastatic Breast Cancer
Applicant:	Eisai Inc.
Date:	Submitted March 30, 2010
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Review Priority:	Priority
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Keywords: overall survival, progression free survival, response rate, metastatic breast cancer

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The applicant submitted the data and final study report of the Study 305 to support a new drug approval indicated for patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and a taxane.

The data and analyses from the current submission showed a 2.5 months improvement in median survival in the primary analysis in the eribulin arm (13.1 months) compared with the TPC arm (10.6 months). The difference was significant with a p-value of 0.041 based on a stratified log-rank test and a HR of 0.81 with 95% CI = (0.66, 0.99).

The results from the 120-safety update confirmed the overall survival (OS) results. The median survival improvement was 2.7 months for the eribulin arm (13.2 months) compared with the TPC arm (10.5 months). The difference was significant with a p-value of 0.014 based on a stratified log-rank test and a HR of 0.81 with 95% CI = (0.68, 0.96).

Based on the data submitted, the study results support the claims in the primary endpoints. Whether the size of the treatment effect from a single study are adequate for approval depends on the risk-benefit assessment and clinical decision.

1.2 Brief Overview of Clinical Studies

Study 305 was a multi-center, Phase 3, open-label, randomized, parallel two-arm multi-national study that enrolled patients with locally recurrent or metastatic breast cancer comparing eribulin with treatment of physician's choice (TPC).

Patients were pre-stratified based on the geographic region, HER2/neu status, and prior treatment with capecitabine. Patients were randomized in a 2:1 ratio to receive either eribulin mesylate as an intravenous (IV) bolus of 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 every 21 days or the Treatment of Physician's Choice (TPC). The TPC was defined as any single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer; or best supportive care or radiotherapy, administered according to local practice, if applicable. Treatment with another investigational agent in the TPC group was not allowed.

The primary study objective was to compare the overall survival (OS) of patients treated with eribulin versus the 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.

1.2 Statistical Issues and Findings

The protocol-specified primary efficacy endpoint was overall survival (OS). The secondary endpoints included progression free survival (PFS), objective response rate (ORR) and duration of response (DoR).

The primary analysis was planned to occur when 411 deaths had been recorded. A formal efficacy interim analysis was performed when 50% of the deaths (206 deaths) had been observed. The final 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. In this report, the primary analysis was conducted with 422 deaths.

The secondary efficacy endpoints analyzed were PFS, ORR, and duration of response. PFS and DoR were analyzed using the same methods as OS. ORR was analyzed using a Fisher's exacted test, and tumor response rates in each group were also estimated by exact Pearson Clopper 2-sided 95% confidence limits. The results of PFS, ORR, and duration of response were based on data by the independent assessment.

A total of 762 patients were randomized to the two arms, with 508 in the eribulin arm, and 254 in the TPC arm.

In the primary analysis, total of 422 deaths were observed. Median survival was 2.5 months longer in the eribulin arm compared with the TPC arm (p-value=0.041). The hazard ratio(HR) based upon a Cox model including the randomization stratification factors as strata was 0.81 with 95% CI = (0.66, 0.99). Median survival was 13.1 months with 95% CI = (11.8, 14.3) in the eribulin arm and 10.6 months with 95% CI= (9.3, 12.5) in the TPC arm.

In the 120-day safety update, total of 589 deaths were observed. The updated analysis showed median survival was 2.7 months longer in the eribulin arm compared with the TPC arm (p-value = 0.014). The hazard ratio (HR) was 0.81 with 95% CI = (0.68, 0.96). The median survival was 13.2 months with 95% CI = (12.1, 14.3) for the eribulin arm compared with 10.5 months with 95% CI = (9.2, 12.0) for the TPC arm.

2. INTRODUCTION

2.1 Overview

Eribulin is a synthetic analog of halichondrin B (HalB), a substance isolated from the rare marine sponge Halichondria okadai. HalB is a large polyether macrolide that exerts potent anti-cancer effects in cell-based and animal models of cancer.

2.1.1 Indication

The indication statement for which marketing approval is being sought was (b) (4) or metastatic breast cancer, previously treated with at least two (b) (4) prior chemotherapy regimens, including an anthracycline and a taxane.

2.1.2 Regulatory History of Drug

The clinical development of eribulin mesylate was conducted under IND 67,193 since January 2003. Meeting with the applicant included an End of Phase 2 Meeting/Breast Cancer in September 2005, a Pre-NDA Meeting in August 2007, an End of Phase 2 Follow-up Meeting/Study E7389-G000-305 in March 2008, and a Pre-NDA Meeting/Study E7389-G000-305 in November 2009.

A Special Protocol Agreement was reached in February 2006 for another study, Study 301 – an open label, randomized trial comparing eribulin to capecitabine in patients with refractory metastatic breast cancer. This study is still ongoing and is expected to finish in (b) (4). The FDA is requesting the final study report and datasets to be submitted upon completion of the study as a Post Marketing Commitment (PMC).

The protocol for Study 305 was discussed in the March 2008 meeting. FDA concerned that this single study might not be robust enough to support NDA approval. The NDA was submitted in March 2010 with data and analyses from a single randomized Phase 3 study, Study 305.

2.2 Data Sources

Data used for review is from the electronic submission received on Jul. 31, 2009. The network path is **\\CDSESUB1\EVSPROD\NDA201532\0000.**

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The data and efficacy analyses from Study 305 will be discussed.

Part of the text, tables and figures presented in this section were adapted from the applicant's Clinical Study Report (CSR).

3.1.1 Study Objectives

The primary objective of the study was to compare the OS of patients treated with eribulin versus 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.

3.1.2 Study Design

Study 305 was a multi-center, phase 3, open-label, randomized study conducted in a total of 135 centers in 19 countries.

Patients were stratified based on the geographic region, HER2/neu status, and prior treatment with capecitabine, and randomized to receive either eribulin mesylate as an intravenous (IV) bolus of 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 every 21 days or the TPC. Patients randomized to receive TPC were treated with either single agent chemotherapy, hormonal or biological therapy, which was available in the investigational center for the treatment of cancer, or, if no such treatment was available, received best supportive care. The use of other investigational drugs, or products not registered for the treatment of cancer was not allowed.

In this study, a 2:1 ratio for randomization for eribulin:TPC was used. An independent data monitoring committee (DMC) was used to allow review of safety of eribulin treatment in the study and to assess interim efficacy data. Prior to randomization, the proposed TPC agent that would have been given if the patient was randomized to TPC had to be defined and confirmed by the investigator using the IVRS.

3.1.3 Efficacy Endpoints

The protocol-specified primary efficacy endpoint was OS. Secondary endpoints were PFS, ORR and DoR.

OS was defined as the time from the date of randomization until death from any cause. PFS was defined as the time from the date of randomization until progressive disease (PD) or death from any cause. Patients who were lost to follow-up were censored at the date last known alive. Patients who were alive on the data cut-off date (May 12, 2009) were censored at the data cut-off date for OS analyses. For PFS analyses, patients who had not progressed on the data cut-off date were censored at that date. ORR was defined as the number of patients with a confirmed CR or confirmed PR divided by the number of patients in the analysis population. DoR was defined as the time from first documented CR or PR until disease progression or death from any cause.

3.1.4 Sample Size Consideration

In the final Study 305 protocol, the sample size consideration was based on the following assumptions:

- In addition to the final analysis based on OS there would be one interim analysis when 50% of the events (206 deaths) had been observed. The trial could be stopped early for superiority or lack of efficacy on overall survival.
- Median survival of 9 months and 12 months in the TPC and Eribulin arms, respectively, i.e. a hazard ratio of 0.75.
- 2:1 randomization scheme.
- 5% two-sided type I error and 80% power
- An average accrual rate of 35 patients per month and an accrual period of 18 months.

The overall death rate in the pooled population was evaluated 15 months after the first patient was recruited. The sample size was increased from 630 patients up to approximately 1,000 patients (approximately 667 in the eribulin arm and approximately 333 in the TPC arm) afterwards. In the final study protocol, it was stated that sample size re-assessment would be done on an ongoing basis. As soon as it became apparent that the 411 deaths would be reached within a reasonable timeframe, recruitment would be stopped. These re-assessments were to be conducted in-house by a statistician who was blinded to treatment assignment. Since there was no formal comparison made between the two groups, there was no alpha adjustment made.

The study enrolled 763 patients upon completion.

Review's Comments:

According to the protocol, the sample size re-estimation was pre-planned at 15 months after the first patient had been recruited. The overall recruitment and death rate in the pooled population were evaluated in-house by a statistician, who was blinded to treatment assignment. The pooled sample suggested that the number of deaths was smaller than expected, and a decision was made to increase the number of patients enrolled from 630 to 1000. However the target number of deaths was not changed. The protocol was changed accordingly, reviewed and agreed by FDA in July 2008.

According to the DMC meeting minutes and previous reviews, recruitment was stopped at 763 patients before Dec. 4, 2008. However, details of the stopping procedure were not reported. As of Jan. 9, 2009, there were 258 deaths recorded, with 166 in the Eribulin arm and 92 in the TPC arm.

3.1.5 Efficacy Analysis Methods

The primary final analysis for OS was a stratified log-rank test. OS was compared between the original randomized treatment groups, irrespective of cross-over, using a two-sided stratified log-rank test at a type I error rate of 0.049. The test was stratified by HER2/neu status, prior capecitabine treatment and geographical region. A Cox regression model was fitted to estimate the hazard ratio which was also adjusted for HER2/neu status, prior capecitabine treatment, geographical region, prior chemotherapy and ER status.

A formal interim analysis was performed when 50% of the events (206 deaths) were observed. To maintain an overall significance level of 0.05, a Lan DeMets implementation of the O'Brien and Fleming alpha spending function was used to create a stopping rule for superior efficacy. With this approach, the nominal significance level of the first interim test was 0.003 and the nominal significance level of the final analysis was 0.049.

The analysis of PFS was based on the independent review of tumor assessments, and tested using a 2-sided stratified log-rank test at 5% significance level.

The analysis of ORR was based on the independent review of disease assessments and a Fisher's exact test. Tumor response rates in each group were also estimated by exact Pearson Clopper 2-sided 95% confidence limits.

The analysis of DoR was based on the independent review of disease assessments and the analysis method was similar to that of PFS.

No statistical analysis plan controlling the overall false positive rate for the secondary endpoints was specified.

3.1.6 Applicant's Results and Statistical Reviewer's Findings/Comments

3.1.6.1 Study Population

Patients enrolled were women, 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.

A total of 762 patients were randomized to the two study arms. Of these patients, 508 were randomized to the eribulin arm, and 254 were randomized to the TPC arm. The patient disposition is summarized in Table 3.1.6.1.1 (adapted from CSR, page 52), and up to the data cut-off date May 12, 2009.

As of May 12, 2009, the percentages of patients who discontinued treatment were 95.3% (484/508) in the eribulin arm and 96.1% (244/254) in the TPC arm. The percentages of patients who discontinued due to adverse events were 9.8% (50/508) in the eribulin arm and 9.4% (24/254) in the TPC arm. Majority of the patients in both treatment arms discontinued due to disease progression.

Table 3.1.6.1.1 Patient Disposition (ITT)

	Treatment Group		Total
	Eribulin N = 508 n (%)[a]	TPC N = 254 n (%)[a]	N = 762 n (%)[a]
Randomized	508	254	762
Intent-to-Treat Population[b]	508 (100.0)	254 (100.0)	762 (100.0)
Safety Population[c]	503 (99.0)	247 (97.2)	750 (98.4)
Response Evaluable Population[d]	468 (92.1)	214 (84.3)	682 (89.5)
Per Protocol Population[e]	459 (90.4)	216 (85.0)	675 (88.6)
Discontinued from study treatment	484 (95.3)	244 (96.1)	728 (95.5)
Reason for discontinuation from study treatment[f]:			
Adverse Events (including toxicity)	50 (9.8)	24 (9.4)	74 (9.7)
Withdrew Consent	10 (2.0)	7 (2.8)	17 (2.2)
Progressive Disease according to RECIST criteria	336 (66.1)	153 (60.2)	489 (64.2)
Clinical progression	61 (12.0)	36 (14.2)	97 (12.7)
Physician's decision	18 (3.5)	13 (5.1)	31 (4.1)
Lost to Follow-up	0 (0)	0 (0)	0 (0)
Death	3 (0.6)	2 (0.8)	5 (0.7)
Other	6 (1.2)	9 (3.5)	15 (2.0)
Survival Status at data cut-off			
Alive	230 (45.3)	104 (40.9)	334 (43.8)
Died	274 (53.9)	148 (58.3)	422 (55.4)
Lost to Follow-up	4 (0.8)	2 (0.8)	6 (0.8)

Abbreviations: TPC = Treatment of Physician's Choice.

a: Percentages are based on all randomized patients.

b: Intent-to-Treat Population: All patients who were randomized irrespective of whether or not they actually received medication.

c: Safety Population: All patients who were randomized and who received at least a partial dose of study treatment.

d: Response Evaluable Population: All patients with measurable disease, defined as the presence of at least one measurable lesion, per Response Evaluation Criteria in Solid Tumors by Independent Review.

e: Per Protocol Population: All patients in the Intent-to-Treat Population who had met the major inclusion Criteria 1 and 2 and who did not have any other specified major protocol violation.

f: Reasons for discontinuation are based on the planned treatment in the ITT Population.

The most common therapy type in the TPC group was chemotherapy, which was planned for 246 (96.9%) patients and actually received by 238 (93.7%) patients. The following table is a summary of the treatments.

Table 3.1.6.1.2 Treatments (ITT)

Treatment	Assigned (%)	Actual (%)
Eribulin	508 (100.0)	503 (99.0)
TPC: Vinorelbine	65 (25.6)	61 (24.0)
TPC: Gemcitabine	46 (18.1)	46 (18.1)
TPC: Capecitabine	45 (17.8)	44 (17.3)
TPC: Taxanes	41 (16.1)	38 (16.1)
TPC: Anthracyclines	24 (9.4)	24 (9.4)
TPC: Hormone therapy	8 (3.1)	9 (3.5)
TPC: Others	25 (9.8)	25 (9.8)

3.1.6.2 Demographic and Other Baseline Characteristics

Demographic and disease characteristics at baseline for the ITT population were summarized by treatment group in Table 3.1.6.2.1 (adapted from the CSR, page 58).

Table 3.1.6.2.1 Demographics and Disease Characteristic at Baseline (ITT)

	Treatment Group		Total
	Eribulin N = 508	TPC N = 254	N = 762
Age (years)			
N	508	254	762
Mean (sd)	54.8 (10.34)	55.9 (10.43)	55.2 (10.37)
Median	55.0	56.0	55.0
Minimum, Maximum	28, 85	27, 81	27, 85
Age distribution, n (%)			
<40 years	34 (6.7)	17 (6.7)	51 (6.7)
≥40 to <65 years	380 (74.8)	180 (70.9)	560 (73.5)
≥65 years	94 (18.5)	57 (22.4)	151 (19.8)
Sex, n (%)			
Female	508 (100.0)	254 (100.0)	762 (100.0)
Race, n (%)			
Black	20 (3.9)	14 (5.5)	34 (4.5)
White	470 (92.5)	233 (91.7)	703 (92.3)
Asian/Pacific Islander	3 (0.6)	2 (0.8)	5 (0.7)
Other	15 (3.0)	5 (2.0)	20 (2.6)
Geographical region, n (%)			
North America/Western Europe/ Australia	325 (64.0)	163 (64.2)	488 (64.0)
Eastern Europe	129 (25.4)	64 (25.2)	193 (25.3)
Latin America /South Africa	54 (10.6)	27 (10.6)	81 (10.6)

Parameter	Treatment Group		Total
	Eribulin N = 508 n (%)	TPC N = 254 n (%)	N = 762 n (%)
HER2/*neu* status (combined FISH and IHC tests), n (%)[b]			
Positive	83 (18.0)	40 (17.2)	123 (17.8)
Negative	373 (81.1)	192 (82.8)	565 (81.6)
Unknown	4 (0.9)	0	4 (0.6)
Not done	48	22	70
ER status, n (%)[b]			
Positive	336 (70.0)	171 (70.4)	507 (70.1)
Negative	143 (29.8)	72 (29.6)	215 (29.7)
Unknown	1 (0.2)	0	1 (0.1)
Not done	28	11	39
PgR status, n (%)[b]			
Positive	254 (56.2)	123 (54.7)	377 (55.7)
Negative	197 (43.6)	102 (45.3)	299 (44.2)
Unknown	1 (0.2)	0	1 (0.1)
Not done	56	29	85
Negative for ER, PgR and HER2/*neu*, n (%)[b]			
Yes	93 (18.3)	51 (20.9)	144 (19.8)
No	380 (78.8)	192 (78.7)	572 (78.8)
Unknown[c]	9 (1.9)	1 (0.4)	10 (1.4)
ECOG performance status, n (%)			
0	217 (42.7)	103 (40.6)	320 (42.0)
1	244 (48.0)	126 (49.6)	370 (48.6)
2	39 (7.7)	22 (8.7)	61 (8.0)

Abbreviation: ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; FISH = Fluorescence in-situ hybridization; HER2/*neu* = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ITT = Intent-to-treat; PgR = progesterone receptor; sd = Standard deviation; TPC = Treatment of Physician's Choice.

Number of prior therapies was also an important baseline factor for this trial. The following table lists the summary of the anti-cancer therapies prior to the trial (adapted from page 63 of the CSR).

Table 3.1.6.2.2 Prior Anti-cancer therapy (ITT)

Parameter	Treatment Group		Total
	Eribulin N = 508	TPC N = 254	N = 762
Number of prior chemotherapy regimens, n (%)			
1	1 (0.2)	0	1 (0.1)
2	65 (12.8)	31 (12.2)	96 (12.6)
3	176 (34.6)	83 (32.7)	259 (34.0)
4	166 (32.7)	79 (31.1)	245 (32.2)
5	85 (16.7)	51 (20.1)	136 (17.8)
≥6	13 (2.6)	9 (3.5)	22 (2.9)
Duration of last chemotherapy (months)			
Median (Minimum, Maximum)[a]	3.57 (0.0, 32.0)	3.50 (0.1, 25.3)	3.53 (0.0, 32.0)
Number of patients who previously received: n (%)			
Taxanes	503 (99.0)	251 (98.8)	754 (99.0)
Anthracyclines	502 (98.8)	250 (98.4)	752 (98.7)
Capecitabine	370 (72.8)	189 (74.4)	559 (73.4)
Number of prior hormonal regimens, n (%)			
1	220 (43.3)	96 (37.8)	316 (41.5)
2	109 (21.5)	65 (25.6)	174 (22.8)
3	60 (11.8)	23 (9.1)	83 (10.9)
4	28 (5.5)	21 (8.3)	49 (6.4)
5	10 (2.0)	1 (0.4)	11 (1.4)
≥6	3 (0.6)	4 (1.6)	7 (0.9)
Number of patients refractory[b] to: n, (%)			
Taxane	410 (80.7)	204 (80.3)	614 (80.6)
Capecitabine	342 (67.3)	174 (68.5)	516 (67.7)
Anthracycline	284 (55.9)	156 (61.4)	440 (57.7)
Prior radiotherapy, n (%)			
Yes	420 (82.7)	195 (76.8)	615 (80.7)
No	88 (17.3)	59 (23.2)	147 (19.3)

Abbreviations: ITT = Intent-to-treat; TPC = Treatment of Physician's Choice.
a: Patients with a zero duration of last chemotherapy were patients who received only a single dose of the last chemotherapy agent that they were receiving prior to starting on study.
b: Refractory was defined as progressed within six months of receiving the therapy.

Reviewer's comments:

The demographic and baseline characteristics of the ITT population are generally balanced over the two arms.

3.1.6.3 Efficacy Analysis

Primary Endpoint Analyses: Overall Survival

The primary endpoint was OS. Table 3.1.6.3.1 summarizes the main efficacy analysis results for final OS data. There were total of 422 deaths observed between the two arms, and 340 patients were still alive at the data cut-off. Since there was an efficacy interim analysis at 50% of the information were observed, the adjusted alpha level for the final log-rank test was 0.049.

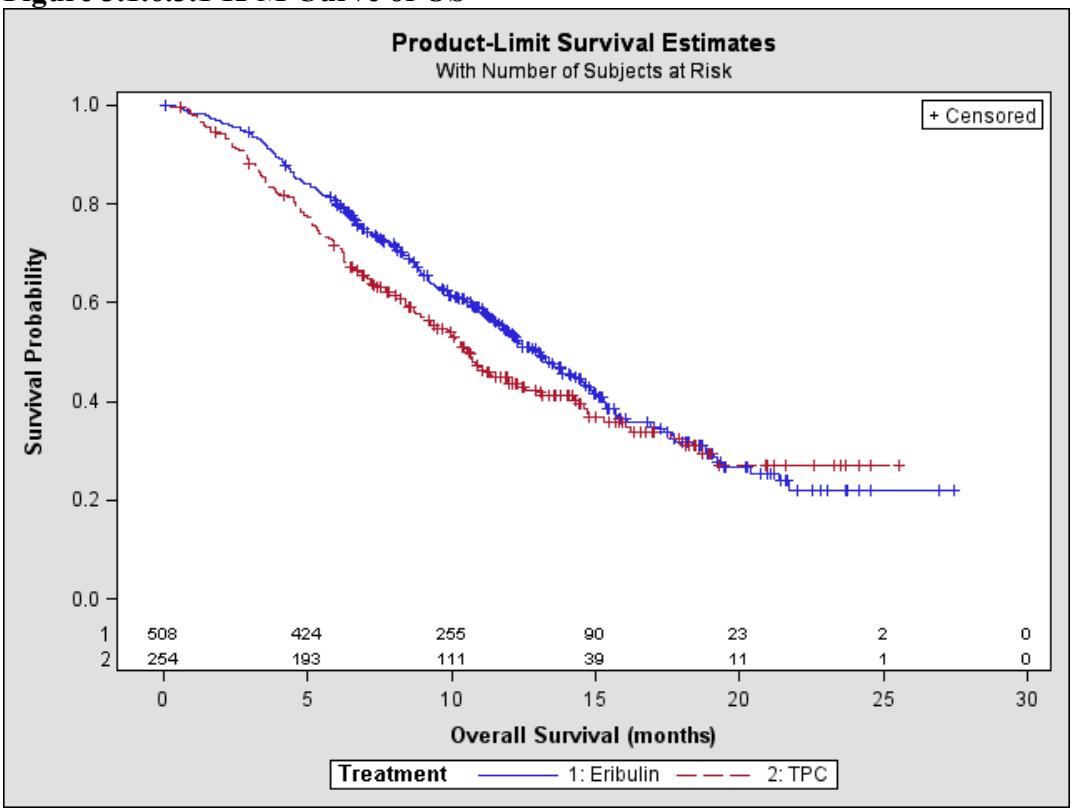
The primary analysis showed the OS was improved with the stratified log-rank test p-value = 0.041. The median survival was 13.1 months for the eribulin arm compared with 10.6 months for the TPC arm. The hazard ratio (HR) was 0.81 with 95% confidence interval (0.66, 0.99).

Table 3.1.6.3.1 Results of OS Primary Analysis

	Eribulin N = 508	**TPC** N= 254
Number of Deaths (%)	274 (53.9%)	148 (58.3%)
Median Survival (95% CI)	13.1 (11.8, 14.3)	10.6 (9.2, 12.5)
p-value	0.041	
HR	0.81 (0.66, 0.99)	

Figure 3.1.6.3.1 shows the estimated Kaplan-Meier curve for the distribution of OS.

Figure 3.1.6.3.1 K-M Curve of OS



Reviewer's comments:

The reviewer conducted sensitivity analysis to check the robustness of the primary analysis results. Most of these analyses were also reported by the applicant.

1. The per protocol (PP) population included patients in the ITT population who met the major inclusion criteria and who did not have any other major protocol violation. A total of 674 patients were included in the PP population, with 49 excluded in the eribulin arm and 38 excluded in the TPC arm from the ITT population. The estimates were similar to those of the ITT population. However, the result from the log-rank test was not statistically significant. The analysis results are summarized below:

Table 3.1.6.3.2 Results of OS Analysis in PP Population

	Eribulin N = 459	TPC N = 216
Number of Deaths (%)	244 (53.2%)	123 (56.9%)
Median Survival (95% CI)	13.1 (11.8, 14.3)	10.6 (9.3, 12.5)
p value	0.066	
HR	0.81 (0.65, 1.02)	

2. Two more sensitivity analyses were performed on the ITT population. The pre-specified final analysis for OS was to be conducted at 411 deaths using a stratified log-rank test on the ITT population. Sensitivity analyses were performed using an un-stratified log-rank test and testing only the first 411 deaths. It was observed that most of these results were consistent to the primary efficacy analysis result. The unstratified log-rank test was not significant, while the test for the first 411 deaths data were showing statistically significant result. The results are summarized in the following table.

Table 3.1.6.3.3 OS Sensitivity Analyses

	N	p-value	HR	95% CI
Stratified	762	0.041	0.809	(0.66, 0.99)
Unstratified	762	0.065	0.829	(0.68, 1.01)
At 411 Deaths	762	0.040	0.807	(0.66, 0.99)

3. Additional sensitivity analyses were also performed on certain subgroups. Please refer to Section 4.2 for results of the subgroup analyses.

Secondary Endpoints Analyses: PFS, ORR and DoR

The secondary endpoints were PFS, ORR and DoR. There was no statistical plan to adjust alpha for multiple comparisons among secondary endpoints. DoR was not based on randomization.

Table 3.1.6.3.2 summarizes the main efficacy analysis results for final PFS data by independent review. There were total of 521 events observed between the two arms at the data cut-off.

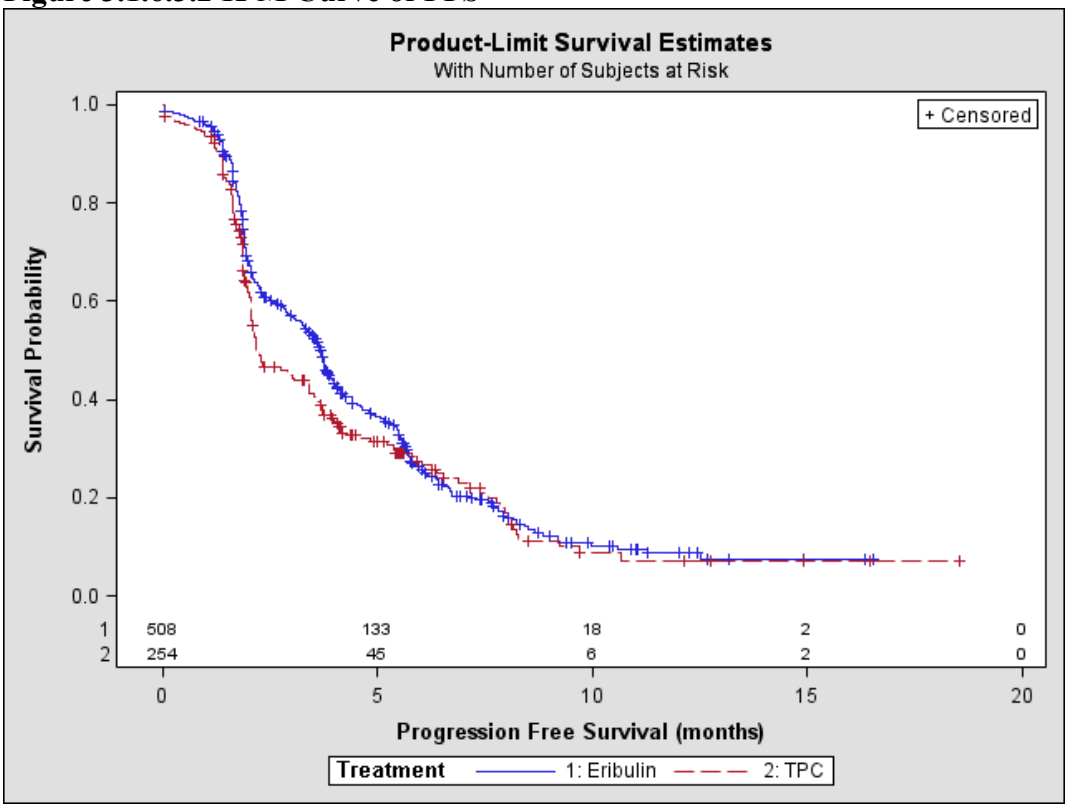
The final analysis showed there was no statistically significant improvement in the median PFS based on a stratified log-rank test (p-value = 0.137). The median PFS was 113 days for the eribulin arm compared with 68 days for the TPC arm. The related HR was 0.87 with 95% CI = (0.71, 1.05). This analysis was not conducted at pre-specified number of events.

Table 3.1.6.3.4 Progression Free Survival

	Eribulin N =508	TPC N = 254
Number of Events (%)	357 (70.3%)	164 (64.6%)
Median PFS (95% CI)	3.7 (3.3, 3.8)	2.2 (2.1, 3.4)
p-value	0.137	
HR	0.87 (0.71, 1.05)	

Figure 3.1.6.3.2 shows the estimated Kaplan-Meier curve for the PFS distribution.

Figure 3.1.6.3.2 K-M Curve of PFS



Objective Response Rate

Response rate was a secondary endpoint planned in the protocol. There were 57 (11.2%) and 10 (3.9%) complete and partial responses reported in the eribulin arm and the TPC arm, respectively. A Fisher's exact test was utilized. The confidence intervals for the response rates were (8.6%, 14.3%) for the eribulin arm and (1.9%, 7.1%) for the TPC arm.

The following table summarized the results for the ORR.

Table 3.1.6.3.5 Objective Response Rate

	Eribulin N=508 (%)	TPC N=254 (%)	p-value
Objective Response Rate (CR+PR)	57 (11.2)	10 (3.9)	0.0006
Complete Response (CR)	3 (0.6)	0	
Partial Response (PR)	54 (10.6)	10 (3.9)	
Stable Disease (SD)	208 (40.9)	96 (37.8)	
Progressive Disease (PD)	190 (37.4)	105 (41.3)	
Non Evaluable (NE)	47 (9.3)	40 (15.8)	
Unknown (UN)	6 (1.2)	3 (1.2)	

Reviewer's comments:

The result of PFS analysis was not statistically significant. However, it showed a similar trend to the result of OS. For the results of ORR analysis, the Fisher's exact test for ORR was significant. However, since no statistical analysis plan was pre-specified to control the overall alpha, the p-values were considered to be nominal. In addition, the response rates were low. There were only 11% patients responded to the eribulin therapy, and less than 1% were complete response.

Duration of Response

Among the 57 patients in the eribulin arm that responded, 31 progressed before the data cut-off date, the median duration of response was 4.2 months with 95% CI (3.8, 5.0). Among the 10 patients in the TPC arm that responded, 3 progressed before the data cut-off date, the median duration of response was 6.7 months with 95% CI = (3.4, 7.0).

Reviewer's comments:

The analysis for DoR was performed on responders only (8.8% of the whole sample size) and was not a randomized comparison.

Updated OS Analysis

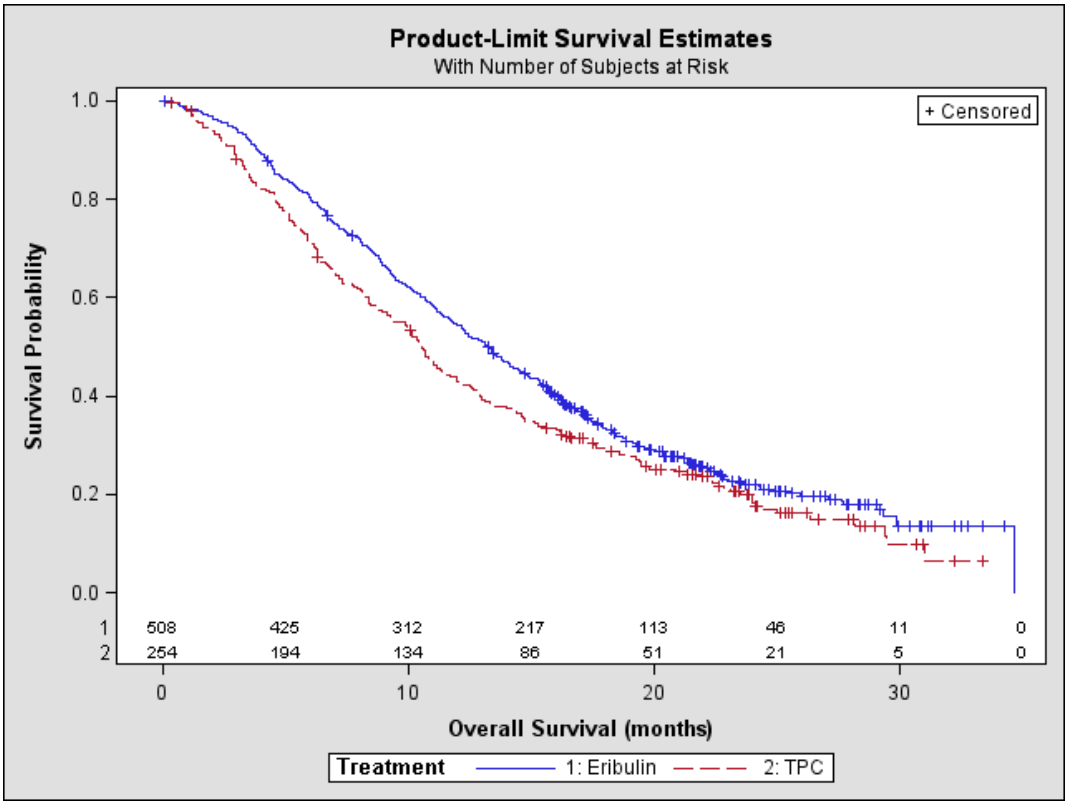
On Jul. 28, 2010 the applicant submitted an updated OS analysis in the 120-day safety report. At the data cut-off date Mar. 3. 2010, there were total of 589 deaths observed between the two arms, which was 77.3% of the enrolled patients. Among these deaths, 386 were in the eribulin arm (76.0%) and 203 (79.9%) were in the TPC arm.

The updated analysis showed the median survival was 2.7 months longer in the eribulin arm compared with the TPC arm (p-value = 0.014). The HR was 0.81 with 95% CI = (0.68, 0.96). The median survival was 13.2 months with 95% CI = (12.1, 14.3) for the eribulin arm compared with 10.5 months with 95% CI = (9.2, 12.0) for the TPC arm.

Table 3.1.6.3.6 Results of OS Updated Analysis

	Eribulin N = 508	**TPC** N = 254
Number of Deaths (%)	386 (76.0%)	203 (79.9%)
Median Survival (95% CI)	13.2 (12.1, 14.3)	10.5 (9.2, 12.0)
p value	0.014	
HR	0.81 (0.68, 0.96)	

Figure 3.1.6.3.3 shows the estimated Kaplan-Meier curve for the distribution of OS.



Reviewer's Comments:

The results from the updated OS analysis confirmed those of primary analysis.

3.2 Evaluation of Safety

Please refer to the Clinical Review of this application for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Since all patients enrolled in the study were females, subgroup analyses for gender were not conducted.

Table 4.1.1 presents the summary statistics of OS by age group (<65 vs. ≥65).

Table 4.1.1 Results of OS Analysis by Age

	Eribulin	TPC
Age < 65		
N	414	197
Number of Deaths (%)	222 (53.6%)	120 (60.9%)
Median Survival (95% CI)	13.0 (11.6, 14.6)	10.3 (8.7, 12.0)
HR	0.79 (0.64, 0.99)	
Age ≥ 65		
N	94	57
Number of Deaths (%)	52 (55.3%)	28 (49.1%)
Median Survival (95%)	13.1 (10.8, 15.3)	11.4 (8.2, NE)
HR	0.96 (0.61, 1.53)	

Table 4.1.2 presents the summary statistics of OS by race (Caucasians vs. Non-Caucasians).

Table 4.1.2 Results of OS Analysis by Race

	Eribulin	TPC
Caucasians		
N	470	233
Number of Deaths	249 (53.0%)	136 (58.4%)
Median Survival	13.1 (12.0, 14.6)	10.7 (9.3, 12.5)
HR	0.80 (0.65, 0.99)	
Non-Caucasians		
N	38	21
Number of Deaths	21 (55.3%)	12 (57.1%)
Median Survival	9.5 (5.7, 14.4)	8.9 (5.7, NE)
HR	1.19 (0.60, 2.37)	

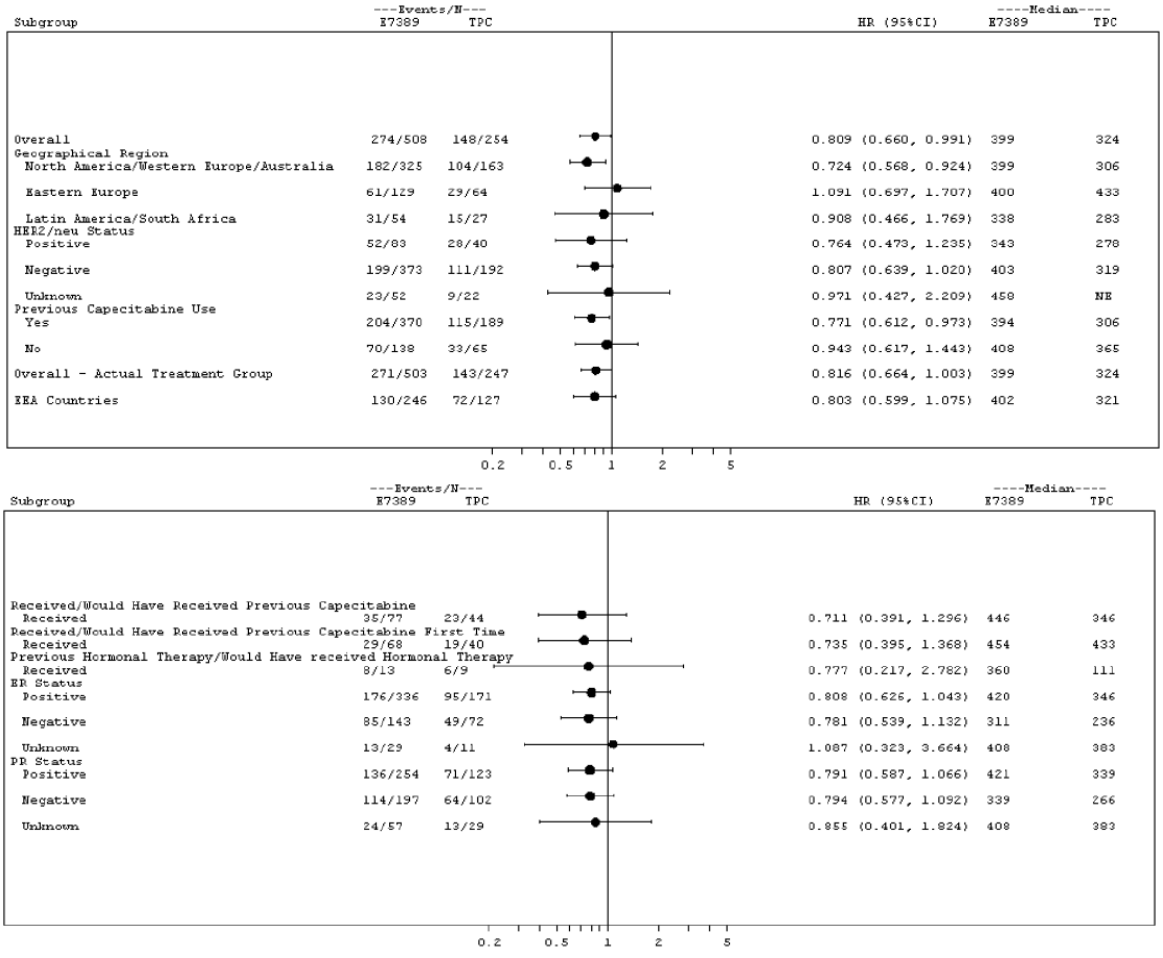
Reviewer's comments:

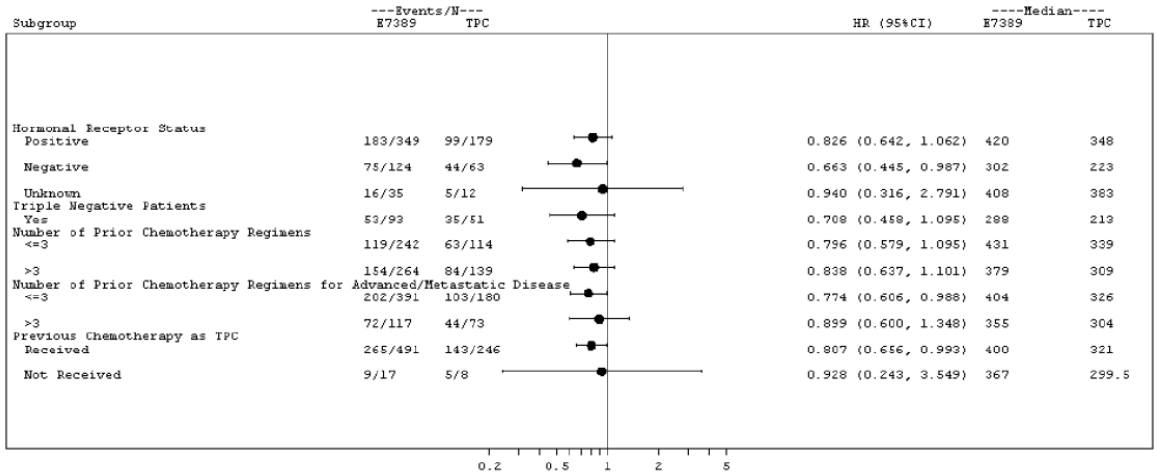
The analyses showed that improvement in the median survival was larger among younger patients (<65 years). Also in the TPC arm, the older group reported a smaller proportion of deaths (49.1% death rate compared with 60.9% death rate from the <65 group). The Caucasians reported a better survival benefit than the non-Caucasians. Both observations were with the caveat that the sample sizes in the age ≥ 65 subgroup and the non-Caucasian subgroup were relatively small.

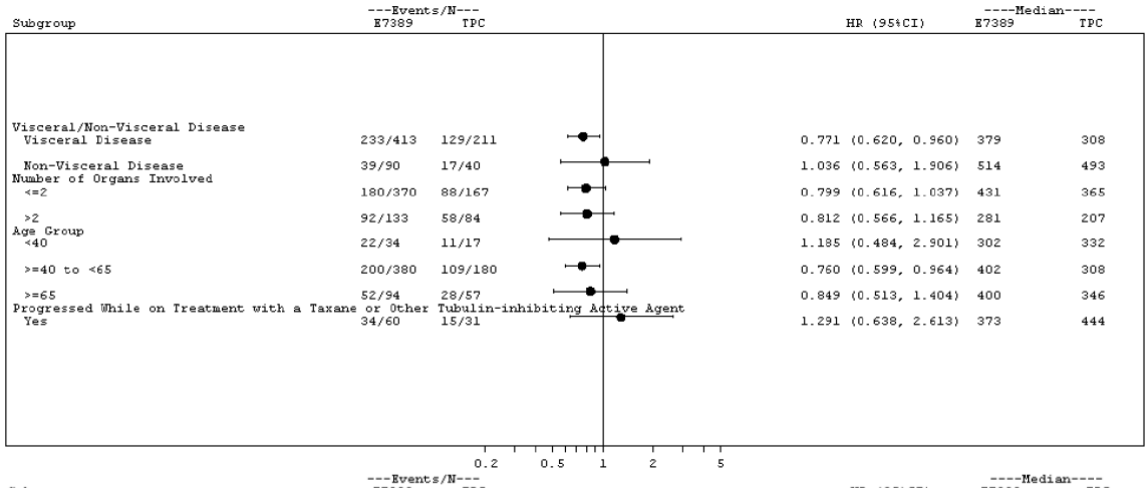
4.2 Other Special/Subgroup Populations

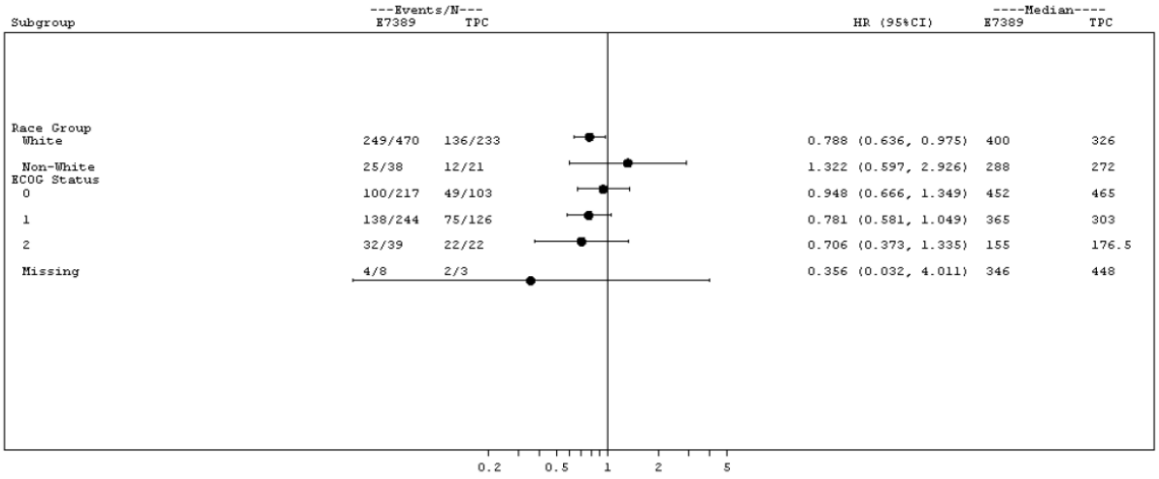
The applicant also reported analysis for certain subgroups. The following figure summarizes the subgroup analysis (adapted from CSR page 77).

Figure 4.2.1 Subgroup Analysis of OS (ITT population)









Reviewer's Comments:

The subgroup analyses for OS were verified by this reviewer. The majority of the subgroup analysis results were consistent with the overall result. Some of the particular subgroups are discussed in detail in the following.

1. The survival effect in the first regional strata, North America/West Europe/Australia showed a stronger result than the overall population. The subgroup analysis for USA patients also showed the same trend. However, the point estimate of HR for the USA patients was 0.93, higher than the overall HR estimate 0.81. This analysis showed that eribulin might not be as effective to the US population compared with the west European/Australian patients. However, the sample size was small in the US.

2. Among other subgroup analyses, patients with prior capecitabine treatment showed a better effect than those without. The HRs were 0.77 with 95% CI = (0.61, 0.97) for patients with prior capecitabine and 0.94 with 95% CI =(0.62, 1.44) for patients without. Since prior capecitabine usage were generally balanced over the two arms, this indicates that eribulin might be more effective to patients with prior capecitabine use.

3. Since HER2 positive is associated with increased disease recurrence and worse prognosis, subgroup analysis were also conducted for HER2 positive and negative patients. Patients with positive HER2 status had a shorter median survival in both arms. However, eribulin showed a trend that it might reduce related risk further for HER2 positive patients. The HRs were 0.76 with 95% CI = (0.47, 1.24) for HER2 positive patients and 0.82 with 95% CI (0.82, 1.03) for HER2 negative patients.

4. For those patients who were ER/PR/HER2 triple negative, eribulin showed a trend to be more effective than TPC, with HR = 0.71 and 95% CI = (0.47, 1.24).

5. In this study there were 403 patients (53.1%) had received more than 3 prior chemotherapies, and for this subgroup the HR was 0.84 with 95% CI = (0.64, 1.10). There were 190 patients (25.0%) had received more than 3 prior chemotherapies in metastatic setting, and for this subgroup the HR was 0.90 with 95% CI = (0.60, 1.35). Though the results were not statistically significant, it showed a trend that eribulin were more effective than TPC.

6. For those patients who had more than 2 organs involved, eribulin showed a trend to be more effective than TPC, with HR = 0.71 and 95% CI = (0.47, 1.24).

7. Patients received same therapy more than once at different time may respond differently new therapies. For patients who did not receive same therapies more than once before entering the trial, either in metastatic setting or any setting, the HR estimates were 0.70, lower than the overall population. This indicates that eribulin might be more effective for these patients.

And the following table summarizes the points discussed above for the subgroup analyses.

Table 4.2.1 Results of OS Subgroup Analyses

Subgroups	N		Median (95% CI)		HR (95% CI)
	Eribulin	TPC	Eribulin	TPC	
N. America / W. Europe / Australia	325	163	13.1 (11.8,14.7)	10.1 (8.4,10.9)	0.73 (0.57, 0.92)
USA	100	46	13.1 (10.7,15.3)	10.7 (7.0,18.0)	0.93 (0.59, 1.46)
w/ Prior Capecitabine Treatment	370	189	12.9 (11.7,14.3)	10.1 (7.7,11.4)	0.77 (0.61, 0.97)
w/o Prior Capecitabine Treatment	138	65	13.4 (11.1,18.4)	12.0 (10.0, NE)	0.94 (0.62, 1.44)
HER2/neu Positive	83	40	11.3 (9.4,12.3)	9.1 (7.3, 13.0)	0.76 (0.47, 1.26)
HER2/neu Negative	373	192	13.2 (12.1, 14.7)	10.5 (8.4,14.2)	0.81 (0.64, 1.02)
Triple Negative	93	51	9.5 (7.1,13.8)	7.0 (4.7,8.9)	0.71 (0.46, 1.10)
w/ Prior >3 Chemos	264	139	12.5 (10.7,13.8)	10.2 (8.2,13.0)	0.84 (0.64, 1.10)
w/ >3 Chemos in Metastatic setting	117	73	11.7 (9.2,13.8)	10.0 (6.0,14.6)	0.90 (0.60, 1.35)
w/ >2 Organs Involved	133	84	9.2 (7.6,11.1)	6.8 (5.7,10.3)	0.81 (0.57, 1.17)
No Repeated Therapy in Any Setting	362	180	13.6 (12.0,14.9)	10.2 (8.4,12.0)	0.70 (0.55, 0.89)
No Repeated Therapy in Metastatic Setting	419	204	13.2 (12.0,14.7)	10.2 (8.4,11.4)	0.70 (0.56, 0.87)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary analysis showed that OS was improved with the stratified log-rank test p-value = 0.041. The median survival was 13.1 months for the eribulin arm compared with 10.6 months for the TPC arm. The hazard ratio (HR) was 0.81 with 95% CI = (0.66, 0.99).

The results from the 120-safety update confirmed the OS results in the primary analysis. The difference p-value was 0.014 from a stratified log-rank test. The median survival was 13.1 for the eribulin arm compared with 10.6 months for the TPC arm. The HR was 0.81 with 95% CI = (0.68, 0.96).

5.2 Conclusions and Recommendations

Based on the data submitted, the study results support the claims in the primary endpoints. Whether the size of the treatment effect is adequate for approval is a clinical decision.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WEISHI YUAN
08/26/2010
This is to replace the previous submitted review. The graphs in the previous review had a typo in the caption

RAJESHWARI SRIDHARA
08/26/2010

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES – TEAM LEADER'S MEMO

NDA/Serial Number:	201532 / 0
Drug Name:	Halaven ® (Eribulin Mesylate)
Indication(s):	(b) (4) or Metastatic Breast Cancer
Applicant:	Eisai Inc.
Dates:	Submitted March 30, 2010
	PDUDA September 30, 2010
Review Priority:	Priority
Biometrics Division:	V (HFD-715)
Primary Reviewer:	Weishi (Vivian) Yuan, Ph. D.
Secondary Reviewer:	Kun He, Statistical Team Leader
Concurring Reviewer:	Rajeshwari Sridhara, Ph. D., Division Director
Medical Division:	Oncology Biologics Products
Clinical Team:	Martha Donoghue, MD, Clinical Reviewer
	Steven Lemery, MD, Team Leader
	Patricia Keegan, MD, Division Director
Project Manager:	Ms. Vaishali Jarral

The Applicant submitted one pivotal trial (the E7389-G000-305 trial) and is seeking a regulatory approval of eribulin for the treatment of patients with (b) (4) or metastatic breast cancer, who had been previously treated with at least two (b) (4) prior chemotherapy regimens, including an anthracyline and a taxane.

The E7389-G000-305 trial (the 305 trial) was an open label, randomized parallel two-arm multi-center study of eribulin versus "treatment of physician's choice" (TPC) in patients with locally recurrent or metastatic breast cancer, who had been previously treated with at least two and a maximum of five prior chemotherapy regimens, including an anthracyline and a taxane, at least two of which must have been given for advanced disease. In addition, patients must have been proven refractory to their most recent chemotherapy regimen, documented by progression on or within six months of therapy. Patients were randomized in a two-to-one ratio to receive eribulin or TPC. Erubilin was given at 1.4 mg/m^2 over two to five minutes intravenously (IV) on Days 1 and 8 of a 21-day cycle, the target dose regimen. TPC was defined as any single-agent chemotherapy, hormonal treatment, or biologic therapy approved for the treatment of cancer; or palliative treatment or radiotherapy, administered according to local practice. In this trial, all patients in the TPC arm received active treatment.

Stratified randomization was used in the 305 trial. The stratification factors were geographic region (North America/Western Europe/Australia, Eastern Europe, or Latin America/South Africa), human epidermal growth factor receptor 2 (HER2/neu) status (positive, negative, or unknown), and prior treatment with capecitabine (yes or no). For all patients, the agent that would be chosen as TPC if the patient were randomized to the TPC arm was defined prior to the randomization. Once the potential TPC therapy had been defined, patients were randomized to either eribulin or TPC treatments.

Patients in the 305 trial were to continue on study treatment until unacceptable toxicity, disease progression (or no further clinical benefit), investigator decision that discontinuation of therapy was in the best interest of the patient, or the patient withdrew consent.

The primary objective of the 305 trial was to compare the overall survival (OS) of patients treated with eribulin versus TPC.

The primary efficacy endpoint in the 305 trial was OS, defined as the date of randomization until the date of death due to any cause. For patients who did not die (i.e., those who were lost to follow-up or who were alive at the date of data cut-off), the time to death was censored at the time of last contact. Secondary endpoints included progression-free survival (PFS), determined from the date of randomization until the date of disease progression or death from any cause assessed by the independent review of tumor assessments, and the objective response rate (ORR), defined as the number of

patients with a confirmed complete response (CR) or partial response (PR) based on the modified RECIST criteria assessed by the independent review divided by the number of patients in the analysis population.

The 305 trial was planned to detect a hazard ratio of 0.75 with 80% power and a two-sided significance level of 0.05, assuming a median OS of 9 months in the TPC arm and 12 months in the eribulin arm. An estimated total of 630 patients (420 in eribulin and 210 in TPC), and a maximum of 411 deaths would be required with an estimated maximum trial duration of 26.5 months. The 305 trial also planned to have a sample size re-estimation at 15 months after the first patient was recruited if the death rate was smaller than expected. In the protocol amendment dated June 5, 2008, the sample size was planned to increase to a maximum of 1000 (667 in eribulin arm and 333 in the TPC arm). The 411 required number of deaths for the primary analysis remained unchanged. The sample size re-assessment would be done on an ongoing basis, conducted in-house by a statistician who was blinded to treatment assignment, and the pooled death rate was communicated to a small group of people for decision-making purposes. Based on the DSMB meeting minutes dated December 18, 2008, enrollment was completed after 763 patients were randomized (one patient in the IVRS database had no treatment record), and 241 deaths had been recorded as of December 1, 2008. The sample size re-assessment was reviewed and accepted by the FDA.

The primary analysis of OS was a stratified log-rank test stratified by those factors used for randomization on the intent-to-treat (ITT) population. The OS statistics would be estimated using Kaplan-Meier curves. The hazard ratio would be estimated by a stratified Cox regression model. The analysis of PFS was the same as that of OS. The analysis of ORR was a Fisher's Exact Test. There was no statistical analysis plan proposed to adjust for multiplicity between the PFS and ORR analyses.

A formal interim analysis of OS was planned at 50% of the deaths (206 deaths) for both superiority and futility purposes. The O'Brien and Fleming alpha spending function was used to adjust alpha, where the nominal level was 0.003 for the interim analysis and 0.049 for the final analysis.

The first patient in the 305 trial was randomized in November 2006, and the last patient was randomized in November 2008. A total of 762 patients were randomized in the 305 trial: 508 in eribulin and 254 in TPC. Twelve patients were discontinued from the trial before the start of treatment (six in the eribulin arm and six in the TPC arm). The demographic and baseline characteristics of the patient population appeared to be balanced. For further details regarding the design, data analyses, and results of the 305 trial, refer to the statistical review for this application by Dr. Vivian Yuan.

The data cut-off for the 305 trial was May 12, 2009, when 422 patients in the ITT population had died. The trial met its primary objective. There were 244 (53.2%) deaths in the eribulin arm and 123 (56.9%) deaths in the TPC arm. Treatment with eribulin

resulted in a 19% risk reduction for death compared with TPC [HR=0.81; (95% CI: 0.66, 0.99); p=0.041]. The median OS was 13.1 months (95% CI: 11.8, 14.3) for eribulin and 10.6 months (95% CI: 9.3, 12.5) for TPC.

Treatment with eribulin resulted in a 13% risk reduction for disease progression compared with TPC [HR=0.87; (95% CI: 0.71, 1.05); p=0.137]. The median PFS was 3.7 months (95% CI: 3.3, 3.9) for eribulin and 2.2 months (95% CI: 2.1, 3.4) for TPC. There was a positive trend for PFS in support of eribulin that did not reach statistical significance. The ORR was 12.2% [(95% CI: 9.4, 15.5); p=0.0006] for patients in the eribulin arm and 4.7% (95% CI: 2.3, 8.4) in the TPC arm. The p-value of 0.0006 was not adjusted for multiplicity.

The Applicant also submitted an updated OS analysis. As described by the Applicant: "Following pre-submission discussions with the regulatory authorities in the European Union, it became evident that the Rapporteurs would expect to see updated survival information from the pivotal Phase 3 study (E7389-G000-305) included in the regulatory submission, and that the data cut-off date should represent a greater level of data maturity than that of the preplanned analysis. Given the need to provide a validated report during the regulatory procedures, a target level of 75% of deaths was chosen for the updated OS cut-off and a survival sweep was initiated at a time to coincide with this estimated event level."

The updated OS analysis was reported at 589 deaths (77.3% of enrolled patients). Based on the updated OS analysis, there were 386 (76.0%) deaths in the eribulin arm and 203 (79.9%) deaths in the TPC arm. Treatment with eribulin resulted in a 19% risk reduction for death compared with TPC [HR=0.81; (95% CI: 0.67, 0.96); p=0.014]. The median OS was 13.2 months (95% CI: 12.1, 14.4) for eribulin and 10.5 months (95% CI: 9.2, 12.0) for TPC.

Although the 305 trial demonstrated that treatment with eribulin resulted in a 19% risk reduction for death compared with TPC for both the protocol specified OS analysis and the updated OS analysis, whether the magnitude of 2.5 months (2.7 months for the updated analysis) improvement in median OS based on only one trial represents a significant clinical benefit will depend on an overall benefit to risk analysis and is deferred to the clinical review team.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KUN HE
08/06/2010

RAJESHWARI SRIDHARA
08/09/2010

August 27, 2010

Three graphs in this review have incorrect wording ("days" should be "months").

This review is superseded by Weishi (Vivian) Yuan's corrected REV-BIOMETRICS-01 (General Review), which was signed-off in DARRTS on August 26, 2010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	201532/0
Drug Name:	Eribulin Mesylate Injection
Indication(s):	(b) (4) or Metastatic Breast Cancer
Applicant:	Eisai Inc.
Date:	Submitted March 30, 2010
	PDUDA September 30, 2010
Review Priority:	Priority
Biometrics Division:	V (HFD-715)
Statistical Reviewer:	Weishi (Vivian) Yuan
Concurring Reviewers:	Kun He, Ph. D., Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Oncology Biologics Products
Clinical Team:	Martha Donoghue, MD, Clinical Reviewer
	Steven Lemery, MD, Team Leader
	Patricia Keegan, MD, Division Director
Project Manager:	Ms. Vaishali Jarral

Keywords: overall survival, progression free survival, response rate, metastatic breast cancer

Table of Contents

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The applicant submitted the data and final study report of the Study 305 to support a new drug approval indicated for patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens, including an anthracycline and a taxane.

The data and analyses from the current submission showed a 2.5 months improvement in median survival in the primary analysis in the eribulin arm (13.1 months) compared with the TPC arm (10.6 months). The difference was significant with a p-value of 0.041 based on a stratified log-rank test and a HR of 0.81 with 95% CI = (0.66, 0.99).

The results from the 120-safety update confirmed the overall survival (OS) results. The median survival improvement was 2.7 months for the eribulin arm (13.2 months) compared with the TPC arm (10.5 months). The difference was significant with a p-value of 0.014 based on a stratified log-rank test and a HR of 0.81 with 95% CI = (0.68, 0.96).

Based on the data submitted, the study results support the claims in the primary endpoints. Whether the size of the treatment effect from a single study are adequate for approval depends on the risk-benefit assessment and clinical decision.

1.2 Brief Overview of Clinical Studies

Study 305 was a multi-center, Phase 3, open-label, randomized, parallel two-arm multi-national study that enrolled patients with locally recurrent or metastatic breast cancer comparing eribulin with treatment of physician's choice (TPC).

Patients were pre-stratified based on the geographic region, HER2/neu status, and prior treatment with capecitabine. Patients were randomized in a 2:1 ratio to receive either eribulin mesylate as an intravenous (IV) bolus of 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 every 21 days or the Treatment of Physician's Choice (TPC). The TPC was defined as any single agent chemotherapy, hormonal treatment or biological therapy approved for the treatment of cancer; or best supportive care or radiotherapy, administered according to local practice, if applicable. Treatment with another investigational agent in the TPC group was not allowed.

The primary study objective was to compare the overall survival (OS) of patients treated with eribulin versus the 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.

1.2 Statistical Issues and Findings

The protocol-specified primary efficacy endpoint was overall survival (OS). The secondary endpoints included progression free survival (PFS), objective response rate (ORR) and duration of response (DoR).

The primary analysis was planned to occur when 411 deaths had been recorded. A formal efficacy interim analysis was performed when 50% of the deaths (206 deaths) had been observed. The final 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. In this report, the primary analysis was conducted with 422 deaths.

The secondary efficacy endpoints analyzed were PFS, ORR, and duration of response. PFS and DoR were analyzed using the same methods as OS. ORR was analyzed using a Fisher's exacted test, and tumor response rates in each group were also estimated by exact Pearson Clopper 2-sided 95% confidence limits. The results of PFS, ORR, and duration of response were based on data by the independent assessment.

A total of 762 patients were randomized to the two arms, with 508 in the eribulin arm, and 254 in the TPC arm.

In the primary analysis, total of 422 deaths were observed. Median survival was 2.5 months longer in the eribulin arm compared with the TPC arm (p-value=0.041). The hazard ratio(HR) based upon a Cox model including the randomization stratification factors as strata was 0.81 with 95% CI = (0.66, 0.99). Median survival was 13.1 months with 95% CI = (11.8, 14.3) in the eribulin arm and 10.6 months with 95% CI= (9.3, 12.5) in the TPC arm.

In the 120-day safety update, total of 589 deaths were observed. The updated analysis showed median survival was 2.7 months longer in the eribulin arm compared with the TPC arm (p-value = 0.014). The hazard ratio (HR) was 0.81 with 95% CI = (0.68, 0.96). The median survival was 13.2 months with 95% CI = (12.1, 14.3) for the eribulin arm compared with 10.5 months with 95% CI = (9.2, 12.0) for the TPC arm.

2. INTRODUCTION

2.1 Overview

Eribulin is a synthetic analog of halichondrin B (HalB), a substance isolated from the rare marine sponge Halichondria okadai. HalB is a large polyether macrolide that exerts potent anti-cancer effects in cell-based and animal models of cancer.

2.1.1 Indication

The indication statement for which marketing approval is being sought was (b) (4) (b) (4) or metastatic breast cancer, previously treated with at least two prior chemotherapy regimens, including an anthracycline and a taxane.

2.1.2 Regulatory History of Drug

The clinical development of eribulin mesylate was conducted under IND 67,193 since January 2003. Meeting with the applicant included an End of Phase 2 Meeting/Breast Cancer in September 2005, a Pre-NDA Meeting in August 2007, an End of Phase 2 Follow-up Meeting/Study E7389-G000-305 in March 2008, and a Pre-NDA Meeting/Study E7389-G000-305 in November 2009.

A Special Protocol Agreement was reached in February 2006 for another study, Study 301 – an open label, randomized trial comparing eribulin to capecitabine in patients with refractory metastatic breast cancer. This study is still ongoing and is expected to finish in March 2011. The FDA is requesting the final study report and datasets to be submitted upon completion of the study as a Post Marketing Commitment (PMC).

The protocol for Study 305 was discussed in the March 2008 meeting. FDA concerned that this single study might not be robust enough to support NDA approval. The NDA was submitted in March 2010 with data and analyses from a single randomized Phase 3 study, Study 305.

2.2 Data Sources

Data used for review is from the electronic submission received on Jul. 31, 2009. The network path is **\\CDSESUB1\EVSPROD\NDA201532\0000.**

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The data and efficacy analyses from Study 305 will be discussed.

Part of the text, tables and figures presented in this section were adapted from the applicant's Clinical Study Report (CSR).

3.1.1 Study Objectives

The primary objective of the study was to compare the OS of patients treated with eribulin versus 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.

3.1.2 Study Design

Study 305 was a multi-center, phase 3, open-label, randomized study conducted in a total of 135 centers in 19 countries.

Patients were stratified based on the geographic region, HER2/neu status, and prior treatment with capecitabine, and randomized to receive either eribulin mesylate as an intravenous (IV) bolus of 1.4 mg/m^2 over 2 to 5 minutes on Days 1 and 8 every 21 days or the TPC. Patients randomized to receive TPC were treated with either single agent chemotherapy, hormonal or biological therapy, which was available in the investigational center for the treatment of cancer, or, if no such treatment was available, received best supportive care. The use of other investigational drugs, or products not registered for the treatment of cancer was not allowed.

In this study, a 2:1 ratio for randomization for eribulin:TPC was used. An independent data monitoring committee (DMC) was used to allow review of safety of eribulin treatment in the study and to assess interim efficacy data. Prior to randomization, the proposed TPC agent that would have been given if the patient was randomized to TPC had to be defined and confirmed by the investigator using the IVRS.

3.1.3 Efficacy Endpoints

The protocol-specified primary efficacy endpoint was OS. Secondary endpoints were PFS, ORR and DoR.

OS was defined as the time from the date of randomization until death from any cause. PFS was defined as the time from the date of randomization until progressive disease (PD) or death from any cause. Patients who were lost to follow-up were censored at the date last known alive. Patients who were alive on the data cut-off date (May 12, 2009) were censored at the data cut-off date for OS analyses. For PFS analyses, patients who had not progressed on the data cut-off date were censored at that date. ORR was defined as the number of patients with a confirmed CR or confirmed PR divided by the number of patients in the analysis population. DoR was defined as the time from first documented CR or PR until disease progression or death from any cause.

3.1.4 Sample Size Consideration

In the final Study 305 protocol, the sample size consideration was based on the following assumptions:

- In addition to the final analysis based on OS there would be one interim analysis when 50% of the events (206 deaths) had been observed. The trial could be stopped early for superiority or lack of efficacy on overall survival.
- Median survival of 9 months and 12 months in the TPC and Eribulin arms, respectively, i.e. a hazard ratio of 0.75.
- 2:1 randomization scheme.
- 5% two-sided type I error and 80% power
- An average accrual rate of 35 patients per month and an accrual period of 18 months.

The overall death rate in the pooled population was evaluated 15 months after the first patient was recruited. The sample size was increased from 630 patients up to approximately 1,000 patients (approximately 667 in the eribulin arm and approximately 333 in the TPC arm) afterwards. In the final study protocol, it was stated that sample size re-assessment would be done on an ongoing basis. As soon as it became apparent that the 411 deaths would be reached within a reasonable timeframe, recruitment would be stopped. These re-assessments were to be conducted in-house by a statistician who was blinded to treatment assignment. Since there was no formal comparison made between the two groups, there was no alpha adjustment made.

The study enrolled 763 patients upon completion.

Review's Comments:

According to the protocol, the sample size re-estimation was pre-planned at 15 months after the first patient had been recruited. The overall recruitment and death rate in the pooled population were evaluated in-house by a statistician, who was blinded to treatment assignment. The pooled sample suggested that the number of deaths was smaller than expected, and a decision was made to increase the number of patients enrolled from 630 to 1000. However the target number of deaths was not changed. The protocol was changed accordingly, reviewed and agreed by FDA in July 2008.

According to the DMC meeting minutes and previous reviews, recruitment was stopped at 763 patients before Dec. 4, 2008. However, details of the stopping procedure were not reported. As of Jan. 9, 2009, there were 258 deaths recorded, with 166 in the Eribulin arm and 92 in the TPC arm.

3.1.5 Efficacy Analysis Methods

The primary final analysis for OS was a stratified log-rank test. OS was compared between the original randomized treatment groups, irrespective of cross-over, using a two-sided stratified log-rank test at a type I error rate of 0.049. The test was stratified by HER2/neu status, prior capecitabine treatment and geographical region. A Cox regression model was fitted to estimate the hazard ratio which was also adjusted for HER2/neu status, prior capecitabine treatment, geographical region, prior chemotherapy and ER status.

A formal interim analysis was performed when 50% of the events (206 deaths) were observed. To maintain an overall significance level of 0.05, a Lan DeMets implementation of the O'Brien and Fleming alpha spending function was used to create a stopping rule for superior efficacy. With this approach, the nominal significance level of the first interim test was 0.003 and the nominal significance level of the final analysis was 0.049.

The analysis of PFS was based on the independent review of tumor assessments, and tested using a 2-sided stratified log-rank test at 5% significance level.

The analysis of ORR was based on the independent review of disease assessments and a Fisher's exact test. Tumor response rates in each group were also estimated by exact Pearson Clopper 2-sided 95% confidence limits.

The analysis of DoR was based on the independent review of disease assessments and the analysis method was similar to that of PFS.

No statistical analysis plan controlling the overall false positive rate for the secondary endpoints was specified.

3.1.6 Applicant's Results and Statistical Reviewer's Findings/Comments

3.1.6.1 Study Population

Patients enrolled were women, 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.

A total of 762 patients were randomized to the two study arms. Of these patients, 508 were randomized to the eribulin arm, and 254 were randomized to the TPC arm. The patient disposition is summarized in Table 3.1.6.1.1 (adapted from CSR, page 52), and up to the data cut-off date May 12, 2009.

As of May 12, 2009, the percentages of patients who discontinued treatment were 95.3% (484/508) in the eribulin arm and 96.1% (244/254) in the TPC arm. The percentages of patients who discontinued due to adverse events were 9.8% (50/508) in the eribulin arm and 9.4% (24/254) in the TPC arm. Majority of the patients in both treatment arms discontinued due to disease progression.

Table 3.1.6.1.1 Patient Disposition (ITT)

	Treatment Group		Total
	Eribulin N = 508 n (%)[a]	TPC N = 254 n (%)[a]	N = 762 n (%)[a]
Randomized	508	254	762
Intent-to-Treat Population[b]	508 (100.0)	254 (100.0)	762 (100.0)
Safety Population[c]	503 (99.0)	247 (97.2)	750 (98.4)
Response Evaluable Population[d]	468 (92.1)	214 (84.3)	682 (89.5)
Per Protocol Population[e]	459 (90.4)	216 (85.0)	675 (88.6)
Discontinued from study treatment	484 (95.3)	244 (96.1)	728 (95.5)
Reason for discontinuation from study treatment[f]:			
Adverse Events (including toxicity)	50 (9.8)	24 (9.4)	74 (9.7)
Withdrew Consent	10 (2.0)	7 (2.8)	17 (2.2)
Progressive Disease according to RECIST criteria	336 (66.1)	153 (60.2)	489 (64.2)
Clinical progression	61 (12.0)	36 (14.2)	97 (12.7)
Physician's decision	18 (3.5)	13 (5.1)	31 (4.1)
Lost to Follow-up	0 (0)	0 (0)	0 (0)
Death	3 (0.6)	2 (0.8)	5 (0.7)
Other	6 (1.2)	9 (3.5)	15 (2.0)
Survival Status at data cut-off			
Alive	230 (45.3)	104 (40.9)	334 (43.8)
Died	274 (53.9)	148 (58.3)	422 (55.4)
Lost to Follow-up	4 (0.8)	2 (0.8)	6 (0.8)

Abbreviations: TPC = Treatment of Physician's Choice.

a: Percentages are based on all randomized patients.

b: Intent-to-Treat Population: All patients who were randomized irrespective of whether or not they actually received medication.

c: Safety Population: All patients who were randomized and who received at least a partial dose of study treatment.

d: Response Evaluable Population: All patients with measurable disease, defined as the presence of at least one measurable lesion, per Response Evaluation Criteria in Solid Tumors by Independent Review.

e: Per Protocol Population: All patients in the Intent-to-Treat Population who had met the major inclusion Criteria 1 and 2 and who did not have any other specified major protocol violation.

f: Reasons for discontinuation are based on the planned treatment in the ITT Population.

The most common therapy type in the TPC group was chemotherapy, which was planned for 246 (96.9%) patients and actually received by 238 (93.7%) patients. The following table is a summary of the treatments.

Table 3.1.6.1.2 Treatments (ITT)

Treatment	Assigned (%)	Actual (%)
Eribulin	508 (100.0)	503 (99.0)
TPC: Vinorelbine	65 (25.6)	61 (24.0)
TPC: Gemcitabine	46 (18.1)	46 (18.1)
TPC: Capecitabine	45 (17.8)	44 (17.3)
TPC: Taxanes	41 (16.1)	38 (16.1)
TPC: Anthracyclines	24 (9.4)	24 (9.4)
TPC: Hormone therapy	8 (3.1)	9 (3.5)
TPC: Others	25 (9.8)	25 (9.8)

3.1.6.2 Demographic and Other Baseline Characteristics

Demographic and disease characteristics at baseline for the ITT population were summarized by treatment group in Table 3.1.6.2.1 (adapted from the CSR, page 58).

Table 3.1.6.2.1 Demographics and Disease Characteristic at Baseline (ITT)

	Treatment Group		Total
	Eribulin N = 508	TPC N = 254	N = 762
Age (years)			
N	508	254	762
Mean (sd)	54.8 (10.34)	55.9 (10.43)	55.2 (10.37)
Median	55.0	56.0	55.0
Minimum, Maximum	28, 85	27, 81	27, 85
Age distribution, n (%)			
<40 years	34 (6.7)	17 (6.7)	51 (6.7)
≥40 to <65 years	380 (74.8)	180 (70.9)	560 (73.5)
≥65 years	94 (18.5)	57 (22.4)	151 (19.8)
Sex, n (%)			
Female	508 (100.0)	254 (100.0)	762 (100.0)
Race, n (%)			
Black	20 (3.9)	14 (5.5)	34 (4.5)
White	470 (92.5)	233 (91.7)	703 (92.3)
Asian/Pacific Islander	3 (0.6)	2 (0.8)	5 (0.7)
Other	15 (3.0)	5 (2.0)	20 (2.6)
Geographical region, n (%)			
North America/Western Europe/ Australia	325 (64.0)	163 (64.2)	488 (64.0)
Eastern Europe	129 (25.4)	64 (25.2)	193 (25.3)
Latin America /South Africa	54 (10.6)	27 (10.6)	81 (10.6)

Parameter	Treatment Group		Total
	Eribulin N = 508 n (%)	TPC N = 254 n (%)	N = 762 n (%)
HER2/*neu* status (combined FISH and IHC tests), n (%)[b]			
Positive	83 (18.0)	40 (17.2)	123 (17.8)
Negative	373 (81.1)	192 (82.8)	565 (81.6)
Unknown	4 (0.9)	0	4 (0.6)
Not done	48	22	70
ER status, n (%)[b]			
Positive	336 (70.0)	171 (70.4)	507 (70.1)
Negative	143 (29.8)	72 (29.6)	215 (29.7)
Unknown	1 (0.2)	0	1 (0.1)
Not done	28	11	39
PgR status, n (%)[b]			
Positive	254 (56.2)	123 (54.7)	377 (55.7)
Negative	197 (43.6)	102 (45.3)	299 (44.2)
Unknown	1 (0.2)	0	1 (0.1)
Not done	56	29	85
Negative for ER, PgR and HER2/*neu*, n (%)[b]			
Yes	93 (18.3)	51 (20.9)	144 (19.8)
No	380 (78.8)	192 (78.7)	572 (78.8)
Unknown[c]	9 (1.9)	1 (0.4)	10 (1.4)
ECOG performance status, n (%)			
0	217 (42.7)	103 (40.6)	320 (42.0)
1	244 (48.0)	126 (49.6)	370 (48.6)
2	39 (7.7)	22 (8.7)	61 (8.0)

Abbreviation: ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; FISH = Fluorescence in-situ hybridization; HER2/*neu* = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ITT = Intent-to-treat; PgR = progesterone receptor; sd = Standard deviation; TPC = Treatment of Physician's Choice.

Number of prior therapies was also an important baseline factor for this trial. The following table lists the summary of the anti-cancer therapies prior to the trial (adapted from page 63 of the CSR).

Table 3.1.6.2.2 Prior Anti-cancer therapy (ITT)

Parameter	Treatment Group		Total
	Eribulin N = 508	TPC N = 254	N = 762
Number of prior chemotherapy regimens, n (%)			
1	1 (0.2)	0	1 (0.1)
2	65 (12.8)	31 (12.2)	96 (12.6)
3	176 (34.6)	83 (32.7)	259 (34.0)
4	166 (32.7)	79 (31.1)	245 (32.2)
5	85 (16.7)	51 (20.1)	136 (17.8)
≥6	13 (2.6)	9 (3.5)	22 (2.9)
Duration of last chemotherapy (months)			
Median (Minimum, Maximum)[a]	3.57 (0.0, 32.0)	3.50 (0.1, 25.3)	3.53 (0.0, 32.0)
Number of patients who previously received: n (%)			
Taxanes	503 (99.0)	251 (98.8)	754 (99.0)
Anthracyclines	502 (98.8)	250 (98.4)	752 (98.7)
Capecitabine	370 (72.8)	189 (74.4)	559 (73.4)
Number of prior hormonal regimens, n (%)			
1	220 (43.3)	96 (37.8)	316 (41.5)
2	109 (21.5)	65 (25.6)	174 (22.8)
3	60 (11.8)	23 (9.1)	83 (10.9)
4	28 (5.5)	21 (8.3)	49 (6.4)
5	10 (2.0)	1 (0.4)	11 (1.4)
≥6	3 (0.6)	4 (1.6)	7 (0.9)
Number of patients refractory[b] to: n, (%)			
Taxane	410 (80.7)	204 (80.3)	614 (80.6)
Capecitabine	342 (67.3)	174 (68.5)	516 (67.7)
Anthracycline	284 (55.9)	156 (61.4)	440 (57.7)
Prior radiotherapy, n (%)			
Yes	420 (82.7)	195 (76.8)	615 (80.7)
No	88 (17.3)	59 (23.2)	147 (19.3)

Abbreviations: ITT = Intent-to-treat; TPC = Treatment of Physician's Choice.
a: Patients with a zero duration of last chemotherapy were patients who received only a single dose of the last chemotherapy agent that they were receiving prior to starting on study.
b: Refractory was defined as progressed within six months of receiving the therapy.

Reviewer's comments:

The demographic and baseline characteristics of the ITT population are generally balanced over the two arms.

3.1.6.3 Efficacy Analysis

Primary Endpoint Analyses: Overall Survival

The primary endpoint was OS. Table 3.1.6.3.1 summarizes the main efficacy analysis results for final OS data. There were total of 422 deaths observed between the two arms, and 340 patients were still alive at the data cut-off. Since there was an efficacy interim analysis at 50% of the information were observed, the adjusted alpha level for the final log-rank test was 0.049.

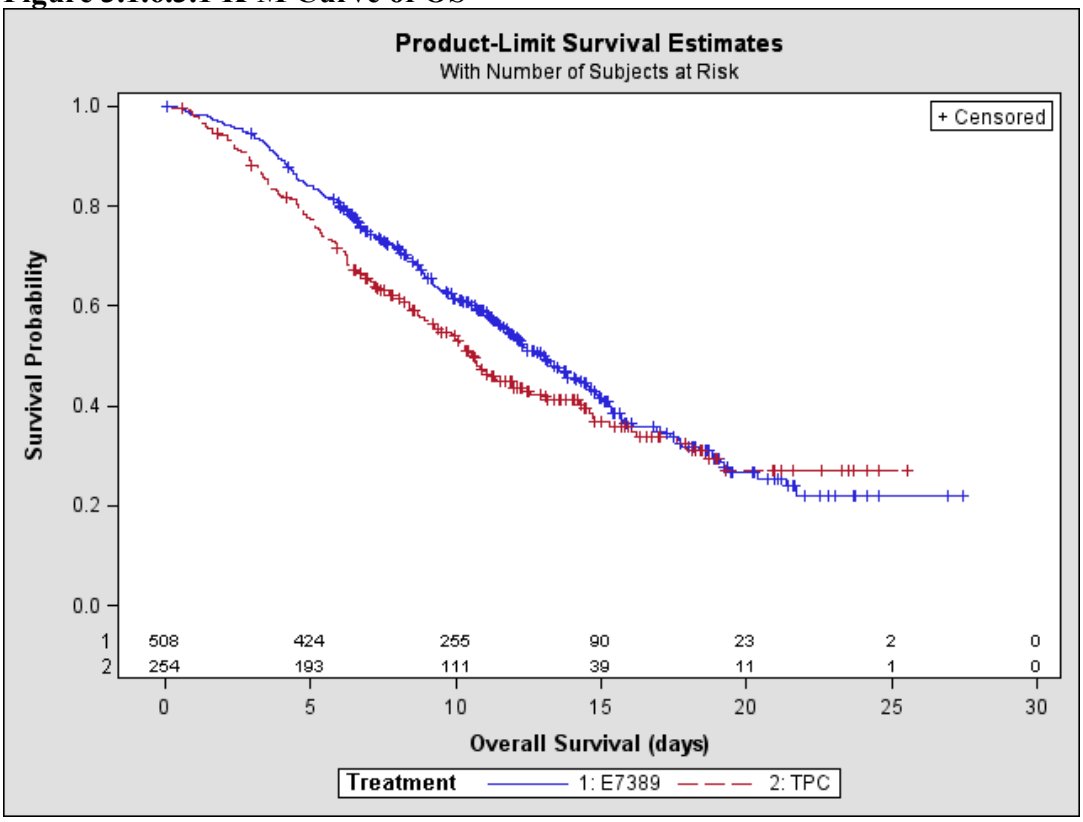
The primary analysis showed the OS was improved with the stratified log-rank test p-value = 0.041. The median survival was 13.1 months for the eribulin arm compared with 10.6 months for the TPC arm. The hazard ratio (HR) was 0.81 with 95% confidence interval (0.66, 0.99).

Table 3.1.6.3.1 Results of OS Primary Analysis

	Eribulin N = 508	**TPC** N= 254
Number of Deaths (%)	274 (53.9%)	148 (58.3%)
Median Survival (95% CI)	13.1 (11.8, 14.3)	10.6 (9.2, 12.5)
p-value	0.041	
HR	0.81 (0.66, 0.99)	

Figure 3.1.6.3.1 shows the estimated Kaplan-Meier curve for the distribution of OS.

Figure 3.1.6.3.1 K-M Curve of OS



Reviewer's comments:

The reviewer conducted sensitivity analysis to check the robustness of the primary analysis results. Most of these analyses were also reported by the applicant.

1. The per protocol (PP) population included patients in the ITT population who met the major inclusion criteria and who did not have any other major protocol violation. A total of 674 patients were included in the PP population, with 49 excluded in the eribulin arm and 38 excluded in the TPC arm from the ITT population. The estimates were similar to those of the ITT population. However, the result from the log-rank test was not statistically significant. The analysis results are summarized below:

Table 3.1.6.3.2 Results of OS Analysis in PP Population

	Eribulin N = 459	TPC N = 216
Number of Deaths (%)	244 (53.2%)	123 (56.9%)
Median Survival (95% CI)	13.1 (11.8, 14.3)	10.6 (9.3, 12.5)
p value	0.066	
HR	0.81 (0.65, 1.02)	

2. Two more sensitivity analyses were performed on the ITT population. The pre-specified final analysis for OS was to be conducted at 411 deaths using a stratified log-rank test on the ITT population. Sensitivity analyses were performed using an un-stratified log-rank test and testing only the first 411 deaths. It was observed that most of these results were consistent to the primary efficacy analysis result. The unstratified log-rank test was not significant, while the test for the first 411 deaths data were showing statistically significant result. The results are summarized in the following table.

Table 3.1.6.3.3 OS Sensitivity Analyses

	N	p-value	HR	95% CI
Stratified	762	0.041	0.809	(0.66, 0.99)
Unstratified	762	0.065	0.829	(0.68, 1.01)
At 411 Deaths	762	0.040	0.807	(0.66, 0.99)

3. Additional sensitivity analyses were also performed on certain subgroups. Please refer to Section 4.2 for results of the subgroup analyses.

Secondary Endpoints Analyses: PFS, ORR and DoR

The secondary endpoints were PFS, ORR and DoR. There was no statistical plan to adjust alpha for multiple comparisons among secondary endpoints. DoR was not based on randomization.

Table 3.1.6.3.2 summarizes the main efficacy analysis results for final PFS data by independent review. There were total of 521 events observed between the two arms at the data cut-off.

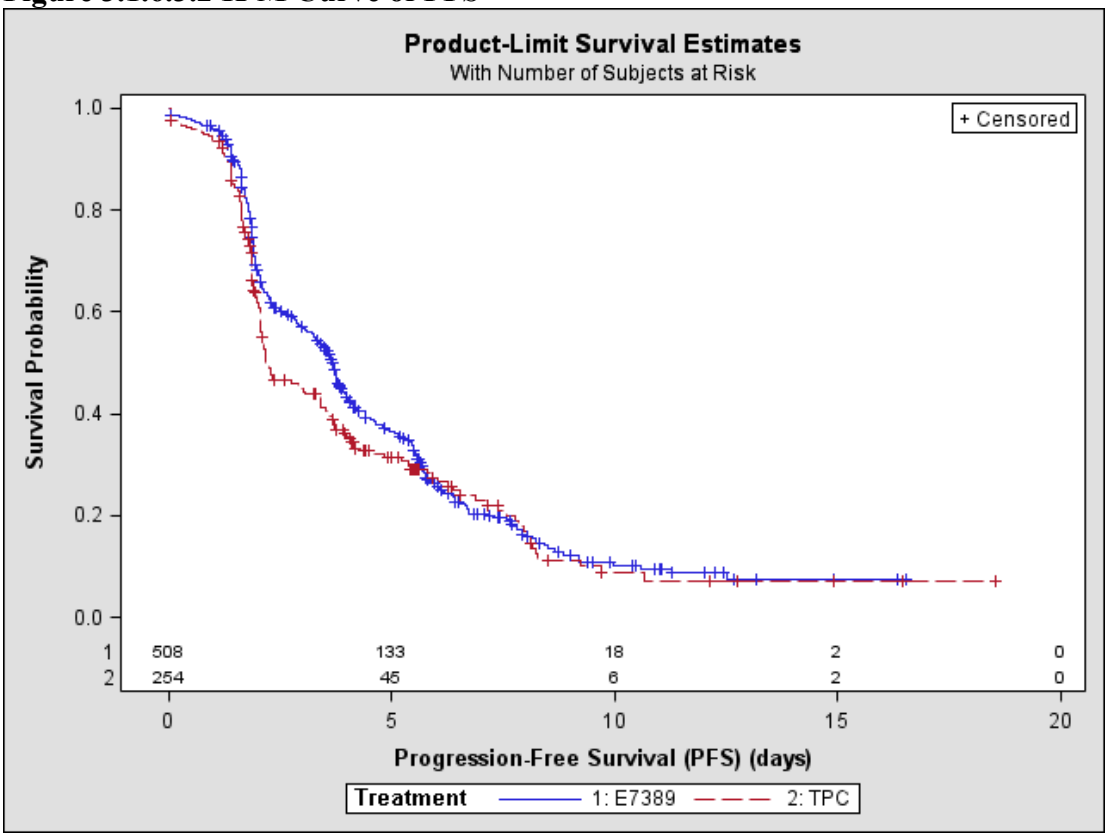
The final analysis showed there was no statistically significant improvement in the median PFS based on a stratified log-rank test (p-value = 0.137). The median PFS was 113 days for the eribulin arm compared with 68 days for the TPC arm. The related HR was 0.87 with 95% CI = (0.71, 1.05). This analysis was not conducted at pre-specified number of events.

Table 3.1.6.3.4 Progression Free Survival

	Eribulin N =508	TPC N = 254
Number of Events (%)	357 (70.3%)	164 (64.6%)
Median PFS (95% CI)	3.7 (3.3, 3.8)	2.2 (2.1, 3.4)
p-value	0.137	
HR	0.87 (0.71, 1.05)	

Figure 3.1.6.3.2 shows the estimated Kaplan-Meier curve for the PFS distribution.

Figure 3.1.6.3.2 K-M Curve of PFS



Objective Response Rate

Response rate was a secondary endpoint planned in the protocol. There were 57 (11.2%) and 10 (3.9%) complete and partial responses reported in the eribulin arm and the TPC arm, respectively. A Fisher's exact test was utilized. The confidence intervals for the response rates were (8.6%, 14.3%) for the eribulin arm and (1.9%, 7.1%) for the TPC arm.

The following table summarized the results for the ORR.

Table 3.1.6.3.5 Objective Response Rate

	Eribulin n=508 (%)	TPC n=254 (%)	p-value
Objective Response Rate (CR+PR)	57 (11.2)	10 (3.9)	0.0006
Complete Response (CR)	3 (0.6)	0	
Partial Response (PR)	54 (10.6)	10 (3.9)	
Stable Disease (SD)	208 (40.9)	96 (37.8)	
Progressive Disease (PD)	190 (37.4)	105 (41.3)	
Non Evaluable (NE)	47 (9.3)	40 (15.8)	
Unknown (UN)	6 (1.2)	3 (1.2)	

Reviewer's comments:

The result of PFS analysis was not statistically significant. However, it showed a similar trend to the result of OS. For the results of ORR analysis, the Fisher's exact test for ORR was significant. However, since no statistical analysis plan was pre-specified to control the overall alpha, the p-values were considered to be nominal. In addition, the response rates were low. There were only 11% patients responded to the eribulin therapy, and less than 1% were complete response.

Duration of Response

Among the 57 patients in the eribulin arm that responded, 31 progressed before the data cut-off date, the median duration of response was 4.2 months with 95% CI (3.8, 5.0). Among the 10 patients in the TPC arm that responded, 3 progressed before the data cut-off date, the median duration of response was 6.7 months with 95% CI = (3.4, 7.0).

Reviewer's comments:

The analysis for DoR was performed on responders only (8.8% of the whole sample size) and was not a randomized comparison.

Updated OS Analysis

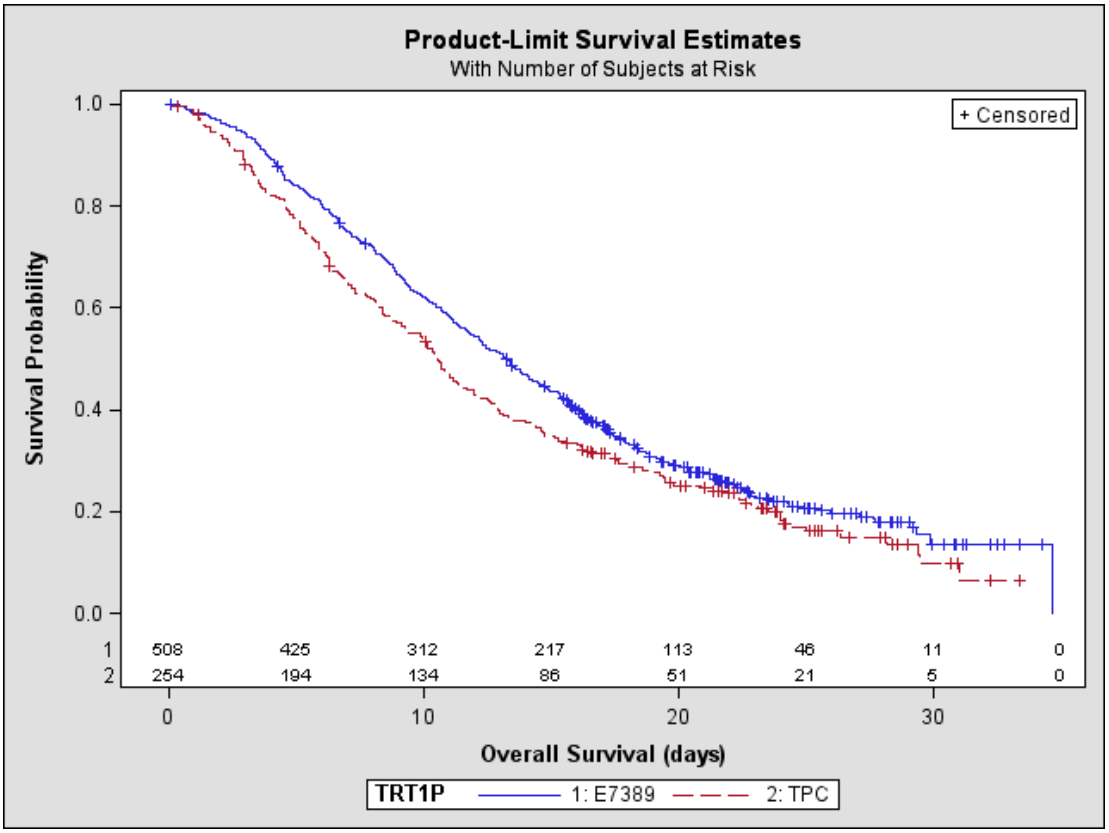
On Jul. 28, 2010 the applicant submitted an updated OS analysis in the 120-day safety report. At the data cut-off date Mar. 3. 2010, there were total of 589 deaths observed between the two arms, which was 77.3% of the enrolled patients. Among these deaths, 386 were in the eribulin arm (76.0%) and 203 (79.9%) were in the TPC arm.

The updated analysis showed the median survival was 2.7 months longer in the eribulin arm compared with the TPC arm (p-value = 0.014). The HR was 0.81 with 95% CI = (0.68, 0.96). The median survival was 13.2 months with 95% CI = (12.1, 14.3) for the eribulin arm compared with 10.5 months with 95% CI = (9.2, 12.0) for the TPC arm.

Table 3.1.6.3.6 Results of OS Updated Analysis

	Eribulin N = 508	**TPC** N = 254
Number of Deaths (%)	386 (76.0%)	203 (79.9%)
Median Survival (95% CI)	13.2 (12.1, 14.3)	10.5 (9.2, 12.0)
p value	0.014	
HR	0.81 (0.68, 0.96)	

Figure 3.1.6.3.3 shows the estimated Kaplan-Meier curve for the distribution of OS.



Reviewer's Comments:

The results from the updated OS analysis confirmed those of primary analysis.

3.2 Evaluation of Safety

Please refer to the Clinical Review of this application for details of the safety evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Since all patients enrolled in the study were females, subgroup analyses for gender were not conducted.

Table 4.1.1 presents the summary statistics of OS by age group (<65 vs. ≥65).

Table 4.1.1 Results of OS Analysis by Age

	Eribulin	TPC
Age < 65		
N	414	197
Number of Deaths (%)	222 (53.6%)	120 (60.9%)
Median Survival (95% CI)	13.0 (11.6, 14.6)	10.3 (8.7, 12.0)
HR	0.79 (0.64, 0.99)	
Age ≥ 65		
N	94	57
Number of Deaths (%)	52 (55.3%)	28 (49.1%)
Median Survival (95%)	13.1 (10.8, 15.3)	11.4 (8.2, NE)
HR	0.96 (0.61, 1.53)	

Table 4.1.2 presents the summary statistics of OS by race (Caucasians vs. Non-Caucasians).

Table 4.1.2 Results of OS Analysis by Race

	Eribulin	TPC
Caucasians		
N	470	233
Number of Deaths	249 (53.0%)	136 (58.4%)
Median Survival	13.1 (12.0, 14.6)	10.7 (9.3, 12.5)
HR	0.80 (0.65, 0.99)	
Non-Caucasians		
N	38	21
Number of Deaths	21 (55.3%)	12 (57.1%)
Median Survival	9.5 (5.7, 14.4)	8.9 (5.7, NE)
HR	1.19 (0.60, 2.37)	

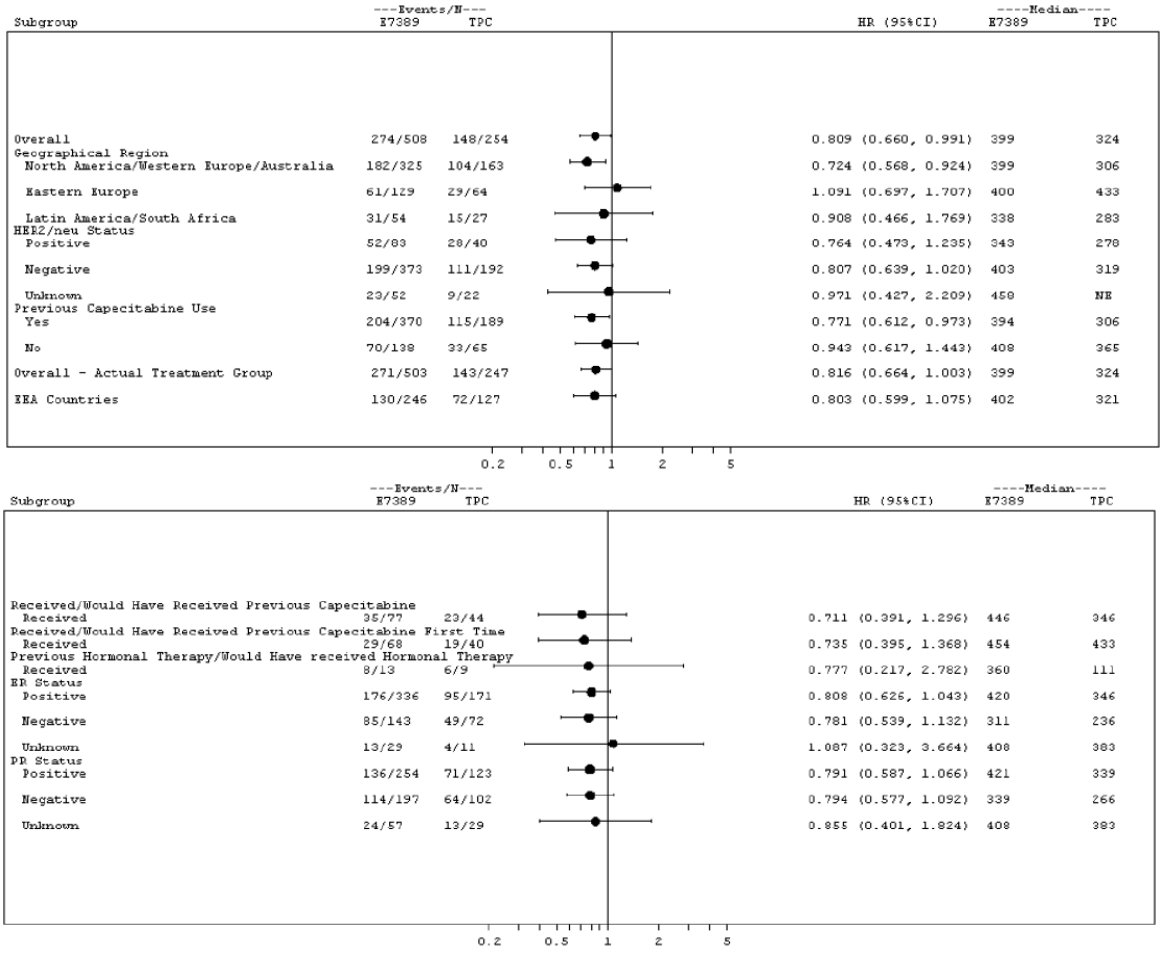
Reviewer's comments:

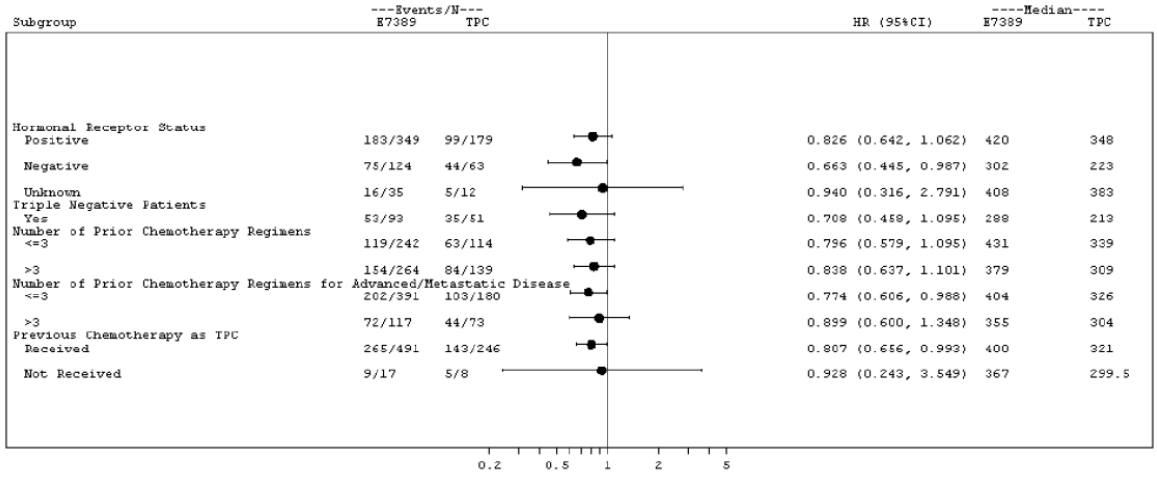
The analyses showed that the median survival was longer among younger patients (<65 years), but the older group reported a smaller proportion of deaths. The Caucasians reported a better survival benefit than the non-Caucasians. Both observations were under the caveat that the sample sizes in the age ≥ 65 subgroup and the non-Caucasian subgroup were relatively small.

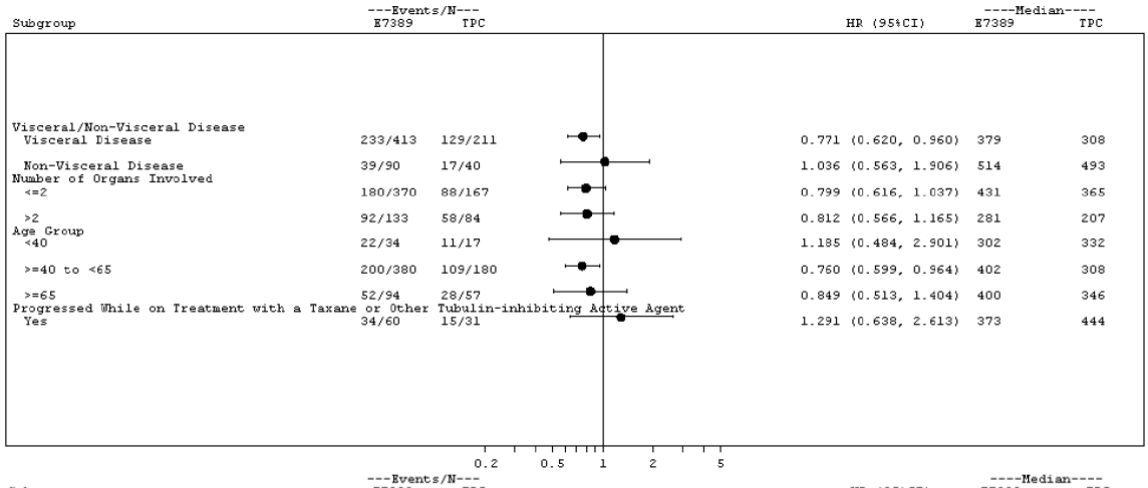
4.2 Other Special/Subgroup Populations

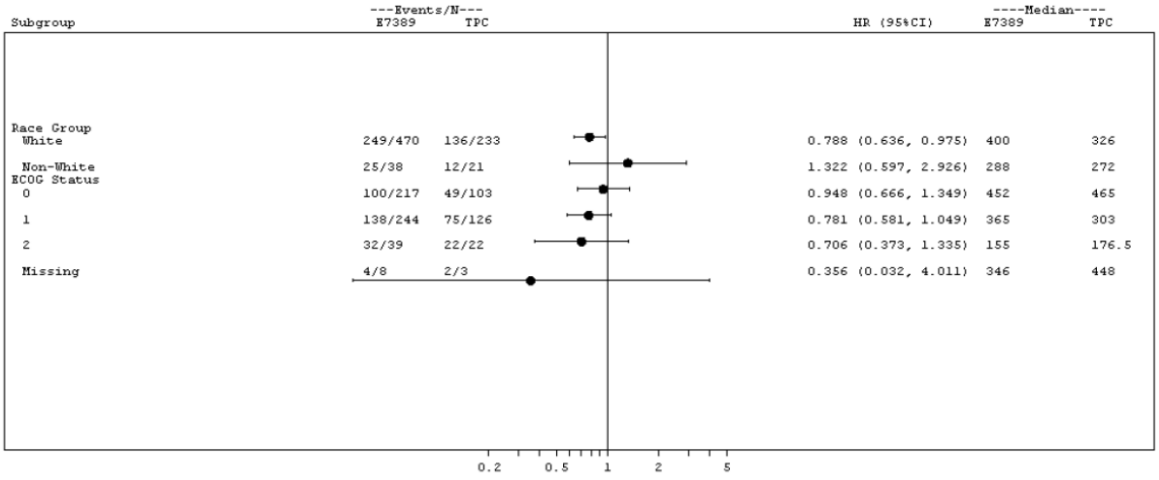
The applicant also reported analysis for certain subgroups. The following figure summarizes the subgroup analysis (adapted from CSR page 77).

Figure 4.2.1 Subgroup Analysis of OS (ITT population)




---Events/N---
Subgroup E7389 TPC HR (95%CI) ----Median---- E7389 TPC
Hormonal Receptor Status
Positive 183/349 99/179 0.826 (0.642, 1.062) 420 348
Negative 75/124 44/63 0.663 (0.445, 0.987) 302 223
Unknown 16/35 5/12 0.940 (0.316, 2.791) 408 383
Triple Negative Patients
Yes 53/93 35/51 0.708 (0.458, 1.095) 288 213
Number of Prior Chemotherapy Regimens
<=3 119/242 63/114 0.796 (0.579, 1.095) 431 339
>3 154/264 84/139 0.838 (0.637, 1.101) 379 309
Number of Prior Chemotherapy Regimens for Advanced/Metastatic Disease
<=3 202/391 103/180 0.774 (0.606, 0.988) 404 326
>3 72/117 44/73 0.899 (0.600, 1.348) 355 304
Previous Chemotherapy as TPC
Received 265/491 143/246 0.807 (0.656, 0.993) 400 321
Not Received 9/17 5/8 0.928 (0.243, 3.549) 367 299.5
0.2 0.5 1 2 5


---Events/N---
Subgroup E7389 TPC HR (95%CI) ----Median---- E7389 TPC
Visceral/Non-Visceral Disease
Visceral Disease 233/413 129/211 0.771 (0.620, 0.960) 379 308
Non-Visceral Disease 39/90 17/40 1.036 (0.563, 1.906) 514 493
Number of Organs Involved
<=2 180/370 88/167 0.799 (0.616, 1.037) 431 365
>2 92/133 58/84 0.812 (0.566, 1.165) 281 207
Age Group
<40 22/34 11/17 1.185 (0.484, 2.901) 302 332
>=40 to <65 200/380 109/180 0.760 (0.599, 0.964) 402 308
>=65 52/94 28/57 0.849 (0.513, 1.404) 400 346
Progressed While on Treatment with a Taxane or Other Tubulin-inhibiting Active Agent
Yes 34/60 15/31 1.291 (0.638, 2.613) 373 444
0.2 0.5 1 2 5


---Events/N---
Subgroup E7389 TPC HR (95%CI) ----Median---- E7389 TPC
Race Group
White 249/470 136/233 0.788 (0.636, 0.975) 400 326
Non-White 25/38 12/21 1.322 (0.597, 2.926) 288 272
ECOG Status
0 100/217 49/103 0.948 (0.666, 1.349) 452 465
1 138/244 75/126 0.781 (0.581, 1.049) 365 303
2 32/39 22/22 0.706 (0.373, 1.335) 155 176.5
Missing 4/8 2/3 0.356 (0.032, 4.011) 346 448
0.2 0.5 1 2 5

Reviewer's Comments:

The subgroup analyses for OS were verified by this reviewer. The majority of the subgroup analysis results were consistent with the overall result. Some of the particular subgroups are discussed in detail in the following.

1. The survival effect in the first regional strata, North America/West Europe/Australia showed a stronger result than the overall population. The subgroup analysis for USA patients also showed the same trend. However, the point estimate of HR for the USA patients was 0.93, higher than the overall HR estimate 0.81. This analysis showed that eribulin might not be as effective to the US population compared with the west European/Australian patients. However, the sample size was small in the US.

2. Among other subgroup analyses, patients with prior capecitabine treatment showed a better effect than those without. The HRs were 0.77 with 95% CI = (0.61, 0.97) for patients with prior capecitabine and 0.94 with 95% CI =(0.62, 1.44) for patients without. Since prior capecitabine usage was generally balanced over the two arms, this indicates that eribulin might be more effective to patients with prior capecitabine use.

3. Since HER2 positive is associated with increased disease recurrence and worse prognosis, subgroup analysis were also conducted for HER2 positive and negative patients. Patients with positive HER2 status had a shorter median survival in both arms. However, eribulin showed a trend that it might reduce related risk further for HER2 positive patients. The HRs were 0.76 with 95% CI = (0.47, 1.24) for HER2 positive patients and 0.82 with 95% CI (0.82, 1.03) for HER2 negative patients.

4. For those patients who were ER/PR/HER2 triple negative, eribulin showed a trend to be more effective than TPC, with HR = 0.71 and 95% CI = (0.47, 1.24).

5. In this study there were 403 patients (53.1%) had received more than 3 prior chemotherapies, and for this subgroup the HR was 0.84 with 95% CI = (0.64, 1.10). There were 190 patients (25.0%) had received more than 3 prior chemotherapies in metastatic setting, and for this subgroup the HR was 0.90 with 95% CI = (0.60, 1.35). Though the results were not statistically significant, it showed a trend that eribulin were more effective than TPC.

6. There were 72 patients who were HER2 positive and received >3 prior chemotherapies. The analysis showed a trend that eribulin might be effective for this subgroup, under the caveat on the small sample size. The HR was 0.77 with 95% CI = (0.41, 1.43).

7. For those patients who had more than 2 organs involved, eribulin showed a trend to be more effective than TPC, with HR = 0.71 and 95% CI = (0.47, 1.24).

8. Patients received same therapy more than once at different time may respond differently new therapies. For patients who did not receive same therapies more than once before entering the trial, either in metastatic setting or any setting, the HR estimates were 0.70, lower than the overall population. This indicates that eribulin might be more effective for these patients.

And the following table summarizes the points discussed above for the subgroup analyses.

Table 4.2.1 Results of OS Subgroup Analyses

Subgroups	N		Median (95% CI)		HR (95% CI)
	Eribulin	TPC	Eribulin	TPC	
N. America / W. Europe / Australia	325	163	13.1 (11.8,14.7)	10.1 (8.4,10.9)	0.73 (0.57, 0.92)
USA	100	46	13.1 (10.7,15.3)	10.7 (7.0,18.0)	0.93 (0.59, 1.46)
w/ Prior Capecitabine Treatment	370	189	12.9 (11.7,14.3)	10.1 (7.7,11.4)	0.77 (0.61, 0.97)
w/o Prior Capecitabine Treatment	138	65	13.4 (11.1,18.4)	12.0 (10.0, NE)	0.94 (0.62, 1.44)
HER2/neu Positive	83	40	11.3 (9.4,12.3)	9.1 (7.3, 13.0)	0.76 (0.47, 1.26)
HER2/neu Negative	373	192	13.2 (12.1, 14.7)	10.5 (8.4,14.2)	0.81 (0.64, 1.02)
Triple Negative	93	51	9.5 (7.1,13.8)	7.0 (4.7,8.9)	0.71 (0.46, 1.10)
w/ Prior >3 Chemos	264	139	12.5 (10.7,13.8)	10.2 (8.2,13.0)	0.84 (0.64, 1.10)
w/ >3 Chemos in Metastatic setting	117	73	11.7 (9.2,13.8)	10.0 (6.0,14.6)	0.90 (0.60, 1.35)
HER2 + & >3 Chemos	49	23	11.5 (9.3,12.3)	9.1 (7.2,13.1)	0.77 (0.41, 1.43)
w/ >2 Organs Involved	133	84	9.2 (7.6,11.1)	6.8 (5.7,10.3)	0.81 (0.57, 1.17)
No Repeated Therapy in Any Setting	362	180	13.6 (12.0,14.9)	10.2 (8.4,12.0)	0.70 (0.55, 0.89)
No Repeated Therapy in Metastatic Setting	419	204	13.2 (12.0,14.7)	10.2 (8.4,11.4)	0.70 (0.56, 0.87)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary analysis showed that OS was improved with the stratified log-rank test p-value = 0.041. The median survival was 13.1 months for the eribulin arm

compared with 10.6 months for the TPC arm. The hazard ratio (HR) was 0.81 with 95% CI = (0.66, 0.99).

The results from the 120-safety update confirmed the OS results in the primary analysis. The difference p-value was 0.014 from a stratified log-rank test. The median survival was 13.1 for the eribulin arm compared with 10.6 months for the TPC arm. The HR was 0.81 with 95% CI = (0.68, 0.96).

5.2 Conclusions and Recommendations

Based on the data submitted, the study results support the claims in the primary endpoints. Whether the size of the treatment effect is adequate for approval is a clinical decision.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WEISHI YUAN
08/09/2010

YUAN L SHEN
08/09/2010
Yuan-Li Shen signs off this document on behalf of Kun He.

RAJESHWARI SRIDHARA
08/09/2010

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 201532 **Applicant: Easai** **Stamp Date: 3/30/2010**

Drug Name: **NDA/BLA Type: original**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	x			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	x			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	x			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	x			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? _yes_____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	x			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	x			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	x			
Appropriate references for novel statistical methodology (if present) are included.	x			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.				
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	x			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Weishi Yuan	04/29/2010
Reviewing Statistician	Date
Kun He	04/29/2010
Supervisor/Team Leader	Date

File name: 5_Statistics Filing Checklist for a New NDA_BLA110207

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201532	ORIG-1	EISAI INC	eribulin mesylate

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/s/

WEISHI YUAN
04/29/2010

KUN HE
04/29/2010