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Clinical Trial Results

A Randomized Phase II Study of Sequential Eribulin Versus Paclitaxel Followed by FAC/FEC as Neoadjuvant Therapy in Patients with Operable HER2-Negative Breast Cancer

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Key Words. Eribulin • Paclitaxel • HER2-negative • Breast cancer • Neoadjuvant chemotherapy

Trial Information

- **ClinicalTrials.gov Identifier:** NCT01593020
- **Sponsor:** Eisai
- **Principal Investigator:** Vicente Valero
- **IRB Approved:** Yes

Lessons Learned

- The combination of eribulin with 5-fluorouracil, either doxorubicin or epirubicin, and cyclophosphamide (FAC/FEC) was not superior to the combination of paclitaxel with FAC/FEC and was associated with greater hematologic toxicity.
- Eribulin followed by an anthracycline-based regimen is not recommended as a standard neoadjuvant therapy in non-metastatic operable breast cancer.

Abstract

Background. Neoadjuvant systemic therapy is the standard of care for locally advanced operable breast cancer. We hypothesized eribulin may improve the pathological complete response (pCR) rate compared with paclitaxel.

Methods. We conducted a 1:1 randomized open-label phase II study comparing eribulin versus paclitaxel followed by 5-fluorouracil, either doxorubicin or epirubicin, and cyclophosphamide (FAC/FEC) in patients with operable HER2-negative breast cancer. pCR and toxicity of paclitaxel 80 mg/m^2 weekly for 12 doses or eribulin 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle for 4 cycles followed by FAC/FEC were compared.

Results. At the interim futility analysis, in March 2015, 51 patients (28 paclitaxel, 23 eribulin) had received at least one dose of the study drug and were thus evaluable for toxicity; of these, 47 (26 paclitaxel, 21 eribulin) had undergone surgery and were thus evaluable for efficacy. Seven of 26 (27%) in the paclitaxel group and 1 of 21 (5%) in the eribulin group achieved a pCR, and this result crossed a futility stopping boundary. In the paclitaxel group, the most common serious adverse events (SAEs) were neutropenic fever (grade 3, 3 patients, 11%). In the eribulin group, nine patients (39%) had neutropenia-related SAEs, and one died of neutropenic sepsis. The study was thus discontinued. For the paclitaxel and eribulin groups, the 5-year event-free survival (EFS) rates were 81.8% and 74.0% (hazard ratio [HR], 1.549; 95% confidence interval [CI], 0.817–2.938; p = .3767), and the 5-year overall survival (OS) rates were 100% and 84.4% (HR, 5.813; 95% CI, 0.647–52.208; p = .0752), respectively.

Conclusion. We did not observe a higher proportion of patients undergoing breast conservation surgery in the eribulin group than in the paclitaxel group. The patients treated with eribulin were more likely to undergo mastectomy and less likely to undergo breast conservation surgery, but the difference was not statistically significant.

As neoadjuvant therapy for operable HER2-negative breast cancer, eribulin followed by FAC/FEC is not superior to paclitaxel followed by FAC/FEC and is associated with a higher incidence of neutropenia-related serious adverse events. ***The Oncologist*** 2021;26:e230–e240

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Table 1. Pathologic response and type of surgery per treatment group

Treatment group	Paclitaxel and FAC/FEC (*n* = 26)	Eribulin and FAC/FEC (*n* = 21)
Residual cancer burden category[a]		
0 (pCR)	7 (27)	1 (5)
I	7 (27)	0 (0)
II	8 (31)	8 (38)
III	4 (15)	12 (57)
Type of surgery		
Mastectomy	17 (65)	16 (76)
Breast conserving surgery	9 (35)	5 (24)

[a]Residual cancer burden (RCB) was calculated by the RCB calculator (by pathologists: http://www3.mdanderson.org/app/medcalc/index.cfm?pagename=jsconvert3).
Abbreviations: FAC/FEC, 5-fluorouracil, either doxorubicin or epirubicin, and cyclophosphamide; pCR, pathologic complete response.

Discussion

Here, we report a first randomized phase II study result that showed the lack of clear efficacy and higher toxicity when eribulin was used as a part of a neoadjuvant chemotherapy regimen in operable HER-2 negative breast cancers. Figure 1 shows Kaplan-Meier plots for EFS and OS by treatment groups. Table 1 shows response data. We do not think this negative result was due to smaller size of the patient groups accrued to each arm, because the study was preplanned to have interim efficacy and toxicity assessments. Although it is disappointing, given the efficacy of eribulin in the metastatic setting and the fact that a larger randomized trial confirmed our results with higher statistical power, we do not recommend a follow-up study.

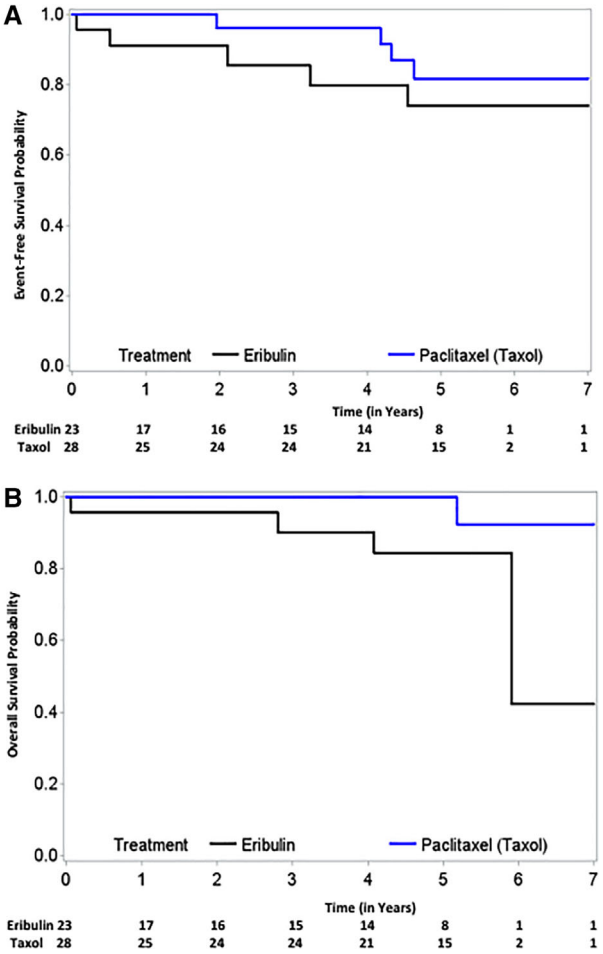

Figure 1. A total of 23 patients in the eribulin arm and 28 patients in the taxol arm were available for long-term clinical outcome measurement. Five-year event-free survival for the eribulin- and paclitaxel-based arms was 74.0% and 81.8%, respectively (A). Five-year overall survival of eribulin- and paclitaxel-based arms, was 84.4% and 100%, respectively (B).

Trial Information

Disease	Breast cancer
Stage of Disease/Treatment	Neoadjuvant
Prior Therapy	None
Type of Study	Phase II, randomized
Primary Endpoint	Complete response rate
Secondary Endpoint	Event-free survival

Additional Details of Endpoints or Study Design

At the time of the first interim futility analysis, 8 (30.8%) of the 26 patients in the paclitaxel group and 1 (4.8%) of the 21 patients in the eribulin group had achieved a pCR (Table 2). The test statistic was $\frac{(0.048-0.308)}{\sqrt{p(1-p)(\frac{1}{21}+\frac{1}{26})}} = -2.25$, where $p = (1+8)/(21+26)$ and it crossed the futility stopping boundary. In an exploratory analysis (not preplanned) comparing outcomes by breast cancer molecular subtype, we found that among the 34 patients with hormone receptor–positive disease, 3 of 18 (17%) in the paclitaxel group and 0 of 16 (0%) in the eribulin group achieved a pCR. Among the 13 patients with triple-negative breast cancer, 4 of 8 (50%) in the paclitaxel group and 1 of 5 (20%) in the eribulin group achieved a pCR. For each disease subtype, the difference in pCR rate between the paclitaxel and eribulin groups was not significant.

Investigator's Analysis

The combination of eribulin and FAC/FEC was not superior to paclitaxel and FAC/FEC and was associated with higher hematological toxicity; therefore, we do not recommend eribulin/FAC/FEC as a standard neoadjuvant therapy in early-stage breast cancer.

Drug Information	
Drug 1	
Generic/Working Name	Eribulin
Trade Name	Halavan
Drug Type	Other
Drug Class	Microtubule-targeting agent
Dose	1.4 mg/m^2
Route	IV, per push
Schedule of Administration	Day 1, day 8, every 21 days × 4 cycles
Drug 2	
Generic/Working Name	Paclitaxel
Trade Name	Taxol
Drug Class	Microtubule-targeting agent
Dose	80 mg/m^2
Route	IV
Schedule of Administration	Weekly x 12 weeks

Patient Characteristics: Paclitaxel Arm	
Number of Patients, Male	0
Number of Patients, Female	28
Stage	II A — 5 II B — 12 III A — 7 III B — 1 III C — 3
Age	Median: 48 years
Number of Prior Systemic Therapies	Median: 0
Performance Status: ECOG	0 — 27 1 — 1 2 — 3 — Unknown —
Other	
Receptor status	ER/PR-postive — 15 ER positive/PR negative — 4 ER neg/PR positive — 1 ER/PR negative — 8
Nuclear grade	Grade 1 — 3 Grade 2 — 10 Grade 3 — 15

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

Patient Characteristics: Eribulin Arm	
Number of Patients, Male	0
Number of Patients, Female	21
Stage	II A — 4 II B — 6 III A — 6 III B — 0 III C — 5

Age	Median: 51 years
Number of Prior Systemic Therapies	Median: 0
Performance Status: ECOG	0 — 20 1 — 1 2 — 3 — Unknown —
Other	ER/PR positive — 13 ER positive/PR negative — 3 ER negative/PR positive — 0 ER/PR negative — 5

Abbreviations: ER, estrogen receptor; PR, progesterone receptor.

Primary Assessment Method

Title	Response: paclitaxel arm
Number of Patients Screened	28
Number of Patients Enrolled	28
Number of Patients Evaluable for Toxicity	28
Number of Patients Evaluated for Efficacy	26
Evaluation Method	RECIST 1.0
Response Assessment CR	*n* = 7 (27%)
Response Assessment PR	*n* = 19 (73%)
(Median) Duration Assessments OS	61 months
Title	Survival: paclitaxel arm
Number of Patients Screened	28
Number of Patients Enrolled	28
Number of Patients Evaluable for Toxicity	28
Number of Patients Evaluated for Efficacy	26
Response Assessment CR	*n* = 8 (31%)
Response Assessment PR	*n* = 18 (69%)
Title	Response: eribulin arm
Number of Patients Screened	26
Number of Patients Enrolled	24
Number of Patients Evaluable for Toxicity	23
Number of Patients Evaluated for Efficacy	21
Evaluation Method	RECIST 1.0
Response Assessment CR	*n* = 1 (5%)
Response Assessment PR	*n* = 20 (95%)
(Median) Duration Assessments OS	61 months
Title	Survival: eribulin arm
Number of Patients Screened	28
Number of Patients Enrolled	28
Number of Patients Evaluable for Toxicity	28
Number of Patients Evaluated for Efficacy	26
Response Assessment CR	*n* = 8 (31%)
Response Assessment PR	*n* = 18 (69%)

Outcome Notes

The median follow-up was 5 years. The median EFS was not reached in either arm, but 5-year event-free survival for the eribulin-based regimen and the paclitaxel-based regimen was 74.0% and 81.8%, respectively. The median OS was 5.9 years for eribulin and was not reached for the paclitaxel arm, and the 5-year overall survival for the eribulin-based regimen and the paclitaxel-based regimen was 84.4% and 100%, respectively.

Adverse Events: Paclitaxel Arm

Name	NC/NA	1	2	3	4	5	All grades
Alopecia	46%	0%	54%	0%	0%	0%	54%
Fatigue	64%	4%	25%	7%	0%	0%	36%
Nausea	81%	4%	11%	4%	0%	0%	19%
Neutrophil count decreased	83%	0%	4%	13%	0%	0%	17%
Paresthesia	78%	0%	18%	4%	0%	0%	22%
Skin and subcutaneous tissue disorders	82%	0%	18%	0%	0%	0%	18%
Constipation	85%	0%	4%	11%	0%	0%	15%
Mucositis oral	96%	0%	4%	0%	0%	0%	4%
Myalgia	96%	0%	4%	0%	0%	0%	4%
Diarrhea	96%	0%	4%	0%	0%	0%	4%
Fever	96%	0%	4%	0%	0%	0%	4%
Vomiting	93%	0%	7%	0%	0%	0%	7%
Alanine aminotransferase increased	93%	0%	7%	0%	0%	0%	7%
Nasal congestion	92%	0%	4%	4%	0%	0%	8%
Pain	96%	0%	4%	0%	0%	0%	4%
Rash acneiform	93%	0%	7%	0%	0%	0%	7%
White blood cell decreased	96%	0%	4%	0%	0%	0%	4%
Abdominal pain	100%	0%	0%	0%	0%	0%	0%
Arthralgia	96%	0%	4%	0%	0%	0%	4%
Aspartate aminotransferase increased	100%	0%	0%	0%	0%	0%	0%
Bladder infection	100%	0%	0%	0%	0%	0%	0%
Dizziness	100%	0%	0%	0%	0%	0%	0%
Edema limbs	96%	0%	4%	0%	0%	0%	4%
Headache	100%	0%	0%	0%	0%	0%	0%
Hyperglycemia	100%	0%	0%	0%	0%	0%	0%
Infections and infestations	100%	0%	0%	0%	0%	0%	0%
Insomnia	96%	0%	4%	0%	0%	0%	4%
Left ventricular systolic dysfunction	96%	0%	0%	4%	0%	0%	4%
Memory impairment	96%	0%	4%	0%	0%	0%	4%
Nail loss	96%	0%	4%	0%	0%	0%	4%
Neutropenic sepsis	100%	0%	0%	0%	0%	0%	0%
Skin infection	96%	0%	4%	0%	0%	0%	4%
Vaginal infection	100%	0%	0%	0%	0%	0%	0%
Vaginal inflammation	96%	0%	4%	0%	0%	0%	4%

See also Tables 2–4 below.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Adverse Events: Eribulin Arm

Name	NC/NA	1	2	3	4	5	All grades
Alopecia	60%	11%	29%	0%	0%	0%	40%
Fatigue	68%	7%	21%	4%	0%	0%	32%
Nausea	75%	7%	18%	0%	0%	0%	25%
Neutrophil count decreased	71%	0%	0%	18%	11%	0%	29%
Paresthesia	96%	0%	4%	0%	0%	0%	4%
Skin and subcutaneous tissue disorders	93%	0%	7%	0%	0%	0%	7%
Constipation	92%	4%	4%	0%	0%	0%	8%
Mucositis oral	82%	4%	14%	0%	0%	0%	18%
Myalgia	81%	11%	4%	4%	0%	0%	19%

Diarrhea	89%	4%	7%	0%	0%	0%	11%
Fever	89%	4%	7%	0%	0%	0%	11%
Vomiting	92%	0%	4%	4%	0%	0%	8%
Alanine aminotransferase increased	96%	0%	0%	4%	0%	0%	4%
Nasal congestion	100%	0%	0%	0%	0%	0%	0%
Pain	96%	0%	4%	0%	0%	0%	4%
Rash acneiform	100%	0%	0%	0%	0%	0%	0%
White blood cell decreased	96%	0%	0%	0%	4%	0%	4%
Abdominal pain	96%	4%	0%	0%	0%	0%	4%
Arthralgia	100%	0%	0%	0%	0%	0%	0%
Aspartate aminotransferase increased	96%	0%	0%	4%	0%	0%	4%
Bladder infection	96%	0%	4%	0%	0%	0%	4%
Dizziness	96%	0%	0%	4%	0%	0%	4%
Edema limbs	100%	0%	0%	0%	0%	0%	0%
Headache	96%	0%	4%	0%	0%	0%	4%
Hyperglycemia	96%	4%	0%	0%	0%	0%	4%
Infections and infestations	96%	0%	4%	0%	0%	0%	4%
Insomnia	100%	0%	0%	0%	0%	0%	0%
Left ventricular systolic dysfunction	100%	0%	0%	0%	0%	0%	0%
Memory impairment	100%	0%	0%	0%	0%	0%	0%
Nail loss	100%	0%	0%	0%	0%	0%	0%
Neutropenic sepsis	96%	0%	0%	0%	0%	4%	4%
Skin infection	100%	0%	0%	0%	0%	0%	0%
Vaginal infection	96%	0%	4%	0%	0%	0%	4%
Vaginal inflammation	100%	0%	0%	0%	0%	0%	0%

See also Tables 2–4 below.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Name	Grade	Attribution
Eribulin, neutropenic sepsis	4	Definite
Eribulin, neutropenic sepsis	4	Definite
Eribulin, neutropenic sepsis	4	Definite
Eribulin, neutropenia	3	Definite
Eribulin, neutropenia	3	Definite
Eribulin, neutropenia	3	Definite
Eribulin, neutropenia	3	Definite
Eribulin, neutropenia	3	Definite
Paclitaxel, neutropenia	3	Definite
Paclitaxel, neutropenia	3	Definite
Paclitaxel, neutropenia	3	Definite
Eribulin, fatigue	3	Probable
Paclitaxel, fatigue	3	Probable
Paclitaxel, fatigue	3	Probable
Eribulin, AST abnormality	3	Probable
Eribulin, ALT abnormality	3	Probable
Eribulin, dizziness	3	Probable
Paclitaxel, LVEF abnormality	3	Probable
Eribulin, myalgia	3	Definite
Paclitaxel, nasal congestion	3	Probable

Paclitaxel, nausea	3	Probable
Eribulin, neutropenic sepsis and death	5	Probable
Paclitaxel, paresthesia	3	Probable
Eribulin, vomiting	3	Probable
Eribulin, white blood cell decreased	4	Definite

If patients received at least one dose of study drug, they were deemed to be evaluable for toxicity. Adverse events including laboratory results were graded according to the National Cancer Institute's CTCAE, version 4.0. Dose-limiting toxicity was defined as occurrence of adverse events that were attributed as possibly, probably, or definitely related to each study drug and occurring within 2 cycles after the first dose: grade 4 thrombocytopenia or grade 4 neutropenia lasting >1 week or any febrile neutropenia; greater than grade 3 nonhematologic toxic effect; or > 14 days of treatment delay due to any grade of therapy-related toxic effects (grade 1–2). For patients with multiple instances of the same adverse event and different grades at different instances, we counted the adverse event only once and assigned the highest grade experienced for that event. Toxicity was evaluated on days 8 and 15 for the first 2 cycles and at the end of each cycle thereafter. Dose modification followed standard care for each taxol and eribulin per U.S. Food and Drug Administration package insert and left up to the treating physician's discretion.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; LVEF, left ventricular ejection fraction.

Assessment, Analysis, and Discussion

Completion	Study terminated before completion
Terminated Reason	Toxicity
Investigator's Assessment	Eribulin/AC as a standard neoadjuvant therapy in early-stage breast cancer is not recommended.

We report the first randomized phase II study comparing eribulin and paclitaxel followed by 5-fluorouracil, either doxorubicin or epirubicin, and cyclophosphamide (FAC/FEC) as neoadjuvant chemotherapy for HER2-negative early-stage breast cancer (Fig. 2). The primary efficacy measure of pathological complete response (pCR) [1–3] assessed by residual cancer burden showed that eribulin was not superior to paclitaxel based on the interim analysis (pCR rate: 4.8% with eribulin and 26.9% with paclitaxel). Because of this lack of superiority at the interim analysis, the study was closed early.

To our surprise, toxicity was greater in the eribulin arm, which was not expected from the metastatic treatment data [4, 5]. Eribulin is approved in metastatic breast cancer, and the increase in toxicity reported for this drug was mainly attributed to the later line introduction of the therapy. However, in our study in early breast cancer, eribulin was associated with higher toxicity.

Several groups have studied eribulin as part of neoadjuvant systemic therapy regimen, especially in triple-negative breast cancer. Kaklamani et al. conducted a phase II trial of carboplatin and eribulin as neoadjuvant treatment in patients with early-stage triple-negative breast cancer. In this study, the combination of carboplatin and eribulin produced a pCR rate of 43%, with mostly grade 1 and 2 toxic effects [6]. Cadoo et al. conducted a phase II trial of the feasibility (defined as the percentage of patients who completed the regimen) of dose-dense doxorubicin/cyclophosphamide (AC) followed by eribulin with and without prophylactic filgrastim in patients with stage I–III, HER2-nonamplified early-stage breast cancer, and showed that eribulin along with AC combination in neoadjuvant therapy for stage I–III patients was feasible in only 72.9% when pegfilgrastim was used and in only 60% when pegfilgrastim was not used [7]. This is in line with the toxicity that was observed in our study. Kaufman et al. conducted a phase III randomized clinical trial of eribulin or capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane [8]. In that trial, eribulin was not superior to capecitabine in terms of either of the coprimary endpoints: median overall survival (15.9 months for eribulin and 14.5 months for capecitabine; hazard ratio [HR], 088; 95% confidence interval [CI], 0.77–1.00; p = .06) or median progression-free survival (4.1 months for eribulin and 4.2 months for capecitabine; HR, 1.08; 95% CI, 0.93–1.25; p = .30).

In terms of the type of surgery, we did not observe an improvement in breast conservation surgery. The patients who were treated with eribulin were more likely to undergo mastectomy and less likely to undergo breast conservation surgery; however, the difference was not statistically significant.

In summary, the combination of eribulin and FAC/FEC was not superior to paclitaxel and FAC/FEC and was associated with higher hematological toxicity; therefore, we do not recommend eribulin/FAC/FEC as a standard neoadjuvant therapy in early-stage breast cancer.

Acknowledgments

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Disclosures

Mariana Chavez-MacGregor: Roche, Pfizer, AstraZeneca, Novartis, Abbott (C/A), Novartis (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

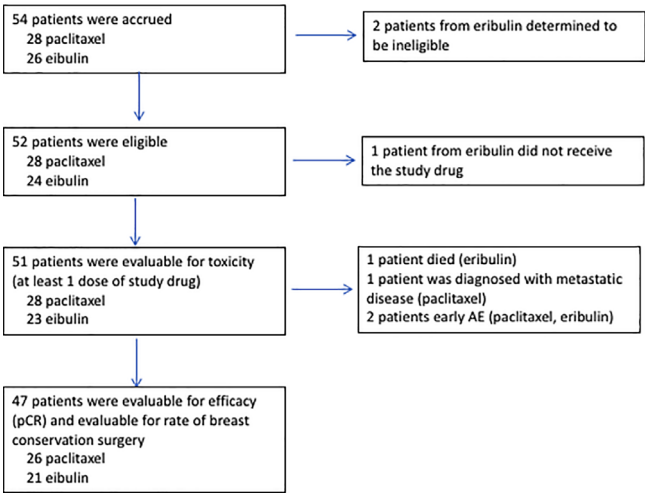

Figure 2. Flow diagram.
Abbreviations: AE, adverse event; pCR, pathological complete response.

Table 2. Sum of individual adverse events by grade and relationship to study treatment

Grade and relationship	Number of events	
	Paclitaxel group (*n* = 28)	Eribulin group (*n* = 23)
Grade 5		
Probable	0	1
Total	0	1
Grade 4		
Definite	0	2
Probable	0	2
Total	0	4
Grade 3		
Definite	6	4
Probable	2	5
Possible	1	1
Unlikely	0	1
Total	9	11
Grade 2		
Definite	35	19
Possible	6	2
Probable	13	11
Unlikely	3	4
Unrelated	2	2
Total	59	38
Grade 1		
Definite	0	8
Probable	3	4
Possible	0	2
Unlikely	0	1
Unrelated	0	1
Total	3	16

Table 3. Severe adverse events by maximum grade experienced[a] in the paclitaxel and eribulin arms

	Grade of toxicity, *n*			
SAE	**3 (Severe)**	**4 (Life threatening)**	**5 (Lethal)**	**Total**
Neutrophil count decreased				
Paclitaxel	3	0	0	3
Eribulin	5	3	0	8
Fatigue				
Paclitaxel	2	0	0	2
Eribulin	1	0	0	1
Alanine aminotransferase increased				
Paclitaxel	0	0	0	0
Eribulin	1	0	0	1
Aspartate aminotransferase increased				
Paclitaxel	0	0	0	0
Eribulin	1	0	0	1
Dizziness				
Paclitaxel	0	0	0	0
Eribulin	1	0	0	1
Left ventricular systolic dysfunction				
Paclitaxel	1	0	0	1
Eribulin	0	0	0	0
Myalgia				
Paclitaxel	0	0	0	0
Eribulin	1	0	0	1
Nasal congestion				
Paclitaxel	1	0	0	1
Eribulin	0	0	0	0
Nausea				
Paclitaxel	1	0	0	1
Eribulin	0	0	0	0
Neutropenic sepsis				
Taxol	0	0	0	0
Eribulin	0	0	1	1
Paresthesia				
Paclitaxel	1	0	0	1
Eribulin	0	0	0	0
Vomiting				
Paclitaxel	0	0	0	0
Eribulin	1	0	0	1
White blood cell decreased				
Paclitaxel	0	0	0	0
Eribulin	0	1	0	1

[a]For patients with multiple instances of the same adverse event and different grades at different instances, we counted the adverse event only once and assigned the highest grade experienced for that event.
[b]No grade 4 or 5 adverse events were observed in the paclitaxel group.
[c]If same patient had more than one episode of toxicity observed during study period, each time was counted as one.
Abbreviation: SAE, serious adverse event.

Table 4. Severe adverse events by maximum grade experienced[a]

		Grade of toxicity					
	Arm	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life threatening)	5 (Lethal)	Total
Alopecia	Taxol	0	15	0	0	0	15
Alopecia	Eribulin	3	8	0	0	0	11
Fatigue	Taxol	1	7	2	0	0	10
Fatigue	Eribulin	2	6	1	0	0	9
Nausea	Taxol	1	3	1	0	0	5
Nausea	Eribulin	2	5	0	0	0	7
Neutrophil count decreased	Taxol	0	1	3	0	0	4
Neutrophil count decreased	Eribulin	0	0	5	3	0	8
Paresthesia	Taxol	0	5	1	0	0	6
Paresthesia	Eribulin	0	1	0	0	0	1
Skin and subcutaneous tissue disorders	Taxol	0	5	0	0	0	5
Skin and subcutaneous tissue disorders	Eribulin	0	2	0	0	0	2
Constipation	Taxol	1	3	0	0	0	4
Constipation	Eribulin	1	1	0	0	0	2
Mucositis oral	Taxol	0	1	0	0	0	1
Mucositis oral	Eribulin	1	4	0	0	0	5
Myalgia	Taxol	0	1	0	0	0	1
Myalgia	Eribulin	3	1	1	0	0	5
Diarrhea	Taxol	0	1	0	0	0	1
Diarrhea	Eribulin	1	2	0	0	0	3
Fever	Taxol	0	1	0	0	0	1
Fever	Eribulin	1	2	0	0	0	3
Vomiting	Taxol	0	2	0	0	0	2
Vomiting	Eribulin	0	1	1	0	0	2
Alanine aminotransferase increased	Taxol	0	2	0	0	0	2
Alanine aminotransferase increased	Eribulin	0	0	1	0	0	1
Nasal congestion	Taxol	0	1	1	0	0	2
Nasal congestion	Eribulin	0	0	0	0	0	0
Pain	Taxol	0	1	0	0	0	1
Pain	Eribulin	0	1	0	0	0	1
Rash acneiform	Taxol	0	2	0	0	0	2
Rash acneiform	Eribulin	0	0	0	0	0	0
White blood cell decreased	Taxol	0	1	0	0	0	1
White blood cell decreased	Eribulin	0	0	0	1	0	1
Abdominal pain	Taxol	0	0	0	0	0	0
Abdominal pain	Eribulin	1	0	0	0	0	1
Arthralgia	Taxol	0	1	0	0	0	1
Arthralgia	Eribulin	0	0	0	0	0	0
Aspartate aminotransferase increased	Taxol	0	0	0	0	0	0
Aspartate aminotransferase increased	Eribulin	0	0	1	0	0	1
Bladder infection	Taxol	0	0	0	0	0	0
Bladder infection	Eribulin	0	1	0	0	0	1
Dizziness	Taxol	0	0	0	0	0	0
Dizziness	Eribulin	0	0	1	0	0	1
Edema limbs	Taxol	0	1	0	0	0	1
Edema limbs	Eribulin	0	0	0	0	0	0

(continued)

Table 4. (continued)

		Grade of toxicity					
	Arm	1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life threatening)	5 (Lethal)	Total
Headache	Taxol	0	0	0	0	0	0
Headache	Eribulin	0	1	0	0	0	1
Hyperglycemia	Taxol	0	0	0	0	0	0
Hyperglycemia	Eribulin	1	0	0	0	0	1
Infections and infestations (other), specify	Taxol	0	0	0	0	0	0
Infections and infestations (other), specify	Eribulin	0	1	0	0	0	1
Insomnia	Taxol	0	1	0	0	0	1
Insomnia	Eribulin	0	0	0	0	0	0
Left ventricular systolic dysfunction	Taxol	0	0	1	0	0	1
Left ventricular systolic dysfunction	Eribulin	0	0	0	0	0	0
Memory impairment	Taxol	0	1	0	0	0	1
Memory impairment	Eribulin	0	0	0	0	0	0
Nail loss	Taxol	0	1	0	0	0	1
Nail loss	Eribulin	0	0	0	0	0	0
Neutropenic sepsis	Taxol	0	0	0	0	0	0
Neutropenic sepsis	Eribulin	0	0	0	0	1	1
Skin infection	Taxol	0	1	0	0	0	1
Skin infection	Eribulin	0	0	0	0	0	0
Vaginal infection	Taxol	0	0	0	0	0	0
Vaginal infection	Eribulin	0	1	0	0	0	1
Vaginal inflammation	Taxol	0	1	0	0	0	1
Vaginal inflammation	Eribulin	0	0	0	0	0	0

[a]For patients with multiple instances of the same adverse event and different grades at different instances, we counted the adverse event only once and assigned the highest grade experienced for that event.
[b]No grade 4 or 5 adverse events were observed in the paclitaxel group.
[c]If same patient had more than one episode of toxicity observed during study period, each time was counted as one.