



Original article

A nationwide, multicenter retrospective study on the effectiveness and safety of eribulin in Korean breast cancer patients (REMARK)



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ABSTRACT

Purpose: Approval of eribulin for metastatic breast cancer was based on data primarily from Western patients, and there is a paucity of data on the effectiveness and safety of eribulin for Asian patients. To determine the effectiveness and safety of eribulin in Korean women with breast cancer in a real-world setting, we conducted a nationwide, multicenter, retrospective study.

Methods: Patients with locally advanced or metastatic breast cancer who were treated with eribulin in 14 centers throughout Korea were included in this study. Eribulin was generally administered at a dose of 1.23 mg/m² (equivalent to 1.4 mg/m² eribulin mesylate) by intravenous infusion for 2–5 min, or as a diluted solution, on Days 1 and 8 of every 21-day cycle. The primary endpoint was progression-free survival (PFS) rate at 6 months. Secondary endpoints included median PFS, overall survival (OS), time-to-treatment failure (TTF), tumor response rate, and incidence of hematologic treatment-emergent adverse events (TEAEs).

Results: The safety and full analysis populations included 398 and 360 (38 had no efficacy data) patients, respectively. The PFS rate at 6 months was 37.8%. Median PFS, OS, and TTF were 134, 631, and 120 days, respectively. Objective response rate, clinical benefit rate, and disease control rate were 18.1%, 50.6%, and 49.4%, respectively. Hematologic TEAEs were reported in 65.1% of patients; neutropenia (56.8%) and anemia (11.3%) were most common.

Conclusion: Real-world effectiveness and safety of eribulin in Korean breast cancer patients were consistent with previous reports; no new safety concerns were identified.

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1. Introduction

Breast cancer is the most commonly diagnosed cancer and a leading cause of death among females worldwide; there were an

List of abbreviations

AE	adverse event
CBR	clinical benefit rate
CR	complete response
DCR	disease control rate
ER	estrogen receptor
FAS	full analysis set
HER2	human epidermal growth factor receptor 2
ORR	objective response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PgR	progesterone receptor
PR	partial response
SAF	safety analysis set
SD	stable disease
TEAE	treatment-emergent adverse event
TTF	time-to-treatment failure

estimated 2.1 million newly diagnosed cases of female breast cancer in 2018 [1]. It is the second most common cancer in Korean women, with 2456 deaths reported in 2016 [2]. Breast cancer rates have been on the rise in past decades, particularly in areas that have historically lower incidences, such as Asia [3]. Since 1999, there has been a trend of increased incidence of breast cancer in Korea [2]. The current 5-year survival rate for patients presenting with metastatic breast cancer is 26% [4].

Eribulin mesylate (hereafter referred to as eribulin) is a unique non-taxane inhibitor of microtubule growth that disrupts mitotic spindle formation, induces an irreversible blockade of mitosis, and leads to cancer cell death by apoptosis [5–10]. It has been shown to be both efficacious and tolerable as a monotherapy in patients with advanced and metastatic breast cancer, improving overall survival (OS) and progression-free survival (PFS) compared with the treating physicians' choice of therapy or capecitabine (in certain patient populations) in phase III clinical studies [11]. These results were further confirmed in a retrospective study of patients who did not meet clinical study eligibility requirements [12].

Based on the findings of two phase III studies, EMBRACE [13] and 301 [14], eribulin was approved in many countries, including Korea, for the treatment of advanced or metastatic breast cancer in patients who have been previously treated with at least two lines of chemotherapy, including an anthracycline and a taxane [15,16]. Eribulin was also recently approved in China for the treatment of locally advanced or metastatic breast cancer, based on the results of the 304 study [17].

In the EMBRACE study, eribulin treatment significantly improved PFS and OS compared with the treating physicians' choice of therapy; of note, fatigue and neutropenia were the most commonly reported adverse events (AEs) in the eribulin-treated group [13]. The 301 study showed a non-significant trend towards improvement in OS for patients treated with eribulin compared with capecitabine, and PFS was similar between the two groups [14]. However, exploratory subgroup analysis showed an overall survival benefit with eribulin treatment in patients with human epidermal growth factor receptor 2 (HER2)-negative, estrogen receptor (ER)-negative, and triple-negative disease (ER, progesterone receptor [PgR], and HER2 negative) [15,18]. Pooled analysis of EMBRACE and 301 demonstrated a significant improvement in OS among patients with HER2-negative and triple-negative disease treated with eribulin [11]. In the recent 304 study,

a multicenter, open-label, randomized phase III trial, which evaluated eribulin versus vinorelbine in 530 Chinese patients with locally recurrent or metastatic breast cancer previously treated with chemotherapy regimens, including an anthracycline and a taxane, eribulin demonstrated a statistically significant extension in PFS (primary endpoint) over vinorelbine according to independent imaging review (hazard ratio: 0.80; 95% confidence interval [CI]: 0.65–0.98; $p = 0.036$) [17].

While these studies were the basis of approval for eribulin, they consisted primarily of Western patients and the only clinical study data of Asian patients were from Japanese metastatic breast cancer patients and, more recently, one study (304 study) in Chinese patients [13–21]. To address the shortage of data from Asian patients, a phase IV clinical study, ESKIMO, was conducted in Korean patients [22]. This study focused on the safety of eribulin treatment, with the primary endpoint being frequency and intensity of treatment-emergent AEs (TEAEs); neutropenia was the most common TEAE [22]. Other studies have also shown that neutropenia is a common hematologic AE associated with eribulin use [13,15,19]. Overall, while the safety data and disease control rates from ESKIMO show that eribulin is generally safe and well-tolerated in Korean patients [22], there is still a paucity of efficacy data. Furthermore, the incidence of neutropenia in clinical practice needs further study; it may be associated with ethnicity as higher rates are reported for Asian patients [19]. This retrospective study (REMARK) was therefore conducted to assess the effectiveness and safety of eribulin in Korean breast cancer patients in a real-world clinical setting.

2. Patients and methods

2.1. Patients

Patients were included in the study if they had confirmed locally advanced or metastatic breast cancer and had been treated with eribulin between June 1, 2014 and December 31, 2016. There were no exclusion criteria. Prior to eribulin administration, all patients were assumed to have been assessed for peripheral neuropathy and tested for a complete blood cell count, as indicated in the label dosing instructions, to check their eligibility for chemotherapy.

2.2. Study design and treatment

This was a retrospective, nationwide, multicenter study conducted across 14 centers throughout Korea between June 1, 2014 and December 31, 2016. Study participants were those who routinely visited the hospital and were prescribed eribulin by their treating physician. The data for this study were obtained by reviewing the past medical records of participating patients. Safety and effectiveness outcomes from patient medical records were collected irrespective of the patient's age, sex, or length of time of eribulin treatment. Data related to treatment patterns were also collected.

In general, eribulin was administered at a clinically recommended dose of 1.23 mg/m² (equivalent to 1.4 mg/m² eribulin mesylate) by intravenous infusion for 2–5 min, or as a diluted solution, on Days 1 and 8 of every 21-day cycle. Dose reductions and delays were acceptable at the treating physician's discretion.

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki, the guidelines of the International Conference on Harmonisation of Pharmaceuticals for Human Use, and the Good Clinical Practice guidelines. The study protocol was reviewed and approved by the institutional review board at each participating center. Because this was a retrospective rather than an interventional study, written informed consent was not required unless specifically requested by an institutional review

board or regulatory authority. This study was registered on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03437083) (NCT03437083).

2.3. Effectiveness and safety

The primary effectiveness endpoint was PFS rate at 6 months. Secondary effectiveness endpoints were median PFS, OS, time-to-treatment failure (TTF), tumor response rate, and safety. Effectiveness according to the line of treatment (early [≤ 2 nd line] vs late [≥ 3 rd line]) and receptor status as measured by PFS rate at 6 months, median PFS, OS, TTF, and tumor response rate was also examined.

The safety endpoint was the incidence of hematologic TEAEs. TEAE grading was based on the description provided in the clinical progress notes and the National Cancer Institute Common Terminology for Adverse Events version 4.0 [23]. Adverse drug reactions were classified by System Organ Class and Preferred Term according to MedDRA® version 21.0. Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

2.4. Statistical analysis

There was no planned sample size as this was a retrospective study. However, the number of breast cancer patients treated with eribulin in Korea between June 1, 2014 and December 31, 2016 was estimated to be approximately 350 based on the internal records of Eisai Korea Inc. (data not shown). The full analysis set (FAS) comprised patients with confirmed locally advanced or metastatic breast cancer who received at least one dose of eribulin and had at least one efficacy evaluation. The safety analysis set (SAF) comprised patients with confirmed locally advanced or metastatic breast cancer who received at least one dose of eribulin and had at least one safety evaluation.

Effectiveness and safety data were evaluated using descriptive statistics; demographic and clinical characteristics were summarized using mean, median, or ratio. Categorical variables were assessed using Chi-square or Fisher’s exact test; continuous variables were assessed using *t*-test or Wilcoxon rank-sum test. PFS, OS, and TTF were assessed using the Kaplan–Meier method and log-rank tests. All statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC).

31. Results

3.1. Patients and treatment

Medical records data from 398 female patients were collected and included in the SAF. Of these, 360 patients were included in the FAS; the remaining 38 patients were excluded because they did not have effectiveness data.

The baseline characteristics of patients in the SAF are shown in [Table 1](#). The mean age \pm standard deviation was 53.0 \pm 9.8 years, the median (range) number of previous chemotherapy regimens for advanced breast cancer was 2 (0–11), and median (range) number of cycles of eribulin administered was 5 (1–34). The mean tumor size at the initial breast cancer diagnosis was 3.7 \pm 2.6 cm, the mean number of nodes was 5.3 \pm 7.2, and 21.0% (81/385) of patients had metastatic disease on presentation. Including patients with unknown receptor status, 50.8% (202/398) were either ER and/or PgR positive, 34.4% (137/398) were ER and PgR negative, 26.1% (104/398) were HER2 positive, and 20.9% (83/398) were triple negative.

Table 1
Baseline characteristics (safety analysis set).

	Total, N = 398
Age (years), mean \pm SD	53.0 \pm 9.8
Weight (kg), mean \pm SD	57.6 \pm 10.3
ER/PgR status	
ER and/or PgR positive	202 (50.8)
ER and PgR negative	137 (34.4)
HER2 negative	235 (59.0)
HER2 positive	104 (26.1)
Triple negative ^a	83 (20.9)
Unknown	59 (14.8)
Most common metastatic sites ^b	
Bone	206 (51.8)
Lung	200 (50.3)
Liver	142 (35.7)
Lymph node	199 (50.0)
Brain	48 (12.1)
Other	71 (17.8)
None	12 (3.0)
No. of prior chemotherapy regimens	
≤ 1	10 (2.5)
2	58 (14.6)
3	114 (28.6)
4	105 (26.4)
5	67 (16.8)
≥ 6	44 (11.1)
No. of prior chemotherapy regimens for advanced disease	
≤ 1	51 (12.8)
2	169 (42.5)
3	98 (24.6)
4	44 (11.1)
5	16 (4.0)
≥ 6	20 (5.0)
Prior anthracycline therapy	393 (98.7)
Prior taxane therapy	394 (99.0)

Data are n (%) unless stated otherwise.

ER, estrogen receptor; HER2, human epidermal growth factor receptor-2; PgR, progesterone receptor; SD, standard deviation.

^a ER, PgR, and HER2 negative.

^b Patients were included in more than one category if applicable.

The treatment pattern of eribulin in the real-world clinical setting is shown in [Table 2](#). The FAS had a mean (standard deviation, range) of 6.6 (4.9, 1–34) treatment cycles, a mean (standard deviation) relative dose intensity of 86.7% (13.8), and 53 (14.8%) patients had a dose reduction. The mean (standard deviation) duration of treatment was 139.0 (108.3) days and the median duration of response was 149 days (95% CI: 95.0, 194.0). The reasons for dose change, dose delay, and dose discontinuation were confirmed for 359 patients and included (n, %): AEs meeting dose reduction/delay criteria (126, 35.1%), AEs not meeting dose reduction/delay criteria (74, 20.6%), progressive disease (PD) (296, 82.5%), and other reason (177, 49.3%).

3.2. Efficacy and safety

The primary effectiveness endpoint of the PFS rate at 6 months was 37.8% (136/360) ([Table 3](#)). When stratified by early (≤ 2 nd line) and late (≥ 3 rd line) use of eribulin, the PFS rates at 6 months were 53.1% (26/49, 95% CI: 38.3, 67.5) and 35.4% (110/311, 95% CI: 30.1, 41.0), respectively. This difference was statistically significant ($P = 0.0176$) (Supplementary file 1: [Supplementary Table 1](#)). PD was reported for 60.3% (217/360) of patients at 6 months, and 1.9% (7/360) of patients had died ([Table 3](#)).

Kaplan–Meier plots of PFS, OS, and TTF are shown in [Fig. 1a–c](#). Median PFS, OS, and TTF were 134 (approximately 4.5 months, 95% CI: 119, 148), 631 (approximately 21 months, 95% CI: 571, 761), and 120 days (approximately 4 months, 95% CI: 98, 133), respectively ([Table 3](#)). Best overall response (n [%]) results showed that 3 (0.8) of

Table 2
Real-world treatment patterns (full analysis set).

Treatment pattern	N = 360
Relative dose intensity (%), mean (SD)	86.7 (13.8)
Dose reduction	53 (14.8)
Treatment cycles, mean (SD, range)	6.6 (4.9, 1–34)
Duration of treatment (days), mean (SD)	139.0 (108.3)
Median duration of response (days [95% CI])	149 (95.0, 194.0)
Reason for dose change, delay, or discontinuation (n = 359)	
AEs meeting dose reduction/delay criteria	126 (35.1)
AEs not meeting dose reduction/delay criteria	74 (20.6)
Progressive disease	296 (82.5)
Other	177 (49.3)

Data are shown as n (%) unless otherwise stated.
AE, adverse event; CI, confidence interval; SD, standard deviation.

Table 3
Primary and secondary effectiveness endpoints (full analysis set).

Endpoint	N = 360	95% CI
Primary endpoint, n (%)		
Progression-free survival rate at 6 months	136 (37.8)	
Progressive disease	217 (60.3)	
Death	7 (1.9)	
Secondary endpoints		
Progression-free survival, days (median)	134	119, 148
Overall survival, days (median)	631	571, 761
Time-to-treatment failure, days (median)	120	98, 133
Best overall response, n (%)		
Complete response	3 (0.8)	
Partial response	62 (17.2)	
Stable disease	113 (31.4)	
Progressive disease	182 (50.6)	
Not evaluable	0 (0.0)	
Objective response rate ^a , n (%)	65 (18.1)	14.2, 22.4
Clinical benefit rate (n = 182) ^b , n (%)	92 (50.6)	43.1, 58.0
Disease control rate ^c , n (%)	178 (49.4)	44.2, 54.7

CI, confidence interval.

^a Complete response + partial response.

^b Complete response + partial response + stable disease for at least 6 months. The number of evaluable patients was 182, which was used as a denominator to calculate the clinical benefit rate.

^c Complete response + partial response + stable disease.

the 360 patients had complete response (CR), 62 (17.2) had partial response (PR), 113 (31.4) had stable disease (SD), and 182 (50.6) had PD (Table 3). The objective response rate (ORR), clinical benefit rate (CBR), and disease control rate (DCR) were 18.1% (65/360; 95% CI, 14.2, 22.4), 50.6% (92/182; 95% CI, 43.1, 58.0), and 49.4% (178/360; 95% CI, 44.2, 54.7), respectively (Table 3).

Significant differences were observed for TTF and ORR ($P = 0.0236$ and $P = 0.0395$, respectively) between the early (≤ 2 nd line, $n = 49$) and late (≥ 3 rd line, $n = 311$) eribulin treatment groups in the FAS; however, the groups showed no significant differences in PFS, OS, best overall response, CBR, or DCR (Supplementary file 1: Supplementary Table 1, Supplementary Fig. 1a–c). When categorized by the receptor status, patients who were hormone receptor (HR)+ and HER2– had the longest (days [95% CI]) median PFS (169 [148, 198]), OS (881 [593, 949]), and TTF (156 [123, 176]) compared with those who were HER2+ (107 [79, 145], 705 [568, 1152], and 92 [76, 134], respectively) or triple negative (121 [79, 134], 485 [285, 672], and 110 [71, 123], respectively) (Supplementary file 1: Supplementary Table 2, Supplementary Fig. 2a–c). Patients with HR+ and HER2– receptor status also showed the best PFS rate at 6 months (48.9%, 67/137), ORR (25.6%, 35/137), and CBR (56.6%, 47/83) compared with those who were HER2+ (34.7% [34/98], 13.3% [13/98], and 43.5% [20/46], respectively) or triple negative (25.7% [19/74], 13.5% [10/74], and 41.4% [12/29], respectively) (Supplementary file 1: Supplementary Table 2). However, for DCR, patients

who were triple negative showed the best response (48.7%, 36/74), followed by those with HR+ and HER2– status (42.6%, 20/47) and HER2+ status (40.85, 40/98) (Supplementary file 1: Supplementary Table 2).

Hematologic TEAEs were reported in 65.1% (259/398) of patients in the SAF and are summarized in Table 4. Of these, neutropenia (56.8%) and anemia (11.3%) were the most frequently reported TEAEs.

4. Discussion

Findings from this study showed the effectiveness of eribulin treatment in Korean patients with advanced or metastatic breast cancer in a real-world clinical setting. Additionally, the real-world safety profile of eribulin was in line with the known safety profile and no new safety concerns were identified.

Overall, the results of our study are comparable with those previously reported. Median PFS (134 days, approximately 4.5 months) was comparable with that reported for previous clinical studies (range: approximately 3–5.1 months) [15,16,20,24,25]. We also report a slightly longer median OS (631 days, approximately 21 months) than previous studies (range: 8.8–15.9 months) [15,16,20,24,25]. In a recent retrospective real-world study of data from 16,703 patients with metastatic breast cancer receiving eribulin as 2nd- to 4th-line therapy, OS in the 3rd- and 4th-line cohorts was significantly improved with eribulin compared with other chemotherapy (11.27 vs 7.65 months, $p = 0.0001$ [3rd line]; 10.91 vs 5.95 months, $p < 0.0001$ [4th line]) [26]. Interestingly, no significant difference was reported for 2nd-line eribulin treatment compared with other chemotherapy; in the present study, there was no significant difference in effectiveness of eribulin between early (≤ 2 nd line) and late (≥ 3 rd line) eribulin treatment groups with respect to OS.

As patient characteristics are difficult to control in the real-world clinical setting, some differences in results may be expected. The TTF of 120 days (approximately 4 months) in our study was comparable with that reported in studies of eribulin treatment in East Asian populations (Taiwan: 3.9 months; Japan: 127 days [approximately 4 months]) [21,27]. Best overall responses were similar among our study (CR, 0.8%; PR, 17.2%; SD, 31.4%; PD, 50.6%) and the studies conducted in Taiwan (CR, 1.8%; PR, 18.8%; SD, 46.3%; PD, 33.0%) and Japan (Watanabe et al.: CR, 1.3%; PR, 15.2%; SD, 33.5%; PD, 49.2%; Tanaka et al.: CR, 3.4%; PR, 20.7%; SD, 27.6%; PD, 48.3%) [20,21,27].

The overall safety profile reported in the present study is similar to what is already known for eribulin treatment in patients with advanced or metastatic breast cancer [13,14,22]. The most common hematological AE was neutropenia (56.8%), followed by anemia and leukopenia (11.3% and 9.8%, respectively), all of which have been previously reported at either similar or higher occurrence rates [13,14,22]. Neutropenia is strongly associated with eribulin use [14,15].

This study had several limitations. First, as this was a retrospective study, there are several inherent biases that cannot be controlled compared with a randomized clinical study. Additionally, we were not able to strictly control the baseline characteristics of the patients, which may have contributed to variations in effectiveness outcomes between this study and other retrospective studies. Secondly, we intended to assess the effectiveness of eribulin treatment according to tumor subtype (receptor status and molecular subtype); however, we were not able to interpret the data because of the high percentage (18.0%) of tumors with an unknown subtype. Finally, no control was set as a clinical factor so there was no guaranteed control of confounding effects; therefore, the current results should be interpreted carefully.

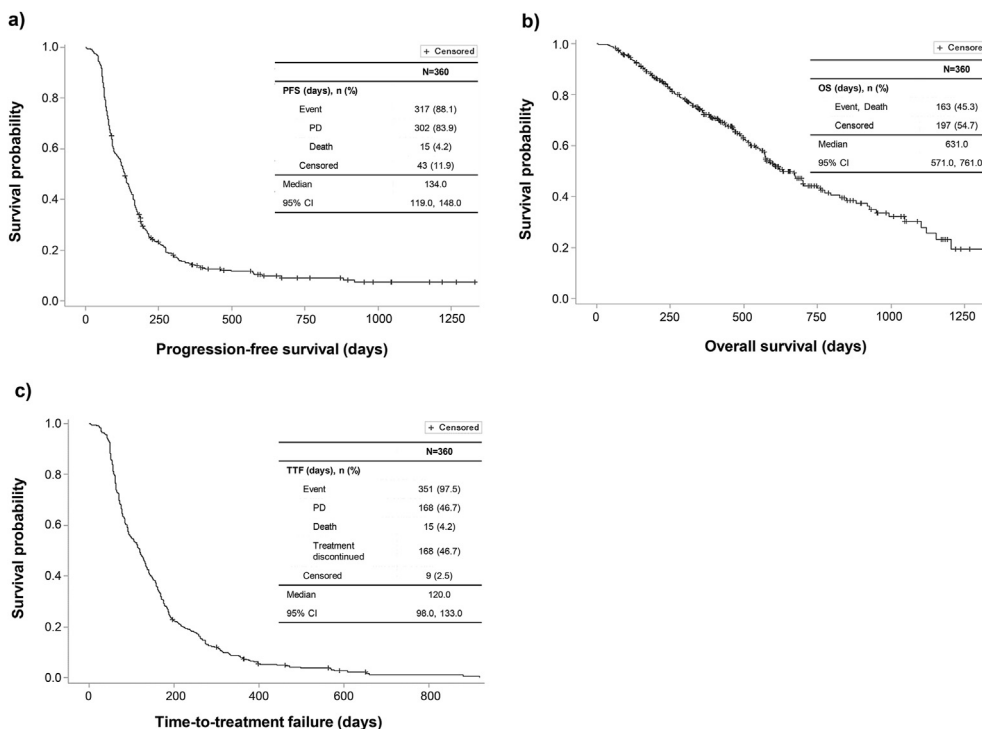


Fig. 1. Kaplan–Meier plots are shown for a) progression-free survival, b) overall survival c) time-to-treatment failure; full analysis set. CI, confidence interval; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TTF, time-to-treatment failure.

Table 4
Summary of adverse events (safety analysis set).

Type of adverse event	N = 398, n (%) [events]
Treatment-emergent adverse events	259 (65.1) [1275]
Adverse drug reaction (related to study drug)	256 (64.3) [1238]
Serious adverse event	42 (10.6) [114]
Serious adverse drug reaction	41 (10.3) [110]
Incidence of hematologic treatment-emergent adverse events, blood, and lymphatic system disorders	248 (62.3)
Neutropenia	226 (56.8)
Anemia	45 (11.3)
Leukopenia	39 (9.8)
Thrombocytopenia	15 (3.8)
Febrile neutropenia	7 (1.8)
Lymphopenia	7 (1.8)
Incidence of hematologic serious adverse events, blood, and lymphatic system disorders	36 (9.1)
Neutropenia	31 (7.8)
Febrile neutropenia	4 (1.0)
Anemia	2 (0.5)
Leukopenia	2 (0.5)
Lymphopenia	2 (0.5)
Thrombocytopenia	2 (0.5)

Treatment-emergent adverse events and serious adverse events were coded according to the system organ class and preferred terms of MedDRA® version 21.0.

The results of this study add to the previously published efficacy and safety data in patients with metastatic breast cancer regardless of treatment line and provide much needed efficacy and safety data for Korean patients. Overall, this retrospective study of Korean patients with advanced or metastatic breast cancer treated with eribulin demonstrated effectiveness and safety results from the real-world clinical setting that are consistent with that reported in previous studies of eribulin in Asian patients and no new safety

concerns were identified. Regarding further work, larger retrospective studies in Korean patients may be warranted to determine possible relationships between the effectiveness of eribulin and tumor subtype.

Ethics approval and consent to participate

The study protocol was approved by the institutional review board at each participating center and the study was conducted in accordance with the Declaration of Helsinki. This was a retrospective study, therefore written informed consent was not required.

Consent for publication

Not applicable.

Data availability

The authors declare that all data supporting the findings of this study are available within the article or from the corresponding author on reasonable request.

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This study was sponsored by Eisai Korea Inc. The sponsor had a role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Authors' contributions

All authors contributed equally to this work, including the experimental design, data collection, data analyses, and manuscript writing and review.

Declaration of competing interest

MYK and JYK are employees of Eisai Korea Inc. All other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2020.09.004>.

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