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Original Article

Safety and Effectiveness of Eribulin in Patients with Advanced or Metastatic Breast Cancer Previously Treated with Anthracyclines and Taxanes in Real-World Clinical Practice: A 6-Year Post-marketing Surveillance Study in South Korea

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Purpose This 6-year post-marketing surveillance (PMS) study was conducted in South Korea to evaluate the real-world safety and effectiveness of eribulin in patients with advanced or metastatic breast cancer previously treated with anthracyclines and taxanes.

Materials and Methods During the study period (17 August 2012 to 16 August 2018), case-report files (CRFs) of patients receiving eribulin were collected. The main study endpoint was to assess the safety of eribulin. Evaluation of the effectiveness of eribulin was an exploratory endpoint. Patients were followed for 1 year after eribulin initiation.

Results CRFs were collected from 64 investigators at 64 sites for 1,079 patients. The safety analysis set (SAS) included 1,001 eribulin recipients; effectiveness was assessed in 244 patients. In the SAS, patients were predominantly female (99.6%), with a median age of 53.0 years, and diagnosed with metastatic breast cancer (92.0%). Eribulin was administered as a median 4th line chemotherapy. A total of 2,124 treatment-emergent adverse events (TEAEs) were reported in 661 patients (66.0%). Neutropenia was the most common TEAE (32.5% of patients), occurring at a median of 9-11 days from initial eribulin administration. Overall response and disease control rates were 31.7% and 95.6%, respectively, and the median duration of eribulin use (time to treatment failure) was 3.0 months.

Conclusion This large real-world PMS analysis in patients with advanced or metastatic breast cancer demonstrated the effectiveness of eribulin and found no new safety concerns relative to safety information from prior clinical and real-world studies, and approvals in South Korea and other countries.

Key words Breast neoplasms, Effectiveness, Eribulin, Postmarketing product surveillance, Real-world, Safety

Introduction

Globally, breast cancer is one of the most common malignancies and is a leading cause of female cancer deaths in 95% of countries [1,2]. In South Korea, there were 259,116 limited-duration prevalent cases on 1 January 2019 (patients who were diagnosed between 1 January 1999 and 31 December 2019 and who were alive on 1 January 2020) [3].

Although newly-emerged targeted and biological therapies have changed the breast cancer treatment paradigm, chemotherapy is still the main treatment option for patients with metastatic triple-negative, human epidermal growth factor receptor 2 (HER2)–positive, or endocrine-resistant hormone receptor (HR)–positive breast cancer [4,5].

Eribulin mesilate, a non-taxane microtubule stabilizer, is a structurally simplified analog of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai* [6-8]. The binding of eribulin to the (+) B-tubulin ends of microtubules differentiates it from other microtubule inhibitors, such as the vinca alkaloids (e.g., vinorelbine) and taxanes (e.g. paclitaxel), which bind the outer surfaces with (+) ends and the inner surface of microtubules, respectively [8]; moreover, the antimitotic effects of eribulin are functionally irreversible at the cellular level, unlike those of paclitaxel and vinblastine [9].

Eribulin is approved for the treatment of patients with locally advanced or metastatic breast cancer, who have progressed after at least two chemotherapeutic regimens, including anthracyclines and taxanes, based on the EMBRACE study [10]. Since being approved in South Korea in January 2013, eribulin has been used for over 10 years. The efficacy and safety of eribulin have been demonstrated in randomized clinical studies [10-13] and, in particular, eribulin showed significant overall survival (OS) benefit in patients

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with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane compared with the conventional chemotherapeutic regimens [10-13]. However, clinical trials contain less than 5% of all cancer patients, and based on inclusion/exclusion criteria, the results are generally confined to younger and healthier patients, which may not reflect the actual use of eribulin in clinical practice.

Therefore, we report data from a prospective 6-year post-marketing surveillance (PMS) study in South Korea, conducted at the request of the Korean Ministry of Food and Drug Safety (MFDS), to confirm the safety and effectiveness of eribulin in patients with advanced or metastatic breast cancer previously treated with anthracyclines and taxanes under real-world clinical practice.

Materials and Methods

1. Study design and participants

This was a nationwide multicenter, prospective, observational study of patients with locally advanced or metastatic breast cancer treated with eribulin in routine clinical practice settings under Korean domestic guidelines. This study included adult patients with locally advanced or metastatic breast cancer who had previously received at least one chemotherapeutic regimen for advanced and/or metastatic disease. As an observational study, all treatment decisions were at the discretion of the treating physician prior to the decision to include the patient in this study.

Patients were enrolled from 64 centers in South Korea and data were collected using case-report files (CRFs) during the 6-year study period from 17 August 2012 to 16 August 2018. The recommended dose of eribulin mesilate was 1.4 mg/m^2 administered intravenously on days 1 and 8 of every 21-day cycle. Safety and clinical outcomes including baseline characteristics for each patient were recorded and patients were followed for 1 year after eribulin initiation.

2. Study endpoints

The main endpoint was to assess the types and incidences of treatment-emergent adverse events (TEAEs) during real-world use of eribulin, including serious and unexpected TEAEs, not previously described in the precautions for use in the product label. An additional exploratory endpoint was to evaluate the effectiveness of eribulin, in terms of time-to-treatment failure (TTF) and response rate, in the real-world setting. For events (death or eribulin discontinuation within 1 year), survival time was calculated as: (earlier of the date of death or eribulin discontinuation date−eribulin first dose date+1)/(365/12), with the result expressed in months. For censored cases (no death and eribulin used for over 1 year), survival time was calculated as: (eribulin discontinuation date−eribulin first dose date+1)/(365/12), with the result expressed in months.

Safety outcomes included the incidence and rates of overall, unexpected, and serious TEAEs. TEAEs were classified by: system organ class (SOC) and preferred term/included term based on the Medical Dictionary for Regulatory Activities (MedDRA) [14]; severity based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [15]; and outcome. In the safety analysis set (SAS), the use and manageability (i.e., rate of change in dose, delay in medication, or treatment withdrawal) of eribulin treatment were recorded. The Anatomical Therapeutic Chemical (ATC) classification system was used to record concomitant medication use.

Disease response, when possible, was assessed in the effectiveness analysis set (EAS) as complete response (CR), partial response, stable disease (SD), disease progression, or unassessable, based on various tumor assessments (e.g., physical examination, X-ray, computerized tomography [CT] scan, magnetic resonance imaging [MRI], positron emission tomography [PET]); the overall disease control rate was defined as the total of the CR, partial response, and SD rates.

At the 1-year follow-up, outcomes were checked such as eribulin continuation/discontinuation, post-eribulin anticancer therapy, patient survival, cause of death, and TEAEs after the 3-month assessment.

3. Statistical analysis

Safety and effectiveness data are presented using descriptive statistics. Categorical data were analyzed with chi-square test or Fisher's exact test, continuous data were analyzed using the t test or Wilcoxon rank sum test. Statistical analyses were conducted using SAS ver. 9.4 (SAS Institute Inc.).

In addition to the overall patient population, analyses were conducted for the three breast cancer subtypes: HR+/HER− [defined as estrogen receptor (ER)+ or progesterone receptor (PR)+ and HER2− (immunohistochemistry [IHC] 0/1 or fluorescence *in situ* hybridization [FISH]−, FISH− confirmed if IHC 2+)], HER2+ (defined as IHC 3+ or FISH+), triple-negative breast cancer (TNBC) (defined as ER−, PR−, HER2−).

Results

1. Patient characteristics

As shown in the flow diagram of study participants (Fig. 1), 1,079 patients were enrolled during the 6-year study period. Of them, 78 (7.2%) were excluded, mainly because of a

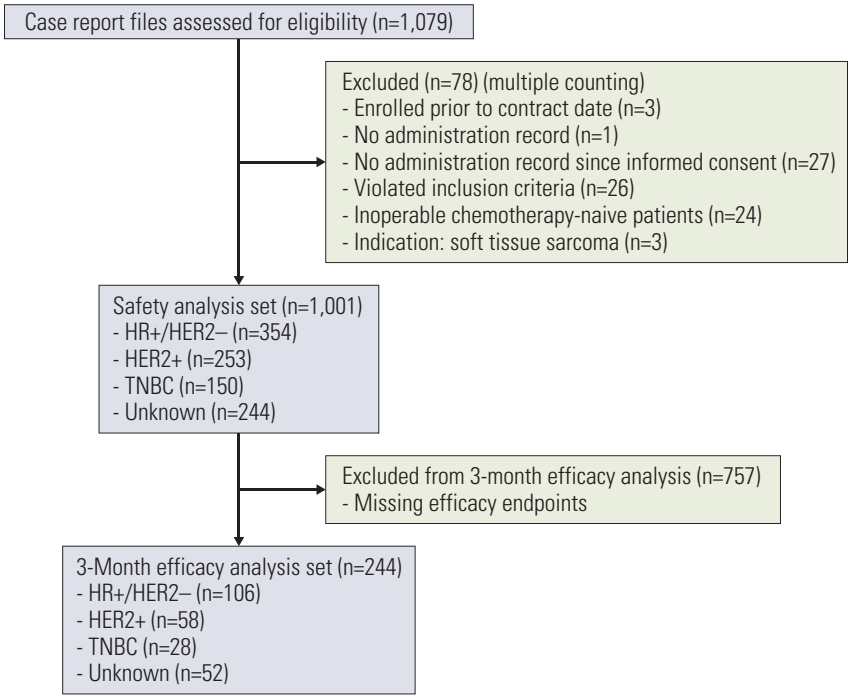

Fig. 1. Patient flow diagram. HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer.

lack of administration record or violation of the inclusion criteria. The remaining 1,001 eribulin recipients were analyzed for safety (SAS) and only 244 were included in the EAS for the effectiveness analysis as 757 patients did not undergo the 3-month eribulin efficacy assessment.

Patients' baseline characteristics are summarized in Table 1. The median age at initiation of eribulin therapy was 53.0 years (range, 26.0 to 85.0 years), most patients were female (99.6%) and had metastatic breast cancer (92.0%). The median duration between breast cancer diagnosis and study entry was 53.6 months (range, 0.3 to 312.0 months). Most patients previously underwent breast cancer surgery (82.2%), adjuvant chemotherapy (62.7%), hormone therapy (59.4%), and radiotherapy (66.2%) before study entry. In particular, taxanes (99.9%), anthracyclines (99.7%), or both taxane and anthracycline (99.6%) were administered in the adjuvant or metastatic setting.

2. Use of eribulin

During the study, the mean eribulin dose was 1.34±0.12 mg/m^2 (median, 1.40 [range, 1 to 10 mg/m^2]), with no significant difference by breast cancer subtype. The median line of therapy when patients initiated eribulin use was 3rd or 4th line (depending on breast cancer subtype) and the overall median duration of eribulin use (referred to as TTF) was 3.0 (2.1 for TNBC and 3.7 for HR+/HER2–) months (Table 2, Fig. 2). After starting eribulin administration, only 217 patients (21.7%) had experienced dose reduction and the majority of them experienced it only once (Table 2). The most common reason for dose reduction/treatment modification was neutropenia.

3. Safety outcomes

A summary of the most common TEAEs by severity is shown in Table 3. In detail, a total of 2,124 TEAEs were reported in 661 (66.0%) patients, including 379 serious TEAEs in 241 (24.1%) patients and most (51.0%) were classified as grade 1 or 2. By outcome, at the time of CRF collection, 87.4% of TEAE cases had recovered or were recovering; 161 (7.6%) had not recovered, and 72 patients with TEAEs had died. 58.8% of the TEAEs were considered to have a relationship with eribulin. Eighteen cases of suspected unexpected serious adverse reactions were reported in 94 patients.

Regardless of causality to eribulin, the most frequent TEAEs by SOC were white cell and reticuloendothelial system disorders (35.1% of patients) followed by body as a whole–general disorders (21.9%), gastrointestinal system disorders (13.5%), respiratory system disorders (12.5%), and central and peripheral nervous system disorders (10.7%). Classified by preferred term, the most frequent TEAE was neutropenia (32.5% of patients) with 22.0% grade 3/4 (Table 3), meanwhile the most common non-hematological TEAEs

Table 1. Patient baseline characteristics and prior treatment/drug exposure

	HR+/HER2– (n=354)	HER2+ (n=253)	TNBC (n=150)	Unknown (n=244)	Total (n=1,001)	p-value
Age (yr), mean±SD	53.22±9.06	52.81±9.02	53.02±10.69	52.31±9.93	52.87±9.52	0.860
Sex						
Male	2 (0.6)	1 (0.4)	0	1 (0.4)	4 (0.4)	> 0.99[a]
Female	352 (99.4)	252 (99.6)	150 (100)	243 (99.6)	997 (99.6)	
Diagnosis						
Locally advanced	25 (7.1)	12 (4.7)	12 (8.0)	31 (12.7)	80 (8.0)	0.362[b]
Metastatic	329 (92.9)	241 (95.3)	138 (92.0)	213 (87.3)	921 (92.0)	
Hormone receptor status: ER						
Negative	20 (5.7)	111 (43.9)	150 (100)	32 (13.1)	313 (31.3)	< 0.001[b]
Positive	334 (94.4)	140 (55.3)	0	89 (36.5)	563 (56.2)	
Unknown	0	0	0	4 (1.6)	4 (0.4)	
Hormone receptor status: PR						
Negative	69 (19.5)	144 (56.9)	150 (100)	48 (19.7)	411 (41.1)	< 0.001[a]
Positive	283 (79.9)	107 (42.3)	0	72 (29.5)	462 (46.2)	
Unknown	1 (0.3)	0	0	5 (2.1)	6 (0.6)	
HER2 status: IHC						
0/1+	296 (83.6)	0	129 (86.0)	3 (1.2)	428 (42.8)	< 0.001[a]
2+	36 (10.2)	14 (5.5)	15 (10.0)	46 (18.9)	111 (11.1)	
3+	0	231 (91.3)	0	0	231 (23.1)	
Unknown	2 (0.6)	0	1 (0.7)	10 (4.1)	13 (1.3)	
HER2 status: FISH						
Negative	89 (25.1)	6 (2.4)	31 (20.7)	2 (0.8)	128 (12.8)	< 0.001[a]
Positive	0	46 (18.2)	0	0	46 (4.6)	
Unknown	0	1 (0.4)	0	11 (4.5)	12 (1.2)	
Prior surgery						
Yes	292 (82.5)	200 (79.1)	126 (84.0)	205 (84.0)	823 (82.2)	0.395[b]
Prior radiotherapy						
Yes	239 (67.5)	163 (64.4)	98 (65.3)	163 (66.8)	663 (66.2)	0.715[b]
Prior hormone						
Yes	316 (89.3)	120 (47.4)	12 (10.0)	144 (59.0)	595 (59.4)	< 0.001[b]
Prior chemotherapy						
Neoadjuvant	56 (15.8)	67 (26.5)	31 (20.7)	55 (22.5)	209 (20.9)	0.006[b]
Adjuvant	217 (61.3)	157 (62.1)	109 (72.7)	145 (59.4)	628 (62.7)	0.041[b]
Prior chemotherapy (exposure)						
Taxanes	354 (100)	253 (100)	150 (100)	243 (99.6)	1,000 (99.9)	NA
Anthracyclines	353 (99.7)	251 (99.2)	150 (100)	244 (100)	998 (99.7)	0.594[b]
Taxane and anthracycline	353 (99.7)	251 (99.2)	150 (100)	243 (99.5)	997 (99.6)	0.594[b]
Setting of previous taxane						
Absent	0	0	0	1 (0.4)	1 (0.1)	0.026[b]
Adjuvant/Neoadjuvant	30 (8.5)	43 (17.0)	19 (12.7)	42 (17.2)	134 (13.4)	
Metastatic	198 (55.9)	137 (54.2)	84 (56.0)	132 (54.1)	551 (31.5)	
Both	126 (35.6)	73 (28.9)	47 (31.3)	69 (28.3)	315 (31.5)	

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were exacerbation of disease (5.0%), fever (4.9%), and generalized weakness (4.1%).

Neutropenia occurred approximately 9-11 days after the initial administration of eribulin and the majority (92%) of grade 3 or higher neutropenia occurred within 3 cycles of eribulin. Of 758 cases of neutropenia, there was no change in eribulin administration in 469 cases (61.9%), the eribulin dose was increased in six cases (0.8%), reduced in 69 cases

Table 1. Continued

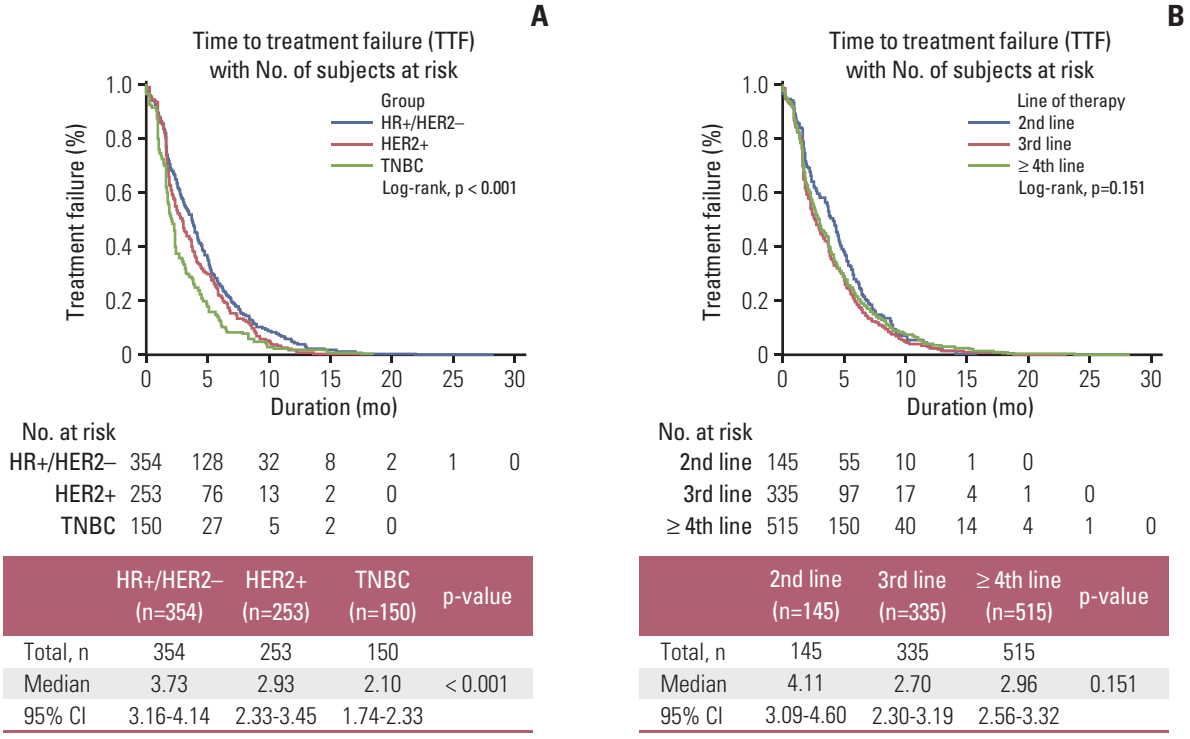
	HR+/HER2– (n=354)	HER2+ (n=253)	TNBC (n=150)	Unknown (n=244)	Total (n=1,001)	p-value
Setting of previous anthracycline						
Absent	1 (0.3)	2 (0.8)	0	0	3 (0.3)	0.206[b]
Adjuvant/Neoadjuvant	137 (38.7)	107 (42.3)	76 (50.7)	117 (48.0)	437 (43.7)	
Metastatic	143 (40.4)	95 (37.6)	45 (30.0)	95 (38.9)	378 (37.8)	
Both	73 (20.6)	49 (19.4)	29 (19.3)	32 (13.1)	183 (18.3)	

Values are presented as number (%) unless otherwise indicated. p-value: results of comparison between the three groups (HR+/HER2–, HER2+, TNBC) excluding 'unknown'. ER, estrogen receptor; FISH, fluorescence *in situ* hybridization; HER2–, human epidermal growth factor receptor 2–negative; HER2+, human epidermal growth factor receptor 2–positive; HR+, hormone receptor–positive; IHC, immunohistochemistry; NA, not available; PR, progesterone receptor; SD, standard deviation; TNBC, triple-negative breast cancer. [a]Fisher's exact test, [b]Chi-square test.

Table 2. Eribulin use, mean dose, and dose reduction

	HR+/HER2– (n=354)	HER2+ (n=253)	TNBC (n=150)	Unknown (n=244)	Total (n=1,001)	p-value
Line of therapy at initiation of eribulin for metastatic disease						
No.	354	253	150	244	1,001	
Mean±SD	3.73±1.41	4.25±1.56	3.77±1.47	3.55±1.37	3.82±1.47	< 0.001[a]
Median	3.00	4.00	3.00	3.00	4.00	
Min-Max	1.00-10.00	2.00-10.00	2.00-10.00	1.00-10.00	1.00-10.00	
Dose of eribulin (mg/m²)						
No.	354	253	150	244	1,001	
Mean±SD	1.33±0.13	1.35±0.10	1.33±0.12	1.34±0.13	1.34±0.12	0.292[a]
Median	1.40	1.40	1.40	1.40	1.40	
Min-Max	0.70-1.40	0.70-1.40	0.81-1.40	0.70-1.40	0.70-1.40	
Time to treatment failure of eribulin (mo)						
No.	354	253	150	244	1,001	
Mean±SD	4.58±3.83	3.93±3.13	3.13±3.10	4.20±3.97	4.10±3.62	< 0.001[a]
Median	3.73	2.93	2.10	3.04	3.02	
Min-Max	0.03-28.27	0.03-17.52	0.03-18.44	0.03-23.80	0.03-28.27	
Dose reduction, n (%)						
No.	354	253	150	244	1,001	
No	262 (74.0)	209 (82.6)	115 (76.7)	198 (81.2)	784 (78.3)	0.091[b]
Yes, once	70 (19.8)	36 (14.2)	30 (20.0)	40 (16.4)	176 (17.6)	
Yes, multiple	22 (6.2)	8 (3.2)	5 (3.3)	6 (2.5)	41 (4.1)	
Patients with early dose reduction, n (%) (during the first 2 cycles)						
No.	92	44	35	46	217	
≤ 2 cycles	50 (54.4)	29 (65.9)	27 (77.1)	22 (47.8)	128 (59.0)	0.507[b]
> 2 cycles	42 (45.7)	15 (34.1)	8 (22.9)	24 (52.2)	89 (41.0)	

Time-to-treatment failure was defined as the time from the first dose of eribulin until the date of treatment discontinuation from any cause. SD, standard deviation. [a]Kruskal-Wallis test, [b]Chi-square test. First dose of eribulin in inoperable chemotherapy (line)=Order of eribulin administration when sorted by the start date of treatment with inoperable chemotherapy. Total period of eribulin administration (days)=End date of the last dose–Start date of the first dose+1. p-value: Comparison between 3 groups (hormone receptor [HR]+/human epidermal growth factor receptor 2 [HER2]–, HER2+, triple-negative breast cancer [TNBC]) excluding 'unknown'.



	HR+/HER2– (n=354)	HER2+ (n=253)	TNBC (n=150)	p-value
Total, n	354	253	150	
Median	3.73	2.93	2.10	< 0.001
95% CI	3.16-4.14	2.33-3.45	1.74-2.33	

	2nd line (n=145)	3rd line (n=335)	≥ 4th line (n=515)	p-value
Total, n	145	335	515	
Median	4.11	2.70	2.96	0.151
95% CI	3.09-4.60	2.30-3.19	2.56-3.32	

Fig. 2. Time to treatment failure by breast cancer subtype (A) and line of eribulin therapy (B). Event: This refers to cases where the patient either passed away or discontinued eribulin treatment within 1 year (the treatment duration is less than 365 days). Censored: This refers to cases where the patient did not pass away and continued using eribulin for more than 1 year (the treatment duration is 365 days or more). Survival time: For events (death or eribulin discontinuation within 1 year): The survival time is calculated as: (earlier of death or eribulin discontinuation date−eribulin first dose date+1)/(365/12), where the result is expressed in months. For censored cases (no death and eribulin used for over 1 year): The survival time is calculated as: (eribulin discontinuation date–eribulin first dose date+1)/(365/12), where the result is also expressed in months. p-value: This is the result of the comparison between the three groups (HR+/HER2–, HER2+, and TNBC). CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer.

(9.1%), and discontinued in 171 cases (22.6%). Initial granulocyte colony stimulating factor for neutropenia was administered at a median of 13 days of the 1st cycle of eribulin.

Adverse events (AEs) resulted in the discontinuation/interruption of eribulin, dose reduction, or death, in 17.0%, 11.0%, and 5.7% of patients, respectively, and the majority of deaths (36/57, 63.2%) were associated with disease progression (Table 4).

In the 1-year follow-up of 742 patients, 60.8% of patients were alive and 35 (4.7%) were still receiving eribulin, which was numerically higher in the ER+/HER2− subgroup (Table 5). After the completion of eribulin administration, 69.7%, 7.8%, and 7.8% of patients received chemotherapy, hormone therapy, and radiotherapy, respectively. Of the 291 deaths, 95.6% were due to disease progression.

4. Effectiveness

A total of 244 patients were available for tumor assessment by image modalities including CT and MRI/other (e.g., PET-CT). Overall response and disease control rates of eribulin were 31.7% and 95.6%, respectively (Fig. 3).

Median TTF was 3.0 months with significant differences by breast cancer subtype but with no statistically significant differences by the lines of eribulin for metastatic breast cancer (Fig. 2).

Discussion

The primary objective of this PMS study was to evaluate the safety of eribulin in more than 1,000 Korean breast cancer patients in real-world clinical practice under the approved indication, with effectiveness in terms of TTF being an exploratory endpoint: Eribulin was found to be well tolerated in routine clinical use showing a similar safety profile as observed in randomized, controlled clinical studies

Table 3. Summary of the most common treatment-emergent adverse events by severity (> 1% of patients)

Preferred term	No. of subjects (n=1,001)							
	Grade 1/2		Grade 3/4		Grade 5		Total	
	Subjects with AE	No. of AEs	Subjects with AE	No. of AEs	Subjects with AE	No. of AEs	Subjects with AE	No. of AEs
Total	510 (51.0)	1,355	342 (34.2)	698	70 (7.0)	71	661 (66.0)	2,124
Hematological								
Neutropenia[a)]	157 (15.7)	288	220 (22.0)	470	0	0	325 (32.5)	758
Febrile neutropenia	4 (0.4)	4	19 (1.9)	22	0	0	23 (2.3)	26
Anaemia	16 (1.6)	19	8 (0.8)	10	0	0	23 (2.3)	29
Thrombocytopenia	10 (1.0)	10	4 (0.4)	4	0	0	11 (1.1)	14
Non-hematological								
Exacerbation of disease	3 (0.3)	3	4 (0.4)	4	43 (4.3)	43	50 (5.0)	50
Fever	45 (4.5)	55	4 (0.4)	5	0	0	49 (4.9)	60
Weakness generalized	36 (3.6)	38	6 (0.6)	6	0	0	41 (4.1)	44
Anorexia	35 (3.5)	36	4 (0.4)	4	0	0	39 (3.9)	40
Liver function test abnormal	32 (3.2)	36	3 (0.3)	3	0	0	35 (3.5)	39
Nausea	30 (3.0)	33	4 (0.4)	4	0	0	34 (3.4)	37
Upper respiratory tract infection	27 (2.7)	31	3 (0.3)	3	0	0	29 (2.9)	34
Coughing	29 (2.9)	32	0	0	0	0	29 (2.9)	32
Dyspnea[b)]	15 (1.5)	16	11 (1.1)	11	3 (0.3)	3	29 (2.9)	30
Diarrhea	22 (2.2)	24	5 (0.5)	5	0	0	26 (2.6)	29
Pain	22 (2.2)	24	3 (0.3)	4	0	0	25 (2.5)	28
Neuropathy peripheral	25 (2.5)	28	0	0	0	0	25 (2.5)	28
Neuropathy	24 (2.4)	27	1 (0.1)	1	0	0	25 (2.5)	28
Dizziness	19 (1.9)	19	1 (0.1)	1	0	0	20 (2.0)	20
Myalgia	20 (2.0)	21	0	0	0	0	20 (2.0)	21
Pleural effusion	9 (0.9)	9	9 (0.9)	12	2 (0.2)	2	20 (2.0)	23
Back pain	17 (1.7)	18	2 (0.2)	2	0	0	19 (1.9)	20
Fatigue	17 (1.7)	18	2 (0.2)	2	0	0	19 (1.9)	20
Constipation	17 (1.7)	19	1 (0.1)	1	0	0	18 (1.8)	20
Headache	15 (1.5)	15	2 (0.2)	2	0	0	17 (1.7)	17
Pneumonia	5 (0.5)	5	4 (0.4)	4	7 (0.7)	7	16 (1.6)	16
Alopecia	13 (1.3)	13	0	0	0	0	13 (1.3)	13
Indigestion	13 (1.3)	15	0	0	0	0	13 (1.3)	15
Shingles	10 (1.0)	10	2 (0.2)	2	0	0	12 (1.2)	12
Skin rash	9 (0.9)	10	3 (0.3)	3	0	0	12 (1.2)	13
Stomatitis	12 (1.2)	12	0	0	0	0	12 (1.2)	12
Insomnia	11 (1.1)	12	0	0	0	0	11 (1.1)	12
Vomiting	8 (0.8)	8	3 (0.3)	4	0	0	11 (1.1)	12

Values are presented as number (%). AE, adverse event. [a)]The term was either 'Neutropenia' or 'Neutrophil count decreased', [b)]Dyspnea (grade 5 cases) evaluated as 'Unlikely' by the investigators.

[10,11,13]. Effectiveness outcomes were consistent with efficacy results observed in EMBRACE [10].

While most therapies have demonstrated comparable safety and efficacy in Asian and non-Asian patients with breast cancer, East Asian patients have an increased incidence of hematologic toxicities, including neutropenia, based on ethnic differences in its etiology and biology [16-18]. Therefore, hematologic safety was a great concern in using eribulin for the treatment of East Asians. This study showed a manageable safety profile in more than 1,000 Korean patients in clinical practice; TEAEs were observed in 66.0% of patients and could be managed with dose reduction and/or delay in medication: only 17.0% and 11.0% of patients required discontinuation/interruption or dose reduction of eribulin.

Table 4. Summary of AE leading to discontinuation/interruption, dose reduction, or death

	HR+/HER2– (n=354)	HER2+ (n=253)	TNBC (n=150)	Unknown (n=244)	Total (n=1,001)
AE leading to discontinuation/interruption					
No. of subjects with AE (%)	77 (21.8)	32 (12.7)	27 (18.0)	34 (13.9)	170 (17.0)
95% Confidence interval	17.56-26.42	8.81-17.38	12.21-25.10	9.85-18.92	14.71-19.46
No. of events, cases	171	54	33	47	305
AE leading to dose reduction					
No. of subjects with AE (%)	47 (13.3)	21 (8.3)	16 (10.7)	26 (10.7)	110 (11.0)
95% Confidence interval	9.92-17.26	5.21-12.41	6.22-16.74	7.08-15.22	9.12-13.09
No. of events, cases	56	25	19	35	135
AE leading to death[a]					
No. of subjects with AE (%)	12 (3.4)	17 (6.7)	10 (6.7)	18 (7.4)	57 (5.7)
95% Confidence interval	1.76-5.85	3.96-10.54	3.24-11.92	4.43-11.41	4.34-7.32
No. of events, cases[a]	12	17	10	18	57

[a]Adverse events (AEs) leading to death by subtype. Hormone receptor (HR)+/human epidermal growth factor receptor 2 (HER2)–: exacerbation of disease (6), dyspnoea (2), death (1), sepsis (1), pneumonia (1), hepatic failure (1). HER2+: exacerbation of disease (13), pneumonia (2), dyspnoea (1), metastases not otherwise specified (1). Triple-negative breast cancer (TNBC): exacerbation of disease (7), pneumonia (1), death (1), thromboembolism (1). Unknown: exacerbation of disease (10), pneumonia (2), metastases not otherwise specified (1), sepsis (1), pericardial effusion (1), metastases to lung (1), embolism pulmonary (1), shock septic (1).

Table 5. Eribulin administration status at 1-year of follow-up

	HR+/HER2– (n=354)	HER2+ (n=253)	TNBC (n=150)	Unknown (n=244)	Total (n=1,001)
Patients with eribulin administration status at 1-year follow-up	267 (36.0)	199 (26.8)	99 (13.3)	177 (23.9)	742 (100)
Eribulin administration status at 1-year follow					
Continuing administration	18 (6.7)	4 (2.0)	4 (4.0)	9 (5.1)	35 (4.7)
Treatment terminated	249 (93.3)	195 (98.0)	95 (96.0)	168 (94.9)	707 (95.3)
Treatment after completion of eribulin administration					
Chemotherapy	174 (65.2)	152 (76.4)	70 (70.7)	121 (68.4)	517 (69.7)
Hormone therapy	30 (11.2)	12 (6.0)	2 (2.0)	14 (7.9)	58 (7.8)
Radiation therapy	16 (6.0)	19 (9.6)	5 (5.1)	18 (10.2)	58 (7.8)
Other therapy	24 (9.0)	13 (6.5)	13 (13.1)	23 (13.0)	73 (9.8)
Unknown	31 (11.6)	14 (7.0)	8 (8.1)	11 (6.2)	64 (8.6)
Status of patients at 1-year follow-up					
Survival	182 (68.2)	122 (61.3)	39 (39.4)	108 (61.0)	451 (60.8)
Dead	85 (31.8)	77 (38.7)	60 (60.6)	69 (39.0)	291 (39.2)

Values are presented as number of patients with eribulin administration status at 1-year follow-up point (persons) (%). Items other than the number of patients with eribulin status at 1-year follow-up point: Percentage calculated based on the number of patients with eribulin status at 1-year follow-up point. HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer.

Moreover, most TEAEs were CTCAE grade 1 or 2 in severity. These safety results are generally consistent with those in previous multinational clinical trials of eribulin in patients with breast cancer (Table 6).

The overall safety profile of eribulin was consistent with that reported in the prescribing information, as well as the established precautions for its use [19]. According to the prescribing information, the most common TEAEs in metastatic breast cancer patients are neutropenia, anemia, asthenia/fatigue, alopecia, peripheral neuropathy, nausea, and constipation, which were also reported in this PMS study [19]. Neutropenia, the most common TEAE, is known to be associated with the use of eribulin and occurred in approximately one-third of patients. The ESKIMO trial reported a much

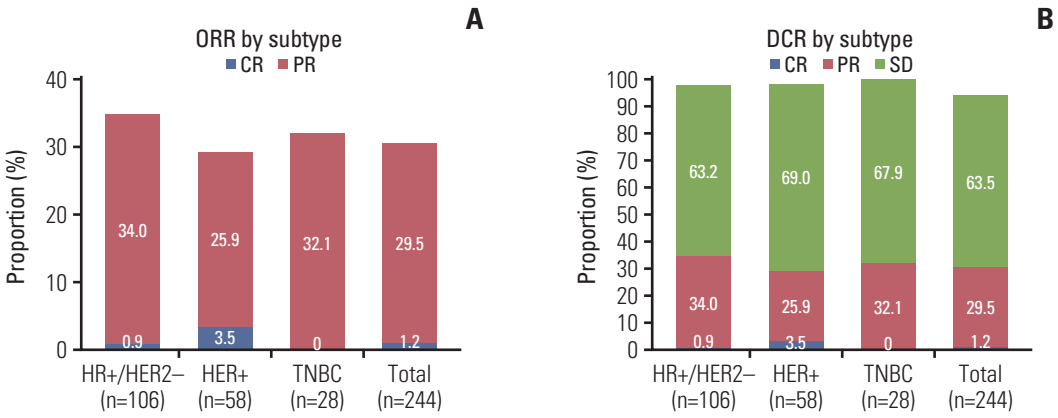


Fig. 3. Eribulin effectiveness: tumor assessment for overall response rate (ORR) by (A) subtype and disease control rate (DCR) by (B) subtype. CR, complete response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PR, partial response; SD, stable disease; TNBC, triple-negative breast cancer.

Table 6. Overview of selected eribulin safety data from pivotal clinical trials and RWE

	Parameter (% of patients)				
	Current Korean PMS (n=1,001)	Study 301 [11] (n=544)	EMBRACE study [10] (n=503)	ESKIMO study [20] (n=101)	RWE [21] (n=272)
TEAEs	66.0	94.1	99.0	NR	NR
Serious TEAEs	24.1	17.5	25.0	19.8	NR
AEs leading to discontinuation	17.0[a)]	7.9	13.0	39.6[b)]	NR
AEs leading to dose reduction	11.0	32.0	29.0	9.9	7.0
AEs leading to death	5.7	4.8	4.0	1.0	NR
Neutropenia, grade 3 or 4	22.0	45.7	45.0	89.1	18.0
Neutropenia, all grades	32.5	54.2	52.0	91.1	31.6
Febrile neutropenia, grade 3 or 4	1.9	2.1	NR	NR	2.9
Febrile neutropenia, all grades	2.3	2.0	5.0	NR	2.9

AEs, adverse events; NR, not reported; PMS, post-marketing surveillance; RWE, real-world evidence; TEAEs, treatment-emergent adverse events. [a)]Dose discontinuation/interruption, [b)]Reported as a dose delay.

higher incidence of neutropenia (> 90%) and this may reflect the large number of patients who were heavily pre-treated; the median number of prior chemotherapeutic regimens was four (range, 2 to 8) and more than 20% of patients were treated with six or more lines of chemotherapeutic regimens [20]. In contrast, the lower occurrence rate of neutropenia in the current PMS study (all grades, 32.5%; grade 3/4, 22.0%) is comparable with that reported in a retrospective, multicenter real-world study in heavily-pretreated patients with metastatic breast cancer in China (all grades, 31.6%; grade 3/4, 18.0%) [21], and may reflect close monitoring of patients and the accumulated experience of clinicians with the use of eribulin.

Peripheral neuropathy is an infrequent but established non-hematological TEAE associated with eribulin. However, peripheral neuropathy in the current study occurred in 2.5% of patients (all grade 1/2) and this incidence is generally similar to that reported in other real-world studies in patients with metastatic breast cancer [21]. Almost all patients enrolled in the current study had previously received taxane-based chemotherapy but no case of grade 3 or higher peripheral neuropathy was observed. The unique mechanism of action of eribulin, which binds to the (+) beta-tubulin ends of microtubules but has no effect on depolymerization [22], may account for the relatively low incidence of peripheral neuropathy compared with taxanes. Eribulin was shown to have a low tendency to induce new-onset peripheral neuropathy or exacerbate preexisting neuropathy compared with

Table 7. Overview of eribulin real-world effectiveness data

Parameter	Current Korean PMS (n=1,001)	Australia [28] (n=266)	China [21] (n=272)	USA [29] (n=513)	China [30] (n=118[a])
Eribulin treatment line	3rd- or 4th-line use at eribulin initiation	3rd- or 4th-line use (54.4% of patients)	5th line Median number of lines of prior chemotherapy was 4 (range, 1 to 10)	3rd-line therapy (78.0% of patients)	3rd-line or later (78.0% of patients)
Median PFS/TTF	TTF: 3 mo (3.7 mo HR+)	NR	PFS 4.1 mo	PFS 6.1 mo	PFS 4.2 mo (eribulin monotherapy 3.4 mo)
Median OS	NR	8.8 (≤ 3rd line); 8.0 (> 3rd line)	NR	10.6 mo	NR
ORR (%)	31.7	NR	17.6	54.4	13.6

HR, hormone receptor; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMS, post-marketing surveillance; TTF, time to treatment failure. [a]Eribulin monotherapy (n=54); eribulin combination therapy (n=64).

taxanes in *in vivo* studies [23,24] and in a randomized phase II study [25].

The administration of chemotherapy carries safety concerns such as accidental extravasation for patients and clinicians. As eribulin is classified as neutral, no extravasation necrosis was observed in our study and only one case out of 1,318 patients experienced extravasation in clinical trials [26]. Despite being administered as an injection, eribulin is not associated with extravasation necrosis unlike anthracyclines, taxanes, and vinca alkaloids (a common and severe adverse event (AE) associated with vinorelbine [27]).

The effectiveness of eribulin in this real-world study aligns with data from previous real-world clinical trials given the between-study differences in reporting outcomes (Table 7). In the EAS, the disease control rate was 95.6% at the time of the 3-month analysis. At 1-year follow-up, 60.8% of patients were alive and 4.7% were still receiving eribulin.

One of the strengths of the current PMS study is that the prospective study design focused on capturing unexpected AEs in real-world clinical practice; this represents a point of difference compared with the majority of other real-world studies of eribulin which were generally retrospective effectiveness analyses. However, in keeping with the design of PMS studies, the key limitations of this analysis stem from voluntary reporting on the case-file records and potentially missing information. These limitations should be considered when interpreting the results. For example, data relating to the status of each patient (e.g., Eastern Cooperative Oncology Group Performance Status, metastatic site) were not collected at the time of eribulin administration. However, the condition of patients in the current study can be inferred from the number of lines of prior chemotherapy and disease duration. There was also a lack of follow-up on effectiveness and, since there are no OS and progression-free survival data, TTF was used as a measure of effectiveness. In addition, there was a large proportion of cases where the breast cancer subtype was reported as 'unknown', reflecting the optional nature of collecting breast cancer subgroup data. Finally, the impact of recently emerging drugs (e.g., CDK4/6 inhibitors, immunotherapy; T-DM1 for HER2+ patients) was not able to be assessed as those drugs were not prescribed during the period covered by the PMS study.

In conclusion, this large real-world analysis reinforced the effectiveness of eribulin and evaluated the safety of eribulin in more than 1,000 patients with metastatic breast cancer, with no new safety concerns relative to safety information from prior studies, and approvals in South Korea and other countries. As shown previously, the most common TEAE was neutropenia. In accordance with the labelled prescribing information, TEAEs were manageable with modification of eribulin treatment.

Ethical Statement

This prospective, multicenter, PMS study of eribulin (Halaven; Eisai Korea Inc., Republic of Korea) in patients with advanced or metastatic breast cancer previously treated with anthracyclines and taxanes, was conducted in South Korea as part of pharmacovigilance activities, as required by the MFDS, including informed consent and institutional review board approval. This study conformed to the provisions of the Declaration of Helsinki and the Pharmaceutical Affairs Law and ministerial ordinance on Good Post-Marketing Study Practice in Korea (the latest Standard for Re-examination of New Drugs).

Author Contributions

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Collected the data: Chae YS, Kwon KA, Lee MH, Ahn MS, Lee KH, Koh SJ, Sohn J, Park KU, Kim MY, Pyo Y, Kim BY, Jung KH.
Contributed data or analysis tools: Chae YS, Kwon KA, Lee MH, Ahn MS, Lee KH, Koh SJ, Sohn J, Park KU, Kim MY, Pyo Y, Kim BY, Jung KH.
Performed the analysis: Chae YS, Kwon KA, Lee MH, Ahn MS, Lee KH, Koh SJ, Sohn J, Park KU, Kim MY, Pyo Y, Kim BY, Jung KH.
Wrote the paper: Chae YS, Kwon KA, Lee MH, Ahn MS, Lee KH, Koh SJ, Sohn J, Park KU, Kim MY, Pyo Y, Kim BY, Jung KH.

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