


# Prognostic and predictive factors of eribulin in patients with heavily pre-treated metastatic breast cancer

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## Abstract

A predictive marker for efficacy of eribulin administered as different lines of treatment in metastatic breast cancer (MBC) has not been identified. We aimed to determine the predictive factors for efficacy of eribulin administered as different lines of treatment in MBC patients.

This retrospective cohort study included 49 heavily pre-treated MBC patients who received either eribulin monotherapy or combination therapy with eribulin and anti-Her2 therapy. Associations between clinical response of eribulin-based treatment, time-to-treatment failure (TTF), and possible predictive markers were investigated.

Patients' median age was 55 years; 65% were ER+; 43% were HER2+; and 16% were triple-negative. Median TTF was 5.23 months and longer in non-visceral metastases patients. Eastern Cooperative Oncology Group (ECOG) status was 0–1; eribulin as ≥2nd-line treatment; eribulin combined with dual blockades; lymphocyte-monocyte ratio (LMR) ≥3; and monocyte-lymphocyte ratio (MLR) <0.4. In patients with eribulin as >3rd-line treatment, univariate analysis showed that ECOG status was 0–1, and LMR ≥3 and MLR <0.4 were associated with a low risk of TTF. Multivariate analysis showed that ECOG status 0–1 was an independent protective factor. Leukopenia and neutropenia were the most common manageable adverse events.

ECOG status is an independent predictor for TTF, while LMR and MLR may have an interactive effect with other biomarkers (e.g., ECOG status) to predict response in MBC patients receiving eribulin as ≥2nd-line treatment.

**Abbreviations:** ALC = absolute lymphocyte count, BC = breast cancer, CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HER-2 = human epidermal growth factor receptor 2, LMR = lymphocyte-monocyte ratio, MBC = metastatic breast cancer, MLR = monocyte-lymphocyte ratio, NLR = neutrophil-lymphocyte ratio, OS = overall survival, PLR = platelet-lymphocyte ratio, TNBC = triple-negative breast cancer, TTF = time-to-treatment failure.

**Keywords:** Eastern Cooperative Oncology Group performance status, eribulin, lymphocyte-monocyte ratio, metastatic breast cancer, time-to-treatment failure

Editor: Nilesch Talele.

The authors have no funding and conflicts of interest to disclose.

This study was approved by the Institutional Review Board of the Taiching Tzu-Chi Hospital, Taiwan (No. REC108-27), which waived the need for patient informed consent because the study classified as retrospective study with expedited review.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Chen PH, Yeh DC, Tung HH, Lin CY. Prognostic and predictive factors of eribulin in patients with heavily pre-treated metastatic breast cancer. *Medicine* 2021;100:47(e27859).

Received: 6 June 2021 / Received in final form: 22 September 2021 / Accepted: 3 November 2021

<http://dx.doi.org/10.1097/MD.0000000000027859>

## 1. Introduction

Approximately half a million people worldwide die from metastatic breast cancer (MBC),<sup>[1]</sup> for which the 5-year survival rate is about 27%.<sup>[2]</sup> Although the survival rate for patients with MBC has reportedly been improving,<sup>[3]</sup> the disease is generally considered to be incurable.<sup>[4,5]</sup> The treatment goal for MBC focuses on prolonging survival and maintaining quality of life by controlling symptoms and minimizing toxicity of treatment.<sup>[6]</sup> Many therapeutic agents have been approved for treatment of breast cancer (BC) in the past 10 years in most developed countries, of which most are targeted agents (e.g., pertuzumab, ado-trastuzumab emtansine, everolimus, bevacizumab, abemaciclib, palbociclib, ribociclib, tucatinib, fam-trastuzumab deruxcan-nxki), and 3 are chemotherapy agents (i.e., eribulin mesylate, ixabepilone, and nab-paclitaxel).<sup>[7]</sup> Most of the new agents are used for the treatment of HER2+ BC, which constitutes about 30% to 35% of all cases of MBC.<sup>[8]</sup> Modest improvements in outcomes have been noted in HR+ MBC, whereas little or no progress has been made in the treatment of triple-negative breast cancer (TNBC).<sup>[9–11]</sup>

The National Comprehensive Cancer Network clinical practice guidelines suggest several preferred chemotherapy regimens, including taxanes (paclitaxel), anthracyclines (doxorubicin and liposomal doxorubicin), antimetabolites (capecitabine and gemcitabine), microtubule inhibitors (eribulin and vinorelbine), and platinum agents.<sup>[6]</sup> Among these, taxanes and anthracyclines are commonly used as first line treatment in neoadjuvant management for early BC<sup>[12]</sup> as well as for advanced BC or MBC.<sup>[5]</sup> However,

chemoresistance is also found commonly in these regimens.<sup>[5,13]</sup> Therefore, novel agents with reduced susceptibility to resistance, higher efficacy and lower toxicities are needed. The agents used for treatment of MBC in patients previously treated with anthracyclines and taxanes include eribulin, ixabepilone, and capecitabine.<sup>[14]</sup> The European Society for Medical Oncology 4<sup>th</sup> international consensus guidelines for advanced BC also suggest that eribulin is one of the preferred choices for patients pre-treated with an anthracycline and a taxane.<sup>[15]</sup>

Eribulin mesylate is a synthetic macrocyclic ketone analog of marine halichondrin B and is a non-taxane microtubule dynamic inhibitor, which induces an irreversible mitotic block at G2-M phases, resulting in apoptosis of cancer cells.<sup>[16–19]</sup> Eribulin was approved by the Food and Drug Administration in the USA in 2010 and in Europe in 2011 for the treatment of MBC previously treated with anthracyclines and taxanes.<sup>[17]</sup> The EMBRACE phase III trial demonstrated a dramatically improved overall survival (OS) in 762 patients with heavily pre-treated MBC, reporting a 19% statistically significant risk reduction (hazard ratio, 0.81, 95% confidence interval [CI], 0.66–0.99;  $P = .041$ ) and manageable toxicity with eribulin treatment compared with physician's choice treatment.<sup>[16]</sup> In a second randomized phase III trial 301, the OS of the eribulin-treated MBC patients was marginally better than in capecitabine-treated patients.<sup>[18]</sup> However, no statistically significant differences were seen in the progression-free survival of the 2 above-mentioned phase III randomized studies (EMBRACE and 301 trials), a pooled analysis from these studies found that eribulin improved OS in MBC patients whose disease had progressed after treatment with at least 2 chemotherapy lines, including anthracyclines and taxanes, in either an adjuvant or metastatic setting.<sup>[16,18,19]</sup> Thus, eribulin may be a useful treatment for patients who have chemotherapy-resistant MBC.

Traditional prognostic factors in BC patients are tumor size, lymph node status, histological grade, hormone receptor status, vascular invasion, human epidermal growth factor receptor 2 (HER-2) overexpression, and age.<sup>[20]</sup> Although many treatment options are available for MBC, physicians often encounter difficulties in choosing the most appropriate treatment because MBC patients respond differently to the same treatments.<sup>[4]</sup> Therefore, effective and readily available predictive markers are urgently needed for the evaluation of therapeutic outcome for MBC.

Previous studies have reported correlations between systemic immunity markers, including neutrophil-lymphocyte ratio (NLR), absolute lymphocyte count (ALC), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR), and lymphocyte-monocyte ratio (LMR) and survival outcomes of patients with BC or MBC.<sup>[21–25]</sup> For MBC patients treated with eribulin, most studies have focused on ALC,<sup>[26,27]</sup> NLR,<sup>[4,28,29]</sup> or both,<sup>[25]</sup> and study results demonstrate that high ALC at baseline is associated with longer survival,<sup>[25,26]</sup> whereas low NLR at baseline is associated with better clinical outcomes.<sup>[4,29]</sup>

However, among all clinical trials that evaluated eribulin in patients previously treated with chemotherapy, none has specifically assessed whether the biomarkers mentioned above can predict the efficacy of eribulin treatment or the prognosis of eribulin-treated MBC patients who have chemoresistant disease. Therefore, this retrospective study sought to find cutoff levels and evaluate the prognostic value of these biomarkers (NLR, ALC, PLR, LMR, & MLR) for therapeutic efficacy of eribulin treatment in MBC patients. The aim of the present study was

to evaluate the efficacy and clinical utility of knowing the immunological status in eribulin-treated MBC patients in a single institution in Taiwan.

## 2. Methods

### 2.1. Study design

In this retrospective cohort study, the demographic, clinical, and laboratory results of 49 patients with MBC who received either eribulin monotherapy or combination therapy with eribulin and anti-HER-2 therapy (trastuzumab or dual blockade) at the Breast Medical Center of Taichung Tzu-Chi Hospital from January 2015 to September 2019. Patient data were collected and their electronic medical records reviewed retrospectively. Included patients had pathologically confirmed locally advanced BC or MBC and had been treated with an anthracycline or taxane regimen before eribulin therapy. Patients with severe comorbidities and/or who had received eribulin only once were excluded. The Eastern Cooperative Oncology Group (ECOG) status and tumor characteristics, including estrogen receptor, progesterone receptor, HER-2, Ki-67, and molecular subtypes (luminal A, luminal B, HER-2 enriched, and TNBC) were recorded. The line of treatment before eribulin was determined. Metastatic sites, including lymph nodes and distant organs, also were recorded and analyzed.

### 2.2. Ethical considerations

The protocol for this study was approved by the Institutional Review Board of the Taichung Tzu-Chi Hospital, Taiwan (No. REC108-27). Since all patient data were deidentified and analyzed retrospectively, patients' informed consent to participate was waived.

### 2.3. Treatment procedures

The treatment consisted of either eribulin monotherapy (over 2–5 minutes) or combination therapy with eribulin and anti-HER-2 therapy (trastuzumab or dual blockade [trastuzumab combined with pertuzumab]), which was administered intravenously at a dose of 1.4 mg/m<sup>2</sup> on days 1 and 8 of a 21-day cycle. Treatment was continued until disease progression, unacceptable toxicity, and patient's or physician's request mandating discontinuation of the drug. Seventeen patients (35%) received treatment with granulocyte colony stimulating factor for chemotherapy-induced neutropenia.

### 2.4. Outcome measures

The primary outcome was the time-to-treatment failure (TTF). TTF was defined as the time from administration of the first eribulin dose until the date of treatment cessation for any reason (including death, disease progression, adverse events, or patient's request).<sup>[30]</sup> The secondary outcome measures were the safety of eribulin and the possible predictive biomarker status of eribulin for MBC. Adverse events were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.<sup>[31]</sup> The ALC, NLR, PLR, MLR, and LMR biomarkers were calculated from patients' baseline laboratory data obtained on the day of or before the day of first eribulin administration. Significant cutoff values of these prognostic factors were found using various cutoff values for further analysis.

**Table 1**  
**Baseline demographic and clinical characteristics of included patients (n=49).**

Characteristics	n (%) or median (range)
Age	55 (33–78)
ECOG status	
G0-G1	42 (86)
G2-G3	7 (14)
Estrogen-receptor status	
Positive	32 (65)
Negative	17 (35)
Progesterone-receptor status	
Positive	12 (24)
Negative	37 (76)
HER2 status	
Positive	21 (43)
Negative	28 (57)
Molecular subtype	
Luminal A	19 (38.77)
Luminal B	12 (24.48)
Her-2 enriched	10 (20.40)
Triple-negative breast cancer	8 (16.32)
Lines of therapy before eribulin	
≤2	10 (20.40)
≥3	39 (79.59)
Most common metastatic sites	
Bone	35 (71.42)
Liver	27 (55.10)
Nodes	23 (46.93)
Lung	19 (38.77)
Pleural effusion	19 (38.77)
Brain	6 (12.24)
Others	5 (10.20)
Number of organs involved	
≤2	25 (51.02)
≥3	24 (48.97)

ECOG = Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2.

**2.5. Statistical analysis**

A retrospective review of clinical and treatment data of all included patients was carried out, and data were entered into a database for further analysis. Patients’ characteristics and clinical

pathological features of tumors, treatment duration, tumor response, and other categorical variables are summarized as number (%), and age is presented as median (range). Median OS (95% CI) for 17 patients and median TTF (95% CI) for all patients were estimated in months were estimated using the Kaplan-Meier method. Associations between ALC, PLR, NLR, LMR, and MLR and survival outcomes and TTF were evaluated using the Kaplan-Meier method plus log-rank test, which are presented as median, 95% CI, and P values. The Cox proportional hazard model was used for univariate and multivariate regression analysis of the relationship between TTF and clinicopathological factors. Statistical assessments were 2-tailed, and P < .05 was considered statistically significant. All statistical analyses were carried out using IBM SPSS statistical software version 24 for Windows (IBM Corp., Armonk, NY).

**3. Results**

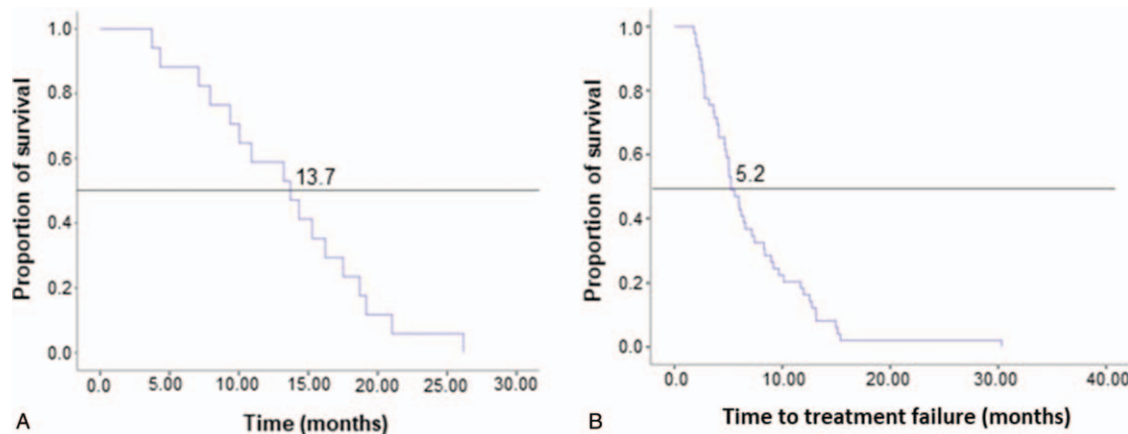
**3.1. Patients’ characteristics**

The patients’ demographic and tumor baseline characteristics are presented in Table 1. Thirty-nine (80%) patients received 3 or more conventional chemotherapy regimens before eribulin treatment, and 10 (20%) patients received eribulin as a 1st- or 2nd-line treatment. Nearly half of the patients (n=24, 49%) had more than 2 sites of metastatic organ involvement.

**3.2. Efficacy of eribulin treatment**

As of September 2019, only 17 (34%) of the included patients had died, so the median OS of the entire 49 patients could not be calculated; the 2-year OS rate of the 17 patients who had died was 66%, and the median OS was 13.7 (9.08–18.3) months (Fig. 1A). The median TTF of the 49 patients was 5.2 (3.9–6.5) months (Fig. 1B).

All 49 patients enrolled in the study were evaluated for efficacy of eribulin treatment. TTF was significantly longer for non-visceral metastases than for the visceral metastases subgroups (11.97 vs 5.23 months [P=.028], Table 2 and Fig. 2B). In other subgroups, TTF was significantly longer in patients with ECOG status <2 vs >2; eribulin as ≥2nd-line treatment; eribulin combined with dual blockades; LMR ≥3; and MLR <0.4 (all



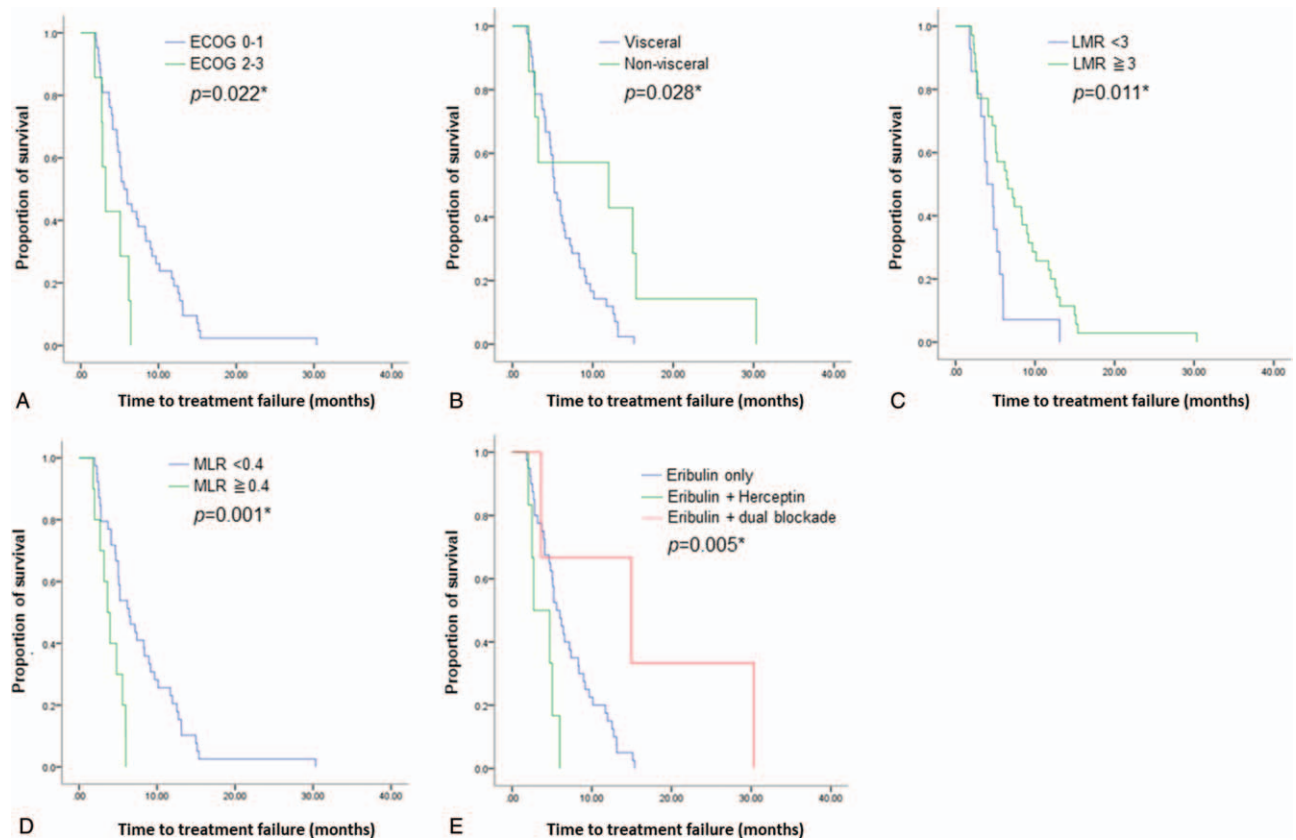
**Figure 1.** Kaplan-Meier curves for overall survival and time-to-treatment failure of metastatic breast cancer patient who had received eribulin treatment. (A) Overall survival (n=17). (B) Time-to-treatment failure (n=49).

**Table 2****Associations between patients' characteristics and time-to-treatment failure in metastatic breast cancer patients (n = 49) treated with eribulin.**

	Patients n (%)	TTF (median months)	95% CI	P value
Age				.446
<60	35 (71)	5.23	4.340–6.120	
≥60	14 (29)	7.40	1.276–13.524	
Hormone receptor				.282
Estrogen-receptor status				
Negative	16 (33)	5.03	4.388–5.672	
Positive	33 (67)	5.97	4.732–7.208	
Progesterone-receptor status				.337
Negative	37 (76)	5.07	4.033–6.107	
Positive	12 (24)	6.17	0.000–12.858	
HER2 status				.571
Negative	33 (67)	5.23	3.289–7.171	
Positive	16 (33)	5.23	2.937–7.523	
Sites of metastases				.590
Bone	35 (71)	5.03	4.337–5.723	
Liver	27 (55)	5.97	4.736–7.204	
Nodes	23 (47)	5.57	3.441–7.699	
Lung	19 (39)	6.43	4.525–8.335	
Pleural effusion	19 (39)	5.03	2.854–7.206	
Brain	6 (12)	3.97	1.209–6.731	
Number of metastatic sites				.563
1	5 (10)	7.17	0.000–15.694	
2	20 (41)	5.23	3.543–6.917	
3–4	20 (41)	5.03	4.489–5.571	
≥5	4 (8)	6.57	0.033–13.107	
Pattern of disease				.028*
Visceral	42 (86)	5.23	4.170–6.290	
Non-visceral	7 (14)	11.97	0.000–34.476	
ECOG status				.022*
0–1	42 (86)	5.57	3.940–7.200	
2–3	7 (14)	3.20	2.174–4.226	
Lines of therapy before eribulin				.028*
1	4 (8)	2.80	1.526–4.074	
2	6 (12)	5.57	3.242–7.898	
3	4 (8)	4.10	1.395–6.805	
4	15 (30)	5.97	4.253–7.687	
≥5	20 (41)	6.00	3.940–8.060	
Treatment regimen				.005*
Eribulin only	40 (82)	5.57	4.206–6.934	
Eribulin + herceptin	6 (12)	2.70	0.059–5.341	
Eribulin + dual blockade	3 (6)	14.97	0.000–33.118	
Inflammatory biomarkers				.055
Absolute lymphocyte count				
<1500	36 (73)	5.0	4.408–5.562	
≥1500 Platelet-lymphocyte ratio	13 (27)	9.17	2.676–15.664	.105
<185	22 (45)	7.40	4.182–10.618	
≥185	27 (55)	4.63	3.701–5.559	
Neutrophil-lymphocyte ratio				0.055
<3	29 (59)	7.17	3.882–10.458	
≥3	20 (41)	3.97	3.386–4.554	.011*
Lymphocyte-monocyte ratio				.001*
<3	14 (29)	3.97	2.137–5.803	
≥3	36 (73)	6.57	4.055–9.085	
Monocyte-lymphocyte ratio				
<0.4	39 (80)	6.43	4.289–8.571	
≥0.4	10 (20)	3.63	2.437–4.823	

CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HER2 = human epidermal growth factor receptor 2, TTF = time-to-treatment failure.

\*  $P < .05$ .



**Figure 2.** Kaplan-Meier curves for time-to-treatment failure in the entire cohort ( $n=49$ ). (A) ECOG 0–1 vs ECOG 2–3; (B) visceral vs non-visceral metastasis; (C) LMR  $<3$  vs LMR  $\geq 3$ ; (D) MLR  $<0.4$  vs MLR  $\geq 0.4$ ; (E) eribulin only vs eribulin + herceptin vs eribulin + dual blockade.  $P < .05$ . ECOG = Eastern Cooperative Oncology Group, LMR = lymphocyte-monocyte ratio, MLR = monocyte-lymphocyte ratio.

$P < .05$ ) (Table 2 and Fig. 2A, C, D, and E). No significant differences were found in TTF according to age, hormone receptor expression (estrogen receptor, progesterone receptor, and HER-2) sites, and number of metastatic organs, ALC, PLR, and NLR between patients treated with eribulin and those who were not (all  $P > .05$ , Table 2).

Univariate Cox regression analysis revealed that patients with non-visceral metastasis; ECOG status  $<2$ ; eribulin as  $\geq 2$ nd-line treatment; eribulin combined with dual blockades; LMR  $\geq 3$ ; or MLR  $<0.4$  had a lower risk of treatment failure than did patients with visceral metastases; ECOG status  $\geq 2$ ; eribulin as a  $\leq 2$ nd-line treatment; eribulin without combined dual blockade; LMR  $<3$ ; and MLR  $\geq 0.4$  (all  $P < .05$ , Table 3). Multivariate Cox regression analysis revealed that ECOG status  $<2$  and eribulin as  $\geq 2$ nd-line treatment were independent protective factors for TTF (all  $P < .05$ , Table 3).

After stratifying by line of therapy before eribulin treatment ( $<3$ rd- and  $\geq 3$ rd-line treatment), univariate Cox regression analysis of patients' characteristics vs TTF revealed no associations between TTF and the numerous characteristics of patients treated with eribulin as  $\leq 3$ rd-line treatment (Table 4). In patients treated with eribulin as  $>3$ rd-line treatment, univariate analysis revealed that ECOG status  $<2$ , LMR  $\geq 3$ , and MLR  $<0.4$  were associated with a lower risk of treatment failure than in patients with ECOG status  $\geq 2$ ; LMR  $<3$ ; and MLR  $\geq 0.4$  (all  $P < .05$ ). However, multivariate analysis revealed that only ECOG status  $<2$  was an independent protective factor for

treatment failure (all  $P < .05$ , Table 5). Similar observations were found in these patients after stratifying by line of therapy before eribulin treatment ( $<2$ nd- and  $\geq 2$ nd-line treatment) (Table S1, S2, Supplemental Digital Content, <http://links.lww.com/MD/G490>).

### 3.3. Safety of eribulin treatment

Hematological and non-hematological toxicities are reported in Table 6. Grade 3 or 4 leukopenia ( $n=15$ , 30%) and neutropenia ( $n=24$ , 48%) were the major hematological adverse events. The most common non-hematological adverse events (grade 1 or 2) were alopecia ( $n=23$ , 47%), mucositis ( $n=11$ , 22%), hand-foot syndrome ( $n=10$ , 20%), and peripheral neuropathy ( $n=6$ , 12%). None of the patients experienced nausea. Seventeen (35%) patients received treatment with granulocyte colony stimulating factor for chemotherapy-induced neutropenia.

## 4. Discussion

The present study is the first to report the efficacy and safety of eribulin administered as various lines of treatment and the possible predictive factors of survival outcomes of heavily pre-treated MBC patients in a real-world setting with an unselected population. The median TTF was 5.23 months. Patients with non-visceral metastasis, ECOG status  $<2$ , eribulin as  $\geq 2$ nd-line treatment, eribulin combined with dual blockades, LMR  $\geq 3$ , or

**Table 3**  
Cox regression analysis of associations between TTF and characteristics of metastatic breast cancer patients (n=49) treated with eribulin.

	HR	95% CI	P value
<i>Univariate analysis</i>			
Age			
<60	Reference		
≥60	0.784	0.418–1.470	.448
Hormone receptor status			
Estrogen receptor			
Negative	Reference		
Positive	0.941	0.518–1.711	.842
Progesterone receptor			
Negative	Reference		
Positive	0.715	0.367–1.392	.324
HER2 status			
Negative	Reference		
Positive	1.191	0.649–2.185	.572
Sites of metastases			
Bone			
Bone	Reference		
Liver	1.019	0.614–1.692	.941
Nodes	0.876	0.517–1.483	.621
Lung	1.001	0.569–1.761	.996
Pleural effusion	1.422	0.803–2.516	.227
Brain	1.587	0.659–3.821	.303
Number of metastatic sites			
1	Reference		
2	1.113	0.410–3.019	.834
3–4	1.643	0.593–4.551	.340
5	1.137	0.296–4.636	.852
Pattern of disease			
Visceral			
Visceral	Reference		
Non-visceral	0.346	0.130–0.921	.034*
ECOG status			
0–1	Reference		
2–3	2.596	1.109–6.082	.028*
Lines of therapy before eribulin			
1	Reference		
2	0.167	0.042–0.671	.012*
3	0.340	0.079–1.467	.148
4	0.200	0.059–0.683	.010*
≥5	0.176	0.052–0.594	.005*
Treatment regimen			
Eribulin only	Reference		
Eribulin + herceptin	3.034	1.212–7.595	.018*
Eribulin + dual blockade	0.264	0.062–1.132	.073
Inflammatory biomarkers			
Absolute lymphocyte count			
<1500	Reference		
≥1500	1.882	0.977–3.628	.059
Platelet-lymphocyte ratio			
<185	Reference		
≥185	0.623	0.349–1.112	.109
Neutrophil-lymphocyte ratio			
<3	Reference		
≥3	1.770	0.978–3.203	.059
Lymphocyte-monocyte ratio			
<3	Reference		
≥3	0.437	0.225–0.845	.014*
Monocyte-lymphocyte ratio			
<0.4	Reference		
≥0.4	3.338	1.526–7.301	.003*
<i>Multivariate analysis</i>			
Pattern of disease			

(continued)

**Table 3**  
(continued).

	HR	95% CI	P value
Visceral			
Visceral	Reference		
Non-visceral	0.627	0.203–1.939	.418
ECOG status			
0–1	Reference		
2–3	4.409	1.717–11.322	.002*
Lines of therapy before eribulin			
1	Reference		
2	0.129	0.024–0.677	.015*
3	0.385	0.074–2.002	.256
4	0.135	0.032–0.577	.007*
≥5	0.140	0.035–0.560	.005*
Treatment regimen			
Eribulin only	Reference		
Eribulin + herceptin	3.365	1.171–9.672	.024*
Eribulin + dual blockade	0.294	0.058–1.487	.139
Lymphocyte-monocyte ratio			
<3	Reference		
≥3	0.763	0.249–2.342	.636
Monocyte-lymphocyte ratio			
<0.4	Reference		
≥0.4	2.125	0.579–7.800	.256

CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, TTF = time-to-treatment failure.

\* $P < .05$ .

MLR  $< 0.4$  had a longer median TTF. In particular, ECOG status  $< 2$  and eribulin as  $\geq 2$ nd-line treatment were independent predictive factors for the efficacy of eribulin treatment. After stratifying by line of therapy before eribulin treatment ( $> 2$ nd or  $> 3$ rd-line treatment), ECOG status  $< 2$  was also an independent predictive factor for the efficacy of eribulin treatment in patients with eribulin as  $> 2$ nd-line treatment but not in patients with eribulin as  $\leq 2$ nd-line treatment. In regression analysis, univariate analysis but not multivariate analysis found that LMR and MLR were associated with the efficacy of eribulin treatment in patients with eribulin as  $> 2$ nd-line treatment but not in patients with eribulin as  $\leq 2$ nd-line treatment.

Patients treated in clinical trials with favorable features often do not represent the general population treated in routine practice, so the present study compared the results of 2 phase III trials<sup>[16,18]</sup> with real-world results in an unselected population. The median age of patients at the initiation of eribulin treatment was 55 years, which was similar to that in 2 phase III trials<sup>[16,18]</sup> and 1 retrospective study.<sup>[32]</sup> The proportion of metastatic organs in these patients was also similar to the characteristics in previously published studies, including that bone, liver, lymph nodes, and lung were the most common 4 metastatic organs in these studies, as in the present study.<sup>[16,32–34]</sup> Specifically, in previous studies, the 1-year survival rate was 58.2%<sup>[34]</sup> and 64.4%,<sup>[18]</sup> respectively; the 2-year survival rate was 65.5% in the present study compared with 58.0%,<sup>[18]</sup> 35.9%,<sup>[34]</sup> and 57.2%.<sup>[30]</sup> Median TTF was longer in the present study (5.23 months) than in previous real-world studies, as follows: a multicenter study conducted in Taiwan, in which TTF was 3.91 months<sup>[30]</sup>; a phase II study conducted in Japan, in which TTF was 4.2 months<sup>[16]</sup>; and a phase III study conducted in Spain, in which TTF was 4.2 months.<sup>[16]</sup> Median OS also was slightly longer in the present study (13.7 months) compared with

**Table 4**

**Univariate Cox regression analysis of associations between TTF and characteristics of metastatic breast cancer patients receiving eribulin as  $\leq$ 3rd line treatment (n = 14).**

	HR	95% CI	P value
Age			
<60	Reference		
$\geq$ 60	0.462	0.122–1.741	.254
Hormone receptor			
Estrogen receptor status			
Negative	Reference		
Positive	2.111	0.661–6.740	.207
Progesterone receptor status			
Negative	Reference		
Positive	0.670	0.084–5.338	.705
HER2 status			
Negative	Reference		
Positive	0.946	0.253–3.538	.934
Number of metastatic sites			
1	Reference		
2	2.871	0.328–25.098	.340
3–4	8.436	0.760–93.691	.083
5	1.582	0.134–18.723	.716
Pattern of disease			
Visceral	Reference		
Non-visceral	0.030	0.000–18.424	.285
ECOG status			
0–1	Reference		
2–3	5.981	0.542–66.047	.144
Inflammatory biomarkers			
Absolute lymphocyte count			
<1500	Reference		
$\geq$ 1500	1.261	0.377–4.220	.707
Platelet-lymphocyte ratio			
<185	Reference		
$\geq$ 185	6.259	0.771–50.482	.086
Neutrophil-lymphocyte ratio			
<3	Reference		
$\geq$ 3	3.420	0.963–12.142	.057
Lymphocyte-monocyte ratio			
<3	Reference		
$\geq$ 3	0.624	0.159–2.448	.499
Monocyte-lymphocyte ratio			
<0.4	Reference		
$\geq$ 0.4	1.603	0.409–6.290	.499

CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, TTF = time-to-treatment failure.

13.1 months in the phase III study<sup>[16]</sup> and less than in the other phase III study (15.9 months),<sup>[19]</sup> probably due to the unselected population in the present study in contrast to selected populations in the randomized trials. This favorable prognostic value may help to explain slightly better TTF results and survival rates in the present retrospective study.

A meta-analysis demonstrated that ECOG status is a significant prognostic factor for metastatic renal cell carcinoma patients.<sup>[35]</sup> Another phase 1 study showed that ECOG status is a potential predictive clinical factor of reduced atezolizumab clinical activity in metastatic TNBC.<sup>[36]</sup> A retrospective study conducted in Italy also confirmed that ECOG status is a predictive factor of eribulin activity in MBC patients.<sup>[28]</sup> Other previous studies have also demonstrated the activity of eribulin across the geographical regions investigated.<sup>[16,33,37]</sup> Differences

**Table 5**

**Cox regression analysis of the association of TTF with characteristics of metastatic breast cancer patients treated with eribulin as  $>$ 3rd line treatment (n = 35).**

	HR	95% CI	P
<i>Univariate analysis</i>			
Age			
<60	1.000		
$\geq$ 60	0.814	0.502–2.407	.814
Hormone receptor expression			
Estrogen receptor status			
Negative	1.000		
Positive	0.774	0.365–1.627	.494
Progesterone receptor status			
Negative	1.000		
Positive	0.608	0.300–1.232	.167
HER2 status			
Negative	1.000		
Positive	1.227	0.610–2.46	.566
Number of metastatic sites			
1	1.000		
2	0.436	0.116–1.638	.219
3–4	0.760	0.217–2.662	.668
5	0.605	0.096–3.815	.593
Pattern of disease			
Visceral	1.000		
Non-visceral	1.848	0.688–4.965	.223
ECOG status			
0–1	1.000		
2–3	2.716	1.048–7.044	.040*
Inflammatory biomarkers			
Absolute lymphocyte counts			
<1500	1.000		
$\geq$ 1500	1.497	0.707–3.170	.292
Platelet-lymphocyte counts			
<185	1.000		
$\geq$ 185	0.934	0.452–1.927	.853
Neutrophil-lymphocyte ratio			
<3	1.000		
$\geq$ 3	1.457	0.720–2.946	.295
Lymphocyte-monocyte ratio			
<3	1.000		
$\geq$ 3	0.390	0.182–0.837	.016*
Monocyte-lymphocyte ratio			
<0.4	1.000	1.609–10.615	.003*
$\geq$ 0.4	4.132		
<i>Multivariate analysis</i>			
ECOG status			
0–1	1.000		
2–3	3.208	1.196–8.605	.021*
Lymphocyte-monocyte ratio			
<3	1.000		
$\geq$ 3	0.541	0.180–1.630	.275
Monocyte-lymphocyte			
<0.4	1.000		
$\geq$ 0.4	2.620	0.700–9.811	.153

CI = confidence interval, ECOG = Eastern Cooperative Oncology Group, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, TTF = time-to-treatment failure.

\*  $P < .05$ .

in efficacy rates between eribulin monotherapy vs treatment of physician's choice may be explained by differences in the type and number of prior chemotherapy regimens received or ECOG performance status at baseline.<sup>[16,33]</sup> Patients' ECOG status of treatment regimens evaluated in each study may differ, which

**Table 6**  
**Toxicity according to National Cancer Institute Common Terminology Criteria Version 5.0.**

Toxicity	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
<b>Hematological</b>			
Neutropenia	33 (67%)	8 (16%)	16 (32%)
Leukopenia	39 (79%)	10 (20%)	5 (10%)
Febrile neutropenia	6 (12%)	–	–
Thrombocytopenia	7 (14%)	3 (6.1%)	–
Anemia	42 (86%)	2 (4%)	–
Transaminitis	24 (48%)	3 (6%)	–
<b>Non-hematological</b>			
Allergy	1 (2%)	–	–
Alopecia	23 (47%)	–	–
Anorexia	2 (4%)	–	–
Fatigue	3 (6%)	–	–
Hand-foot syndrome	10 (20%)	–	–
Mucositis	11 (22%)	–	–
Peripheral neuropathy	6 (12%)	–	–
Nausea	–	–	–
Vomiting	4 (8%)	–	–
Diarrhea	3 (6%)	–	–
Constipation	1 (2%)	–	–
Edema	7 (14%)	–	–

may also contribute to the differences found in efficacy rates between studies. Similarly, the present study demonstrated that the main result from time-to-event analysis was the associations found between TTF and tumor burden and clinical conditions. That is, multivariate Cox regression analysis revealed that ECOG 0–1 was a protective factor for the prediction of TTF in all patients or patients receiving eribulin as >2nd or >3rd line treatment. Even if patients with an ECOG status of 2 or 3 were relatively few in the present study population, these results strengthen the role of these clinical characteristics (e.g., ECOG status) as clinical determinants in real-world decision-making.

Measures of systemic inflammatory response, including NLR, PLR, LMR, and MLR, are found to be independent factors predictive of prognosis,<sup>[21,38–41]</sup> or response to chemotherapy<sup>[22,23,42,43]</sup> in treating various types of malignant tumors, and of the occurrence or prognosis of non-malignant diseases.<sup>[44,45]</sup> Eribulin improves the immune microenvironment by producing an antitumor effect through the epithelial-mesenchymal transition, acting as an inhibiting mechanism and promoting tumor vascular remodeling.<sup>[46,47]</sup> The present study evaluated LMR, which has been reported previously to be associated with prognosis and response to chemotherapeutic agents in BC,<sup>[22,23,43]</sup> but no correlation was found between LMR and survival. However, results of the present study showed further that LMR and MLR were associated with TTF in MBC patients who had received eribulin as >3rd line treatment, but in multivariate analysis, no correlation was found between LMR and TTF. These results suggest that LMR and MLR have an interactive effect with other biomarkers (e.g., ECOG status) to predict the response of eribulin administered as various lines of treatment.

Consistent with the results of previous studies, the present study found that neutropenia and leukopenia were the most common adverse events associated with eribulin use.<sup>[18,33,43,48]</sup> Another retrospective study conducted in Taiwan found similar results.<sup>[30]</sup> The incidence of hematologic and grade 3 or 4

adverse events was like that in other studies,<sup>[16,18]</sup> except that the total incidence of febrile neutropenia (grade 3 or 4) with eribulin was lower in the present study (0%) than that reported by Cortes et al<sup>[16]</sup> (5%), in which patients had received more prior lines of chemotherapy. The rate of neutropenia in our patients also was much lower than the rate reported for a Korean population<sup>[49]</sup> and for Japanese populations.<sup>[33,48]</sup> Neutropenia in the present study population was managed with dose delays, reductions, and granulocyte colony-stimulating factor according to clinical practice, and no deaths resulted from neutropenia.

Although further studies are needed to identify the molecular, genetic, environmental, and socioeconomic factors accounting for the slightly better efficacy and tolerance of eribulin in our patients than in previously reported studies, this may be because the National Health Insurance System of Taiwan requires certification of the quality of care in all hospitals. This policy may have contributed to the improved care and survival of the cancer patients reported herein.<sup>[50]</sup> Fewer and less severe adverse events occurred in patients in the present study, which may be a result of 2 mg being the highest dosage for each single injection, a decision made to control costs.

We acknowledge that the present study has several limitations, including the retrospective study design, which may have led to confounding errors or bias. The present study also had a single treatment arm without comparators, and it was a single-site experience with a moderately sized study population, which may limit generalizations to other locations or populations.

## 5. Conclusions

This study reports real-world experience with unselected patients in an Asian country, enhancing current knowledge of eribulin in the treatment of MBC. Eribulin is shown to be safe and effective for the treatment of Taiwanese women with MBC who had previously received at least 1 chemotherapy regimen in either the adjuvant or the metastatic setting. ECOG status appears to be an independent predictive biomarker for efficacy of eribulin at various lines of treatment, while LMR and MLR may have interactive effects with other biomarkers (e.g., ECOG status) to predict eribulin efficacy when administered as various lines of treatment.

## Author contributions

PHC, HHT, CYL, and DCY contributed to the study design, collecting the patient data, interpretation of the data, and drafting the manuscript. PHC and CYL contributed to the literature review, literature integration, and statistical analysis. HHT supervised all the work. All authors read and approved the final manuscript.

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