

Prediction of Survival after Eribulin Chemotherapy for Breast Cancer by Absolute Lymphocyte Counts and Progression Types

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Research

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Abstract

Background: In the RECIST diagnostic criteria, the concepts of progression by pre-existing disease (PPL) and progression by new metastases (PNM) have been proposed to distinguish between the progression types of cancer refractory to treatment. According to the tumor biology of cancer progression forms, the "PPL" form indicates invasion and the "PNM" form indicates metastasis. On the other hand, recent studies have focused on the clinical importance of inflammatory markers as indicators of the systemic tumor immune response. In particular, absolute lymphocyte counts (ALC) is an indicator of the host's immune response. Thus, we developed a new measure that combined progression form with ALC. In this study, we clinically validated the combined assessment of progression form and ALC in eribulin chemotherapy.

Methods: From August 2011 to April 2019, a total of 486 patients with locally advanced or metastatic breast cancer (MBC) underwent treatment. In this study, only 88 patients who underwent chemotherapy using eribulin were included. The antitumor effect was evaluated based on the RECIST criteria, version 1.1. To measure ALC, peripheral blood samples collected before eribulin treatment were used. The cut-off value for ALC in this study was 1,500 / μ L, based on previous studies.

Results: The PPL group (71 patients, 80.7%) had significantly longer PFS ($p=0.022$, log-rank) and OS ($p<0.001$, log-rank) than the PNM group (17 patients, 19.3%). In the 51 patients with $ALC < 1500/\mu$ L, the PPL group had a significantly better prognosis than the PNM group (PFS: $p=0.035$, OS: $p<0.001$, log-rank, respectively). On the other hand, in the 37 patients with $ALC \geq 1500/\mu$ L, the PPL group had a better OS compared to the PNM group ($p=0.055$, log-rank), but there was no significant difference in PFS between the two groups ($p=0.541$, log-rank). Furthermore, multivariate analysis that validated the effect of OS showed that high ORR and "high-ALC and PPL" were factors for a good prognosis ($p<0.001$, HR=0.321) ($p=0.036$, HR=0.290).

Conclusions: In breast cancer patients with eribulin chemotherapy, good systemic immune status, such as $ALC \geq 1500/\mu$ L, was associated with less progression, particularly metastasis, and better prognosis. Furthermore, the biomarker "high-ALC and PPL" was particularly useful as a prognostic marker following eribulin chemotherapy.

Background

The Response Evaluation Criteria for Solid Tumors (RECIST) plays an important role in determining the response to chemotherapy for solid tumors as well as the treatment strategy [1]. In the RECIST diagnostic criteria, the concepts of progression by pre-existing disease (PPL) and progression by new metastases (PNM) have been proposed to distinguish between the progression types of cancer refractory to treatment [2, 3]. Since both PPL and PNM are evaluated as "progression disease (PD)" by the RECIST diagnostic criteria, the difference in the form of progression has not influenced the choice of treatment. However, according to the tumor biology of cancer progression forms, the "PPL" form indicates invasion and the "PNM" form indicates metastasis. Our previous study showed that patients with PPL who had good tumor immune microenvironment conditions had a good prognosis after eribulin chemotherapy [4].

On the other hand, recent studies have focused on the clinical importance of inflammatory markers as indicators of the systemic tumor immune response [5, 6]. The *in vivo* inflammatory response contributes to cancer progression. The peripheral blood neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR) of cancer patients have been proposed as indicators of the systemic inflammatory

response [7–11]. In addition, several studies have reported that these factors predicted the prognosis of various carcinomas [12–15]. These inflammatory markers reflect a systemic tumor immune response. In particular, absolute lymphocyte counts (ALC) is an indicator of the host's immune response.

In a phase III clinical trial on patients with locally advanced or metastatic breast cancer (MBC), eribulin significantly prolonged the overall survival (OS) (study 305, EMBRACE) [16]. Furthermore, the survival curve showed a characteristic pattern called the delayed separation curve in immunotherapy. Thus, this pattern may reflect the effects of eribulin on tumor immune response. A retrospective analysis of this trial showed that ALC was a useful marker in predicting the therapeutic effect of eribulin chemotherapy [17]. Additionally, real-world data on MBC patients treated with eribulin have reported on NLR, ALC prognosis, and predictors of therapeutic efficacy [18, 19].

We hypothesized that the combination of both the "form of PD" and the "host's immune systemic marker, ALC" was a more sensitive indicator than ALC alone. Thus, we developed a new measure that combined progression form with ALC. In this study, we clinically validated the combined assessment of progression form and ALC in eribulin chemotherapy.

Methods

Patient background

From August 2011 to April 2019, a total of 486 patients with MBC underwent treatment at the Osaka City University Hospital. In this study, only 88 patients who underwent chemotherapy using eribulin were included, and 380 patients who were administered other drug therapies, such as endocrine therapy or other chemotherapy regimens, and 18 patients who dropped out due to surgery or adverse events, were excluded (**Fig. 1**). This dataset was partially used in previous studies [20–22].

The median follow-up time was 478 days (range: 50–2267 days). Based on the efficacy of this regimen, the objective response rate (ORR), OS, and progression-free survival (PFS) were determined. ORR was evaluated by adding complete response (CR) and partial response (PR). OS was defined as the time from the date of treatment initiation to death (daily). PFS was defined as the time from the date of treatment initiation to the date of death or PD confirmation, whichever was earlier (daily). The antitumor effect was evaluated based on the RECIST criteria, version 1.1 [1].

The chemotherapy regimen consisted of one course of treatment for 21 days (three weeks), and eribulin mesylate (1.4 mg/m^2) was intravenously administered on days 1 and 8 [16, 23]. This protocol was followed repeatedly until PD was evaluated or therapy was discontinued due to severe adverse events. Chemotherapy was administered in all cases on an outpatient basis. Hematoxylin and eosin (H.E.) staining was used to identify tumor morphology (histological classification and nuclear grade). In addition, the expression of estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and Ki67 was assessed on immunohistology.

Classification based on progression types

According to RECIST guidelines, PPL is described as an increase by at least 20% in the sum of the diameter of the lesion evaluated, or an absolute increase of 5 mm or more in the sum of the diameter from the lowest sum of the

diameter to date [2, 3]. PNM was defined as a new lesion, indicative of disease progression, identified during a follow-up session. If PPL and PNM were observed simultaneously during the evaluation, it was considered a PNM.

Blood sample analysis

To measure ALC, peripheral blood samples collected before eribulin treatment were used. The percentage of white blood cells was measured using a Coulter LH750 blood analyzer (Beckman Coulter, Brea, CA, USA). The cut-off value for ALC in this study was 1,500 / μ L, based on previous studies [17, 18, 24]. ALC values \geq 1,500 / μ L were considered high, while values below 1,500 / μ L were low.

Statistical Analysis

We used SPSS® Statistics version 25 statistical software (IBM, Armonk, NY, USA) for the statistical analysis. To analyze whether clinical parameters were associated with ALC, the chi-square test or Fisher's exact test was used as appropriate. The association with survival was analyzed using Kaplan-Meier plots and the log-rank test. Cox proportional hazards models were used to calculate univariate and multivariate hazard ratios (HRs) for the study parameters with 95% confidence intervals (CIs). The selection of variables in the multivariate analysis included a backward stepwise method. For all statistical tests, a p-value of less than 0.05 was considered statistically significant.

Ethics statement

This study complies with the provisions of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). This study consisted of a retrospective chart review. While receiving treatment, patients provided written informed consent for the use of patient data in later research studies. This research protocol was approved by the Ethics Committee of Osaka City University (#926).

Results

Differences in progression types and prognostic analysis

Among the 106 MBC patients who received chemotherapy with eribulin, 88 were included in the study, and 18 patients were excluded. Among them, 17 patients (19.3%) were PNM and 71 patients (80.7%) were PPL. The PPL group had significantly longer PFS ($p = 0.022$, log-rank) and OS ($p < 0.001$, log-rank) than the PNM group (Fig. 2).

Absolute lymphocyte counts and differences in progression types

Among the 88 patients, 37 (42.0%) were included in the high-ALC group and 51 (58.0%) were in the low-ALC group. Among the 17 patients in the PNM group, 5 were classified in the high-ALC group (29.4%) and 12 were in the low-ALC group (70.6%). Among the 71 patients in the PPL group, 32 (45.1%) were classified in the high-ALC group and 39 (54.9%) were in the low-ALC group. When the groups were divided based on the difference in ALC, there was no significant difference between the clinicopathological parameter and ALC (Table 1).

Table 1

Correlations between absolute lymphocyte counts and clinicopathological parameters in 88 patients with eribulin chemotherapy for locally advanced or metastatic breast cancer.

Parameters	All breast cancer (n = 88)			Progression due to new metastasis (n = 17)			Progression due to pre-existing lesions (n = 71)		
	High (n = 37)	Low (n = 51)	<i>p</i> - value	High (n = 5)	Low (n = 12)	<i>p</i> - value	High (n = 32)	Low (n = 39)	<i>p</i> - value
Age at chemotherapy									
≤ 63	24 (64.9%)	28 (54.9%)		3 (60.0%)	6 (50.0%)		21 (65.6%)	22 (56.4%)	
> 63	13 (35.1%)	23 (45.1%)	0.348	2 (40.0%)	6 (50.0%)	0.563	11 (34.4%)	17 (43.6%)	0.293
Degree of progress									
Locally advanced	11 (29.7%)	13 (25.5%)		1 (20.0%)	5 (41.7%)		10 (31.3%)	8 (20.5%)	
Visceral metastases	26 (70.3%)	38 (74.5%)	0.659	4 (80.0%)	7 (58.3%)	0.395	22 (68.7%)	31 (79.5%)	0.301
HR (ER and/or PgR) status									
Negative	12 (32.4%)	21 (41.2%)		1 (20.0%)	6 (50.0%)		11 (34.4%)	15 (38.5%)	
Positive	25 (67.6%)	30 (58.8%)	0.403	4 (80.0%)	6 (50.0%)	0.278	21 (65.6%)	24 (61.5%)	0.722
HER2 status									
Negative	33 (89.2%)	47 (92.2%)		5 (100.0%)	12 (100.0%)		28 (87.5%)	35 (89.7%)	
Positive	4 (10.8%)	4 (7.8%)	0.633	0 (0.0%)	0 (0.0%)	-	4 (12.5%)	4 (10.3%)	0.527
Ki67									
Low	21 (56.8%)	30 (58.8%)		2 (40.0%)	4 (33.3%)		19 (59.4%)	26 (66.7%)	
High	16 (43.2%)	21 (41.2%)	0.846	3 (60.0%)	8 (66.7%)	0.605	13 (40.6%)	13 (33.3%)	0.526
Nuclear grade									
1, 2	24 (64.9%)	38 (74.5%)		3 (60.0%)	8 (66.7%)		21 (65.6%)	30 (76.9%)	

HR, hormone receptor. ER, estrogen receptor. PgR, progesterone receptor. HER2, human epidermal growth factor receptor. ORR, objective response rate.

Parameters	All breast cancer (n = 88)			Progression due to new metastasis (n = 17)			Progression due to pre-existing lesions (n = 71)		
	High (n = 37)	Low (n = 51)	p- value	High (n = 5)	Low (n = 12)	p- value	High (n = 32)	Low (n = 39)	p- value
3	13 (35.1%)	13 (25.5%)	0.328	2 (40.0%)	4 (33.3%)	0.605	11 (34.4%)	9 (23.1%)	0.292
Objective Response Rate									
ORR	23 (62.2%)	18 (35.3%)		3 (60.0%)	2 (16.7%)		20 (62.5%)	16 (41.0%)	
non-ORR	14 (37.8%)	33 (64.7%)	0.013	2 (40.0%)	10 (83.3%)	0.117	12 (37.5%)	23 (59.0%)	0.072

HR, hormone receptor. ER, estrogen receptor. PgR, progesterone receptor. HER2, human epidermal growth factor receptor. ORR, objective response rate.

Effects of ALC and differences in progression type upon prognosis

In the 51 patients with ALC < 1500/μl, the PPL group had a significantly better prognosis than the PNM group (PFS: p = 0.035, OS: p < 0.001, log-rank, respectively) (**Fig. 3**). On the other hand, in the 37 patients with ALC ≥ 1500/μl, the PPL group had a better OS compared to the PNM group (p = 0.055, log-rank), but there was no significant difference in PFS between the two groups (p = 0.541, log-rank).

A univariate analysis that validated the effect of OS showed that high ORR, high-ALC, and “high-ALC and PPL” were factors for a good prognosis (p < 0.001, HR = 0.310, 95% CI: 0.170–0.568) (p = 0.027, HR = 0.505, 95% CI: 0.275–0.926) (p = 0.009, HR = 0.407, 95% CI: 0.208–0.795) (**Fig. 4**). Receiver operating characteristic (ROC) analysis showed that the results for “high-ALC and PPL” [area under the curve (AUC): 0.666] were better than those for the ALC (AUC: 0.639), “low-ALC and PPL” (AUC: 0.455), “high-ALC and PNM” (AUC: 0.473), and “low-ALC and PNM” (AUC: 0.406) (**Fig. 5**). Furthermore, multivariate analysis demonstrated that ORR was the strongest independent factor for a favorable prognosis (p < 0.001, HR = 0.321, 95% CI: 0.171–0.602). In addition, “high-ALC and PPL” was another independent factor for a favorable prognosis (p = 0.036, HR = 0.290, 95% CI: 0.091–0.923) (Table 2).

Table 2

Univariate and multivariate analysis with respect to overall survival in 88 patients with eribulin chemotherapy for locally advanced or metastatic breast cancer.

Parameters	Univariate analysis			Multivariate analysis			
		Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Age at chemotherapy	≤ 63 vs. >63	0.653	0.366–1.164	0.148			
Degree of progress	Locally advanced vs. Visceral metastases	0.622	0.328–1.178	0.144			
HR (ER and/or PgR)	Positive vs. Negative	0.630	0.359–1.107	0.108			
HER2	Positive vs. Negative	0.366	0.089–1.506	0.164			
Ki67	≤ 14% vs. >14%	1.401	0.803–2.446	0.235			
Nuclear grade	1, 2 vs. 3	1.501	0.842–2.673	0.168			
Objective Response Rate	ORR vs. non-ORR	0.310	0.170–0.568	< 0.001	0.321	0.171–0.602	< 0.001
ALCs	≥ 1500/μl vs. <1500/μl	0.505	0.275–0.926	0.027	0.424	0.138–1.300	0.133
Progression	Progression due to pre-existing lesions and High-ALCs vs. Others	0.407	0.208–0.795	0.009	0.290	0.091–0.923	0.036
Progression	Progression due to pre-existing lesions and Low-ALCs vs. Others	1.183	0.667–2.097	0.565			
Progression	Progression due to new metastasis and High-ALCs vs. Others	1.681	0.600–4.712	0.323			
Progression	Progression due to new metastasis and Low-ALCs vs. Others	1.885	1.039–3.422	0.037	1.654	0.846–3.234	0.142

HR, hormone receptor. ER, estrogen receptor. PgR, progesterone receptor. HER2, human epidermal growth factor receptor. ORR, objective response rate. ALC: absolute lymphocyte count. CI, Confidence interval.

Discussion

Eribulin chemotherapy for MBC patients has been shown to prolong OS in international phase III clinical trials (Study 305, EMBRACE) [16]. Prolonging OS in MBC, which is biologically mild and has more treatment options, is difficult. Bevacizumab combination therapy has a high response rate and has been shown to improve PFS, but it did not significantly affect OS (E2100, AVADO, RIBBON-1) [25–28]. Meanwhile, eribulin chemotherapy benefitted MBC patients by improving the OS. However, there was no significant difference in PFS, and the reason for this is

being investigated [16]. The modulating effect of eribulin on the tumor microenvironment through tumor vascular remodeling and epithelial-mesenchymal transition (EMT) suppression is a possible mechanism for OS prolongation [29–31]. In our previous study, which analyzed tissue specimens collected after eribulin treatment, tumor microenvironment (TME) improvement, such as reduced tumor hypoxia and EMT suppression, was observed in the responders [32]. Furthermore, a study using the same tissue specimens showed decreased expression of programmed cell death protein (PD)-1, programmed death ligand-1 (PD-L1), and forkhead box P3 (FOXP3) as well as increased expression of CD8 [33]. The eribulin-resistant MDA-MB-231 breast cancer cell line also showed lower CD274 (PD-L1) expression than the parental cell line [34]. These results indicated an improvement in tumor immunity with eribulin chemotherapy.

ALC and NLR, which are indicators of systemic tumor immune response, have been reported to be prognostic and predictive of therapeutic response in patients treated with eribulin. This was supported by the results of the EMBRACE study [17–19, 24]. We have also shown that local and systemic tumor immune responses are linked via transforming growth factor- β (TGF- β) [20].

The RECIST diagnostic criteria for PD were divided into PPL and PNM. Those with PNM had a worse prognosis than those with PPL in Studies 305 and 301 [3]. PNM is associated with peripheral tissue invasion and metastasis to other organs, explaining the poor prognostic course. On the other hand, PPL is associated with peripheral tissue invasion only, without metastasis [2–4, 35]. In other words, differences in progression patterns are related to dynamic changes in the TME.

The rates of PNM in this study were 13.5% (5/37) in high-ALC cases ($ALC \geq 1500/\mu\text{l}$) and less than 23.5% (12/51) in low-ALC cases ($ALC < 1500/\mu\text{l}$). That is, patients with higher ALC had a lesser form of PNM progression. Although ALC is a useful biomarker for eribulin chemotherapy, its mechanism has not been validated until now. The results of our study suggest that a good systemic immune status contributes to benefit in terms of OS. A good local tumor immune microenvironment reduces the progression of PNM. Our previous study showed that systemic and local tumor immune responses were linked to eribulin chemotherapy [20], and the present study showed that the form of progression was a factor.

Furthermore, the use of the combination of "form of PD" and "host's immune systemic marker, ALC" was more sensitive than using ALC alone. In particular, high ALC and PPL were independent favorable prognostic factors for overall survival. Good systemic immune status and progressive forms of PPL suggested a good prognosis.

This study had limitations since it involved a retrospective cohort analysis with a small sample size. However, this is the first report to capture the mechanism behind the role of ALC as a useful biomarker in eribulin chemotherapy in a progressive form of cancer. We developed a new biomarker, "high-ALC and PPL", which was found to be more sensitive than ALC alone. In the future, these biomarkers should also be considered in clinical practice to determine the best treatment options.

Conclusions

In breast cancer patients with eribulin chemotherapy, good systemic immune status, such as $ALC \geq 1500/\mu\text{l}$, was associated with less progression, particularly metastasis, and better prognosis. Furthermore, the biomarker "high-ALC and PPL" was particularly useful as a prognostic marker following eribulin chemotherapy.

Abbreviations

ALC: absolute lymphocyte count, AUC: area under the curve, CI: confidence interval, CR: complete response, EMT: epithelial-mesenchymal transition, ER: estrogen receptor, H.E.: hematoxylin and eosin, FOXP3: forkhead box P3, HER2: human epidermal growth factor receptor 2, HR: hazard ratio, LMR: lymphocyte-monocyte ratio, MBC: locally advanced or metastatic breast cancer, NLR: neutrophil-lymphocyte ratio, ORR: objective response rate, OS: overall survival, PD: progression disease, RECIST: Response Evaluation Criteria for Solid Tumors, ROC: receiver operating characteristic, PD-L1: programmed death ligand-1, PFS: progression-free survival, PgR: progesterone receptor, PLR: platelet-lymphocyte ratio, PNM: progression by new metastases, PPL: progression by pre-existing disease, PR: partial response, TME: tumour microenvironment, TGF- β : transforming growth factor- β .

Declarations

Ethics approval and consent to participate

A written informed consent to participate in the study was obtained from each subject in accordance with the declaration of Helsinki principles. Each patient or the patient's family was fully informed of the investigational nature of this study and provided their written, informed consent. The study protocol was approved by the Ethics Committee of Osaka City University (approve number #926).

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors were involved in the preparation of this manuscript. TM collected the data and wrote the manuscript. SK, YA, WG, KT, RK, AY, and SI performed the operation and designed the study. TM and SK summarized the data and revised the manuscript. MS, HT, KH, and MO provided a substantial contribution to the study design, performed the operation, and revised the manuscript. All authors read and approved the final manuscript.

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Figures

Fig. 1 Morisaki T. et al.

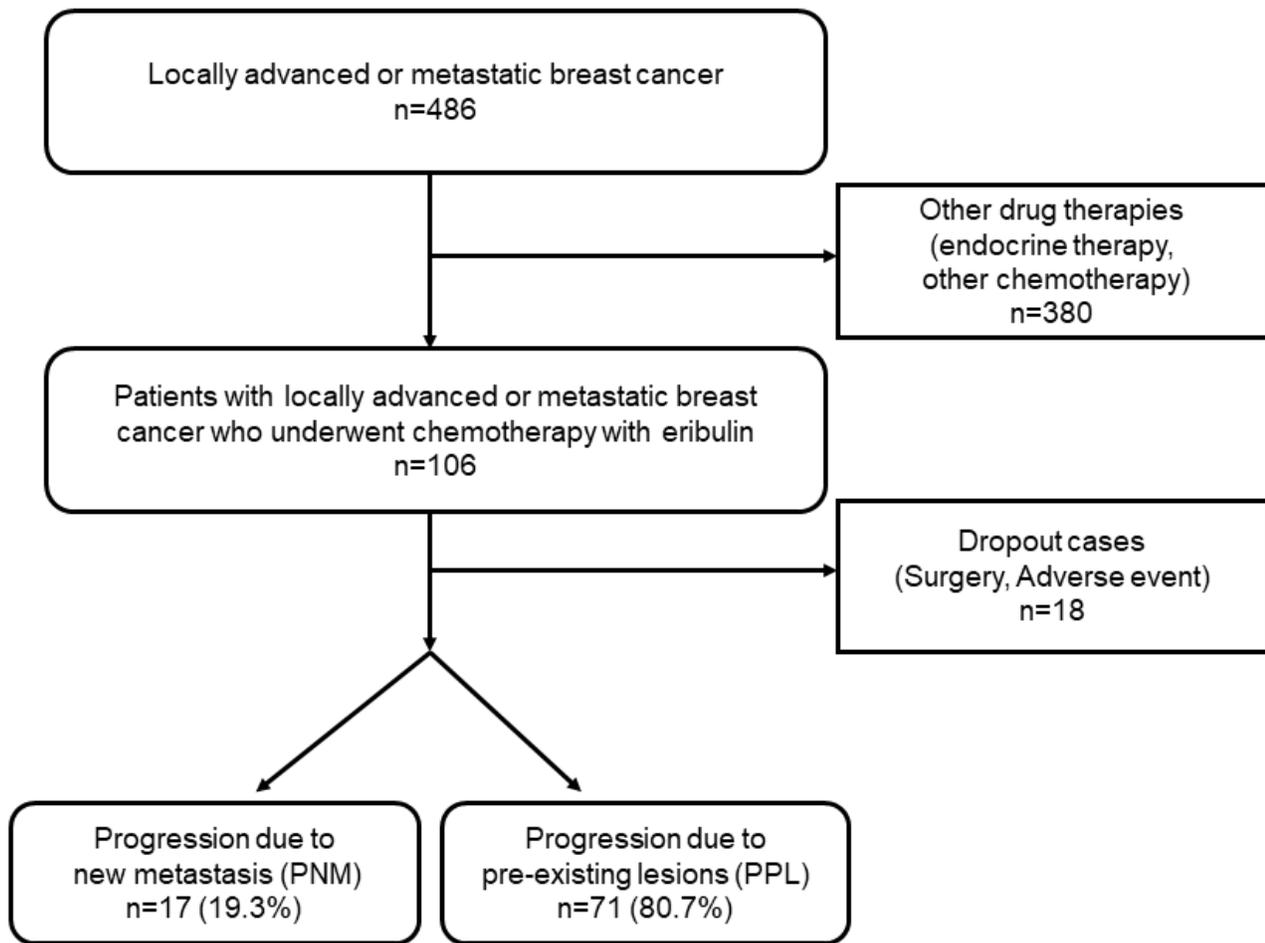


Figure 1

A total of 486 patients with MBC underwent treatment at the Osaka City University Hospital. In this study, only 88 patients who underwent chemotherapy using eribulin were included, and 380 patients who were administered other drug therapies, such as endocrine therapy or other chemotherapy regimens, and 18 patients who dropped out due to surgery or adverse events, were excluded

Fig. 2 Morisaki T. et al.

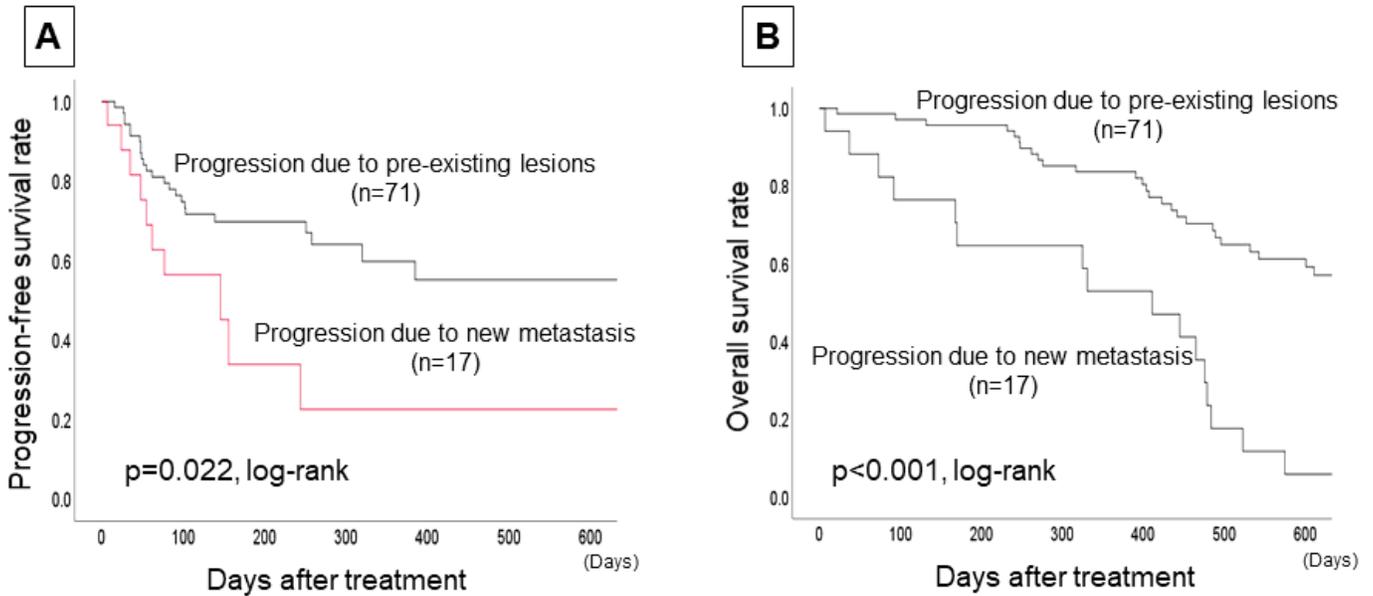


Figure 2

Among the 106 MBC patients who received chemotherapy with eribulin, 88 were included in the study, and 18 patients were excluded. Among them, 17 patients (19.3%) were PNM and 71 patients (80.7%) were PPL. The PPL group had significantly longer PFS ($p=0.022$, log-rank) and OS ($p<0.001$, log-rank) than the PNM group

Fig. 3 Morisaki T. et al.

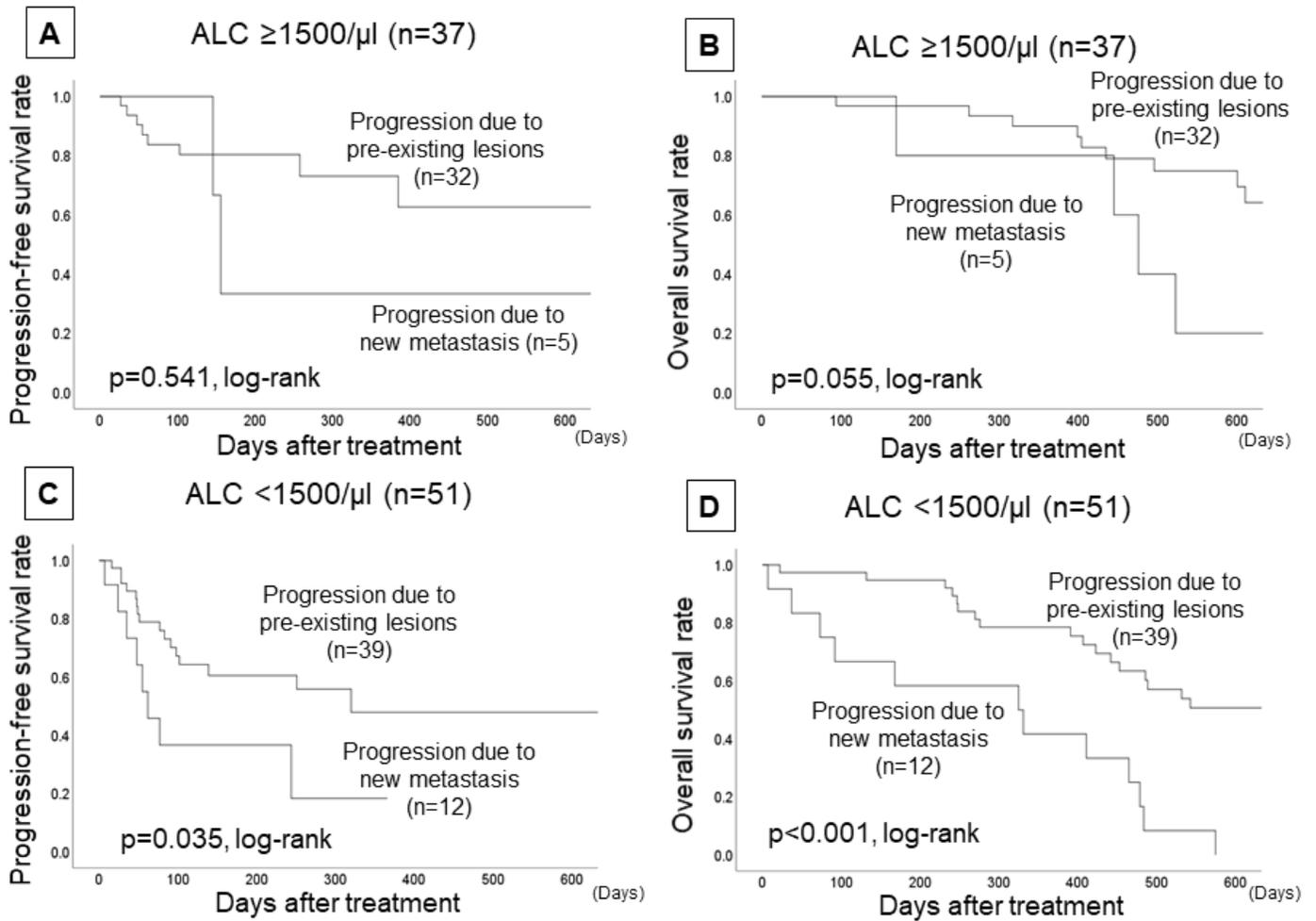


Figure 3

In the 51 patients with ALC $< 1500/\mu\text{l}$, the PPL group had a significantly better prognosis than the PNM group (PFS: $p=0.035$, OS: $p<0.001$, log-rank, respectively)

Fig. 4 Morisaki T. et al.

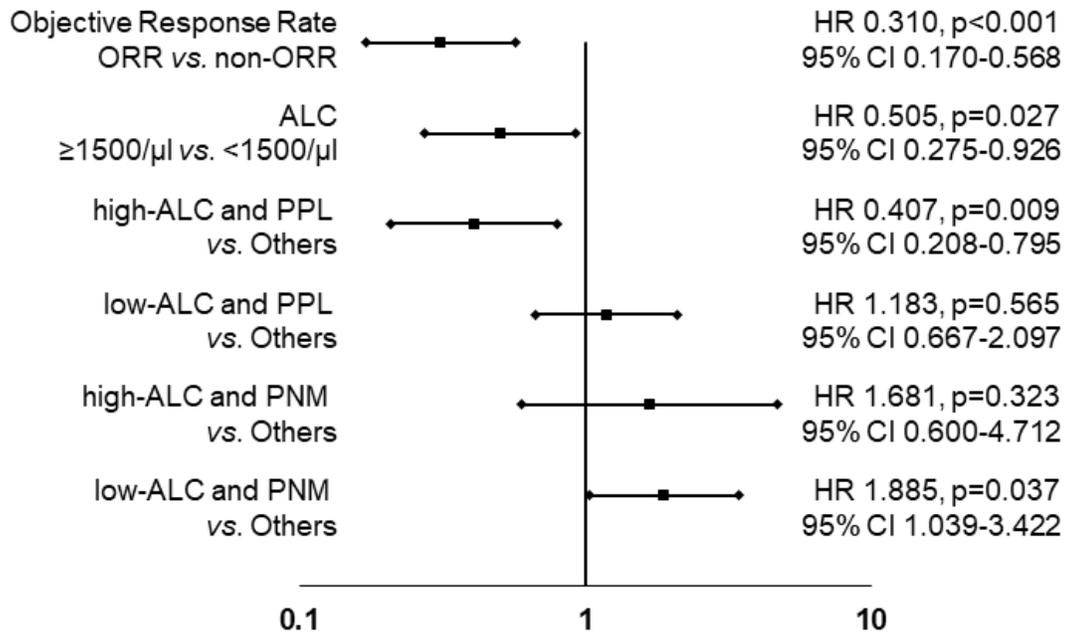


Figure 4

A univariate analysis that validated the effect of OS showed that high ORR, high-ALC, and “high-ALC and PPL” were factors for a good prognosis (p<0.001, HR=0.310, 95% CI: 0.170-0.568) (p=0.027, HR=0.505, 95% CI: 0.275-0.926) (p=0.009, HR=0.407, 95% CI: 0.208-0.795)

Fig. 5 Morisaki T. et al.

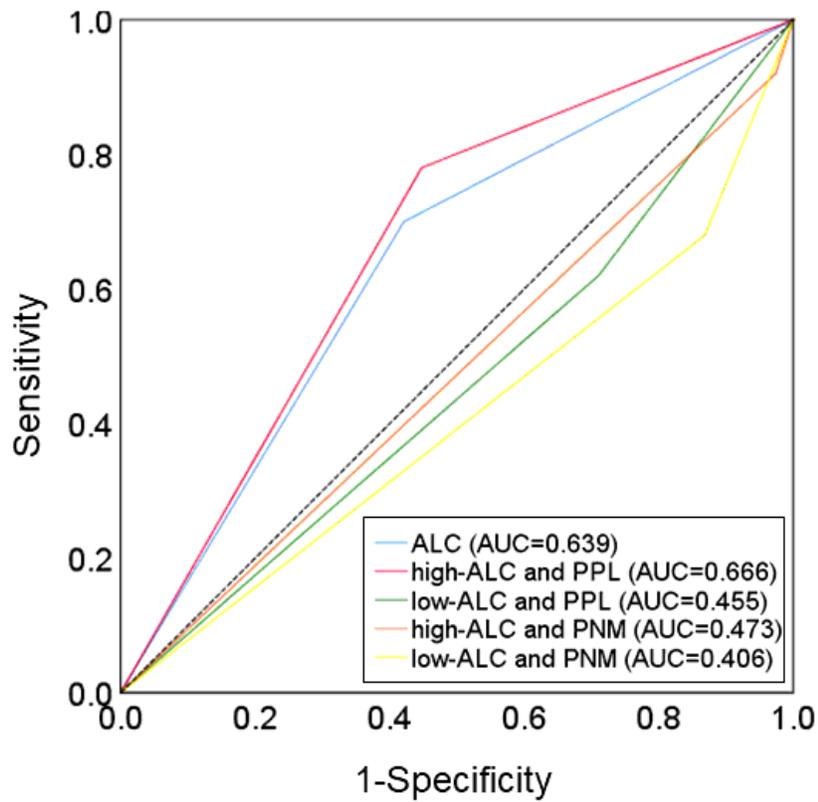


Figure 5

Receiver operating characteristic (ROC) analysis showed that the results for “high-ALC and PPL” [area under the curve (AUC): 0.666] were better than those for the ALC (AUC: 0.639), “low-ALC and PPL” (AUC: 0.455), “high-ALC and PNM” (AUC: 0.473), and “low-ALC and PNM” (AUC: 0.406)