


Clinical Predictive Factors for the Efficacy of Everolimus in Patients With Hormone Receptor-Positive, HER2-Negative Advanced Breast Cancer: A Multicenter Retrospective Cohort Study in Japan

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ABSTRACT

PURPOSE: To investigate the clinical predictive factors for the efficacy of everolimus (EVE) for advanced/metastatic breast cancer (AMBC).

METHODS: Routine practice data of consecutive patients with AMBC who received EVE at 5 institutions in western Japan were retrospectively analyzed in this cohort study (study registration no.: UMIN 000032569). The correlation among time to treatment failure (TTF), overall survival (OS), and clinical background was investigated via univariate and multivariate analyses using Cox hazards model for the clinically important variables.

RESULTS: A total of 134 patients were included in the analysis. The median TTF and OS were 5.2 months (95% confidence interval [CI]: 4.1–6.4) and 27.3 months (95% CI: 23.7–30.9), respectively. Multivariate analysis showed that dose reduction of EVE from any initial dose was associated with a longer TTF (hazard ratio [HR]: 0.52; 95% CI: 0.32–0.84, $P = .007$). Meanwhile, very low hormone sensitivity (ie, relapse within the first 2 years during adjuvant endocrine therapy or progression within 3 months of endocrine therapy immediately before EVE) was associated with a shorter TTF (HR: 2.48; 95% CI: 1.49–4.10, $P < .001$). In the analysis of stratified treatment outcomes, TTF was longer in the group with <3 liver metastases and in groups other than the very low hormone sensitivity group, regardless of the treatment line of EVE.

CONCLUSIONS: Low hormone sensitivity and ≥ 3 liver metastases were important prognostic factors for the efficacy of EVE. EVE may be less effective in patients with AMBC with these factors, and as such, chemotherapy should be administered instead.

KEYWORDS: Everolimus, advanced breast cancer, hormone sensitivity, cohort study

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Introduction

The phosphatidylinositol-3-kinase (PI3K)–Akt pathway is involved in the cell proliferation of various malignant tumors through the mammalian target of rapamycin (mTOR), which is a serine/threonine kinase. The mTOR inhibitor everolimus (EVE) acts by forming a complex with FKBP12 intracellularly, thus inhibiting phosphorylation of S6K1 and 4EBP by binding to the mTOR complex 1 and suppressing tumor growth.^{1,2}

In the randomized phase III BOLERO-2 trial, EVE plus exemestane significantly improved progression-free survival (PFS) compared to placebo plus exemestane for patients with post-menopausal hormone receptor-positive, human epidermal growth factor-2 (HER2)-negative advanced/metastatic breast cancer (AMBC) who developed resistance to non-steroidal

aromatase inhibitors (hazard ratio [HR]: 0.45; 95% confidence interval [CI]: 0.38–0.54; $P < .0001$).³ However, EVE induces characteristic adverse events, such as stomatitis, interstitial pneumonitis, and abnormal glucose metabolism, leading to treatment discontinuation in approximately 20% of cases and requiring special precautions.⁴ Therefore, despite being an effective drug, EVE is sometimes challenging to administer given the difficulty in managing its side effects.

Although some reports suggest the usefulness of biomarkers,^{5,6} currently, there are no clinically available ones to predict the efficacy of EVE. For this reason, its optimal timing is mostly based on the sensitivity to previous endocrine therapy (ET) or metastatic tumor burden. Furthermore, the recently reported effectiveness of cyclin-dependent kinase (CDK) 4/6



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inhibitors⁷⁻⁹ makes the sequence of ET for AMBC complicated. To date, limited data about the clinical application of EVE have been reported in Japan, including in poor treatment candidate patients such as the elderly or those with reduced organ function who are unlikely to be eligible for clinical trials. Therefore, in this study, we investigated the routine practice data for patient characteristics, sensitivity to ET, tumor burden, and safety, and the relationship between these factors and the efficacy of EVE before CDK4/6 inhibitors were available.

Methods

Patient recruitment and study design

Between March 17, 2014 (EVE approval date for AMBC in Japan) and October 30, 2017, consecutive patients with AMBC who received EVE at 5 institutions in western Japan (Hyogo Cancer Center, Hiroshima City Hiroshima Citizens Hospital, Kobe City Medical Center General Hospital, Kyoto University Hospital, and Tenri Hospital) were recruited. The data for these cases were extracted from the electronic medical record of each institution and reviewed. Thereafter, a total of 141 patients were enrolled in this study. Among these, 7 patients were excluded: 3 because of HER2 positivity, 2 because the administration period of EVE was less than 7 days, 1 because of no prior ET administration before EVE administration, and 1 owing to male breast cancer. Finally, 134 patients were included in the analysis. The baseline characteristics of the patients are shown in Table 1.

This is a retrospective study registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry managed by the National University Hospital Council of Japan (Registration no.: UMIN 000032569). The institutional review board of each participating institution approved the study design, and the need for written informed consent was waived owing to the retrospective nature of the study. Moreover, in compliance with the Japanese ethical guidelines, the research information is published on each institution's website. The cut-off for data collection was November 30, 2017.

Treatment

EVE was given in combination with aromatase inhibitors (exemestane in 132 cases and letrozole in 2 cases). Depending on the patient's condition, EVE was administered at a reduced dose or interrupted at the discretion of the attending physician. Dose modification of EVE from the standard dose of 10 mg is shown in Table 2. Treatment was continued until unacceptable toxicity or disease progression.

Pathological assessment

ER and HER2 status were defined according to the American Society of Clinical Oncology (ASCO)/College of American Pathologists guideline^{10,11} in each institution from the primary

site or metastatic site specimens, or both. The specimen obtained most recently before EVE administration was adopted for the breast cancer subtype.

Evaluation of efficacy

Time to treatment failure (TTF), overall survival (OS), and the correlation among TTF, OS, and clinical characteristics were evaluated. Time to treatment failure was defined as the interval between the first and last days of EVE administration, and OS was defined as the period of survival after the initiation of EVE treatment.

Definition of hormone sensitivity

Hormone sensitivity (HS) before EVE was categorized into 4 groups (Figure 1), which is the modified version presented by Piccart at the 2nd Advanced Breast Cancer Conference in Lisbon.¹² In this categorization, we define "Very low-HS," "Low-HS," "Medium-HS," and "High-HS" as follows:

"Very low-HS": the relapse within first 2 years during adjuvant ET, or progression within 3 months of ET for AMBC immediately before EVE.

"Low-HS": the relapse after first 2 years during adjuvant ET, or progression within 3 to 9 months of ET for AMBC immediately before EVE.

"Medium-HS": the relapse within a year since completion of adjuvant ET, or progression within 9 to 24 months of ET for AMBC immediately before EVE.

"High-HS": the relapse after a year since completion of adjuvant ET, or progression after 24 months of ET for AMBC immediately before EVE.

Definition of the predicting model

We considered liver metastasis and HS to be important factors for treatment outcomes and created a flow chart that divided the patients into 5 groups by adding the PS and the treatment line of EVE, which are robust prognostic factors (Figure 2).

Statistical analysis

TTF and OS were estimated using the Kaplan-Meier method. Univariate and multivariate analyses of TTF and OS were performed using Cox hazards model. All statistical analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY, USA), and significance was set at $P < .05$.

Results

Treatment outcomes

At the data cut-off date, 109 patients had completed EVE therapy, and the remaining 25 under ongoing treatment were

Table 1. Patient characteristics.

CHARACTERISTIC	VALUE, NO. (%)
Median age (range), y	63.5 (32–85)
ECOG PS	
0	69 (51.5)
1	46 (34.3)
2	17 (12.7)
3	2 (1.5)
Hormone receptor status	
ER+/PgR+	97 (72.4)
ER+/PgR–	36 (26.9)
ER+/PgR (unknown)	1 (0.7)
Disease-free interval, y	
Stage IV	33 (24.6)
<2	19 (14.2)
2-5	45 (33.6)
5-8	14 (10.4)
≥8	23 (17.2)
Treatment lines of EVE, median	5 (1–17)
1	3 (2.2)
2	16 (11.9)
3	28 (20.9)
4	15 (11.2)
≥5	72 (53.7)
History of chemotherapy	
Yes	99 (73.9)
No	35 (26.1)
Reason of discontinuation of EVE	
Adverse event	32 (23.9)
PD	63 (47.0)
Others	4 (3.0)
Ongoing	35 (26.1)
Administration period of the most recent ET before EVE (months)	
≤3	33 (24.6)
3-9	52 (38.8)
9-24	36 (26.9)
>24	9 (6.7)
Adjuvant ET	4 (3.0)

Table 1. (Continued)

CHARACTERISTIC	VALUE, NO. (%)
Most recent ET before EVE	
SERD	59 (44.0)
SERM	24 (17.9)
AI	45 (33.6)
Others	6 (4.5)
No. of metastatic sites	
<3	99 (73.9)
≥3	35 (26.1)
Metastatic site	
Liver	
1-2	22 (16.4)
≥3	23 (17.2)
No	89 (66.4)
Malignant pleural effusion	
Yes	12 (9.0)
No	122 (91.0)
Bone	
Yes	84 (62.7)
No	50 (37.3)
Brain ^a	
Yes	8 (6.0)
No	126 (94.0)

Abbreviations: AI, aromatase inhibitor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor; ET, endocrine therapy; EVE, everolimus; PD, progressive disease; PgR, progesterone receptor; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.

^aBrain metastases were well controlled.

censored. The median TTF and OS were 5.2 months (95% CI: 4.1–6.4) and 27.3 months (95% CI: 23.7–30.9), respectively.

Univariate and multivariate analyses for TTF and OS

The following categorical variables that can affect outcomes were used as covariates of analysis: (1) age <70 or ≥70 years; (2) performance status (PS) 0 and 1 or 2 and 3; (3) >3 or ≤3 lines of EVE treatment; (4) with or without history of chemotherapy before EVE administration; (5) with or without dose modification; (6) positive or negative progesterone receptor status; (7) very low HS or any other category of sensitivity; (8) very low and low HS or any other category of sensitivity; and (9) factors related to tumor burden, such as

the number of liver metastases, malignant pleural effusion, and ≥ 3 metastatic sites.

Univariate analysis for TTF showed that dose reduction from any initial dose of EVE was associated with a significantly longer TTF (HR: 0.57; 95% CI: 0.37-0.89, $P = .0129$), while very low HS (HR: 2.41; 95% CI: 1.55-3.74, $P < .001$) (Figure 3A) and the presence of ≥ 3 liver metastases (HR: 1.92; 95% CI 1.17-3.16, $P = .01$) were associated with a significantly

Table 2. Dose modification of everolimus.

EVE administration at reduced dose	
7.5 mg	17 (12.7%)
5.0 mg	38 (28.3%)
Dose reduction from the start of EVE	
10 mg \rightarrow 7.5 mg	1 (0.7%)
10 mg \rightarrow 5.0 mg	24 (17.9%)
10 mg \rightarrow 2.5 mg	1 (0.7%)
7.5 mg \rightarrow 5.0 mg	6 (4.5%)
7.5 mg \rightarrow 2.5 mg	2 (1.5%)
5 mg \rightarrow 2.5 mg	5 (3.7%)
Dose increase from the start of EVE	
5.0 mg \rightarrow 10 mg	4 (2.9%)
5.0 mg \rightarrow 7.5 mg	1 (0.7%)
No dose modification	40 (29.9%)

Abbreviation: EVE, everolimus.

shorter TTF. On multivariate analysis, dose reduction from any initial dose of EVE was associated with a longer TTF (HR: 0.52; 95% CI: 0.32-0.84, $P = .007$), while very low HS was associated with a shorter TTF (HR: 2.48; 95% CI: 1.49-4.10, $P < .001$; Table 3).

In the univariate analysis for OS, shorter OS was associated with the following covariates: PS ≥ 2 (HR: 2.59; 95% CI: 1.27-5.27, $P = .009$), EVE administration at more than the third line (HR: 3.50; 95% CI: 1.55-7.89, $P = .003$), history of chemotherapy (HR: 3.45; 95% CI: 1.23-9.66, $P = .018$), very low HS (HR: 2.21; 95% CI: 1.20-4.07, $P = .011$) (Figure 3B), very low or low HS (HR: 5.31; 95% CI: 2.20-12.8, $P < .001$), and the presence of ≥ 3 liver metastases (HR: 1.92; 95% CI: 1.17-3.16, $P = .01$). In contrast, dose reduction from the start of EVE was associated with longer OS (HR: 0.47; 95% CI: 0.23-0.95, $P = .036$). However, no variables were associated with OS in the multivariate analysis (Table 3).

Prognostic outcomes in predicting model

In the analysis of stratified treatment outcomes among each group, which was shown in Figure 2, TTF was longer in the groups with < 3 liver metastases and in the low, medium, or high (not very low) HS groups (Groups 1 and 2), regardless of the treatment line of EVE (Figure 4).

Safety

Stomatitis and pneumonitis, which are important adverse events of EVE, occurred in 93 (69.4%) and 29 (21.6%) patients, respectively (any grade). Moreover, treatment was discontinued due to adverse events in 32 patients (23.9%).

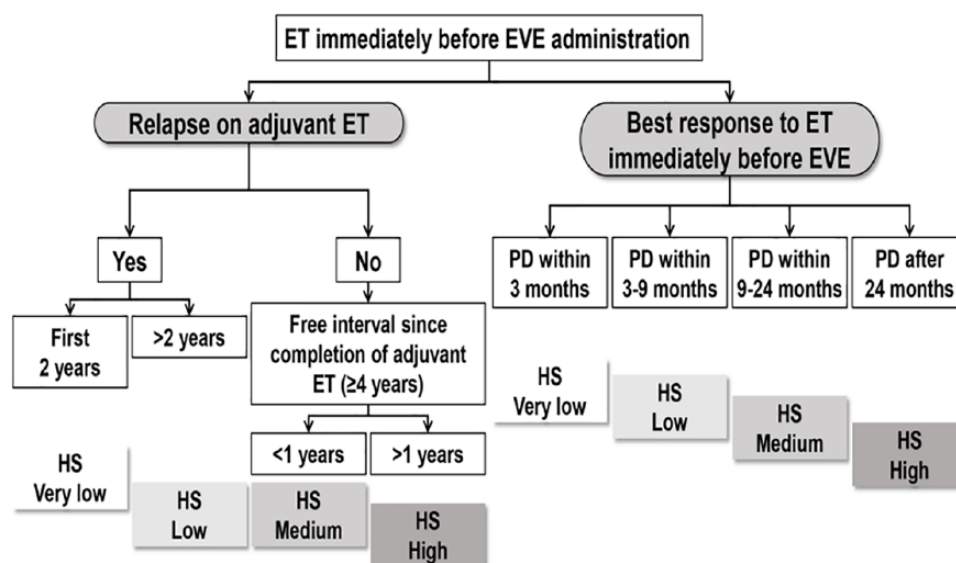


Figure 1. Probabilities of hormone sensitivity immediately before starting EVE. ET indicates endocrine therapy; EVE, everolimus; HS, hormone sensitivity; PD, progressive disease.

Discussion

In this study, the median TTF in unelected patients was 5.2 months, which is similar to that reported in previous real-world cohort studies (4.0-5.7 months).¹³⁻¹⁵ The shorter treatment duration compared to that in the BOLERO-2 trial can be attributed to the high proportion of heavily treated patients in our study (ie, 14.2% of patients had PS 2 or 3 and 53.7% of patients had more than 4 previous treatments of EVE). The reason why EVE was administered to more than half of the patients with the later treatment line was that EVE was used immediately after being approved to the later line patients who had been waiting for this drug in this cohort.

One of the interesting results is that in the multivariate analysis, dose reduction from any initial dose of EVE was associated with a longer TTF. Pouget et al¹³ also showed that patients with dose adaptation tended to have a longer TTF in their cohort study. The reason by which dose reduction is correlated with a longer TTF is uncertain. However, we hypothesize that the adverse effects of patients with dose reduction after EVE initiation might be well managed, leading to better outcomes. Furthermore, patients with very low hormone sensitivity immediately before EVE administration had a shorter TTF than those with not very low hormone sensitivity, although there were no specific variables associated with OS in the multivariate analysis. Regarding hormone sensitivity, the ABC2 guideline defines “primary endocrine resistance” as relapse during the first 2 years of ET or progression within the first 6 months of first-line ET for AMBC while on ET. Meanwhile, “secondary endocrine resistance” is defined as a relapse while on adjuvant ET after the first 2 years, a relapse within 12 months of completing adjuvant ET, or disease progression ≥ 6 months after initiating ET for MBC while on ET.¹⁶ Moreover, the ASCO guideline has recommended taking into account prior ET in the choice of subsequent-line ET.¹⁷

In addition to these criteria, Piccart categorized disease progression within 3 months after the initiation of first-line ET for MBC as very low hormone sensitivity.¹² In our modified algorithm, patients with very low hormone sensitivity had significantly poorer prognosis than those with other levels of hormone sensitivity. In these patients, cell proliferation may occur independently of ER and mTOR pathway signaling; therefore, different treatment strategies, such as chemotherapy, should be used.

Tumor burden is also an important factor in deciding the appropriateness of ET administration because hormone

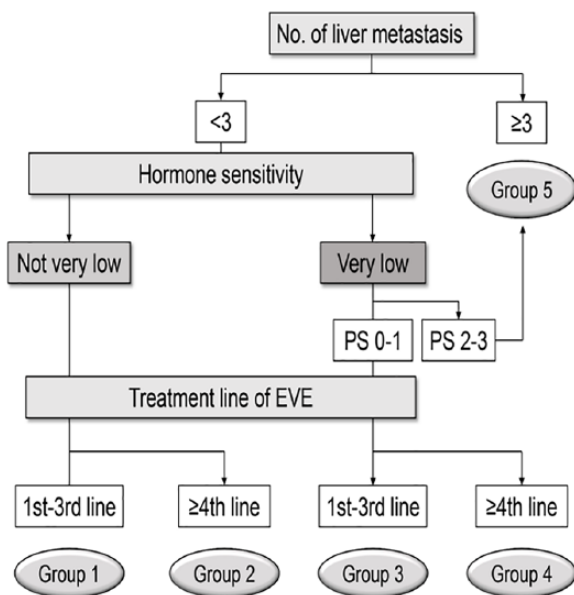


Figure 2. Flow chart for prognostic outcome. EVE indicates everolimus; PS, performance status.

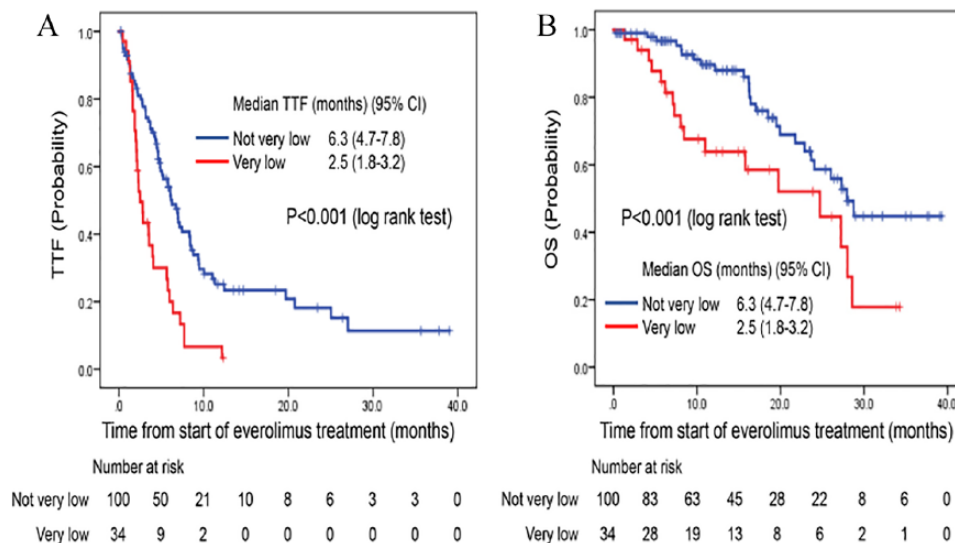


Figure 3. (A) Kaplan-Meier plot for TTF according to hormone sensitivity (very low vs not very low). (B) Kaplan-Meier plot for OS according to hormone sensitivity (very low vs not very low). CI indicates confidence interval; OS, overall survival; TTF, time to treatment failure.

Table 3. Univariate and multivariate analyses for TTF and OS.

VARIABLE	REFERENCE GROUP	TTF			OS			
		UNIVARIATE		MULTIVARIATE	UNIVARIATE		MULTIVARIATE	
		HR (95% CI)	P VALUE	HR (95% CI)	HR (95% CI)	P VALUE	P VALUE	
Age ≥70y	<70	1.16 (0.72–1.85)	.544	1.17 (0.68–2.01)	0.62 (0.27–1.38)	.566	0.39 (0.16–1.00)	.050
PS ≥2	PS <2	1.43 (0.83–2.46)	.195	0.76 (0.39–1.46)	2.59 (1.27–5.27)	.410	1.38 (0.58–3.30)	.470
ER+/PgR+	ER+/PgR–	1.11 (0.71–1.74)	.642	1.03 (0.64–1.65)	0.83 (0.42–1.63)	.902	0.54 (0.25–1.16)	.112
EVE line >3	≤3	1.40 (0.92–2.14)	.115	0.97 (0.59–1.61)	3.50 (1.55–7.89)	.902	2.34 (0.91–6.03)	.078
History of chemotherapy: Yes	No	1.38 (0.87–2.21)	.174	1.33 (0.75–2.35)	3.45 (1.23–9.66)	.331	2.48 (0.80–7.76)	.118
EVE administration at reduced dose	No	0.98 (0.66–1.47)	.924	1.19 (0.74–1.90)	1.02 (0.54–1.96)	.471	1.77 (0.81–3.85)	.151
Dose reduction from the start of EVE	No	0.57 (0.37–0.89)	.012	0.52 (0.32–0.84)	0.47 (0.23–0.95)	.007	0.58 (0.26–1.27)	.174
Hormone sensitivity: very low	Others	2.41 (1.55–3.74)	<.001	2.48 (1.49–4.10)	2.21 (1.20–4.07)	<.001	1.90 (0.97–3.71)	.061
Hormone sensitivity: very low or low	Others	1.28 (0.84–1.95)	.252		5.31 (2.20–12.8)	<.001		
No. of metastatic sites ≥3	<3	1.16 (0.75–1.81)	.505	0.97 (0.58–1.61)	1.32 (0.68–2.58)	.894	1.77 (0.76–4.13)	.186
Liver metastases: Yes	No	1.29 (0.85–1.96)	.226		1.28 (0.68–2.39)	.449		
No. of liver metastases ≥3	<3	1.92 (1.17–3.16)	.010	1.49 (0.82–2.71)	2.51 (1.21–5.20)	.189	1.34 (0.53–3.36)	.537
Malignant pleural effusion: Yes	No	1.18 (0.61–2.27)	.623	1.03 (0.50–2.13)	1.14 (0.35–3.70)	.930	1.75 (0.48–6.42)	.402

Abbreviations: CI, confidence interval; ER, estrogen receptor; EVE, everolimus; HR, hazard ratio; OS, overall survival; PgR, progesterone receptor; PS, performance status; TTF, time to treatment failure.

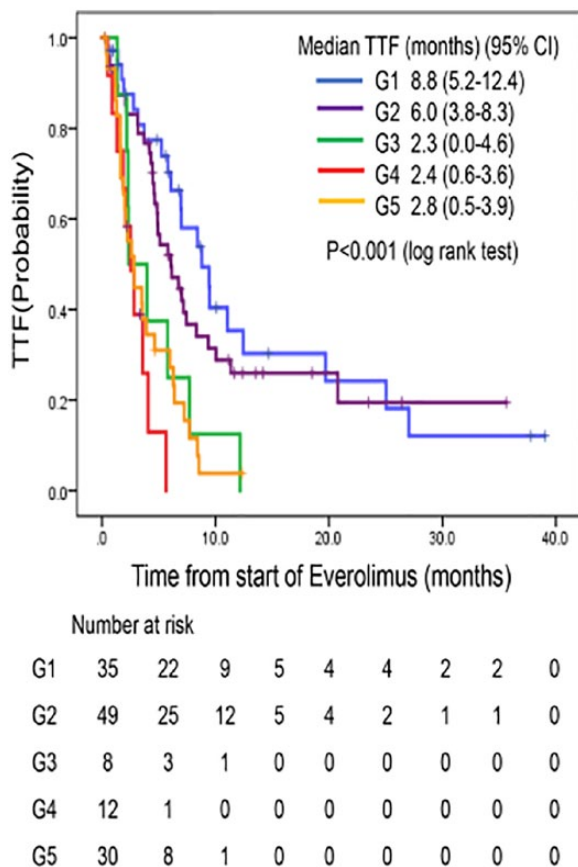


Figure 4. Kaplan-Meier plot for TTF according to prognostic groups in Figure 2. CI indicates confidence interval; G, group; TTF, time to treatment failure.

sensitivity can be decreased due to intra- or inter-tumoral heterogeneity as the tumor burden increases.¹⁸ Thereafter, a high tumor burden leads to visceral crisis, where chemotherapy is a definite indication. In this study, the following factors were considered clinically important as they could directly lead to visceral crisis and affect hormone sensitivity: liver metastases, pleuritis carcinomatosa with pleural effusion, and metastasis to >3 organs. Our findings show that EVE may be appropriate for patients with <3 liver metastases and low, medium, or high hormone sensitivity.

The limitations of this study are as follows. First, it is a retrospective study, and PFS data based on Response Evaluation Criteria in Solid Tumors (RECIST) could not be obtained. Second, the sample size was small (134 cases). However, our data are important in determining the appropriateness of ET because there are currently no available biomarkers that can be used, although some studies have reported *ESR1* and *PIK3CA* as potential candidate biomarkers.^{19,20} Furthermore, with the advent of CDK4/6 inhibitors, the sequence of ET for AMBC and the timing of EVE have become complicated. Although we cannot address all these issues in this study, we believe that the indications for shifting from hormone therapy to chemotherapy were clearly identified.

In conclusion, EVE may be less effective in patients with AMBC with a short duration (<3 months) of ET immediately before EVE administration and those with ≥ 3 liver metastases. Therefore, chemotherapy should be selected for these patients. These findings should be verified in future prospective studies.

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Author Contributions

YK planned, analyzed, and submitted the study. TK planned the study and collected data. YK collected data. KH collected data. HY collected data. SO collected data. ST collected data. MT supervised the analysis. All investigators have seen and approved the final version of the manuscript.

Ethical Approval

This study was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

The need for informed consent was waived owing to the retrospective nature of the study.

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