Real-World Efficacy of Everolimus in ER+/HER2– Metastatic Breast Cancer Following CDK4/6 Inhibitors: A Multicenter Registry-Based Study

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Objective

Everolimus combined with endocrine therapy[1)] is one of the standard treatment options for patients who develop resistance to CDK4/6 inhibitors. However, prospective studies and real-world evidence regarding the efficacy of everolimus in patients previously treated with CDK4/6 inhibitors remain limited[2-4)]. This retrospective study evaluated the clinical outcomes of everolimus in such patients and aimed to identify factors associated with treatment response.

Methods

We conducted a retrospective, registry-based analysis using data from the Advanced Breast Cancer Database (ABCD) Project, coordinated by the Japan Breast Cancer Research Group (JBCRG). Of 184 patients treated with everolimus plus endocrine therapy between January 2019 and March 2025, 169 ER+/HER2– cases with prior CDK4/6 inhibitor exposure and complete data were included. Collected variables included age, performance status, treatment line, reason for treatment discontinuation, best response, menopausal status, recurrence type, BRCA1/2 mutation status, histology, ER/PgR/HER2 expression, Ki-67 index, prior chemotherapy, antibody–drug conjugate (ADC) use, and type and duration of prior CDK4/6 inhibitor therapy. Sites and number of metastatic organs were also assessed. Time to treatment failure (TTF) and overall survival (OS) were measured from everolimus initiation. Clinicopathologic factors influencing TTF were evaluated by univariate and multivariate Cox proportional hazards analyses. Factors independently associated with shorter TTF were defined as risk factors. Kaplan–Meier methods and log-rank tests were used for survival comparisons.

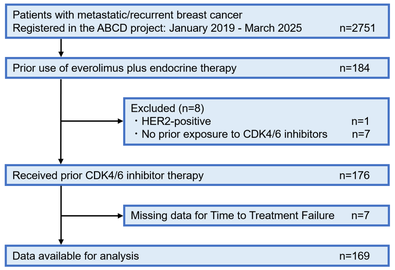


Figure 1. Patient flow of this study.

Table 1. Patient characteristics

	Overall (N=169)		Overall (N=169)
Age, median (range)	63 (31-84)	**Ki-67 index**	
Performance Status (%)		Mean (range)	27.5 (1-80)
0	95 (73.1)	Unknown	54
1	25 (19.2)	**Line of treatment with everolimus (%)**	
2	9 (6.9)	≤ 3 line	104 (61.5)
3	1 (0.8)	≥ 4 line	65 (38.5)
Unknown	39	**Prior use of CDK4/6 inhibitor (%)**	
Reason for termination of treatment (%)		Palbociclib only	94 (55.6)
Adverse event	29 (17.2)	Abemaciclib only	41 (24.3)
Progression Disease	108 (63.9)	Palbociclib and Abemaciclib	34 (20.1)
Unknown/others	32 (18.9)	**Time to treatment failure of prior CDK4/6 inhibitor (%)**	
Best treatment effect (%)		< 1 year	86 (50.9)
Complete Response	1 (0.9)	≥1 year	83 (49.1)
Partial Response	9 (7.8)	**History of treatment with chemotherapy (%)**	
Stable Disease	43 (37.4)	Yes	52 (30.8)
Progression Disease	62 (53.9)	No	117 (69.2)
Unknown	54	**History of treatment with Antibody-Drug-Conjugate (%)**	
Menopause status (%)		Yes	2 (1.2)
Postmenopausal	159 (96.4)	No	167 (98.8)
Premenopausal	6 (3.6)	**Liver metastasis (%)**	
Unknown	4	Yes	69 (40.8)
Type of metastasis (%)		No	100 (59.2)
De-novo StageIV	51 (30.2)	**Lung metastasis (%)**	
Locally advanced	1 (0.6)	Yes	58 (34.3)
Post-operative recurrence	117 (69.2)	No	111 (65.7)
BRCA1/2 pathogenic variant status (%)		**Bone metastasis (%)**	
Present	5 (5.6)	Yes	108 (63.9)
Absent	84 (94.4)	No	61 (36.1)
Unknown	80	**Brain metastasis (%)**	
Histology (%)		Yes	3 (1.8)
Invasive ductal carcinoma	143 (87.7)	No	166 (98.2)
Invasive lobular carcinoma	15 (9.2)	**Distant lymph node metastasis (%)**	
Others	5 (3.1)	Yes	47 (27.8)
Unknown	6	No	122 (72.2)
ER status (%)		**Pleural metastasis (%)**	
1-9%	3 (1.9)	Yes	28 (16.6)
≥10%	158 (98.1)	No	141 (83.4)
Unknown	8	**Bone only metastasis (%)**	
PgR status (%)		Yes	21 (12.4)
<1%	38 (23.6)	No	148 (87.6)
1-9%	23 (14.3)	**Number of metastatic organs (%)**	
≥10%	100 (62.1)	0	3 (1.8)
Unknown	8	1	32 (18.9)
HER2 low (IHC* 1+ or 2+/ISH negative)**		2	84 (49.7)
Yes	99 (63.1)	3	34 (20.1)
No	58 (36.9)	4	12 (7.1)
Unknown	12	5	4 (2.4)

IHC: Immunohistochemistry, ISH: in-situ Hybridization

Results

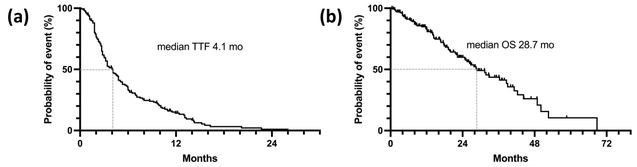


Figure 2. Kaplan–Meier curves of all patients: (a) median TTF 4.1 months; (b) median OS 28.7 months.

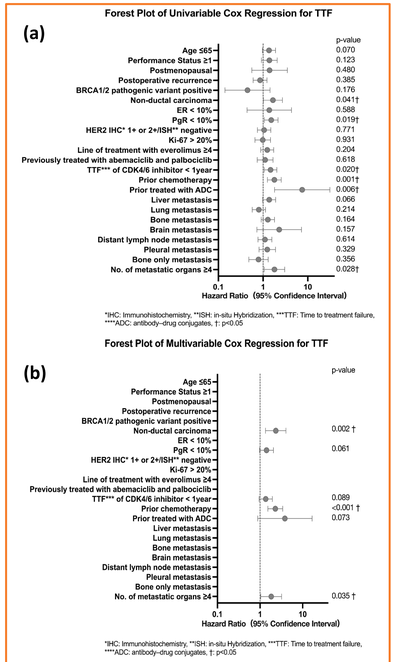


Figure 3. Forest plots of univariable analysis**(a)** and multivariable analysis**(b)** Cox regression analysis for time to treatment failure.

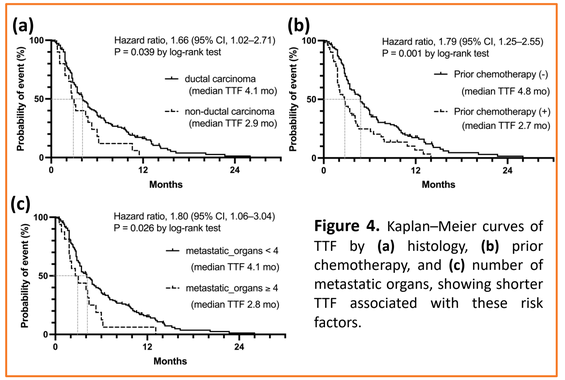
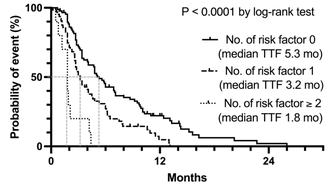


Figure 4. Kaplan–Meier curves of TTF by **(a)** histology, **(b)** prior chemotherapy, and **(c)** number of metastatic organs, showing shorter TTF associated with these risk factors.



No. of risk factor	Hazard ratio*
0	-
1	1.88 (95%CI, 1.32-2.69)
≥2	5.64 (95%CI, 2.82-11.28)

* vs No. of risk factor 0

Figure 5. A Kaplan–Meier curve showed that TTF decreased stepwise with increasing number of risk factors, with median TTFs of 5.3, 3.2, and 1.8 months for 0, 1, and ≥2 risk factors, respectively.

Summary

The median TTF was 4.1 months, and the median OS was 28.7 months. The median TTF was comparable to previously reported PFS (3.8–6.0 months)[2-4)], while OS was longer (15.6–16.0 months)[2-4)]. Univariate analysis identified several prognostic factors significantly associated with shorter TTF: non-ductal histology, PgR <10%, TTF of CDK 4/6 inhibitor <1year, previous chemotherapy or ADC use, and ≥4 metastatic organs (all $p < 0.05$). In multivariate analysis, non-ductal histology (HR 2.34, p=0.002), prior chemotherapy (HR 2.28, p<0.001), and ≥4 metastatic organs (HR 1.83, p=0.035) remained significant predictors of inferior TTF. A progressive decline in TTF was observed with increasing numbers of risk factors (log-rank $p < 0.05$).

Conclusions

This study demonstrated the efficacy of everolimus after CDK4/6 inhibitors in ER+/HER2– metastatic breast cancer and identified clinicopathologic factors associated with reduced treatment durability, informing therapeutic decisions. To our knowledge, this is the largest reported cohort, supporting the reliability and generalizability of our findings.

Fundings

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Conflict of interest

The author declare no conflict of interest.

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