Breast Cancer
https://doi.org/10.1007/s12282-020-01095-y

ORIGINAL ARTICLE

The efficacy of sequential second-line endocrine therapies (ETs) in postmenopausal estrogen receptor-positive and HER2-negative metastatic breast cancer patients with lower sensitivity to initial ETs

Takayuki Iwamoto[1] · Tomomi Fujisawa[2] · Tadahiko Shien[1] · Kazuhiro Araki[3] · Kentaro Sakamaki[4] · Takafumi Sangai[5] · Yuichiro Kikawa[6] · Shintaro Takao[7] · Reiki Nishimura[8] · Masato Takahashi[9] · Tomohiko Aihara[10] · Hirofumi Mukai[11] · Naruto Taira[1]

Received: 23 January 2020 / Accepted: 11 April 2020

Abstract

Purpose Second-line endocrine therapy (ET) for estrogen receptor (ER)-positive and human epidermal growth factor 2 (HER2)-negative metastatic breast cancer (MBC) is offered based on the response to first-line ET. However, no clinical trials have evaluated the efficacy and safety of secondary ETs in patients with poor responses to initial ET. This study evaluated the efficacy of second-line ET in ER-positive and HER2-negative postmenopausal MBC patients with low or very low sensitivity to initial ET.

Methods This multicenter prospective observational cohort study evaluated the response of 49 patients to second-line ETs in postmenopausal MBC patients with low or very low sensitivity to initial ET. The primary endpoint was the clinical benefit rate (CBR) for 24 weeks.

Results Of the 49 patients assessed, 40 (82%) received fulvestrant in the second line, 5 (10%) received selective estrogen receptor modulators, 3 (6%) received aromatase inhibitors (AIs) alone, and 1 received everolimus with a steroidal AI. The overall CBR was 44.9% [90% confidence interval (CI): 34.6–57.6, $p=0.009$]; CBR demonstrated similar significance across the progesterone receptor-positive ($n=39$, 51.3%, 90% CI: 39.6–65.2, $p=0.002$), very low sensitivity ($n=17$, 58.8%, 90% CI: 42.0–78.8, $p=0.003$), and non-visceral metastases ($n=25$, 48.0%, 90% CI: 34.1–65.9, $p=0.018$) groups. The median progression-free survival was 7.1 months (95% CI: 5.6–10.6).

Conclusion Second-line ET might be a viable treatment option for postmenopausal patients with MBC with low and very low sensitivity to initial ET. Future studies based on larger and independent cohorts are needed to validate these findings.

Keywords Metastatic breast cancer · Endocrine therapies · Estrogen receptor-positive · HER2-negative · Resistance

Introduction

Breast cancer with inoperable distant metastasis or recurrence has a poor prognosis. Therefore, therapies for metastatic breast cancers (MBCs) intend to prolong survival and improve the quality of life [1, 2]. Systemic therapies play a major role in the treatment of MBC, but local therapies including surgery and radiotherapy play less important roles. Overall, therapeutic strategies are selected based on the age, disease-free interval, extent of disease, and the biology of breast cancers, including hormone receptor (HR) and human epidermal growth factor 2 (HER2) status and extent of the disease. Among the novel chemotherapeutic agents and targeted therapies, first-line endocrine therapy (ET) continues to be the gold standard for treating HR-positive and HER2-negative MBC as it provides a good quality of life with a lower incidence of adverse events. Unfortunately, certain patients fail to respond to first-line ET owing to resistance [3]. Second-line therapies after initial ET are offered based on the response to first-line ET [4], as the durations of response to second and subsequent-lines of therapy are substantially

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12282-020-01095-y) contains supplementary material, which is available to authorized users.

✉ Takayuki Iwamoto
tiwamoto@md.okayama-u.ac.jp

Extended author information available on the last page of the article

Published online: 11 May 2020

lower than those of the prior therapy [5, 6]. Patients with good responses to first-line ET should be offered ET in the second line [4]. Conversely, those not responding to first-line ET are usually offered chemotherapy instead, owing to the likelihood of primary or acquired resistance [3]. However, there is no clear clinical definition of resistance to ET.

A new classification developed by the second International Consensus Guidelines for Advanced Breast Cancer (ABC2) clarifies ET sensitivity based on the clinical response to initial ET. These guidelines propose the following classification of ET sensitivity in HR-positive ABC based on the time from ET induction to progression [7]: patients with recurrence during the first two years after the induction of adjuvant ET or with progression during the first three months after the induction of first-line ET are considered to have "very low" ET sensitivity, whereas those with recurrence at two to five years after the initiation of adjuvant ET or progression within three to nine months after the initiation of first-line ET are considered to have "low" sensitivity [3]. The others are stratified into medium or high sensitivity groups. In patients with "very low" or "low" endocrine sensitivity based on the ABC2 criteria, the clinical advantages of second-line ET remain unclear. To our knowledge, no clinical trials have evaluated the efficacy and safety of the numerous available secondary ETs in patients with poor response to initial ET. Previously, we reported the reasons for selection of secondary ETs in this unique subgroup [8]. Majority of patients and physicians selected secondary ET based on its therapeutic effect, while 28% based on the side effects.

The mechanisms of action of recently developed ETs for breast cancer differ from those of the existing drugs. Fulvestrant lacks partial agonistic effects on ER, unlike tamoxifen; instead, it downregulates ER expression in breast cancer cells, and is therefore classified as a selective estrogen receptor downregulator (SERD) [3, 9, 10]. Everolimus is a mammalian target of rapamycin (mTOR) inhibitor; mTOR is situated downstream in the PI3K/AKT pathway and is a key signaling molecule that mediates cancer cell proliferation. In breast cancer that has acquired resistance to non-steroidal aromatase inhibitors, progression-free survival (PFS) can be extended by the combined administration of mTOR inhibitors with other endocrine therapies [11–13]. However, the preferred endocrine agents in the second-line setting have not been well identified. Accordingly, this study aimed to evaluate the efficacy and safety of second-line ETs and various agents used to treat ER-positive and HER2-negative postmenopausal MBC with unfavorable clinical responses to primary ET (i.e. "low" or "very low" sensitivity to primary ET); it also intended to determine the clinical characteristics of individual tumor types in terms of the efficacy of second-line ET.

Methods

Patients and study design

This multicenter prospective observational study, namely, HORSE-BC, included patients receiving second-line ETs between February 2016 and January 2017 [8, 14]. The study protocol was approved by our institutional review boards, and all patients provided written informed consent. The inclusion criteria were as follows: (1) postmenopausal patients with histologically diagnosed breast cancer, (2) a diagnosis of either (a) stage IV breast cancer and inoperable distant metastasis at the first visit or (b) breast cancer with progression or recurrence caused by distant metastasis after treatment with curative intent, with or without measurable lesions, (3) patients planning to receive ET for MBC, (4) those with Eastern Cooperative Oncology Group performance status (PS) scores of zero to one, (5) those who received previous ET using any agent, either as (a) continuous postoperative adjuvant therapy with recurrence within five years after starting ET or (b) initial treatment for MBC with disease progression within nine months after starting ET, (6) either received no previous chemotherapy for breast cancer or pre- or postoperative chemotherapy within the past six months, (7) received no previous radiotherapy for breast cancer within the past 14 days. Cases in which $\geq 1\%$ of the tumor cells stained positive for ER were considered ER-positive, and HER2-negative cases were defined as having immunohistochemistry scores of 0/1 + or gene copy numbers < 2.0. "Very low" sensitivity to initial ET was defined as recurrence within the first two years during adjuvant ET or progression within three months of initial ET for ABC. "Low" sensitivity to initial ET was defined as the recurrence after first two to five years during adjuvant ET or progression within three to nine months of initial ET for ABC.

The treatment choices included various agents that are approved by the Japanese regulatory authority for use as ET for postmenopausal breast cancer. The various treatment strategies were thoroughly explained by the attending physician and the final decision was made by the patients. The safety of the patients and efficacy of the strategy were closely monitored. The treatment groups included a SERM group [those who received tamoxifen or toremifene, which are selective estrogen receptor modulators (SERMs)], an AI group (those who received anastrozole, letrozole, or exemestane), a SERD group [those who received fulvestrant, which is a selective estrogen receptor downregulator (SERD)], and an mTORi group (those who received any ET with everolimus, which is an mTOR inhibitor).

The primary endpoint was the clinical benefit rate (CBR), defined as achievement of a complete response

(CR), partial response (PR), or stable disease (SD) for 24 weeks. The secondary endpoints included the following: (1) response rate (RR): the proportion of patients whose best overall response in the target population with measurable lesions was CR or PR in 6 months, (2) PFS: the period from the registration day to either the day on which progression was determined or the day of death from any cause, whichever was earlier, (3) overall survival (OS): the period from the day of registration to death from any cause, (4) time to treatment failure (TTF): the period from the day of registration to either the day when progression was determined, death occurred from any cause, or the day of discontinuation of the protocol treatment, whichever was earlier, (5) time to chemotherapy (TTC): the period from the day of registration to the day of first administration of chemotherapy, (6) adverse events observed from registration to the discontinuation of protocol treatment, evaluated in all treated cases using the common terminology criteria for adverse events version 4.0. The therapeutic effect was evaluated by imaging methods such as computed tomography after 3 or 6 months from the initiation of second-line treatment. The response evaluation criteria in solid tumors version 1.1 was used for assessment. All clinical data and disease characteristics were collected with the use of a case-report form. This trial has been registered in the UMIN Clinical Trials Registry, UMIN000019556.

Statistical analyses

Secondary ET for breast cancer with low-sensitivity to ET provides a CBR of at least 30% using newer endocrine agents; the expected CBR was 50%. The null hypothesis of a CBR of 30% was tested with a one-sided α of 5%. Further, 90% confidence intervals (CIs) were calculated for hypothesis tests. Assuming the use of an accurate binomial test, the required number of cases with $\alpha = 0.05$ (one-tailed) and $\beta = 0.2$ was estimated to be 43. Univariate analyses of predictive factors with respect to the CBR for 6 months were performed for hypothesis tests with a one-sided α of 5% and 90% CIs. Similarly, predictive factors for response rate for six months was calculated. These analyses for predictive factors were pre-planned. Survival curves were shown by the Kaplan–Meier method.

Results

Patient characteristics

A total of 56 patients were enrolled, of whom 7 were excluded based on the inclusion criteria. Overall, data from 49 patients were analyzed further. The patient characteristics are shown in Table 1. The median age was 65.8 (range 41–88) years and the median body mass index was 23.9 (16.4–31.9) kg/m^2. All patients were ER-positive and 80% (39/49) were progesterone receptor (PgR)-negative. Most patients had a baseline PS of zero or one, 89.8% (44/49) and 10.2% (5/49) had invasive ductal and lobular carcinoma, respectively. Further, 6.1% (3/49) were TNM stage I, 38.8% (19/49) were stage II, 36.7% (18/49) were stage III, and 18.4% (9/49) were stage IV based on staging at the initial diagnosis. Of the patients 49.0% (24/49) had visceral metastases, whereas the others had non-visceral metastases including those of the bone and lymph nodes; 36.7% (18/49) had single metastatic sites, and the remaining had multiple sites. Postoperative recurrence was detected in 81.6% (40/49); the median duration of adjuvant ET was 30.5 (5.3–58.9) months. Of patients with postoperative recurrence, 50% (20/40) received adjuvant/neo adjuvant chemotherapy. De novo stage IV breast cancer was observed in 18.4% (9/49); the median duration of first-line ET was 5 (2.3–10.8) months. Overall, 88.1% (37/42), 4.8% (2/42), and 7.1%(3/42) received non-steroidal AIs, steroidal AIs, and SERM as adjuvant ET, respectively. In de novo stage IV cases, 88.9% (8/9) were treated with AIs or SERM [11.1% (1/9)] in the first-line. Overall, of the total cases, 40 (81.6%, 40/49), 5 (10.2%), 5 (6.1%), and 1 (2.0%) received fulvestrant, SERMs, an mTOR inhibitor with a steroidal AI, and AI alone, respectively, in the second-line setting. Of the patients who had a very low response, 76.5% (13/17) experienced recurrence within the first two years during adjuvant ET and 23.5% (4/17) experienced progression within three months of the initial ET for metastatic breast cancer. Of patients who had a low response, 84.3% (27/32) experienced recurrences at two to five years after the initiation of adjuvant ET and 15.6% (5/32) experienced progression within three to nine months after the initiation of first-line ET.

CBR and RR

The overall CBR was 44.9% (90% CI: 34.6–57.6, $p = 0.009$), with similar significance across the following subgroups: PgR-positive: $n = 10$, 51.3%, 90% CI: 39.6–65.2, $p = 0.002$; very low sensitivity: $n = 17$, 58.8%, 90% CI: 42.0–78.8, $p = 0.003$; non-visceral metastases: $n = 25$, 48.0%, 90% CI: 34.1–65.9, $p = 0.018$) (Table 2). The CBR in PgR-negative patients was not statistically significant. As shown in Table 3, the overall RR was 8.2% (90% CI: 4.1–17.7%). The RR was relatively favorable in the very low sensitivity ($n = 17$, 11.8%, 90% CI: 5.0–32.6%) and PgR-negative (10.0%, 90% CI 3.7–39.4%) subgroups. The fulvestrant group demonstrated a relatively poor RR ($n = 40$, 2.5%, 90% CI: 0.9–11.3%).

Table 1 Patient characteristics

	Number	
Registered patients	56	
Eligible patients	49	
Patients in our analytic cohort ($N=49$)		
	Mean	Mini–max
Age (years)	65.8	41–88
BMI (kg/m^2)	23.9	16.4–31.9
	Number	%
ER		
Positive	49	100.0
Negative	0	0.0
PgR		
Positive	10	20.4
Negative	39	79.6
PS		
0	41	83.7
1	7	14.3
2	1	2.0
Staging at initial diagnosis		
I	3	6.1
II	19	38.8
III	18	36.7
IV	9	18.4
Histological type		
IDC	44	89.8
ILC	5	10.2
Metastatic site		
Visceral	24	49.0
Non-visceral	25	51.0
Liver	15	30.6
Lung	12	24.5
Bone	24	49.0
Lymph node	18	36.7
Sensitivity to primary ET		
Very low	17	34.7
Low	32	65.3
Adjuvant endocrine therapy		
Tamoxifen	3	7.1
Letrozole	20	47.6
Anastrozole	17	40.5
Exemestane	2	4.8
First-line ET (stage IV)		
Tamoxifen	1	11.1
Letrozole	6	66.7
Anastrozole	2	22.2
Second-line ET		
Fulvestrant	40	81.6
SERM	5	10.2
AI	3	6.1
mTORi + AI	1	2.0

BMI body mass index; *ER* estrogen receptor; *PgR* progesterone receptor; *PS* performance status; *IDC* invasive ductal carcinoma; *ILC* invasive lobular carcinoma; *ET* endocrine therapy; *SERM* selective estrogen receptor modulators; *AI* aromatase inhibitor; *mTORi* mTOR inhibitor

Prognostic data

The median follow-up time was 10.8 months. The median PFS of the entire cohort ($n=49$) was 7.1 (95% CI: 5.6–10.6) months, and the 1-year PFS rate was 34.1% (95% CI: 21.2–47.4%; Fig. 1a). The one-year OS, TTF, and TTC rates were 93.8% (95% CI: 82.0–98.0%; Fig. 2a), 32.0% (95% CI: 19.5–45.2%; Fig. 3a), and 73.2% (95% CI: 57.4–83.9%; Supplementary figure 1a), respectively. In the fulvestrant-only subgroup ($n=40$), the median PFS was 6.7 (95% CI: 5.6–9.6) months and the 1-year PFS rate was 30.0% (95% CI: 16.8–44.4%; Fig. 1b). The 1-year OS, TTF, and TTC rates were 94.9% (95 CI: 81.2–98.7%; Fig. 2b), 27.5% (95% CI: 14.9–41.7%; Fig. 3b), and 69.9% (95% CI: 52.0–82.2%; Supplementary figure 1b), respectively.

Adverse events

The adverse events (≥ grade 3) are presented in Table 4. A total of twelve AEs were observed in this cohort. In the fulvestrant group (total patients $N=40$), abnormal blood levels of aspartate transaminase, total bilirubin, gamma-glutamyltransferase, and fatigue were reported. In the AI group ($N=3$), two and one patients had depression and insomnia, respectively, whereas in the everolimus with exemestane group ($N=1$), one, one, two, and one patients had interstitial pneumonia, appetite loss, fatigue (one patient had it twice), and oral mucositis, respectively.

Discussion

To our knowledge, this is the first study to assess the efficacy of sequential second-line ETs in postmenopausal ER-positive and HER2-negative MBC with lower endocrine sensitivity. We first evaluated the clinical significance of the efficacy of second-line ETs in ER-positive and HER2-negative postmenopausal MBC in cases where primary ET did not demonstrate favorable clinical benefits with relative safety. Over 20 years have elapsed since the Hortobagyi algorism was established [4], and additional next-generation ETs

Table 2 Predictive factors for clinical benefit rate for 6 months

	Number of samples	%	90% CI			*p* value
All	49	44.9	34.6	–	57.6	0.009
Fulvestrant	40	40.0	29.2	–	54.2	0.063
PgR-positive	10	51.3	39.6	–	65.3	0.002
PgR-negative	39	20.0	8.7	–	50.7	0.617
Very low sensitivity	17	58.8	42.0	–	78.8	0.003
Low sensitivity	32	39.4	27.8	–	55.2	0.088
Visceral	24	41.7	28.2	–	60.3	0.074
Non-visceral	25	48.0	34.1	–	65.9	0.018

PgR progesterone receptor

Table 3 Predictive factors for response rate for 6 months

	Number of samples	%	90% CI		
All	49	8.2	4.1	–	17.7
Fulvestrant	40	2.5	0.9	–	11.3
PgR positive	10	7.7	3.6	–	18.7
PgR negative	39	10.0	3.7	–	39.4
Very low sensitivity	17	11.8	5.0	–	32.6
Low sensitivity	32	6.1	2.5	–	17.9
Visceral	24	8.3	3.5	–	24.0
Non-visceral	25	8.0	3.4	–	23.1

PgR progesterone receptor

have been available for routine clinical use for HR-positive and HER2-negative MBC. Fulvestrant, a selective estrogen receptor degrader, was selected for the majority of patients in our cohort; a lack of cross-reactivity with tamoxifen or AIs was observed. Therefore, cancers that progress during ET might remain sensitive to fulvestrant [15, 16]. Ellis et al. reported that in the first-line setting, fulvestrant (500 mg) improves outcomes of HR-positive advanced breast cancer compared to those with AIs [17]. The clinical efficacy of first-line fulvestrant (500 mg) is also supported by the results of the phase III double-blind FALCON trial, which assessed patients with locally advanced or metastatic breast cancers using a strict definition for ET-naïve disease [13]. There might be some distinct resistant mechanisms between aromatase inhibitor and fulvestrant. Although aromatase inhibition is prone to resistance generated by *ESR1* mutations [18], fulvestrant does seem to retain activity against tumors that harbor an *ESR1* mutation [19]. Further study is needed to clarify these mechanisms. Our results provide additional data on the clinical efficacy of second-line ET, and fulvestrant in particular, for patients with poor response to first-line ETs. Unfortunately, the considerably small sample sizes of the individual ET subgroups (i.e. SERMs, mTOR inhibitors, and AIs) in our cohort might not provide adequate statistical power; future trials on various agents,

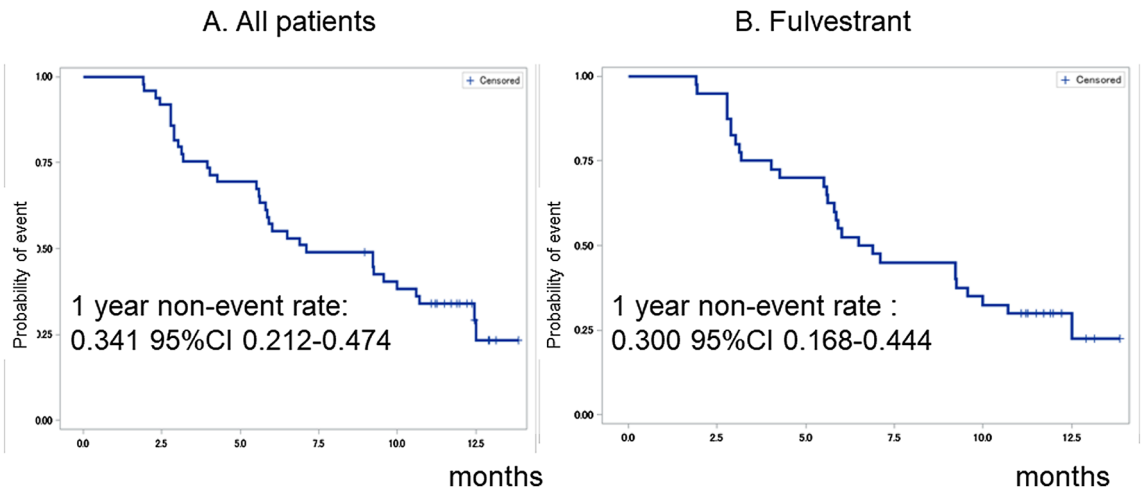

Fig. 1 Kaplan–Meier curves for progression free survival. **a** All patients ($N=49$), **b** fulvestrant ($n=40$). *CI* confidence interval

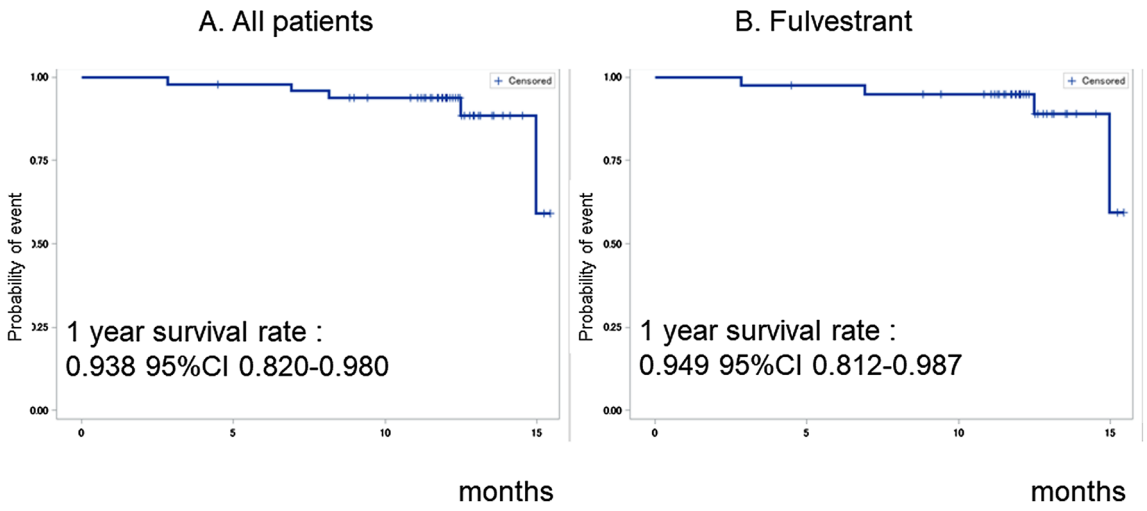

Fig. 2 Kaplan–Meier curves for overall survival. **a** All patients ($N=49$), **b** fulvestrant ($n=40$). *CI* confidence interval

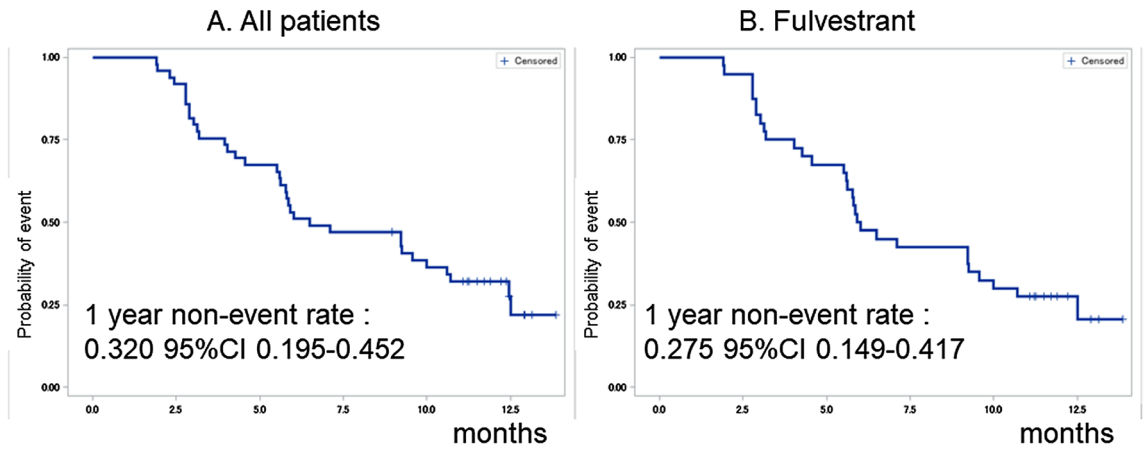

Fig. 3 Kaplan–Meier curves for time to treatment failure. **a** All patients ($N=49$), **b** fulvestrant ($n=40$). *CI* confidence interval

including cyclin-dependent kinase (CDK) inhibitors in addition to SERMs, mTOR inhibitors, and AIs, are warranted in the second-line setting after the endocrine responses of low sensitivity to first-line ET.

We subsequently evaluated the predictive factors (non-visceral metastases, PgR-positivity, and very low sensitivity; P value <0.05) for the efficacy of second-line ETs as secondary endpoints. Sub-analyses from prospective randomized trials in the first-line setting have already demonstrated the clinical efficacy of fulvestrant in patients with non-visceral metastases; however, no significant clinical differences were observed between fulvestrant and AIs alone in cases with visceral metastases [13]. It is essential to emphasize that this was a sub-analysis of a prospective randomized control trial [13]. Since this was not a primary endpoint, it was not clear whether the unique biological characteristics of fulvestrant confer selective efficacy for non-visceral or visceral metastases. However, our findings agree with that of the previously reported data. The prognostic value of "PgR-positivity" has also been discussed previously. PgR-positivity was found to be associated with good outcomes in HR-positive breast cancers, indicating better baseline prognoses than in PgR-negative cases. The predictive value of PgR expression regarding the benefit from ET has also been evaluated [20, 21]. Subgroup analysis from the same clinical trial showed that PgR-positivity resulted in superior PFS (hazard ratio: 0·728, CI: 0·561–0·944) in patients treated with fulvestrant compared to that with AI alone [13]. Similar to our observations, these previous reports demonstrated good predictive value of PgR-positivity. Interestingly, "very low sensitivity" defined as recurrence within 2 years during adjuvant ET or progression within 3 months of initial ET, was also found to be a favorable predictive factor in our cohort. In the case of classical ET, the majority of this subset with "very low

Table 4 Adverse events for the second line hormone therapy (≥ grade 3)

Adverse events	Number of events
Fulvestrant ($n=40$)	
AST	1
Total bilirubin	1
γ-GTP	1
Fatigue	1
AI ($n=3$)	
Depression	2
Insomnia	1
Everolimus + exemestane ($n=1$)	
Interstitial pneumonia	1
Appetite loss	1
Fatigue	2
Oral mucositis	1

AST aspartate transaminase, *γ-GTP* gamma-glutamyltransferase

sensitivity" might receive first-line chemotherapy instead of second-line ETs after progression on the first-line ET [4]. The Hortobagyi algorism [4] was based on classical, and not next-generation ETs and targeted therapies [including, SERD, inhibitors of mTOR, poly ADP ribose polymerase (PARP), CDK, and immune checkpoints]. New agents with distinct mechanisms of action might help to establish next-generation treatment strategies, and these analyses of predictive markers need to be interpreted with caution. Previous reports suggest that ET with CDK inhibitors are effective for treating both visceral and non-visceral HR-positive and HER2-negative MBC in the first or second-line settings [22–24]. Distinct predictive markers need to be evaluated for various agents (i.e. SERMs, SERD, AIs, CDK inhibitors, and PARP inhibitors) and settings (i.e. neoadjuvant, adjuvant, and first/second or later-line therapies). Our findings also need to be validated in other independent datasets.

Our study has certain limitations. First, the sample size was small; therefore, our findings should be interpreted with caution. The heterogeneity of treatments (fulvestrant, SERMs, steroidal AI with an mTOR inhibitor, and AI) in our cohort might have affected the results. We performed only univariate analyses in this study and did not have enough sample size for multivariate analyses. Confounding factors might impact on our results. Moreover, the study did not aim to compare different treatment regimens. Assuming the use of an accurate binominal test with $\alpha=0.05$ (one-tailed) and $\beta=0.2$, none of the subgroups (fulvestrant, SERMs, mTOR inhibitor, and AI) had 43 patients. Further, the recommended second-line ET regimen could not be identified as the fulvestrant group with 40 cases as the largest subgroup. Second, being a cohort study, only registered patients were selected and cases might not have always been evenly distributed to each cohort. This hidden bias could misrepresent findings to readers. Despite these limitations, our finding that second-line ETs provide clinical benefits for patients with poor sensitivities to initial ET was clinically significant, as the total number assessed in our cohort exceeded the minimum number of estimated cases.

In conclusion, this study showed that second-line ET was effective and might be a valid option for the sequential treatment of postmenopausal women with MBC with low and very low sensitivity to initial ET. Future studies based on larger and independent cohorts are needed to evaluate the predictive values of these treatment strategies and covariates. Since prospective randomized control trials might not be feasible for this small population with low sensitivity to first-line ETs, cohort studies might be more suitable.

Acknowledgements This study was conducted as a research support project of the General Incorporated Association of Comprehensive Support Project for Oncological Research of Breast Cancer (CSPOR-BC). We would like to thank Editage (www.editage.com) for English language editing.

Funding This study was funded by AstraZeneca.

Compliance with ethical standards

Conflict of interest TI, TF, TShien, KA, KS, TSangai, ST, RN, TA, HM, and NT declare no conflict of interest. YK received an honorarium from Eizai, Chugai, Novartis, Taiho, Pfizer, and Eli Lilly. MT received an honorarium from AstraZeneca, Eli Lilly, Eizai, and Pfizer, and research funding from Eizai, Kyowa Hakko Kirin, Taiho, and Nippon kayaku.

Ethical approval All procedures performed in studies involving human participants were 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 Informed consent was obtained from all individual participants included in the study.

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Affiliations

Takayuki Iwamoto[1] · Tomomi Fujisawa[2] · Tadahiko Shien[1] · Kazuhiro Araki[3] · Kentaro Sakamaki[4] · Takafumi Sangai[5] · Yuichiro Kikawa[6] · Shintaro Takao[7] · Reiki Nishimura[8] · Masato Takahashi[9] · Tomohiko Aihara[10] · Hirofumi Mukai[11] · Naruto Taira[1]

1 Department of Breast and Endocrine Surgery, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

2 Department of Breast Oncology, Gunma Prefectural Cancer Center, Gunma, Japan

3 Department of Medical Oncology, Gunma Prefectural Cancer Center, Gunma, Japan

4 Department of Biostatistics and Bioinformatics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

5 Department of Breast and Thyroid Surgery, Chiba University Hospital, Chiba, Japan

6 Department of Breast Surgery, Kobe City Medical Center General Hospital, Kobe, Japan

7 Department of Breast Surgery, Hyogo Cancer Center, Hyogo, Japan

8 Department of Breast Oncology, Kumamoto Shinto General Hospital, Kumamoto, Japan

9 Department of Breast Surgery, National Hospital Organization Hokkaido Cancer Center, Hokkaido, Japan

10 Breast Center, Aihara Hospital, Osaka, Japan

11 Division of Breast and Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan