

Factors associated with overall survival after recurrence in patients with ER-positive/HER2-negative breast cancer: An ad-hoc analysis of the JBCRG-C06 Safari study

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Abstract

Background

The Safari study (UMIN 000015168) was a retrospective, multicenter study in which 1072 consecutive cases of estrogen receptor-positive (ER+) advanced breast cancer (ABC) treated using 500 mg fulvestrant were registered. We previously reported the relationship between the patient factors and overall survival (OS) after the diagnosis using the same cases and the same factors for the analysis of time to treatment failure (TTF) in patients with ER + ABC. The current study is an ad-hoc analysis that focused on the relationship between the patient factors and OS after recurrence by adding factors generally associated with OS after recurrence.

Methods

The OS after recurrence in patients with ER + human epidermal growth factor receptor 2 negative (HER2-) recurrent breast cancer was analyzed via univariate and multivariate analyses with a Cox proportional hazards model.

Results

A total of 598 cases were used for the analysis of OS after recurrence. Multivariate analysis revealed that favorable OS (median, 6.4 years) was significantly correlated with long time from recurrence to fulvestrant use (≥ 3 years), low nuclear or histological grade (G3 vs. G1), long TTF of initial palliative endocrine therapy (≥ 12 months), and long time to initial palliative chemotherapy (≥ 2 years).

Conclusion

In patients with ER + HER2 - recurrent breast cancer who received endocrine therapy as the primary palliative treatment, the low proliferation activity of the tumor at the first diagnosis, sensitivity to initial endocrine therapy after the recurrence, and long time to the initiation of chemotherapy might be correlated with the favorable OS after recurrence.

Trial registration:

University Hospital Medical Information Network: UMIN 000015168, 2014/09/16

Introduction

The biology of recurrent breast cancer might be different from that observed at the time of initial diagnosis [1, 2]. In addition, some ER + recurrent cases will show endocrine therapy resistance owing to the use of adjuvant endocrine therapy [3, 4]. For estrogen receptor-positive (ER+) recurrent breast cancer, in addition to endocrine monotherapy, various molecular targeted therapeutic agents have become available in combination with endocrine therapy, such as mammalian target of rapamycin (mTOR) inhibitors, cyclin dependent kinase (CDK) 4/6 inhibitors, and phosphoinositide 3-kinase inhibitors [5, 6]. Therefore, the identification of factors associated with prognosis after recurrence of ER + breast cancer is important for planning the treatment strategy after recurrence. However, although many studies have evaluated the factors that predict recurrence and prognosis at the time of the initial diagnosis [7], only a few studies have determined the factors associated with prognosis after recurrence at the time of recurrence [2, 8, 9].

In the Safari study, we established a database of more than 1,000 cases of ER + advanced breast cancer (ABC), including locally advanced and metastatic breast cancer [10]. The main aim of the Safari study was to explore the factors that influenced time to treatment failure (TTF) of fulvestrant, and the results have been reported previously [11]. Next, we focused on ER+/ human epidermal growth factor receptor 2 negative (HER2-) cases and conducted a TTF subgroup analysis [12]. Then, we performed overall survival (OS) analysis using the same cases and the same factors used in the main TTF analysis [13], because we wanted to compare the factors associated with TTF and factors associated with OS. The factors that were correlated with both long TTF and long OS after fulvestrant use were a long time from ABC diagnosis to fulvestrant use (≥ 3 years), no prior palliative chemotherapy before fulvestrant use, and a low nuclear or histological grade [13].

In the current study, we analyzed the factors correlated with OS after recurrence by using the database of the Safari study, with a focus on recurrent ER+/HER2 - breast cancer cases. HER2 + cases were excluded from this analysis, because even among patients with ER + breast cancer, those with HER2 + cases and those with HER2 - cases have different prognostic properties. De novo Stage IV cases were also excluded because of the lack of data about adjuvant endocrine therapy, adjuvant chemotherapy, and disease-free interval (DFI). In addition, as the biology of de novo Stage IV cancer and recurrent breast cancer may be different, we focused on recurrent cases in the current analysis.

Analysis was performed by adding factors suspected to be involved in the prognosis after recurrence to the factors in the previously reported analysis of OS. Adjuvant chemotherapy (yes vs. no) and adjuvant endocrine therapy (yes vs. no) may be correlated with the prognosis after recurrence [14]. In addition, we suspected that the TTF of initial palliative endocrine therapy (≥ 12 vs. <12 months) and the time to initial palliative chemotherapy (≥ 2 vs. < 2 years) might be prognostic factors, so we added them to the analysis factors. Therefore, the current study aimed to determine the factors correlated with OS after recurrence of ER+/HER2 - recurrent breast cancer.

Methods

Analysis of OS after recurrence

The cohort and design of the Safari study (UMIN 000015168) were previously described using TTF analysis [11, 12] and OS analysis [13]. In brief, the Safari study was a multicenter cohort study of all patients who received fulvestrant between November 25, 2011, when fulvestrant was launched in Japan, and December 31, 2014. A total of 1072 patient's data were collected from 16 sites registered in the Japan Breast Cancer Research Group (JBCRG). When the study was initiated, only data about second-line treatment with fulvestrant were available, so most of the patients had received second-line or later treatment. We analyzed the factors affecting TTF and/or OS in cases of advanced ER + breast cancer in Japan (JBCRG-C06 Safari).

The study was conducted in compliance with the Declaration of Helsinki, "Guidelines for Clinical Evaluation Methods of Anti-Cancer Drugs," and "Ethical Guidelines for Epidemiology Research (revised on December 1, 2008)." Patients received postoperative follow-up and treatment after recurrence according to the National Comprehensive Cancer Network guidelines (version 4, 2018) [15] and the Japanese Breast Cancer Society guidelines [16]. The data cut-off was April 30, 2018. This study was registered as UMIN 000015168.

We analyzed OS after recurrence by using the same previously reported factors of OS analysis [13], as follows: patient age (≥ 60 vs. <60 years), treatment line of fulvestrant (≥ 4 th vs. 3rd vs. 1st and 2nd), time from recurrence to fulvestrant use (≥ 3 vs. <3 years), visceral metastasis (yes vs. no), nuclear or histological grade (G2 vs. G1 and G3 vs. G1), progesterone receptor (PgR) expression (positive vs. negative), and DFI (≥ 5 vs. <5 years). In this analysis, we excluded the previously reported factor "prior palliative chemotherapy use" (yes vs. no) [11–13]. "Prior palliative chemotherapy use" referred to any chemotherapy received after the diagnosis of ABC to the start of fulvestrant. It was decided that "whether chemotherapy was administered before one type of endocrine therapy (fulvestrant)" was not suitable for searching for factors correlated with the prognosis after recurrence. In addition, "prior palliative chemotherapy use" was considered to be confounded with the "time to initial palliative chemotherapy," which is the period between primary endocrine therapy and chemotherapy, as described below.

We added the following factors to the analysis, which were expected to be correlated with OS after recurrence: adjuvant chemotherapy (yes vs. no), adjuvant endocrine therapy (yes vs. no), TTF of initial palliative endocrine therapy (≥ 12 vs. <12 months), time to initial palliative chemotherapy (≥ 2 vs. <2 years). The "time to initial palliative chemotherapy" was defined as the period from the beginning of initial palliative endocrine therapy to subsequent chemotherapy (Supplementary Fig. S1) [17, 18]. If the primary palliative treatment was chemotherapy, those cases were excluded from this analysis. In the current study, the cut-off values for the factors were the same as those used for OS analysis, as we reported previously [13]. The cut-off value of the factor newly added in this analysis was the median value.

Statistical analysis

The OS after recurrence was defined as the period between primary palliative endocrine therapy and the time of death. Kaplan–Meier curves were used for OS analysis. The surviving cases by the time of data cut-off were censored at the last confirmation date. We evaluated the correlation between factors and OS after recurrence by using the Cox hazards model. First, univariate analysis was performed, and multivariate analysis was performed using factors with $P < 0.1$. Hazard ratios (HRs) with 95% confidence intervals (CIs) and P -values were determined. All analyses were two-sided, and $P < 0.05$ was considered statistically significant. To compare the three groups considering outcomes, we used a Bonferoni correction for adjusting the type I error (α) of hypothesis testing. We considered two-sided P -values < 0.025 to be statistically significant.

Results

Patient demographics

Figure 1 shows the patient flowchart. Of the 1072 patients enrolled in the Safari study, we excluded 37 cases treated with fulvestrant combined with other therapies (chemotherapy or new investigational drugs) and 4 cases of ER – cancer, leaving 1031 cases eligible for OS efficacy analysis [13].

In the current analysis of OS after recurrence, 174 cases of de novo metastatic or unresectable locally advanced were excluded.

In addition, we excluded 112 cases treated with chemotherapy as the first palliative treatment. Finally, 598 cases were eligible for this analysis.

Table 1 shows the characteristics of the patient included in this analysis. The median age at recurrence was 60 years. Fulvestrant was most often used for later-line treatment. Visceral metastases at the time of first recurrence were observed in 240 patients (40.1%), and there were 114 cases of PgR – cancer (19.1%) and 40 cases with unknown PgR status (6.7%). The TTF after the initial treatment with palliative endocrine therapy was < 12 months in 302 patients (50.5%), ≥ 12 months in 291 patients (48.7%), and unknown in 5 patients (0.8%). The time to initial palliative chemotherapy was < 2 years in 196 patients (32.8%) and ≥ 2 years in 217 cases (36.3%); 185 patients (30.9%) did not receive any palliative chemotherapy.

Table 1
Patient characteristics

	OS after recurrence dataset
Characteristic	<i>n</i> = 598
Age (recurrent diagnosis), years	
Median	61
Range	29–91
Age group (recurrent diagnosis), <i>n</i> (%)	
<60	259 (43.3)
≥60	339 (56.7)
Treatment line of fulvestrant	
First	12 (2.0)
Second	140 (23.4)
Third	159 (26.6)
Fourth or more	287 (48.0)
Time from recurrence to fulvestrant use, years	
Median	2.8
Range	0–24.3
Time from recurrence to fulvestrant use, group, years	
<3	313 (52.3)
≥3	285 (47.7)
DFI, years	
Median	5.6
Range	0–30.3
DFI, group, years	
<5	268 (44.8)

Results are given as *n* (%) unless otherwise indicated.

OS, overall survival; DFI, disease-free interval; ER, estrogen receptor; PgR, progesterone receptor; TTF, time to treatment failure.

	OS after recurrence dataset
≥5	330 (55.2)
Visceral metastasis	
No	358 (59.9)
Yes	240 (40.1)
Nuclear or histological grade	
1	201 (33.6)
2	139 (23.2)
3	76 (12.7)
NA	182 (30.4)
Hormonal receptor	
ER(+) PgR(-)	114 (19.1)
ER(+) PgR(+)	444 (74.2)
ER(+) PgR(NA)	40 (6.7)
Adjuvant chemotherapy	
No	249 (41.6)
Yes	349 (58.4)
Adjuvant endocrine therapy	
No	95 (15.9)
Yes	503 (84.1)
TTF of initial endocrine therapy, months	
Median	11.9
Range	0.1–226.4
TTF of initial endocrine therapy, group, months	
<12	302 (50.5)

Results are given as n (%) unless otherwise indicated.

OS, overall survival; DFI, disease-free interval; ER, estrogen receptor; PgR, progesterone receptor; TTF, time to treatment failure.

	OS after recurrence dataset
≥12	291 (48.7)
NA	5 (0.8)
Time to initial palliative chemotherapy, years	
Median	2.1
Range	0–23.0
Time to initial palliative chemotherapy, group, years	
<2	196 (32.8)
≥2	217 (36.3)
No chemotherapy use	185 (30.9)
Results are given as n (%) unless otherwise indicated.	
OS, overall survival; DFI, disease-free interval; ER, estrogen receptor; PgR, progesterone receptor; TTF, time to treatment failure.	

Analysis of outcomes

The median OS was 6.4 years (95% CI: 5.9–7.1 years; Supplementary Fig. S2). Table 2 shows the results of univariate and multivariate analyses of factors affecting OS after recurrence. Univariate analysis revealed that favorable OS after recurrence was correlated with young age (< 60 years), early treatment line of fulvestrant, long time from recurrence to fulvestrant use (≥ 3 years), low nuclear or histologic grade (G2 vs. G1 and G3 vs. G1), no adjuvant chemotherapy, no adjuvant endocrine therapy, long TTF of initial palliative endocrine therapy (≥ 12 months), and long time to initial palliative chemotherapy (≥ 2 years; $P < 0.1$). In contrast, visceral metastasis, PgR, and DFI were not correlated with OS after recurrence. PgR expression had a P -value of < 0.1 for (NA vs. negative) but not for (positive vs. negative); therefore, PgR expression was not included in the factors for multivariate analysis. The TTF of initial palliative endocrine therapy did not have a P -value of < 0.1 for (NA vs. < 12 months) but the P -value was < 0.1 for (≥ 12 vs. < 12 months); hence, we added the TTF of initial palliative endocrine therapy to the factors for multivariate analysis. On multivariate analysis, long time from recurrence to fulvestrant use (≥ 3 years; $P < 0.0001$), low nuclear or histologic grade (G1 > G3; $P < 0.0001$), long TTF of initial palliative endocrine therapy (≥ 12 months; $P < 0.0001$), and long time to initial palliative chemotherapy (≥ 2 years; $P = 0.009$) were correlated with favorable OS (Table 2).

Table 2

Univariate and multivariate Cox proportional hazards regression models for OS from recurrence (n = 598)

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (≥ 60 vs. <60 years)	1.51 (1.23–1.85)	< 0.0001	1.23 (1.00–1.53)	0.051
Treatment line of fulvestrant (≥ 4 th vs. 3rd vs. 1st and 2nd)	0.70 (0.61–0.79)	< 0.0001	0.97 (0.84–1.12)	0.67
Time from recurrence to fulvestrant use (≥ 3 vs. <3 years)	0.17 (0.13–0.22)	< 0.0001	0.26 (0.20–0.35)	< 0.0001
Visceral metastasis (yes vs. no)	1.13 (0.92–1.38)	0.24		
Nuclear or histological grade				
Grade 2 vs. Grade 1	1.49 (1.14–1.94)	0.003	1.04 (0.80–1.37)	0.76
Grade 3 vs. Grade 1	2.31 (1.72–3.12)	< 0.0001	1.87 (1.37–2.54)	< 0.0001
NA vs. Grade 1	0.56 (0.43–0.72)	< 0.0001	0.59 (0.45–0.77)	< 0.0001
PgR				
Positive vs. negative	1.08 (0.83–1.40)	0.58		
NA vs. negative	0.63 (0.39–1.01)	0.06*		
DFI (≥ 5 vs. <5 years)	0.89 (0.73–1.08)	0.24		

OS, overall survival; CI, confidence interval; HR, hazard ratio; PgR, progesterone receptor; DFI, disease-free interval; TTF, time to treatment failure

Factors that were significant ($P < 0.1$) on the univariate analysis were used as explanatory variables in the multivariate analysis.

* PgR expression had a P-value of < 0.1 for (NA vs. negative) but not for (positive vs. negative); therefore, PgR expression was not included in the factors for multivariate analysis.

† The TTF of initial palliative endocrine therapy did not have a P-value of < 0.1 for (NA vs. <12 months) but the P-value was < 0.1 for (≥ 12 vs. <12 months); hence, we added the TTF of initial palliative endocrine therapy to the factors for multivariate analysis.

‡ Cases that were not treated with palliative chemotherapy were treated as missing values.

	Univariate analysis		Multivariate analysis	
Adjuvant chemotherapy (yes vs. no)	1.29 (1.06–1.58)	0.01	1.13 (0.91–1.39)	0.26
Adjuvant endocrine therapy (yes vs. no)	1.80 (1.36–2.38)	< 0.0001	1.20 (0.89–1.63)	0.24
TTF of initial palliative endocrine therapy				
(≥ 12 vs. <12 months)	0.37 (0.30–0.45)	< 0.0001	0.57 (0.45–0.74)	< 0.0001
(NA vs. <12 months)	0.41 (0.13–1.27)	0.12 [†]	1.20 (0.38–3.86)	0.76
Time to initial palliative chemotherapy				
(≥ 2 vs. <2 years)	0.35 (0.28–0.44)	< 0.0001	0.69 (0.52–0.91)	0.009
(NA [‡] vs. <2 years)	0.36 (0.27–0.47)	< 0.0001	0.51 (0.38–0.68)	< 0.0001
OS, overall survival; CI, confidence interval; HR, hazard ratio; PgR, progesterone receptor; DFI, disease-free interval; TTF, time to treatment failure				
Factors that were significant ($P < 0.1$) on the univariate analysis were used as explanatory variables in the multivariate analysis.				
* PgR expression had a P-value of < 0.1 for (NA vs. negative) but not for (positive vs. negative); therefore, PgR expression was not included in the factors for multivariate analysis.				
† The TTF of initial palliative endocrine therapy did not have a P-value of < 0.1 for (NA vs. <12 months) but the P-value was < 0.1 for (≥ 12 vs. <12 months); hence, we added the TTF of initial palliative endocrine therapy to the factors for multivariate analysis.				
‡ Cases that were not treated with palliative chemotherapy were treated as missing values.				

The Kaplan–Meier curve showed that a long TTF of initial palliative endocrine therapy (≥ 12 months) was significantly correlated with favorable OS ($P < 0.0001$; Fig. 2). In addition, OS was better after recurrence with a long time to initial palliative chemotherapy (≥ 2 years) than after a short time (< 2 years; $P < 0.0001$; Fig. 3).

Discussion

The current study was a subgroup analysis of the previously reported Safari study (UMIN 000015168) [13], which examined the association between clinicopathological factors and OS in patients with ER + ABC whose treatment history included fulvestrant. In the current study, we analyzed the factors that affected OS after recurrence in only HER2 – recurrent cases. The median OS after recurrence was 6.4 years, which is longer than that reported in Japanese studies (4–5 years) [8, 9] and in Western studies (< 5

years) that used a similar cohort [19]. It is possible that the Safari study included cases with a relatively good prognosis because most cases had a history of using second-line or later fulvestrant. At the time of enrollment in the Safari study, only the CONFIRM trial [20], in which fulvestrant was effective as the second-line endocrine treatment, included results of the phase III trial for 500 mg fulvestrant. In addition, Japanese patients with recurrent breast cancer have a relatively good prognosis, which is discussed in more detail in the OS analysis of our previously reported Safari study [13].

The main purpose of this subgroup analysis was to determine factors that were correlated with OS after recurrence, as the factors aid in determining the treatment strategy of the cases after recurrence. In the current study, multivariate analysis revealed that low nuclear or histological grade were correlated with a long prognosis after recurrence, similar to that observed in previous studies [14]. In addition, although the difference was not statistically significant, a better prognosis was found at a young age ($P=0.051$). This has also been reported in previous studies [14, 22]. In contrast, we were unable to determine why patients with long time from recurrence to fulvestrant use had good prognosis after recurrence. There are possibly two reasons for this long prognosis after recurrence. The first reason is that the long prognosis may be because the endocrine therapy given before the administration of fulvestrant might have been effective and that the endocrine therapy could be administered for a long period before fulvestrant use; thus, the sensitivity of these cases to endocrine therapy should be high and OS after recurrence should be long. The second reason may be that the tumor grows very slowly after recurrence, regardless of whether endocrine therapy is effective. Univariate analysis showed that “the use of fulvestrant in the later line” may result in a longer OS after recurrence, but multivariate analysis contradicted this finding because “a long time from recurrence to fulvestrant use” would be confounded with “the use of fulvestrant in the later line.”

The current study also showed that a long TTF of initial palliative endocrine therapy was correlated with favorable OS after recurrence. This finding may be explained by the fact that cases with high endocrine sensitivity at the time of recurrence have a favorable OS after the recurrence. Moreover, the correlation between long TTF of initial palliative endocrine therapy and favorable OS after recurrence may be owing to the biological feature of slow tumor growth after recurrence, irrespective of whether endocrine therapy was effective. The reason for this is the same as those explained in the previous paragraph. Regardless of whichever of the two reasons is applicable, this information is possibly useful for choosing subsequent therapy. If the initial palliative endocrine TTF is long enough, no aggressive treatment may be needed. In addition, the results showed a favorable OS after the recurrence of cases in which the period was long between the first palliative endocrine therapy and the initial palliative chemotherapy. Thus, the period at which endocrine therapy is administered after recurrence may also predict the prognosis of the case.

Although the survival time after recurrence of breast cancer has been prolonged, the disease is still difficult to cure [23]. The ASCO Statement states that in advanced incurable cancer care, disease-directed therapy, symptom management, and attention QOL must be considered [24]. A long time to initial palliative chemotherapy allows endocrine therapy with few adverse events to be continued for a long

period of time, which directly leads to maintenance of QOL in patients with recurrent breast cancer. In order to prolong the time to initial palliative chemotherapy, the tumor should be sensitive to endocrine therapy at the time of recurrence, but it is also important that the tumor is stable without rapid growth (so-called tumor dormancy [15]). Tumor dormancy requires that, among other things, there is no heterogeneity of the tumor, there are no genetic or epigenetic changes that result in the tumor becoming resistant to endocrine therapy, angiogenesis is suppressed, the metastatic site is not fatal, and the tumor is neither high volume nor critical [26–28]. In the current study, it is speculated that patients with a long time to initial palliative chemotherapy had favorable OS because these conditions were met. However, it is unlikely that the patients with time to initial palliative chemotherapy of 2 years or more, as shown in this study, will have a highly favorable prognosis with a median OS of 8.8 years after recurrence. It is just speculation, but long-term exposure to endocrine therapy may have improved OS because of some effect, such as an immune response, that is not already known as an endocrine therapy.

Previous studies showed that PgR [21, 29], DFI [21, 29, 30], visceral metastasis [8, 21, 22, 29, 30], and adjuvant chemotherapy [14, 21, 29, 30] were associated with OS after recurrence. However, the current study did not find any correlation between these factors and OS after recurrence.

The reason may be that the database used in this study included cases with a relatively good prognosis wherein patients received fulvestrant after the second-line or later endocrine therapy.

We hypothesized that cases that responded well to endocrine therapy after recurrence would be eligible, regardless of the status of PgR, DFI, organ metastasis, and adjuvant chemotherapy. In other words, among recurrent cases with PgR – status, short DFI, visceral metastases, and adjuvant chemotherapy, the treatment of those suspected to have a low endocrine sensitivity would already be converted to chemotherapy before using fulvestrant. Therefore, these cases may not be included in this dataset.

As previously reported, the limitations of the Safari study were the retrospective nature of the study and the lack of a comparative treatment group [11–13]. The current study was considered to reflect real clinical practice. Moreover, because the database includes only cases treated with fulvestrant, it does not reflect the entire population of ER + ABC and is hence a highly selected population. The study was also limited by the fact that other endocrine therapies were not considered. Furthermore, only recurrent cases were included, because we wanted to determine how the DFI, initial palliative endocrine therapy, and the time between initial palliative endocrine therapy and initial palliative chemotherapy would affect OS after recurrence.

Conclusion

The proliferative activity of the tumor at the first diagnosis, the sensitivity of initial endocrine therapy after recurrence, and the period between initial endocrine therapy and the initiation of chemotherapy may be correlated with OS after recurrence in patients with ER+/HER2 – recurrent breast cancer who received endocrine therapy as the first palliative treatment.

Abbreviations

ER: estrogen receptor; ABC: advanced breast cancer; OS: overall survival; TTF: time to treatment failure; HER2: human epidermal growth factor receptor 2; mTOR: mammalian target of rapamycin; CDK: cyclin dependent kinase; DFI: disease-free interval; JBCRG: Japan Breast Cancer Research Group; PgR: progesterone receptor; HRs: Hazard ratios; Cis: confidence intervals

Declarations

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Author's contributions

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Manuscript writing: All authors

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Availability of data and materials

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

Ethics approval and consent to participate

The study was conducted in compliance with the Declaration of Helsinki, “Guidelines for Clinical Evaluation Methods of Anti-Cancer Drugs,” and “Ethical Guidelines for Epidemiology Research (revised on December 1, 2008).” Study protocol was approved by the institutional review board (IRB) of Matsuyama Red Cross Hospital (No. 426) and other 15 study sites as follows; Kumamoto University Graduate School of Medical Sciences, NHO Shikoku Cancer Center, Kitakyushu Municipal Medical Center, The Cancer Institute Hospital of JFCR, Hiroshima City Hiroshima Citizens Hospital, Niigata Cancer Center Hospital, Toranomon Hospital, Kyushu Cancer Center, Showa University School of Medicine, Hirosaki Municipal Hospital, Aichi Cancer Center Hospital, Gunma Prefectural Cancer Center, JCHO Kurume General Hospital, Hokkaido University Hospital, and Sagara Hospital Miyazaki.

As this observational study contained neither investigational intervention nor human-derived specimens, all boards of above facilities waived the need for written informed consent in accordance with the Japanese government’s Ethical Guidelines for Medical and Health Research Involving Human Subjects, which allow for the opt-out opportunity for the secondary use of existing clinical medical records.

Consent for publication

Not applicable.

Competing interest

H.K. received honoraria from Pfizer, Chugai, AstraZeneca and Eisai; Y.Y. received honoraria from Chugai, Pfizer, AstraZeneca, research funding from Chugai; S.S. received honoraria from Kyowa Kirin, Chugai, Eli Lilly, AstraZeneca, Pfizer, Eisai, Takeda and Novartis, research funding from Chugai and Taiho; N.M. received honoraria from Chugai, AstraZeneca, Pfizer, Eli Lilly, Eisai and Takeda, research funding from Chugai, AstraZeneca, Kyowa-Kirin, MSD, Novartis, Pfizer, Eli Lilly, Eisai, Nippon-Kayaku and Daiichi Sankyo; T.N. has received honoraria from Eli Lilly, Chugai and Novartis; K. Aogi received honoraria from Chugai, Eisai, AstraZeneca, Taiho, Novartis, Daiichi Sankyo, Mochida, Ono and Eli Lilly, research funding from Chugai, Eisai, Takeda and Sanofi; Y.I. received research funding from AstraZeneca, Chugai, Daiichi Sankyo, MSD and Eli Lilly; S.O. received honoraria from Pfizer, Eli Lilly, AstraZeneca, Chugai and Eisai; N.S. received personal fees from Chugai Pharmaceutical, Eisai, Pfizer, Sysmex, TAIHO PHARMACEUTICAL CO., LTD., Kyowa Kirin Co., Ltd., Eli Lilly Japan K.K, T.T. received honoraria from Daiichi-Sankyo, Chugai, Kyowa Kirin, Eisai, Pfizer, Eli Lilly and Celltrion, research funding from Daiichi-Sankyo, Chugai, Kyowa Kirin, Eisai, Ono, Bristol-Myers Squibb, MSD, Merck Serono, Taiho and Novartis; E.T. received honoraria from Chugai, Eli Lilly and AstraZeneca; S.N. received honoraria from AstraZeneca, Chugai and Pfizer, scholarship donations from Chugai, Daiichi Sankyo, Eisai and Taiho; S.M. received honoraria from AstraZeneca, Bristol-Myers Squibb, Chugai, Eli Lilly, Nippon Boehringer Ingelheim and Taiho, research funding from Nippon Boehringer Ingelheim; H.Y. received honoraria from Pfizer; T.Y. received honoraria from Chugai, Eisai and Eli Lilly; M.T. received honoraria from Pfizer, AstraZeneca, Eli Lilly, research funding from Taiho, Shimadzu, Kyowa-Kirin, Pfizer, Chugai, AFI, JBCRG, AstraZeneca, C&C, Nippon Kayaku, Astellas, Bizicom, Termo, others from Eli Lilly; S.O. received honoraria from AstraZeneca, Eisai, Eli

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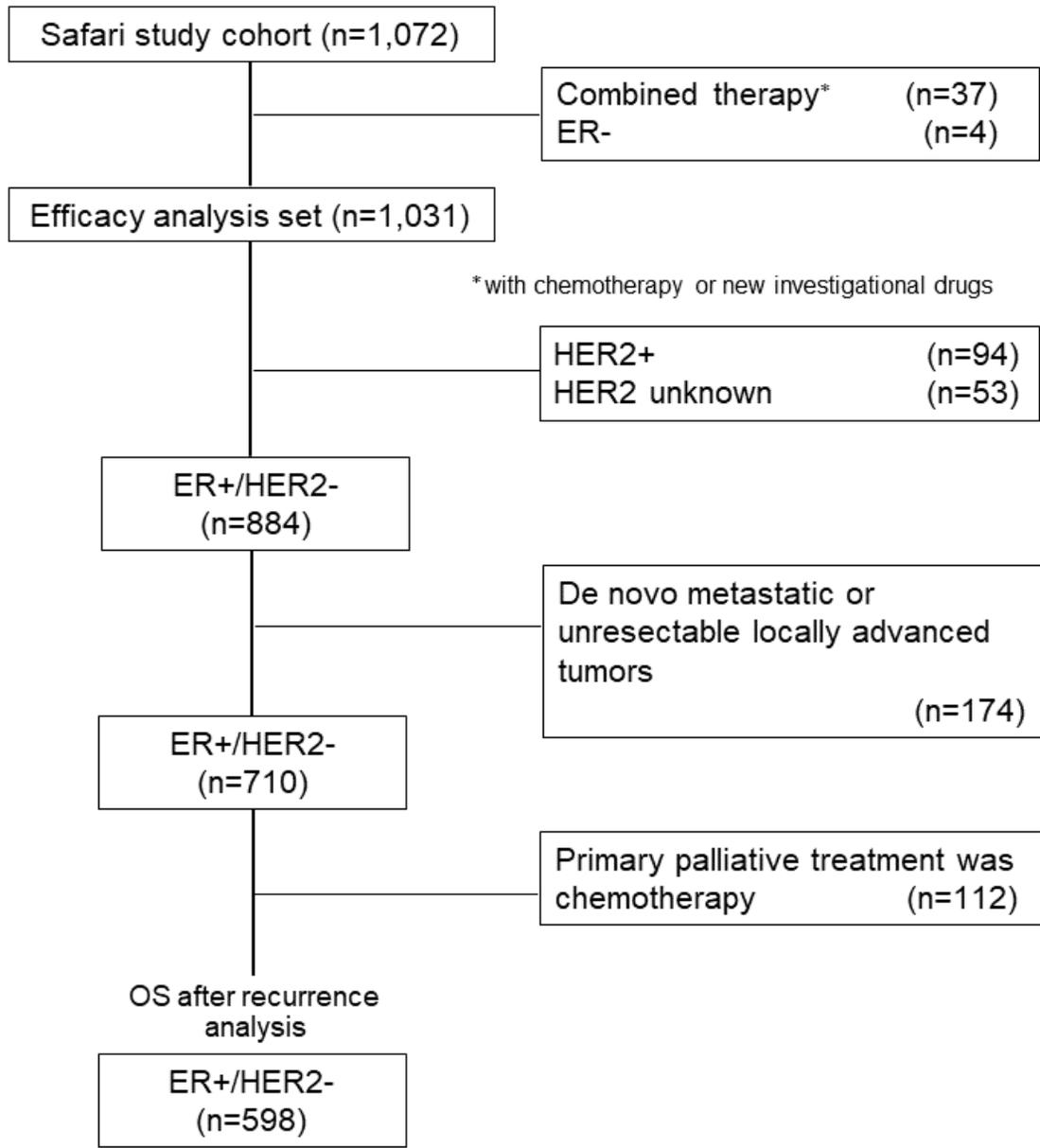
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Figures

Fig. 1

Patient flow diagram

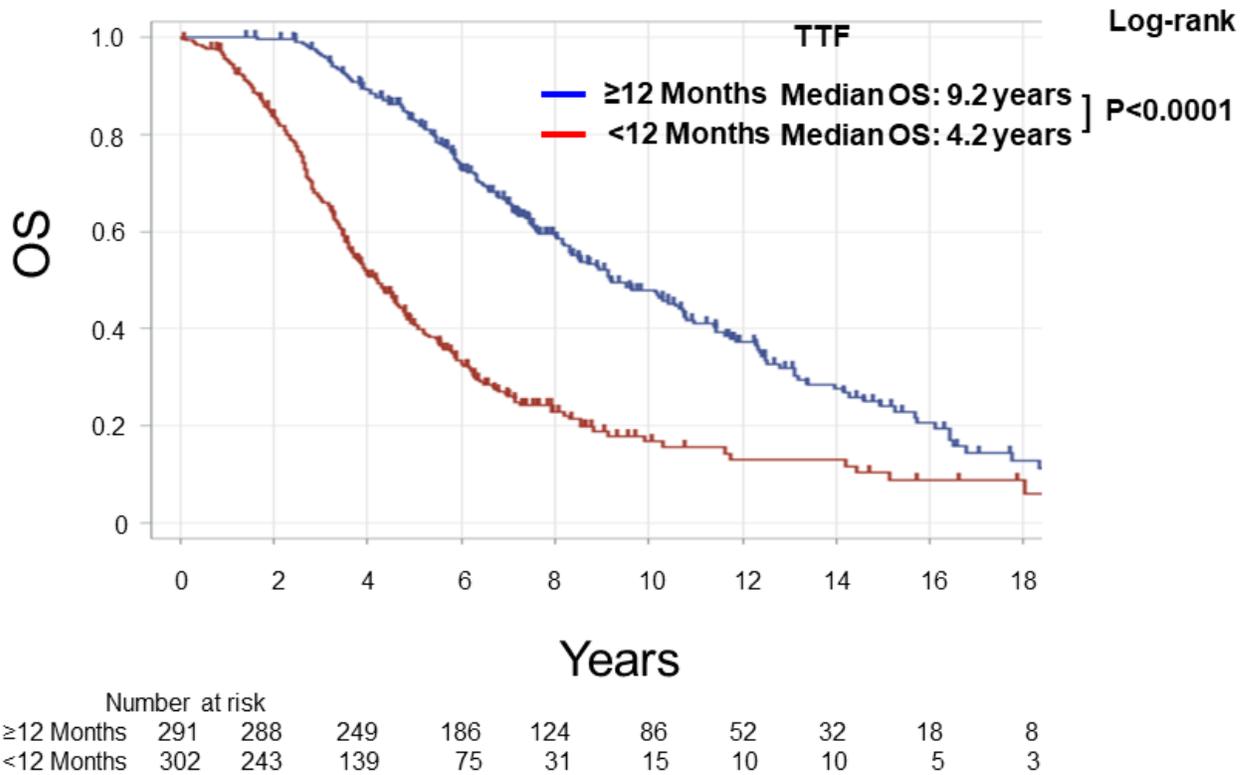


OS, overall survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2

Figure 1

Patient flow diagram. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; OS, overall survival

Fig. 2
OS: TTF of initial palliative endocrine therapy



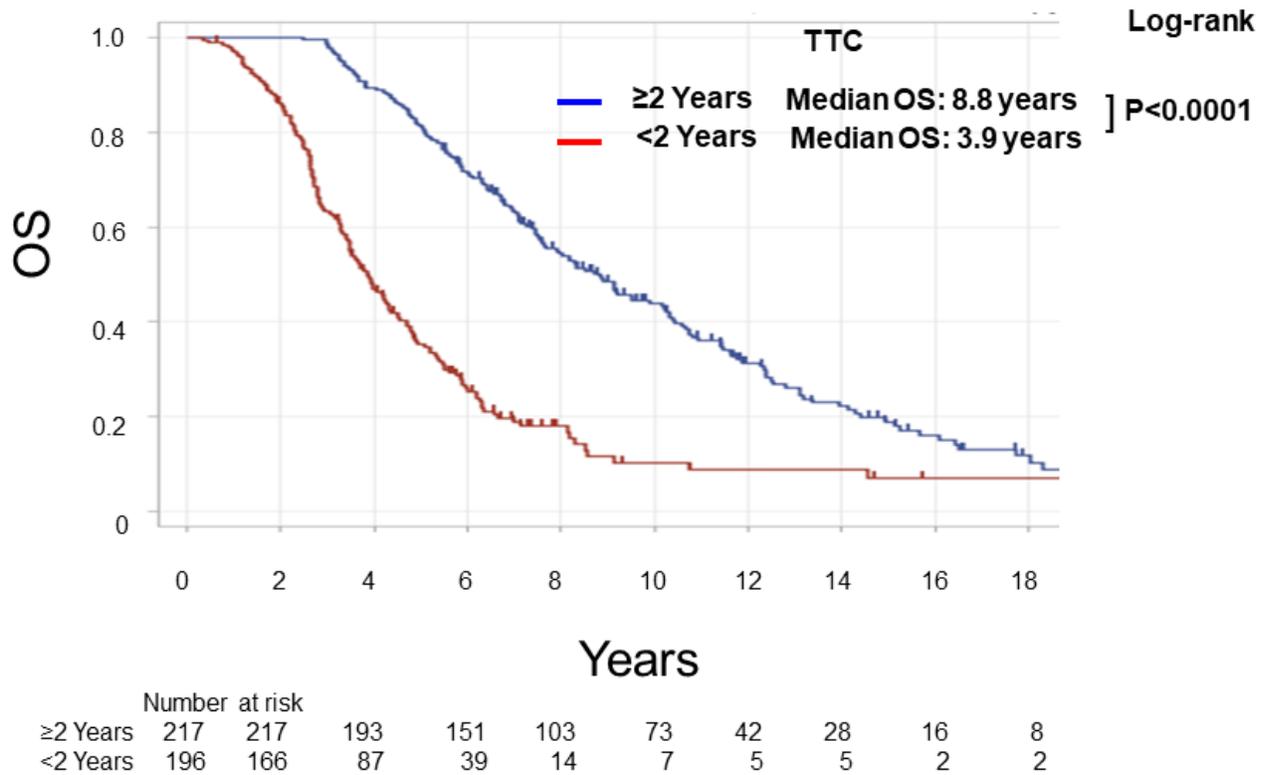
OS, overall survival; TTF, time to treatment failure

Figure 2

Kaplan–Meier estimates for OS after recurrence by the TTF of initial palliative endocrine therapy (≥ 12 vs. < 12 months). Blue line: TTF of initial palliative endocrine therapy ≥ 12 months, red line: TTF of initial palliative endocrine therapy < 12 months. OS, overall survival; TTF, time to treatment failure

Fig. 3

OS: Time to initial palliative chemotherapy



OS, overall survival; TTC, time to initial palliative chemotherapy

Figure 3

Kaplan–Meier estimates for OS after recurrence by the time to initial palliative chemotherapy (≥ 2 vs. < 2 years). Blue line: time to initial palliative chemotherapy ≥ 2 years, red line: time to initial palliative chemotherapy < 2 years, green line: no chemotherapy. OS, overall survival; TTC, time to initial palliative chemotherapy

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