Fulvestrant 500 mg in postmenopausal patients with metastatic breast cancer: the initial clinical experience

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Abstract

Background: Fulvestrant 500 mg is currently approved for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer after failure of prior endocrine therapies.

Methods: A total of 117 postmenopausal women with metastatic breast cancer, who experienced progression after previous endocrine therapies, were treated with fulvestrant 500 mg between January 2012 and June 2014. Clinical response, time to progression (TTP) and adverse events were investigated.

Results: Ninety-nine patients had recurrent breast cancer and 18 patients had stage IV disease. Patients had received a median of two endocrine therapies and a median of two chemotherapies, prior to fulvestrant. There were 10 patients with partial response, 39 patients with long stable disease, 18 patients with stable disease, and 50 patients with progressive disease, so that the objective response rate was 8.5%, with a clinical benefit rate of 41.9%. The median TTP was 6.1 months. The absence of liver metastases, a small number of previous chemotherapies, and the longer duration of first-line endocrine therapy were positively correlated with TTP in univariate analysis. In multivariate analysis, a significant association was observed between TTP and duration of first-line endocrine therapy. Serious adverse events were observed in one patient with pulmonary embolism and in one patient with psychiatric symptoms.

Conclusions: Fulvestrant 500 mg is an effective and well-tolerated treatment for

postmenopausal women with metastatic breast cancer that had progressed after prior endocrine therapies. Patients with acquired resistance to endocrine therapies might be good candidates for fulvestrant therapy regardless of the number of prior endocrine treatments.

Abbreviations

ER, estrogen receptor; PgR, progesterone receptor; HER2, human epidermal growth factor receptor type 2; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; TTP, time to progression; SERM, selective estrogen receptor modulator

Introduction

The purpose of the treatment of metastatic breast cancer is to guarantee a good quality of life and prolong survival of patients. Sequential use of endocrine therapies remains the essential strategy for treatment of hormone receptor-positive advanced breast cancers, with a new treatment prescribed following progression [1]. Selective estrogen receptor modulators (SERMs), such as tamoxifen and toremifene, and aromatase inhibitors are commonly used for endocrine treatment.

Fulvestrant, a 17β-estradiol analog, is a selective estrogen receptor (ER) antagonist without known agonistic properties that downregulates cellular levels of ER in a dose-dependent manner [2-4]. Two phase III trials comparing fulvestrant 250 mg with aromatase inhibitor anastrozole in postmenopausal women with advanced breast cancer that had progressed or recurred after prior tamoxifen therapy showed that both treatments have similar efficacy and an acceptable safety profile with a low incidence of withdrawals [5, 6]. Therefore, fulvestrant was originally approved at a monthly dose of 250 mg in 70 countries except Japan. However, a dose-dependent effect was subsequently shown in the CONFIRM study [7]. This phase III study is a randomized, double-blind, placebo-controlled trial that was designed to assess the efficacy and safety of fulvestrant 500 mg versus fulvestrant 250 mg in patients who progressed following prior anti-estrogen or aromatase inhibitor therapy. Progression-free survival was 6.5 months in the 500 mg group compared with 5.5 months in the 250 mg group, demonstrating a dose-dependent relationship. The benefit was further

confirmed in a follow-up analysis with improved overall survival in the 500 mg group compared with that in the 250 mg group [8]. Notably, the dose-dependent clinical efficacy seen in this trial was not associated with a dose-dependent increase in toxicity, with no substantial differences in toxicity between the treatment groups. In addition to the CONFIRM study, the phase II FINDER1 and FINDER2 studies were conducted on Japanese and European populations, respectively [9, 10]. Although the relatively small sample sizes did not permit a confirmation of improved efficacy of fulvestrant 500 mg in the individual studies, the data raised concerns on ethnic differences in the efficacy and tolerability profiles of fulvestrant. In 2011 these studies led to the approval in Japan of the 500 mg dose for the treatment of postmenopausal women with hormone receptor-positive metastatic breast cancer after failure of prior endocrine therapy. However, there are only few studies on the efficacy and safety of fulvestrant 500 mg in metastatic breast cancer.

In the present study, we report our experience with fulvestrant 500 mg in postmenopausal women with metastatic breast cancer that had progressed after previous endocrine therapies. The effectiveness and safety of fulvestrant 500 mg were retrospectively investigated.

Patients and methods

Patients and treatment

A retrospective review was carried out on a total of 117 postmenopausal women (97 women at the Cancer Institute Hospital and 20 women at the Hokkaido University Hospital) with metastatic breast cancer, who experienced progression after prior endocrine therapies and were treated with fulvestrant 500 mg between January 2012 and June 2014 (Table 1). Most patients were heavily pretreated prior to fulvestrant therapy (median prior endocrine therapies or chemotherapies = 4, Table 2). Patients were given fulvestrant 500 mg as two 5-mL intramuscular injections, one in each buttock, on days 0, 14, and 28 and every 28 days thereafter. Patients with HER2-positive disease were treated in addition with trastuzumab.

Clinical responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). CT and/or MRI and bone scintigraphy were used to evaluate response to fulvestrant therapy for patients with bone metastasis only, and the results were included in this study. Clinical benefit rate was defined as the sum of all patients experiencing complete response (CR), partial response (PR) or stable disease (SD) lasting 6 months or more. Time to progression (TTP) and safety were also retrospectively analyzed. TTP was defined as the time from the date of fulvestrant treatment commencement to the documented date of progression. Adverse events were evaluated using the National Cancer Institute Common Toxicity Criteria, version 4.0.

Statistical analysis

SPSS was used for all statistical analyses. Estimation of survival was performed using the Kaplan-Meier method, and differences between survival curves were assessed with the log-rank test. Univariate and multivariate analyses with Cox proportional hazards regression models were used to identify independent prognostic factors in all patients. *P* values < 0.05 were considered to be significant.

Results

Patients' characteristics

Of 117 patients, 99 (84.6%) had recurrent breast cancer and 18 (15.4%) had stage IV disease (Table 1). Median age at the time of the start of fulvestrant therapy was 62 years (range, 41–85 years). There were 91 (77.8%) patients with ER or progesterone receptor (PgR) -positive and HER2-negative tumors, and 10 (8.5%) patients with tumors that were ER or PgR-positive and HER2-positive. There were 71 (60.7%) patients with both visceral and bone metastases, 35 (29.9%) patients with visceral involvement without bone metastases, and 11 (9.4%) patients with bone metastases without visceral involvement.

Previous treatments

The previous endocrine treatment regimens, in the adjuvant and metastatic setting, and the numbers of previous endocrine and chemotherapy regimens for metastatic breast cancer prior to treatment with fulvestrant 500 mg are listed in Table 2. Thirty-six patients (30.8%) had relapsed during adjuvant endocrine therapy. Prior to fulvestrant therapy, 47 patients (40.2%) had received SERMs and 104 patients (88.9%) had received aromatase inhibitors in the metastatic setting. All patients had undergone endocrine therapy and 30 patients (25.6%) had not received chemotherapy in the metastatic setting prior to fulvestrant. Patients had received a median of two endocrine therapies and a median of two chemotherapies. Twenty-two patients (18.8%) received fulvestrant 500 mg as the second-line

endocrine therapy, 45 patients (38.5%) as the third-line, and 37 patients (31.6%) as the forth-line. Sixty-three patients (53.8%) had received first-line endocrine therapy for 5.5 months or more and 18 patients (15.4%) had received first-line endocrine therapy for less than 5.5 months. The median follow-up from the recurrence or first appearance of advanced breast cancer was 77.2 months (range, 0.9–290.5 months).

Response to fulvestrant therapy and survival

There were 10 patients (8.5%) with PR, 39 patients (33.3%) with long SD, 18 patients (15.4%) with SD, and 50 patients (42.7%) with progressive disease with fulvestrant therapy, so that the objective response rate was 8.5%, with a clinical benefit rate of 41.9% (Table 3). The median TTP of patients who received fulvestrant therapy was 6.1 months (range, 0.3–26.2 months, Fig. 1).

A Kaplan-Meier analysis showed that patients without liver metastases had longer TTP during fulvestrant therapy compared with the others (Fig. 2a). Median duration of TTP was 6.7 months in patients without liver metastases and 3.3 months in patients with liver metastases (p = 0.0038). In order to identify a clinically meaningful cutoff point for the duration of first-line endocrine therapy that could be used to analyze TTP, various durations were tested using the Kaplan-Meier method and were analyzed by the log-rank test. When the cutoff point was set at 5.5 months for first-line endocrine therapy duration, a Kaplan-Meier analysis showed that patients who responded to first-line endocrine therapy (duration ≥ 5.5

months) displayed longer TTP during fulvestrant therapy compared with those with a duration of first-line endocrine therapy less than 5.5 months (Fig. 2b). Median TTP was 7.0 months in patients with duration of first-line endocrine therapy ≥ 5.5 months and 4.7 months in patients with duration of first-line endocrine therapy < 5.5 months ($p = 0.026$). Median TTP in patients who relapsed during adjuvant endocrine therapy was 5.0 months (Fig. 2b). TTP was longer in patients who relapsed during adjuvant endocrine therapy than in those with first-line endocrine therapy duration < 5.5 months, although this was not statistically significant. Univariate analysis showed that the absence of liver metastases ($p = 0.005$), a small number of previous chemotherapies ($p = 0.017$), and the longer duration of first-line endocrine therapy ($p = 0.016$) were positively correlated with TTP (Table 4). In multivariate analysis, a significant association was observed between TTP and duration of first-line endocrine therapy ($p = 0.026$, Table 4).

Adverse events

Adverse events occurred in 26 (22.2%) out of 117 patients (Table 5). The most commonly reported adverse events were gastrointestinal disturbances (n = 9, 7.7%) and joint disorders (n = 8, 6.8%). Serious adverse events were observed in one patient with pulmonary embolism (grade 3) and in one patient with psychiatric symptoms (grade 3).

Discussion

Our experience with fulvestrant 500 mg was reported in postmenopausal advanced breast cancer that had progressed after previous endocrine therapies. Although most patients were heavily treated prior to fulvestrant therapy, our study showed a clinical benefit rate of fulvestrant of 41.9% and TTP of 6.1 months, which are equivalent to that observed in the CONFIRM (45.6% and 6.5 months, respectively) [7] and the FINDER1 (46.8% and 6.0 months, respectively) [9] studies in patients who experienced progression after first-line endocrine therapy.

Sequential use of endocrine therapies is fundamental for treatment of hormone receptor-positive advanced breast cancer [1]. While various endocrine therapies are indicated for postmenopausal breast cancer, nonsteroidal aromatase inhibitors have been primarily used as first-line therapy for recurrence. Subsequent endocrine agents for patients who are refractory to aromatase inhibitors have been investigated for the past decade. There are several options, such as a steroidal aromatase inhibitor exemestane [11, 12], SERMs [13, 14], fulvestrant 250 mg [15], fulvestrant 500 mg [7, 9, 10], and an endocrine agent in combination with the mTOR inhibitor everolimus [16, 17]. Although a steroidal aromatase inhibitor exemestane has been used as a control arm after failure of nonsteroidal aromatase inhibitors in several phase II and phase III trials, clinical benefit rates seem not high (18.0–31.5%) [14-16] compared with SERMs (41.3–48.7%) [13, 14], fulvestrant 500 mg (45.6–47.8%) [7, 9, 10], and an endocrine agent in combination with everolimus (33.4–61.1%) [16, 17]. Therefore,

when choosing a subsequent endocrine therapy, it is critical to select one with a different mechanisms of action from the prior therapy [14]. Furthermore, it is important to guarantee a good quality of life during the subsequent endocrine therapy.

In our present cohort, all patients were treated with aromatase inhibitors and/or SERMs prior to fulvestrant 500 mg. Moreover, 81.2% of patients were treated with fulvestrant as third- or later-line of endocrine therapy. In addition to endocrine therapies, 74.4% of patients were pretreated with chemotherapies. Thus, patients with heavily pretreated metastatic breast cancer were included. Although a small number of previous chemotherapies was positively correlated with TTP, the number of previous endocrine therapies did not affect TTP in our analysis. In addition, we showed that patients who could be treated with first-line endocrine therapy for 5.5 months or more had significant longer TTP compared with those with first-line endocrine therapy duration less than 5.5 months. Therefore, patients with acquired resistance to endocrine therapies might be good candidates for fulvestrant therapy regardless of the number of prior endocrine treatments. Furthermore, recurrent patients during adjuvant endocrine therapy might also be better candidates for fulvestrant therapy than those with a shorter duration of first-line endocrine therapy, because in our analysis TTP was longer in patients who relapsed during adjuvant endocrine therapy than in those with first-line endocrine therapy duration < 5.5 months.

Recently, *ESR1* mutations were identified in ER-positive metastatic breast tumors, especially in those with acquired resistance to aromatase inhibitors, but were not detected in

primary tumors. Several studies showed that constitutively active *ESR1* ligand-binding domain mutations in pretreated advanced ER-positive breast cancers confer partial resistance to antiestrogens such as tamoxifen and fulvestrant, and higher doses of these drugs could inhibit mutant ERα tumors [18-20]. Yamamoto and colleagues demonstrated that high-dose toremifene (120 mg daily) was effective in patients with metastatic breast cancer who showed progression of the disease during aromatase inhibitors therapy, although the mechanisms of action of high-dose toremifene have not fully been understood [14, 21]. It is suggested that high-dose SERMs and fulvestrant 500 mg might be effective in tumors with constitutively active *ESR1* mutations.

Finally, our results showed that patients with liver metastases had shorter TTP than those without liver metastases during fulvestrant 500 mg therapy. Because most patients with liver metastases received chemotherapies before fulvestrant therapy and duration of first-line endocrine therapy was not long, we considered that the absence of liver metastases was not correlated with TTP in multivariate analysis, and that it was not an independent prognostic factor for TTP. Further studies are needed to verify this observation and to understand the mechanisms of resistance to fulvestrant.

In conclusion, our study indicates that fulvestrant 500 mg is an effective and well-tolerated treatment for postmenopausal women with metastatic breast cancer that had progressed after prior endocrine therapies. Patients with acquired resistance to endocrine therapies might be good candidates for fulvestrant therapy regardless of the number of prior

endocrine treatments.

Conflict of interest statement

H. Yamashita received research funding from AstraZeneca. The other authors have no conflict of interest.

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Figure legends

Figure 1: Time to progression (TTP) Kaplan-Meier curve in 117 patients treated with fulvestrant 500 mg therapy. The median TTP was 6.1 months (range, 0.3–26.2 months).

Figure 2: (a) Time to progression (TTP) Kaplan-Meier curves according to the absence and presence of liver metastases. The median TTP in patients without liver metastases was 6.7 months and that in patients with liver metastases was 3.3 months (p = 0.0038). **(b)** TTP Kaplan-Meier curves according to the duration of first-line endocrine therapy. Median TTP was 7.0 months in patients with duration of first-line endocrine therapy ≥ 5.5 months, 4.7 months in patients with duration of first-line endocrine therapy < 5.5 months, and 5.0 months in patients who relapsed during adjuvant endocrine therapy.

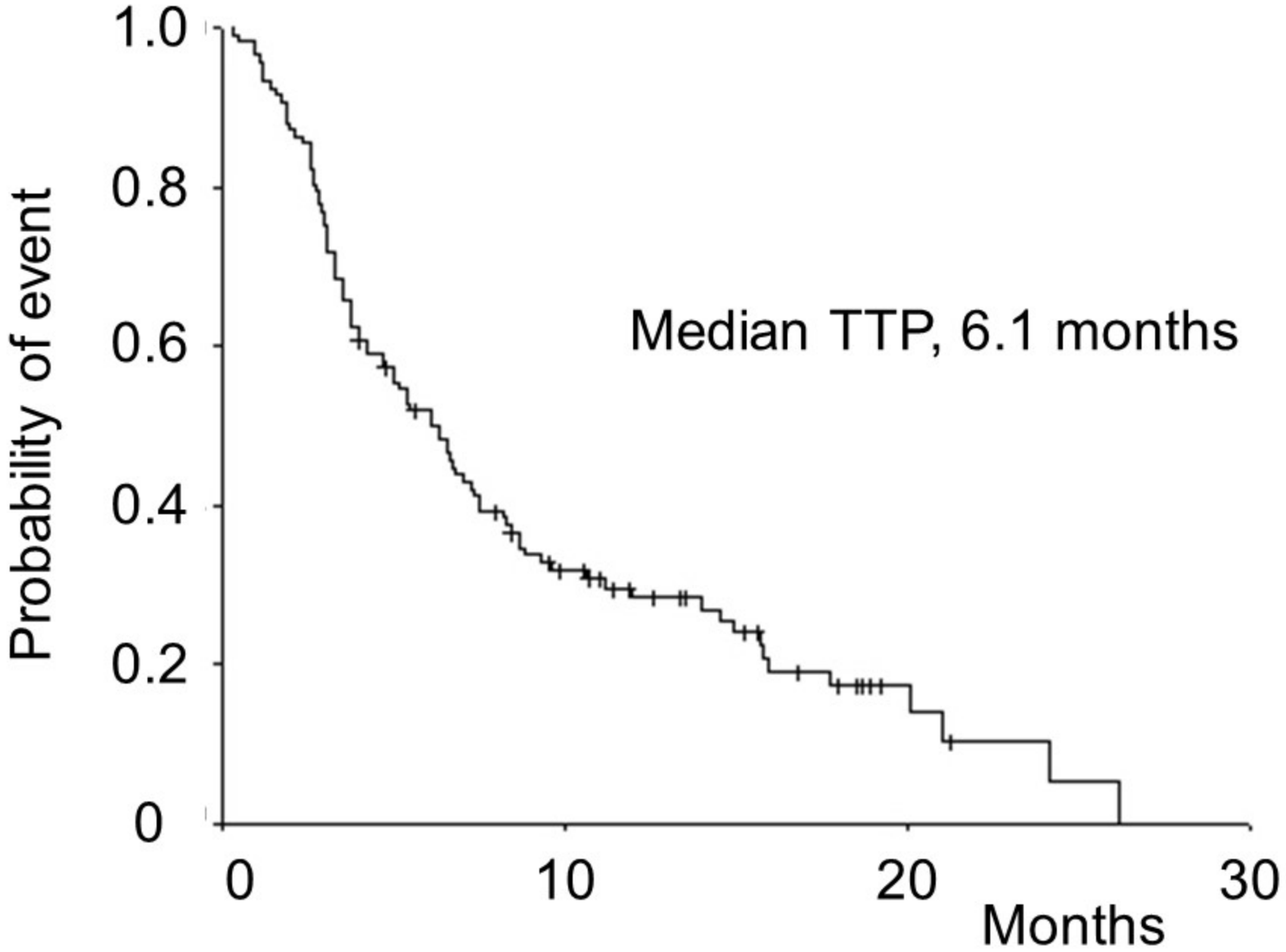
1.0
0.8
0.6
0.4
0.2
0
Probability of event
Median TTP, 6.1 months
0
10
20
30
Months

Figure 1

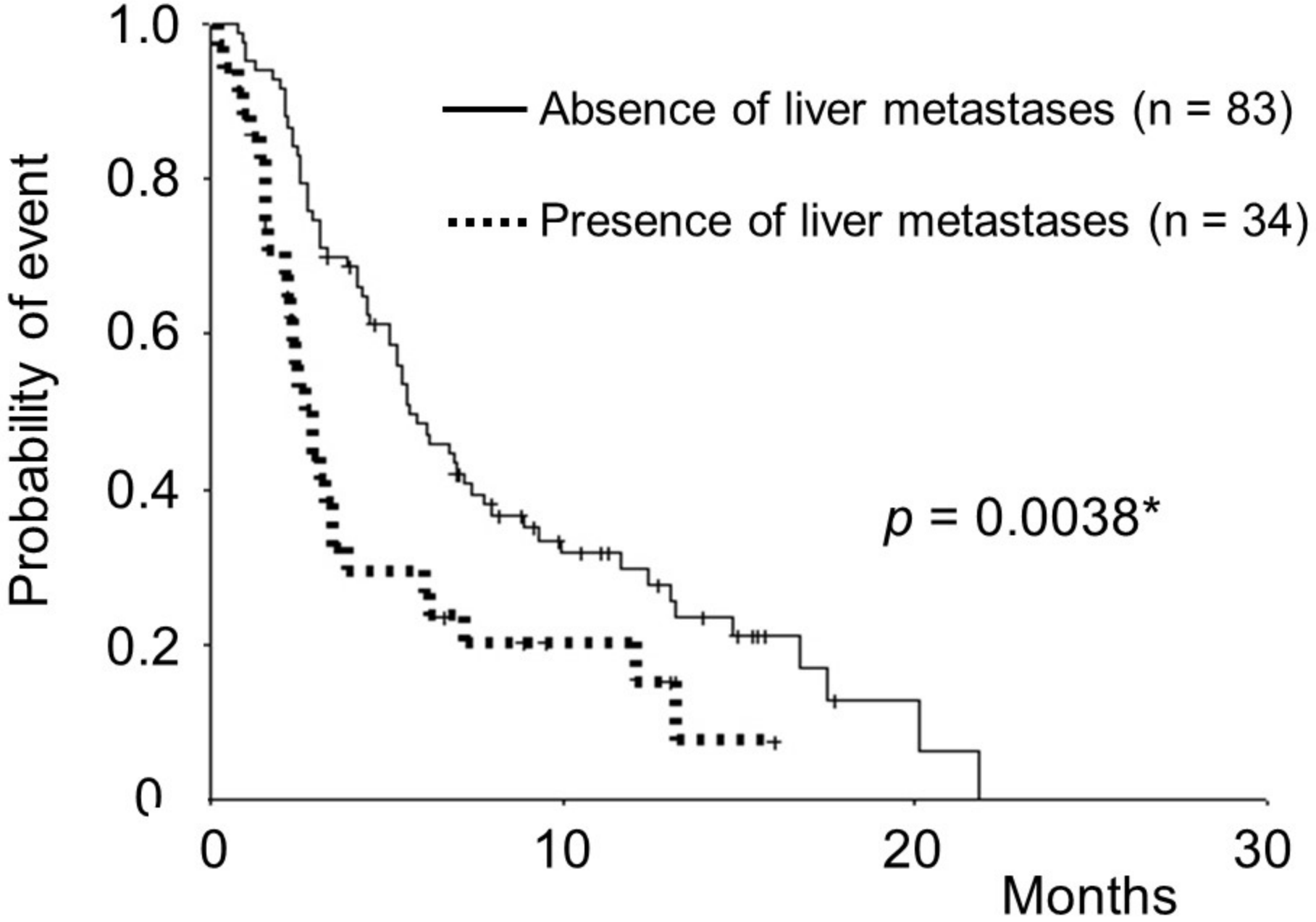
1.0
0.8
0.6
0.4
0.2
0
Probability of event
Absence of liver metastases (n = 83)
Presence of liver metastases (n = 34)
p = 0.0038*
0
10
20
30
Months

Figure 2a

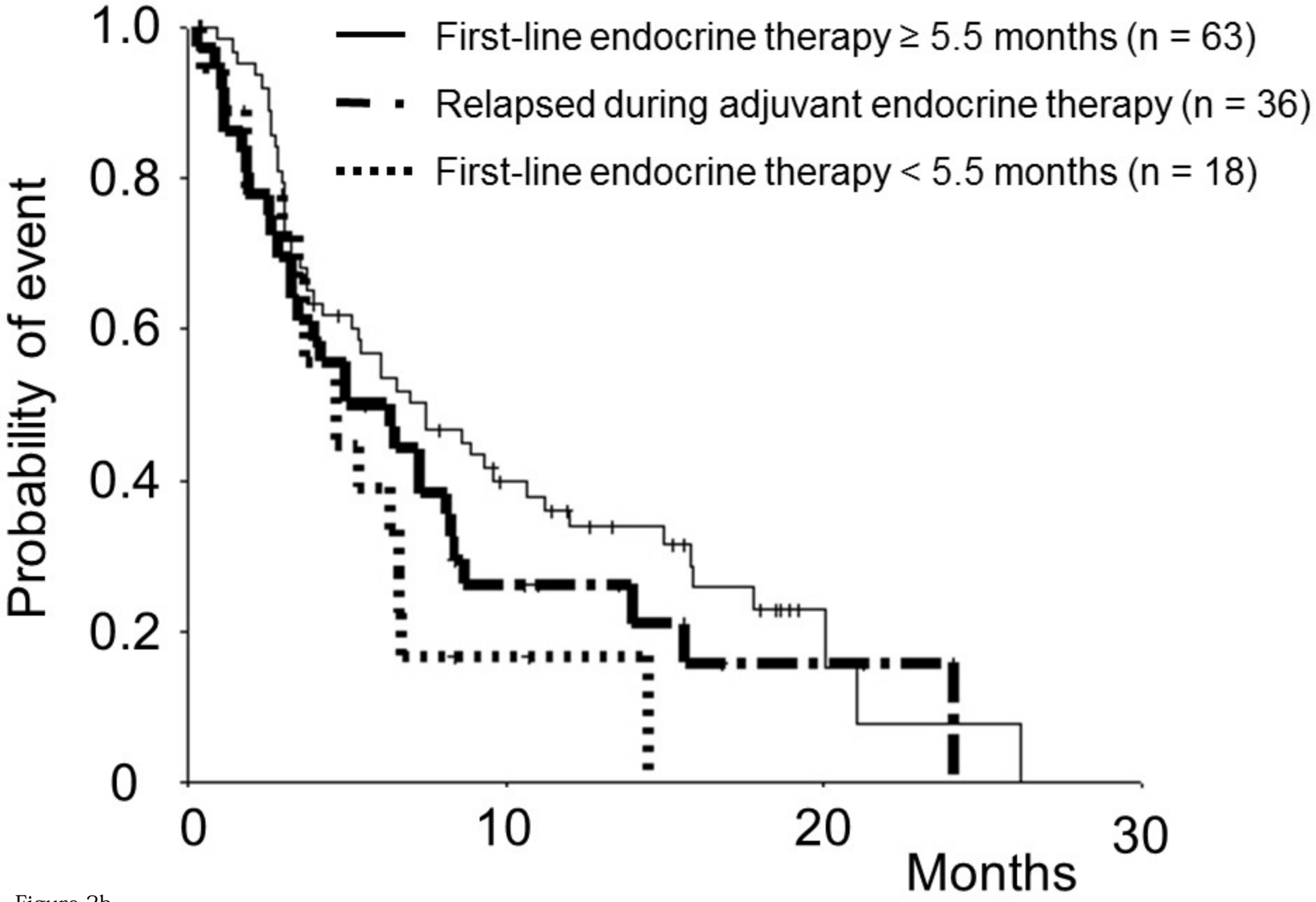
First-line endocrine therapy ≥ 5.5 months (n = 63)
Relapsed during adjuvant endocrine therapy (n = 36)
First-line endocrine therapy < 5.5 months (n = 18)
Probability of event
1.0
0.8
0.6
0.4
0.2
0
0
10
20
30
Months

Figure 2b

Table 1: Characteristics of patients

	Number of patients	%
Total	117	
Age, median (range)	62 (41–85)	
Hormone receptor and HER2 status		
ER and/or PgR-positive and HER2-negative	91	77.8
ER and/or PgR-positive and HER2-positive	10	8.5
unknown	16	13.7
Stage IV	18	15.4
Recurrence	99	84.6
Disease free interval		
< 5 years	40	40.4
5–10 years	33	33.3
≥ 10 years	26	26.3
Metastatic site		
bone	80	68.4
liver	34	29.1
lung	43	36.8
brain	6	5.1
other	45	38.5
Number of disease sites		
1–2	65	55.6
3–4	47	40.2
5–6	5	4.3

Table 2: Prior treatments

	Number of patients	%
Adjuvant endocrine therapies	99	
Tamoxifen	32	32.3
Aromatase inhibitors	24	24.2
Tamoxifen followed by aromatase inhibitors	14	14.1
LHRH agonist	1	1.0
None	46	46.5
Previous endocrine therapies for metastatic breast cancer		
Relapse during adjuvant endocrine therapy	36	
Tamoxifen	12	33.3
Aromatase inhibitors	19	52.8
Tamoxifen followed by aromatase inhibitors	5	13.9
Metastatic setting		
SERMs (tamoxifen and/or toremifene)	47	40.2
Aromatase inhibitors	104	88.9
LHRH agonist + aromatase inhibitor	3	2.6
Medoxyprogesterone acetate	6	5.1
Number of previous therapies for metastatic breast cancer		
Total number of previous therapies, median (range)	4 (1–12)	
1–2	23	19.7
3–4	43	36.8
5–6	24	20.5
≥ 7	27	23.1
Endocrine therapies, median (range)	2 (1–5)	
1 (second line)	22	18.8
2 (third line)	45	38.5
3 (forth line)	37	31.6
4 (fifth line)	11	9.4
5 (sixth line)	2	1.7
Chemotherapies, median (range)	2 (0–9)	
0	30	25.6
1	24	20.5
2	18	15.4
≥ 3	45	38.5
Duration of first-line endocrine therapy		
≥ 5.5 months	63	53.8
< 5.5 months	18	15.4
Relapsed during adjuvant endocrine therapy	36	30.8

LHRH agonist, luteinizing hormone-releasing hormone agonist; SERM, selective estrogen receptor modulator

Table 3: Response to fulvestrant

Response	Number of patients	%
Complete response	0	0
Partial response	10	8.5
Long stable disease (≥ 24 weeks)	39	33.3
Clinical benefit†	49	41.9
Stable disease (< 24 weeks)	18	15.4
Progressive disease	50	42.7

†Clinical benefit defined as complete response + partial response + long stable disease.

Table 4: Univariate and multivariate analysis of factors predicting time to progression during fulvestrant treatment

	Univariate			Multivariate		
	HR	95%CI	*p*	HR	95%CI	*p*
Age	1.000	0.973-1.028	0.999			
HER2 status	1.007	0.785-1.292	0.956			
Stage IV/Recurrence	1.455	0.791-2.677	0.228			
Disease-free interval	1.000	0.996-1.004	0.884			
Metastatic sites	1.056	0.759-1.468	0.746			
Presence of liver metastases	1.899	1.214-2.970	0.005*	1.318	0.708-2.452	0.384
Number of disease sites	1.073	0.868-1.326	0.516			
Number of previous endocrine therapies	0.955	0.769-1.185	0.674			
Number of previous chemotherapies	1.113	1.019-1.214	0.017*	1.011	0.893-1.145	0.861
Duration of first-line endocrine therapy	0.988	0.978-0.998	0.016*	0.988	0.978-0.999	0.026*

HR, hazard ratio; CI, confidence interval

*$p < 0.05$ is considered significant.

Table 5: Adverse events

	Grade 1	Grade 2	Grade 3	Grade 4
Injection site reactions	3			
Gastrointestinal disturbances	9			
Hot flushes	2			
Joint disorders	7	1		
Peripheral neuropathy of lower limbs	2			
Thromboembolic events			1	
Psychiatric symptoms			1	