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Examination of the Efficacy of Fulvestrant 500 mg Targeting Estrogen Receptor-Positive Postmenopausal Metastatic Breast Cancer: Prospective Observational Study (PerSeUS BC03 Study)

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Abstract

This multi-institutional prospective cohort study aimed to examine the efficacy and safety of 500 mg of Fulvestrant (Ful-500) in postmenopausal Estrogen Receptor (ER)-positive Advanced or Recurrent Metastatic Breast Cancer (AMBC). Patients with second, third or fourth-line Endocrine Therapy (ET) were recruited. From August 2013 to June 2016, participants were administered Ful-500 as two 5-mL intramuscular injections on days 0, 14, and 28 and thereafter, every 28 days until disease progression. The primary endpoint was Progression-Free Survival (PFS). Overall Response Rate (ORR), Clinical Benefit Rate (CBR), and safety were the secondary endpoints. For PFS, the Kaplan-Meier method was used to estimate the survival curve with a threshold Median Survival Time (MST) of 3 months and an expected MST of 5.5 months, at a one-sided significance level of 0.05 and power of 0.8. All statistical tests were two-sided. A 5% error was used in the PFS analysis. Of the 51 enrolled patients, 46 (second-line: 31, third-line: 10, fourth-line: 5) were analyzed. The median PFS duration was 8.5 months (95% confidence interval [CI], [5.6-14.5]). Furthermore, the 90% CI of the mean PFS was 5.6-14.5 months. The lower 90% CI value was higher than the median PFS (3 months) threshold, signifying that Ful-500 use was effective in these patients. The ORR and CBR values were 6.5% (3/46) and 71.7% (33/46), respectively. Adverse events, all grades 1-2, were observed in 15 cases (32.6%). Ful-500 use was effective and safe in second to fourth-line ET for ER-positive postmenopausal AMBC.

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Introduction

Breast cancer is the most commonly diagnosed cancer among women and the leading cause of cancer-related death, worldwide [1]. More than two-thirds of breast cancer patients have the Estrogen Receptor (ER)-positive form of the disease [2,3]. The main treatment aims for Advanced or Metastatic Breast Cancer (AMBC) are survival prolongation and Quality of Life (QOL) improvement. For postmenopausal women with ER-positive locally AMBC, Endocrine Therapy (ET) is recommended, particularly in cases with non-life-threatening situations as seen in the Hortobagyi algorithm [4]. As first-line drugs, third-generation aromatase inhibitors (AIs; Anastrozole, Letrozole, or Exemestane) are widely used due to their safety and clinical superiority to tamoxifen in terms of the time to progression [5-8]. However, another agent Fulvestrant with a different mechanism of action, has been developed, which is a selective ER degrader, that blocks ER function by inducing its degradation [9,10]. In second-line ET, 250 mg of Fulvestrant (Ful-

250) has been shown to yield a Progression-Free Survival (PFS) rate which is similar to that observed for several AIs [11-14]. In particular, recent clinical trials have demonstrated that the administration of 500 mg of Fulvestrant (Ful-500) is more effective than Ful-250 for postmenopausal hormone receptor-positive Metastatic Breast Cancer (MBC) patients [15,16]. Fulvestrant, administered in three dose regimens (approved dose, loading dose, and high dose) and used in second-line ET, has demonstrated similar efficacy and tolerability in both Japanese and western populations, with analyses determining the optimal dose at 500 mg of Fulvestrant [17,18].

In Japan, Fulvestrant has been used for postmenopausal MBC patients since its approval in 2011. In fact, it has been widely used for ER-positive AMBC patients in second-line therapy and higher. Safari-a large-scale retrospective cohort study was conducted to investigate the current status of Fulvestrant use in Japan [19]. While that study seems to reflect the real-world status of Fulvestrant use in Japan, there is a lack of prospective data concerning the efficacy and safety of Fulvestrant in the country. In the FALCON study, the use of Ful-500 as a first-line drug for MBC led to a PFS duration greater than 16 months [20,21], indicating that monotherapy with Ful-500 may be useful in ER-positive AMBC. However, few reports have focused on the efficacy of Ful-500 in clinical practice. Accordingly, we performed a prospective cohort study focusing on the efficacy and safety of Ful-500 monotherapy as part of second to fourth-line ET for ER-positive postmenopausal AMBC patients.

Materials and Methods

The PerSeUS BC03 study (UMIN000011976) is a multicenter, phase II, prospective cohort study. The primary endpoint of the study was the evaluation of the PFS in patients treated with Ful-500, and the secondary endpoints were Objective Response Rate (ORR), Clinical Benefit Rate (CBR), and safety.

Patients

Eligible patients included postmenopausal women with MBC who had demonstrated ER-positivity in the primary or metastatic tumor tissue (≥ 1% positive staining by immunohistochemistry on local laboratory testing) [22]. In addition, patients were required to have second, third, or fourth-line ET. Second-line endocrine therapy was to have relapsed during, or within 12 months after the completion of, adjuvant endocrine therapy; be in progression while on ET that was started more than 12 months after prior adjuvant endocrine therapy; or be in progression while on ET administered for de novo advanced disease. The provision of any form of chemotherapy for AMBC was not allowed. Patients had to have a survival prognosis greater than 6 months. In addition, patients had to have measurable disease, as assessed by RECIST version 1.1 [23], or non-measurable lesions, as clinically identified by bone scintigraphy, Positron Emission Tomography-Computed Tomography (PET-CT), Computed Tomography (CT), or Magnetic Resonance Imaging (MRI). The Eastern Cooperative Oncology Group performance status of all patients was 0, 1 or 2, due to the presence of only bone metastasis. All patients exhibited adequate organ function. Those with uncontrolled life-threatening metastatic diseases such as severe liver metastasis, brain metastasis, carcinomatous lymphangitis and inflammatory breast cancer, allergies to Fulvestrant, and a history of previous Fulvestrant use were excluded. All patients provided written informed consent for participation. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee or review board of each participating institution.

Table 1: Summary of patient's characteristic.

Characteristics	Efficacy analysis sets n=46 (%)
Age (years)	
Median	69
Range	[45-82]
Performance Status	
0	37 (80.4)
1	9 (19.6)
Metastatic pattern	
Recurrent	35 (76.1)
de novo metastatic	11(23.9)
Treatment lines	
Second	31 (67.4)
Third	10 (20.4)
Fourth	5 (12.2)
MBC diagnosis to F500 use (years)	
Median	1.8
Range	[0.0-13.4]
Hormonal receptor	
ER(+) PgR(+)	34 (73.9)
ER(+) PgR(-)	9 (19.6)
ER(+) PgR(NA)	3 (6.5)
HER2	
Negative	39 (84.9%)
Positive	2 (4.3%)
Missing	5 (10.8%)
Visceral metastasis	
Yes	19 (41.3)
No	27 (58.7)
Central nerve metastasis	
Yes	0 (0.0)
No	49 (100.0)
Period from diagnosis to Fulvestrant use (months)	
Second	8
Third	25
Fourth	49

Abbreviation: MBC: Metastatic Breast Cancer; ER: Estrogen Receptor; PgR: Progesterone Receptor

Study treatment

From August 2013 to June 2016, eligible patients were administered Ful-500 (high dose) as two 5-mL intramuscular injections on days 0, 14, and 28, and then every 28 days thereafter. Treatment with Ful-500 was continued until disease progression or until any other discontinuation criterion was met.

Study assessments

The primary endpoint was PFS. CBR, ORR, and safety were the secondary endpoints. Efficacy was assessed using PFS, ORR (defined by Complete Response [CR] and Partial Response [PR]) and CBR (defined by complete response, partial response and Stable Disease [SD] lasting longer than 24 weeks). Generally, in clinical trials, measurable metastatic sites such as the lung, liver and lymph node are required, whereas most bone metastases are non-measurable. Measurable lesions were estimated by CT or MRI (≤ 5-mm slice). All patients were followed-up every 12 weeks for progression. In this study, based on RECIST criteria, the unequivocal progression of non-CR/non-Progressive Disease (PD) lesions was evaluated by a combination of several modalities (e.g. CT, MRI, PET/CT and bone scintigraphy [24]), tumor marker levels, and worsening symptoms. Patients with non-measurable lesions diagnosed as non-CR/non-PD were classified as having SD [23].

Safety was evaluated by the assessment of Adverse Events (AEs) classified according to the National Cancer Institute-Common Toxicity Criteria for AEs (version 4.0) at the baseline and at four-week intervals thereafter.

Table 2: Efficacy of Ful-500.

Total	CR	PR	SD ≥ 24W	PD	NE	ORR [95% CI]	CBR [95% CI]
46	0	3	19	22	2	3 (6.5%)	22 (47.8%)
						[1.4%, 17.9%]	[32.9%, 63.1%]

Abbreviation: CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Overall Response Rate; NE: Not Evaluable; CBR: Clinical Benefit Rate; CI: Confidence Interval

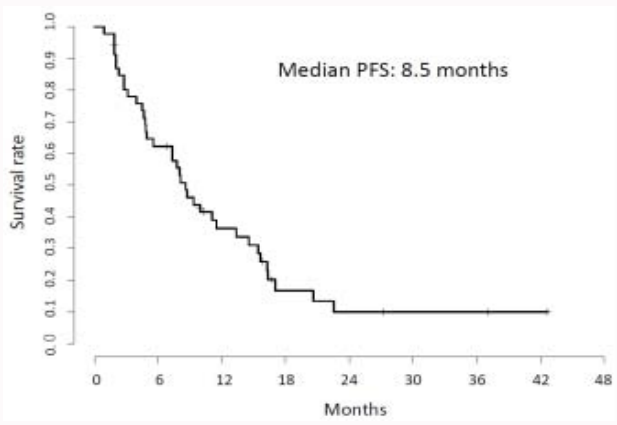

Figure 1: Kaplan-Meier plot of progression-free survival in all cases. Abbreviation: PFS: Progression Free Survival

Statistical analysis

For PFS, the Kaplan-Meier method was used to estimate the survival curve. Assuming a threshold Median Survival Time (MST) of 3 months and an expected MST of 5.5 months, the required sample size was 48, at a significance level of 0.05 (one-sided) and power of 0.8. Therefore, the target sample size was set at 50. All statistical tests were two-sided and a 5% error was used in the PFS analysis.

Results

Patients

In total, 51 patients were recruited from seven institutes. Five patients were excluded: one patient refused the administration of Fulvestrant after registration, one was administered another drug before registration and three had a performance status of 2-4. Overall, 46 patients were analyzed.

The participants' baseline characteristics are shown in Table 1. Their median age was 69 years. Recurrence was observed in 35 cases (76%) and de novo metastasis in 11 (24%), in whom the treatment lines were as follows second: 31, third: 10, and fourth: 5. All patients had ER-positive disease and 34 patients (73.9%) showed progesterone receptor-positivity. Two cases showed HER2-positivity (and ER-positivity). Recurrent metastasis was observed in 35 cases, with advanced disease observed in 11 (56.6%). Nineteen patients (41.3%) showed visceral involvement.

The median PFS was 8.5 months (95% confidence interval [CI]: 5.6-14.5 months) (Figure 1). The 90% CI was 5.6-14.5 months. The lower 90% CI (5.6 months) limit was higher than the threshold MST of 3 months, suggesting that this protocol was effective.

The ORR and CBR, as listed in Table 2, were 6.5% (95% CI; 1.4-17.9%) and 47.8% (95% CI; 32.9-63.1%), respectively.

The PFS duration in the recurrent metastasis cases (n=35) was 8.0 months (95% CI: 4.9-15.4), while that for the advanced disease cases (n=11) was 8.7 months (95% CI: 7.3-NA) (Figure 2a). Furthermore, the PFS associated with second-line (n=31), third-line (n=10) and fourth-line (n=5) ET was 8.1 months (95% CI: 4.9-15.4), 7.8 months (95% CI: 2.3-NA) and 14.5 months (95% CI: 13.4-NA), respectively. The durations from AMBC diagnosis to Ful-500 use in the second, third, and fourth-line ET groups were 8, 25, and 49 months, respectively.

Table 3: Adverse events.

	Grade 1	Grade 2	Grade 3	Grade 4	%
Injection site reaction	3	1	0	0	8.7
Backpain	3	1	0	0	8.7
Arthralgia	2	1	0	0	6.5
Appetite loss	1	1	0	0	4.3
Thrombocytopenia	0	1	0	0	2.2
Agitation	0	1	0	0	2.2
Cognitive disturbance	0	1	0	0	2.2
Thirst	0	1	0	0	2.2
Lower limb pain	1	0	0	0	2.2
Myalgia	1	0	0	0	2.2
Nausea	1	0	0	0	2.2
Fatigue	1	0	0	0	2.2
Headache	1	0	0	0	2.2
Hot flush	1	0	0	0	2.2
Rash	1	0	0	0	2.2
Melena	1	0	0	0	2.2

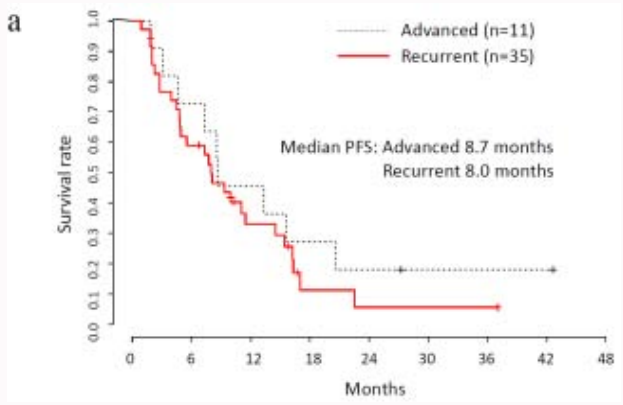

Figure 2a: Kaplan-Meier plot of progression-free survival in advanced and recurrent disease cases.

Safety

Table 3 lists the incidence of prespecified AEs due to Ful-500 use. AEs were reported in 15 of 46 cases (32.6%). However, all the AEs were of grade 1 or 2. AEs of ≥ grade 2 included: injection site reactions: 4 (8.7%), back pain: 4 (8.7%), arthralgia: 3 (6.5%), and anorexia: 2 (4.3%). There were no notable changes in either the clinical chemistry or vital signs, and electrocardiography values.

Discussion

For AMBC patients, the sequential use of ETs, especially the use of a subsequent therapy with a mechanism of action that differs from that in the case of the prior therapy is important to obtain a beneficial effect in the maintenance of a good QOL and prolonged survival [25].

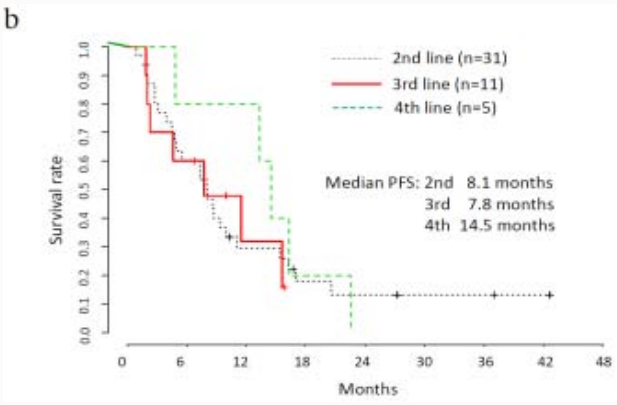

Figure 2b: Kaplan-Meier plot of progression-free survival (second *vs.* third *vs.*fourth-line).
Abbreviation: PFS: Progression-Free Survival

The sequential administration of first-line Anastrozole followed by tamoxifen is effective in the treatment of postmenopausal women with advanced breast cancer [26]. Previous studies have demonstrated the efficacy of Fulvestrant in the degradation of ERs when included in second-line ET or higher. Namely, Ful-500 is more effective than Ful-250 and non-steroidal AIs [13,17,18]. Additional data, which confirmed the dose escalation of Fulvestrant, determined that Ful-500 provides a statistically significant improvement in both PFS (6.5 months) and overall survival (22.8 months) without an increase in toxicity [17,18]. Eventually, the loading dose of Ful-500 (on days 1, 14 and 28, followed by administration every 28 days thereafter) is now the recommended dose. With the publication of the aforementioned reports, Fulvestrant use was approved in Japan in 2011. However, there is lack of adequate data on the efficacy of Ful-500 in clinical practice.

To clarify the real-world status of Ful-500 use in Japan, Kawaguchi et al [19]. conducted a large retrospective cohort study including 1,031 patients from 16 institutions [19]. That analysis, in which first-line treatment was provided to 2.0%, second-line ET to 22.7%, third-line ET to 26.7%, and ≥ fourth-line to 48.6% of patients, demonstrated a median Time to Failure (TTF) of 5.4 months. Multivariate analyses demonstrated there was a significant statistical association between a longer TTF and several characteristics such as earlier treatment line, duration from AMBC diagnosis to Ful-500 use greater than 3 years, absence of prior palliative chemotherapy, and disease-free interval greater than 2 years. They concluded that patients with ER-positive MBC may benefit from Fulvestrant therapy early in their treatment course.

In MBC, metastatic lesions are located in various sites, particularly in non-measurable bone metastasis cases. In this study, the enrollment of patients with non-measurable lesions was allowed; in such cases, the unequivocal progression of non-CR/non-PD lesions was evaluated according to RECIST (version 1.1) criteria using a combination of clinical observation and several modalities such as CT, MRI, PET/CT, bone scintigraphy, and tumor marker level estimation. In this paper, we evaluated the real-world impact of Ful-500 for AMBC using a prospective cohort study of patients receiving second to fourth-line ET. In spite of the small sample size, the median PFS was 8.7 months, which was statistically significant; this may be attributed to the fact that our population comprised 33 patients (71.1%) who received second-line ET, which is totally different from the Safari study. In detail, the PFS values associated with each line of ET were: 8.1 months for second-line, 7.1 months for third-line, and 14.5 months for fourth-line ET. Interestingly, the PFS for fourth-line ET was longer than that for second and third-line ET. In terms of the duration from AMBC diagnosis to Ful-500 use, the values for second, third, and fourth-line ET were 8, 25, and 49 months, respectively. In the ER-positive AMBC patients, the survival duration was about 4 years; in the setting of fourth-line ET (49 months), this duration is considerably long. In other words, patients requiring fourth-line therapy continued to have a high sensitivity to ET, resulting in longer disease-free survival rates [27,28]. Of note, among five patients receiving fourth-line ET, one had bilateral lung and cervical lymph node metastasis, suggesting that endocrine monotherapy may be effective so long as the function of the ER is normal and it is sensitive to estrogen irrespective of the metastatic site.

As seen in Table 3, AEs were observed in 15 of 46 cases (32.6%). They were all grades 1-2 AEs, with infusion-related reactions and back pain the most commonly cited (8.7%). This AE profile was recoverable and similar to that reported previously [17]. There was no case in which Ful-500 discontinuation was required owing to AE presentation. These results indicate that Ful-500 is safe for use and tolerable in patients with PS 0/1 requiring second to fourth-line ET, even in elderly populations.

Recent strategic advances for hormone-receptor positive AMBC include the establishment of molecular targeted agents. Combination therapy using Ful-500 and Palbociclib as second-line ET yielded a PFS of 9.5 months, with a 73% occurrence rate of grades 3-4 AEs [29,30]. The present study, accomplished under similar conditions, yielded PFS duration of 8.7 months with recoverable AEs. If Ful-500 monotherapy is effective, it may serve as an economical treatment option for AMBC. Namely, monotherapy using Ful-500 may be useful for ER-positive AMBC patients in the presence of hormone sensitivity.

In summary, Ful-500 was found to be effective and tolerable in ER-positive AMBC patients. Attention should be paid to the selection of therapeutic strategies based on the associated efficacy, QOL, and economic performance.

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Competing Financial Interests

Outside of this work, KY has received grants and personal fees from Taiho Pharmaceutical Co., Ltd., Pfizer Inc., Chugai Pharmaceutical Co., Ltd., and Yakult Honsha Co., Ltd., grants from Bristol-Myers Squibb and Kyowa Hakko Kirin Co., Ltd., honoraria from Taiho Pharmaceutical Co., Ltd., Pfizer Inc., Chugai Pharmaceutical Co., Ltd., Kyowa Hakko Kirin Co., Ltd., and Yakult Honsha Co., Ltd., and had a consultant or advisory relationship with Taiho Pharmaceutical Co., Ltd. and La Roche, Ltd.

References

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Piñeros M, et al. Global and regional estimates of the incidence and mortality for 38 cancers: GLOBOCAN 2018. Lyon: International Agency for Research on Cancer/World Health Organization; 2018.

2. Anderson WF, Katki HA, Rosenberg PS. Incidence of breast cancer

in the United States: current and future trends. J Natl Cancer Inst. 2011;103(18):1397-402.

3. Yamashita H, Iwase H, Toyama T, Takahashi S, Sugiura H, Yoshimoto N, et al. Estrogen receptor-positive breast cancer in Japanese women: trends in incidence, characteristics, and prognosis. Ann Oncol. 2011;22(6):1318-25.

4. Hortobagyi GN. Treatment of breast cancer. N Engl J Med. 1998;339(14):974-84.

5. Bonneterre J, Buzdar A, Nabholtz JM, Robertson JFR, Thürlimann B, von Euler M, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. Cancer. 2001;92(9):2247-58.

6. Mouridsen H, Gershanovich M, Sun Y, Pérez-Carrión R, Boni C, Monnier A, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol. 2001;19(10):2596-606.

7. Mouridsen H, Gershanovich M, Sun Y, Perez-Carrion R, Boni C, Monnier A, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol. 2003;21(11):2101-9.

8. Paridaens RJ, Dirix LY, Beex LV, Nooij M, Cameron DA, Cufer T, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organization for Research and Treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol. 2008;26(30):4883-90.

9. Johnston SJ, Cheung KL. Fulvestrant-A novel endocrine therapy for breast cancer. Curr Med Chem. 2010;17(10):902-14.

10. Nathan MR, Schmid P. A review of fulvestrant in breast cancer. Oncol Ther. 2017;5(1):17-29.

11. Osborne CK, Pippen J, Jones SE, Parker LM, Ellis M, Come S, et al. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol. 2002;20(16):3386-95.

12. Howell A, Robertson JF, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg UR, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. J Clin Oncol. 2002;20(16):3396-403.

13. Chia S, Gradishar W, Mauriac L, Bines J, Amant F, Federico M, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol. 2008;26(10):1664-70.

14. Johnston SR, Kilburn LS, Ellis P, Dodwell D, Cameron D, Hayward L, et al. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. Lancet Oncol. 2013;14(10):989-98.

15. Ohno S, Rai Y, Iwata H, Yamamoto N, Yoshida M, Iwase H, et al. Three dose regimens of fulvestrant in postmenopausal Japanese women with advanced breast cancer: results from a double-blind, phase II comparative study (FINDER1). Ann Oncol. 2010;21(12):2342-7.

16. Pritchard KI, Rolski J, Papai Z, Mauriac L, Cardoso F, Chang J, et al. Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2). Breast Cancer Res Treat. 2010;123(2):453-61.

17. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol. 2010;28(30):4594-600.

18. Di Leo A, Jerusalem G, Petruzelka L, Torres R, Bondarenko IN, Khasanov R, et al. Final overall survival: fulvestrant 500 mg *vs*. 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst. 2014;106(1):djt337.

19. Kawaguchi H, Masuda N, Nakayama T, Aogi K, Anan K, Ito Y, et al. Outcomes of fulvestrant therapy among japanese women with advanced breast cancer: a retrospective multicenter cohort study (JBCRG-C06; Safari). Breast Cancer Res Treat. 2017;163(3):545-54.

20. Robertson JFR, Bondarenko IM, Trishkina E, Lawrence DM, Alexey P, Shparyk MY, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet. 2016;388(10063):2997-3005.

21. Noguchi S, Ellis MJ, Robertson JFR, Thirlwell J, Fazal M, Shao Z. Progression-free survival results in postmenopausal Asian women: subgroup analysis from a phase III randomized trial of fulvestrant 500 mg vs anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON). Breast Cancer. 2018;25(3):356-64.

22. Japan Breast Cancer Society. General rules for clinical and pathological study of breast cancer in Japan (18th edition). Kanehara syuppan; 2018.

23. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

24. Li D, Lv H, Hao X, Dong Y, Dai H, Song Y. Prognostic value of bone scan index as an imaging biomarker in metastatic prostate cancer: a meta-analysis. Oncotarget. 2017;8(48):84449-58.

25. Iwase H, Yamamoto Y. Clinical benefit of sequential use of endocrine therapies for metastatic breast cancer. Int J Clin Oncol. 2015;20(2):253-61.

26. Thürlimann B, Robertson JF, Nabholtz JM, Buzdar A, Bonneterre J; Arimidex Study Group. Efficacy of tamoxifen following anastrozole ('Arimidex') compared with anastrozole following tamoxifen as first line treatment for advanced breast cancer in postmenopausal women. Eur J Cancer. 2003;39(16):2310-7.

27. Kobayashi K, Ito Y, Matsuura M, Fukada I, Horii R, Takahashi S, et al. Impact of immunohistological subtypes on the long-term prognosis of patients with metastatic breast cancer. Surg Today. 2016;46(7):821-6.

28. Cardoso F, Senkus E, Costa A, Papadopoulos E, Aapro M, André F, et al. 4th ESO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 4). Ann Oncol. 2018;29(8):1634-57.

29. Turner NC, Ro J, André F, Loi S, Verma S, Iwata H, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med. 2015;373:209-19.

30. Cristofanilli M, Turner NC, Bondarenko I, Ro J, Im SA, Masuda N, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol. 2016;17(4):425-39.