—Original—

Effectiveness of Changing the Class of Molecularly Targeted Agent after Disease Progression during Initial Molecularly Targeted Therapy for Luminal Advanced/Metastatic Breast Cancer

Satoko Nakano[1], Akemi Mibu[1], Shunsuke Kato[1,2], Shigeo Yamaguchi[1,3], Yuna Suzuki[1,4], Kaoru Tanimura[1,4] and Masataka Sano[5]

[1]Department of Breast Surgery, Kawaguchi Municipal Medical Center, Saitama, Japan
[2]Medical Oncology Department, Juntendo University, Tokyo, Japan
[3]Surgical Department, Keio University School of Medicine, Tokyo, Japan
[4]Division of Breast and Endocrine Surgery, Department of Surgery, Nihon University School of Medicine, Tokyo, Japan
[5]Faculty of Commerce, Takushoku University, Tokyo, Japan

Background: The emergence of molecularly targeted agents (MTAs) has altered the treatment landscape for hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2−) advanced breast cancer (ABC)/metastatic breast cancer (MBC). Multiple guidelines recommend molecularly targeted therapy as first-line treatment for HR+/HER2− ABC/MBC. However, optimal treatment for disease progression during MTA therapy remains undetermined. This study evaluated the suitability of different MTA types for this patient subgroup.

Methods: In this retrospective study, we analyzed the electronic health records of 56 patients with HR+/HER2− ABC/MBC receiving treatment with palbociclib, abemaciclib, or everolimus in our center between April 2014 and June 2021.

Results: Overall, 39, 14, and 35 regimens using palbociclib, abemaciclib, and everolimus, respectively, were identified. Three and 53 patients were premenopausal and postmenopausal, respectively. MTAs were included in the 1st-11th lines of treatment. Time to failure (TTF) was significantly different among the three MTAs. In contrast, TTF did not significantly differ among the 50 regimens that included CDK4/6 inhibitors, with/without prior mTOR inhibitor use, and the 35 regimens that included mTOR inhibitors, with/without prior CDK4/6 inhibitor use.

Conclusions: The sequential use of different MTA classes did not affect the TTF of another MTA. mTOR inhibitor + exemestane is a favorable treatment option after CDK4/6 inhibitor + hormone therapy, and CDK4/6 inhibitor + hormone therapy is suitable for patients previously treated with mTOR inhibitor + exemestane. Although this study was retrospective and conducted at a single center, the present findings are useful for treatment selection in clinical practice. (J Nippon Med Sch 2023; 90: 179–185)

Key words: breast cancer, cyclin-dependent kinase, drug resistance, mammalian target of rapamycin, molecularly targeted therapy

Introduction

The emergence of molecularly targeted therapies has changed the treatment landscape for luminal-type advanced breast cancer (ABC)/metastatic breast cancer (MBC). The combination of molecularly targeted agents (MTAs) and hormonal therapy is effective for treating hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2−) ABC/MBC. In clinical trials[1–8], cyclin-dependent kinase (CDK) 4/6 inhibitors such as palbociclib, abemaciclib, and ribociclib, which are

Correspondence to Satoko Nakano, MD, PhD, Department of Breast Surgery, Kawaguchi Municipal Medical Center, 180 Nishi-Araijuku, Kawaguchi, Saitama 333–0833, Japan
E-mail: s.nakano@kawaguchi-mmc.org
https://doi.org/10.1272/jnms.JNMS.2023_90-205
Journal Website (https://www.nms.ac.jp/sh/jnms/)

a new class of MTAs, have shown promising results. Another effective MTA for endocrine-resistant ABC/MBC is the mammalian target of rapamycin (mTOR) inhibitor everolimus[9]. These MTAs significantly improve progression-free survival (PFS) in patients with HR+/HER2− ABC/MBC. Therefore, combining an MTA with an aromatase inhibitor or fulvestrant is recommended as the first-line treatment by the guideline for ABC[10], the National Comprehensive Cancer Network (NCCN)[11], and clinical practice guidelines in Japan[12,13]. However, there is no consensus regarding subsequent treatment after development of progressive disease (PD) with first-line MTA. Given the nature of the disease, such treatment is urgently needed. To validate the use of different types of MTAs, this retrospective study analyzed data from patients who received either MTA for HR+/HER2− ABC/MBC at our center.

Materials and Methods

Patients and Study Design

Using an opt-out approach we collected data from the electronic health records of 60 patients with HR+/HER2− ABC/MBC who were treated with an MTA (namely, palbociclib, abemaciclib, or everolimus) between April 2014 and June 2021 at Kawaguchi Municipal Medical Center. On initiating treatment with MTA, 4 patients were excluded because they experienced PD or withdrew without blood sampling or an imaging examination. All patients were treated with combined MTA and hormone agent. With regard to drug choice, MTAs are considered superior, except when visceral crisis develops. Because of the possibility of cross-resistance, MTAs with very different mechanisms of action should be selected. When a CDK4/6 inhibitor was used, an mTOR inhibitor-another class of MTA-was the first drug of choice for subsequent therapy. The MTA and hormonal agents were selected at the physician's discretion, in accordance with the concerns mentioned above.

The patient data collected included age, menopausal status, recurrence sites, lines of treatment, treatments after metastasis, number of MTA treatments, time to failure (TTF), hormonal agents for combination therapy, and outcomes. MTA dose was reduced as necessary, according to the dose modification criteria[14–16]. Patients treated with CDK4/6 inhibitors visited the hospital once every 2 weeks for monitoring of complete blood count and reporting of any adverse events (AEs), until the target dose was achieved. After 2 months of CDK4/6 inhibitor treatment at the same dose, the frequency of hospital visits was reduced to once a month. Patients treated with everolimus also visited the hospital once a month for monitoring of complete blood counts, blood glucose, and other AEs. The institutional review board of the Kawaguchi Municipal Medical Center approved this study (approval number: 2021-28), which was performed in accordance with the principles of the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective design of the study.

Statistical Analysis

Standard descriptive statistics were used to report data on patient characteristics and tolerability outcomes. Results were considered statistically significant if $P < 0.05$. Analyses were performed using Statistical Analysis System, University Edition (SAS Institute Japan Ltd, Tokyo, Japan).

Results

A total of 56 patients underwent MTA therapy. Median age at the start of MTA therapy was 60 years (range: 39-91 years). Three women were premenopausal, and 53 were postmenopausal. The most common metastatic site was the bone (n = 28), followed by the lung/pleura and lymph nodes (n = 21, both); the least common metastatic site was the liver (n = 8). MTAs were included in the first to 11th lines of treatment. An MTA was administered to 11 patients in the first or second line of treatment and to 45 patients in the third and subsequent lines. Moreover, 35, 15, and 6 patients received treatment with 1, 2, and all 3 of the abovementioned MTAs, and 34, 14, 5, and 3 patients were treated with 1, 2, 3, and 4 regimens with MTAs, respectively (**Table 1**).

A total of 88 regimens were used, and palbociclib, abemaciclib, and everolimus were administered to 39, 14, and 35 patients, respectively. The mean and median TTF of all MTAs were 226.3 and 171 days, respectively. The TTF values were 279, 217, and 171 days in patients treated with palbociclib, abemaciclib, and everolimus, respectively ($P = 0.045$). Palbociclib, abemaciclib, and everolimus were administered to 11 (28.2%), 3 (21.4%), and 5 (14.3%) patients, respectively, for more than 1 year of TTF ($P = 0.348$) (**Table 2**).

Figure 1 shows the TTF values for the 56 patients.

Until December 2017, the primary MTA was an mTOR inhibitor. However, after approval of a CDK4/6 inhibitor in Japan, it was used as the first-line MTA in almost all cases. Except for the 12 patients who continue to use the first-line MTA therapy at this writing, the next treatments after the first-line MTA were other MTA types combined

Table 1 Patient characteristics

Characteristics	Number of patients (n = 56)
Mean age in years (median, range)	63 (60, 39–91)
Menopausal status, n	
Premenopausal	3
Postmenopausal	53
Metastatic site, n	
Bone	28
Lung/pleura	21
Liver	8
Lymph node	21
Local	6
Chest wall	1
Brain	1
Others	4
Mean number of prior chemotherapy treatments (median, range)[a]	1.3 (0, 0–7)
Treatment line in which the first MTA was introduced (1st–11th line)	
1st and 2nd line	11 patients
3rd line or later	45 patients
Number of MTAs administered	
1	35 patients
2	15 patients
3	6 patients
Prior MTA	
CDK4/6 inhibitor	35 patients
mTOR inhibitor	21 patients
Number of regimens with MTAs	
1	34 patients
2	14 patients
3	5 patients
4	3 patients

[a] Data for one patient were not available.
Abbreviations: CDK, cyclin-dependent kinase; MTA, molecularly targeted agent; mTOR, mammalian target of rapamycin

with hormone therapy in 15 patients (34%), chemotherapy in 14 patients (32%), hormone monotherapy in 8 patients (18%), and best supportive care in 6 patients (14%). Among patients included in the 50 regimens using CDK 4/6 inhibitor, TTF was not significantly different, regardless of prior use of an mTOR inhibitor (P = 0.408). Among patients included in the 35 regimens using mTOR inhibitor, TTF was also not significantly different, regardless of prior use of CDK4/6 inhibitors (P = 0.183) (**Table 3**).

In 21 patients who were treated with more than 2 MTAs, no correlation was found between the TTF of the initial and next MTAs (correlation coefficient: 0.211). Furthermore, no significant difference was found in the TTF for the next MTA when the TTF of the initial MTA was longer or shorter than 6 months (definition of endocrine resistance)[10] (P = 0.154) (**Fig. 2**).

Discussion

MTA therapy has become the standard for HR+/HER2– ABC/MBC in patients without visceral crisis[10–13]. Several clinical trials have reported that CDK4/6 inhibitors and mTOR inhibitors are both more effective than single-hormone therapy.

Although data are limited on which patient groups are best suited for specific MTAs, Bøttcher reported that with respect to AEs CDK4/6 inhibitors are preferable for initial use[17]. In the present study, TTF was significantly longer for CDK4/6 inhibitors than for mTOR inhibitors, although the MTA treatment line varied. In the absence of controversy, multiple guidelines indicate that CDK4/6 inhibitors should be considered as the first MTA op-

Table 2 TTF according to MTA

	Palbociclib	Abemaciclib	Everolimus	Total
Number of regimens	39	14	35	88
Mean TTF in days (median, range)	279 (202, 35–1,043)	216.8 (147.5, 21–538)	171 (137, 11–511)	226.3 (171, 11–1,043)
Treatment ongoing	10	5	1	16
Number of patients with TTF ≥ 1 year	11 (28.2%)	3 (21.4%)	5 (14.3%)	19 (21.6%)
Combination partner	Letrozole, 21 Fulvestrant, 13 Fulvestrant + LH-RH agonist, 3 Anastrozole, 2	Letrozole, 7 Fulvestrant, 4 Fulvestrant + LH-RH agonist, 2 Letrozole + LH-RH agonist, 1	Exemestane, 30 Tamoxifen, 2 Anastrozole, 3	

Abbreviations: TTF, time to failure; MTA, molecularly targeted agent; LH-RH, luteinizing hormone-releasing hormone

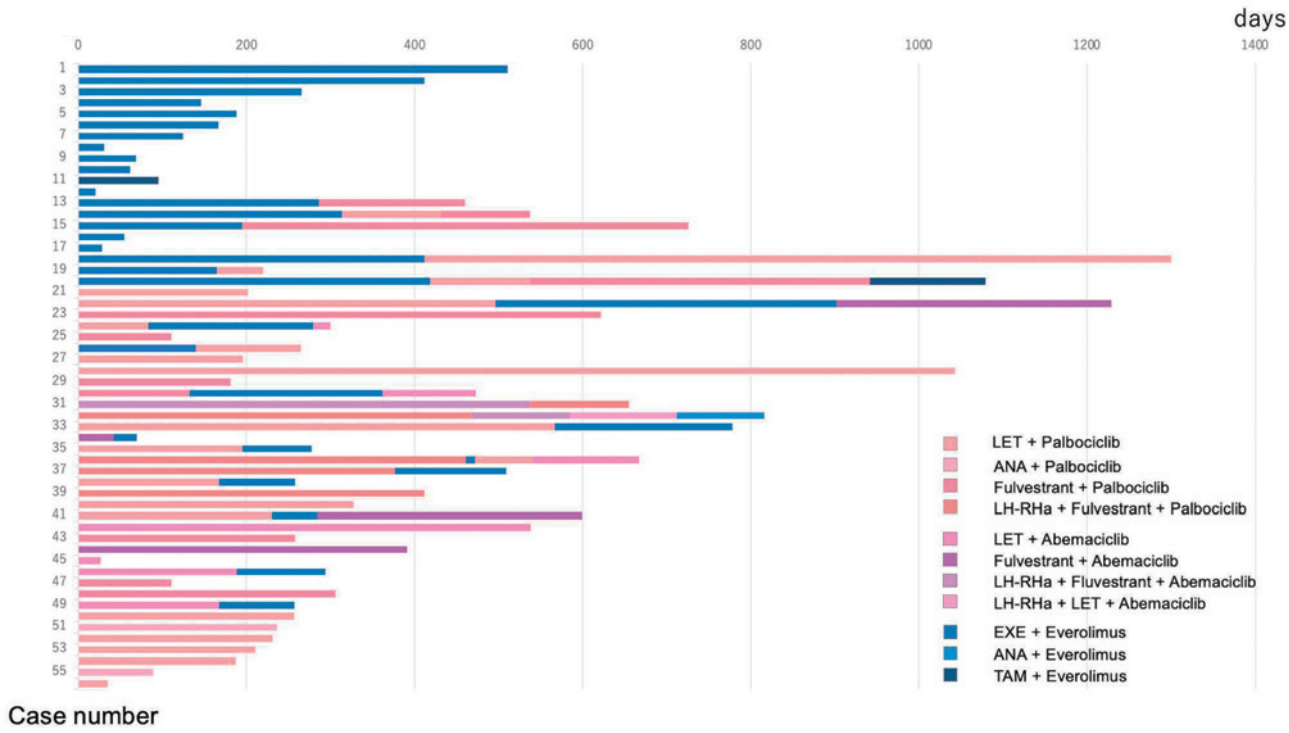

Fig. 1 Bar graph of TTF for all patients
Abbreviations: TTF; time to failure

tion[10–13]. Abemaciclib was approved in Japan only 3 years previously. However, we have patients with PD during first-line MTA treatment, and the best treatment option is unclear. In addition, subsequent treatments should be selected in accordance with cases encountered in clinical practice. In deciding the next treatment for PD during MTA therapy, the mechanism of hormone and MTA resistance should be considered. CDK4/6 inhibitors halt progression of the cell cycle by inhibiting CDK involved in cell-cycle regulation and exhibit an antitumor effect. Findings from basic research[18] suggest that when cancer cells become resistant to a CDK4/6 inhibitor, switching to another CDK4/6 inhibitor is ineffective; however, no data from relevant clinical trials have been reported. When resistance to a CDK4/6 inhibitor develops, inhibition of further upstream pathways with PI3K/AKT/mTOR pathway inhibitors is likely to be effective. Studies of the use of multiple MTAs combined with hormone therapy (triplet therapy[19,20]) and a new class of MTA are ongoing[21,22]. Several cohort studies have reported the potential utility of this approach. Cook et al. found that neither PFS nor overall survival during mTOR inhibitor ad-

Table 3 TTF in patients with CDK4/6 inhibitor treatment with or without previous mTOR inhibitor treatment and TTF in patients with a mTOR inhibitor treatment with or without previous CDK4/6 inhibitor treatment

	CDK4/6 inhibitor		mTOR inhibitor	
	Prior mTOR inhibitor	No prior mTOR inhibitor	Prior CDK4/6 inhibitor	No prior CDK4/6 inhibitor
n (days)	15	35	14	21
Average TTF	232.5	288.1	134.1	195.6
Median TTF	125	230	105	165
Range	21–888	27–1,043	11–406	21–511

Abbreviations: CDK, cyclin-dependent kinase; mTOR, mammalian target of rapamycin TTF, time to failure

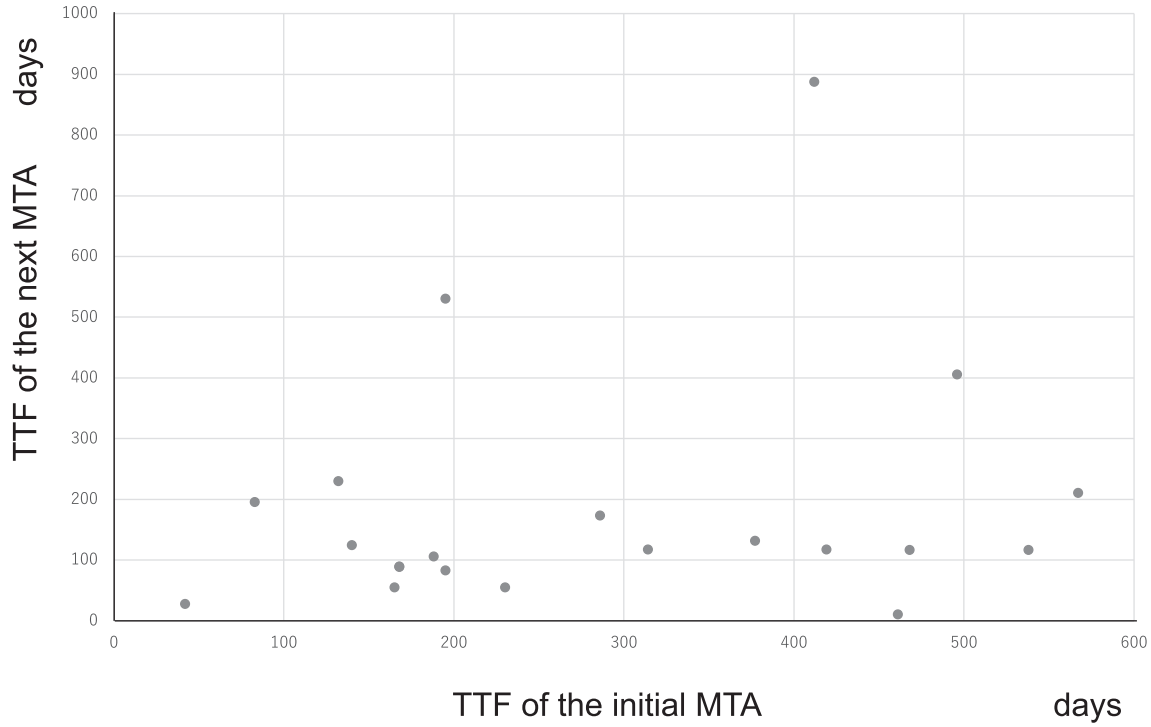

Fig. 2 Correlation between TTF values for the initial and subsequent MTA
The correlation coefficient was 0.211.
Abbreviations: TTF, time to failure; MTA, molecularly targeted agent

ministration differed in relation to previous use of CDK 4/6 inhibitors[23]. At our center, too, the TTF of mTOR inhibitors was not associated with prior use of CDK4/6 inhibitors. In Japan, everolimus was approved 3 years before the approval of CDK4/6 inhibitors. Therefore, all patients were treated with an mTOR inhibitor as the first-line MTA before the study period. The TTF of CDK4/6 inhibitors did not differ in relation to prior mTOR inhibitor use, in contrast to the findings of Dhakal et al.[24] We reported data from an HR+/HER2− ABC/MBC case series at our center. MTAs are used for treatment of hormone-sensitive breast cancer. Endocrine sensitivity significantly affects MTA efficacy. Therefore, we examined correlations of TTF for MTAs with the (1) TTF for adjuvant hormone therapy, (2) TTF for hormone therapy used immediately before MTA administration, and (3) TTF for all hormone therapies used before MTA administration. The TTF of adjuvant hormone therapy correlated with that of the MTA administered[25]. This suggested that if the TTF of the initial MTA is long, the next MTA may also be effective. However, the correlation of TTFs for initial and subsequent MTAs was not significant. Additionally, given that the cutoff for endocrine resistance is PD at 6 months of initial endocrine therapy, we examined whether a difference existed in the TTF of the next MTA when the TTF of the initial MTA was shorter or

longer than 6 months. No significant difference was found, possibly because the resistance of the hormone and MTA was not evaluated separately and the sample size was small.

High-quality clinical trials are expected to identify the next treatment. However, because luminal-type breast cancer progresses slowly, the findings of clinical trials will not be reported for some time. These clinical trials are designed as analyses of real-world evidence rather than as prospective randomized clinical trials and are conducted by major medical societies, such as the American Society of Clinical Oncology and European Society for Medical Oncology[26–29].

The present study is limited because it was retrospective, the data were collected at a single center, and the sample size was small. In clinical practice, patients were treated on the basis of findings from basic research and retrospective cohort studies. Our result-that TTF did not markedly differ among of MTAs regardless of prior use of different MTA types-was consistent with the findings of other retrospective cohort studies. Our findings are essential information on the clinical effectiveness of changing the type of MTA for patients with PD after initial MTA treatment.

Acknowledgements: We thank all our coworkers who were involved in treating patients with breast cancer in our hospital.

Conflict of Interest: None.

References

1. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375(20):1925−36. doi: 10.1056/NEJMoa1607303. PubMed PMID: 27959613.
2. Cristofanilli M, Turner NC, Bondarenko I, 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. doi: 10.1016/S1470-2045(15)00613-0. PubMed PMID: 26947331.
3. Turner NC, Ro J, André F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med. 2015;373(3):209−19. doi: 10.1056/NEJMoa1505270. PubMed PMID: 26030518.
4. Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. N Engl J Med. 2018;379(20):1926−36. doi: 10.1056/NEJMoa1810527. PubMed PMID: 30345905.
5. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med. 2016;375(18):1738−48. doi: 10.1056/NEJMoa1609709. PubMed PMID: 27717303.
6. Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. J Clin Oncol. 2018;36(24):2465−72. doi: 10.1200/JCO.2018.78.9909. PubMed PMID: 29860922.
7. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol. 2017;35(25):2875−84. doi: 10.1200/JCO.2017.73.7585. PubMed PMID: 28580882.
8. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol. 2017;35(32):3638−46. doi: 10.1200/JCO.2017.75.6155. PubMed PMID: 28968163.
9. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†. Ann Oncol. 2014;25(12):2357−62. doi: 10.1093/annonc/mdu456. PubMed PMID: 25231953.
10. Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol. 2020;31(12):1623−49. doi: 10.1016/j.annonc.2020.09.010. PubMed PMID: 32979513.
11. NCCN [Internet]. Plymouth Meeting (PA): NCCN; c2023. Guidelines Detail: Breast Cancer. 2023 [cited 2022 Jan 2]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
12. Clinical practice guideline for systemic treatment of breast cancer [Internet]. Tokyo: Table of contents for pharmacotherapy. Japan Breast Cancer Society; 2021. 2021 Mar 31 [cited 2022 Jan 2]. Available from: https://jbcs.xsrv.jp/guidline/2018/index/yakubutu
13. Shimoi T, Nagai SE, Yoshinami T, et al. Correction to: The Japanese Breast Cancer Society Clinical Practice Guidelines for systemic treatment of breast cancer. Breast Cancer. 2018 ed. 2021;28(4):985−6. doi: 10.1007/s12282-021-01252-x. PubMed Central PMCID: 33886078.
14. PfizerPRO [Internet]. New York (NY): Pfizer; c2023. Dosing & Monitoring: Recommended dose modifications for IBRANCE. [cited 2022 Jun 14]. Available from: https://ibrance.pfizerpro.com/dosing/modifications
15. Highlights of prescribing information [Internet]. Indianapolis (IN): Lilly USA, LLC; 2017. VERZENIO. [cited 2022 Jun 14]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208716s006s007s008lbl.pdf
16. Highlights of prescribing information [Internet]. Stein: Novartis Pharma Stein AG; 2012. AFINITOR;. [cited 2022 Jun 14]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022334s016lbl.pdf
17. Bøttcher TM, Cold S, Jensen AB. Treatment of advanced HR+/HER2− breast cancer with new targeted agents in combination with endocrine therapy: a review of efficacy and tolerability based on available randomized trials on everolimus, ribociclib, palbociclib and abemaciclib. Acta Oncol. 2019;58(2):147−53. doi: 10.1080/0284186X.2018.1532603. PubMed PMID: 30375908.
18. Iida M, Toyosawa D, Nakamura M, et al. Different mechanism of CDK4/6 inhibitor resistance between ribociclib and abemaciclib. Poster session presented at: Proceedings of the 2019 San Antonio breast cancer sympo-

sium. 2019;Dec 10 - Dec 14:Texas (TX).
19. Bardia A, Modi S, Oliveira M, et al. Triplet therapy with ribociclib, everolimus, and exemestane in women with HR+/HER2- advanced breast cancer. Cancer Res. 2016;76: P6-13-01.
20. O'Shaughnessy J, Thaddeus Beck J, Royce M. Everolimus-based combination therapies for HR+, HER2- metastatic breast cancer. Cancer Treat Rev. 2018;69:204−14. doi: 10.1016/j.ctrv.2018.07.013. PubMed PMID: 30092555.
21. Fabrice A, Eva MC, Dejan J. Overall survival results from SOLAR-1, a Phase 3 study of Alpelisib + fulvestrant for HR+, HER2-Advanced Breast Cancer. N Engl J Med. 2019;380:1929−40.
22. Rugo HS, Lerebours F, Ciruelos E, et al. Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. Lancet Oncol. 2021;22(4): 489−98. doi: 10.1016/S1470-2045(21)00034-6. PubMed PMID: 33794206.
23. Cook MM, Al Rabadi L, Kaempf AJ, Saraceni MM, Savin MA, Mitri ZI. Everolimus plus exemestane treatment in patients with metastatic hormone receptor-positive breast cancer previously treated with CDK4/6 inhibitor therapy. Oncologist. 2021;26(2):101−6. doi: 10.1002/onco.13609. PubMed PMID: 33230905.
24. Dhakal A, Matthews CM, Levine EG, et al. Efficacy of palbociclib combinations in hormone receptor-positive metastatic breast cancer patients after prior everolimus treatment. Clin Breast Cancer. 2018;18(6):e1401−5. doi: 10.1016/j.clbc.2018.04.015. PubMed PMID: 29778787.
25. Nakano S, Imawari Y, Mibu A, Kato S, Yamaguchi S, Sano M. Horumon kanjusei yousei, Her2 insei no shinkousaihatsunyugan ni taisuru bunshihyourekichiryouyaku no Time to failure ni kanrensuru inshi [Factors associated with time to failure of molecular targeted therapies for hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced/metastatic breast cancer]. Japanese. Proceedings of the 29th Annual Meeting of the Japanese Breast Cancer Society; 2021 Jul 1 - Jul 3; Yokohama. Tokyo: Japanese Breast Cancer Society. 2021. p. 73.
26. Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. J Natl Cancer Inst. 2017;109(11). doi: 10.1093/jnci/djx187. PubMed PMID: 29059439.
27. Visvanathan K, Levit LA, Raghavan D, et al. Untapped potential of observational research to inform clinical decision making: American Society of Clinical Oncology Research Statement. J Clin Oncol. 2017;35(16):1845−54. doi: 10.1200/JCO.2017.72.6414. PubMed PMID: 28358653.
28. ESMO Oncology Pro Educational Portal for Oncologists [Internet]. Lugano: ESMO; c2023. [cited 2021 Mar 2]. Available from: https://oncologypro.esmo.org
29. Wedam S, Fashoyin-Aje L, Bloomquist E, et al. FDA approval summary: palbociclib for male patients with metastatic breast cancer. Clin Cancer Res. 2020;26(6):1208−12. doi: 10.1158/1078-0432.CCR-19-2580. PubMed PMID: 31649043.

(Received, June 21, 2022)
(Accepted, December 2, 2022)
(J-STAGE Advance Publication, February 21, 2023)