Use of molecular targeted therapy for hormone receptor-positive, human epidermal growth factor 2-negative metastatic breast cancer in real-world clinical practice

Running title: Targeted therapy for HR+, HER2- MBC

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Abstract

**Background:** The emergence of molecular targeted therapies (MTTs) has altered the treatment landscape of hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2-) metastatic breast cancer (MBC). The objective of this study was to describe treatment patterns, clinical outcomes, and safety profiles among patients with HR+/HER2- MBC treated with palbociclib, abemaciclib, or everolimus in a clinical practice setting.

**Methods:** Forty-five patients with HR+/HER2- MBC were enrolled; of these, 40 received molecular targeted therapy (MTT) in ≥3rd lines and 5 received treatment in the 1st/2nd line. The results were compared with clinical trials.

**Results:** Median progression-free survival (PFS) in all patients was 5.3 months (95% confidence interval [CI] 2.8–8.4), and a similar PFS was found for patients receiving 1st/2nd line (5.5 months, 95% CI 1.8–) and ≥ 3rd line (5.1 months, 95% CI 2.8–9.4) treatments. Eleven patients continued with the same regimen for >1 year; treatment is ongoing for 15 patients. In 23 patients (51%), everolimus was administered prior to cyclin-dependent kinase (CDK) 4/6 inhibitors. The most frequent grade 3 or higher adverse event (AE) with CDK4/6 inhibitors was neutropenia, whereas AEs ≥ grade 3 with everolimus included *Pneumocystis* pneumonia, sepsis, and stomatitis.

**Conclusions:** Molecular targeted therapy (MTT) was mostly used in ≥ 3rd lines, and PFS of patients receiving 1st/2nd line and ≥ 3rd line treatments was similar; however, this study included heavily treated patients and a limited number of cases. Treatment options should take into consideration the maximal benefit to the patient based on the results of clinical trials.
Keywords: Hormone receptor-positive, Molecular targeted therapy, Palbociclib, Abemaciclib, Everolimus
Introduction

The treatment landscape of luminal type metastatic breast cancer (MBC) has changed owing to the emergence of molecular targeted therapies (MTTs)\(^1\). Hormonal or endocrine therapy (ET) is commonly prescribed in patients with luminal type, non-life-threatening MBC owing to fewer adverse events (AEs), lower costs, and less frequent hospital visits. However, many patients fail to respond to ET or eventually develop endocrine resistance\(^2\). According to the Advanced Breast Cancer 4 guidelines, the combination of molecular targeted agents (MTAs) and hormonal agents is an effective strategy in treating endocrine-resistant hormone receptor-positive (HR+), human epidermal growth factor 2-negative (HER2-) MBC\(^1\). Cyclin-dependent kinase (CDK) 4/6 inhibitors, such as palbociclib, abemaciclib, and ribociclib, are a new class of molecular targeted agents that have shown promising results in clinical trials\(^3\)-\(^10\). Palbociclib and abemaciclib were approved in Japan in December 2017 and November 2018, respectively. Another molecular targeted agent that has demonstrated efficacy in endocrine-resistant MBC is the mammalian target of rapamycin (mTOR) inhibitor, everolimus. Everolimus was approved in March 2014 in Japan. Compared to exemestane monotherapy, the combination of everolimus and exemestane significantly improved progression-free survival (PFS) in HR+, HER2- MBC patients progressing on non-steroidal aromatase inhibitors\(^11\). The safety profile of these MTTs is highly variable.

Despite the promising results, MTA is not commonly prescribed in the 1\(^{\text{st}}\) and 2\(^{\text{nd}}\) line setting in clinical practice;\(^{12\text{-}15}\) ET remains the preferred choice of treatment, especially for elderly patients. This may be attributed to the relatively better safety profile of ET than that of MTT. From a clinician’s perspective, patients must receive the most
beneficial treatment considering factors such as the duration until treatment failure, the patient’s comorbidity, and financial constraints. Here, we retrospectively analyzed patients who were administered MTAs for HR+, HER2- MBC in our hospital, and compared these data with results from clinical trials. We aimed to describe treatment patterns, clinical outcomes, and safety profiles among patients with HR+/HER2- advanced breast cancer and/or MBC treated with palbociclib, abemaciclib, or everolimus in a clinical practice setting.

**Materials and Methods**

In June 2020, data were collected (using the opt-out approach) from the electronic records of patients with HR+/HER2- MBC who received treatment with MTA (everolimus, palbociclib, or abemaciclib) at the Kawaguchi Municipal Medical Center from April 2014 to May 2020. Patients were treated with a combination of MTA and endocrine agent, with no concurrent anti-cancer therapy. The selection of MTA was made at the physician’s discretion. Data collected from the patients included age, menopausal status, adjuvant therapy, recurrence pattern, lines of treatment, prior treatments, the number of MTA, PFS, dose reduction parameters, outcomes, and AEs (per common terminology for adverse events v5.0 criteria)\(^\text{16}\). Doses of the MTAs were reduced as necessary, according to the dose modification criteria. Patients who received treatment with CDK4/6 inhibitors visited the hospital once every 2 weeks for a complete blood count check and to report any AEs, until the adequate dose was identified. After 2 months of treatment with the same dose of CDK4/6 inhibitor, the frequency of hospital visits was reduced to once a month. Patients who received treatment with everolimus visited the hospital once a month for monitoring complete
blood counts, blood sugar, and other AEs. This study was approved by the institutional review board of the Kawaguchi Municipal Medical Center (approval number 2020-2) and was performed in compliance with the Declaration of Helsinki. Informed consent was waived due to the retrospective nature of the study.

Data were reported in a manner similar to that in the PALOMA-3 main scientific paper. Standard descriptive statistics were used to report the data related to patient characteristics and tolerability outcomes. The Kaplan-Meier method was used to estimate the PFS. External reference data were used from Cristofanilli et al. to compare our findings with real-world data. Results were considered statistically significant if $P < 0.05$. Analyses were performed using SAS University Edition.

**Results**

From April 2014 to May 2020, 45 patients with HR+/HER2- MBC were treated with either palbociclib, abemaciclib, or everolimus (60 treatment regimens). The combination partners for different MTAs that have been authorized for use in Japan include exemestane with everolimus, letrozole or fulvestrant with palbociclib, and NSAI or fulvestrant with abemaciclib. In premenopausal patients, CDK4/6 inhibitors are used only with fulvestrant, in conjunction with a luteinizing hormone-releasing hormone agonist.

The average age of patients who received any type of MTA was 61 years (range, 39–91 years). Forty-two patients were postmenopausal and three were premenopausal. Metastatic sites are shown in Table 1. Besides adjuvant therapy, the number of chemotherapy regimens administered to the patients ranged from zero to eight. Seven
(15.6%) patients received MTT just before the best supportive care. The MTAs were administered in lines ranging from 1\textsuperscript{st} to 16\textsuperscript{th}. Only 5 patients were administered MTT in either the 1\textsuperscript{st} or 2\textsuperscript{nd} line, whereas 40 patients received MTT in the following lines.

Thirty-four patients received treatment with one MTA, 10 received two MTAs, and 1 received all three MTAs. Twenty-two patients had received a CDK4/6 inhibitor prior to an mTOR inhibitor, and 23 had received an mTOR inhibitor prior to CDK4/6 inhibitor therapy (Table 1). These data were compared with those of the PALOMA-3 population\textsuperscript{5}.

Palbociclib, abemaciclib, and everolimus were administered to 28, 5, and 27 patients, respectively, among 45 patients. Average time-to-failure (TTF), the number of patients who received the same regimen for >1 year, and combination partner in each MTA are shown in Table 2. The median PFS was 5.5 months among patients receiving 1\textsuperscript{st} and 2\textsuperscript{nd} lines of treatment and 5.1 months among those receiving 3\textsuperscript{rd} or later lines of treatment. Nine patients had a PFS > 1 year, and MTT was introduced in the 5.9\textsuperscript{th} line of treatment on average (Table 3). The median PFS in this study was 5.3 months (95\% confidence interval [CI] 4.9–15.1), compared with 9.5 months in the PALOMA-3 study (95\% CI 9.2–11.0) (Figure 1). Eleven patients received more than two MTAs. The sequential data of PFS are shown in Figure 2 and have been classified by the prior MTA received.

The most frequent AE (severity ≥ grade 3) associated with palbociclib treatment was neutropenia (Table 4). Of the 28 patients receiving palbociclib, 21 (75\%) required dose reduction or prolongation of interval. Although diarrhea was the most common AE associated with abemaciclib reported in clinical trials, there was no case of diarrhea with ≥ grade 3 observed in this study. Serious AEs, such as \textit{Pneumocystis} pneumonia, sepsis, and Fanconi syndrome were recognized for everolimus, although they were few, and
none was of grade 5 severity.

Discussion

In this study, we observed that MTTs for HR+/HER2- MBC were mostly used in 3rd line or later treatments, mainly because MTT was initially used in late lines. This could be due to the tendency to delay or avoid chemotherapy in elderly patients and the timing of MTT being first available in Japan and introduced to the back-log of heavily treated patients. The PALOMA-3 study\textsuperscript{4-6} compared fulvestrant and a combination of fulvestrant and palbociclib as a 2nd line treatment, whereas the PALOMA-2 study\textsuperscript{3} compared letrozole and a combination of letrozole and palbociclib as a 1st line treatment for HR+/HER2- advanced breast cancer and/or MBC patients. In our study, palbociclib was the most used and most of the patients were treated in 3rd line or later; thus, the PALOMA-3 study was chosen for comparison rather than PALOMA-2. Despite the limited number of cases of older and heavily treated patients in our study compared to the PALOMA-3 study, the median PFS using MTT in the late lines was similar to that in the early lines. The PFS in the 1st and 2nd line patients was low; however, the patients had no visceral metastases. Although the number of patients was limited, follow-up data from ongoing treatment will help us to further understand and evaluate these observations.

In our study, 9 (20\%) patients received MTT for longer than 1 year and it was introduced in these patients on average in the 5.9th line. Compared with the patients in the PALOMA-3 study\textsuperscript{4}—who received the 2nd line combination therapy and showed a PFS of 11.2 months—the patients in our study were heavily treated and older. However,
some of the patients in our study showed PFS that was comparable to that observed in the PALOMA-3 study. Analysis of the Kaplan-Meier curves showed that PFS of the patients in our study was close to that of patients in the PALOMA-3 study\(^4\) as analyzed by hormone monotherapy curves. It is noteworthy that PFS in our study declined immediately after the introduction of MTT, suggesting that some of the patients were administered MTT just before offering best supportive care. MTTs should be used in early lines of treatment before hormone sensitivity is lost.

There were only 11 cases of sequential treatment with MTTs in our study, including cases that are still ongoing. Since the mTOR inhibitor became available earlier than CDK4/6 inhibitors, there were slightly more cases in which the mTOR inhibitor was used first (23 vs. 22 cases for mTOR vs. CDK4/6 inhibitor, respectively) and one of the CDK4/6 inhibitors was used later in progressive disease. However, with the increasing number of CDK4/6 inhibitors now available, it is expected that these inhibitors will be used first more often in the near future. Sequential treatment of progressive disease with prior MTT will likely be more significant. When resistance to CDK4/6 inhibitors is observed, mTOR or PI3K inhibitors may be effective\(^{17-19}\). Some reports state that the use of prior MTT affects efficacy outcomes\(^{12-15}\); however, changing the treatment from a CDK4/6 inhibitor to an mTOR inhibitor has been shown to maintain the treatment effect\(^{20}\).

When a different treatment option is called for, we need to refer to known basic mechanisms of drug action or resistance because there is little available evidence from clinical trials to guide the next treatment choice. According to Iida et.al., cross-resistance can occur between two CDK4/6 inhibitors\(^{21}\); therefore, it would be better to
choose an agent with a different mechanism of action in the next treatment step. In our study, there were no cases in which one CDK 4/6 inhibitor was switched for another.

Combinations of MTA and hormone therapy have also been studied, demonstrating that hormones have the same effect whether used with or without MTA. Furthermore, PFS was shown to increase when MTA was used in combination with hormones rather than using MTA alone. Therefore, if possible, it is better to change both MTA and the hormonal agent to avoid the chances of cross-resistance. Results of ongoing clinical trials are expected.

Palbociclib is known to prevent cell proliferation by arresting the cell cycle; hence, neutropenia is easy to recover from after withdrawal of palbociclib. Febrile neutropenia is also experienced in clinical practice. Grade 3 or higher AEs are usually handled with dose modification criteria of the administered drug. Dose reduction was required for 75% of the patients who received palbociclib in this study. One- and two-step reduction was achieved for 32% and 29% of the patients, respectively. For 14% of the patients, the duration of the withdrawal was prolonged even after a two-step dose reduction. Variations in the safety profile of palbociclib exist for patients of different races; the incidence of various AEs was higher in Asian or Japanese patients than in the overall population.

Compared to palbociclib, abemaciclib does not require treatment withdrawal, which in turn reduces the complexity of the treatment schedule. However, according to a post-marketing investigation of abemaciclib in Japan, 17 of 4100 patients (0.4%) developed grade 5 interstitial lung disease, showing both organizing pneumonia and diffuse alveolar damage patterns, including some rapidly progressed cases. This is an important observation since the clinical trials of abemaciclib did not report interstitial
lung disease as an AE. There is no evidence of whether this observation is related to ethnicity. It is important to take special precautions to prevent severe AEs, especially in early lines of treatment. An examination of blood samples is recommended, including KL-6 levels and a chest CT scan, prior to the use of MTT. Additionally, clinical symptoms such as dyspnea and cough should be checked carefully during treatment.

When using everolimus, serious safety-related complications including *Pneumocystis* pneumonia, sepsis, and Fanconi syndrome were observed in our study, and treatment had to be discontinued or changed. Interstitial lung disease is another AE reported for everolimus, with relatively slow progression\textsuperscript{11}; however, there was no case of this AE in our study.

The effectiveness of MTT for HR+ HER2- MBC is convincing according to many clinical trials. Moreover, clinical trials employing a triplet combination of two MTTs and an ET, and new targeted agents with different mechanisms of action, have been conducted with the expectation of better results. However, MTT is sometimes difficult to introduce to patients with complications and elderly patients because of potential AEs, complex treatment schedules, frequent hospital visits, and costs in clinical practice. The current study included mainly patients with >3\textsuperscript{rd} line treatments with MTT because these cases had accumulated immediately after MTT was approved. As a result, the median PFS was shorter than that observed in the PALOMA-3 study.

There were some limitations in our study. First, the study was conducted at a single center and data were collected from electronic medical records. Second, the sample size was small and included some patients who are still receiving treatment as well as patients who received MTT just before the best supportive care. Despite the limited number of cases of older and heavily treated patients in the clinical practice setting,
20% of the patients obtained PFS longer than 1 year in our study. Treatment should be chosen to maximize benefits for each patient with HR+ HER2- MBC.
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Figure Legends:

Fig. 1. Kaplan-Meier curves of progression-free survival of patients in this study and in the PALOMA-3 study. The PALOMA-3 study data were adjusted according to the original data published by Turner et al. 5,6

Fig. 2. Progression free survival for each molecular targeted agent. Patients received (upper) mammalian target of rapamycin (mTOR) inhibitor treatment prior to initiation of cyclin-dependent kinase (CDK) 4/6 inhibitor treatment or (lower) CDK4/6 inhibitor treatment prior to initiation of mTOR inhibitor treatment. An “→” indicates treatment is ongoing.
Tables:

Table 1. Patient characteristics

| Characteristics                      | This study (n = 45) |
|--------------------------------------|--------------------|
| Average age in years (median, range) | 61 (59, 39–91)     |
| Menopausal status                    |                    |
| Premenopausal                        | 3 patients         |
| Postmenopausal                       | 42 patients        |
| Metastatic site                      |                    |
| Bone                                 | 23                 |
| Lung/pleura                          | 17                 |
| Liver                                | 6                  |
| Lymph node                           | 19                 |
| Local                                | 4                  |
| Chest wall                           | 1                  |
| Brain                                | 1                  |
| Unknown                              | 3                  |
| Average number of prior chemotherapy treatments (median, range)<sup>a</sup> | 1.9 (1, 0–8)       |

**Line introduced MTT (1<sup>st</sup>–16<sup>th</sup> line)**

- 1<sup>st</sup> and 2<sup>nd</sup> line: 5 patients
- 3<sup>rd</sup> line or later: 40 patients
| Number of molecular targeted agents administered |
|-----------------------------------------------|
| 1                                             | 34 patients |
| 2                                             | 10 patients |
| 3                                             | 1 patient   |

| Prior molecular targeted agent                |
|-----------------------------------------------|
| CDK 4/6 inhibitor                              | 22 patients |
| mTOR inhibitor                                 | 23 patients |

*Data for one patient were not available.*
Table 2. Time-to-failure (TTF) in each targeted agent

|                          | Palbociclib | Abemaciclib | Everolimus |
|--------------------------|-------------|-------------|------------|
| **Number of treatments** | 28          | 5           | 27         |
| **Average TTF in**       |             |             |            |
| **months (median, range)**| 8.2 (6.5, 0-22) | 4.9 (3.2, 0.3-16) | 6.2 (5.5, 0.3-18) |
| **Treatment ongoing**    | 10          | 3           | 2          |
| **Number of patients with TTF ≥1 year** | 6 (21.4%) | 1 (20.0%) | 4 (14.8%) |
| **Combination partner**  | Letrozole, 16 | Letrozole, 3 | Exemestane, 24 |
|                          | Fulvestrant, 10 | Fulvestrant, 1 | Others, 3 |
|                          | Fulvestrant + LH-RH agonist, 2 | Fulvestrant + LH-RH agonist, 1 |

LH-RH; luteinizing hormone-releasing hormone
Table 3. Progression-free survival (PFS) in early and late lines of treatment

| Line of therapy                     | Median PFS                      |
|-------------------------------------|---------------------------------|
| 1\(^{st}\) and 2\(^{nd}\) (5 cases) | 5.5 months (ongoing; 2 cases)   |
| 3\(^{rd}\) or later (40 cases)     | 5.1 months (ongoing; 8 cases)   |
| All patients                        | 5.3 months                      |

Number of patients who received molecular targeted therapy for >1 year

9 (20%)

Average and median line of introducing molecular targeted agents in patients with PFS > 1 year (range)

5.7, 5.9 (3-10)
Table 4. Summary of adverse events for 45 patients (60 treatment regimens)

| Number of patients using each molecular targeted agent | Palbociclib | Abemaciclib | Everolimus |
|---------------------------------------------------------|-------------|-------------|------------|
|                                                         | 28          | 5           | 27         |

| Adverse events (severity ≥ grade 3), n                  | Neutropenia, 12 | Vomiting, 1 | Pneumocystis pneumonia, 1 |
|--------------------------------------------------------|----------------|-------------|------------------------|
|                                                        | Leukocytopenia, 1 | Abdominal pain, 1 | Sepsis, 1 |
|                                                        | Febrile neutropenia, 1 | Increase of hepatobiliary enzyme, 1 | Stomatitis, 1 |
|                                                        | Anemia, 1 | | Fanconi syndrome, 1 |
|                                                        | Vomiting, 1 | Leukocytopenia, 1 | Gastrointestinal disorders, 1 |
|                                                        | Chronic renal failure, 1 | Malaise, 1 | Increased blood sugar, 1 |

| Dose reduction, n (%)                                  | 21 (75%) | 3 (60%) | 2 (7%) |
|--------------------------------------------------------|----------|---------|--------|
| 1-dose level reduction: 9 (32%)                        |          |         | 50% reduction: 2 (7%) |
| 2-dose level reduction: 8 (29%)                        |          |         |        |
| 2-dose level reductions                                |          |         |        |
| + prolongation of interval: 4 (14%)                    |          |         |        |

| Treatment discontinuation, n (%)                       | 3 (11%) | 2 (40%) | 2 (7%) |
|--------------------------------------------------------|---------|---------|--------|
Fig. 1

Comparison of progression-free survival probability between different treatments:
- Blue line: Palbociclib + Fulvestrant in the PALOMA-3 study (n = 347)
- Gray line: This study (n = 45)
- Red line: Placebo + Fulvestrant in the PALOMA-3 study (n = 174)

Y-axis: Progression-free survival probability (%)
X-axis: Time (months)
Fig. 2

- **mTOR inhibitor (month)** to **CDK4/6 inhibitor (month)**:
  - Everolimus + Exemestane or others: 12, 10, 9
  - Palbociclib + Letrozole: 13, 5, 5
  - Palbociclib + Fulvestrant: 5, 4, 3
  - Abemaciclib + Letrozole: 16, 17, 2

- **CDK4/6 inhibitor (month)** to **mTOR inhibitor (month)**:
  - Everolimus + Exemestane or others: 4, 6, 5
  - Palbociclib + Letrozole: 16, 12, 6
  - Palbociclib + Fulvestrant: 2, 1
  - Abemaciclib + Letrozole: 5, 3