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ORIGINAL RESEARCH

Current Treatment Patterns Among Postmenopausal Women with HR+/HER2− Metastatic Breast Cancer in US Community Oncology Practices: An Observational Study

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ABSTRACT

Introduction: Recent approval of novel agents has changed the treatment landscape for post menopausal women with hormone receptor-positive (HR+) and human epidermal growth factor receptor-2 negative (HER2−) metastatic breast cancer (mBC). The objective of this study was to describe contemporary treatment patterns among postmenopausal women with HR+/HER2− mBC in the real-world setting.

Methods: Data were collected from 64 community oncologists in the US between February and June 2017 using an online medical records extraction tool. Physicians reviewed medical records and provided information on patient demographics and disease characteristics, and treatment regimens. Treatment patterns were described overall and separately by line of therapy and type of treatment received. Discontinuation rates were estimated using Kaplan–Meier analyses to account for censoring.

Results: Data were collected on 401 patients. Mean age at the time of mBC diagnosis was 67 years. In the first-line setting, 52.4% of patients received a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor-based regimen, most commonly with an aromatase inhibitor (AI) (39.2%) or fulvestrant (10.0%); 30.2% received endocrine therapy, most commonly an AI (21.4%) or fulvestrant (5.2%) in monotherapy, while 12.7% received a chemotherapy-based regimen. In the second-line setting, 42.9% of patients received a CDK4/6 inhibitor-based regimen, 18.4% received endocrine therapy, and 22.4% received a chemotherapy-based regimen. The 18-month discontinuation rate was 34.5% for patients receiving a CDK4/6 inhibitor-based regimen and 45.8% for patients receiving endocrine monotherapy.

Conclusion: CDK4/6 inhibitor-based regimens were the most commonly prescribed treatment in both first- and second-line settings. A wide variety of treatment sequences were observed

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which suggests an absence of a standard of care for postmenopausal women with HR+/HER2− mBC in real-world practice.

Keywords: CDK4/6 inhibitor; Chemotherapy; Endocrine therapy; Hormone-positive; Metastatic breast cancer; Oncology; Postmenopausal; Real-world

INTRODUCTION

Breast cancer (BC) is a leading cause of cancer-related deaths among women [1]. In 2017, an estimated 252,710 new cases of invasive BC were expected to be diagnosed in women in the United States (US) [1]. Although as many as 90% of women with early stage localized BC achieve long-term disease-free survival, women diagnosed with metastatic BC (mBC) have substantially lower survival rates [1, 2].

Although often referred to as a single disease, mBC has distinct histological and molecular subtypes that differ in terms of risk factors, response to treatments and outcomes. Hormone receptor-positive (HR+) and human epidermal growth factor receptor-2-negative (HER2−) are the most common histological subtypes diagnosed in approximately 70% of patients, and account for most of the deaths from the disease [3]. Other important prognostic factors include age and menopausal status which impact disease characteristics and outcomes, as well as choice of treatment [4].

Endocrine therapy has long been the recommended first-line treatment for HR+/HER2− mBC. Following disease progression, patients may receive an alternative single-agent endocrine therapy followed by chemotherapy. Chemotherapy is typically recommended when there is clear evidence of resistance to endocrine therapy or when there is a need for rapid disease control [4].

Recently, novel agents, notably cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, have changed the treatment landscape of the disease [5]. CDK4/6 inhibitor therapies have shown improved progression-free survival compared to endocrine therapy alone. Palbociclib was the first CDK4/6 inhibitor to be approved by the Food and Drug Administration (FDA) in the US, in February 2015, for use in combination with letrozole as first-line treatment for advanced HR+/HER2− BC in postmenopausal women [6, 7]. It was later approved in combination with fulvestrant for use in second or further lines of therapy for women with HR+/HER2− advanced or mBC who relapsed or progressed during prior endocrine therapy [8]. In 2017, two new CDK4/6 inhibitors, ribociclib and abemaciclib, were also approved for the treatment of postmenopausal women with HR+/HER2− advanced or mBC [9, 10]. The updated 2017 National Comprehensive Cancer Network (NCCN) guidelines include recommendations for palbociclib or ribociclib, in combination with an aromatase inhibitor (AI), as first-line treatment options for postmenopausal women with recurrent or stage IV HR+/HER2− BC. In addition, abemaciclib (alone or with fulvestrant) is recommended as a second-line therapy for these patients [4].

Given the changing landscape of treatments for HR+/HER2− mBC among postmenopausal women, it is important to understand the treatments used in current clinical practice and the drivers of different treatment choices. The objective of this study was to describe contemporary treatment patterns in US clinical practice for postmenopausal women with HR+/HER2− mBC.

METHODS

Data Source

This observational, retrospective study was based on data collected from community oncologists using an online survey and patient medical chart review. Oncologists in the US were invited by email to participate in the study. Participating oncologists were asked to provide clinical information on a maximum of 10 patients from their practice. The data collection period spanned February to June 2017, and was conducted using an online medical record extraction tool that was developed for this study. Data collected from physicians did not include any patient-identifying information

and the study was exempted from full review by the New England Institutional Review Board. This study is based on retrospective data and does not include any interaction with human participants or animals performed by any of the authors.

Study Sample

Patients were eligible if they: (1) were women diagnosed with HR+ and HER2− or HER2-equivocal de novo or recurrent mBC between March 2015 and January 2016 (allowing for a potential follow-up of 12 months); (2) were postmenopausal at the time of initiation of first-line therapy for HR+/HER2− mBC; (3) had never been enrolled in a clinical trial for the treatment of BC; and (4) had complete medical and treatment-related information from the date of HR+/HER2− mBC diagnosis available to the participating physician.

Data Collection and Study Measures

Physicians provided information on their practice, including size, setting, location, specialty, and treatment preferences. For each selected patient, physicians reviewed medical records and provided detailed information on patient demographics, BC history (e.g., diagnosis date, tumor stage at diagnosis), comorbidities, and treatment patterns, including information on first- and second-lines of therapy for mBC such as treatment regimens, treatment changes, and reasons for treatment changes.

Physician characteristics and treatment preferences were summarized. Patient treatment patterns and treatment sequences were also described for all patients. After exploring reported treatment patterns, patients were categorized into four groups based on the first-line treatment received: (1) CDK4/6 inhibitor-based regimen (only palbociclib was approved at the time of the data collection), (2) endocrine monotherapy, (3) chemotherapy-based regimen, or (4) other treatment regimen. Patient characteristics were summarized overall and separately by treatment group. Discontinuation rates were estimated using Kaplan–Meier analyses to account for censoring of patients who were still on treatment at the time of the data collection.

RESULTS

Physician Characteristics

A total of 64 US oncologists participated in the study. Nearly all physicians (95.3%) worked at community-based practices with most practice sizes of 2–9 oncologists/subspecialists (54.7%) or 10 or more oncologists/subspecialists (40.6%). All four US census regions were represented, with the majority of practices in a suburban (45.3%) or urban (42.2%) setting. Almost all physicians (90.6%) reported having practiced oncology for more than 10 years.

Table 1 describes the treatment preferences for first-line therapy for mBC of the responding physicians in their current practice. The majority (67.2%) of physicians ranked CDK4/6 inhibitors + endocrine therapy as their top treatment option in their current practice, citing good efficacy profile (93.0%) and good tolerability profile (60.5%) as reasons for this treatment choice. Endocrine monotherapy was the preferred first-line treatment option for mBC for 26.6% of physicians who cited good tolerability profile (100%), good efficacy profile (88.2%), and their familiarity with this regimen (52.9%) as reasons for this treatment choice. Chemotherapy as monotherapy was preferred by 6.3% of physicians with the majority (75%) citing good efficacy profile as the main reason for choosing this treatment option as a first-line therapy for treatment of mBC (Table 1).

Patient Characteristics

A total of 401 women met the inclusion criteria and were included in the analyses. The average age of patients at the time of mBC diagnosis was 67 years; patients receiving endocrine monotherapy were older (71.6 years). The majority of patients were Caucasian (70.6%) and 55.1% had Medicare, while 41.1% were covered by commercial or private insurance. Patients who received endocrine monotherapy

Table 1 Physician treatment preferences and reasons

Most commonly prescribed first-line therapy for the treatment of mBC with associated reasons, *n* (%)	**Physicians (*n* = 64)**
CDK4/6 inhibitor + endocrine therapy	43 (67.2%)
Good efficacy profile	40 (93.0%)
Good tolerability profile	26 (60.5%)
Convenience of treatment administration	15 (34.9%)
Patients prefer CDK4/6 inhibitor + endocrine therapy over endocrine monotherapy	11 (25.6%)
Patients prefer CDK4/6 inhibitor + endocrine therapy over chemotherapy	11 (25.6%)
Per institutional guidelines	9 (20.9%)
Insurance requirement	1 (2.3%)
Endocrine monotherapy	17 (26.6%)
Good tolerability profile	17 (100.0%)
Good efficacy profile	15 (88.2%)
Familiarity with regimen	9 (52.9%)
Insurance requirement	6 (35.3%)
Lower out-of-pocket cost for the patient	8 (47.1%)
Convenience of treatment administration	7 (41.2%)
Per institutional guidelines	4 (23.5%)
Patients prefer endocrine monotherapy over CDK4/6 inhibitor + endocrine therapy	6 (35.3%)
Patients prefer endocrince monotherapy over chemotherapy	4 (23.5%)
Patients prefer endocrine monotherapy over mTOR inhibitor	2 (11.8%)
Chemotherapy as monotherapy	4 (6.3%)
Good efficacy profile	3 (75.0%)
Good tolerability profile	2 (50.0%)
Symptomatic bulky disease	2 (50.0%)
Visceral crisis	2 (50.0%)
Per institutional guidelines	2 (50.0%)
Convenience of treatment administration	1 (25.0%)
Need for rapid response	2 (50.0%)
Insurance requirement	1 (25.0%)
Lower out-of-pocket cost for the patient	1 (25.0%)

Responding physicians were allowed to select more than one reason for preferring a treatment option. Other treatment options, including mTOR inhibitor + endocrine therapy, and other therapy (to specify), were presented but were not selected by any physician as the most commonly prescribed first-line therapy for the treatment of mBC
mBC metastatic HR+/HER2− breast cancer, *CDK4/6* cyclin-dependent kinase 4/6

Table 2 Description of patient demographic and clinical characteristics

	All patients (n = 401)	CDK4/6 inhibitor patients (n = 210)	Endocrine only patients (n = 121)	Any chemotherapy patients (n = 51)	Other regimen patients (n = 19)
Demographic characteristics at mBC diagnosis					
Age (years)					
Mean (SD)	67.0 (9.4)	65.4 (8.6)	71.6 (10.0)	63.3 (8.6)	64.1 (5.5)
Median [range]	67.0 [34, 92]	66.0 [34, 89]	72.0 [35, 92]	63.0 [43, 84]	63.0 [49, 72]
Race, n (%)					
Asian	22 (5.5%)	15 (7.1%)	4 (3.3%)	1(2.0%)	2(10.5%)
Black	86 (21.4%)	44 (21.0%)	32 (26.4%)	7 (13.7%)	3 (15.8%)
Caucasian	28 (70.6%)	146 (69.5%)	83 (68.6%)	41 (80.4%)	13 (68.4%)
Native American	2 (0.5%)	1 (0.5%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Pacific Islander	1 (0.2%)	1 (0.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Unknown	1 (0.2%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Other	6 (1.5%)	3 (1.4%)	0 (0.0%)	2 (3.9%)	1 (5.3%)
Type of insurance[a], n (%)					
Commercial/private insurance	65 (41.1%)	89 (42.4%)	33 (27.3%)	32 (62.7%)	11 (57.9%)
Medicare	221 (55.1%)	114 (54.3%)	79 (65.3%)	20 (39.2%)	8 (42.1%)
Medicaid	63 (15.7%)	38 (18.1%)	20 (16.5%)	3 (5.9%)	2 (10.5%)
Military insurance (VA or active military)	2 (0.5%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
No insurance	1 (0.2%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Unknown/not sure	3 (0.7%)	0 (0.0%)	3 (2.5%)	0 (0.0%)	0 (0.0%)
Karnofsky performance status (KPS) at first-line-therapy initiation,[b] n (%)					
100%	33 (8.2%)	18 (8.6%)	11 (9.1%)	3 (5.9%)	1 (5.3%)
90%	53 (13.2%)	28 (13.3%)	17 (14.0%)	3 (5.9%)	5 (26.3%)
80%	133 (33.2%)	81 (38.6%)	28 (23.1%)	19 (37.3%)	5 (26.3%)
70%	105 (26.2%)	55 (26.2%)	27 (22.3%)	17 (33.3%)	6 (31.6%)
60%	46 (11.5%)	22 (10.5%)	19 (15.7%)	5 (9.8%)	0 (0.0%)
50%	13 (3.2%)	3 (1.4%)	7 (5.8%)	3 (5.9%)	0 (0.0%)
40%	11 (2.7%)	2 (1.0%)	8 (6.6%)	0 (0.0%)	1 (5.3%)
30%	5 (1.2%)	1 (0.5%)	2 (1.7%)	1 (2.0%)	1 (5.3%)
20%	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
10%	1 (0.2%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Not recorded in medical record	1 (0.2%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0 (0.0%)
Metastatic sites present at first-line therapy initiation,[a] n (%)					
Bone	292 (72.8%)	149 (71.0%)	98 (81.0%)	31 (60.8%)	14 (73.7%)
Bone only (with or without lymph nodes)	162 (40.4%)	83 (39.5%)	68 (56.2%)	7 (13.7%)	4 (21.1%)
Brain	17 (4.2%)	9 (4.3%)	1 (0.8%)	6 (11.8%)	1 (5.3%)
Chest wall	39 (9.7%)	25 (11.9%)	9 (7.4%)	3 (5.9%)	2 (10.5%)
Kidney	3 (0.7%)	2 (1.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)
Liver	92 (22.9%)	45 (21.4%)	20 (16.5%)	20 (39.2%)	7 (36.8%)
Lungs	157 (39.2%)	87 (41.4%)	29 (24.0%)	30 (58.8%)	11 (57.9%)
Lymph nodes	115 (28.7%)	71 (33.8%)	20 (16.5%)	20 (39.2%)	4 (21.1%)
Pancreas	2 (0.5%)	1 (0.5%)	0 (0.0%)	1 (2.0%)	0 (0.0%)

Table 2 continued

	All patients (n = 401)	CDK4/6 inhibitor patients (n = 210)	Endocrine only patients (n = 121)	Any chemotherapy patients (n = 51)	Other regimen patients (n = 19)
Skin	16 (4.0%)	7 (3.3%)	7 (5.8%)	2 (3.9%)	0 (0.0%)
Other[c]	16 (4.0%)	6 (2.9%)	4 (3.3%)	6 (11.8%)	0 (0.0%)
Any visceral organ (kidney, liver, lungs, pancreas)	192 (47.9%)	105 (50.0%)	38 (31.4%)	35 (68.6%)	14 (73.7%)
Patients diagnosed with de-novo mBC, n (%)	223 (55.6%)	124 (59.0%)	75 (62.0%)	22 (43.1%)	2 (10.5%)
Time from primary BC to mBC among patients previously diagnosed with early stage breast cancer (months)	**All patients (n = 178)**	**CDK4/6 inhibitor patients (n = 86)**	**Endocrine only patients (n = 46)**	**Any chemotherapy patients (n = 29)**	**Other regimen patients (n = 17)**
Mean (SD)	65.4 (57.0)	52. 9 (48.8)	96.9 (68.2)	72.2 (52.7)	31.9 (17.9)
Median [range]	51 [1, 312]	38 [2, 283]	85.4 [8, 312]	57.9 [5, 224]	33.3 [1, 77]

mBC metastatic breast cancer, *CDK4/6* cyclin-dependent kinase 4/6
[a] Responding physicians were allowed to select more than one option
[b] Physicians could report performance status based on KPS or ECOG; since KPS was more frequently used, all scores were transferred to KPS
[c] Other metastatic sites at first-line initiation include mediastinum, omentum, peritoneum, stomach, abdominal carcinomatosis, adrenal, ascites, interstinal implants, spleen, pleural effusion, and pleura

in the first-line were more likely to be Medicare-insured (65.3%)—which is highly correlated with age, while those receiving chemotherapy were more likely to be covered by commercial or private insurance (62.7%). Prior to first-line therapy, the majority of patients (80.8%) had Karnofsky performance status (KPS) $\geq$ 70%. Patients who used endocrine monotherapy in the first-line tended to have poorer KPS scores, with 14.9% reporting KPS $\leq$ 50%. The most common sites of metastases at first-line initiation were bone (72.8%; 40.4% of patients had bone-only metastases), followed by lungs (39.2%) and lymph nodes (28.7%). Patients receiving endocrine monotherapy were most likely to have bone-only metastases (56.2%), while patients receiving chemotherapy or other regimens were most likely to have metastases in visceral organs (68.6% and 73.7%, respectively) (Table 2).

Treatment Characteristics

In first-line therapy, 52.4% of the patients received a CDK4/6-based regimen, most commonly with an AI (39.2%) or fulvestrant (10.0%), 30.2% received endocrine therapy, most commonly an AI (21.4%) or fulvestrant (5.2%) in monotherapy, while 12.7% received a chemotherapy-based regimen. In second-line therapy, 42.9% of patients received a CDK4/6 inhibitor-based regimen, 18.4% received endocrine therapy, 22.4% received a chemotherapy-based regimen, and 16.3% received other treatment regimens (everolimus + endocrine therapy). The most common regimens were palbociclib with fulvestrant (23.1%) or with an AI (17.7%) (Table 3).

Among the 147 patients with at least two lines of therapy, the most common treatment sequences observed were an AI followed by CDK4/6 inhibitor with fulvestrant (13.6%), chemotherapy followed by CDK4/6 inhibitor with an AI (10.3%), and CDK4/6 inhibitor with an AI, followed by chemotherapy (8.8%) or by everolimus with an AI (8.8%) (Table 4).

Slightly over half of all patients (53.1%) were still receiving first-line therapy at the time of data collection, 65.7% of patients were receiving a CDK4/6 inhibitor-based regimen, 53.7% were receiving endocrine monotherapy, and 5.9% were receiving chemotherapy. Overall, the median time to discontinuation for first-line

therapy was 19.4 months. Among patients using endocrine monotherapy in the first line, the median duration was 18.7 months, while, for patients receiving chemotherapy, it was 5.6 months (consistent with 4–6 cycles of 28 days). For patients who received a CDK4/6 inhibitor in first line, median duration was not reached because the majority of patients were censored (still on treatment at the time of data collection).

The 18-month discontinuation rate for patients receiving a CDK4/6 inhibitor-based regimen was 34.5%, 45.8% for patients receiving endocrine monotherapy, and 92.9% for patients receiving chemotherapy in first-line therapy. The most common reason for discontinuing first-line therapy was disease progression or sub-optimal response, given for 72.3% of patients overall, 80.6% of patients receiving CDK4/6 inhibitors and 89.3% of patients receiving endocrine therapy. Among patients receiving chemotherapy in the first line, the majority (56.3%) discontinued because they had completed the planned duration of therapy (Table 5).

DISCUSSION

This study evaluated real-world treatment patterns among postmenopausal women with HR+/HER2− mBC. The results showed that, in both first-line and second-line settings, CDK4/6 inhibitor-based regimens were the most commonly prescribed treatment with just over half of patients receiving CDK4/6 inhibitors, mostly with AI or fulvestrant in the first line. However, endocrine therapy and chemotherapy were also used for a considerable proportion of patients as first-line therapies.

Several clinical trials have demonstrated the effectiveness of CDK4/6 inhibitors in the treatment of postmenopausal women with HR+/HER2− mBC. These studies have shown significantly longer progression-free survival in patients treated with CDK4/6 inhibitors compared to those treated with endocrine therapy alone [11–13]. However, despite improved outcomes demonstrated for patients using CDK4/6 inhibitor therapies, 30% of patients in the present study were observed to receive endocrine monotherapy and 13% chemotherapy-based regimens in the first line for HR+/HER2− mBC; however, the results of the physician survey indicated that treatment patterns may already be changing. Approximately two-thirds of physicians reported CDK4/6 inhibitors to be the most commonly prescribed first-line therapy for the treatment of mBC in their current practice. The difference between the physician survey results and the patient-level data, where approximately 50% of patients were treated with CDK4/6 inhibitors in the first line, may be partly explained by the lag between the time patients started therapy (up to 2 years before the data collection) and the time physicians answered the survey. It is likely that the proportion of patients receiving CDK4/6 inhibitors will increase over time as physicians become more familiar with these agents and their benefits, particularly since two additional CDK4/6 inhibitors, ribociclib and abemaciclib, have recently been approved.

For postmenopausal women with HR +/HER2- mBC, the NCCN guidelines recommend a number of options for first-line therapy, including a CDK4/6 inhibitor—palbociclib or ribociclib—in combination with AI, or single-agent therapy with an AI, a selective estrogen receptor (ER) modulators (i.e., tamoxifen or toremifene), or a selective ER down-regulator (i.e., fulvestrant). Patients who had prior endocrine therapy within 1 year are recommended to consider a different endocrine therapy, possibly with a CDK4/6 inhibitor, or mTOR inhibitor, and those in visceral crises are recommended chemotherapy. Patients are recommended to continue first-line therapy until progression or unacceptable toxicity, at which time they may consider another line of endocrine therapy (if not endocrine refractory). Chemotherapy is only recommended for women with a need for rapid response, symptomatic visceral disease, or suspected endocrine resistance [4]. Several of the treatment regimens observed in this study were not consistent with these guideline recommendations. For example, 30% of patients received endocrine therapy, 12% received chemotherapy-based regimens in the first line, and some received palbociclib in combination with chemotherapy.

Table 3 Description of treatment regimens for mBC by line of therapy

Treatment regimen, *n* (%)	First-line therapy (*n* = 401)	Second-line therapy (*n* = 147)
CDK4/6 inhibitor-based regimen	210 (52.4%)	63 (42.9%)
Palbociclib + aromatase inhibitor	157 (39.2%)	26 (17.7%)
Palbociclib + fulvestrant	40 (10.0%)	34 (23.1%)
Palbociclib in monotherapy	3 (0.7%)	0 (0.0%)
Palbociclib + endocrine therapy + chemotherapy	9 (2.2%)	3 (2.0%)
Palbociclib + chemotherapy	1 (0.2%)	0 (0.0%)
Endocrine monotherapy	121 (30.2%)	27 (18.4%)
Aromatase inhibitor	86 (21.4%)	5 (3.4%)
Fulvestrant	21 (5.2%)	19 (12.9%)
Aromatase inhibitor + fulvestrant	11 (2.7%)	3 (2.0%)
Tamoxifen	2 (0.5%)	0 (0.0%)
Aromatase inhibitor + tamoxifen	1 (0.2%)	0 (0.0%)
Chemotherapy-based regimen	51 (12.7%)	33 (22.4%)
Taxane-based regimen	34 (8.5)	17 (11.6%)
Taxane monotherapy	11 (2.7%)	11 (7.5%)
Platinum + taxane	10 (2.5%)	4 (2.7%)
Gemcitabine + taxane	2 (0.5%)	1 (0.7%)
Cyclophosphamide + taxane	5 (1.2%)	0 (0.0%)
ACT with or without aromatase inhibitor	3 (0.7%)	0 (0.0%)
Cyclophosphamide + aromatase inhibitor + Taxane	1 (0.2%)	0 (0.0%)
Endocrine therapy + taxane	1 (0.2%)	1 (0.7%)
Capecitabine + taxane	1 (0.2%)	0 (0.0%)
Capecitatine with or without endocrine therapy	11 (2.7%)	10 (6.8%)
Other[a]	6 (1.5%)	6 (4.1%)
Other regimen		
Everolimus + endocrine therapy[b]	17 (4.2%)	24 (16.3%)
Bevacizumab-based regimen	2 (0.5%)	0 (0.0%)

mBC metastatic HR+/HER2− breast cancer, *ACT* anthracycline + cyclophosphamide + taxane, *CDK4/6* cyclin-dependent kinase 4/6

[a] Other chemotherapy-based regimens included vinorelbine monotherapy, anthracycline + cyclophosphamide, bevacizumab + cyclophosphamide, cyclophosphamide + fluorouracil + methotrexate, gemcitabine monotherapy, eribulin monotherapy

[b] One patient received everolimus in combination with fulvestrant in second-line therapy; all other patients received it in combination with an aromatase inhibitor

Table 4 Description of treatment sequences for mBC

	All patients with at least two lines of therapy ($n = 147$) (%)
AI → CDK4/6 + fulvestrant	20 (13.6)
AI → fulvestrant	7 (4.8)
AI → CDK4/6 + AI	5 (3.4)
Chemotherapy → CDK4/6 + AI	15 (10.3)
Chemotherapy → chemotherapy	9 (6.3)
Chemotherapy → CDK4/6 + fulvestrant	6 (4.2)
Chemotherapy → fulvestrant	3 (2.1)
Chemotherapy → AI	3 (2.0)
CDK4/6 + AI → everolimus + AI	13 (8.8)
CDK4/6 + AI → chemotherapy	13 (8.8)
CDK4/6 + AI → fulvestrant	8 (5.4)
CDK4/6 + fulvestrant → everolimus + AI	4 (2.7)
Fulvestrant → chemotherapy	5 (3.5)
Fulvestrant → CDK4/6 + AI	4 (2.7)
Everolimus + AI → CDK4/6 + fulvestrant	5 (3.4)

mBC metastatic HR+/HER2− breast cancer, *AI* aromatase inhibitor, *CDK4/6* cyclin-dependent kinase 4/6

Previous studies on treatment patterns among women with HR+/HER2− mBC have also reported inconsistencies with guideline recommendations. For example, despite NCCN recommendations that endocrine therapy should be used as first-line therapy in women with HR+/HER2− mBC, a US study based on commercial health plan data from 2008 to 2013 found that more than 50% of women with HR+/HER2− mBC were treated with first-line chemotherapy [14]. In another US study based on claims data from 2002 to 2012, 40% of postmenopausal women with HR+/HER2− mBC received chemotherapy as first-line therapy; among those who used endocrine therapy in the first line, most received only one line of endocrine therapy before discontinuation or transition to chemotherapy [15]. Similarly, in a European chart review study from 2014, 30% of patients used chemotherapy in first line, a higher proportion than expected considering the HR+ tumor molecular profile and chemotherapy-related toxicities [16]. Moreover, it was reported that 22% of patients in that study would have been recommended by treatment guidelines to continue hormonal therapy for their second line of therapy, but instead received chemotherapy [16].

The present study uses more recent data that include novel CDK4/6 inhibitors as current treatment options. Results suggest considerable deviation from guideline recommendations and significant heterogeneity in the treatment of postmenopausal women with HR+/HER2− mBC. In this study, a variety of treatment sequences, including 35 different treatment regimens in the first line, were observed. Some treatment regimens, such as the combination of palbociclib with chemotherapeutic agents, may be unconventional.

The inconsistencies between guideline recommendations and real-world practice may be partly attributed to the considerable heterogeneity in metastatic disease characteristics as well as the lack of clarity in some components of guideline recommendations (e.g., definition of treatment response or disease progression) that may leave treatment options open to physicians' interpretation. While there may be individual patient-specific reasons for these inconsistencies, the absence of a standard of care that is consistently implemented in clinical practice points to an unmet need for treatment options in this patient population.

This study has some limitations. First, although physicians were instructed to randomly select patients who met the inclusion criteria, selection bias may exist if physicians were biased towards selecting patients they had seen more recently or who had better or worse outcomes. In addition, due to the non-randomized nature of the sample, the choice of treatment could be endogenous to patient characteristics or physician preferences. Second, since patients were observed over a relatively short time period, the information on

Table 5 Description of treatment characteristics for mBC (first-line of therapy)

	All patients (n = 401)	CDK4/6 inhibitor patients (n = 210)	Endocrine only (n = 121)	Any chemotherapy (n = 51)	Other regimens (n = 19)
Therapy duration (months),[a] median	19.4	–	18.7	5.6	11.2
The patient is still receiving this therapy, n (%)	213 (53.1%)	138 (65.7%)	65 (53.7%)	3 (5.9%)	7 (36.8%)
The patient died while on this therapy, n (%)	4 (2.1%)	1 (1.4%)	1 (1.8%)	1 (2.1%)	1 (8.3%)
Discontinuation rate following therapy initiation, (%)					
3 months	3.2%	0.0%	1.7%	21.6%	0.0%
6 months	10.3%	2.9%	5.0%	51.0%	15.8%
9 months	22.6%	10.6%	17.5%	80.4%	31.6%
12 months	32.2%	20.7%	25.8%	86.3%	52.6%
18 months	46.9%	34.5%	45.8%	92.9%	63.2%

Reasons for discontinuation (multiple options could be selected),[b,c] n (%)	All Patients (n = 188)	CDK4/6 inhibitor (n = 72)	Endocrine only (n = 56)	Any chemotherapy (n = 48)	Other regimens (n = 12)
Any indicator of disease progression or sub-optimal response	136 (72.3%)	58 (80.6%)	50 (89.3%)	18 (37.5%)	10 (83.3%)
Disease progression	126 (67.0%)	53 (73.6%)	49 (87.5%)	15 (31.3%)	9 (75.0%)
Deterioration of patient's quality of life	15 (7.9%)	6 (8.2%)	4(7.1%)	4 (8.3%)	1 (8.3%)
Deterioration of patient's functional status	9 (4.8%)	6 (8.3%)	0 (0.0%)	2 (4.2%)	1 (8.3%)
Suboptimal response	3 (1.6%)	2 (2.8%)	0 (0.0%)	1 (2.1%)	0 (0.0%)
Death	4 (2.1%)	1 (1.4%)	1 (1.8%)	1 (2.1%)	1 (8.3%)
Patient completed planned duration of therapy	29 (15.4%)	2 (2.8%)	0 (0.0%)	27 (56.3%)	0 (0.0%)
Lack of adherence	7 (3.7%)	5 (6.9%)	0 (0.0%)	1 (2.1%)	1 (8.3%)
Development or worsening of comorbid conditions	6 (3.2%)	4 (5.6%)	1 (1.8%)	1 (2.1%)	0 (0.0%)
Non-severe adverse event	5 (2.7%)	5(6.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Severe adverse event	3 (1.6%)	0 (0.0%)	1 (1.8%)	2 (4.2%)	0 (0.0%)
Patient high out-of-pocket burden	3 (1.6%)	1 (1.4%)	1 (1.8%)	0 (0.0%)	1 (8.3%)
Inconvenience of treatment administration	3 (1.6%)	2 (2.8%)	0 (0.0%)	1 (2.1%)	0 (0.0%)
Potential drug–drug interactions	1 (0.5%)	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Treatment is no longer reimbursed	2 (1.1%)	1 (1.4%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
Other patient-driven reason[d]	3 (1.6%)	2 (2.8%)	1 (1.8%)	0 (0.0%)	0 (0.0%)
Other physician-driven decision[d]	2 (1.1%)	0 (0.0%)	1 (1.8%)	1 (2.1%)	0 (0.0%)

mBC metastatic HR+/HER2− breast cancer, *CDK4/6* cyclin-dependent kinase 4/6

[a] Time to line of therapy discontinuation was assessed using Kaplan–Meier analyses. Patients who did not discontinue the line of therapy or died while of therapy were censored at last follow-up. Median duration was not reported if fewer than 50% of patients discontinued treatment. Kaplan–Meier analysis was not performed for third-line therapy because no patients discontinued treatment

[b] Responding physicians were allowed to select more than one option

[c] Among patients who discontinued or died while on therapy

[d] Other patient-driven reasons for discontinuing include "moved away" and "noncompliance". Other physician-driven reasons include "better therapies available" and "excellent partial remission"

treatment duration was limited. Third, the study did not consider prior use of antineoplastic therapy in the adjuvant or neo-adjuvant setting, which may impact the treatments considered for mBC. Finally, given the relatively small number of physicians who participated in the study, the results may not be fully

representative of community oncology practices in the US.

CONCLUSION

The treatment landscape for postmenopausal women with HR+/HER2− mBC is rapidly changing. Half of postmenopausal women with HR+/HER2− mBC were treated with CDK4/6 inhibitors in this study, a proportion that is likely to increase given the recent approval of two new CDK4/6 inhibitor agents. Further studies are needed to evaluate the uptake of these novel agents into real-world practice, as well as their outcomes in the real world.

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Compliance with Ethics Guidelines. This study is based on retrospective data and does not include any interaction with human participants or animals performed by any of the authors.

Data Availability. The datasets analyzed during the current study are available from the corresponding author upon reasonable request. Please note that institutional review board confirmation will be needed before the data can be shared with additional parties.

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