Hormone receptor–positive, HER2-negative metastatic breast cancer: redrawing the lines

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ABSTRACT

Estrogen receptor modulators and estrogen deprivation have become standards of care for hormone receptor–positive metastatic breast cancer. However, after traditional first-line endocrine monotherapy treatment, the disease typically progresses despite the initial high rate of clinical benefit. Multiple studies have aimed at optimizing treatment strategies to improve upon clinical benefit beyond the traditional single-agent endocrine treatment. With the availability of new data and novel therapies, the clinical practice challenge becomes how best to define the optimal treatment sequence to maximize clinical benefit. In this review, we present treatment options clinically relevant to the management of hormone-positive, HER2-negative metastatic breast cancer, and we propose a treatment algorithm based on the current literature.

Key Words Antineoplastic agents, hormonal therapy, combined chemotherapy protocols, breast neoplasms, drug therapy, metastasis

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INTRODUCTION

Survival rates for women with metastatic breast cancer (mBCa) are improving, especially for those whose tumours express the estrogen or progesterone hormone receptors (HRs) or the human epidermal growth factor receptor 2 (HER2)1,2. The most common subtype of breast cancer is HR-positive breast cancer, which accounts for approximately 60%–70% of all cases3. Oophorectomy was first shown to cause regression of unresectable breast cancer in 1896, and since then, estrogen receptor modulation and estrogen deprivation have become standards of care for HR-positive mBCa4,5.

Unfortunately, despite the high rate of clinical benefit from initial endocrine treatment, disease progression typically occurs after 1 year of traditional first-line endocrine monotherapy3. Multiple studies have aimed at optimizing treatment strategies to further improve on clinical benefit beyond traditional single-agent endocrine therapy. However, with more recent positive data available, the clinical practice challenge has become how to define the optimal treatment sequence to maximize clinical benefit. In this review, we present treatment options clinically relevant to the management of HR-positive, HER2-negative mBCa, and we propose a treatment algorithm based on the current literature.

METHODS

Reports of systematic reviews and randomized controlled trials from 1990 to 2017 in the MEDLINE database and in abstracts from the San Antonio Breast Cancer Symposium, American Society of Clinical Oncology meetings, and European Society for Medical Oncology meetings were reviewed for available data about endocrine treatment in mBCa. Reference lists from recent review articles and guidelines were scanned for additional citations, and known updates of the included evidence were obtained as available. Abstracts and full articles in English were included. Clinically relevant data were selected by the authors for description and discussion.

RESULTS

Current Endocrine Treatment Approach for HR-Positive, HER2-Negative mBCa

Targeting the estrogen receptor is one of the most important treatment strategies used to control endocrine-sensitive mBCa3,5,6. Endocrine treatment strategies include medications that lower estrogen production, modulate signalling through the estrogen receptor, or antagonize and degrade the estrogen receptor itself5. Additionally, novel drugs given in combination with endocrine treatment are...
now available and have also been incorporated into clinical practice. Endocrine therapy might be suitable for patients with HR-positive, HER2-negative mBCa who have low-burden disease (that is, bone as a single site of metastatic disease, or nonthreatening visceral burden) and for those who have experienced a long disease-free interval (that is, beyond 2 years) to enrich for more endocrine-responsive disease. Patients with rapidly progressive visceral disease or with a risk or evidence of end-organ dysfunction or significant disease-related symptoms should be offered chemotherapy. The choice of endocrine agent should be based on menopausal status, comorbidities, prior adjuvant therapy, drug availability, patient preference, and drug safety profile.

Postmenopausal Patients

First-Line Treatment Options for HR-Positive, HER2-Negative mBCa

In the past, based on positive results in randomized trials and subsequent meta-analyses, single-agent endocrine therapy was the mainstay of first-line treatment for HR-positive, HER2-negative mBCa. The two most effective endocrine monotherapy treatment choices in the first-line setting are either aromatase inhibitors (AIs) or selective estrogen receptor degraders (Fulvestrant). Those endocrine agents have also now been studied in combination with inhibitors of cyclin-dependent kinases 4 and 6 (CDK 4/6) with some synergy with endocrine agents.

AIs: The AIs block the aromatase enzyme, which normally converts naturally occurring androgens into estrogenic compounds, mainly in peripheral tissues. Their use ultimately leads to less available estrogen to stimulate the growth of HR-positive breast cancer cells.

A 2006 meta-analysis of twenty-three randomized trials (8504 patients) showed the efficacy of AIs as a first-line treatment for mBCa in postmenopausal women (Table 1). Despite in vitro and pharmacodynamic data noting increased potency of aromatase inhibition with letrozole, no clinically meaningful data have demonstrated outcome superiority in comparisons of letrozole with the other AIs. In one trial involving 128 women with advanced breast cancer, the comparison between exemestane and anastrozole resulted in a similar overall response rate (ORR) of 15% in both groups and similar overall survival (OS) durations of 30.5 months and 33.3 months respectively. Data in the adjuvant setting comparing letrozole with anastrozole also showed similar outcomes with both agents.

Fulvestrant: Fulvestrant is a selective estrogen receptor degrader that blocks estrogen receptor dimerization and DNA binding, increases estrogen receptor turnover, and inhibits nuclear uptake of the receptor. Initially approved as a single-agent monthly intramuscular injection (250 mg per injection), a higher 500 mg dose with a loading dose was proved in the CONFIRM trial to be more effective and is now the preferred dose. Table 1 describes the phase II FIRST and the phase III FALCON trials that demonstrated the role of single-agent fulvestrant in the first-line setting for postmenopausal patients. The FALCON study included only endocrine treatment–naïve patients with mBCa, but did allow for one prior line of chemotherapy in the advanced disease setting.

Fulvestrant Plus Anastrozole: The fact and SWOG S0226 trials explored fulvestrant–anastrozole as first-line combination therapy, but with conflicting results, as Table 1 shows. The SWOG S0226 trial enrolled more endocrine-naïve patients and, in addition, used the more effective 500 mg fulvestrant regimen; those differences might explain the difference in outcomes. Additional studies are needed to clarify those discrepancies and to determine whether combination therapy with fulvestrant–anastrozole is truly superior to anastrozole or fulvestrant alone.

CDK 4/6 Inhibitors Plus Endocrine Therapy: Knowledge of the molecular heterogeneity of breast cancer has led to the identification of the role that cell-cycle signalling plays in breast cancer oncogenesis—in particular, for patients with HR-positive mBCa. The CDKs drive cell-cycle progression and control transcriptional processes. The dysregulation of multiple CDK family members commonly occurs in human cancer. The cyclin D–CDK4/6–retinoblastoma protein–INK4 axis is particularly disrupted, facilitating cancer cell proliferation, thus leading to research targeting CDK 4/6 as a therapeutic approach.

Palbociclib was the first oral small-molecule CDK 4/6 inhibitor to be developed. It is known to arrest cells in GI phase by blocking phosphorylation of retinoblastoma protein at CDK 4/6–specific sites.

Preclinical studies suggested growth-inhibitory activity in HR-positive breast cancer cells and potential synergy with endocrine agents.

The PALOMA-1 trial, an open-label randomized phase II study of letrozole (2.5 mg daily) with or without palbociclib (125 mg daily on days 1–21 of a 4-week cycle) as first-line therapy, demonstrated activity and clinical benefit for the combination. Postmenopausal women with HR-positive, HER2-negative mBCa who had received no systemic treatment for their advanced disease were eligible to participate (n = 165). At the time of the final analysis, progression-free survival (PFS) was superior in the palbociclib–letrozole group compared with the letrozole-only group (median: 20.2 months (range: 13.8–27.5 months) vs. 10.2 months (range: 5.7–12.6 months); hazard ratio: 0.49; 95% confidence interval: 0.32 to 0.75; one-sided p = 0.0004). Grade 3 or 4 neutropenia was reported in 45 of 83 patients (54%) in the palbociclib–letrozole group compared with 1 of 77 patients (1%) in the letrozole group, leucopenia in 16 patients (19%) compared with none, and fatigue in 4 patients (4%) compared with 1 (1%). No cases of febrile neutropenia or neutropenia-related infections were reported during the study. Based on those results, palbociclib–letrozole received U.S. Food and Drug Administration accelerated approval in February 2015 as first-line therapy for HR-positive, HER2-negative mBCa.

In an underpowered analysis, the OS results of the PALOMA-1 trial were presented at the 2017 American Society of Clinical Oncology meeting, demonstrating a nonsignificant difference in OS for palbociclib–letrozole compared...
| Regimen and study | Pts (n) | Arms | Outcome | Overall response rate | Progression-free survival | Overall survival |
|-------------------|---------|------|---------|-----------------------|---------------------------|-----------------|
| **Aromatase inhibitors (AIs)** | | | | | | |
| Meta-analysis of 23 randomized trials⁶ | 8504 | AIs vs. tamoxifen, AIs vs. other endocrine therapies | Not reported | Not reported | Superior with AIs compared with tamoxifen (HR: 0.89; 95% CI: 0.80 to 0.99) and with other endocrine therapies (HR: 0.86; 95% CI: 0.79 to 0.94) |
| **Fulvestrant** | | | | | | |
| Phase II FIRST trial⁸-¹⁰ | 205 | Fulvestrant vs. anastrozole | Similar clinical benefit rate: 72.5% for fulvestrant, 67% for anastrozole (OR: 1.3; 95% CI: 0.72 to 2.38) | Significantly longer time to treatment progression for fulvestrant: 23.4 months vs. 13.1 months (HR: 0.66; 95% CI: 0.47 to 0.92) | Superior with fulvestrant: 54.1 months vs. 48.4 months (HR: 0.70; 95% CI: 0.50 to 0.98) |
| Phase III FALCON trial¹¹ | 462 | Fulvestrant vs. anastrozole | Similar: 46% for fulvestrant, 45% for anastrozole (OR: 1.07; 95% CI: 0.72 to 1.61; p=0.7290) | Fulvestrant arm superior in the overall population: 16.6 months vs. 13.8 months (HR: 0.797; 95% CI: 0.637 to 0.999; p=0.0486) | Fulvestrant arm superior for patients with no visceral disease: 22.3 months vs. 13.8 months (HR: 0.59; 95% CI: 0.42 to 0.84) |
| | | | No apparent differences between the two arms for patients with visceral disease: 13.8 months vs. 15.9 months (HR: 0.99; 95% CI: 0.74 to 1.33) | | |
| **Fulvestrant plus anastrozole** | | | | | | |
| Phase III FACT trial¹² | 514 | Anastrozole alone or in combination with fulvestrant | Similar: 33.6% for anastrozole alone, 31.8% for the combination (OR: 0.92; 95% CI: 0.54 to 1.58; p=0.76) | Similar time to progression: 10.8 months for the combination, 10.2 months for anastrozole (HR: 0.99; 95% CI: 0.81 to 1.20) | Similar: 37.8 months for the combination, 38.2 months for anastrozole (HR: 1.0; 95% CI: 0.76 to 1.32) |
| Phase III SWOG S0226 trial¹³ | 707 | Anastrozole alone or in combination with fulvestrant | Similar: 27% for the combination, 22% for anastrozole alone; p=0.26 | Superior with combination therapy: 15 months vs. 13.5 months (HR: 0.80; 95% CI: 0.68 to 0.94) | Superior with combination therapy: 47.7 months vs. 41.3 months (HR: 0.81; 95% CI: 0.65 to 1.00) |
| **Inhibitors of cyclin-dependent kinases 4 and 6 plus endocrine therapy** | | | | | | |
| Phase III PALOMA-2 trial¹⁴,¹⁵ | 666 | Palbociclib plus letrozole vs. placebo plus letrozole | Superior with palbociclib–letrozole: 42.1% vs. 34.7%, p=0.031 | Superior with palbociclib–letrozole: 24.8 months vs. 14.5 months (HR: 0.58; 95% CI: 0.46 to 0.72; p<0.000001) | Not reported |
TABLE I

| Regimen and study | Overall response rate | Progression-free survival | Overall survival |
|-------------------|-----------------------|---------------------------|-----------------|
|                   |                      |                           |                 |
| Inhibitors of cyclin-dependent kinases 4 and 6 plus endocrine therapy continued | Not reported | Not reported | Not reported |
| Phase III MONALEESA-2 trial (NCT02422615) | Superior with ribociclib–letrozole: 54.5% vs. 38.8%, *p* = 0.0014 | Superior with ribociclib–letrozole: 25.3 months vs. 16 months (HR: 0.568; 95% CI: 0.457 to 0.704; *p* = 9.63 × 10⁻⁹) | Not reported |
| Phase III MONALEESA-3 trial (NCT02136279) | Not reported | Not reached in the abemaciclib–anastrozole or letrozole arm | Not reported |
| Phase III MONARCH 3 trial | Superior with abemaciclib plus anastrozole or letrozole: 59% vs. 44%, *p* = 0.004 | Not reached in the placebo arm | Not reached in the placebo arm |

**HR2 = human epidermal growth factor receptor 2; Pr = patients; AI = aromatase inhibitor; HR = hazard ratio; CI = confidence interval; OR = odds ratio.**

with letrozole only [median: 37.5 months (range: 31.4–47.8 months) vs. 34.5 months (range: 27.4–42.6 months); hazard ratio: 0.897; 95% confidence interval: 0.623 to 1.294; *p* = 0.281]. Additionally, 78.6% of patients in the palbociclib–letrozole arm compared with 86.4% in the letrozole arm received post-study systemic therapy, and more patients in the letrozole arm received 3 or more lines of therapy (37% vs. 18%)²⁹.

Subsequent phase III trials in the first-line setting for postmenopausal patients were developed with palbociclib (PALOMA-2), ribociclib (MONALEESA-2), and abemaciclib (MONARCH 3), as described in Table I²⁵–²⁹. Those trials excluded patients who had received prior therapy for advanced disease, but did not exclude patients who had been exposed to prior neoadjuvant or adjuvant treatment, including prior endocrine treatment, provided that the disease-free interval after exposure to a nonsteroidal AIs was more than 12 months. The results of all studies of CDK 4/6 inhibitors in association with endocrine therapy in the first-line setting were consistent, showing increased rates of ORR and PFS, with the OS data still being immature.

**Second-Line Treatment Options for HR-Positive, HER2-Negative mBCa**

For a patient experiencing disease progression after initial endocrine therapy, ongoing endocrine treatment is a reasonable option provided that symptoms from underlying metastatic disease are not present, that the disease continues to be slowly progressive, and that the patient experienced a reasonable response to first-line endocrine therapy. Patients with rapidly progressive or life-threatening metastatic disease should be treated with palliative chemotherapy instead³. However, it is important to point out that data published so far with respect to the second-line treatment of HR-positive, HER2-negative mBCa do not inform the question of how best to sequence therapy after progression on CDK 4/6 inhibitors. Table II summarizes the most relevant data for postmenopausal patients in the second-line setting.

**CDK 4/6 Inhibitors Plus Endocrine Therapy:** Table II lists combination trials of CDK 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) with endocrine therapy in the second-line setting²⁸–³⁰,³¹.

The first reported trial of this combination was palbociclib–fulvestrant in the PALOMA-3 trial, in which superior ORR and PFS rates favoured the combination²⁰,²¹. Eligible patients included those experiencing disease relapse or progression during treatment with prior endocrine therapy for advanced disease or within 12 months of completion of adjuvant therapy. Notably, premenopausal or perimenopausal women (21% of the trial population) were included and received goserelin together with the study treatment.

Interestingly, a description of patterns of disease progression and subsequent therapies and an analysis of the effect of the study treatment on subsequent therapies for participants in the PALOMA-3 trial were presented at the 2016 San Antonio Breast Cancer Symposium³¹. In both the palbociclib–fulvestrant and the placebo–fulvestrant groups, the most common sites of disease progression were liver (75.3% (*n* = 149) and 72.3% (*n* = 94) respectively) and...
### TABLE II
Summary of trials in postmenopausal patients with hormone receptor–positive, HER2-negative metastatic breast cancer in the second-line setting

| Regimen and study                      | Pts  | Arms                              | Outcome                                      |
|----------------------------------------|------|-----------------------------------|----------------------------------------------|
|                                        | (n)  | Overall response rate             | Progression-free survival | Overall survival |
| **Inhibitors of cyclin-dependent kinases 4 and 6 plus endocrine therapy** |      |                                   |                               |                 |
| Phase III PALOMA-3 trial\[30,31\]       | 521  | Palbociclib and fulvestrant vs. placebo and fulvestrant | Superior with palbociclib–fulvestrant: 24.6% vs. 10.9% (OR: 2.69; 95% CI: 1.43 to 5.26; two-sided \( p=0.001 \)) | Superior with palbociclib–fulvestrant: 9.5 months vs. 4.6 months (HR: 0.46; 95% CI: 0.36 to 0.59; \( p<0.001 \)) | Not reported |
| Phase III MONALEESA-3 trial (NCT02422615) | Not reported | Ribociclib and fulvestrant vs. placebo and fulvestrant | Not reported | Not reported | Not reported |
| Phase III MONARCH 2 trial\[12\]        | 669  | Abemaciclib and fulvestrant vs. placebo and fulvestrant | Superior with abemaciclib–fulvestrant: 35.2% vs. 16.1%, \( p<0.001 \) | Superior with abemaciclib–fulvestrant: 16.4 months vs. 9.3 months (HR: 0.553; 95% CI: 0.449 to 0.681; log-rank \( p<0.0000001 \)) | Not reported |
| **Everolimus with exemestane**         |      |                                   |                               |                 |
| Phase III BOLERO-2 trial\[33–35\]      | 724  | Everolimus and exemestane vs. exemestane plus placebo | Superior with everolimus–exemestane: 9.5% vs. 0.4% | Similar: 16.4 months vs. 9.3 months (HR: 0.553; 95% CI: 0.449 to 0.681; log-rank \( p<0.0000001 \)) |                 |
| **Everolimus plus fulvestrant**        |      |                                   |                               |                 |
| Phase II PrECOG 0102 trial\[36\]       | 130  | Everolimus plus fulvestrant vs. placebo plus fulvestrant | Not reported | Similar: 8% for everolimus–fulvestrant, 8% for fulvestrant–placebo, 4% for exemestane, \( p=0.17–1.00 \) |                 |
| **Aromatase inhibitors**               |      |                                   |                               |                 |
| Phase III trial\[37\]                  | 713  | Letrozole vs. anastrozole          | Superior with letrozole: 19.1% vs. 12.3%, \( p=0.013 \) | Similar: 22 months for letrozole, 20.3 months for anastrozole, \( p=0.624 \) |                 |
| Qualitative systematic review\[38\]    | Nine studies | Exemestane                        | Ranged from 2% to 19%, with a clinical benefit rate that ranged from 12% to 55% | Time to progression: 3.7 months to 5.2 months | 15.2 months |
| **Fulvestrant as a single agent or in combination with AI** |      |                                   |                               |                 |
| Phase III SoFEA trial\[39\]           | 723  | Fulvestrant plus anastrozole vs. fulvestrant plus placebo vs. exemestane alone | Similar: 8% for fulvestrant–anastrozole, 4% for fulvestrant–placebo, 1% for exemestane, \( p=0.05 \) | Similar: 20.2 months for fulvestrant–anastrozole, 21.6 months for exemestane, \( p<0.05 \) |                 |
bone [27.8% (n = 55) and 33.1% (n = 43) respectively]. The most commonly used post-progression regimens in the palbociclib–fulvestrant and placebo–fulvestrant patients were everolimus [15.2% (n = 30) and 23.1% (n = 30) respectively], capecitabine [28.8% (n = 57) and 24.6% (n = 32)], paclitaxel [11.1% (n = 22) and 17.7% (n = 23)], and exemestane with or without everolimus [17.2% (n = 34) and 21.5% (n = 28)]. The treatment effect for palbociclib–fulvestrant appears to be retained through the immediate next line of treatment after progression. The analysis showed that, for patients with post-study disease progression, the median time until the start of subsequent follow-up treatment was longer in the palbociclib group than in the placebo group. The end of the immediate follow-up therapy was also later in the palbociclib group, regardless of post-treatment modality.

Ribociclib is also being evaluated in this setting in the monaleesa-3 trial, a phase III trial in the first- or second-line setting in which ribociclib is being compared with placebo–fulvestrant, with no reported results to date (see NCT02422615 at http://ClinicalTrials.gov).

Abemaciclib was studied in the phase III monarch2 trial, which enrolled women with hr-positive, her2-negative advanced breast cancer who progressed while receiving neoadjuvant or adjuvant endocrine therapy, at 12 months or fewer from end of adjuvant endocrine therapy, or on first-line endocrine therapy for mbc and who had not received chemotherapy for metastatic disease.52 Patients were stratified by metastatic site (visceral, bone only, or other) and resistance to prior endocrine therapy (primary vs. secondary). Premenopausal and perimenopausal patients received a gonadotropin-releasing hormone agonist. Abemaciclib–fulvestrant was superior to fulvestrant alone for ORR and PFS.

**Everolimus–Exemestane:** Studies show that the mtor (mechanistic target of rapamycin) inhibitor everolimus is an option, in combination with endocrine therapy, in postmenopausal women for the treatment of AI-resistant hr-positive mbc. The bolero-2 trial described the benefit of everolimus plus the steroidal AI exemestane for ORR and PFS, as described in Table II. The trial enrolled women who had progressed on AIs.

**Everolimus–Fulvestrant:** The phase II JCOG 0102 trial demonstrated a benefit in PFS in favour of combined everolimus–fulvestrant compared with placebo–fulvestrant in postmenopausal women with hr-positive mbc resistant to AI therapy (Table II)56.

**AIs:** In the second-line setting, as evidenced in the first line, the nonsteroidal AIs show no differences in efficacy.37 When it comes to exemestane in the second-line setting after progression on a nonsteroidal AI, there is evidence of drug efficacy as described in Table II.38

**Fulvestrant As a Single Agent or in Combination with an AI:** Most of the trials evaluating fulvestrant in the second-line setting were designed to use a lower dose of fulvestrant (250 mg monthly) than the dose that the CONFIRM trial proved to be superior23,42,43. At the lower dose, no benefit was seen when fulvestrant was compared with
**Tamoxifen:** The available data assessing the benefit of tamoxifen in the second-line setting are limited, but activity has been described for this drug (Table II)\(^40\).

**Third- or Later-Line Therapy**

For women who progress after two lines of endocrine therapy, treatment must be individualized based on prior treatment response, tumor burden, and preferences for treatment. In general, patients who have progressed after multiple lines (>3) of endocrine therapy should likely receive chemotherapy. However, for patients who are asymptomatic with slowly progressive disease, continuation of endocrine therapy is a reasonable strategy\(^3\). Additionally, new studies of monotherapy with CDK 4/6 inhibitors have shown promising responses in later-line settings.

**CDK 4/6 Inhibitors As Single Agents**

Recent data from a single-arm phase II trial in hormone receptor–positive, HER2-negative metastatic breast cancer demonstrated activity for palbociclib as a single agent after a median of 2 prior cytotoxic regimens described for that agent. The overall clinical benefit rate was 19%. Grades 3 and 4 toxicities included neutropenia (51%), anemia (5%), and thrombocytopenia (22%). No tumor biomarker identified a sensitive population\(^44\).

Abemaciclib showed activity after a median of 3 lines of prior systemic treatment, as demonstrated in the single-arm phase II MONARCH 1 study, which was designed to evaluate the single-agent activity and adverse event profile of that drug. The ORR was 19.7%, the clinical benefit rate was 42.4%, the median PFS was 6.0 months, and the median OS was 17.7 months. The most common adverse events of any grade were diarrhea, fatigue, and nausea\(^49\).

**Pre- and Perimenopausal Patients**

Historically, for pre- and perimenopausal patients with hormone receptor–positive, HER2-negative metastatic breast cancer, data are available for ovarian suppression alone, for single-agent tamoxifen, for ovarian suppression plus tamoxifen, and for ovarian suppression plus AIs\(^46–50\). However, recent data now show the benefits of the addition of targeted agents to endocrine therapy compared with endocrine monotherapy, as described in Table III.

**Adverse Events With Combination Therapy Using Endocrine and Targeted Agents**

The combination of endocrine treatment with targeted agents has shown increased response rates and improved PFS in many trials. However, combination therapy is associated with increased toxicity, which has to be considered when choosing the optimal therapy for each individual patient based on comorbidities, preferences, burden of disease, financial and social supports, and drug availability. Table IV summarizes the adverse events observed with targeted therapy.

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**TABLE III**

| Regimen and study | Phase | Arms | Randomization | Pre Randomization | Ovs | Line | Outcome | Progression-free survival | Overall survival |
|-------------------|-------|------|---------------|-------------------|-----|------|---------|--------------------------|----------------|
| **Ribociclib** | Phase III | MONALEESA-7 trial\(^1\) | 627 (100% pre- and perimenopausal) | 1:1 | Superior with ribociclib–tamoxifen vs. ribociclib–placebo plus goserelin | 1st | Superior with ribociclib combination; (HR: 0.553; 95% CI: 0.449 to 0.681; \(p<0.0000001\)) | Not reported | Not reported |
| **Palbociclib** | Phase III | PALOMA-3 trial\(^1\) | 521 (21% pre- and perimenopausal) | 1:1 | Superior with palbociclib–fulvestrant vs. placebo–fulvestrant plus goserelin (placebo) | 2nd | Superior with palbociclib–fulvestrant: (OR: 2.69; 95% CI: 1.43 to 5.26; \(p<0.001\)) | Superior with palbociclib–fulvestrant: (HR: 0.46; 95% CI: 0.36 to 0.59; \(p<0.001\)) | Superior with palbociclib–fulvestrant: (HR: 0.553; 95% CI: 0.449 to 0.681; \(p<0.0000001\)) |
| **Abemaciclib** | Phase III | MONARCH 2 trial\(^1\) | 669 (16% pre- and perimenopausal) | 1:1 | Superior with abemaciclib–fulvestrant vs. placebo–fulvestrant plus goserelin (placebo) | 2nd | Superior with abemaciclib–fulvestrant: (HR: 0.553; 95% CI: 0.449 to 0.681; \(p<0.0000001\)) | Not reported | Not reported |
### TABLE IV  Summary of adverse events in phase III trials of targeted agents in combination with endocrine therapy in patients with hormone receptor–positive, HER2-negative metastatic breast cancer

| Variable | In first line | Study drug | In second line+ |
|----------|--------------|------------|----------------|
| Study name | PALOMA-2,14,15 MONALEESA-2,16–18 MONALEESA-7,51 MONARCH 3,19 | Palbociclib | Ribociclib | Ribociclib | Abemaciclib |
| Class of drug | CDK 4/6 inhibitor | CDK 4/6 inhibitor | CDK 4/6 inhibitor | CDK 4/6 inhibitor |
| In combination with ... | Letrozole | Letrozole | Tamoxifen or NSAI–goserelin | Letrozole or anastrozole |
| Adverse events in combination arm (%) | | | | |
| All grades a | | | | |
| Neutropenia | 79.5 | 74.3 | 75.8 | 41.3 | 81 | 46 |
| Febrile neutropenia | 1.8 | 1.5 | 2.1 | 0.3 | 1 | 1.4 |
| Fatigue | 37.4 | 36.5 | 40.1 | 38.5 | 32 | 45.1 |
| Nausea | 35.1 | 51.5 | 31.6 | 39.9 | 37 |
| Arthralgia | 33.3 | 29.9 | | | |
| Alopecia | 32.9 | 33.2 | | | |
| Infections | 50.3 | 39.1 | 43 | | | |
| Diarrhea | 35 | 81.3 | 86.4 | | | |
| Increased LFTs | 9.3 | | | | | |
| Increase in QTcF | 2.7 | 6.9 | | | | |
| Hot flashes | 34 | | | | | |
| Abdominal pain | | | | 35.4 | | |
| Stomatitis | | | | 59 | | |
| Rash | | | | 39 | | |
| Decreased appetite | | | | 31 | | |
| Pneumonitis | | | | 16 | | |
| Grades 3–4 b | | | | | | |
| Any | 75.7 | 81.2 | NR | 55 | NR | 60.5 | NR |
| Neutropenia | 66.5 | 59.3 | 60.6 | 21.1 | 65 | 26.5 | |
| Diarrhea | 9.5 | | | 13.4 | | | |

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a Reaching 30% or clinically relevant.
b Reaching more than 10% or clinically relevant.

HER2 = human epidermal growth factor receptor 2; CDK = cyclin-dependent kinase; mTOR = mechanistic target of rapamycin; NSAI = nonsteroidal aromatase inhibitor; LFTs = liver function tests; QTcF = QT interval, corrected; NR = not reported.
The adverse events most commonly seen with Cdk 4/6 inhibitors in combination with endocrine therapy in phase III trials were neutropenia, infections, fatigue, and nausea. Rates of febrile neutropenia were low in all trials. In particular, trials of ribociclib showed increased values in liver function tests and prolongation of QTcF interval, and abemaciclib trials showed higher rates of diarrhea. The use of mtor inhibitors was associated with the risk of stomatitis, rash, fatigue, diarrhea, decreased appetite, and pneumonitis.

**DISCUSSION AND SUMMARY**

In recent years, a significant evolution has occurred in the management of HR-positive mbc. Given the emerging evidence, it is now essential to optimize therapy and to choose a treatment sequence strategy that considers both patient- and tumour-related factors.

In general, endocrine therapy represents the mainstay for most patients with HR-positive mbc, with palliative chemotherapy being reserved for life-threatening advanced disease or patients with visceral crisis. Endocrine monotherapy is still considered an effective treatment option, especially for patients whose disease course is more indolent (for example, a disease-free interval prolonged beyond 2 years) or for patients presenting with de novo low-burden and non-visceral metastatic disease. Combination therapy with endocrine and targeted agents, including either Cdk 4/6 inhibitors or mtor inhibitors, is now considered a treatment option in patients who do not meet the foregoing criteria for chemotherapy or endocrine monotherapy. We propose an algorithm based on the inclusion criteria in the key studies described in our review, on current guidelines, on the efficacy information available to date, and on results from important subgroups evaluated in the relevant studies (Figure 1)

Although the first-line treatment approach might be more straightforward, many questions remain unanswered, including the ideal treatment sequence that will optimize survival based on tumour biology and de novo or acquired treatment resistance factors. In routine clinical practice, clinicians and patients have to evaluate several factors beyond those that can be considered in our algorithm, including quality of life, patient preference, and access to therapies.

In Canada, based on the Ontario Drug Benefit list price, the approximate costs of a 28-day course of treatment were CA$39 for letrozole, CA$36 for anastrozole, CA$37 for exemestane, and CA$10 for tamoxifen. The addition of palbociclib at the recommended dose of 125 mg once daily for 21 days, followed by 7 days off treatment, adds CA$6250 per 28-day course at the list price and brings a need for monthly monitoring and bloodwork for neutropenia, together with the associated costs. Based on those findings, cost-effectiveness analyses of new targeted agents are needed to implement them in routine mbc care and in various health care systems. For instance, based on the paloma-2 trial, a Swiss cost-effectiveness study evaluated the burden of the addition of palbociclib to letrozole in mbc. The results showed that a considerable price reduction for palbociclib would be needed to make the drug cost-effective, given the estimated additional annual cost of approximately US$22 million to the system. By themselves, some drugs might therefore bring an additional amount to the total treatment cost that might not be affordable for patients, health care systems, and government funding bodies.

It is also important to point out that the treatment of HR-positive, HER2-negative mbc is rapidly evolving; results from ongoing clinical trials expected to be published in the next few years will most likely affect our proposed

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**FIGURE 1** Treatment algorithm for patients with hormone receptor–positive, HER2 (human epidermal growth factor receptor 2)–negative metastatic breast cancer.
treatment algorithm. Lastly, the hope is that, in the genomic era, novel predictive biomarkers other than HRs and HER2 will be available to narrow the population of patients who will ultimately derive the greatest magnitude of benefit with the addition of the new targeted agents delivered on a backbone of hormonal therapy.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood Current Oncology’s policy on disclosing conflicts of interest, and we declare the following interests: AJ reports personal fees from Pfizer, personal fees from Eli Lilly, personal fees from Novartis, and personal fees from Roche, and personal fees from AstraZeneca during the conduct of the study. SC reports personal fees and other from Novartis, personal fees and other from Pfizer, personal fees and other from AstraZeneca, and personal fees and other from Hoffman-La Roche outside the submitted work. SV reports membership on advisory boards for Amgen, AstraZeneca, Pfizer, Novartis, Roche, Spectrum, and Daiichi during the conduct of the study. AM has no declarations to make.

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REFERENCES

1. Chia SK, Speers CH, D’yachkova Y, et al. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer* 2007;110:973–9.
2. Giordano SH, Budzar AJ, Smith TL, Kau SW, Yang Y, Hortobagyi GN. Is breast cancer survival improving? *Cancer* 2004;100:44–52.
3. National Comprehensive Cancer Network (nccn). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Ver. 2.2016. Fort Washington, PA: nccn; 2016. [Current version available online at: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (free registration required); cited 17 August 2016]
4. Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *Lancet* 1896;148:162–5.
5. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med* 2003;348:2431–42. [cited 17 August 2016]
6. Mauri D, Pavlidis N, Polyzos NP, Ioannidis JP. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. *J Natl Cancer Inst* 2006;98:1285–91.
7. Cardoso F, Costa A, Senkus E, et al. 3rd ESMO–ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). *Ann Oncol* 2017:16–33. [Erratum in: *Ann Oncol* 2017;28:3111]
8. Robertson JF, Llombart-Cussac A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. *J Clin Oncol* 2009;27:4530–5.
9. Robertson JF, Lindemann JP, Llombart-Cussac A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized “FIRST” study. *Breast Cancer Res Treat* 2012;136:503–11.
10. Ellis MJ, Llombart-Cussac A, Feltl D, et al. Fulvestrant 500 mg versus letrozole 1 mg for the first-line treatment of advanced breast cancer: overall survival analysis from the phase III FIRST study. *J Clin Oncol* 2015;33:3781–7.
11. Robertson JFR, Bondarenko IM, Trishkina E, 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;388:2997–3005.
12. Bergh J, Jönsson PE, Lidbrink EK, et al. FACT: an open-label randomised phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. *J Clin Oncol* 2012;30:1919–25.
13. Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. *N Engl J Med* 2012;367:435–44.
14. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016;375:1925–36.
15. Kish JK, Ward MA, Garofalo D, et al. Early utilization pattern of palbociclib 1 year post-approval in the United States [abstract P6-16-05]. *Cancer Res* 2017;77(suppl):.
16. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016;375:1738–48.
17. United States, Department of Health and Human Services, Food and Drug Administration (FDA). Home > Drugs > Drug Approvals and Databases > Approved Drugs > Ribociclib (Kisqali) [Web page]. Silver Spring, MD: FDA; 2017. [Available at: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm546438.htm; cited 6 June 2017]
18. Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase 3 trial of first-line ribociclib + letrozole in hormone receptor-positive (HR+), HER2-negative (HER2–) advanced breast cancer (ABC) [abstract 1038]. *J Clin Oncol* 2017;35:. [Available online at: https://meetinglibrary.asco.org/record/153081/abstract; cited 21 March 2018]
19. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 2017;35:3638–46.
20. Geisler J, Haynes B, Anker G, Dowsett M, Lønning PE. Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study. *J Clin Oncol* 2002;20:751–7.
21. Sainsbury R. Aromatase inhibition in the treatment of advanced breast cancer: is there a relationship between potency and clinical efficacy? *Br J Cancer* 2004;90:1733–9.
22. Smith I, Yardley D, Burris H, et al. Comparative efficacy and safety of adjuvant letrozole versus anastrozole in postmenopausal patients with hormone receptor–positive, node-positive early breast cancer: final results of the randomized phase III Femara Versus Anastrozole Clinical Evaluation (FACE) trial. *J Clin Oncol* 2017;35:1056–8.
23. Di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. *J Natl Cancer Inst* 2014;106:di337.
24. Finn RS, Aleshin A, Slamon DJ. Targeting the cyclin-dependent kinases (cdk) 4/6 in estrogen receptor–positive breast cancers. *Breast Cancer Res* 2016;18:17.
25. Vidula N, Rugo HS. Cyclin-dependent kinase 4/6 inhibitors for the treatment of breast cancer: a review of preclinical and clinical data. *Clin Breast Cancer* 2016;16:8–17.
26. Finn RS, Dering J, Conklin D, et al. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor–positive human breast cancer cell lines in vitro. *Breast Cancer Res* 2009;11:R77.
27. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/IRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015;16:25–35.

28. United States, Department of Health and Human Services, Food and Drug Administration (FDA). Home > Drugs > Drug Approvals and Databases > Approved Drugs > Palbociclib (Ibrance) [Web page]. Silver Spring, MD: FDA; 2015. [Available at: https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm549978.htm; cited 17 August 2016]

29. Finn RS, Crown J, Lang I, et al. Overall survival results from the randomized phase II study of palbociclib (p) in combination with letrozole (l) versus letrozole alone for frontline treatment of HR+/HER2– advanced breast cancer (PALOMA-1; TRIO-18) [abstract 1001]. *J Clin Oncol* 2017;35:425–39. [Available online at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.15_suppl.1001; cited 9 February 2018]

30. Turner NC, Bo J, André F, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015;373:209–19.

31. 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 randomized controlled trial. *Lancet Oncol* 2016;17:425–39.

32. 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;35:2875–84.

33. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012;366:520–9.

34. 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;25:2357–62.

35. Yardley DA, Noguchi S, Pritchard KI, et al. Everolimus plus exemestane in postmenopausal patients with HR+ breast cancer: BOLERO-2 final progression-free survival analysis. *Adv Ther* 2013;30:870–84.

36. Kornblum NS, Manola J, Klein P, et al. PRECOG 0012: a randomized, double-blind, phase II trial of fulvestrant plus everolimus or placebo in post-menopausal women with hormone receptor–positive, HER2-negative metastatic breast cancer resistant to aromatase inhibitor therapy [abstract S1-02]. Presented at: 39th Annual San Antonio Breast Cancer Symposium; San Antonio, TX, U.S.A.: 6–10 December 2016. [Available online at: https://www.absabstracts.com/sabcs16/view.php?nu=SABCS16L_952&terms=; cited 4 June 2017]

37. Rose C, Vitoraya O, Pluzanska A, et al. An open randomised trial of second-line endocrine therapy in advanced breast cancer: comparison of the aromatase inhibitors letrozole and anastrozole. *Eur J Cancer* 2003;39:2318–27.

38. Beresford M, Tumur I, Chakrabarti J, Barden J, Rao N, Makris A. A qualitative systematic review of the evidence base for non-cross-resistance between steroidal and non-steroidal aromatase inhibitors in metastatic breast cancer. *Clin Oncol (R Coll Radiol)* 2011;23:209–15.

39. Johnston SR, Kilburn LS, Ellis P, et al. on behalf of the soFEA investigators. 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;14:989–98.

40. Chiari PG, B, Robertson JF, Nabholz JM, Buzdar A, Bonner J on behalf of the 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;39:2310–17.

41. Turner NC, André F, Cristofanilli M, et al. Treatment progression in women with endocrine-resistant HR+/HER2– advanced breast cancer who received palbociclib plus fulvestrant in PALOMA-3 [abstract P4-22-06]. *Cancer Res* 2017;77:.

42. Howell A, Pippen J, Elledge RM, et al. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma: a prospectively planned combined survival analysis of two multicenter trials. *Cancer* 2005;104:236–9.

43. Chia S, Gaidarshar W, Mauriac L, 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;26:1664–70.

44. DeMichele A, Clark AS, Tan KS, et al. CDK 4/6 inhibitor palbociclib (PD0332991) in RB+ advanced breast cancer: phase II activity, safety, and predictive biomarker assessment. *Clin Cancer Res* 2015;21:995–1001.

45. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2– metastatic breast cancer. *Clin Cancer Res* 2017;23:5218–24.

46. Taylor CW, Green S, Dalton WS, et al. Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an Intergroup study. *J Clin Oncol* 1998;16:999–9.

47. Sunderland MC, Osborne CK. Tamoxifen in premenopausal patients with metastatic breast cancer: a review. *J Clin Oncol* 1991;9:1283–97.

48. Klijn JG, Blamey RW, Boccardo F, Tominaga T, Duchateau L, Sylvester R on behalf of the Combined Hormone Agents Trialists’ Group and the European Organization for Research and Treatment of Cancer. Combined tamoxifen and luteinizing hormone–releasing hormone (LH-RH) agonist versus LH-RH agonist alone in premenopausal advanced breast cancer: a meta-analysis of four randomized trials. *J Clin Oncol* 2001;19:343–53.

49. Carlson RW, Theriault R, Schurman CM, et al. Phase II trial of anastrozole plus goserelin in the treatment of hormone receptor–positive, metastatic carcinoma of the breast in premenopausal women. *J Clin Oncol* 2010;28:3917–21.

50. Park HI, Ro J, Lee KS, et al. Phase II parallel group study showing comparable efficacy between premenopausal metastatic breast cancer patients treated with letrozole plus goserelin and postmenopausal patients treated with letrozole alone as first-line hormone therapy. *J Clin Oncol* 2010;28:2705–11.

51. Rugo HS, Rumble BR, Macrae E, et al. Endocrine therapy for hormone receptor–positive metastatic breast cancer: American Society of Clinical Oncology guideline. *J Clin Oncol* 2016;34:3069–103.

52. Pan-Canadian Oncology Drug Review (pCODR). *Initial Economic Guidance Report: Palbociclib (Ibrance) for Advanced Breast Cancer*. Toronto, ON: pCODR; 2016.

53. Matter-Walstra K, Schwenkglenks M, Brauchli P, Klingbiel D, Dedes KJ. A cost-effectiveness analysis of palbociclib plus letrozole as first-line treatment for estrogen receptor–positive, HER2-negative, metastatic breast cancer [abstract S57]. *J Clin Oncol* 2016;34: [Available online at: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.S57; cited 9 February 2018]