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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 cases[3]. 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 MBCa[4,5].

Unfortunately, despite the high rate of clinical benefit from initial endocrine treatment, disease progression typically occurs after 1 year of traditional first-line endocrine monotherapy[3]. 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 MBCa[3,5,6]. Endocrine treatment strategies include medications that lower estrogen production, modulate signalling through the estrogen receptor, or antagonize and degrade the estrogen receptor itself[6]. Additionally, novel drugs given in combination with endocrine treatment are

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now available and have also been incorporated into clinical practice[3]. 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[3,7]. 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[3,7]. The choice of endocrine agent should be based on menopausal status, comorbidities, prior adjuvant therapy, drug availability, patient preference, and drug safety profile[3,7].

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[3]. 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)[3]. Table I summarizes the most relevant data in the first-line setting for postmenopausal patients.

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[6] of twenty-three randomized trials (8504 patients) showed the efficacy of AIs as a first-line treatment for MBCa in postmenopausal women (Table I). 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[20]. For instance, 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[21]. Data in the adjuvant setting comparing letrozole with anastrozole also showed similar outcomes with both agents[22].

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[23]. Although 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[23]. Table I 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[8–11] 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[11].

Fulvestrant Plus Anastrozole: The FACT and SWOG S0226 trials explored fulvestrant–anastrozole as first-line combination therapy, but with conflicting results, as Table I shows[12,13]. 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[24]. The CDKs drive cell-cycle progression and control transcriptional processes[24,25]. 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[24,25]. Palbociclib was the first oral small-molecule CDK 4/6 inhibitor to be developed. It is known to arrest cells in G1 phase by blocking phosphorylation of retinoblastoma protein at CDK 4/6–specific sites[24–26]. Preclinical studies suggested growth-inhibitory activity in HR-positive breast cancer cells and potential synergy with endocrine agents[26].

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[27]. 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[27]. 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[28].

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

TABLE I Summary of trials in postmenopausal patients with hormone receptor–positive, HER2-negative metastatic breast cancer in the first-line setting

Regimen and study	Pts (*n*)	Arms	Outcome		
			Overall response rate	Progression-free survival	Overall survival
Aromatase inhibitors (AIs)					
Meta-analysis of 23 randomized trials[6]	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 trial[8–10]	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 trial[11]	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)	Not reported
Fulvestrant plus anastrozole					
Phase III FACT trial[12]	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 trial[13]	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 trial[14,15]	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 Continued

Regimen and study	Pts (*n*)	Arms	Outcome		
			Overall response rate	Progression-free survival	Overall survival
Inhibitors of cyclin-dependent kinases 4 and 6 plus endocrine therapy continued					
Phase III MONALEESA-2 trial[16–18]	668	Ribociclib plus letrozole vs. placebo plus letrozole	Superior with ribociclib–letrozole: 54.5% and 38.8%, $p<0.001$	Superior with ribociclib-letrozole: 25.3 months vs. 16 months (HR: 0.568; 95% CI: 0.457 to 0.704; $p=9.63\times10^{-8}$)	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 3 trial[19]	493	Abemaciclib or placebo combined with either anastrozole or letrozole	Superior with abemaciclib plus anastrozole or letrozole: 59% vs. 44%, $p=0.004$	Not reached in the abemaciclib plus anastrozole or letrozole arm vs. 14.7 months in the placebo arm (HR: 0.543; 95% CI: 0.409 to 0.723; $p=0.000021$)	Not reported

HER2 = human epidermal growth factor receptor 2; Pts = 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 I[14–19]. 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 AI 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 instead[3]. 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 setting[30–32,41].

The first reported trial of this combination was palbociclib–fulvestrant in the PALOMA-3 trial, in which superior ORR and PFS rates favoured the combination[30,31]. 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 Symposium[41]. 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 (*n*)	Arms	Outcome		
			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 (21% pre- and peri-menopausal)	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=0·0012)	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[32]	669 (16.1% pre- and peri-menopausal)	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%	Superior with everolimus–exemestane: 7.8 months vs. 3.2 months (HR: 0.45; 95% CI: 0.38 to 0.54)	Similar: 31 months for everolimus–exemestane, 26.6 months for exemestane–placebo; (HR: 0.89; 95% CI: 0.73 to 1.10)
Everolimus plus fulvestrant					
Phase II PrECOG 0102 trial[36]	130	Everolimus plus fulvestrant vs. placebo plus fulvestrant	Not reported	Superior with everolimus–fulvestrant: 10.4 months vs. 5.1 months (HR: 0.61; 95% CI: 0.4 to 0.92)	Not reported
Aromatase inhibitors					
Phase III trial[37]	713	Letrozole vs. anastrozole	Superior with letrozole: 19.1% vs. 12.3%, p=0.013	Similar time to progression: 5.7 months vs. 5.7 months, p=0.92	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, 8% for fulvestrant–placebo, 4% for exemestane, p=0.17–1.00	Similar: 4.4 months for fulvestrant–anastrozole, 4.8 months for fulvestrant–placebo, 3.4 months for exemestane, p>0.05	Similar: 20.2 months for fulvestrant–anastrozole, 19.4 months for fulvestrant–placebo, 21.6 months for exemestane, p>0.05

TABLE II Continued

Regimen and study	Pts (*n*)	Arms	Outcome		
			Overall response rate	Progression-free survival	Overall survival
Tamoxifen					
Combined analysis of two randomized trials[40]	137	Second-line tamoxifen after first-line anastrozole	For tamoxifen: 10%, with a clinical benefit rate of 49% (ORR plus stable disease for 6 months or more)	Not reported	Not reported

HER2 = human epidermal growth factor receptor 2; Pts = patients; OR = odds ratio; CI = confidence interval; HR = hazard ratio; AI = aromatase inhibitor; ORR = overall response rate.

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 MONARCH 2 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 MBCa and who had not received chemotherapy for metastatic disease[32]. 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 MBCa. 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 PRECOG 0102 trial demonstrated a benefit in PFS in favour of combined everolimus–fulvestrant compared with placebo–fulvestrant in postmenopausal women with HR-positive, HER2-negative MBCa resistant to AI therapy (Table II)[36].

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 superior[23,42,43]. At the lower dose, no benefit was seen when fulvestrant was compared with

AIs. Furthermore, the combination of fulvestrant (250 mg monthly) with anastrozole did not show any advantage compared with fulvestrant (250 mg monthly) or an AI alone as second-line treatment, as seen in the phase III SoFEA trial described in Table II[39].

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, tumour 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 mBCa positive for retinoblastoma protein that evaluated palbociclib as a single agent after a median of 2 prior cytotoxic regimens demonstrated activity for that agent. The overall clinical benefit rate was 19%. Grades 3 and 4 toxicities included neutropenia (51%), anemia (5%), and thrombocytopenia (22%). No tumour 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[45].

Pre- and Perimenopausal Patients

Historically, for pre- and perimenopausal patients with HR-positive, HER2-negative mBCa, 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.

TABLE III Summary of trials in pre- and perimenopausal patients with hormone receptor–positive, HER2-negative metastatic breast cancer

Regimen and study	Pts (*n*)	Randomization	Arms	Line	Outcome		
					Overall response rate	Progression-free survival	Overall survival
Inhibitors of cyclin-dependent kinases 4 and 6 inhibitors plus endocrine therapy							
Phase III MONALEESA-7 trial[a]	672	(100% pre- and perimenopausal)	Ribociclib–tamoxifen or ribociclib–nonsteroidal AI vs. ribociclib–placebo (plus goserelin)	1st	Superior with ribociclib combination: 50.9% vs. 36.4%, p=0.000317	Superior with ribociclib combination: 23.8 months vs. 13 months (HR: 0553; 95% CI: 0.441 to 0.694)	Not reported
Phase III PALOMA-3 trial[31,41]	521	(21% pre- and perimenopausal)	Palbociclib–fulvestrant vs. placebo–fulvestrant (plus goserelin if pre- or perimenopausal)	2nd+	Superior with palbociclib–fulvestrant: 24.6% vs. 10.9% (OR: 2·69; 95% CI: 1.43 to 5.26; two-sided p=0.0012)	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 MONARCH 2 trial[32]	669	(16.1% pre- and perimenopausal)	Abemaciclib–fulvestrant vs. placebo–fulvestrant (plus goserelin if pre- or perimenopausal)	2nd	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

[a] Tripathy D, Sohn J, Im S, *et al.* First-line ribociclib or placebo combined with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor–positive, HER2-negative advanced breast cancer: results from the randomized phase III MONALEESA-7 trial [abstract GS2-05]. Presented at: 2016 San Antonio Breast Cancer Symposium; 6–10 December 2016; San Antonio, TX, U.S.A.

HER2 = human epidermal growth factor receptor 2; Pts = patients; AI = aromatase inhibitor; HR = hazard ratio; CI = confidence interval; OR = odds ratio.

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	Study drug						
	In first line				In second line+		
	Palbociclib	Ribociclib	Ribociclib	Abemaciclib	Palbociclib	Abemaciclib	Everolimus
Study name	PALOMA-2[14,15]	MONALEESA-2[16–18]	MONALEESA-7[51]	MONARCH 3[19]	PALOMA-3[30,31]	MONARCH2 [32]	BOLERO-2[33–35]
Class of drug	CDK 4/6 inhibitor	CDK 4/6 inhibitor	CDK 4/6 inhibitor	CDK 4/6 inhibitor	CDK 4/6 inhibitor	CDK 4/6 inhibitor	mTOR inhibitor
In combination with ...	Letrozole	Letrozole	Tamoxifen or NSAI–goserelin	Letrozole or anastrozole	Fulvestrant (plus goserelin if pre- or perimenopausal)	Fulvestrant (plus goserelin if pre- or perimenopausal)	Exemestane
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	39	39.9	37
Nausea	35.1	51.5	31.6	38.5	32	45.1	31
Arthralgia	33.3		29.9				
Alopecia	32.9	33.2					
Infections		50.3		39.1	43		
Diarrhea		35		81.3		86.4	34
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	

[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 MBCa. 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 MBCa, 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)[52].

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[51] 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 MBCa 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 MBCa[53]. 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 MBCa is rapidly evolving; results from ongoing clinical trials expected to be published in the next few years will most likely affect our proposed

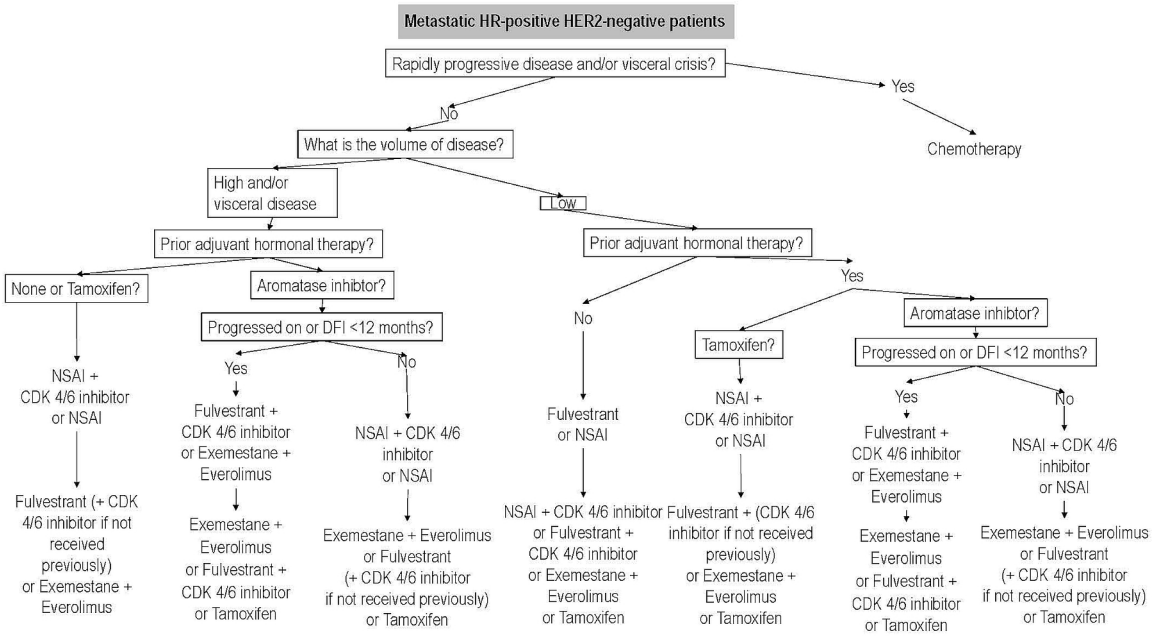

FIGURE 1 Treatment algorithm for patients with hormone receptor–positive, HER2 (human epidermal growth factor receptor 2)–negative metastatic breast cancer.

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: AAJ reports personal fees from Pfizer, personal fees from Eli Lilly, personal fees from Novartis, personal fees from Roche, and personal fees from AstraZeneca (all outside the submitted work, for medical consultation services). CBM reports grants and personal fees from Eli Lilly, grants and personal fees from Pfizer, grants and personal fees from Novartis, and grants 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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