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Overall survival and progression-free survival with endocrine therapy for hormone receptor-positive, HER2-negative advanced breast cancer: review

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Abstract: We reviewed randomized phase II/III trials comparing first- or second-line endocrine therapy as monotherapy or in combination with targeted therapies for treatment of postmenopausal patients with hormone receptor-positive advanced breast cancer. First-line was defined as treatment for endocrine therapy-naïve advanced breast cancer or advanced disease treated with endocrine therapy in the adjuvant/neoadjuvant setting. Second-line was defined as endocrine therapy for advanced breast cancer following disease progression on endocrine therapy for advanced disease. Publications reporting progression-free survival (PFS)/time to progression (TTP) or overall survival (OS) for FDA-approved agents anastrozole, exemestane, fulvestrant 250 mg, fulvestrant 500 mg, letrozole (0.5 and 2.5 mg), megestrol acetate, and tamoxifen as monotherapy, or in combination with everolimus, palbociclib or ribociclib, were assessed. First-line monotherapy with anastrozole, fulvestrant 500 mg or letrozole 2.5 mg significantly improved PFS/TTP *versus* comparator endocrine therapy; however, only fulvestrant 500 mg improved OS. For endocrine therapy in combination with targeted therapies, palbociclib plus letrozole 2.5 mg, and ribociclib plus letrozole 2.5 mg significantly improved PFS *versus* letrozole 2.5 mg alone first-line. For second-line monotherapies, exemestane, fulvestrant 500 mg and letrozole 2.5 mg significantly improved PFS/TTP *versus* comparator endocrine therapy; only fulvestrant 500 mg and letrozole 2.5 mg improved OS. For second-line combination therapies, everolimus plus exemestane, and palbociclib plus fulvestrant 500 mg, improved PFS *versus* endocrine therapy alone. In both first- and second-line settings, aromatase inhibitors demonstrated PFS benefits *versus* comparator endocrine therapy; however, fulvestrant 500 mg was the only endocrine therapy included in our review to show both PFS and OS advantages compared with other endocrine therapies. Targeted agents in combination with endocrine therapy have demonstrated PFS improvements both first- and second-line; OS data are awaited.

Keywords: advanced breast cancer, aromatase inhibitor, endocrine therapy, fulvestrant, hormone receptor-positive, overall survival, progression-free survival

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Introduction

Approximately 250,000 new cases of breast cancer are diagnosed each year,[1] and over two-thirds of these patients will be categorized as having hormone receptor-positive disease.[2] For patients with hormone receptor-positive advanced breast cancer, clinical guidelines recommend sequential treatment with endocrine therapy, unless they are experiencing visceral crises and/or endocrine resistance is known or suspected.[3–5]

In addition, the targeted therapies everolimus, an allosteric inhibitor of mammalian target of rapamycin (mTOR),[6] and most recently palbociclib, a

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cyclin-dependent kinase 4/6 (CDK 4/6) inhibitor,[7,8] have been approved for use in combination with endocrine therapies in either the first- or second-line setting.[9,10] In addition, the CDK 4/6 inhibitor ribociclib, in combination with letrozole, has recently received FDA Breakthrough Therapy designation for the first-line treatment of hormone receptor-positive, human epidermal growth factor receptor 2- (HER2-) negative advanced or metastatic breast cancer.[11]

In order for these agents to gain approval for treatment, regulatory authorities have required robust evidence of efficacy using endpoints including progression-free survival (PFS)/time to progression (TTP) and overall survival (OS), each of which is subject to some limitations. OS is considered to be a more objective measure than other outcomes,[12] but requires large patient cohorts and extensive follow-up times. OS may also be influenced by subsequent post-trial therapies, particularly in settings such as breast cancer where many effective treatments are available, and could be confounded by deaths not attributable to cancer.

PFS/TTP values are derived from tumor-based assessments, and can be obtained in a shorter time frame than OS; therefore, these outcome measures may be more suited to accelerated approval schemes. Moreover, these measures are not influenced by post-trial therapies, unlike OS. However, there is a potential for bias, particularly if treatment is not blinded.[12] In an ideal scenario, PFS/TTP may be regarded as a surrogate for OS; however, evidence suggests that these measures can diverge and are only moderately correlated.[13]

In light of the recent approval of new therapies for the treatment of hormone receptor-positive advanced breast cancer, and the lack of direct comparisons between these agents, the aim of this review is to evaluate efficacy outcomes data, in terms of both published TTP/PFS and OS, from randomized clinical trials of endocrine therapy for hormone receptor-positive advanced breast cancer in both the first- and second-line settings.

Methods

A literature review was conducted using the MEDLINE database in order to identify randomized, controlled phase II or phase III trials that compared endocrine therapies as monotherapies or in combination with targeted therapies in the first- or second-line treatment of postmenopausal patients with hormone receptor-positive advanced breast cancer. For the purposes of this analysis, first-line treatment was defined as first endocrine therapy for advanced breast cancer. In this context, patients may have received prior adjuvant endocrine therapy for early disease. Second-line treatment was defined as endocrine therapy for advanced breast cancer following disease progression on endocrine therapy for advanced disease.

The search strategy included terms applicable to the patient population (postmenopausal women with locally advanced or metastatic breast cancer) and any publications identified during the literature review that reported TTP/PFS or OS data for the following endocrine monotherapies were eligible for further assessment: anastrozole 1 mg, exemestane 25 mg, fulvestrant 250 mg, fulvestrant 500 mg, letrozole 0.5 mg, letrozole 2.5 mg, megestrol acetate 160 mg, and tamoxifen 20 mg. Data for endocrine therapy in combination with available targeted therapies everolimus 10 mg and palbociclib 125 mg, which have been recently approved, and ribociclib 600 mg, were also included. Data were evaluated from publications reporting either the primary or follow-up analyses. Only English-language publications were reviewed and no date restrictions were applied. No congress abstracts were reviewed. Studies that focused on hormone receptor-positive, HER2-positive disease and publications presenting data for combinations of endocrine therapies with novel treatments, such as inhibitors of HER-2, histone deacetylase (HDAC), insulin-like growth factor receptor (IGFR) and phosphatidyl-inositol 3-kinase (PI3K), were not included. Studies with HER2 unknown or HER2-negative status were included.

For each relevant publication identified, OS and TTP/PFS, median duration of treatment and/or follow up, and details of prior therapies or responsiveness to prior therapies are presented. For the purpose of this review, statistical significance was attributed according to the level of significance described in each study.

Results

First-line treatment

From our literature review, we identified primary or secondary publications reporting TTP/PFS results from 12 randomized, controlled trials of

first-line endocrine therapy (Table 1); of these, three and seven studies reported results of phase II and III trials, respectively (phase not disclosed for two studies).

The range of PFS/TTP reported was 8.2–13.8 months with anastrozole (from six studies),[14,16–18,21,24,29] 16.6–23.4 months with fulvestrant 500 mg (from two studies),[21,22,24] 6.8 months with fulvestrant 250 mg (from one study),[20] 6.1–13.8 months with exemestane (from three studies),[17–19] 9.4–14.7 months with letrozole 2.5 mg (from four studies)[11,25,27,28] and 5.6–8.3 months with tamoxifen (from five studies).[14,16,19,20,25,29]

Based on the published hazard ratios (HRs), statistically significant advantages in TTP/PFS were observed for anastrozole *versus* tamoxifen in one phase III, randomized, double-blind study [HR 1.44, 95% confidence interval (CI) 1.16–not reported; $p = 0.005$];[29] fulvestrant 500 mg *versus* anastrozole in one phase II, randomized, open-label study (HR 0.66, 95% CI 0.47–0.92; $p = 0.01$)[21] and one phase III, double-blind, randomized study (HR 0.797, 95% CI 0.637–0.999; $p = 0.0486$);[24] and letrozole 2.5 mg *versus* tamoxifen (HR 0.72; $p < 0.0001$)[25] in one phase III, randomized, double-blind study.

In terms of targeted therapies, the combination of palbociclib plus letrozole 2.5 mg significantly increased PFS *versus* letrozole 2.5 mg alone in one phase II, randomized, open-label study (HR 0.49, 95% CI 0.32–0.75; $p = 0.0004$)[27] and one phase III, randomized, double-blind study (HR 0.58, 95% CI 0.46–0.72; $p < 0.001$).[28] In one phase III randomized, double-blind study, ribociclib plus letrozole 2.5 mg was associated with significantly longer PFS compared with letrozole 2.5 mg alone (HR 0.56, 95% CI 0.43–0.72; $p < 0.0001$).[11]

Across the publications evaluated, the ranges of reported OS values for endocrine therapies in the first-line setting were 38.5–60.1 months with anastrozole (five studies);[15,17,18,23] 19.9 months, 37.2 months and median not reached with exemestane (three studies);[17–19] 36.9 months with fulvestrant 250 mg (one study);[20] 54.1 months with fulvestrant 500 mg (one study);[23] 33.3–34 months with letrozole 2.5 mg (two studies);[26,27] and 30–43.3 months with tamoxifen (five studies).[14,15,19,20,25,29]

A significant OS advantage was observed for tamoxifen *versus* fulvestrant 250 mg (HR 1.29, 95% CI 1.01–1.64; $p = 0.04$) in one randomized, double-blind study,[20] for anastrozole *versus* megestrol acetate in a combined analysis of two phase III studies (HR 0.78, 97.5% CI 0.60–<1.0, $p = 0.025$)[30] and for fulvestrant 500 mg *versus* anastrozole (HR 0.70, 95% CI 0.50–0.98; $p = 0.04$) in one phase II, randomized, open-label study.[23] Data in the phase III FALCON study comparing fulvestrant 500 mg *versus* anastrozole[24] were not of sufficient maturity at the time of data cut-off for an analysis of median OS (HR 0.88; 95% CI 0.63–1.22; $p = 0.4277$).

OS in a phase II, randomized, open-label study of palbociclib in combination with letrozole 2.5 mg was 37.5 months,[27] which was not significantly different to OS achieved with letrozole 2.5 mg alone (HR 0.81, 95% CI 0.49–1.35; $p = 0.42$); however, it must be noted that this study was not powered for OS. In the phase III, randomized, double-blind PALOMA-2 study of palbociclib in combination with letrozole 2.5 mg, data were not mature for an analysis of OS.[28] Interim data from the phase III, randomized, double-blind MONALEESA-2 trial of ribociclib in combination with letrozole 2.5 mg *versus* letrozole 2.5 mg alone were not sufficiently mature to allow an analysis of OS.[11]

Second-line treatment

In total, 14 studies were identified that reported PFS/TTP with endocrine therapy alone in the second-line setting (Table 2); of these, three and seven studies reported results of phase II and III trials, respectively (phase not disclosed for three studies).

The ranges of PFS/TTP reported were 3.4–5.1 months with anastrozole (from four studies);[30,35,36] 3.2–4.7 months with exemestane (from three studies);[31,32,34] 3.1–6.0 months with fulvestrant 250 mg (from five studies);[34–36,39,41,42] 3.8–6.5 months with fulvestrant 500 mg (from four studies);[7,39,41,42] 3.3–5.1 months with letrozole 0.5 mg (from two studies);[43,44] 3.4–5.6 months with letrozole 2.5 mg (from two studies);[43,44] 4.5 months with tamoxifen (from one study);[45] and 3.8–5.5 months with megestrol acetate (from four studies).[30,31,44]

Significant advantages in PFS/TTP were observed within individual studies for exemestane *versus* megestrol acetate (4.7 *versus* 3.8 months; HR not reported, $p = 0.037$),[31] fulvestrant 500 mg *versus*

Table 1. Randomized controlled trials of endocrine therapies for the treatment of postmenopausal women with hormone receptor-positive advanced breast cancer in the first-line setting.

Study	Treatment	Patient characteristics	Median (months); HR (95% CI)	
			PFS/TTP	OS/TTD
TARGET[14,15] Randomized, double-blind study conducted at 83 sites in Europe, Australia, New Zealand, South America and South Africa	Anastrozole 1 mg ($n = 340$) *versus* tamoxifen 20 mg ($n = 328$)	Endocrine therapy for early breast cancer was permitted, but patients could not receive tamoxifen within 12 months before entry Mean age (range): 67 (34–91) *versus* 66 (41–92) years Prior adjuvant endocrine therapy: 9.1% *versus* 6.1% Prior adjuvant chemotherapy: 18.8% *versus* 18.9% Prior adjuvant endocrine therapy and chemotherapy: 2.9% *versus* 4.6% HER2 status not reported	8.2 *versus* 8.3; HR 0.99 (0.86–NR); $p = 0.941$ Median follow up: 19 months	38.5 *versus* 40.9; HR 0.94 (0.79–NR); $p =$ NR Median follow up NR
Bonneterre 2001[15,16] Phase III, randomized, double-blind study conducted at 97 sites in the US and Canada	Anastrozole 1 mg ($n = 171$) *versus* tamoxifen 20 mg ($n = 182$)	Endocrine therapy or chemotherapy for early breast cancer was permitted, but patients could not receive tamoxifen within 12 months before entry Median age (range): 68 (30–88) *versus* 67 (40–92) years Prior adjuvant endocrine therapy: 12.3% *versus* 11.0% Prior adjuvant chemotherapy only: 18.7% *versus* 20.3% Prior adjuvant endocrine therapy and chemotherapy: 8.8% *versus* 7.1% HER2 status not reported	11.1 *versus* 5.6; HR 1.44 (1.16–NR); $p = 0.005$ Median follow up: 17.7 months	40.4 *versus* 38.5; HR 1.02 (0.81–NR); $p =$ NR Median follow up NR
Nabholtz 2003[15,16] A combined analysis	Anastrozole 1 mg ($n = 511$) *versus* tamoxifen 20 mg ($n = 510$)	Endocrine therapy or chemotherapy for early breast cancer was permitted, but patients could not receive tamoxifen within 12 months before entry Median age (range): 67 (30–91) *versus* 67 (40–92) years Prior adjuvant endocrine therapy: 10.2% *versus* 7.8% Prior adjuvant chemotherapy: 18.8% *versus* 19.4% Prior adjuvant endocrine therapy and chemotherapy: 4.9% *versus* 5.5% HER2 status not reported	8.5 *versus* 7.0; HR 1.13 (1.00–NR); $p = 0.103$ Median follow up: 18.2 months	39.2 *versus* 40.1; HR 0.97 (0.84–NR); $p =$ NR Median follow up: 43.7 months
Llombart-Cussac 2012[17] Phase II, randomized, open-label study conducted at 13 sites in Spain	Exemestane 25 mg ($n = 51$) *versus* anastrozole 1 mg ($n = 52$)	Prior tamoxifen permitted if initiated 24 months before recurrence Median age (range): 68 (45–94) *versus* 73 (46–85) years Prior adjuvant tamoxifen: 51.0% *versus* 50.5% HER2 status not reported	6.1 *versus* 12.1; HR 1.13 (0.75–1.72); $p = 0.558$ Median follow up: 9.1 months	19.9 *versus* 48.3; HR 1.33 (0.78–2.25); $p = 0.296$ Median follow up NR
Iwata 2013[18] Phase III, randomized, double-blind study conducted at 64 sites in Japan	Exemestane 25 mg ($n = 149$) *versus* anastrozole 1 mg ($n = 149$)	Mean age (range): 63 (44–95) *versus* 64 (45–94) years Prior adjuvant tamoxifen: 16.8% *versus* 16.8% HER2 positive: 6.1% *versus* 6.4%	13.8 *versus* 11.1; HR 1.01 (0.77–1.32) Median follow up NR	NR *versus* 60.1; HR 1.06 (0.73–1.54) Median follow up NR

Table 1. (Continued)

Study	Treatment	Patient characteristics	Median (months); HR (95% CI)	
			PFS/TTP	OS/TTD
EORTC[19] Phase III, randomized, open-label study conducted at 81 sites in Europe	Exemestane 25 mg ($n = 182$) *versus* tamoxifen 20 mg ($n = 189$)	Recurrence-free interval after tamoxifen had to be ⩾6 months Median age (range): 63 (37–86) *versus* 62 (37–87) years Prior systemic therapy: Prior chemotherapy only: 20.9% *versus* 20.1% Prior endocrine therapy only: 11.5% *versus* 8.5% Prior chemotherapy and endocrine therapy: 9.3% *versus* 13.2% Prior adjuvant chemotherapy: 24.2% *versus* 27.0% Prior chemotherapy for MBC: 4.4% *versus* 4.2% Prior adjuvant chemotherapy and also chemotherapy for MBC: 1.6% *versus* 2.1% Prior adjuvant tamoxifen: 20.9% *versus* 20.6% HER2 status not reported	9.9 *versus* 5.8; Median follow up: 29 months	37.2 *versus* 43.3; Median follow up: 29 months
Howell 2004[20] Randomized, double-blind study conducted at 171 centers worldwide	Fulvestrant 250 mg ($n = 313$) *versus* tamoxifen 20 mg ($n = 274$)	Adjuvant endocrine therapy was not permitted within 12 months before trial entry Median age (range): 67 (43–93) *versus* 66 (43–92) years Prior adjuvant tamoxifen: 22.0% *versus* 24.8% Prior adjuvant chemotherapy: 22.7% *versus* 24.1% HER2 status not reported	6.8 *versus* 8.3; HR 1.18 (0.98–1.44); $p = 0.088$ Median follow up: 14.5 months	36.9 *versus* 38.7; HR 1.29 (1.01–1.64); $p = 0.04$ Median follow up: 31.1 months
FIRST[21–23] Phase II, randomized, open-label, multicenter, parallel-group study conducted at 62 centers in nine countries	Fulvestrant 500 mg ($n = 102$) *versus* anastrozole 1 mg ($n = 103$)	Prior endocrine therapy for early disease allowed, providing this had been completed >12 months before randomization Median age (range): 66 (40–89) *versus* 68 (48–87) years Prior adjuvant endocrine therapy (>12 months prior to randomization): 27.5% *versus* 22.3% Prior endocrine therapy: 28.4% *versus* 22.3% Prior chemotherapy for advanced breast cancer: 0% *versus* 0% Prior adjuvant chemotherapy for early breast cancer: 28.4% *versus* 24.3% HER2 positive: 18.6% *versus* 18.4%	23.4 *versus* 13.1; HR 0.66 (0.47–0.92); $p = 0.01$ Median follow up: 18.8 months *versus* 12.9 months	54.1 *versus* 48.4; HR 0.70 (0.50–0.98); $p = 0.04$ Median follow up: NR
FALCON[24] Phase III, randomized, double-blind study conducted at 113 centers in 20 countries in Asia, Europe, North America, South America and South Africa	Fulvestrant 500 mg ($n = 230$) *versus* anastrozole 1 mg ($n = 232$)	No prior endocrine therapy was permitted Median age (range): 64 (38–87) *versus* 62 (36–90) years Prior chemotherapy for locally advanced/metastatic disease: 16% *versus* 19% Prior endocrine therapy: 1% *versus* 0.4% HER2 positive: 0% *versus* <1%	16.6 *versus* 13.8; HR 0.797 (0.637–0.999); $p = 0.0486$	NM *versus* NM (31% maturity)

(Continued)

Table 1. (Continued)

Study	Treatment	Patient characteristics	Median (months); HR (95% CI)	
			PFS/TTP	OS/TTD
International Letrozole Breast Cancer Group[25,26] Phase III, randomized, double-blind, parallel-group study conducted at 201 centers in 29 countries	Letrozole 2.5 mg ($n = 453$) *versus* tamoxifen 20 mg ($n = 454$)	Patients with disease relapse or recurrence within 12 months of completion of adjuvant antiestrogen therapy were excluded Median age (range): 65 (31–96) *versus* 64 (31–93) years Any prior chemotherapy: 29% *versus* 34% Prior adjuvant chemotherapy: 21% *versus* 23% Prior chemotherapy for advanced disease: 9% *versus* 11% Prior adjuvant endocrine therapy: 19% *versus* 18% HER2 status not reported	9.4 *versus* 6.0; HR 0.72 (NR); $p < 0.0001$ Median follow up: 32 months	34 *versus* 30; $p = 0.53$ Median follow up: 32 months
PALOMA-1[27] Phase II, randomized, open-label, multicenter study conducted at 50 sites in 12 countries	Letrozole 2.5 mg + palbociclib 125 mg ($n = 84$) *versus* letrozole 2.5 mg ($n = 81$)	Disease-free interval >12 months: 30% *versus* 37% Median age (range): 63 (54–71) *versus* 64 (56–70) years Prior chemotherapy: 40% *versus* 46% Prior endocrine therapy: 32% *versus* 35% Tamoxifen: 29% versus 30% Anastrozole: 10% *versus* 14% Letrozole: 2% *versus* 1% Exemestane: 5% *versus* 2% All patients were HER2-negative	20.2 *versus* 10.2; HR 0.49 (0.32–0.75); $p = 0.0004$ Median follow up: 29.6 months *versus* 27.9 months	37.5 *versus* 33.3; HR 0.81 (0.49–1.35); $p = 0.42$ Median follow up: 29.6 months *versus* 27.9 months
PALOMA-2[28] Phase III, randomized, double-blind, multicenter study conducted at 186 centers in 17 countries	Letrozole 2.5 mg + palbociclib 125 mg ($n = 444$) *versus* letrozole 2.5 mg ($n = 222$)	Disease-free interval >12 months: 40.1% *versus* 41.9% Median age (range): 62 (30–89) *versus* 61 (28–88) years Prior chemotherapy: 48.0% *versus* 49.1% Prior endocrine therapy: 56.1% *versus* 56.8% Tamoxifen: 47.1% *versus* 44.1% Anastrozole: 12.6% *versus* 13.1% Letrozole: 8.1% *versus* 7.2% Exemestane: 6.8% *versus* 5.9% All patients were HER2-negative	24.8 *versus* 14.5; HR 0.58 (0.46–0.72); $p < 0.001$ Median follow up: 23 months	NM
MONALEESA-2[11] Phase III, randomized, double-blind, multicenter study conducted at 223 centers in 29 countries	Letrozole 2.5 mg + ribociclib 600 mg ($n = 334$) *versus* letrozole 2.5 mg ($n = 334$)	Disease-free >24 months: 60.5% *versus* 58.4% Median age (range): 62 (23–91) *versus* 63 (29–88) years Prior chemotherapy: 44% *versus* 43% Prior endocrine therapy: 52% *versus* 51% Anastrozole: 14% *versus* 13% Exemestane: 6% *versus* 7% Letrozole: 10% *versus* 7% Tamoxifen: 42% *versus* 43% All patients were HER2-negative	Not reached *versus* 14.7; HR 0.56 (0.43–0.72); $p < 0.0001$ Prior endocrine therapy: non-steroidal AI and others ($n = 53$): HR 0.45 (0.19–1.04) Tamoxifen or exemestane ($n = 293$): HR 0.57 (0.39–0.83) No prior endocrine therapy ($n = 322$); HR 0.57 (0.38–0.85) Median follow up: 15.3 months	NM

AI, aromatase inhibitor; CI, confidence interval; HR, hazard ratio; MBC, metastatic breast cancer; NM, not matured; NR, not reported; OS, overall survival; PFS, progression-free survival; TTD, time to death; TTP, time to progression.

Table 2. Randomized controlled trials of endocrine therapies for the treatment of postmenopausal women with hormone receptor-positive advanced breast cancer in the second-line setting.

Study	Treatment	Patient characteristics	Median (months); HR (95% CI)	
			PFS/TTP	OS/TTD
Buzdar 1998[30] A combined analysis of two randomized, parallel-group, multicenter studies conducted at 49 centers in North America and 73 centers in Europe, Australia and South Africa	Anastrozole 1 mg ($n = 263$) *versus* megestrol acetate 160 mg ($n = 253$)	Median disease-free interval: 127 weeks *versus* 165 weeks Mean age (SD): 65 (10.9) *versus* 65 (9.9) years Prior chemotherapy: 37.3% *versus* 35.2% Prior adjuvant endocrine therapy: 47.9% *versus* 40.3% Prior endocrine therapy for advanced disease: 52.1% *versus* 59.7% Hormone receptor status unknown: 23.6% *versus* 25.3% Relapse during prior tamoxifen: 46.0% *versus* 40.3% HER2 status not reported	4.8 *versus* 4.6; HR 0.94 (0.76–1.16):[a] $p = 0.49$ Median follow up: 31.2 months	26.7 *versus* 22.5; HR 0.78 (0.60–1.0);[a] $p < 0.025$ Median follow up: 31.2 months
Kaufman 2000[31] Phase III, randomized, double-blind, parallel-group, multicenter study conducted at 144 centers in 19 countries	Exemestane 25 mg ($n = 366$) *versus* megestrol acetate 160 mg ($n = 403$)	Median disease-free interval: 46 *versus* 48 months Median (range) age: 65 (35–89) *versus* 65 (30–91) years Prior adjuvant chemotherapy: 28.4% *versus* 26.8% Prior chemotherapy for advanced disease: 15.8% *versus* 16.6% HER2 status not reported	4.7 *versus* 3.8; $p = 0.037$ Median follow up: 11.3 months	NR *versus* 28.4; $p = 0.039$ Median follow up: 11.3 months
BOLERO-2[6,32,33] Phase III, randomized, double-blind, multicenter study conducted at 189 centers in 24 countries	Exemestane 25 mg + everolimus 10 mg ($n = 485$) *versus* exemestane 25 mg ($n = 239$)	Disease-free interval >24 months: 56% *versus* 54% Median age (range): 62 (34–93) *versus* 61 (28–90) years Prior neoadjuvant or adjuvant chemotherapy: 44% *versus* 40% Prior chemotherapy for MBC: 26% *versus* 26% Previous antiestrogens: Any: 57% *versus* 59% Tamoxifen: 47% *versus* 49% Fulvestrant: 17% *versus* 16% All patients were HER2-negative	7.8 *versus* 3.2; HR 0.45 (0.38–0.54); $p < 0.0001$ Median follow up: 17.7 months	31.0 *versus* 26.6; HR 0.89 (0.73–1.10); $p = 0.143$ Median follow up: 39.3 months
EFECT[34] Phase III, randomized, double-blind study conducted at 138 centers worldwide	Fulvestrant 250 mg + loading dose ($n = 351$) *versus* exemestane 25 mg ($n = 342$)	Median age (range): 63 (38–88) *versus* 63 (32–91) years Prior adjuvant chemotherapy: 42% *versus* 49% Prior chemotherapy for MBC: 25% *versus* 22% Prior adjuvant endocrine therapy: 62% *versus* 58% Prior endocrine therapy for advanced disease: 89% *versus* 86% HER2 status not reported	3.7 *versus* 3.7; HR 0.93 (0.82–1.13); $p < 0.65$ Median follow up: 13 months	NR

(Continued)

Table 2. (Continued)

Study	Treatment	Patient characteristics	Median (months); HR (95% CI)	
			PFS/TTP	OS/TTD
Trial 0020[35] Phase III, randomized, open-label, multicenter, parallel-group study conducted at 83 centers in Europe, Australia and South Africa	Fulvestrant 250 mg ($n = 222$) *versus* anastrozole 1 mg ($n = 229$)	Mean age (range): 63 (35–86) *versus* 64 (33–89) years Prior chemotherapy: 42.3% *versus* 42.8% Prior endocrine therapy for advanced disease: 56.8% *versus* 56.3% Prior adjuvant endocrine therapy: 54.5% *versus* 52.0% HER2 status not reported	5.5 *versus* 5.1: HR 0.98 (95.14% CI 0.80–1.21); $p = 0.84$ Median follow up: 14.4 months	NR
Trial 0021[36] Phase III, randomized, double-blind, double-dummy, multicenter, parallel-group study conducted in North America	Fulvestrant 250 mg ($n = 206$) *versus* anastrozole 1 mg ($n = 194$)	Mean age (range): 63 (33–89) *versus* 62 (36–94) years Prior chemotherapy: 62.6% *versus* 62.9% Prior endocrine therapy for advanced disease: 53.4% *versus* 50.0% Prior adjuvant endocrine therapy: 59.2% *versus* 59.8% HER2 status not reported	5.4 *versus* 3.4; HR 0.92 (95.14% CI 0.74–1.14); $p = 0.43$ Median follow up: 16.8 months	NR
Trial 0020 and Trial 0021 combined[37,38] A combined analysis of two phase III, randomized, multicenter studies conducted in North America (Study 21), and Europe, Australia and South Africa (Study 20)	Fulvestrant 250 mg ($n = 428$) *versus* anastrozole 1 mg ($n = 423$)	Mean age (range): 63 (33–89) *versus* 63 (33–94) years Prior chemotherapy: 52.1% *versus* 52.0% Prior endocrine therapy for advanced disease: 55.1% *versus* 53.4% Prior adjuvant endocrine therapy: 56.8% *versus* 55.6% HER2 status not reported	5.5 *versus* 4.1; HR 0.95 (94.14% CI 0.82–1.10); $p = 0.48$ Median follow up: 15.1 months	27.4 *versus* 27.7; HR 0.98 (0.84–1.15); $p = 0.809$ Median follow up: 27.0 months
CONFIRM[39,40] Phase III, randomized, double-blind, multicenter, parallel-group study conducted at 128 centers in 17 countries	Fulvestrant 500 mg ($n = 362$) *versus* fulvestrant 250 mg ($n = 374$)	Median age: 61 *versus* 61 years Relapse during prior adjuvant endocrine therapy: 48.3% *versus* 45.2% Relapse 0–12 months after adjuvant endocrine therapy: 4.4% *versus* 7.2% Relapse >12 months after adjuvant endocrine therapy: 9.9% *versus* 13.9% Relapse during *de novo* advanced disease: 35.9% *versus* 33.4% HER2 status not reported	6.5 *versus* 5.5; HR 0.80 (0.68–0.94); $p = 0.006$ Median follow up NR	26.4 *versus* 22.3; HR 0.81 (0.69–0.96); $p = 0.02$ 75% survival analysis

Table 2. (Continued)

Study	Treatment	Patient characteristics	Median (months); HR (95% CI)	
			PFS/TTP	OS/TTD
FINDER 1[41] Phase II, randomized, double-blind, multicenter, parallel-group study conducted at 40 centers in Japan	Fulvestrant 250 mg ($n = 45$) *versus* fulvestrant 250 mg + loading dose ($n = 51$) *versus* fulvestrant 500 mg ($n = 47$)	Median age (range): 61 (50–77) *versus* 62 (43–86) *versus* 61 (45–83) years Prior chemotherapy: 55.6% *versus* 72.5% *versus* 70.2% Prior endocrine therapy: 100.0% *versus* 100.0% *versus* 100.0% Relapse during adjuvant endocrine therapy: 40.0% *versus* 33.3% *versus* 59.6% Relapse 0–12 months after adjuvant endocrine therapy: 11.1% *versus* 3.9% *versus* 0% Relapse >12 months after adjuvant endocrine therapy: 22.2% *versus* 29.4% *versus* 12.8% Relapse during endocrine therapy for *de novo* advanced disease: 26.7% *versus* 33.3% *versus* 25.5% HER2-positive: 13.3% *versus* 2.0% *versus* 14.9%	6.0 *versus* 7.5 *versus* 6.0 Median follow up NR	NR
FINDER 2[42] Phase II, randomized, double-blind, multicenter, parallel-group study conducted at 34 centers in eight countries	Fulvestrant 250 mg ($n = 47$) *versus* fulvestrant 250 mg + loading dose ($n = 51$) *versus* fulvestrant 500 mg ($n = 46$)	Median age (range): 63 (42–88) *versus* 69 (38–85) *versus* 67 (49–85) years Prior chemotherapy: 59.6% *versus* 49.0% *versus* 56.5% Prior endocrine therapy: Anastrozole: 38.3% *versus* 29.4% *versus* 37.0% Tamoxifen: 59.6% *versus* 70.6% *versus* 58.7% Exemestane: 23.4% *versus* 23.5% *versus* 34.8% Relapse during adjuvant endocrine therapy: 51.1% *versus* 35.3% *versus* 32.6% Relapse 0–12 months after adjuvant endocrine therapy: 4.3% *versus* 5.9% *versus* 2.2% Relapse >12 months after adjuvant endocrine therapy: 10.6% *versus* 23.5% *versus* 19.6% Relapse during first-line endocrine treatment for *de novo* advanced disease: 34.0% *versus* 35.3% *versus* 43.5% HER2 positive: 4.3% *versus* 2.0% *versus* 6.5%	3.1 *versus* 6.1 *versus* 6.0 Median follow up NR	NR

(Continued)

Table 2. (Continued)

Study	Treatment	Patient characteristics	Median (months); HR (95% CI)	
			PFS/TTP	OS/TTD
PALOMA-3[7,8] Phase III, randomized, double-blind, multicenter study conducted at 144 centers in 17 countries	Fulvestrant 500 mg + palbociclib 125 mg ($n = 347$) *versus* fulvestrant 500 mg ($n = 174$)	Included postmenopausal patients as well as perimenopausal and premenopausal patients rendered postmenopausal through the use of goserelin throughout the study. Disease-free interval >24 months: 79.1% *versus* 76.6% Median age (range): 57 (30–88) *versus* 56 (29–80) years Documented sensitivity to prior endocrine therapy: 79.0% *versus* 78.2% Prior aromatase inhibitor: 85.3% *versus* 86.8% Prior tamoxifen: 60.8% *versus* 59.8% Prior neoadjuvant or adjuvant chemotherapy: 41.5% *versus* 43.1% Prior chemotherapy for MBC: 30.8% *versus* 36.2% Number of prior lines of therapy for MBC: 0: 24.2% *versus* 25.9% 1: 38.0% *versus* 40.2% 2: 25.9% *versus* 24.7% >2: 11.8% *versus* 9.2% All patients were HER2-negative	9.5 *versus* 4.6 HR 0.46 (0.36–0.59); $p < 0.0001$ Median follow up: 8.9 months	NM
Gershanovich 1998[43] Randomized, open-label, multicenter study conducted at 86 centers in 11 countries	Letrozole 0.5 mg ($n = 192$) *versus* letrozole 2.5 mg ($n = 185$) *versus* aminoglutethimide 500 mg ($n = 178$)	Disease-free interval ⩾24 months: 64.6% *versus* 61.6% *versus* 59.0% Median age: 64 *versus* 66 *versus* 65 years Prior chemotherapy: 53.1% *versus* 47.6% *versus* 43.8% Prior endocrine therapy: 100.0% *versus* 99.5% *versus* 100.0% Relapsed on adjuvant endocrine therapy: 35.4% *versus* 36.8% *versus* 39.9% Progressed on therapeutic endocrine therapy: 64.6% *versus* 62.7% *versus* 60.1% HER2 status not reported	3.3 *versus* 3.4 *versus* 3.2 RR for letrozole 2.5 mg *versus* letrozole 0.5 mg; $p = 0.3$ RR for letrozole 2.5 mg *versus* aminoglutethimide: 0.72 (0.57–0.92); $p = 0.008$ Median follow up: 20 months	21 *versus* 28 *versus* 20 RR for letrozole 2.5 mg *versus* letrozole 0.5 mg 0.74 (0.56–0.98); $p = 0.04$ RR for letrozole 2.5 mg *versus* aminoglutethimide: 0.64 (0.49–0.85); $p = 0.002$ RR for letrozole 0.5 mg *versus* aminoglutethimide: 0.86; $p = 0.28$ Median follow up: 20 months

Table 2. (Continued)

Study	Treatment	Patient characteristics	Median (months); HR (95% CI)	
			PFS/TTP	OS/TTD
Dombernowsky 1998[44] Randomized, double-blind study conducted in 91 centers in ten countries	Letrozole 0.5 mg ($n = 188$) *versus* letrozole 2.5 mg ($n = 174$) *versus* megestrol acetate 160 mg ($n = 189$)	Disease-free interval ⩾24 months: 63.3% *versus* 60.9% *versus* 58.2% Mean age (SD): 64.6 (10.5) *versus* 63.6 (9.1) *versus* 64 (9.5) years Prior chemotherapy: 39.4% *versus* 31.0% *versus* 40.2% Prior adjuvant chemotherapy: 21.8% *versus* 20.7% *versus* 21.7% Prior endocrine therapy: 65.4% *versus* 67.2% *versus* 67.7% Prior adjuvant endocrine therapy: 34.6% *versus* 32.8% *versus* 32.3% HER2 status unknown	5.1 *versus* 5.6 *versus* 5.5 RR for letrozole 0.5 mg *versus* letrozole 2.5 mg: 1.35 (1.04–1.75); $p = 0.02$ RR for letrozole 0.5 mg *versus* megestrol acetate: 1.04 (0.81–1.32); $p = 0.78$ RR for letrozole 2.5 mg *versus* megestrol acetate: 0.80 (0.62–1.02); $p = 0.07$ Median follow up: 33 months	21.5 *versus* 25.3 *versus* 21.5 RR for letrozole 0.5 mg *versus* letrozole 2.5 mg: 1.34 (1.02–1.76); $p = 0.03$ RR for letrozole 0.5 mg *versus* megestrol acetate: 1.12 (0.87–1.44): $p = 0.38$ RR for letrozole 2.5 mg *versus* megestrol acetate: 0.82 (0.63–1.08); $p = 0.15$ Median follow up: 45 months
TAMRAD[45] Phase II, randomized, open-label, multicenter study conducted in France	Tamoxifen 20 mg + everolimus 10 mg ($n = 54$) *versus* tamoxifen 20 mg ($n = 57$)	Median age (range): 63 (41–81) *versus* 66 (42–86) years Prior adjuvant aromatase inhibitor therapy: 39% *versus* 42% Prior aromatase inhibitor for MBC (first-line): 69% *versus* 65% Prior adjuvant tamoxifen: 33% *versus* 42% Prior adjuvant chemotherapy: 46% *versus* 56% Prior chemotherapy for MBC (first-line): 24% *versus* 26% Primary endocrine resistance: 48% *versus* 49% Secondary endocrine resistance: 50% *versus* 51% HER2 positive: 7.0% *versus* 2.0%	8.6 *versus* 4.5; HR 0.54 (0.36–0.81); $p = 0.0021$ Median follow up: 23.7 months *versus* 24.2 months	NR *versus* 32.9; HR 0.45 (0.24–0.81); $p = 0.007$ Median follow up: 23.7 months *versus* 24.2 months

CI, confidence interval; HR, hazard ratio; MBC, metastatic breast cancer; NC, not calculated; NM, not matured; NR, not reported; OS, overall survival; PFS, progression-free survival; RR, risk ratio; SD, standard deviation; TTD, time to death; TTP, time to progression.
[a]97.5% CI.

fulvestrant 250 mg (HR 0.80, 95% CI 0.68–0.94; $p = 0.006$),[39] letrozole 2.5 mg *versus* aminoglutethimide (risk ratio 0.72; 95% CI 0.57–0.92; $p = 0.008$),[43] and letrozole 2.5 mg *versus* letrozole 0.5 mg (risk ratio 1.35; 95% CI 1.04–1.75; $p = 0.02$).[44]

In the phase II TAMRAD study, the combination of tamoxifen and everolimus was compared with tamoxifen alone and demonstrated an improvement in TTP (HR 0.54, 95% CI 0.36–0.81; $p = 0.0021$).[45] In the phase III BOLERO-2 study, the addition of everolimus to exemestane significantly increased PFS compared with exemestane alone (HR 0.45; 95% CI 0.38–0.54; $p < 0.0001$).[32] Palbociclib in combination with fulvestrant 500 mg significantly improved PFS *versus* fulvestrant 500 mg alone (HR 0.46; 95% CI 0.36–0.59; $p < 0.0001$) in the phase III PALOMA-3 study.[7,8]

OS with second-line endocrine monotherapy ranged from 26.7 to 27.7 months with anastrozole (from two studies);[30,37] 26.6 months and median not reached with exemestane (from two studies);[31,33] 22.3–27.4 months with fulvestrant 250 mg (from two studies);[37,40] 26.4 months with fulvestrant 500 mg (from one study);[40] 21–21.5 months with letrozole 0.5 mg (from two studies);[43,44] 25.3–28 months with letrozole 2.5 mg (from two studies);[43,44] 32.9 months with tamoxifen (from one study);[45] and 21.5–28.4 months with megestrol acetate (from three studies).[30,31,44]

OS advantages were observed within individual studies for fulvestrant 500 mg *versus* fulvestrant 250 mg (HR 0.81; 95% CI 0.69–0.96; $p = 0.02$);[40] letrozole 2.5 mg *versus* letrozole 0.5 mg in two studies (risk ratio 0.5 *versus* 2.5 mg, 1.34; 95% CI 1.02–1.76; $p = 0.03$[44]; and risk ratio 2.5 *versus* 0.5 mg, 0.74; 95% CI 0.56–0.98; $p = 0.04$);[43] anastrozole *versus* megestrol acetate (HR 0.78; 97.5% CI 0.60–1.0; $p < 0.025$) in one study;[30] and exemestane *versus* megestrol acetate ($p = 0.039$) in one study.[31]

In the small phase II TAMRAD trial, the combination of everolimus and tamoxifen suggested an improvement in OS for the combination compared with tamoxifen alone (HR 0.45; 95% CI 0.24–0.81; $p = 0.007$).[45] However, in the much larger phase III BOLERO-2 trial, the addition of everolimus to exemestane therapy did not significantly increase OS compared with exemestane alone (HR 0.89; 95% CI 0.73–1.10; $p = 0.14$).[33] OS data for the combination of palbociclib with fulvestrant was not mature at the time of publication of the final analysis results.[7]

Discussion

We conducted a comprehensive literature review with the objective of providing an overview of efficacy in terms of TTP/PFS and OS findings from randomized controlled studies evaluating approved endocrine therapies (as monotherapy and in combination with targeted therapies) for the first- and second-line treatment of postmenopausal women with hormone receptor-positive advanced breast cancer. As the objective of this review was to evaluate the PFS and OS data for approved endocrine therapies, we do not review quality of life, toxicity, cost, definitions of endocrine resistance or analyses of biomarkers.

In the first-line setting, anastrozole, fulvestrant 500 mg and letrozole 2.5 mg were reported to significantly improve PFS/TTP *versus* a comparator endocrine therapy.[21,24,25,29] In this setting, fulvestrant 500 mg also provided a significant OS advantage compared with anastrozole in a phase II study, although the analysis of OS was not prespecified.[23]

Concerning first-line targeted therapies, palbociclib in combination with letrozole 2.5 mg (PALOMA-1 study) significantly improved PFS compared with letrozole 2.5 mg alone; however, OS data were not significantly different between treatment arms and this phase II study was not powered to demonstrate OS benefit.[27] In the phase III PALOMA-2 study, PFS improvement was demonstrated for the combination of palbociclib and letrozole 2.5 mg *versus* letrozole 2.5 mg alone. Data were not sufficiently mature to allow an analysis of OS (this will be the subject of a follow-up analysis).[28] In a recently published phase III study, a significant improvement in PFS with ribociclib in combination with letrozole 2.5 mg compared with letrozole 2.5 mg alone was reported;[11] however, OS data from this study were not mature at the time of the interim analysis.

Exemestane, fulvestrant 500 mg, anastrozole and letrozole 2.5 mg as second-line treatment of hormone receptor-positive advanced breast cancer were reported to significantly improve PFS/TTP over a comparator endocrine therapy.[31,39,43,44] Subsequent significant OS advantages *versus* comparators were observed for fulvestrant 500 mg,

anastrozole and letrozole 2.5 mg, and exemestane.[30,31,40,43,44] Of note, fulvestrant 500 mg and letrozole 2.5 mg demonstrated OS advantages compared with fulvestrant 250 mg and letrozole 0.5 mg, respectively.[40,43,44] The mTOR inhibitor everolimus in combination with tamoxifen improved TTP and OS *versus* tamoxifen alone in the small phase II TAMRAD trial.[45] The combination of everolimus with exemestane in the phase III BOLERO-2 study improved PFS *versus* exemestane as a single agent;[32] however, this finding did not translate into improved OS,[33] although it must be noted that this study was powered to detect statistical significance with an 8-month improvement in OS. Results of the phase III PALOMA-3 study demonstrated that palbociclib in combination with fulvestrant 500 mg significantly improved PFS compared with fulvestrant 500 mg alone.[7,8] OS data from this study are pending and are awaited with interest.

Fulvestrant 500 mg is the only endocrine therapy of those included in our review that showed improvements in both PFS/TTP and OS in both the first- and second-line treatment of postmenopausal women with hormone receptor-positive advanced breast cancer compared with other endocrine therapies. Fulvestrant 500 mg was associated with improved OS *versus* anastrozole in the phase II FIRST study (54.1 *versus* 48.4 months, respectively). However, this finding should be interpreted with caution, given the limitations of the OS analysis in this study, which only included a small number of patients.[23] Confirmation of the significant improvement in PFS seen in the phase II FIRST study with fulvestrant over anastrozole was demonstrated in the recently published phase III FALCON study.[24] Furthermore, results of a post hoc analysis of data in the FALCON study demonstrated that the improvement in PFS with fulvestrant versus anastrozole was greater in patients with non-visceral disease compared with patients with visceral disease; however, further studies are required to confirm this finding. Of note, patients in this study had not received any prior endocrine therapy, a patient population for which there is a paucity of data,[46] which limits the generalizability of the findings.

Our analysis included an evaluation of studies reporting the comparative efficacy of endocrine therapies as monotherapy. However, it should be noted that few studies have investigated the efficacy of combinations of endocrine therapies *versus* endocrine therapy alone.[47] To our knowledge, no significant differences in efficacy have been reported with endocrine therapy combinations over monotherapy,[48,49] with the exception of one study that demonstrated significant improvement in PFS for a combination of anastrozole and fulvestrant *versus* anastrozole alone.[50] Consequently, no definitive changes to clinical practice based on these findings have occurred.

Furthermore, in order to optimize treatment for individual patients, it is important to consider the impact of treatment on several factors in addition to efficacy, including quality of life, treatment-related adverse events and cost; however, a review of these aspects is beyond the scope of this article.

Key limitations of our data set include the substantial heterogeneity in the patient populations and the paucity of available information describing patients' prior exposure to endocrine therapy, number of previous treatments (chemotherapy and endocrine therapy) and duration of response to prior therapy, which make cross-trial comparisons difficult.

In this review, first-line treatment has been uniformly defined as first endocrine therapy for advanced breast cancer; however, prior adjuvant endocrine treatment was allowed in many studies. Therefore this does not represent first exposure to endocrine treatment, and may have biologic consequences that are not appropriately addressed in these studies. Prior exposure to endocrine therapy may therefore be a more precise parameter by which studies could be classified;[47] however, given the limitations described above, this would be difficult to ascertain for all studies included in this analysis.

It should be highlighted that the patient populations included in these trials would be expected to include a subpopulation of patients with hormone receptor-positive and HER2-positive advanced or metastatic breast cancer; however, few studies reported these data. According to the most recent guidelines, treatment recommendations for these patients include anti-HER2 therapy in combination with chemotherapy or endocrine therapy,[51] thus the presence of this cohort in the studies may have a confounding, albeit small, effect. For this reason, studies excluding these patients may provide a more representative population in which to evaluate the efficacy of endocrine therapies.

In addition, this literature review confined its evaluation to the efficacy of endocrine treatment in postmenopausal women only, with the exception of the PALOMA-3 trial, which also included premenopausal and perimenopausal patients who were rendered postmenopausal through administration of a gonadotropin-releasing hormone (GnRH) agonist goserelin for the duration of the study.[7,8] Treatment recommendations suggest that premenopausal women with advanced breast cancer should follow the same treatment algorithm as postmenopausal women with additional ovarian suppression;[51] however, there is underrepresentation of premenopausal women in clinical trials, and inclusion of this patient population in future trial designs would benefit clinical practice. To date, data on the use of endocrine therapy as a treatment for premenopausal women with advanced breast cancer are limited; however, the results of the PALOMA-3 trial suggested similar PFS with palbociclib plus fulvestrant in these patient subgroups compared with postmenopausal women.[7,8] Moreover, the results of the phase III, randomized MONALEESA-7 study [ClinicalTrials.gov identifier: NCT02278120] of ribociclib or placebo plus tamoxifen and goserelin or an aromatase inhibitor in premenopausal women are eagerly awaited.

An important conclusion to be drawn from the available evidence base is that fulvestrant is currently the best available single-agent endocrine therapy, as demonstrated in the FALCON trial.[24] It is expected that fulvestrant will form the backbone of future combination strategies attempting to modulate endocrine resistance. The results of the ongoing phase II randomized, open-label PARSIFAL study [ClinicalTrials.gov identifier: NCT02491983] of palbociclib combined with fulvestrant or letrozole in advanced breast cancer, once available, will help to inform these strategies. It should be acknowledged that regardless of the findings of this analysis and despite OS data not being available, the addition of a CDK 4/6 inhibitor to an aromatase inhibitor is often selected as a preferred treatment choice based on the improvements in PFS seen with these combinations.

With the increasing number of alternative options for treating hormone receptor-positive advanced breast cancer, one critical aspect that warrants further investigation is how best to sequence each of the available therapies. Unfortunately, we have been unable to perform trials addressing this particular and very important issue. As patients derive additional benefits from current treatments and are able to receive more lines of therapy after an initial progression, it remains a significant challenge to demonstrate OS benefits in this scenario. This issue should be considered in the design and interpretation of future trials and in the regulatory criteria for drug approval.

In conclusion, our literature review reports on the use of endocrine therapy as first- and second-line treatment of postmenopausal women with hormone receptor-positive advanced or metastatic breast cancer. Patient selection strategies, development of predictive biomarkers, longer time frame follow-up information from reported studies, adequate data on lines of therapy after progression and the results of ongoing large randomized studies will add to the evidence base in this therapy area.

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Conflict of interest statement

Dr. Barrios has received honoraria from, and provided consultancy/advisory services to, AstraZeneca, Novartis, Pfizer and Roche. Dr. Reinert declares that he has no conflict of interest.

References

1. Howlader N, Noone AM, Krapcho M, *et al.* SEER Cancer Statistics Review, 1975–2012: estimated new cancer cases and deaths for 2015, http://seer.cancer.gov/csr/1975_2012 (2015, accessed 25 May 2017).
2. Lim E, Metzger-Filho O and Winer EP. The natural history of hormone receptor-positive breast cancer. *Oncology* 2012; 26: 688–694, 696.
3. Burstein HJ, Temin S, Anderson H, *et al.* Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical

Practice Guideline focused update. *J Clin Oncol* 2014; 32: 2255–2269.

4. Cardoso F, Costa A, Senkus E, *et al*. 3rd ESO-ESMO International Consensus Guidelines for Advanced Breast Cancer (ABC 3). *Breast* 2017; 31: 244–259.
5. Robertson JFR. Fulvestrant (Faslodex®): how to make a good drug better. *Oncologist* 2007; 12: 774–784.
6. Baselga J, Campone M, Piccart M, *et al*. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012; 366: 520–529.
7. Cristofanilli M, Turner NC, Bondarenko I, *et al*. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol* 2016; 17: 425–439.
8. Turner NC, Ro J, André F, *et al*. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015; 373: 209–219.
9. US Food and Drug Administration. Everolimus prescribing information, http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2150f73a-179b-4afc-b8ce-67c85cc72f04 (2015, accessed 25 May 2017).
10. US Food and Drug Administration. Palbociclib prescribing information, https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=86718885-da44-4d3d-b3ca-06cbcedcffd8 (2015, accessed 25 May 2017).
11. 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: 1738–1748.
12. Saad ED and Buyse M. Overall survival: patient outcome, therapeutic objective, clinical trial end point, or public health measure? *J Clin Oncol* 2012; 30: 1750–1754.
13. Burzykowski T, Buyse M, Piccart-Gebhart MJ, *et al*. Evaluation of tumor response, disease control, progression-free survival, and time to progression as potential surrogate end points in metastatic breast cancer. *J Clin Oncol* 2008; 26: 1987–1992.
14. Bonneterre J, Thürlimann B, Robertson JFR, *et al*. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol* 2000; 18: 3748–3757.
15. Nabholtz JM, Bonneterre J, Buzdar A, *et al*. Anastrozole (Arimidex™) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. *Eur J Cancer* 2003; 39: 1684–1689.
16. Bonneterre J, Buzdar A, Nabholtz JM, *et al*. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer* 2001; 92: 2247–2258.
17. Llombart-Cussac A, Ruiz A, Antón A, *et al*. Exemestane versus anastrozole as front-line endocrine therapy in postmenopausal patients with hormone receptor-positive, advanced breast cancer: final results from the Spanish Breast Cancer Group 2001–03 phase 2 randomized trial. *Cancer* 2012; 118: 241–247.
18. Iwata H, Masuda N, Ohno S, *et al*. A randomized, double-blind, controlled study of exemestane versus anastrozole for the first-line treatment of postmenopausal Japanese women with hormone-receptor-positive advanced breast cancer. *Breast Cancer Res Treat* 2013; 139: 441–451.
19. Paridaens RJ, Dirix LY, Beex LV, *et al*. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol* 2008; 26: 4883–4890.
20. Howell A, Robertson JFR, Abram P, *et al*. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. *J Clin Oncol* 2004; 22: 1605–1613.
21. Robertson JFR, Lindemann JPO, 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: 503–511.
22. Robertson JFR, 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: 4530–4535.
23. Ellis MJ, Llombart-Cussac A, Feltl D, *et al*. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: overall survival analysis from the phase II FIRST study. *J Clin Oncol* 2015; 33: 3781–3787.
24. 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.

25. Mouridsen H, Gershanovich M, Sun Y, *et al*. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001; 19: 2596–2606.

26. Mouridsen H, Gershanovich M, Sun Y, *et al*. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003; 21: 2101–2109.

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/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015; 16: 25–35.

28. Finn RS, Martin M, Rugo HS, *et al*. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016; 375: 1925–1936.

29. Nabholtz JM, Buzdar A, Pollak M, *et al*. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. *J Clin Oncol* 2000; 18: 3758–3767.

30. Buzdar AU, Jonat W, Howell A, *et al*. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. *Cancer* 1998; 83: 1142–1152.

31. Kaufmann M, Bajetta E, Dirix LY, *et al*. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. The Exemestane Study Group. *J Clin Oncol* 2000; 18: 1399–1411.

32. 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: 870–884.

33. 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: 2357–2362.

34. Chia S, Gradishar 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: 1664–1670.

35. Howell A, Robertson JFR, Quaresma Albano J, *et al*. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol* 2002; 20: 3396–3403.

36. Osborne CK, Pippen J, Jones SE, *et al*. Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. *J Clin Oncol* 2002; 20: 3386–3395.

37. 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: 236–239.

38. Robertson JFR, Osborne CK, Howell A, *et al*. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. *Cancer* 2003; 98: 229–238.

39. Di Leo A, Jerusalem G, Petruzelka L, *et al*. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol* 2010; 28: 4594–4600.

40. 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: djt337.

41. Ohno S, Rai Y, Iwata H, *et al*. Three dose regimens of fulvestrant in postmenopausal Japanese women with advanced breast cancer: results from a double-blind, phase II comparative study (FINDER1). *Ann Oncol* 2010; 21: 2342–2347.

42. Pritchard KI, Rolski J, Papai Z, *et al*. Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2). *Breast Cancer Res Treat* 2010; 123: 453–461.

43. Gershanovich M, Chaudri HA, Campos D, *et al*. Letrozole, a new oral aromatase inhibitor:

randomised trial comparing 2.5 mg daily, 0.5 mg daily and aminoglutethimide in postmenopausal women with advanced breast cancer. *Ann Oncol* 1998; 9: 639–645.

44. Dombernowsky P, Smith I, Falkson G, *et al*. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998; 16: 453–461.
45. Bachelot T, Bourgier C, Cropet C, *et al*. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. *J Clin Oncol* 2012; 30: 2718–2724.
46. Martin M, Lopez-Tarruella S and Gilarranz YJ. Endocrine therapy for hormone treatment-naïve advanced breast cancer. *Breast* 2016; 28: 161–166.
47. Reinert T and Barrios CH. Optimal management of hormone receptor positive metastatic breast cancer in 2016. *Ther Adv Med Oncol* 2015; 7: 304–320.
48. Bergh J, Jönsson PE, Lidbrink EK, *et al*. FACT: an open-label randomized 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: 1919–1925.
49. Johnston SRD, Kilburn LS, Ellis P, *et al*. 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: 989–998.
50. Mehta RS, Barlow WE, Albain KS, *et al*. Combination anastrozole and fulvestrant in metastatic breast cancer. *N Engl J Med* 2012; 367: 435–444.
51. Cardoso F, Costa A, Norton L, *et al*. ESO-ESMO 2nd International Consensus Guidelines for Advanced Breast Cancer (ABC2). *Ann Oncol* 2014; 25: 1871–1888.

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