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-naive 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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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.

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.

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.

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; 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; 0.0004); 27 and one phase III, randomized, double-blind study (HR 0.58, 95% CI 0.46–0.72; p < 0.001). 26 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; 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, 95% CI 0.60–0.95; 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) |
|------------------------------|------------------------------------|----------------------------------------------------------------------------------------|------------------------------|
|                              |                                    | Median (months); HR (95% CI)                                                           | PFS/TTP                      |
|                              |                                    |                                                                                       | OS/TTD                       |
| TARGET14,15                  | Anastrozole 1 mg                   | Endocrine therapy for early breast cancer was permitted, but patients could not receive tamoxifen within 12 months before entry | 8.2 versus 8.3; HR 0.99 (0.86–NR); p = 0.941 | 38.5 versus 40.9; HR 0.94 (0.79–NR); p = NR |
| Randomized, double-blind study conducted at 83 sites in Europe, Australia, New Zealand, South America and South Africa | versus tamoxifen 20 mg [n = 328] | 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 | Median follow up: 19 months | Median follow up NR |
| Bonneterre 200115,16         | Anastrozole 1 mg                   | Endocrine therapy or chemotherapy for early breast cancer was permitted, but patients could not receive tamoxifen within 12 months before entry | 11.1 versus 5.6; HR 1.44 (1.16–NR); p = 0.005 | 40.4 versus 38.5; HR 1.02 (0.81–NR); p = NR |
| Phase III, randomized, double-blind study conducted at 97 sites in the US and Canada | versus tamoxifen 20 mg [n = 182] | 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 | Median follow up: 17.7 months | Median follow up NR |
| Nabholtz 200315,16           | Anastrozole 1 mg                   | Endocrine therapy or chemotherapy for early breast cancer was permitted, but patients could not receive tamoxifen within 12 months before entry | 8.5 versus 7.0; HR 1.13 [1.00–NR]; p = 0.103 | 39.2 versus 40.1; HR 0.97 [0.84–NR]; p = NR |
| A combined analysis          | versus tamoxifen 20 mg [n = 510]   | 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 | Median follow up: 18.2 months | Median follow up: 43.7 months |
| Llombart-Cussac 201217       | Exemestane 25 mg                   | Prior tamoxifen permitted if initiated 24 months before recurrence | 6.1 versus 12.1; HR 1.13 [0.75–1.72]; p = 0.558 | 19.9 versus 48.3; HR 1.33 [0.78–2.25]; p = 0.296 |
| Phase II, randomized, open-label study conducted at 13 sites in Spain    | [n = 51] versus anastrozole 1 mg  | Median age [range]: 68 [45–71] versus 73 [46–85] years Prior adjuvant tamoxifen: 51.0% versus 50.5% HER2 status not reported | Median follow up: 9.1 months | Median follow up NR |
|                             | [n = 52]                           |                                                                                       |                              |                              |
| Iwata 201318                | Exemestane 25 mg                   | 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]; p = NR | NR versus 60.1; HR 1.06 [0.73–1.54]; p = NR |
| Phase III, randomized, double-blind study conducted at 64 sites in Japan | [n = 149] versus anastrozole 1 mg | Median follow up: 19 months |                              |                             |
|                             | [n = 149]                           |                                                                                       |                              |                             |
| Study           | Treatment                                             | Patient characteristics                                                                 | Median (months); HR (95% CI)                  |
|-----------------|-------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------------------|
| EORTC19         | Exemestane 25 mg (n = 182) versus tamoxifen 20 mg (n = 189) | Recurrence-free interval after tamoxifen had to be ≥ 6 months                             | 9.9 versus 5.8; Median follow up: 29 months   |
|                 |                                                       | Median age (range): 63 (37–86) versus 62 (37–87) years                                   | 37.2 versus 43.3; Median follow up: 29 months |
|                 |                                                       | 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                                                                 |                                               |
| Howell 200420   | Fulvestrant 250 mg (n = 313) versus tamoxifen 20 mg (n = 274) | Adjuvant endocrine therapy was not permitted within 12 months before trial entry          | 6.8 versus 8.3; HR 1.18 [0.98–1.44]; p = 0.088|
|                 |                                                       | Median age (range): 67 (43–93) versus 66 (43–92) years                                   | 36.9 versus 38.7; HR 1.29 [1.01–1.64]; p = 0.04|
|                 |                                                       | Prior adjuvant tamoxifen: 22.0% versus 24.8%                                             | 54.1 versus 48.4; HR 0.70 [0.50–0.98]; p = 0.04|
|                 |                                                       | Prior adjuvant chemotherapy: 22.7% versus 24.1%                                          | 31.1 months                                   |
|                 |                                                       | HER2 status not reported                                                                 |                                               |
| FIRST21–23      | 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 | 23.4 versus 13.1; HR 0.66 [0.47–0.92]; p = 0.01|
|                 |                                                       | Median age (range): 66 (40–89) versus 68 (48–87) years                                   | 54.1 versus 48.4; HR 0.70 [0.50–0.98]; p = 0.04|
|                 |                                                       | Prior adjuvant endocrine therapy (>12 months prior to randomization): 27.5% versus 22.3% | 31.1 months                                   |
|                 |                                                       | 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%                                                         |                                               |
| FALCON24        | Fulvestrant 500 mg (n = 230) versus anastrozole 1 mg (n = 232) | No prior endocrine therapy was permitted                                                | 16.6 versus 13.8; HR 0.797 [0.637–0.999]; p = 0.046       |
|                 |                                                       | Median age (range): 64 (38–87) versus 62 (38–90) years                                   | NM versus NM (31% maturity)                   |
|                 |                                                       | Prior chemotherapy for locally advanced/metastatic disease: 16% versus 19%                |                                               |
|                 |                                                       | Prior endocrine therapy: 1% versus 0.4%                                                   |                                               |
|                 |                                                       | HER2 positive: 0% versus <1%                                                               |                                               |
### Table 1. (Continued)

| Study                                      | Treatment                                      | Patient characteristics                                                                 | Median (months); HR (95% CI) | OS/TTD |
|--------------------------------------------|-----------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------|--------|
| **International Letrozole Breast Cancer Group**<sup>25,26</sup> | Letrozole 2.5 mg (<sup>n</sup> = 453) versus tamoxifen 20 mg (<sup>n</sup> = 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); <i>p</i> < 0.0001 | 34 versus 30; <i>p</i> = 0.53 |
| **PALOMA-1**<sup>27</sup> | Letrozole 2.5 mg + palbociclib 125 mg (<sup>n</sup> = 84) versus letrozole 2.5 mg (<sup>n</sup> = 81) | Disease-free interval: >12 months: 30% versus 37%; Median age [range]: 63 [56–71] 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); <i>p</i> = 0.0004 | 37.5 versus 33.3; HR 0.81 (0.49–1.35); <i>p</i> = 0.42 |
| **PALOMA-2**<sup>28</sup> | Letrozole 2.5 mg + palbociclib 125 mg (<sup>n</sup> = 444) versus letrozole 2.5 mg (<sup>n</sup> = 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); <i>p</i> < 0.001 | NM |
| **MONALEESA-2**<sup>31</sup> | Letrozole 2.5 mg + ribociclib 600 mg (<sup>n</sup> = 334) versus letrozole 2.5 mg (<sup>n</sup> = 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: 16% 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); <i>p</i> < 0.0001 | 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)                                                                 |
|-------------------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
|                   |                                                                           | Median disease-free interval: 127 weeks versus 165 weeks                               | PFS/TTP 4.8 versus 4.6; HR 0.94 (0.76–1.16); p = 0.49                                      |
|                   |                                                                           | Mean age [SD]: 65 [10.9] versus 65 [9.9] years                                         | OS/TTD 26.7 versus 22.5; HR 0.78 [0.60–1.0]; p < 0.025                                     |
|                   |                                                                           | Prior chemotherapy: 37.3% versus 35.2%                                                | Median follow up: 31.2 months                                                              |
|                   |                                                                           | Prior adjuvant endocrine therapy: 47.9% versus 40.3%                                   | Median follow up: 31.2 months                                                              |
|                   |                                                                           | 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                                                               |                                               |
| Buzdar 199830     | 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                                                               |                                               |
| Kaufman 200031    | Exemestane 25 mg (n = 366) versus megestrol acetate 160 mg (n = 403)     | Median disease-free interval: 46 versus 48 months                                       | PFS/TTP 4.7 versus 3.8; p = 0.037                                                          |
|                   |                                                                           | Median [range] age: 65 [35–89] versus 65 [30–91] years                                | OS/TTD NR versus 28.4; p = 0.039                                                          |
|                   |                                                                           | Prior adjuvant chemotherapy: 28.4% versus 26.8%                                       | Median follow up: 11.3 months                                                              |
|                   |                                                                           | Prior chemotherapy for advanced disease: 15.8% versus 16.6%                           | Median follow up: 11.3 months                                                              |
|                   |                                                                           | HER2 status not reported                                                               |                                               |
| BOLERO-26,32,33   | Exemestane 25 mg + everolimus 10 mg (n = 485) versus exemestane 25 mg (n = 239) | Disease-free interval >24 months: 56% versus 54%                                      | PFS/TTP 7.8 versus 3.2; HR 0.45 [0.38–0.54]; p < 0.001                                  |
|                   |                                                                           | Median [range]: 62 [34–93] versus 61 [28–90] years                                     | OS/TTD 31.0 versus 26.6; HR 0.89 [0.73–1.10]; p = 0.14                                  |
|                   |                                                                           | Prior neoadjuvant or adjuvant chemotherapy: 44% versus 40%                            | Median follow up: 17.7 months                                                              |
|                   |                                                                           | Prior chemotherapy for MBC: 26% versus 26%                                            | Median follow up: 39.3 months                                                              |
|                   |                                                                           | Previous antiestrogens:                                                               |                                               |
|                   |                                                                           | Any: 57% versus 59%                                                                   |                                               |
|                   |                                                                           | Tamoxifen: 47% versus 49%                                                             |                                               |
|                   |                                                                           | Fulvestrant: 17% versus 16%                                                           |                                               |
|                   |                                                                           | All patients were HER2-negative                                                       |                                               |
| EFECT34           | Fulvestrant 250 mg + loading dose (n = 351) versus exemestane 25 mg (n = 342) | Median age [range]: 63 [38–88] versus 63 [32–91] years                               | PFS/TTP 3.7 versus 3.7; HR 0.93 [0.82–1.13]; p < 0.65                                  |
|                   |                                                                           | Prior adjuvant chemotherapy: 42% versus 49%                                           | OS/TTD NR                                                                                  |
|                   |                                                                           | Prior chemotherapy for MBC: 25% versus 22%                                            | Median follow up: 13 months                                                               |
|                   |                                                                           | Prior adjuvant endocrine therapy: 62% versus 58%                                      |                                               |
|                   |                                                                           | Prior endocrine therapy for advanced disease: 89% versus 86%                         |                                               |
|                   |                                                                           | HER2 status not reported                                                               |                                               | (Continued)
### Table 2. (Continued)

| Study | Treatment | Patient characteristics | Median (months); HR (95% CI) |
|-------|-----------|-------------------------|-------------------------------|
| **Trial 0020**<sup>25</sup> | Fulvestrant 250 mg (<i>n</i> = 222) versus anastrozole 1 mg (<i>n</i> = 229) | Mean age (range): 63 [35–86] versus 64 [33–89] years | 5.5 versus 5.1; HR 0.98 (95.14% CI 0.80–1.21); <i>p</i> = 0.84 | 14.4 months |
| Phase III, randomized, open-label, multicenter, parallel-group study conducted at 83 centers in Europe, Australia and South Africa | Prior chemotherapy: 42.3% versus 42.8% | | Median follow up: NR | |
| | Prior endocrine therapy for advanced disease: 56.8% versus 56.3% | | | |
| | Prior adjuvant endocrine therapy: 54.5% versus 52.0% | | | |
| | HER2 status not reported | | | |
| **Trial 0021**<sup>26</sup> | Fulvestrant 250 mg (<i>n</i> = 206) versus anastrozole 1 mg (<i>n</i> = 194) | Mean age (range): 63 [33–89] versus 62 [36–94] years | 5.4 versus 3.4; HR 0.92 (95.14% CI 0.74–1.14); <i>p</i> = 0.43 | 16.8 months |
| Phase III, randomized, double-blind, double-dummy, multicenter, parallel-group study conducted in North America | Prior chemotherapy: 62.6% versus 62.9% | | Median follow up: NR | |
| | Prior endocrine therapy for advanced disease: 53.4% versus 50.0% | | | |
| | Prior adjuvant endocrine therapy: 59.2% versus 59.8% | | | |
| | HER2 status not reported | | | |
| **Trial 0020 and Trial 0021 combined**<sup>27,28</sup> | Fulvestrant 250 mg (<i>n</i> = 428) versus anastrozole 1 mg (<i>n</i> = 423) | Mean age (range): 63 [33–89] versus 63 [33–94] years | 5.5 versus 4.1; HR 0.95 (94.14% CI 0.82–1.10); <i>p</i> = 0.48 | 15.1 months |
| A combined analysis of two phase III, randomized, multicenter studies conducted in North America (Study 21), and Europe, Australia and South Africa (Study 20) | Prior chemotherapy: 52.1% versus 52.0% | | Median follow up: 27.0 months | |
| | Prior endocrine therapy for advanced disease: 55.1% versus 53.4% | | | |
| | Prior adjuvant endocrine therapy: 56.8% versus 55.6% | | | |
| | HER2 status not reported | | | |
| **CONFIRM**<sup>29,30</sup> | Fulvestrant 500 mg (<i>n</i> = 362) versus fulvestrant 250 mg (<i>n</i> = 374) | Median age: 61 versus 61 years | 6.5 versus 5.5; HR 0.80 [0.68–0.94]; <i>p</i> = 0.006 | NR |
| Phase III, randomized, double-blind, multicenter, parallel-group study conducted at 128 centers in 17 countries | Relapse during prior adjuvant endocrine therapy: 48.3% versus 45.2% | | Median follow up NR | |
| | 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 | | | |
| | 26.4 versus 22.3; HR 0.81 [0.69–0.96]; <i>p</i> = 0.02 | | 75% survival analysis | |
### Table 2. (Continued)

| Study                        | Treatment                                                                 | Patient characteristics                                                                 | Median (months); HR (95% CI)       |
|------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-----------------------------------|
| **FINDER 1**<sup>41</sup>    | 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 |
| **FINDER 2**<sup>42</sup>    | 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 |
Table 2. (Continued)

| Study | Treatment | Patient characteristics | Median (months); HR (95% CI) |
|-------|-----------|-------------------------|-------------------------------|
|       |           |                         | PFS/TTP                       | OS/TTD                  |
| **PALOMA-3**<sup>3,8</sup> | 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 |
| **Gershanovich 1998**<sup>1,3</sup> | 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 |
| Study                  | Treatment                                                                 | Patient characteristics                                                                 | Median (months), HR (95% CI)                                                                 |
|-----------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
|                       |                                                                           |                                                                                         | PFS/TTP                                                                                      | OS/TTD                                                                                      |
| **Dombernowsky 1998** | Letrozole 0.5 mg \(n = 188\) versus letrozole 2.5 mg \(n = 174\) versus megestrol acetate 160 mg \(n = 189\) | Disease-free interval \(\geq 24\) months: 63.3\% versus 60.9\% versus 65.8\% | 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]; \(p = 0.78\)         |
|                       |                                                                           | Mean age [SD]: 64.6 [10.5] versus 63.6 [9.1] versus 64.9 years                        | RR for tamoxifen versus letrozole 2.5 mg: 0.5 mg versus megestrol acetate: 1.04 [0.81–1.32]; \(p = 0.78\)     |
|                       |                                                                           | Prior chemotherapy: 39.4\% versus 31.0\% versus 40.2\%                              | RR for letrozole versus megestrol acetate: 0.80 [0.62–1.02]; \(p = 0.07\)                   | RR for letrozole versus megestrol acetate: 0.82 [0.63–1.08]; \(p = 0.15\)               |
|                       |                                                                           | Prior adjuvant chemotherapy: 21.8\% versus 20.7\% versus 21.7\%                     | Median follow up: 23.7 months versus 24.2 months                                             | Median follow up: 23.7 months versus 24.2 months                                             |
|                       |                                                                           | 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                                                                  |                                                                                             |                                                                                             |
| **TAMRAD**            | 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                              | RR for tamoxifen + everolimus versus tamoxifen: 0.54 [0.36–0.81]; \(p = 0.002\)            | RR for tamoxifen + everolimus versus tamoxifen: 0.45 [0.24–0.81]; \(p = 0.007\)         |
|                       |                                                                           | Prior adjuvant aromatase inhibitor therapy: 39\% versus 42\%                         | Median follow up: 23.7 months versus 24.2 months                                             | Median follow up: 23.7 months versus 24.2 months                                             |
|                       |                                                                           | Prior aromatase inhibitor for MBC [first-line]: 69\% versus 65\%                     |                                                                                             |                                                                                             |
|                       |                                                                           | Prior adjuvant tamoxifen: 33\% versus 42\%                                         |                                                                                             |                                                                                             |
|                       |                                                                           | Prior adjuvant chemotherapy: 44\% 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\%                                                    |                                                                                             |                                                                                             |

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.

a97.5\% CI.
fulvestrant 250 mg (HR 0.80, 95% CI 0.68–0.94; \( p = 0.006 \))\(^6\), letrozole 2.5 mg versus aminogluthethimide (risk ratio 0.72; 95% CI 0.57–0.92; \( p = 0.008 \))\(^4\) and letrozole 2.5 mg versus letrozole 0.5 mg (risk ratio 1.35; 95% CI 1.04–1.75; \( p = 0.02 \))\(^4\).

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; \( p = 0.0021 \))\(^5\). 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; \( p < 0.0001 \))\(^2\). 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\(^7\).

OS with second-line endocrine monotherapy ranged from 26.7 to 27.7 months with anastrozole (from two studies);\(^3\) 26.6 months and median not reached with exemestane (from two studies);\(^3,31,33\) 22.3–27.4 months with fulvestrant 250 mg (from two studies);\(^3,40\) 26.4 months with fulvestrant 500 mg (from one study);\(^4\) 21–21.5 months with letrozole 0.5 mg (from two studies);\(^3,34\) 25.3–28 months with letrozole 2.5 mg (from two studies);\(^3,34\) 32.9 months with tamoxifen (from one study);\(^4\) and 21.5–28.4 months with megestrol acetate (from three studies).\(^3,30,31,44\)

OS advantages were observed within individual studies for fulvestrant 500 mg versus fulvestrant 250 mg (HR 0.81; 95% CI 0.69–0.96; \( p = 0.02 \));\(^4\) 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; \( p = 0.03 \));\(^4\) and risk ratio 2.5 versus 0.5 mg, 0.74; 95% CI 0.56–0.98; \( p = 0.04 \));\(^4\) anastrozole versus megestrol acetate (HR 0.78; 97.5% CI 0.60–1.0; \( p < 0.025 \)) in one study;\(^3\) and exemestane versus megestrol acetate (\( p = 0.039 \)) in one study.\(^3\)

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; \( p = 0.007 \)).\(^4\) 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; \( p = 0.14 \)).\(^3\) 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.\(^2,21,24,25,29\) 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{45} The combination of everolimus with exemestane in the phase III BOLERO-2 study improved PFS versus exemestane as a single agent;\textsuperscript{32} however, this finding did not translate into improved OS,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{47} To our knowledge, no significant differences in efficacy have been reported with endocrine therapy combinations over monotherapy,\textsuperscript{48,49} with the exception of one study that demonstrated significant improvement in PFS for a combination of anastrozole and fulvestrant versus anastrozole alone.\textsuperscript{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;\textsuperscript{37} 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,\textsuperscript{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. Treatment recommendations suggest that premenopausal women with advanced breast cancer should follow the same treatment algorithm as postmenopausal women with additional ovarian suppression; 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. 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. 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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