Systematic literature review of clinical trials of endocrine therapies for premenopausal women with metastatic HR+ HER2− breast cancer

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Abstract
Several endocrine-based therapies have recently been evaluated as treatments for premenopausal women with hormone-receptor-positive/human-epidermal-growth-factor-receptor 2 negative (HR+/HER2−) metastatic breast cancer (mBC). We conducted a systematic review and assessed the feasibility of an indirect treatment comparison (ITC) to characterize the comparative efficacy of endocrine-based therapies in this setting. A systematic literature review (SLR) of Medline, EMBASE, Cochrane Library and key conferences was performed to identify randomized clinical trials (RCTs) satisfying the following criteria: (a) included pre/perimenopausal women with HR+/HER2− mBC, (b) included endocrine-based therapies, (c) reported efficacy, safety, or quality of life outcomes, and (d) was published in 2007 or later (when HER2 testing was standardized). The clinical and methodological similarities across trials were assessed to evaluate the feasibility of an ITC. Four RCTs (PALOMA-3, MONARCH-2, KCSG BR10-04 and MONALEESA-7) and eight regimens (palbociclib + fulvestrant + goserelin, fulvestrant + goserelin, abemaciclib + fulvestrant + gonadotropin-releasing hormone agonist [GnRHa], fulvestrant + GnRHa, anastrozole + goserelin, goserelin, ribociclib + NSAI/tamoxifen + goserelin and NSAI/tamoxifen + goserelin) were selected. MONALEESA-7 was the only phase 3 trial investigating endocrine-based therapies as first-line in only pre/perimenopausal women with HR+/HER2− mBC; the other three trials focused on the ET-failure setting and their pre/perimenopausal populations were relatively small. ITCs were methodologically unfeasible due to critical differences in treatment settings and lack of common comparators across trials. Therefore, we were not able to characterize the relative efficacy of the different endocrine-based therapies available in the premenopausal HR+/HER2− mBC setting. This systematic review provides a comprehensive assessment of the available trial evidence on the efficacy and safety of endocrine-based therapies.
therapies for premenopausal women with HR+/HER2− mBC. Only four trials have reported relevant data in this setting, and MONALEESA-7 is currently the only trial focused on premenopausal HR+ HER2− mBC in the first-line setting.

**KEYWORDS**

hormone receptor positive/human epidermal growth factor receptor-2 negative (HR+/HER2−), metastatic breast cancer, premenopausal, systematic literature review

1 | INTRODUCTION

Breast cancer (BC) is the most common cancer among women in the United States, with approximately 252,710 new cases and 40,610 deaths in 2017.1 Hormone receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2−) is the most common BC subtype, accounting for approximately 70% of BC cases.2 More than 90% of BC cases are detected in early stage (stage I-II), with approximately one-quarter diagnosed in premenopausal women,3 although the majority of cases progress to advanced or metastatic disease.4 A recent study reported that about one third of de novo metastatic BC (mBC) cases were diagnosed in premenopausal women.5

Typically, younger women are diagnosed with BC less often than older women. For instance, 20% of all breast cancers in the USA are diagnosed in women younger than 50 years,6 although in other regions, such as the Middle East and Latin America, the estimated percentages are almost 50%.7,8 However, BC in premenopausal women tend to be more often diagnosed in a higher stage compared to BC in postmenopausal women,9,10 partly due to the lack of routine screening mammography guidelines for younger women. Also, younger women tend to have tumors with a more aggressive phenotype and poor prognostic features; recent studies have reported that women <40 years had worse survival outcomes than women of older age groups.10,11

Large registrational trials assessing the efficacy of endocrine therapy for mBC have generally excluded premenopausal women. As a result, clinical data for premenopausal women remains remarkably limited and treatment recommendations for premenopausal patients has been largely based on studies in the postmenopausal population. Consequently, current treatment guidelines for premenopausal patients often recommend chemotherapy or surgical castration, thus converting these patients to postmenopausal from a physiological perspective. Therefore, the task of finding optimal strategies for endocrine-based therapies in premenopausal HR+/HER2− mBC remains an important challenge.

Among premenopausal women with mBC, the National Comprehensive Cancer Network (NCCN) guidelines recommend tamoxifen or toremifene alone, or ovarian ablation or suppression (eg, goserelin) plus endocrine-based therapy, similar to guidelines for postmenopausal women.12 The endocrine-based therapy options include endocrine monotherapy (ET) and ET + targeted therapy (TT, eg, palbociclib, ribociclib and abemaciclib) in the first-line setting or after failure with ET. Since BC in premenopausal women tends to be more aggressive, chemotherapy (CT) can also be part of the first-line treatment plan.13,14

Recent phase 3 trials in this setting include PALOMA-3,15 MONARCH-2,16 and MONALEESA-7.17 PALOMA-3 is a phase 3 randomized controlled trial (RCT) that assessed the efficacy and safety of palbociclib + fulvestrant + goserelin vs placebo + fulvestrant + goserelin in a subgroup of 108 pre/perimenopausal women with HR+/HER2− mBC who had progressed on prior ET. The median progression-free survival (PFS) in the palbociclib and placebo arms were 9.5 and 5.6 months respectively (hazard ratio [HR], 0.50). MONARCH-2 is a phase 3 RCT that compared abemaciclib + fulvestrant + GnRHa (gonadotropin-releasing hormone agonist, eg, goserelin) vs placebo + fulvestrant+GnRHa in a subgroup of 114 pre/perimenopausal women. The median PFS in the abemaciclib arm was not yet reached as of the latest report, and was 10.5 months for the placebo arm (HR = 0.45). Finally, MONALEESA-7 is also a phase 3 RCT that compared ribociclib + NSAI/tamoxifen + goserelin vs placebo + NSAI/tamoxifen + goserelin as the first-line therapy among premenopausal women with HR+/HER2− mBC. The PFS in the ribociclib and placebo arms was 23.8 and 13.0 months respectively (HR = 0.55). This is the first phase 3 trial investigating a CDK4/6 inhibitor in only pre/perimenopausal women with mBC in the first-line setting, and included a large population of 672 patients.

Despite the abundance of evidence in the postmenopausal setting,18 limited data exist regarding the efficacy of endocrine-based therapies among premenopausal women with HR+/HER2− mBC. With the recent changes in the treatment landscape in this setting, there is a need for patients, clinicians, and payers to assess the relative benefits and risks of the emerging and currently available endocrine-based therapies. Such an evaluation has to comprehensively examine all the available evidence to characterize the comparative efficacy of the treatments. However, given the lack of head-to-head comparison data of endocrine-based therapies for HR+/HER2− mBC, indirect comparison methods (eg, network meta-analysis [NMA]) can be used to synthesize information on multiple treatment alternatives across different RCTs to evaluate the comparative efficacy and safety of all these treatments.

To conduct these indirect treatment comparisons (ITC), a comprehensive literature search is needed to assess the feasibility of such analyses. To our knowledge, no previous study has performed a systematic literature review (SLR) of ETs in premenopausal women with HR+/HER2− mBC, nor examined the comparative efficacy and safety of these treatments via ITC. Therefore, the objectives of this study were to systematically review the literature to summarize the evidence on
efficacy and safety of existing endocrine-based therapies for premenopausal HR+/HER2− mBC, and to evaluate the feasibility of an ITC to quantitatively synthesize their efficacy and safety in this setting.

2 | METHODS

2.1 | Literature search

A SLR of RCTs of endocrine-based therapies among premenopausal women with HR+/HER2− mBC was conducted. A series of searches were undertaken in the following data bases and time ranges to identify RCTs in HR+/HER2− mBC: MEDLINE (2007-December 26, 2017), MEDLINE (R) In-Process (2007-December 26, 2017), EMBASE (2007 week 1-2017 week 52), Cochrane Database of Systematic Reviews (CDSR) (2007-December 19 2017), Cochrane Central Register of Controlled Trials (CENTRAL) (2007-November 2017), and Database of Abstracts of Reviews of Effects (DARE) (2007-2017). The search also included the following conference proceedings: American Society for Clinical Oncology (ASCO) annual meeting (2015-2017), American Association for Cancer Research (AACR) annual meeting (2015-2017), ASCO Breast Cancer Symposium (ASCO BC) (2015-2017), San Antonio Breast Cancer Symposium (SABCS) (2015-2017), European CanCer Organisation (ECCO), European Breast Cancer Conference (EBCC) (2015-217), and European Society of Medical Oncology (ESMO) (2015-2017).

To reduce patient heterogeneity, the search was restricted to articles published on or after 2007, the year the American Society of Clinical Oncology/College of American Pathologists developed the guidelines for standardizing HER2 testing.19 The SLR was designed, performed, and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.20 Study quality was assessed using the Cochrane Collaboration's tool for assessing risk of bias.21

The inclusion and exclusion criteria (Table 1) were defined a priori. Based on the inclusion and exclusion criteria listed in Table 1, the literature screening was conducted in two levels. At Level I screening, all titles/abstracts for the identified studies were reviewed for clear exclusion criteria. Abstracts about which reviewers were uncertain were included in the Level II full-text screening. For the abstracts that passed Level I screening, the corresponding full-text articles were retrieved for further review during Level II screening. The same inclusion and exclusion criteria used in the Level I screening was applied in Level II screening. Additionally, any relevant systematic review or meta-analysis articles published during the past 3 years were reviewed to identify additional studies. The reasons for exclusion were recorded for excluded articles. The studies excluded for different reasons were summarized at each level of screening.

2.2 | Data extraction

Study level information (eg, trial acronym, population), PFS outcomes (eg, HR and standard errors) and the reported baseline characteristics were extracted from selected studies. To ensure accuracy of the study selection and data extraction, literature screening and data extraction were performed by two researchers independently. A third researcher was consulted to reach a consensus if there was a disagreement on inclusion/exclusion decisions or extracted data. For the MONARCH-2 trial, the outcome data were obtained from the more recent reports at ASCO 2018,16 and for MONALEESA-7, the extracted data were supplemented with information in the Clinical Study Report (CSR).

2.3 | Indirect treatment comparison assessment

To evaluate the feasibility of an ITC (eg, network meta-analysis or match-adjusted indirect comparison), included studies were examined to assess their clinical and methodological similarities. The between-trial similarity of the following elements were inspected during this assessment: patient population (eg, disease status, HR, and HER2 status); outcomes reported (eg, availability and definitions); and interventions compared (including line of therapy [first-line vs second-line]). A network diagram was created to show the sources of evidence available for the analysis and to evaluate the possibility of conducting a network meta-analysis.

3 | RESULTS

3.1 | Study selection

The SLR identified three journal articles and three conference abstracts that met the eligibility criteria (Figure 1). Two journal articles corresponded to PALOMA 3 trial,15,22 and one journal article corresponded to the MONARCH-2 trial.23 The three identified conference abstracts corresponded, respectively, to the PALOMA-3 trial,24 MONALEESA-7 trial,17 and KCSG BR 10-04 trial.25

The baseline characteristics of the selected trials are summarized in Table 2. The sample size per treatment arm of premenopausal women in the identified trials was relatively small (range, 36-72), except for the MONALEESA-7 trial (335-337). Age distributions across trials were largely similar clinically. Patients in the MONALEESA-7 trial were slightly healthier compared to those in the KCSG BR10-04 trial, as indicated by the greater proportion of patients with ECOG = 0. MONALEESA-7 trial is the only trial in the first-line treatment setting for metastatic disease, whereas the patient population in the other trials had progressed after prior ET either in the metastatic setting, and in the case of MONARCH 2, patients either progressed ≤12 months after adjuvant ET or while receiving ET for mBC.

Key outcomes from all the selected trials are shown in Table 3, although several of these outcomes were not reported for some of the trials. PFS HR for the premenopausal population was reported in PALOMA-3 (palbociclib vs placebo arm: 0.50 [0.29-0.87]), MONARCH-2 (abemaciclib vs placebo arm: 0.45, [0.26-0.75]), KCSG BR 10-04 (fulvestrant + goserelin vs goserelin: 0.61 [0.37-1.00]; anastrozole + goserelin vs goserelin: 0.98 [0.62-1.55]) and MONALEESA-7 (ribociclib vs placebo arm: 0.55 [0.44-0.69]).

PALOMA-3, MONARCH-2 and MONALEESA-7 reported median PFS, while KCSG BR 10-04 reported TTP. The median time
to progression or death is longer in MONALEESA-7 compared to the other three trials, partly due to the former trial being in the first-line setting. Overall response rate (ORR) was larger in MONARCH-2 compared to MONALEESA-7 and PALOMA-3. Only MONALEESA-7 reported quality of life outcomes in the premenopausal population.

Although there were differences between the PALOMA-3 and MONARCH-2 trials (eg, reference arms were slightly different [in

**TABLE 1** Eligibility criteria used in the search strategy

| Clinical effectiveness | Inclusion criteria | Exclusion criteria |
|------------------------|-------------------|-------------------|
| Population             | Population consists of premenopausal women with HR+ HER2− ABC | Population does not consist of premenopausal HR+ HER2− subtype, or no outcomes separately for this subtype |
|                        |                   | Population does not consist of premenopausal ABC, or mixed population, but no results separately for premenopausal ABC |
| Interventions          | The interventions will include at least one of the following therapies, either as monotherapy or as part of a combination therapy: **Endocrine therapy** • letrozole • anastrozole • exemestane • tamoxifen • fulvestrant **Targeted therapy** • palbociclib • ribociclib/LEE011 • abemaciclib **Chemotherapy** • capecitabine • doxorubicin • paclitaxel • docetaxel • cyclophosphamide • eribulin | Studies do not include the drugs of interest |
| Outcomes               | At least one of the following outcomes is reported: **Efficacy outcomes** • Overall survival (OS) • Progression-free survival (PFS) • Time to progression (TTP) • Overall response rate (ORR) **Safety outcomes** • Adverse events (AEs) • Serious AEs (SAEs) • Discontinuation due to AE • All-cause discontinuation **HRQOL outcomes** • European Organization for Research and Treatment of Cancer Breast Cancer-Specific Quality of Life Questionnaire (EORTC QLQ-BR23) • Functional assessment of cancer therapy for breast cancer (FACT-B) • EQ-5D • Other QoL measures | Studies do not report outcomes of interest |
| Trial design           | Trial design is RCT | Trial design consists of: Single-arm trials Case reports Editorials & opinion pieces Reviews |
| Language restrictions  | Studies are in English | Studies are in English |
| Publication year       | Studies have been published between 2007 and January 5, 2018 | Studies have been published before 2007 |

Abbreviation(s): ABC, advanced breast cancer; EQ-5D, Euroqol 5 dimensions; HR+ HER2− ABC, hormone receptor-positive/human epidermal growth factor receptor-2 negative; HRQOL, health-related quality of life; QoL, quality of life; RCT, randomized control trial.
MONARCH-2 it was not specified that goserelin was the only GnRHα used], and patients had different prior treatment history [more patients in MONARCH-2 progressed within 12 months of adjuvant ET]), a naïve comparison of the PFS HR between these two trials indicates that abemaciclib + fulvestrant + GnRHα (HR = 0.45) is associated with a lower hazard of progression or death than palbociclib + fulvestrant + goserelin (HR = 0.50). However, due to the small sample size limitation, the confidence intervals around these estimates are large and overlapping.

3.2 Quality assessment

Quality assessment of the identified RCTs were based on the criteria described in Table 4, adapted from the “Systematic reviews: CRD’s guidance for undertaking reviews in health care” (University of York Centre for Reviews and Dissemination). The included trials were all well-conducted and the risk of bias was low to moderate, with concealment of allocation (with the exception of KCSG BR10-04).

3.3 Indirect treatment comparison

Figure 2 shows the disconnected network of the four identified trials, corresponding to the PFS HR outcome (the only outcome reported for all trials). In order to form a fully connected network, strong clinical assumptions are needed, such as “pooling” endocrine-based therapies (ie, assume that the clinical efficacies of the comparator arms in PALOMA-3 [fulvestrant + goserelin], MONARCH-2 [fulvestrant + GnRHα] and MONALEESA-7 [NSAI/tamoxifen + goserelin] are all similar in terms of PFS). Moreover, MONALEESA 7 is in the first-line (ET-naïve) setting, while all other studies are in the ET-failure setting. Hence, to be able to compare the ribociclib arm with the rest of the therapies, it would have to be assumed that the PFS HRs are similar in the first-line and second line settings. This difference in treatment settings also limits the validity of an indirect comparison via a matching-adjusted indirect comparison approach.

4 DISCUSSION

The treatment landscape for premenopausal women with HR+/HER2− mBC is rapidly changing as treatments previously approved in the postmenopausal setting are now being also assessed in premenopausal women. Hence, there is a need for patients, clinicians, and payers to assess the relative benefits and risks of the emerging and currently available endocrine-based therapies in the premenopausal setting. To that end, we conducted a SLR and assessed the feasibility of an indirect comparison of the available evidence. To our knowledge, this is the first SLR in this clinical and therapeutic setting.

The literature search indicated that only four RCTs (PALOMA-3, MONARCH-2, KCSG BR10-04, and MONALEESA-7) have assessed the effectiveness of endocrine-based therapies in premenopausal women with HR+/HER2− mBC. MONALEESA-7 is the first phase 3 trial investigating a CDK4/6 inhibitor (ribociclib) as first-line endocrine-based therapy in only pre/perimenopausal women with
| Characteristics | PALOMA-3* | MONARCH-2 | KCSG BR10-04* | MONALEESA-7* |
|-----------------|---------|---------|---------------|-------------|
| Trial phase     | III     | III     | II            | III         |
| Sample size, N  | 72      | 36      | 72            | 42          |
| Age (y)         | Median (Range) NR | 46 (32-57) | 47 (32-66) | 42.9 (28.0-53.0) |
| Race/Ethnicity, N (%) | White | 37 (51.4) | 21 (58.3) | 14 (38.1) |
|                 | Asian   | 31 (43.1) | 13 (36.1) | 51 (70.8) |
|                 | Black   | NR      | NR           | NR          |
|                 | Native American | NR | NR | NR |
|                 | Other   | 4 (5.6) | 2 (5.6) | 7 (9.7) |
|                 | Unknown | NR | NR | NR |
| Performance status, N (%) | ECOG 0 | NR | NR | NR |
|                 | ECOG 1  | NR | NR | NR |
|                 | ECOG 2  | NR | NR | NR |
|                 | ECOG >2 | NR | NR | NR |
|                 | Missing | NR | NR | NR |
| Prior therapy, N (%) | Endocrine therapy | 72 (100.0) | 36 (100.0) | 72 (100.0) |
|                 | Chemotherapy | 23 (31.9) | 12 (33.3) | NR |
|                 | Cancer stage, N (%) | Locally advanced | NR | NR | NR |
|                 | Metastatic | NR | NR | 72 (100.0) |

Abbreviation(s): ECOG, Eastern Cooperative Oncology Group; GnRHa, gonadotropin-releasing hormone agonist (eg, goserelin); NR, not reported; NSAI, nonsteroidal aromatase inhibitor.

*Baseline characteristics are for the entire trial population. Trials with * have 100% pre- or peri-menopausal population or report baseline characteristics for the pre- or peri-menopausal population.

#Age was reported as number and percentage for the following age groups: ≤40, 40-50, and >50 y old.

The data has been extracted from the 2018 ASCO Annual Meeting Presentation.

Other includes Black, Native American and etc when these categories have not been reported separately.

Prior (neo) adjuvant endocrine therapy.

Previous chemotherapy in metastatic setting. Subjects are counted for each treatment of metastatic disease (± neoadjuvant) received.

Calculated as the sum of chemotherapy for (neo) adjuvant only and advanced disease.
| Characteristics\(^a\) | PALOMA-3 | MONARCH-2 | KCSG BR10-04 | MONALEESA-7 |
|-----------------------|-----------|-----------|-------------|-------------|
| Trial phase           | Trial phase III | Trial phase III | Trial phase III | Trial phase III |
| Sample size, N        | 72        | 36        | 72          | 42          | 44          | 47          | 47          | 335         | 337         |
| PFS hazard ratio      | 0.50      | NA        | 0.45        | 0.61        | 0.37        | 0.62       | 0.98        | 0.55        | NA          |
| 95% CI                | (0.29-0.87)| NA        | (0.26-0.75)| (0.37-1.00)| (0.62-1.55)| NA         | (0.44-0.69)| NA         |
| Median PFS (mo)       | 9.5       | 5.6       | Not reached | 10.5        | NR          | NR         | NR          | NR          | NR          |
| TTP hazard ratio      | NR        | NR        | NR          | NR          | NR          | NR         | NR          | NR          | NR          |
| Median TTP (mo)       | NR        | NR        | NR          | 16.3        | 14.5        | 13.5       | NR          | NR          | NR          |
| OS hazard ratio       | NR        | NR        | NR          | NR          | 0.60        | 0.52       | NR          | 0.92        | NA          |
| 95% CI                | NR        | NR        | NR          | (0.28-1.32) | (0.23-1.19)| NR         | (0.6-1.4)| NA         |
| Median OS (mo)        | NR        | NR        | NR          | Not reached\(^b\) | Not reached\(^b\) | 53.5      | Not Reached\(^b\) | 29.4        |
| 95% CI                | NR        | NR        | NR          | NR          | NR          | NR         | NR          | NR          | (28.2, NE) |
| ORR, N (%)            | 18 (25.0) | 4 (11.1)  | 31 (43.1)\(^d\) | 8 (19.0)\(^d\) | NR\(^c\)    | NR\(^c\)  | NR\(^c\)    | 137 (40.9) | 100 (29.7) |
| CBR, N (%)            | 50 (69.4)| 16 (44.4)| 56 (77.8)\(^d\) | 29 (69.0)\(^d\) | NR\(^c\)    | NR\(^c\)  | NR\(^c\)    | 265 (79.1) | 235 (69.7) |
| Overall AEs, N (%)    | 71 (98.6)| 35 (97.2)| 70 (98.6)    | 40 (95.2)    | NR          | NR         | NR          | 329 (98.2) | 317 (94.1) |
| Overall SAEs, N (%)   | 10 (14.1)| 7 (19.4)  | 8 (11.3)     | 2 (4.8)      | NR          | NR         | NR          | 60 (17.9)  | 39 (11.6)  |
| Discontinuation due to AE, N (%) | 4 (5.6) | 0 (0.0)  | 4 (5.6)     | 0 (0.0)      | NR          | NR         | NR          | 21 (6.3)  | 12 (3.6)  |
| All-cause discontinuation, N (%) | NR | NR | NR | NR | NR | NR | NR | 161 (48.1) | 216 (64.1) |
| EORTC QLQ-C30 hazard ratio | NR | NR | NR | NR | NR | NR | NR | 0.7\(^e\) | NA\(^e\) |
| EORTC QLQ-B23 hazard ratio | NR | NR | NR | NR | NR | NR | NR | 0.68\(^e\) | NA\(^e\) |
| FACT-B hazard ratio   | NR        | NR        | NR          | NR          | NR          | NR         | NR          | NR          | NR          |
| EQ-SD                 | NR        | NR        | NR          | NR          | NR          | NR         | NR          | NR          | NR          |

Abbreviation(s): AE, adverse event; CBR, clinical benefit rate; GnRHa, gonadotropin-releasing hormone agonist (e.g., goserelin); NA, not applicable; NE, not estimable; NR, not reported; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SAE, serious AE; TTP, time to progression.
\(^a\)Sample size and outcomes correspond to the pre- or peri-menopausal population.
\(^b\)Median OS was not reached.
\(^c\)The poster has information for partial response and stable response, but not for complete response. Therefore we cannot derive ORR and CBR values.
\(^d\)The reported ORR and CBR values pertain to the ITT population.
\(^e\)There was a delay in the time to definitive 10% deterioration for the global health status/quality of life scale in the ribociclib arm vs the placebo arm.
mBC, whereas the other three trials focused on the ET-failure setting. As MONALEESA-7 focused solely on premenopausal women, this trial had a large population size, while the other three trials featured relatively small premenopausal patient populations and as a result their power to detect clinically relevant treatment effects may be limited. Notwithstanding, the PALOMA-3, MONARCH-2, and MONALEESA-7 trials consistently indicated that combining a CDK4/6 inhibitor with an endocrine monotherapy (fulvestrant, tamoxifen or NSAI) and a GnRHa (eg, goserelin) led to improvements in PFS and ORR in premenopausal women with HR+/HER2− mBC.

In assessing the feasibility of a formal ITC, it was determined that the treatments in these trials do not form a connected network, unless strong clinical assumptions are granted. ITCs via an NMA were deemed methodologically unfeasible given the critical differences in treatment settings (MONALEESA-7 is in the first-line (ET-naïve) setting, while all other studies are in the ET-failure setting), in addition to the disconnected geometry of the evidence network. The unfeasibility of this indirect comparison is also in part due to the inconsistency in the endocrine therapy partner (goserelin vs any GnRHa), which indicates that some trials (eg, MONARCH-2) may have not been designed primarily to show a benefit of their investigational treatment in premenopausal women. The PALOMA-3 and MONARCH-2 trials did not focus exclusively on the premenopausal population and their PFS results correspond to subgroup analysis that may be underpowered (in the case of MONARCH-2, the subgroup analyses in the premenopausal population was not pre-specified in the study protocol).

One of the limitations of the present study is that, due to the lack of clinical trial data available for the premenopausal HR+/HER2− mBC population, we could not perform an ITC of all the therapies in the studies identified in the literature search. Hence, it was not feasible to assess the relative efficacy of the different treatments available in this setting. Additionally, there were gaps in the reporting of patient characteristics or outcomes for the premenopausal population in some of the identified studies.

5 | CONCLUSIONS

To conclude, this systematic literature evaluation provides a comprehensive review of the available clinical trial evidence on the efficacy and safety of ET as treatments for premenopausal women with HR+/HER2− mBC. The search demonstrated the paucity of RCTs focusing on premenopausal HR+ HER2− mBC, with only four trials having reported relevant data in this setting. MONALEESA-7...
is currently the only phase 3 trial focused on premenopausal HR+/HER2− mBC in the first-line setting. Efficacy results from the selected trials indicated that combining a CDK4/6 inhibitor with an endocrine monotherapy and a GnRHa led to improvements in PFS and ORR in premenopausal women with HR+/HER2− mBC in the first-line and ET-failure settings.

**CONFLICT OF INTEREST**

OP-L, RA, OL, and ED are employees of Analysis Group Inc, which has received consultancy fees from Novartis. AAD, EP, and DC are employees of Novartis and may own stock/stock options. JAO received consultancy fees from Novartis.

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