

Targeted Therapy for Premenopausal Women with HR⁺, HER2⁻ Advanced Breast Cancer: Focus on Special Considerations and Latest Advances

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Abstract

The incidence of advanced breast cancer in premenopausal women is increasing, and breast cancer in younger women is often more aggressive and has a worse prognosis compared with breast cancer in older women. Premenopausal women with hormone receptor–positive (HR⁺) breast cancer are frequently under-represented in clinical trials, and treatment strategies in the premenopausal setting are usually extrapolated from data from postmenopausal patients, with the addition of ovarian function suppression to endocrine therapy in HR⁺ disease. However, the underlying biology of breast cancer in premenopausal women can be different from postmenopausal women, and treatment strategies should ideally be specifically tested in premenopausal patients. Recent phase III trials have now investigated cyclin-dependent kinase 4/6

(CDK4/6) inhibitors in premenopausal patients with HR⁺, HER2⁻ advanced breast cancer: Palbociclib and abemaciclib have been tested in a subset of premenopausal patients in the PALOMA-3 and MONARCH-2 studies, and ribociclib has been tested in the phase III MONALEESA-7 trial, which was entirely dedicated to premenopausal women. This comprehensive review summarizes the differences in the biology of HR⁺, HER2⁻ breast cancer in the premenopausal population compared with the postmenopausal population; discusses special considerations for treatment of premenopausal women; and reviews the evidence from clinical trials investigating endocrine therapy, other targeted treatments, and ovarian function suppression in the HR⁺, HER2⁻ advanced breast cancer setting. *Clin Cancer Res*; 1–13. ©2018 AACR.

Introduction

While breast cancer is predominantly seen in older, postmenopausal women (>50 years), the incidence of advanced breast cancer (ABC) in younger, premenopausal women is increasing (1). In the United States, 20% of all breast cancers are diagnosed in women <50 years (2), and in 20- to 39-year-old women, the incidence of distant breast cancer increased by 2% per year between 1978 and 2008 (1). Worldwide, breast cancer is the most common cancer in women (3), accounting for almost half of cancer diagnoses in women <50 years (4), and is the leading cause of cancer-related deaths in women <45 years (5). Approximately two thirds of tumors in women <40 years are identified as hormone receptor–positive (HR⁺; refs. 6–8), and younger women with HR⁺ tumors have a worse prognosis than older women (9, 10). However, premenopausal women with HR⁺, HER2⁻ breast cancer are often under-represented in clinical trials (9).

Treatment strategies for HR⁺, HER2⁻ breast cancer in premenopausal women are usually extrapolated from data from postmenopausal patients, with the addition of ovarian function suppression (OFS) to endocrine therapy (ET; refs. 11, 12); how-

ever, this might not be the best strategy given differences in tumor biology and other special considerations (discussed in detail below). In the postmenopausal, HR⁺, HER2⁻ ABC setting, the treatment landscape has changed considerably in recent years; targeted therapies that can be added to ET to improve efficacy and delay endocrine resistance include the cyclin-dependent kinase 4/6 (CDK4/6) inhibitors ribociclib, palbociclib, and abemaciclib, and the mTOR inhibitor everolimus. In the postmenopausal first-line setting, the addition of palbociclib to letrozole increased median progression-free survival (PFS) from 14.5 to 24.8 months in PALOMA-2 (13), the addition of ribociclib to letrozole increased median PFS from 16.0 to 25.3 months in MONALEESA-2 (14), and the addition of abemaciclib to a nonsteroidal aromatase inhibitor (NSAI) prolonged PFS (median PFS not reached vs. 14.7 months) in MONARCH-3 (15). In the second-line setting and beyond, the addition of palbociclib to fulvestrant resulted in a longer median PFS compared with fulvestrant alone in PALOMA-3 (11.2 vs. 4.6 months, respectively; ref. 16), as did abemaciclib and fulvestrant compared with fulvestrant alone in MONARCH-2 (median PFS 16.4 vs. 9.3 months, respectively; ref. 17). Also in the hormone-refractory setting, the addition of everolimus to exemestane resulted in a longer median PFS compared with exemestane alone (7.8 months vs. 3.2 months, respectively) in BOLERO-2 (18).

There is a need for dedicated studies in premenopausal patients with ABC to derive an evidence-based approach to tailor treatment to young women. Before MONALEESA-7, the last randomized trial dedicated to the treatment of premenopausal women with HR⁺, HER2⁻ ABC, and not testing only OFS modalities, was published in 2000 (19). In this review, we discuss the special considerations for the premenopausal patient population, review the evidence for treatment decisions in premenopausal

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women with HR⁺, HER2⁻ ABC, and provide insights on how the treatment landscape may evolve for these patients in the future. Treatment of HER2-positive and triple-negative breast cancer is reviewed elsewhere (20, 21).

Special Considerations for the Premenopausal Patient Population

Tumor biology

Premenopausal patients with HR⁺, HER2⁻ ABC present with both a tumor biology and clinical response profile that is distinct from that seen in postmenopausal patients (9). Compared with postmenopausal breast cancer, the tumor characteristics in premenopausal breast cancer often include: (i) a more advanced cancer stage at diagnosis (8), possibly resulting from the lack of routine screening in this age group (22, 23), (ii) higher tumor grades, larger tumor sizes, and the presence of positive axillary lymph nodes (6, 8), and (iii) presence of more aggressive breast cancer subtypes including HER2-overexpressing tumors, and triple-negative disease [estrogen receptor (ER)-negative, progesterone receptor-negative, and HER2⁻; ref. 8]. Poorer clinical outcomes associated with premenopausal breast cancer include: (i) increased risk of recurrence in younger women (1.5 times greater risk before the age of 40 compared with after 40 years; refs. 8, 24), and (ii) greater risk of death due to breast cancer than older women (4, 8). A large database study found that premenopausal patients with breast cancer had significantly higher levels of the proliferation marker Ki67 compared with their postmenopausal counterparts (25). Furthermore, a unique breast cancer gene expression profile was observed in another study of premenopausal HR⁺ disease, with differences in copy number, DNA methylation, and somatic mutations compared with older, postmenopausal patients (26). Specifically, *ESR1*, *MAT2B*, *CTSS*, *DDR2*, and *GALNTL2* were the top genes found to be hypermethylated in premenopausal ER⁺ tumors compared with postmenopausal tumors (26). In addition, five genes had significantly different mutation rates (*CDH1*, *GATA3*, *MLL3*, *GPS2*, *PIK3CA*) in premenopausal versus postmenopausal ER⁺ tumors (26). It is interesting to note that in a study of serial liquid biopsies, methylation of *ESR1* in circulating tumor cells significantly correlated with a lack of response to everolimus plus exemestane (27). Although this is one small study, it indicates a role for methylation of key genes in treatment responses and the need for more robust biomarker data.

Quality of life

Health-related quality of life (HRQoL) is an important factor in the treatment of premenopausal women with metastatic breast cancer as QoL scores have been shown to be predictive of survival, with better mood and physical wellbeing significantly associated with longer survival (28). Compared with age-matched survivors of other cancers, young women (<50 years) surviving breast cancer had worse HRQoL with significantly lower global health scores, as well as poorer emotional, social, and cognitive functioning scales, assessed by the EORTC QLQ-C30 questionnaire in a cross-sectional study of 2,224 breast cancer survivors, 8,504 noncancer controls, and 2,205 survivors of other cancer (29). Young women with breast cancer also experienced more fatigue and insomnia than survivors of other cancers (29). In addition, in a longitudinal study, younger women reported significantly more distress related to treatment adverse events

(AE), particularly vasomotor dysfunction, dyspareunia, vaginal dryness, and persistent sexual disinterest (30). Following surgery or systemic therapy for breast cancer, poor body image and reduced sexual functioning is common in young women (31). Mastectomy, hair loss due to chemotherapy, weight gain or loss, poor mental health, low self-esteem, and a partner's difficulty in understanding their feelings have all been attributed to body image problems in young, sexually active women with breast cancer (31, 32). Younger women may also have more difficulty adjusting to their breast cancer diagnosis and report symptoms of distress, depression, and anxiety more frequently than older women (30, 33, 34). Young women with newly diagnosed breast cancer often have fertility concerns, and studies have suggested that patients are not receiving appropriate information regarding fertility prior to the start of treatment (35). Fertility concerns have been associated with depression in young patients with breast cancer (36), and as mood is linked with survival of patients with metastatic breast cancer (28), depression related to unaddressed reproductive concerns could affect treatment outcomes in young women. Younger women may also have children to care for and careers to manage; therefore, the impact of breast cancer on their financial situation and day-to-day life can be substantial and difficult to cope with, which may add to the social, emotional, and psychologic dysfunction associated with their diagnosis and treatment (11, 33).

Impact of treatment on menopausal status

Abrupt, premature menopause (which can be temporary or permanent) can be triggered by breast cancer treatment and can be distressing for younger patients (30). Approximately one third of young women with breast cancer experience onset of menopause due to treatment for stage I–IV disease (30). For HR⁺ ABC, OFS is a recommended part of the treatment protocol (and required for use of AIs; refs. 12, 37) and the resulting premature menopause can have a direct effect on the HRQoL of young patients (36). Premature menopause can have more severe symptoms than the normal aging process, and patients aged ≤40 years were significantly more distressed by hot flashes associated with premature menopause than older women ($P = 0.0007$; ref. 30). In a study examining tamoxifen plus OFS in premenopausal women with early breast cancer, side effects included hot flashes, sweating, decreased libido, vaginal dryness, insomnia, depression, musculoskeletal symptoms, hypertension, and diabetes, which were greater in the combination group compared with those who received tamoxifen alone (38). Medically induced menopause from OFS is usually temporary, with the return of normal ovarian function more likely in younger women (39). Chemotherapy can also result in medically induced menopause, and up to 40% of women aged under 40 years, and 70%–90% of women aged over 40 years, go into permanent menopause as a result of chemotherapy (39). Women who experience premature menopause, regardless of cause, are at increased risk of overall mortality, cardiovascular diseases, neurological diseases, and osteoporosis, among others (40).

Treatment Options in Premenopausal HR⁺ Advanced Breast Cancer

It is generally accepted that young age alone is not a reason to prescribe more aggressive treatment and/or favor chemotherapy over sequential ET (11). Because of the lack of proven standards of

care for advanced disease in young women, the Second International Consensus Guidelines for Breast Cancer in Young Women (BCY2) recommend that treatment not differ from older women (11). However, the special considerations discussed above should be considered when developing a treatment plan for premenopausal women, and treatment decisions should ideally be based on clinical data obtained specifically in the premenopausal population. On the basis of current data, ET (with/without a CDK4/6 inhibitor) is the recommended option for all HR⁺ advanced disease, with the addition of OFS for first-line treatment of premenopausal women (11, 12, 37, 41). OFS can be accomplished with gonadotropin-releasing hormone agonists (GnRHa) such as goserelin or leuprolide, which are injected monthly, or with surgical oophorectomy. According to the guidelines, treatment options for disease that has progressed on first-line ET include additional rounds of ET, palbociclib, or abemaciclib plus fulvestrant, everolimus plus exemestane, or chemotherapy, depending on previous treatment (11, 12, 37). A possible treatment sequence for premenopausal women with HR⁺, HER2⁻ ABC based on current guidelines and our insights is presented in Fig. 1.

First-line treatment options

ET with targeted therapy (CDK4/6 inhibitors). The cell-cycle checkpoint is regulated by the cyclin D-CDK4/6-p16-retinoblastoma pathway and commonly dysregulated in cancer; CDK4/6 inhibitors bind to CDK4 and CDK6 and prevent phosphorylation of retinoblastoma, which downstream leads to cell-cycle arrest at G₁ (42). Addition of CDK4/6 inhibitors to ET in the first-line treatment of HR⁺, HER2⁻ ABC in postmenopausal women has led to significant gains in PFS compared with ET alone (13, 14, 16, 17). Similar results were recently reported in premenopausal breast cancer.

In MONALEESA-7, the first phase III randomized, placebo-controlled trial of a CDK4/6 inhibitor plus ET fully dedicated to premenopausal women with HR⁺, HER2⁻ ABC in the first-line setting (Table 1), 672 premenopausal women were randomized to receive either ribociclib plus ET (tamoxifen or NSAI depending on previous treatment) plus goserelin ($n = 335$) or placebo plus ET plus goserelin ($n = 337$; ref. 43). The trial demonstrated that PFS was significantly prolonged with the addition of ribociclib to ET plus goserelin (median PFS 23.8 vs. 13.0 months, HR 0.55, $P < 0.0001$; ref. 43). In addition, PFS subgroup analysis showed a benefit for adding ribociclib to both ET partners; tamoxifen ($n = 177$) had an HR of 0.59 [95% confidence interval (CI) 0.39–0.88] and NSAI ($n = 495$) had a HR of 0.57 (95% CI, 0.44–0.74; ref. 43). The safety profile of the ribociclib combinations was manageable, and was similar to other studies of ribociclib (Table 1). Furthermore, addition of ribociclib to ET plus goserelin improved HRQoL (as assessed by delayed deterioration of patient-reported HRQoL and improved pain scores; ref. 43). Although addition of a CDK4/6 inhibitor to first-line ET in the postmenopausal advanced disease setting maintains HRQoL compared with placebo, such an improvement in health status during treatment compared with placebo has not been observed (44, 45). It has been found that pain is detrimental to the quality of life of patients with breast cancer, particularly those with ABC (46). Consequently, the clinically meaningful decrease in pain scores in women treated with ribociclib in MONALEESA-7 could represent a treatment breakthrough. Consistent with this, ribociclib received Breakthrough Therapy designation from the FDA for initial treatment of pre- or perimenopausal women with HR⁺, HER2⁻ ABC, based on the MONALEESA-7 data (47).

Tamoxifen with OFS. The evidence supporting use of tamoxifen plus OFS (GnRHa) comes from a meta-analysis published in

Figure 1.

Insights for possible treatment sequence for premenopausal women with HR⁺, HER2⁻ advanced breast cancer (not all treatments approved by the FDA). ^aRecommended in ASCO and ABC3, but not NCCN. The FACT trial testing fulvestrant plus anastrozole compared with anastrozole included women receiving OFS in addition to postmenopausal women without OFS (82). ^bThere are no data to support use of a CDK4/6i-based treatment after progression on a CDK4/6i-based treatment. ^c“Up to three” is the number of regimens specified by NCCN. Abbreviations: ABC3, 3rd international guidelines for advanced breast cancer; ASCO, American Society of Clinical Oncology; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; HR⁺, hormone receptor-positive; NCCN, National Comprehensive Cancer Network; NSAI, nonsteroidal aromatase inhibitor; OFS, ovarian function suppression; SERD, selective estrogen receptor degrader; SERM, selective estrogen receptor modulator.

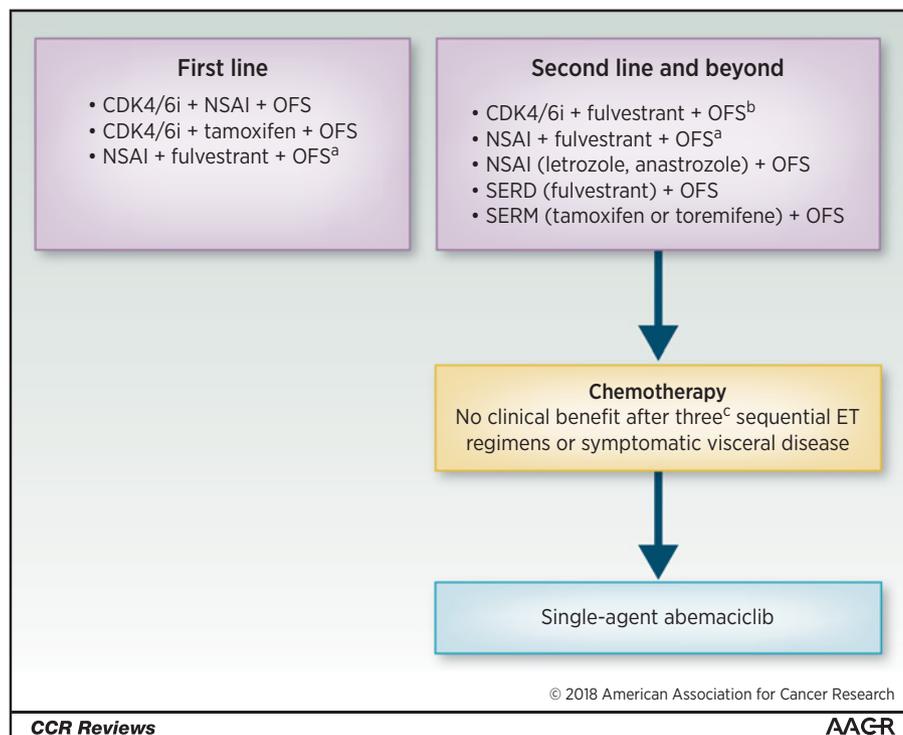


Table 1. Key completed trials in premenopausal women with HR⁺ ABC: first-line ET^a

Study	Description	N ^b	Proportion of patients with HER2 ⁻ disease (%)	Treatments tested	Prior therapies allowed	Results of primary endpoint	Adverse events
CDK4/6 inhibitors MONALEESA-7/NCT02278120 (43)	Phase III; RCT	672	100	Ribociclib + (tamoxifen or NSA) + goserelin vs. placebo + (tamoxifen or NSA) + goserelin	Adjuvant ET/CT and CT for MBC	Median PFS (months): 23.8 ribociclib arm vs. 13.0 placebo arm	>30% all grade (ribociclib arm/ placebo arm) Neutropenia 76%/8% Hot flash 34%/34% Nausea 32%/20% Leukopenia 31%/7%
Tamoxifen EORTC	Meta-analysis: overall (48)	506	NS	GnRHa + tamoxifen vs. GnRHa	Adjuvant ET/CT	Median OS (months): ≈35 combined arm vs. ≈30 GnRHa	NS
	International RCT (79)	318	NS	Goserelin + tamoxifen vs. goserelin	Adjuvant ET/CT	ORR: ^c 38% vs. 31%	>15% ^d either arm (combined arm/ goserelin arm) Hot flashes 72%/74% Vaginal discharge 18%/13% Vaginal soreness 18%/18% NS
AIs Qingdao University (51)	Retrospective	35	83	Buserelin + tamoxifen vs. buserelin vs. tamoxifen	Adjuvant ET/CT	ORR: 48% vs. 28% vs. 34%	NS
				Goserelin + tamoxifen vs. goserelin vs. oophorectomy + tamoxifen vs. oophorectomy	Adjuvant ET/CT	ORR: ^c 45% vs. 27.2% vs. 11.1% vs. 46.6%	>40% ^d any arm Hot flashes 91%/78%/72%/67% Headache 50%/35%/41%/33% Depression 50%/35%/33%/33% Irritability 41%/44%/22%/20%
Chinese Academy of Medical Sciences (54)	Retrospective: first-line subset	52 (n = 36, 1L)	67	Letrozole + goserelin	Adjuvant ET/CT and ET/CT for MBC	First-line subset: CBR: 75.0%	>10% ^e Fatigue 20% Hot flashes 20% Abdominal pain 14% Nausea 11% Hot flashes 15% Nausea 12%

(Continued on the following page)

Table 1. Key completed trials in premenopausal women with HR⁺, ABC: first-line ET³ (Cont'd)

Study	Description	N ^b	Proportion of patients with HER2 ⁻ disease (%)	Treatments tested	Prior therapies allowed	Results of primary endpoint	Adverse events
NCT00186121 (52)	Phase II; single arm	35	91	Anastrozole + goserelin	Adjuvant ET/CT and CT for MBC	ORR: ^f 37.5%	>20% ^g Hot flashes 59% Arthralgia 53% Fatigue 50% Headache 31% Alopecia 25% NS
Nottingham Breast Unit (53) Sun Yat-sen University Cancer Center (50)	Observational Retrospective: case control	36 80	NS 73	Anastrozole + goserelin ET (tamoxifen then AI) + goserelin vs. tamoxifen	NS Adjuvant CT and CT for ABC required, radiotherapy allowed	CBR: ^c 67% Median PFS (months): 27.9 goserelin arm vs. 16.9 tamoxifen	NS NS
Fulvestrant Medical University of Vienna (61)	Observational: first-line subset	26 ^h (n = 8, 1L)	88	Fulvestrant 250 mg + goserelin	Adjuvant ET/CT and ET/CT for MBC	First-line subset: CBR: 87.5%	>10% ^g Hot flashes 15% Joint pain 12%
Ovarian suppression/ablation NCT00293540 (70)	Phase III; RCT	249	NS	Mid-luteal-phase oophorectomy + tamoxifen vs. mid-follicular-phase oophorectomy + tamoxifen	Adjuvant ET/CT	Median OS: 2.14 years mid-luteal vs. 2.00 years mid-follicular	NS
NCT01073865 (69)	Phase III; RCT	222	NS	Tamoxifen + goserelin 10.8 mg (every 12 weeks) vs. tamoxifen + goserelin 3.6 mg (every 4 weeks)	Adjuvant ET/CT	24-week rate of PFS: 62% (10.8 mg) vs. 60% (3.6 mg)	>10% either arm ^d (10.8 mg/3.6 mg) Hot flashes 14%/20% Nasopharyngitis 12%/8%

Abbreviations: 1L, first-line; ABC, advanced breast cancer; AI, aromatase inhibitor; CBR, clinical benefit rate; CT, chemotherapy; EORTC, European Organisation for Research and Treatment of Cancer; ET, endocrine therapy; GnRH_a, gonadotropin-releasing hormone agonist; HR⁺, hormone receptor-positive; MBC, metastatic breast cancer; NS, not stated; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized-controlled trial.

^aData cannot be compared between trials due to differences in study designs and populations. Dose of goserelin was 3.6 mg unless otherwise specified.

^b100% of patients in all studies were either premenopausal or perimenopausal.

^cPrimary endpoint was not stated.

^dGrade not reported.

^eNo grade 3 or 4 adverse events reported.

^fORR = complete response + partial response.

^gNo grade 4 adverse events reported.

^hAn additional four patients who were enrolled in the study did not receive treatment and were not included in the analysis.

2001. The study analyzed data from randomized clinical trials that tested OFS (GnRHa) compared with the selective ER modulator tamoxifen plus OFS; 506 premenopausal women with ABC were included in the meta-analysis and the median follow-up time was 6.8 years (Table 1). There was a significant survival benefit (HR, 0.78; $P = 0.02$), and a significant benefit in PFS (HR, 0.70; $P = 0.0003$), in using combined treatment (48). The largest of the trials included in the meta-analysis reported similar safety profiles for combination treatment compared with GnRHa alone, and no additional safety signals were found for combination treatment in the metastatic setting (48). Tamoxifen remains a commonly prescribed treatment for premenopausal HR⁺ ABC, although these data are more than a decade old (12). In the MONALEESA-7 trial discussed above, addition of ribociclib to tamoxifen plus goserelin significantly prolonged PFS (43). Of note, while studies have demonstrated that tamoxifen plus OFS is better than tamoxifen alone, whether tamoxifen plus a CDK4/6 inhibitor provides greater benefit with OFS than without is unclear, and requires additional investigation as it may obviate the need for OFS in premenopausal patients receiving tamoxifen with a potent CDK4/6 inhibitor.

Aromatase inhibitors with OFS. In the past 10 years, aromatase inhibitors (AI) have largely replaced tamoxifen for the treatment of HR⁺ breast cancer in postmenopausal patients. However, in premenopausal women, estrogen continues to be produced by the ovaries, rendering AIs less effective (49). Thus, OFS is required for use of AIs for premenopausal women (11, 12, 37). The American Society of Clinical Oncology (ASCO) guidelines state that premenopausal women who develop metastatic disease while on or within 12 months of adjuvant tamoxifen treatment should be switched to an AI plus GnRHa (12). It is interesting to note that in MONALEESA-7 the median PFS of ribociclib plus NSAI was 27.5 months, while the median PFS of ribociclib plus tamoxifen was 22.1 months; however, comparison of NSAI with tamoxifen was not the intent of the study and so caution must be taken with any interpretation (43). A retrospective study examining ET with/without OFS directly after chemotherapy for metastatic breast cancer reported a median PFS of 27.9 months for AI plus OFS and 16.9 months for tamoxifen ($N = 80$; ref. 50).

Four single-arm studies have investigated the use of AI plus OFS for first-line treatment of HR⁺ ABC in premenopausal women (Table 1). The combination of letrozole or anastrozole plus goserelin in the first-line setting resulted in median PFS/time to progression (TTP) ranging from 8.3 months to 12 months; however, patient numbers were small ($n = 35$ each) and none of the studies were randomized (51–54). The results of the MONALEESA-7 trial showed that the addition of ribociclib to NSAIs plus goserelin is superior to the ET combination alone, (43) and these results may change the first-line treatment option for premenopausal women.

Treatment options following progression on ET

ET with targeted therapy (CDK4/6 inhibitors). No randomized trial has investigated CDK4/6 inhibitors for second-line therapy and beyond specifically in premenopausal HR⁺ breast cancer. However, two large phase III trials investigating CDK4/6 inhibitors combined with fulvestrant for treatment of HR⁺, HER2⁻ ABC in patients whose disease had progressed on ET, allowed enrollment of premenopausal women provided they also used

GnRHAs. In the phase III, randomized PALOMA-3 trial, addition of palbociclib to fulvestrant led to a significant improvement in median PFS in the approximately 20% of patients who were premenopausal (9.5 vs. 5.6 months, HR 0.50, $P = 0.013$; $n = 108$; ref. 55). Nearly half of all patients enrolled in PALOMA-3 had received prior treatment with both tamoxifen and AIs, and in the premenopausal subset there was a greater proportion of patients in the palbociclib arm who had received two or more lines of therapy for advanced disease than in the placebo arm (41.7% vs. 27.8%, respectively; ref. 55). MONARCH-2 investigated the combination of abemaciclib plus fulvestrant (and GnRHa in premenopausal women) versus placebo plus fulvestrant (17). The HR for PFS in the premenopausal population ($n = 114$, 17% of study population) favors abemaciclib plus fulvestrant over placebo (0.415, 95% CI, 0.246–0.698; ref. 17), additional results are pending. Of note, all the patients enrolled in the PALOMA-3 and MONARCH-2 trials were CDK4/6 inhibitor treatment naïve, and the role of CDK4/6 inhibitor in patients who have disease progression on a prior CDK4/6 inhibitor is unclear.

AIs. Two single-arm, phase II clinical trials have investigated AIs plus goserelin for the treatment of HR⁺ ABC in premenopausal women whose disease had progressed on ET, and a further two observational and two retrospective trials have been performed (Table 2). As in the first-line setting, numbers of patients included have been small (range 13–52), and no head-to-head comparisons in a randomized setting have been completed. Although it is not possible to compare across studies due to differences in design and patient populations, median PFS of premenopausal patients receiving AIs plus goserelin in the post-ET setting has been similar to median PFS seen in the first line in this patient population. Median PFS/TTP for letrozole or anastrozole or exemestane (all with goserelin) ranged from 7.3 months to 13 months (54, 56–58); the longest PFS was seen with use of exemestane in a mixed population receiving the treatment in the first or second line (57). Prior tamoxifen treatment was allowed in all these studies.

Fulvestrant. The selective ER degrader fulvestrant is indicated for the treatment of HR⁺, HER2⁻ locally advanced or metastatic breast cancer in postmenopausal women who have not previously received ET, or who have disease progression on ET. It is also approved for treatment of HR⁺, HER2⁻ ABC in combination with palbociclib or abemaciclib in women whose disease progressed after ET; the recommended dose is 500 mg (59, 60).

To our knowledge, there are no randomized trials that have evaluated efficacy of single-agent fulvestrant (with/without OFS) versus AI or tamoxifen in premenopausal women with HR⁺ breast cancer. However, small studies have investigated efficacy of fulvestrant with OFS in patients who had previously received tamoxifen or AIs. One small single-arm study ($n = 26$) reported that fulvestrant 250 mg combined with goserelin resulted in a clinical benefit rate of 58% in patients who had previously received tamoxifen or AIs for early or advanced breast cancer (Table 2; ref. 61). The subset of patients receiving treatment in the first line also showed a promising clinical benefit rate, although the numbers are very small ($n = 8$; Table 1). Additional data on the use of fulvestrant 500 mg plus goserelin in the post-ET setting can be taken from the placebo arm of PALOMA-3, as discussed above.

Table 2. Key completed trials including premenopausal women with HR⁺, ABC, treatment following progression on ET^a

Study	Line of ET treatment for ABC	Description	N	Proportion of premenopausal patients (%)	Proportion of patients with HER2 disease (%)	Treatments tested	Prior therapies allowed	Results of primary endpoint	Adverse events
CDK4/6 inhibitors MONARCH-2/ NCT02107703 (17)	1-2	Phase III; RCT	669	17% (n = 114)	100	Abemaciclib + fulvestrant + GnRHa vs. fulvestrant + GnRHa	Adjuvant ET/CT, IL ET or CT for ABC	PFS hazard ratio for abemaciclib vs. placebo: ^b 0.415 95% CI 0.246-0.698	Results in the premenopausal population have not yet been published
PALOMA-3/ NCT01942135 (55)	1-2+	Phase III; RCT	521	21% (n = 108)	100	Palbociclib + fulvestrant + goserelin vs. placebo + fulvestrant + goserelin	Adjuvant ET/CT, ET for ABC, IL CT for ABC	Median PFS (months): ^c 9.5 palbociclib arm vs. 5.6 placebo arm	>30% all grade (palbociclib arm/ placebo arm) ^d Neutropenia 86%/6% Leukopenia 56%/3% Infections 48%/33% Nausea 41%/36% Stomatitis 37%/17% Fatigue 35%/31%
AI Chinese Academy of Medical Sciences (54)	1-2	Retrospective	52	100	67	Letrozole + goserelin	Adjuvant ET/CT and ET/CT for MBC	Overall: ORR: ^e 21.1% CBR: 71.1% Second-line subset: CBR: 56.3%	>10% ^f Hot flashes 15% Nausea 12%
JMTO BC08-01 (56)	1-2	Phase II	37	100	97	Anastrozole + goserelin	Tamoxifen + GnRHa, CT for EBC or MBC	ORR: ^e 18.9%	>15% ^f Hot flashes 24% Sweating 19% Joint pain 16% NS
Nottingham Breast Unit (81)	2	Observational	16	100	NS	Anastrozole + goserelin for MBC	Tamoxifen + goserelin for MBC	ORR: ^{e,g} 75%	>20% ^h Hot flashes 55% Arthralgia 52% Fatigue 39% Myalgia 21% NS
ChiCTR-ONC-13003946 (57)	1-2	Phase II	44	100	89	Exemestane + goserelin	Adjuvant ET/CT and ET/CT for MBC	Median PFS (months): 13	
Nottingham Breast Unit (53)	2+	Observational	13	100	NS	Exemestane + goserelin	Anastrozole + goserelin for ABC required, prior tamoxifen allowed	CBR: ^a 38%	
Kyushu University (58)	2	Retrospective	14	100	100	AI + GnRHa	Tamoxifen + GnRHa, CT for EBC or MBC	CBR: 71.4%	>10% ^h Decrease in joint range of motion 21% Hot flashes 14% Headache 14%

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Table 2. Key completed trials including premenopausal women with HR⁺ ABC: treatment following progression on ET^a (Cont'd)

Study	Line of ET treatment for ABC	Description	N	Proportion of premenopausal patients (%)	Proportion of patients with HER2 ⁻ disease (%)	Treatments tested	Prior therapies allowed	Results of primary endpoint	Adverse events
Fulvestrant Medical University of Vienna (61)	1-3+	Observational	26 ^b	100	88	Fulvestrant 250 mg + goserelin	Adjuvant ET/CT and ET/CT for MBC	CBR: 57.7%	>10% ^h Hot flashes 15% Joint pain 12%
Ovarian suppression/ablation Seoul National University Hospital (63)	1-4	Retrospective	66	100	100	NSAI + BSO vs. NSAI + GnRHa	Not restricted	Median PFS (months): 17.2 BSO vs. 13.3 GnRHa	NS

Abbreviations: 1L, first-line; ABC, advanced breast cancer; AI, aromatase inhibitor; BSO, bilateral-salpingo oophorectomy; CBR, clinical benefit rate; CI, confidence interval; CT, chemotherapy; EBC, early breast cancer; ET, endocrine therapy; GnRHa, gonadotropin-releasing hormone agonist; HR⁺, hormone receptor-positive; MBC, metastatic breast cancer; NS, not stated; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; PFS, progression-free survival; RCT, randomized-controlled trial.

^aData cannot be compared between trials due to differences in study designs and populations. Dose of goserelin was 3.6 mg unless otherwise specified.

^bHazard ratio for premenopausal population is presented; however, the primary endpoint of MONARCH-2 was PFS in the intention-to-treat population of the entire study.

^cPFS for premenopausal population is presented; however, the primary endpoint of PALOMA-3 was PFS in the intention-to-treat population of the entire study.

^dAdverse events are from the premenopausal subgroup of the study.

^eORR = complete response + partial response.

^fNo grade 3 or 4 adverse events reported.

^gPrimary endpoint was not stated.

^hNo grade 4 adverse events reported.

ⁱAn additional four patients who were enrolled in the study did not receive treatment and were not included in the analysis.

OFS

The ASCO guidelines for the treatment of HR⁺ metastatic breast cancer with ET state unequivocally that OFS should be used in premenopausal patients and that there are no clinically important data for using ET without OFS in women who remain premenopausal (12).

OFS with GnRHAs versus surgical oophorectomy. OFS with GnRHa is considered equivalent to surgical oophorectomy based on a previous phase III trial comparing the two treatments in premenopausal women with HR⁺ metastatic breast cancer (12, 37). There were no significant differences in overall survival or failure-free survival for either the goserelin or oophorectomy arms; median survival was 37 months and 33 months, respectively (HR 0.80; 95% CI, 0.53–1.20; ref. 62). While in the past, surgical oophorectomy was associated with morbidity due to surgical complications, advances in laparoscopic surgery have decreased the invasiveness and related complications of the procedure (63).

Incomplete OFS while using GnRHAs has been reported from multiple early and advanced breast cancer studies (52, 63, 64). However, it is difficult to compare data from individual studies as the tests used to measure estradiol vary in sensitivity (11, 12). Most studies do not routinely measure estradiol, follicle-stimulating hormone (FSH), or luteinizing hormone, and even if they did, there is no consensus on the optimal level of hormones for ET (12). The SOFT/TEXT early breast cancer studies have raised concerns over incomplete OFS during adjuvant treatment (38, 65), and the NCCN guidelines for early breast cancer have now taken this into account by specifying particular subgroups of patients (based on risk categories and previous treatments) for whom OFS would likely benefit the most (37). The latest data show that toxicity is worse with the addition of OFS to tamoxifen; however, both analyses of SOFT or SOFT/TEXT support the use of adjuvant OFS for some women (66, 67). It remains to be seen whether these findings will impact future treatment guidelines for ABC.

Frequency of GnRHa administration. Because of the lack of data at the time of publication, current guidelines recommend monthly administration of GnRHAs over 3-monthly regimens (11, 12, 37). However, injection of goserelin can be a painful procedure and monthly painful procedures could impact treatment adherence (68, 69). The results of a phase III, noninferiority study (NCT01073865, Table 1) of monthly (3.6 mg) versus 3-monthly (10.8 mg) injections of goserelin (plus tamoxifen) in 222 premenopausal women showed no difference in 24-week PFS rate in either arm, supporting use of 3-monthly injections (69). In addition, both goserelin regimens resulted in similar mean serum estradiol concentrations (20.3 pg/mL for 10.8 mg goserelin and 24.8 pg/mL for 3.6 mg; ref. 69). In a retrospective study not restricted to line (Table 2), oophorectomy plus an NSAI was compared with a GnRHa plus NSAI in 66 premenopausal women with metastatic disease (63). Although there was no statistical significance, median PFS was numerically higher in women treated with oophorectomy compared with those treated with a GnRHa (17.2 vs. 13.3 months, respectively $P = 0.245$; ref. 63). In addition, 9 of 19 patients who received a GnRHa plus NSAI, and had hormone levels assessed at the time of disease progression, had FSH and estradiol in the premenopausal range (63). The authors noted that premenopausal patients with advanced disease who wish to avoid painful injections of GnRHAs might

Table 3. Ongoing clinical trials including premenopausal women with HR⁺, HER2⁻ ABC^a

Study name/ID	Phase	N ^b	Patient population	Line of ET treatment for ABC	Treatments tested ^c	Primary endpoint	Secondary endpoints	Recruiting status ^a
Studies dedicated to premenopausal women								
FATIMA/NCT02917005	II	160	Premenopausal women	1	Palbociclib + exemestane + goserelin vs. exemestane + goserelin	PFS	ORR, CBR, OS, safety	Not yet recruiting
NCT02592746	II	122	Premenopausal women	1	Palbociclib + exemestane + GnRHa OR capecitabine	PFS	NS	Recruiting
LEO/NCT02344550	II	137	Premenopausal women	1-2	Everolimus + letrozole + leuporelin vs. letrozole + leuporelin	PFS	ORR, CBR, OS, safety	Recruiting
PEER/NCT02990845	I/II	25	Premenopausal women	1-2	Pembrolizumab (PD-1 antibody) + exemestane + leuprolide	PFS rate at 8 months	Safety, CBR, ORR, DoR	Not yet recruiting
Studies including premenopausal women								
ComplEEment-1/NCT02941926	III	3,000	Males, and pre- and postmenopausal women	1	Ribociclib + letrozole + goserelin	Safety and tolerability	TTP, ORR, CBR, HRQoL	Recruiting
CLEE01XDE01/NCT03096847	III	500	Males, and pre- and postmenopausal women	1	Ribociclib + letrozole + goserelin	CBR	PFS, OS, ORR, HRQoL	Recruiting
PALINA/NCT02692755	II/III	35	Black, African, or African-American women aged ≥18 years ^d	1	Palbociclib + letrozole	Hematologic safety	CBR, dose adjustments due to neutropenia	Recruiting

Abbreviations: ABC, advanced breast cancer; CBR, clinical benefit rate; DoR, duration of response; GnRHa, gonadotropin-releasing hormone agonist; HR⁺, hormone receptor–positive; HRQoL, health-related quality of life; NS, not stated; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; TTP, time to progression.

^aClinicalTrials.gov accessed on December 21, 2017.

^bEstimated study enrollment.

^cTreatments listed in the table are for premenopausal women enrolled in the studies. Treatments for other patient populations not listed.

^dThis trial does not specify menopausal status of eligible women and so was assumed to allow enrollment of premenopausal women, since no restrictions were stated.

consider laparoscopic oophorectomy, and that patient preference for treatment should be taken into consideration (63).

Timing of oophorectomy. Given the uncertainty over the effect that timing of the oophorectomy during the menstrual cycle had on the long-term outcomes, a phase III trial (NCT00293540, Table 1) compared mid-luteal phase and mid-follicular phase oophorectomy, followed by tamoxifen as first-line treatment in 249 premenopausal women with HR⁺ ABC (70). The trial demonstrated that there were no significant differences in overall survival or PFS in the two arms of the study (70).

Ongoing Clinical Trials That Include Premenopausal Women

Multiple trials of targeted treatment for HR⁺, HER2⁻ ABC in premenopausal women have been initiated; however, most are phase I or phase II. Of the four ongoing trials dedicated to premenopausal women, two phase II studies are investigating palbociclib plus exemestane in the first line, one phase II study is investigating everolimus plus letrozole in the first and second lines, and one phase I/II study is investigating pembrolizumab (PD-1 antibody) plus exemestane in the first and second lines, and all require a GnRHa (Table 3). Currently, three phase III trials of interventions for HR⁺, HER2⁻ ABC allow enrollment of premenopausal women; two are investigating ribociclib plus letrozole plus goserelin; and one is investigating palbociclib plus letrozole (Table 3). A further 10 ongoing phase II studies allow enrollment of premenopausal women; combinations include CDK4/6 inhibitors plus AIs or fulvestrant, the PI3K inhibitor buparlisib plus tamoxifen, and the mTOR inhibitor everolimus plus ET. Most of these studies require a GnRHa.

Future Perspectives

Although the guideline recommendations state ET as the preferred first-line treatment for HR⁺, HER2⁻ ABC (11, 12), in routine practice up to 43% of all patients with HR⁺, HER2⁻ ABC are receiving first-line chemotherapy (71, 72). This proportion increased to 59% for premenopausal women in one study (71), despite worse outcomes being reported with first-line chemotherapy compared with ET (72). The lack of data from phase III clinical trials for the treatment of premenopausal women could be contributing to this discrepancy between treatment recommendation in expert guidelines and real-world practice. The results of the MONALEESA-7 trial are a significant advancement in treatment for premenopausal women with HR⁺, HER2⁻ ABC; the median PFS of 23.8 months in the ribociclib arm is the longest reported PFS in a prospective trial in this patient population and the treatment benefit of adding ribociclib was consistent across patient subgroups. These data, along with those from a subset of premenopausal patients in the PALOMA-3 and MONARCH-2 trials, show there is a clear benefit of adding a CDK4/6 inhibitor to ET for the premenopausal population.

However, there are several unanswered questions. First, the role of CDK4/6 inhibitors in patients who have disease progression on a prior CDK4/6 inhibitor is unclear and may require careful consideration of second-line options if resistance to CDK4/6 inhibitors occurs, such as with the development of acquired *RB1* mutations (73). Second, whether OFS is needed when combining a potent CDK4/6 inhibitor with tamoxifen or fulves-

Table 4. Ongoing phase III clinical trials including premenopausal women with HR⁺, HER2⁻ EBC^a

Study name/ID	Phase	N ^b	Patient population	Line of ET treatment for EBC	Treatments tested	Primary endpoint	Secondary endpoints	Recruiting status ^a
PENELOPE-B/NCT01864746	III	1,250	Pre- and postmenopausal women	1	Palbociclib + ET vs. placebo + ET	iDFS	iDFS excluding second non-breast cancers, DDFS, OS, safety, PROs, QALY, PK	Ongoing, not recruiting
RxPONDER/NCT01272037	III	10,000	Women aged ≥ 18 years ^c	1	Tamoxifen, anastrozole, letrozole, or exemestane with or without CT	Recurrence score	DDFS, local disease-free interval, OS, toxicity	Ongoing, not recruiting
NCT01674140	III	1,900	Males, and pre- and postmenopausal women	1	ET + everolimus vs. placebo + ET	iDFS	OS, DRFS, toxicity	Recruiting
NCT02535221	III	234	Premenopausal women 35–55 years old	1	Goserelin + tamoxifen + AI vs. epirubicin + CTX + 5-FU	Ultrasound response rate	Pathologic response rate	Recruiting
PALLAS/NCT02513394	III	4,600	Males, and pre- and postmenopausal women	1–2	Palbociclib vs. ET	iDFS	Safety, DRFS, locoregional RFS, OS	Recruiting

Abbreviations: 5-FU, 5-fluorouracil; AI, aromatase inhibitor; CT, chemotherapy; CTX, cyclophosphamide; DDFS, distant disease-free survival; EBC, early breast cancer; ET, endocrine therapy; HR⁺, hormone receptor–positive; iDFS, invasive disease-free survival; OS, overall survival; PK, pharmacokinetics; PROs, patient-reported outcomes; QALY, quality-adjusted life-years; RFS, recurrence-free survival.

^aClinicalTrials.gov accessed on December 21, 2017.

^bEstimated study enrollment.

^cThis trial does not specify menopausal status of eligible women and so was assumed to allow enrollment of premenopausal women, since no restrictions were stated.

trant is currently unclear, and needs investigation in additional clinical trials. Third, the pattern of disease progression in premenopausal women with ABC is different with a higher prediction for brain metastasis, and this could impact therapeutic selection and efficacy (74). Fourth, while immunotherapy agents such as checkpoint inhibitors have not shown much success in HR⁺ breast cancer, the role of these agents in premenopausal ABC is unclear. Studies such as the ongoing PEER trial investigating pembrolizumab will be important to determine the potential future role for immunotherapies (Table 3). Fifth, the role of observed differences in the biology of premenopausal tumors on the impact of treatment outcome is currently unknown. As mentioned before, premenopausal breast cancer has a different gene expression, somatic mutation, and methylation profile than postmenopausal breast cancer (25, 26), and this could impact the efficacy and safety of targeted agents; more information is needed to understand the clinical impact of these differing genomic profiles. Although one study found a significant correlation with *ESR1* methylation and everolimus treatment outcome, the remarkable similarity in the results of CDK4/6 inhibitors plus ET in pre- and postmenopausal women indicates that for this class of agents, treatment success may be independent of major differences in tumor biology in genomically unselected premenopausal women (17, 43, 55, 75). This may not be the case for all treatments and further research is needed to understand the biological determinants of treatment outcome. Finally, use of CDK4/6 inhibitors may also move into adjuvant therapy for premenopausal women with HR⁺, HER2⁻ early breast cancer, as several phase III trials that include premenopausal women have been initiated (Table 4). However, the earliest anticipated completion date for studies investigating CDK4/6 inhibitors is 2020, so it may take some time for adjuvant use to be approved.

CDK4/6 inhibitors are the greatest breakthrough in the treatment of HR⁺, HER2⁻ ABC since the approval of the mTOR inhibitor everolimus. However, novel treatment strategies are still required for when progression occurs on the currently available therapeutic options and to extend the survival of patients. PI3K inhibitors and immunotherapies are currently under investigation in breast cancer, and could enter the treatment landscape in the future (76, 77). Chimeric antigen receptor-modified T cells directed against c-Met were recently tested in patients with metastatic breast cancer in a proof-of-concept study (2 of the 6

patients in the study had HR⁺, HER2⁻ disease; ref. 78). Histologic evaluations of tumors from 2 patients showed extensive tumor necrosis at the injection site, and a phase I study (NCT03060356) is now underway (78). Although the current advances are promising, to save the lives of premenopausal women with ABC, new targets must be uncovered and new treatment strategies should be specifically tested in premenopausal women.

Conclusions

Treatment options for premenopausal women with HR⁺, HER2⁻ ABC are expanding, and results from trials of CDK4/6 inhibitors may effect a paradigm shift. The results of MONALEESA-7 demonstrate significant gains in PFS with ribociclib added to goserelin and ET (43). The safety profile of CDK4/6 inhibitors in premenopausal women appears to be manageable, with discontinuations due to AEs occurring in just 4% of patients receiving ribociclib plus ET and 6% of patients receiving palbociclib plus fulvestrant, compared with 3% and 0% of patients in the placebo arms, respectively. These data have clear implications for treatment decisions, and provide evidence for a new standard of care in premenopausal women. The flexibility of the ET partner gives premenopausal women more treatment choices, allowing a customized plan that can take patient preference as well as tumor biology into consideration, thus offering a true personalized and precision oncology approach.

Disclosure of Potential Conflicts of Interest

A. Bardia reports receiving a commercial research grant from Biothernostics and is a consultant/advisory board member for Genentech, Immunomedics, Merck, Novartis, Pfizer, Radius Health, and Spectrum Pharma. S. Hurvitz reports receiving commercial research grants from Amgen, Bayer, Biomarin, Boehringer Ingelheim, Cascadian, Dignatana, Genentech/Roche, GlaxoSmithKline, Lilly, MacroGenics, Medivation, Merrimack, Novartis, OBI Pharma, Pfizer, PUMA, and Seattle Genetics. No other potential conflicts of interest were disclosed.

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