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SUPPLEMENT ARTICLE

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Optimizing care for younger women with hormone receptor-positive, HER2-negative metastatic breast cancer

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Abstract

Treatment strategies for hormone receptor-positive (HR^+), human epidermal growth factor receptor 2-negative ($HER2^-$) metastatic breast cancer in young women (<40 years at diagnosis) have traditionally been extrapolated from data obtained from trials conducted either exclusively or predominantly in the postmenopausal setting. These young patients are usually treated with ovarian function suppression (OFS) + endocrine therapy (ET) ± targeted therapy, except if there is a concern about endocrine resistance or a need to gain rapid disease control due to the onset of visceral crisis. This review examines evidence that supports the use of a cyclin-dependent kinase 4/6 inhibitor, in combination with OFS and ET, when treating premenopausal or perimenopausal women with $HR^+/HER2^-$ metastatic breast cancer. This includes data from the MONALEESA-7 study (treating only premenopausal/perimenopausal women in the first-line setting), and the results of subgroup analyses from the PALOMA-3 and MONARCH-2 trials. We also consider a number of age-specific challenges that younger breast cancer patients can face, highlighting the importance of a multidisciplinary approach to ongoing care.

KEYWORDS
CDK4/6 inhibitor, endocrine therapy, HER2-negative, hormone receptor-positive, metastatic breast cancer, psychosocial, supportive care, younger women

1 | INTRODUCTION

In Australia, each year approximately 5% of women diagnosed with breast cancer are less than 40 years of age at the time of their diagnosis.[1] Breast cancer in these younger women can be more complex to treat than breast cancer in older women. Younger women are more likely to present with aggressive, higher-grade and more advanced-stage disease and tend to have poorer prognoses.[2–7] Due to their age, younger women with breast cancer also often have to contend with a variety of other challenges or concerns (e.g. the development of treatment-related menopausal symptoms and/or loss of fertility; concerns about the impact of their diagnosis and treatment on relationships, their ability to parent young children and/or continue to work), which may necessitate additional assessment, monitoring and support.[2,3,5,6,8–11]

The fact that younger patients are likely to have more advanced disease at diagnosis may be partly due to later diagnoses. A delayed diagnosis can be due to a number of factors, including the absence of routine screening for healthy, average-risk young women; the presence of a low index of suspicion on the part of patients and/or their primary

healthcare providers; and the denser nature of breast tissue in younger women, which makes it more difficult to detect breast cancer via mammography or ultrasound.[2,4,6,11]

The tendency for breast cancer to be more aggressive in younger patients and so more difficult to treat than in older patients is consistent with evidence that breast cancer may be biologically different in younger women.[12,13] For example, at a molecular level, it is known that younger women are more likely to harbor germline BRCA1 or BRCA2 mutations than older individuals with the disease;[12,13] and, more recently, estrogen receptor-positive (ER^+) tumors from premenopausal patients have been found to be molecularly distinct from ER^+ tumors from postmenopausal patients, in terms of gene expression, DNA methylation, copy number and somatic mutation patterns.[6,14]

The impact that pregnancy may have on breast cancer outcomes is another important consideration. Patients diagnosed with breast cancer either during or shortly after pregnancy tend to have poorer prognoses.[13,15] It is possible that the hormonal milieu and large increase in female sex hormones during pregnancy modulates the breast microenvironment in a way that stimulates more aggressive tumor growth.[13] An alternative hypothesis is that the processes of breast involution that occur following childbirth result in more aggressive breast cancer biology.[13]

The relationship between younger age and worse breast cancer outcomes appears to be particularly evident among women with luminal (hormone receptor-positive; HR^+) breast cancers[2,12,16] and the majority of breast cancers among women aged <40 years are luminal cancers (luminal A or luminal B).[6,12] In this review, we summarize current treatment recommendations for younger patients who have been diagnosed with HR^+, human epidermal growth factor receptor 2-negative ($HER2^-$) metastatic breast cancer, drawing particular attention to recently reported phase III clinical trial data that support the use of a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor, in combination with endocrine therapy (ET) and ovarian function suppression (OFS), when treating such individuals in the first-line metastatic setting (Table 1). We also discuss some of the age-specific considerations that need to be kept in mind when managing younger breast cancer patients, and emphasize the importance of utilizing a multidisciplinary approach in their ongoing care.

2 | RECOMMENDED APPROACHES TO TREATMENT

The key goals when treating younger women with $HR^+/HER2^-$ metastatic breast cancer are not only to prolong survival, but also to delay disease progression, optimize symptom control and minimize treatment-related toxicity, thereby helping patients maintain an acceptable quality of life (QoL).[2,17,18] This helps patients continue to do the things they want to do, and need to do, for themselves and the people around them, for as long as possible. It is notable that QoL scores have been shown to have prognostic value in the treatment of premenopausal women with metastatic breast cancer, with better mood and physical wellbeing being significantly associated with longer survival.[6,19]

A key strategy when seeking to maintain or improve a patient's QoL is to delay disease progression, as disease progression in patients with metastatic breast cancer is likely to be associated with an increase in symptoms, a decline in physical function and/or psychological distress, thereby negatively affecting health-related QoL.[20] There are data suggesting that an important independent predictor of anxiety in this clinical setting is a patient's physical symptom burden.[21] Thus, minimizing patients' symptoms, by delaying disease progression, may not only help them feel better physically, but also psychologically; at least in terms of the level of anxiety they may be experiencing.

A further way to help patients with metastatic breast cancer maintain an acceptable QoL is to minimize treatment-related toxicity and associated adverse events.

2.1 | First-line therapy for advanced $HR^+/HER2^-$ breast cancer

ET remains the preferred first-line treatment for advanced $HR^+/HER2^-$ breast cancer, unless there is concern about endocrine resistance or a need to gain rapid disease control due to the onset of visceral crisis.[2,6,22,23] Adding a targeted therapy to ET has been shown to improve efficacy and delay the development of endocrine resistance.[6,22,23] Targeted therapies include CDK4/6 inhibitors (ribociclib, palbociclib and abemaciclib), the mTOR inhibitor everolimus and the phosphatidylinositol 3-kinase (PI3K) inhibitor alpelisib (approved for use in combination with fulvestrant as a treatment for postmenopausal women and men with $HR^+/HER2^-$, PIK3CA-mutated metastatic breast cancer, after progression on or after an endocrine-based regimen).[6,23,24]

The development of potent, selective, orally bioavailable CDK4/6 inhibitors has transformed the care of patients with advanced $HR^+/HER2^-$ breast cancer.[6,25,26] Each of the available CDK4/6 inhibitors – ribociclib, palbociclib and abemaciclib – has been shown to be effective and generally well tolerated when used in combination with ET in both the first-line[25–34] and second-line settings.[25–28,33–38] Combining CDK4/6 inhibitors with ET is now the standard first-line treatment option for these patients and may also be considered a standard option in the second-line setting (i.e. for patients who have previously received ET alone in the first-line setting), given the significant improvements in PFS that have been observed among patients in key clinical trials of this combination.[22,27,28] Importantly, there is now evidence that combining CDK4/6 inhibitors with ET improves overall survival when treating patients with $HR^+/HER2^-$ metastatic breast cancer.[36,37,39]

The preferred endocrine partner when using CDK4/6 inhibitor therapy in the first-line setting is typically a nonsteroidal aromatase inhibitor. However, the demonstrated efficacy of CDK4/6 inhibitor + fulvestrant therapy when used to treat advanced $HR^+/HER2^-$ breast cancer, including overall survival data from the MONALEESA-3 and MONARCH-2 studies (which each enrolled patients in the first- or

TABLE 1 Phase III clinical trials of CDK4/6 inhibitor therapy that included pre/perimenopausal patients with advanced HR$^+$/HER2$^-$ breast cancer[32,34,35,37–39,47,48]

Study	Population	Median PFS	Median overall survival[a]
First-line setting			
MONALEESA-7[32,39] NSAI or tamoxifen[b] + Ribociclib or placebo + Goserelin	*N* = 672 premenopausal or perimenopausal patients First-line (could have had first-line of chemotherapy for aBC)	Overall cohort[32] 23.8 months *vs* 13.0 months HR = 0.55 (95% CI, 0.44–0.69) *P* < 0.0001	Overall cohort[39] NE months *vs* 40.9 months HR = 0.71 (95% CI, 0.54–0.95) *P* = 0.00973
Second-line setting			
MONARCH-2[34,37,47] Fulvestrant + Abemaciclib or placebo (pre/perimenopausal patients also received goserelin)	*N* = 669, including 134 premenopausal or perimenopausal patients First-line or second-line (relapsed on neoadjuvant ET or on/within 1 year of adjuvant ET; or progressed on first-line ET) No chemotherapy for aBC; not more than 1 ET for aBC	Overall cohort[34] 16.4 months *vs* 9.3 months HR = 0.553 (95% CI, 0.449–0.681) *P* < 0.001 Pre/perimenopausal[47] NR months *vs* 10.5 months HR = 0.446 (95% CI, 0.264–0.754) *P* = 0.002	Overall cohort[37] 46.7 months *vs* 37.3 months HR = 0.757 (95% CI, 0.606–0.945) *P* = 0.01
PALOMA-3[35,38,48] Fulvestrant + Palbociclib or placebo (pre/perimenopausal patients also received goserelin)	N = 521, including 108 premenopausal or perimenopausal patients 2nd-line (relapsed or progressed during prior ET) Patients were allowed to have received 1 prior line of chemotherapy for aBC	Overall cohort[38] 11.2 months *vs* 4.6 months HR = 0.50 (95% CI, 0.40–0.62) *P* < 0.0001 Pre/perimenopausal[48] 9.5 months *vs* 5.6 months HR = 0.50 (95% CI, 0.29–0.87) *P* = 0.013	Overall cohort[38] 34.9 months *vs* 28.0 months[c] HR = 0.81 (95% CI, 0.64–1.03) *P* = not significant

NOTE: This table presents data from three different clinical trials.
Abbreviations: aBC, advanced breast cancer; ET, endocrine therapy; HR, hazard ratio; NE, not estimable; NSAI, nonsteroidal aromatase inhibitor.
[a] Median follow up for overall survival analyses: 34.6 months in MONALEESA-7;[39] 47.7 months in MONARCH-2;[37] 44.8 months in PALOMA-3.[38]
[b] Ribociclib is not indicated for concomitant use with tamoxifen.
[c] Median overall survival = 39.7 months *vs* 29.7 months among subset of 410 patients deemed sensitive to previous endocrine therapy (HR = 0.72; 95% CI, 0.55–0.94); sensitivity to previous endocrine therapy was defined as either a documented clinical benefit (complete response, partial response or stable disease for ≥24 weeks) from ≥1 previous endocrine therapy regimen in the context of metastatic disease or the receipt of ≥24 months of adjuvant ET before recurrence.[38]

second-line settings), suggest that combining a CDK4/6 inhibitor with fulvestrant may also be an appropriate first-line option to consider in certain situations, such as when a patient has progressed on adjuvant aromatase inhibitor therapy.[33,34,36,37,40]

2.2 | Specific advice regarding the treatment of younger patients

International consensus guidelines recommend that the treatment for HR$^+$ metastatic breast cancer in young women (aged < 40 years at diagnosis) should be similar to the treatment that would be recommended for postmenopausal women with the same type and extent of disease, provided the patient has been rendered chemically or surgically postmenopausal.[2,22,41] This is largely because younger, premenopausal women with advanced HR$^+$ breast cancer have been excluded from, or underrepresented in, clinical trials of treatment for advanced HR$^+$ breast cancer.[2,6,23] As a result, recommended treatment strategies have had to be extrapolated from data obtained from trials conducted either exclusively or predominantly in the postmenopausal setting.[6,23]

The currently recommended first-line treatment for HR$^+$ metastatic breast cancer in young women, even in the presence of visceral disease, is OFS (or oophorectomy) + ET ± targeted therapy, unless there is concern about endocrine resistance or a need to gain rapid disease control due to the onset of visceral crisis (severe organ dysfunction and/or rapid progression of disease with the threat of impending organ dysfunction).[2,22,41] This recommended "endocrine therapy first" approach reflects the lack of evidence that chemotherapy prolongs survival in this situation (*vs* use of ET) and its likely greater toxicity compared with ET.[42,43] Consensus guidelines also indicate that a patient's age should not, in itself, determine the intensity of systemic treatment (i.e. that being younger is not, in itself, a reason for patients to be prescribed chemotherapy).[2,6,44]

The optimal choice of treatment for any individual patient is influenced by multiple factors, including the biological characteristics of the disease, the sites of metastases, the disease burden and the pace of disease progression. In cases of relapsed disease, it will also be influenced by the patient's previous therapy, the duration of that therapy and the disease-free and treatment-free intervals. The patient's symptoms, comorbidities, performance status, predicted ability to tolerate particular treatments or dosing regimens and other QoL considerations also need to be taken into consideration when making treatment decisions, as do the patient's own preferences (especially when the likely benefits of treatment are modest or when there is likely to be little difference between treatment options).[2,22]

2.3 | Addressing the evidence gap

Given the age-related differences in tumor biology that appear to exist between younger, premenopausal women and older, postmenopausal individuals, treatment decisions for premenopausal women with HR$^+$ disease should ideally be based on trial data from predominately premenopausal cohorts of women with HR$^+$ disease. In the absence of such data, it cannot be certain that use of a particular treatment will result in similar outcomes, in terms of efficacy or toxicity profile, to those observed when the same therapy is used to treat postmenopausal women.

The phase III MONALEESA-7 study[32,39] is notable in this regard. The MONALEESA-7 study investigators randomized 672 premenopausal or perimenopausal women (aged 18–59 years), with advanced HR$^+$/HER2$^-$ breast cancer, to receive either ribociclib or placebo, in combination with ET (nonsteroidal aromatase inhibitor [NSAI] or tamoxifen), as well as goserelin; none had received prior ET for advanced disease, but they could have received up to one line of chemotherapy.[32] Follow up in this double-blind study revealed that the addition of ribociclib significantly improved PFS, compared with placebo (median 23.8 months *vs* 13.0 months; hazard ratio [HR] = 0.55; 95% CI, 0.44–0.69; $P < 0.0001$).[32] The HR was similar regardless of whether patients were treated with ribociclib + NSAI (HR = 0.57; 95% CI, 0.44–0.74]) or ribociclib + tamoxifen (HR = 0.59; 95% CI, 0.39–0.88]), and a PFS benefit was observed within nearly every evaluated patient subgroup (Table 2).[32]

The median duration of PFS among ribociclib-treated MONALEESA-7 study participants (23.8 months) was the longest reported PFS outcome in a prospective treatment trial conducted in this patient population.[6] Moreover, the overall PFS benefit (*vs* placebo) was similar to that observed during phase III trials of CDK4/6 inhibitor + ET in postmenopausal women with advanced disease,[29–32] suggesting that the impact of CDK4/6 inhibitor therapy may not be substantially affected by age-related differences in tumor biology.[6]

MONALEESA-7 also represents the first clinical trial in which use of a CDK4/6 inhibitor + ET has been associated with a statistically significant overall survival benefit (*vs* use of ET alone).[28,39] Specifically, use of ribociclib + ET (NSAI or tamoxifen) + goserelin was associated with a 29% reduction in risk of death, *versus* use of ET + goserelin (HR = 0.71; 95% CI, 0.54–0.95; $P = 0.00973$; Figure 1).[39,45] A similar overall survival benefit was observed among patients with lung or liver metastases at study entry (n = 342; HR = 0.73; 95% CI, 0.50–1.05), with the addition of CDK4/6 inhibitor to ET being associated with a 47% reduction in mortality risk among those who had liver metastases and whose ET had been NSAI therapy ($n = 170$; HR = 0.531; 95% CI, 0.321–0.877).[39,46] In addition, the treatment was associated with: a significantly improved time to definitive deterioration of patient-reported health-related QoL score (HR = 0.70; 95% CI, 0.53–0.92; $P = 0.004$); a durable and clinically meaningful reduction in pain score (*vs* baseline, from as early as 8 weeks after treatment initiation); and a similar adverse event profile to that observed in previous trials of ribociclib + ET.[6,29,32]

The use of a CDK4/6 inhibitor in the treatment of premenopausal or perimenopausal women with HR$^+$/HER2$^-$ metastatic breast cancer is also supported by the results of subgroup analyses from the MONARCH-2 and PALOMA-3 clinical trials.[47,48]

The MONARCH-2 study was a phase III, double-blind, placebo-controlled clinical trial, in which 669 patients with advanced HR$^+$/HER2$^-$ breast cancer were randomized to receive fulvestrant plus either abemaciclib or placebo; each had progressed while receiving neoadjuvant or adjuvant ET, ≤12 months after completing adjuvant ET or while receiving first-line ET for metastatic disease.[34] A total of 72 premenopausal or perimenopausal study participants – each of whom also received a gonadotropin-releasing hormone (GnRH) agonist – were randomized to fulvestrant + abemaciclib, whereas 42 were randomized to fulvestrant + placebo. Overall, use of the CDK4/6 inhibitor was associated with a significant PFS benefit (median PFS = 16.4 months *vs* 9.3 months; HR = 0.553; 95% CI, 0.449–0.681; $P < 0.001$); and it improved PFS regardless of whether study participants were pre/perimenopausal (HR = 0.415; 95% CI, 0.246–0.698) or postmenopausal (HR = 0.580; 95% CI, 0.463–0.726).[34] A later analysis of data from the pre/perimenopausal patients revealed that use of the CDK4/6 inhibitor was associated with a significant PFS benefit (median PFS = not reached in the fulvestrant + abemaciclib arm *vs* 10.5 months in the fulvestrant + placebo arm; HR = 0.446; 95% CI, 0.264–0.754; $P = 0.002$).[47]

The PALOMA-3 study was a phase III, double-blind, placebo-controlled clinical trial, in which 521 women, of any menopausal status, with advanced HR$^+$/HER2$^-$ breast cancer that had progressed on prior ET or recurred within 12 months of stopping adjuvant ET were randomized to receive fulvestrant plus either palbociclib or placebo; 108 study participants were premenopausal or perimenopausal and also received goserelin.[35,48] It should be noted that the PALOMA-3 study participants were a more heavily pretreated group than those enrolled in the MONALEESA-7 or MONARCH-2 studies (e.g. 34% had received prior chemotherapy in the metastatic setting *vs* 14% in MONALEESA-7 and none in MONARCH-2).[32,34,35] Follow up revealed that the median PFS for pre/perimenopausal women in the palbociclib arm of the study ($n = 72$) was 9.5 months, versus 5.6 months among women in the placebo arm ($n = 36$; HR = 0.50; 95% CI, 0.29–0.87; $P = 0.013$).[48] A similar PFS benefit was also

TABLE 2 CDK4/6 inhibitor therapy for pre/perimenopausal patients with advanced HR$^+$/HER2$^-$ breast cancer: Effect on risk of disease progression or death, compared with placebo (data from MONALEESA-7 study)[a,32]

	Ribociclib + ET[b] (events/patients)	Placebo + ET[b] (events/patients)	HR (95% CI)
Endocrine therapy partner			
NSAI	92/248	132/247	0.57 (0.44–0.74)
Tamoxifen[c]	39/87	55/90	0.59 (0.39–0.88)
Age			
<40 years	42/98	61/88	0.44 (0.29–0.67)
≥40 years	89/237	126/249	0.59 (0.45–0.78)
ECOG performance status			
0	87/245	134/255	0.55 (0.42–0.72)
≥1[d]	43/87	51/79	0.50 (0.32–0.77)
Hormone receptor status			
ER and PR positive	105/286	149/286	0.57 (0.45–0.74)
Other	26/49	38/51	0.44 (0.26–0.77)
Presence of liver or lung metastases			
Yes	75/173	109/170	0.50 (0.38–0.68)
No	56/162	78/167	0.64 (0.45–0.91)
Bone-only disease			
Yes	25/81	33/78	0.70 (0.41–1.19)
No	106/254	154/259	0.53 (0.42–0.69)
Number of metastatic sites			
<3	76/219	106/216	0.60 (0.44–0.81)
≥3	55/116	81/121	0.50 (0.35–0.72)
Prior chemotherapy for advanced disease			
Yes	22/47	29/47	0.55 (0.31–0.95)
No	109/288	158/290	0.57 (0.44–0.72)
All patients	131/335	187/337	0.55 (0.44–0.69)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; ET, endocrine therapy (NSAI or tamoxifen; ribociclib is not indicated for concomitant use with tamoxifen); HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; PR, progesterone receptor.
[a] Each of the subgroup analyses presented was prespecified in the study protocol.
[b] All study participants also received goserelin.
[c] Ribociclib is not indicated for concomitant use with tamoxifen.
[d] One patient had an ECOG performance status of 2.

observed among postmenopausal study participants ($n = 413$; median PFS = 9.9 months *vs* 3.9 months; HR = 0.45; 95% CI, 0.34–0.59; $P < 0.0001$).[48]

Several other clinical trials of targeted therapy involving pre/perimenopausal women with HR$^+$/HER2$^-$ advanced breast cancer have been initiated and are ongoing. However, most are phase I or phase II studies. Those that have enrolled exclusively pre/perimenopausal cohorts include three phase II studies that are designed to evaluate OFS + ET + CDK4/6 inhibitor in the first-line treatment setting, and one phase I/II trial of OFS + ET + pembrolizumab (anti-PD-1 immunotherapy) in the first- and second-line settings (Table 3).

2.4 | Managing patient expectations

Metastatic breast cancer is still generally regarded as being incurable and life-limiting.[17,22,23] It is important to ensure that patients with HR$^+$/HER2$^-$ metastatic breast cancer understand this when discussing treatment options, and what treatment or life goals it may or may not be realistic to set.

Many people with advanced cancer want to know how their diagnosis will affect their life expectancy. Patients diagnosed with HR$^+$/HER2$^-$ metastatic breast cancer can be informed that, although incurable, their disease is highly treatable and many people with advanced disease can continue to live and maintain an acceptable

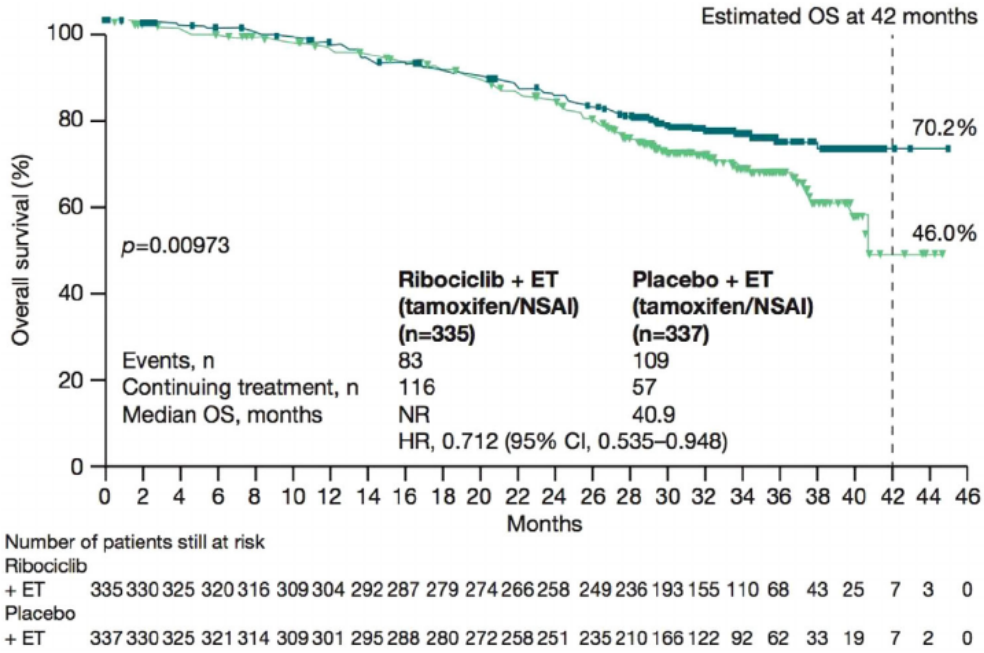

FIGURE 1 CDK4/6 inhibitor therapy for pre/perimenopausal patients with advanced HR$^+$/HER2$^-$ breast cancer: Effect on overall survival during MONALEESA-7 study.[a,b45]

[a]Intent-to-treat population; second interim analysis. The MONALEESA-7 study enrolled pre/perimenopausal patients with advanced HR$^+$/HER2$^-$ breast cancer (none had received prior endocrine therapy for advanced disease, but they could have received up to one line of chemotherapy for advanced disease; ~40% had *de novo* disease at study entry); all were randomized to receive ribociclib (a CDK4/6 inhibitor) in combination with either nonsteroidal aromatase inhibitor (NSAI) or tamoxifen; all patients also received goserelin.[32,39]

NOTE: HR = 0.70 (95% CI, 0.50–0.98) among patients who received NSAI ± ribociclib (n = 495); and 0.79 (95% CI, 0.45–1.38) among patients who received tamoxifen ± ribociclib (n = 177).[39]

[b] Ribociclib is not indicated for concomitant use with tamoxifen.

Abbreviations: ET, endocrine therapy (NSAI or tamoxifen; ribociclib is not indicated for concomitant use with tamoxifen); HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival.

[Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Ongoing clinical trials restricted to pre/perimenopausal women with advanced HR$^+$/HER2$^-$ breast cancer[a]

Study	Population	Treatment arms	Primary endpoint
FATIMA NCT02917005 (recruiting) Phase II RCT Open-label	First-line (N = 160) Premenopausal HR$^+$/HER2$^-$ LA or MBC	Palbociclib + Exe + goserelin Exe + goserelin	PFS
RIGHT Choice NCT03839823 (recruiting) Phase II RCT Open-label	First-line (N = 222) Pre/perimenopausal HR$^+$/HER2$^-$ inoperable LA or MBC	Ribociclib + ET + goserelin Chemotherapy (PC)	PFS
NCT02592746 (active, not recruiting) Phase II RCT Open-label	First-line (N = 182) Premenopausal HR$^+$ MBC	Palbociclib + Exe + GnRH agonist Capecitabine	PFS
PEER NCT02990845 (recruiting) Phase I/II pilot Open-label	First- and second-line (N = 25) Premenopausal HR$^+$/HER2$^-$ LA or MBC	Pembrolizumab + Exe + leuprolide	PFS rate at 8 months

Abbreviations: ET, endocrine therapy; Exe, exemestane; GnRH, gonadotropin-releasing hormone; LA, locally advanced; MBC, metastatic breast cancer; PC, physicians' choice; RCT, randomized controlled trial.

[a] A selection of studies that are currently recruiting and/or active, and for which recruitment status is currently known (as per US National Library of Medicine, ClinicalTrials.gov; accessed 10 June 2020).

quality of life for extended periods (sometimes many years).[22] It has been suggested that presenting patients with three possible scenarios ("worst case" [e.g. ≤ one-quarter of the median overall survival], "typical" [e.g. half to double the median overall survival] and "best case" [e.g. ≥3 times the median overall survival]) may be better than offering a single estimate of likely life expectancy.[49,50] This type of information helps patients with advanced cancer evaluate possible treatment options, set appropriate goals and optimize use of their remaining time, and may also help to minimize any negative impact on a patient's mood or sense of hopefulness.[50]

3 | SUPPORTIVE CARE CONSIDERATIONS

Follow-up care for younger women with HR$^+$/HER2$^-$ metastatic breast cancer should generally be the same as that for older individuals with the same disease.[2] However, it is important to recognize that women diagnosed with breast cancer at a younger age may face a variety of challenges, concerns and needs that are related to their age, and which may require specific additional assessments, monitoring and support.[2,3,5,6,8–11] These may include concerns or needs related to their:

- Diagnosis, including the unexpectedness of the diagnosis at an age when breast cancer is uncommon and the sense of isolation or frustration that may result if age-appropriate support is not readily available.
- Treatment (e.g. the development of treatment-induced menopause and associated symptoms; loss of fertility; issues related to treatment adherence).
- Family or home life (e.g. young women are more likely to be parenting young children at the time of their diagnosis and treatment, and having to explain their diagnosis and treatment to their children; young patients may be concerned or distressed about the possibility of not seeing their children grow up; they may be concerned about their children's genetic risk of breast cancer; younger patients may also be caring for parents or having to help their parents cope with their daughter's diagnosis).
- Self-esteem or body image, and the potential impact of the diagnosis and its treatment on relationships, sexual function and intimacy.
- Employment status and their ability to manage personal or family finances, remembering that younger women are more likely to be at the start or middle of their working life and less likely to be approaching retirement or already retired (vs older individuals).
- Other ongoing survivorship issues, including issues related to symptom management, which may adversely affect their physical, mental or psychosocial wellbeing.

Challenges, concerns or needs such as those mentioned above are not always adequately identified or addressed (e.g. young women commonly have unmet psychosocial needs following a breast cancer diagnosis) and may help to explain why younger women with breast cancer report symptoms of distress, depression and anxiety more frequently than older women.[2,6,8–10,23]

3.1 | Managing psychological and psychosocial health

Patients' mental health and psychosocial wellbeing should be regularly assessed as part of routine care after a breast cancer diagnosis, with appropriate treatment, referrals and/or other supportive measures being initiated as required.[2,10]

Clinical practice guidelines recommend that patients with breast cancer be screened for anxiety and depression on an ongoing basis, the risk of each being increased either by the use of particular treatments for breast cancer (e.g. endocrine therapies, chemotherapy) or the impact (psychological, emotional) of the cancer diagnosis itself.[51] The use of brief, validated assessment tools (e.g. the Patient Health Questionnaire) is recommended, particularly during periods of transition (e.g. when a patient is receiving her diagnosis, at hospital discharge, etc.).[10,51] A published screening guideline from the American Society of Clinical Oncology contains a comprehensive list of validated screening tools; use of standardized protocols for psychological referral has also been recommended to ensure that patients receive timely and appropriate treatment for identified symptoms of psychological morbidity and/or psychosocial distress.[10,52]

3.2 | Premature infertility and menopausal symptoms

Young women with HR$^+$/HER2$^-$ metastatic breast cancer are typically initiated on treatment that induces premature menopause (e.g. OFS + ET; or chemotherapy).[2,6] All young women who have been diagnosed with breast cancer should be advised about the risks, associated symptoms and implications of premature menopause, as well as informed about available and approved ameliorative therapies; and appropriate referrals (e.g. for counseling, for symptom management) should also be made when necessary.[2]

The abrupt onset of treatment-related menopause can be particularly distressing for younger patients, in view of its potential symptoms and impact on QoL, and patients should be counseled, monitored, treated and supported accordingly.[2,6] Premature menopausal symptoms may include vasomotor symptoms (e.g. hot flushes), sleep disturbance, mood changes, fatigue and weight gain, as well as genitourinary symptoms and impaired sexual function (e.g. vaginal dryness, dyspareunia and/or persistent loss of libido).[2,6,53–55] Hormone replacement therapy for these and other menopausal symptoms (symptoms that can be more severe or persistent than those associated with the onset of natural menopause) should generally be avoided for women with ER$^+$ breast cancer, due to concern about the potential for promoting disease progression, so it is important to be able to discuss non-hormonal treatment options with these patients.

TABLE 4 Effect of oral oxybutynin on the severity and frequency of hot flushes over seven weeks (interim data) [a,62,63]

	Placebo	Oxybutynin 2.5 bid	Oxybutynin 5 bid[b]
Mean change in hot flush score	−5.1 (SD 9.7)	−10 (SD 7.4)*	−16.2 (SD 5.1)***
Mean change in average weekly number of hot flushes	−2.3 (SD 3.9)	−4.6 (SD 3.1)**	−7.0 (SD 4.0)***

* $P = 0.003$ *vs* placebo.
** $P = 0.002$ *vs* placebo.
*** $P < 0.001$ *vs* placebo.
[a] Interim data from first 104 patients for which at least one post-baseline evaluation was available. Study investigators enrolled 150 patients who had experienced hot flushes ≥28 times per week, over >30 days, and which were severe enough to prompt them to seek treatment; all were women with a history of breast cancer or who had a concern about taking estrogen due to a fear of developing breast cancer; 62% were on tamoxifen or an aromatase inhibitor for the duration of the study; four withdrew before starting treatment (excluded from analyses). Patients took their assigned oxybutynin doses on days 8–49.
NOTE: Hot Flush-Related Daily Interference Scale scores also revealed that patients in both oxybutynin arms experienced an improvement with regard to the following measures: work, social activities, leisure activities, sleep, relations, life enjoyment and overall quality of life.
[b] 2.5 mg bid for 1 week (days 8–14), followed by 5 mg bid (days 15–49).

Hot flushes are commonly experienced by young women on ET for breast cancer. The range of treatment options for hot flushes in this clinical setting includes:

- Nonpharmacological interventions (e.g. avoidance or minimization of exposure to identified triggers, such as stress, caffeine, spicy food, hot rooms or hot baths; management of psychological contributors; stress management; relaxation training; cognitive behavior therapy; use of effective cooling options).[53,54]
- Specific dietary supplements, such as a fixed combination of black cohosh (isopropanolic *Cimicifuga racemosa* extract) and St John's wort.[55]
- Gabapentin.[54,56,57]
- Clonidine.[54,58,59]
- Appropriate selective serotonin reuptake inhibitors (SSRIs; note that some SSRIs, such as paroxetine and fluoxetine, are likely to interfere with the metabolism of tamoxifen, resulting in reduced production of its main active metabolite, and should be avoided when patients are on this ET).[54,55,58–61]
- Oxybutynin (Table 4).[54,62,63]
- Stellate ganglion block (limited supporting study data, but case reports/series indicate that there are some patients for whom nothing else works and for whom this option provides relief).[54,64,65]

Each of the above treatments is potentially helpful, and more than one may be used to achieve the desired clinical effect. Potential side effects and drug-drug interactions associated with each option should be considered when making treatment recommendations. Care should also be taken to avoid use of treatments or complementary therapies that may exert estrogenic effects or otherwise be deemed contraindicated for use in a patient with HR^+ breast cancer.

Another common menopausal symptom is vaginal dryness, which can make sexual intercourse painful and adversely affect QoL.[54] A number of strategies can be suggested or implemented to help patients affected by this symptom. For example:

- Simple vulval care strategies may be helpful in this situation (e.g. avoidance of irritants [such as soap, detergents and other products with perfumes or dyes], the use of soap-free washes and/or use of appropriate moisturizers and lubricants).[54]
- Patients experiencing dyspareunia may benefit from self-application of an appropriate topical anesthetic (e.g. 4% aqueous lignocaine) to the mucosa of the vulvar vestibule (vaginal introitus) prior to engaging in sexual intercourse.[54,66]
- Exploration of non-penetrative sexual practices and/or the accessing of appropriate relationship or sexual health counseling might also be beneficial.

If a patient remains unresponsive to nonhormonal interventions for vaginal dryness and discomfort with sexual activity, consideration may also be given to prescribing vaginal estrogens (in consultation with the treating oncologist), using a dose low enough to avoid detectable systemic absorption and thereby minimize any systemic effect (e.g. ultra-low-dose estriol, compounded), or vaginal dehydroepiandrosterone (DHEA; i.e. vaginal DHEA pessaries [6.5 mg/day, compounded]).[54,67–69]

3.3 | Genetic testing and lifestyle advice

Referral for genetic counselling and possible testing should also be considered when managing younger women diagnosed with breast cancer, given that these younger women are more likely to harbor germline BRCA1 or BRCA2 mutations than older individuals with the disease.[2,12,70,71] Indeed, it has been suggested that genetic counseling should be offered to all young women with breast cancer (as per local/national guidelines, resources and testing availability), especially if they have a family history suggestive of a hereditary cancer predisposition.[44,70]

More generally, young women with advanced $HR^+/HER2^-$ breast cancer – like all patients with cancer – should be strongly encouraged to adopt a healthy lifestyle, including: the avoidance of smoking; the limiting of daily alcohol intake; and the maintenance of a healthy body weight (BMI 19–25).[2] A recently published Clinical Oncology Society of Australia position statement recommends that tailored, supervised exercise (i.e. under the guidance of an accredited exercise specialist, such as a physiologist or physiotherapist, who has experience working with individuals who have had a cancer diagnosis) also be routinely prescribed for all patients with cancer, including those with metastatic disease, as a component of routine cancer care.[72] There is now a

considerable body of literature indicating that exercise is a safe and effective intervention for counteracting some of the adverse physical and psychological effects of cancer and its treatment.[72,73] Not only does available data indicate that patients with cancer who engage in greater levels of exercise experience fewer and/or less severe treatment-related adverse effects than those who do not, but we also know that appropriate exercise can help mitigate cancer-related fatigue and may also improve functional capacity and QoL.[73–77]

3.4 | A multidisciplinary approach is important

It is well recognized that multidisciplinary care is necessary to comprehensively meet the often-complex medical and psychosocial needs of patients living with advanced breast cancer; and current therapeutic guidelines therefore recommend a multidisciplinary approach to the management of young women with breast cancer – one that includes provision of suitably tailored, age-appropriate psychosocial support.[2,5,10,22,44]

Ideally, young women with advanced breast cancer should be cared for by dedicated multidisciplinary teams, preferably within specialized breast services, to help ensure that each patient's specific diagnostic, therapeutic, psychological and psychosocial issues or concerns are appropriately addressed.[2,5,44] The multidisciplinary team may include a medical oncologist, radiation oncologist, breast and plastic surgeon, radiologist, pathologist, general practitioner, breast cancer nurse, pain specialist, clinical psychologist and geneticist/genetic counselor, as well as gynecological, fertility, sexual therapy and psychosocial experts.[2,22] The early involvement of palliative care services is also recommended to help manage patients' symptoms, facilitate better physical and role functioning, improve QoL and plan for end-of-life care.[10,22,78] It has been noted that young women with metastatic cancer are likely to benefit from earlier referral for palliative care, and all women with a high symptom burden stand to benefit from multidisciplinary palliative care.[10]

4 | SUMMARY AND CONCLUSIONS

Breast cancer in younger women is complex to treat and generally associated with a poorer prognosis when compared to breast cancer in older women. In addition to prolonging survival, one of the main goals when treating younger women with $HR^+/HER2^-$ metastatic breast cancer is to help them maintain an acceptable QoL for as long as possible, by delaying disease progression, controlling symptoms, minimizing treatment-related toxicity and offering suitably tailored, age-appropriate psychosocial support. Actively striving to implement and facilitate genuinely multidisciplinary, patient-centered models care and follow up is likely to assist in this regard.

The currently recommended first-line treatment for young women with HR^+ metastatic breast cancer remains OFS + ET ± targeted therapy, unless there is concern about endocrine resistance or a need to gain rapid disease control due to the onset of visceral crisis. The use of CDK4/6 inhibitors in the treatment of premenopausal or perimenopausal women with $HR^+/HER2^-$ metastatic breast cancer is now supported by phase III clinical trial data. This includes data from the MONALEESA-7 study, as well as the results of subgroup analyses from the PALOMA-3 and MONARCH-2 trials. The MONALEESA-7 study, conducted in the first-line treatment setting, is particularly notable in that it enrolled an exclusively premenopausal or perimenopausal patient population and represents the first clinical trial in which the addition of a CDK4/6 inhibitor to ET for advanced $HR^+/HER2^-$ breast cancer has been associated with a statistically significant overall survival benefit.

DISCLOSURES

RDB has served as an investigator on CDK inhibitor trials, is a member of advisory boards for Novartis, Eli Lilly and Roche and has received speaker honoraria from Novartis, Roche, Amgen, Eli Lilly and Genomic Health.

RH has served as an investigator on CDK inhibitor trials, has participated in advisory boards for Novartis, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck Sharp and Dohme, Pfizer and Roche; and has received speaker honoraria from Novartis, Merck Sharp and Dohme, AstraZeneca, Roche, Bristol Myers Squibb, and Boehringer Ingelheim.

EL has received research funding from Novartis and Bayer Pharmaceuticals, and has participated in advisory boards for Pfizer, Novartis, Roche, Eisai and Lilly.

NZ has participated in advisory boards for Lilly and Eisai, has received speaker honoraria from Novartis, Pfizer and Amgen, and has served as an investigator on CDK4/6 inhibitor trials.

BY has served as an investigator on CDK inhibitor trials, is a member of advisory boards for Novartis and Roche and has received speaker honoraria from Novartis, Roche and Eisai.

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