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REVIEW

Extended adjuvant endocrine therapy in early breast cancer: finding the individual balance

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Endocrine therapy (ET) is a cornerstone in the management of patients with hormone receptor-positive early breast cancer, which accounts for over 70% of cases worldwide. The efficacy of adjuvant ET for 5 years in reducing the risk of recurrence and improving survival outcomes is well documented. However, the risk for late relapses, occurring >5 years after initial treatment, has prompted exploration of longer treatment durations. Extending ET beyond the traditional 5-year period offers additional benefit in reducing the risk of recurrence and improving long-term outcomes. Nevertheless, determining the optimal duration and identifying suitable candidates for extended therapy is often nuanced. This review aims to comprehensively evaluate the current landscape of extended ET in breast cancer management. It provides an overview of the rationale behind extending endocrine treatment in both premenopausal and postmenopausal women, with a focus on clinical trials and observational studies supporting extended therapy. Furthermore, it emphasizes the significance of considering associated toxicities in patient management. It also explores novel strategies involving the combination of ET with new drugs, leading to an evolution of treatment paradigms that may make the need for extended therapy obsolete.

Key words: breast cancer, hormone receptor-positive, extended endocrine therapy, adjuvant, early setting, predictive tools

INTRODUCTION

Hormone receptor-positive breast cancer (BC) is defined by the positive expression of estrogen receptors (≥1%) and/or progesterone receptors (≥1%).[1-3] This subtype stands as the most common, accounting for almost 70% of all BC diagnoses.[4] Adjuvant endocrine therapy (ET) with tamoxifen, a selective estrogen receptor modulator (SERM), demonstrated its impact in reducing risk of relapse in early BC.[5] Comparably, aromatase inhibitor (AI) can further reduce this risk by ∼30%.[6,7] A standard duration of 5 years of adjuvant ET is indicated for all hormone receptor-positive BC, unless contraindicated.[2]

Despite such approach, risk of relapse in patients with hormone receptor-positive BC remains even 20 years after the initial diagnosis. In a meta-analysis led by the Early Breast Cancer Trialists Collaborative Group (EBCTCG) on >80 trials and 80 000 patients, the rate of distant relapse at 15 years after finishing 5 years of adjuvant ET ranged from 13% to 41%, according to disease stage and tumour grade, and the tumour diameter and nodal status represented the strongest prognostic factors.[8] Thus, extended adjuvant ET (EET) has been the subject of intense research activity in the last few years. The choice of the type and duration of ET for each patient in clinical practice is multifactorial and must consider, among others, patient menopausal status, risk of recurrence, ET toxicity profile, and patient preferences.[2]

This review evaluates the current landscape of EET in BC, highlighting the rationale for extending treatment in premenopausal and postmenopausal women based on clinical trials and observational studies. We also discuss associated toxicities and explore novel combination strategies with new drugs to inform evolving treatment approaches (Figure 1).

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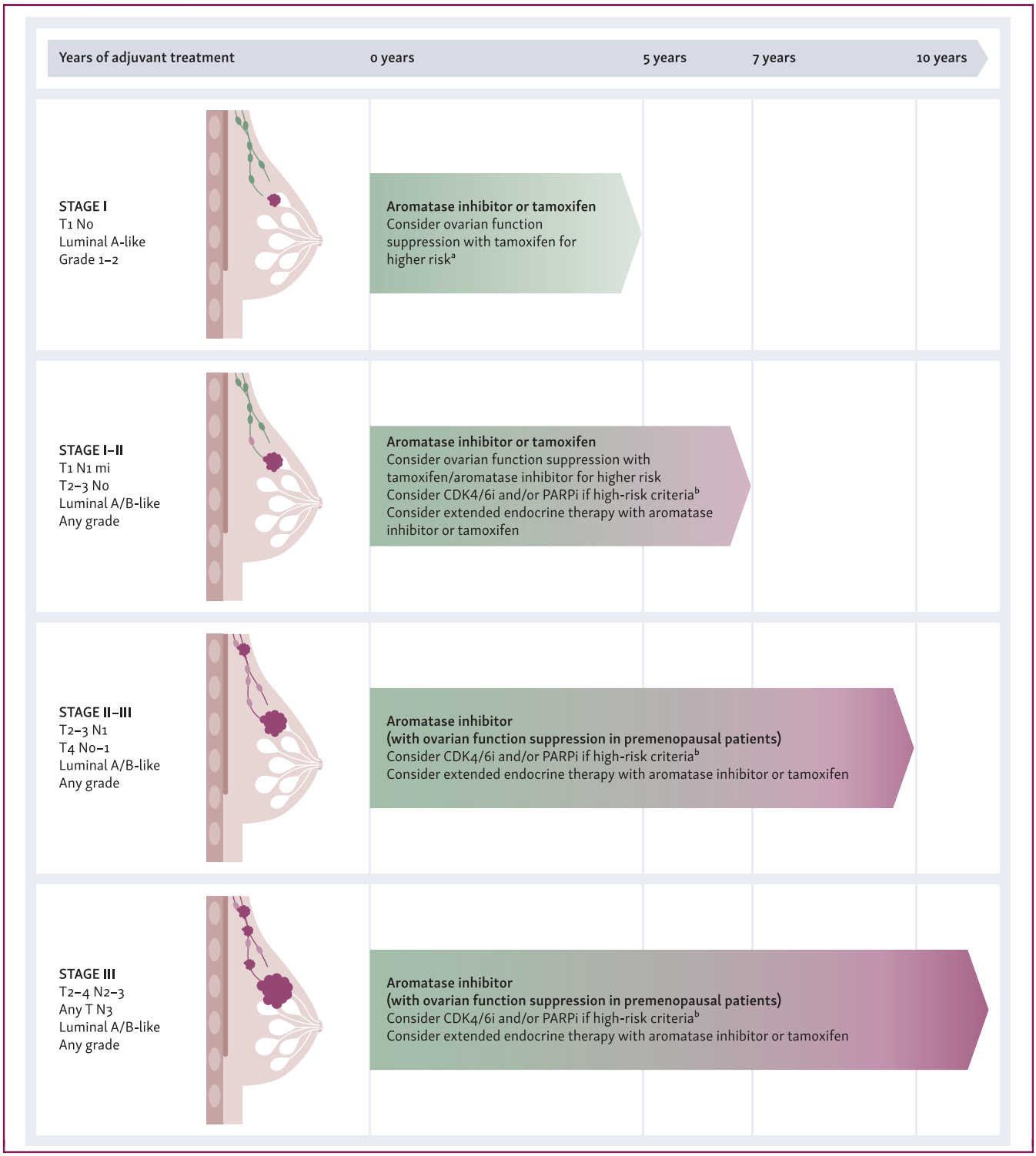

Figure 1. Summary of recommendations for adjuvant endocrine therapy for hormone receptor-positive/HER2-negative breast cancer.
AI, aromatase inhibitor; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ET, endocrine therapy; OFS, ovarian function suppression; PARPi, poly (ADP-ribose) polymerase inhibitor; Tam, tamoxifen.
[a]Higher-risk characteristics include intermediate to high-grade or higher-risk genomic signature, lower ER expression, higher baseline Ki67, or lack of decline in Ki67 with preoperative ET.
[b]High-risk criteria defined according to the inclusion criteria of the monarchE, NATALEE, and OlympiA trials—for more complete information, please refer to Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057. Created with BioRender.com.

PREMENOPAUSAL WOMEN

Menopausal status is a clear prognostic factor in patients with hormone receptor-positive early BC, even for late recurrences.[8,9] Evaluating menopausal status before starting adjuvant ET is crucial, as ongoing ovarian estrogen production influences therapy choice. In patients with

chemotherapy-induced amenorrhea, testing follicle-stimulating hormone and oestradiol levels can help assess menopausal state, though these levels may temporarily mimic postmenopausal status, with ovarian function potentially recovering up to 2 years after chemotherapy.[10] Though this hormonal change has a direct impact on the choice of the best adjuvant ET,[11,12] adjuvant tamoxifen remains a standard approach in premenopausal patients.[5]

Given the greater reduction in recurrence risk with an AI compared with tamoxifen in postmenopausal women,[6] studies questioned the effect of ovarian function suppression (OFS) in premenopausal patients with hormone receptor-positive BC, along with its combination with an AI or a SERM. A combined analysis of the SOFT and TEXT studies demonstrated significantly higher 12-year rates of disease-free survival (DFS) but not overall survival (OS) when comparing exemestane plus OFS and tamoxifen plus OFS.[13] High-risk patients exposed to chemotherapy benefit more from combining OFS with AI.[13] These results establish OFS as an important consort to adjuvant ET in premenopausal women.[1] Additionally, a meta-analysis of four randomized clinical trials (RCTs) indicated a lower 5-year recurrence rate with OFS with AI compared with tamoxifen (6.9% versus 10.1%, $P = 0.0005$).[7]

As referred, the choice of adjuvant ET in premenopausal women include tamoxifen alone, or OFS combined with tamoxifen or AI.[11,12] Escalating treatment with cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) and poly (ADP-ribose) polymerase inhibitors (PARPi) has shown benefits in high-risk patients,[14-16] but the optimal duration of adjuvant ET beyond the 5 years remains unclear. The composite-risk Subpopulation Treatment Effect Pattern Plot score was designed to illustrate the similarities between patients in SOFT and TEXT with characteristics of the patient tested regarding response to ET + OFS in a median follow-up of 8-9 years. The composite-risk value was obtained from a Cox model that incorporated age, nodal status, tumour size, grade and estrogen receptor, progesterone receptor, and Ki-67 labelling index expression levels. Although not a prediction model, it allows the clinician to better understand those in need of escalating therapy in the first 5 years, as this score provides knowledge of absolute improvements in 8-year freedom from distant recurrence with exemestane plus OFS versus tamoxifen plus OFS or tamoxifen alone. As the potential benefit of escalating ET is higher in high recurrence risk, these patients may benefit from ET (available at https://rconnect.dfci.harvard.edu/CompositeRiskSTEPP/).[17]

Current literature on selection of EET in premenopausal patients rely solely on subgroup analyses conducted within RCTs (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057).

EET after upfront 5 years of tamoxifen

The ATLAS trial explored the benefit of 5 additional years of tamoxifen versus no EET following an initial 5 years of tamoxifen. In total, 12 894 women with early BC were enrolled, but only 1058 (8%) of them were identified as premenopausal at the time of trial enrolment.[18] In the overall population, EET resulted in reduced risk of recurrence [rate ratio (RR) 0.85, standard error (SE) 0.05, $P = 0.001$]. BC-specific mortality (RR 0.84, SE 0.06, $P = 0.006$) and overall mortality (RR 0.89, SE 0.04, $P = 0.01$) were also improved (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057).[18] When analysing the subgroup of premenopausal patients, similar results have been shown, where 64 of 326 patients (20%) in the EET arm and 73 of 304 patients (24%) in the control arm experienced recurrences after 10 years from randomization (RR 0.81, SE 0.15).

Similarly, the aTToM study evaluated the benefit of extending tamoxifen therapy to 10 years after 5 years of tamoxifen therapy, without age or menopausal state restriction. Overall, continuation of tamoxifen reduced BC recurrence ($P = 0.003$) and BC mortality ($P = 0.05$) (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057). It is worth noting that the study was initially presented as an abstract and has not been formally published, with the data on the premenopausal population remaining undisclosed.[19]

A third but negative study, the NSABP B-14 trial, aimed to assess the efficacy of EET with tamoxifen after 5 years of tamoxifen. It is of note that this trial enrolled only patients with node-negative disease. A total of 1172 women were enrolled of whom 26% were aged <50 years. This trial demonstrated no benefit for EET, regardless of age.[20]

As menopausal status fluctuates over the standard 5-year adjuvant ET period, trials beyond this timeframe for postmenopausal patients randomize those who were premenopausal at diagnosis and became postmenopausal during this period. It is the case of the NCIC CTG—MA.17 trial, designed to evaluate the efficacy of EET with 5-year letrozole in postmenopausal women who have completed 5 years of adjuvant tamoxifen (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057).[21] Among the 5166 patients included, 877 were categorized as premenopausal when starting adjuvant tamoxifen. Overall, EET with letrozole notably increased DFS and revealed a marginal advantage in distant DFS (DDFS) for premenopausal women. It is of note that premenopausal women at diagnosis experienced a greater DFS benefit with letrozole in EET than those postmenopausal at diagnosis [hazard ratio (HR) 0.26, $P = 0.0003$ versus HR 0.67, $P = 0.006$; respectively].[22] Premenopausal patients with positive nodes had a significant difference between letrozole and placebo in 4-year DFS [93.8% versus 85.0%, HR 0.40, 95% confidence interval (CI) 0.18-0.85]. Results on premenopausal women with negative nodes cannot be analysed due to the fact that no events were observed in the letrozole arm, while 15.0% of premenopausal patients in the placebo arm had a 4-year DFS event.[22]

EET after ovarian function suppression

There are no data so far supporting the continuation of ET beyond the fifth year in premenopausal patients treated

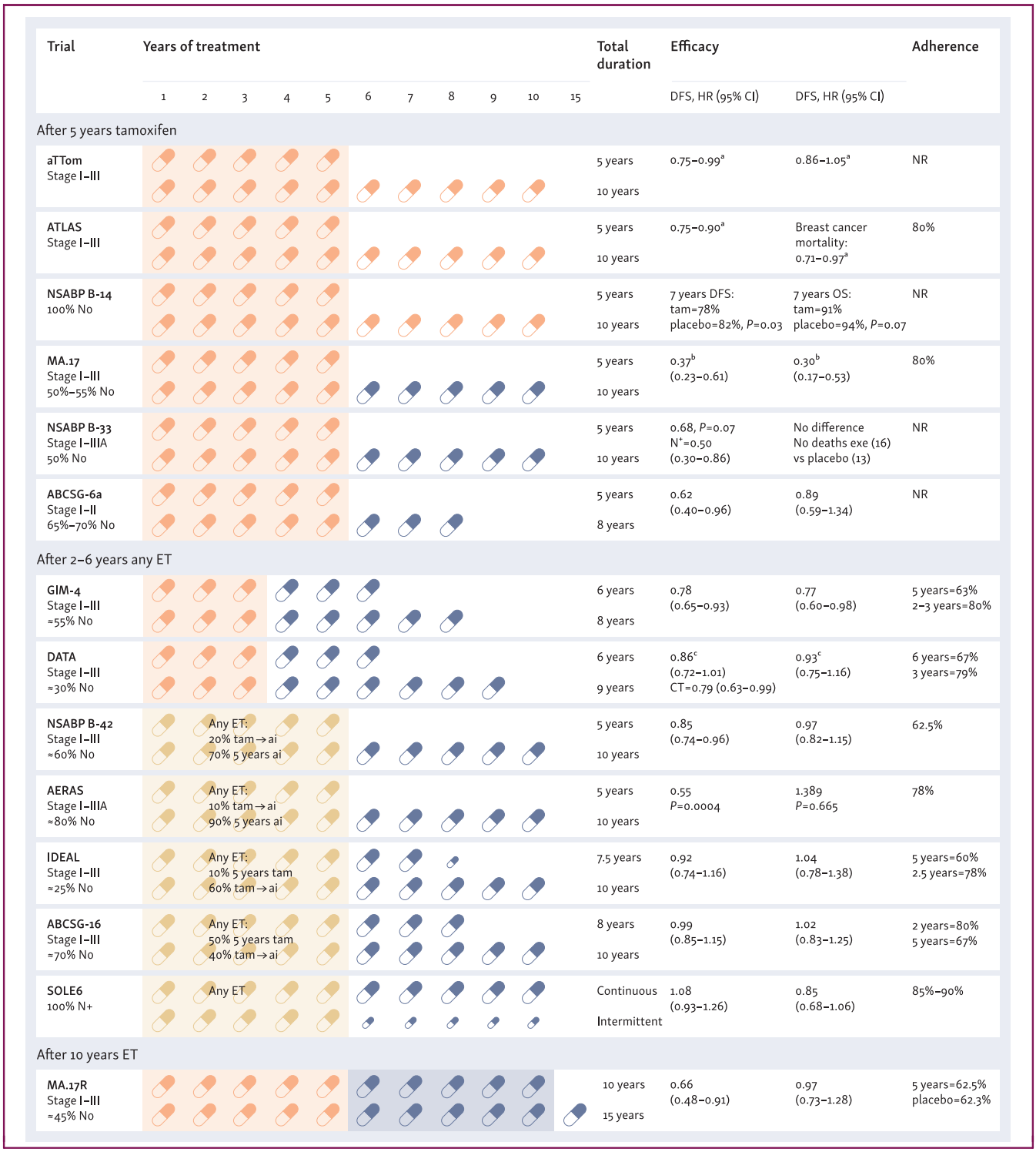

Figure 2. Summary of extended adjuvant endocrine therapy trials for hormone receptor-positive/HER2-negative breast cancer. The solid fill background represents the period before trial randomization. The pills are colour-coded as follows: orange for tamoxifen, blue for AI, and yellow for any ET before randomization. For more detailed information on the clinical trials design and results, please consult Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057.
AI, aromatase inhibitor; CI, confidence interval; CT, chemotherapy; DFS, disease-free survival; ET, endocrine therapy; Exe, exemestane; HR, hazard ratio; N+, node positive disease; NR, not reported; OS, overall survival; Tam, tamoxifen.
[a]The trials of extended tamoxifen therapy showed a time-dependent HR. After 10 years (i.e. 5 years after random assignment), the HR was 0.75 for DFS, but it was lower in earlier years of follow-up.
[b]Adjusted Cox models for unbalanced demographic and disease characteristics.
[c]Starting 3 years after randomization.

with 5 years of OFS in combination with either tamoxifen or exemestane. EET in these patients must be based on patient-adapted risk—benefit ratio and menopausal status after the first 5 years of adjuvant ET.[2,12]

A phase II study aiming to answer this question had been initiated by including patients who had already received >4.5 years of OFS to receive an additional 2 years of OFS; however, enrolment was discontinued after only 16 patients had been included out of a planned 50 patients, and the main reason was the difficulty for patients to tolerate OFS longer than the first 5 years. Poor accrual suggests that young women may not be highly motivated to pursue longer time of OFS and that future studies of this approach may be challenging.[23]

EET in premenopausal patients is currently a subject of debate. This is due to lack of data on the benefit of EET in patients with a high risk of recurrence who received 5 years of OFS with tamoxifen or AI. It is in such populations where potential candidates for EET reside. Furthermore, there are no available data on the benefit of EET in premenopausal patients who received targeted drugs, such as CDK4/6i or PARPi. However, new trials involving oral selective estrogen receptor degraders (SERDs), such as CAMBRIA-1 (NCT05774951) and CAMBRIA-2 (NCT05952557), mandate the use of OFS for premenopausal women (in the experimental arm for CAMBRIA-1 and for both arms in CAMBRIA-2), which will provide future data on extending OFS beyond 5 years.[24,25]

POSTMENOPAUSAL WOMEN

Over 70% of new cases of BC were diagnosed in women over the age of 55 years in 2022 in the United States.[26] As in premenopausal women, the continuation of ET beyond 5 years must be based on the risk—benefit ratio, depending on risk of recurrence, previous treatments, competing comorbidities, side-effects, and patient's preference (Figure 1).[27] Based on the upfront strategy taken for the first 5 years of adjuvant ET, different options for the extended period have been studied (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057).

EET after upfront 5 years of tamoxifen

Two studies have evaluated an additional 5 years of tamoxifen after an initial 5 years of tamoxifen: ATLAS[18] and aTTom trials (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057). Both studies demonstrated a reduction in recurrence, BC mortality, and OS, with RR dependent on time [in ATLAS, BC outcomes presented an RR of 0.90 (95% CI 0.79-1.02) during years 5-9 and 0.75 (0.62-0.90) in later years].[18,19]

Alternatively, the EET can be proposed with 5 years of AI after 5 years of tamoxifen. Two trials, the MA.17[28-30] and the NSABP B-33[31] studies, investigated this option (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057). In MA.17, risk of relapse, locoregional and distant, was reduced with EET by 4.6% and 2.9%, respectively (5-year DFS, HR 0.37, 95% CI 0.23-0.61; 5-year DDFS, HR 0.38, 95% CI 0.20-0.73).[28,29] This benefit was seen independently of lymph node status and previous use of chemotherapy. Improvement in OS was demonstrated only in the subgroup of patients with axillary lymph node involvement (node-positive: HR 0.61, 95% CI 0.38-0.98; node-negative: HR 1.52, 95% CI 0.76-3.06).[28,30] In the NSABP B-33 study, where 44% of patients crossed over from placebo to AI after unblinding, there was no difference in OS. However, exemestane exhibited a tendency for better DFS, particularly in node-positive disease (DFS, HR 0.50, 95% CI 0.30-0.86).[31]

In the ABCSG-6a trial, patients who remained disease free after 5 years of tamoxifen were randomized to receive either 3 years of anastrozole or no further treatment (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057). Risk of recurrence, local and distant, was reduced with additional treatment (HR 0.62, 95% CI 0.40-0.96).[32]

EET after sequencing tamoxifen and AI

After 2-3 years of tamoxifen, patients can be proposed to switch to 2-3 years of AI (total of 5 years of adjuvant ET) or extended adjuvant AI to a total of 7/8 years of adjuvant ET (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057). In the GIM-4 trial, a total duration of 8 years of ET led to significant advantages in both invasive DFS (iDFS) and OS, with absolute increases of 5% and 4%, respectively.[33] It should be noted that patients with stage I-III histologically proven and operable invasive hormone receptor-positive BC were eligible and ~40% of the patients included had node-positive disease. DFS benefit was more pronounced in patients 55 years old or more, and with node-negative disease.[33] The greater benefit in node-negative patients may result from the timing of randomization, which occurred after 2-3 years of tamoxifen; high-risk patients, such as those with node-positive disease, may have already experienced recurrence by that point and thus were not eligible for enrolment.

In the NSABP B-42[34,35] and AERAS[36,37] trials, postmenopausal women were randomized to an additional 5 years of AI after 5 years of adjuvant ET (sequencing tamoxifen and AI, or just AI) (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057). In both studies the exposure to tamoxifen was low. In NSABP B-42, ~70% of patients received >4 years of AI as previous therapy. Those who received tamoxifen presented a better DFS (HR 0.75, 95% CI 0.57-0.99; versus no tamoxifen, HR 0.91, 0.75-1.10), and for the entire population, the benefit in DFS was only seen after a median follow-up of 10 years.[34,35] In the AERAS trial, although only 10% of patients had received tamoxifen, 10 years of adjuvant ET was associated with a 7.5% absolute reduction at 5-year DFS.[36,37] Neither study demonstrated OS advantages.

In trying to understand the adequate time duration of EET, the DATA study demonstrated a better tendency favouring EET with 6 years of anastrozole in DFS compared with 3 years of anastrozole (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057).[38] An exploratory subgroup analysis revealed a greater benefit with 6 years of EET in patients who had received chemotherapy (10-year DFS, absolute benefit of 3.9%).[38]

Two studies compared 7-7.5 years to 10 years of EET with no improvements in outcomes, DFS or OS (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057). In the IDEAL trial, 60% of patients were previously treated with sequential tamoxifen and AI, and 25% did not have nodal involvement.[39] In the ABCSG-16 trial, 40% received sequential and 30% presented positive lymph node disease.[40] More recently, a prospective-retrospective translational study of IDEAL demonstrated that patients at high risk of recurrence assessed by the Breast Cancer Index (BCI) derived an absolute benefit of 9.8% on recurrence with 10 years of adjuvant ET (HR 0.42, 95% CI 0.21-0.84, $P = 0.011$).[41] However, these findings suggest that patients who receive AI upfront are unlikely to gain additional benefit from extending ET beyond 7-8 years, emphasizing the need for careful patient selection in determining EET duration.

EET after 10 years of ET

In the MA.17R, 1918 postmenopausal women who had already completed a full 10 years of adjuvant ET [4.5-6 years of tamoxifen (∼70%) followed by 4.5-6 years of AI] were randomized to receive an additional 5 years of letrozole or placebo (Figure 2 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105057).[42] Despite DFS favouring EET ($P = 0.01$), distant recurrence differences were modest (4.4% for letrozole versus 5.5% for placebo) and no OS benefit was demonstrated.[42]

Alternative regimens

Trying to overcome secondary resistance to ET, the SOLE trial assessed the superiority of intermittent versus continuous letrozole, for an additional 5 years in postmenopausal women who were relapse free after 4-6 years of adjuvant ET.[43,44] The biological rational was based on animal models, where resistance was reversed with intermittent treatment with AI. The trial did not meet its primary endpoint, with similar 7-year DFS (HR 1.03, $P = 0.64$) and similar rates of reported adverse events (AEs) in both arms.[43,44] Intermittent administration was associated with less symptom worsening during the first year of treatment, particularly hot flushes, vaginal problems, musculoskeletal pain, sleep disturbances, physical well-being, and mood alterations.[45] Although not designed for non-inferiority, intermittent administration might be considered for women experiencing decreased quality of life (QoL) due to symptom burden.

Haddad et al. showed a threefold increase in risk of BC events, for patients who presented higher levels of estrone or oestradiol while on anastrozole therapy.[46] Among postmenopausal women, they studied the role of high doses of anastrozole in patients with inadequate suppression of estrogen levels (∼30% of the population in the study). With dose escalation, the majority achieved adequate values of suppression.[46] Hence, we are now facing a shift in the paradigm of the standard doses of ET, especially in the concept of 'one size fits all'.

NEW COMBINATIONS

New targeted agents such as CDK4/6i or PARPi have contributed for important improvements in survival outcomes for the metastatic setting. Several trials evaluated the role of these compounds in the adjuvant setting (Table 1).

Initial findings from the PALLAS and Penelope-B trials, which investigated the use of palbociclib in combination with adjuvant ET in high-risk patients, failed to show improved outcomes, and therefore, palbociclib is not approved in the adjuvant setting.[14,47-50] On the contrary, in the monarchE trial, the addition of 2 years of abemaciclib to ET showed an absolute increase of 7.6% and 6.7% in 5-year iDFS and DDFS, respectively.[15,51] Likewise, the results for the NATALEE trial showed that ribociclib induces an absolute benefit of 3.3% and 2.2% in terms of iDFS and DDFS, respectively, at 3 years ($P < 0.005$) and follow-up of patients continue in this trial.[16,52] Of note, ∼30% of patients eligible for NATALEE would not be eligible for monarchE.

In the OlympiA trial, adjuvant olaparib demonstrated significant survival benefits in patients with germline BRCA 1/2 pathogenic or likely pathogenic variants in human epidermal growth factor receptor 2 (HER2)-negative BC, with a 9.9% increase in 3-year iDFS and 3.4% increase in 4-year OS.[14,53] These benefits also exist in the subgroup of hormone receptor-positive BC patients, although with limited data due to their smaller representation in the trial (18.2%).[14,53] For patients eligible for both CDK4/6i and olaparib, the best option or sequence is yet unknown.[54] The 2024 European Society for Medical Oncology (ESMO) guidelines do not recommend combining the two therapies, but do consider the possibility of sequential therapy starting with olaparib.[1]

The implications of extended duration of ET combined with CDK4/6i remain uncertain, as the carry-over effect of these drugs is not well established. In monarchE, 2 years of abemaciclib has impacted iDFS at 5 years, while palbociclib did not seem to present the same effect in the Penelope-B trial.[49,51] Currently, the long-term impact of the addition of these agents is still unknown. Patients included in these four trials will receive at least 5 years of ET. However, how many will extend adjuvant treatment with ET is not clear. Moreover, since these patients are at high risk, it is advisable to continue EET for at least 7-8 years and in some cases up to 10 years.

Table 1. Summary of trials of ET combined with CDK4/6 or PARP inhibitors in hormone receptor-positive/HER2-negative breast cancer

	PALLAS[47,48,107]	Penelope-B[49,108]	monarchE[15,51,109,110]	NATALEE[16,52,111]	OlympiA[14,53,112]
Trial design					
Sex	Men and women	Women	Men and women	Men and women	Men and women
Menopausal status	Pre- and postmenopausal	Pre- and postmenopausal	Pre- and postmenopausal	Pre- and postmenopausal	Pre- and postmenopausal
Disease severity	Stage II Stage III N0-N3	Residual invasive disease after NACT ≥16 weeks (including 6 weeks of taxane) CPS+EG ≥3 or 2 if ypN+ N0-N3	Cohort 1 ≥4 ALN or 1-3 ALN and tumour size ≥5 cm and/or G3 Cohort 2 1-3 ALN and Ki-67 ≥20%	Stage III Stage IIB and IIA N1 Stage IIA N0 G3 or N0 G2 and Ki-67 ≥20% or high risk by genetic test	Neoadjuvant group TNBC: non-pCR HR+/HER2−[a]: non-pCR and CPS+EG score ≥3 Adjuvant group TNBC: ≥pT2 or ≥pN1 HR+/HER2−[a]: ≥4 ALN
ET partner	AI or Tam (±LHRH agonist)	Standard adjuvant ET (AI, Tam ± LHRH agonist)	Standard adjuvant ET (AI, Tam ± LHRH agonist)	LET or ANA (±LHRH agonist)	Standard adjuvant ET for HR+/HER2−
Dose	Palbociclib 125 mg q.d. (3 weeks on/1 week off)	Palbociclib 125 mg q.d. (3 weeks on/1 week off)	Abemaciclib 150 mg b.i.d.	Ribociclib 400 mg q.d. (3 weeks on/1 week off)	Olaparib 300 mg b.i.d.
Duration of TKI	2 years	∼13 months	2 years	3 years	1 year
Baseline characteristic					
Age					
Median (min-max)	52 (45-61) years	49 (22-76) years	51 (23-89) years	52 (24-90) years	42 (36-49) years
Menopausal status					
Men and pre-	54%[b]	47%	43%	44%	62%
Postmenopausal	56%	53%	57%[c]	56%	38%
Anatomical stage					
IIA/IIB	17%/34%	—	12%/14%	20%/20%	57%[d]/15%[d]
III	49%	—	74%	60%	22%[d]
Nodal status at diagnosis					o
N0/N1/N2-3	13%/49%/38%	11%[e]/69%[e]/20%[e]	0%/40%/66%	27%/41%/19%	NR
Prior (neo)adj CT	83%	100%[e]	98%	88%	100%
Study efficacy					
Median follow-up	31 months	43 months	54 months	28 months	42 months
iDFS					
3 years	88.2% versus 88.5%	81.2% versus 77.7%	89.2% versus 84.4%	90.4% versus 87.1%	86.1% versus 77.3%
HR	0.96 (0.81-1.14)	0.93 (0.74-1.17)	0.68 (0.60-0.77)	0.75 (0.62-0.91)	0.63 (0.50-0.78) HR+/HER2−, 0.68 (0.40-1.13)
DDFS					
3 years	89.3% versus 90.7%	NR	90.9% versus 86.7%	90.8% versus 88.6%	88.0% versus 81.0%
HR	1.05 (0.87-1.28)		0.68 (0.59-0.77)	0.74 (0.60-0.91)	0.61 (0.48-0.77) HR+/HER2−, 0.69 (0.40-1.18)
OS					
3 years	96.8% versus 96%	93.6% versus 90.5%	Immature data	Immature data	92.8% versus 89.1%
HR	1.32 (0.98-1.78)	0.87 (0.61-1.22)	0.90 (0.75-1.09)	0.76 (0.54-1.07)	0.68 (0.47-0.97) HR+/HER2−, 0.90 (0.50-1.78)

Toxicity	PALLAS Any grade	PALLAS Grade ≥3	Penelope-B Any grade	Penelope-B Grade ≥3	monarchE Any grade	monarchE Grade ≥3	NATALEE Any grade	NATALEE Grade ≥3	OlympiA Any grade	OlympiA Grade ≥3
Neutropenia, %	83.5	62.0	95.7	70.0	26.3	19.7	62.1	43.8	16.0	4.9
Diarrhoea, %	16.7	0.7	18.3	0.2	75.7	7.8	14.2	0.6	17.6	0.3
Nausea, %	19.4	0.2	23.7	0.3	29.1	0.5	23.0	0.2	56.9	13.3
Fatigue, %	41.0	2.1	66.4	2.7	38.0	2.9	21.9	0.7	40.1	1.8
Arthralgia, %	38.2	1.1	41.2	0.8	26.2	0.3	36.5	1.0	9.2	0.2
QT prolongation, %	—	—	—	—	—	—	4.2	0.2	—	—
Discontinuation rate	44.9%		17.5		27.7%		19%		10.8%	

AI, aromatase inhibitor; ALN, axillary lymph node; ANA, anastrozole; b.i.d., twice daily; CDK4/6, cyclin-dependent kinase 4/6; CPS+EG, clinical pathological staging-estrogen receptor grading; CT, chemotherapy; DDFS, distant disease-free survival; ET, endocrine therapy; G, grade; HR, hazard ratio; HR+/HER2−, hormone receptor-positive/human epidermal growth factor receptor 2-negative; iDFS, invasive disease-free survival; LET, letrozole; LHRH, luteinizing hormone-releasing hormone; N, node; NACT, neoadjuvant CT; NR, not reported; OS, overall survival; PARP, poly (ADP-ribose) polymerase; pCR, pathological complete response; q.d., once daily; Tam, tamoxifen; TKI, tyrosine-kinase inhibitor; TNBC, triple-negative breast cancer.

[a]In OlympiA, 18.2% of patients had HR+/HER2− BC (results are presented for both TNBC and HR+/HER2− BC).

[b]Men not included.

[c]In monarchE, all men were considered postmenopausal.

[d]Pathological staging only in the adjuvant group.

[e]Clinical nodal status by sonography.

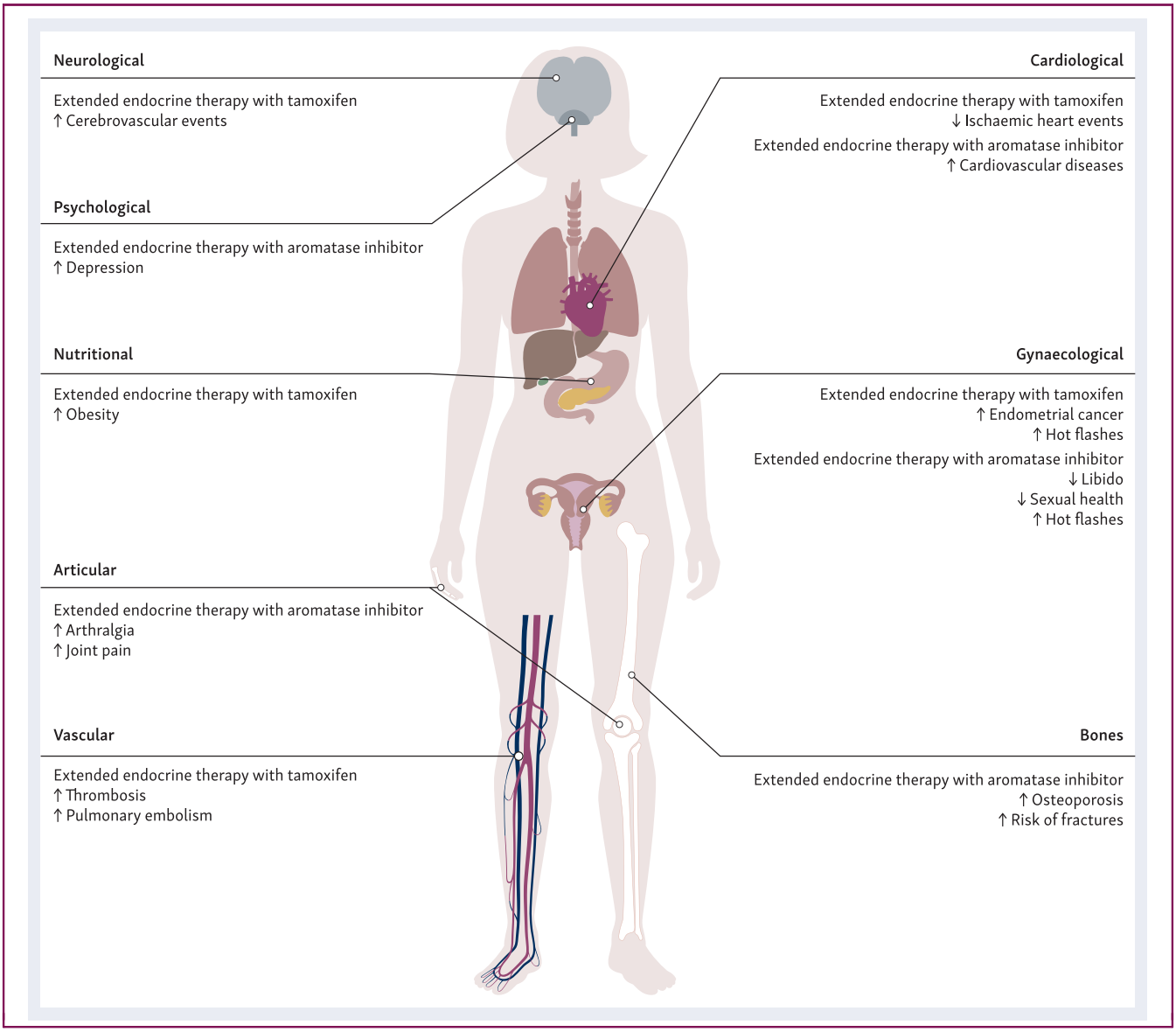

Figure 3. Toxicity of standard duration of ET versus extended ET.
AI, aromatase inhibitor; EET, extended endocrine therapy; Tam, tamoxifen. Created with BioRender.com.

ADVERSE EVENTS AND TOXICITIES

Despite the demonstrated benefit on clinical outcomes,[55] adjuvant ET with tamoxifen or AI is associated with side-effects that can negatively impact QoL and treatment adherence (Figure 3).[56] Early discontinuation and non-adherence to ET have been linked to increased mortality in BC survivors[57] and the rate of discontinuation range from 31% to 73% after 5 years of adjuvant ET.[58] Importantly, early discontinuation is also substantial within the first 5 years, varying between 35% and 50%.[56,59] Therefore, continuous monitoring of side-effects and optimizing their management are paramount.

Osteoporosis and bone fractures

Circulating estrogens play a crucial role in regulating bone turnover by influencing osteoblastic and osteoclastic activities.[60] Consequently, estrogen deficiency increases the rate of bone loss leading to osteoporosis and a higher risk of bone fractures. In postmenopausal women, adjuvant tamoxifen plays an estrogen-agonistic effect on bone, reducing bone loss.[61] However, its effects on bone density can vary depending on the menopausal status. In premenopausal women it can induce bone loss, especially in the lumbar spine, increasing the risk of osteoporosis.[62,63] Bone fracture rates were similar in 10 versus 5 years of adjuvant tamoxifen (RR 0.86, 95% CI 0.61-1.21).[18]

Bone-related toxicities seem to be higher in patients receiving EET with AI. In trials such as MA.17 and ABCSG-6a, where patients switched from tamoxifen to extended AI therapy, differences were observed in fracture rates. The ABCSG-6a trial, which involved an additional 3 years of AI, showed similar fracture incidence between treatment arms (0.8% for observation versus 1.1% for anastrozole),[32]

whereas the MA.17 trial, with an additional 5 years of AI, reported increased clinical fractures (5.2% versus 3.1%, $P = 0.02$) and diagnoses of osteoporosis (5.3% versus 1.6%, $P < 0.0001$).[29] Moreover, in trials with sequential ET with tamoxifen followed by AI, such as GIM-4, DATA, and AERAS, increased rates of fractures, osteoporosis, and osteopenia were consistently observed.[33,37,38] However, the NSABP-42 trial reported similar incidence of osteoporotic fractures (4.8% versus 5.4%).[34] For those treated with AI for 10 years, such as in the MA.17R trial, even with bisphosphonate use, prolonged AI therapy for 10 years was associated with a higher incidence of fractures, highlighting the ongoing risk despite preventive measures (14% versus 9%, $P = 0.001$).[42] In addition to findings from individual trials, two meta-analyses, of 7 and 11 RCTs, revealed an increase in bone fractures in the group of patients treated with extended AI [odds ratio (OR) 1.34, 95% CI 1.16-1.55; and OR 1.33, 95% CI 1.18-1.59, respectively].[64,65]

Given the significant impact of EET on bone health, in both premenopausal and postmenopausal women, it is crucial to clearly explain the potential risks of bone loss and fractures to all patients before the start of treatment. Implementing proactive strategies and lifestyle modification to prevent osteoporosis and fractures is essential to reduce the risk of complications associated with EET. Weight-bearing exercises, adequate calcium and vitamin D intake, and smoking cessation can significantly contribute to maintain bone health.[63,66] Additionally, close monitoring of bone density and early intervention with pharmacological agents are key components of fracture prevention strategies.[63,67]

Endometrial cancer

The use of tamoxifen is associated with an increased risk of endometrial cancer and the incidence appears to increase when prolonging therapy beyond 5 years.[5,68] The aTTom trial showed an increased risk of endometrial cancer with 10 years of tamoxifen versus 5 years (RR 2.20, 95% CI 1.31-2.34) with more endometrial cancer death (1.1% versus 0.6%, absolute hazard 0.5%, $P = 0.02$).[19] Similarly, in the ATLAS trial, endometrial cancer incidence during years 5-14 was 3.1% in the prolonged tamoxifen arm versus 1.6% in the control arm (RR 1.74, 95% CI 1.30-2.34).[18]

Cardiovascular adverse events

Circulating estrogens play a role in cardiometabolic health. Among patients with early BC, cardiovascular death emerges as a significant competing risk, in particular for older woman 5 years after the diagnosis.[69] Lowering circulating estrogen levels is associated with detrimental effects on both blood vessels and myocardium.[70] Ten years of tamoxifen use was associated with higher rates of pulmonary embolus (RR 1.87, 95% CI 1.13-3.07) and lower rates of ischaemic heart disease (RR 0.75, 95% CI 0.60-0.95). Additionally, the risk of stroke was similar in the two arms (RR 1.06, 95% CI 0.83-1.36).[18] Compared with tamoxifen, the use of AI is associated with higher incidence of cardiovascular disease, and prolonged therapy is associated with even higher risk.[64,71]

The impact of EET on cardiovascular toxicity is still controversial. The MA.17 trial revealed no significant difference in cardiovascular events between treatment arms (4.1% versus 3.1%, $P = 0.17$).[29] In sequential ET trials such as GIM-4 and DATA, no disparities in cardiovascular events were observed, while GIM-4 showed a higher incidence of grade 1 hypertension (1.8% versus 0.7%).[33,38] However, the NSABP B-42 study reported increased thrombotic events following prolonged letrozole therapy (HR 1.85, 95% CI 1.18-2.88).[34] On the other hand, the MA.17R trial, involving 10 years of AI therapy, showed no significant difference in cardiovascular events (12% versus 10%, $P = 0.21$).[42] These findings emphasize the necessity for tailored approaches to mitigate cardiac toxicity risks in patients with hormone receptor-positive BC undergoing EET.

Quality of life and adherence

QoL and adherence are critical considerations in the use of EET. Ferreira et al. revealed that QoL deterioration can persist up to 2 years after diagnosis, with ET having a more significant negative impact than chemotherapy.[72] This underscores the need for careful patient selection when considering ET escalation, as long-term QoL impacts may influence treatment tolerance. Persistent, bothersome symptoms, such as insomnia, fatigue, menopausal symptoms, and arthralgia, often lead to early discontinuation of ET. Pistilli et al. further highlighted adherence issues, finding that 16% of patients had tamoxifen serum levels below the adherence threshold, despite more than half of these patients self-reporting adherence.[73] Nonadherent patients demonstrated significantly shorter DDFS.[73] Although there is limited evidence on QoL specifically in EET, smaller studies, such as that by Kool et al.[74], provide some insights. Larger prospective cohorts, such as the CANTO study (NCT01993498),[75] may offer valuable insights into patient-reported outcomes in EET, addressing the ongoing need to balance efficacy with tolerability in long-term therapy.

PREDICTING LATE RELAPSES

Hormone receptor-positive BC is the most susceptible subtype of late recurrences,[8,9] with around 20%-40% of patients developing distant metastasis, half of which occur 5 or more years after the primary tumour diagnosis.[76] This underscores the importance of predicting the personal risk and of adjusting adjuvant ET accordingly. Continuing adjuvant ET beyond 5 years must be considered based on a risk—benefit assessment, as EET is associated with AEs that must be weighed in the therapeutic decision. While traditional criteria such as tumour size, lymph node involvement, and tumour grade consistently correlate with late recurrences,[77-79] determining which patients are at real risk of late recurrences remains challenging. In recent years, various tools have emerged to aid physicians in this effort, assessing both adjuvant treatment benefit and risk of late BC recurrences.

Online clinical tools

The Clinical Treatment Score post-5 years (CTS5) is a freely accessible online tool designed to estimate the risk of late recurrences in postmenopausal patients who have completed 5 years of adjuvant ET without recurrence.[80] Developed according to clinicopathological parameters from the ATAC trial as the training set and the Breast International Group (BIG) 1-98 trial as the testing set,[81,82] CTS5 uses tumour size and grade, number of involved nodes, and patients' age at diagnosis to identify patients at higher risk of recurrence and for whom EET can be useful.[80,83] A retrospective study by Richman et al. found a 10-year distant relapse risk of 2.9% for the CTS5-low group, compared with 7.2% for the intermediate-risk and 12.9% for the high-risk groups, suggesting patients with a higher CTS5 risk may benefit substantially from adjuvant ET beyond 5 years.[84]

Genomic testing

To date, several genomic multi-parametric tests have been designed to assess an individual's risk of BC recurrence by analysing the expression profile of specific cancer-related genes. The OncotypeDX, PAM50, MammaPrint, and EndoPredict assays have been developed based on intrinsic tumour biology to try to predict the benefit of de-escalating adjuvant chemotherapy.[85] However, many of these tests are not created to predict late recurrences in addition to early recurrences (relapse <5 years after initial treatment) and only a few have shown to be prognostic for late relapses (Table 2).[79]

OncotypeDX, a well-established multi-gene assay, assesses the risk of recurrence in women with hormone receptor-positive BC. In the transATAC trial, it was not predictive of late distant recurrences (years 5-10) when adjusted for clinical parameters.[78,113] The PAM50 Prosigna assay added prognostic information for distant late recurrences and was more effective than OncotypeDX.[114] The MammaPrint assay has also been evaluated in many subgroups of patients, but the prognostic information added by this assay is limited to the first 5 years after diagnosis and there are no solid data regarding the potential role of MammaPrint in informing the potential benefits of EET.[116] The EndoPredict assay and EPclin score have been developed with the aim of combining the EndoPredict score with clinical information, such as nodal status and tumour size.[115] Both are available as continuous scores or categorized into low- and high-risk groups. These signatures have been specifically investigated for their association with late distant recurrences, with EPclin demonstrating superior predictive accuracy compared with the genomic score alone.[115]

Patients with negative lymph nodes or 1-3 positive lymph nodes and who have already completed 5 years of adjuvant ET may have EET-guided decision based on their BCI.[117] BCI is an RT—PCR test that can be carried out on formalin-fixed, paraffin-embedded BC tissue and integrates two biomarkers based on the expression of both genes that assess tumour responsiveness to ET (HOXB13 : IL17BR ratio) and the molecular grade index (MGI), which consists of the average expression of five cell cycle-associated genes. The BCI test is able to provide a quantitative estimate of the risk of late distant recurrences 5 years after diagnosis and the cumulative risk of distant recurrence over 10 years, and a prediction of the probability of benefit from EET.[117] An exploratory analysis was also carried out to further clarify which of the two components of the BCI score predicts late distant recurrences, and results showed that only the HOXB13 : IL17BR ratio significantly predicted late recurrences.[118] MGI seems not to be prognostic for late distant recurrences, similarly to proliferation-related tumour markers such as Ki67 or clinical tumour grade.[78]

Although these tests provide insights for predicting late recurrences, the decision to continue ET beyond the first 5

Table 2. Principal genomic tests and their clinical validations to investigate predictive and prognostic value of late recurrence

	Oncotype DX[78,113]	Prosigna (PAM50)[114]	EndoPredict[115]	MammaPrint[116]	Breast Cancer Index (BCI)[41,117,118]
Type of assay	21-gene recurrence score Centralized	50-gene assay Decentralized	12-gene assay Decentralized	70-gene assay Centralized	2-gene ratio (H/I) and molecular grade index Decentralized
Tissue sample	FFPE	FFPE	FFPE	Fresh frozen or FFPE	FFPE
Technique	qRT-PCR	qRT-PCR	qRT-PCR	DNA microarray and qRT-PCR	qRT-PCR
Results presentation	Low-, intermediate-, and high-risk groups	Continuous variable	Dichotomous: Low and high-risk groups	Dichotomous: Good and poor prognosis	Continuous variable
Clinical validation for late recurrence	TransATAC trial ($n = 785$ patients)	TransATAC trial ($n = 785$ patients) ABCSG-8 ($n = 1246$ patients)	ABCSG-6 and ABCSG-8 trials ($n = 1702$ patients)	ABCSG-8 ($n = 658$ patients)	TransATTOM ($n = 583$) MA-17 ($n = 249$ patients) IDEAL ($n = 454$ patients) NSABP-B42 ($n = 2179$ patients)
Clinical application of the assay	Early relapses Predictive and Prognostic for pN0 and pN1 (1-3 positive nodes)	Early and late relapses Prognostic for pN0 and pN1 (1-3 positive nodes)	Early and late relapses Prognostic for pN0 and pN1 (1-3 positive nodes)	Early relapses Prognostic for pN0 and pN1 (1-3 positive nodes)	Early and late relapses Predictive and prognostic of benefit of extended adjuvant ET

FFPE, formalin-fixed paraffin-embedded; qRT-PCR, real-time quantitative reverse transcription PCR.

years must always account for the context of the single patient.

OPEN QUESTIONS

In the context of hormone receptor-positive/HER2-negative advanced BC, patients who progressed on CDK4/6i do not seem to derive the same benefit from continuing standard ET. As so, several novel ETs are being studied: SERDs (e.g. elacestrant), complete estrogen receptor antagonists (CERANs; e.g. palazestrant; NCT04505826, NCT05508906, NCT05266105), proteolysis-targeting chimera (PROTAC, e.g. vepdegestrant/ARV-471), selective estrogen receptor covalent antagonists (SERCAs; e.g. H3B-6545; NCT04288089), SERMs (e.g. lasofoxifene; NCT01042379, NCT05696626).[86] Some of these drugs are already being tested in clinical trials in patients with early disease, in particular oral SERD, PROTAC, and SERM (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105057).[87-100] Trials such as CAMBRIA-1 and EMBER-4 are searching the added value of new anti-estrogen-receptor therapies in patients already treated for 2-5 years with standard ET ± CDK4/6i.[101] Additionally, the coopERA study, a phase II trial, has shown promising results for oral SERDs plus palbociclib, demonstrating significant reductions in Ki67 levels after 2 weeks of neoadjuvant therapy.[102]

The introduction of immunotherapy in hormone receptor-positive/HER2-negative BC is supported by early results from KEYNOTE 756 and CHECKMATE 7FL.[103,104] The combination of anti-programmed cell death protein 1 agents with neoadjuvant chemotherapy increased rates of pathological complete response compared with placebo. However, with short follow-up durations, long-term efficacy remains unclear, particularly with EET. Additionally, the potential for combining these therapies with CDK4/6i and their additional/synergistic effect is still under investigation. Moreover, antibody—drug conjugates are being explored in an earlier setting of BC and a new generation of CDK4/6i is coming, more selective for CDK4[105] or even CDK2[106] (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105057). The impact of these combinations in adjuvant ET, particularly EET, is not known and will remain unknown, until the follow-up for these trials is long enough to allow some conclusions.

CONCLUSIONS

The broad investigation of EET through several trials has left the search for the optimal agent and treatment duration somewhat unclear. Such complexities are pronounced in premenopausal women, where ongoing debates persist due to lack of strong evidence, particularly in patients who have received OFS with tamoxifen or AIs during the first 5 years of adjuvant ET. Conversely, in postmenopausal patients, there is evidence in favour of prolonging adjuvant ET, particularly among those with an increased risk of recurrence (such as the use of adjuvant chemotherapy or the presence of positive lymph nodes) and those who have been exposed to tamoxifen during the first 5 years of treatment; however, high rates of hot flushes, vaginal symptoms, and the increased risk of osteoporosis (particularly in cases treated with long-lasting AI) underline the delicate balance between therapeutic benefits and adverse effects, potentially leading to lower rates of patient compliance.

Supporting the choice of prolonged treatment means balancing the QoL against the costs of toxicity (Figure 1).

The evolving therapeutic landscape for patients with hormone receptor-positive BC is witnessing the integration of new targeted agents like CDK4/6i and PARPi, adding complexity to the search for evidence supporting prolonged ET. While the standard minimum duration of adjuvant therapy in these trials is 5 years, patients have the option to extend this treatment. However, due to the relatively short follow-up periods in trials assessing these new agents, the long-term impact (over 10-15 years) of incorporating these treatments remains uncertain and should be confirmed. As research progresses, it becomes imperative to bridge these knowledge gaps to refine and personalize the approach to prolonged adjuvant ET, ensuring optimal outcomes for patients with BC in the constantly evolving landscape of oncology.

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