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The optimal duration of adjuvant endocrine therapy in early luminal breast cancer: A concise review

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ABSTRACT

Patients with luminal early breast cancer are at risk of relapse, even after five years of adjuvant endocrine therapy. To date, no biomarkers have been clinically validated to identify those patients at risk of late recurrence, who might benefit from extended adjuvant endocrine therapy. In recent decades, multiple clinical trials have tested the role of extending adjuvant endocrine therapies in patients with luminal disease. However, the data currently at our disposal are conflicting. This article reviews all the major trials concerning extended adjuvant endocrine regimens, and formulates some general conclusions and hypotheses of future study.

Setting the scene

Endocrine therapy (ET) is the cornerstone of the adjuvant management of luminal early breast cancer (eBC), a group of breast cancer characterized by positive expression of hormone receptors (HR+). Possible therapies include tamoxifen, aromatase inhibitors (AIs) or, in pre-menopausal patients, ovarian function suppression (OFS), achieved by surgery (oophorectomy) or by GnRH agonists [1]. For some time, five years of adjuvant ET was considered optimal, and became the standard of care for all patients [1]. However, luminal BC is a tumor characterized by a significant rate of late local or distance recurrences. Recurrences can occur after ten years of follow-up [2], with about two-thirds of cancer-related deaths occurring beyond five years from diagnosis [3]. A recent large meta-analysis [4] accounting for 88 trials and 62,923 women with luminal eBC showed that after the standard duration for 5 years of adjuvant ET, the risk of local and distant recurrence persisted throughout the entire study period, up to 20 years from diagnosis. The risk of distant recurrence was strongly and positively correlated with tumor size (T) and nodal involvement (N), whereas tumor grade and Ki-67 status had only a moderate independent predictive value. Conversely, hormone receptor and human epidermal growth factor receptor type 2 (HER2) status were not predictive.

These observations raise the issue as to the necessity of extending adjuvant ET, and of identifying those patients who may benefit from extension. These fundamental questions have been addressed by numerous trials that evaluate the efficacy of various extended adjuvant ET regimens and their respective toxicity and tolerability profiles. The results of these trials are conflicting and as such, the issue of the best strategy and sequence of adjuvant ET is still debated. As a result, there are many different algorithms in current clinical practice [5–7]. The purpose of this article is to review the literature regarding the efficacy and toxicity of extended adjuvant ET in eBC.

A review of the literature: analysis of efficacy

Extending tamoxifen therapy beyond five years

Initially, five years was established as the standard duration of adjuvant tamoxifen administration [8]. One of the first attempts at extending adjuvant ET was to prolong tamoxifen up to ten years from the diagnosis of eBC. Following the publication of encouraging results from a 1984 pilot study [9], Tormey and colleagues performed a small randomized trial to assess the efficacy of maintaining adjuvant tamoxifen beyond five years in women with node-positive luminal eBC. A longer time to relapse was associated with continuing tamoxifen beyond five years, but without statistical significance ($p = 0.81$) [10]. This approach was again recently investigated by two large trials, ATLAS and aTTom, with both providing clear evidence that ten years of tamoxifen improves recurrence free survival (RFS) and overall survival (OS) compared to five years. ATLAS randomized 15,244 women to ten versus

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five years of adjuvant tamoxifen. After a median follow-up of 7.6 years, the experimental group showed a reduction of BC recurrence of 3% (18% vs 21%, relative risk [RR] 0.84, 95% CI 0.76–0.94), with the protective effect emerging after the 10-year treatment period, regardless of age and nodal status (RR 0.90, 95% CI 0.79–1.02 during years 5–9; RR 0.70, 95% CI 0.62–0.90 in subsequent years) [11]. Similarly, the aTTom trial randomized approximately 7,000 women to receive ten versus five years of adjuvant tamoxifen, showing a subsequent approximate 4% reduction in the rate of recurrence (28% vs 32%, p = 0.003) in favour of extended therapy. Regarding BC mortality, aTTom demonstrated a 3% reduction in the tamoxifen-extension group compared to the five-year duration group (21% vs 24% respectively; 392 vs 443 events, p = 0.06). However, it should be noted that HR status was untested in a significant proportion of enrolled patients (approximately 60%) [12], raising the possibility that significant bias potentially exists within this cohort.

In contrast with these findings, the NSABP B-14 study [13] and the Scottish Adjuvant Tamoxifen Trial [14] failed to demonstrate the improvement of RFS and OS prolonging tamoxifen treatment beyond 5 years. NSABP B-14 randomized 1172 pre and post-menopausal patients with luminal eBC who had already received five years of adjuvant tamoxifen to receive tamoxifen for an additional five years (n = 593) or placebo (n = 579). After a median follow-up of 7 years, the hazard ratio of DFS was 1.3 (p = 0.03) regardless of tumor size and ER/PR levels, with an OS of 94% in patients who received extended therapy, versus 91% in the placebo-group (p = 0.07) [13]. The Scottish trial included a substudy (the “duration trial”) that specifically assessed the benefit of continuing tamoxifen for an indefinite duration beyond the first five years (n = 173) versus cessation after the five years of initial therapy (n = 169). This substudy reported a similar RFI between the two arms (HR 1.36, 95% CI 0.95–1.95, p = 0.12) and similar OS (HR 1.32, 95% CI 0.93–1.88, p = 0.12) [14]. Despite these contrasting results, main international guidelines such as NCCN and ESMO include the option of prolonging tamoxifen up to 10 years in patients at high risk of recurrence [5,7].

AIs after tamoxifen

The value of utilizing an AI after previous ET with tamoxifen in the adjuvant setting has been explored in at least five major clinical trials. Among these, MA.17 was the first large trial aimed to investigate the impact of letrozole for five years after five years of initial tamoxifen in postmenopausal patients with luminal eBC. This randomized, double-blind, placebo-controlled phase III trial enrolled 5187 patients, regardless of nodal status. After a median follow-up of 2.5 years, an interim analysis showed an improved disease-free survival (DFS) in the experimental arm (HR 0.58, 95% CI 0.45–0.76) with a 39% reduction of the risk of distant metastasis and a 43% reduction in overall recurrence or new contralateral BC [15]. However, after an early unblinding of the study, 61% of the placebo group crossed-over to letrozole, requiring additional statistical analysis to avoid considering almost two thirds of patients as censored events after such a short follow-up. Therefore, in addition to intention-to-treat (ITT) analyses, Jin and colleagues [16] applied two different statistical approaches: the inverse probability of censoring weighted (IPCW), and the “Shao, Chang and Chow model” (SCC), both previously described elsewhere [17,18]. Both these statistical models adjusted for the effect of crossover from placebo to letrozole, and confirmed that letrozole was statistically significantly superior to placebo in terms of DFS (HR 0.52, 95% CI 0.45–0.61 for IPCW analysis and HR 0.58 95% CI 0.47–0.62 for SCC analysis) and OS (HR 0.61, 95% CI 0.52–0.71 for IPCW analysis and HR 0.76 95% CI 0.60–0.96 for SCC analysis). The NSABP B33 trial [19] evaluated the role of two extra years of adjuvant exemestane after five years of tamoxifen. Following the publication of the MA.17 interim analysis, this study was closed early after randomising 1562 patients. The study was unblinded after a median follow-up of only 2.5 years with subsequent crossover to exemestane by a substantial proportion of patients. The authors reported a non-significant 2% absolute DFS in favour of exemestane arm (p = 0.07). However, the lack of statistical power caused by the early termination of the trial limits the interpretation of the results.

The DATA trial evaluated the efficacy of six versus three years of anastrozole after 2–3 years of adjuvant tamoxifen in 1660 post-menopausal patients with eBC [20]. The five-year DFS, the primary endpoint of the study, favoured the 6-year arm, but was not statistically significant (HR 0.79, 95% CI 0.62–1.02, p = 0.066). However, unplanned subgroup analyses of patients at high risk of recurrence showed interesting results. In node-positive patients, the adapted DFS was 84% in the 6-year arm versus 76% in 3-year arm (HR 0.64, 95% CI 0.46–0.89, p = 0.0075). In patients with nodal involvement and large tumors (≥T2,) the adapted DFS was 83% in 6-year arm versus 69% in 3-year arm (HR 0.53, 95% CI 0.53–0.82, p = 0.0031). Results from ABCSG 6a [21] (N = 856) demonstrated a benefit of extending adjuvant ET with anastrozole for three years after five years of tamoxifen in post-menopausal women in terms of reducing the risk of locoregional or distant recurrence, or contralateral BC (HR 0.62, 95% CI 0.40–0.96, p = 0.031). There was also a statistically non-significant improvement in OS (HR 0.89, 95% CI 0.53–1.34, p = 0.570).

The MA.17R study [22] was conceived as an extension of the MA.17 trial, evaluating the efficacy of extending adjuvant ET with letrozole (five or ten years’ duration) in 1918 postmenopausal women with luminal eBC. The study design initially envisaged enrolling only women who received an AI in the first phase of adjuvant ET, but later also included patients who received tamoxifen initially. At the end of the enrollment, 68.5% of patients had received tamoxifen. After a first extension of ET with letrozole, patients were further randomized to either five years of letrozole or placebo. The authors reported a higher five-year DFS with the extension of adjuvant treatment with letrozole compared to placebo (95% vs 91%). The DFS advantage was mainly attributable to a decreased rate of contralateral BC. The difference in five-year OS were not significant between patients groups (93% vs 94%, p = 0.83).

AIs after AIs and other strategies

Multiple other trials have evaluated the effectiveness of adjuvant ET extension with AIs after initial AI therapy. The recent NSABP-B42 trial was a randomized, double-blind, placebo-controlled study that randomized 1,959 postmenopausal women with luminal eBC to receive five years of letrozole after five years of initial AI therapy, or previous tamoxifen subsequently switched to an AI. After a median follow-up of 6.9 years, there was a 15% relative risk reduction in DFS in the experimental arm, which did not reach the pre-specified level for statistical significance set as 0.0418 (HR 0.85, 95% CI 0.73–0.99, p = 0.048) [23]. Moreover, the extension of ET did not improve OS. However, the authors reported a statistically significant improvement in the breast cancer free-interval (BCFI) (29% reduction in BC recurrence or contralateral BC risk) and a 28% reduction in the cumulative risk of distant recurrence (BCFI: HR 0.71, 95% CI, 0.22–0.81, p = 0.007; distant-recurrence-free-survival: HR 0.72, 95% CI 0.53–0.97, p = 0.03). Contrastingly, no difference in DFS or OS was observed with the extension of ET with letrozole for 2.5 or 5 years subsequent to five years of standard initial adjuvant ET (tamoxifen or AIs) in the IDEAL study (N = 1824) [24]. However, a subgroup analysis suggested a major advantage with ET extension in patients with node-positive disease [25].

At the 2017 San Antonio Breast Cancer Symposium, results from the ABCSG-16 study were presented [26]. This phase III trial enrolled 3,484 postmenopausal women with luminal eBC to receive an initial five years of standard adjuvant ET consisting of either tamoxifen, AIs or switching from tamoxifen to AIs, and thereafter to receive anastrozole for a further two (n = 377) or five (n = 380) years. The primary

endpoint was DFS. The difference between DFS rates between the two arms was not statistically significant (71.1% for 2 years versus 70.3% for 5 years, HR 0.997, 95% CI 0.86–1.15, p = 0.982). No difference between the two arms in terms of OS was observed.

The SOLE trial evaluated an alternative approach to ET extension with letrozole, comparing a strategy of intermittent dosing with that of continuous therapy. In 4,884 postmenopausal patients, intermittent administration (9 months on, 3 months off) of letrozole for a further five years after 5–6 years of standard ET reduced the risk of recurrence to a similar extent as continuous administration (DFS 85.8%, 95% CI 84.2–87.2 in the intermittent arm vs 87.5%, 95% CI 56.0–88.8, HR 1.08, 95% CI 0.93–1.26 for continuous dosing, p = 0.31) [27]. These results suggest that intermittent administration of extended AI may represent a feasible option, particularly in patients with poor tolerance to therapy. One of the most interesting data emerging from SOLE is the influence exerted by the previous adjuvant therapy on the subsequent efficacy of letrozole in the period following the fifth year [28]. Continuous administration of letrozole improved outcomes in patients who had previously received tamoxifen, whilst intermittent administration improved OS in patients who received letrozole in the first phase of ET. A potential explanation could be that greater control of micro-metastatic disease is achieved with intermittent administration after AIs, due to resensitization of neoplastic cell clones to letrozole during the therapeutic breaks [29].

Finally, a very recent meta-analysis by Gray and colleagues [30] examined data from 12 randomized trials (24,912 women) comparing 3–5 years of AIs versus no treatment following at least five years of initial adjuvant ET. Preliminary data, presented in abstract form, showed that extended adjuvant therapy using AIs following five years of standard ET (tamoxifen, AIs or switching) provided better outcomes in terms of recurrence rate and BC mortality overall. This effect was observed in all predefined subgroups according to prior ET, site of recurrence, age, nodal status, tumor size, grade and duration of follow-up. The definitive data of this meta-analysis are yet to be published, but if confirmed, may further cement the role of AIs in the extension of adjuvant ET.

All the major trials concerning extension of ET are summarized in Table 1.

Prolongation of ovarian suppression with GnRH analogues

Ovarian function suppression (OFS) obtained by administration of gonadotropin-releasing-hormone analogues (GnRHa) represents an additional ET option in pre-menopausal women [31]. Despite numerous trials to evaluate the effectiveness of GnRHa therapy in the adjuvant setting, the optimal duration has not been established. On the basis of the available data, OFS should be given for at least two years [7] but not exceed five years [32–34].

Toxicity, tolerability and compliance

The extension of adjuvant ET is associated with problems of long-term toxicity and tolerability, and, consequently, of compliance. Prolongation of tamoxifen is known to increase the risk of thromboembolism and uterine neoplasms, but also prevents osteoporosis in postmenopausal patients. Both the ATLAS and the aTTom studies reported increases in the risk of endometrial cancer. The aTTom study reported a RR of 2.20 (p < 0.0001) with a 0.5% increase in absolute risk of related deaths (p = 0.02). Conversely, ATLAS showed a doubling of endometrial cancer cases. The incidence of endometrial cancer was 1.6% in control group, and 3.1% in extension group. Similarly, a doubling of mortality rates from 0.2% to 0.4% was observed. Furthermore, in both studies, approximately 40% of patients assigned to receive tamoxifen for ten years discontinued therapy prematurely due to adverse events [11,12].

The addition of AIs after initial ET with AIs or tamoxifen is generally characterized by an increase in the side effects typical of this class of drugs, such as osteopenia, osteoporosis, bone fractures, dyslipidemia, cardiovascular events, arthralgias and myalgias. MA.17 reported osteoporosis to be significantly more frequent in the extension arm (8.1% vs 6.0%, p = 0.003), although there was no significant difference in terms of osteoporotic fractures (5.3% vs 4.6%, p = 0.25) [15]. Similarly, in MA.17R, significant bone demineralization (measured by bone densitometry) was reported in the extension group (loss of density −3.2% vs +1.4%, p < 0.001) [22]. In NSABP-B42, extended ET with letrozole was associated with an increased risk of arterial thrombotic events (HR 1.85, p = 0.007), whilst the rate of osteoporotic fractures

Table 1
Synoptic table of the principal clinical trials on extended adjuvant endocrine therapy in women with hormonal-sensitive early breast cancer.

Trial	Therapy	n	Population	Menopausal status	DFS	Follow-up (years)	Absolute benefit	HR
ATLAS	Tam x 5y	6846	HR+	Pre and post	79%	8	3%	0.84
	Tam x 10y		Any N		82%			p = 0.002
aTTom	Tam x 5y	6953	HR+	Pre and post	76%	9	3%	0.86
	Tam x 10y		Any N		79%			p = 0.003
MA.17	Tam x5y → Placebo x5y	5187	HR+	Post	89.8%	5.4	4.6%	0.58
	Tam x5y → AI x 5y		Any N		94.4%			p < 0.001
MA.17R	Tam x0-5y → AI x5y → PBO	1918	HR+	Post	91%	6.3	4%	0.66
	Tam x0-5y → AI x 5y → AI x 5y		Any N		95%			p = 0.01
NSABP B14	Tam x 5y → PBO	1172	HR+	Pre and post	86%	7	6%	1.3
	Tam x 5 y → Tam x 5 y		N –		92%			p = 0.03
NSABP – B33	Tam x 5y → PBO x5y	1598	HR+	Post	89%	2.5	2%	0.68
	Tam x 5y → AI x 5y		Any N		91%			p = 0.07
NSABP – B42	AI x5y or AI/Tam x5y → AI x5y	3966	HR+	Post	84.7%	6.9	3%	0.85
	AI x 5y or AI/Tam x5y → PBO		Any N		81.3%			p = 0.048
DATA	Tam x2-3y → AI x6y	1912	HR+	Post	83%	4.1	4%	0.79
	Tam x2-3y → AI x3y		Any N		79%			p = 0.07
IDEAL	Tam, AI or AI/Tam x 5y → AI x2.5y	1824	HR+	Post	84.7%	6.6	3%	0.96
	Tam, AI or AI/Tam x 5y → AI x5y		Any N		87.9%			p = 0.70
ABCSG-6a	Tam x 5y (+/− AG) → Ana x3y	856	HR+	Post	92.9%	5.2	4.7%	0.62
	Tam x 5y (+/− AG) → stop		Any N		88.2%			p = 0.31
ABCSG16	Tam, AI or AI/Tam x 4-6y → Ana x2y	3484	HR+	Post	71.1%	8.8	−0.8%	1.007
	Tam, AI or AI/Tam x 4-6y → Ana x5y		Any N		70.3%			p = 0.925
SOLE	ET x 4/6y → AI x 5y (cont)	4884	HR+	Post	85.8%	5	1.7%	1.08
	ET x 4/6y → AI x 5y (9 m ON, 3 m OFF)		Any N		87.5%			p = 0.31

Abbreviations: DFS: disease free survival, HR: hazard ratio, HR+: hormonal sensitive, n: number of patients enrolled, N: num Tam: tamoxifen, AI: aromatase inhibitors, PBO: placebo; y: years, AG: aminoglutethimide, Ana: anastrozole, ET: endocrine therapy, cont: continuing, m: months, p: p-value.

was similar between the two arms [23]. In ABCSG-16 trial [26] 6.3% of patients on 5 years extended AI had experienced bone fractures. The difference on fracture-events between 2-year and 5-year groups was 27 events (71 fractures in 2-year arm and 98 fractures in 5-year arm). Authors' conclusions were that prolonged treatment with AI (anastrozole) could be a risk for fractures.

The DATA and IDEAL trials reported a low number of adverse events, mainly grade 1–2 [20,24]. Finally, the SOLE trial, contrary to intuition, reported a higher number of Grade 3 and above adverse events in patients receiving intermittent AI therapy (43.5% Vs 41.6%) [27].

A comprehensive meta-analysis [35] considered results from seven trials comprising 16,349 patients regarding the toxicity of extending ET with AIs. As may be expected, extension was associated with an increased of risk of cardiovascular events (odds ratio [OR] = 1.18, p = 0.05), bone fractures (OR = 1.34, p < 0.001) and treatment discontinuation due to side effects (OR = 1.45, p < 0.001). There was also a statistically insignificant increase in the rate of deaths without BC recurrence. Moreover, extended use of AIs was correlated with a numerical excess of deaths without BC recurrence (OR = 1.11, p = 0.34) [35]. These results suggest that the potential, not yet definitively demonstrated survival advantage of extending ET with AIs may be at least partially offset by an increase in non-BC-related mortality, leading to a similar OS rate between the treatment groups.

To reduce the side effects of AI there are different strategies, including calcium and vitamin D supplementation, increase of physical activity and antiresorptive therapies with bisphosphonates or denosumab. Recent data from a meta-analysis of randomised trials of bisphosphonates as adjuvant systemic therapy for eBC (18,866 women) by the Early Breast Cancer Trialists' Collaborative Group [36] showed a reduction of risk of fracture in postmenopausal patients from 7.3% to 6.3% (RR = 0.85, p = 0.02). Similarly, adjuvant denosumab 60 mg every 6 months reduces the risk of clinical fractures in postmenopausal patients receiving AIs for eBC, as shown in the ABCSG-18 trial, a prospective double-blind, placebo-controlled multicenter phase 3 study in which 3420 patients with HR+ eBC received treatment with AIs and placebo or denosumab [37]. Time to first clinical fracture was significantly delayed in the experimental arm compared with placebo arm (HR 0.5, p < 0.0001).

Compliance in sequential treatments is generally low, particularly in women aged under 40 years (HR 1.51, 95% CI 1.23–1.85) [38]. This issue is particularly important in the adjuvant setting considering that non-adherence influences clinical outcomes [39]. An interesting finding in this regard emerges from the SOLE trial, which reported a 24% discontinuation rate in both treatment arms, despite the hypothesis that intermittent administration would result in better compliance due to time spent off treatment [27].

In this context we can consider also a strategy of ET de-escalation to reduce treatment burden, side effects and, consequently, compliance rate. However, while several clinical trials are exploring the role of de-escalation of chemotherapy or anti-HER2 therapy in the adjuvant setting, little is known about the effective role of ET de-escalation in patients with HR+ eBC with high risk of recurrence. In the 15th St. Gallen International Breast Cancer Consensus Conference (2017), the Panel stressed the weight of patient preference and tolerability in the decision to extend the ET treatment over 5 years [40].

Tools to predict risk of late recurrence

An ideal risk stratification tool aims to maximize the benefits to patients who could benefit from the extension of adjuvant ET, whilst avoiding unnecessary exposure to side effects in patients who have already derived the majority of potential benefit within the first 5 years of treatment.

The St Gallen 2017 conference [40] recently addressed the issue of adjuvant ET extension, with 89% of the expert panel approving extended therapy for at least five years. A further 66% was in favour of extending ET until 15 years in patients considered to be at high risk of relapse, but the definition of “high risk of relapse” proved controversial.

Many previous studies have led to the identification of different sets of genes related to late relapses, including ESR1, ESR2, EGFR, BCL2, AR, p53 and TP3 [41,42]. In clinical practice there are a number of available tools to stratify relapse risk, starting with the usual clinicopathological characteristics of the primary tumor, to validated molecular assays such as Oncotype DX, the Prediction Analysis of Microarray 50 (PAM50), and other genomic signatures (Mammaprint, EndoPredict). In particular, the 21-Gene Recurrence Score of Oncotype DX seems to be a strong predictor for late recurrence (> 5 years from diagnosis) in patients with high ER expression levels [43]. PAM50 has also been shown to be a reliable tool to predict late distant recurrence [44].

The EndoPredict (EP) multigene test combines the expression of three proliferative and five ER-associated genes. Its result is expressed as “EPclin”, a recurrence risk score which also accounts for clinical parameters such as nodal status and tumor size. In transATAC, the cohort derived from the ATAC population for translational substudies, the EPclin score was able to provide prognostic information in both early (within five years of diagnosis) and late (beyond five years from diagnosis) recurrences [45]. In this cohort, the low-risk group of patients after 5 years of adjuvant ET has an absolute risk of distant metastases of 1.8% between five and ten years of follow-up, suggesting they might have sufficiently treated with only five years of adjuvant ET.

The Breast Cancer Index (BCI) is a score that combines two independent markers: the HOXB13/IL17BR (H/I) gene-expression ratio, and the molecular-grade index (MGI). In the MA.17 population, both BCI and H/I (but not MGI) were predictive of late recurrence, and HOXB13 expression at diagnosis was predictive of benefit from extended use of letrozole [46]. The BCI was also evaluated in the transATAC cohort as a prognostic marker of late distant relapse. It was shown to be a strong independent marker of late-distant relapses in patients without nodal involvement at diagnosis [47]. The use and role of these tools are summarized in Table 2.

Despite these encouraging results, the routine use of such assays is limited by availability and prohibitive costs. They are not yet recommended for guiding therapy of HR+ eBC beyond five years of diagnosis. Moreover, as they are derived from analysis of the primary tumor only, they do not provide information about the potential presence of micrometastatic disease in the periphery, especially following years of local and systemic adjuvant therapy. Indeed, after five years of adjuvant ET, it is reasonable to assume that, if there are dormant micro metastatic subclones present increasing the risk of subsequent late relapses, these may have been selected by ET pressure and acquired endocrine resistance. Assuming this hypothesis, it may be sensible to combine clinical pathological and genomic risk stratification criteria with additional tools. This approach addresses not only assumptions of theoretical risk of relapse, but also monitors for detection of residual disease. For example, one such additional method may involve the detection of circulating tumor cells (CTC) or ctDNA after five years of adjuvant ET, and possibly also the presence of clonal/subclonal gene mutations associated with conferring endocrine resistance. In so doing, the detection of circulating biomarkers in this second time-point (after five years of adjuvant ET) could provide not only prognostic, but also predictive information. This would allow the identification of patients with endocrine-sensitive micrometastatic disease who may benefit from extended adjuvant ET, whilst possibly also identifying those with mutations associated with endocrine resistance. In this context, studies are ongoing to evaluate the role of potential circulating biomarkers to address these open issues.

Sparano and colleagues [48] recently published results of a prospective evaluation of a CTC identification assay (CellSearch system) used to determine the risk of BC late relapse after five years of adjuvant ET. The evaluated population was derived from the E5103 trial, a

Table 2
Synoptic table of molecular diagnostic tests most commonly available in clinical practice (other than ER, PR and HER2).

Assay	Endorsed use	Endorsed by	Not endorsed but used by supporting data
OncotypeDX – 21 genes recurrence score	HR+, estimate risk of recurrence, selection for adjuvant chemotherapy	ASCO, NCCN, St Gallen	Prediciton of recurrence after 5 years from diagnosis
Prosigna PAM50	HR+, estimate risk of recurrence, selection for adjuvant chemotherapy	ASCO, NCCN, St Gallen	Prediciton of recurrence after 5 years from diagnosis
Breast Cancer Index (BCI)	HR+, estimate risk of recurrence, selection for adjuvant chemotherapy	ASCO, St Gallen	Prediciton of recurrence after 5 years from diagnosis. Prediction of benefit from extensed endocrine therapy
EndoPredict (EP score)	HR+, estimate risk of recurrence, selection for adjuvant chemotherapy	ASCO, St Gallen	Prediciton of recurrence after 5 years from diagnosis
MammaPrint	HR+, estimate risk of recurrence, selection for adjuvant chemotherapy	St Gallen	Prediction of chemotherapy sensitivity in HR+ breast cancer
Ki67 expression (ICH)	HR+, estimate risk of recurrence, selection for adjuvant chemotherapy	St Gallen	Prediction of chemotherapy sensitivity

Abbreviations: HR+: expression of estrogen receptor, ASCO: American Society of Clinical Oncology, NCCN: National Comprehensive Cancer Network, St Gallen: St Gallen Practice Guidelines, ICH: immunohistochemistry.

double-blind, phase III, negative trial that enrolled 4994 patients with node-positive or high-risk node-negative HER2– eBC to estimate the invasive-disease-free survival (IDFS) after adjuvant therapy with doxorubicin/cyclophosphamide-paclitaxel chemotherapy alone or in combination with bevacizumab [49]. A blood sample was obtained approximately five years after diagnosis from 547 women included in this pre-specified secondary analysis. The CTC assay was positive in 5.1% of all cases, and 6.5% of all patients had a clinical relapse. At multivariate analysis, a positive CTC assay result was associated with a higher risk of recurrence (HR 13.1, 95% CI 4.7–36.3). No clinicopathological features related to the primary tumor were predictive of CTC assay results. Moreover, risk stratification based on CTC assay results surpassed the twofold higher late relapse risk showed by multiparameter gene expression assays of the primary tumor. Despite several limitations of this study, such as the small sample size, the short median follow-up time (2.6 years after the first five years from diagnosis) and the evaluation of CTC in a single time point, this is the first study evaluating a CTC assay in the early detection of late clinical recurrence after five years of adjuvant therapy.

Identification of ctDNA after five years of adjuvant ET is understood as a sign of micrometastatic disease [50], but may also allow for the analysis of genomic mutations, leading to a more tailored therapy. In a recent prospective study, Garcia-Murillas and colleagues [51] evaluated the prognostic power of single or repetitive ctDNA measurements in 55 patients with eBC, first identifying somatic mutations in the primary tumors, and then sequencing selected mutations in plasma ctDNA via personalized digital PCR. Detection of ctDNA after the completion of neoadjuvant therapy was strongly associated with relapse. Of those patients with detectable ctDNA during follow-up, 80% relapsed, whereas 96% of those without detectable ctDNA remained free from relapse. Recurrences could be predicted early, with a median anticipation-time of 7.9 months (range: 0–14 months) over clinical relapse. These results suggest that a super-sensitive assay to detect patient-specific mutations in ctDNA may be of clinical value in anticipating the diagnosis of relapse. However, once positive ctDNA results are known, it is unknown whether it is best to respond by re-directing treatment in order to impede the possible eventuality of macrometastatic disease, or to simply increase clinical monitoring in order to detect metastatic/recurrent disease at its earliest clinical stage. No data exists that suggests that extensive monitoring of micrometastatic disease leads to a benefit in terms of overall or disease-free-survival.

This is further complicated by the fact that the mutation rates in hot-spot mutations of frequently altered genes in ctDNA tends to be very low in the adjuvant setting, as has been recently demonstrated in the context of ESR1 mutations by a recent French study, which evaluated the frequency of ESR1 mutations in ctDNA both following completion of adjuvant ET, and at the point of first relapse [52]. Interestingly, no circulating ESR1 mutation was detectable at the end of five years of ET versus 5.3% at first relapse, suggesting detection of ESR1 mutations before relapse may not be clinically feasible.

PIK3CA is the second-most commonly mutated gene in luminal BC [53]. Although PIK3CA mutations are generally associated with lower recurrence and mortality rates [54,55], these mutations frequently have a clonal distribution. Therefore, these mutations present in the majority of cancer cells, and may represent a better marker of early relapse than mutations in ESR1, which are frequently sub-clonal. Although some studies have investigated the detection rate of PIK3CA in ctDNA and its prognostic significance [56,57], to date, data regarding the prognostic and predictive value of PIK3CA mutations in ctDNA after at least five years of adjuvant ET remains scarce.

Despite numerous efforts to detect circulating late-relapse biomarkers, as yet none of these has been clinically validated. As such, the decision to extend adjuvant ET beyond five years is still based mainly on clinicopathological factors related to the primary tumor, such as tumor size and nodal status. Biomarker discovery is therefore still considered a field that requires further confirmation from translational and clinical research.

Perspectives and conclusions

In the context of precision medicine, therapeutic decisions – including the evaluation of the optimal duration of adjuvant ET – should increasingly be based on the individual disease risk profile and counterbalanced with the patient's ability to tolerate treatment, as well as their distinct personal wishes. In all likelihood, the therapeutic landscape of adjuvant ET could soon be changed by the results of ongoing trials such as PALLAS (NCT02513394), UNIRAD (NCT01805271) and SWOG 1207 (NCT01674140), which are aimed to evaluate the role of other agents such as CDK4/6 inhibitors (PALLAS) or mTOR inhibitors (UNIRAD and SWOG 1207) in the adjuvant setting in patients at high risk of relapse.

Contributions

All authors contributed to the conception, drafting, and critical review of the manuscript and provided final approval.

Conflict of interest statement

ALD: AstraZeneca, Lilly, Pfizer (consultant), Novartis (consultant and speaker).

All other authors: no conflicts of interest.

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