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Tailoring adjuvant endocrine therapy in early breast cancer: When, how, and how long?

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ABSTRACT

Endocrine therapy represents the gold standard for the adjuvant treatment of luminal-like early breast cancer, but its personalization is still a major point of debate. To define the most appropriate therapeutic strategy, both the patient's menopausal status at the moment of diagnosis and the individual risk of disease recurrence should be taken into account. Five years of therapy with tamoxifen represent the standard of care for low-risk pre/perimenopausal patients, whilst the combination of ovarian suppression with tamoxifen or an aromatase inhibitor should be considered for high-risk patients. Also, to high-risk patients, an extended strategy can be proposed. Postmenopausal patients, instead, should receive an upfront aromatase inhibitor and an extended strategy can be considered for a high risk of disease recurrence.

Aim of this review is to set a focus on the major studies investigating the optimal type and duration of adjuvant endocrine therapy and evaluate emerging options.

Introduction

In more than 90 % of cases, breast cancer (BC) is diagnosed in early stage, when the disease has not extended beyond the mammary gland and the loco-regional lymph-nodes (N) [1]. Luminal-like BC is the most common molecular subtype, representing up to 70 % of the diagnoses [2].

An estrogen receptor (ER) expression at immunohistochemistry (IHC) $\geq$ 1 % defines BC as ER positive. BCs with an ER expression between 1 and 10 % are referred to as "ER-low" and they have been shown to share biological features with triple negative BC (TNBC), in terms of potential resistance to endocrine therapy (ET) and immune landscape. However, although limited, there is current evidence in favor of the employment of ET also for patients with ER-low BC [3,4].

Adjuvant treatment landscape has recently significantly changed, in relation to the increased deployment of genomic assays in the clinical practice. In particular, Oncotype and MammaPrint are extensively employed to evaluate the likelihood of BC recurrence and therefore determine which patients can be safely treated with ET alone, thereby underlying its pivotal role in this setting.

ET, tailored upon the patient's menopausal status and the individual risk of BC recurrence, represents the mainstay of adjuvant systemic treatment for luminal-like early BC [5].

Premenopausal status

Endocrine agents

Monotherapy with tamoxifen (Tam) for a minimum of 5 years [5] is one of the potential options for pre/perimenopausal luminal-like early BC. When taken regularly, Tam has demonstrated to lower BC recurrence risk throughout the first 10 years and to lower BC mortality risk by almost one third during the first 15 years from the beginning of ET. Such a benefit is observed also for tumors with weak ER expression, but not for ER negative diseases [4,6].

Ovarian function suppression (OFS) can be achieved through removal or irradiation of the ovaries or, more commonly, by using the luteinizing hormone-releasing hormone agonists (LHRHa). In recent

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years, its role has been explored in association with both Tam or an aromatase inhibitor (AI) [7].

There are three main trials in which Tam was compared with the combination of Tam and OFS in premenopausal patients with early BC [8–10]: if the small sample size and the predominantly low-risk patients, led to the early closure of the E-3193 INT-0142 trial with no conclusions derived regarding the survival benefit of adding Tam to OFS [8], positive results were, instead, observed with the SOFT and the ASTRRA trials [10,11].

The SOFT trial randomized 3,066 patients in pre-menopause to receive either Tam alone or Tam plus OFS or exemestane (steroidal AI) plus OFS for a total of 5 years of adjuvant ET [9]. At approximately 8 years of follow-up, a significantly higher disease-free survival rate (DFS rate 83.2 % vs 78.9 %. HR 0.76; 95 % confidence interval [CI], 0.62 to 0.93; p-value = 0.009) and overall survival rate (OS rate 93.3 % vs 91.5 %. HR 0.67; 95 % CI, 0.48 to 0.92; p-value = 0.01) was shown in women treated with Tam plus OFS with respect to those who received Tam alone. Of note, the greatest survival benefits of adding OFS to ET were reported for patients treated with neoadjuvant or adjuvant chemotherapy (CT), for those who were less than 35 year old at the moment of diagnosis and for the subpopulation with HER2-positive BC [9,11].

In the ASTRRA trial, 1,293 premenopausal patients previously treated with neoadjuvant or adjuvant CT, received Tam for 5 years either in monotherapy or in association with the LHRHa goserelin (administered for 2 years). At approximately 5 years of follow-up, a significant benefit in the DFS (DFS rate 91.1 % vs 87.5 %. HR 0.69; 95 % CI, 0.48 to 0.97; p-value = 0.033) and OS rate (OS rate 99.4 % vs 97.8 %. HR 0.31; 95 % CI, 0.10 to 0.94; p-value = 0.029) was reported for the group treated with Tam plus OFS [10].

Also in the ASTRRA trial, the survival advantage of adding OFS to Tam was observed in a population of patients all treated with chemotherapy, thereby considered at high risk of BC recurrence (i.e. younger patients < 35 year old and/or with tumor grade [G] 2 or 3 and/or with lymph-node involvement (N positive; N +) [10].

Many studies, including the aforementioned SOFT trial, tried to evaluate if AIs, employed generally in the adjuvant setting for postmenopausal women, could have a role also in the pre/perimenopausal setting, combined to OFS, in high-risk patients [11–13].

In the ABCSG-12 trial, a total of 1,803 patients with early luminal-like BC were randomized to receive goserelin plus either anastrozole or Tam with or without zoledronic acid for a total of 3 years of adjuvant ET [12]. At almost 8 years of follow-up, a greater DFS rate was reported when combining zoledronic acid to ET (DFS rate 88.4 % vs 85 %. HR 0.77; 95 % CI, 0.60–0.99; p-value = 0.042), whereas no difference was observed between patients treated with anastrozole as compared to patients treated with Tam, (HR for DFS 1.13; 95 % CI, 0.88–1.45; p-value = 0.335). Moreover, a greater, but non-significant, OS rate was observed in patients that received zoledronic acid (OS 96.7 % vs 94.5 %. HR 0.66; 95 % CI, 0.43–1.02; p-value = 0.064) but, looking at the overall survival outcomes in patients treated with anastrozole versus those treated with Tam, a negative impact was observed in the first group (51 versus 35 deaths, respectively; HR 1.63; 95 % CI, 1.05–2.52; p-value = 0.030) [14].

In the HOBOE trial, 1,605 premenopausal women with early BC were allocated to receive for 5 years adjuvant ET consisting of the LHRHa triptorelin with either Tam, letrozole or letrozole plus zoledronic acid. At 5 years, the DFS rates were 85.4 %, 93.2 % and 93.3 %, respectively and, focusing upon the comparison between Tam and letrozole, a non-significant benefit was found in favor of letrozole (DFS HR 0.72; 95 % CI, 0.44–1.12). OS was similar amongst the three treatment arms (log-rank test, p-value = 0.14) [13].

Positive results were observed when combining the results of the SOFT and TEXT trials [11]. The TEXT trial randomized 2,672 premenopausal patients to receive either Tam plus OFS or exemestane plus OFS for a total of 5 years of adjuvant ET. The combined analysis of these two trials revealed, after 8 and 9 years of follow up, respectively, that DFS (DFS rate 86.8 % vs 82.8 %. HR 0.77; 95 % CI 0.67–1.05; p-value=<0.001) and freedom from distant recurrence (91.8 % vs 89.7 %. HR 0.80; 95 % CI 0.66–0.96; p-value = 0.02) were significantly increased, when combining exemestane to OFS [11].

Recently, at the 2021 San Antonio Breast Cancer Symposium (SABCS), the updated results of this combined analysis at a median follow up of 12 and 13 years, respectively, were presented. As reported, a persistently reduced risk of BC recurrence was observed when combining OFS with Tam or exemestane for 5 years, with the greatest benefit among patients who received exemestane. Furthermore, OFS addition to ET reduced the long-term mortality risk. Of note, low-risk patients (not treated with CT) had a 12-year OS greater than 95 % independently from the ET received (including Tam in monotherapy), thus supporting the use of Tam alone in this subgroup of patients [15].

Data from these 4 trials (ABCSG-12, HOBOE, SOFT and TEXT) were pooled in a recently published *meta*-analysis which compared AIs versus Tam in patients in pre-menopause with luminal-like eBC receiving OFS. A reduced risk of BC recurrence was reported for women treated with an AI with respect to those treated with Tam (RR 0.79; 95 % CI 0.69–0.90; p-value = 0.0005), with the greatest advantage observed in the first 4 years, when the type of ET received was different [16].

As a matter of fact, the risk definition for choosing the appropriate ET between AI + OFS with respect to Tam + OFS is multifactorial rather than driven by single features. The composite risk score and STEPP analyses performed in the SOFT and TEXT cohorts showed that women with the lowest composite risk (who did not receive CT) did not have a differential benefit across endocrine regimes. Instead, an improved 5-year breast cancer-free interval (BCFI) with exemestane plus OFS over Tam was observed in the subgroup with the highest composite risk [17].

Taken together, these findings support the use of the combination of an AI and OFS as the best therapeutic option in high-risk patients. On the other hand, low-risk patients can be safely treated with Tam alone.

However, as both ET and OFS are not devoid of adverse events, when proposing an adjuvant therapy the aspects relating to the safety profile of the endocrine agents as well as the patient's preferences must be taken into due consideration. [8,18,19] (Fig. 1) (Table 1).

The optimal strategy: 10 years of Tam, 5 years of Tam plus 5 years of AI or 5 years of Tam?

When defining the most appropriate therapeutic strategy, also the optimal duration of adjuvant ET should be defined. Patients at high risk of BC recurrence that have received 5 years of ET with Tam in monotherapy (due to contraindications or intolerance to OFS), could eventually extend the duration of the ET to a total of 10 years, with either 5 more years of Tam [20,21] or 5 more years of an AI (if they have entered menopause during the adjuvant setting) [22].

The ATLAS study randomized 12,894 women treated with adjuvant Tam for 5 years to either discontinue the treatment or to receive Tam for another 5 years. In the 6.846 patients with ER positive BC, the extended therapy with Tam reduced BC recurrence risk (RR 0.84; 95 % CI, 0.76–0.94; p-value = 0.002), BC mortality (331 versus 397 deaths, p-value = 0.01) and overall mortality (639 versus 722 deaths, p-value = 0.01), although an absolute increased risk of endometrial cancer related mortality of 0.2 % was registered [20].

Similarly, the aTToM trial, in which 6,953 patients that had received for at least 4 years adjuvant ET with Tam were assigned to continue the therapy for another 5 years or to suspend it, reported that, at a median follow up of 9 years, the extended therapy with Tam led to a lower recurrence rate (28 % vs 32 %; RR for recurrence 0.85, 95 % CI, 0.76–0.95; p-value = 0.003). A non-significantly reduced BC mortality rate and an increased risk for endometrial cancer (102 events versus 45 events, respectively; Rate ratio 2.20, p-value=<0.0001) and endometrial cancer related mortality (1.1 % versus 0.6 %, p-value = 0.02) were registered for the extended strategy [21,23].

In both these trials, the reduced risk of recurrence reported by

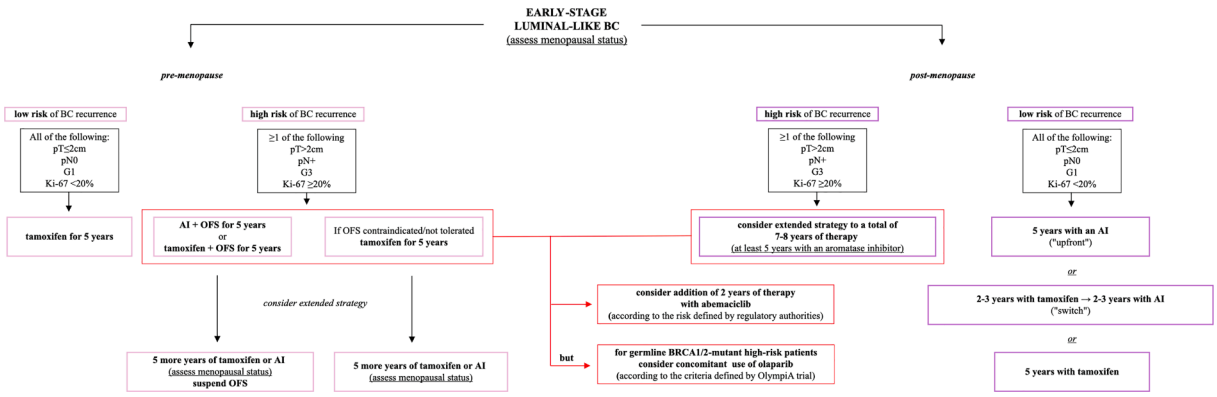

Fig. 1. Flowchart for adjuvant endocrine therapy in early breast cancer patients according to menopausal status and recurrence risk. Abbreviations: breast cancer (BC), aromatase inhibitor (AI), ovarian function suppression (OFS).

extending adjuvant ET was particularly evident starting from year 10 [20,21,23].

If a high-risk patient has completed 5 years of adjuvant ET with Tam and has, in the meanwhile, entered menopause, 5 additional years of ET with an AI could be proposed. The MA.17 trial allocated 5,187 patients (of which approximately 17 % were premenopausal at diagnosis but had postmenopausal status before study entry) who had been treated for at least 5 years with adjuvant Tam, to receive either letrozole of placebo for another 5 years. The extended therapy with letrozole led to a significantly longer DFS (HR 0.58; 95 % CI, 0.45–0.76; p-value=<0.001) and distant DFS (DDFS HR 0.60; 95 % CI, 0.43–0.84; p-value = 0.002) and, in patients with N + BC, also a greater OS was reported (HR 0.61; 95 % CI, 0.38–0.98; p-value = 0.04) [22]. This survival benefit was observed in both patients who were postmenopausal and those who were premenopausal at the time of BC diagnosis, but it was particularly relevant in the latter (HR 0.26; 95 % CI, 0.13–0.55; p-value = 0.0003), at the cost of an increased occurrence of arthralgias (24 % versus 16 %, p-value = 0.004) [24].

The design of the NSABP B-33 trial was very similar, as it randomized postmenopausal women that had received adjuvant Tam for at least 5 years, to receive either exemestane or placebo for another 5 years. The publication of the results of the MA.17 trial, however, led to the early closure of this study and all the patients allocated in the control group, were proposed to receive exemestane in the extended setting [25].

Thereby, according to these data, an extended strategy should be proposed to high-risk (i.e., presence of at least one of these findings: pT > 2 cm, pN+, Ki-67 ≥ 20 %, G3) premenopausal patients who have received 5 years of Tam alone in the adjuvant setting. As there is no data regarding the extended use of OFS, to those patients who have completed 5 years of ET with the combination strategy, could be eventually offered to receive 5 additional years of Tam or an AI, depending upon the menopausal status [26] (Fig. 1) (Table 1).

Postmenopausal status

Endocrine agents

Postmenopausal patients candidate for adjuvant ET are generally offered an AI, considering that, when compared to Tam, AIs have demonstrated to further reduce the risk of BC recurrence and mortality in this subpopulation [27]. In case of intolerance or contraindications to the AIs, however, also 5 years of Tam could be proposed to the patient [5].

AIs in this setting can be taken either continuously for 5 years ("upfront" strategy) or for 2–3 years after 2–3 years of adjuvant ET with Tam ("switch" strategy) [5]. In fact, no relevant difference in terms of survival outcomes had been observed with these 2 different schedules, as reported by both a 2015 EBCTCG *meta*-analysis of clinical trials and by the Italian study FATA-GIM3 [27,28] (Fig. 1).

The EBCTCG *meta*-analysis compared the survival outcomes in patients with luminal-like early BC receiving different schedules of adjuvant ET and it showed that 5 years of ET "upfront" with an AI lower the risk of BC recurrence (10-year recurrence risk 19.1 % versus 22.7 %) and death (RR 0.85; 95 % CI, 0.75–0.96, p-value = 0.010) compared to 5 years of Tam. Also, using AIs in the "switch" strategy reduced in a significant way the recurrence rate in comparison to 5 years of Tam (17 % versus 19 %) and a lower BC related mortality (RR 0.84; 95 % CI, 0.71–0.96; 2p-value = 0.015) and overall mortality (RR 0.82; 95 % CI, 0.73–0.91; 2p-value = 0.0002) was observed in favor of the "switch" strategy. Finally, when comparing the "upfront" and the "switch" strategies, a modest, and yet significantly lower recurrence risk in favor of the "upfront" strategy was reported only in the first 2 years of adjuvant ET, when the ET differed among the 2 patients groups (RR 0.74; 95 % CI, 0.62–0.89; 2p-value = 0.002), whilst comparable recurrence rates were observed in the subsequent 3 years of ET, when all patients were receiving an AI (RR 0.99; 95 % CI, 0.85–1.15). BC related mortality or overall mortality were similar amongst the two strategies [27].

The FATA-GIM3 study confirmed the results obtained by the aforementioned *meta*-analysis: 3,697 postmenopausal women were randomized to receive anastrozole, exemestane or letrozole "upfront" for 5 years or Tam for 2 years with a subsequent switch to one of the AIs for the remaining 3 years of adjuvant ET. No significant differences in DFS were reported at 5 years of median follow up amongst the 2 different therapeutic modalities [DFS rate 88.5 % versus 89.8 % in the "switch" and "upfront" schedule, respectively (HR 0.89, 95 % CI, 0.73–1.08; p-value = 0.23]. Moreover, no differences in OS were observed [OS rate 95.3 % versus 96.8 % in the "switch" and "upfront" schedule, respectively (HR 0.72. 95 % CI, 0.51–1.00; p-value = 0.052)]. Besides for confirming the equal efficacy of the "switch" and "upfront" schedules of administration of the AIs, this study also demonstrated the equal efficacy of the three AIs in terms of both DFS and OS (DFS rates 90.0 % versus 88.0 % versus 89.4 % and OS rates 95.9 % versus 95.7 % versus 96.6 % for anastrozole, exemestane and letrozole, respectively) [28].

The optimal duration: 5, 7, 10 or 15 years?

Although different studies have evaluated the efficacy of different schedules and extensions of adjuvant ET in this setting of patients, the critical question about the optimal duration of the therapy is still open.

Comparing 5 to 7–8 years

The DATA trial randomized 1,912 postmenopausal patients that were treated with 2–3 years of adjuvant Tam, to receive anastrozole for 3 or 6 years. DFS rates at 5 years were comparable amongst the two arms (DFS rate 83.1 % versus 79.4 %. HR 0.79; 95 % CI, 0·62-1.02]; p-value = 0·066) and adverse outcomes, such as osteopenia and osteoporosis, were

Table 1
Main trials evaluating type and duration of adjuvant endocrine therapy. Abbreviations: tamoxifen (Tam), ovarian function suppression (OFS), aromatase inhibitors (AIs), DFS (disease-free survival), HR (hazard ratio), IDFS (invasive disease-free survival).

Menopausal Status	Study	Treatment	Duration of Treatment	Results
pre-menopause	ASTRRA	Tam vs Tam + OFS	5 years	DFS 87.5 % vs 91.1 %, HR 0.69; 95 % CI, 0.48 to 0.97; p-value = 0.033
	combined analysis of SOFT and TEXT	Tam vs Tam + OFS vs exemestane + OFS (SOFT) Tam + OFS vs exemestane + OFS (TEXT)	5 years	DFS 86.8 % in exemestane + OFS vs 82.8 % in Tam + OFS, HR 0.77; 95 % CI 0.67–1.05; p-value=<0.001
	ABCSG-12	Tam + OFS vs anastrozole + OFS +/- zoledonic acid	3 years	no difference in DFS events for Tam vs anastrozole, HR 1.13; 95 % CI, 0.88–1.45; p-value = 0.335
	HOBOE	Tam + OFS vs letrozole + OFS vs letrozole + zoledronic acid + OFS	5 years	no difference in DFS events for Tam vs letrozole, HR 0.72; 95 % CI, 0.44–1.12
	ATLAS	Tam	10 vs 5 years	Recurrence Rate 25.1 % vs 21.4 %, RR 0.84; 95 % CI, 0.76–0.94; p-value = 0.002
	aTToM	Tam	10 vs 5 years	Recurrence Rate 32 % vs 28 %, RR 0.85. 95 % CI, 0.76–0.95; p-value = 0.003
	Ma.17	Tam + Letrozole	5 years of Tam + 5 years of Letrozole vs 5 years of Tam	DFS 94 % vs 96.4 %, HR 0.58; 95 % CI, 0.45–0.76; p-value = <0.001
	monarchE	abemaciclib + any ET	2 years of abemaciclib/ placebo + 5–10 years of any ET	IDFS 92.2 % vs 88.7 %, HR 0.75. 95 % CI, 0.60–0.93; p-value = 0.01
	OlympiA	olaparib	1 year	IDFS 85.9 % vs 77.1 %, HR 0.58; 99.5 % CI, 0.41–0.82; p-value=<0.001
post-menopause	FATA-GIM3	AIs	5 years "upfront" vs 5 years "switch"	DFS 89.8 % vs 88.5 %, HR 0.89. 95 % CI, 0.73–1.08; p-value = 0.23
	DATA	AIs	5 vs 7–8 years	DFS 83.1 % vs 79.4 %, HR 0.79; 95 % CI, 0.62–1.02; p-value = 0.066
	GIM4	AIs	5 vs 7–8 years	DFS 62 % vs 67 %, HR 0.78; 95 % CI, 0.65–0.93; p-value = 0.006
	AERAS	AIs	5 vs 10 years	DFS 84.4 % vs 91.9 %, HR 0.548; p-value = 0.0004
	NSABP-B42	AIs	5 vs 10 years	DFS 72 % vs 76 %, HR 0.84; 95 % CI, 0.74–0.96; p-value = 0.011
	IDEAL	AIs	7 vs 10 years	163 vs 152 DFS events, HR 0.92; 95 % CI, 0.78–1.45
	SALSA (ABCSG16)	AIs	7 vs 10 years	DFS 73.6 % vs 73.9 %, HR 0.99; 95 % CI; 0.85–1.15; p-value = 0.90
	MA.17R	AIs	10 vs 15 years	DFS 88 % vs 90 %, HR 0.8; 95 % CI, 0.63–1.01; p-value = 0.06
	SOLE	AIs	10 years "intermittent schedule" vs 10 years "continuous schedule"	DFS 81.4 % vs 81.5 %, HR 1.03; 95 % CI, 0.91–1.17; p-value = 0.64
	monarchE	abemaciclib + any ET	2 years of abemaciclib/ placebo + 5–10 years of any ET	IDFS 92.2 % vs 88.7 %, HR 0.75. 95 % CI, 0.60–0.93; p-value = 0.01
	OlympiA	olaparib	1 year	IDFS 85.9 % vs 77.1 %, HR 0.58; 99.5 % CI, 0.41–0.82; p-value = <0.001

commonly reported for women allocated to the extended arm. However, a benefit in DFS in favor of the extended arm was reported for patients with N + disease (DFS 84.4 % versus 76.2 %. HR 0.64; 95 % CI, 0.46–0.89; p-value = 0.0075) and with T ≥ 2 cm (DFS 82.7 % versus 69.2 %. HR 0.53; 95 % CI, 0.53–0.82; p-value = 0.0031). OS rates at 5 years were similar (OS 90.8 % versus 90.4 %. HR 0.91; 95 % CI, 0.65–1.29; p-value = 0.60) [29].

Particularly relevant in this setting is the GIM4 trial, in which 2,056 postmenopausal patients treated with 2–3 years of adjuvant Tam were allocated to receive either 2–3 years (5 years of ET in total, control group) or 5 years (7–8 years of ET in total, extended group) of letrozole [30]. This trial showed a higher DFS (12-year DFS rate 67 % versus 62 %, HR 0.78; 95 % CI, 0.65–0.93; p-value = 0.006) and, for the first time in this setting, also a higher OS (12-year OS rate 88 % versus 84 %, HR 0.77, 95 % CI, 0.60–0.98; p-value = 0.036) in the extended arm, at the cost of an increased occurrence of arthralgias and osteoporosis [31].

Comparing 5 to 10 years

In the AERAS trial, 1,697 patients with early BC in post-menopause, that had received adjuvant anastrozole for 5 years either with the "upfront" or the "switch" strategy, were randomized to either receive anastrozole for 5 additional years or to discontinue the therapy. A comparable OS was obtained in the two treatment arms (5-year OS rate 99.5 % versus 99.6 %. HR 1.389; p-value = 0.665), but a higher DFS and DDFS was found in the extended arm (5-year DFS rate 91.9 % versus 84.4 %, HR 0.548; p-value = 0.0004 and 5-year DDFS rate 97.2 % versus 94.3 %, HR 0.514; p-value = 0.0077), at the cost of an increased occurrence of osteoporosis and bone fractures [32].

The NSABP B42 trial was similarly designed, as 3,966 postmenopausal women that had received adjuvant ET for 5 years with an AI either with the "upfront" or the "switch" strategy, were randomized to receive either letrozole or placebo for the subsequent 5 years. At 7 years of follow-up, no significant difference in terms of DFS was observed between the extended and the control arm [33]. However, the updated results of this trials were recently discussed at the SABCS and the 10-year DFS rate resulted significantly improved in the extended arm (DFS 76 % versus 72 %. HR 0.84; 95 % CI, 0.74–0.96; p-value = 0.011), whilst no significant difference was reported in terms of OS rates (OS 86.1 % versus 85.5 %. HR 0.97; 95 % CI, 0.82–1.16; p-value = 0.77). Also, the risk of osteoporotic fractures was not increased in the extended arm [34].

Comparing 7 to 10 years

The SALSA (ABCSG16) trial randomized 3,470 women who had received any adjuvant ET for 5 years to be treated with anastrozole for another 2 years (total of 7 years of ET) or for another 5 years (total of 10 years of ET). At 10 years from randomization, this trial demonstrated similar DFS (DFS rate 73.6 % versus 73.9 %, HR 0.99; 95 % CI; 0.85–1.15; p-value = 0.90) and OS (OS rate 87.5 % versus 87.3 %, HR 1.02; 95 % CI, 0.83–1.25) rates, if the extended therapy lasts for 7 or for 10 years. However, the 10-year extended strategy was associated with a higher risk of osteoporotic bone fractures (HR 1.35; 95 % CI, 1.00–1.84) [35].

In the IDEAL trial, 1,824 women who had received 5 years of any kind of adjuvant ET were randomized to prolong the ET with letrozole for another 2.5 or 5 years. DFS (HR 0.92; 95 % CI, 0.78–1.45) and OS (HR 1.04; 95 % CI, 0.78–1.38) did not significantly vary in the two treatment arms after 6 years of follow up [36].

Comparing 10 to 15 years

The MA.17R trial randomized 1,918 patients who had received at least 4 years of adjuvant ET with an AI (preceded in most cases by a therapy with Tam) to receive letrozole or placebo for the subsequent 5 years. Thereby, in this trial, more than two thirds of the randomized population had already received 10 years of adjuvant ET: the primary aim was to assess the efficacy (in terms of DFS) of a 15-year extended strategy versus a 10-year extended strategy. At the post-hoc analysis, performed to include also death (both BC-related and related to any cause) in the definition of DFS (as it had been previously excluded), no statistically significant difference was observed amongst the two arms, but bone related adverse events were more common in the 15-year extended strategy group [40,41].

Intermittent versus continuous extended therapy

A total of 4,884 women that had received from 4 to 6 years of adjuvant ET were randomized in the SOLE trial to receive letrozole either continuously for another 5 years or intermittently (every day for 9 months, followed by 3 months of suspension in the first 4 years and then every day for the entire fifth year) [42], on the line of pre-clinical data that had demonstrated how the transient suspension of the ET allows to delay the onset of endocrine resistance and to prolong the benefits of the ET [43]. This study failed in demonstrating that the intermittent administration of the therapy can improve the DFS compared to the continuous administration (7-year DFS rate 81.4 % versus 81.5 %, HR 1.03; 95 % CI, 0.91–1.17; p-value = 0.64). However, it showed that there is not a greater risk of distant recurrence if, in the extended setting, the therapy is taken intermittently or continuously [7-year distant recurrence-free interval (DRFI) 91.6 % versus 90.4 %, HR 0.91. 95 % CI, 0.76–1.10; p-value = 0.35] [44].

Thereby, according to the results of all the aforementioned trials, it can be postulated that, to postmenopausal patients that have completed 5 years of adjuvant ET and at high risk of disease recurrence, according to the individual tolerance to the therapy, an extended strategy should be proposed. In particular, 7–8 years of adjuvant ET in total (of which at least 5 years with an AI) seem to represent the best option in terms of both survival benefit and tolerability (Fig. 1) (Table 1).

The potential role of genomic and clinical scores

Genomic tests (i.e., Oncotype and Mammaprint) are extensively utilized in women with N negative (N-) eBC to determine if they could benefit from adjuvant CT or if they could be successfully managed with ET only.

Breast Cancer Index (BCI) is another multigene signature that can be proposed to patients that have completed 5 years of adjuvant ET to predict the benefit of an extended strategy [37].

The Clinical Treatment Score post-5 years (CTS5), instead, is a score that is obtained by evaluating four parameters (T, N, G and patient's age) to evaluate the risk of distant recurrence. In women in postmenopause that have received 5 years of adjuvant ET, CTS5 could be proposed to assess the risk of late recurrence and eventually consider an extended strategy [38].

However, used in the patients enrolled in the IDEAL trial, only BCI was found to be predictive of a benefit from the extended strategy, whilst CTS5 did not [37]. There is currently no evidence regarding the employment of other genomic signatures in this setting.

The personalization of ET escalation will, moreover, leverage future liquid biopsy-based technologies focused on the detection and characterization of minimal residual disease and ultra-deep sequencing [39].

Role of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors in high-risk early BC

CDK4/6 inhibitors have revolutionized the treatment of metastatic luminal-like BC considering the outcome benefit obtained when used in combination to ET [45].

Their role has been subsequently explored also in the early setting by three main studies: PALLAS and Penelope-B (with postneo/adjuvant palbociclib) and monarchE (with adjuvant abemaciclib), while the results of the NataLEE trial, exploring the role of ribociclib, have not been published yet.

Both the PALLAS and Penelope-B studies failed in demonstrating that adjuvant palbociclib, in combination to standard ET, can provide a survival benefit compared to ET alone [46,47].

Positive results were, instead, obtained with the monarchE trial. A total of 5,637 women with high-risk early BC [defined according to clinical characteristics, such as T, N, G, and Ki-67 expression] were randomized to receive either standard ET alone or ET in association with abemaciclib (taken for two years).

These patients were divided in two cohorts:

- Cohort 1 (accounting approximately for 91 % of all randomized patients) included women with either $\geq$ 4 axillary lymph-nodes involved or that had from 1 to 3 axillary lymph-nodes involved with either G3 or pT $\geq$ 5 cm.
- Cohort 2, instead, included patients with 1 to 3 axillary lymph-nodes involved and Ki-67 $\geq$ 20 %, G1 or G2 and with pT $<$ 5 cm [48].

Considering both cohorts, the study demonstrated that abemaciclib in association to ET significantly improves the invasive DFS (IDFS) compared to ET alone (HR 0.75; 95 % CI, 0.60–0.93; p-value = 0.01) with an IDFS rate at 2 years of 92.2 % versus 88.7 % in favor of the abemaciclib arm. Such a benefit was consistent in both pre- and postmenopausal patients and independent from the Ki-67 status that revealed to have a prognostic rather than predictive value [48,49].

Currently, abemaciclib is recommended by the American Food and Drug Administration (FDA) and the European Medical Agency (EMA) in the adjuvant setting, in combination to standard ET, for the management of early BC patients at high-risk of disease recurrence, according to the

criteria defined by both regulatory authorities (Fig. 1) (Table 1).

Role of poly(ADP-ribose) polymerase (PARP) inhibitors

PARP inhibitors have demonstrated to provide a survival benefit in patients with different kinds of solid tumors harboring mutations in the tumor suppressor genes *BRCA1* and *BRCA2* [50].

In the OlympiA trial, a total of 1,836 *BRCA1/2*-mutant early BC patients (of which almost 18 % had a luminal-like molecular profile) were randomized to receive either adjuvant olaparib or placebo, for the purpose of evaluating its efficacy also in the adjuvant setting. These patients had received at least 6 cycles of neoadjuvant or adjuvant CT and those with luminal-like BC were permitted to receive standard ET concomitantly to the experimental treatment [51].

A significant improvement in IDFS was observed in the patients treated with olaparib, with a 3-year IDFS rate of 85.9 % versus 77.1 % in the control group (Table 1). To note that this survival benefit was consistent in all the subgroups, including those patients with the luminal-like molecular profile [51].

Recently, at the 2022 ESMO Virtual Plenary, the OS data from the OlympiA trial were reported and adjuvant olaparib was associated with a significant improvement in OS compared to placebo, with a 4-yeas OS of 89.8 % versus 86.4 %.

These results are of crucial importance for the subgroup of patients with the triple negative molecular profile, which represented up to 82 % of the randomized cohort: for these patients, in fact, the standard of care in the adjuvant setting is still represented by CT, irrespective from *BRCA1/2* mutational status. However, it is also interesting to postulate what could be the implications of these results in the management of luminal-like early BC patients harboring *BRCA1/2* germline mutations.

Recently, olaparib has been approved by FDA (not yet by EMA) for use in the adjuvant setting for women with high-risk *BRCA1/2*-mutant early HER2 negative BC that have received neoadjuvant or adjuvant CT. In view of the OS benefit observed in the OlympiA study, it is reasonable to imagine a priority for the use of olaparib over abemaciclib in high-risk patients with luminal-like disease. Given that the monarchE study allowed abemaciclib to be initiated within 16 months of surgery, sequential use of the two agents (i.e., olaparib followed by abemaciclib) could be considered in selected cases.

Conclusions

Adjuvant endocrine therapy represents the cornerstone for the management of early luminal-like early breast cancer.

In premenopausal patients with low-risk disease, 5 years of therapy with tamoxifen represent the standard of care. For intermediate/high-risk patients, the combination of ovarian suppression with tamoxifen or an aromatase inhibitor should be considered. Also, in patients at high-risk of disease recurrence, an extended strategy (for a total of 10 years of therapy) can be proposed, with either tamoxifen or an aromatase inhibitor, according to the menopausal status. Currently, the role of extended ovarian suppression is still unclear.

Postmenopausal patients should receive an upfront aromatase inhibitor. An extended strategy should be considered in high-risk patients, always evaluating the individual tolerance to the therapy. In this setting, 7–10 years of adjuvant endocrine therapy (of which at least 5 years with an aromatase inhibitor), seem to represent the best option.

Finally, to high-risk patients, according to local regulatory authorities, two years of adjuvant abemaciclib could be proposed in association to conventional endocrine therapy.

CRediT authorship contribution statement

Linda Cucciniello: Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Lorenzo Gerratana:** Conceptualization, Formal analysis, Writing – original draft, Writing – review & editing. **Lucia Del Mastro:** Conceptualization, Formal analysis, Writing – review & editing. **Fabio Puglisi:** Conceptualization, Formal analysis, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: F. P. reports research grant/funding from AstraZeneca, Eisai, personal fees from AstraZeneca, Roche, Amgen, Lilly, Novartis, Pfizer, outside the submitted work; L.G. reports non-financial support from Menarini Silicon Biosystems, personal fees from Lilly, outside the submitted work; L. D.M. reports non-financial support from Roche, Celgene, Pfizer, personal fees from Genomic Health, Pfizer, Seattle Genetics, Pierre Fabre, Lilly, Roche, Novartis, MSD, Eisai, Ipsen, Takeda, outside the submitted work. The remaining author declares no competing interests.

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