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Review

Solving current dilemmas in the adjuvant endocrine treatment of pre- and perimenopausal women with an estrogen receptor positive breast cancer

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In pre- and perimenopausal women with ER-positive HER2 negative breast cancer, 5 years of adjuvant tamoxifen (TAM) has been the standard of care for years. However, in some of these women with sufficiently high risk, we now consider extending (to 10 years TAM) and/or escalating endocrine treatment with ovarian function suppression (OFS) that can be combined safely with TAM but also with one of the three aromatase inhibitors (AIs). In this review, we will summarize our current policy on how to select patients at sufficient risk for relapse to consider OFS. We will also discuss the available data related to the choice of combining OFS with TAM or an AI, when to consider extended endocrine therapy, as well as the potential benefits of adding bone agents as part of treatment of these young patients.

Keywords

ER-positive; HER2-negative; Ovarian function suppression; Adjuvant endocrine therapy; Premenopausal patients; Extended; Bone agents

1. Introduction

Female sex steroids are important for breast cancer pathogenesis. Two historical experiences from milestone papers showed the importance of ovarian ablation in breast cancer treatment. Long before estradiol and the estrogen receptor (ER) were described [1, 2], in 1895 sir Beatson reported an improved overall survival (OS) in late-stage breast cancer patients following ovarian castration. In 1996, before TAM treatment and ER evaluation were standard of care, an Early Breast Cancer Trialists' Collaborative group (EBCTCG) meta-analysis was published in which 13 studies that began before 1990 were analyzed, comparing ovarian ablation or suppression versus control. This meta-analysis confirmed a 6.3% improved 15 years OS with ovarian ablation in premenopausal early breast cancer patients (15 years OS 52.4% vs. 46.1%, $p < 0.05$), mainly when patients were under age 50 and in those patients not being treated with adjuvant chemotherapy (CT) [3]. Indeed, post-CT amenorrhea occurs in 60–80% of premenopausal women [4, 5] and predicts a better DFS in ER+ breast cancer [5, 6] confirming a chemocastration effect.

The ZIPP (Zoladex in Premenopausal Patients) trial randomized 2710 patients (mean age 44.6 years; 54% confirmed ER+, 42% pN+, 43% adjuvant CT), between August 1987 and March 1999, into one of four treatment groups (goserelin for 2 years vs. TAM 20 or 40 mg for 2 years vs. goserelin + TAM versus no adjuvant endocrine treatment (ET)). After 12 years follow-up, OFS with goserelin significantly lowered the risk of dying from breast cancer in non-TAM users by 8.5% compared to those not given goserelin (95% CI, 2.2 to 13.7, $p = 0.036$). In TAM users, addition of goserelin reduced death by –2.6% (95% CI = –6.6 to 2.1), however this was not statistically significant [7]. Following the 1998 EBCTCG meta-analysis confirming 5 years rather than 2 years of adjuvant TAM as the new standard of care in premenopausal women, the aforementioned OFS trials rapidly lost their applicability in modern practice [8].

New randomized controlled trials (RCTs) soon studied the value of OFS in the modern context of adjuvant CT, 5 years TAM $\pm$ adjuvant CT, but remained hampered by methodological issues (in particular unknown ER status) and design flaws (e.g., treatment allocation issues, retrospective ER staining, lack of archived tumor specimens for ER assessment) [9]. The ABC trial (enrolled 1993–2000, n = 2144, randomized OFS yes/no) reported after 5.9 years median follow-up failed to demonstrate a benefit from OFS, but still 40% of patients lacked ER status and a non-significant effect was suggested in an unplanned subgroup analysis of women <40 years [10]. At the same time, a pooled analysis [11] (n = 11906, 16 trials) focusing only on premenopausal breast cancer patients with known ER status reported a statistically significant reduction in recurrence rates by 12.7% and death after recurrence by 15.1% with the addition of LHRH agonists to TAM, CT, or both [11]. Triple combination LHRH agonist + TAM + CT compared to CT alone was associated

with the greatest relative risk reduction for recurrence –26.7% (p = 0.001) and for death after recurrence –24.4% (p = 0.01) [11]. LHRH-agonist use as the only systemic adjuvant therapy was reported as having similar efficacy to CT with a relative decrease of 28% in recurrence, but the trial was underpowered (p = 0.08). The largest effects were predominantly seen in young women aged ≤40 years after CT, complementary to their higher chances of ovarian function recovery post CT [12].

New data and results soon followed, allowing improvement in patient treatment. CMF-based CT regimens were changing rapidly to more effective and less ovarian toxic anthracycline-taxane based regimens. Also, it was unclear to what extent the use of AIs could be introduced in premenopausal women when combined with OFS. Optimal duration of OFS was additionally questioned.

A new series of studies started in early 2000 and recently reported mature data. Today use of OFS in premenopausal women with ER+ early breast cancer is largely informed by two large phase III trials (SOFT and TEXT) in which adjuvant CT was a stratification factor [13–15]. Other smaller recent trials will be discussed and interpreted as well.

In the Suppression of Ovarian Function Trial (SOFT), 3066 women were randomized to 5 years TAM alone, 5 years TAM + OFS, or 5 years exemestane (EXE) + OFS (by triptorelin 3.75 mg every 28 days for 5 years unless relapse or intolerance). The study allowed goserelin 3.6 mg every 28 days when intolerance for triptorelin, and non-reversible bilateral surgical oophorectomy or bilateral ovarian irradiation as alternative for OFS [16]. Women were randomized within 12 weeks after surgery if no CT was given or within 8 months after completing CT only if biochemical proof of remaining or regaining premenopausal ovarian function (between 2 weeks and 8 months following CT completion). In the Tamoxifen and Exemestane Trial (TEXT), 2672 women were randomized to 5 years OFS + TAM or 5 years OFS + EXE following surgery, but in contrast to SOFT, OFS was started concurrently with CT (if administered) with triptorelin 3.75 mg every 28 days for 5 years (bilateral oophorectomy or ovarian irradiation were only allowed after at least 6 months of triptorelin). In both TEXT and SOFT, ER+ was defined as ≥10% cells staining positive (in contrast to the usual ≥1% threshold). In both trials disease-free survival (DFS) was the primary outcome and a planned combined SOFT-TEXT analysis was foreseen. DFS was defined as the time from randomization to invasive local (including recurrence restricted to the breast after breast conserving treatment), regional or distant relapse, invasive contralateral breast cancer, appearance of a second (non-breast) primary tumor, or death from any cause, whichever occurs first. Secondary outcomes were breast cancer-free interval (BCFI) (defined as the time from randomization to invasive breast cancer recurrence (local, regional, or distant) or invasive contralateral breast cancer; or censored at date of last follow up) and distant recurrence-free interval (DRFI) (defined as the time from randomization to breast cancer recurrence at a distant site; or censored at date of last follow-up).

1.1 Trials comparing TAM vs. OFS + TAM

Comparing OFS + TAM versus TAM alone is studied in SOFT, but also in the smaller ECOG E3193 [17] and ASTRRA trial [18].

The E3193 study randomized 345 low risk patients (pT <3 cm and pN0, 0% CT) to 5 years TAM ± 5 years OFS and reported after 9.9 years median follow-up. The study was terminated early due to slow accrual after NSABP-20 recommended CT in breast cancer patients under age 50. Although underpowered, OFS did not show statistically significant benefits in this low risk population (TAM vs. TAM + OFS DFS 5 years 87.9% vs. 89.7% (p = 0.62), OS 5 years 95.2% vs. 97.6% (p = 0.67) [17].

ASTRRA randomized 1293 South Korean patients aged ≤45 years all receiving (neo-) adjuvant CT and remaining premenopausal (biochemically determined) to 5 years TAM ± 2 years OFS (goserelin). After a median follow-up of 63 months, 5 years DFS rates were statistically significantly better in the TAM + OFS group 91.1% vs. 87.5% (p = 0.033). The estimated 5 years OS rate was 99.4% in the TAM + OFS group and 97.8% in the TAM-only group (HR = 0.31; 95% CI, 0.10 to 0.94; p = 0.029) confirming the benefit of OFS in these young women exposed to adjuvant CT [18].

In SOFT [15], OFS + TAM compared to TAM statistically significantly improved the primary endpoint of DFS (8 years DFS +4.3%, 83.2% vs. 78.9% (p = 0.009)). The absolute effect was larger in CT treated patients (8 years DFS +5.3%, 76.7% vs. 71.4%) versus those who did not receive CT (+3.2%, 90.6 vs. 87.4%). HER2 positive breast cancers exhibited the largest benefit (8 years DFS +17.1%, 85.4% vs. 68.3%). Heterogeneity by HER2 status was confirmed (p = 0.04), noting that only 12% of all patients included in SOFT were HER2-positive. Of these patients only 60.1% received HER2-directed therapy. Although OFS + TAM compared to TAM showed no statistically improved freedom from distant recurrence (all patients at 8 years +1%, 89.4% vs. 88.4%; CT treated patients +2.1%, 82.1% vs. 80%; HER2+ patients +11.0%, 89.6% vs. 78.6%), overall survival was statistically significantly improved with the addition of OFS to TAM (all patients 8 years OS +1.8%, 93.3% vs. 91.5%; CT treated patients 8 years OS +4.3%, 89.4% vs. 85.1%; HER2+ patients 8 years OS +9.1%, 95.1% vs. 86.0%). The improved OS without improvement in distant recurrences was surprising, also keeping in mind that there were very few deaths in SOFT after 8 years median follow-up and 25/225 were non breast cancer related deaths: 3 in the TAM + OFS group, 10 in the TAM group and 12 in the AI + OFS group [19, 20]. A number of questions arise, for example: do patients with preclinical distant metastasis benefit to a larger extent from early OFS or endocrine therapy in combination compared with OFS at the time of distant metastasis diagnosis, in terms of prolonging survival? Do subsequent therapy choices differ between these two groups? What about HER2-status?

In conclusion, SOFT, E3193 and ASTRRA all support the role of OFS for 2 to 5 years, mainly in CT-treated patients, HER2 positive patients or young age (<35–40 years) who remain premenopausal after CT, while a clinically-meaningful benefit in lower-risk patients seems negligible.

1.2 Trials comparing OFS + TAM versus OFS + AI

The combined TEXT + SOFT data together with the ABCSG-12 and the HOBOE trials generated data on whether an AI is superior to TAM in the presence of OFS.

ABCSG-12 randomized 1803 premenopausal patients, of whom 90% were CT-naïve. The trial used a factorial design, all 4 arms re-

ceived goserelin, and only 3 years of endocrine therapy was given: OFS + TAM, OFS + TAM + zoledronate (ZOL), OFS + anastrozole (ANA), OFS + ANA + ZOL. The trial reported final data after a median follow-up of 94.4 months. The addition of ZOL significantly improved DFS +3.4% (88.4% ZOL + ET vs. 85% ET alone ($p = 0.04$)). Risk of death did not differ significantly between ET alone and ZOL + ET (5.6% vs. 3.9%). There was no significant difference in DFS between patients assigned TAM versus ANA (87% vs. 85.2%), but OS was significantly worse with ANA than with TAM (94.1% vs. 96.3%) [21, 22].

The phase III HOBOE trial [23] randomized 1065 premenopausal patients with ER positive breast cancer to 5 years of OFS + TAM, OFS + LETRO, OFS + ZOL + LETRO (all OFS with triptorelin). With a median follow-up of 64 months, the trial reported statistically significantly different 5 years DFS of 85.4% (OFS + TAM), 93.2% (OFS + LETRO) and 93.3% (OFS + LETRO + ZOL). Although the hazard ratio (HR) for DFS was significantly in favor of OFS + ZOL + LETRO vs. OFS + TAM (HR = 0.52 (95% CI, 0.34 to 0.80; $p = 0.003$)), significant improvement was not found for OFS + LETRO versus OFS + TAM (HR = 0.72 (95% CI, 0.48 to 1.07; $p = 0.06$)). There was no statistically significant difference in OS.

Most recently, the 8-year update of the combined SOFT and TEXT trials including 4690 patients, provided additional perspectives on whether to prefer an AI or TAM in combination with OFS [15]. Again, these trials noticed an overall DFS event rate that was substantially lower than originally anticipated [24], likely again due to advances and changes in (neo-)adjuvant systemic treatments (ATLAS trial, aTTom trial, dose dense chemotherapy, anti-HER2 targeted therapies). Additionally, in TEXT and SOFT the characteristics of enrolled patients were more favorable than anticipated: the enrollment of lower-risk, older premenopausal patients would also lead to lower-than-expected event rates [24].

Significantly better DFS, BCFI and DRFI were observed favoring EXE + OFS versus TAM + OFS, but heterogeneity of effect by HER2 status ($p = 0.014$) revealed this was only observed for HER2 negative breast cancer [15]. Overall, in patients with HER2 negative cancers, 8-y% were better for EXE + OFS for DFS (+5.4%; 88.1% vs. 82.7%), BCFI (+5.6%; 90.5% vs. 84.9%) and DRFI (+3.4%, 93% vs. 89,6%). For HER2 positive cancers, 8-year DFS was better for TAM + OFS (79.7% OFS + AI vs. 82.9% OFS + TAM) based on the subgroup analysis of 642 patients. Overall survival in HER2 positive cancers however was better for OFS + TAM versus OFS + AI (8-year OS 93.7% vs. 89.5% (HR = 1.19 (95% CI; 1.05–3.46)). However, absolute improvements can be as large as 10–15% in 8-year estimated DRFI as will be discussed further (Regan Risk score) [25].

Time will tell whether the lower distant recurrences with OFS + EXE will translate into a significant OS benefit, which is currently not the case. Note that at this moment, OS seems slightly worse in SOFT (8-year OS 88.7%) than in TEXT (8-year OS 91.7%) for patients receiving CT and EXE. Recall that these numbers cannot be compared in absolute terms since follow-up in TEXT begins from the start of adjuvant therapy, while in SOFT follow-up begins from completion of chemo and regaining of ovarian function up to 8 months later. Some of the TEXT patients may have become menopausal from CT and would never have been included in SOFT. These patients would not rely on adequate OFS with a GnRH analogue compared with SOFT patients that all have functioning ovaries post CT. SOFT patients were more susceptible to the possibility of inadequate OFS with a GnRH analogue; biochemical and clinical monitoring of menopausal status may play a role for these patients (SOFT-EST trial). Also in SOFT, and somewhat contradictory compared to TAM only, OFS+TAM (but not OFS + AI) has resulteds in better OS, while OFS + AI (but not OFS + TAM) has resulted in less distance recurrence. Do patients on OFS + AI with potential inadequate OFS develop more aggressive recurrent tumors or does AI use select ESR1 mutated tumor clones [19]? Although a 5 years standard duration of treatment was not used in this trial, ABCSG-12 as well showed a similar discordant DFS/OS result with worse OS but equivalent DFS comparing OFS + AI versus OFS + TAM [19]. Further follow-up in SOFT/TEXT is necessary (Table 1, Ref. [15, 17, 18, 21, 23]).

2. In which patients do we consider OFS with tamoxifen or AI

We currently know that with more than 8 years of follow-up:

(a) OFS combined with TAM compared to TAM alone was associated with a statistically significant risk reduction of approximately 25% for DFS and OS (but not for DRFI) overall, although the absolute benefits were only a few percentage points as described in the introduction.

(b) OFS + AI compared to OFS + TAM was associated with a statistically significant risk reduction of approximately 30–35% for DFS, DRFI, freedom from breast cancer (but not for OS) overall. The effect was driven by HER2 negative breast cancers. Again, the absolute benefits were only a few percentage points as described earlier.

In our daily clinic, we now need to balance benefits of endocrine escalation adding OFS (reducing relapse risk) with the potential short- and long-term risks and side effects (as described further in this manuscript).

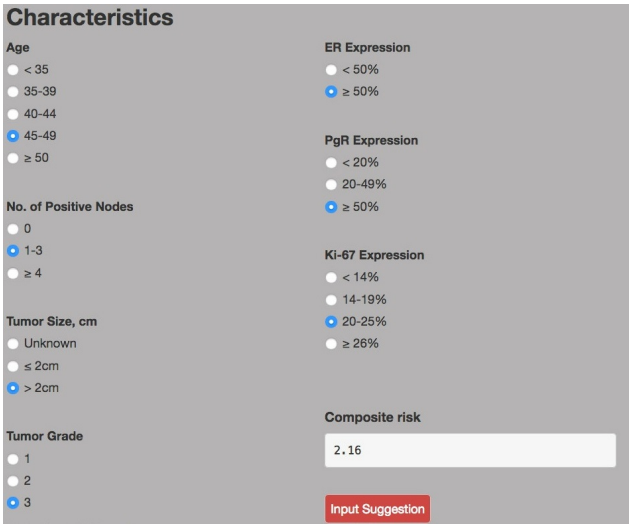

Fig. 1. An example of the facilitating tool "Regan Risk Score" — patient characteristics.

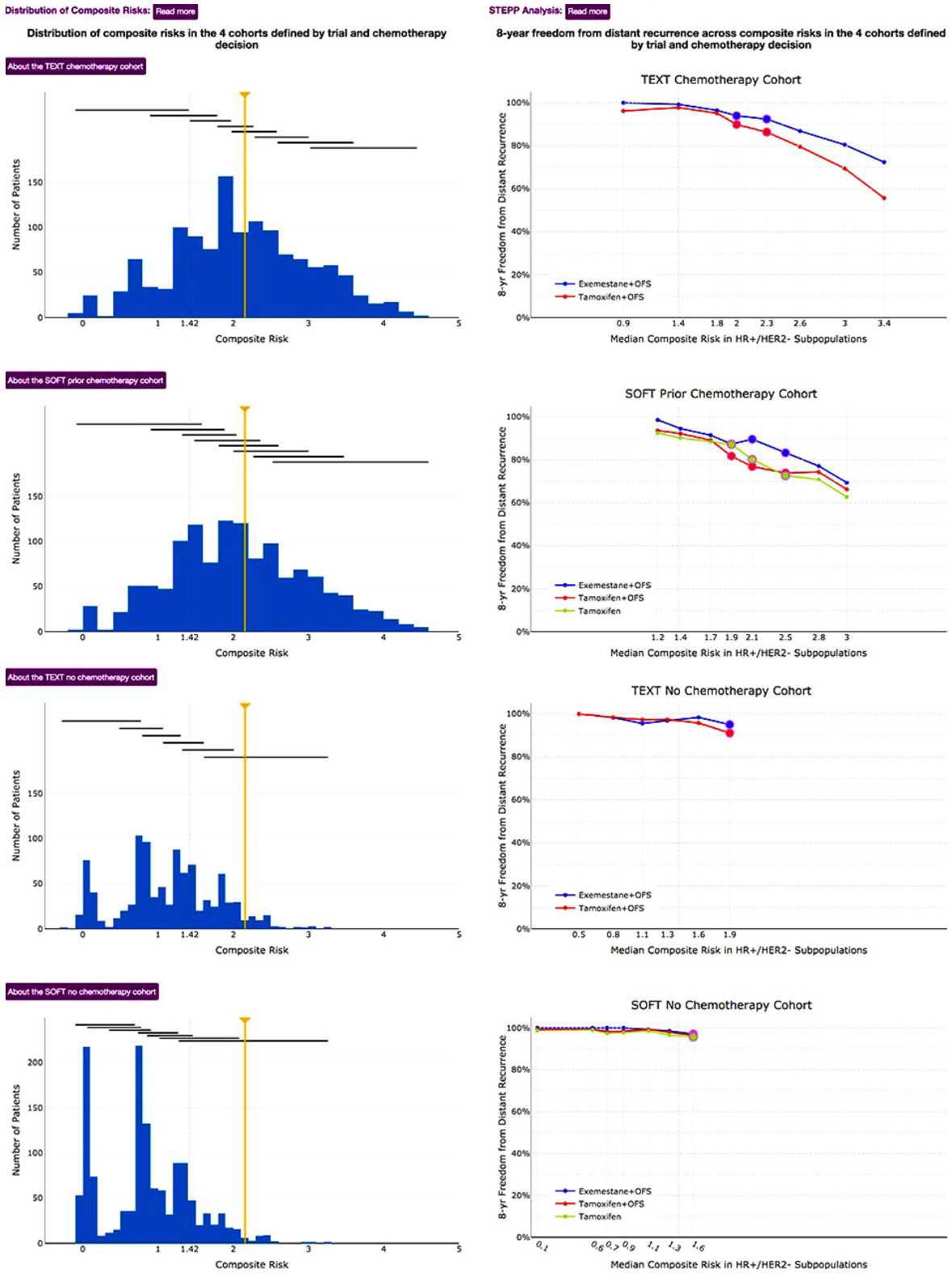

Fig. 2. An example of the facilitating tool "Regan Risk Score" - results. "STEPP illustrates the pattern of 8-year freedom from distant recurrence (Kaplan-Meier estimates) according to composite risk as a continuum in subpopulations (which are indicated by horizontal lines in the adjacent histogram, and plotted in STEPP at the median value in each subpopulation). The enlarged highlighted points correspond to the subpopulations containing the calculated composite risk (which are also indicated by the orange line intersecting the horizontal lines in the adjacent histogram). Moving over the points will show the estimated 8-year value with 95% confidence interval. Gray dotted vertical line: the median value of composite risks (1.42) across all 4 cohorts combined, used as a common reference point, as there are expected differences in the composite risk distributions among the 4 cohorts based on differences in characteristics" [25, 27, 28]. In the 4 curves below, 4 different cohorts are shown, based on differences in characteristics; (1) TEXT subpopulation with CT, (2) SOFT subpopulation with prior CT, (3) TEXT subpopulation without CT, (4) SOFT subpopulation without CT. The curves are comparative and show differences inbetween in function of the composite risk.

Table 1. Overview of different discussed trials.

	Study	N	Population	Definition of menopause	Comparison	Median follow-up	Disease free survival	Overall survival
ECOG E3193 [17]	Open-label, randomized phase III trial	345	All T <3 cm and pN0, 0% CT	Last cycle <6 m. Prior hysterectomy: ≤55 years with normal E2 level	5 years TAM alone or 5 years OFS + TAM	9.9 years	5-year rate 87.9% vs. 89.7% (p = 0.62)	5-year rate: 95.2% vs. 97.6% (p = 0.67)
ASTRRA [18]	Open-label, prospective, randomized, multicenter, phase III trial	1293	South Korean, ≤45 years, stage I–III, 100% CT	FSH >30 or menses <24 m postchemo	5 years TAM alone or 5 years TAM + 2 years OFS	63 months	5-year 87.5% vs. 91.1% (p = 0.033)	5-year 97.8% vs. 99.4% (p = 0.029)
SOFT [15]	Open-label, randomized, multicenter, phase III trial	3066	53% CT (OFS sequentially)	Premenopausal E2 level or menses <12 w postop or <8 m postC	5 years TAM alone (1), 5 years OFS + TAM (2), 5 years OFS + EXE (3)	8 years	8-year 78.9% vs. 83.2% vs. 85.9%	8-year 91.5% vs. 93.3%, 92.1%
TEXT [15]	Open-label, randomized, multicenter, phase III trial	2672	60% CT (OFS concomitant)	E2 or menses <12 w postop	5 years OFS + TAM or 5Yofs + EXE	9 years	8-year 82.8% vs. 86.8% (p < 0.001)	8-year 93.3% vs. 93.4% (p = 0.84)
ABCSG-12 [21]	Randomised, controlled, open-label, two-by-two factorial, multicenter trial	1803	Stage I–II, 90% CT naïve, 75% pT1G1, 66% pN0	Last menses <1y, or FSH and LH premeno	3 years OFS + TAM, 3 years OFS + TAM + ZOL, 3 years OFS + ANA, 3 years OFS + ANA + ZOL	62 months	* ET alone vs. ET + ZOL (88% vs. 92%, p = 0.008) * OFS + TAM vs. OFS + ANA (80.2% vs. 78.6%, p = 0.591)	* ET alone vs. ET + ZOL (95% vs. 97%, p = 0.09) * OFS + ANA vs. OFS + TAM (94% vs. 89.8%, p = 0.02)
HOBOE [23]	Open-label, multicenter, three-arm randomised phase III study	1065	≥18 years, any T-size and N status, CT allowed	Last menses <1 year. No determination of FSH/LH/E	5 years OFS + TAM, 5 years OFS + LETRZOZOLE, 5 years OFS + ZOL + LETROZOLE	64 months	5-year 85.4% vs. 93.2% vs. 93.3% (p = 0.008)	95.2% vs. 96.9% vs. 97.7% (p = 0.14)

SOFT, TEXT and ABCSG-12 data suggest that although the relative benefits associated with OFS are equally present across the overall population studied, they translate into worthwhile absolute benefits mainly in high-risk subgroups. Although formal criteria to define high risk are not present, it is reasonable to use the administration of (neo) adjuvant CT as a surrogate marker for 'high risk'. In clearly low risk (= no recommendation for adjuvant CT) or clearly high risk (= strong recommendation for CT), the need for OFS is discussed below, as well for the intermediate risk group (= borderline indication for CT). Given the heterogeneity of effects in SOFT/TEXT by HER2 status, these tumors are discussed separately below.

2.1 HER2 positive

Most patients with (ER positive) HER2 positive breast cancer will receive CT and can be considered at sufficiently high risk to consider OFS + TAM. As discussed earlier, statistical analysis demonstrated that HER2 positive compared to negative breast cancers benefitted to a statistically significant greater extent from OFS + TAM compared to TAM in SOFT. In addition, there was no benefit from OFS + AI (8-year DFS 79.9%) compared to OFS + TAM (8-year DFS 82.9%) (HR 1.18 (95% CI; 0.80–1.71)) in the combined SOFT + TEXT analysis for HER2 positive cancers, while OS was even worse for OFS + AI (34 deaths out of 298 patients) versus OFS + TAM (16 deaths out of 280 patients) (8-year OS 89.5% vs. 93.7% (HR 1.19 (95% CI; 1.05–3.46)) [14, 15, 20]. This is concordant with results from the HOBOE trial, also demonstrating heterogeneity of effect by HER2 status, showing no superior outcome with an AI compared to TAM in HER2 positive breast cancer patients with OFS [23]. These two subgroup analyses show that AI (+ OFS) is not superior to TAM (+ OFS) in premenopausal patients in contrast to the postmenopausal setting, and that there are even hints for slight superiority of TAM + OFS in HER2+ premenopausal patients. We would conclude that OFS seems to be very relevant, both TAM + OFS and AI + OFS are valid options in premenopausal HER2+ patients, with a slight preference for TAM + OFS, but of course adaptable to tolerance, risk factors, and personal preference [26].

2.2 HER2 negative

An important tool in facilitating the choice (i.e., estimating benefits) of whether to start OFS or not (SOFT-data: TAM versus OFS + TAM), or whether to prefer TAM or an AI in addition to OFS (SOFT and TEXT data), is the Regan Risk Score [25, 27]. This web based application is available at https://rconnect.dfci.harvard.edu/CompositeRiskSTEPP/ and integrates patient age, factors determining NPI (tumour size, nodal status, disease grade) and levels of tumour expression of estrogen receptor, progesterone receptor and Ki-67) [25]. Its use enables estimating the magnitude of benefit (up to 10–15% absolute improvement in 8 years freedom from distant recurrence) of escalating endocrine therapy in premenopausal women with HR-positive (HER-2 negative) breast cancer. Fig. 1 and Fig. 2 . shows an example of this tool.

2.2.1 Low risk

Patients with sufficiently low risk to forego CT may have little absolute benefit, although even pT1N0 low grade tumors may experience up to 10% distant metastasis relapse in years 5–20 [29]. The available follow-up in recent OFS trials however is currently insufficient to predict clinically-significant benefits at such a timeframe in this setting. TAM for 5–10 years remains standard of care and some of these patients could perhaps even forego TAM treatment in case of ultra-low genomic scores, although these data were generated in postmenopausal setting and this is not implemented in daily clinic as for now [30, 31]. In rare low-risk cases, where contraindications exist for both TAM and an AI, OFS only treatment could be considered [11].

2.2.2 Intermediate risk

Some of the patients included in SOFT/TEXT that received CT would no longer receive CT by today's standards. Indeed, since prospective randomized trials demonstrated the clinical usefulness of genomic profiling (MINDACT, TAILORx, RxPONDER [32]), we are now able to safely omit adjuvant CT in some clinical high-risk cases. In TAILORx, adjuvant CT may still yield some modest (±5%) benefits in premenopausal young women with low risk genomic scores and up to 3 positive lymph nodes, as these benefits were mainly seen around age 46–50 years and therefore believed to be related to CT-induced menopause [32–37]. These patients may perhaps forego adjuvant CT and still largely derive the modest CT benefit through escalation of their endocrine treatment with OFS.

Also in rather high risk patients that refuse or cannot tolerate CT, OFS can at least partially compensate for the lost benefit of adjuvant CT.

However, it remains difficult to further identify intermediate risk candidates for OFS. Only when given OFS + EXE (but not when given OFS + TAM), chemo naïve patients in SOFT (n = 1419) derived a clinically meaningful benefit compared to TAM alone; this was the case only for DFS (8-year DFS 92.5% vs. 87.4% (HR = 0.58 (95% CI 0.38–0.88)), as no benefits were found for freedom from distant recurrence (8 years 97.8%, 99.3%, 97.8%) or overall survival (97.9%, 97.7%, 98.8%) [20]. In TEXT patients who received CT, the average absolute improvement in freedom from distant recurrence with OFS + EXE versus OFS + TAM was 5.1%. STEPP analysis in the Regan Risk Score showed an increasing benefit as the composite risk increased, reaching more than 15% benefit in the subpopulation with the highest composite risk.

In IBCSG 11–93, four cycles of adjuvant CT (AC/doxorubicin or epirubicin plus cyclophosphamide) added to OFS + TAM for 5 years versus OFS + TAM for 5 years alone were compared in 174 premenopausal patients with node-positive, ER positive early breast cancer. The trial however was closed before the target accrual was reached due to low accrual rate. After 10 years median follow-up, this trial showed no difference for DFS (HR = 1.02 (95% CI; 0.57–1.83), $p = 0.94$) or OS (HR = 0.97 (95% CI; 0.44–2.16), $p = 0.94$).

In contrast, a worse OS was seen in the mainly chemo naïve ABCSG-12 trial (n = 1803, 90% no chemo) with OFS + AI versus OFS + TAM (89.8% vs. 94%, $p = 0.02$) although these women received a currently substandard duration of only 3 years endocrine treatment [21]. Given also the small absolute improvements in chemo-naïve patients in SOFT and TEXT, it often remains difficult to decide whether the benefit of OFS (+TAM/AI) is clinically meaningful, but the Regan Risk Score can be helpful [27].

2.2.3 High risk

High risk appreciation by today's standards may not entirely rely on the same variables and knowledge that was available in the SOFT

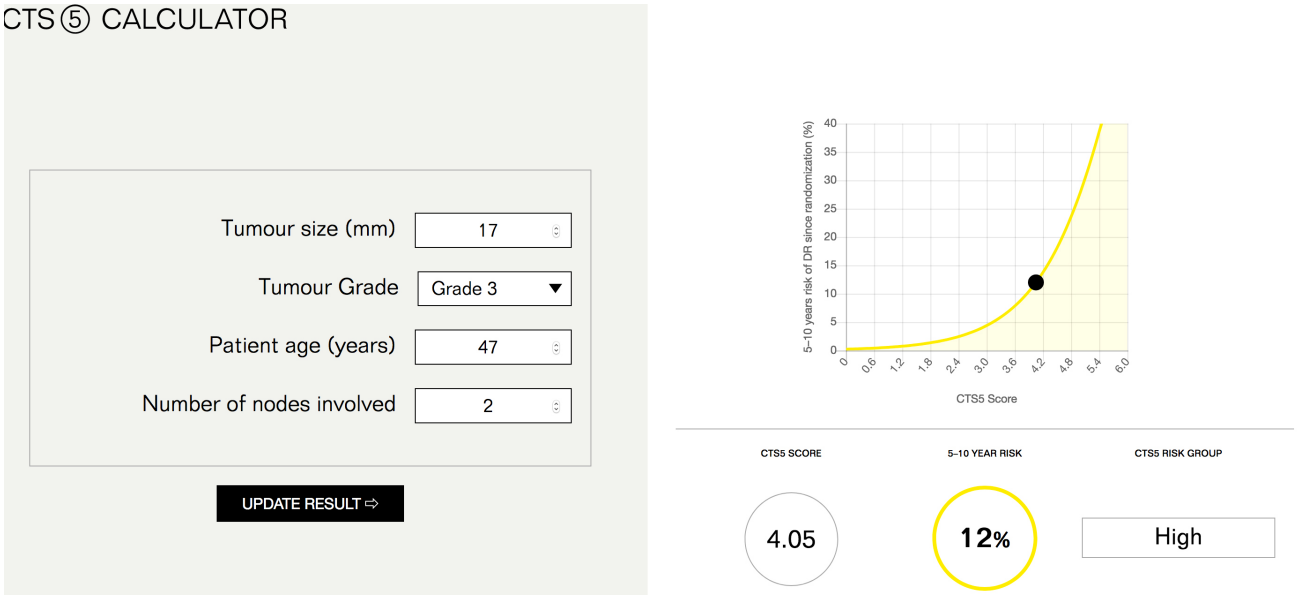

Fig. 3. An example of the CTS-5 score; a tool which may be helpful, by giving prognostic value, in selecting postmenopausal patients at high risk for late relapse where extended endocrine treatment may be considered [63, 64].

and TEXT era. We now also include genomic information in addition to ER expression, grade and proliferation (biologic features) together with tumour stage in a so-called integrated model, to decide the need for (neo-)adjuvant CT [38]. Some clinical high risk (premenopausal) patients with genomic low risk might nowadays be considered intermediate risk (see intermediate risk). For example in the MINDACT trial, clinical high risk was defined as per Adjuvant! Online expected 10-year OS <92% with endocrine treatment alone, based on grade, node and tumor size [39].

Here, the Regan Risk score facilitates the choice between TAM or an AI in addition to OFS [27].

3. Definition and surveillance of menopausal status

A variety of definitions for menopause are used across different breast cancer trials (Table 1, Ref. [15, 17, 18, 21, 23]). Menopause is difficult to define, but following the NCCN guidelines, reasonable criteria are any of the following: [40]

- Prior bilateral oophorectomy

- Age ≥60 years

- Age <60 years and amenorrheic for ≥12 months in the absence of CT, TAM or OFS AND follicle-stimulating hormone (FSH) and plasma estradiol level in postmenopausal range.

Post CT amenorrhoea in premenopausal women is not a reliable indicator of ovarian menopausal status. These women may still have or recover an intact ovarian function years later, and for this reason, efficient non-hormonal contraception should be discussed. Serial FSH/estradiol measurements could be considered in case an AI is given, since ovarian function recovery is relevant even beyond age 45 years [41–43] and more frequent when AIs are given [44–46]. Inferior OS and DRFI have been reported with AI use in case of ovarian function recovery as compared to women remaining in definitive amenorrhoea following CT [42].

It remains unclear to what extent we need to decrease estradiol levels in women under (OFS+) AI and to what extent we need surveillance for ovarian function recovery [47]. In SOFT, only a minority of women were subject to serial FSH/LH and estradiol measurements (SOFT-EST substudy) with highly-sensitive gas chromography assays [48]. With these highly-sensitive assays, approximately 20% of patients on EXE + triptorelin exhibited values above an oestradiol threshold of 2.72 pg/mL, which represents a level reported in postmenopausal patients on AIs. Others have shown however that the use of different assays yielded similar efficacy in determining ovarian function recovery [43]. More data in this field are needed to make further recommendations but we recommend mechanical contraception (independent of LHRH agonist) and follow FSH and E2 every 3–4 months if amenorrheic. There are limited data on hormonal contraceptive use in breast cancer survivors. A recent retrospective study assessed the risk of recurrence with hormonal contraceptive use in premenopausal breast cancer survivors. Data of 1370 women were assessed, of which 97 women received a prescription for a form of hormonal contraception. Between groups, no difference in recurrence was seen, 6.19% users vs. 6.67% non-users (p = 0.83) [49]. Additional research for definitive recommendations is necessary.

4. OFS modalities, timing and duration

4.1 Modalities

Both in TEXT and SOFT, triptorelin 3.75 mg every 28 (±3) days was initiated for 5 years. In case of intolerance, goserelin 3.6 mg every 28 days was allowed. Immediate bilateral surgical oophorectomy or bilateral ovarian irradiation (3 Gy/fraction for 4 fractions, 3 Gy/fraction for 5 fractions) were allowed in SOFT. In TEXT, bilateral oophorectomy or ovarian irradiation was allowed only after at least 6 months of triptorelin. GnRH analogues administered with 3 monthly intervals were not allowed [50].

4.2 Timing

- PRE chemo in case of pregnancy wish (ovarian protection) [51]
- Concurrently with chemo (TEXT)
- Sequentially with chemo (SOFT) <8 months
- Sequentially with chemo (ASTRRA) <24 months

Since ASTRRA revealed a similar efficacy compared to SOFT (hazard ratio) with OFS started as late as 2 years post CT, initiation of OFS can be considered until 2y post CT.

4.3 Duration 2 years, 5 years or early discontinuation

Although SOFT and TEXT offered a full 5 years of OFS, ASTRRA revealed similar efficacy (hazard ratio) with only 2 years OFS. No studies directly comparing 2 years versus 5 years are available. Although 5 years OFS is proposed to the patients in SOFT and TEXT, as many as 20% stopped OFS early [20]. Taken together with ASTRRA data, one might question whether a full 5 years OFS is superior to only 2–3 years.

5. What about extended therapy?

As of today, no randomized trials assessed extended endocrine therapy for premenopausal women following 2–5 years OFS specifically. We do know however that ER+ breast cancer carries a high risk for late distant relapses (up to 10–41% risk over 20 years) and death after only 5 years of endocrine therapy [29]. Given we only consider OFS in patients at sufficiently high risk, extended endocrine therapy in these patients will be considered by many of us and risks and benefits need to be balanced carefully (discussed further). We also need to reconsider endocrine treatment options in patients prematurely stopping OFS and rely on their menopausal status at that moment, always taking into account patient preferences, balancing risk/side effects with benefits, and prioritise adherence (also discussed below).

In case these women remain premenopausal after completing or prematurely stopping OFS, extended TAM monotherapy totaling 10 years of endocrine treatment can be considered [38]. Results from the ATLAS and aTTom trials clearly demonstrated that 10 years of TAM versus 5 years of TAM resulted in a significant reduction in breast cancer recurrence of approximately 4% (ER+ subgroup, 15 years recurrence 25.1% versus 21.4%), and a reduced breast cancer mortality (15 years 15.0% versus 12.2%)) [41, 52, 53]. These findings were independent of age, stage or menopausal status. Of note, fewer than 10% of patients in ATLAS were premenopausal, but these premenopausal women had at least similar (numerically even better) recurrence rates with extended TAM compared to postmenopausal women (4.4% vs. 2.7%, $p = 0.79$) [52, 54, 55].

In case women that completed or prematurely stopped OFS have become definitively menopausal, both extended TAM but also extended AI can now be considered [38]. The only data to guide our decisions here come however from trials including women that went into menopause naturally and no trials compared AI's with TAM directly in the extended setting.

The 2018 EBCTCG meta-analysis [56] (n = 24912 patients) reported statistically significant benefits of extended AI use following 5 years of prior endocrine therapy. The benefit depended on the type of prior endocrine therapy and the extended AI benefit was most apparent following 5 years TAM, with a 33% risk reduction for any recurrence (5 years gain 3.6%); 23% for distant recurrence (5 years gain 1.5%) and 23% for breast cancer mortality (5 years gain 0.8%) (all $p < 0.05$). Extended AI benefit following previous 5 years AI improved recurrence free survival but not OS.

Tools such as the CTS-5 score may be helpful in selecting patients at high risk for late relapse where extended endocrine treatment may be considered, but they carry prognostic, not predicitive, value only, and overestimate risk particularly in high-risk patients [57, 58]. Fig. 3 shows an example of this tool (same patient characteristics were used as in Fig. 1). Recently, the Breast Cancer Index (BCI) has been accepted by the NCCN as the first predictive (and prognostic) biomarker for extended endocrine treatment [59]. It is a gene expression-based signature that consists of two functional biomarker panels, the HOXB13/IL17BR (H/I) ratio and the molecular grade index (MGI), that interrogate important estrogen signaling and proliferation pathways in breast cancer [53, 54, 60]. BCI was validated on data from trials MA.17, trans-aTTom, IDEAL and STOCKHOLM and carries both prognostic and predictive value for response to extended use of an AI following 5 years TAM [61], extended use of TAM following TAM (all node positive) [53] and extended AI following AI or TAM [62]. In daily clinic, the CTS-5 score may help us select those (postmenopausal) patients that have a sufficiently high risk for late relapse to consider assessing BCI that predicts benefit from extended endocrine treatment.

6. Bone targeting agents in premenopausal patients at diagnosis

Oestradiol is an important regulator of bone metabolism. Endocrine therapy causes relatively rapid decreases in circulating oestradiol concentrations or competitively inhibits oestradiol action in bone, adversely affecting bone health in the majority of women with early breast cancer [65]. Use of bone-targeting agents is of importance not only in reducing skeletal morbidity in the metastatic setting but is also beneficial in reducing AI-induced accelerated bone loss and in preventing metastases, mainly bone metastases, resulting in improved breast cancer specific mortality (even in ER-negative breast cancer) [66].

The EBCTCG published a meta-analysis of individual patient data from 18766 breast cancer patients included in 26 randomized trials of adjuvant bisphosphonates. They showed that adjuvant bisphosphonates (i.v. Zoledronate, daily oral Clodronate or daily oral Ibandronate specifically) compared to placebo reduced distant recurrences (10-year risk −1.4%, $p = 0.03$); this effect was mainly because of a reduction in bone recurrence (10-year risk −1.2%, $p = 0.004$). Additionally a reduced breast cancer mortality (10-year risk −1.8%, $p = 0.04$) and similar all-cause mortality reduction (10-year risk −1.5%, $p = 0.06$) was seen [66]. However, almost all benefits were restricted to postmenopausal women or those receiving OFS, with clinically-important benefits in overall breast cancer recurrence, bone recurrence and breast-cancer specific mortality. This meta-analysis, which included data from HOBOE, did sensitivity analyses of the possible relevance of age and menopausal status. This analysis omitted the hypothesis-generating ABCSG-12 and AZURE, which showed significant benefit only in postmenopausal women [21, 66, 67].

These bisphosphonates will also lower the risk of cancer treatment-induced bone loss (from chemotherapy, radiotherapy and/or hormonal therapy). Denosumab (60 mg twice yearly) can

be considered for this indication as well, but did not result in improved outcomes from a prognostic perspective [68]. Bisphosphonates may be the preferred agents as they are active in prevention and treatment of AI bone loss while they are associated with improved outcome as well [69, 70]. Zoledronate, typically initiated alongside adjuvant chemotherapy, is administered every 6 months, or daily oral ibandronate or clodronate can be considered. The optimum duration of treatment is uncertain and bisphosphonate duration of 2 years vs. >2 years had similar treatment effects (hazard ratios) [71].

7. Adverse events and adherence

Observational data on long-term health outcome with the use of elective oophorectomy in benign gynaecological hysterectomy patients suggest an association with increased long-term overall mortality and cardiovascular risk. In the Nurse's Health Study for example, with over 28 years of follow-up, all cause mortality was 16.8% in women with hysterectomy and bilateral oophorectomy versus 13.3% of women who had ovarian conservation [72]. Although not all data are in agreement, and although observational data do not imply causal effects, the negative effect of elective oophorectomy seems in particular present in patients younger than 45 years. We need to keep these data in mind when considering OFS in breast cancer patients, knowing (very) long-term follow-up is not provided in these OFS trials. On the other hand, we cannot compare elective oophorectomy in a benign gynaecology setting with (mostly temporary) OFS in the adjuvant setting of breast cancer. The benefits of OFS were described earlier, but they also depend on patient adherence and on side effects which will be discussed now.

7.1 Description of adverse effects

Despite the benefits of both escalated (OFS) and extended endocrine therapy, side effects should not be underestimated [73]. Adverse effects are common and influence long-term adherence to treatment impacting prognosis. The recent ELENA study reported that patients judge a median absolute gain of 22% in survival necessary to make adjuvant ET worthwhile based on an untreated 5 years survival rate expectation of 60% [74].

Ribi *et al.* [75] reported on patient-reported outcomes in the SOFT trial. A total of 1722 patients, randomly assigned to TAM + OFS or TAM alone, completed a quality of life (QoL) form consisting of global and symptom indicators at baseline, every 6 months for 24 months and annually during year 3 to 6. Patients on TAM + OFS were more affected by endocrine symptom burden (loss of sexual interest and sleep disturbance at 6m, vaginal dryness up to 60 m) than patients on TAM alone during the first 24 months although these differences for most endocrine symptoms diminished after 2 years and were no longer clinically relevant after 5 years. Changes in global QoL indicators from baseline were small and similar between treatment groups over the whole treatment period. The effect of OFS on impaired symptom-specific QoL, treatment burden and coping effort during the first 2 years of treatment was less pronounced for patients who received prior CT. Of the total sample, 19% of patients ceased TAM and 21% discontinued Triptorelin prematurely.

A similar analysis of SOFT & TEXT from Bernhard *et al.* [76] showed that patients assigned to AI + OFS reported significantly more adverse effects of bone or joint pain, vaginal dryness, greater loss of sexual interest and difficulties becoming aroused. Patients assigned to TAM + OFS reported more complaints of hot flushes, sweats and vaginal discharge. In general, patients reported considerable changes in key endocrine symptoms in the short-, mid- and long-term, but differences between the randomized treatments were small. The changes in global QoL domains were similar between the randomized treatment groups [76].

The "Co-SOFT substudy" assessed the objective cognitive function and patient-reported outcomes at randomisation (T0) and 1 year later (T1) [77]. They showed no significant difference in the changes in the composite cognitive function scores between the OFS+TAM/EXE groups and the TAM alone group regardless of prior CT status, and adjusting for baseline characteristics. However, the study did not have adequate power to detect a small to moderate effect on cognitive function.

In conclusion, the results of these studies show an additional harmful effect of adding OFS to TAM on endocrine symptom burden in premenopausal women. The effect of OFS on QoL, treatment burden and coping effort during the first 2 years was less for patients who received prior CT (those that benefit the most from OFS). From a QoL perspective, as measured in SOFT/TEXT, there is no strong indication to favour either AI + OFS or TAM + OFS. However, it remains unclear to what extent current QoL assessments are sensitive enough to capture differences in tolerability of AI + OFS vs. TAM + OFS which can be more pronounced in real-world populations. Differential effects of the treatments on short- and long-term should be discussed with each patient individually.

Endocrine treatment escalation and extension may make patients more more susceptible to (early) treatment discontinuation. For all women enrolled in SOFT and TEXT an adherence analysis was done. Nonadherence with therapy was higher in women younger than 35 years. The cumulative incidence of nonadherence with oral endocrine therapy in women younger than 35 years at 1 year was 11%, increasing to approximately 17%, 23%, and 25% at 2, 3, and 4 years. For those ≥35 years old, it was 9%, 14%, 18%, and 21%, respectively [78]. A systematic review from C. Murphy *et al.* [79] in 2012 concerning adherence to adjuvant hormonal therapy in breast cancer patients showed that in RCT's early discontinuation of TAM ranged from 13 to 28% and discontinuation of AI ranged from 8 to 24%. However, treatment discontinuation outside of a study context may range from 31 to 73%. The top reasons for stopping endocrine treatment are arthralgia, thromboembolic events, hot flushes and gastrointestinal symptoms both for TAM and AI users [80]. Perhaps only 80–85% of patients will take adjuvant hormonal treatment for the full duration at the optimal schedule, with younger women being at increased risk of non-adherence [81] and early discontinuation or non-adherence has been shown to be associated with inferior prognosis [81, 82].

7.2 Management of adverse effects

As mentioned above, nonadherence and early discontinuation of therapy is frequent. Guidance for the patient by clinicians is essential.

7.2.1 Patient education

Thorough information about the therapy and the possible adverse effects at the beginning of therapy, as well as education of

preventive measures (e.g., *hot flushes: less caffeine [83], less spicy food, … *vaginal atrophy: cotton underwear, no use of soap vaginally, … [84]).

7.2.2 Pharmacological products

Sometimes switching the endocrine agent can be a solution (e.g.,: switch letrozole to anastrozole, exemestane or to TAM).

In other situations, treatment of side effects such as vaginal dryness or hot flushes is recommended. In addition to preventive measures, we can help patients with some medications (e.g., *vaginal atrophy: hydrating healing non hormonal vaginal creams [85], lidocaine cream, gabapentin [86], CO_2 laser [87],…, *hot flushes: anti-depressants, anticholinergic medication (oxybutynin [88]), purified cytoplasmic extracts of pollen,…). Pharmacological treatment of complaints of arthralgia are more difficult, support with analgesic medication is possible, though a specific treatment is not available [89, 90].

7.2.3 Psychophysical techniques

Encouragement of physical activity and healthy diet can help for the general well-being. A systematic review from Lu *et al.* [91] analysed data of 9 studies involving a total of 743 patients. All studies compared exercise programs with usual care among breast cancers survivors taking AI. Results indicated that exercise relieved musculoskeletal symptoms (pain, stiffness and grip strength) and improved quality of life.

Also mindfulness and acupuncture are more recently proving their relevance as a treatment and as a tool for enhancing psychological well-being [92, 93].

8. Conclusions

In premenopausal women at sufficiently high risk, all treatment options considered in postmenopausal women are available when combined with OFS. An OS benefit for HER2+ breast cancer patients comparing OFS + TAM vs. TAM is seen. In HER2+ patients there seems to be no benefit from OFS + AI compared to OFS + TAM in SOFT/TEXT and HOBOE, with even a slight preference to use OFS + TAM. However, caution is necessary since this a subgroup analysis of ~10% of the trial patients, and besides only 60.1% of these patients received HER2 targeted therapy. More solid comparative data between OFS + TAM and OFS + AI for premenopausal HER2+ patients is needed to draw solid conclusions. In HER2- breast cancer patients at higher risk of relapse, an improved prognosis is seen with OFS + AI compared to OFS + TAM, and the Regan risk score and use of BCI may respectively help in estimating an individual's prognosis and benefit from extended endocrine treatment. Nonetheless, we should always consider short- and long-term adverse effects, and no survival benefits of OFS + AI compared to OFS + TAM have been shown so far. Longer follow-up is needed to evaluate whether sufficient improvements in breast cancer related mortality will surpass the long-term increased risk of cardiovascular mortality associated with (definitive) castration at early age.

Abbreviations

AI, aromatase inhibitors; BCFI, breast cancer-free interval; BCI, breast cancer index; BTAs, bone-targeted agents; CMF, Cyclophosphamide Methotrexate Fluorouracil; CT, chemotherapy; DFS, disease free survival; DRFI, distant recurrence-free interval; ET, endocrine therapy; EXE, exemestane; LETRO, letrozole; NCCN, National Comprehensive Cancer Network; OFS, ovarian function suppression; OS, overall survival; RCTs, randomized controlled trials; SREs, skeletal-related events; TAM, Tamoxifen; QoL, quality of life; ZOL, zolendronate.

Author contributions

PN gave a virtual talk on this subject during the online breast cancer conference: 'MBC symposium 2020'. KS took the initiative to write this paper and analyzed the current known results on this subject. Both PN and OB are shared senior authors. ES, MVH, SH, KP, HW, MR, OB and PN contributed to the editing and rewriting of the manuscript before submission. MR edited the manuscript for use of the English language. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

As a formality a request was made at the ethical commission of KU Leuven. Automatically approved since this concerns a literature study, reference number MP017337.

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Conflict of interest

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