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REVIEW

Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials

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Abstract Five years of adjuvant hormonal therapy is the standard of care in early breast cancer (BC) expressing oestrogen receptors (ER+). Prolonged duration of adjuvant endocrine therapy is implemented to prevent recurrence and death; in particular, its carryover effect may prevent very late events. This meta-analysis compares the efficacy of 5 years of hormonal therapy alone with that of additional years of hormonal therapy, in patients with early BC. Randomised trials comparing 5 years versus more than 5 years of hormonal therapy in BC were identified by electronic searches of PubMed, EMBASE, ISI Web of Science and the Cochrane Central Register of Controlled Trials. Meta-analysis was performed using the fixed- or random-effects models. The primary endpoints were overall survival (OS), BC-specific survival (BCSS) and relapse-free survival (RFS) reported as odds ratios (ORs) and 95 % confidence interval (CI). Eight trials, including 29,138 patients, were identified. Overall, in ER+ BCs, extended endocrine therapy beyond 5 years of tamoxifen significantly improved OS (OR, 0.89; 95 % CI 0.80–0.99; $P = 0.03$), BCSS (OR, 0.78; 95 % CI 0.69–0.9; $P = 0.0003$) and RFS (OR 0.72; 95 % CI 0.56–0.92; $P = 0.01$) compared with 5 years of hormonal therapy alone. Loco-regional and distant relapses were reduced by 36 and 13 %, respectively. Compared with 5 years of tamoxifen, additional adjuvant endocrine therapy reduced risk of death and relapse of ER+ BC by ~10 and 30 %, respectively. This strategy should be considered in patients free of disease after 5 years of hormonal therapy.

Keywords Tamoxifen · Aromatase inhibitors · Adjuvant therapy · Breast cancer · Extended duration · Five years · Ten years

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Introduction

Adjuvant endocrine therapy of tamoxifen (TAM) for 5 years reduces risk of death and recurrence by ~30 and 40 %, respectively, in early breast cancer (BC). Five years are confirmed to be the preferred length of adjuvant TAM in randomised trials [1, 2].

The risk reduction effect of endocrine therapy is detectable even after 15 years from initiation of TAM (carryover effect) [1] in oestrogen receptor positive (ER+) BCs. This late effect of hormonal therapy is potentially of benefit for patients with ER+ BC associated with late relapse 10 years after diagnosis [3]. In particular, BC mortality risk is reduced with TAM by approximately one-third in years after the tenth [1, 2].

For evidence that 5 years of TAM are better than two in terms of recurrence and mortality [2], several extended, adjuvant trials compare 5 years of TAM with 5 years of TAM plus an additional period of treatment with TAM or an aromatase inhibitor. The ATLAS study, for example, randomised more than 12,000 BC patients to five additional years of TAM or observation after cessation of the standard 5 years of TAM [4]. A decrease in late BC and overall mortality was observed, after a mean of 7.6 years of follow-up after the first 5 years of TAM. This benefit was observed at the expense of a moderate increase in endometrial cancer risk (3.1 vs. 1.6 %), but with a minimal

increase in endometrial cancer mortality (0.2 %). In the ATTOM study [5], 10 years of TAM reduced risk of BC relapse ($P = 0.003$), BC mortality ($P = 0.05$) and overall mortality ($P = 0.1$), and the magnitude of benefit was greater after the ninth year.

Following the advent of aromatase inhibitors, extended adjuvant trials were designed with these agents after 5 years of TAM. Among these, the MA 17 trial [6], which randomised women to letrozole or placebo after 5 years of TAM, showed a significant reduction in relapse at 64 months of median follow-up (despite 66 % of placebo patients taking letrozole after unblinding), with similar overall survival (OS). The influence of treatment with letrozole in the placebo arm after unblinding was analysed separately and, adjusting for treatment crossover, extended use of letrozole lead to a significant benefit in disease-free survival (DFS) and OS [7].

To aggregate these data on extended adjuvant endocrine therapy beyond 5 years, we undertook a meta-analysis of published studies reporting outcome of patients with BC randomised to extended (>5 years) or standard duration adjuvant therapy. The aim was to determine whether a longer period of adjuvant hormonal therapy (with either TAM or an aromatase inhibitor), after at least 5 years of an initial course of endocrine treatment, is associated with reduced risk of death and relapse.

Methods

Data sources

Trials were identified by electronic searches of the Cochrane Controlled Trials Register, PubMed, ISI Web of Science and EMBASE. In addition, we manually searched reference lists and major conference proceedings (without date limitations). This search strategy included the following terms: (breast cancer OR breast carcinoma) and (tamoxifen OR letrozole OR exemestane OR anastrozole) and (extended OR duration OR longer OR continued OR '5 years' OR '10 years' OR prolonged OR continuing) and (randomised OR randomised).

Study selection

We include all randomised controlled trials that compare a fixed duration (5 years) with an extended course of endocrine therapy (more than 5 years) in patients with histologically confirmed early BC. The randomisation may have been carried out at the start of endocrine therapy (year 0) or after the initial (standard) course of endocrine therapy (year 5) in patients free of disease. Temporal-limit searches were from inception to 11 June 2013. Only articles in English and involving humans were considered.

Data extraction

Study selection, data extraction and data entry were performed by two authors independently (FP and AC). Differences were resolved by consensus with a third author (SB).

The following information was extracted from each article: (i) basic information including journal, year of publication and author names; (ii) demographic characteristics of patients, including median age, nodal status, menopausal status and hormonal status of primary tumours; (iii) study information, including sample size, study design and study endpoints; (iv) treatment information (including treatment regimens in control and experimental arms) and (v) outcomes (rates or number of events) for OS, relapse-free survival (RFS), breast cancer-specific survival (BCSS), non-cancer-related mortality, loco-regional and distant RFS (LR-RFS and D-RFS).

Outcome measures

Primary outcomes were OS (time to randomisation to all causes of death), BCSS (time to randomisation to BC death after recurrence) and RFS (time to randomisation to any BC relapse excluding contralateral BC). Secondary outcomes included non-cancer-related mortality (any death without recurrence not related to BC), LR-RFS (any local or regional relapse due to BC) and D-RFS (any distant relapse due to BC).

Data synthesis and statistical analysis

This study is a meta-analysis of published trials (aggregate data meta-analysis). The number of events was extrapolated directly from the survival curves or survival rates when outcomes of interest were not reported by authors. Summary statistics of patients achieving a specific event with odds ratios (ORs) and 95 % CI were calculated using both the fixed effect model/Mantel–Haenszel method with minimal heterogeneity in the variables among studies, and the DerSimonian–Laird [8] method (random effects model) when there was significant heterogeneity. Each publication was weighted according to sample size. The χ^2 and I^2 test methods were utilised for between-study heterogeneity of the ORs. Statistically significant differences were defined as <0.1 for χ^2 P, and greater than 50 % for the I^2 test. Forest plots were generated using standard techniques to summarise the included studies, with horizontal lines representing 95 % CI the area of each square representing the weighting and position of each square, demonstrating the

OR point estimate. Sensitivity analyses were performed for OS, BCSS and RFS analyses according to type of agent (T vs. aromatase inhibitors), ER+ status, nodal status (N+ vs. N−) and menopausal status (pre- vs. postmenopausal status). A two-tailed P value < 0.05 was considered statistically significant.

Publication bias

Potential publication biases were evaluated by funnel plots for OS, which assessed the relative symmetry of individual study estimates around the overall estimate, followed by Begg's and Egger's tests, other than the 'Trim and Fill' method.

All statistical analyses were performed with Review Manager 5.1 (Review Manager (RevMan) [computer program] version 5.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008) and Comprehensive Meta Analysis software (version 2.2.064; July 27, 2011).

Results

We identified 4,192 references through electronic searches. After exclusion of duplicate publications and irrelevant trials, ten references remained for evaluation. Finally, eight publications were included in the review [3–5, 9–13]; seven report the results of clinical trials in full-text publications and one is a conference abstract (Table 1). The French study of Delozier et al. was excluded (two publications) because the control arm consists of only 2–3 years of TAM only. All the included trials were phase III studies and required completion of 5 years of TAM before randomisation, except ABCSG 6a, which included patients randomised to 5 years of TAM or TAM + aminogluthetimide. The experimental arms included TAM in five studies, and letrozole, anastrozole and exemestane in each remaining case, respectively. Tamoxifen was generally prescribed for five more years except in ECOG and Scottish trials, where it continued until death or relapse. In the aromatase inhibitor studies, randomised patients were administered letrozole or exemestane for 5 years (vs. placebo) and anastrozole for 3 years (vs. observation). In MA 17 and NSABP B-33, 66 and 44 % of patients in the control arms accepted the active experimental drugs after unblinding. Data from the ATTOM study were not included in ER+ analysis because these patients ($n = 2{,}775$ with ER+ BC) were not analysed apart from patients with ER unknown data ($n = 4{,}198$). In the ECOG trial, the number of events in the ER+ population was not calculated, because only P value was provided; however, in the two treatment arms, OS was similar. Conversely, 3 % of patients in the B-33 study and 31 patients in ABCSG 6a were included despite ER status was negative or unknown. Median duration of follow-up ranged from 30 months to 15 years.

In the MA 17 trial, DFS, which included contralateral BCs, replaced RFS. However, these events were excluded, if possible, from analysis of RFS. In the Scottish trial, only systemic relapses were available at last follow-up. In ECOG trials, time to relapse included any recurrence with contralateral new primary BCs (excluded if numerically specified). In these trials, mixed relapses were not included if not specified singly.

The total number of patients included in this meta-analysis is 29,138, with $n = 14{,}540$ receiving TAM for 5 years and $n = 14{,}598$ receiving extended endocrine therapy either with TAM ($n = 21{,}554$) or an aromatase inhibitor ($n = 7{,}584$). A consort diagram of the stepwise identification of eligible studies is detailed in Fig. 1.

Primary endpoints: OS, BCSS and RFS

Overall, eight trials were available for OS analysis. Using a fixed effect model, the aggregate results for OS were not significant (OR = 0.95, 95 % CI 0.89–1.01, $P = 0.09$; P for heterogeneity = 0.21). According to ER status (six trials available), the results for OS were significant for ER+ patients in the extended arm (OR = 0.89, 95 % CI 0.8–0.99, $P = 0.03$; P for heterogeneity = 0.1, fixed effect model; Fig. 2). Data according to nodal (OS data for N−/N+ disease available in three trials) and menopausal status (OS data for pre- and postmenopausal women available in one and four trials) were not significantly different in the experimental and control arms. Data were also similar according to type of agent.

Data for BCSS were available in seven trials. The results were significant, with OR = 0.87 (95 % CI 0.81–0.95, $P = 0.001$; P for heterogeneity = 0.33, fixed effect model). In ER+ populations, BCSS was significantly better with extended hormonal therapy compared to 5 years of TAM (OR = 0.78, 95 % CI 0.69–0.90, $P = 0.0003$; P for heterogeneity = 0.7, fixed effect model; Fig. 3). No further subgroup analysis was possible for lack of data on nodal and menopausal status. The result for BCSS was significant for TAM but not for aromatase inhibitor studies.

RFS was increased with extended hormonal therapy (similarly with TAM or an aromatase inhibitor) with OR of 0.79 (95 % CI 0.68–0.92, $P = 0.002$; P for heterogeneity = 0.02, random effects model). According to subgroup analysis, RFS was significantly better for the experimental arm in ER+ (OR 0.72, $P = 0.01$; Fig. 4), N+ (OR 0.76, $P < 0.0001$) and postmenopausal women (OR 0.8, $P < 0.0001$). The results for BCSS, but not for OS, in ER+ population remained significant even under the random effect model.

Table 1 Characteristics of included trials

Authors [Ref.]	Type of study and primary endpoint	No. of patients	Median age exp vs. ctr arms (years)	Median follow-up (years)	N+/ER+ (exp vs. ctr arms)	Premenopausal/ postmenopausal (% exp vs. ctr)	Schedule of treatment (exp vs. ctr)	Treatment before randomization	Outcome benefit					
									OS	RFS	BCSS	LR-RFS	D-RFS	Not CRM
Tormey et al. [12]	Phase III/TTR (E4181 & E5181)	194 (87 + 107)	NR	5.6	100/73 vs. 100/72	57/43 vs. 53/47	TAM[a] vs. obs	TAM × 5 y + CT	No	√ in ER+[b]	No	No	No	No
Stewart et al. [11]	Phase III/OS-BCSS-TSR (Scottish Trial)	342	64 vs. 63	15	24.8/38 vs. 20.7/38[c]	23/77 vs. 27/73	TAM[a] vs. obs	TAM × 5 y or at relapse	No	No	No	No	No	No
Fisher et al. [13]	Phase III/DFS-OS (NSABP B-14)	1,172	56 vs. 56	81 mo	0/100 vs. 0/100	27/73 vs. 25/74	TAM × 5 y vs. plac	TAM × 5 y	No	√ in ER+[d]	No	No	No	No
Jakesz et al. [10]	Phase III/RFS (ABSCG 6a)	856	67.8 vs. 68.5	62.3 mo	34.1/95.9 vs. 31.1/96.8	0/100 vs. 0/100	ANA × 3 y vs. obs	TAM or TAM + aminoglut.	No	√	No	√	√	No
Ingle et al. [6]	Phase III/DFS (MA 17)	5,187	62.4 vs. 62	64 mo	46/97.4 vs. 46/97.4	0/100 vs. 0/100	LET × 5 y vs. plac	TAM × 4.5–6 y + CT (46 %)	No[e]	√[d]	No	√	No	No
Mamounas et al. [9]	Phase III/DFS (NSABP B-33)	1,598	51 vs. 49 % ≥ 60	30 mo	48/97 vs. 48/97	0/100 vs. 0/100	EXE × 5 y vs. plac	TAM × 57–66 mo + CT (55 %)	No	√	No	√	No	No
Davies et al. [4]	Phase III/OS (ATLAS)	12,894	51 vs. 51 % < 55 y	7.6	41/53 vs. 40/53	8/90 vs. 8/90	TAM × 5 y vs. obs	TAM × 5 y	√ in ER+	√	√	√ in ER+	No	No
Gray [5]	Phase III/OS (ATTOM)	6,953	NR	NR	39.6 % ER+ overall	NR	TAM × 5 y vs. obs	TAM × ≥4 y	No	√	No	NR	NR	No

TTR time to relapse, *BCSS* breast cancer-specific survival, *TSR* time to systemic relapse, *NR* not reported, *y* years, *N+* node positive primary breast cancer, *ER+* oestrogen and/or progesterone receptor positive, *TAM* tamoxifen, *OS* overall survival, *LR-RFS* loco-regional relapse-free survival, *DRFS* distant relapse-free survival, *RFS* relapse-free survival, *not CRM* not cancer-related mortality, *ANA* anastrozole, *CT* chemotherapy, *plac* placebo, *Mo* months, *aminoglut* aminoglutethimide, *LET* letrozole, *EXE* exemestane

[a] Until death or relapse

[b] Time to relapse

[c] ≥20 fmol/mg cytosol protein

[d] Only DFS significant

[e] Only in node positive

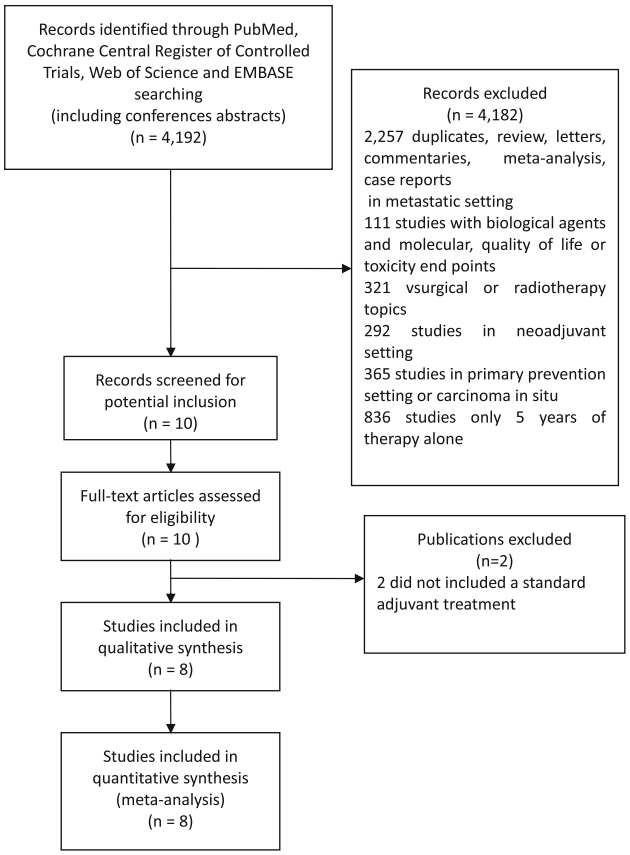


Fig. 1 Selection of publications included in the pooled analysis

Secondary endpoints: non-cancer-related mortality, LR-DFS, D-DFS

Non-cancer-related mortality was similar in the two groups, even though there were 30 more events in the extended endocrine therapy arm. The risks of loco-regional (excluding contralateral primaries) and distant relapses were 36 % ($P = 0.02$) and 13 % ($P = 0.02$), respectively, less in the experimental arm.

Publication bias

Funnel plot and both Begg's and Egger's tests were performed to determine publication bias of the selected studies for OS analysis in the ER+ population (Fig. 5). The shapes of the funnel plots showed no evidence of clear asymmetry (Begg's test $P = 0.25$ and Egger's test $P = 0.24$). Using the 'Trim and Fill' method to account for asymmetric studies in the funnel plot had no effect on the OR for OS (OR = 0.84).

Discussion

This trial-level meta-analysis of eight randomised studies, comparing extended versus standard (5 years) duration of adjuvant hormonal therapy for BC, shows that prolonging treatment beyond 5 years of TAM is useful in terms of survival and relapse. In particular, OS and BCSS with prolonged therapy are significantly better in ER+ disease (11 and 22 % less risk of death, respectively), even though data from the ATTOM trial, which recently presented its updated analysis for almost 7,000 women, were not included, because two-thirds of BCs were of unknown ER status. Relapse rate is also better (about 30 % reduced risk in ER+ populations) with prolonged treatment, in particular for loco-regional recurrence.

Data for this meta-analysis comes from ~30,000 (mainly postmenopausal) women, randomised, after 5 years of TAM, to further TAM (or to an aromatase inhibitor) versus no further therapy. The results are significant, in particular for TAM in BC mortality; however, the results are probably biased in extended trials with aromatase inhibitors, because crossover was permitted to women in the control arm after unblinding. Also, OS benefit in the ER+ subgroup is comparable with TAM or with an aromatase inhibitor when trials are analysed separately. Similarly, even the benefit in RFS is equally strong with the two classes of agents.

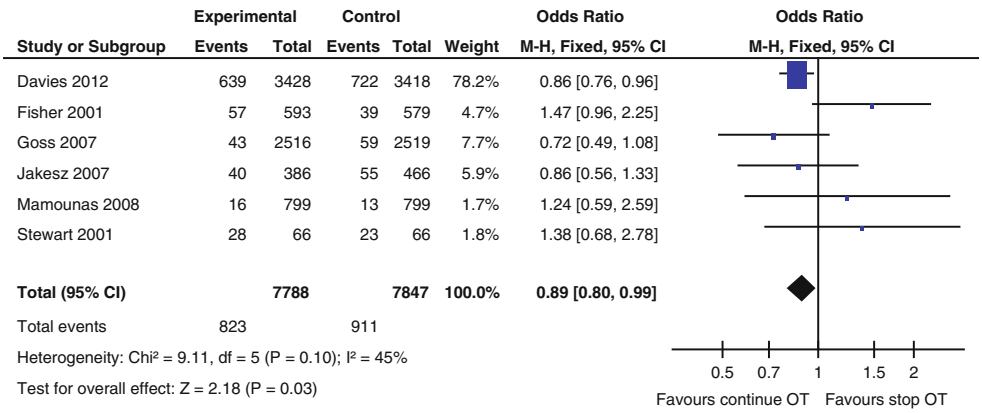


Fig. 2 The forest plots of OR with 95 % CIs for OS in ER+ population with >5 years of endocrine therapy

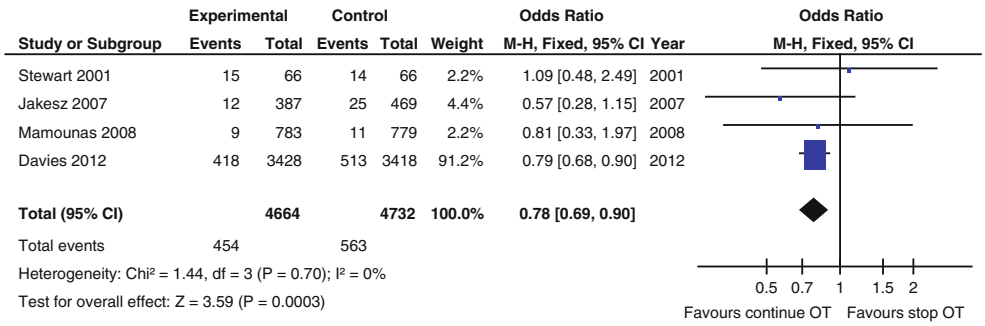
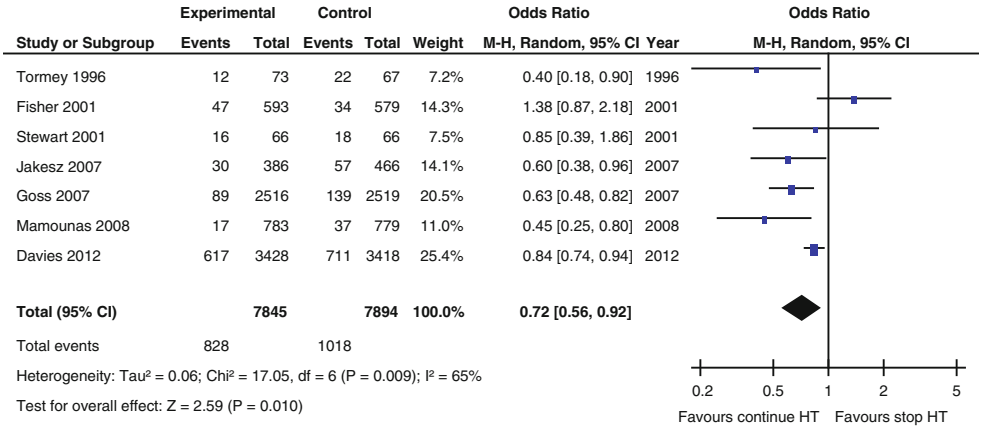


Fig. 3 The forest plots of OR with 95 %CIs for BCSS in ER+ population with >5 years of endocrine therapy

Fig. 4 The forest plots of OR with 95 %CIs for RFS in ER+ population with >5 years of endocrine therapy



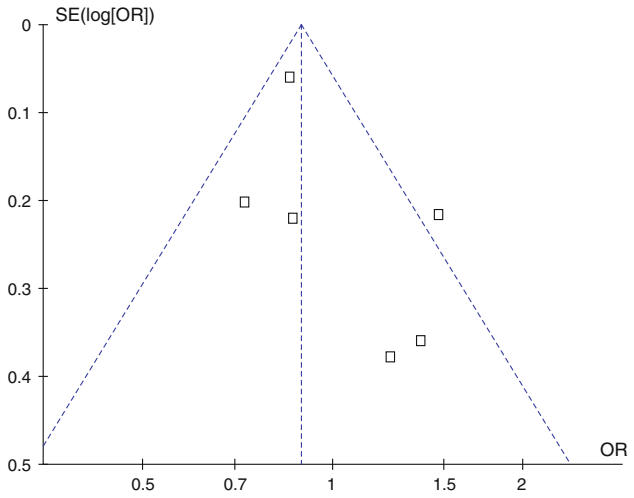


Fig. 5 Funnel plot for publication bias in OS analysis (ER+ population)

These results lead to several additional considerations. First, use of extended endocrine therapy, after 5 years of TAM, ameliorates OS in ER+ BCs only. The results for survival, however, are probably underestimated in magnitude, likely because of the short follow-up and the good prognosis of some (low risk) ER+ BCs that remained disease-free after 5 years of TAM; their outcome is little affected by additional years of therapy. Further, in aromatase inhibitor trials, where the control arm, after unblinding, received a large percentage of the active drugs, the OS benefit was not significant in all studies. This means that the magnitude of survival benefit in this meta-analysis could have been even greater if a population with only higher risk features were enroled, and crossover were not permitted at all. In MA 17, after re-analysis adjusting for treatment crossover, the results for OS were significant (hazard ratios (HR) = 0.61) [7].

Second, to prevent late events (those occurring after 10 years of follow-up), a prolonged hormonal therapy course (of at least five more years) is necessary to increase the carryover effect on survival and to obtain a further, albeit small, OS benefit compared with 5 years of TAM alone. This is shown in the results of the ATTOM trial, where BC mortality and overall mortality are significantly reduced, in particular after the ninth year. Similarly, the HRs for DFS in the MA 17 study in fact progressively decreased over the 48-month treatment period to a remarkably low level of 0.19 in favour of letrozole. The decreasing trend in HRs was highly significant ($P < 0.0001$), indicating greater benefit the longer the patient received letrozole, at least for 48 months' duration [14]. In this setting, whether adherence to extended treatment is critical to obtaining this result is presently unknown.

Third, not BC-related mortality is little affected, even if a larger number of events are observed in the experimental arm. In ATLAS analysis, not BC mortality is not significantly worse after 10 years of the TAM arm. Finally, reduction in relapse is stronger for loco-regional than for distant ones. This may be explained by ER discordance between primary BC and distant metastasis: in this case, extended endocrine therapy may have been less protected from ER− disease relapse [15–18], allowing for emergence of more ER− metastases.

Several questions remain unanswered. The ideal candidate for extended adjuvant therapy is presently unknown. Analysis of survival according to nodal and menopausal status is limited by sparse data availability. RFS conversely is significantly better with more endocrine therapy in N+ and postmenopausal patients. This is expected, because N+ BCs are associated with increased risk of recurrence and death, and postmenopausal women are more commonly associated with ER+ tumours, with consequent larger benefit. In the most recently published *Lancet* meta-analysis of individual patient data from TAM trials [1], the absolute benefit of 5 years of TAM was largest in N+ and older (postmenopausal) patients. In ATLAS and MA 17 trials, the overall benefit in recurrence was similar in two arms, but slightly numerically superior in N+ disease. In MA 17, premenopausal women at diagnosis who became postmenopausal after adjuvant chemotherapy derived the greatest benefit from letrozole [19].

The ideal agent for extended treatment is under debate. The largest body of evidence in this meta-analysis comes from the TAM trials (>20,000 patients). However, if more data were available for aromatase inhibitors, different or even better results for the survival analysis could have been obtained. Shifting to an aromatase inhibitor could in fact revert to secondary resistance; however, switching data are available in trials for only a total of 5 years of treatment duration (e.g., BIG 1–98 study). Comparison between TAM and aromatase inhibitors is still pending in the extended setting, and determining which strategy is more suitable after 5 years of an aromatase inhibitor is still challenging. An NCIC trial is currently comparing letrozole versus placebo after 5 years of letrozole [20].

Our analysis has several limitations. First, it is a meta-analysis of published studies, with outcomes derived (or calculated) directly from publications. Thus, proper subgroup analysis, including adjusting for baseline factors such as nodal and menopausal status, age, or other pathological features is not possible with the information available. Second, clear differences among the two endocrine classes of agents are not conclusive, because results for TAM-treated patients are much more numerically abundant than data with aromatase inhibitors. Third, follow-up times are different among the trials, and in particular, are shorter for aromatase inhibitors. This limitation may not have captured some late deaths or relapses typically observed in this disease. Our results, however, are significant for both mortality and RFS, with little heterogeneity for survival analysis.

Further follow-up of these trials is needed to confirm our results. A balance between risk and benefits must be carefully performed in cases of prolonged duration of treatment; nevertheless, not cancer-related mortality is not worse with prolonged therapy, according to our analysis.

In conclusion, extended endocrine therapy is an opportunity for women with ER+ BC to reduce their risk of death or relapse. To which ER+ BC patients this treatment is better suited is presently unknown. In the mean time, a detailed discussion of the pros and cons of this strategy must be performed with women with ER+ early BC who have completed 5 years of TAM.

Conflict of interest All authors disclose any potential conflicts of interest.

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