REVIEW

Efficacy and toxicity of extended aromatase inhibitors after adjuvant aromatase inhibitors-containing therapy for hormone-receptor-positive breast cancer: a literature-based meta-analysis of randomized trials

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Abstract

Background Endocrine therapy with aromatase inhibitors (AIs) is the cornerstone of adjuvant systemic treatment for post-menopausal patients with hormone receptor-positive breast cancer. It has become clear that hormone receptor-positive breast cancer carries a consistent risk of relapse up to 15 years after diagnosis. Extended duration of adjuvant AIs therapy after completing initial standard adjuvant AIs-containing therapy may prevent late recurrence and death. We performed a meta-analysis to assess the real impact of the extended adjuvant therapy with AIs.

Methods A literature-based meta-analysis of the randomized controlled trials (RCTs) was undertaken. Relevant publications from PubMed, Embase, Cochrane Library, and abstracts from American Society of Clinical Oncology (ASCO) and San Antonio Breast Cancer (SABCS) symposia were searched. The endpoints were disease-free survival (DFS), overall survival (OS), local recurrence, distant recurrence, contralateral breast cancer, non-breast cancer-related death, and toxicity.

Results Eight trials comprising 15,966 patients met the inclusion criteria. The pooled analysis revealed a significant improvement in DFS (RR = 0.79; 95% CI 0.68–0.91), distant recurrence (RR = 0.75; 95% CI 0.58–0.96), and contralateral breast cancer (RR = 0.53; 95% CI 0.40–0.70) in the extended AIs group. While there was not significant improvement in OS (RR = 1.00, 95% CI 0.99–1.01), non-breast cancer-related death (RR = 1.16, 95% CI 0.96–1.41), and local recurrence (RR = 0.82; 95% CI 0.64–1.06), the subgroup analysis showed that the patient with tumor size > 2 cm (HR = 0.74, RD = − 0.31, P = 0.05 vs. HR = 0.85, RD = − 0.16, P = 0.20), node positive status (HR = 0.77, RD = − 0.27, P = < 0.0001 vs. HR = 0.89, RD = − 0.12, P = 0.19) and previous chemotherapy use (HR = 0.75, RD = − 0.29, P = 0.003 vs. HR = 0.91, RD = −0.10, P = 0.44) would get a greater DFS benefit with extended AIs. Longer treatment with AIs was associated with an increased risk ratio of bone pain (RR = 1.26, RD = 0.04, P = 0.003), bone fractures (RR = 1.59, RD = 0.02, P = 0.002), osteoporosis (RR = 1.53, RD = 0.07, P = 0.005), myalgia (RR = 1.26, RD = 0.04, P = 0.02), and treatment discontinuation for adverse events (RR = 1.51, RD = 0.06, P = 0.0009).

Conclusion After initial standard AIs-containing adjuvant therapy, extended AIs therapy could further bring a DFS benefit for postmenopausal patients with early breast cancer, especially in the patients with high-risk characteristics.

Keywords Breast cancer · Hormone-positive · Adjuvant endocrine therapy · Aromatase inhibitors · Extended adjuvant AIs therapy

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Abbreviations

RCTs	Randomized controlled trials
ASCO	American Society of Clinical Oncology
SABCS	San Antonio Breast Cancer
RR	Risk ratio
HR	Hazard ratio
RD	Risk difference
CI	Confidence intervals
ER	Estrogen receptor
PR	Progesterone receptor
N±	Node positive or negative
DFS	Disease-free survival
OS	Overall survival
LR	Local recurrence
DR	Distant recurrence
CBC	Contralateral breast cancer
NBCD	Non-breast cancer-related death
TAM	Tamoxifen
ANA	Anastozole
LET	Letrozole
AIs	Aromatase inhibitors
OFS	Ovarian function suppression
AG	Aminoglutethimide
COMB	Combination
mo	Month
plac	Placebo

Background

Hormonal therapy is the cornerstone of adjuvant systemic treatment for patients with hormone receptor-positive breast cancer. Possible therapies include tamoxifen, aromatase inhibitors (AIs) or, in pre-menopausal patients, ovarian function suppression (OFS) achieved by surgery (oophorectomy) or by GnRH agonists [1]. Multiple large clinical trials have showed that 5 years of adjuvant endocrine therapy substantially reduces the risks of locoregional and distant recurrence, contralateral breast cancer, death from breast cancer, and death from any cause [2–4].

Despite the success of adjuvant endocrine therapy, still 50 % of all recurrences occur after the first 5 years [5]. In recent decades, multiple clinical trials have tested the role of extending adjuvant endocrine therapies in patients with hormone receptor-positive disease. Extended adjuvant endocrine therapy with either tamoxifen or AIs after 5 years of initial tamoxifen treatment has been shown to improve the disease-free survival (DFS) in early-stage breast cancer [6–9].

However, the EBCTCG meta-analysis has shown that the adjuvant therapy containing AIs in the first 5 years of adjuvant therapy was superior to tamoxifen monotherapy [4]. Nowadays AIs are one of the most commonly used

treatments in adjuvant endocrine therapy for postmenopausal women with breast cancer [10–12], which has achieved good therapeutic effects. Thus, whether it is necessary to adopt extended adjuvant AIs therapy after completing AIs-containing therapy is not clear. The MA.17R is the first study to examine the role of extended AIs therapy for up to 10 years. After a median follow-up of 6.3 years, the study showed a significant reduction in DFS in favor of letrozole (HR 0.66, $P = 0.01$). These results provide support for consideration of extended AIs therapy in all women who have tolerated standard adjuvant AIs-containing therapy. However, the NSABP B-42 trial showed that letrozole therapy did not significantly prolong DFS in patients who had remained free of breast cancer after completing 5 years of AIs-containing therapy.

In view of the variability in results in trials of extended adjuvant AIs therapy, the true benefit of this treatment
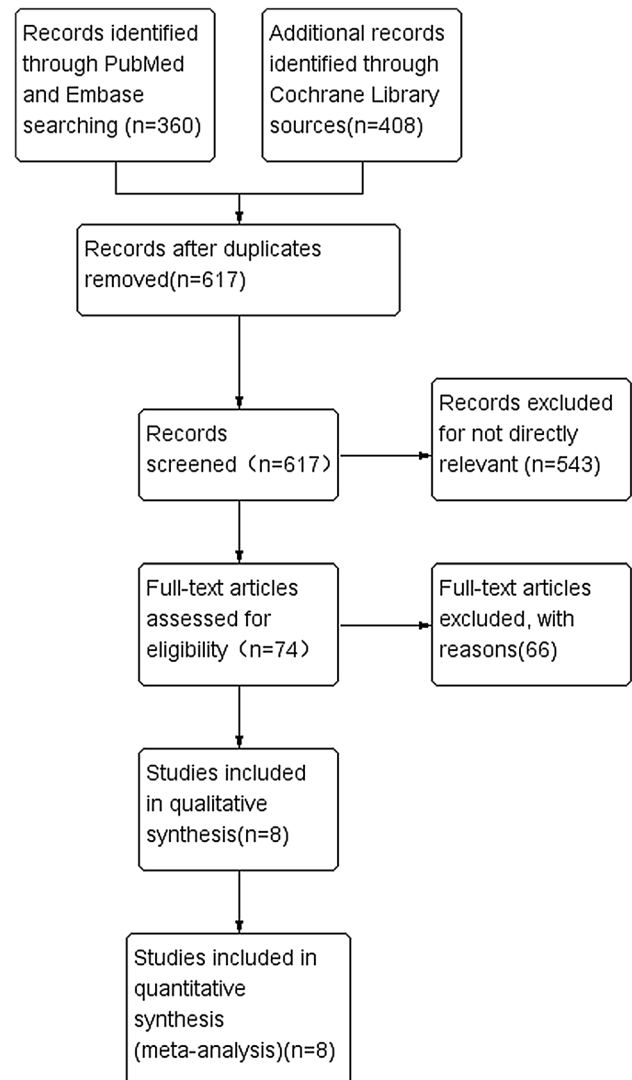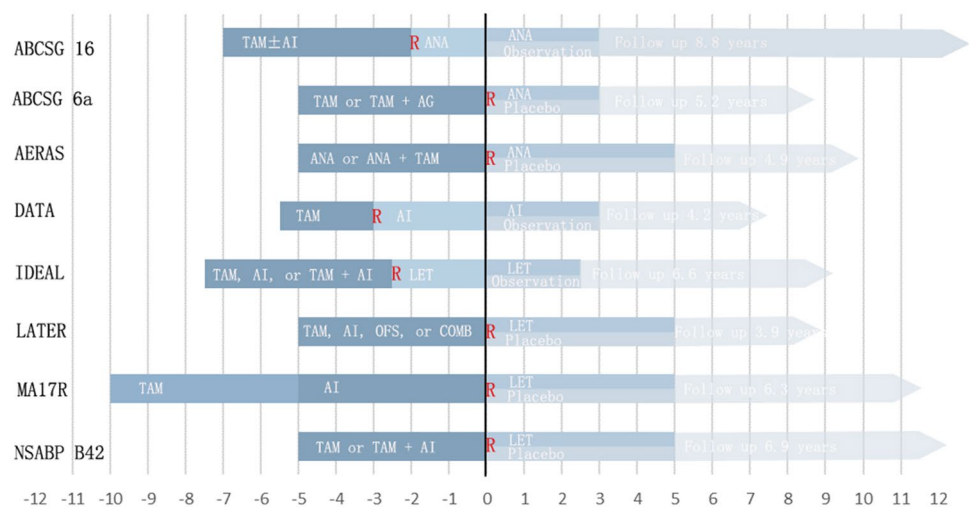

Fig. 1 Flow chart of the literature selection process of included studies

Fig. 2 Treatment strategies of included studies

strategy is unknown. Here, we report a meta-analysis of randomized trials to assess the differences in efficacy and toxicity of the extended adjuvant AIs therapy after completing the initial standard AIs-containing therapy.

Methods

A systematic literature review of the published RCTs was performed and the meta-analysis was conducted in accordance with the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This meta-analysis did not require any review of protocols or registration.

Data sources and search strategy

PubMed, Embase, and Cochrane Library were used to identify all eligible trials. Keywords used were: "breast cancer", "endocrine therapy", "extended or continued or prolonged", "aromatase inhibitor". Furthermore, we searched abstracts and presentations reported from annual meetings of the American Society of Clinical Oncology (ASCO) or the San Antonio Breast Cancer Symposium (SABCS) to collect relevant unpublished studies. Lastly, all review articles and the cross referenced manuscripts from retrieved articles were screened for relevant studies.

Inclusion criteria

We included all the RCTs which met the following criteria: RCT's that were published in English, patients of any age with hormone receptor-positive early or locally advanced breast cancer, RCT's which investigated the outcomes of extended adjuvant AIs-containing therapy in postmenopausal women who had remained free of breast cancer after completing AIs-containing therapy, assessed the DFS, OS,

local recurrence, distant recurrence, contralateral breast cancer, non-breast cancer-related death, and toxicity. There was no time restriction on publication dates.

Exclusion criteria

Studies, which were not RCTs, case series, reviews, letters, editorials, non-peer reviewed studies, and duplicates were excluded from the analysis.

Data extraction

Articles were retrieved from databases using mentioned keywords. Selection of articles was done in 3 steps. The Endnote X7 Resources Management Software was used to organize, study titles and abstracts, and identify duplicates. After removing duplicates, the titles of all articles reviewed and articles that didn't match with inclusion criteria were removed. For the next step, the abstract and the full-text of the articles were studied and checked based on inclusion criteria and study objectives. The study selection and quality assessment were done by two researchers independently, and in case of disagreement the subject was referred to a third person. Information extracted from the articles was summarized in the extraction form.

Risk of bias assessment

Review Manager 5.3 from the Cochrane Collaboration was used to assess the risk of bias in individual studies. Uniform criteria were recommended by the Cochrane Collaboration, which included six items: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential bias as previously used were applied in our meta-analysis.

Table 1 Characteristics of included studies and outcome events

Type of study and primary endpoint	No. of patients	Median age (exp versus ctr) (years)	Median follow-up (years)	T1/≥T2 (exp versus ctr)[a]	N+/N− (exp versus ctr)	Grade 1and2/Grade3 (exp versus ctr)	ER and PR positive/ER or PR positive (exp versus ctr)	Chemotherapy/no Chemotherapy (exp versus ctr)	Schedule of treatment (exp versus ctr)	Treatment before randomization	Outcome benefit					
											DFS	OS	LR	DR	CBC	NBCD
Phase III/DFS (ABCSG16)	3468	64	105.9 mo	2507/961	1167/2301	NR	2683	1000	ANA * 5 years versus ANA*2 years	TAM±AI * 5 years	✓	NR	NR	NR	NR	NR
Phase III/RFS (ABCSG6a)	856	67.8 versus 68.5	62.3 mo	241/146 versus 296/173	132/255 versus 146/323	308/79 versus 377/92	309/62 versus 359/95	NR	ANA * 3 years versus plac	TAM or TAM + aminoglut * 5 years	✓	✓	✓	✓	✓	✓
Phase III/DFS (AERAS)	1697	64.3 versus 64.5	4.9 years	449/391 versus 437/406	190/650 versus 176/667	NR	500 versus 507	313/499 versus 311/487	ANA * 5 years versus plac	ANA or TAM+ANA * 5 years	✓	✓	✓	✓	✓	✓
Phase III/DFS (DATA)	1860	57.7 versus 57.6	4.2 years	376/450 versus 383/449	561/266 versus 551/282	569/229 versus 573/238	627/200 versus 633/200	565/262 versus 570/263	ANA * 6 years versus ANA * 3 years	TAM * 2–3 years	✓	✓	✓	✓	✓	✓
Phase III/DFS (IDEAL)	1821	NR	6.6 years	NR	669/235 versus 665/237	524/296 versus 536/270	697/182 versus 712/160	626/287 versus 617/291	LET * 5 years versus LET * 2.5 years	TAM or AI or TAM+AI * 5 years	✓	✓	✓	✓	✓	✓
Phase III/DFS (LATER)	360	65.0 versus 64.0	3.9 years	132/48 versus 114/63	56/112 versus 65/105	31/144 versus 24/153	138/43 versus 142/37	75/106 versus 86/93	LET * 5 years versus plac	AI, TAM, OFS, or sequential combination * 5 years	✓	✓	✓	✓	✓	✓
Phase III/DFS (MA.17R)	1918	65.6 versus 64.8	6.3 years	553/399 versus 535/414	492/446 versus 494/448	NR	726/219 versus 721/229	561/398 versus 557/402	LET * 5 years versus plac	TAM → AI * 4–6 years	✓	✓	✓	✓	✓	✓
Phase III/DFS (NSABP42)	3923	no	6.9 years	NR	838/1145 versus 849/1134	NR	NR	NR	LET * 5 years versus plac	AI or AI+ TAM * 5 years	✓	✓	✓	✓	✓	✓

ER: estrogen receptor, *PR*: progesterone receptor, *N±*: node positive or negative, *DFS*: disease-free survival, *OS*: overall survival, *LR*: local recurrence, *DR*: distant recurrence, *CBC*: contralateral breast cancer, *NBCD*: non-breast cancer-related death, *TAM*: tamoxifen, *ANA*: anastrozole, *LET*: letrozole, *AI*: aromatase inhibitor, *OFS*: ovarian function suppression, *mo* month, *plac* placebo, *NR*: not reported

[a] T1 indicates that the tumor is <20 mm in its greatest dimension, ≥ T2 indicates that the tumor is ≥ 20 mm in its greatest dimension.
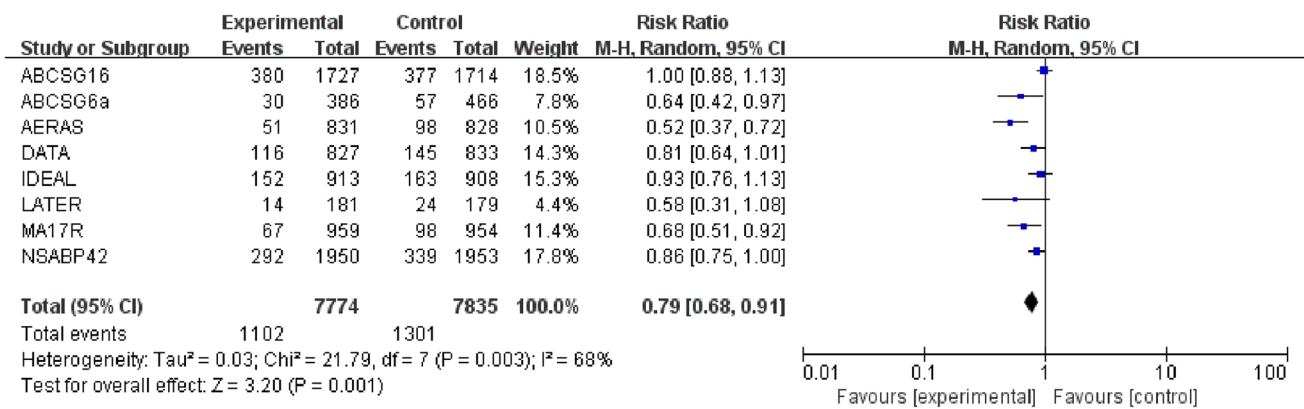
Fig. 3 Forest plots of RR for DFS in patients treated with extended adjuvant AIs-containing therapy versus placebo

Statistical analyses

The differences between the two groups were estimated by the pooled RR and HR along with 95% CIs. The summary RR or HR estimates were conducted using a random or fixed effect model. Subgroup analyses were performed to detect the influence of stratification factors and other baseline characteristics. Statistical heterogeneity was estimated by the I^2 statistic as follows: $I^2 < 30\%$ meant "low heterogeneity"; I^2 between 30 and 50% denoted "moderate heterogeneity"; $I^2 > 50\%$ represented "substantial heterogeneity." A fixed effect model was used if the heterogeneity was low or moderate. Otherwise, the random effect model was reported after exploring the cause of heterogeneity. All calculations were performed by Review Manager Version 5.3 software (The Cochrane Collaboration, Oxford, UK). All tests mentioned below were 2-tailed and a P value of $< .05$ was considered to be statistically significant for all analyses.

Results

According to the search strategy established by us, 708 records were retrieved totally from PubMed, Embase, and Cochrane Library. After removing the duplicates and irrelevant records, 74 full-text articles were available for the meta-analysis. However, 66 studies were excluded after full-text article assessment, leaving a total of 8 RCTs that contained sufficient details or met the inclusion criteria (Fig. 1) [13–20]. The majority of the included studies evaluated the effects of further extension of adjuvant AIs therapy which had completed the AIs-containing therapy, and detailed treatment strategies were shown in Fig. 2. All studies' characteristics have been summarized in Tables 1.
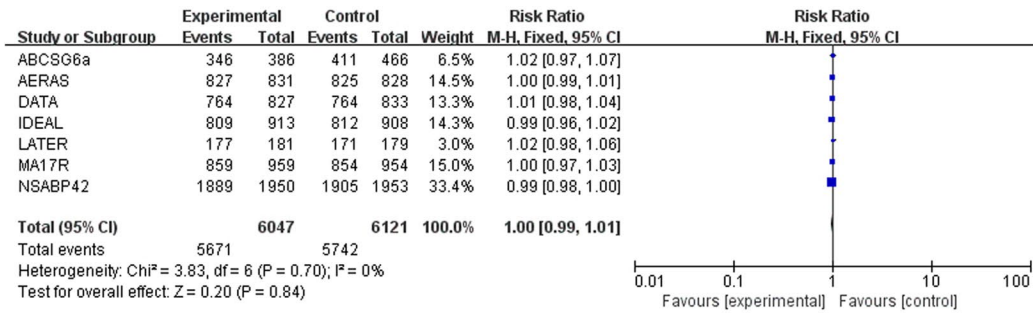
Disease-free survival (DFS) and overall survival (OS)

All 8 RCTs enrolling 15,966 postmenopausal patients were available for the analysis of DFS at the end of the observation period. The random effects model was used because there were high heterogeneities ($I^2 = 68\%$, $P = 0.003$) between these data. The pooled data showed that extended endocrine therapy with AIs improved DFS when compared to control (RR = 0.79; 95% CI 0.68–0.91; Fig. 3).
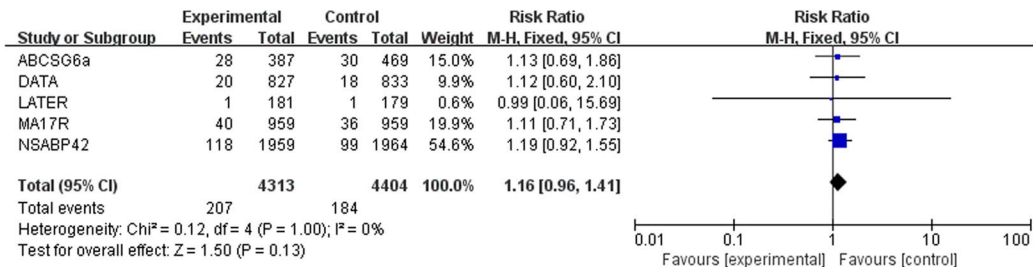
Data for OS were available in 7 trials, and OS was similar in the two groups. The fixed effects model was used for the analysis of the OS data due to the presence of low heterogeneity ($I^2 = 0\%$) between the trials. The pooled analysis revealed that extended AIs therapy did not decrease the risk of death from any cause (RR = 1.00, 95% CI 0.99–1.01; Fig. 4a), as well as non-breast cancer-related death (RR = 1.16, 95% CI 0.96–1.41; $I^2 = 0\%$, fixed effects model Fig. 4b). Regarding local recurrence, we also found that extended therapy did not significantly improve the local recurrence (RR = 0.82; 95% CI 0.64–1.06; $I^2 = 42\%$, fixed effects model Fig. 4c), while the distant recurrence and contralateral breast cancer were increased with extended endocrine therapy, and the RR of distant recurrence and contralateral breast cancer was 0.75 (95% CI 0.58–0.96; $I^2 = 58\%$, random effects model Fig. 4d) and 0.53 (95% CI 0.40–0.70; $I^2 = 0\%$, fixed effects model Fig. 4e).

Subgroup analysis

Several subgroups analyses were performed, however, with only fewer number of studies reporting effects of size in the subgroups. Table 2 shows that the benefits of extended AIs therapy for postmenopausal women with breast cancer in reducing recurrence were associated with tumors that are > 2 cm (HR = 0.74, RD = − 0.31, P = 0.05 vs. HR = 0.85, RD = − 0.16, P = 0.20), node positive status (HR = 0.77, RD = − 0.27, P = < 0.0001 vs. HR = 0.89, RD = − 0.12, P =

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ABCSG6a	346	386	411	466	6.5%	1.02 [0.97, 1.07]
AERAS	827	831	825	828	14.5%	1.00 [0.99, 1.01]
DATA	764	827	764	833	13.3%	1.01 [0.98, 1.04]
IDEAL	809	913	812	908	14.3%	0.99 [0.96, 1.02]
LATER	177	181	171	179	3.0%	1.02 [0.98, 1.06]
MA17R	859	959	854	954	15.0%	1.00 [0.97, 1.03]
NSABP42	1889	1950	1905	1953	33.4%	0.99 [0.98, 1.00]
Total (95% CI)		**6047**		**6121**	**100.0%**	**1.00 [0.99, 1.01]**
Total events	5671		5742			

Heterogeneity: Chi² = 3.83, df = 6 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.20 (P = 0.84)
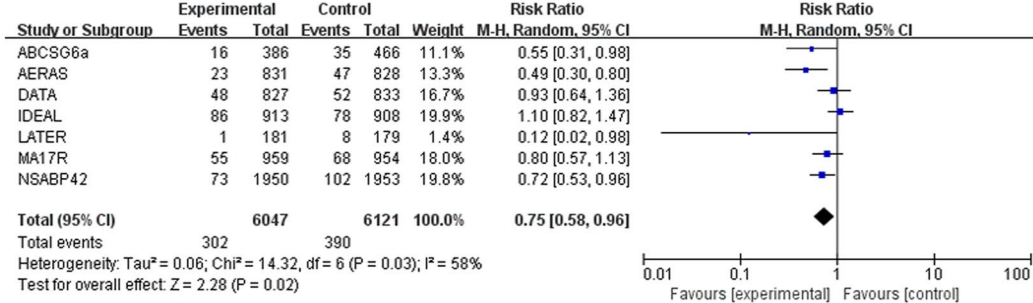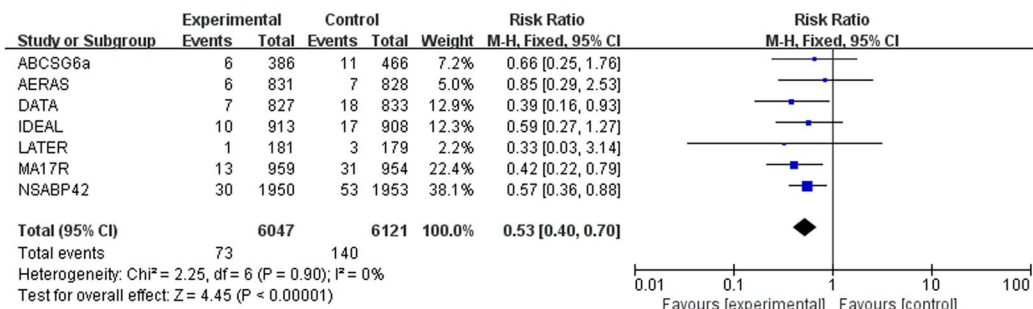
A Overall survival

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ABCSG6a	28	387	30	469	15.0%	1.13 [0.69, 1.86]
DATA	20	827	18	833	9.9%	1.12 [0.60, 2.10]
LATER	1	181	1	179	0.6%	0.99 [0.06, 15.69]
MA17R	40	959	36	959	19.9%	1.11 [0.71, 1.73]
NSABP42	118	1959	99	1964	54.6%	1.19 [0.92, 1.55]
Total (95% CI)		**4313**		**4404**	**100.0%**	**1.16 [0.96, 1.41]**
Total events	207		184			

Heterogeneity: Chi² = 0.12, df = 4 (P = 1.00); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)

B Non-breast cancer-related death

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ABCSG6a	10	386	15	466	10.4%	0.80 [0.37, 1.77]
AERAS	15	831	32	828	24.6%	0.47 [0.25, 0.86]
DATA	12	827	7	833	5.4%	1.73 [0.68, 4.36]
IDEAL	14	913	12	908	9.2%	1.16 [0.54, 2.49]
LATER	0	181	4	179	3.5%	0.11 [0.01, 2.03]
MA17R	19	959	28	954	21.6%	0.68 [0.38, 1.20]
NSABP42	36	1950	33	1953	25.3%	1.09 [0.68, 1.74]
Total (95% CI)		**6047**		**6121**	**100.0%**	**0.82 [0.64, 1.06]**
Total events	106		131			

Heterogeneity: Chi² = 10.28, df = 6 (P = 0.11); I² = 42%
Test for overall effect: Z = 1.49 (P = 0.14)

C Local recurrence

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ABCSG6a	16	386	35	466	11.1%	0.55 [0.31, 0.98]
AERAS	23	831	47	828	13.3%	0.49 [0.30, 0.80]
DATA	48	827	52	833	16.7%	0.93 [0.64, 1.36]
IDEAL	86	913	78	908	19.9%	1.10 [0.82, 1.47]
LATER	1	181	8	179	1.4%	0.12 [0.02, 0.98]
MA17R	55	959	68	954	18.0%	0.80 [0.57, 1.13]
NSABP42	73	1950	102	1953	19.8%	0.72 [0.53, 0.96]
Total (95% CI)		**6047**		**6121**	**100.0%**	**0.75 [0.58, 0.96]**
Total events	302		390			

Heterogeneity: Tau² = 0.06; Chi² = 14.32, df = 6 (P = 0.03); I² = 58%
Test for overall effect: Z = 2.28 (P = 0.02)

D Distant recurrence

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
ABCSG6a	6	386	11	466	7.2%	0.66 [0.25, 1.76]
AERAS	6	831	7	828	5.0%	0.85 [0.29, 2.53]
DATA	7	827	18	833	12.9%	0.39 [0.16, 0.93]
IDEAL	10	913	17	908	12.3%	0.59 [0.27, 1.27]
LATER	1	181	3	179	2.2%	0.33 [0.03, 3.14]
MA17R	13	959	31	954	22.4%	0.42 [0.22, 0.79]
NSABP42	30	1950	53	1953	38.1%	0.57 [0.36, 0.88]
Total (95% CI)		**6047**		**6121**	**100.0%**	**0.53 [0.40, 0.70]**
Total events	73		140			

Heterogeneity: Chi² = 2.25, df = 6 (P = 0.90); I² = 0%
Test for overall effect: Z = 4.45 (P < 0.00001)

E Contralateral breast cancer

◀**Fig. 4** Forest plots of RR for **a** OS, **b** Non-breast cancer-related death, **c** local recurrence, **d** distant recurrence and **e** contralateral breast cancer in patients treated with extended adjuvant AIs-containing therapy versus placebo

0.19) and previous chemotherapy use (HR = 0.75, RD = −0.29, P = 0.003 vs. HR = 0.91, RD = −0.10, P = 0.44). However, the benefits of extended AIs therapy were statistically significant regardless of whether the initial endocrine therapy includes tamoxifen (HR = 0.82, RD = −0.20, P = 0.01 vs. HR = 0.81, RD = −0.21, P = 0.0002). Furthermore, the reduction in the risk of recurrence achieved with extended AIs therapy for postmenopausal women with breast cancer was demonstrated regardless of whether previous AIs had been used for 5 years (HR = 0.81, RD = −0.22, P = 0.02 vs. HR = 0.78, RD = −0.25, P = 0.01).

Toxicity

7 out of 8 trials reported toxicity and adverse events. Table 3 summarizes the common adverse events reported in the included trials. Our meta-analysis showed as was expected that extension was associated with an increase of risk of bone pain (RR = 1.26, RD = 0.04, P = 0.003, I^2 = 12%), bone fractures (RR = 1.59, RD = 0.02, P = 0.002, I^2 = 56 %), osteoporosis (RR = 1.53, RD = 0.07, P = 0.005, I^2 = 91%), and myalgia (RR = 1.26, RD = 0.04, P = 0.02, I^2 = 57%). In contrast, we did not observe a statistically significant increase in the RR of cardiovascular events (RR = 1.07, RD = 0, P = 0.41, I^2 = 12%) and hypertension (RR = 0.99, RD = 0, P = 0.92, I^2 = 32%) with longer durations of AIs. It was evident that bone pain, arthralgia, myalgia, osteoporosis, and fracture were higher in the extended AIs therapy group, while the cardiovascular adverse events did not increase significantly. Discontinuation of treatment for adverse events was reported in five studies [14, 16, 17, 19, 20]. Pooled data showed that longer duration of therapy with AIs was associated with a 51% increased RR for therapy discontinuation for adverse events compared with placebo or no treatment (RR = 1.51, RD = 0.06, P = 0.0009, I^2 = 72%) (Table 3).

Risk of bias in included RCT studies

Full details about the risk of bias in RCT studies were shown in Fig. 5. For allocation concealment, the risk of bias was unclear in 3 RCTs with an allocation scheme that was not mentioned in the trials; in 1 study the risk of bias was low, whereas in the other 5 studies the risk of bias was high. For the performance bias, the risk of bias was unclear in 3 RCT studies and high in another one. For the detection bias, the risk was unclear in 1 study.

Due to the small number of trials that were included (< 10), no publication bias or sensitivity analysis was performed.

Discussion

The study shows that hormone receptor-positive early breast cancer recurrences continued to occur steadily throughout the study period from 5 to 20 years after 5 years of adjuvant endocrine therapy. Due to good therapeutic result and long-term toxicity of endocrine therapy of AIs, extending endocrine therapy is not routinely recommended for all patients [21, 22]. Multiple studies have assessed the hypothesis that extending the duration of endocrine therapy will result in reduction of breast cancer recurrences. Data are currently available from studies which included treatment initially with AIs-containing therapy for postmenopausal women with early breast cancer and randomized them either to ongoing AIs or placebo. Results of these studies have been mixed leading to an uncertainty regarding the benefit of extended adjuvant endocrine therapy.

The debates concerning extended adjuvant AIs therapy is obvious. The trials such as MA.17R, AERAS, and ABCSG 6a have shown a significant advantage deriving from extended endocrine therapy with AIs beyond initial AIs-containing therapy, particularly in the group of patients with higher risk of recurrence [23]. However, such improvement has not been confirmed in more recent studies. For example, NSABP B42, DATA, LATER, ABCSG 16, and IDEAL trials all failed to show an improvement in DFS and OS. Here, we report on a published data meta-analysis of eight randomized trials, showing that extended adjuvant therapy using AIs following initial AIs-containing therapy (tamoxifen, AIs or switching) in postmenopausal women provided better outcomes in terms of recurrence rate. In particular, DFS, distant recurrence and contralateral breast cancer with extended therapy were significantly better in early hormone-positive breast cancer. However, those benefits did not translate to survival benefit. Above all, the recurrence of contralateral breast cancer was significantly decreased in patients treated with extended AIs therapy. It could be argued that the extended adjuvant endocrine therapy with AIs after initial adjuvant AIs-containing therapy was a secondary prevention rather than the actual adjuvant therapy, preventing relapse of the earlier breast cancer. This preventive effect has already been shown in multiple clinical trials in healthy women without breast cancer using AIs [24–27].

In our meta-analysis, those events which were associated with substantial morbidity and mortality or commonly reported in trials would be chosen. The addition of AIs after initial adjuvant AIs-containing therapy is generally

Table 2 Subgroup analysis for DFS

Subgroups analysis	Included studies	Individual studies HR/RD (95%CI)	Subgroups effects HR/RD (95%CI)	P
Recurrence versus tumor status				
T1	AERAS	0.60 (0.35,1.03)/−0.51 (−1.06, 0.03)	0.85 (0.66,1.09)/−0.16 (−0.41, 0.09)	0.20
	DATA	0.91 (0.60,1.38)/−0.09 (−0.51, 0.32)		
	IDEAL	0.95 (0.65,1.39)/−0.05 (−0.43, 0.33)		
T2 and T3/4	AERAS	0.52 (0.32,0.85)/−0.65 (−1.15, −0.16)	0.74 (0.54,1.00)/−0.31 (−0.61, −0.00)	0.05
	DATA	0.72 (0.52,1.00)/−0.33 (−0.66, −0.00)		
	IDEAL	0.94 (0.68,1.29)/−0.06 (−0.38, 0.26)		
Recurrence versus nodal status				
pN positive	ABCSG6a	0.61 (0.34, 1.10)/−0.49 (−1.08, 0.09)	0.77 (0.67, 0.87)/−0.27 (−0.40, −0.14)	< 0.0001
	AERAS	0.51 (0.34, 0.76)/−0.67 (−1.08, −0.27)		
	DATA	0.75 (0.56, 1.00)/−0.29 (−0.58, 0.00)		
	IDEAL	0.82 (0.65, 1.04)/−0.20 (−0.43, 0.03)		
	NSABP B-42	0.85 (0.68, 1.06)/−0.16 (−0.38, 0.06)		
pN negative	ABCSG6a	0.61 (0.31, 1.19)/−0.49 (−1.16, 0.17)	0.89 (0.75, 1.06)/−0.12 (−0.29, 0.06)	0.19
	AERAS	0.69 (0.35, 1.35)/−0.37 (−1.04, 0.30)		
	DATA	0.94 (0.59, 1.50)/−0.06 (−0.53, 0.40)		
	IDEAL	1.41 (0.86, 2.31)/0.34 (−0.15, 0.84)		
	NSABP B-42	0.86 (0.69, 1.07)/−0.15 (−0.37, 0.07)		
Recurrence versus histological grade				
Grade 1 and 2	ABCSG6a	0.59 (0.36, 0.97)/−0.53 (−1.03, −0.03)	0.80 (0.66, 0.98)/−0.22 (−0.42, −0.02)	0.03
	DATA	0.81 (0.59, 1.11)/−0.21 (−0.52, 0.10)		
	IDEAL	0.89 (0.65, 1.21)/−0.12 (−0.42, 0.19)		
Grade 3	ABCSG6a	0.73 (0.29, 1.84)/−0.31 (−1.24, 0.61)	0.93 (0.69, 1.24)/−0.08 (−0.37, 0.21)	0.61
	DATA	0.80 (0.51, 1.26)/−0.22 (−0.68, 0.23)		
	IDEAL	1.10 (0.73, 1.66)/0.10 (−0.32, 0.51)		
Recurrence versus receptors status				
ER and PR positive	ABCSG6a	0.32 (0.18, 0.56)/−1.14 (−1.71, −0.57)	0.70 (0.48, 1.03)/−0.35 (−0.74, 0.03)	0.07
	AERAS	0.84 (0.57, 1.25)/−0.17 (−0.57, 0.22)		
	DATA	0.70 (0.53, 0.92)/−0.36 (−0.63, −0.08)		
	IDEAL	1.03 (0.79, 1.34)/0.03 (−0.23, 0.29)		
ER or PR positive	ABCSG6a	2.93 (1.18, 7.29)/1.08 (0.16, 1.99)	0.91 (0.45, 1.86)/−0.09 (−0.80, 0.62)	0.80
	AERAS	0.38 (0.19, 0.77)/−0.97 (−1.67, −0.27)		
	DATA	1.18 (0.71, 1.96)/0.17 (−0.34, 0.67)		
	IDEAL	0.63 (0.37, 1.07)/−0.46 (−0.99, 0.07)		
Recurrence versus chemotherapy use				
Yes	AERAS	0.53 (0.32, 0.88)/−0.63 (−1.14, −0.13)	0.75 (0.62, 0.91)/−0.29 (−0.49, −0.10)	0.003
	DATA	0.68 (0.50, 0.93)/−0.39 (−0.70, −0.07)		
	IDEAL	0.90 (0.68, 1.20)/−0.11 (−0.39, 0.18)		
No	AERAS	0.58 (0.33, 1.02)/−0.54 (−1.11, 0.02)	0.91 (0.71, 1.16)/−0.10 (−0.34, 0.15)	0.44
	DATA	1.08 (0.71, 1.64)/0.08 (−0.34, 0.50)		
	IDEAL	0.96 (0.67, 1.38)/−0.04 (−0.41, 0.32)		
Recurrence versus previous TAM use				
TAM-AI	AERAS	0.60 (0.18, 1.99)/−0.51 (−1.71, 0.69)	0.82 (0.70, 0.96)/−0.20 (−0.35, −0.04)	0.01
	DATA	0.79 (0.62, 1.01)/−0.24 (−0.48, 0.01)		
	IDEAL	0.97 (0.73, 1.29)/−0.03 (−0.32, 0.26)		
	NSABP B-42	0.75 (0.57, 0.99)/−0.29 (−0.56, −0.01)		
AI	AERAS	0.55 (0.39, 0.78)/−0.60 (−0.94, −0.25)	0.81 (0.69, 0.94)/−0.21 (−0.37, −0.06)	0.0002
	IDEAL	0.80 (0.53, 1.21)/−0.22 (−0.64, 0.19)		
	NSABP B-42	0.91 (0.75, 1.10)/−0.09 (−0.29, 0.10)		
Recurrence versus previous AI duration				

Table 2 (continued)

Subgroups analysis	Included studies	Individual studies HR/RD (95%CI)	Subgroups effects HR/RD (95%CI)	P
≥5 years	AERAS	0.55 (0.39, 0.78)/−0.60 (−0.94, −0.25)	0.81 (0.67, 0.97)/−0.22 (−0.40, −0.03)	0.02
	IDEAL	0.91 (0.72, 1.15)/−0.09 (−0.33, 0.14)		
	MA.17R	0.80 (0.63, 1.01)/−0.22 (−0.46, 0.01)		
	NSABP B-42	0.91 (0.75, 1.10)/−0.09 (−0.29, 0.10)		
<5 years	AERAS	0.60 (0.18, 1.99)/−0.51 (−1.71, 0.69)	0.78 (0.64, 0.94)/−0.25 (−0.44, −0.06)	0.01
	DATA	0.79 (0.59, 1.05)/−0.24 (−0.52, 0.05)		
	IDEAL	1.06 (0.50, 2.25)/0.06 (−0.69, 0.81)		
	NSABP B-42	0.75 (0.57, 0.99)/−0.29 (−0.56, −0.01)		

characterized by an increase in the adverse effects typical of this class of drugs, such as osteoporosis, bone pain, bone fractures, hypertension, cardiovascular events, arthralgias, myalgias and so on. The adverse events of endocrine therapy might increase due to the extended therapy. As expected, extended AIs therapy was associated with an increased RR of death without recurrence in our meta-analysis, although this was not statistically significant (1.16, $P = 0.13$).

Our exploratory subgroup analyses showed that tumor size ($\geq$ T2), node positive status, previous chemotherapy use, and histological grade 1 and 2 status were independent predictors of DFS. Due to the inclusion of data from the ABCSG6a trial, histological grade 1 and 2 became an independent risk factor. However, we cannot draw firm conclusions according to the data of ABCSG Trial 6a. Because in this trial, aminoglutethimide which was used as an initial adjuvant AIs-containing therapy was no longer commonly used in the adjuvant setting now. Our results also showed that, although initial adjuvant AIs therapy was adequate for 5 years, extended use of AIs could get more benefits of DFS. Meanwhile, the potential therapeutic toxicity indicates that extended endocrine therapy was not a feasible option for all patients. A balance between toxicities and benefits must be carefully performed in cases of extended duration of therapy. Gene-expression profiles might help to identify patients who were at sufficient risk of developing late

Table 3 Toxicity related major adverse events

Outcome	RCTs	RR	RD	P	I^2 (%)
Bone pain	3	1.26	0.04	0.003	12
Arthralgia	6	1.13	0.05	0.20	92
Myalgia	3	1.26	0.04	0.02	57
Osteoporosis	5	1.53	0.07	0.005	91
Fracture	7	1.59	0.02	0.002	56
Cardiovascular	4	1.07	0	0.41	12
Hypertension	3	0.99	0	0.92	32
Discontinuation	5	1.51	0.06	0.0009	72

recurrences to increase efficacy and compliance [28–31]. Patients with high-risk characteristics might benefit from extended therapy.

However, it is unclear why there is a lack of extended therapy effect of survival benefit. One reason might be that events not correlated with disease recurrence could overtake the ones related to breast cancer morbidity and mortality, thus masking the actual experimental treatment benefit. Nevertheless, our results showed that extended use of AIs was not correlated with a numerical excess of deaths without breast cancer recurrence (RR = 1.16, $P = 0.13$). The other reason might be that, as we all know, endocrine therapy has a carryover effect with an absolute survival benefit which increases over time and becomes extremely significant in the second decade after diagnosis, when compared to the first 5 years of follow-up [4, 9]. It becomes therefore clear that an adequate follow-up period is paramount in the attempt to evaluate the benefit of extended adjuvant endocrine treatment. In this context, the carryover effect could have been lost as the follow-up period is too short.

Our work has some important limitations. First, this is a literature-based rather than an individual patient–based meta-analysis. Thus, proper subgroup analysis, including adjusting for baseline factors such as nodal and tumor size, previous chemotherapy use, the duration of initial adjuvant AIs therapy or other pathological features are not possible with the information available. Second, follow-up times are different among the trials, and in particular they are shorter for AIs. This limitation may not have captured some late deaths or relapses typically observed in this disease. Third, the heterogeneity of the outcome measures definitions across the trials, which could impact the final results. However, even in the presence of high heterogeneity between trials design characteristics, endocrine therapy duration and type, as well as differences in the outcome measures definition, our data suggest a general benefit of extended adjuvant therapy with AIs, in particular, in the patients with the high recurrence risk.

Fig. 5 Risk of bias: a summary table for each risk of bias item for each study

Conclusion

After initial AIs-containing adjuvant therapy, extended AIs therapy could further bring a DFS benefit for postmenopausal patients with early breast cancer, especially in the patients with high-risk characteristics. And no matter how long the duration of initial AIs-containing adjuvant therapy and whether the initial endocrine therapy included tamoxifen, extended use of AIs would lead to a further reduction in DFS. Although extended AIs therapy might increase the

therapeutic toxicity and discontinuation of therapy, there were no statistically significant excess of deaths without breast cancer recurrence among patients receiving longer durations of AIs.

Compliance with ethical standards

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