Original Study

Extended Adjuvant Therapy With Aromatase Inhibitors for Early Breast Cancer: A Meta-analysis of Randomized Controlled Trials

Ling Xu,[1,2] Zhuo Zhang,[1] Qian Xiang,[1] Qianxin Liu,[1] Xuening Duan,[2] Yinhua Liu,[2] Yimin Cui[1]

Abstract

This meta-analysis aimed to assess the efficacy and toxicity of extended adjuvant aromatase inhibitors (AIs) in early breast cancer. Seven randomized clinical trials that involved 16,926 patients were selected for analysis. The results showed that extended AI therapy could significantly improve disease-free survival, especially for contralateral breast cancer recurrence. In addition, there were no significant differences between AIs and control for overall survival and serious adverse events.

Background: Aromatase inhibitors (AIs) are widely used for early breast cancer, whereas the efficacy and safety of extended AI adjuvant therapy compared with shorter AI therapy, observation, or placebo remains controversial. We conducted a quantitative meta-analysis to summarize available randomized controlled trials (RCTs) regarding the efficacy and safety of extended AI therapy for early breast cancer. **Materials and Methods:** We systematically searched PubMed, EmBase, and the Cochrane library to select studies published through March 2018. Studies designed as RCTs and that investigated overall survival (OS) or disease-free survival (DFS) for extended AI and shorter AI therapy, observation, or placebo were included. Hazard ratio (HR) and relative risk (RR) with 95% confidence intervals (CIs) were employed to pool analysis according to data type. **Results:** We identified 7 RCTs that involved 16,926 patients with early breast cancer. The summary HRs indicated that extended treatment with AIs was not associated with OS (HR, 0.95; 95% CI, 0.82-1.10; $P = .488$), whereas it could significantly improve DFS as compared with shorter AI therapy, observation, or placebo (HR, 0.75; 95% CI, 0.66-0.86; $P < .001$). Treatment with extended AIs significantly reduced contralateral breast cancer recurrence (RR, 0.46; 95% CI, 0.34-0.64; $P < .001$), whereas it has no significant effect on distant metastatic recurrence (RR, 0.80; 95% CI, 0.64-1.00; $P = .055$), and locoregional recurrence (RR, 0.76; 95% CI, 0.53-1.08; $P = .127$). There were no significant differences between treatment with extended AIs and control for grade 3 or more adverse events. **Conclusion:** Extended AI therapy could significantly improve DFS, especially for contralateral breast cancer recurrence. There were no significant differences between treatment with AIs and control for OS, distant metastatic and locoregional recurrence, and serious adverse events.

Clinical Breast Cancer, Vol. 19, No. 5, e578-88
Keywords: Aromatase inhibitor, Breast cancer, Extended adjuvant endocrine therapy

Introduction

Breast cancer is the most common cancer in women both in developed and developing countries; it has the highest number of diagnosed cases and is the second leading cause of cancer deaths in women.[1] Early stage breast cancer contributed to nearly one-quarter of the new cases, and hormone receptor-positive breast cancer is the most common subtype. Adjuvant endocrine therapy is widely used and has contributed to a significant improvement in overall survival (OS) and has reduced the risk of recurrence.[2,3] Five years of tamoxifen therapy has been the standard adjuvant endocrine therapy for both pre- and postmenopausal women. Although patients who received 1 to 2 years of tamoxifen therapy had a significantly reduced risk of recurrence and breast cancer-related mortality, there were greater improvements in recurrence rates and breast cancer-related mortality in patients with 5 years of tamoxifen.[3]

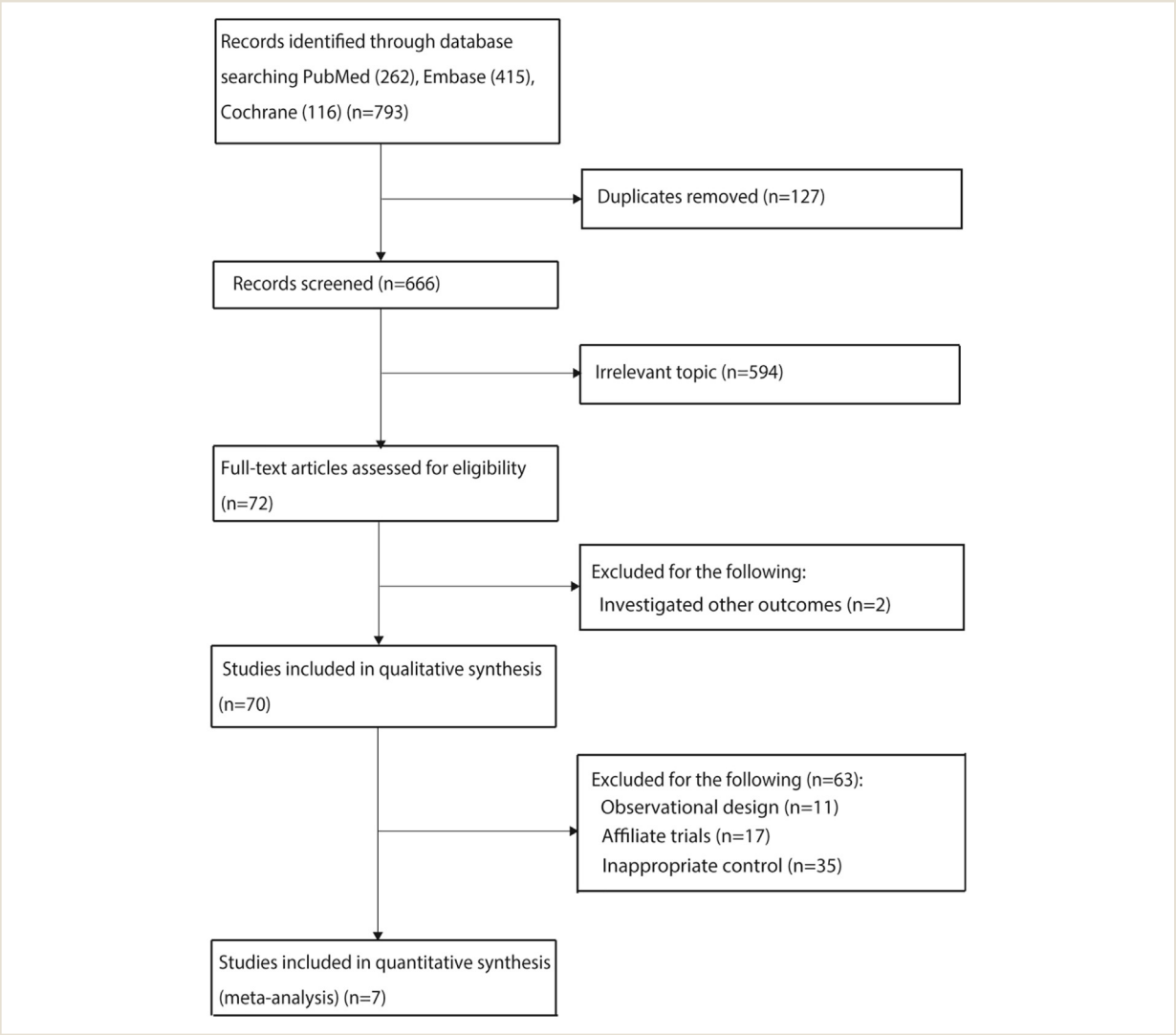
[1]Department of Pharmacy
[2]Breast Disease Center, Peking University First Hospital, Beijing, China

Submitted: Jul 31, 2018; Revised: Feb 26, 2019; Accepted: Mar 16, 2019; Epub: Apr 19, 2019

Address for correspondence: Yimin Cui, MD, PhD, Department of Pharmacy, Peking University First Hospital, 6 Dahongluochang St, Xicheng District, Beijing, 100034, China
E-mail contact: cui.pharm@pkufh.com

1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2019.03.005

Figure 1 Flow Diagram of the Literature Search and Trial Selection Process



Currently, numerous trials have already investigated either aromatase inhibitors (AIs) or longer endocrine therapy following an initial 5 years of tamoxifen, but the treatment effects of extended AI therapy for early stage breast cancer are limited and inconclusive.[4-6]

Currently, clear evidence suggests adjuvant endocrine therapy on extended tamoxifen treatment for women with hormone receptor-positive early breast cancer.[7] The study conducted by the Early Breast Cancer Trialist's Cooperative Group suggested that AIs as adjuvant endocrine therapy, whether continuous or sequential regimens, was more effective than tamoxifen monotherapy for reducing the risk of recurrence and breast cancer-related mortality.[8] Several prospective randomized controlled trials (RCTs) have already investigated whether extended AIs may reduce the risk of recurrence and improvement in OS, whereas other RCTs have revealed inconsistent results. Clarifying the highest efficacy of treatment regimens is particularly important in patients with early stage breast cancer, as it has not been definitively determined. Therefore, we conducted this comprehensive, quantitative meta-analysis of the available RCTs to determine the efficacy and safety of extended AIs for patients with early stage breast cancer.

Materials and Methods

Data Sources, Search Strategy, and Selection Criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement issued in 2009 (See Supplemental Table 1 in the online version for the Checklist).[9] Studies with an RCT design and that investigated the efficacy and safety of extended adjuvant therapy with AIs for early stage breast cancer were potentially eligible for inclusion in this meta-analysis, and no restrictions were placed on published language and publication status. Three electronic databases, including PubMed, EmBase, and the Cochrane library, were searched for trials published through March 2018. The core search terms included "adjuvant" AND ("aromatase inhibitor"

Table 1 Baseline Characteristics of Trials Included in This Meta-analysis

Study	Publication Year	Sample Size	Mean Age, y	Node-positive, %	Tumor Size[a] (T1 and T2)	Grade 3, %	Intervention	Control	Prior Endocrine Therapy	Prior Chemotherapy, %	Follow-up, mos	Jadad Scale
ABCSG 6a[18]	2007	856	68.2	32.5	98.1%	20.0	Anastrozole 3 y	None	Tamoxifen alone 5 y, 52.6%; Tamoxifen 5 y plus aminoglutethimide first 2 y with tamoxifen, 47.4%	NA	62.3	3
MA.17R[19]	2016	1918	65.1	53.4	90.5%;	NA	Letrozole 5 y	Placebo	Tamoxifen, 79.3%; AIs, 100% (5.0 y)	58.3	75.6	4
MA.17[20]	2005	5170	62.0	45.6	NA	NA	Letrozole 5 y	Placebo	Tamoxifen, 100%; median duration usage 5y	45.3	30.0	4
B-33[21]	2008	1598	60.0	48.0	99.0%	NA	Exemestane 5 y	Placebo	Tamoxifen, 100%; duration, 57-67 months	55.0	30.0	4
DATA[22]	2017	1660	57.6	66.2	92.9%	28.5	Anastrozole 6 y	Anastrozole 3 y	Tamoxifen, 100%; 2-3 y	68.4	49.0	3
NSABP B-42[23]	2017	3923	>60.0	42.6	NA	NA	Letrozole 5 y	Placebo	5 y endocrine therapy: AIs, 60.9%; Sequence of tamoxifen and AIs, 39.1%	NA	83.0	4
IDEAL[24]	2018	1801	55.0-65.0	73.1	NA	NA	Letrozole 5 y	Letrozole 2.5 y	5 y endocrine therapy: Tamoxifen, 11.6%; AIs, 24%; Sequence of tamoxifen and AIs, 60%; Unknown, 4.4%	NA	78.0	3

Abbreviations: AIs = aromatase inhibitors; NA = not available.
[a]Tumor size: T1 ≤ 2 cm, T2 > 2 cm and ≤ 5 cm.

OR "tamoxifen") AND "extended" AND "breast cancer." Manual searches of reference lists from potential included studies were performed to select any additional potential studies to be included. The initial study selection process was based on title, study design, disease status, control, and investigated outcomes.

The literature search and study selection were conducted independently by 2 reviewers (L.X. and Z.Z.) according to a standardized approach, and any disagreement was resolved by group discussion until a consensus was reached. The inclusion criteria of this meta-analysis are as follows: (1) Patient status: all patients with early stage breast cancer; (2) Intervention: the intervention group received extended adjuvant therapy with AIs; (3) Control: the control group received a shorter period of AI therapy, placebo, or observation; (4) Outcomes: the primary outcomes were OS and disease-free survival (DFS), whereas the secondary outcomes included specific recurrence events and grade 3 or greater adverse events; and (5) Study design: all the included studies should be designed as RCTs. Observational studies were excluded owing to various confounders that might affect the treatment effects between extended AIs and control.

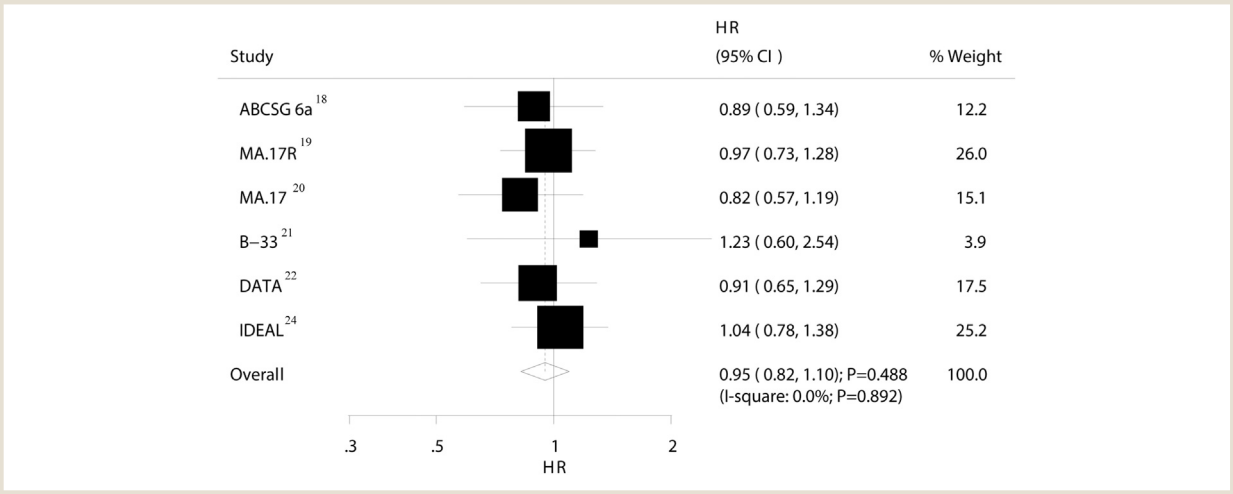
Data Collection and Quality Assessment

The data collection and quality assessment processes were undertaken by 2 reviewers (Z.Z. and Q.L.) independently, and any inconsistencies were examined by the corresponding author referring to the original studies. The data items abstracted included the study group's name, publication year, sample size, mean age, node-positive status, tumor size, percentage of grade 3 or greater adverse events, intervention, control, prior endocrine therapy, percentage of prior chemotherapy, follow-up duration periods, and investigated outcomes. The Jadad scale, which is comprehensive and has been partially validated for evaluating the quality of RCTs in meta-analysis, was used to assess methodological quality.[10] The Jadad scale is based on the following 5 items: randomization (1 or 0), concealment of the treatment allocation (1 or 0), blinding (1 or 0), completeness of follow-up (1 or 0), and the use of intention-to-treat analysis (1 or 0). The range of the scoring system (from 0 to 5) has been developed for assessment, and the trial was regarded as high study quality if the study scored 4 or more on the Jadad scale.

Statistical Analysis

The primary outcomes, which included OS and DFS, were abstracted based on the hazard ratio (HR) and its 95% confidence interval (CI) in each individual trial. In addition, the secondary outcomes, including specific recurrence events and grade 3 or greater adverse events, the crude data, or the effect estimate (relative risk [RR]) were abstracted from each trial. The summary results for the extended AIs versus control were calculated by using the random-effects model.[11,12] The heterogeneity among included trials was calculated using the I^2 and Q statistic, and a P value less than .10 was considered to indicate significant heterogeneity.[13] The sensitivity analyses for OS and DFS were calculated to assess the impact of a single trial on the overall analysis by sequentially excluding each individual trial. Subgroup analysis for OS was based on study level, and stratified factors included sample size, age, percentage of positive nodes, intervention duration, control, prior endocrine therapy, follow-up duration, and study quality. Moreover, nearly all of the

Figure 2 Effect of Extended AI Therapy on OS



Abbreviations: AI = aromatase inhibitors; CI = confidence interval; HR = hazard ratio; OS = overall Survival.

included trials reported stratified results for DFS based on several factors; therefore, subgroup analysis for DFS was conducted based on sample size, age, node status, tumor grade, estrogen receptor (ER)/progesterone receptor (PR) status, intervention duration, control, prior chemotherapy, prior endocrine therapy, tumor size, follow-up duration, and study quality. The *P* value for heterogeneity between subgroups were evaluated using the χ^2 test and meta-regression.[14] Publication biases for OS and DFS were evaluated by using funnel plots and the Egger[15] and Begg test[16] results. If *P* values of publication biases were less than .10, the trim and fill method was employed to adjust for publication bias.[17] The significance level (α) was 0.05 in 2-sided testing for all summary results, and all of the statistical analyses were undertaken using STATA software (version 10.0; Stata Corporation, College Station, TX).

Results

Literature Search

The flowchart of the study selection process is presented in Figure 1. We identified 793 articles during the initial electronic search, of which 721 were excluded, including duplicates and irrelevant studies. The full text of 72 screened articles were retrieved, and 65 studies were excluded owing to factors including observational design of the study, reporting the same population as another study, inappropriate controls within the study, and investigating other outcomes (lipid profiles) in the study. Finally, 7 RCTs including 16,926 patients with early stage breast cancer were selected for quantitative analysis.[18-24] No additional eligible study was observed by a manual search of the reference lists of relevant articles.

Study Characteristics

Table 1 summarizes the baseline characteristics of studies and patients with early stage breast cancer. The studies were published between 2005 and 2018, and 856 to 5170 patients were included in each trial. The mean age of patients in each individual trial ranged from 57.6 to 68.2 years, and the percentage of patients who were node-positive ranged from 32.5% to 73.1%. In 4 trials, the intervention group received 5 years of letrozole, 2 trials reported on patients who received 3 or 6 years of anastrozole, and the remaining 1 trial reported on patients who received 5 years of exemestane. In addition, 2 of the included trials compared extended AI therapy with shorter AI therapy; the remaining 5 trials compared extended AIs with placebo or observation. Study quality was assessed using the Jadad scale; 4 trials had a score of 4, whereas the remaining 3 trials had a score of 3.

OS

Data relating the effect of extended AIs on OS were available in 6 RCTs. There was no significant difference between extended AIs and control for OS (HR, 0.95; 95% CI, 0.82-1.10; $P = .488$; with no evidence of heterogeneity) (Figure 2). Sensitivity analysis indicated that the conclusion was not changed after sequential exclusion of each study from the overall analyses (see Supplemental Figure 1 in the online version). The results of subgroup analyses were consistent with overall analysis and remained without significant differences (Table 2).

DFS

Data relating to the effect of extended AIs on DFS were available in 7 RCTs. The summary result indicated that extended AIs significantly improved DFS (HR, 0.75; 95% CI, 0.66-0.86; $P < .001$; with moderate heterogeneity) (Figure 3). A sensitivity analysis was conducted for DFS, and after each study was sequentially excluded from the pooled analysis, the conclusion was not affected by the exclusion of any specific study (see Supplemental Figure 2 in the online version). Although there was significant improvement of DFS mostly in subsets, we noted that extended AIs did not affect DFS if the pooled study sample size was $\geq$ 3000, and

Table 2 Subgroup Analyses for OS and PFS

Outcomes	Group	HR (95% CI)	*P* Value	Heterogeneity, %	*P* Value for Heterogeneity	*P* Value for Heterogeneity Between Subgroups
OS			Sample size			
	≥3000	0.82 (0.57-1.18)	.291	—	—	.393
	<3000	0.98 (0.84-1.14)	.760	0.0	.918	
			Age, y			
	≥60	0.96 (0.82-1.12)	.607	0.0	.809	.783
	<60	0.91 (0.65-1.28)	.590	—	—	
			Percentage of node positive, %			
	≥50.0	0.98 (0.82-1.16)	.811	0.0	.839	.550
	<50.0	0.89 (0.69-1.15)	.377	0.0	.618	
			Intervention duration, y			
	≥5.0	0.96 (0.82-1.12)	.595	0.0	.816	.737
	<5.0	0.89 (0.59-1.34)	.578	—	—	
			Control			
	Shorter AI	0.98 (0.79-1.23)	.890	0.0	.557	.678
	Placebo or none	0.93 (0.77-1.12)	.426	0.0	.764	
			Prior endocrine therapy, y			
	≥5.0	0.96 (0.82-1.12)	.607	0.0	.809	.783
	<5.0	0.91 (0.65-1.28)	.590	—	—	
			Follow-up duration, y			
	≥5.0	0.98 (0.82-1.17)	.833	0.0	.825	.572
	<5.0	0.90 (0.71-1.14)	.385	0.0	.616	
			Study quality			
	High	0.94 (0.76-1.16)	.543	0.0	.574	.848
	Low	0.96 (0.79-1.17)	.701	0.0	.769	
DFS			Sample size			
	≥ 3000	0.72 (0.50-1.03)	.070	81.8	.019	.934
	<3000	0.77 (0.67-0.89)	<.001	13.2	.330	
			Age, y			
	≥60	0.81 (0.71-0.93)	.003	0.0	.828	.913
	<60	0.82 (0.69-0.98)	.027	0.0	.709	
			Node status			
	Positive	0.73 (0.64-0.83)	<.001	10.2	.351	.382
	Negative	0.83 (0.64-1.07)	.144	51.8	.053	
			Tumor grade			
	3	0.93 (0.69-1.24)	.609	0.0	.517	.404
	Other	0.80 (0.66-0.98)	.032	0.0	.521	
			ER/PR status			
	Positive/positive	0.66 (0.48-0.90)	.009	76.8	.002	.180
	Other	1.03 (0.58-1.81)	.923	56.5	.043	
			Intervention duration, y			
	≥5.0	0.76 (0.66-0.88)	<.001	44.8	.107	.307
	<5.0	0.62 (0.40-0.96)	.032	—	—	
			Control			
	Shorter AI	0.86 (0.73-1.02)	.074	0.0	.373	.140
	Placebo or none	0.70 (0.59-0.83)	<.001	43.9	.129	
			Prior chemotherapy			
	Yes	0.71 (0.60-0.84)	<.001	11.5	.340	.360
	No	0.80 (0.66-0.97)	.024	25.9	.249	

Table 2 Continued

Outcomes	Group	HR (95% CI)	*P* Value	Heterogeneity, %	*P* Value for Heterogeneity	*P* Value for Heterogeneity Between Subgroups
	Prior endocrine therapy, y					
	≥5.0	0.74 (0.63-0.87)	<.001	50.3	.073	.868
	<5.0	0.79 (0.62-1.01)	.063	—	—	
	Tumor size, cm					
	>2	0.76 (0.55-1.06)	.104	46.9	.152	.489
	<2	0.88 (0.68-1.13)	.317	0.0	.911	
	Follow-up duration, y					
	≥5.0	0.80 (0.69-0.94)	.006	34.0	.209	.081
	<5.0	0.69 (0.57-0.83)	<.001	20.3	.285	
	Study quality					
	High	0.71 (0.58-0.86)	.001	53.7	.091	.326
	Low	0.81 (0.68-0.98)	.030	24.7	.265	

Abbreviations: AI = aromatase inhibitor; CI = confidence interval; DFS = disease-free survival; ER = estrogen receptor; HR = hazard ratio; OS = overall survival; PR = progesterone receptor.

for patients who were node-negative, had tumor grade 3, had either ER or PR (but not both) positive, were part of a control group with shorter AIs, had prior endocrine therapy < 5.0 years, and also regardless of tumor size (Table 2).

Recurrence in Specific Sites

The breakdown for the number of studies available for each outcome was 6, 6, and 6 trials for contralateral breast cancer, distant metastatic, and locoregional recurrence, respectively. Overall, we noted that extended AI therapy significantly reduced the risk of contralateral breast cancer recurrence (RR, 0.46; 95% CI, 0.34-0.64; $P < .001$) (Figure 4), whereas it had no significant effect on distant metastatic recurrence (RR, 0.80; 95% CI, 0.64-1.00; $P = .055$) (Figure 4) and locoregional recurrence (RR, 0.76; 95% CI, 0.53-1.08; $P = .127$) (Figure 4).

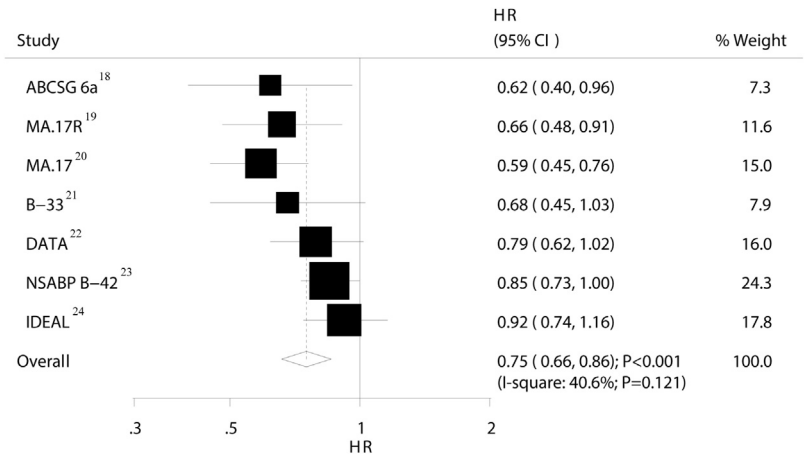
Adverse Events

The summary results of extended AI therapy and control on the risk of grade 3 or greater adverse events are shown in Table 3. We noted no significant differences for all specific adverse events between extended AI therapy and control for early stage breast cancer.

Publication Bias

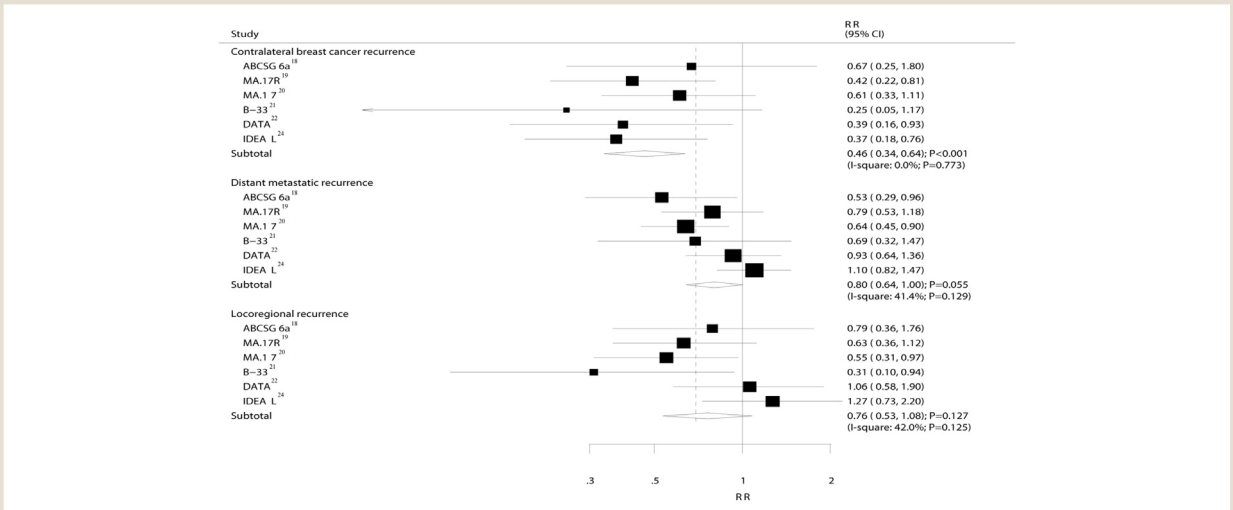
The funnel plots for OS and DFS are shown in Figure 5. The Egger and Begg test results showed no evidence of publication bias for OS (*P* value for Egger, 0.805; *P* value for Begg, 1.000). Although the Begg test showed no evidence of publication bias for DFS ($P = .230$), the Egger test showed potential evidence of publication bias for DFS ($P = .097$). The conclusions were not changed for DFS after adjustment for publication bias by using the trim and fill method (HR, 0.75; 95% CI, 0.66-0.86; $P < .001$) (Figure 6).

Figure 3 Effect of Extended AI Therapy on DFS



Abbreviations: AI = aromatase inhibitors; CI = confidence interval; DFS = disease-free Survival; HR = hazard ratio.

Figure 4 Effect of Extended AI Therapy on Specific Recurrence Events



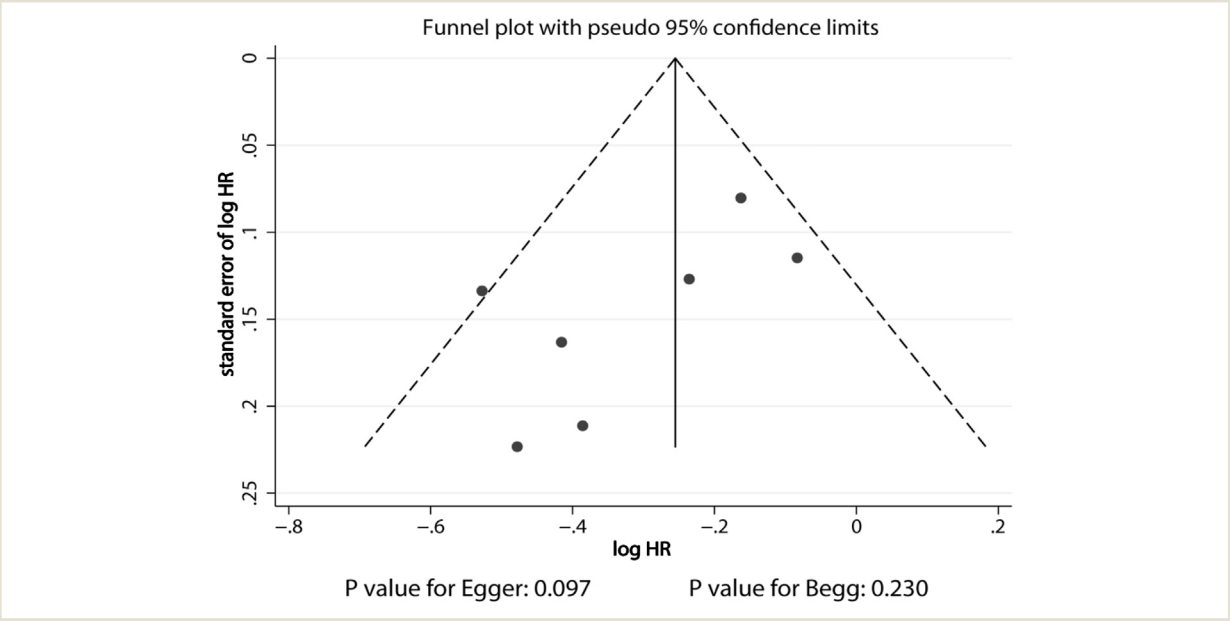
Abbreviations: AI = aromatase inhibitors; CI = confidence interval; DFS = disease-free Survival; RR = relative risk.

Table 3 Summary Results for Grade 3 or More Adverse Events

Outcomes	Events in Intervention	Events in Control	RR (95% CI)	*P* Value
Asthenia, somnolence	6	1	7.27 (0.88-60.14)	.066
Allergy, cutaneous toxicity, skin rash	5	0	13.32 (0.74-240.22)	.079
Hair loss	7	2	2.96 (0.21-40.96)	.419
Diarrhea	16	10	1.55 (0.71-3.38)	.275
Nausea	10	9	1.95 (0.12-30.87)	.635
Edema	5	4	1.25 (0.34-4.66)	.737
Hypertension	55	68	0.81 (0.57-1.15)	.241
Hot flashes/flushes	11	5	2.01 (0.72-5.61)	.181
Fatigue	26	17	1.52 (0.82-2.83)	.182
Anorexia	1	4	0.25 (0.03-2.24)	.215
Constipation	6	3	2.00 (0.50-8.00)	.325
Vaginal bleeding	2	5	0.40 (0.08-2.06)	.274
Infection	27	15	1.80 (0.96-3.38)	.066
Arthritis	13	6	2.13 (0.79-5.71)	.134
Hypercholesterolemia	2	6	0.33 (0.07-1.65)	.179
Dizziness	13	7	1.86 (0.74-4.66)	.185
Insomnia	2	2	1.00 (0.14-7.11)	.998
Depression	20	13	1.45 (0.61-3.44)	.394
Headache	22	26	0.85 (0.48-1.49)	.567
Arthralgia or myalgia	141	116	1.22 (0.94-1.57)	.127
Bone pain	18	19	0.95 (0.50-1.81)	.878
Dyspnea	18	21	0.86 (0.46-1.61)	.634
Bone fractures	39	30	1.46 (0.61-3.48)	.398
Osteoporosis	13	10	1.06 (0.24-4.65)	.942
Cardiovascular	45	50	0.91 (0.61-1.34)	.623
Back pain	4	5	0.80 (0.21-2.95)	.733

Abbreviations: CI = confidence interval; RR = relative risk.

Figure 5 Funnel Plots for overall Survival and Disease-free Survival

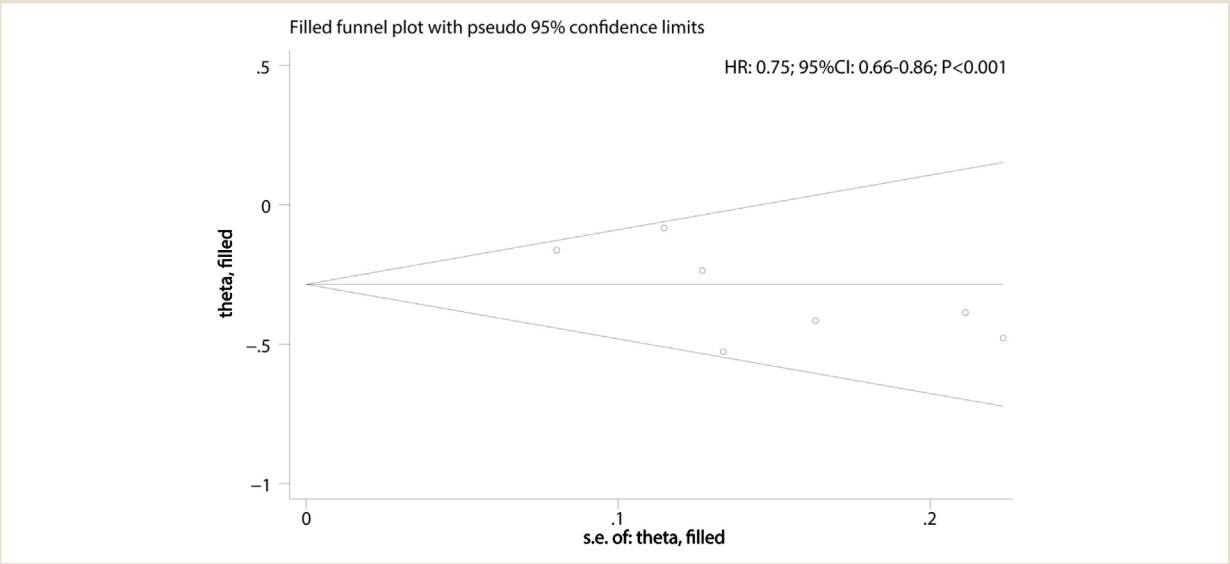


Abbreviation: HR = hazard ratio.

Discussion

The present meta-analysis was based on RCTs and explored the efficacy and safety of extended AIs for early stage breast cancer. This large quantitative study included 16,926 patients with early stage breast cancer from 7 RCTs with a broad range of populations. We noted that patients who received extended AI therapy significantly improved their DFS and reduced the risk of contralateral breast cancer recurrence. However, extended AI therapy had little or no effect on OS, distant metastatic recurrence, locoregional recurrence, and grade 3 or greater adverse events. The results of sensitivity analyses for OS and DFS were stable and consistent with the overall analyses. Finally, the results of stratified analysis for OS showed a

Figure 6 Trim and fill Adjustment of Disease-free Survival



Abbreviations: CI = confidence interval; HR = hazard ratio; s.e. = standard error.

non-significant difference between extended AIs and controls in all subsets.

The study quality assessment of each included trial based on randomization, blinding, allocation concealment, withdrawals and dropouts, and use of intention-to-treat analysis. Most of the included studies provided clear information on randomization, withdrawals and dropouts, and use of intention-to-treat analysis, whereas other items of blinding and allocation concealment differed among included trials, which might contribute to the heterogeneity across the included trials. The results of subgroup analyses based on study quality was calculated; therefore, the recommendations of this meta-analysis for early stage breast cancer were reliable.

A previous meta-analysis based on RCTs found that extended AI therapy was significantly associated with similar improvements in DFS in all subsets.[25] In addition, they point out that patients who were node-positive and had larger tumors acquired a greater effect size and higher absolute benefits in the extended AI group. However, stratified analyses based on study level were not calculated, and the outcomes of OS and grade 3 or greater adverse events were not described in the previous meta-analysis. Therefore, we conducted a quantitative meta-analysis of available RCTs to evaluate the efficacy and safety of extended AIs for early stage breast cancer.

There was no significant difference between extended AI therapy and control for OS, and all of the included trials reported consistent results. In this study, the summary HR was less than 1 for OS, and 4 of the included trials reported similar results. However, these protective trends of extended AIs were not obvious and require further validation. The reason for this non-significant difference could be owing to lower mortality events in patients with early stage breast cancer, which could result in a broad 95% CI (ie, no statistically significant difference). Furthermore, the various percentages of prior chemotherapy could affect the treatment effect on OS between treatment with extended AIs and controls for early stage breast cancer.

The summary results indicated that extended AI therapy could significantly improve DFS. However, several studies included in our study reported inconsistent results. The B-33 trial suggested that extended AI therapy resulted in non-statistically significant improvement in DFS, whereas it could significantly improve relapse-free survival. The reason for this could be that extended AI therapy was more pronounced in reducing relapse-free survival events than in reducing DFS events. Further, the DATA trial (extended adjuvant aromatase inhibition after sequential endocrine therapy) did not recommend extended AIs after 5 years of sequential endocrine therapy in postmenopausal women with hormone receptor-positive breast cancer. They point out that the preventive effect of extended AIs on DFS mainly focused on secondary primary breast cancers.[6] These results were consistent with the summary results of specific recurrence events.

Subgroup analysis indicated that extended AI therapy has no significant effect on OS in all subsets, whereas it had significantly improved DFS in multiple subsets. Notably, there was no significant effect on DFS if the study sample size was $\geq$ 3000, and involved patients who were node-negative node, had tumor grade 3, were ER- or PR-positive (but not both), were a control group with shorter duration of AIs, had prior endocrine therapy $<$ 5.0 years, and regardless of tumor size. The reasons for these could be owing to a smaller number of trials in these subsets and thus the associated lower statistical power. Further, the greater effects of extended AIs mainly focused on node-positive and ER-/PR-positive patients. In addition, the absolute effect relative to shorter duration of AIs was smaller as compared with placebo or observation. Extended AI therapy given in patients who underwent prior endocrine therapy $\geq$ 5.0 years has greater effectiveness owing to the large number of trials included in this subset and was associated with stable pooled results. Finally, not all included trials provided the stratified results based on several pre-defined factors.

Several strengths of our study should be highlighted. First, only prospective RCTs were included, which could overestimate the treatment effect in observational studies. Second, the treatment effect of extended AIs therapy was quantitatively determined based on a large sample size. Third, the study provided pooled results that investigated the effects of extended AI therapy on OS and grade 3 or greater adverse events. Finally, the treatment effects of extended AIs on OS and DFS according to baseline characteristics of the study or patients were conducted.

The limitations of our study are as follows: (1) moderate heterogeneity for DFS among included trials was observed owing to patients with different characteristics; (2) specific grade 3 or greater adverse events were available in few trials, and the event rate was lower than expected; therefore, we found no significant differences between extended AIs and control for adverse events; (3) publication bias is inevitable owing to this study being based on published studies; and (4) the analysis was based on pooled data, whereas more detailed analyses were not calculated.

Conclusion

The findings of this meta-analysis suggested that extended AI therapy has no significant effect on OS, whereas it could significantly improve DFS for patients with early stage breast cancer. Further, this significantly reduced recurrence events focused on contralateral breast cancer. Future large-scale trials should be conducted focused on OS in patients with early stage breast cancer with longer follow-up duration periods.

Clinical Practice Points

- AIs are widely used for early breast cancer, whereas the efficacy and safety of extended AI adjuvant therapy compared with shorter AI therapy, observation, or placebo remains controversial.
- A previous meta-analysis based on RCTs found extended AI therapy was significantly associated with similar improvements in DFS in all subsets.[25] Furthermore, they point out that patients with node-positive and larger tumors acquired greater effect size and higher absolute benefits in the extended AI group. However, stratified analyses based on study level was not calculated, and the outcomes of OS and grade 3 or greater adverse events were not illustrated in the previous meta-analysis.
- This meta-analysis showed that extended AI therapy could significantly improve DFS for patients with early breast cancer, especially significantly reduced contralateral breast cancer recurrence, and there were no significant differences between AIs and control for OS, distant metastatic, and locoregional recurrence, and grade 3 or more adverse events.
- We believe this study provides clinicians with the confidence of recommending extended adjuvant AIs because of the significant

reduction of contralateral breast cancer and no additional serious adverse events.

Acknowledgments

This work was supported by National Key R&D Program of China (grant numbers No. 2016YFC0901302 and No. 2016YFC0904900).

Disclosure

The authors declare that they have no conflict of interest.

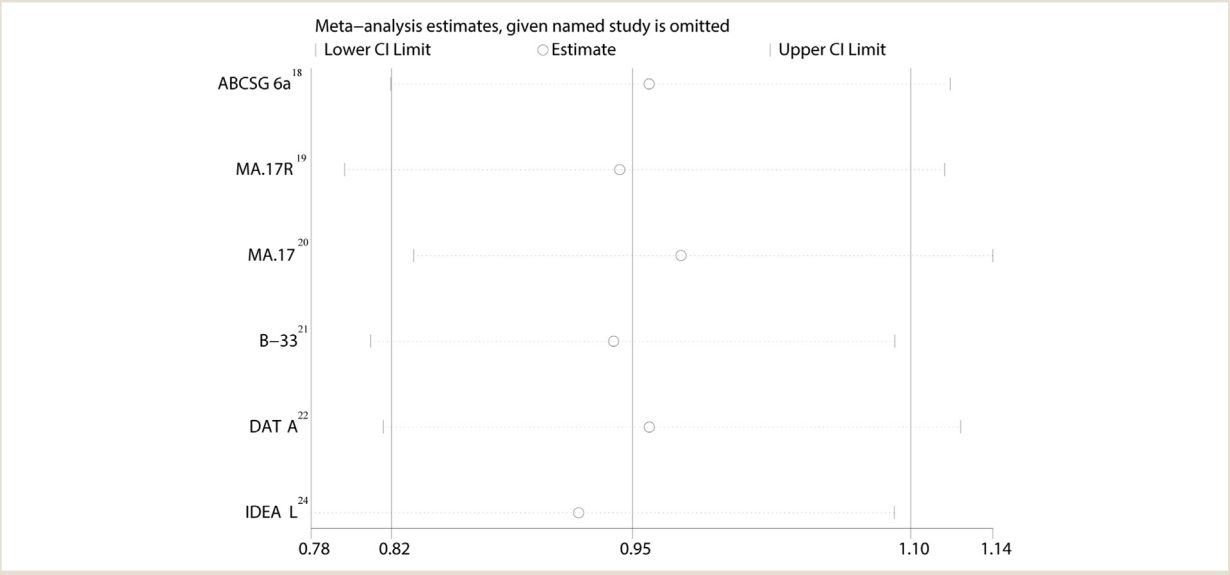
Supplemental Data

Supplemental materials accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2019.03.005.

References

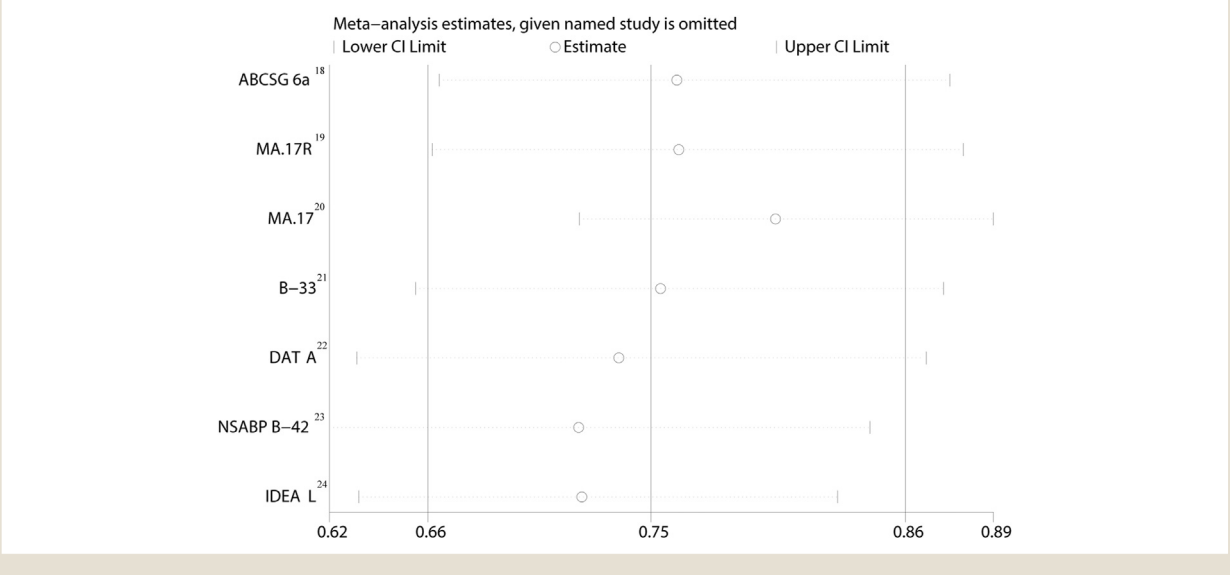
1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; 136:E359-86.
2. Kohler BA, Sherman RL, Howlader N, et al. Annual report to the nation on the status of cancer, 1975-2011, featuring incidence of breast cancer subtypes by race/ethnicity, poverty, and state. *J Natl Cancer Inst* 2015; 107:djv048.
3. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; 365:1687-717.
4. Jin H, Tu D, Zhao N, Shepherd LE, Goss PE. Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover. *J Clin Oncol* 2012; 30:718-21.
5. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003; 349:1793-802.
6. Davies C, Pan H, Godwin J, et al; Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) Collaborative Group. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet* 2013; 381:805-16.
7. Burstein HJ, Temin S, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology clinical practice guideline focused update. *J Clin Oncol* 2014; 32:2255-69.
8. Early Breast Cancer Trialists' Collaborative Group. Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet* 2015; 386:1341-52.
9. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009; 62:1006-12.
10. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17:1-12.
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7:177-88.
12. Ades AE, Lu G, Higgins JP. The interpretation of random-effects meta-analysis in decision models. *Med Decis Making* 2005; 25:646-54.
13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; 327:557-60.
14. Deeks J, Altman DG, Bradburn M. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, eds. *Systematic Reviews in Health Care: Meta-analysis in Context. 2nd Edition of systematic reviews*. London: BMJ Publishing Group; 2001:285-312.
15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629-34.
16. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50:1088-101.
17. Duval S, Tweedie R. A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis. *J Am Stat Assoc* 2000; 95:89-98.
18. Jakesz R, Greil R, Gnant M, et al; Austrian Breast and Colorectal Cancer Study Group. Extended adjuvant therapy with anastrozole among postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a. *J Natl Cancer Inst* 2007; 99:1845-53.
19. Goss PE, Ingle JN, Pritchard KI, et al. Extending aromatase-inhibitor adjuvant therapy to 10 years. *N Engl J Med* 2016; 375:209-19.
20. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005; 97:1262-71.
21. Mamounas EP, Jeong JH, Wickerham DL, et al. Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. *J Clin Oncol* 2008; 26:1965-71.
22. Tjan-Heijnen VCG, van Hellemond IEG, Peer PGM, et al; Dutch Breast Cancer Research Group (BOOG) for the DATA Investigators. Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial. *Lancet Oncol* 2017; 18:1502-11.
23. Mamounas EP, Bandos H, Lembersky BC, et al. A randomized, double-blinded, placebo-controlled clinical trial of extended adjuvant endocrine therapy (tx) with letrozole (L) in postmenopausal women with hormone-receptor (+) breast cancer (BC) who have completed previous adjuvant tx with an aromatase inhibitor (AI): results from NRG Oncology/NSABP B-42. *Cancer Res* 2017; 77, Abstract S1-05.
24. Blok EJ, Kroep JR, Meershoek-Klein Kranenbarg E, et al, IDEAL Study Group. Optimal duration of extended adjuvant endocrine therapy for early breast cancer: results of the IDEAL trial (BOOG 2006-05). *J Natl Cancer Inst* 2018:110.
25. Goldvaser H, AlGorashi I, Ribnikar D, et al. Efficacy of extended adjuvant therapy with aromatase inhibitors in early breast cancer among common clinicopathologically-defined subgroups: a systematic review and meta-analysis. *Cancer Treat Rev* 2017; 60:53-9.

Supplemental Figure 1 Sensitivity Analysis for Overall Survival



Abbreviation: CI = confidence interval.

Supplemental Figure 2 Sensitivity Analysis for Disease-free survival



Abbreviation: CI = confidence interval.