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Original Research

Meta-analyses of phase 3 randomised controlled trials of third generation aromatase inhibitors versus tamoxifen as first-line endocrine therapy in postmenopausal women with hormone receptor-positive advanced breast cancer



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Received 23 August 2020; received in revised form 23 November 2020; accepted 24 November 2020

Available online 7 January 2021

KEYWORDS

Advanced breast cancer;
HR positive;
1st line endocrine therapy;
meta-analyses of RCTs;
tamoxifen;
3rd generation AIs

Abstract Background: Four randomised controlled trials (RCTs) in postmenopausal women with advanced breast cancer (ABC) comparing aromatase inhibitors (AIs) versus the selective estrogen receptor modulator tamoxifen, each individually reported significantly longer progression-free survival (PFS) but none showed a significant difference in overall survival (OS). In these trials between 6.8% and 55% of tumours were hormone receptor (HR) status unknown or negative. This meta-analysis restricted the comparison to HR-positive (HR+) tumours.

Methods: Anonymised individual patient data were obtained from three RCTs, EORTC (exemestane versus tamoxifen), Study 0027 and Study 0030 (both anastrozole versus tamoxifen). For the remaining RCT (Femara Study PO25; letrozole versus tamoxifen), odds ratio (OR) or hazard ratio (HzR), with confidence intervals were obtained from the clinical study report, for patients with HR+ tumours, in addition to published data. In total, data were obtained from 2296 patients; 1560 (68%) had HR+ ABC.

Findings: The OR for clinical benefit rate was 1.56, in favour of AIs ($p < 0.001$). The duration of clinical benefit was not significantly increased by AIs (HzR 0.88; $p = 0.08$). For PFS the

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HzR (0.82) was in favour of AIs ($p = 0.007$). However, for OS the HzR (1.05) was not significantly different between AIs and tamoxifen ($p = 0.42$).

Interpretation: Although third generation AIs put significantly more patients into ‘clinical benefit’, their tumours were not controlled for significantly longer. Overall, while this resulted in a significantly greater PFS in favour of the AIs, this did not translate into improvement in OS.

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Introduction

In postmenopausal women, around 70% of all breast cancer diagnoses are hormone receptor (HR)-positive (HR+), and are candidates for endocrine therapy (ET) [1].

The use of tamoxifen (TAM), an anti-estrogen, for the treatment of patients with advanced breast cancer (ABC), was first reported in 1971 [2]. It was approved in the UK in 1973 and in the USA in 1977. TAM was the first of a class of endocrine agents called selective estrogen receptor modulators (SERMs), which can act as antagonists of the estrogen receptor in breast cancers, but also have partial agonist activity on other organs (e.g. bone, uterus).

The first generation aromatase inhibitor (AI), aminoglutethimide, which was a non-selective inhibitor of the enzyme aromatase in postmenopausal women, resulted in ~90% reduction in circulating estrogen levels and was approved for clinical use in 1980. Aminoglutethimide was compared to TAM in randomised controlled trials (RCTs) and essentially showed no difference in efficacy [3–5]. To overcome drawbacks of the non-specificity and side effects of aminoglutethimide, more potent and specific AIs were developed, such as the second-generation 4-hydroxyandrostenedione (formestane) [6]. In addition to looking for improved specificity, agents which gave more complete suppression of aromatase activity, such as vorozole and fadrozole, were also required. Third generation AIs developed were either steroidal (e.g. exemestane) or non-steroidal (e.g. anastrozole, letrozole) agents. These third generation AIs, exemestane [7], anastrozole [8–10] and letrozole [11,12], were compared to TAM in the first-line setting of patients with ABC. All of the studies reported increased progression-free survival (PFS) for the AIs versus TAM, but no individual study reported an increased overall survival (OS). In these comparative trials, the percentage of patients with HR positive (+) tumours ranged from 93.2% [7] to 45% [9,10].

Here, we report the first meta-analysis of all Phase 3, multicentre, international randomised controlled trials (RCTs) that compared third generation AIs with TAM (20 mg) as first-line endocrine therapy, restricted to advanced breast patients with HR+ tumours only. Given the large number of patients pooled here, the present meta-analyses allowed not only to compare AI versus

TAM in terms of OS, but it also allowed us to address the fundamental question of whether the PFS benefit from AIs arises as a result of either reducing de novo resistance (i.e. increasing the number of patients achieving clinical benefit (CB) in the first 6 months) or delaying the acquired resistance to first-line hormonotherapy (i.e. by lengthening the duration of clinical benefit [DoCB]), or from the combination of both mechanisms? For example, a new drug which increased the CBR significantly (i.e. less de-novo resistance within 6 months) but made no difference to acquired resistance (i.e. produced the same duration of CB) could result in a significantly improved PFS. Equally, an alternative drug which had the same CBR (i.e. the same de-novo resistance within 6 months) but which took longer for the tumour to develop acquired resistance (i.e. longer duration of CB) could also result in a significantly improved PFS. However, the reason for the improved PFS in both cases would be biologically and therapeutically different.

Methods

This meta-analysis included data from 4 large, Phase 3, international, multicentre, RCTs of first-line endocrine monotherapy for the treatment of locally advanced/metastatic breast cancer in postmenopausal women, available data for analysis also included the status of visceral/non-visceral metastases (Fig. 1). All trials were run in compliance with regulatory

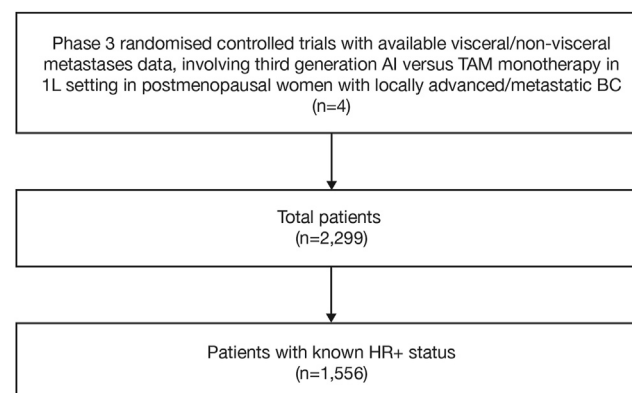


Fig. 1. Study-selection flow chart. 1L = first line. AI = aromatase inhibitor. BC = breast cancer. HR+ = hormone receptor-positive. TAM = tamoxifen.

requirements for registration of endocrine agents. Each trial included TAM as the control/comparator arm: EORTC (European Organisation for Research and Treatment of Cancer group) evaluated exemestane versus TAM treatment in 371 patients at 81 worldwide centres [7], Study 0027 evaluated anastrozole versus TAM in 668 patients in 83 European, Oceanic, South African and South American centres [9,10], Study 0030 evaluated anastrozole versus TAM in 353 patients at 97 North American centres [8] and Femara Study PO25 (letrozole study) evaluated letrozole versus TAM in 907 patients at 201 centres in 29 countries [11,12].

The percentage of patients with known HR+ tumours varied between studies. In the EORTC trial there were 346/371 (93%) patients with known HR+ tumours, while in Study 0027, 0030 and the letrozole study there were 298/668 (45%), 313/353 (89%) and 599/907 (66%) patients with known HR+ tumours, respectively.

Anonymised IPD from three RCTs that compared third generation AIs with TAM as first-line ET in patients with known HR+ ABC, including the EORTC (exemestane vs TAM) and Study 0027 and Study 0030 (both anastrozole vs TAM) was included. Anonymised IPD was not available for the letrozole versus TAM study and so data including odds ratio (OR) or hazard ratio (HzR), with confidence intervals (Cis), were obtained from the clinical study report (CSR) provided by Novartis, for patients with HR+ tumours in the letrozole study (letrozole versus TAM), in addition to relevant data from peer review publications.

These RCTs were reviewed for the following clinical outcomes, in patients with clinically confirmed HR+ breast cancer, clinical benefit rate (CBR), DoCB, PFS and OS. CBR was defined as the proportion of patients who experienced a best objective response of complete response, partial response or stable disease for >24 weeks. Objective response was defined as the proportion of patients who achieved a best objective response of complete response or partial response. Response criteria were assessed by the study physician using either the International Union against Cancer or World Health Organization criteria. DoCB was measured for patients who achieved a CB, in terms of the time it took for the tumour to progress in this subgroup of patients. PFS was the time from randomisation to disease progression, death or censored at last follow-up if alive and not progressed. OS was the time from commencement of the study to death of the individual patient or censored at the time last known to be alive.

Details of the RCTs used in this meta-analysis, including patient numbers, ages, tumour sites, HR status, are shown in Table 1.

Statistical analysis

A two-stage IPD/aggregate data meta-analysis was used. The Peto method for pooled ORs was used to calculate *p* values, OR and CIs for CBR. The Yusuf Peto method was used to calculate *p*-values, HzRs and CI for PFS, OS and DoCB [13]. Significance was tested at 5%.

Table 1
Summary of the study populations included in the meta-analysis.

Study	Design	Stratified by	Adj. ET (%)	n	No. Pts	VM n (%)	VLM n (%)	Md age yrs	HR+ pts (%)	n	AI	Disease Type	Resp. criteria	Resp Time (mths)	Bisphosphonates allowed
0027 [1]	DBDD	No	76 (11)	668	227 (34)	63 (9)	67	298 (45)	Ana	Meas nMeas	UICC	#3	Last 127 pts recruited		
0030 [2]	DBDD	Centre	69 (20)	353	170 (48)	43 (12)	68	313 (89)	Ana	Meas nMeas	UICC	#3	Last 82 pts recruited		
PO25 [3]	DBDD	No	167 (18)	907	402 (44)	115 (13)	65	599 ⁱ (66)	Let	Meas nMeas UnAss	UICC	3	Treatment of bone mets		
EORTC [4]	OL	Centre, Adj Tam, MBC Chemo, Site of mets	78 (21)	371	175 (47)	N/A	63	346 (93)	Exe	Meas	WHO	*3	None		

DBDD = Double blind, double dummy, OL = Open label.

VM(%) = % patients with visceral mets. VLM(%) = % patients with specifically liver mets.

N/A = not available.

ANA = Anastrozole, Let = Letrozole, Exe = Exemestane.

Mes = measurable, nMes = non-measurable but assessable, UnAss = Unassessable for response but assessed for progression.

Response assessment criteria: UICC - International Union Against Cancer; WHO - World Health Organisation.

Response time (assessment frequency) [#] 0027 & 0030 - included 4 weekly clinical examination to 6 months; * EORTC - one additional assessment in first 6 months (ie assessed at 2, 4 & 6 months).

*Mean age reported. [†]Data for HR+ patients were only available for TTP (used for PFS meta-analysis); for other endpoints, aggregate data were used in the meta-analysis. AI = aromatase inhibitor. EORTC = European Organisation for Research and Treatment of Cancer. ET = endocrine therapy. HR+ = hormone receptor-positive. PFS = progression-free survival. TTP = time to progression.

Following the test for heterogeneity: Tarone's test (CBR) and Cochrane's Q (PFS, OS and DoCB), a fixed-effects model was fitted throughout. For CBR, DoCB and OS, the model was fitted with and without the letrozole trial, for which IPD were not available. For the letrozole study the HzR and CI for OS were not available from the published manuscript. The group log-rank test was calculated from a table in the CSR for OS, the HzR was then estimated by indirect methods based on the test statistic and the number of deaths in each group.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, the writing of the report, or the decision to submit the paper for publication.

Results

A summary of the study populations included in this meta-analysis, including HR status, are shown in Table 1.

Overall, as shown in Fig. 2, more patients achieved a CB with an AI compared with TAM, with the letrozole study included in the analysis: OR 1.56 (95% CI 1.29–1.89; $p < 0.001$); the advantage was maintained and nearly identical after excluding data from the letrozole study: OR 1.51 (95% CI 1.11–2.05; $p = 0.008$).

As shown in Fig. 3, as far as the duration of the clinically relevant therapeutic benefit is concerned, this meta-analysis demonstrated that the DoCB, while

numerically slightly higher for AI, is non-significantly different from TAM for all of the RCTs, either by including: HzR 0.88 (95% CI 0.75–1.02) $p = 0.08$ or excluding data from the letrozole study: HzR 0.93 (95% CI 0.76–1.13; $p = 0.46$).

For PFS, Fig. 4 shows that there is a statistically significant difference between AIs and TAM, in favour of AIs, HzR 0.82 (95% CI 0.71–0.95; $p = 0.007$). Of note, the HzR and CIs for patients in the letrozole study were available, so that there was no need to run the model for PFS excluding data from the letrozole study.

Finally, as shown in Fig. 5, the OS was not significantly different between AIs and TAM: HzR 1.05 (95% CI 0.93–1.20; $p = 0.43$). Running the model excluding data from the letrozole study also resulted with no significant difference between AIs and TAM for OS: HzR 1.06 (95% CI 0.87–1.29) $p = 0.56$. The results from the meta-analysis are summarised in Table 3.

Discussion

In this meta-analysis, third generation AIs (anastrozole, letrozole and exemestane) produced significantly greater increases in CBR and PFS than TAM, in postmenopausal women with HR+ ABC. This shows that more patients had their tumours controlled with an AI, and the effect of AI treatment was not simply to keep the same number of tumours which respond to TAM in clinical benefit for longer (ie prolong the time to acquired resistance). It is not simply the same tumours that respond to different endocrine agents. Clearly, from

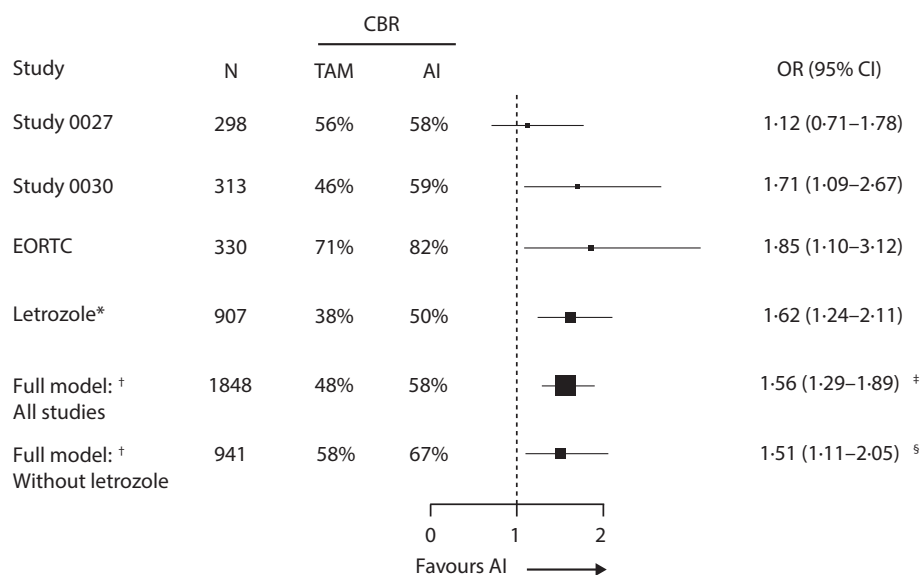


Fig. 2. Forest plot of CB with AI versus TAM. Reference for comparison was tamoxifen. *According to final CSR 2002 (included HR status unknown). †Fixed effect for study was included in the full model. ‡Fixed effect $p < 0.001$; heterogeneity test $p = 0.45$. §Fixed effect $p = 0.008$; heterogeneity test $p = 0.29$. AI = aromatase inhibitor. CBR = clinical benefit rate. CI = confidence interval. CSR = clinical study report. EORTC = European Organisation for Research and Treatment of Cancer. HR = hormone receptor. OR = odds ratio. TAM = tamoxifen.

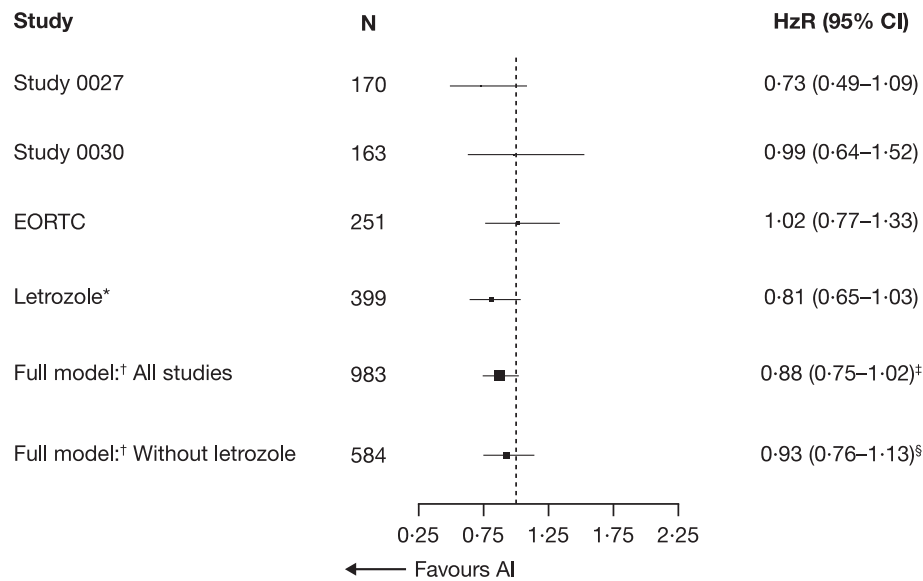


Fig. 3. Forest plot of DoCB with AI versus TAM. Reference for comparison was TAM. *According to final CSR 2002 (includes HR status unknown). [†]Fixed effect for study was included in the full model. [‡]Fixed effect $p = 0.08$; heterogeneity test $p = 0.45$. [§]Fixed effect $p = 0.46$; heterogeneity test $p = 0.39$. AI = aromatase inhibitor. CI = confidence interval. CSR = clinical study report. DoCB = duration of clinical benefit. EORTC = European Organisation for Research and Treatment of Cancer. HR = hormone receptor. HzR = hazard ratio. TAM = tamoxifen.

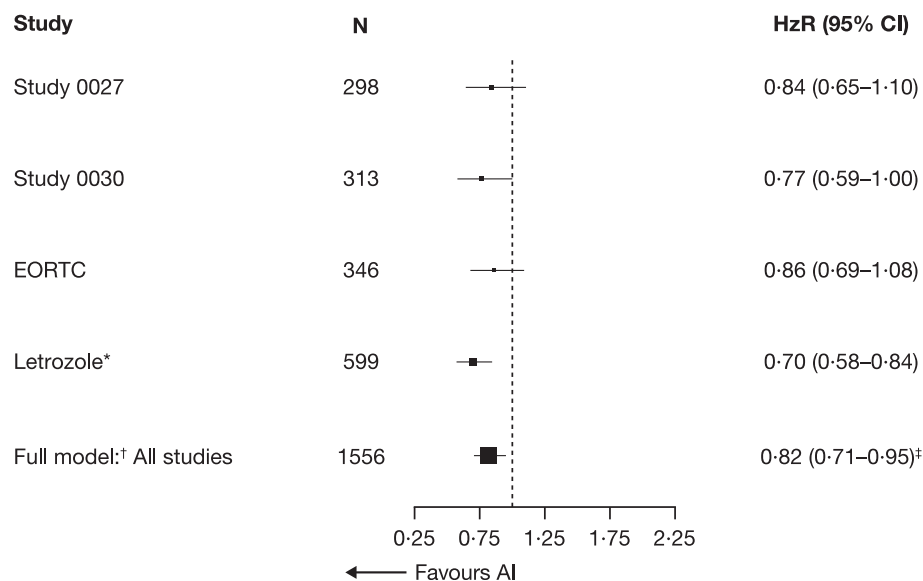


Fig. 4. Forest plot of PFS with AI versus TAM. Reference for comparison was TAM. *According to Mouridsen *et al.* (2001) [11]. [†]Fixed effect for study was included in the full model. [‡]Fixed effect $p = 0.007$; heterogeneity test $p = 0.88$. AI = aromatase inhibitor. CI = confidence interval. EORTC = European Organisation for Research and Treatment of Cancer. HzR = hazard ratio. PFS = progression-free survival. TAM = tamoxifen.

previous crossover studies, it appears that the majority of tumours responding to one of these agents may also respond to another. However, choosing an AI instead of TAM by clinicians in the in first-line setting is clinically important as it increases the number of patients who benefit from ET as well as the duration of tumour control, by prolonging PFS. The CBR in the EORTC trial was 71% and 82% for TAM and AI, respectively,

which was significantly higher than the CBR for either agents (AI and TAM) in the remaining trials (CBR range 46%–59%). There were differences between the EORTC study and the other studies including the EORTC study being open label, including only measurable disease and not allowing use of bisphosphonate therapy throughout the study. In addition, the percentage of patients with liver metastases, which are

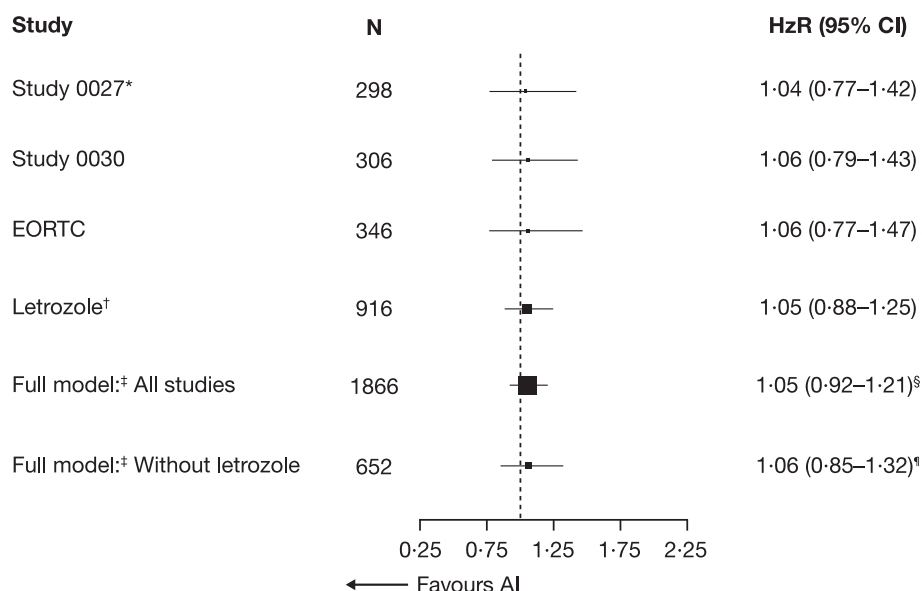


Fig. 5. Forest plot of OS with AIs versus TAM. Reference for comparison was TAM. * Estimated by indirect methods using group log-rank statistics, based on results presented in the CSR. † Fixed effect for study was included in the full model. ‡ Fixed effect $p = 0.425$; heterogeneity test $p = 1.00$. § Fixed effect $p = 0.562$; heterogeneity test $p = 1.00$. AI = aromatase inhibitor. CI = confidence interval. EORTC = European Organisation for Research and Treatment of Cancer. HzR = hazard ratio. OS = overall survival. TAM = tamoxifen.

less hormone sensitive site of metastases was not specifically reported in the EORTC study. Some or all of these factors might have contributed to this difference in CBR rate but it is noted that, despite the difference in the absolute CBR, in the EORTC study, like the others, the CBR was higher in the AI treated arm.

Despite increased CBR and PFS, there was no associated improvement in OS with AIs versus TAM. This was true with or without the inclusion of data from the letrozole study, the HzR = 1.05 and 1.06 respectively.

It is worth noting that for the letrozole and anastrozole studies, the study design differed slightly in the

Table 2

AI vs TAM - HR status in Study 0027, 0030 and EORTC.

AI vs TAM				
HR status in Study 0027, 0030 and EORTC				
Study	Patients	HR +	HR-	Unknown ^a
Study 0027	668	298	..	370
Study 0030	353	313	..	40
EORTC	371	346	1	24
Study by treatment	Patients	HR +	HR-	Unknown ^a
Study 0027: AI	340	154	..	186
Study 0027: TAM	328	144	..	184
Study 0030: AI	171	151	..	20
Study 0030: TAM	182	162	..	20
EORTC: AI	182	168	..	14
EORTC: TAM	189	178	1	10
Study by treatment	HR+/known CB ^b	CB, n	CBR	
Study 0027: AI	154	90	58%	
Study 0027: TAM	144	80	56%	
Study 0030: AI	151	89	59%	
Study 0030: TAM	162	74	46%	
EORTC: AI	159	130	82%	
EORTC: TAM	171	121	71	

AI = aromatase inhibitor. CB = clinical benefit. CBR = clinical benefit rate. EORTC = European Organisation for Research and Treatment of Cancer. HR = hormone receptor. HR+ = hormone receptor-positive. HR- = hormone receptor-negative. IPD = individual patient data. TAM = tamoxifen.

^a IPD for HR status for Study 0027 and 0030 was HR+ or other, so HR status for these studies are presented as HR+ or unknown.

^b IPD for clinical benefit status was only reported for 330/346 of HR+ patients in the EORTC.

Table 3

Summary of clinical outcomes of the studies included in the meta-analysis.

Study	Treatment (TAM vs)	CBR OR (95% CI)	DoCB HzR (95% CI)	PFS HzR (95% CI)	OS HzR (95% CI)
Study 0027	Anastrozole	1.12 (0.71–1.78)	0.73 (0.49–1.09)	0.84 (0.65–1.10)	1.05 (0.69–1.60)
Study 0030	Anastrozole	1.71 (1.09–2.67)	0.99 (0.64–1.52)	0.77 (0.59–1.00)	1.06 (0.796–1.43)
EORTC	Exemestane	1.85 (1.10–3.12)	1.02 (0.77–1.33)	0.86 (0.69–1.08)	1.06 (0.77–1.47)
Study PO25	Letrozole	1.62 (1.24–2.11)	0.81 (0.65–1.03)	0.70 (0.58–0.84)	1.05 (0.88–1.25)
Full model: all studies		1.56 (1.29–1.89)	0.88 (0.75–1.02)	0.82 (0.71–0.95)	1.05 (0.93–1.20)
p value		<0.001	0.08	0.007	0.425
Full model: without letrozole		1.51 (1.11–2.05)	0.93 (0.76–1.13)	NA	1.06 (0.87–1.29)
p value		0.008	0.46	NA	0.562

CBR = clinical benefit rate. CI = confidence interval. DoCB = duration of clinical benefit. EORTC = European Organisation for Research and Treatment of Cancer. HzR = hazard ratio. NA = not available. OR = odds ratio. OS = overall survival. PFS = progression-free survival. TAM = tamoxifen.

post-progression survival protocol with the initial randomised ET. In the letrozole study, progression of disease, at the discretion of the investigator if they deemed the patient was suitable for further ET, the patient could be switched to the alternative treatment in a double-blind fashion (optional crossover) [11,12]. However, in the anastrozole and exemestane studies there was no proposed crossover design and patients were simply unblinded, further treatment was left to the discretion of the investigator and follow-up was until death [8,9]. Of the 907 patients in the intent-to-treat population in the letrozole study, 453 patients were allocated letrozole therapy and 454 were allocated TAM. Patient baseline characteristics were well balanced in the two treatment arms. On the final reported analysis, median follow-up of 32 months with a maximum observation period of 57 months, 48 patients were still receiving letrozole and 27 patients were still receiving TAM [12]. Of the 832 patients who discontinued treatment, 239 letrozole-treated patients and 228 TAM-treated patients entered crossover (around 51%). There was no significant difference in OS, which at that time, the authors of that study concluded that this might be due to the large proportion (51%) of patients crossing over to the alternative treatment, following disease progression.

A combined analysis of Study 0027 and Study 0030 (anastrozole versus TAM), median follow-up of 43.7 months, reported on the OS in a total of 1021 patients randomised into the 2 studies (combined analysis; anastrozole 1 mg; n = 511; TAM 20 mg; n = 510) [14]. A subsequent retrospective review reported that ~26% of patients crossed over to the alternative treatment [15]. Despite the fact that only a minority of patients crossed over there was still no survival advantage reported for either the whole cohort (HzR = 0.97; lower 95% CL = 0.84) or for the ER+/PR+ cohort (HzR = 1.00; lower 95% CL = 0.83) [14], adding further support to the results of this meta-analysis, that patients treated with AIs appear to have increased CB with longer PFS compared with those treated with TAM, although this does not result in significantly longer duration of control (DoCB) or increased OS.

This meta-analysis was performed on patients with HR+ tumours only. We were not able to identify the individual patients or the percentage of HR+ patients in the RCTs who crossed over. However, based on the 51% and 26% reported for the intent-to-treat populations in the letrozole and anastrozole studies, respectively, it would appear that the absence of a survival advantage was not due to crossover by patients to the alternative ET. This is different from the adjuvant setting where the use of AI for 5 years versus TAM for 5 years, results in significantly fewer breast cancer recurrences and significantly fewer deaths (both breast cancer mortality and deaths from any cause) [16].

These findings differ from those with the SERD, fulvestrant 500 mg, which has been reported to show a significant improvement in PFS and OS versus the AI, anastrozole, in ABC. Indeed, the first Phase 3 trial of fulvestrant 500 mg, which showed a significant PFS (HzR = 0.81) and OS (HR = 0.80) advantage versus against fulvestrant 250 mg in the second-line ET setting, was the CONFIRM study [17,18]. Fulvestrant 250 mg had previously been shown to be statistically equivalent to an AI (anastrozole) in the combined analysis of the two Phase 3 trials of fulvestrant 250 mg versus anastrozole in the second-line (post-TAM) setting [19–22]. Indirectly, fulvestrant 500 mg was thought to be better than an AI in the second-line setting. The FIRST study, an open-label Phase 2 study in the first-line ET setting not only showed a significant PFS advantage (HzR = 0.66; $p = 0.01$) but also a significant OS advantage (HzR = 0.70; $p = 0.04$) [23–25]. The Phase 3 FALCON trial has also shown a significant improvement in PFS (HzR = 0.797, $p < 0.05$); the OS data was immature with only 31% of deaths [26]. However, if the advantage noted in PFS (HzR = 0.797) in the FALCON trial is again translated into OS, then the study is powered for this to be statistically significant. Fulvestrant, as a SERD, degrades the ER but tumours can still respond to subsequent ETs—either when it is used at an initial dose of 250 mg [27] or the currently approved dose of 500 mg [24].

Up until 2000 and the studies of third generation AIs versus TAM reported here, different ETs (e.g. TAM,

megestrol acetate, aminoglutethimide) were thought to be of similar efficacy and the sequence of treatments was selected based on side-effects rather than efficacy. We now know that endocrine agents are not all equally efficacious. This meta-analysis has shown that AIs, compared to TAM, appear to induce a response/CB in more patients, but not significantly longer DoCB; with DoCB the CI does cross 1 and so potentially interesting therapeutic effects on DoCB cannot be ruled out. Using an AI in first-line setting translates into significantly better PFS, but without improvement in OS. From data thus far with the SERD, fulvestrant 500 mg, it appears that improvement in PFS translates into a significant improvement in OS. There is also currently data which suggests that endocrine agents with different mechanisms of action (e.g. estrogen receptor ‘blockers’, SERM and SERD, have a greater effect on non-visceral metastases than AIs) [28]. Taken together, these results suggest that the type of endocrine agent (with differing mechanisms of action), sites of disease (i.e. non-visceral, visceral non-liver and visceral liver metastases) and also mechanism of resistance (e.g. ESR1 mutation induction, growth factor pathway induction) are all important in selecting which ET to use. At the present time, fulvestrant 500 mg appears to have the advantage in all these issues—having shown significant improvement in PFS and OS compared with anastrozole, particularly in non-visceral, and recently in visceral non-liver metastases, compared to visceral liver disease and in the fact that the SERD does not appear to induce ESR1 mutation, at least in the vast majority of tumours.

As reported in a previous publication [29], why would one select an inferior endocrine agent in first line?—unless of course there is sequencing data to show that a particular sequence yields better outcomes in the end, including survival. Such sequence data does not yet exist and as such we should always use our best endocrine agent for the setting.

The present meta-analysis shows that AIs used in first-line setting are superior, in terms of PFS, to the SERM, TAM, in patients with HR+ ABC. However, given the recent data we have on fulvestrant 500 mg—i.e. improvement in both PFS and OS over anastrozole—the latter AI cannot be considered the most efficacious ET in the first-line setting of HR+ ABC. Combination therapies involving CDK-blocking agents will also have to consider these issues in future studies. At present the SERD, fulvestrant 500 mg, seems to be an efficient first-line monodrug therapy, which could represent a privileged first-line choice for most patients. Future studies should focus on optimising therapeutic sequences of hormonotherapy (fulvestrant vs steroidal or non-steroidal AI) and aim at identifying subgroups of patients most likely to respond to one of these modalities, for example patients with non-visceral disease versus those with or without liver visceral

disease. Prospective RCTs would be needed to definitively solve these questions.

Strengths and limitations of this meta-analysis

A major strength is the meta-analysis includes only known HR+ tumours, the intended target of endocrine therapy, which makes the results relevant in current practice where ET is now recommended based on known HR+ status. A second major strength is that the meta-analysis clearly shows that the sequence of starting with tamoxifen or an AI impacts initial disease control (i.e. PFS) but has no significant impact on overall survival. A minor limitation is that the sequence of therapies post-progression was not identical in all four studies but the reproducible HR for OS in all 4 studies indicates this was not a significant factor.

A further strength is the meta-analysis allowed dissection of the PFS results to show that the bigger effect was that AIs placed more tumours in CB rather than significantly prolonging DoCB. This opens new lines of translational and clinical research.

Selecting only the HR+ tumours may be seen as a limitation in that it could introduce possible elements of bias. As a statistical comment this may be correct but equally, randomising tumours which are HR negative or unknown (and potentially triple negative) itself introduces an element of bias. By removing the HR negatives or unknowns not only does the meta-analysis focus on the appropriate tumour type (i.e. HR+) but removes inappropriate tumours equally from both arms. Table 2 shows that the number of patients on TAM or AI in each study is almost equal (as would be expected in a RCT) and that the number of patients with HR+ tumours on TAM or AI are likewise almost equal in both arms. This supports that the subgroup of HR+ tumours are not imbalanced in the meta-analysis by removing the HR negatives and unknowns.

A further limitation would be that the meta-analysis does not look at side effects. The authors did not have access to these data and furthermore all 4 studies individually reported both drugs were well-tolerated, and none of the studies statistically compared the side-effect profiles. The adjuvant setting where the number of patients are much greater and the duration of treatment is on average longer and as such provide a more accurate description of the side-effect profiles and significant differences between TAM and AIs. Other limitations are two different criteria for assessing tumour response (i.e. WHO and UICC), but as both have been used for registration of drugs this would seem minor. Also one study (EORTC) was open label and had a higher ORR for both AI and TAM compared to the double-blinded studies: this could be viewed as a limitation, but the relative improvement in OR and CBR with the AI compared to TAM was similar to that seen in the double-blind trials.

Overall the strengths of the meta-analysis markedly outweigh the limitations.

Author contribution

JFRR conducted the literature review and designed the study. JFRR and RP provided study materials. JFRR and CC collected and assembled the data. JFRR wrote the first draft of the report with input from RJP, JL, IB and CC. All authors were involved in data analysis, data interpretation, drafting and revising the manuscript, and provided approval of the final draft for submission.

Funding

This work was funded by the University of Nottingham.

Data files and accessibility

The datasets that support the findings of this study are not publicly available, but will be made available upon reasonable request from the corresponding author, Prof John Robertson, email address: John.Robertson@nottingham.ac.uk. The data may be obtained upon request for specific use as long as the request is in keeping with the terms of the agreement under which the University of Nottingham received the data. In accordance with the agreement under which Nottingham University gained approval to use the data, permission for sharing the data beyond those permitted in the agreement is not approved.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: John FR Robertson has received consultancy fees from, and has performed contracted research on behalf of, AstraZeneca, Bayer, Novartis, Carrick Therapeutics and Oncimmune; has given expert testimony for AstraZeneca, holds stock with Oncimmune and FaHRAS, and stock options with Carrick Therapeutics. Christine Campbell, Ian Bradbury and Robert Paridaens have no conflicts of interest to declare. Jasmine Lichfield is a previous employee and current stockholder of AstraZeneca.

Acknowledgments

This work was funded by the University of Nottingham. The authors would like to thank AstraZeneca and EORTC for making the study data available. The authors would also like to thank Novartis for making the letrozole study report available. The figures were

produced by CMC Connect, McCann Health Medical Communications, for a poster presented at the 2018 SABCS meeting, and was funded by AstraZeneca in accordance with Good Publication Practice (GPP3) guidelines.

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