

New Aromatase Inhibitors as Second-Line Endocrine Therapy in Postmenopausal Patients with Metastatic Breast Carcinoma

A Pooled Analysis of the Randomized Trials

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BACKGROUND. New aromatase inhibitors (AI) (second-generation: formestane and fadrozole; third-generation: letrozole, anastrozole, vorozole, and exemestane) have been tested in several controlled clinical trials after tamoxifen failure in metastatic breast carcinoma (MBC). They have resulted in better survival compared with megestrol acetate (MEG) in a number of studies. The authors performed a pooled analysis including all the Phase III trials published between 1996 and 2004 evaluating the AIs approved or not by the Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medical Products (EMA) as second-line endocrine therapy (ET) for patients with MBC.

METHODS. The overall response rate (ORR) and time to disease progression (TTP) were considered the primary end points, whereas toxicity was regarded as a secondary objective. Relative risk, 95% confidence interval, and heterogeneity were derived using 2 methods.

RESULTS. No significant differences in ORR and TTP were noted in the entire group of 9 trials comparing AI with MEG (3908 patients) and in the 6 trials comparing nonsteroidal AI and MEG (2415 patients). AI yielded significantly more hot flashes than MEG ($P = 0.004$) but caused significantly less toxicity than MEG in weight gain ($P = 0.001$), dyspnea ($P = 0.008$), and peripheral edema ($P = 0.03$). Significant heterogeneity for nausea, weight gain, dyspnea, and peripheral edema was registered. When steroidal AIs were excluded from the toxicity analysis, nausea maintained its strongly significant heterogeneity ($P = 0.0002$), whereas weight gain, dyspnea, and peripheral edema lost their significance.

CONCLUSIONS. This pooled analysis suggested that AIs in second-line ET for patients with MBC do not seem to add any significant benefit to MEG in terms of ORR and TTP. With regard to toxicity, the findings in the current study showed that weight gain, dyspnea, and peripheral edema are more frequent with the use of MEG, whereas hot flashes were more represented using AI. *Cancer* 2005;104:1335–42. © 2005 American Cancer Society.

KEYWORDS: metastatic breast carcinoma, aromatase inhibitors, metaanalysis, pooled analysis, comprehensive review.

Tamoxifen has been the most widely used endocrine drug for the management of all stages of breast carcinoma in women with estrogen-dependent tumors, regardless of age and menopausal status.^{1–3} This antiestrogen agent has been considered the standard first-line endocrine therapy (ET) for postmenopausal patients with metastatic breast carcinoma (MBC) until the publication of the Phase III trials using the new aromatase inhibitors (AI).^{4–6} According to their

structure, selective AI are classified as steroidal (sAI) or nonsteroidal (nsAI), and, with respect to their commercial development and chemical features, as first-generation, second-generation, and third-generation agents.⁷ The sAI include formestane, a drug requiring parenteral administration, which is no longer available, and exemestane, an oral agent. nsAI include aminoglutethimide, fadrozole, vorozole, anastrozole, and letrozole. The sAI agents competitively bind to the active site of aromatase and cause irreversible inhibition of enzyme activity, whereas the binding of the nsAI is reversible. This difference is of potential clinical relevance, because some evidence has demonstrated that there is a lack of cross-resistance between the sAI and nsAI.⁸ Third-generation AI have excellent pharmacologic profiles, with better tolerability and no significant drug interactions.⁹ Trials with second-generation inhibitors (fadrozole, formestane) and one trial with a third-generation agent, vorozole, now withdrawn from clinical studies, failed to show any clinical advantage over megestrol acetate (MEG).^{10–13} Vorozole is no longer used in clinical development, fadrozole is available only in Japan, and formestane is still considered a suitable alternative to progestins but has recently been withdrawn from commerce.

Third-generation inhibitors have become the established second-line endocrine option after tamoxifen failure for patients with estrogen receptor-positive MBC, because a series of trials have shown that they could be more effective than MEG, despite some differences in the presented results.^{14–18} The clinical benefit with anastrozole, letrozole, and exemestane over MEG was generally small and the results among AI slightly different.¹⁹ A metaanalysis gathered data from three randomized trials comparing AI with MEG.²⁰ The current analysis demonstrated a survival advantage in favor of AI, with a relative risk (RR) of death of 0.79 (95% confidence interval [95% CI], 0.69–0.91), but excluded trials presenting negative results. However, no pooled analysis has yet evaluated the overall response rate (ORR) and time to disease progression (TTP) of all the Phase III trials including old and new AI (second-generation AI: formestane and fadrozole; third-generation AI: vorozole, letrozole, anastrozole, and exemestane) approved or not by the Food and Drug Administration (FDA) or European Agency for the Evaluation of Medical Products (EMA) as second-line ET for postmenopausal patients with MBC. The aim of our analysis was to estimate in all published randomized trials the RR of ORR, TTP, and, when possible, adverse events of AI compared with MEG as second-line hormonal therapy after tamoxifen failure in postmenopausal women with MBC.

MATERIALS AND METHODS

Outcome Definition

We considered second or third-generation AI as the experimental arm and MEG as the standard comparator arm. Analysis was conducted to determine eventual significant differences in primary and secondary outcomes. The primary outcomes were ORR and TTP. The secondary outcome was toxicity evaluated in at least seven of nine trials comparing AI versus MEG. In particular, we investigated hot flashes, nausea, constipation, weight gain, peripheral edema, and dyspnea. All calculations were independently performed by two different investigators. All outcomes were computed and analyzed using two different methods.

Trial Identification Criteria

We gathered all the prospective randomized Phase III trials published as formal articles in peer-reviewed journals until December 31, 2004. In these trials, postmenopausal patients with advanced-stage breast carcinoma or MBC progressive to tamoxifen treatment were randomized to receive AI versus standard treatment (MEG). No Phase II trials were collected. Letters/editorials and studies on AI given as adjuvant/neoadjuvant ET were excluded.

Search Strategy

Randomized clinical trials were collected through a search of Medline (PubMed; available from URL: www.ncbi.nlm.nih.gov/PubMed). The key words used for research were metastatic or advanced breast cancer, aromatase inhibitors, AI, steroidal, non-steroidal, anastrozole, fadrozole, letrozole, vorozole, exemestane, formestane, review, metanalysis, meta-analysis, pooled analysis, randomized, phase III, comprehensive review, systematic review, hormonal, endocrine. Beyond computer browsing, review and original articles were also scanned in the reference sections to search for missing trials.

Data Extraction Methods

From each study, we obtained the rate and number of complete (CR) and partial responses, the median TTP, and the rate and number of toxicity events. Statistical combination of results was performed using two methods: Method A, as suggested by Simes,²¹ and Method B, based on the inverse variance and Mantel-Haenszel methods.²²

Method A

A ratio of median times to event was calculated for each study and its log was then combined using weights based on the sample size of each trial accord-

TABLE 1

Trials of Selective Aromatase Inhibitors Compared with Megestrol Acetate Included in the Current Analysis

Authors	Year	No. of patients	Trial	Primary/secondary end points
Buzdar et al. ^{10a}	1996	683	Fadrozole 2 mg vs. MEG 160 mg	ORR/TTP
Thurlimann et al. ¹²	1997	177	Formestane 250 mg vs. MEG 160 mg	ORR/TTF
Bezuda et al. ^b	1998	96	Fadrozole 2 mg vs. MEG 160 mg	ORR, TTP, TTF, OS/QOL, safety
Buzdar et al. ¹⁴	1998	516	Anastrozole 1 mg vs. MEG 160 mg	ORR, TTP, safety/OS, TTF
Dombrowsky et al. ¹⁵	1998	364	Letrozole 2.5 mg vs. MEG 160 mg	ORR/TTP, TTF, CB, OS
Goss et al. ¹¹	1999	452	Vorozole 2.5 mg vs. MEG 160 mg	ORR/TTP, OS, safety, QOL
Kaufmann et al. ¹⁷	2000	769	Exemestane 25 mg vs. MEG ^a 160 mg	ORR/TTP, TTF, CB, OS
Freue et al. ¹³	2000	547	Formestane 250 mg vs. MEG 160 mg	ORR/TTP, TTF, OS
Buzdar et al. ¹⁶	2001	400	Letrozole 2.5 mg vs. MEG ^a 160 mg	ORR/TTP, TTF, OS
Total		3908		

MEG: megestrol acetate; ORR: overall response rate; TTP: time to disease progression; TTF: time to treatment failure; OS: overall survival; QOL: quality of life; CB: clinical benefit.

^a Two Phase III grouped trials.

^b The trial by Bezuda et al. (Bezuda WR, Gudgeon A, Falkson G, et al. Fadrozole versus megestrol acetate: a double-blind randomized trial in advanced breast cancer. *Oncology*, 1998;55:416–420) was excluded from the current analysis because other studies have recently been negatively audited. However, the relative risk in the pooled analysis is the same with or without these data.

ing to a fixed-effect model approach. The 95% CI were then calculated using critical values of the t-distribution with $k-1$ degree of freedom, where k was the number of studies. In case of response (ORR and CR) and toxicity, we used the same method, obtaining the log of RR given by the ratio between rates in the two arms. The heterogeneity among trials was tested with the Q statistics, computing the square distance of each study from the combined effect and weighting these values with the inverse of variance of each study. The Q statistics was then compared with the chi-square distribution with $k-1$ degree of freedom, in which k was the number of studies. We calculated variances as indicated for RR.²³ The lack of significance of this test may justify the use of a fixed-effect model to calculate Q statistics. In case of time to event, we estimated the number of events at 6 months, assuming an exponential distribution of survival time. This approach appears to be quite reliable because median TTP values are generally very close to 6 months.²⁴

Method B

This second approach was based on the inverse variance and Mantel-Haenszel methods. The log of relative RR was estimated for each considered end point. Estimated events at 6 months were used when considering TTP. By this method, it was possible to apply a fixed-effect model as well as a random-effect model according to the inverse variance and the Mantel-Haenszel method.²⁴ To test for heterogeneity between trials, the Q statistics was used. The significance of the heterogeneity test suggests preference for the random-effect estimation for a more appropriate evaluation of the results. Patients were accounted and filled in the 2×2 tables using the intention-to-treat assign-

ment. Results were depicted in all Method B figures as conventional metaanalysis forest plots. The Method B calculations were accomplished using the Comprehensive Metaanalysis software, version 1.0.23 (CMA, Biostat, Englewood, NJ).²⁴

RESULTS

Selected Trials

Trials selected for the analysis are summarized in Table 1. Nine Phase III prospective randomized trials including 3908 women and comparing AI with MEG^{10–17} were performed from 1996 to 2004. All were published as original articles in peer-reviewed journals. The primary and secondary end points are indicated in Table 1. All arms within each trial were well balanced for pretreatment characteristics of the patients. Hot flashes results were present in all trials (AI vs. MEG), nausea and dyspnea in 8 trials (3731 patients),^{10,11,13–17} constipation in 7 trials (3184 patients),^{10,11,14–17} peripheral edema in 7 trials (2962 patients),^{10,11,13–16} and weight gain in 7 trials (2456 patients).^{11–16} Overall, 1942 patients were enrolled in AI arms and 1966 in MEG arms. The median number of patients per trial was 200 (range, 86–403 patients). The median follow-up varied much among trials (9.9–45 months). In the AI arms, TTP ranged from 3 months to 6 months. In the MEG arms, it ranged from 3 months to 5.6 months.

Combined Analysis

All outcomes and their statistical significance computed by both methods are listed in Table 2. Risk ratios are to be interpreted as follows: RR < 1.0 favors the AI group, whereas RR > 1.0 favors the MEG group. Comparing AI with MEG in the overall population, the

TABLE 2
Combined Results of Pooled Analysis (Methods A and B): Primary Endpoints

Outcome	Events		Method A		Method B		Method A	Method B
	Treated	Control	RR (95% CI)	Overall effect of (chi-square)	RR (95% CI)	Overall effect of (chi-square)	Heterogeneity test (P value)	
AI vs. MEG								
ORR	215/1942	241/1966	1.07 (0.88–1.29)	$P = 0.41$	1.06 (0.90–1.25)	$P = 0.46$	8.61 (0.38)	8.75 (0.36)
TTP	697/1942	734/1966	1.00 (0.89–1.12)	$P = 0.99$	1.00 (0.93–1.09)	$P = 0.93$	10.55 (0.23)	10.63 (0.22)
nsAI vs. MEG								
ORR	142/1209	128/1206	1.10 (0.84–1.46)	$P = 0.39$	1.13 (0.90–1.41)	$P = 0.29$	5.51 (0.36)	5.73 (0.33)
TTP	399/1209	450/1206	0.95 (0.85–1.07)	$P = 0.32$	0.96 (0.87–1.07)	$P = 0.47$	4.23 (0.52)	4.41 (0.49)
sAI vs. MEG								
ORR	109/733	113/760	1.02 (0.57–1.81)	$P = 0.90$	0.99 (0.78–1.27)	$P = 0.95$	2.60 (0.27)	2.44 (0.29)
TTP	298/733	284/760	1.08 (0.69–1.69)	$P = 0.51$	1.08 (0.95–1.22)	$P = 0.24$	4.86 (0.09)	4.16 (0.12)

RR: relative risk; 95% CI: 95% confidence interval; chi-square: chi-square test; AI: aromatase inhibitors; MEG: megestrol acetate; ORR: overall response rate; TTP: time to disease progression; nsAI: non-steroidal aromatase inhibitors; sAI: steroidal aromatase inhibitors.

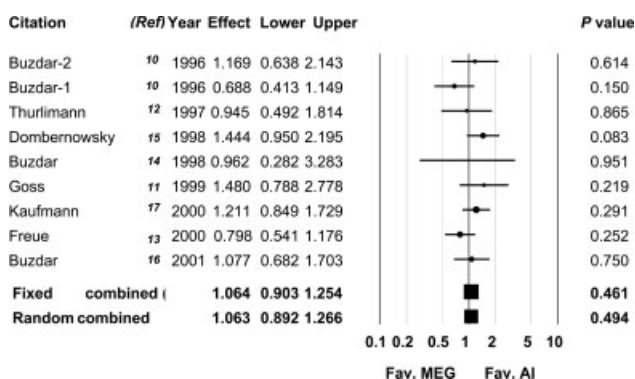


FIGURE 1. Aromatase inhibitor (AI) versus megestrol acetate (MEG): overall response rate relative risk (RR) (3908 patients). Ref: reference; Effect: RR; Fixed: fixed-effect model; Random: random-effect model; Fav.: favors.

ORR RR values were 1.07 (95% CI, 0.88–1.29) and 1.06 (95% CI, 0.90–1.25) using Methods A and B, respectively (Table 2) (Fig. 1). Therefore, no significant benefit was detected for AI versus MEG using both methods ($P = 0.41$ and $P = 0.46$, respectively). The same impact was seen for TTP, in which the RR values were 1.00 (95% CI, 0.89–1.12; $P = 0.99$) and 1.00 (95% CI, 0.93–1.09; $P = 0.93$) (Table 2) (Fig. 2). No significance was registered for other comparisons performed (nsAI vs. MEG, sAI vs. MEG) as displayed in Table 2 and Figures 3–6. When computed by the Mantel-Haenszel estimation, results were definitively comparable with those already described and plotted as shown in Figures 3–6.

Toxicity analysis was exclusively computed with Method A (Table 3). In the overall population, AI significantly yielded more hot flashes than MEG (RR = 1.64; 95% CI, 1.23–2.18 [$P = 0.004$]). A borderline significance regarding nausea was present as well (RR

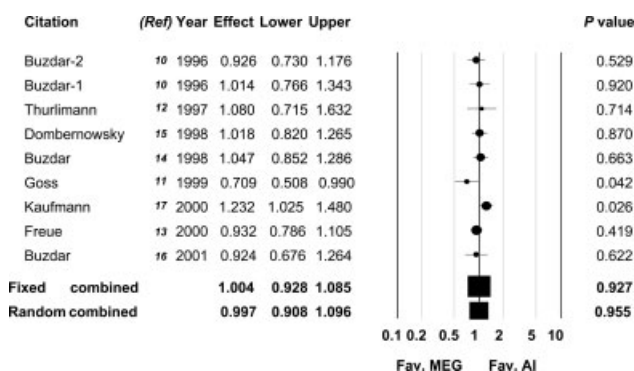


FIGURE 2. Aromatase inhibitor (AI) versus megestrol acetate (MEG): time to disease progression relative risk (RR) (3908 patients). Ref: reference; Effect: RR; Fixed: fixed-effect model; Random: random-effect model; Fav.: favors.

= 1.41; 95% CI, 0.99–2.00 [$P = 0.05$]). Conversely, AI caused significantly less toxicity than MEG in weight gain (RR = 0.18; 95% CI, 0.09–0.35 [$P = 0.001$]), dyspnea (RR = 0.20; 95% CI, 0.07–0.55 [$P = 0.008$]), and peripheral edema (RR = 0.52; 95% CI, 0.31–0.90 [$P = 0.03$]). No significant difference was seen with regard to constipation ($P = 0.38$). nsAI significantly yielded more hot flashes than MEG (RR = 1.53; 95% CI, 1.04–2.25 [$P = 0.03$]) as well as the overall comparison. nsAI led to a significantly less toxicity rate than MEG in weight gain (RR = 0.19; 95% CI, 0.09–0.42 [$P = 0.006$]), dyspnea (RR = 0.41; 95% CI, 0.25–0.66 [$P = 0.006$]), and peripheral edema (RR = 0.66; 95% CI, 0.43–1.00 [$P = 0.05$]) as well as the overall comparison. No significant differences were noted with regard to constipation ($P = 0.62$) and nausea ($P = 0.14$).

Heterogeneity analysis yielded noteworthy results. In the overall comparison, significant heteroge-

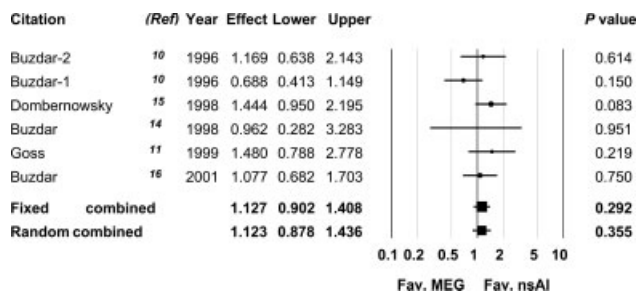


FIGURE 3. Nonsteroidal aromatase inhibitor (nsAI) versus megestrol acetate (MEG): overall response rate relative risk (RR) (2415 patients). Ref: reference; Effect: RR; Fixed: fixed-effect model; Random: random-effect model; Fav.: favors.

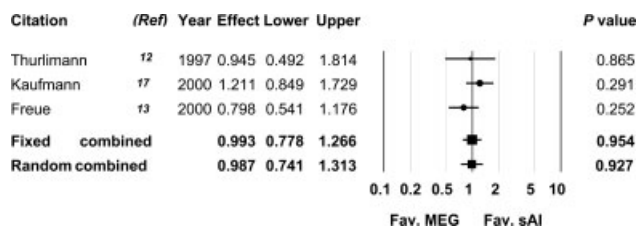


FIGURE 5. Steroidal aromatase inhibitor (sAI) versus megestrol acetate (MEG): overall response rate relative risk (RR) (1493 patients). Ref: reference; Effect: RR; Fixed: fixed-effect model; Random: random-effect model; Fav.: favors.

neity for peripheral edema, nausea, weight gain, and dyspnea was registered. The last three side effects had extremely significant heterogeneity effects ($P = 0.0005$, $P = 0.00008$, and $P < 0.00001$, respectively). When sAI were ruled out from the analysis, nausea maintained its strongly significant heterogeneity ($P = 0.0002$), whereas the other three side effects lost their significance ($P = 0.51$, $P = 0.16$, and $P = 0.31$, respectively). This phenomenon would indirectly indicate that the major contribution to the significant heterogeneity in the overall analysis regarding toxicity could be conferred by sAI.

DISCUSSION

AI have been shown to be superior to tamoxifen as initial therapy in MBC,⁴⁻⁶ whereas other investigations have evaluated their potential benefits in the adjuvant and preventive treatment of early and primary breast carcinoma.²⁵⁻²⁸ The nsAI anastrozole and letrozole and the sAI exemestane are considered to be superior to MEG for the clinical outcome of women with advanced-stage breast carcinoma who have progressed despite continuing tamoxifen treatment. It should be noted that the comparisons made so far between AI and MEG are indirect, and there have been some limitations in making such comparisons. One

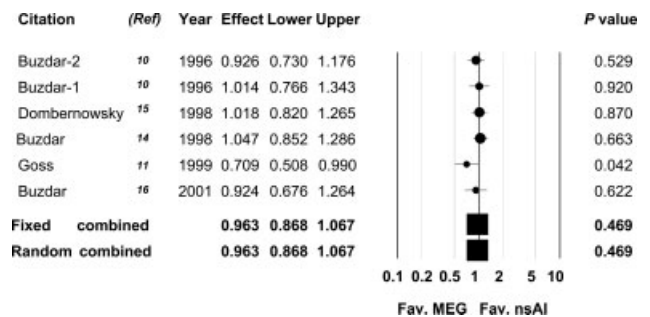


FIGURE 4. Nonsteroidal aromatase inhibitor (nsAI) versus megestrol acetate (MEG): time to disease progression relative risk (RR) (2415 patients). Ref: reference; Effect: RR; Fixed: fixed-effect model; Random: random-effect model; Fav.: favors.

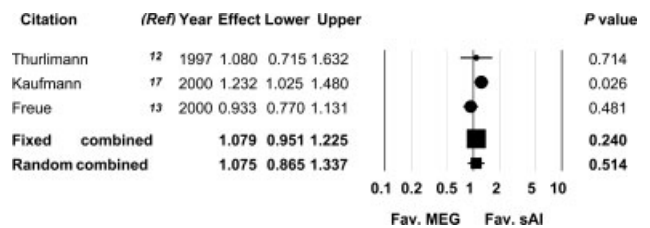


FIGURE 6. Steroidal aromatase inhibitor (sAI) versus megestrol acetate (MEG): time to disease progression relative risk (RR) (1493 patients). Ref: reference; Effect: RR; Fixed: fixed-effect model; Random: Random-effect model; Fav.: favors.

important factor to consider is that conditions across studies were different (e.g., in the length of time of drug dosing or in the characteristics of the recruits). Metaanalysis can represent a step forward, because data coming from similar and comparable studies are pooled, leading to a statistical synthesis of a quantitative summary. Therefore, it would be of great interest to see the results of a metaanalysis comparing AI with MEG with regard to their efficacy and tolerability for women with MBC after tamoxifen failure. The quantitative results and their statistical analysis are the most useful information capable of guiding physicians to shift from a standard clinical attitude to an experimental mentality.

In the reported metaanalyzed Phase III trials, ORR is often the primary study endpoint, although OS analysis is regularly performed and always represents a secondary objective. In particular, in eight studies analyzed comparing AI with MEG,^{10-13,15-17} ORR was considered the primary endpoint, whereas in one study only,¹⁴ both ORR and TTP were regarded as primary endpoints. Whether overall survival can represent the most appropriate endpoint for evaluating the superiority of experimental treatments over standard therapy in patients with MBC remains controver-

TABLE 3
Combined Results of Pooled Analysis (Method A): Secondary End-Points

Outcome	Events		RR (95% CI)	Overall effect of (chi-square)	Heterogeneity test (P value)
	Treated	Control			
AI vs. MEG					
Hot flashes	228/1942	139/1966	1.64 (1.23–2.18)	$P = 0.004$	12.19 (0.14)
Constipation	121/1575	122/1609	0.80 (0.47–1.35)	$P = 0.38$	11.00 (0.09)
Nausea	274/1851	189/1880	1.41 (0.99–2.00)	$P = 0.05$	26.14 (0.0005)
Peripheral edema	109/1485	164/1477	0.52 (0.31–0.90)	$P = 0.03$	12.74 (0.047)
Weight gain	40/1228	143/1228	0.18 (0.09–0.35)	$P = 0.001$	26.23 (0.00008)
Dyspnea	118/1851	274/1880	0.20 (0.07–0.55)	$P = 0.008$	80.24 (< 0.00001)
nsAI vs. MEG					
Hot flashes	157/1209	102/1206	1.53 (1.04–2.25)	$P = 0.03$	8.38 (0.13)
Constipation	118/1209	112/1206	1.07 (0.77–1.48)	$P = 0.62$	5.99 (0.31)
Nausea	213/1209	160/1206	1.40 (0.85–2.31)	$P = 0.14$	24.61 (0.0002)
Peripheral-edema	107/1209	154/1206	0.66 (0.43–1.00)	$P = 0.05$	5.96 (0.31)
Weight gain	21/861	103/871	0.19 (0.09–0.42)	$P = 0.006$	2.33 (0.51)
Dyspnea	117/12090	249/1206	0.41 (0.25–0.66)	$P = 0.006$	7.85 (0.16)

RR: relative risk; 95% CI: 95% confidence interval; chi-square: chi-square test; AI: aromatase inhibitors; MEG: megestrol acetate; nsAI: non-steroidal aromatase inhibitors.

sial. The FDA considers survival and quality of life (QOL) benefit the cornerstone for approval of new anticancer drugs in the U.S., whereas the EMEA accepts a prolongation in TTP as a primary requirement for new drug registration in the European Union. Although the date of disease progression may be dependent on the evaluation methods and schedules used and by knowledge of the therapy received, TTP as a study endpoint might be regarded as the most sensitive parameter to assess the efficacy of a new drug in patients with advanced-stage disease, especially when the TTP increase is associated with an ORR increase and/or with improvement in QOL. We chose TTP as the primary end point because in MBC, survival estimation could be affected by several factors such as previous or subsequent chemotherapy or hormonal treatments or crossover design.²⁹

The impact of AI as second-line therapy in MBC has been already investigated in a systematic review²⁰ with results supporting the superiority of these drugs over MEG. However, Messori et al.²⁰ published this metaanalysis of survival data from only three randomized trials.^{14,15,17} The authors pooled individual patient data from the North American and European trials of anastrozole,¹⁴ letrozole,¹⁵ and exemestane¹⁷ compared with MEG. The trial of letrozole versus MEG by Buzdar et al.¹⁶ was not included because it was published after completion of the Messori et al. metaanalysis. This analysis found that treatment with AI compared with MEG prolonged survival, with an RR of death of 0.79 (95% CI, 0.69–0.91; $P = 0.0011$). Our analysis of abstracted data from nine trials using AI as a second-line endocrine option after tamoxifen failure

in comparison to MEG did not detect a statistically significant improvement in ORR or TTP. Stratifying for type of AI (sAI and nsAI), no significant difference in efficacy was observed between the two groups. Whatever method was applied (Method A or Method B), this systematic review suggests that AI do not confer any added benefit when compared with MEG in terms of ORR or TTP. We would have expected to see relatively little heterogeneity within each trial's results, with most of the heterogeneity being observed between trials dissimilar with respect to the key characteristics. No significant heterogeneity was checked concerning each trial's interaction with Method A and Method B.

Thromboembolic phenomena, weight gain, dyspnea, hypertension, edema, sweating, and vaginal hemorrhage are all observed more commonly in MEG-treated patients compared with those receiving AI. Conversely, the most common adverse event of the third-generation inhibitors are nausea, emesis, hot flashes, fatigue, diarrhea, and headache. There have been no direct comparisons concerning toxicity among anastrozole, letrozole, and exemestane but indirect comparisons have demonstrated that these three agents are generally well tolerated, and the incidence of side effects is reported to be similar. However, exemestane treatment is also associated with weight gain, which may be due to its steroidal structure. In our pooled analysis, we chose the most frequently reported side effects, to obtain reliable comparisons of toxicity caused by AI with that caused by MEG. Our findings resemble those already reported in the literature, with weight gain, dyspnea, and edema

being more frequent with the use of MEG whereas hot flashes and nausea (borderline significance) were more represented with the use of AI. It is noteworthy that when steroidal AI were excluded from the analysis, nausea maintained its strongly significant heterogeneity, whereas weight gain, dyspnea, and peripheral edema lost their significance. This phenomenon would indirectly assess that the major contribution to the significant heterogeneity in the overall analysis regarding toxicity could be conferred by steroidal AI. In fact, anastrozole and letrozole generally exhibit negligible steroid-like effects, whereas the androgenic properties of exemestane may be a possible drawback and may warrant caution, especially if prolonged treatment is envisaged. It is also important to note that the assessment of toxicity in these metaanalyzed trials is confounded by the finding that the patients were no longer taking tamoxifen. In these studies, the discontinuation rate, which can be seen as a surrogate for overall toxicity, has been reported to be lower with AI than with MEG.

Lacking the strength of evidence for a benefit by AI compared with MEG, it would be critical to reanalyze the cost-effectiveness analyses performed for AI versus MEG as second-line ET of MBC, which have produced controversial results. For example, anastrozole and exemestane have been considered appropriate choices compared with MEG for second-line hormonal treatment of MBC even after sensitivity analysis testing.³⁰ Conversely, letrozole has been reported to have comparable overall costs and anastrozole to be slightly more costly than MEG while providing at least equivalent quality-adjusted disease progression-free survival.³¹ These data were derived from the findings that anastrozole and exemestane improved survival and letrozole prolonged time to treatment failure compared with MEG in this clinical setting.

Based on the presented results, AI appear to be equivalent to MEG as a second-line endocrine option in MBC, because no significant benefit in terms of ORR or TTP was observed using the inhibitors. Concerning the toxicity profile, sAI should be distinguished from nsAI before making any comparison with MEG. These findings should be taken into account in the oncology practice during the clinical decision-making process.

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