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Aromatase inhibitors versus tamoxifen for management of postmenopausal breast cancer in the advanced disease and neoadjuvant settings☆

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Abstract

The third-generation aromatase inhibitors anastrozole, exemestane and letrozole have become firmly established as the agents of choice in patients with tamoxifen-resistant tumors. Large, well-conducted, double-blind clinical trials directly comparing the non-steroidal aromatase inhibitors anastrozole and letrozole with tamoxifen in the advanced disease setting have matured. Based on these trials, there is sufficient evidence to choose one of these agents over tamoxifen because of a superior time to disease progression and acceptable toxicity which includes a lower incidence of thromboembolic complications. Information for the steroidal aromatase inhibitor exemestane will be forthcoming from a phase III trial which has completed accrual. Consistent with the findings in the advanced disease setting, a double-blind trial comparing letrozole with tamoxifen in the neoadjuvant setting revealed superiority for letrozole in terms of clinical response rate. This provides a strong impetus for further study of the aromatase inhibitors in the preoperative setting.

Keywords: Aromatase inhibitors; Anastrozole; Exemestane; Letrozole; Tamoxifen; Clinical trials

1. Introduction

It has been a quarter century since tamoxifen emerged as the endocrine agent of choice for postmenopausal women with metastatic carcinoma of the breast. Prior to the introduction of tamoxifen, the standard of treatment was high-dose estrogens. The acceptance of tamoxifen as preferable to estrogen therapy was based not on a superior efficacy but rather improved tolerability as was demonstrated in phase III trials [1,2]. In our trial, we documented a significantly higher incidence of serious toxicity, defined as severe nausea or emesis, moderate to severe edema, congestive heart failure or phlebitis for patients receiving diethylstilbestrol (DES) compared with tamoxifen [1]. An update of this trial performed after 95% of the patients had died revealed no significant difference between the two agents in terms of response rates and time to progression [3]. Survival, however, was modestly but significantly longer for women initially treated with DES (adjusted $P = 0.039$) rather than tamoxifen with median survivals of 3.0 years versus 2.4 years and 5-year survivals of 35 and 16%, respectively. Thus, the major change in clinical practice of utilizing tamoxifen as the agent of choice in metastatic disease was based on superior tolerability of this agent relative to estrogen therapy.

The introduction of the third-generation aromatase inhibitors, viz. the non-steroidal agents anastrozole and letrozole and the steroidal agent exemestane, into clinical practice began with their evaluation in the setting of tamoxifen-resistant disease. Phase III clinical trials in this setting comparing these agents with megestrol acetate demonstrated not only improved tolerability, but also improved efficacy in outcome parameters for the three aromatase inhibitors [4–6]. Based on these phase III studies, the third-generation aromatase inhibitors replaced megestrol acetate as the agent-class of choice in women who have experienced disease progression on tamoxifen and one could choose either a non-steroidal or a steroidal agent. Lending support for the enthusiasm for use of the third-generation aromatase inhibitors were previous phase III trials evaluating first and second-generation agents. The second-generation aromatase inhibitor fadrozole was compared with megestrol acetate in two multiinstitutional double-blind prospective randomized trials and the outcome parameters of response rate, time to progression and survival were not significantly different [7]. On the other hand, letrozole at the currently

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recommended dose of 2.5 mg daily was found to be significantly superior to the first-generation aromatase inhibitor aminoglutethimide in terms of time to progression, time to treatment failure and overall survival [8].

Investigation of aromatase inhibitors has moved into disease settings in which the patients' tumors are not resistance to tamoxifen. The purpose of this review was to examine the main body of evidence addressing the therapeutic value of the third-generation aromatase inhibitors relative to tamoxifen in the advanced disease and neoadjuvant settings. It must be emphasized that the goal of this exercise was to examine for consistency across well-conducted randomized phase III trials and that direct cross-trial comparisons are not intended or appropriate.

2. Materials and methods

The materials reviewed include the findings of three randomized phase III clinical trials: two trials compared anastrozole with tamoxifen and one trial compared letrozole with tamoxifen. The two trials comparing anastrozole with tamoxifen are the tamoxifen or arimidex randomized group efficacy and tolerability (TARGET) trial that was conducted at 83 sites in Europe, Australia, New Zealand, South America and South Africa [9] and the North American trial (NAT) that was conducted at 97 sites in the US and Canada [10]. These two trials were designed for a later combined analysis that has been reported by Bonneterre et al. [11]. Mouridsen et al. [12] reported the results of their randomized trial comparing letrozole and tamoxifen that was conducted at 201 centers in 29 countries. In addition to these three phase III trials, a randomized phase II trial of exemestane and tamoxifen is only commented upon as no phase III trial data are currently available. All of these trials are reviewed in substantial detail by other authors in this issue.

The unadjusted progression hazard ratio (aromatase inhibitor:tamoxifen) and its corresponding two-sided 95% confidence interval were taken from the publication of the trial results. A point and interval estimate of the difference in response rates among treatment groups within a given trial and the difference in the proportion of patients who reported a particular toxicity within a given trial were calculated by using the properties of the binomial distribution.

3. Pivotal trials in advanced breast cancer

A major strength of these three pivotal trials comparing anastrozole or letrozole with tamoxifen [9,10,12] is that they were double-blind, multi-center and multi-national phase III clinical trials. The trials differed in terms of whether they were designed to demonstrate equivalency or superiority, the patient population accrued, their definition of time to progression, and whether there was the option to crossover to the alternative study treatment at the time of progression.

The two anastrozole versus tamoxifen trials [9,10] were designed as equivalency trials with the primary endpoints being time to progression (time from randomization to objective disease progression or death, whichever came first) and objective response rate [complete response (CR) plus partial response (PR), according to UICC criteria, on two consecutive assessments at least 4 weeks apart]. Crossover to the alternative regimen was not a part of the trial design. The trials were designed to conclude that the treatments were equivalent in terms of time to progression if a 20% or greater advantage for tamoxifen could be ruled out, and in terms of objective response rates if difference of more than 10% in favor of tamoxifen could be ruled out. An additional primary endpoint was tolerability. Secondary endpoints were time to treatment failure, response duration and clinical benefit (CR plus PR plus stable disease for at least 24 weeks) duration. A total of 1021 patients were entered on the two trials with 668 patients enrolled on TARGET and only 353 patients on NAT which was stopped early because of the rapid accrual on TARGET. These trials differ in terms of the proportion of patients with tumors known to be estrogen receptor (ER) and/or progesterone receptor (PgR) positive. Only 45% of those entered on TARGET but 89% of those on the NAT were ER and/or PgR positive. Considering these two trials combined, the proportion of patients with ER- and/or PgR-positive tumors was 60%, 14% had received prior adjuvant endocrine therapy and no one had received prior chemotherapy for advanced disease. The analysis examined for this review had been performed at a median follow-up of 18.2 months.

The letrozole versus tamoxifen trial [12] was designed as a superiority trial with the primary endpoint being time to progression. Time to progression was defined as the time from randomization to a 25% or more increase in existing lesions, appearance of new lesions, clinical deterioration due to breast cancer, death due to breast cancer, or death of unknown cause while receiving treatment or within 6 weeks of discontinuing treatment. An optional crossover to the alternative treatment was available maintaining the double-blind aspect. The trial was powered to identify a progression hazard ratio (letrozole:tamoxifen) of less than 0.80. Secondary endpoints were objective response rates, duration of response, clinical benefit duration, time to treatment failure, time to response, number of deaths and overall survival. A total of 939 patients were entered. The proportion of patients with ER- and/or PgR-positive tumors was 66%. Prior adjuvant antiestrogen therapy had been given to 18% of patients and 10% had received chemotherapy for advanced disease. The analysis examined for this review had been performed at a median study duration of about 18 months.

The combined cohort of anastrozole trials and the letrozole trial in advanced breast cancer appear similar in terms of their double-blind design, number of patients enrolled, proportion of patients with hormone receptor-positive disease, and maturity of data. The trials differed in terms of their objectives (equivalency versus superiority), definition

of time to progression and option for crossover to the alternative study agent at progression.

4. Outcomes in pivotal trials in advanced breast cancer

Time to progression was a common primary endpoint for both the anastrozole and letrozole trials. Fig. 1 displays the point estimates for the progression hazard ratio (aromatase inhibitor:tamoxifen) with 95% confidence intervals for both the intent-to-treat and ER- and/or PgR-positive cohorts in the combined anastrozole versus tamoxifen trials and in the letrozole versus tamoxifen trial. In each instance, the estimate favors the aromatase inhibitor. In the intent-to-treat analysis, anastrozole was not worse than tamoxifen and letrozole was better than tamoxifen. Considering the hormone receptor-positive cohorts, both anastrozole and letrozole were superior to that of tamoxifen in that the 95% confidence interval for the progression hazard ratio did not include 1.0. From these data, it can be concluded that there is a consistency of findings that these aromatase inhibitors are superior to tamoxifen in terms of an increased time-to-disease progression.

Point and interval estimates of the differences in overall response rates and clinical benefit rates are presented in Fig. 2. Letrozole was found to have significantly higher rates than tamoxifen (the 95% confidence intervals of the difference in rates do not cross zero). The overall response rate for anastrozole appears to be similar to that for tamoxifen while the clinical benefit rate appears to be somewhat better for anastrozole relative to tamoxifen. Thus, there is a consistency that these aromatase inhibitors are superior or at least similar to tamoxifen in terms of overall response and clinical benefit rates.

Toxicity is an important element in determining the therapeutic index. Fig. 3 presents the point and interval estimates of the differences in incidence of three selected adverse events, viz. thromboembolic events, nausea and hot flushes. The incidences of nausea and hot flushes were not found to differ between the aromatase inhibitors and tamoxifen.

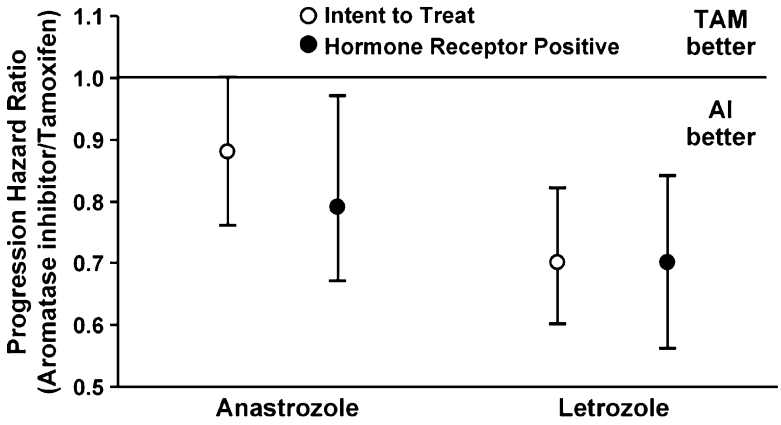

Fig. 1. Estimated progression hazard ratios (aromatase inhibitor:tamoxifen) and corresponding 95% confidence intervals in intent-to-treat and hormone receptor-positive cohorts of the pivotal trials in advanced breast cancer comparing anastrozole and letrozole with tamoxifen. Adapted from [11,12].

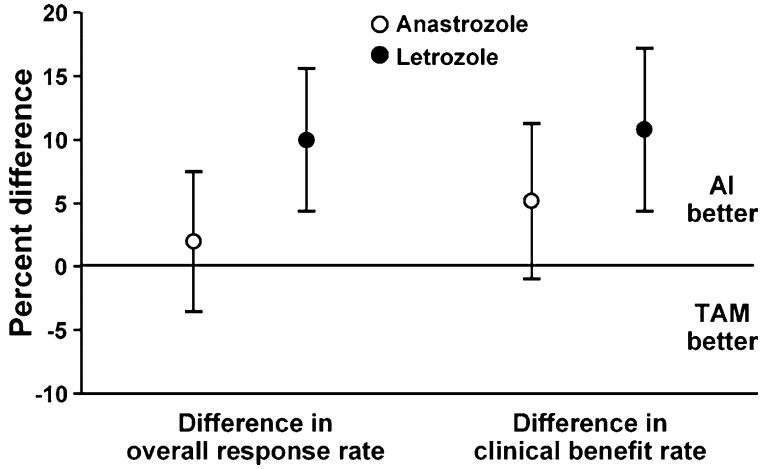

Fig. 2. Differences (aromatase inhibitor minus tamoxifen) in overall response rates and clinical benefit rates with 95% confidence intervals in pivotal trials in advanced breast cancer. Adapted from [11,12].

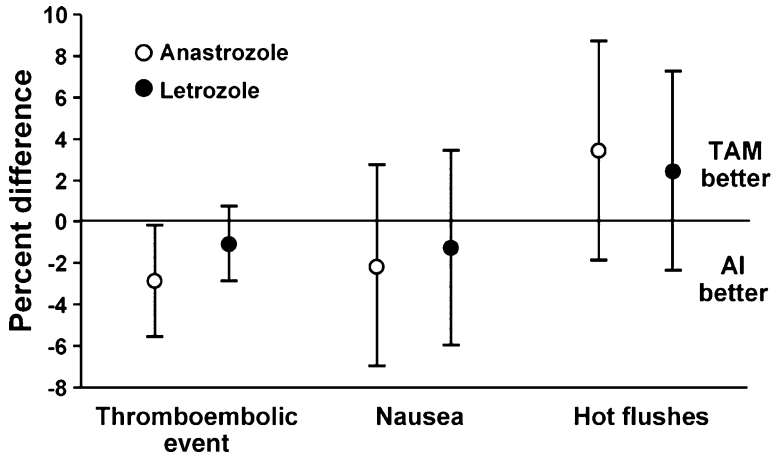

Fig. 3. Differences (aromatase inhibitor minus tamoxifen) in the incidence of selected adverse events and 95% confidence interval in the intent-to-treat cohort of the pivotal trials in advanced breast cancer comparing anastrozole and letrozole with tamoxifen. Adapted from [11,12].

Although nausea and hot flushes can be very troublesome, thromboembolic events can be life-threatening and the lower incidence of this adverse event favors the aromatase inhibitors over tamoxifen. A case can be made that even greater insight into adverse events can be obtained from large adjuvant trials where the interpretation is less likely to be confounded by signs and symptoms related to disease. In this regard, the recently reported arimidex, tamoxifen alone and in combination (ATAC) trial [13] provides substantial information relating to the incidences of adverse events seen with one of the aromatase inhibitors under consideration, anastrozole, relative to tamoxifen. In this large study involving 9366 patients, anastrozole was associated with a significantly lower incidence of hot flushes, vaginal discharge, vaginal bleeding, ischemic cerebrovascular events, any venous thromboembolic events, deep venous thromboses including pulmonary emboli and endometrial cancer. Alternatively, tamoxifen was associated with a significantly lower incidence of musculoskeletal disorders and fractures. There was no significant difference between anastrozole and tamoxifen in incidence of nausea and vomiting, fatigue/tiredness, mood disturbances, ischemic cardiovascular disease or cataracts. Thus, based on the findings from the pivotal trials in advanced disease and the ATAC trial [13] one can conclude that the adverse event profile for the non-steroidal aromatase inhibitors does not detract from the superiority seen in time to progression. The lower incidence of the potentially serious thromboembolic events adds to the therapeutic index favoring the aromatase inhibitors over tamoxifen in the advanced disease setting.

A randomized phase II trial of the steroidal aromatase inhibitor exemestane and tamoxifen conducted by the European Organization for Research and Treatment of Cancer [14] revealed a numerically higher response rate for exemestane. This result led to a phase III study comparing exemestane with tamoxifen. Accrual has been completed to this trial and results are awaited with interest.

Survival data are available for both the anastrozole and letrozole studies. The survival analyses for the TARGET and NAT are available from the US Food and Drug Administration (http://www.fda.gov/cder/foi/nda/2000/20-5415006_Arimidex_statr.pdf) and no significant difference were seen between the two agents in either study. An analysis of the survival data for the letrozole trial was presented at the San Antonio Breast Cancer Symposium in December 2001. No significant difference was seen (log-rank test $P = 0.53$). An early separation of the survival curves was identified and a Wilcoxon test, which emphasizes early events, was employed to assess survival difference but the results of this test did not achieve statistical significance with $P = 0.079$. Survival analysis is problematic in phase III trials examining a new agent in the first-line endocrine therapy setting. Fig. 4 illustrates the reality of a randomized trial evaluating two agents such as, for example, agent A representing an aromatase inhibitor and agent B representing tamoxifen. It can be seen that time to progression (TTP) is a proximate endpoint not confounded by other treatments. Whether planned, as in the case of the letrozole trial, or not, a substantial proportion of patients will be treated

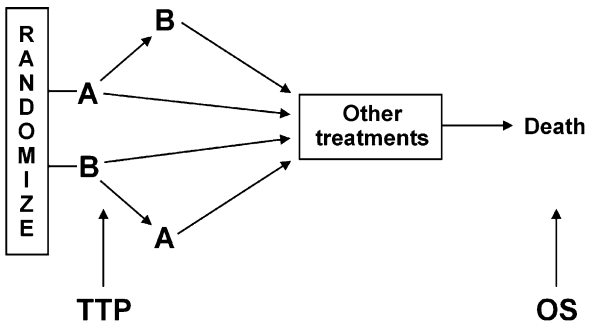

Fig. 4. Sequencing issues when evaluating survival in randomized trials comparing aromatase inhibitors with tamoxifen. TTP: time to progression; OS: overall survival.

with the alternative agent after progression. The endpoint of survival is also confounded by multiple other systemic therapies. Whereas a clearly documented survival would be of great interest, time to progression remains a valuable and valid endpoint upon which to judge the efficacy of a new endocrine therapy, in this case aromatase inhibitors, in the advanced disease setting.

5. Aromatase inhibitors versus tamoxifen in the neoadjuvant setting

A series of phase II studies of neoadjuvant endocrine therapy at the Edinburgh Breast Unit in Scotland have demonstrated the efficacy of the third-generation aromatase inhibitors anastrozole, exemestane and letrozole and suggested a higher level of efficacy than tamoxifen based on ultrasound assessment of reduction in tumor volume [15]. Eiermann et al. [16] reported what must be considered the major trial to date addressing the question of relative value of aromatase inhibitors and tamoxifen in the neoadjuvant setting. This multi-center, multi-national, double-blind, double-dummy randomized trial enrolled 334 eligible postmenopausal patients with untreated primary breast cancer and clinical stage of T2-4a-c, N0-2, M0 who were considered inoperable or not candidates for breast conserving surgery. These patients were randomized to 4 months of treatment with either letrozole or tamoxifen prior to surgery. The primary endpoint was objective response rate (CR plus PR) based on measurements made clinically by palpation of the breast. Secondary endpoints included the response rates at 4 months as determined by mammography and by ultra-sonography and the percentage of patients who underwent breast conserving surgery. Fig. 5 displays the point and interval estimates of the differences in response rates between patients randomized to letrozole and tamoxifen according to the different methods of evaluation. Although the lower bound of difference approaches zero for the

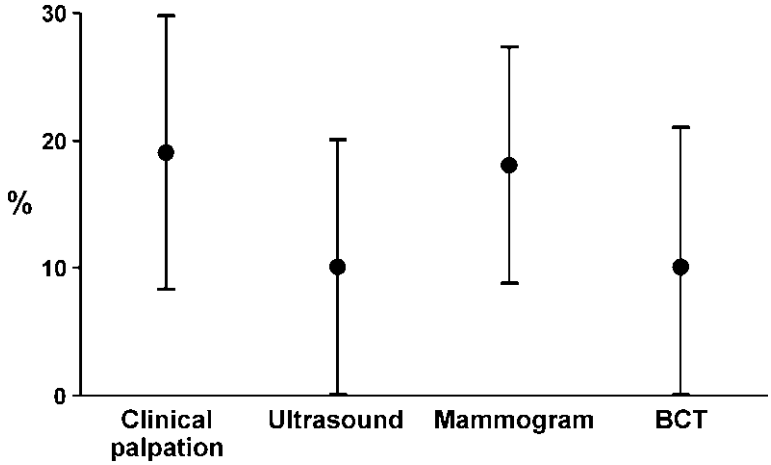

Fig. 5. Differences (letrozole minus tamoxifen) in tumor response rates by method of assessment and breast conservation therapy (BCT) rates, with 95% confidence intervals, in trial of neoadjuvant therapy with letrozole or tamoxifen. Adapted from [16].

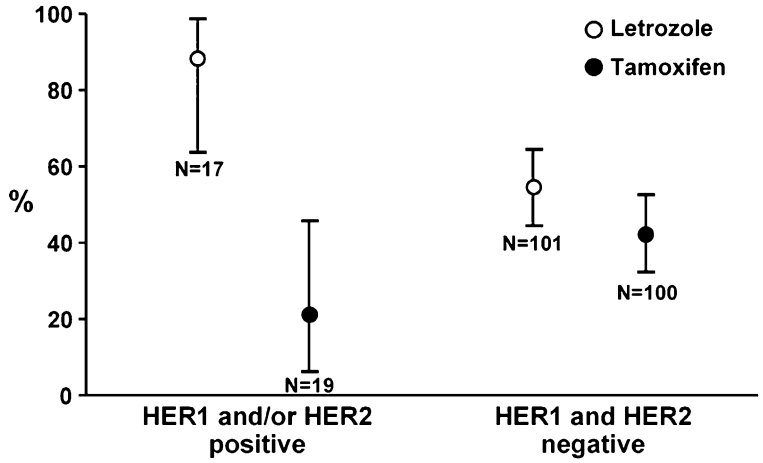

Fig. 6. Clinical response rates with 95% confidence intervals in ER-positive patients according to HER1 and HER2 status for neoadjuvant therapy with letrozole and tamoxifen. Adapted from [17].

ultrasound and the breast conserving surgery rate, there was a clear advantage for letrozole in terms of response rates based on clinical breast examination and mammographic assessment. The credibility of these findings indicating superiority for letrozole is substantially enhanced by the fact the trial was performed in a double-blind fashion.

An important aspect of the Eiermann et al. trial [16] discussed above was central laboratory testing for ER, PgR, HER1 (ErbB-1) and HER2 (ErbB-2). The impact of these markers on response was reported by Ellis et al. [17]. A patient's tumor was considered to have HER1 and/or HER2 positive (i.e. overexpressed) if immunohistochemistry was scored as 2+ or 3+. Fig. 6 displays the observed response rates, with 95% confidence intervals, according to HER1 and HER2 status for both letrozole and tamoxifen. Considering patients confirmed to be ER-positive, the difference in response were the greatest and highly statistically significant for those women whose tumors overexpressed HER1 and/or HER2 while the response rates were higher for letrozole in the HER1 and HER2 negative cohort but not significantly so. Subset analysis is of value for hypothesis generation and these findings are of greatest value in providing leads for designing future investigations into signaling pathways employed by breast cancers.

6. Conclusions

Based on well-designed, well-conducted, adequately powered, double-blind randomized clinical trials, several conclusion can be drawn with confidence regarding the role of the third-generation non-steroidal aromatase inhibitors vis a vis tamoxifen in women with breast cancer in the advanced disease and neoadjuvant settings. In advanced breast cancer, reasonable and sufficient evidence exists, based on a superior time to progression and acceptable toxicity including a lower incidence of thromboembolic events, to choose a third-generation aromatase inhibitor over tamoxifen. Determination of relative merits of the two aromatase inhibitors, anastrozole and letrozole, would require a randomized trial in which they were directly compared. Conclusions regarding the steroidal aromatase inhibitor exemestane must await the results of the phase III trial which has recently completed accrual. In the neoadjuvant setting, letrozole has demonstrated superiority against tamoxifen in a prospective randomized double-blind trial and the clinical response advantage seen with letrozole is consistent with the findings in advanced disease. The findings from this trial provide a strong impetus to further define the role of the aromatase inhibitors in the neoadjuvant setting.

References

[1] J.N. Ingle, D.L. Ahmann, S.J. Green, J.H. Edmonson, H.F. Bisel, L.K. Kvols, W.C. Nichols, E.T. Creagan, R.G. Hahn, J. Rubin, S. Frytak, Randomized clinical trial of diethylstilbestrol versus tamoxifen in postmenopausal women with advanced breast cancer, N. Engl. J. Med. 304 (1981) 16–21.

[2] H.J. Stewart, A.P.M. Forrest, J.M. Gunn, T. Hamilton, A.O. Langlands, I.J. McFadyen, M.M. Roberts, The tamoxifen trial—a double-blind comparison with stilboestrol in postmenopausal women with advanced breast cancer, in: H.T. Mouridsen, T. Palshof (Eds.), Breast Cancer: Experimental and Clinical Aspects, Pergamon Press, Oxford, 1980, pp. 83–88.

[3] P.P. Peethambaram, J.N. Ingle, V.J. Suman, L.C. Hartmann, C.L. Loprinzi, Randomized trial of diethylstilbestrol vs. tamoxifen in postmenopausal women with metastatic breast cancer. An updated analysis, Breast Cancer Res. Treat. 54 (1999) 117–122.

[4] A.U. Buzdar, W. Jonat, A. Howell, S.E. Jones, C.P. Blomqvist, C.L. Vogel, W. Eiermann, J.M. Wolter, M. Steinberg, A. Webster, D. Lee, Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials, Cancer 83 (1998) 1142–1152.

[5] P. Dombernowsky, I. Smith, G. Falkson, R. Leonard, L. Panasci, J. Bellmunt, W. Bezwoda, G. Gardin, A. Gudgeon, M. Morgan, A. Fornasiero, W. Hoffmann, J. Michel, T. Hatschek, T. Tjabbes, H.A. Chaudri, U. Hornberger, P.F. Trunet, Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate, J. Clin. Oncol. 16 (1998) 453–461.

[6] M. Kaufmann, E. Bajetta, L.Y. Dirix, L.E. Fein, S.E. Jones, N. Zilembo, J.-L. Dugardyn, C. Nasurdi, R.G. Mennel, J. Cervek, C. Fowst, A. Polli, E. di Salle, A. Arkhipov, G. Piscitelli, L.L. Miller, G. Massimini, Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial, J. Clin. Oncol. 18 (2000) 1399–1411.

[7] A.U. Buzdar, R. Smith, C. Vogel, P. Bonomi, A.M. Keller, G. Favis, M. Mulagha, J. Cooper, Fadrozole HCl (CGS-16949A) versus megestrol acetate treatment of postmenopausal patients with metastatic breast carcinoma. Results of two randomized double blind controlled multiinstitutional trials, Cancer 77 (1996) 2503–2513.

[8] M. Gershanovich, H.A. Chaudri, D. Campos, H. Lurie, A. Bonaventura, M. Jeffrey, F. Buzzi, I. Bodrogi, H. Ludwig, P. Reichardt, N. O'Higgins, G. Romieu, P. Friederich, M. Lassus, Letrozole, a new oral aromatase inhibitor: randomized trial comparing 2.5 mg daily, 0.5 mg daily and aminoglutethimide in postmenopausal women with advanced breast cancer, Ann. Oncol. 9 (1998) 639–645.

[9] J. Bonneterre, B. Thurlimann, J.F.R. Robertson, M. Krzakowski, L. Mauriac, P. Koralewski, I. Vergote, A. Webster, M. Steinberg, M. von Euler, Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the tamoxifen or arimidex randomized group efficacy and tolerability study, J. Clin. Oncol. 18 (2000) 3748–3757.

[10] J.M. Nabholtz, A. Buzdar, M. Pollak, W. Harwin, G. Burton, A. Mangalik, M. Steinberg, A. Webster, M. von Euler, Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial, J. Clin. Oncol. 18 (2000) 3758–3767.

[11] J. Bonneterre, A. Buzdar, J.-M.A. Nabholtz, J.F. Robertson, B. Thurlimann, M. von Euler, T. Sahmoud, A. Webster, M. Steinberg, Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. Results of two randomized trials designed for combined analysis, Cancer 92 (2001) 2247–2258.

[12] H. Mouridsen, M. Gershanovich, Y. Sun, R. Perez-Carrion, C. Boni, A. Monnier, J. Apffelstaedt, R. Smith, H.P. Sleeboom, F. Janicke, A. Pluzanska, M. Dank, D. Becquart, P.P. Bapsy, E. Salminen, R. Snyder, M. Lassus, J.A. Verbeek, B. Staffler, H.A. Chaudri-Ross, M. Dugan, Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer:

results of a phase III study of the International Letrozole Breast Cancer Group, J. Clin. Oncol. 19 (2001) 2596–2606.

[13] The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group, Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial, Lancet 359 (2002) 2131–2139.

[14] L. Dirix, M.J. Piccart, C. Lohrisch, L. Beex, M. Nooij, D. Cameron, L. Biganzoli, T. Cufer, C. Yague, L. Duchateau, J. Lobelle, R. Paridaens, Efficacy of and tolerance to exemestane (E) versus tamoxifen (T) in first line hormone therapy (HT) of postmenopausal metastatic breast cancer (MBC) patients (pts): a European Organisation for the Research and Treatment of Cancer (EORTC Breast Group) phase II trial with Pharmacia and Upjohn, Proc. Am. Soc. Clin. Oncol. 20 (2001) 29a.

[15] J.M. Dixon, Neoadjuvant therapy: surgical perspectives, in: W.R. Miller, J.N. Ingle (Eds.), Endocrine Therapy in Breast Cancer, Marcel Dekker, New York, 2002, pp. 197–212.

[16] W. Eiermann, S. Paepke, J. Appfelstaedt, A. Llombart-Cussac, J. Eremin, J. Vinholes, L. Mauriac, M. Ellis, M. Lassus, H.A. Chaudri-Ross, M. Dugan, M. Borgs, Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study, Ann. Oncol. 12 (2001) 1527–1532.

[17] M.J. Ellis, A. Coop, B. Singh, L. Mauriac, A. Llombert-Cussac, F. Janicke, W.R. Miller, D.B. Evans, M. Dugan, C. Brady, E. Quebe-Fehling, M. Borgs, Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for erbB-1- and/or erbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial, J. Clin. Oncol. 19 (2001) 3808–3816.