Neoadjuvant endocrine therapy for breast cancer: past, present and future

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Combined treatments together with surgery, radiotherapy, chemotherapy, and endocrine therapy have contributed substantially to the improved survival rate in breast cancer. For more than 2 decades, tamoxifen has been the standard endocrine agent for hormone receptor-positive tumors. Third-generation aromatase inhibitors have, however, now proven to be superior to tamoxifen in the adjuvant and, more recently, the neoadjuvant treatment of postmenopausal patients. They have especially improved the surgical management of large or inoperable locally advanced breast tumors. Other advantages of neoadjuvant endocrine therapy are just emerging, but there are still many unanswered questions regarding its optimal use in this setting. A need to define how to select the patients who will benefit most from these therapies, the optimal duration of treatment, the best method to evaluate the treatment response achieved, the existence of predictive factors for response, or the superiority of certain endocrine agents over others has been observed. Other questions regarding which complementary local and systemic treatments should be administered after neoadjuvant endocrine therapy or which efficacy endpoints should be evaluated in clinical trials are also of interest. To answer as many of these questions as possible, we have carried out a critical analysis of the current literature on the use of endocrine therapy in the neoadjuvant setting of breast cancer. In this review, we outline the rationale for its use, and consider data published to date to further clarify how to optimize its administration. ***Anti-Cancer Drugs*** **19:339–347 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Endocrine therapy for breast cancer has been used since the last century, as it was shown that oopherectomy caused regression of advanced breast cancer [1]. Later, endocrine therapies including adrenalectomy and hypophysectomy, and the use of estrogens and androgens, were developed. In the 1970s, tamoxifen became the standard treatment for hormone receptor (HR)-positive breast tumors and has been used for more than two decades [2,3]. Nowadays, it is known that tamoxifen may reduce the annual breast cancer death rate by 31% in estrogen receptor (ER)-positive tumors [4].

As estrogens are the major hormones supporting the growth of breast cancer, the goal of endocrine therapy is to block the cell growth pathways that are stimulated after ER activation. This objective can be achieved either by inhibiting estrogen from binding to its specific receptor or by inhibiting its synthesis. Tamoxifen is a competitive inhibitor of estradiol binding to the ER. It has mixed agonist and antagonist effects. Although the agonist effect may be beneficial because it prevents bone demineralization, it can also lead to significant side effects such as endometrial cancer or thromboembolism [5]. Other agents that are currently playing a pivotal role in endocrine therapy include aromatase inhibitors, which act throughout the estrogen synthesis pathway. After menopause, estrogens are mainly synthesized outside the ovaries by the conversion of androgenic substrates via the aromatase enzyme. Aromatase inhibitors inactivate this enzyme thereby decreasing the synthesis of estrogens. According to the chronological order in which they were developed, aromatase inhibitors are classified as first-generation, second-generation, and third-generation compounds. First-generation compounds are represented by aminoglutethimide, but its use is limited owing to its toxicity and lack of selectivity [6]. Second-generation aromatase inhibitors, such as formestane and fadrozole, were substituted by third-generation compounds, which showed greater potency and specificity along with oral availability and reduced side effects [7]. These third-generation compounds are currently in use today and may

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be further classified into type 1 inhibitors, such as exemestane, which is steroidal and binds irreversibly to its site of action, and type 2 inhibitors, such as anastrozole and letrozole, which are nonsteroidal and bind reversibly to the enzyme [8].

To date, third-generation aromatase inhibitors have been demonstrated to be superior to tamoxifen in the treatment of postmenopausal women with breast cancer in the metastatic and the adjuvant setting of the disease. In the metastatic setting, several prospective randomized trials have compared anastrozole, letrozole, or exemestane with tamoxifen as first-line treatment and have demonstrated statistically significant clinical benefits in favor of aromatase inhibitors [9–13]. In the adjuvant setting, at least three randomized studies have shown a benefit from switching to an aromatase inhibitor after 2–3 years of tamoxifen [14–16]; and two studies have demonstrated the superiority of aromatase inhibitors over tamoxifen when administered as initial therapy in the adjuvant setting [17,18]. As a consequence, the American Society of Clinical Oncology guidelines recommend that, to lower the risk of tumor recurrence, adjuvant therapy for postmenopausal women with HR-positive breast cancer should include an aromatase inhibitor [19].

Neoadjuvant therapy, also called primary, induction, or preoperative therapy, is increasingly used in the treatment of breast cancer. Recently, an international expert panel has updated the indications for the neoadjuvant systemic treatment of operable breast cancer [20]. Although it was already widely accepted that neoadjuvant treatment was the standard treatment for locally advanced breast cancer, they also considered that it should be a standard option for primary operable disease. This is because of the main clinical advantages of neoadjuvant therapy, which has been demonstrated to reduce tumor size, thereby allowing the resection of previously inoperable tumors, or to enhance the chances for carrying out breast-conserving surgery (BCS) in large operable tumors initially destined for mastectomy, without compromising survival rates [21]. Other than surgical improvements, neoadjuvant therapy offers additional advantages. Although adjuvant therapy requires much larger patient numbers and longer follow-up periods to ascertain its effectiveness, tumor responses following neoadjuvant therapy can be directly evaluated. It therefore permits the prediction of subsequent sensitivity to a given agent in the adjuvant setting, or an early change of therapy in the case of resistance [22]. It also provides insights into the molecular mechanisms of breast cancer and corresponding interactions with different anticancer compounds, as well as the opportunity to search for molecular biomarkers that might be of value in predicting outcome. As a result, information obtained from neoadjuvant therapy is expanding our knowledge ultimately to ensure the most appropriate choice of therapy for each patient.

Administration of endocrine therapies preoperatively has proven effectiveness in HR-positive postmenopausal women [23–27]. Many unanswered questions are however, still present concerning their use in this setting such as how to select the patients who will benefit most from these therapies, the optimal duration of treatment, the best method to evaluate the treatment response achieved, the existence of predictive factors for this response or the superiority of certain endocrine agents over others. To answer as many of these questions as possible, we have carried out a critical analysis of the current literature on the use of endocrine therapy in the neoadjuvant setting of breast cancer.

Which data support the use of neoadjuvant endocrine therapy in patients with breast cancer?

Tamoxifen was first tested as primary therapy in elderly or frail patients with the intention of avoiding surgery rather than as a neoadjuvant agent. Three important randomized trials compared tamoxifen alone versus surgery alone [28–30]. Generally, the conclusion drawn from these trials was that tamoxifen alone led to a higher rate of local failure, and that the optimal treatment for elderly patients with operable breast cancer should, whenever possible, include a surgical procedure. This conclusion was further supported by other trials where tamoxifen alone was compared with surgery followed by tamoxifen [31–33]. None of these studies, however, showed any overall survival differences between tamoxifen, surgery or the combination of both, and hence hormone therapy alone remains as an ethical approach in those patients for whom surgery is not recommended. Subsequent research has focused on whether neoadjuvant endocrine therapy was able to improve surgical outcomes rather than to replace it.

Only one study reported direct comparison of neoadjuvant endocrine therapy versus neoadjuvant chemotherapy in postmenopausal HR-positive patients with breast cancer [34]. Patients were assigned to receive either chemotherapy (four cycles of doxorubicin and paclitaxel every 3 weeks) or endocrine therapy with an aromatase inhibitor (anastrozole or exemestane for 3 months). Objective responses and disease-free survival at 3 months were similar between both treatment groups, although a tendency toward more breast-conserving surgeries was observed in the endocrine treatment arm (33 versus 24%, $P = 0.058$). The authors concluded that neoadjuvant endocrine therapy was an effective and safe alternative to neoadjuvant chemotherapy in postmenopausal women with HR-positive breast cancer.

Unfortunately, there are no published studies that compare preoperative endocrine therapy followed by surgery versus surgery followed by endocrine therapy, in the way that the National Surgical Adjuvant Breast and

Bowel Project B-18 trial did successfully with chemotherapy [35]. Only one study [36] partially achieved this by comparing neoadjuvant chemoendocrine with adjuvant chemoendocrine therapy. Treatment assignment was carried out according to menopausal and HR status. ER-negative patients received chemotherapy, whereas ER-positive patients received goserelin if they were premenopausal or formestane if they were postmenopausal. No improvement in survival benefit was seen between the neoadjuvant and adjuvant approaches.

In summary, it is well established that adjuvant endocrine therapy is the most effective adjuvant treatment for postmenopausal women with ER-positive breast cancer [4], and it is recognized that neoadjuvant therapy is as safe and effective as the same treatment administered postoperatively [20,35,37]. In spite of the lack of specific data with endocrine therapies, it would be logical to assume that neoadjuvant endocrine therapy should be at least as effective as chemotherapy in postmenopausal women with ER-positive breast cancer.

Which patients with breast cancer should receive neoadjuvant endocrine therapy?

Nowadays, the routine administration of neoadjuvant endocrine therapy is acceptable for postmenopausal patients with ER-positive tumors that are large but operable or locally advanced ($T \geq 3$ cm). In these patients, neoadjuvant endocrine therapy has been demonstrated to improve surgical outcome [23–26]. Neoadjuvant endocrine therapy is also recommended for elderly or frail patients for whom chemotherapy, surgery, or even radiotherapy is not suitable, but who nevertheless require a control of their breast cancer [38].

Current evidence to date indicates that HR status (and especially ER status) should be the most important criterion by which to select the patients who will benefit most with neoadjuvant endocrine therapy. Within ER-positive patients, those with an ER Allred scored of 6 and more are most likely to respond [24,26,39,40]. This enhanced responsiveness in tumors with higher HR levels has been demonstrated with all endocrine compounds (tamoxifen, letrozole, anastrozole, and exemestane). It is, however, believed that aromatase inhibitors are able to induce response in tumors with even lower levels of ER, whereas tamoxifen does not [39].

It is hypothesized that for some groups of the population with ER-positive tumors for which chemotherapy provides little benefit, endocrine therapy may be more effective [41]. Recently, the National Surgical Adjuvant Breast and Bowel Project and Genomic Health Inc. established a 21-gene expression assay that was used to demonstrate that approximately 50% of women with node-negative HR-positive breast cancer had an excellent prognosis after being treated with adequate local treatment and tamoxifen, and that they were unlikely to derive any further benefit from chemotherapy [42]. In this regard, the Z1031 trial designed by the American College of Surgeons Oncology Group will try to identify the patient population in which the response to aromatase inhibitors would be sufficiently high to be competitive against chemotherapy. This should identify additional patient groups, which would benefit from neoadjuvant endocrine therapy.

No data available to support the use of neoadjuvant endocrine therapy in premenopausal healthy women with ER-positive breast cancer outside clinical trials are present. Clinical trials that are assessing whether administration of an aromatase inhibitor in addition to ovarian suppression will improve the outcome for these women are, however, ongoing [43].

Has any endocrine agent demonstrated superiority in the neoadjuvant setting of breast cancer?

To date, five randomized clinical trials have compared the efficacy of third-generation aromatase inhibitors with tamoxifen, and all of them have reported benefits by different clinical endpoints in favor of the aromatase inhibitor arm (Table 1). In the first clinical trial reported [23], 4 months of letrozol (2.5 mg/day) was compared with tamoxifen (20 mg/day) as neoadjuvant treatment for women with HR-positive tumors that were inoperable or who were ineligible for BCS. Letrozole was superior to tamoxifen in terms of clinical and radiologic response rates as well as the rate of BCS.

Another three trials compared the efficacy of anastrozole with tamoxifen. Two of them have been reported in full [24,25], and the third has been published in abstract form [40]. The IMPACT (Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen) trial [24] randomized operable or locally advanced ER-positive patients to receive anastrozol (1 mg/day), tamoxifen (20 mg/day), or a combination of both over a period of 3 months. The overall, response rates were not significantly different between the three treatment arms; however, in those patients assessed to require mastectomy at baseline, 46% of patients in the anastrozole arm were able to undergo BCS, whereas only 22% of patients in the control arm could do so ($P = 0.03$). The Pre-Operative 'Arimidex' Compared with Tamoxifen trial [25] compared anastrozole with tamoxifen, but in this trial patients could receive chemotherapy along with the endocrine treatment. Initial results revealed that response rates were higher with anastrozole than with tamoxifen in those patients receiving a chemoendocrine treatment, and this was so when response was evaluated clinically (49 versus 36%, $P = 0.04$) or by ultrasound (37 versus 24%, $P = 0.03$). Moreover, significantly more patients were

Table 1 Main randomized trials comparing third-generation aromatase inhibitors with tamoxifen in the neoadjuvant treatment of breast cancer

Trial	Patients	Treatment	Response rate			Surgical improvement
			Clinical	Mammography	Ultrasound	
P024 [23,39]	*n*=337; HR+	T: 20 mg/day	36%	16%	25%	35%
	Inoperable or ineligible for BCS	L: 2.5 mg/day	55%	34%	35%	45%
	4 months of treatment	*P* value T versus L	<0.001	<0.001	0.042	0.022
IMPACT [24]	*n*=330; ER+	T: 20 mg/day	36%	–	20%	31% 22%[b]
	Postmenopausal, operable or LABC	A: 1 mg/day	37%	–	24%	44% 46%[b]
	3 months of treatment	A+T	39%	–	28%	24% 26%[b]
		P value T versus A	NS	–	NS	NS 0.03
PROACT [25]	*n*=451; HR+	T: 20 mg/day	40%	–	27%	31%
	Large, operable (T2/3, N0–2, M0) or potentially operable (T4b, N0-2, M0)	A: 1 mg/day	50%, *P*=0.08	–	36%, *P*=0.07	43%, *P*=0.04
	3 months of treatment	T+CT	36%	–	24%	–
		A+CT	49%, *P*=0.04	–	37%, *P*=0.03	–
Semiglazov *et al.*[a] [40]	*n*=87; HR+	T: 20 mg/day	44%	36%	30%	28%
	T2N1, T3N0–1, T4N0M0	A: 1 mg/day	70%	56%	44%	42%
	3 months of treatment	T+A	49%	40%	32%	30%
		P value T versus A	0.048	0.058	0.072	0.056
Semiglazov *et al.*[a] [26]	*n*=151; ER+	T	40%	37%	37%	20%
	3 months of months	E: 25 mg/day	76%	64%	61%	37%
		P value T versus E	0.05	0.082	0.092	0.05

A, anastrozole; BCS, breast-conserving surgery; CT, chemotherapy; E, exemestane; ER+, estrogen receptor-positive; HR+, hormone receptor-positive; IMPACT, Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen; L, letrozole; LABC, locally advanced breast cancer; NS, not significant; PROACT, Pre-Operative 'Arimidex' Compared with Tamoxifen; T, tamoxifen.

[a]Preliminary data.

[b]Surgeon assessment of feasible breast-conserving surgery.

able to undergo BCS if treated with anastrozole rather than with tamoxifen (43 versus 31%, $P = 0.04$). The third trial [40] compared anastrozole with tamoxifen or the combination of both in postmenopausal HR-positive women; and the aromatase inhibitor again achieved a significantly improved clinical response rate in comparison with tamoxifen (70 versus 44%, $P = 0.048$).

Lastly, one randomized trial of exemestane versus tamoxifen has been published to date in abstract form [26]. A total of 151 patients with ER-positive breast cancer were randomly assigned to receive exemestane (25 mg/day) or tamoxifen for 3 months. The exemestane arm showed significantly higher clinical response (76 versus 40%, $P = 0.05$) and BCS rates (37 versus 20%, $P = 0.05$) than the tamoxifen arm.

Regarding safety issues, the third-generation aromatase inhibitors seem to be well tolerated with a low incidence of serious short-term adverse events. Some of the most common events include headaches, hot flushes, or vaginal dryness. Few data regarding long-term effects of these compounds are observed, but they may include a higher incidence of osteoporosis and fractures in comparison with tamoxifen [11,44]. Also, they may provoke different effects on lipid profiles that need further investigation. Unlike tamoxifen, there is no evidence of an increased risk of uterine carcinoma or venous thromboembolism with third-generation aromatase inhibitors [45].

In summary, these trials have clearly demonstrated the superiority of aromatase inhibitors over tamoxifen in the neoadjuvant treatment of breast cancer, and have established rates of BCS between 40 and 50%. Unfortunately, there are no large, direct clinical studies that compare third-generation aromatase inhibitors among themselves. Indirect comparisons among different trials would not be appropriate owing to the wide variability of selection criteria and treatment schedules used in those trials. Results are pending for the American College of Surgeons Oncology Group Z1031 trial, in which the efficacy of neoadjuvant exemestane (25 mg/day), anastrozole (1 mg/day), and letrozole (2.5 mg/day) is being compared in postmenopausal women with breast cancer [46].

Which is the optimal duration of neoadjuvant endocrine therapy?

The optimal duration of neoadjuvant endocrine therapy has not yet been established [20]. At this point in time, few clinical trials with endocrine therapies have examined this question in the neoadjuvant setting, and no definitive conclusions have be drawn from any of them.

In a small clinical trial [47], 33 postmenopausal women with HR-positive breast cancer ineligible for BCS were treated preoperatively with 2.5 mg daily of letrozole for a minimum of 4 months and a maximum of 8 months. Overall, the response rate was 57% for patients receiving treatment for 4 months and 90% for those who were treated for a longer period. Moreover, longer treatment periods resulted in significant tumor size reductions ($P = 0.0393$). Another phase II trial with letrozole as primary therapy in 70 patients was designed to determine optimal treatment duration. A high overall clinical response rate of 83% was achieved after a median time of endocrine treatment of 6 months [48]. Lastly, a phase II trial in which 55 patients ineligible for BCS were treated preoperatively with exemestane during 6 months demonstrated an overall clinical response rate of 45% with a pathological complete response (pCR) rate of 5% [27].

Overall, these studies show that at least 4 months of neoadjuvant endocrine therapy should be administered, and that longer treatments might certainly improve response rates. Provided that there is a strict follow-up to detect any possible case of disease progression early, it seems reasonable to prolong endocrine treatment for 6–12 months, especially in those patients who are responding and in whom a BCS may be achieved.

How should response be evaluated after neoadjuvant endocrine therapy?

One unresolved problem with neoadjuvant endocrine therapy is the lack of a reliable marker of response. Clinical measurements are inaccurate because of poor reproducibility and observer variability, but other methods of response assessment do not seem to be much better [49]. As shown in Table 1, tumor responses in all randomized clinical trials carried out with neoadjuvant endocrine therapy were measured by clinical examination (palpation or caliper). Complementary radiological assessments such as mammography, ultrasound, or both were also carried out [23–26,40]. It is noteworthy that in all cases response rates were higher with clinical examination than with imaging procedures. It seems that either clinical assessment overestimates response or radiological methods underestimate it, perhaps owing to residual fibrosis and lack of specifity [50]. Unfortunately, none of these studies have reported data regarding comparison between the actual tumor size obtained after surgical resection and the estimated size by those methods.

Nevertheless, it is important to monitor tumor size during treatment to exclude disease progression. In this case, it should be taken into account that ultrasound is considered to be more accurate than mammography, at least in assessing tumor size in breasts with high density [51]. For those tumors showing no clear resolution, a magnetic resonance imaging could be an alternative, as it substantially improves the prediction of pathologic tumor response to preoperative treatments [52].

One concern with neoadjuvant endocrine therapy is the low rate of pCRs obtained. In fact, the majority of the studies have not reported these data in their publications, probably because no pCRs were achieved in most of them. In the P024 trial [23], the pCR rates observed in both breast and axilla were 0.59% for tamoxifen and 0.65% for letrozole. In the randomized trial that compared tamoxifen with exemestane [26], the pCR rate was 2.7% for tamoxifen and 2.6% for exemestane, although it is not known if these were assessed only in the breast or in both the breast and the axilla. It is true that neoadjuvant chemotherapy also results in lower rates of pCR in ER-positive [41,53] rather than in ER-negative patients, but they are not as low as those seen with endocrine therapies. One reason may be that the difference between the antitumor mechanisms of chemotherapy (cytotoxic) and endocrine therapy (antiproliferative) may have an effect on the type of response. It is also possible that a more appropriate selection of patients, with a tumor genetic profile that is more sensitive to the endocrine treatment, or the administration of longer neoadjuvant endocrine treatments, would result in improved rates of pCRs. Whatever the reason is, it does not seem that pCR rate is an important efficacy endpoint in neoadjuvant endocrine trials to date owing to the low rates achieved.

Lastly, it has been mentioned that clinical immunohistochemical markers and gene expression profiles may predict response to neoadjuvant systemic therapies [20]. In the case of endocrine therapies, as already discussed, those ER-positive tumors in which the Allred scored is 6 or higher are most likely to respond to whichever endocrine agent is administered [24,26,39,40]. The subset of patients with ER-positive disease who also express epidermal growth factor receptor 1(ErbB-1) and/or ErbB-2 also seems to respond better to aromatase inhibitors than to tamoxifen [24,54,55]. Another interesting histological marker may be invasive lobular carcinoma which, although it seems to respond less well than invasive ductal carcinomas to neoadjuvant therapy, may have better long-term outcomes [56].

One of the biological markers that has been most intensively studied is the tumor expression of Ki67, a nuclear proliferation marker, which seems to show the most promising ability to predict not only response but also other long-term outcomes used in the adjuvant setting [54,57]. Interestingly, associations between changes in Ki67 and HRs were noted in the IMPACT trial, independently of the endocrine agent used (tamoxifen, anastrozole, or the combination of both). A positive relationship between ER level and Ki67 suppression was

observed, as well as a greater reduction in Ki67 expression in progesterone receptor (PR)-positive compared with PR-negative tumors [58]. On the other hand, while higher baseline Ki67 expression was not related to outcome, higher Ki67 expression after 2 weeks of endocrine therapy was significantly associated with lower 5-year recurrence-free survival [57]. This finding indicates that for long-term outcome prediction, an overall low level of Ki67 expression in response to the endocrine treatment, rather than the percentage change of expression from baseline levels, is more relevant. Moreover, absolute values of Ki67 after 2 weeks of treatment were significantly lower with anastrozole than with tamoxifen or with the combination, which correlated with improved outcomes in the anastrozole-treated patients. This means that Ki67 level in biopsy samples taken 2 weeks after treatment may be used to evaluate tumor responses to therapy, even if Ki67 levels were not assayed before treatment.

Gene expression profiling has been shown to predict prognosis of breast cancer as well as responses to particular chemotherapy regimens. The detection of a large number of genes in the tumor samples is achieved using DNA microarrays. A multigene assay for prediction of prognosis after adjuvant tamoxifen therapy is commercially available, although it is restricted to tamoxifen-treated patients with node-negative, ER-positive breast cancer [59]. Breast cancer subtypes have been differentiated according to their specific gene expression patterns. The main subtypes are luminal A, luminal B, basal-like, normal-like, and human epidermal growth factor receptor-2 [60–62]. Luminal A tumors have higher expression of ER-related genes and lower expression of proliferative genes and, consequently, are indicated for endocrine therapy; whereas luminal B tumors are more proliferative, and patients with this type of tumor may benefit from chemotherapy in combination with endocrine therapy [61]. The specific responses of these breast cancer subtypes have been investigated but results have been disappointing. Luminal tumors had a low pCR rate (6%) following neoadjuvant paclitaxel and doxorubicin-containing chemotherapy [62]. Following doxorubicin neoadjuvant chemotherapy, tumors of the luminal A subtype showed low frequency of progressive disease, whereas luminal B subtype tumors showed high frequency of progressive disease, but otherwise no other consistent associations between response to chemotherapy and tumor subtype have been observed [63]. It will be of great interest to include patients with luminal breast cancer subtypes, especially luminal A subtype, in neoadjuvant endocrine therapy clinical trials, to determine if this patient population would respond more effectively to endocrine treatments.

In summary, the primary clinical indication for neoadjuvant endocrine therapy remains the downstaging of large tumors to avoid mastectomy and to increase operability. Therefore, BCS rate should be one of the main efficacy endpoints of those clinical trials that assess endocrine therapy in the neoadjuvant setting. In addition, tumor response should be evaluated alongside the treatment, at least to exclude disease progression. Different clinical and radiological techniques to assess tumor response should be used to ensure accurate assessments. Despite the key role that pCR plays in neoadjuvant chemotherapy trials, it does not seem to play the same role in neoadjuvant endocrine therapy studies. Other surrogate biological markers of response for neoadjuvant endocrine trials are needed that are able to predict long-term outcomes. Finally, further research is needed to understand better all those potential predictive markers that will help to identify patients who will benefit the most from neoadjuvant endocrine therapy.

Which complementary treatments should be administered after neoadjuvant endocrine therapy?

It has been well established in the aforementioned trials that the optimal management of postmenopausal ER-positive breast cancer patients should include surgery if it is not contraindicated, and in fit elderly patients for whom life expectancy is longer than 24 months [28–33]. Although the rate of BCS procedures will be increased with neoadjuvant endocrine therapy, not all treated patients will be candidates for this procedure. In fact, the selection criteria for BCS after neoadjuvant endocrine therapy should be similar to those used after neoadjuvant chemotherapy [20]. The M.D. Anderson Prognostic Index (MDAPI) has recently been developed, which may help in the clinical decision-making process to select the most appropriate surgical procedure for the patient as well as other treatment strategies in a multimodality approach [64]. To date, it is known that there is an increased risk of locoregional and/or ipsalateral breast tumor recurrence in those patients with advanced nodal involvement at diagnosis, residual tumor larger than 2 cm, multifocal residual disease, and/or lymphovascular space invasion [64,65]. This fact should be taken into account when deciding upon the convenience of additional locoregional treatments such as radiotherapy.

One of the major advantages of neoadjuvant therapy is that it gives information about the tumor that can be used to individualize adjuvant treatment after surgery. Although this fact has been further exploited with neoadjuvant chemotherapy [66,67], this has not been the case for neoadjuvant endocrine therapy. In the P024 trial [23], the adjuvant treatment to be administered after surgery was at the discretion of the investigators. In the IMPACT trial [24], the same endocrine agent (tamoxifen or anastrozole) given as neoadjuvant treatment was to be continued in the adjuvant setting for a total of 5 years. In those patients who received the combination of both (tamoxifen and anastrozole), the

choice of switching to either tamoxifen or anastrozole was offered to them. Also, patients who had BCS and/or involved axillary lymph nodes after mastectomy received radiotherapy and patients younger than 70 years of age with high-risk disease were offered adjuvant chemotherapy. In the PROACT study [25], concomitant chemotherapy in the neoadjuvant and the adjuvant setting was permitted, and the same endocrine agent was taken by the patient for 5 years after surgery. No information regarding the other two randomized trials is available as they have been reported only in abstract form [26,40].

In spite of the lack of data on this regard, it should be taken into account that the Early Breast Cancer Trialists' Collaborative Group [4] has clearly established that patients with HR-positive tumors should receive endocrine therapy after surgery; and that it seems logical that those patients who have responded to a previous endocrine agent in the neoadjuvant setting should remain with the same hormone for 5 years after surgery. For those patients for whom there was no response, a change in the endocrine agent or even the administration of adjuvant chemotherapy may be of value.

Conclusion and future directions

Neoadjuvant endocrine therapy is active in patients with HR-positive breast cancer, and has a significantly higher efficacy in tumors with elevated expression of ERs. Third-generation aromatase inhibitors have been proven to be superior to tamoxifen in the neoadjuvant setting of postmenopausal women with breast cancer. Clinical trials administering neoadjuvant aromatase inhibitor therapies in postmenopausal women with hormone-sensitive large operable breast tumors have resulted in increased rates both of BCS and mastectomies in previously inoperable locally advanced tumors. Within ER-positive patients, very high levels of ER predict better response rate to endocrine therapy. Aromatase inhibitors have been shown to induce response with lower levels of ER, whereas tamoxifen does not [39]. Additionally, neoadjuvant endocrine therapy is the standard of care for patients with hormonosensitive tumors and comorbid conditions that make them too frail for surgery and/or chemotherapy, a situation that occurs often but not exclusively in elderly patients [38].

Neoadjuvant endocrine therapy for breast cancer is just emerging and a number of questions remain to be resolved in ongoing or future clinical trials. Some of the key questions include the optimal duration of treatment, which according to current literature is between 6 and 12 months, whether the patient is responding, and whether there is a possibility of carrying out more conservative surgery of the breast. Other questions include the best way to assess response and the efficacy endpoints of neoadjuvant endocrine therapy trials. In our opinion, the rate of BCS achieved should be one of the most important endpoints, along with response rate, measured accurately with clinical and radiological techniques. Complementary local and systemic treatments such as surgery, chemotherapy, and radiotherapy should be administered after neoadjuvant endocrine therapies taking into account the criteria developed for neoadjuvant chemotherapy [64]. Although there is a lack of data from randomized trials, it seems logical in responding patients to keep the same endocrine agent for 5 years in the adjuvant setting; and to change it in nonresponding patients.

Regarding future directions of research, there is a high expectation of being able to discern which of the three main aromatase inhibitors (exemestane, letrozole, and anastrozole) offers a better efficacy profile in the neoadjuvant treatment of breast cancer, and it is expected that this question will shortly be clarified with the results of the American College of Surgeons Oncology Group Z1031 trial. Other current clinical trials of neoadjuvant endocrine therapy are evaluating the role of clinical immunohistochemical markers and gene expression before and after endocrine therapy, and it will be interesting to see whether they may predict not only response rate but also long-term outcomes.

It will be of interest as well to determine the efficacy of other treatments in combination with neoadjuvant endocrine therapy, such as chemotherapy or biologic agents targeting vascular endothelial growth factor or blocking ErbB-2 receptor. In addition, there are other factors that need to be considered in neoadjuvant endocrine therapy such as the treatment of premenopausal women with HR-positive breast cancer who require additional ovarian suppression with luteinizing hormone-releasing hormone agonists.

Another antiestrogen agent, fulvestrant, is presently being evaluated in the neoadjuvant setting in a large European Organization for Research and Treatment of Cancer randomized trial. It does not have the partial agonist effects of tamoxifen [68] and has proven efficacy in tamoxifen-resistant disease and aromatase inhibitor-resistant disease [69,70].

Finally, additional studies in selected groups of patients are needed to confirm the use of neoadjuvant endocrine therapy as a possible alternative to chemotherapy in routine practice.

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References

1 Beatson GT. On the treatment of inoperable cases of carcinoma of the mamma: suggestion for a new method of treatment, with illustrative cases. *Lancet* 1896; **2**:104–107.

2 Kiang DT, Kennedy BJ. Tamoxifen (antiestrogen) therapy in advanced breast cancer. *Ann Intern Med* 1977; **87**:687–690.

3 Legha SS, Buzdar AU, Hortobagyi GN, Wiseman C, Benjamin RS, Blumenschein GR. Tamoxifen. Use in treatment of metastatic breast cancer refractory to combination chemotherapy. *JAMA* 1979; **242**:49–52.

4 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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**:1687–1717.

5 Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, *et al*. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005; **97**:1652–1662.

6 Wells SA Jr, Santen RJ, Lipton A, Haagensen DE Jr, Ruby EJ, Harvey H, *et al*. Medical adrenalectomy with aminoglutethimide: clinical studies in postmenopausal patients with metastatic breast carcinoma. *Ann Surg* 1978; **187**:475–484.

7 Brodie AM. Aromatase inhibitors in the treatment of breast cancer. *J Steroid Biochem Mol Biol* 1994; **49**:281–287.

8 Chowdhury S, Ellis PA. Recent advances in the use of aromatase inhibitors for women with postmenopausal breast cancer. *J Br Menopause Soc* 2005; **11**:96–102.

9 Paridaens R, Therasse P, Dirix L, Beex L, Piccart M, Cameron D, *et al*. First line hormonal treatment (HT) for metastatic breast cancer (MBC) with exemestane (E) or tamoxifen (T) in postmenopausal patients (pts) – a randomized phase III trial of the EORTC breast group. *Proc Am Soc Clin Oncol* 2004; **22**: abstract 515.

10 Paridaens R, Dirix L, Lohrisch C, Beex L, Nooij M, Cameron D, *et al*. Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. *Ann Oncol* 2003; **14**:1391–1398.

11 Bonneterre J, Thürlimann B, Robertson JF, Krzakowski M, Mauriac L, Koralewski P, *et al*. 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* 2000; **18**:3748–3757.

12 Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, Mangalik A, *et al*. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multi-center randomized trial. Arimidex study group. *J Clin Oncol* 2000; **18**: 3758–3767.

13 Mouridsen H, Gershanovich M, Sun Y, Pérez-Carrión R, Boni C, Monnier A, *et al*. 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* 2001; **19**:2596–2606.

14 Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, Jones SE, *et al*. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (intergroup exemestane study): a randomised controlled trial. *Lancet* 2007; **369**:559–570.

15 Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, *et al*. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005; **366**:455–462.

16 Boccardo F, Rubagotti A, Guglielmini P, Fini A, Paladini G, Mesiti M, *et al*. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Updated results of the Italian tamoxifen anastrozole (ITA) trial. *Ann Oncol* 2006; **17 (suppl 7)**:vii10–vii14.

17 Coates AS, Keshaviah A, Thürlimann B, Mouridsen H, Mauriac L, Forbes JF, *et al*. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *J Clin Oncol* 2007; **25**:486–492.

18 Baum M, Buzdar A, Cuzick J, Forbes J, Houghton J, Howell A, *et al*. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer* 2003; **98**:1802–1810.

19 Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, *et al*. American Society of Clinical Oncology Technology Assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor positive breast cancer: status report 2004. *J Clin Oncol* 2005; **23**:619–629.

20 Kaufmann M, Hortobagyi GN, Goldhirsch A, Scholl S, Makris A, Valagussa P, *et al*. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: an update. *J Clin Oncol* 2006; **24**:1940–1949.

21 Mauriac L, MacGrogan G, Avril A, Durand M, Floquet A, Debled M, *et al*. Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with a 124-month median follow-up. Institut Bergonie Bordeaux Groupe Sein (IBBGS). *Ann Oncol* 1999; **10**:47–52.

22 Wenzel C, Locker GJ, Bartsch R, Pluschnig U, Hussian D, Zielinski CC, *et al*. Preoperative second line chemotherapy induces objective responses in primary breast cancer. *Wien Klin Wochenschr* 2005; **117**:48–52.

23 Eiermann W, Paepke S, Appfelstaedt J, Llombart-Cussac A, Eremin J, Vinholes J, *et al*. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. *Ann Oncol* 2001; **12**:1527–1532.

24 Smith IE, Dowsett M, Ebbs SR, Dixon JM, Skene A, Blohmer JU, *et al*. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol* 2005; **23**:5108–5116.

25 Cataliotti L, Buzdar AU, Noguchi S, Bines J, Takatsuka Y, Petrakova K, *et al*. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor positive breast cancer: the Pre-Operative 'Arimidex' Compared to Tamoxifen (PROACT) trial. *Cancer* 2006; **106**:2095–2103.

26 Semiglazov V, Kletsel A, Semiglazov V, Zhiltzova E, Ivanov V, Dashyan G, *et al*. Exemestane versus tamoxifen as neoadjuvant endocrine therapy for postmenopausal women with ER+ breast cancer (T2N1–2, T3N0–1, T4N0M0). *J Clin Oncol* 2005; **23**:530.

27 Gil M, Barnadas A, Cirera L, Tusquets I, Muñoz M, Arcusa A, *et al*. Primary hormonal therapy with exemestane in patients with breast tumors greater than 3 cm in diameter: results of a Spanish multicenter phase II trial. *J Clin Oncol* 2004; **22**:603.

28 Gazet JC, Ford HT, Coombes RC, Bland JM, Sutcliffe R, Quilliam J, *et al*. Prospective randomized trial of tamoxifen versus surgery in elderly patients with breast cancer. *Eur J Surg Oncol* 1994; **20**:207–214.

29 Fentiman IS, Christiaens MR, Paridaens R, Van Geel A, Rutgers E, Berner J, *et al*. Treatment of operable breast cancer in the elderly: a randomised clinical trial EORTC 10851 comparing tamoxifen alone with modified radical mastectomy. *Eur J Cancer* 2003; **39**:309–316.

30 Robertson JF, Ellis IO, Elston CW, Blamey RW. Mastectomy or tamoxifen as initial therapy for operable breast cancer in elderly patients: 5-year follow-up. *Eur J Cancer* 1992; **28A**:908–910.

31 Mustacchi G, Ceccherini R, Milani S, Pluchinotta A, De Matteis A, Maiorino L, *et al*. Tamoxifen alone versus adjuvant tamoxifen for operable breast cancer of the elderly: long-term results of the phase III randomized controlled multicenter GRETA trial. *Ann Oncol* 2003; **14**:414–420.

32 Fennessy M, Bates T, MacRae K, Riley D, Houghton J, Baum M. Late follow-up of a randomized trial of surgery plus tamoxifen versus tamoxifen alone in women aged over 70 years with operable breast cancer. *Br J Surg* 2004; **91**:699–704.

33 Bates T, Riley DL, Houghton J, Fallowfield L, Baum M. Breast cancer in elderly women: a cancer research campaign trial comparing treatment with tamoxifen and optimal surgery with tamoxifen alone. The elderly breast cancer working party. *Br J Surg* 1991; **78**:591–594.

34 Semiglazov VF, Semiglazov VV, Dashyan GA, Ziltsova EK, Ivanov VG, Bozhok AA, *et al*. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor positive breast cancer. *Cancer* 2007; **110**:244–254.

35 Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A, Fisher ER, *et al*. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998; **16**:2672–2685.

36 Gazet JC, Ford HT, Gray R, McConkey C, Sutcliffe R, Quilliam J, *et al*. Estrogen-receptor-directed neoadjuvant therapy for breast cancer: results of a randomised trial using formestane and methotrexate, mitozantrone and mitomycin C (MMM) chemotherapy. *Ann Oncol* 2001; **12**:685–691.

37 Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst* 2005; **97**:188–194.

38 Macaskill EJ, Renshaw L, Dixon JM. Neoadjuvant use of hormonal therapy in elderly patients with early or locally advanced hormone receptor-positive breast cancer. *Oncologist* 2006; **11**:1081–1088.

39 Ellis MJ, Coop A, Singh B, Mauriac L, Llombert-Cussac A, Jänicke F, *et al*. 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* 2001; **19**:3808–3816.
40 Semiglazov V, Semiglazov VV, Ivanov VG, Ziltsova EK, Dashyan GA, Kletzel A, *et al*. Anastrazol (A) versus tamoxifen (T) versus combine (A + T) as neoadjuvant endocrine therapy of postmenopausal breast cancer patients. *Proc Am Soc Clin Oncol* 2003; **22**:3538a.
41 Kuerer HM, Newman LA, Smith TL, Ames FC, Hunt KK, Dhingra K, *et al*. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol* 1999; **17**:460–469.
42 Wong ZW, Ellis MJ. First-line endocrine treatment of breast cancer: aromatase inhibitor or antiestrogen? *Br J Cancer* 2004; **90**:20–25.
43 Pollow K, Schoenegg W, Koelbl H, Kreienberg R, Dubois A, Elling D, *et al*. Safety and tolerability of adjuvant exemestane plus goserelin with or without tibolone in receptor-positive, node-negative primary breast cancer in premenopausal women: the final results of the randomized multicenter ADAGIO pilot study. *Proc Am Soc Clin Oncol* 2004; **22**:594.
44 Harper-Wynne C, Ross G, Sacks N, Salter J, Nasiri N, Iqbal J, *et al*. Effects of the aromatase inhibitor letrozole on normal breast epithelial cell proliferation and metabolic indices in postmenopausal women: a pilot study for breast cancer prevention. *Cancer Epidemiol Biomarkers Prev* 2002; **11**:614–621.
45 Jonat W, Hilpert F, Kaufmann M. Aromatase inhibitors: a safety comparison. *Expert Opin Drug Saf* 2007; **6**:165–174.
46 Ma CX, Ellis MJ. Neoadjuvant endocrine therapy for locally advanced breast cancer. *Semin Oncol* 2006; **33**:650–656.
47 Paepke S, Tulusan A, Kiesel L, Bastert G, Jaenicke FK, Bouterfa H, *et al*. A multi-center study of pre-operative treatment with letrozole for optimal duration of treatment in postmenopausal women with ER and/or PGR positive breast cancer. *Proc Am Soc Clin Oncol* 2003; **22**:321a.
48 Llombart-Cussac A, Galan A, Fuster C, Buch E, Carañana V, Rodriguez-Lescure A, *et al*. Phase II trial with letrozole (2.8 mg) to maximal response as neoadjuvant endocrine therapy in postmenopausal patients with ER/PgR$^+$ operable breast cancer. *The Breast* 2007; **16** (**Suppl 1**):S49–S50.
49 Beresford MJ, Ravichandran D, Makris A. Neoadjuvant endocrine therapy in breast cancer. *Cancer Treat Rev* 2007; **33**:48–57.
50 Herrada J, Iyer RB, Atkinson EN, Sneige N, Buzdar AU, Hortobagyi GN. Relative value of physical examination, mammography, and breast sonography in evaluating the size of the primary tumor and regional lymph node metastases in women receiving neoadjuvant chemotherapy for locally advanced breast carcinoma. *Clin Cancer Res* 1997; **3**:1565–1569.
51 Fasching PA, Heusinger K, Loehberg CR, Wenkel E, Lux MP, Schrauder M, *et al*. Influence of mammographic density on the diagnostic accuracy of tumor size assessment and association with breast cancer tumor characteristics. *Eur J Radiol* 2006; **60**:398–404.
52 Bollet MA, Thibault F, Bouillon K, Meunier M, Sigal-Zafrani B, Savignoni A, *et al*. Role of dynamic magnetic resonance imaging in the evaluation of tumor response to preoperative concurrent radiochemotherapy for large breast cancers: a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2007; **69**:13–18.
53 Ring AE, Smith IE, Ashley S, Fulford LG, Lakhani SR. Oestrogen receptor status, pathological complete response and prognosis in patients receiving neoadjuvant chemotherapy for early breast cancer. *Br J Cancer* 2004; **91**:2012–2017.
54 Ellis MJ, Coop A, Singh B, Tao Y, Llombart-Cussac A, Jänicke F, *et al*. Letrozole inhibits tumor proliferation more effectively than tamoxifen independent of HER1/2 expression status. *Cancer Res* 2003; **63**: 6523–6531.
55 Zhu L, Chow LW, Loo WT, Guan XY, Toi M. Her2/neu expression predicts the response to antiaromatase neoadjuvant therapy in primary breast cancer: subgroup analysis from celecoxib antiaromatase neoadjuvant trial. *Clin Cancer Res* 2004; **10**:4639–4644.
56 Cristofanilli M, Gonzalez-Angulo A, Sneige N, Kau SW, Broglio K, Theriault RL, *et al*. Invasive lobular carcinoma classic type: response to primary chemotherapy and survival outcomes. *J Clin Oncol* 2005; **23**:41–48.
57 Dowsett M, Smith IE, Ebbs SR, Dixon JM, Skene A, A'Hern R, *et al*. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. *J Natl Cancer Inst* 2007; **99**:167–170.
58 Dowsett M, Ebbs SR, Dixon JM, Skene A, Griffith C, Boeddinghaus I, *et al*. Biomarker changes during neoadjuvant anastrozole, tamoxifen, or the combination: influence of hormonal status and HER-2 in breast cancer – a study from the IMPACT trialists. *J Clin Oncol* 2005; **23**:2477–2492.
59 Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, *et al*. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004; **351**:2817–2826.
60 Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, *et al*. Molecular portraits of human breast tumours. *Nature* 2000; **406**:747–752.
61 Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, *et al*. Repeated observation of breast tumor subtypes in independent gene expression data sets. *Proc Natl Acad Sci U S A* 2003; **100**:8418–8423.
62 Rouzier R, Perou CM, Symmans WF, Ibrahim N, Cristofanilli M, Anderson K, *et al*. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res* 2005; **11**:5678–5685.
63 Sorlie T, Perou CM, Fan C, Geisler S, Aas T, Nobel A, *et al*. Gene expression profiles do not consistently predict the clinical treatment response in locally advanced breast cancer. *Mol Cancer Ther* 2006; **5**:2914–2918.
64 Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Outlaw ED, Strom EA, *et al*. Breast conservation after neoadjuvant chemotherapy. *Cancer* 2005; **103**:689–695.
65 Chen AM, Meric-Bernstam F, Hunt KK, Thames HD, Oswald MJ, Outlaw ED, *et al*. Breast conservation after neoadjuvant chemotherapy: the MD Anderson cancer center experience. *J Clin Oncol* 2004; **22**:2303–2312.
66 Von Minckwitz G, Blohmer J, Vogel P, Hanusch C, Eidtmann H, Hilfrich J, *et al*. Comparison of neoadjuvant 6 versus 8 cycles of docetaxel/ doxorubicin/cyclophosphamide (TAC) in patients early responding to TACx2: the GEPARTRIO Study. *J Clin Oncol* 2006; **24**:576.
67 Smith IC, Heys SD, Hutcheon AW, Miller ID, Payne S, Gilbert FJ, *et al*. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. *J Clin Oncol* 2002; **20**:1456–1466.
68 Robertson JF, Come SE, Jones SE, Beex L, Kaufmann M, Makris A, *et al*. Endocrine treatment options for advanced breast cancer – the role of fulvestrant. *Eur J Cancer* 2005; **41**:346–356.
69 Robertson JF. ICI 182,780 (Fulvestrant) – the first oestrogen receptor down-regulator – current clinical data. *Br J Cancer* 2001; **85** (**Suppl 2**): 11–14.
70 Johnston SR, Martin LA, Dowsett M. Life following aromatase inhibitors – where now for endocrine sequencing? *Breast Cancer Res Treat* 2005; **93** (**Suppl 1**):S19–S25.