Estrogen Receptor Expression and Docetaxel Efficacy in Patients with Metastatic Breast Cancer: A Pooled Analysis of Four Randomized Trials

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ABSTRACT

Background. Differences in the efficacy of various chemotherapies in patients with estrogen receptor (ER)⁺ metastatic breast cancer are not well understood. In the present study, we assessed the efficacy of docetaxel in patients with metastatic breast cancer according to ER expression.

Methods. The efficacy of docetaxel in terms of the response rate and progression-free survival (PFS) time was analyzed according to ER expression in four randomized trials comparing a docetaxel-based regimen with a non-taxane regimen that included a total of 1,631 patients. The odds ratio for tumor response was estimated with logistic regression and a hazard ratio (HR) for PFS was estimated with Cox proportional hazards models.

Findings. ER expression was assessable in 1,037 patients included in these trials (64%). ER was expressed

in 601 tumors (58%). Docetaxel was associated with a similarly higher response rate in both patients with ER⁺ (odds ratio, 2.90; 95% confidence interval [CI], 1.72–4.87) and patients with ER[−] (odds ratio, 2.55; 95% CI, 1.44–4.51) disease. The lower hazard for disease progression with docetaxel was also similar in ER⁺ (HR, 0.82; 95% CI, 0.67–1.00) and ER[−] (HR, 0.86; 95% CI, 0.70–1.07) cancers. The effect of docetaxel was not different in ER⁺ and ER[−] disease, in terms of both the response rate and PFS time (interaction test, $p = .77$ and $p = .93$).

Interpretation. Docetaxel produces a higher response rate and lower risk for disease progression to a statistically similar extent in both patients with ER⁺ and patients with ER[−] metastatic breast cancer. *The Oncologist* 2010;15:476–483

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INTRODUCTION

The outcome of patients with metastatic breast cancer has improved during the past 20 years [1]. This improvement has been attributed, in part, to the use of new chemotherapy agents, including taxanes [2, 3], as well as novel endocrine agents, including the aromatase inhibitors [4, 5], and, more recently, targeted therapies such as trastuzumab [6]. Estrogen receptor (ER) expression is one of the key criteria to define endocrine sensitivity and select patients for front-line endocrine therapy. The use of endocrine therapy as first-line treatment in patients with ER⁺ disease is supported by its favorable therapeutic index in the metastatic setting [7] and by the lack of evidence for greater benefit from chemotherapy than from endocrine therapy [8]. Based on these data, most clinical guidelines currently recommend that the vast majority of patients with ER⁺ metastatic breast cancer be offered front-line endocrine therapy [9, 10].

Although several new chemotherapeutic agents have been evaluated and approved for metastatic breast cancer treatment in the past 15 years, it is not clear whether or not, and to what extent, these new drugs improve the outcome of ER⁺ metastatic breast cancer patients. Several studies performed in both the preoperative [11] and adjuvant [12] settings have suggested that docetaxel has substantial antitumor activity in patients with ER⁺ disease. In the National Surgical Adjuvant Breast and Bowel Project B-27 trial [11], docetaxel in the preoperative setting led to a higher pathological complete response rate, 14% versus 5%, in patients with ER⁺ disease ($p < .001$). In the adjuvant setting, docetaxel provided a 30% lower risk for death in patients with ER⁺ disease in a pooled analysis of two randomized trials [12].

The efficacy of docetaxel in patients with metastatic breast cancer has been established by four different randomized trials [13–16]. Nevertheless, these trials did not report docetaxel efficacy according to ER expression, and it is therefore unclear whether the use of this drug would lead to a significant therapeutic advance in the subset of patients with ER⁺ metastatic breast tumors.

In the present study, we analyzed the efficacy of docetaxel according to ER expression in four randomized phase III trials that evaluated this drug in the metastatic setting [13–16].

PATIENTS AND METHODS

Patients

The present study is a combined analysis of four randomized trials that evaluated the efficacy of docetaxel in patients with metastatic breast carcinoma [13–16]. Only

studies comparing docetaxel with a nontaxane regimen were taken into account. The inclusion criteria and study design are available in the original reports [13–16]. Briefly, the TAX303 trial [13] included 326 patients who were previously treated with an alkylating agent in either the adjuvant or metastatic setting. Prior treatment with anthracyclines or with more than one line of chemotherapy for metastatic disease was an exclusion criterion. The TAX304 trial [14] included 392 patients who were previously treated with anthracyclines either as adjuvant treatment or as first-line chemotherapy for metastatic disease. Trials TAX306 [15] and TAX307 [16] recruited 429 and 484 patients, respectively, and included patients who had never received chemotherapy in the metastatic setting. In total, these four trials included 1,631 patients. ER expression was assessable in 1,037 of these 1,631 patients (64%), who represent the denominator for these analyses. Individual patient data devoid of personal identifying elements were provided by Sanofi-Aventis to the investigators upon request by F.A.

Treatments

The TAX303 trial [13] compared docetaxel (100 mg/m², days 1–21) with doxorubicin (50 mg/m², days 1–21). The TAX304 trial [14] compared docetaxel (100 mg/m², days 1–21) with a combination of mitomycin (12 mg/m² every 6 weeks) and vinblastine (6 mg/m² every 3 weeks). The TAX306 trial [15] compared the AT regimen (doxorubicin, 50 mg/m², combined with docetaxel, 75 mg/m²) with an AC regimen (doxorubicin, 60 mg/m², combined with cyclophosphamide, 600 mg/m²). The TAX307 trial [16] compared a TAC regimen (docetaxel, 75 mg/m²; doxorubicin, 50 mg/m²; cyclophosphamide, 500 mg/m² on day 1, every 21 days) with a FAC regimen (5-fluorouracil, 500 mg/m²; doxorubicin, 50 mg/m²; cyclophosphamide, 500 mg/m² on day 1, every 21 days).

Statistical Analyses

We analyzed the efficacy of docetaxel defined by the objective tumor response rate and progression-free survival (PFS) duration. Tumor response was defined as a partial or complete response according to World Health Organization criteria [17]. The PFS time was measured from the date of randomization to the date of disease progression or death from any cause. The disease-free interval was defined as the time from the initial diagnosis of breast cancer to the time of the initial diagnosis of metastatic breast cancer. We first considered each study separately. The odds ratios for tumor response associated with docetaxel were estimated from logistic regression models that included terms for docetaxel, ER status, menopausal status, number of metastases, site of metas-

Table 1. Patient characteristics

Characteristic	ER ⁺ disease (<i>n</i> = 601)	ER ⁻ disease (<i>n</i> = 436)	ER status unknown (<i>n</i> = 594)
Median age (min–max), yrs	54 (25–77)	52 (28–75)	53 (30–78)
Disease-free interval (min–max) ^a	39 (0–229)	21 (0–205)	35 (0–463)
Menopausal status			
Yes	450 (83%)	308 (75%)	441 (78%)
No	94 (17%)	102 (25%)	124 (22%)
Unknown	57	26	29
<i>n</i> of metastatic sites			
0	5 (1%)	2 (1%)	2 (0.3%)
1	138 (23%)	102 (23%)	109 (18%)
2	194 (32%)	156 (36%)	199 (34%)
3	134 (22%)	103 (24%)	170 (29%)
4	90 (15%)	56 (13%)	97 (16%)
5	27 (5%)	15 (3%)	12 (2%)
6	11 (2%)	1 (0.2%)	5 (1%)
7	2 (0.3%)	1 (0.2%)	0 (0%)
Visceral metastasis ^b			
Yes	394 (66%)	286 (66%)	354 (60%)
No	203 (34%)	148 (34%)	239 (40%)
Unknown	4	2	1
Progesterone receptor			
Yes	392 (76%)	68 (18%)	3 (50%)
No	124 (24%)	303 (82%)	3 (50%)
Unknown	85	65	588
Trial			
TAX303 (<i>n</i> = 326)	99 (16%)	89 (20%)	138 (23%)
TAX304 (<i>n</i> = 392)	162 (27%)	117 (27%)	113 (19%)
TAX306 (<i>n</i> = 429)	121 (20%)	102 (23%)	206 (35%)
TAX307 (<i>n</i> = 484)	219 (36%)	128 (29%)	137 (23%)

^aDefined as the interval between the initial diagnosis and metastatic relapse.

^bDefined as metastasis in the liver, lung, or brain.

tasis (visceral versus other), and the disease-free interval. Modeling was repeated for each study by ER subgroups. All four studies were then combined, and the odds ratio for tumor response associated with docetaxel was estimated from a logistic regression model that included terms for study, docetaxel, ER status, menopausal status, number of metastases, sites of metastasis, and the disease-free interval. We then tested for an interaction between docetaxel and ER status with the likelihood ratio test. PFS was considered similarly with Cox proportional hazards models. Analyses were performed with SAS 9.1 (SAS Institute, Cary, NC) and S-Plus 7 (Insightful Corp., Seattle, WA). *p*-values <.05 were considered statistically significant.

RESULTS

Patient Characteristics

ER was expressed in 601 of 1,037 assessable tumors (58%). Patient characteristics are reported in Table 1 for patients with ER⁺ disease (*n* = 601), ER⁻ disease (*n* = 436), and unknown ER status (*n* = 594). Patients with unknown ER status had a lower rate of visceral metastasis (60% versus 66%) and were more likely to be from trial TAX306. The disease-free interval after the initial diagnosis was higher in patients with ER⁺ disease (39 months) than in those with ER⁻ disease (21 months). A higher proportion of postmenopausal patients was observed among those with ER⁺

Table 2. Efficacy of docetaxel in terms of response rate according to trial and ER expression

	TAX303 (<i>n</i> = 188) OR (95% CI)	TAX304 (<i>n</i> = 279) OR (95% CI)	TAX306 (<i>n</i> = 223) OR (95% CI)	TAX307 (<i>n</i> = 347) OR (95% CI)	Overall (<i>n</i> = 1,037) OR (95% CI)
ER ⁺ disease (<i>n</i> = 601)	2.14 (0.63–7.31)	6.49 (1.66–25.25)	6.17 (2.00–18.97)	1.30 (0.53–3.14)	2.89 (1.72–4.87)
ER [−] disease (<i>n</i> = 436)	3.28 (0.89–12.12)	5.56 (1.30–23.73)	4.70 (1.20–18.45)	1.36 (0.51–3.60)	2.54 (1.43–4.50)
Overall (<i>n</i> = 1,037)	2.64 (1.09–6.39)	5.06 (1.94–13.18)	3.86 (1.78–8.37)	1.42 (0.75–2.70)	2.65 (1.82–3.86)

Abbreviations: CI, confidence interval; ER, estrogen receptor; OR, odds ratio.

disease than among those with ER[−] disease (83% versus 75%; *p* = .004). Two hundred twenty-eight (52%) and 299 (50%) patients with ER[−] and ER⁺ disease, respectively, were treated with docetaxel either as a single agent or in combination therapy.

Efficacy of Docetaxel in the Overall Population

Considering the four pooled studies, the tumor response rates were 34.1% and 47.2% among patients who did not receive and did receive docetaxel, respectively. After adjustment for other (menopausal status, number of metastases, site of metastasis [any visceral versus other], and disease-free interval) characteristics, the odds ratio for tumor response associated with docetaxel was 2.66 (95% confidence interval [CI], 1.83–3.87). In this pooled analysis, docetaxel was also associated with a 15% lower hazard for disease progression (HR, 0.85; 95% CI, 0.73–0.97).

Docetaxel Efficacy According to ER Expression

We report the odds ratios for tumor response for each trial according to ER expression in Table 2. Among patients with ER⁺ disease, the odds ratios for tumor response associated with docetaxel were 2.1 (95% CI, 0.63–7.31), 6.5 (95% CI, 1.66–25.253), 6.2 (95% CI, 2.00–18.974), and 1.3 (95% CI, 0.53–3.14) in trials TAX303, TAX304, TAX306, and TAX307, respectively. The absolute differences in response rate were 17.4%, 26.1%, 22.1%, and 4.7% in trials TAX303, TAX304, TAX306, and TAX307, respectively. Among all ER⁺ patients, the tumor response rate was 31.1% among patients who did not receive docetaxel and 46.8% among patients who did receive docetaxel. For patients with ER⁺ tumors, the odds ratio for tumor response associated with docetaxel was 2.90 (95% CI, 1.72–4.87). Similarly, among all ER[−] patients, tumor response rates were 29.3% and 44.7% among patients who did not receive and did receive docetaxel, respectively. For patients with ER[−] tumors, the odds ratio for response associated with docetaxel was 2.55 (95% CI, 1.44–4.51). The odds ratio associated with the interaction between do-

cetaxel and ER status was 1.12 (95% CI, 0.53–2.37; *p* = .77).

We next considered whether docetaxel had a different effect in terms of PFS in patients with ER⁺ and ER[−] disease. Figure 1 reports the PFS curves according to trial and ER expression. Table 3 reports the lower hazard for disease progression associated with docetaxel, according to trial and ER expression. When the four studies were pooled, docetaxel was associated with an 18% (HR, 0.82; 95% CI, 0.67–1.00) and 14% (HR, 0.86; 95% CI, 0.70–1.07) lower hazard for disease progression in patients with ER⁺ and ER[−] disease, respectively. As reported in Table 3, the risk differences were heterogeneous among trials. These risk reductions ranged from 0.61 (0.43–0.85) to 1.13 (0.70–1.83) in patients with ER⁺ disease and from 0.65 (0.42–0.98) to 1.20 (0.76–1.88) in patients with ER[−] disease. The test for interaction between docetaxel and ER expression did not indicate any difference in the relative benefit of docetaxel between the two groups in terms of PFS (HR for interaction, 0.99; 95% CI, 0.75–1.31; *p* = .93).

DISCUSSION

The optimal use of chemotherapy, including the sequencing and choice of drugs in patients with ER⁺ metastatic breast cancer is still a matter of controversy [9, 10]. Although there is clear evidence that chemotherapy induces tumor responses in patients with ER⁺ metastatic breast cancer, only a few studies have specifically evaluated the relative efficacy of chemotherapy drugs or combination regimens by ER expression. Most of these studies were small and relatively underpowered to examine this question [18–22]. Two of these studies suggested that ER[−] tumors were more likely to respond than ER⁺ disease [18, 19]. This is consistent with results from adjuvant and neoadjuvant clinical trials that indicated greater general chemotherapy sensitivity in ER[−] cancers. However, we recently reported that the inclusion of docetaxel in adjuvant chemotherapy resulted in statistically similar longer survival times for both ER[−] and ER⁺ breast cancer patients in a pooled analysis of several randomized trials [12]. In this manuscript, we examined

Figure 1. Progression-free survival according to trial and estrogen receptor (ER) expression.
Abbreviations: A, doxorubicin; C, cyclophosphamide; F, 5-fluorouracil; T, docetaxel.

Table 3. Hazard of disease progression associated with docetaxel according to trial and ER expression

	TAX303 (n = 188) HR^a (95% CI)	TAX304 (n = 279) HR (95% CI)	TAX306 (n = 223) HR (95% CI)	TAX307 (n = 347) HR (95% CI)	Overall (n = 1,037) HR (95% CI)
ER ⁺ disease (n = 601)	0.74 (0.47–1.18)	0.61 (0.43–0.85)	1.13 (0.70–1.83)	1.05 (0.73–1.50)	0.82 (0.67–1.00)
ER [−] disease (n = 436)	1.01 (0.64–1.59)	0.69 (0.45–1.05)	1.20 (0.76–1.88)	0.65 (0.42–0.98)	0.86 (0.70–1.07)
Overall (n = 1,037)	0.84 (0.61–1.16)	0.65 (0.51–0.84)	1.18 (0.85–1.63)	0.85 (0.65–1.12)	0.84 (0.73–0.97)

^aHR associated with the performance of docetaxel.

Abbreviations: CI, confidence interval; ER, estrogen receptor; HR, hazard ratio.

whether or not we could detect differential clinical benefit from docetaxel by ER status in metastatic breast cancer.

For patients with ER⁺ tumors, the odds ratio for tumor response associated with docetaxel was 2.90 (95% CI, 1.72–4.87), and for ER[−] patients it was 2.55 (95% CI, 1.44–4.51). There was no significant interaction between docetaxel response and ER status in the pooled analysis. The relative reduction in the hazard for disease progression with the inclusion of docetaxel was also similar for ER⁺ (HR, 0.82; 95% CI, 0.67–1.00) and ER[−] (HR, 0.86; 95% CI, 0.70–1.07) cancers in the pooled analysis. However, there was heterogeneity among the individual trials—HRs for disease progression with docetaxel ranged from 0.61 (0.43–0.85) to 1.13 (0.70–1.83) in patients with ER⁺ disease. This indicates that the relative efficacy of docetaxel varied from trial to trial. At least one other study including 478 patients also demonstrated substantial antitumor activity for docetaxel in ER⁺ cancers; in fact, that study reported a statistically significantly higher response rate in patients with ER⁺ cancers (29%) than in those with ER[−] tumors (20%) ($p = .04$) [23]. However, these data are not consistent with results reported with paclitaxel [18], in which patients with ER[−] disease are more likely to benefit from this drug. Several hypotheses could explain this apparent discrepancy. First, paclitaxel and docetaxel could present different mechanisms of resistance. Second, a difference in the percentage of highly proliferative disease across trials could contribute to such a discrepancy.

Recent molecular assays clearly demonstrated that a subset of ER⁺ cancers is highly sensitive to chemotherapy. A high *Oncotype DX* recurrence score, luminal B molecular class, or high genomic grade index are molecular characteristics of this subset [24–26]. In a recent analysis from the Breast Cancer International Research Group 001 trial, docetaxel efficacy was indeed shown to be more pronounced in patients with Ki67-expressing ER⁺ breast cancer [27]. To what extent these molecular assays could help to select patients for chemotherapy or endocrine therapy in the first-line treatment of advanced breast cancer patients remains to be addressed.

One of the arguments in support of endocrine therapy as front-line treatment for ER⁺ metastatic breast cancer patients is the favorable balance between toxicity and efficacy. This is particularly relevant for patients who are asymptomatic or have only minimal symptoms from their cancer. On the other hand, chemotherapy in general presents side effects. This consideration underlines the importance of evaluating quality-adjusted survival in future trials that would address the issue of chemotherapy efficacy in patients with ER⁺ metastatic breast cancer [28, 29].

This study did not address the overall survival benefit from docetaxel as a function of ER status because of a lack of statistical power, together with many potential biases, including crossover treatment. It is notoriously difficult to demonstrate survival differences in metastatic breast cancer patients. Most patients receive multiple sequential lines of therapy after participation in a clinical trial, and these subsequent treatments, often including off-study crossover therapy, confound possible effects on survival. Also, most of the studies are underpowered in the metastatic setting to detect small survival differences [30].

Several studies have suggested that the level of ER expression could be predictive of resistance to adjuvant chemotherapy [31]. Some guidelines recommend considering this parameter when selecting patients for chemotherapy both in the adjuvant [32] and metastatic [10] settings. Unfortunately, quantitative levels of ER positivity were not available for the present study. We therefore were unable to examine whether patients with strongly ER⁺ tumors benefit less (or more) from a docetaxel-containing regimen than less ER⁺ cases.

Finally, the study is limited by a potential bias related to the selection of ER⁺ breast cancer patients included in chemotherapy trials. Because most of the guidelines recommend endocrine therapy for patients with ER⁺ metastatic breast cancer, and luminal A breast cancers have a better natural history than luminal B disease, we cannot exclude the fact that ER⁺ disease candidates for chemotherapy trials represent a subset of more aggressive disease (i.e., visceral metastases, high tumor grade, luminal B disease). Simi-

larly, human epidermal growth factor receptor (HER)-2 was not assessable in the present study. Because HER-2 is associated with greater chemosensitivity, we cannot know whether patients with HER-2–overexpressing ER⁺ breast cancer benefit from docetaxel. This bias in selecting patients for chemotherapy trials could explain the high response rates observed in ER⁺ cancer patients in these four trials. This phenomenon was previously reported in the adjuvant setting [33], where it was shown that differences in biological characteristics across trials might explain differences in trials results. Furthermore, none of the patients in these four studies received docetaxel as adjuvant therapy. However, today some patients receive docetaxel-containing adjuvant chemotherapy, and therefore to what extent the current findings apply to this patient population is unknown. Another potential limitation of the current study relates to the fact that the number of patients who received first-line endocrine therapy is unknown.

Overall, this pooled analysis of four different randomized trials confirms that docetaxel is an effective chemotherapy agent for ER⁺ metastatic breast cancer. It improves both the response rate and PFS time. The magnitude of these benefits in patients with ER⁺ disease is the same as that observed in patients with ER[−] metastatic disease. Whereas this study does not suggest that docetaxel is a universally required treatment in this setting, we rather suggest that it may be particularly appropriate for selected patients.

This study provides a rationale to molecularly redefine the benefits of chemotherapy in women with metastatic ER⁺ breast cancer. Future studies should evaluate the relative benefits of chemotherapy among molecularly defined populations with metastatic breast cancer, ideally with tissue samples derived from metastatic sites, interrogated with new molecular tools, including *Oncotype DX* [24], immunohistochemical panels to define luminal subtypes [27], genomic grade [26], or DLD30 [34]. Such studies would potentially improve patient and therapeutic selection for patients with ER⁺ metastatic breast cancer.

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REFERENCES

- Andre F, Slimane K, Bachelot T et al. Breast cancer with synchronous metastases: Trends in survival during a 14-year period. *J Clin Oncol* 2004;22:3302–3308.
- Valero V, Hortobagyi GN. Are anthracycline-taxane regimens the new standard of care in the treatment of metastatic breast cancer? *J Clin Oncol* 2003;21:959–962.
- Lebwohl DE, Canetta R. New developments in chemotherapy of advanced breast cancer. *Ann Oncol* 1999;10(suppl 6):139–146.
- Bonnetterre J, Thurlimann B, Robertson JF 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.
- Mouridsen H, Gershonovich M, Sun Y et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: Analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003;21:2101–2109.
- Marty M, Cognetti F, Maraninchi D et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: The M77001 study group. *J Clin Oncol* 2005;23:4265–4274.
- Bonnetterre J, Buzdar A, Nabholz JM et al.; Arimidex Writing Committee; Investigators Committee Members. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer* 2001;92:247–2258.
- Stockler M, Wilcken NR, Ghersi D et al. Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. *Cancer Treat Rev* 2000;26:151–168.
- Kataja VV, Colleoni M, Bergh J.; ESMO Guidelines Task Force. ESMO minimum clinical recommendations for diagnosis, treatment and follow-up of locally recurrent or metastatic breast cancer (MBC). *Ann Oncol* 2005;16(suppl 1):i10–i12.
- Beslija S, Bonnetterre J, Burstein H et al. Second consensus on medical treatment of metastatic breast cancer. *Ann Oncol* 2007;18:215–225.
- Bear HD, Anderson S, Brown A et al.; National Surgical Adjuvant Breast and Bowel Project Protocol B-27. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: Preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. *J Clin Oncol* 2003;21:4165–4174.
- Andre F, Broglio K, Roche H et al. Estrogen receptor expression and efficacy of docetaxel-containing adjuvant chemotherapy in patients with node-positive breast cancer: Results from a pooled analysis. *J Clin Oncol* 2008;26:2636–2643.
- Chan S, Friedrichs K, Noel D et al.; 303 Study Group. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol* 1999;17:2341–2354.
- Nabholz JM, Senn HJ, Bezwoda WR et al. Prospective randomized trial of

- docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline-containing chemotherapy. 304 Study Group. *J Clin Oncol* 1999;17:1413–1424.
- 15 Nabholz JM, Falkson C, Campos D et al.; TAX 306 Study Group. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: Results of a randomized, multicenter, phase III trial. *J Clin Oncol* 2003;21:968–975.
 - 16 Mackey JR, Paterson A, Dirix LY. Final results of the phase III randomized trial comparing docetaxel (T), doxorubicin (A) and cyclophosphamide (C) to FAC as first line chemotherapy for patients with metastatic breast cancer [abstract 137]. *Proc Am Soc Clin Oncol* 2002;21:35a.
 - 17 Miller AB, Hoogstraten B, Staquet M et al. Reporting results of cancer treatment. *Cancer* 1981;47:207–214.
 - 18 Harris LN, Broadwater G, Lin NU et al. Molecular subtypes of breast cancer in relation to paclitaxel response and outcomes in women with metastatic disease: Results from CALGB 9342. *Breast Cancer Res* 2006;8:R66.
 - 19 Rosner D, Lane WW, Nemoto T. Differential response to chemotherapy in metastatic breast cancer in relation to estrogen receptor level. Results of a prospective randomized study. *Cancer* 1989;64:6–15.
 - 20 Van Poznak C, Tan L, Panageas KS et al. Assessment of molecular markers of clinical sensitivity to single-agent taxane therapy for metastatic breast cancer. *J Clin Oncol* 2002;20:2319–2326.
 - 21 Bennett JM, Muss HB, Doroshow JH et al. A randomized multicenter trial comparing mitoxantrone, cyclophosphamide, and fluorouracil with doxorubicin, cyclophosphamide, and fluorouracil in the therapy of metastatic breast carcinoma. *J Clin Oncol* 1988;6:1611–1620.
 - 22 Sjöström J, Krajewski S, Franssila K et al. A multivariate analysis of tumour biological factors predicting response to cytotoxic treatment in advanced breast cancer. *Br J Cancer* 1998;78:812–815.
 - 23 Alexandre J, Bleuzen P, Bonnetterre J et al. Factors predicting for efficacy and safety of docetaxel in a compassionate-use cohort of 825 heavily pretreated advanced breast cancer patients. *J Clin Oncol* 2000;18:562–573.
 - 24 Paik S, Tang G, Shak S et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006;24:3726–3734.
 - 25 Rouzier R, Perou CM, Symmans WF et al. Breast cancer molecular subtypes respond differently to preoperative chemotherapy. *Clin Cancer Res* 2005;11:5678–5685.
 - 26 Tordai A, Wang J, Andre F et al. Evaluation of biological pathways involved in chemotherapy response in breast cancer. *Breast Cancer Res* 2008;10:R37.
 - 27 Hugh J, Hanson J, Cheang MC et al. Breast cancer subtypes and response to docetaxel in node-positive breast cancer: Use of an immunohistochemical definition in the BCIRG 001 trial. *J Clin Oncol* 2009;27:1168–1176.
 - 28 Cole BF, Gelber RD, Gelber S et al. Polychemotherapy for early breast cancer: An overview of the randomised clinical trials with quality-adjusted survival analysis. *Lancet* 2001;358:277–286.
 - 29 Adjuvant Breast Cancer Trials Collaborative Group. Polychemotherapy for early breast cancer: Results from the international adjuvant breast cancer chemotherapy randomized trial. *J Natl Cancer Inst* 2007;99:506–515.
 - 30 Di Leo A, Bleiberg H, Buyse M. Overall survival is not a realistic end point for clinical trials of new drugs in advanced solid tumors: A critical assessment based on recently reported phase III trials in colorectal and breast cancer. *J Clin Oncol* 2003;21:2045–2047.
 - 31 Albain K, Barlow W, O'Malley F et al. Concurrent versus sequential chemohormonal therapy versus T alone for postmenopausal, node-positive, estrogen and/or progesterone receptor-positive breast cancer: Mature outcomes and new biologic correlates on phase III intergroup trial 0100 [abstract 37]. Presented at the 27th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 8–11, 2004.
 - 32 Goldhirsch A, Glick JH, Gelber RD et al. Meeting highlights: International expert consensus on the primary therapy of early breast cancer 2005. *Ann Oncol* 2005;16:1569–1583.
 - 33 Pusztaï L, Broglio K, Andre F et al. Effect of molecular disease subsets on disease-free survival in randomized adjuvant chemotherapy trials for estrogen receptor-positive breast cancer. *J Clin Oncol* 2008;26:4679–4683.
 - 34 Hess KR, Anderson K, Symmans WF et al. Pharmacogenomic predictor of sensitivity to preoperative chemotherapy with paclitaxel and fluorouracil, doxorubicin, and cyclophosphamide in breast cancer. *J Clin Oncol* 2006;24:4236–4244.