The Oncologist®
Breast Cancer

First-Line Chemotherapy for HER-2–Negative Metastatic Breast Cancer Patients Who Received Anthracyclines as Adjuvant Treatment

ALESSANDRO MORABITO,[a] MARIA CARMELA PICCIRILLO,[a] KATIA MONACO,[a] CARMEN PACILIO,[b] FRANCESCO NUZZO,[b] PAOLO CHIODINI,[c] CIRO GALLO,[c] ANDREA DE MATTEIS,[b] FRANCESCO PERRONE,[a] FOR THE NCI NAPLES BREAST CANCER GROUP

[a]Clinical Trials Unit and [b]Medical Oncology C, National Cancer Institute, Naples, Italy; [c]Department of Medicine and Public Health, Second University of Naples, Italy

Key Words. Metastatic breast cancer • Adjuvant anthracyclines • First-line chemotherapy • Taxanes

Disclosure: No potential conflicts of interest were reported by the authors, planners, reviewers, or staff managers of this article.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the value of retreatment with anthracyclines for HER-2–negative metastatic breast cancer patients who received anthracyclines as adjuvant treatment.
2. Discuss the role of liposomal anthracyclines, taxanes, and combinations without anthracyclines and taxanes, or innovative treatments, including target-based agents.
3. Comment on the weakness and quality of available evidence.

CME Access and take the CME test online and receive 1 *AMA PRA Category 1 Credit*™ at CME.TheOncologist.com

ABSTRACT

The treatment decision for patients with metastatic breast cancer who have received anthracyclines within the course of adjuvant chemotherapy is troublesome, particularly if trastuzumab and hormonal treatment are not indicated. In the first part of this review we discuss the value of retreatment with anthracyclines, a topic that has been indirectly evaluated by retrospective studies with conflicting results and within a small phase III trial with a negative outcome. Evidence on liposomal anthracyclines is also reviewed. In the second part of the review, alternative options of first-line chemotherapy are discussed. These include taxanes as single agents, taxanes in combination with other cytotoxic drugs, combinations without anthracyclines and taxanes, and innovative treatments including target-based agents. Both the amount and the quality of evidence on these treatments are poor. Few phase III studies are available and most of them have been performed with registrative aims sponsored by the companies who own the winning drug. Beyond indications derived from such studies, there is a great need for more clinical research in this setting. *The Oncologist* 2007;12:1288–1298

Correspondence: Francesco Perrone, M.D., Ph.D., Clinical Trials Unit, National Cancer Institute, Via Mariano Semmola, 80131 Naples, Italy. Telephone: 390815903522; Fax: 390817702938; e-mail: francesco.perrone@uosc.fondazionepascale.it Received July 20, 2007; accepted for publication October 5, 2007. 1083-7159/2007/$30.00/0 doi: 10.1634/theoncologist.12-11-1288

Introduction

"Madam, unfortunately you have already received anthracyclines during adjuvant treatment that has failed . . .". This incipit is being more and more frequently used in clinic, following the demonstration by the Early Breast Cancer Trialists' Collaborative Group that anthracycline-based adjuvant polychemotherapy (e.g., with fluorouracil, doxorubicin, and cyclophosphamide [FAC] or fluorouracil, epirubicin, and cyclophosphamide [FEC]) reduces the annual breast cancer death rate by about 38% for women younger than 50 years and by about 20% for those aged 50–69 years [1]. There is no doubt that breast cancer relapse after the most effective adjuvant treatment has been given (even acknowledging that the efficacy of taxanes has been recently demonstrated) is an unfortunate condition, for at least two reasons: first, the dismal prognosis of metastatic breast cancer, and second, the intrinsic difficulty in the choice of first-line chemotherapy approach to metastatic disease. Is rechallenge with anthracycline-containing regimens effective? Which alternative options should be considered? Such questions are particularly relevant when hormonal treatment has failed or is not indicated and for human epidermal growth factor receptor (HER)-2–negative metastatic breast cancer patients. In fact, for those with HER-2–positive tumors, trastuzumab plus taxanes [2, 3] or vinorelbine [4] can be considered standard combinations.

To answer the above questions, we performed a critical literature review, trying to summarize the best available evidence and focusing on pitfalls and biases that actually exist.

Methods

Data for this review were identified in December 2006, through MEDLINE, PubMed, and by systematic searches of conference proceedings from the 2002–2006 American Society of Clinical Oncology (ASCO) Annual Meetings and San Antonio Breast Cancer Symposium; one trial, previously identified as an abstract, has since been published, at the beginning of 2007, and the extended paper was considered for the review. Studies were eligible if they were published in the English language and reported results of randomized controlled trials investigating the role of a first-line chemotherapy regimen in patients who had received adjuvant anthracyclines. Selected phase II studies were also included if they supplied relevant information regarding the actual perspectives of clinical research. The level and grade of recommendation according to the Oxford Centre for Evidence Based Medicine (Table 1) have been applied to qualify the available evidence [5]. Subsequent to the peer-review process, some studies presented at the ASCO 2007 Annual Meeting were added to the review.

Table 1. Levels of evidence and grades of recommendation by Oxford Centre for Evidence-Based Medicine (May 2001)

Level	Type of evidence
1a	From a systematic review of multiple, well-designed, high-power, randomized, controlled trials
1b	From at least one well-designed, randomized, controlled trial with a narrow confidence interval
1c	From at least one well-designed, randomized, controlled trial in which all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it
2a	From a systematic review of cohort studies
2b	From at least one well-designed cohort study (including low-quality randomized controlled trials)
2c	From "outcomes" research
3a	From a systematic review of case-control studies
3b	From at least one well-designed case-control study
4	From case series (and poor quality cohort and case-control studies)
5	From expert opinion without explicit critical appraisal, or based on physiology, bench research, or "first principles"
Grade	**Grading of recommendation**
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level

Is Rechallenge with Anthracycline-Containing Regimens Effective in First-Line Therapy?

There are four available retrospective studies tackling this question [6–9], whose details have been summarized in Table 2. All followed the same schema, which was a retrospective analysis of the prognostic impact of previous adjuvant chemotherapy on the outcome of first-line chemotherapy with anthracycline-based regimens. All the studies included a group of patients who had received no adjuvant chemotherapy and another group who had received chemo-

Table 2. Activity of first-line anthracycline-containing regimens and prior adjuvant therapy

Study	*n* of patients	Adjuvant treatment	First-line chemotherapy Type	OS (mos)	TTP (mos)	RR (%)
Kardinal et al. (1988) [6]	425	Chemotherapy naive ($n = 379$)	CAF	19.6	10.6	59
		CMF-like ($n = 32$) or L-PAM ($n = 10$) or anthracycline based ($n = 2$) or others ($n = 2$)		17.5	9.4	50
Venturini et al. (1996) [7]	326	Chemotherapy naive ($n = 144$)	CEF	21.1[a]	11.4[a]	58[a]
		CMF-like ($n = 143$)		15.3	8.8	43
		Anthracycline based ($n = 39$)		15.8	6.6	44
Pierga et al. (2001) [8]	1,430	Chemotherapy naive ($n = 992$)	Anthracycline based	26[a]	14[a]	66[a]
		CMF-like ($n = 190$) or anthracycline based ($n = 165$)		19	10	56
Gennari et al. (2004) [9]	291	Chemotherapy naive ($n = 101$)	ET	27.5	12.5	68
		CMF ($n = 109$)		23.8	11	63
		Anthracyclines ($n = 81$)		20.2	10.2	67

[a]Statistically significant difference.
Abbreviations: CAF, cyclophosphamide, doxorubicin, and fluorouracil; CEF, cyclophosphamide, epirubicin, and fluorouracil; CMF, cyclophosphamide, methotrexate, and fluorouracil; ET, epirubicin and paclitaxel; L-PAM, melphalan; OS, overall survival; RR, response rate; TTP, time to progression.

therapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) or CMF-like regimens in the majority of cases, or anthracyclines. First-line treatment was homogeneous in three studies. All the studies included analyses for at least three outcomes: objective response rate, time to progression, and overall survival time. Results were consistent across the three outcomes in all the studies, and there was a trend toward a worse outcome for patients who had received adjuvant chemotherapy that was statistically significant for all endpoints in two studies [7, 8]. However, given the nonrandomized allocation of adjuvant chemotherapy, these findings could merely represent a selection bias, because patients with worse baseline prognosis could have been preferentially selected for adjuvant chemotherapy. No study found any difference between CMF-based and anthracycline-containing regimens for their impact on the outcome of first-line treatment with anthracyclines. So, the overall message coming from these studies is that rechallenge with anthracycline-based chemotherapy should not be excluded because of previous adjuvant chemotherapy, even if it already included anthracyclines. It was suggested, however, that the efficacy could be lower than for patients who had not received adjuvant chemotherapy.

To the best of our knowledge, only one study with a prospective design tackled the question of rechallenge with anthracycline-containing regimens [10]. It was a small randomized phase III trial comparing the efficacy of epirubicin plus docetaxel (ED) with that of docetaxel (D) alone as first-line chemotherapy of metastatic breast cancer patients pretreated with epirubicin in the adjuvant or neoadjuvant setting. Antitumor efficacy was similar in the two arms, while ED produced significantly worse toxicity in terms of leukopenia, nausea, and stomatitis (Table 3). Because of slow enrolment, the trial was closed before reaching the planned sample size and was substantially underpowered. A Bayesian post hoc analysis for the efficacy of ED was performed and showed that the predictive probability of a better response rate for the ED group than for the D group, if the trial had been brought to its completion, was equal to 0.0334 (Fig. 1), strengthening the conclusion of no greater activity of the ED treatment. All these findings lead us to not recommend the use of anthracycline-containing regimens as first-line therapy in anthracycline-pretreated metastatic breast cancer patients (level of evidence 2bB).

Is There a Role for Liposomal Anthracyclines?

It has been suggested that liposomal anthracyclines (pegylated and nonpegylated) maintain the efficacy of conventional anthracyclines and have a more favorable toxicity profile [11]. Lack of crossresistance with conventional anthracyclines has been demonstrated in preclinical studies [12]. A phase II trial has recently shown that pegylated liposomal doxorubicin (PLD) as a single agent retains some

Table 3. Summary of efficacy outcomes in the phase III trial of epirubicin and docetaxel versus docetaxel [10]

Endpoint	ED ($n = 26$)	D ($n = 25$)	p[a]
Objective response rate, % (95% exact CI)	72 (51–88)	79 (58–93)	.82[b]
Progression-free survival			.70[c]
Events, *n* (%)	22 (85)	23 (92)	
Median (95% CI), months	9 (7–13)	11 (9–15)	
Overall survival			.64[c]
Events, *n* (%)	15	15	
Median (95% CI), months	18 (15 to NA)	21 (18 to NA)	

[a]One-tailed *p*-value.
[b]From Fisher's exact test.
[c]From log-rank test.
Abbreviations: CI, confidence interval; ED, epirubicin plus docetaxel; D, docetaxel; NA, not available.

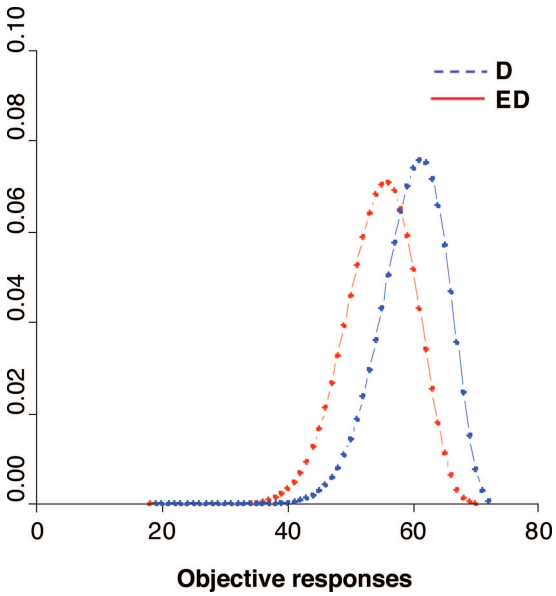

Figure 1. Predictive distributions of total number of responses for the epirubicin and docetaxel (ED) and docetaxel alone (D) arm in the trial of Pacilio et al. [10]. The predictive distribution for total responses in ED is positioned on the left, in a region of substantially fewer responses than that of D; therefore, the probability of a difference in response rates favoring ED is very low.

activity in patients with metastatic breast cancer previously treated with anthracyclines; the rate of success, including patients with an objective response and durable stable disease, was 24%, and there was no difference between patients who received PLD >12 months and those who received PLD ≤12 months after the last anthracycline treatment for metastatic disease (25% versus 24.1%, respectively) [13]. A new strategy for the use of liposomal anthracyclines was presented at the ASCO 2007 Annual Meeting by Alba et al. [14], who performed a phase III trial testing the efficacy of maintenance therapy with PLD for metastatic breast cancer patients who had not progressed after first-line chemotherapy with anthracyclines and taxanes. The authors found that maintenance therapy with PLD produced a significantly longer median time to progression (5 versus 8.3 months; hazard ratio [HR], 0.54; 95% CI, 0.38–0.77; $p = .0006$), with manageable toxicity. However, because of the selection of nonprogressive patients, this study cannot be interpreted as proof in favor of a lack of crossresistance, nor can it respond to whether or not it is opportune to treat patients who have received standard anthracyclines in their past with liposomal anthracyclines.

High response rates were reported in studies combining PLD with docetaxel [15, 16], paclitaxel [17], gemcitabine [18], and vinorelbine [19, 20]; in all these cases, of course, the other drug might have played a key role in determining the activity of the combination. The role of PLD in combination with docetaxel as compared with docetaxel alone is being assessed within a randomized phase III trial (the Doxil-BCA-3001 trial) that has already completed patient enrolment [21].

The activity of nonpegylated liposomal doxorubicin in the first-line treatment of metastatic breast cancer patients who have received prior adjuvant doxorubicin was evaluated in a retrospective analysis [22]. Data were pooled from two prospective, randomized, phase III clinical trials, comparing nonpegylated liposomal doxorubicin with conventional doxorubicin in combination with cyclophosphamide and as single agents, respectively [23, 24]. Significant differences for the overall response rate (31% versus 11%; $p = .04$) and median time to treatment failure (4.2 versus 2.1 months; $p = .001$) in favor of nonpegylated liposomal doxorubicin were observed, while there was no difference in survival. Moreover, treatment with nonpegylated liposomal doxorubicin was associated with a significantly lower risk for developing cardiotoxicity as compared with con-

ventional doxorubicin ($p = .001$). Such an analysis, although suggestive, has many limitations because of the pooling procedure of two subgroups from two different trials.

In summary, definitive data are not yet available to state whether the liposomal formulations are a worthwhile strategy for retreatment with anthracyclines.

Which Alternatives Can Be Considered for First-Line Chemotherapy of HER-2–Negative Metastatic Breast Cancer Patients Who Have Relapsed After Adjuvant Anthracyclines?

Taxanes as Single Agents

Both docetaxel and paclitaxel can be given as a single agent or in combination with other cytotoxic drugs (Table 4).

Docetaxel is the only single agent for which a survival advantage has been demonstrated in anthracycline-pretreated patients, within a comparison versus mitomycin C plus vinblastine. In that trial, advantages in the response rate and time to progression were also demonstrated [25]. Similar results were found in a phase III trial comparing docetaxel with sequential methotrexate and 5-fluorouracil, where docetaxel was more effective in terms of response rate and time to progression [26]. There is only one available head-to-head comparison between docetaxel and paclitaxel used as single agents with U.S. Food and Drug Administration–approved doses and schedules [27]. In that trial, docetaxel was superior to paclitaxel in terms of time to progression (5.7 versus 3.6 months; $p < .0001$), response duration (7.5 versus 4.6 months; $p = .01$), and survival (15.4 versus 12.7 months; $p = .03$) (level of evidence IbA). Moreover, a cost-effectiveness analysis of that study, considering clinical efficacy, quality-adjusted life-years, and direct medical costs in the United Kingdom as endpoints, showed that docetaxel is cost-effective compared with paclitaxel [28]. A way to deliver higher doses of paclitaxel and to improve its efficacy could be the binding of the drug to 130-nM albumin (nab-paclitaxel). In a study presented at the 2007 ASCO Annual Meeting, nab-paclitaxel (either weekly at a dose of 150 mg/m^2 or 3-weekly at a dose of 300 mg/m^2) resulted in a longer progression-free survival interval than with 3-weekly docetaxel, with a better safety profile [29]. To confirm these results, nab-paclitaxel (150 mg/m^2 weekly) will be compared with docetaxel (100 mg/m^2 every 3 weeks) in a large-scale, randomized phase III trial.

For both taxanes, a weekly schedule has been proposed. Weekly docetaxel was studied in a randomized phase II trial and was less toxic than and similarly active to the standard 3-weekly schedule [30]. Weekly paclitaxel resulted in a higher response rate (40% versus 28%; $p = .017$) and longer time to progression (9 versus 5 months; $p = .0008$) than with a standard 3-weekly schedule in the Cancer and Leukemia Group B 9840 trial [31]. These results were confirmed by the first results of the Anglo-Celtic IV study, showing that, for a matched total dose, weekly paclitaxel produced a higher response rate than the 3-weekly schedule (42% versus 27%; $p = .002$) [32]. Further, in a phase II trial dedicated to elderly patients, weekly paclitaxel produced a relatively high response rate of 54%, but also a quite high rate of cardiotoxicity (15% grade ≥ 2) that was not predictable at baseline [33]. In the adjuvant setting, the E1199 trial showed no difference in disease-free survival when comparing taxanes (paclitaxel versus docetaxel) or schedules (every 3 weeks versus weekly) [34]. Of note, the disease-free survival time was significantly longer in the weekly paclitaxel and every-3-week docetaxel arms, compared with the every-3-week paclitaxel arm. Therefore, head-to-head comparisons of the two taxanes given weekly as well as randomized trials comparing weekly taxanes with classic 3-weekly schemes or new formulations of taxanes could be useful in the metastatic setting to better define their efficacies and their roles in clinical practice.

Taxanes Combined with Other Cytotoxic Drugs

Capecitabine, gemcitabine, and platinum salts have been combined with taxanes in several studies.

A longer time to progression (6.1 versus 4.2 months; $p = .0001$) and survival time (14.5 versus 11.5 months; $p = .01$) were found when comparing the combination of capecitabine (1,250 mg/m^2 twice daily on days 1–14) and docetaxel (75 mg/m^2 on day 1, every 3 weeks) with single-agent docetaxel (100 mg/m^2) [35]. However, the toxicity of this combination was severe, particularly for gastrointestinal side effects and hand–foot syndrome; more patients in the combination arm required dose reductions, and subgroup analyses showed that patients >60 years of age were particularly at risk for treatment interruption because of side effects. A later retrospective analysis of the study suggested that lowering the dose of capecitabine and docetaxel can improve tolerability and reduce the rate of treatment interruptions without losing the efficacy advantage over single-agent docetaxel [36]. In contrast, sequential use of the two drugs does not seem to be a useful strategy to overcome toxicity. Two trials were reported at the 2006 ASCO Annual Meeting comparing sequential with combined treatment; in the first one, the combination was superior to the sequential scheme in terms of response rate, time to progression, and survival [37]; in the second one, also including paclitaxel as an alternative to docetaxel, the objective

Table 4. Regimens evaluated in phase III clinical trials dedicated to anthracyclines-pretreated metastatic breast cancer patients

Study	*n* of patients	Treatment line	Treatment arms	Median OS (mos)	Median TTP (mos)	RR (%)	Main differences in toxicity profile
Nabholtz et al. (1999) [25][b]	392	First and second	Docetaxel (D) versus vinblastine + mitomycin (VM)	11.4,[a] 8.7	4.7,[a] 2.7	30,[a] 11.6	More neutropenia with D and thrombocytopenia with VM
Sjöström et al. (1999) [26][b]	283	First and second	Docetaxel (D) versus methotrexate + fluorouracil (MF)	10.4, 11.1	6.3,[a] 3.0	42,[a] 21	More leukopenia, neuropathy edema, asthenia, and skin toxicity with D
O'Shaughnessy et al. (2002) [35][b]	511	First, second, and third	Capecitabine + docetaxel (CD) versus docetaxel (D)	14.5,[a] 11.5	6.1,[a] 4.2	42,[a] 30	More stomatitis, diarrhea, and HFS with CD and neutropenic fever, myalgia, and arthralgia with D
Albain et al. (2004) [39][b,c]	529	First	Gemcitabine + paclitaxel (GP) versus paclitaxel (P)	18.5,[a] 15.8	5.4,[a] 3.5	39,[a] 25	More hematological toxicity with GP
Jones et al. (2005) [27][b]	449	First and second	Paclitaxel (P) versus docetaxel (D)	12.7, 15.4[a]	3.6, 5.7[a]	25, 31	More hematological and nonhematological toxicities with D
Chan et al. (2005) [40][b,c]	305	First and second	Gemcitabine + docetaxel (GD) versus capecitabine + docetaxel (CD)	NR	8.1, 8.1	32, 32	More diarrhea, mucositis, HFS, and drug-related discontinuation with CD
Miller et al. (2005) [54][b,c]	682	First	Paclitaxel + bevacizumab (PB) versus paclitaxel (P)	HR, 0.64	11,[a] 6.1	28.2,[a] 14.2	More hypertension, proteinuria, and neuropathy with PB
Beslija et al. (2006) [37][c]	100	First	Capecitabine + docetaxel (CD) versus capecitabine→docetaxel (C→D)	22,[a] 19	9.3,[a] 7.7	68,[a] 40	More HFS and stomatitis with CD
Soto et al. (2006) [38][c]	368	First and second	Capecitabine→taxanes versus capecitabine + paclitaxel or capecitabine + docetaxel	24+, 24+, 24+	8.4, 6.7, 8.1	46, 65,[a] 74[a]	More alopecia in the combination arms
Mavroudis et al. (2006) [47][c]	114	Salvage	Gemcitabine + vinorelbine (GV) versus capecitabine (C)	NR	3.7, 5.8	25.8, 24.1	More hematological toxicity with GV; more common HFS with C
Pacilio et al. (2006) [10]	51	First	Epirubicin + docetaxel (ED) versus docetaxel (D)	18, 21	9, 11	72, 79	More leukopenia, nausea, and stomatitis with ED
Batist et al. (2006) [22]	68	First	Nonpegylated liposomal doxorubicin (M) versus doxorubicin (A) (pooled data)	16, 15	4.5, 3.4	31,[a] 11	More cardiac toxicity with A
Martin et al. (2007) [46]	252	First, second, and third	Gemcitabine + vinorelbine (GV) versus vinorelbine (V)	NR	6.3,[a] 4.1	37,[a] 25	More hematological toxicity with GV
Vahdat et al. (2007) [49][b,c]	752	Second and third	Ixabepilone + capecitabine (IC) versus capecitabine (C)	NR	5.8,[a] 4.2	35,[a] 14	More hematologic toxicity, peripheral neuropathy, and myalgia with IC

[a]Statistically significant difference.
[b]Profit study.
[c]Study reported only as abstract as of December 2006.
Abbreviations: HFS, hand–foot syndrome; HR, hazard ratio; NR, not reported; OS, overall survival; RR, response rate; TTP, time to progression.

response rate was significantly higher in the combination arms (65% and 74% versus 46%), while there was no difference in terms of the progression-free and overall survival times [38]. On this basis, the docetaxel plus capecitabine combination, at moderated doses (950 mg/m^2 twice daily on days 1–14 and 60 mg/m^2 on day 1, respectively, every 3 weeks), can be considered for the treatment of fit patients with anthracycline-pretreated metastatic breast cancer (level of evidence IbA).

Two trials have been performed testing the combination of taxanes with gemcitabine. The first one, which led to registration of gemcitabine in breast cancer, showed a longer time to progression (5.4 versus 3.5 months) and survival time (18.5 versus 15.8 months) for the combination of paclitaxel plus gemcitabine compared with single-agent paclitaxel [39]. The combination therapy produced more grade 4 hematological toxicities, while nonhematological toxicities were manageable in both arms. As of September 1, 2007, an extended paper of this registrative trial had not been published. The second trial failed to demonstrate superiority of the combination of gemcitabine plus docetaxel over capecitabine plus docetaxel; the median progression-free survival time (35 weeks) and response rate (32%) were the same in both arms [40]. The safety profile seemed to favor gemcitabine plus docetaxel, thanks to a lower occurrence of drug-related discontinuation (13% versus 28%), less grade 3 hand–foot syndrome (0% versus 26%), less grade 3–4 diarrhea (7% versus 18%), and less grade 3–4 mucositis (4% versus 17%). An extended publication is awaited for this study as well.

Finally, several phase II studies combining taxanes with platinum salts have suggested that such combinations are active and well tolerated in metastatic breast cancer, with varying degrees of activity according to the different schedules used and the proportion of anthracycline-resistant patients [41]. In a phase III study, the combination of paclitaxel and carboplatin showed no significant difference in survival as compared with paclitaxel and epirubicin; however, only 25% of patients in that study had received adjuvant anthracyclines [42]. Thus, the level of recommendation of such a combination for this subgroup of patients remains low (level of evidence IbB).

Combinations Without Anthracyclines and Taxanes

Treatment options for those patients who develop metastatic disease after having received adjuvant anthracyclines and taxanes are controversial.

The combination of gemcitabine and vinorelbine represents an attractive schedule, as a result of its activity and favorable safety profile. Response rates in the range of 21%–54% have been reported in phase II studies, depending on patient characteristics, dose and schedule of the two drugs, and type of previous chemotherapy administered [43–45]. A recently published phase III study, including metastatic breast cancer patients previously treated with anthracyclines and taxanes, at their first, second, or third line of treatment, demonstrated a significant advantage with the combination of the two drugs over vinorelbine alone in terms of the progression-free survival time (6 versus 4 months, respectively; $p = .0028$), while the survival duration (15.9 versus 16.4 months; $p = .805$) and response rate (36% versus 26%; $p = .093$) were not different [46]. The incidence of hematological toxicity was significantly higher with the combination of the two drugs, while the incidence of nonhematological toxicity was low and manageable in both arms (level of evidence IbA). However, it was reported at the 2006 ASCO Annual Meeting that the same combination (with slight differences in the schedule) was not superior to single-agent capecitabine [47].

A new option for treatment is the epothilones, a novel class of antineoplastic agents with low susceptibility to tumor resistance mechanisms and demonstrated clinical activity in patients pretreated with anthracyclines, taxanes, and capecitabine [48]. A randomized phase III trial, dedicated to patients pretreated with anthracyclines and taxanes, recently demonstrated that the combination of ixabepilone and capecitabine resulted in a longer progression-free survival time (median, 5.8 versus 4.2 months, respectively; $p = .0003$) and higher response rate (35% versus 14%, respectively; $p < .0001$), as compared with capecitabine alone, with manageable toxicity [49]. These results support that ixabepilone plus capecitabine can be effective for patients with anthracycline- and taxane-resistant metastatic breast cancer.

Other combinations of cytotoxic drugs have been evaluated in phase II studies. For instance, the combination of vinorelbine and capecitabine has been shown to have antitumor activity (response rate, 37%–55%) with limited toxicity, even after previous treatment with anthracyclines and taxanes [50, 51]. Combinations of vinorelbine or gemcitabine with platinum salts have produced high response rates but with a significant burden of hematological toxicity, often requiring dose reduction and treatment discontinuation [52].

What Is the Role of Target-Based Agents?

The increased knowledge of the molecular mechanisms that regulate cancer cell proliferation and survival has produced new biological drugs with specific molecular targets that are currently in clinical development in breast cancer and

could shortly become part of the first-line treatment for patients with metastatic disease.

Bevacizumab, a humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF)-A ligand, is the most mature target-based agent with antiangiogenetic activity. However, a phase III trial of bevacizumab plus capecitabine versus capecitabine alone in anthracycline- and taxane-pretreated patients failed to show a difference in progression-free and overall survival times despite a significant twofold higher response rate [53]. Subsequently, a large, international phase III trial of the Eastern Cooperative Oncology Group (E2100) tested the addition of bevacizumab to first-line paclitaxel [54]. Almost all of the patients had tumors that did not overexpress HER-2. The first interim data analysis, which led to early stopping of the study, showed that the addition of bevacizumab to paclitaxel resulted in a higher response rate, 28.2% versus 14.2%, and longer median progression-free survival time, nearly 11 versus 6.1 months, with an HR of progression of 0.50 (95% CI, 0.40–0.62) in favor of patients receiving bevacizumab. More neuropathy was seen in women receiving the combination therapy than in those receiving paclitaxel alone (20.5 versus 14.2%; $p = .01$), but this finding might be a result of the longer exposure to paclitaxel in the combination arm. Although longer follow-up is required, early data suggest that the overall survival time is longer with the addition of bevacizumab to paclitaxel (HR, 0.67; 95% CI, 0.50–0.92).

The small molecules that inhibit the tyrosine kinase activity of VEGF receptors (VEGFRs) represent another opportunity for treatment targeting the VEGF pathway. Sunitinib, targeting the VEGFRs, platelet-derived growth factor receptor β and c-Kit, is being evaluated in metastatic breast cancer patients resistant to anthracyclines and taxanes. Preliminary data show a good safety profile and sufficient activity, with four partial responses and five cases of stable disease in 23 patients [55]. Several phase III trials are evaluating the efficacy of the addition of sunitinib to docetaxel, trastuzumab, and capecitabine and comparing sunitinib with chemotherapy or sunitinib and paclitaxel with paclitaxel and bevacizumab. Moreover, phase I–II studies are ongoing with vatalanib, a potent inhibitor of all known VEGFR tyrosine kinases, and sorafenib, a dual inhibitor of Raf kinase and VEGFRs [56].

Although agents directed against the epidermal growth factor receptor (EGFR) have shown early clinical activity, initial phase II studies have suggested that the EGFR tyrosine kinase inhibitors gefitinib and erlotinib are not sufficiently active as single agents in heavily pretreated metastatic breast cancer patients [57–59]. However, in patients resistant to tamoxifen, gefitinib might have a therapeutic effect [60]. Finally, there is evidence regarding the synergy of anti-EGFR therapy and chemotherapy. Namely, a 54% response rate (95% CI, 45%–75%) with the combination of gefitinib and docetaxel as first-line treatment of women with metastatic breast cancer was reported in a phase II trial [61].

Pitfalls and Quality of Available Evidence

On the basis of the evidence that we have collected and presented in the above paragraphs, we consider that the amount and the quality of the available data on which therapeutic decisions should be based are particularly dismal. Considering patients who have not received taxanes as adjuvant, we have found 10 phase III studies. Of these, one, conducted by our group, indicates that rechallenge with anthracyclines is probably not worthwhile; five studies were reported only at ASCO meetings, but they have not been published yet as extended papers; and the remaining four studies have been all sponsored by the pharmaceutical industry holding the license of the winner drug.

At best, according to the Oxford Centre for Evidence-Based Medicine recommendation [5], we can give a grade A recommendation for single-agent docetaxel (four trials available with consistent results, of which three were sponsored by the pharmaceutical industry) and for the combination of capecitabine and docetaxel (two trials available, of which one was sponsored by the pharmaceutical industry and the other one is not yet published). For patients who are not eligible both for anthracyclines and taxanes, we can give a grade A recommendation for gemcitabine plus vinorelbine.

There can be several reasons for such poor evidence. First of all, the clinical problem has become important quite recently, because of advances in adjuvant chemotherapy. Second, the academic interest for this setting of research has been very low during recent years. This can be explained by the interest in more innovative target-based drugs. It is also possible that interest has been lowered by the feeling that testing different combinations or sequences of known chemotherapeutic agents has a very low chance of significantly changing the outcome of metastatic breast cancer patients who have already failed most effective drugs in the adjuvant setting. As a consequence, only trials proposed by industries with registrative aims have been pursued. In the long run, this could bias our knowledge, because of a possible prevalence of positive results [62] and a low number of trials addressing strategies or hypotheses that might be clinically relevant, although not consistent with the direct interests of the pharmaceutical industry. Finally, another reason for the weakness of the current evidence is that some trials have not been published yet as extended papers, although some of these studies were pre-

sented 2 or 3 years ago at ASCO meetings. Even accepting that all the phase III studies cited above will be rapidly published with results superimposable to those previously presented, the overall judgment on the poorness of the knowledge in this field would not change substantially.

Future Perspectives and Conclusions

The most desired perspective by clinical oncologists is the possibility of predicting patient-by-patient which is the best treatment option on the basis of biological characteristics of the tumor. In the field that we are addressing (chemotherapy of metastatic breast cancer already pretreated with anthracyclines) such a perspective is quite far from being realized. It has been suggested that amplification of the topoisomerase-IIα gene is a positive marker for efficacy of anthracycline-based chemotherapy [63], but there are no data to support its testing as a tool to decide about retreatment with anthracyclines after failure of these drugs in the adjuvant setting. Mutations of the *p53* gene have been proposed as predictive of lower sensitivity to anthracyclines [64]. Such mutations are quite frequent among the so-called triple-negative tumors (i.e., those that are estrogen receptor, progesterone receptor, and HER-2 negative), corresponding to the basal-like subgroup identified through molecular subtyping [65]. Consistently, such tumors are less sensitive to anthracyclines [66]. Triple-negative tumors also share phenotypical and molecular features with *BRCA-1*-related cancers [67]. A retrospective analysis has recently shown that the presence of *BRCA-1* mutations in triple-negative breast cancer decreases anthracycline-based chemotherapy efficacy [68]. Such results, if confirmed, would discourage the use (and even more, the rechallenge) of anthracyclines. However, neither topoisomerase-IIα nor *p53* or *BRCA-1* is currently used in clinical practice for treatment decisions.

In conclusion, while we acknowledge that the most interesting trials for the future are those testing the activity and the efficacy of newer target-based agents, we believe that efforts should also be made to improve the quality of the evidence on which we still decide the treatment for many thousands of breast cancer patients. Some unsolved questions remain, including the use of weekly schedules or sequential strategies, optimal modalities of combinations of target-based agents, appropriate patient selection possibly based on molecular features of the tumor, and evaluation of surrogate biomarkers of activity. A renewed interest in this kind of research by academic organizations could play an important role in addressing these issues.

Appendix

The following are members of the NCI-Naples Breast Cancer Group who contributed to this manuscript: Cell Biology and Preclinical Models Unit: Nicola Normanno, Amelia D'Alessio, Monica Rosaria Maiello, Adele Carotenuto, Gianfranco De Feo, Anna Maria Rachiglio; Clinical Trials Unit: Francesco Perrone, Alessandro Morabito, Ermelinda De Maio, Massimo Di Maio, Mario Iaccarino, Maria Carmela Piccirillo, Katia Monaco, Jane Bryce, Fabiano Falasconi, Antonia Del Giudice; Medical Oncology C: Andrea de Matteis, Francesca Di Rella, Adriano Gravina, Vincenzo Labonia, Gabriella Landi, Francesco Nuzzo, Carmen Pacilio, Emanuela Rossi, Rosa Fiore; Nuclear Medicine: Secondo Lastoria, Corradina Caracò, Luigi Aloj; Pathology: Gerardo Botti, Maurizio Di Bonito, Maria Pia Curcio, Franca Formichelli, Franca La Vecchia, Maria Staiano; Pharmacy: Maria Rosaria Salzano, Piera Maiolino; Radiology: Alfredo Siani, Teresa Petrosino, Rosaria Rubulotta, Paolo Vallone, Mauro Matta Ceraso, Antonella Petrillo, Orlando Catalano, Fabio Sandomenico; Radiotherapy: Brunello Morrica; Senology: Giuseppe D'Aiuto, Franca Avino, Immacolata Capasso, Massimiliano D'Aiuto, Claudio Longo, Massimo Rinaldo, Renato Thomas; Department of Medicine and Public Health (Second University of Naples): Ciro Gallo, Giuseppe Signoriello, Paolo Chiodini.

Acknowledgments

The Clinical Trials Unit and the Division of Medical Oncology C of the National Cancer Institute of Naples have received funding from the nonprofit "Associazione Italiana per la Ricerca sul Cancro - AIRC" for research projects on breast cancer.

References

1 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.

2 Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–792.

3 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.

4 Chan A. A review of the use of trastuzumab (Herceptin) plus vinorelbine in metastatic breast cancer. Ann Oncol 2007;18:1152–1158.

5 Phillips B, Ball C, Sackett DL et al. Levels of evidence and grades of recommendation. Centre for Evidence-Based Medicine: Oxford-Centre for Evidence Based Medicine, 2001. Available at http://www.cebm.net/index.aspx?o=1025. Accessed September 1, 2007.

6 Kardinal CG, Perry MC, Korzun AH et al. Responses to chemotherapy or

chemohormonal therapy in advanced breast cancer patients treated previously with adjuvant chemotherapy. A subset analysis of CALGB Study 8081. Cancer 1988;61:415–419.

7 Venturini M, Bruzzi P, Del Mastro L et al. Effect of adjuvant chemotherapy with or without anthracyclines on the activity and efficacy of first-line cyclophosphamide, epidoxorubicin, and fluorouracil in patients with metastatic breast cancer. J Clin Oncol 1996;14:764–773.

8 Pierga JY, Asselain B, Jouve M et al. Effect of adjuvant chemotherapy on outcome in patients with metastatic breast carcinoma treated with first-line doxorubicin-containing chemotherapy. Cancer 2001;91:1079–1089.

9 Gennari A, Bruzzi P, Orlandini C et al. Activity of first-line epirubicin and paclitaxel in metastatic breast cancer is independent of type of adjuvant therapy. Br J Cancer 2004;90:962–967.

10 Pacilio C, Morabito A, Nuzzo F et al. Is epirubicin effective in first-line chemotherapy of metastatic breast cancer (MBC) after an epirubicin-containing adjuvant treatment? A single centre phase III trial. Br J Cancer 2006;94:1233–1236.

11 Rivera E. Liposomal anthracyclines in metastatic breast cancer: Clinical update. ***The Oncologist*** 2003;8(suppl 2):3–9.

12 Vail DM, Amantea MA, Colbern GT et al. Pegylated liposomal doxorubicin: Proof of principle using preclinical animal models and pharmacokinetic studies. Semin Oncol 2004;31(suppl 13):16–35.

13 Al-Batran SE, Bischoff J, von Minckwitz G et al. The clinical benefit of pegylated liposomal doxorubicin in patients with metastatic breast cancer previously treated with conventional anthracyclines: A multicentre phase II trial. Br J Cancer 2006;94:1615–1620.

14 Alba E, Ruiz-Borrego M, Martin M et al. Maintenance therapy with PLD following standard chemotherapy for MBC significantly prolongs TTP in a multicenter phase III randomized trial: GEICAM 2001–01 study. Proc Am Soc Clin Oncol 2007;25(18 suppl):33s.

15 Morabito A, Gattuso D, Stani SC et al. Safety and activity of the combination of pegylated liposomal doxorubicin and weekly docetaxel in advanced breast cancer. Breast Cancer Res Treat 2004;86:249–257.

16 Alexopoulos A, Karamouzis MV, Stavrinides H et al. Phase II study of pegylated doxorubicin (Caelyx) and docetaxel as first-line treatment in metastatic breast cancer. Ann Oncol 2004;15:891–895.

17 Jones V, Finucane D, Rodriguez R et al. Phase II study of weekly paclitaxel (Taxol) and liposomal doxorubicin (Doxil) in patients with locally advanced and metastatic breast cancer. Proc Am Soc Clin Oncol 2000;19:113a.

18 Rivera E, Valero V, Arun B et al. Phase II study of pegylated liposomal doxorubicin in combination with gemcitabine in patients with metastatic breast cancer. J Clin Oncol 2003;21:3249–3254.

19 Ardavanis A, Mavroudis D, Kalbakis K et al. Pegylated liposomal doxorubicin in combination with vinorelbine as salvage treatment in pretreated patients with advanced breast cancer: A multicentre phase II study. Cancer Chemother Pharmacol 2006;58:742–748.

20 Martin M, Garcia-Donas J, Casado A et al. Phase II study of pegylated liposomal doxorubicin plus vinorelbine in breast cancer with previous anthracycline exposure. Clin Breast Cancer 2004;5:353–357.

21 A Study of Docetaxel Monotherapy or Doxil®/Caelyx® and Docetaxel in Patients with Advanced Breast Cancer. Available at http://www.clinicaltrials.gov/ct/show/NCT00091442. Accessed April 4, 2007.

22 Batist G, Harris L, Azarnia N et al. Improved anti-tumor response rate with decreased cardiotoxicity of non-pegylated liposomal doxorubicin compared with conventional doxorubicin in first-line treatment of metastatic breast cancer in patients who had received prior adjuvant doxorubicin: Results of a retrospective analysis. Anticancer Drugs 2006;17:587–595.

23 Batist G, Ramakrishnan G, Rao CS et al. Reduced cardiotoxicity and preserved antitumor efficacy of liposome-encapsulated doxorubicin and cyclophosphamide compared with conventional doxorubicin and cyclophosphamide in a randomized, multicenter trial of metastatic breast cancer. J Clin Oncol 2001;19:1444–1454.

24 Harris L, Batist G, Belt R et al. Liposome-encapsulated doxorubicin compared with conventional doxorubicin in a randomized multicentre trial as first-line therapy of metastatic breast carcinoma. Cancer 2002;94:25–36.

25 Nabholtz J-M, 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.

26 Sjöström J, Blomqvist C, Mouridsen H et al. Docetaxel compared with sequential methotrexate and 5-fluorouracil in patients with advanced breast cancer after anthracycline failure: A randomised phase III study with crossover on progression by the Scandinavian Breast Group. Eur J Cancer 1999;35:1194–1200.

27 Jones SE, Erban J, Overmoyer B et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 2005;23:5542–5551.

28 Jones SE, Benedict A, Cameron D et al. Cost-effectiveness of docetaxel compared to paclitaxel in metastatic breast cancer: A UK health economic analysis. Proc Am Soc Clin Oncol 2007;25(18 suppl):52s.

29 Gradishar WJ, Krasnojon D, Cheporov S et al. Randomized comparison of weekly or every-3-week nab-paclitaxel vs. every-3-week docetaxel as 1st-line therapy in patients with metastatic breast cancer. Proc Am Soc Clin Oncol 2007;25(18 suppl):40s.

30 Tabernero J, Climent MA, Lluch A et al. A multicentre, randomised phase II study of weekly or 3-weekly docetaxel in patients with metastatic breast cancer. Ann Oncol 2004;15:1358–1365.

31 Seidman AD, Berry D, Cirrincione C et al. CALGB 9840: Phase III study of weekly (W) paclitaxel (P) via 1-hour (h) infusion versus standard (S) 3h infusion every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomized for T in HER2 normal MBC. Proc Am Soc Clin Oncol 2004;22(14 suppl):6s.

32 Verril MW, Lee J, Cameron DA et al. Anglo-Celtic IV: First results of a UK National Cancer Research Network randomised phase 3 pharmacogenetic trial of weekly versus 3 weekly paclitaxel in patients with locally advanced or metastatic breast cancer. Proc Am Soc Clin Oncol 2007;25(18 suppl):33s.

33 Del Mastro L, Perrone F, Repetto L et al. Weekly paclitaxel as first-line chemotherapy in elderly advanced breast cancer patients: A phase II study of the Gruppo Italiano di Oncologia Geriatrica (GIOGer). Ann Oncol 2005;16:253–258.

34 Sparano JA, Wang M, Martino S et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in operable breast cancer: Results of Intergroup Trial E1199. Proc Am Soc Clin Oncol 2007;25(18 suppl):6s.

35 O'Shaughnessy J, Miles D, Vukelja S et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. J Clin Oncol 2002;20:2812–2823.

36 Leonard R, O'Shaughnessy J, Vukelja S et al. Detailed analysis of a randomized phase III trial: Can the tolerability of capecitabine plus docetaxel be improved without compromising its survival advantage? Ann Oncol 2006;17:1379–1385.

37 Beslija S, Obralic N, Basic H et al. Randomized trial of sequence vs. combination of capecitabine (X) and docetaxel (T): XT vs T followed by X after

progression as first line therapy for patients (pts) with metastatic breast cancer (MBC). Proc Am Soc Clin Oncol 2006;24(18 suppl):18s.

38 Soto C, Torrecillas S, Reyes S et al. Capecitabine (X) and taxanes in patients (pts) with anthracycline-pretreated metastatic breast cancer (MBC): Sequential vs. combined therapy results from a MOSG randomized phase III trial. Proc Am Soc Clin Oncol 2006;24(18 suppl):20s.

39 Albain KS, Nag S, Calderillo-Ruiz G et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs. paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival. Proc Am Soc Clin Oncol 2004;22(14 suppl):5s.

40 Chan S, Romieu G, Huober J et al. Gemcitabine plus docetaxel (GD) versus capecitabine plus docetaxel (CD) for anthracycline-pretreated metastatic breast cancer (MBC) patients (pts): Results of a European phase III study. Proc Am Soc Clin Oncol 2005;23(16 suppl):24s.

41 Decatris MP, Sundar S, O'Byrne KJ. Platinum-based chemotherapy in metastatic breast cancer: Current status. Cancer Treat Rev 2004;30:53–81.

42 Fountzilas G, Kalofonos HP, Dafni U et al. Paclitaxel and epirubicin versus paclitaxel and carboplatin as first-line chemotherapy in patients with advanced breast cancer: A phase III study conducted by the Hellenic Cooperative Oncology Group. Ann Oncol 2004;15:1517–1526.

43 Nicolaides C, Dimopoulos MA, Samantas E et al. Gemcitabine and Vinorelbine as second-line treatment in patients with metastatic breast cancer progressing after first-line taxane-based chemotherapy: A phase II study conducted by the Hellenic Cooperative Oncology Group. Ann Oncol 2000; 11:873–875.

44 Morabito A, Filippelli G, Palmeri S et al. The combination of gemcitabine and vinorelbine is an active regimen as second-line therapy in patients with metastatic breast cancer pretreated with taxanes and/or anthracyclines: A phase I-II study. Breast Cancer Res Treat 2003;78:29–36.

45 Rossi E, Perrone F, Labonia V et al. Is gemcitabine plus vinorelbine active in second-line chemotherapy of metastatic breast cancer? A single-center phase 2 study. Oncology 2003;64:479–480.

46 Martín M, Ruiz A, Muñoz M et al. Gemcitabine plus vinorelbine versus vinorelbine monotherapy in patients with metastatic breast cancer previously treated with anthracyclines and taxanes: Final results of the phase III Spanish Breast Cancer Research Group (GEICAM) trial. Lancet Oncol 2007;8:219–225.

47 Mavroudis D, Ardavanis A, Boukovinas I et al. A multicenter randomized study comparing vinorelbine plus gemcitabine versus capecitabine monotherapy as salvage treatment in patients with advanced breast cancer pretreated with taxane and anthracycline chemotherapy: A preliminary report. Proc Am Soc Clin Oncol 2006;24(18 suppl):42s.

48 Thomas E, Perez EA, Mukhopadhyay P et al. Phase II trial of ixabepilone in patients with metastatic breast cancer (MBC) who are resistant to an anthracycline, a taxane and capecitabine. Proc Am Soc Clin Oncol 2006; 24(18 suppl):42s.

49 Vahdat LT, Thomas E, Li R et al. Phase III trial of ixabepilone plus capecitabine compared to capecitabine alone in patients with metastatic breast cancer (MBC) previously treated or resistant to an anthracycline and resistant to taxanes. Proc Am Soc Clin Oncol 2007;25(18 suppl):33s.

50 Welt A, von Minckwitz G, Oberhoff C et al. Phase I/II study of capecitabine and vinorelbine in pretreated patients with metastatic breast cancer. Ann Oncol 2005;16:64–69.

51 Nole F, Catania C, Munzone E et al. Capecitabine/vinorelbine: An effective and well-tolerated regimen for women with pretreated advanced-stage breast cancer. Clin Breast Cancer 2006;6:518–524.

52 Nagourney RA, Link JS, Blitzer JB et al. Gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed breast cancer patients. J Clin Oncol 2000;18:2245–2249.

53 Miller KD, Chap LI, Holmes FA et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005;23:792–799.

54 Miller KD, Wang M, Gralow J et al. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first line therapy for locally recurrent or metastatic breast cancer: A trial coordinated by the Eastern Cooperative Oncology Group (E2100). Breast Cancer Res Treat 2005; 94(suppl 1):S6.

55 Schneider BP, Miller KD. Angiogenesis of breast cancer. J Clin Oncol 2005;23:1782–1790.

56 Morabito A, De Maio E, Di Maio M et al. Tyrosine kinase inhibitors of vascular endothelial growth factor receptors in clinical trials: Current status and future directions. ***The Oncologist*** 2006;11:753–764.

57 von Minckwitz G, Jonat W, Fasching P et al. A multicentre phase II study on gefitinib in taxane- and anthracycline-pretreated metastatic breast cancer. Breast Cancer Res Treat 2005;89:165–172.

58 Baselga J, Albanell J, Ruiz A et al. Phase II and tumor pharmacodynamic study of gefitinib in patients with advanced breast cancer. J Clin Oncol 2005;23:5323–5333.

59 Winer E, Cobleigh M, Dickler M et al. Phase II multicenter study to evaluate the efficacy and safety of Tarceva (erlotinib, OSI-774) in women with previously treated locally advanced or metastatic breast cancer. Breast Cancer Res Treat 2002;76(suppl 1):S115.

60 Robertson JFR, Gutteridge E, Cheung KL et al. Gefitinib (ZD1839) is active in acquired tamoxifen (TAM)-resistant oestrogen receptor (ER)-positive and ER negative breast cancer: Results from a phase II study. Proc Am Soc Clin Oncol 2003;22:7.

61 Ciardiello F, Troiani T, Caputo F et al. Phase II study of gefitinib in combination with docetaxel as first-line therapy in metastatic breast cancer. Br J Cancer 2006;94:1604–1609.

62 Als-Nielsen B, Chen W, Gluud C et al. Association of funding and conclusions in randomized drug trials: A reflection of treatment effect or adverse events? JAMA 2003;290:921–928.

63 Coon JS, Marcus E, Gupta-Burt S et al. Amplification and overexpression of topoisomerase IIalpha predict response to anthracycline-based therapy in locally advanced breast cancer. Clin Cancer Res 2002;8:1061–1067.

64 Di Leo A, Tanner M, Desmedt C et al. p-53 gene mutations as a predictive marker in a population of advanced breast cancer patients randomly treated with doxorubicin or docetaxel in the context of a phase III trial. Ann Oncol 2007;18:997–1003.

65 Perou CM, Sorlie T, Eisen MB et al. Molecular portraits of human breast tumours. Nature 2000;406:747–752.

66 Cleator S, Heller W, Coombes RC. Triple-negative breast cancer: Therapeutic options. Lancet Oncol 2007;8:235–244.

67 Turner N, Tutt A, Ashworth A. Hallmarks of 'BRCAness' in sporadic cancers. Nat Rev Cancer 2004;4:814–819.

68 Petit T, Wilt M, Rodier J et al. Are BRCA1 mutations a predictive factor for anthracycline-based neoadjuvant chemotherapy response in triple negative breast cancers? Proc Am Soc Clin Oncol 2007;25(18 suppl):580.