Multiple-Treatments Meta-analysis of Chemotherapy and Targeted Therapies in Advanced Breast Cancer

Davide Mauri, Nikolaos P. Polyzos, Georgia Salanti, Nicholas Pavlidis, John P. A. Ioannidis

Background Many systemic nonhormonal regimens have been evaluated across several hundreds of randomized trials in advanced breast cancer. We aimed to quantify the relative merits of these regimens in prolonging survival.

Methods We performed a systematic review of all trials that compared different regimens involving chemotherapy and/or targeted therapy in advanced breast cancer (1973–2007). Regimens were categorized a priori into different treatment types. We performed multiple-treatments meta-analysis and calculated hazard ratios for each treatment category relative to monotherapy with old agents (ie, regimens not including anthracyclines, anthracenediones, vinorelbine, gemcitabine, capecitabine, taxanes, marimastat, thalidomide, trastuzumab, lapatinib, or bevacizumab).

Results We identified 370 eligible randomized trials (54 189 patients), of which 172 (31 552 patients) compared different types of treatment. Survival data from 148 comparisons pertaining to 128 of the 172 trials (26 031 patients, 22 different types of treatment) were available for inclusion in the multiple-treatments meta-analysis. Compared with single-agent chemotherapy with old nonanthracycline drugs, anthracycline regimens achieved 22%–33% relative risk reductions in mortality (ie, hazard ratio [HR] for standard-dose anthracycline-based combination: 0.67, 95% credibility interval [CrI] 0.57–0.78). Several newer regimens achieved further benefits (eg, HR [95% CrI] 0.67 [0.55–0.81] for single-drug taxane, 0.64 [0.53–0.78] for combination of anthracyclines with taxane, 0.49 [0.37–0.67] for taxane-based combination with capecitabine or gemcitabine), and similar benefits were seen with several regimens including molecular targeted treatments. Most regimens had very similar efficacy profiles (<5% difference in HR) as first- and subsequent-line therapies.

Conclusions Stepwise improvements in efficacy of chemotherapy and targeted treatments cumulatively have achieved major improvements in the survival of patients with advanced breast cancer. Many options that can be used in first and subsequent lines of therapy have comparable efficacy profiles.

J Natl Cancer Inst 2008;100:1780–1791

The morbidity band mortality impact of breast cancer is very large worldwide (1-3) and treatment can be challenging. Many pharmacological compounds and administration modalities have been developed for the treatment of advanced breast cancer (4). Key milestones in the systemic treatments for breast cancer were the introduction of hormonal treatment in the 1940s (5), combined chemotherapy in 1969, and anthracyclines in 1972 (6). In the 1990s, gemcitabine, vinorelbine, and capecitabine also entered clinical care, followed by taxanes. Additional expensive targeted treatments were introduced in the last decade.

Although progress has been achieved in the field and patients live longer, the relative merits of the many different chemotherapy and targeted treatment regimens are not well understood. Hundreds of trials have been conducted to compare treatments for advanced breast cancer, but because each has compared only two or a few treatments, it is difficult to integrate information on the relative efficacy of all tested regimens. This integration is important because different regimens vary both in cost and in toxicity. Therefore, we performed a comprehensive systematic review of chemotherapy and targeted treatment regimens in advanced breast cancer and evaluated, through a multiple-treatments meta-analysis (7,8), the relative merits of the many different regimens used to prolong survival in advanced breast cancer patients. Data were analyzed on all eligible trials as well as separately for first- and subsequent-line treatment.

Affiliations of authors: Clinical Trials and Evidence-Based Medicine Unit, Department of Hygiene and Epidemiology (DM, NPP, GS, JPAI) and Department of Medical Oncology (DM, NP), University of Ioannina School of Medicine, Ioannina, Greece; Department of Medical Oncology, Lamia Polyclinic, Lamia, Greece (DM); Biomedical Research Institute, Foundation for Research and Technology—Hellas, Ioannina, Greece (JPAI); Institute for Clinical Research and Health Policy Studies, Department of Medicine, Tufts Medical Center, Tufts University School of Medicine, Boston, MA (JPAI).

Correspondence to: John P. A. Ioannidis, MD, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina 45110, Greece (e-mail: jioannid@cc.uoi.gr).

See "Funding" and "Notes" following "References."

DOI: 10.1093/jnci/djn414

Methods

Identification of Randomized Studies

We searched for randomized studies in any language in PubMed and the Cochrane Central Registry of Controlled Trials looking for studies with the key words mammary or breast that also contained the search terms cancer, malign*, neoplasm*, or carcinoma*. The last search update was done on October 9, 2007. PubMed searches used the restriction limit: randomized controlled trial. We searched the reference lists of every primary study and also retrieved previous meta-analyses addressing comparisons of regimens in advanced breast cancer. Considering the recent introduction of targeted treatment agents and the paucity of information available to date on these agents, we ensured that electronic searches would not miss any major reports of eligible studies by hand-searching the volumes published from 2004 to 2007 inclusive of the three journals with the highest number of electronically identified cancer trials (9). Furthermore, because recent trials with novel or targeted treatment agents may still be unpublished, we also reviewed abstract books and presentations of major recent meetings in 2006–2007 of the American Society of Clinical Oncology, the European Society of Clinical Oncology, and the European Cancer Conference to identify any other trial that had presented final (not preliminary) data on drugs that were already studied in the published trials and comparisons that would be eligible for consideration in the multiple-treatments meta-analysis. Earlier meeting abstracts were not included.

Eligibility Criteria

We considered all randomized trials that compared at least two arms of different regimens involving chemotherapy and/or targeted treatments in patients with advanced breast adenocarcinoma in any line of treatment. Advanced-stage disease was defined by the presence of metastatic or recurrent disease that was not amenable to surgical treatment. We excluded trials on earlier stages of the disease (when trials included both advanced and earlier stage, we included only the relevant population) and trials comparing regimens in breast malignancies other than adenocarcinoma (inflammatory breast cancer, sarcoma, etc). We also excluded nonrandomized and pseudo-randomized trials (eg, those with alternate allocation of subjects). If trials included other concomitant interventions such as hormonal treatment, surgery, radiotherapy, or radioisotopic treatment that differed systematically between the investigated arms, they were excluded. Whenever reports pertained to sets of patients that overlapped, only the report with longest follow-up (having the largest number of events) was used in the analysis.

Data Extraction

From each eligible trial, we recorded authors' names, journal and year of publication, country of origin (as noted in their affiliations), years of patient enrolment, sample size (randomized and analyzed) per arm, performance status, regimens used, line of treatment, additional treatments given to both arms, and information pertaining to study design (whether the trial reported the mode of randomization, allocation concealment, description of withdrawals per arm, and blinding). We also recorded the median survival per arm and whether there was any statistically significant difference ($P < .05$) in median survival between any compared arms.

For trials comparing different types of treatment (as defined below), we also extracted or estimated the logarithm of the hazard ratio for death and its variance. We used the hazard ratio and 95% confidence intervals from Cox regressions, as reported or retrieved by contacting the investigators. Unadjusted hazard ratios were preferred over multivariable ones. If only the variance of the hazard ratio was unavailable, we calculated it using the log-rank *P* value. When neither hazard ratio nor variance was available, we estimated the variance as $(T_1 + T_2)^2/[(E_1 + E_2)T_1T_2]$, where E_1 and E_2 are the number of events and T_1 and T_2 the number of randomly assigned patients in each arm, and then estimated the log(HR), such that it would have the *P* value of the log-rank test (10). When *P* values were unavailable, the hazard ratio was approximated by the ratio of median survivals.

Data were independently extracted by two investigators (D. Mauri and N. P. Polyzos). Discrepancies were discussed with a third investigator (J. P. A. Ioannidis). J. P. A. Ioannidis and G. Salanti also cross-checked against the original articles all the data entered into calculations.

Categories for Analyses

In our analysis, we grouped the regimens into the following nine categories: anthracyclines, anthracenediones, non-taxane novel chemotherapy agents (vinorelbine, gemcitabine, or capecitabine), taxanes, marimastat, thalidomide, trastuzumab, lapatinib, and bevacizumab. Other compounds, such as cyclophosphamide,

CONTEXT AND CAVEATS

Prior knowledge

Although many nonhormonal regimens for advanced breast cancer have been evaluated across hundreds of randomized clinical trials, the relative merits of these regimens were not known with precision.

Study design

Multiple-treatments meta-analysis of survival data based upon direct and indirect comparisons to estimate hazard ratios for different chemotherapy regimens as first- and subsequent-line treatments relative to older nonanthracycline single-agent therapy.

Contribution

This study quantified the survival gains of 21 different classes of therapy relative to older single-agent therapy.

Implications

Whether used in first or subsequent lines of therapy, many classes of modern breast cancer therapy, including anthracyclines, taxanes, novel non-taxane agents, and molecular targeted therapies used in the context of single-agent or combination therapy, produce gains in absolute survival over older single agents.

Limitations

A comprehensive understanding of the effectiveness of newer molecular targeted therapies will require additional trial information. The extent of intertrial variability and its effect on the results of the meta-analysis cannot be known with certainty.

From the Editors

fluorouracil, methotrexate, mitomycin, vincristine, and vinblastine, and all other agents not included in the previous categories were grouped in a miscellaneous category as old agents.

Considering that combined chemotherapy has been demonstrated to produce statistically significant survival advantages over monotherapy (4,11), all categories of drugs analyzed were further split into combination therapies (when two or more different agents were given together) or monotherapies. Regimens using lower dosages of anthracyclines may be inferior to those using higher doses (4); thus, anthracycline-based regimens were further split into low and standard vs high doses. The anthracycline dose equivalence for doxorubicin and epirubicin was derived from isodose studies (12). For monotherapy, we considered as low dose a 21-day dose intensity of less than 60 mg/m^2 doxorubicin or less than 78 mg/m^2 epirubicin. For combination treatment, we designated low dose as a 21-day dose intensity of less than 45 mg/m^2 doxorubicin or less than 58 mg/m^2 epirubicin. For mitoxantrone monotherapy, we designated as low dose a 21-day dose intensity of less than 12 mg/m^2; a low dose for combination regimens was a 21-day dose intensity of less than 8 mg/m^2.

Statistical Analyses

We generated descriptive statistics for trial and study population characteristics across all eligible trials. We described the types of comparisons and how these had evolved over time. We used the probability of interspecific encounter (PIE) and PIE′ metrics to evaluate the diversity of the network, and the *C* metric to measure co-occurrence. Details of these metrics have been described previously (13). In brief, a PIE of less than 0.75 suggests that there is lack of diversity, which could be due to either few regimens or large unevenness of available evidence across the represented regimens. The PIE′ index divides PIE by the maximum possible PIE given the number of regimens and thus removes the effect of the number of regimens in the estimation of diversity. The *C* test, based on a permutation procedure, examines whether there are pairs of regimens in the networks that are systematically preferred or avoided, after accounting for the overall frequency of representation of each regimen in the network.

Quantitative analyses of mortality were limited to trials that compared different types of chemotherapy. In the multiple-treatments meta-analyses, we also performed subgroup analyses for first- and subsequent-line treatment.

We conducted a series of "head-to-head" meta-analyses with a random effects model. Between-study heterogeneity was estimated using the I^2 statistic; typically, values greater than 50% are considered large, 25%–50% modest, and less than 25% low heterogeneity. These estimates can have large uncertainty, especially in the presence of few trials, and should be interpreted cautiously (14).

Multiple-treatments meta-analysis synthesizes information from a network of trials (7,10). It combines direct and indirect evidence on the relative effectiveness of two interventions A and B, respecting randomization. Direct evidence comes from trials of A vs B. Indirect evidence, through an "intermediate" comparator C, comes by combining trials of A vs C and of C vs B; many intermediate comparators are possible. Combination of the many sources of evidence increases precision. Combination of direct and indirect evidence for any given treatment comparison can be extended over a complex network of multiple treatments. We assumed a common heterogeneity parameter τ^2 across all comparisons. The model applied to analyze the data is a Bayesian consistency model as described in reference 7. From each trial (denoted with *i*) with, say, three randomized chemotherapy arms (say A, B, and C), we extract two hazard ratios (in log scale) with their associated variances. We then model the observed $\log(HR_{AB,i})$, $\log(HR_{AC,i})$, which compare the effectiveness of A to B and C, respectively, as:

$$\begin{pmatrix} \log(HR_{AB,i}) \\ \log(HR_{AC,i}) \end{pmatrix} \sim N\left(\begin{pmatrix} \theta_{AB,i} \\ \theta_{AC,i} \end{pmatrix}, \begin{pmatrix} v_{AB,i} & c \\ c & v_{AC,i} \end{pmatrix} \right),$$

where v denotes the sample variance and c is the sample covariance between the log hazard ratios. The random effects $\theta_{AB,i}$, $\theta_{AC,i}$ are subsequently combined across all studies that address the same comparison as:

$$\begin{pmatrix} \theta_{AB,i} \\ \theta_{AC,i} \end{pmatrix} \sim N\left(\begin{pmatrix} \mu_{AB} \\ \mu_{AC} \end{pmatrix}, \begin{pmatrix} 1 & 0.5 \\ 0.5 & 1 \end{pmatrix} \tau^2 \right),$$

where μ is the summary effect of a specific comparison and τ^2 is the between-study variance. In the simpler case, where a study has two arms only, the distributions above reduce to one dimension. The idea described above extends to all reported regimen comparisons. In the Bayesian framework, effect sizes are estimated along with 95% credibility intervals.

Multiple-treatments meta-analysis assumes that the different sources of evidence are coherent (8,15–17). On the top of the estimation of heterogeneity in each head-to-head comparison, we also estimate the incoherence (disagreement between direct and indirect evidence) in each closed loop in the network. Except for one loop with modest incoherence, no incoherence was noted.

Analyses were conducted in WinBUGS 1.4 (MRC Biostatistics Unit, Cambridge, UK; http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml) and S-PLUS 8 (Insightful Corporation, Seattle, WA; http://www.insightful.com).

Results

Eligible Trials

The 13 651 scrutinized reports yielded 367 eligible trials (Figure 1). Another three eligible trials were identified from recent major meetings, bringing the total to 370 trials with 54 189 randomly assigned patients (Table 1). Trials had been published for a period of 35 years (1973–2007), and most included only two arms. Two-thirds addressed first-line treatment, and patients with poor performance status were either absent or a small minority in most trials. Most trials had been performed in the United States or Europe, with approximately a quarter involving several countries. Details on the regimens used over time appear in Supplementary Table 1 (available online,) and detailed study design information on all the 370 trials is available from the authors upon request.

Of the 370 trials, 32 presented formally statistically significant differences between arms in the original report (Supplementary Table 2, available online). Of 198 trials comparing regimens that were categorized as the same type of treatment in our protocol,

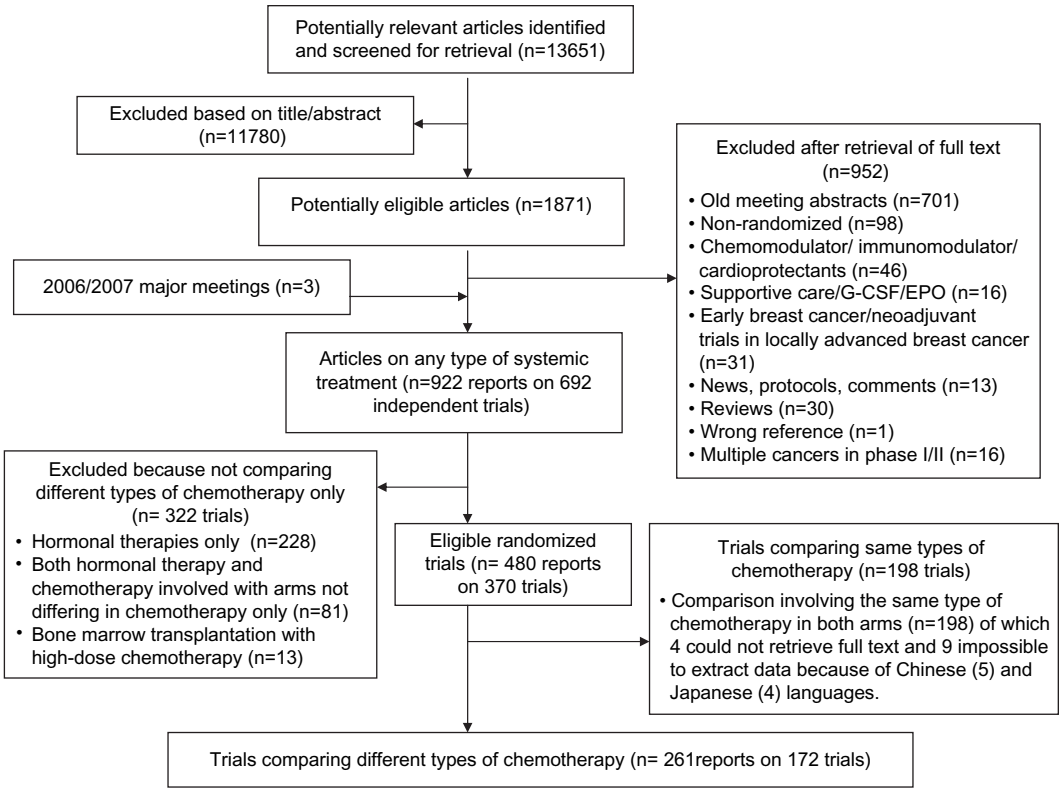

Figure 1. Flow chart for trial selection for multiple-treatments meta-analysis of chemotherapy and targeted therapies for advanced breast cancer. Trials comparing the same types of chemotherapy were defined as those that compared regimens that were considered the same type of treatment in our protocol.

only 8 (4%) presented formally statistically significant results. The other 172 trials with 31 552 patients compared different types of treatment (Figure 1; Table 1).

Comparisons of Different Types of Treatment

Of the 172 trials, survival data could be analyzed in 128 trials, representing 26 031 randomly assigned patients, of whom 25 850 were analyzed in the trials (Supplementary Table 3, available online) (18–144). Data from 121 of these trials could be obtained from published reports, and data from the other seven were obtained by contacting investigators (37,64,75,76,98,114,127). The 44 trials without analyzable survival information included 5521 patients and were mostly small phase 2 trials that did not collect or present survival data. The meta-analysis included 148 comparisons (18 trials had more than two eligible arms).

Twenty-two different types of treatment were represented in the 148 comparisons. The geometry of the network of comparisons was complex (Figure 2). Older regimens generally had somewhat more data than the more recently introduced regimens (Figure 2, A). The PIE index for the network is 0.88, and the PIE′ is 0.96. Moreover, although regimens involving older agents had been thoroughly compared against each other, most regimens involving novel agents, taxanes, and/or targeted treatments (the regimens introduced more recently and thus shown with larger circles in Figure 2, B) had been compared against one or few other comparator regimens. The co-occurrence index C was 132 ($P < 0.001$), which suggests that there is a clear preference for specific comparisons (or avoidance for others), aside from what would be expected according to the relative representation of each regimen in the network.

Direct Comparisons

For 22 different types of chemotherapy, 231 different comparisons are theoretically possible, but only 45 of these (20%) had been performed (Table 2). Only 10 of these comparisons had been made in more than three trials; thus, the results of these analyses should be interpreted very cautiously. Formally statistically significant differences were seen in 10 analyses, and an estimate consistent with large heterogeneity ($I^2 > 50\%$) was seen in five comparisons; uncertainty in the heterogeneity estimates is unavoidably large with few trials per analysis.

In particular, old agents as monotherapy were formally statistically inferior to novel non-taxane agents, low-dose anthracycline-based combinations, standard-dose anthracycline, and combinations of the same old agents. Formally statistically significant improvement in survival with the use of combined agents vs single agents was found in six comparisons; conversely, monotherapy with novel non-taxane agents fared better than combinations of old agents. The combination of old agents was statistically significantly inferior to standard-dose anthracycline-based combinations as well but was better than low-dose anthracycline monotherapy. Survival benefits were observed when taxanes were combined with novel non-taxane agents or trastuzumab (Table 2).

Multiple-Treatments Meta-analysis

Data derived from direct and indirect evidence were analyzed in the multiple-treatment meta-analysis. Results are expressed for convenience as hazard ratio relative to the regimen of monotherapy with an old agent (Table 3). Taxanes in combination with novel agents, trastuzumab, or old agents, had the largest decrease in mortality risk (hazard ratios [HRs] 0.49, 0.50, and 0.53, respectively). Considerable survival benefits, relative to monotherapy

Table 1. Characteristics of the eligible trials*

Characteristics	All trials (n = 370)	Trials eligible for MTM (n = 172)
No. of eligible patients	54 189	31 552
Median sample size (IQR)	104 (53–201)	141 (87–262)
Year of publication		
1971–1980	51	28
1981–1990	111	53
1991–2000	118	51
2001–2007	90	40
Number of eligible arms†		
Two	309	136
Three	44	29
Four or more	16	7
Previous chemotherapy, No. (%)	140 (40)‡	55 (32)
Including PS >2, No. (%)	105 (37)‡	62 (46)‡
Had more than 10% of patients with PS >2, No. (%)	24 (8)‡	9 (7)‡
Countries involved (investigator affiliations)		
Multiple countries	95	52
United States	85	41
Italy	41	16
United Kingdom	28	14
France	22	7
Japan	14	1
China	10	0
Germany	9	4
Denmark	9	6
Other	57	31

* MTM = multiple-treatments meta-analysis; IQR = interquartile range; PS = performance status.

† Fifteen trials (of which 12 were eligible for multiple-treatments meta-analysis) also included additional arms that would not be eligible for the systematic review.

‡ Data are not available for all trials, percentages calculated based on trials with available information.

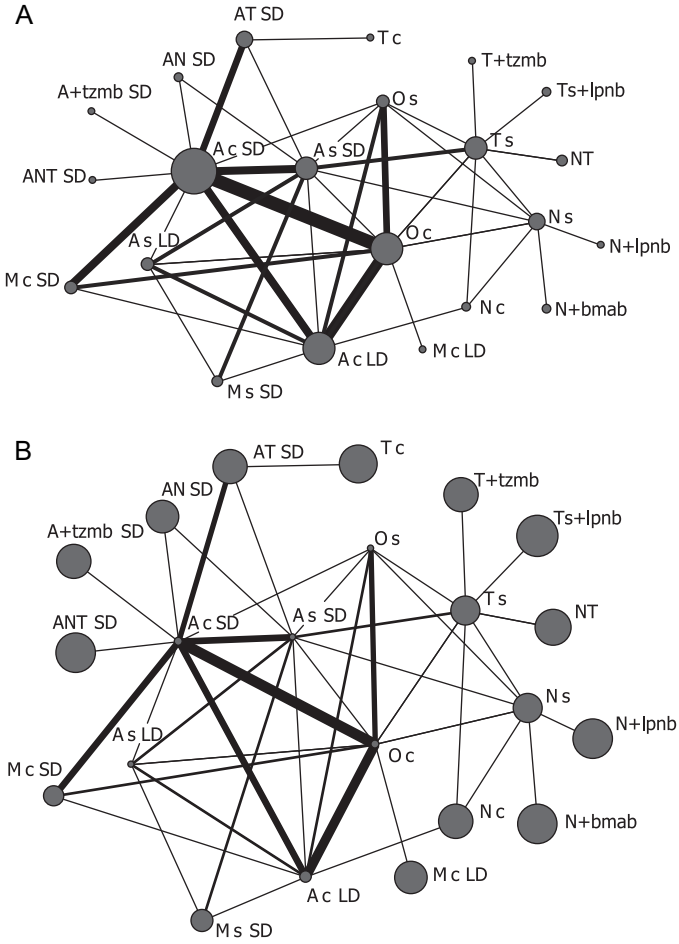

Figure 2. Network of eligible comparisons for the multiple-treatments meta-analysis. Thickness of connecting lines indicates the number of available comparisons. **A**) The size of each node is proportional to the amount of information (sample size). **B**) A larger node means more recent year of first publication of a trial for this type of regimen. Ac LD = low-dose anthracycline (combination regimen); Ac SD = standard-dose anthracycline (combination regimen); As LD = low-dose anthracycline (single agent); As SD = standard-dose anthracycline (single agent); A+tzmb SD = standard-dose anthracycline + trastuzumab; AN SD = standard-dose anthracycline + novel non-taxane agents; ANT SD = standard-dose anthracycline + novel non-taxane agents + taxanes; AT SD = standard-dose anthracycline + taxanes; Mc LD = low-dose mitoxantrone (combination regimen); Mc SD = standard-dose mitoxantrone (combination regimen); Ms SD = standard-dose mitoxantrone (single agent); Nc = novel non-taxane agents (combination regimen); Ns = novel non-taxane agents (single agent); N+bmab = novel non-taxane agents + bevacizumab (single agent); N+lpnb = novel non-taxane agents + lapatinib; NT = novel non-taxane agents + taxanes; Oc = old agents (combination regimen); Os = old agents (single agent); Tc = taxanes (combination regimen); Ts = taxanes (single agent); T+tzmb = taxanes + trastuzumab; Ts+lpnb = taxanes + lapatinib.

with an old agent, were observed for taxanes in combination with lapatinib, anthracyclines, or both anthracycline + novel non-taxane agents (HRs = 0.57, 0.64, and 0.56, respectively). Combination of trastuzumab with standard-dose anthracyclines offered similar benefits (HR = 0.55). Taxanes as single agents and standard-dose anthracyline-based combinations reduced mortality risk by approximately one-third (HR = 0.67). Old combination regimens without anthracyclines or taxanes achieved a 25% relative risk reduction in mortality.

Therapy line–specific effect estimates were similar to estimates for all available comparisons regardless of line. Effect estimates for the overall analysis and first-line trials only typically differed by less than 5%. Subsequent-line treatment data were more sparse and thus less conclusive, but the overall pattern did not differ, with the exception of a trend for lower efficacy for anthracycline-based combinations when compared with the first-line setting (Table 3).

When plotting hazard ratios as a function of the year of publication of the first trial that used each type of treatment (Figure 3), it appeared that early regimens such as combination of old agents and anthracycline-based regimens achieved a 25%–30% relative risk reduction, with little further progress for two decades; the introduction of additional agents attained larger (30%–50%) relative risk reductions.

Discussion

Our meta-analysis quantifies the progress achieved in the treatment of advanced breast cancer with nonhormonal systemic treatment in the last 35 years. Several regimens have shown effectiveness, and for some of them, the treatment effects are practically indistinguishable in magnitude. Given that subsequent lines of treatment

Table 2. Estimates of effect (HR and uncertainty 95% CI) for mortality in 45 direct comparisons*

Arm 1	Arm 2	No. of studies	No. of patients	HR† (95% CI)	I^2 (%)
Low-dose anthracycline (combination regimen)	Standard-dose anthracycline (combination regimen)	16	3347	1.05 (0.98 to 1.13)	0
Low-dose anthracycline (combination regimen)	Low-dose anthracycline (single agent)	4	725	0.93 (0.83 to 1.05)	0
Low-dose anthracycline (combination regimen)	Standard-dose anthracycline (single agent)	1	115	0.90 (0.62 to 1.32)	NA
Low-dose anthracycline (combination regimen)	Standard-dose mitoxantrone (combination regimen)	2	440	0.79 (0.58 to 1.07)	51
Low-dose anthracycline (combination regimen)	Standard-dose mitoxantrone (single agent)	1	260	0.89 (0.67 to 1.18)	NA
Low-dose anthracycline (combination regimen)	Novel non-taxane agents (combination regimen)	1	84	1.08 (0.67 to 1.75)	NA
Low-dose anthracycline (combination regimen)	Old agents (combination regimen)	19	2257	0.96 (0.86 to 1.08)	23
Low-dose anthracycline (combination regimen)	Old agents (single agent)	3	458	0.82‡ (0.68 to 1.00)	0
Standard-dose anthracycline (combination regimen)	Low-dose anthracycline (single agent)	2	565	0.87 (0.73 to 1.04)	0
Standard-dose anthracycline (combination regimen)	Standard-dose anthracycline (single agent)	8	1030	0.84‡ (0.74 to 0.96)	0
Standard-dose anthracycline (combination regimen)	Standard-dose anthracycline + trastuzumab	1	281	1.22 (0.91 to 1.63)	NA
Standard-dose anthracycline (combination regimen)	Standard-dose anthracycline + novel non-taxane agents	1	170	1.03 (0.73 to 1.45)	NA
Standard-dose anthracycline (combination regimen)	Standard-dose anthracycline + novel non-taxane agents + taxanes	1	243	1.18 (0.80 to 1.77)	NA
Standard-dose anthracycline (combination regimen)	Standard-dose mitoxantrone (combination regimen)	9	1322	0.95 (0.84 to 1.08)	9
Standard-dose anthracycline (combination regimen)	Old agents (combination regimen)	14	2529	0.89‡ (0.80 to 0.98)	11
Standard-dose anthracycline (combination regimen)	Old agents (single agent)	1	60	1.14 (0.60 to 2.18)	NA
Standard-dose anthracycline (combination regimen)	Standard-dose anthracycline + taxanes	9	2201	1.06 (0.89 to 1.27)	62
Low-dose anthracycline (single agent)	Standard-dose anthracycline (single agent)	5	202	1.03(0.70 to 1.54)	63
Low-dose anthracycline (single agent)	Standard-dose mitoxantrone (single agent)	2	99	0.77(0.50 to 1.17)	0
Low-dose anthracycline (single agent)	Old agents (combination regimen)	2	88	1.54‡(1.01 to 2.32)	0
Standard-dose anthracycline (single agent)	Standard-dose anthracycline + novel non-taxane agents	2	687	1.09 (0.93 to 1.29)	0.
Standard-dose anthracycline (single agent)	Standard-dose anthracycline + taxanes	1	454	0.98 (0.79 to 1.22)	NA
Standard-dose anthracycline (single agent)	Standard-dose mitoxantrone (single agent)	3	621	0.87 (0.65 to 1.18)	61
Standard-dose anthracycline (single agent)	Novel non-taxane agents (single agent)	2	698	0.75 (0.46 to 1.22)	84
Standard-dose anthracycline (single agent)	Old agents (combination regimen)	1	64	1.26 (0.71 to 2.25)	NA
Standard-dose anthracycline (single agent)	Old agents (single agent)	2	155	0.52‡ (0.35 to 0.77)	10
Standard-dose anthracycline (single agent)	Taxanes (single agent)	3	1110	1.02 (0.89 to 1.17)	0
Standard-dose anthracycline + taxanes	Taxanes (combination regimen)	1	327	1.20 (0.88 to 1.64)	NA
Standard-dose anthracycline + taxanes	Taxanes (single agent)	1	459	1.07 (0.88 to 1.30)	NA
Low-dose mitoxantrone (combination regimen)	Old agents (combination regimen)	1	312	0.92 (0.61 to 1.41)	NA
Standard-dose mitoxantrone (combination regimen)	Novel non-taxane agents (single agent)	1	65	1.06 (0.65 to 1.72)	NA
Standard-dose mitoxantrone (combination regimen)	Old agents (combination regimen)	3	116	0.88 0.68 to 1.14)	0
Novel non-taxane agents (combination regimen)	Novel non-taxane agents (single agent)	1	251	1.04 (0.78 to 1.38)	NA
Novel non-taxane agents (combination regimen)	Taxanes (single agent)	1	176	1.07 (0.71 to 1.59)	NA
Novel non-taxane agents (single agent)	Novel non-taxane agents + bevacizumab	1	462	1.04 (0.77 to 1.40)	NA
Novel non-taxane agents (single agent)	Novel non-taxane agents + lapatinib	1	324	1.09 (0.69 to 1.72)	NA
Novel non-taxane agents (single agent)	Old agents (combination regimen)	3	482	0.78‡ (0.62 to 0.97)	0
Novel non-taxane agents (single agent)	Old agents (single agent)	1	179	0.67‡ (0.47 to 0.97)	NA
Novel non-taxane agents (single agent)	Taxanes (single agent)	1	41	1.56 (0.69 to 3.53)	NA
Novel non-taxane agents + taxanes	Taxanes (single agent)	3	1140	0.76‡ (0.66 to 0.88)	0
Old agents (combination regimen)	Old agents (single agent)	9	950	0.72‡ (0.55 to 0.95)	72
Old agents (combination regimen)	Taxanes (single agent)	4	1076	1.10 (0.82 to 1.47)	76
Old agents (single agent)	Taxanes (single agent)	1	81	1.72 (0.82 to 3.61)	NA
Taxanes (single agent)	Taxanes + trastuzumab	2	374	1.32‡ (1.06 to 1.65)	0
Taxanes (single agent)	Taxanes + lapatinib	1	579	1.16 (0.93 to 1.46)	NA

* Forest plots are available in Supplementary Figure 1 (available online). NA = not applicable (one trial); HR = hazard ratio; CI = confidence interval.

† HR estimates less than 1.00 suggest that arm 1 has better survival.

‡ $P < .05$.

can confer similar relative benefits as the first-line setting, one can exploit the survival benefits conferred by several effective regimens used in sequential fashion. For example, if three regimens are used, each one prolonging survival by 1 year for a patient who would have had 1 year of survival without effective treatment, life expectancy may be quadrupled. The availability of multiple effective options suggests that it is essential to identify appropriate indications for timely changes of regimens in patients in whom treatment is no longer effective.

Progress in chemotherapeutic treatment of advanced breast cancer has been stepwise. After the achievement of a 25% reduction in the risk of death in 1975 with the use of anthracycline-based combination regimens (145), little additional progress was made for almost two decades. Subsequently, several new agents (vinorelbine, gemcitabine, capecitabine, taxanes, and molecular targeted treatments) were introduced that proved more effective (59,85,146–148). These agents have not yet been tested in all possible combinations. Moreover, less data have been collected on combinations involving these newer agents than are available for the standard earlier treatments. Comparisons for which there is at present little or no data should be the focus of future investigations so that more direct evidence about the relative merits of these regimens can be obtained.

Interventions should be tailored to the individual patient, and benefits should be weighed against adverse events for each treatment. Toxicity should not be underestimated. For example,

Table 3. Multiple-treatments meta-analysis and subgroup analyses by line of treatment

Treatment	All available comparisons in any line (n = 148), HR (95% CrI)	Survival gain over Os* (mo)	First-line comparisons (n = 107), median HR (95% CrI)	Subsequent-line comparisons (n = 41), median HR (95% CrI)
Old agents (single agent)	1.00 (referent)		1.00 (referent)	1.00 (referent)
Novel non-taxane agents + taxanes	0.49 (0.37 to 0.67)	12.5	0.52 (0.32 to 0.86)	0.47 (0.30 to 0.71)
Taxanes + trastuzumab	0.51 (0.35 to 0.72)	11.5	0.51 (0.33 to 0.79)	0.56 (0.35 to 0.90)
Taxanes (combination regimen)	0.53 (0.34 to 0.85)	10.6	0.54 (0.32 to 0.90)	—
Standard-dose anthracycline + trastuzumab	0.55 (0.36 to 0.84)	9.8	0.54 (0.34 to 0.88)	—
Standard-dose anthracycline + novel non-taxane agents + taxanes	0.56 (0.34 to 0.94)	9.4	0.56 (0.32 to 0.98)	—
Taxanes + lapatinib	0.57 (0.38 to 0.86)	9.1	—	—
Standard-dose anthracycline + taxanes	0.64 (0.53 to 0.78)	6.8	0.64 (0.50 to 0.83)	—
Standard-dose anthracycline + novel non-taxane agents	0.65 (0.49 to 0.85)	6.5	0.67 (0.46 to 0.97)	0.64 (0.41 to 1.03)
Taxanes (single agent)	0.67 (0.55 to 0.81)	5.9	0.67 (0.50 to 0.91)	0.65 (0.49 to 0.87)
Standard-dose anthracycline (combination regimen	0.67 (0.57 to 0.78)	5.9	0.67 (0.54 to 0.81)	0.74 (0.55 to 0.99)
Novel non-taxane agents + lapatinib	0.68 (0.38 to 1.23)	5.6	0.69 (0.39 to 1.22)	0.62 (0.33 to 1.12)
Low-dose mitoxantrone (combination regimen)	0.69 (0.41 to 1.18)	5.4	—	—
Low-dose anthracycline (combination regimen)	0.70 (0.61 to 0.81)	5.1	0.70 (0.57 to 0.85)	0.76 (0.57 to 1.01)
Standard-dose anthracycline (single agent)	0.71 (0.60 to 0.84)	4.9	0.74 (0.58 to 0.94)	0.72 (0.55 to 0.94)
Novel non-taxane agents + bevacizumab (single agent)	0.71 (0.45 to 1.12)	4.9	—	0.64 (0.39 to 1.06)
Novel non-taxane agents (combination regimen)	0.72 (0.53 to 0.99)	4.7	0.65 (0.35 to 1.18)	0.69 (0.46 to 1.04)
Novel non-taxane agents (single agent)	0.74 (0.60 to 0.91)	4.2	1.08 (0.69 to 1.68)	0.66 (0.50 to 0.88)
Old agents (combination regimen)	0.75 (0.65 to 0.85)	4.0	0.75 (0.63 to 0.90)	0.72 (0.54 to 0.95)
Standard-dose mitoxantrone (combination regimen)	0.75 (0.62 to 0.90)	4.0	0.74 (0.59 to 0.94)	0.71 (0.41 to 1.26)
Low-dose anthracycline (single agent)	0.78 (0.64 to 0.94)	3.4	0.80 (0.62 to 1.03)	0.79 (0.54 to 1.18)
Standard-dose mitoxantrone (single agent)	0.82 (0.64 to 1.06)	2.6	0.81 (0.56 to 1.18)	0.85 (0.58 to 1.26)

* Absolute prolongation of survival with various regimens for a patient with an anticipated survival on an old agent (single agent) of 1 y; it is calculated as [(12/HR) − 12] mo. CrI = credibility interval; HR = hazard ratio; Os = old agents (single agent).

taxane-based combinations that include capecitabine and gemcitabine cause serious hematologic toxicity, diarrhea, mucositis, hand–foot syndrome, neurosensory disorders, and fatigue (39,125,128). Administration of anthracycline with trastuzumab was associated with major cardiotoxicity (84), and preliminary data (149) suggest that the combination of gefitinib with docetaxel is very toxic. Very few patients with poor performance status, who may be especially susceptible to adverse effects, have been enrolled in recent trials.

Our meta-analysis includes data on results of treatment with trastuzumab, bevacizumab, and lapatinib as of October 2007. The available data on lapatinib and bevacizumab in particular are quite limited. After data freeze and analysis, a trial on 722 patients (150) was published, showing no statistically significant survival benefit with bevacizumab + paclitaxel vs paclitaxel, but clear benefit was seen for disease progression. It is possible that many patients switched treatment upon disease progression and that this may have eroded any survival difference. With many available treatment options and early switches to other effective agents, differences in survival by intention to treat may become small. Cautious optimism as to the effectiveness of molecular targeted treatments is needed until more data accumulate, and it is important to correctly identify the patients who would benefit from them. Targeted therapies are not appropriate for all breast cancer patients. Trastuzumab and lapatinib are effective in treating HER2-positive cancers, but these account only for approximately 20% of breast cancers (129). Although molecular targeted therapies have an increasing range of applications for different cancers, trials with less impressive results (not stopped early) may still be ongoing, and the complete picture of effectiveness and toxicity has not yet emerged.

Overall, it would be useful to design trials that fill in important gaps for key treatment comparisons that have minimal or no information. For some treatment comparisons in the examined network of treatments, no direct evidence was available, and thus, evaluation of incoherence (ie, the extent of disagreement between direct and indirect evidence) was also impossible.

Furthermore, it has to be considered that over time, anthracycline- and taxane-based chemotherapy has been increasingly used for the treatment of early-stage disease. Thus, estimates of the relative merits of these agents in the advanced setting could be in part biased by when the study was conducted.

Also in the last three decades, there has been much change in supportive care of cancer patients. Thus, there is uncertainty as to the validity of the transitivity assumption (ie, that the treatment effect of a regimen does not change over time) for early introduced regimens. Would the relative risk reduction be the same as several decades ago, if early trials were to be repeated? Obviously, repetition of the trials is not feasible for ethical reasons. Changes in supportive care and other adjunct management would certainly change the absolute survival for both compared arms, but there is no strong reason to believe that these changes would influence the relative performance of the compared regimens, and it is the relative performance of one regimen vs the other that enters in the multiple-treatments meta-analysis calculations.

A possible limitation of the current analysis is that it is based on published group data, rather than individual patient information.

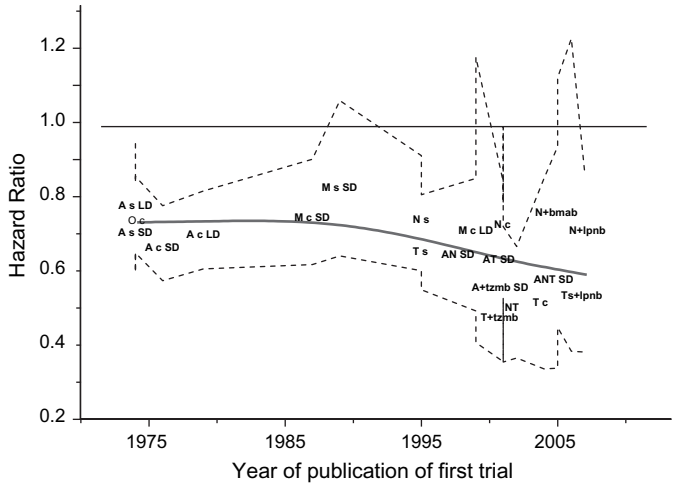

Figure 3. Hazard ratios for mortality using monotherapy, with old agent as the reference comparator as a function of the first year of publication of a trial for each type of treatment. The abbreviated name of each regimen is placed at the point representing the first year of publication, and the hazard ratio estimated from the multiple-treatments meta-analysis. Also shown is a **spline fitted line**. In **dashed lines** are the piecewise 95% credibility intervals. Ac LD = low-dose anthracycline (combination regimen); Ac SD = standard-dose anthracycline (combination regimen); As LD = Low-dose anthracycline (single agent); As SD = standard-dose anthracycline (single agent); A+tzmbSD = standard-dose anthracycline + trastuzumab; AN SD = standard-dose anthracycline + novel non-taxane agents; ANT SD = standard-dose anthracycline + novel non-taxane agents + taxanes; AT SD = standard-dose anthracycline + taxanes; Mc LD = low-dose mitoxantrone (combination regimen); Mc SD = standard-dose mitoxantrone (combination regimen); Ms SD = standard-dose mitoxantrone (single agent); Nc = novel non-taxane agents (combination regimen); Ns = novel non-taxane agents (single agent); N+bmab = novel non-taxane agents + bevacizumab (single agent); N+lpnb = novel non-taxane agents + lapatinib; NT = novel non-taxane agents + taxanes; Oc = old agents (combination regimen); Tc = taxanes (combination regimen); Ts = taxanes (single agent); T+tzmb = taxanes + trastuzumab; Ts+lpnb = taxanes + lapatinib.

However, we have included patients across a rather narrow range of prognoses, namely, metastatic breast cancer (stage IV). Individual patient data might allow a more detailed appraisal of outcomes at different risk groups (151). Still, the power to detect effect modifications might still be limited even with individual patient information in such a complex network of multiple treatments. The available data for each regimen are relatively limited, and thus, strong inferences about the specific superiority of one particular regimen should be avoided. Finally, given the retrospective nature of the meta-analysis, publication bias and selective reporting biases cannot be excluded. Although such biases may affect sporadic comparisons, they are unlikely to refute the overall picture of progress. Prospective registration of trials has been adopted in the last few years. Registration, if complete and transparent, would allow updating this and similar analyses with more comprehensive information and keeping track of the improvements in the treatment of advanced breast cancer.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin.* 2005;55(2):74–108.
2. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. *CA Cancer J Clin.* 2007;57(1):43–66.
3. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. *Ann Oncol.* 2007;18(3):581–592.
4. Fossati R, Confalonieri C, Torri V, et al. Cytotoxic and hormonal treatment for metastatic breast cancer: a systematic review of published randomized trials involving 31 510 women. *J Clin Oncol.* 1998;16(10):3439–3460.
5. Haddow A, Watkinson JM, Paterson E, et al. Influence of synthetic oestrogens upon advanced malignant disease. *Br Med J.* 1944;2(4368):393–408.
6. Arcamone F, Penco S, Vigevani A, et al. Synthesis and antitumor properties of new glycosides of daumomycinone and adriamycinone. *J Med Chem.* 1975;18(7):703–707.
7. Salanti G, Higgins J, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. *Stat Methods Med Res.* 2008;17(3):279–301.
8. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ.* 2005;331(7521):897–900.
9. Hopewell S, Clarke M, Lusher A, Lefebvre C, Westby M. A comparison of handsearching versus MEDLINE searching to identify reports of randomized controlled trials. *Stat Med.* 2002;21(11):1625–1634.
10. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. *Health Technol Assess.* 2005;9(26):1–134, iii–iv.
11. Rivera E, Smith RE Jr. Trends in recommendations of myelosuppressive chemotherapy for the treatment of breast cancer: evolution of the national comprehensive cancer network guidelines and the cooperative group studies. *Clin Breast Cancer.* 2006;7(1):33–41.
12. Launchbury AP, Habboubi N. Epirubicin and doxorubicin: a comparison of their characteristics, therapeutic activity and toxicity. *Cancer Treat Rev.* 1993;19(3):197–228.
13. Salanti G, Kavvoura FK, Ioannidis JP. Exploring the geometry of treatment networks. *Ann Intern Med.* 2008;148(7):544–553.
14. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med.* 2002;21(11):1539–1558.
15. Baker SG, Kramer BS. The transitive fallacy for randomised trials: if A bests B and B bests C in separate trials, is A better than C? *BMC Med Res Methodol.* 2002;2:13.
16. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat Med.* 2002;21(16):2313–2324.
17. Ioannidis JP. Indirect comparisons: the mesh and mess of clinical trials. *Lancet.* 2006;368(9546):1470–1472.
18. Cavalli F, Pedrazzini A, Martz G, et al. Randomized trial of 3 different regimens of combination chemotherapy in patients receiving simultaneously a hormonal treatment for advanced breast cancer. *Eur J Cancer Clin Oncol.* 1983;19(11):1615–1624.
19. Lorusso V, Vici P, Bianco AR. Combination chemotherapy with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) versus CNF (mitoxantrone, 5-fluorouracil, cyclophosphamide) in advanced breast cancer: a multicenter randomized study. *Int J Oncol.* 1993;4(2):531–535.
20. Hori T, Kodama H, Nishimura S. A randomized study comparing oral and standard regimens for metastatic breast cancer. *Oncol Rep.* 2001;8(5):1067–1071.
21. Nemoto T, Rosner D, Diaz R, et al. Combination chemotherapy for metastatic breast cancer: comparison of multiple drug therapy with 5-fluorouracil, cytoxan and prednisone with adriamycin or adrenalectomy. *Cancer.* 1978;41(6):2073–2077.
22. Dieras V, Marty M, Tubiana N, et al. Phase II randomized study of paclitaxel versus mitomycin in advanced breast cancer. *Semin Oncol.* 1995;22 (4 suppl 8):33–39.
23. Rubens RD, Knight RK, Hayward JL. Chemotherapy of advanced breast cancer: a controlled randomized trial of cyclophosphamide versus a four-drug combination. *Br J Cancer.* 1975;32(6):730–736.
24. Nielsen D, Dombernowsky P, Skovsgaard T, et al. Epirubicin or epirubicin and vindesine in advanced breast cancer. A phase III study. *Ann Oncol.* 1990;1(4):275–280.
25. Cocconi G, Bisagni G, Bacchi M, et al. A comparison of continuation versus late intensification followed by discontinuation of chemotherapy in advanced breast cancer. A prospective randomized trial of the Italian Oncology Group for Clinical Research (G.O.I.R.C.). *Ann Oncol.* 1990;1(1):36–44.

26. Smalley RV, Lefante J, Bartolucci A, et al. A comparison of cyclophosphamide, adriamycin, and 5-fluorouracil (CAF) and cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, and prednisone (CMFVP) in patients with advanced breast cancer. *Breast Cancer Res Treat.* 1983;3(2): 209–220.
27. Zekan PJ, Muss HB, Capizzi RL, et al. High-dose cyclophosphamide and 5-fluorouracil versus vincristine, doxorubicin, and cyclophosphamide in advanced carcinoma of the breast. A phase III study of the Piedmont Oncology Association (POA). *Cancer.* 1984;54(11):2338–2343.
28. Pavesi L, Preti P, Da Prada G, et al. Epirubicin versus mitoxantrone in combination chemotherapy for metastatic breast cancer. *Anticancer Res.* 1995;15(2):495–501.
29. Harper-Wynne C, English J, Meyer L, et al. Randomized trial to compare the efficacy and toxicity of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) with methotrexate mitoxantrone (MM) in advanced carcinoma of the breast. *Br J Cancer.* 1999;81(2):316–322.
30. Moiseenko VM, O'Reilly SM, Dalbot DC, et al. A comparative randomized phase-II study of Xeloda (capecitabine) and paclitaxel in patients with breast cancer progressing after anthracycline antibiotics. *Vopr Onkol.* 2000; 46(3):285–289.
31. 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(8):1194–1201.
32. Bishop JF, Dewar J, Toner GC, et al. Initial paclitaxel improves outcome compared with CMFP combination chemotherapy as front-line therapy in untreated metastatic breast cancer. *J Clin Oncol.* 1999;17(8):2355–2364.
33. Falkson G, Gelman RS, Tormey DC, Taylor SG IV, Falkson HC. Mitomycin and tamoxifen versus mitolactol, doxorubicin, and tamoxifen in patients with previously treated breast cancer. *Cancer Treat Rep.* 1985; 69(7–8):755–760.
34. Brufman G, Colajori E, Ghilezan N, et al. Doubling epirubicin dose intensity (100 mg/m2 versus 50 mg/m2) in the FEC regimen significantly increases response rates. An international randomised phase III study in metastatic breast cancer. The Epirubicin High Dose (HEPI 010) Study Group. *Ann Oncol.* 1997;8(2):155–162.
35. Athanassiou A. Dose intensification by using human recombinant granulocyte-macrophage colony stimulating factor in advanced breast cancer patients. *Eur J Gynaecol Oncol.* 1996;17(5):411–413.
36. Pouillart P, Follézou JY, Palangie T, Feuilhade F, George C, Richards E. Long-term results of a randomised trial comparing regimens of cyclophosphamide and fluorouracil with either mitoxantrone or doxorubicin in patients with advanced breast cancer. *Eur J Cancer.* 1994;30A(5):715–716.
37. Oshaughnessy JA, Blum J, Moiseyenko V, et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. *Ann Oncol.* 2001;12(9): 1247–1254.
38. Heidemann E, Stoeger H, Souchon R, et al. Is first-line single-agent mitoxantrone in the treatment of high-risk metastatic breast cancer patients as effective as combination chemotherapy? No difference in survival but higher quality of life were found in a multicenter randomized trial. *Ann Oncol.* 2002;13(11):1717–1729.
39. 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(12):2812–2823.
40. Andersson M, Daugaard S, von der Maase H, Mouridsen HT. Doxorubicin versus mitomycin versus doxorubicin plus mitomycin in advanced breast cancer: a randomized study. *Cancer Treat Rep.* 1986;70(10):1181–1186.
41. Venturino A, Comandini D, Simoni C, et al. Is salvage chemotherapy for metastatic breast cancer always effective and well tolerated? A phase II randomized trial of vinorelbine versus 5-fluorouracil plus leucovorin versus combination of mitoxantrone, 5-fluorouracil plus leucovorin. *Breast Cancer Res Treat.* 2000;60(3):195–200.
42. Paridaens RJ, Biganzoli L, Bruning P, et al. Paclitaxel versus doxorubicin as first-line single-agent chemotherapy for metastatic breast cancer: a European Organization for Research and Treatment of Cancer randomized study with cross-over. *J Clin Oncol.* 2000;18(4):724–733.
43. Brambilla C, De Lena M, Rossi A, Valagussa P, Bonadonna G. Response and survival in advanced breast cancer after two non-cross-resistant combinations. *Br Med J.* 1976;1(6013):801–804.
44. Cowan JD, Neidhart J, McClure S, et al. Randomized trial of doxorubicin, bisantrene, and mitoxantrone in advanced breast cancer: a Southwest Oncology Group study. *J Natl Cancer Inst.* 1991;83(15):1077–1084.
45. Henderson IC, Allegra JC, Woodcock T, et al. Randomized clinical trial comparing mitoxantrone with doxorubicin in previously treated patients with metastatic breast cancer. *J Clin Oncol.* 1989;7(5):560–571.
46. Habeshaw T, Paul J, Jones R, et al. Epirubicin at two dose levels with prednisolone as treatment for advanced breast cancer: the results of a randomized trial. *J Clin Oncol.* 1991;9(2):295–304.
47. Gottlieb JA, Rivkin SE, Spigel SC, et al. Proceedings: superiority of adriamycin over oral nitrosoureas in patients with advanced breast carcinoma. A Southwest Cancer Chemotherapy Group study. *Cancer.* 1974; 33(2):519–526.
48. Biganzoli L, Cufer T, Bruning P, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: the European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. *J Clin Oncol.* 2002;20(14):3114–3121.
49. Canellos GP, Pocock SJ, Taylor SG III, Sears ME, Klaasen DJ, Band PR. Combination chemotherapy for metastatic breast carcinoma. Prospective comparison of multiple drug therapy with L-phenylalanine mustard. *Cancer.* 1976;38(5):1882–1886.
50. Kolaric K, Vukas D, Potrebica V. Combination of cyclophosphamide, adriamycin and platinum (CAP) versus 5-fluorouracil, adriamycin and cyclophosphamide (FAC) as primary treatment in metastatic breast cancer: results of a prospective randomized study. *Tumori.* 1989;75(2):132–136.
51. Ingle JN, Pfeifle DM, Green SJ, et al. Randomized clinical trial of doxorubicin alone or combined with mitolactol in women with advanced breast cancer and prior chemotherapy exposure. *Am J Clin Oncol.* 1985;8(4): 275–282.
52. Tormey DC, Weinberg VE, Leone LA, et al. A comparison of intermittent vs. continuous and of adriamycin vs. methotrexate 5-drug chemotherapy for advanced breast cancer. A Cancer and Leukemia Group B study. *Am J Clin Oncol.* 1984;7(3):231–239.
53. Chang YC, Falkson G, Tormey DC, Crowley J. A pilot study of mitomycin-C and tamoxifen (MT) versus dibromodulcitol, adriamycin, and tamoxifen (DAT). *Am J Clin Oncol.* 1982;5(5):521–525.
54. 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(10):1611–1620.
55. Lawton PA, Spittle MF, Ostrowski MJ, et al. A comparison of doxorubicin, epirubicin and mitozantrone as single agents in advanced breast carcinoma. *Clin Oncol (R Coll Radiol).* 1993;5(2):80–84.
56. Creagan ET, Green SJ, Ahmann DL, Ingle JN, Edmonson JH, Marschke RF Jr. A phase III clinical trial comparing the combination cyclophosphamide, adriamycin, cisplatin with cyclophosphamide, 5-fluorouracil, prednisone in patients with advanced breast cancer. *J Clin Oncol.* 1984;2(11): 1260–1265.
57. Cummings FJ, Gelman R, Tormey DC, DeWys W, Glick J. Adriamycin plus vincristine alone or with dibromodulcitol or ICRF-159 in metastatic breast cancer. *Cancer Clin Trials.* 1981;4(3):253–260.
58. Vogel CL, Smalley RV, Raney M, et al. Randomized trial of cyclophosphamide, doxorubicin, and 5-fluorouracil alone or alternating with a "cycle active" non-cross-resistant combination in women with visceral metastatic breast cancer: a Southeastern Cancer Study Group project. *J Clin Oncol.* 1984;2(6):643–651.
59. Jones S, Winer E, Vogel C, et al. Randomized comparison of vinorelbine and melphalan in anthracycline-refractory advanced breast cancer. *J Clin Oncol.* 1995;13(10):2567–2574.
60. Leonard RC, Cornbleet MA, Kaye SB, et al. Mitoxantrone versus doxorubicin in combination chemotherapy for advanced carcinoma of the breast. *J Clin Oncol.* 1987;5(7):1056–1063.

61. Dogliotti L, Berruti A, Buniva T, et al. Lonidamine significantly increases the activity of epirubicin in patients with advanced breast cancer: results from a multicenter prospective randomized trial. *J Clin Oncol.* 1996; 14(4):1165–1172.
62. Kolarić K, Vukas D, Roth A, Potrebica V, Cervek J, Cerar O. Cyclophosphamide, adriamycin and platinum (CAP) combination chemotherapy, a new effective approach in the treatment of disseminated breast cancer. Preliminary report. *Tumori.* 1985;71(2):159–165.
63. Hainsworth JD, Jolivet J, Birch R, Hopkins LG, Greco FA. Mitoxantrone, 5-fluorouracil, and high dose leucovorin (NFL) versus intravenous cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) in first-line chemotherapy for patients with metastatic breast carcinoma: a randomized phase II trial. *Cancer.* 1997;79(4):740–748.
64. Bastholt L, Dalmark M, Gjedde SB, et al. Dose-response relationship of epirubicin in the treatment of postmenopausal patients with metastatic breast cancer: a randomized study of epirubicin at four different dose levels performed by the Danish Breast Cancer Cooperative Group. *J Clin Oncol.* 1996;14(4):1146–1155.
65. Muss HB, Richards F II, Jackson DV, et al. Vincristine, doxorubicin, and cyclophosphamide versus low-dose intravenous cyclophosphamide, methotrexate, and 5-fluorouracil in advanced breast cancer: a randomized trial of the Piedmont Oncology Association. *Cancer.* 1982;50(11):2269–2274.
66. Tormey DC, Gelman R, Band PR, et al. Comparison of induction chemotherapies for metastatic breast cancer. An Eastern Cooperative Oncology Group trial. *Cancer.* 1982;50(7):1235–1244.
67. 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(1):6–15.
68. Rosner D, Nemoto T, Lane WW. A randomized study of intensive versus moderate chemotherapy programs in metastatic breast cancer. *Cancer.* 1987;59(5):874–883.
69. Costanza ME, Weiss RB, Henderson IC, et al. Safety and efficacy of using a single agent or a phase II agent before instituting standard combination chemotherapy in previously untreated metastatic breast cancer patients: report of a randomized study—Cancer and Leukemia Group B 8642. *J Clin Oncol.* 1999;17(5):1397–1406.
70. Nabholtz 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(5):1413–1424.
71. Stewart DJ, Evans WK, Shepherd FA, et al. Cyclophosphamide and fluorouracil combined with mitoxantrone versus doxorubicin for breast cancer: superiority of doxorubicin. *J Clin Oncol.* 1997;15(5):1897–1905.
72. Chan S, Friedrichs K, Noel D, et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. *J Clin Oncol.* 1999;17(8):2341–2354.
73. Bonneterre J, Roché H, Monnier A. Docetaxel vs 5-fluorouracil plus vinorelbine in metastatic breast cancer after anthracycline therapy failure. *Br J Cancer.* 2002;87(11):1210–1215.
74. Romero A, Rabinovich MG, Pérez JE, et al. Alternating versus sequential therapy in advanced breast cancer. *Medicina (B Aires).* 1987;47(3):243–248.
75. Joensuu H, Holli K, Heikkinen M. Combination chemotherapy versus single-agent therapy as first- and second-line treatment in metastatic breast cancer: a prospective randomized trial. *J Clin Oncol.* 1998;16(12): 3720–3730.
76. Gebbia V, Testa A, Valenza R, et al. Levo folinic acid and 5-fluorouracil plus high dose epidoxorubicin as first line treatment for metastatic breast carcinoma. *Anticancer Res.* 1993;13(1):141–144.
77. Carmo-Pereira J, Costa FO, Henriques E. Single-drug vs combination cytotoxic chemotherapy in advanced breast cancer: a randomized study. *Eur J Cancer.* 1980;16(12):1621–1625.
78. Ebbs SR, Saunders JA, Graham H, A'Hern RP, Bates T, Baum M. Advanced breast cancer. A randomised trial of epidoxorubicin at two different dosages and two administration systems. *Acta Oncol.* 1989;28(6): 887–892.
79. Gundersen S, Kvinnsland S, Klepp O, Kvaløy S, Lund E, Høst H. Weekly adriamycin versus VAC in advanced breast cancer. A randomized trial. *Eur J Cancer Clin Oncol.* 1986;22(12):1431–1434.
80. Coates A, Gebski V, Bishop JF, et al. Improving the quality of life during chemotherapy for advanced breast cancer. A comparison of intermittent and continuous treatment strategies. *N Engl J Med.* 1987;317(24):1490–1495.
81. Focan C, Andrien JM, Closon MT, et al. Dose-response relationship of epirubicin-based first-line chemotherapy for advanced breast cancer: a prospective randomized trial. *J Clin Oncol.* 1993;11(7):1253–1263.
82. Andersson M, Madsen EL, Overgaard M, Rose C, Dombernowsky P, Mouridsen HT. Doxorubicin versus methotrexate both combined with cyclophosphamide, 5-fluorouracil and tamoxifen in postmenopausal patients with advanced breast cancer—a randomised study with more than 10 years follow-up from the Danish Breast Cancer Cooperative Group. Danish Breast Cancer Cooperative Group (DBCG). *Eur J Cancer.* 1999;35(1):39–46.
83. Hausmaninger H, Lehnert M, Steger G, et al. Randomised phase II study of epirubicin-vindesine versus mitoxantrone-vindesine in metastatic breast cancer. *Eur J Cancer.* 1995;31A(13–14):2169–2173.
84. Jassem J, Pieńkowski T, Płuzańska A, et al. Doxorubicin and paclitaxel versus fluorouracil, doxorubicin, and cyclophosphamide as first-line therapy for women with metastatic breast cancer: final results of a randomized phase III multicenter trial. *J Clin Oncol.* 2001;19(6):1707–1715.
85. 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(11):783–792.
86. Norris B, Pritchard KI, James K, et al. Phase III comparative study of vinorelbine combined with doxorubicin versus doxorubicin alone in disseminated metastatic/recurrent breast cancer: National Cancer Institute of Canada Clinical Trials Group Study MA8. *Clin Oncol.* 2000;18(12): 2385–2394.
87. Ackland SP, Anton A, Breitbach GP, et al. Dose-intensive epirubicin-based chemotherapy is superior to an intensive intravenous cyclophosphamide, methotrexate, and fluorouracil regimen in metastatic breast cancer: a randomized multinational study. *J Clin Oncol.* 2001;19(4):943–953.
88. Cook AM, Chambers EJ, Rees GJ. Comparison of mitozantrone and epirubicin in advanced breast cancer. *Clin Oncol (R Coll Radiol).* 1996;8(6): 363–366.
89. Ingle JN, Mailliard JA, Schaid DJ, et al. Randomized trial of doxorubicin alone or combined with vincristine and mitomycin C in women with metastatic breast cancer. *Am J Clin Oncol.* 1989;12(6):474–480.
90. Green JA, Slater AJ, Campbell IR, Kelly V. Advanced breast cancer: a randomized study of doxorubicin or mitoxantrone in combination with cyclophosphamide and vincristine. *Breast Cancer Res Treat.* 1996;39(2): 155–163.
91. Steiner R, Stewart JF, Cantwell BM, Minton MJ, Knight RK, Rubens RD. Adriamycin alone or combined with vincristine in the treatment of advanced breast cancer. *Eur J Cancer Clin Oncol.* 1983;19(11):1553–1557.
92. Erkisi M, Bilkay BC, Seyrek E, Hazar B, Burgut R. Refractory breast cancer: a comparison of two different chemotherapy regimens. *J Chemother.* 1997;9(6):442–445.
93. Capotorto AM, Pavesi L, Pedrazzoli P, et al. Randomized, controlled, multicenter phase III trial of standard-dose fluorouracil-epirubicin-cyclophosphamide (FEC), compared with time-intensive FEC (FEC-G) and mitoxantrone-methotrexate mitomycin C (MMM-G) in metastatic breast carcinoma. *J Chemother.* 2003;15(2):184–191.
94. Gasparini G, Dal Fior S, Panizzoni GA, Favretto S, Pozza F. Weekly epirubicin versus doxorubicin as second line therapy in advanced breast cancer. A randomized clinical trial. *Am J Clin Oncol.* 1991;14(1):38–44.
95. Ahmann DL, Schaid DJ, Ingle JN, et al. A randomized trial of cyclophosphamide, doxorubicin, and prednisone versus cyclophosphamide, 5-fluorouracil, and prednisone in patients with metastatic breast cancer. *Am J Clin Oncol.* 1991;14(3):179–183.
96. Cocconi G, Bisagni G, Bella M, et al. Comparison of CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) with a rotational crossing and a sequential intensification regimen in advanced breast cancer: a prospective randomized study. *Am J Clin Oncol.* 1999;22(6):593–600.
97. Spittle MF, Hill BT, Ostrowski MJ, et al. A randomized, prospective, comparative, multicentre trial of a single combination versus alternating combinations of antitumour drugs in advanced breast cancer. *Eur J Cancer Clin Oncol.* 1987;23(8):1155–1162.

98. Berruti A, Bitossi R, Gorzegno G, et al. Time to progression in metastatic breast cancer patients treated with epirubicin is not improved by the addition of either cisplatin or lonidamine: final results of a phase III study with a factorial design. *J Clin Oncol.* 2002;20(20):4150–4159.
99. Sledge GW, Neuberg D, Bernardo P, et al. Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). *J Clin Oncol.* 2003;21(4):588–592.
100. Nabholtz JM, Falkson C, Campos D, et al. 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(6):968–975.
101. Blajman C, Balbiani L, Block J, et al. A prospective, randomized phase III trial comparing combination chemotherapy with cyclophosphamide, doxorubicin, and 5-fluorouracil with vinorelbine plus doxorubicin in the treatment of advanced breast carcinoma. *Cancer.* 1999;85(5):1091–1097.
102. Skeel RT, Andersen JW, Tormey DC, et al. Combination chemotherapy of advanced breast cancer. Comparison of dibromodulcitol, doxorubicin, vincristine, and fluoxymesterone to thiotepa, doxorubicin, vinblastine, and fluoxymesterone: an Eastern Cooperative Oncology Group study. *Cancer.* 1989;64(7):1393–1399.
103. Fraser SC, Dobbs HJ, Ebbs SR, Fallowfield LJ, Bates T, Baum M. Combination or mild single agent chemotherapy for advanced breast cancer? CMF vs epirubicin measuring quality of life. *Br J Cancer.* 1993; 67(2):402–406.
104. Carmo-Pereira J, Costa FO, Henriques E, et al. A comparison of two doses of adriamycin in the primary chemotherapy of disseminated breast carcinoma. *Br J Cancer.* 1987;56(4):471–473.
105. Estaban E, Lacave AJ, Fernández JL, et al. Phase III trial of cyclophosphamide, epirubicin, fluorouracil (CEF) versus cyclophosphamide, mitoxantrone, fluorouracil (CNF) in women with metastatic breast cancer. *Breast Cancer Res Treat.* 1999;58(2):141–150.
106. Nielsen D, Dombernowsky P, Larsen SK, Hansen OP, Skovsgaard T. Epirubicin or epirubicin and cisplatin as first-line therapy in advanced breast cancer. A phase III study. *Cancer Chemother Pharmacol.* 2000;46(6): 459–466.
107. French Epirubicin Study Group. A prospective randomized phase III trial comparing combination chemotherapy with cyclophosphamide, fluorouracil, and either doxorubicin or epirubicin. *J Clin Oncol.* 1988;6(4):679–688.
108. French Epirubicin Study Group. A prospective randomized trial comparing epirubicin monochemotherapy to two fluorouracil, cyclophosphamide, and epirubicin regimens differing in epirubicin dose in advanced breast cancer patients. *J Clin Oncol.* 1991;9(2):305–312.
109. Italian Multicentre Breast Study. Phase III randomized study of fluorouracil, epirubicin, and cyclophosphamide vs fluorouracil, doxorubicin, and cyclophosphamide in advanced breast cancer: an Italian multicentre trial. *J Clin Oncol.* 1988;6(6):976–982.
110. Ejlertsen B, Mouridsen HT, Langkjer ST, et al. Phase III study of intravenous vinorelbine in combination with epirubicin versus epirubicin alone in patients with advanced breast cancer: a Scandinavian Breast Group trial (SBG9403). *J Clin Oncol.* 2004;22(12):2313–2320.
111. Icli F, Akbulut H, Uner A, et al. Cisplatin plus oral etoposide (EoP) combination is more effective than paclitaxel in patients with advanced breast cancer pretreated with anthracyclines: a randomised phase III trial of Turkish Oncology Group. *Br J Cancer.* 2005;92(4):639–644.
112. Bonneterre J, Dieras V, Tubiana-Hulin M, et al. Phase II multicentre randomised study of docetaxel plus epirubicin vs 5-fluorouracil plus epirubicin and cyclophosphamide in metastatic breast cancer. *Br J Cancer.* 2004;91(8):1466–1471.
113. Keller AM, Mennel RG, Georgoulias VA, et al. Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer. *J Clin Oncol.* 2004;22(19):3893–3901.
114. Zielinski C, Beslija S, Mrsic-Krmpotic Z, et al. Gemcitabine, epirubicin, and paclitaxel versus fluorouracil, epirubicin, and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: a Central European Cooperative Oncology Group International, multicenter, prospective, randomized phase III trial. *J Clin Oncol.* 2005;23(7):1401–1408.
115. 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(4):792–799.
116. 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(10):1517–1526.
117. Lyman GH, Green SJ, Ravdin PM, et al. A Southwest Oncology Group Randomized Phase II Study of doxorubicin and paclitaxel as frontline chemotherapy for women with metastatic breast cancer. *Breast Cancer Res Treat.* 2004;85(2):143–150.
118. Buyukunal E, Derman U, Serdengecti S, Berkarda B. A clinical trial of mitoxantrone (novantrone) versus doxorubicin (adriamycin) in combination chemotherapy for metastatic breast cancer. *Chemioterapia.* 1987;6(5): 377–379.
119. Feher O, Vodvarka P, Jassem J, et al. First-line gemcitabine versus epirubicin in postmenopausal women aged 60 or older with metastatic breast cancer: a multicenter, randomized, phase III study. *Ann Oncol.* 2005;16(6): 899–908.
120. 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(19):4265–4274.
121. Langley RE, Carmichael J, Jones AL, et al. Phase III trial of epirubicin plus paclitaxel compared with epirubicin plus cyclophosphamide as first-line chemotherapy for metastatic breast cancer: United Kingdom National Cancer Research Institute trial AB01. *J Clin Oncol.* 2005;23(33):8322–8330.
122. Bontenbal M, Creemers GJ, Braun HJ, et al. Phase II to III study comparing doxorubicin and docetaxel with fluorouracil, doxorubicin, and cyclophosphamide as first-line chemotherapy in patients with metastatic breast cancer: results of a Dutch Community Setting Trial for the Clinical Trial Group of the Comprehensive Cancer Centre. *J Clin Oncol.* 2005;23(28): 7081–7088.
123. 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(3):219–225.
124. Geyer CE, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med.* 2006;355(26): 2733–2743.
125. Moen MD, Wellington K. Gemcitabine: in combination with paclitaxel in the first-line treatment of metastatic breast cancer. *Am J Cancer.* 2005;4(5): 327–323.
126. Pandya KJ. Phase III study of standard combination versus rotating regimen of induction chemotherapy in patients with hormone insensitive metastatic breast cancer: an Eastern Cooperative Oncology Group intergroup study (E3185). *Am J Clin Oncol.* 2007;30(2):113–125.
127. Stockler M, Sourjina T, Grimison P, et al. A randomized trial of capecitabine (C) given intermittently (IC) rather than continuously (CC) compared to classical CMF as first-line chemotherapy for advanced breast cancer (ABC). *J Clin Oncol. (2007 ASCO Annual Meeting Proceedings Part I).* 2007;25(18S):1031.
128. 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). *J Clin Oncol. (2006 ASCO Annual Meeting Proceedings Part I).* 2006;24(18S):571.
129. Di Leo A, Gomez H, Aziz Z, et al. Lapatinib (L) with paclitaxel compared to paclitaxel as first-line treatment for patients with metastatic breast cancer: a phase III randomized, double-blind study of 580 patients. *J Clin Oncol. (2007 ASCO Annual Meeting Proceedings Part I).* 2007; 25(18S):1011.
130. Falkson G, Tormey DC, Carey P, Witte R, Falkson HC. Long-term survival of patients treated with combination chemotherapy for metastatic breast cancer. *Eur J Cancer.* 1991;27(8):973–977.

131. Chlebowski RT, Smalley RV, Weiner JM, Irwin LE, Bartolucci AA, Bateman JR. Combination versus sequential single agent chemotherapy in advanced breast cancer: associations with metastatic sites and long-term survival. The Western Cancer Study Group and the Southeastern Cancer Study Group. *Br J Cancer*. 1989;59(2):227–230.
132. Smalley RV, Carpenter J, Bartolucci A, Vogel C, Krauss S. A comparison of cyclophosphamide, adriamycin, 5-fluorouracil (CAF) and cyclophosphamide, methotrexate, 5-fluorouracil, vincristine, prednisone (CMFVP) in patients with metastatic breast cancer: a Southeastern Cancer Study Group project. *Cancer*. 1977;40(2):625–632.
133. Smalley RV, Bartolucci AA. Variations in responsiveness and survival of clinical subsets of patients with metastatic breast cancer to two chemotherapy combinations. *Eur J Cancer*. 1980;16(suppl 1):141–146.
134. Vaughn CB, Green SJ, O'Bryan R, et al. VP-16 + adriamycin vs. adriamycin alone in advanced adenocarcinoma of the breast, phase II, a randomized trial: a Southwest Oncology Group study. *Med Pediatr Oncol*. 1988; 16(5):312–319.
135. Aisner J, Weinberg V, Perloff M, et al. Chemotherapy versus chemoimmunotherapy (CAF v CAFVP v CMF each +/− MER) for metastatic carcinoma of the breast: a CALGB study. Cancer and Leukemia Group B. *J Clin Oncol*. 1987;5(10):1523–1533.
136. Falkson G, Gelman RS, Leone L, Falkson CI. Survival of premenopausal women with metastatic breast cancer. Long-term follow-up of Eastern Cooperative Group and Cancer and Leukemia Group B studies. *Cancer*. 1990;66(7):1621–1629.
137. Nemoto T, Horton J, Simon R, et al. Comparison of four-combination chemotherapy programs in metastatic breast cancer: comparison of multiple drug therapy with cytoxan, 5-FU and prednisone versus cytoxan and adriamycin, versus cytoxan, 5-FU and adriamycin, versus cytoxan, 5-FU and prednisone alternating with cytoxan and adriamycin. *Cancer*. 1982; 49(10):1988–1993.
138. Cummings FJ, Gelman R, Skeel RT, et al. Phase II trials of Baker's antifol, bleomycin, CCNU, streptozotocin, tilorone, and 5-fluorodeoxyuridine plus arabinosyl cytosine in metastatic breast cancer. *Cancer*. 1981;48(3): 681–685.
139. Thormey DC, Falkson G, Simon RM, et al. A randomized comparison of two sequentially administered combinations to a single regimen in metastatic breast cancer. *Cancer Clin Cancer Clin Trials*. 1979;2(2):247–256.
140. Pannuti F, Iafelice G, Martoni A, Fruet F, Angelelli B, Casadei M. A new six-drug antiblastic regimen (R 14) at low doses (micropolychemotherapy) compared to CMF in the treatment of metastatic breast cancer: phase III study. *Chemioterapia*. 1984;3(4):216–219.
141. Cummings FJ, Gelman R, Horton J. Comparison of CAF versus CMFP in metastatic breast cancer: analysis of prognostic factors. *J Clin Oncol*. 1985;3(7):932–940.
142. Ahmann DL, Bisel HF, Hahn RG. A phase 2 evaluation of 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (NSC 95441) in patients with advanced breast cancer. *Cancer Res*. 1974;34(1):27–30.
143. Ahmann DL, Bisel HF, Hahn RG. Phase II clinical trial of isophosphamide (NSC-109724) in patients with advanced breast cancer. *Cancer Chemother Rep*. 1974;58(6):861–865.
144. Ahmann DL, Schaid DJ, Bisel HF, Hahn RG, Edmonson JH, Ingle JN. The effect on survival of initial chemotherapy in advanced breast cancer: polychemotherapy versus single drug. *J Clin Oncol*. 1987;5(12): 1928–1932.
145. De Lena M, Brambilla C, Morabito A, Bonadonna G. Adriamycin plus vincristine compared to and combined with cyclophosphamide, methotrexate, and 5-fluorouracil for advanced breast cancer. *Cancer*. 1975;35(4): 1108–1115.
146. Carmichael J, Possinger K, Phillip P, et al. Advanced breast cancer: a phase II trial with gemcitabine. *J Clin Oncol*. 1995;13(11):2731–2736.
147. Blum JL, Jones SE, Buzdar AU, et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol*. 1999;17(2):485–493.
148. Holmes FA, Walters RS, Theriault RL, et al. Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer. *J Natl Cancer Inst*. 1991;83(24):1797–1805.
149. Engebraaten O, Natarajan V, Lokkevik E, et al. A randomized phase II trial with gefitinib and docetaxel in metastatic breast cancer: an evaluation of the treatment regimen and the factors associated with toxicity. San Antonio Breast Cancer Symposium 2006. Available at: http://www.sabcs.org. Accessed January 13, 2008. Abstract 1093.
150. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med*. 2007; 357(26):2666–2676.
151. Trikalinos TA, Ioannidis JP. Predictive modeling and heterogeneity of baseline risk in meta-analysis of individual patient data. *J Clin Epidemiol*. 2001;54(3):245–252.

Funding

There was no funding source for this study.

Notes

The original idea was developed by J. P. A. Ioannidis and N. Pavlidis. All the authors participated in the design of the study; D. Mauri, N. P. Polyzos, and J. P. A. Ioannidis participated in data extraction; G. Salanti and J. P. A. Ioannidis performed the statistical analyses; all the authors interpreted the results; D. Mauri and J. P. A. Ioannidis wrote the manuscript and all other authors commented critically on it. All the authors approved the final version. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

All authors declare that they have no conflicts of interest.

We are grateful to Dr Evangelos Briasoullis for helpful discussions and to Dr Lamprini Tsali for help in data collection.

Manuscript received March 24, 2008; revised August 20, 2008; accepted October 16, 2008.