Bevacizumab in metastatic breast cancer: a meta-analysis of randomized controlled trials

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Breast Cancer Res Treat (2010) 122:1–7
DOI 10.1007/s10549-009-0727-0

REVIEW

Bevacizumab in metastatic breast cancer: a meta-analysis of randomized controlled trials

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Received: 6 August 2009 / Accepted: 29 December 2009 / Published online: 9 January 2010

Abstract: Numerous studies have demonstrated that angiogenesis and in particular VEGF over-expression play an essential role in the progression and metastatic potential of breast cancer. Bevacizumab is a humanized recombinant monoclonal antibody that specifically blocks the binding of VEGF to high-affinity receptors and it has been recently used for the treatment of metastatic breast cancer. We conducted a meta-analysis to synthesize available evidence for use of bevacizumab in metastatic breast cancer patients. Systematic review and meta-analysis of available trials. Primary outcomes were overall survival, progression free survival (PFS) and objective response rate (ORR). Five trials were identified with 3,163 eligible patients. Combination of bevacizumab and chemotherapy resulted in a statistically significant improvement in PFS (HR = 0.70, 95% CI 0.60–0.82, $P = 9.3 \times 10^{-6}$) and ORR (RR = 1.26, 95% CI 1.17–1.37, $P = 9.96 \times 10^{-9}$) compared with chemotherapy alone. Differences in objective response rates were substantial independently by the type of chemotherapy used, while PFS advantages were observed only for taxanes. The pooled HR for overall survival did not show significant advantage for the use of bevacizumab compared to placebo arm (HR = 0.90, 95% CI 0.80–1.03, $P = 0.119$). This meta-analysis shows that the addition of bevacizumab to chemotherapy offers meaningful improvement in PFS and ORR in patients with metastatic breast cancer. Bevacizumab treatment might be suggested for treatment of 1st line metastatic breast cancer, but more data are needed until statistical overall survival differences will be documented and firm guideline recommendation could be given.

Keywords Advanced · Metastatic · Breast cancer · Bevacizumab · Meta-analysis · Avastin · Chemotherapy

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Introduction

Despite the use of hormonal agents and chemotherapy, metastatic disease remains largely incurable with a median survival of 2–3 years from the time of diagnosis [1].

Numerous studies have demonstrated that angiogenesis and in particular VEGF over-expression play an essential role in the growth, progression and metastatic potential of breast cancer [2–5]. Thereafter, VEGF became a fundamental target of anti-angiogenic therapy.

Bevacizumab is a humanized recombinant monoclonal antibody that specifically blocks the binding of VEGF to high-affinity receptors [6]. In metastatic breast cancer patients, randomized controlled trials evaluated bevacizumab as first-line treatment showed improvements in tumor response rate and progression-free survival (PFS)

when added to chemotherapy [7–9]. However, none of the trials showed significant survival benefit with the use of bevacizumab partially because all those trials were designed to detect differences regarding progression-free survival events.

Therefore, we conducted a meta-analysis to synthesize available evidence for use of bevacizumab in metastatic breast cancer patients in terms of overall survival, progression free survival and response rate.

Materials and methods

Identification of randomized trials

We searched PubMed, ISI Thompson, and The Cochrane Library to identify all relevant randomized controlled trials (RCTs), comparing chemotherapy with or without bevacizumab in metastatic breast cancer. Keywords employed in the search process included avastin; bevacizumab; breast or mammary; cancer, malign*, neoplasm*, or carcinoma. The last search update was on June 3, 2009.

The reference lists of all relevant articles of this topic were examined manually for other relevant articles missed by the electronic searches. Because recent trials with bevacizumab may still be unpublished, we also searched electronically the major international congresses proceedings (American Society of Clinical Oncology Annual Meeting, San Antonio Breast Cancer Symposium, the European Cancer Conference).

Eligibility criteria

Eligibility and exclusion criteria were prespecified. We included all randomized controlled trials that evaluated the administration of bevacizumab plus chemotherapy versus chemotherapy alone. All cytotoxic chemotherapy regimens were considered eligible for the meta-analysis, provided that the same drugs were given at the same dose in all study arms and that the arms differed systematically only regarding bevacizumab administration. Articles in all languages were considered.

We excluded dose escalating studies, phase I or I/II trials and non-randomized studies. We also excluded trials testing the neoadjuvant administration of bevacizumab.

Data extraction and outcomes

From each eligible trial, we recorded authors' names, journal and year of publication, country of origin, years of patient enrolment, sample size, regimens used, chemotherapy and bevacizumab dosing and scheduling, line of treatment, additional treatments given to both arms, follow-up period, the number of outcome events and information pertaining to study design, mode of randomization, blinding, allocation concealment, and withdrawals description.

Two authors (A.V and D.M.) extracted data independently and reached consensus on all items. Disagreement on specific studies between the two reviewers was resolved through discussion.

The three outcomes of interest were (1) overall survival (OS), defined as the time from random assignment to death from any cause; (2) progression-free survival (PFS) defined as the time from randomization to disease progression or death from any cause; and (3) objective response rate (ORR) defined as the sum of partial and complete response rates. For the overall survival and progression-free survival we synthesized extracted HRs and respective standard errors, whereas for the outcome of objective response rate we used available data from 2×2 tables.

Statistical analysis

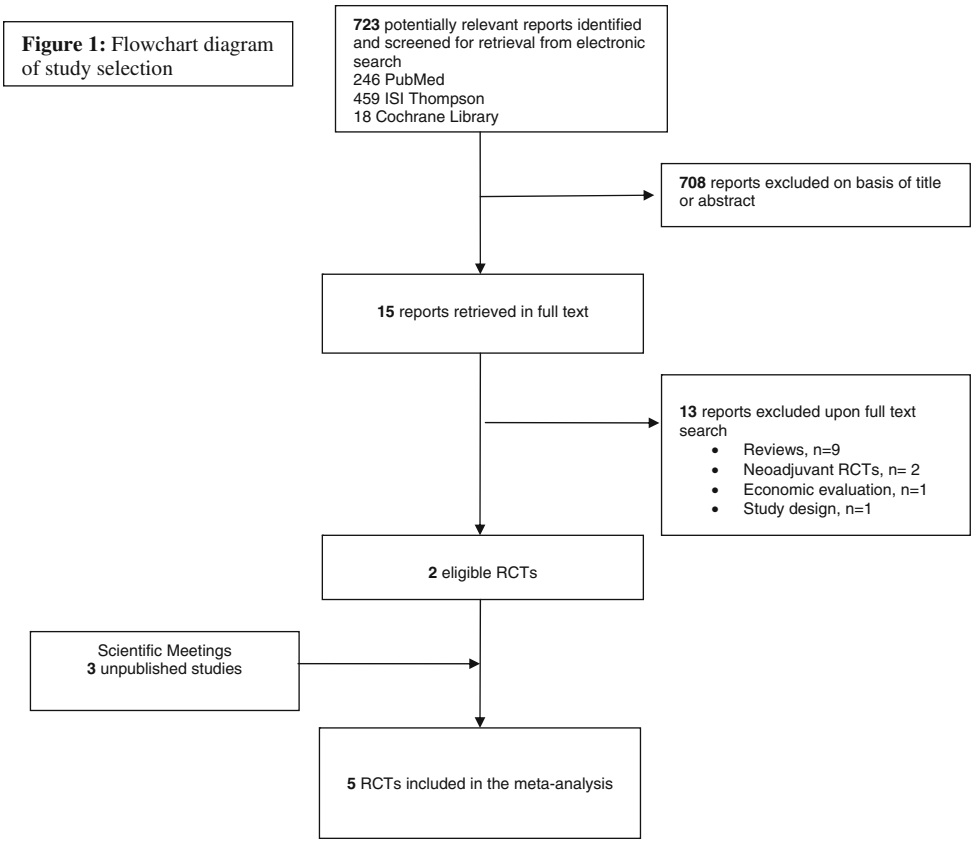
Hazard ratios and their 95% confidence intervals (CI) for treated versus control groups were retrieved from each primary study. In case these data were not available in primary reports we derived HR and their 95% CIs using Tierney methodology when applicable. We used the DerSimonian-Laird random effects model [10] to calculate the overall effect size when more than two studies were available. A random effects model assumes that each study has its own true effect size, whereas a fixed effects model assumes that there is only one true effect size. Since most studies were expected to have differences in clinical settings, methodology, etc., we preferred a random effects model. The presence of statistical heterogeneity was assessed with Cochran's Q test (considered significant for $P < 0.10$) [11] and quantified using I^2 and respective 95% CIs [12]. For I^2 values $\geq$50% indicate large heterogeneity and values $\geq$75% indicate very large (extreme) heterogeneity [13]. Finally, we synthesized separately studies based on the type of comparative chemotherapy treatment used, e.g. taxanes.

Results

Description of eligible trials

The trial flow is summarized in Fig. 1. The search yielded 723 studies and after scrutinizing title and abstract 15 papers were selected for full text evaluation (Fig. 1). We identified two eligible trials published in full text [7, 14] and three eligible trials presented only in major conferences [8, 9, 15]. Even considering that survival data for two

Fig. 1 Flowchart diagram of study selection



trials (AVADO and RIBBON-1) [8, 9] was premature at the time of abstract presentation (ASCO 2009), since only 2 months intercourse between abstract presentation and our data-analyses, no further data were requested from primary investigators. Thus, we included five studies in the meta-analysis, including a total of 3,163 patients, with 1,932 patients in the chemotherapy-plus bevacizumab arm and 1,231 patients in the chemotherapy alone arm.

Two of the studies were described as double-blinded [8, 9]. We were able to evaluate other quality characteristics of eligible trials in only two studies published in full text [7, 14]. Both studies provided in detail withdrawals description, only one [7] described in detail the mode of randomization while none of them reported allocation concealment.

One of the studies was a three-arm trial [8]. In this trial, patients were randomized to receive placebo or bevacizumab in two different doses, 15 or 7.5 mg/kg. Since hazard ratios for OS and PFS were given separately for the two dosage bevacizumab arms versus the placebo comparator arm, to avoid double counting of placebo arm, only data from 15 mg/kg dosage versus placebo arms were included in the meta-analyses for OS and PFS. The choice was driven by the fact that in the 15 mg/kg arm bevacizumab was used at the same dose density used in other trials included in present meta-analysis. The arm of 7.5 mg/kg was used instead of the 15 mg/kg one in sensitivity analyses.

In addition, one study [9] reported separate analyses for patients received capecitabine plus bevacizumab versus placebo and those who received anthracycline-based chemotherapy or taxanes plus bevacizumab versus placebo. We also considered this trial as two different two-arm studies. The key trial characteristics are listed in Table 1.

Progression-free survival

All but one trial [15] reported this outcome representing a total of 3,108 patients. The combination of bevacizumab and chemotherapy resulted in a statistically significant improvement in PFS compared with chemotherapy alone (HR = 0.70, 95% CI = 0.60–0.82, P-value = 9.3×10^{-6}) (Fig. 2). There was significant statistical heterogeneity between individual trials (Q test P-value = 0.023, I^2 = 65%; 95% CI 8–87%). Using the 7.5 mg/kg instead yielded similar results (data not shown).

The subgroup analysis based on type of chemotherapy showed that the combination of bevacizumab with taxanes led to statistical significant improvement of PFS (HR =

Table 1 Key trial characteristics

Author, study name [ref]	Year	Study arms	Bevacizumab schedule	No. of patients	Line of treatment	Primary endpoint
Miller, E2100 [7]	2007	Paclitaxel		326	1st	PFS
		Paclitaxel + bevacizumab	10 mg/kg iv every 2 weeks	347		
Pivot, AVADO [8]	2009	Docetaxel		241	1st	PFS
		Docetaxel + bevacizumab	7.5 mg/kg iv every 3 weeks	248		
		Docetaxel + bevacizumab	15 mg/kg iv every 3 weeks	247		
Robert, RIBBON-1 [9]	2009	Capecitabine + placebo		206	1st	PFS
		Capecitabine + bevacizumab	15 mg/kg iv every 3 weeks	409		
Robert, RIBBON-1 [11]	2009	Taxanes or anthracyclines + placebo		207	1st	PFS
		Taxanes or anthracyclines + bevacizumab	15 mg/kg iv every 3 weeks	415		
Miller, AVF2119g [12]	2005	Capecitabine		230	>1st	PFS
		Capecitabine + bevacizumab	15 mg/kg iv every 3 weeks	232		
Burstein [13]	2005	Methotrexate + cyclophosfamide		21	>1st	RR
		Methotrexate + cyclophosphamide + bevacizumab	10 mg/kg iv every 2 weeks	34		

ref reference, *mg* milligrams, *kg* kilograms, *PFS* progression-free survival, *RR* response rate

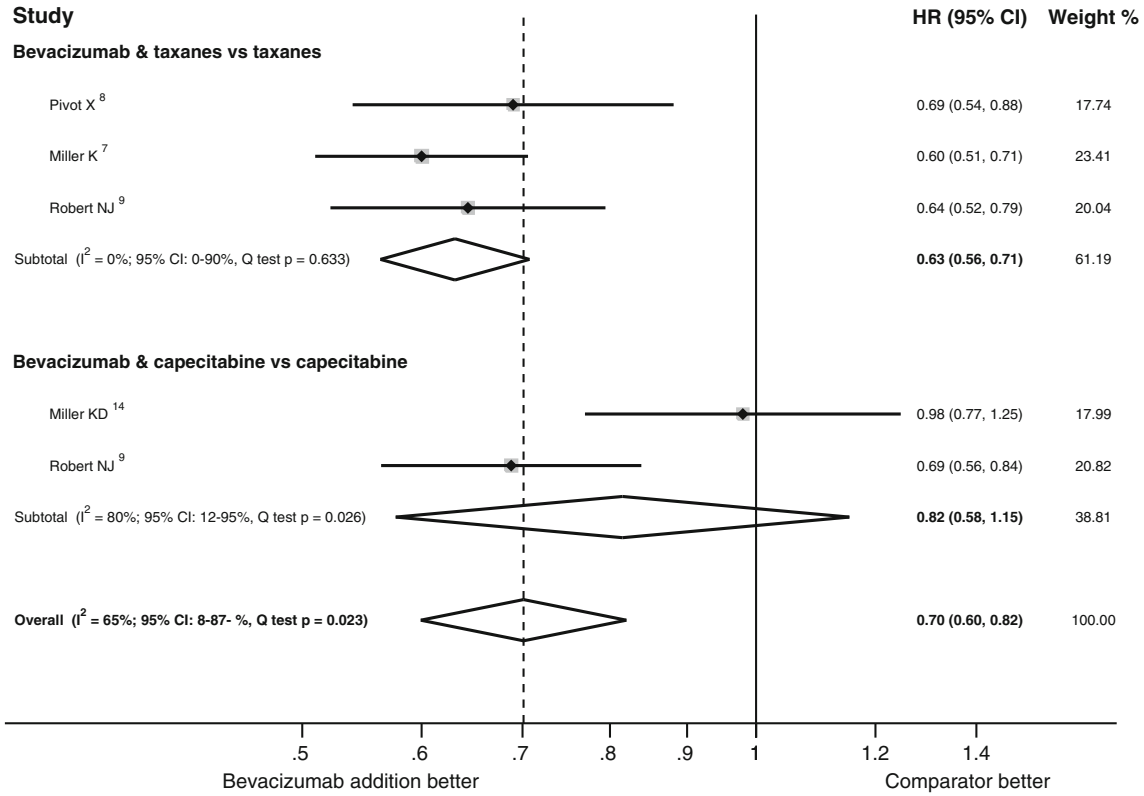


Fig. 2 Forest plots for progression-free survival (PFS) for the use of bevacizumab versus non-use. Each study is shown by the point estimate of the hazard ratio (*square*) and 95% confidence interval for the hazard ratio (*extending lines*); the pooled hazard ratio and 95% CI by random-effects calculations are shown by *diamonds*. For all plots, a HR < 1 (on the left of the *black line*) corresponds to results in favor of bevacizumab arm

0.63, 95% CI 0.56–0.71, *P*-value = 2.4×10^{-15}) while combination of bevacizumab with capecitabine does not improve PFS statistically significant (HR = 0.82, 95% CI 0.58–1.15, *P*-value = 0.249). However, this difference did not reach statistical significance (*P*-value of difference between groups: 0.158).

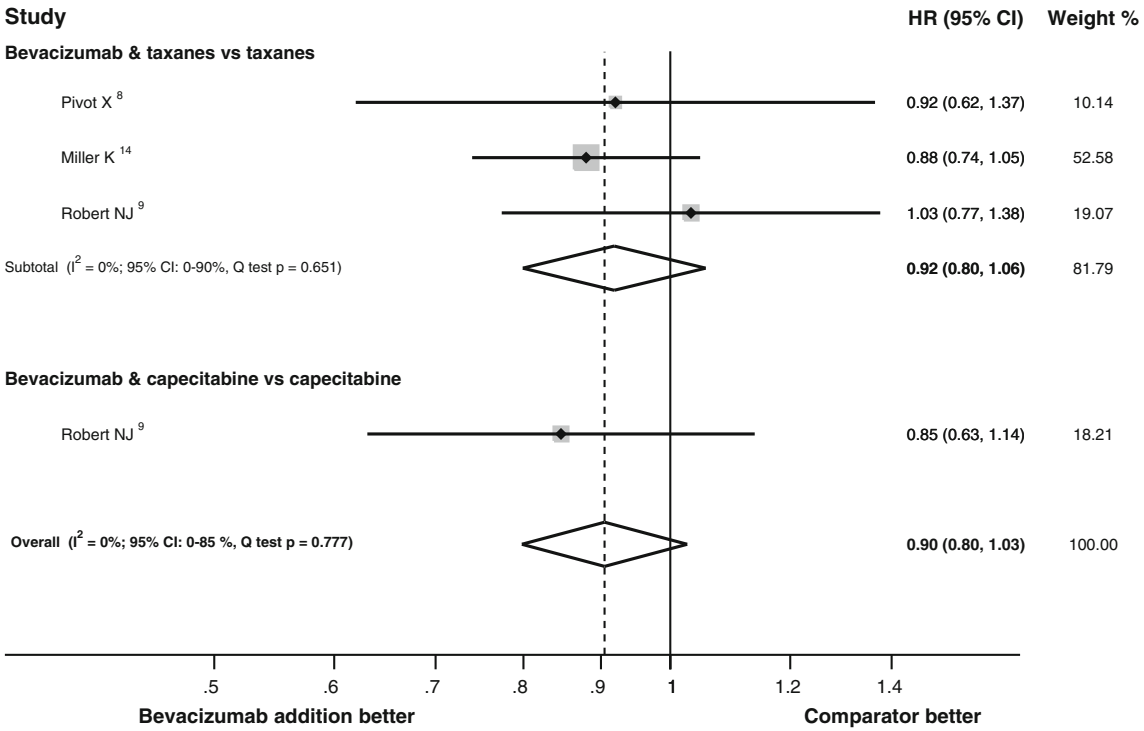


Fig. 3 Forest plots for overall survival (OS) for the use of bevacizumab versus non-use in advanced breast cancer. Each study is shown by the point estimate of the hazard ratio (*square*) and 95% confidence interval for the hazard ratio (*extending lines*); the pooled hazard ratio and 95% CI by random-effects calculations are shown by *diamonds*. For all plots, a HR < 1 (on the left of the *black line*) corresponds to results in favor of bevacizumab arm

Overall survival

Four studies [7–9, 14] reported or had data available to calculate hazard ratio including totally 2,646 patients.

The pooled HR for overall survival did not show significant advantage for the use of bevacizumab compared to placebo arm (pooled HR = 0.90, 95% CI 0.80–1.03, *P*-value = 0.119; Q test *P*-value: 0.777; $I^2 = 0\%$, 95% CI 0–85%) (Fig. 3). Using the 7.5 mg/kg arm yielded borderline statistically significant results (HR = 0.88, 95% CI 0.76–1.00, *P*-value = 0.046; Q test *P*-value: 0.433; $I^2 = 0\%$, 95% CI 0–85%). Only the subgroup of taxanes had enough studies to synthesize. The pooled HR was very similar to the overall one (HR: 0.92, 95% CI 0.80–1.06).

Objective response rate

All the five studies [7–9, 14, 15] included in the meta-analysis reported data on objective response rate. The RR was 1.26 with an associated 95% CI of 1.17–1.37 (*P*-value 9.96×10^{-9}; Q test *P*-value: 0.091; $I^2 = 47\%$; 95% CI 0–79%), corresponding to a statistically significant increase in response for the addition of bevacizumab therapy (Fig. 4). Differences in objective response rates were substantial independently by the type of chemotherapy use in combination with bevacizumab (taxanes agents, capecitabine or metronomic treatment with Methotrexate + Cyclophosfamide) (Fig. 4).

First- and second-line setting

Only few data were available to evaluate the use of bevacizumab in first and second line of treatment. When response rate data were analyzed we found that three studies included in the meta-analysis reported first line data ($n = 2{,}646$) [7–9], and two studies reported second-line data (517) [14, 15].

The objective response rate RR for the use of bevacizumab in the 1st line of treatment was 1.23 with an associated 95% CI of 1.13–1.33 (*P*-value 3.87×10^{-7}; Q test *P*-value: 0.136; $I^2 = 46\%$; 95% CI 0–82%) corresponding to a statistical significant increase in response for the addition of bevacizumab therapy. Analogous objective response rate advantages were observed for the use of bevacizumab in the second line of treatment: RR 1.466 with an associated 95% CI of 1.24–1.34 (*P*-value = 0.000011; Q test *P*-value: 0.91; $I^2 = 0\%$).

Unfortunately, no study reported OS data for second line of treatment, thereafter the retrieved data (pooled HR = 0.90, 95% CI 0.80–1.03, *P*-value = 0.119; Q test *P*-value: 0.777; $I^2 = 0\%$, 95% CI 0–85%) strictly pertain the first-line setting. Similarly, when PFS was analyzed, only one

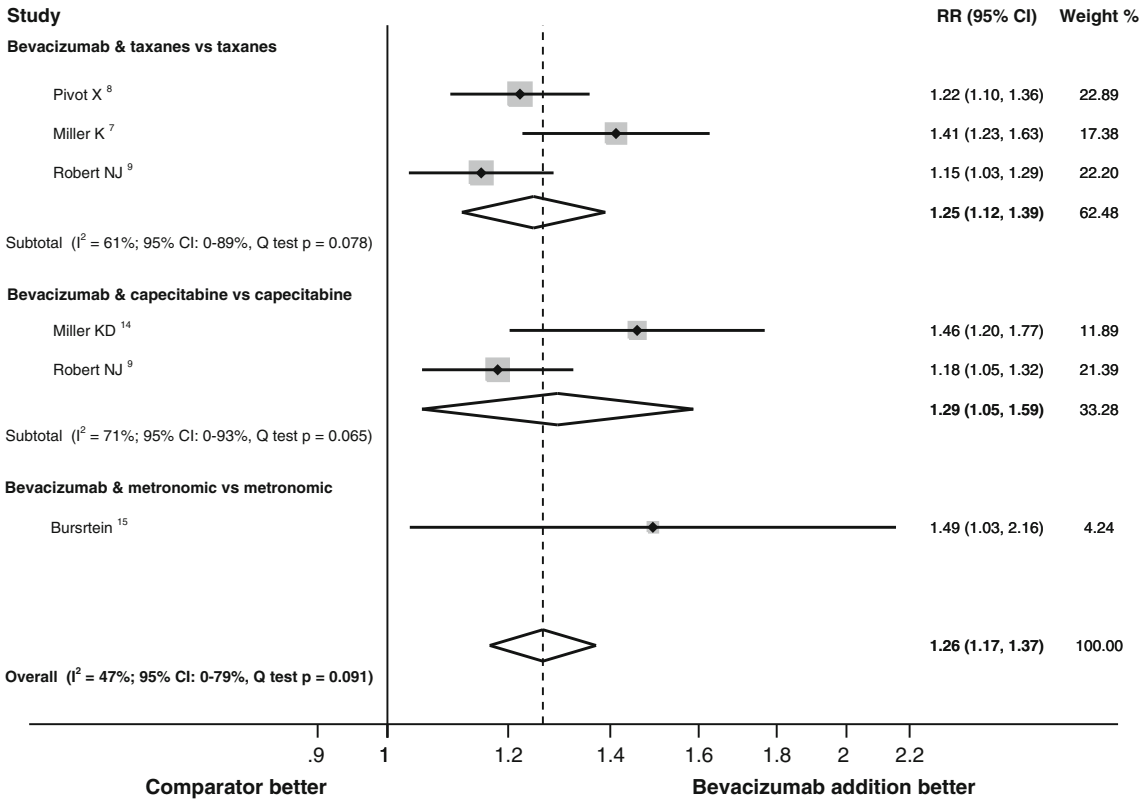


Fig. 4 Forest plot for objective response rate (ORR) for the use of bevacizumab versus non-use in advanced breast cancer. Each study is shown by the point estimate of the risk ratio (*square*) and respective 95% CI (*extending lines*); the pooled risk ratio and 95% CI by random-effects calculations are shown by *diamonds*. For all plots, a RR > 1 (on the left of the *black line*) corresponds to results in favor of bevacizumab arm. Burstein trial was a small phase 2 randomized trial. Due to predefined stopping roles, control arm was stopped at the interim analysis. Consequently, only 42 patients were randomized (21 per arm), while last accrued 13 patients were enrolled in the investigational arm. Due to his small sample size, Burstein trial have not any impact on final result of present meta-analysis. Anyhow these data were included in meta-analysis for the completeness of systematic review on available randomized evidence for the use of bevacizumab in advanced breast cancer

study [14] reported data on second-line setting; consequently, no subgroup analysis was performed.

Discussion

This meta-analysis summarizes all the current randomized evidence of the potential benefit with the addition of bevacizumab to chemotherapy for metastatic breast cancer. Data from our meta-analysis confirm that the addition of bevacizumab to chemotherapy regimens provides substantial benefit for women with metastatic breast cancer in terms of progression-free survival and objective response but not in overall survival. We also found that the combination of bevacizumab with taxanes has beneficial effect in PFS while the combination of bevacizumab with capecitabine does not reach statistical differences. It is possible that taxanes may have synergistic effect with bevacizumab as proposed by preclinical data [16]. Anyhow it should be considered that pooled HR results for capecitabine were influenced by Miller report [14], which used bevacizumab in heavily pretreated patients. Indeed, individually, all but Miller [14] trials contained in this study reported that bevacizumab improves PFS when added to chemotherapy for MBC, but all positive PFS trials used bevacizumab in first line of treatment. A possible explanation is that VEGF alone decreases in importance when more numerous and redundant pathways of angiogenesis become effective as breast cancer progresses [17, 18]. A direct consequence of this theory is that anti-VEGF agents might provide their greatest benefit in patients with early disease, which might be the rationale for recommending bevacizumab in first-line setting.

On the other hand, overall survival is the gold standard endpoint for clinical benefit in cancer patients, while PFS is a surrogate endpoint. In this setting, none of the trials included in our analyses revealed improvement in overall survival, and pooled HR analyses revealed only a positive trend without reaching statistical significance. Under these assumptions, solid recommendation of bevacizumab in first-line MBC could not be given until overall survival trend will be translated in statistical significant advantages.

Undoubtedly improvements in PFS may have independent value to patients, and many investigators have questioned the fact that OS should be the standard to evaluate drug benefits. On these bases a fair recommendation for the use of bevacizumab seems reasonable, anyhow these controversies do not diminish the importance of answering the OS question.

Several limitations need to be considered when interpreting our results. First, our approach was based on data abstracted from publications and not on individual patient data (IPD) which might define more clearly treatment benefits [19]. Second, most trials that we identified were reported in an abstract form only, which made it difficult both to extract complete data for analyses and to examine study quality characteristics. Furthermore, two studies were excluded from survival analysis since we could not retrieve any survival data. Anyhow these studies are unlikely to change our results since one study [15] had extremely small sample size and in the second one [14] no overall survival differences between the two arms were reported. Finally, we did not test formally for publication bias because we had few studies [20], but we cannot exclude the possibility of delayed publication of negative studies or no publication at all. Furthermore, we have to consider that if different benefits are expected as first versus refractory therapy (or with different chemotherapy partners), the meta-analysis may decrease important differences, thus limiting the benefits of more effective settings (e.g. combinations or line of treatment). Similarly if the survival benefits of a drug are maintained in second or more line of treatment, the eventual crossover of the drug after disease progression may obscure and render null the survival benefits that were amenable with the former line of treatment. Thereafter, meta-analysis technique may sometimes be inappropriate to quantify the eventual benefits of a certain drugs.

Admitting these restrictions, the results of this meta-analysis show that the addition of bevacizumab to chemotherapy offers a clinically meaningful and statistically significant improvement in PFS and ORR in patients with metastatic breast cancer but does not benefit overall survival. Bevacizumab treatment might be suggested for treatment of 1st line metastatic breast cancer, but more data are needed until statistical overall survival differences will be documented and firm guideline recommendation could be given.

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