Original Article
Multikinase inhibitor in combination with chemotherapy in the treatment of advanced breast cancer-a meta-analysis

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Abstract: Background: Multikinase inhibitors in combination with chemotherapy have recently been evaluated in patients with advanced breast cancer (ABC) in the adjuvant treatment, but limited data are available. We performed a meta-analysis of prospective randomized controlled trials to evaluate both the efficacy and safety of approved multikinase inhibitors combined with chemotherapy in the treatment of ABC. Methods: Relevant literature search were performed comprehensively up to June 2015. The endpoints were progression-free survival (PFS), overall survival (OS), overall response rate (ORR) and grade 3 or 4 adverse event (AEs). The available data were pooled and evaluated using Stata 12.0 (StataCorp, College Station, USA). Results: Seven randomized controlled trials (RCTs) with 1694 patients were included. Our pooled results showed that, compared to chemotherapy alone, multikinase inhibitors in combination with chemotherapy improved the PFS [hazard ratio (HR), 0.74; 95% confidence interval (CI), 0.63-0.84; $P<0.001$] and ORR [odds ratios (OR), 1.66; 95% CI, 1.35-2.05; $P<0.001$], but this did not correspond to an improvement in OS (HR, 1.02; 95% CI, 0.84-1.19; $P<0.001$). Additionally, a higher incidence of grades 3/4 hypertension, diarrhea, hand-foot syndrome, rash, stomatitis, and mucositis were observed in multikinase inhibitor-based therapy. Conclusions: Our results suggested that the combination of multikinase inhibitors and chemotherapy benefits ABC patients in PFS and ORR, but not OS, and may also have resulted in increased AEs.

Keywords: Advanced breast cancer, chemotherapy, multikinase inhibitor, meta-analysis

Introduction

Breast cancer is the most common cancer in women worldwide. Although adjuvant treatment in breast cancer has made much progress, many women still develop tumor relapse. Advanced breast cancer (ABC) is still considered an incurable malignancy, and the prognostic is poor [1]. The combination of chemotherapy has demonstrated clinical benefits compared with single-agent regimens, but toxicity was also increased. The development of new treatment strategies is therefore essential for patients with ABC. In recent years, angiogenesis inhibitors have become one of the most promising avenues for treating cancer, as angiogenesis plays a crucial component of tumor growth and metastasis [2-4]. In case of breast cancer, inhibition of angiogenesis has become a target of treatment strategy. Several

therapies targeting angiogenesis are in development. To date, bevacizumab is the only anti-angiogenic that has been approved for use in advanced breast cancer, which is a humanized monoclonal antibody that binds to vascular endothelial growth factor (VEGF), a primary angiogenic factor [5, 6]. Phase III E2100 study was initially demonstrated improved treatment response and PFS with the use of bevacizumab plus paclitaxel as first-line treatment for patients with HER2-negative locally advanced or metastatic breast cancer [7]. However, there was no significant improvement in OS. The follow-up studies also demonstrated statistically significant improvements in PFS without an OS benefit when adding bevacizumab to standard chemotherapy in advanced breast cancer patients, and the PFS benefit was limited. Furthermore, the frequency of common adverse events was higher and more serious with the

use of bevacizumab [8, 9]. Thus, the US Food and Drug Administration (FDA) revoked bevacizumab's conditional approval for breast cancer in 2011.

In view of the experience with bevacizumab, a number of orally multi-target antiangiogenic kinase inhibitors with multiple molecular targets have been developed as an alternative option for ABC, e.g., sorafenib, sunitinib, vandetanib, axitinib. In addition to the vascular epithelial growth factor receptor (VEGFR) tyrosine kinases, these agents potently inhibit a wide range of tyrosine kinases, including fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), epidermal growth factor receptor (EGFR), and their respective receptors involved in angiogenesis [10-13]. Since multiple pathways and multiple steps involved in tumorigenesis, these molecular and pharmacokinetic properties could lead to potential differences in the efficacy and safety profile of multikinase inhibitors. The use of multikinase inhibitors in combination with first-line or second-line chemotherapy agents for the treatment of advanced renal cell carcinomas (RCC) and unresectable hepatocellular carcinomas (HCC) are indicated, and is being evaluated for patients with ABC in several phase II~III studies. Results from these studies were encouraging, however, estimates of the efficacy and safety failed to reach consensus, and there was an absence of strong supporting evidence from single clinical trial. We conducted a meta-analysis of randomized controlled trials to make an objective evaluation of the efficacy and safety of multikinase inhibitor plus chemotherapy in ABC.

Materials and methods

Search strategy

Literature search were applied to PubMed, EMBASE, the Cochrane Library Databases, American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) and China Biological Medicine Database (CBM), with the search terms "breast cancer" and "kinase inhibitor". For example, for PubMed, the search strategy was based on combinations of the following terms: (breast cancer, breast carcinoma [MESH], breast cancer or breast carcinoma [TEXT WORD]) AND (multitargeted kinase inhibitor [TEXT WORD] or sorafenib [TEXT WORD] or axitinib

[TEXT WORD] or vandetanib [TEXT WORD] or sunitinib [TEXT WORD] or cediranib [TEXT WORD] or pazopanib [TEXT WORD] or dovitinib [TEXT WORD] or afatinib [TEXT WORD] or BIBF1120 [TEXT WORD] or motesanib [TEXT WORD]). The PubMed search strategy was adapted in other databases. All searches were up to date to June 2015, without any language restrictions. In addition, related keywords and their synonyms were included in our search strategy and reference lists were scanned for additional publications. Only randomized controlled trials were included. Letters, conference abstracts, reviews and grey literature to the journal editors were excluded because of the limited data presented.

Study selection

From the studies obtained in the above search, inclusion criteria for primary studies were as follows: (1) prospective, randomized, placebo-controlled clinical trial assessed multitargeted antiangiogenic tyrosine kinase inhibitors in combination with chemotherapy versus chemotherapy alone or with placebo for locally advanced or metastatic breast cancer. (2) The primary outcomes endpoint was to evaluate the PFS or OS. The secondary outcome was ORR and AEs. The exclusion criteria were: (1) non-randomized control study, or lack of the control group; (2) studies not reporting any efficacy measures; (3) studies with many cases lost during the follow-up period; (4) reviews, letters, or conference papers; (5) data cannot be extracted; (6) duplicate articles; (7) studies were not conducted in humans.

Data extraction

Data extraction was performed independently by two authors (Tan and Zeng) according to the inclusion criteria listed above. The two authors were blinded to publication details, and all extracted data had to be agreed upon by them. The information retrieved from the reports including study design, the first author, year of publication, methodological quality, number of patients, patients characteristics, hazard ratios (HR) and their 95% confidence intervals (CI) for PFS and OS, number of patients acquired overall response assessed with Response Evaluation Criteria In Solid Tumors (RECIST), data on adverse effects, and details of subgroup analysis were extracted. When multiple publications of the same trial were identified,
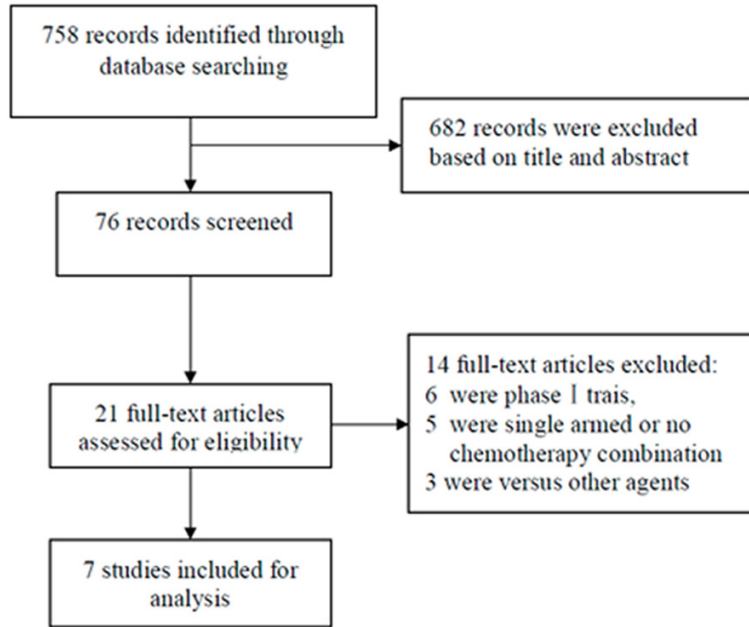
Figure 1. Flow chart for identification and inclusion of trials for this meta-analysis.

ing the methods reported by Parmar et al. [15]. A statistical test with a *P* value of <0.05 was considered to be significant. HR of >1 indicates more progression or deaths in the multi-kinase inhibitor group, and OR of >1 reflects more overall response or more toxicities in the multikinase inhibitor group. Statistical heterogeneity among studies was evaluated using the chi-square test and Q test statistic. When no heterogeneity between studies ($P>0.1$, or $I^2<50\%$), The pooled HR and proportion were estimated using fixed-effects model or, random effects model were used in case of significant heterogeneity between estimates ($P<0.1$, or $I^2>50\%$).

data were extracted and reported as a single trial.

Qualitative assessment

The quality of each retrieved study was independently assessed by two of the authors (Zeng and Qin), in accordance with the Quality of Reporting of Meta-analyses (QUOROM) statement [14]. Details include sequence generation of randomization, allocation concealment, blinding of outcome assessors and reporting of an intention-to-treat analysis. Trials were considered to be of low quality if they met none of the items, of mode rate quality if they reported on less than three items, and if they reported on three or four items, indicated good quality. Any disagreement was resolved by discussion among reviewers.

Statistical analysis

All statistical analyses were performed using Stata 12.0 (StataCorp, College Station, USA). Survival outcome data were polled using the time to-event HR and their 95% CI as the operational measure, while OR for objective response to treatment and different types of toxicity was calculated. When these statistical variables were not given explicitly in an article, they were calculated from available numerical data us-

Results

Identification and characteristics of studies

From 758 citations identified by database searches, seven eligible RCTs [16-22] involving a total of 1694 patients were included in this meta-analysis (**Figure 1**). A definite diagnosis of ABC was made based on histological evidence or a combination of several imaging modalities. All the RCTs were placebo-controlled, among them, sorafenib was used in three studies [20-22], and the other four trails were treated with motesanib [16], axitinib [17], sunitinib [18] and vandetanib [19], respectively. Six trails [16, 18-22] evaluated PFS, and four trails [18, 20-22] assessed OS, all of the seven trails reported ORR and AEs. Chemotherapy plus other multikinase inhibitors, e.g., cediranib, pazopanib, dovitinib, afatinib and BIBF1120, have not been performed in RCTs yet. Among the included patients, 879 patients received multikinase inhibitor plus chemotherapy, and 815 patients received chemotherapy plus placebo. The characteristics of the seven included studies are shown in **Table 1**.

Methodological quality of studies

According to the QUOROM statement [14], The methodological qualities were good in six stud-

Table 1. Baseline characteristics of the seven eligible randomized trials in this meta-analysis

First author	Martin M [16]	Rugo HS [17]	Bergh J [18]	Boer K [19]	Baselga J [20]	Gradishar WJ [21]	Schwartzberg LS [22]
Year	2011	2011	2012	2012	2012	2013	2013
Population	Asia, Europe, North America, Oceania	North-America, Europe, India	NC	Hungary, South Africa, Spain, Sweden, Taiwan	Spain, France, Brazil	India, the United States, Brazil.	The-United States
Phase	II	II	III	II	IIB	IIB	IIB
Sample size (T/P, n)	185 (91/94)	168 (112/56)	593 (296/297)	64 (35/29)	229 (115/114)	237 (119/118)	160 (81/79)
Therapy line	First	First	First	Second	First/Second	First	First/Second
Treatment	MOT+PAC vs. PLA+PAC	AXI+DOC vs. PLA+DOC	SUN+DOC vs. PLA+DOC	VAN+DOC vs. PLA+DOC	SOR+CAP vs. PLA+CAP	SOR+PAC vs. PLA+PAC	SOR+GEM/CAP vs. PLA+GEM/CAP
Mean age (T/P, years)	55.3/53.0	55/56	54/56	54/57	55.1/54.4	50.6/53.1	53.5/54.2
Untreated antiangiogec inhibitors before	Yes	Yes	Yes	Yes	Yes	Yes	NO
Blinding	Double-blind	Double-blind	Open-label	Double-blind	Double-blind	Double-blind	Double-blind
Multicenter	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Survival analysis	PFS	PFS	PFS/OS	PFS	PFS/TTP/OS	PFS/TTP/OS	PFS/TTP/OS
Hazard	Reported	Reported	Reported	Reported	Reported	Reported	Reported
Ratios	in text	in text	in text	in text	in text	in text	in text

T, multikinase inhibitor group; P, Placebo group; NC, No Clear; MOT: Motesanib; AXI: Axitinib; SUN: Sunitinib; VAN: Vandetanib; SOR: Sorafenib; PLA: Placebo; DOC: Docetaxel; PAC: Paclitaxel; GEM: Gemcitabine; CAP: Capecitabine.

Table 2. Methodological quality assessment: internal validity of included studies

Study	Description of random allocation	Concealment of random allocation	Blinding of those assessing treatment effects	Intention-to-treat analysis
Martin M [16]	+	+	+	+
Rugo HS [17]	+	+	+	+
Bergh J [18]	-	+	-	+
Boer K [19]	+	+	+	+
Baselga J [20]	+	+	+	-
Gradishar WJ [21]	+	+	+	+
Schwartzberg LS [22]	+	+	+	+

ies [16, 17, 19-22], moderate in one studies [18] (**Table 2**).

Progression-free survival

Six studies reported the PFS data. There was no significant heterogeneity between the studies (P=0.26; I^2=23.2%) and the pooled HR based on fixed-effect model was 0.74 (95% CI, 0.63-0.84; P<0.001), representing the addition of multikinase inhibitor to chemotherapy resulted in a significant improvement in PFS versus placebo (**Figure 2**).

Overall survival

Four of the 7 trials reported OS data. There was no significant heterogeneity between each study (P=0.53, I^2=0.0%), and a fixed-effects model meta-analysis were used. There was no significant improvement in multikinase inhibitors plus chemotherapy for OS, with a pooled HR of 1.02 (95% CI, 0.84-1.19; P<0.001) (**Figure 3**).
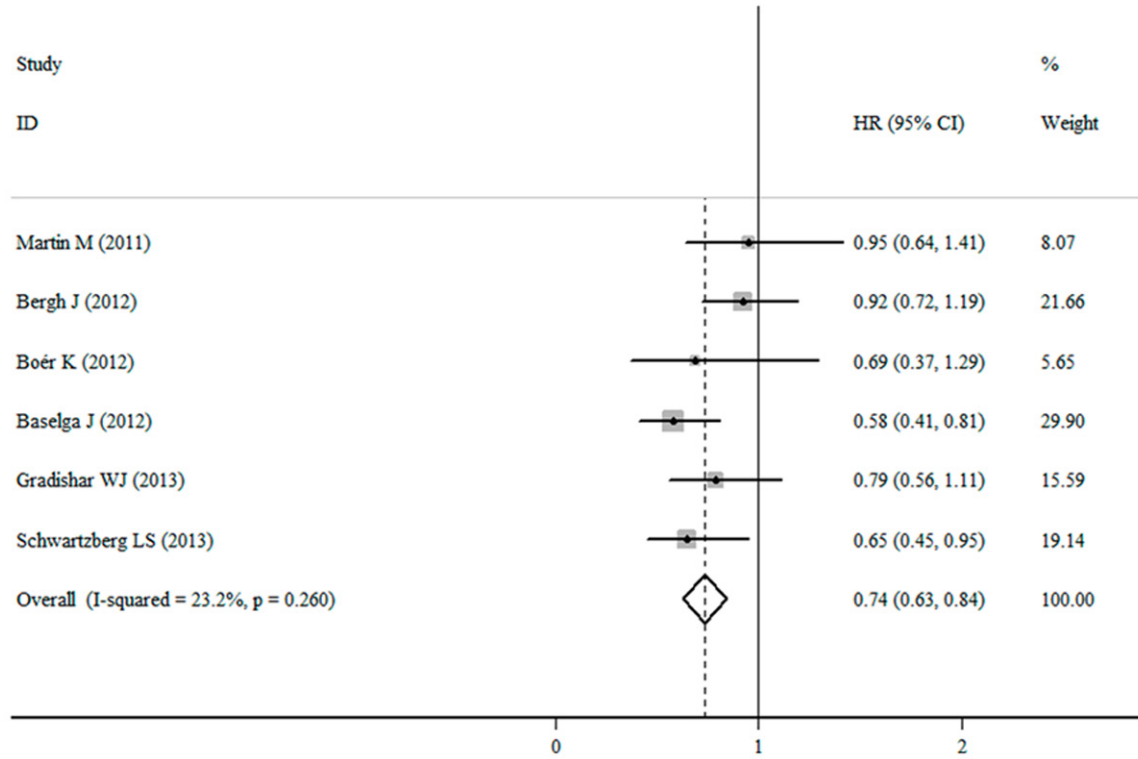
Overall response rate

The ORR was demonstrated in all seven trials. There was no significant heterogeneity between each study (P=0.84, I^2=0.0%), and a fixed-effects model meta-analysis were used. The pooled OR value was 1.66 (95% CI, 1.35-2.05; P<0.001) (**Figure 4**), represented that multikinase inhibitors plus chemotherapy significantly improved the ORR.
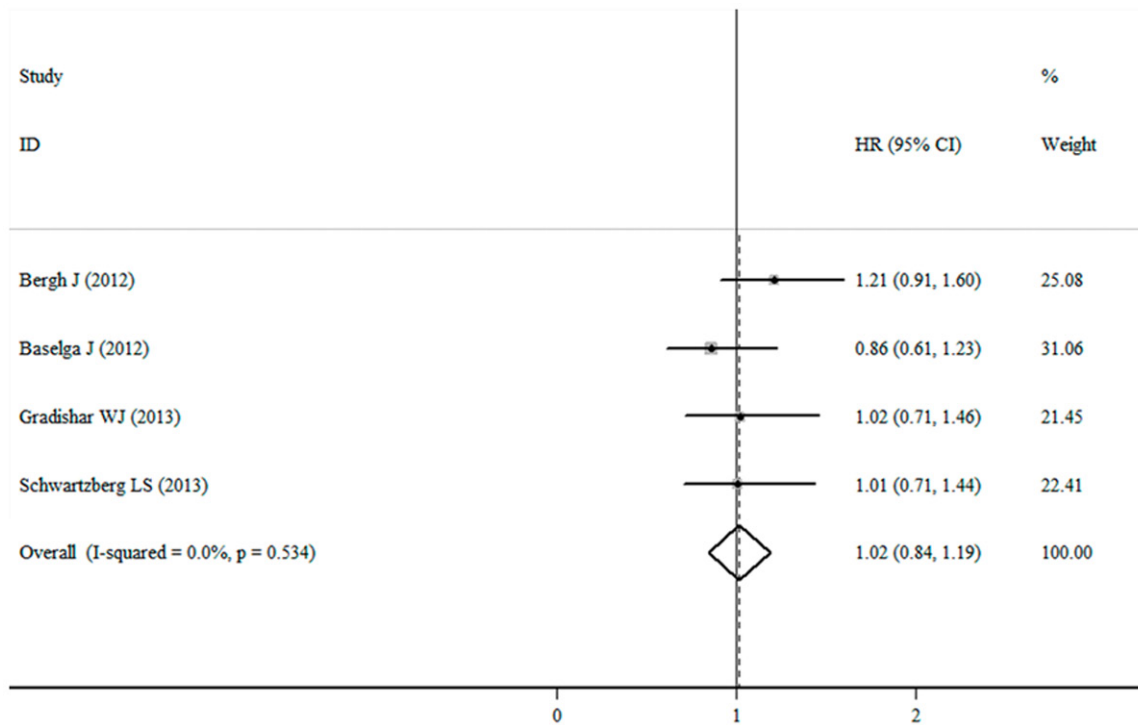
Adverse events

All seven trials included multiple adverse events after treatment. **Table 3** summarizes

Study
ID

HR (95% CI)   %
                    Weight

Martin M (2011)   0.95 (0.64, 1.41)   8.07

Bergh J (2012)   0.92 (0.72, 1.19)   21.66

Boér K (2012)   0.69 (0.37, 1.29)   5.65

Baselga J (2012)   0.58 (0.41, 0.81)   29.90

Gradishar WJ (2013)   0.79 (0.56, 1.11)   15.59

Schwartzberg LS (2013)   0.65 (0.45, 0.95)   19.14

Overall (I-squared = 23.2%, p = 0.260)   0.74 (0.63, 0.84)   100.00

0   1   2

Figure 2. Comparison of PFS between multikinase inhibitors combined with chemotherapy and chemotherapy alone.

Study
ID

HR (95% CI)   %
                    Weight

Bergh J (2012)   1.21 (0.91, 1.60)   25.08

Baselga J (2012)   0.86 (0.61, 1.23)   31.06

Gradishar WJ (2013)   1.02 (0.71, 1.46)   21.45

Schwartzberg LS (2013)   1.01 (0.71, 1.44)   22.41

Overall (I-squared = 0.0%, p = 0.534)   1.02 (0.84, 1.19)   100.00

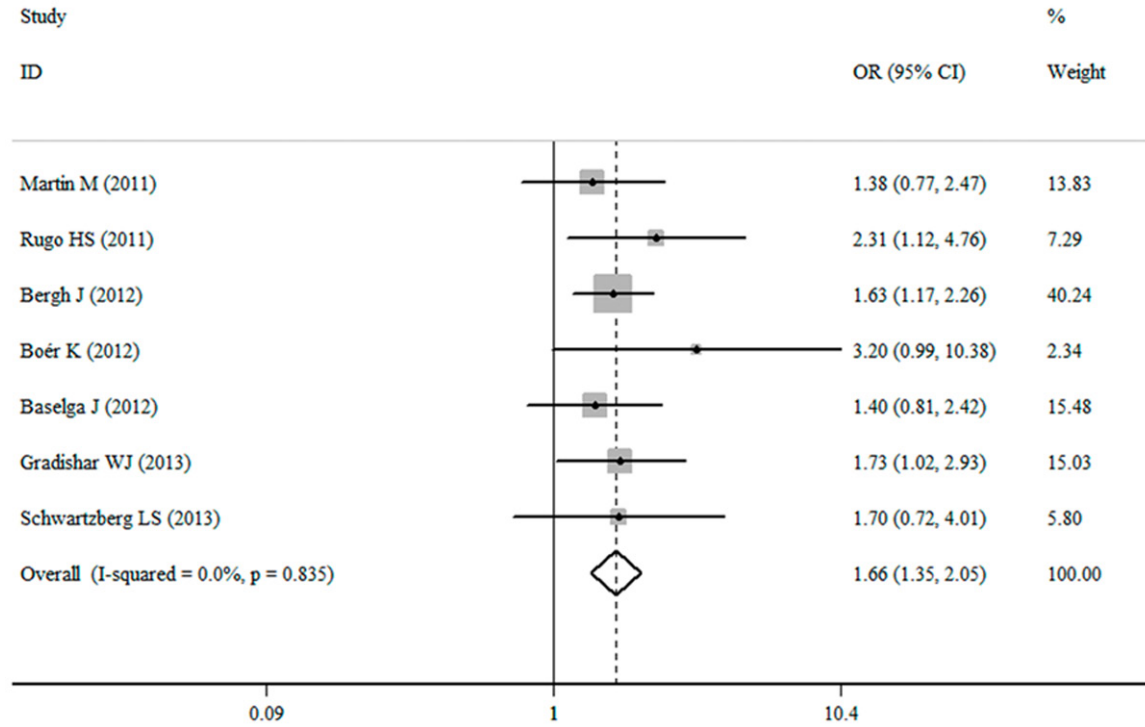0   1   2

Figure 3. Comparison of OS between multikinase inhibitors combined with chemotherapy and chemotherapy alone.

the major AEs occurring in patients of either treatment arm for grade 3/4. The pooled rela-tive risk (RR) of our meta-analyses showed that the risks of hypertension, diarrhea, hand-foot

Figure 4. Comparison of ORR between multikinase inhibitors combined with chemotherapy and chemotherapy alone.

Table 3. Outcome of grade 3/4 toxicity meta-analysis comparing multikinase inhibitors combined with chemotherapy versus chemotherapy alone

| Adverse Event	No. of evaluable trials	Combination group incidence of AEs (No. %)	Monotherapy group incidence of AEs (No. %)	Combination group vs. Monotherapy group	
				RR (95% CI)	p value
Hypertension	6	26/722 (3.6)	4/656 (0.6)	4.81 (1.85-12.51)	0.001
Diarrhea	7	78/837 (9.3)	20/774 (2.6)	3.4 (2.16-5.65)	<0.001
Hand-foot Syndrome	4	165/601 (27.5)	24/600 (4.0)	7.86 (3.10-19.92)	<0.001
Rash	6	26/745 (3.5)	5/685 (0.7)	3.54 (1.59-7.87)	0.002
Stomatitis	6	50/725 (6.9)	5/662 (0.8)	6.34 (2.88-13.98)	<0.001
Alopecia	4	1/531 (0.2)	1/467 (0.2)	0.51 (0.03-7.91)	0.626
Asthenia	4	26/666 (3.9)	28/608 (4.6)	0.96 (0.29-3.16)	0.950
Fatigue	7	83/837 (9.9)	46/774 (5.9)	1.66 (1.18-2.34)	0.004
Mucositis	5	31/712 (4.4)	11/596 (1.8)	2.35 (1.19-4.63)	0.014
Nausea	6	8/725 (1.1)	14/662 (2.1)	0.52 (0.22-1.22)	0.135
Vomiting	5	14/692 (2.0)	6/633 (0.9)	1.90 (0.78-4.63)	0.159
Neutrogena	6	252/726 (34.7)	190/718 (26.5)	1.51 (0.90 -2.56)	0.122

AEs, adverse events; RR, relative risk; CI, confidence interval.

syndrome, rash, mucositis and stomatitis were significantly higher in patients receiving multikinase inhibitors in combination with chemotherapy. The risk of alopecia, asthenia, fatigue, nausea and vomiting were comparable between two treatment arms.

Sensitivity analysis

Excluding the open-label study [18] did not alter the results for PFS and OS. Among the remaining trials, the pooled HR for PFS was 0.68 (95% CI, 0.56-0.81; *P*<0.001), and OS was 0.95
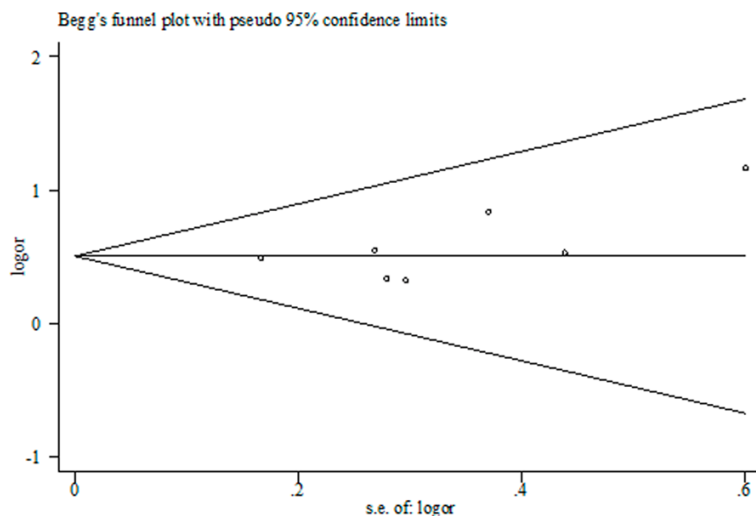
Figure 5. Funnel plot of Begg's among all included studies in this meta-analysis.

(95% CI, 0.75-1.15; *P*<0.01). Similarly, excluding this study did not alter ORR and AEs.

Publication bias

Begg's funnel plot was prepared for the 7 studies to check the publication bias in this meta-analysis. Publication bias was not found in all included studies according to the funnel plot (**Figure 5**).

Discussion

The role of multikinase inhibitors that target angiogenesis is being explored in ABC. Oral multikinase inhibitor monotherapy studies had demonstrated encouraging but limited activity [23], and now were generally developed for use in combination with chemotherapy. Several prospective, randomized, placebo-controlled trials were developed to investigate the efficacy of multikinase inhibitor when added to selected chemotherapies in ABC. But the results were varied. Martin et al. [16] demonstrated PFS and ORR for motesanib plus paclitaxel and placebo plus paclitaxel did not differ significantly. In the SOLTI-0701 study [21], significant PFS and TTP benefit for sorafenib plus capecitabine as first- or second-line treatment were reported. In contrast, sorafenib plus first-line paclitaxel did not significantly improve PFS in the NU07B1 study [20]. In AC01B07 trial [22], sorafenib were added to gemcitabine or capecitabine in patients with HER2-negative ABC whose dis-

ease progressed during or after bevacizumab, both PFS and time to progression (TTP) were prolonged in the sorafenib arm. Bergh et al. [18] demonstrated the combination of sunitinib and docetaxel improved ORR but did not prolong either PFS or OS when given to an unselected HER2-negative cohort as first-line treatment, and Boer et al. [19] also revealed that efficacy benefit was not different for vandetanib plus docetaxel. In another study, Rugo et al. [17] found that the addition of axitinib to docetaxel did not improve TTP in first-line ABC treatment, but improved ORR. To help resolve the controversy over the benefits of multikinase inhibitors plus chemotherapy, we carried out a meta-analysis of all the RCTs, which allowed us to maximize the sample size. To our best knowledge, it is the first time that a comprehensive and detailed meta-analysis has assessed the efficacy of multikinase inhibitors plus chemotherapy for ABC.

In the present study, the pooled statistical data showed that multikinase inhibitors plus chemotherapy significantly improved the PFS (pooled HR=0.74) and ORR (pooled OR=1.66) among the patients in the studies. Conversely, the combination of multikinase inhibitors and chemotherapy did not result in a significant improvement in OS (pooled HR=1.02). Furthermore, the use of multikinase inhibitors was associated with infrequent but serious adverse events.

Overall, the development program for multikinase inhibitors in ABC has demonstrated encouraging activity when used in combination with select chemotherapies. Nevertheless, we grouped all multikinase inhibitors together, with no distinction as to individual agents. With the exception of differences in PFS among the various multikinase inhibitors, the different spectrums and mechanism of action of multikinase inhibitors, and the unselected patient population, may result in different outcome. In these seven trials, the patients in four trials [16, 20-22] were HER2-negative breast cancer, and

another three did not mention HER2 status, but the efficacy was similar. Subgroup analyses based on stratification factors and other baseline characteristics, such as age, hormone receptor status, did not identify any patient subpopulations with statistically significant improvements. However, patients who had received prior adjuvant chemotherapy tend to benefit in the multikinase inhibitor arms [17, 18, 20, 21]. Therefore, improving future trials of targeted therapies will involve increased collection of biologic samples to enable study of predictive markers that may allow the targeting of these agents to be optimized. Unfortunately, at present, there are no proven biomarkers for selecting patients with ABC who would benefit from antiangiogenic therapy. Additional research to identify a patient population that might benefit from multikinase inhibitors therapies is required.

OS as an endpoint in advanced breast cancer studies has been a topic of controversy among regulatory authorities and clinicians [24]. In the present study, four studies assessed OS as a secondary end point, but none of these trials demonstrated an improvement in OS with the addition of multikinase inhibitors. The improvements in PFS and ORR with the addition of multikinase inhibitors did not translate into prolonged OS, sunitinib in combination with docetaxel even showing a trend toward shorter survival [16]. This result was similar with the results of previous studies that assessed the multikinase inhibitors-chemotherapy regimen for patients with other solid tumors [24, 25]. One possibility is that the differences of post-progression treatments between groups may confound the OS outcome. Other possible explanations include statistical chance or potential imbalances in baseline prognostic factors, and it is also conceivable that treatment with multikinase inhibitors adversely impacted postprogression survival, either through effects on tumor growth or toxicities, but there was no evidence of post progression deaths related to drug toxicity [26]. Rugo et al. [17] and Bergh et al. [18] considered that one possible explanation for the lower than expected activity of the combination regimen in the present study could be that the agent with demonstrated clinical activity in advanced breast cancer was used at a lower dose than was administered in the monotherapy arm.

Thus, to better define the impact of anti-angiogenics on OS benefit for first- or second-line treatments would probably require a large clinical trial that possibly defines or controls for subsequent treatment regimens. Future studies should also analyze the possible toxicity that may influence the OS after therapies.

Although the addition of multikinase inhibitors to chemotherapy showed some activity in patients with ABC, the safety profile and tolerability of this regimen present substantial challenges to the further development, and the dose of multikinase inhibitors used in these trials resulted in unacceptable toxicity for many patients. Based on the result of this meta-analysis, increased rates of some AEs were observed in the multikinase inhibitor arm, including hypertension, diarrhea, hand-foot syndrome and stomatitis. The incidence of alopecia, asthenia, fatigue, mucositis, nausea and vomiting were comparable between treatment arms. Grade 3/4 AEs that occurred more frequently in the multikinase inhibitors arm than in the placebo arm included diarrhea, hand-foot syndrome, rash and stomatitis. The included trials also showed that dose interruptions and reductions were consistently more common in the multikinase inhibitor arm than in the placebo arm.

There are several limitations in the present study, due primarily to the chemotherapy regimens and multikinase inhibitors varied in the studies. Individual chemotherapy combine with single multikinase inhibitor was not compared with the same chemotherapy alone because of the relatively low number of RCTs and patients, and different multikinase inhibitors may lead to different clinical benefits. Besides, although we included studies without language restrictions, in order to avoid local literature bias, the number of included studies was quite small. We were unable to increase this number even after systematically searching the databases five months after the original searches. Thus selective publication bias may exist.

Implications for future practice and study: this meta-analysis suggests that the addition of multikinase inhibitors to selected first or second-line chemotherapies provide statistically significant improvements in PFS and ORR, lack of an OS benefit. The frequencies of common AEs of grade 3/4 were often higher with the

combination. The multikinase inhibitor-chemotherapy regimen evaluated in this study is therefore not recommended for conventional treatment of patients with ABC, until further investigation and much larger-scale RCTs with long-term follow-up were performed.

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Disclosure of conflict of interest

None.

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