Bevacizumab Addition in Neoadjuvant Treatment Increases the Pathological Complete Response Rates in Patients with HER-2 Negative Breast Cancer Especially Triple Negative Breast Cancer: A Meta-Analysis

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Abstract

Background
Neoadjuvant therapy is administered to breast cancer patients as an induction process before surgery or radiotherapy to reduce tumor size. Human epidermal growth factor receptor-2 (HER-2) negative breast cancer lacks effective standard target therapy. Bevacizumab has a controversial role in the treatment of breast cancer and we conduct a meta-analysis to evaluate the value of adding bevacizumab in neoadjuvant regimen.

Methods
Potentially eligible studies were retrieved using PubMed, EMBASE and Medline. Clinical characteristics of patients and statistical data with pathological complete response (pCR) data were collected. Then a meta-analysis model was established to investigate the correlation between administration of bevacizumab in neoadjuvant therapy and pCR rates in HER-2 negative breast cancer.

Results
Seven eligible studies and 5408 patients were yielded. The pCR rates for “breast” or “breast plus lymph node” were similar. In subgroup analysis, we emphasized on patients with triple-negative breast cancer (TNBC). In the criterion of “lesions in breast” the pooled ORs was 1.55 [1.29, 1.86], P<0.00001 and regarding to the evaluation criterion of “lesions in breast
and lymph nodes”, the pooled ORs was 1.48 [1.23, 1.78], P<0.0001, in favor of bevacizu-
mab administration.

Conclusion
According to our pooled results, we finally find that bevacizumab addition as a neoadjuvant 
chemotherapy component, for induction use with limited cycle to improve the pCR rates and 
patients may avoid long-term adverse event and long-term invalid survival improvement. 
Especially in subgroup analysis, pCR rates could be improved significantly and physicians 
could consider bevacizumab with caution. As patients could avoid the adverse event 
caused by long-term using of bevacizumab, long-term quality of life improvement may be 
achieved, especially in TNBC.

Introduction
Breast cancer can be subdivided into human epidermal growth factor receptor 2 (HER-2) posi-
tive and HER-2 negative breast cancer due to the important molecular marker HER-2, and 
around 10%–17% is defined as triple-negative breast cancer (TNBC) that is also negative for 
estrogen and progesterone receptors It confers a high risk of recurrence and mortality [1]. 
Neoadjuvant treatment (NT), also called primary systemic treatment, is administered to breast 
cancer patients as an induction process before surgery or radical radiotherapy to reduce tumor 
size by allowing for more women to become candidates for breast conserving therapy.

Pathological complete response (pCR) in the breast could be defined as that there is no his-
tologic evidence of invasive tumor foci in the surgical breast specimen (ypT0ypN0/is), while 
pCR in the breast and axillary nodes was defined as the absence of histologic evidence regard-
ing invasive tumor cells in the surgical breast specimen, axillary nodes identified after neoadju-
vant chemotherapy (ypT0ypN0). The pCR rate after NT appears to correlate with improved 
survival outcome including disease-free (DFS) and overall survival (OS) in local advanced 
breast cancer patients, and what is more important is that it could act effectively as an indicator 
for operation [2]. Several recent studies and trials suggested pCR rate used as a surrogate 
marker for trials comparing different schedules of primary systemic therapy.

Nowadays, choice of treatment for cancer is to combine traditional chemo-radiotherapy 
with addition of target therapy. For breast cancer, trastuzumab [3, 4] and everolimus [5]w e r e 
demonstrated to improve the clinical remission rate and survival outcomes in the long-term 
 scale. In a phase III trial, 54.8% HER-2 positive patients receiving trastuzumab plus chemother-
apy achieved pCR, but only 19.3% HER-2 positive patients who received chemotherapy alone 
achieved pCR [6]. The addition of trastuzumab has almost doubled the pCR rates in patients 
with HER-2 positive breast cancer [6–8].

Meanwhile, bevacizumab, a monoclonal antibody aimed to target vascular endothelial 
growth factor receptor (VEGFR), still has a controversial role in the treatment of breast cancer. 
In 2008, Bevacizumab was approved by US Food and Drug Administration (FDA) to treat 
patients with metastatic breast cancer, which at that time was under an accelerated plan that 
allows for approval based on data that are not complete enough for the full approval. Later on, 
the approval of bevacizumab was revoked in 2011 because further studies demonstrated that 
there was no significant difference regarding overall survival or quality-of-life [9, 10]. Some 
recent studies demonstrated increased pathological complete response (pCR) rates when add-
ing bevacizumab to the NT in patients with Her-2 negative expression, especially in triple-
negative breast cancer (TNBC) type. Bevacizumab was chosen as a candidate choice to further increase the rate of pCR rates in patients with the Her2-negative subtypes.

Previous studies demonstrate that pCR rates ranged from 18% to 61% in various chemotherapy regimens or with different ER/PR expression status. Some conflicting reports still remain in these studies, although patients who received both carboplatin and bevacizumab had the highest pCR rates, the combination did not demonstrate any synergy. The objective of this study was to perform a meta-analysis of recent clinical trials to evaluate the potential value of bevacizumab in NT for patients with HER-2 negative status.

Materials and Methods

Search strategy

Pubmed, Medline and EMBASE were searched for the last time on Jun 25, 2016. The search strategy included the following keywords, which are variably combined by “breast cancer”, “neoadjuvant”, “bevacizumab”, and “pathological complete response”.

Selection criteria

Studies were considered eligible if they met all of the following inclusion criteria, (i) all the patients were local advanced breast cancer patients receiving NT, (ii) receptor expression pattern included were HER-2 negative, (iii) the research investigated the data regarding pCR rate, which is the measurement of the effect of bevacizumab schedule, and (iv) study designs were prospective randomized controlled trials or case control studies. Studies were excluded based on any of the following criteria, (i) were review articles, case report or letters, (ii) lacked key information for calculation pooled ORs from pCR, (iii) single arm studies without control, and (iv) with duplicated data regarding one population.

Data extraction

All included studies were independently reviewed by two investigators (Huang JW and Ma XL) for data extraction. If there was any discrepancy, we discussed it and further to reach a consensus. The data were independently extracted from eligible studies by two investigators (Huang JW and Ma XL). The primary data were odds ratio (OR) with 95% confidence interval (CI) of pCR after neoadjuvant chemotherapy regimen, with bevacizumab or not.

The additional data obtained from these articles included, first author, publication year, patient source (region), percentage of treatment regimen with bevacizumab, study type, TNM stage, details of neoadjuvant chemotherapy regimens, methods to determine pCR, patients number, who achieved pCR /total patients number in bevacizumab and control group respectively, pCR rates. The statistical data for OR regarding the relationship between bevacizumab administration and pCR rate were also obtained, such as patients number, who achieved pCR /total patients number in bevacizumab and control group respectively.

Statistical Methods. The pCR number/total numbers were required in our analysis. The included studies provided the remission and total number of patients in both bevacizumab and control group, and we utilized these primary data to calculate pooled ORs using methods developed by Williamson et al. (2002) [11], and Tierney et al. (2007) [12].

In analysis of pCR rates in patients, the significant outcome was defined as a P value <0.05. A pooled ORs >1 frequently indicated the administration of bevacizumab was related to a relatively better pCR rates. Therefore, we use the term "positive" to describe that bevacizumab administration in neoadjuvant regimen could predicting a better pathological complete response outcome, and "negative" for no correlation between the two neoadjuvant
chemotherapy regimens. P<0.10 or I^2>50% indicates that heterogeneity existing in pooled ORs result (Higgins et al., 2003) [13]. When homogeneity was fine (p≥0.10, I^2≤50%), a fixed-effects model was applied to secondary analysis; otherwise, a random-effects model was chosen. In terms of publication bias, if the p value greater than 0.10, then the publication bias was accepted in the analysis.

All the earlier calculated ORs were used as measure index to describe the correlation between pCR rates with Bevacizumab adding. The calculation process for the current meta-analysis was performed using REVIEW MANAGER (version 5.0 for Windows; the Cochrane collaboration, Oxford, UK). With regard to publication bias, it was measured using the Begg’s funnel plot, which was performed by STATA 11.0 (STATA Corporation, College Station, TX).

Result

Eligible Studies

The initial search yielded 176 studies in PubMed, Medline and EMBASE. After a reviewing the abstracts, 27 potentially relevant studies were identified as eligible candidates and underwent a full-text review. Eighteen studies were excluded for the following reasons: three were reviews, eleven were single arm clinical trials without comparison statistics, two were not related to pathologic response rate and three studies were in vitro experiment (Fig 1).

Finally, eight eligible published articles were included [14–20]. In addition, 11 single arm clinical trials containing bevacizumab administration without control has been included as well [16, 21–30]. These eligible control studies were published from 2009 to 2015 and included a total of 5408 patients, ranging from 36 to 1916 per study (median, 703). Five included studies involving eight sets of data related to pooled ORs for pCR rates within breast (ypT0ypN0/is) and five studies with six sets of data dealing with OR data related to pCR rates in the breast and axillary lymph node (ypT0ypN0). The basic clinical characteristics of patients and other useful information were shown in Table 1.

Correlation between Bevacizumab administration status and pathological complete response

Seven sets of accommodated data showed pathological complete response in patients who were scheduled to receive neoadjuvant chemotherapy plus bevacizumab or neoadjuvant chemotherapy alone. As two different definitions of pCR rates are common: one assessment rule is that no noninvasive residuals could be found in breast (ypT0ypN0/is) and another suggests that no residuals in breast and axillary lymph nodes (ypT0ypN0), we assessed both conditions respectively.

After integrating data, we found that pooled ORs to predict the pCR rates for both “breast” and “breast plus lymph node” were similar and the mathematic value for two settings were 1.51 [1.29, 1.77], (I^2 = 40%, P<0.00001) and 1.44 [1.28, 1.62], (I^2 = 0%, P<0.00001), respectively. (Fig 2)

Subgroup analysis

In subgroup analysis, we emphasized the patients with triple-negative breast cancer. In the group of “pCR in the breast (ypT0ypN0/is)”, the pooled ORs is 1.55 [1.29, 1.86], (I^2 = 0%, P<0.00001) and in terms of the evaluation group of “pCR in the breast and axillary nodes (ypT0ypN0/is)”, the pooled ORs was 1.48 [1.23, 1.78], (I^2 = 0%, P<0.00001). Both standards were effective for prediction patient pCR rates after administration of bevacizumab as a component for neoadjuvant chemotherapy (p<0.05). (Fig 3, Table 2)
Results of single arm studies

Eleven studies aimed to evaluate the remission rate of one group of people with HER-2 negative breast cancers and/or triple-negative subgroup [19, 21–28]. The basic characteristics, including first author, publication year, patient source (region), percentage of treatment regimen with bevacizumab, study type, TNM stage, details of neoadjuvant chemotherapy regimens, methods to determine pCR, patients number who achieved pCR and pCR rate were shown in Table 3.
Table 1. Basic clinical characteristics of patients.

| Author          | Diagnostic method | Date  | Attitude | Study design | +/- Beva | Age | Type of breast cancer | Receptor status | Treatment regimen | Stage | pCR define criteria | Beva group | Without beva group | pCR rate |
|-----------------|-------------------|-------|----------|--------------|----------|-----|-----------------------|----------------|-------------------|-------|--------------------|------------|-------------------|----------|
| Bahri S         | MRI               | 2009  | Negative | Non-RCT      | 16/20    | 48  | IDC and ILC           | HER-2 negative | +/- Beva          | Stage II-V     | Breast            | 5          | 17                | 8        |
| Harry D. Bear   | Core biopsy       | 2012  | Positive | RCT          | 60/4/902 |     | HER-2 negative        | all regimens-AC  | +/- Beva          | Breast          | 204               | 591        | 168               | 595      | 34.5               |
| Bahri S         | MRI               | 2009  | Negative | Non-RCT      | 16/20    | 48  | IDC and ILC           | HER-2 negative | +/- Beva          | Stage II-V     | Breast            | 5          | 17                | 8        |
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| Bahri S         | MRI               | 2009  | Negative | Non-RCT      | 16/20    | 48  | IDC and ILC           | HER-2 negative | +/- Beva          | Stage II-V     | Breast            | 5          | 17                | 8        |
| Harry D. Bear   | Core biopsy       | 2012  | Positive | RCT          | 60/4/902 |     | HER-2 negative        | all regimens-AC  | +/- Beva          | Breast          | 204               | 591        | 168               | 595      | 34.5               |

IHC, immunohistochemistry; RCT, randomized controlled clinical trial; IDC, invasive ductal cancer; ILC, infiltrating lobular cancer; IDLC, invasive ductal-lobular cancer; IBC, invasive breast carcinoma; TNBC, triple negative breast cancer; beva, bevacizumab; +/- beva, with or without bevacizumab; pCR, pathologic complete response; Dox, docetaxel; AC, doxorubicin + cyclophosphamide; EC, etoposide + carboplatin; Nab-paclitaxel, Abraxane-Ab + a new formulation of albumin-bound nanoparticle of paclitaxel; Ca, carboplatin; NR, not reference.

doi:10.1371/journal.pone.0160148.t001
The pCR rates ranged from 9%-37% in the breast (ypT0ypN0/is) and 18%-42% for breast and/or axillary lymph nodes, while the rates were 55% for breast and various from 47%-50% in the breast and/or axillary lymph nodes (ypT0ypN0). (Table 4)

Assessment of publication bias. On the basis of Begg’s funnel plot, p value greater than 0.10 indicates that the publication bias was accepted in the analysis. According to the Begg’s funnel plot analysis, publication bias did not emerge in the pCR in the breast of HER-2 negative breast cancer cohort (0.325), pCR in the breast and axillary lymph nodes of HER-2 negative breast cancer cohort (0.805), pCR in the breast of TNBC cohort (0.573) or pCR in the breast and axillary lymph nodes of TNBC cohort (0.573). (Fig 4)

Discussion

Whether adding bevacizumab into standard neoadjuvant chemotherapy regimen could benefit patients with HER-2 negative breast cancer is controversial, discrepant results regarding bevacizumab addition or not was reported previously. Thus, we conducted a meta-analysis to find the out effect of adding this monoclonal antibody as a target component together with basic chemotherapy. According to our study result, we approved the value of adding bevacizumab into neoadjuvant chemotherapy regimen for patients with HER-2 negative breast cancer, especially people with triple-negative breast cancer (TNBC), which is consistent with previous studies [28, 31, 32].

Marker expression could be used to direct drug administration especially for target therapy, and the utility of target therapy could significantly increase the survival outcomes [33–35] with
largely improved quality of life [36, 37]. In breast cancer, HER-2 is a widely used marker for categorizing, as HER-2 positive expression state is in favor of the usage of trastuzumab [38, 39]. Bevacizumab, a monoclonal antibody proposed to target against vascular endothelial growth factor (VEGF) A and could impair the effect of VEGFR and go against the activated genes of angiogenesis [40, 41]. HER-2 negative breast cancer, especially TNBC are highly invasive type for their high ability of proliferation and enhanced level of VEGFR to prompt angiogenesis [42, 43]. However, as bevacizumab has poor selective characteristics, the toxicity and adverse event are long been discussed. The long-time administration of bevacizumab is difficult for patients to continue, because of the common, high-grade (grade 3 or higher) toxicity and adverse events such as diarrhea, hypertension, and peripheral sensory neuropathy [44].

The dose, time and duration for bevacizumab delivery are three quite important factors influencing the treatment regimen decision. In details, the number of cycle patients received, the utility of bevacizumab in neoadjuvant or adjuvant chemotherapy, and the finish time of it would have considerable effect on the combination with basic chemotherapy and patient remission, survival outcomes. As what was shown from the pooled results, the addition of bevacizumab would improve the pCR rates. Though the CT-NeoBC pooled analysis demonstrated that patients, whoever achieved pathological complete response either in the breast (ypT0ypN0/is) or in the breast and axillary lymph nodes (ypT0ypN0) group had improved survival [45]. It has been demonstrated before that patients, regardless of benefitting from short-term pCR or not, seem to fail to show an inspiring outcomes as no significance has been found regarding the invasive disease-free survival and overall survival [46]. In one recent meta-analysis, the neoadjuvant bevacizumab delivery could improve PFS but not OS regarding to years of survival [47]. However, one previous study reported an opposite result that whether patients achieve pCR after neoadjuvant chemotherapy had a strong positive correlation with surgical rates and survival outcomes (p < 0.05) [48], which give us further clue that patients with pCR after neoadjuvant chemotherapy could increase surgical rate and may further improve the survival outcomes.

While the role of pCR rates to become an independent surrogate marker for predicting survival outcomes is controversial, previous evidence showed established advantage of neoadjuvant chemotherapy (only chemotherapy was administrated) of converting patients who were initially ineligible for breast conserving operations into candidate of this operation on both sides of shrinkage of solid tumor and decrease the incidence of positive nodes [49–51], which is thought to be the first treatment for cancer patients without distant metastasis. Thus, pCR rates after effective neoadjuvant chemotherapy, as in our analysis, the combination of chemotherapy plus bevacizumab, could provide an indication for breast-conserving surgery. In a recent report from National Cancer Database showed that patients who reached pCR, the lumpectomy rate was higher compared to patients who did not achieve pCR (41.0% vs. 26.8%, p < 0.001). In addition, Rouzier et al reported that whether patients had complete pCR after neoadjuvant chemotherapy could be an independent predict factor of loco-regional recurrence in patients who underwent breast conserving surgery or mastectomy [52].

Table 2. pCR (95% CI) for evaluation the use of bevacizumab in neoadjuvant treatment.

| Receptor status          | pCR definition                        | Study N. | Model | HR (95% CI)     | P value | Heterogeneity (I², p) | Conclusion |
|-------------------------|---------------------------------------|----------|-------|-----------------|---------|------------------------|------------|
| HER-2 negative          | pCR in the breast                     | 9        | Fixed | 1.51 [1.29, 1.77]| <0.00001| 40%, 0.10              | Positive   |
| HER-2 negative          | pCR in the breast and axillary nodes  | 7        | Fixed | 1.44 [1.28, 1.62]| <0.00001| 0%, 0.82               | Positive   |
| Triple-negative         | pCR in the breast                     | 5        | Fixed | 1.55 [1.29, 1.86]| <0.00001| 0%, 0.46               | Positive   |
| Triple-negative         | pCR in the breast and axillary nodes  | 5        | Fixed | 1.48 [1.23, 1.78]| <0.0001 | 0%, 0.55               | Positive   |

N, number; HER-2, human epidermal growth factor receptor-2; pCR, pathological complete response; CI, confidence interval.

doi:10.1371/journal.pone.0160148.t002
### Table 3. Basic patients’ characteristics regarding clinical data.

| Author                  | Diagnostic method     | Receptor status  | Date   | Study design     | Stage            | Treatment                      | pCR definition criteria       | Bevacizumab group | pCR rate (%) |
|-------------------------|-----------------------|------------------|--------|------------------|------------------|------------------------------|-------------------------------|------------------|--------------|
| Mrozek E. bu (28)       | Core biopsy           | HER-2 negative   | 2014   | Single-arm phase II trial | Stage II-III     | Nab-P + Ca + beva            | Breast and/or axillary lymph nodes | 6               | 33           |
|                         |                       |                  |        |                  |                  |                              |                               | 6               | 18%          |
| Priya Rastogi (24)      | Core biopsy           | HER-2 negative   | 2011   | Single-arm phase II trial | Stage III A-III C | ATC + Cap — beva             | Breast                        | 4               | 45%          |
|                         |                       |                  |        |                  |                  |                              |                               | 12              | 50%          |
| Sanchez-Rovira (25)     | Core biopsy           | HER-2 negative   | 2013   | Single-arm phase II trial | Stage II A-III C | AC-Dox + beva               | Breast                        | 16              | 66%          |
|                         |                       |                  |        |                  |                  |                              |                               | 66              | 24%          |
| Issam Makhou (31)       | SLNB                  | HER-2 negative   | 2013   | Single-arm phase II trial | Stage II A-III C | ATC + beva               | Breast                        | 13              | 31%          |
|                         |                       |                  |        |                  |                  |                              |                               | 66              | 24%          |
| Clavarezzo M (21)       | Core biopsy           | HER-2 negative   | 2013   | Single-arm phase II trial | Stage III A-III C | FCE + T + beva             | Breast and/or axillary lymph nodes | 10              | 49%          |
|                         |                       |                  |        |                  |                  |                              |                               | 49              | 21%          |
| Jeon Hor Chen (17)      | MRI-guided biopsy     | HER-2 negative   | 2007   | Stage II-IV      |                  | AC + beva                  | Breast                        | 1               | 4%           |
|                         |                       |                  |        |                  |                  |                              |                               | 5               | 25%          |
| Makhou (21)             | Core biopsy           | HER-2 negative   | 2014   | Single-arm phase II trial | Stage II-III     | ATC + beva               | Breast                        | 10              | 37%          |
|                         |                       |                  |        |                  |                  |                              |                               | 10              | 37%          |
| Kim HN (28)             | SLNB                  | HER-2 negative   | 2013   | Single-arm phase II trial | Stage II-III     | Dox + Ca + beva            | Breast and/or axillary lymph nodes | 8               | 49%          |
|                         |                       |                  |        |                  |                  |                              |                               | 19              | 42%          |
| Greul R (31)            | Sentinel node biopsy  | HER-2 negative   | 2009   | Single-center, phase II | Stage II-III     | Doo + Ca + beva            | Breast                        | 4               | 18%          |
|                         |                       |                  |        |                  |                  |                              |                               | 16              | 22%          |
| Guarneri V (21)         | Core-needle biopsy    | TNBC             | 2015   | Single-arm phase II trial | Stage II-III     | Ca-T + beva               | Breast and/or axillary lymph nodes | 22              | 44%          |
|                         |                       |                  |        |                  |                  |                              |                               | 44              | 50%          |
| Bertucci F (21)         | Core biopsy           | HER-2 negative   | 2016   | Single-arm phase II trial | Stage II-III     | FCE + T + beva             | Breast and/or axillary lymph nodes | 19              | 100%         |
|                         |                       |                  |        |                  |                  |                              |                               | 100             | 100%         |

pCR, pathologic complete response; SLNB, sentinel lymph node biopsy; nab-P, nanoparticle albumin-bound paclitaxel; beva, bevacizumab; Ca, carboplatin; FCE, 5-fluorouracil, epirubicin and cyclophosphamide; AC, doxorubicin + cyclophosphamide; ATC, doxorubicin + docetaxel + cyclophosphamide; ATC+Cap, doxorubicin + docetaxel + cyclophosphamide + capcitabine; FCE+T, 5-fluorouracil, epirubicin + cyclophosphamide + Taxol; Dox, docetaxel; CaT, carboplatin + Paclitaxel.

doi:10.1371/journal.pone.0160148.t003
In concordance with our result, pCR could be improved in neoadjuvant treatment regimen, which contains bevacizumab and integrating studies described above, we think that pCR is a valuable surrogate marker predicting breast conserving surgery and would further increase quality of life. Thus, based on these clinical trials, short-term results support the adjuvant bevacizumab administration while long-term results go against with the benefit for patients. Thus, for bevacizumab delivery sequence: patients could benefit a lot from neoadjuvant chemotherapy, which plays a role in only 1–2 cycles induction, and after this induction therapy, patients who had better pCR outcomes. Take sever toxicity and patients tolerance into consideration, this short cycle of induction regimen, compared with relative long cycle adjuvant chemotherapy, would be optimal schedule for patients in case of efficiency and toxicity.

Table 4. pCR (95% CI) for evaluation the response rate of adding bevacizumab in single-arm study.

| Receptor status                      | pCR definition                        | Study N. | Response rate range (%) | Mean±SD response rate (%) |
|--------------------------------------|---------------------------------------|----------|--------------------------|----------------------------|
| HER-2 negative                       | pCR in the breast                     | 5        | 9–37                     | 23.3±11.5                  |
| HER-2 negative                       | pCR in the breast and axillary nodes  | 4        | 18–42                    | 26.3±10.8                  |
| Triple-negative                      | pCR in the breast                     | 1        | 55                       | 55±0                       |
| Triple-negative                      | pCR in the breast and axillary nodes  | 5        | 42–50                    | 46.5±3.3                   |

N, number; HER-2, human epidermal growth factor receptor-2; pCR, pathological complete response; CI, confidence interval; SD, standard deviations.

doi:10.1371/journal.pone.0160148.t004

Fig 4. Estimated Begg’s funnel plots of publication bias regarding pCR in the breast of HER-2 negative breast cancer cohort, breast and axillary lymph nodes of HER-2 negative breast cancer cohort, breast of TNBC cohort, breast and axillary lymph nodes of TNBC cohort respectively.

doi:10.1371/journal.pone.0160148.g004
In subgroup analysis, patients with TNBC showed better pCR outcomes compared with the whole population. In previous studies, in the result of [NSABP] B-40 trial, patients with TNBC receiving standard chemotherapy plus bevacizumab had significant higher pCR rates compared with no bevacizumab group (P = 0.003). Whereas, GBG44, another randomized controlled study showed no significance between patients with or without bevacizumab (P = 0.43). In accordance with previous studies, our pooled result, with a larger population, indicated that adding of bevacizumab as a component in neoadjuvant chemotherapy would benefit patient with pCR and confer them more opportunities for breast surgery. The pCR is even more important in this subgroup, as data from National Cancer Database showed a strong correlation between improved outcomes in patients with aggressive breast cancer subtypes (TNBC and Her-2 positive breast cancer) and the pCR achievement [15]. One recent meta-analysis of randomized trials regarding bevacizumab plus chemotherapy versus chemotherapy alone to treat non-metastatic breast cancer showed similar trends with ours [53].

In spite that those VEGFR blockers may enhance the severe bleeding after surgery, bevacizumab administration as a neoadjuvant component may be a high risk factor, Cortés J et al demonstrated that the surgery could be performed on patients with metastatic breast cancer who underwent bevacizumab therapy before, for the low risk of severe bleeding or wound-healing complications after the surgery [54].

In addition, as this is a meta-analysis, some limitations still exist. Primarily, only published data within those prospective or retrospective studies were included in our meta-analysis, without individual data. In addition, we combined both retrospective and the randomized trials in our meta-analysis and this could also contribute to the bias of this meta-analysis as these two type of studies may not be the same and result in data mixed bias. Also, in pooled data calculation process, we prefer multivariate data if they were available. Otherwise, our calculate data is from the univariate data without adjusting with some other influencing factors, such as age, sex, and Histologic grade. This would bring in a source of bias, for multivariate studies tests the prognostic value independently while univariate studies consider single factor.

Currently, the cost of bevacizumab is a big obstacle preventing its using. Small molecule target therapies designed for breast cancer (including TNBC), such as trastuzumab, are now approved or under clinical trials. Thus, we need further clinical trials to confirm the effectiveness and bright future of bevacizumab. If neoadjuvant regimens contain bevacizumab are really effective and improve pCR or even survival outcomes, the effect outweighs the cost and we could consider bevacizumab.

Conclusion
In spite of all the limitations and biases of our meta-analysis, we finally find that bevacizumab addition as a neoadjuvant chemotherapy component, for induction use with limited cycle to improve the pCR rates and patients may avoid long-term adverse event and long-term invalid survival improvement. Especially in subgroup analysis, pCR rates could be improved significantly and physicians could consider bevacizumab with caution. As patients could avoid the adverse event caused by long-term using of bevacizumab, long-term quality of life improvement may be achieved, especially in TNBC. Combined with current results, more clinical trials could also focus on the choice of chemotherapy, that is, the effect of bevacizumab plus which chemotherapy could improve pCR rates obviously in a relative cost-effective way.

Supporting Information
S1 PRISMA Checklist.
(DOC)
Author Contributions

Conceptualization: LL.
Data curation: LL.
Formal analysis: XW.
Investigation: XW JH.
Methodology: XM.
Resources: YC LL.
Software: XM JH.
Supervision: LL.
Validation: XW.
Visualization: JZ.
Writing – original draft: XM JH.
Writing – review & editing: JZ.

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