Review

Effectiveness of Added Targeted Therapies to Neoadjuvant Chemotherapy for Breast Cancer: A Systematic Review and Meta-analysis

Mona Pathak,[1] Sada Nand Dwivedi,[2] S.V.S. Deo,[3] Bhaskar Thakur,[1] Vishnubhatla Sreenivas,[2] G.K. Rath[4]

Abstract

Over the past several years, targeted therapy has been increasingly used in the management of breast cancer. Reported results for targeted therapies are variable, as some randomized controlled trials (RCTs) reported a strong effect, whereas others reported no or minimal effect on the outcomes. Accordingly, the present study aimed to assess the effect of the addition of targeted therapies to neoadjuvant chemotherapy on tumor response rates, breast conserving surgeries, and survival outcomes. PubMed and the Cochrane register of clinical trials were searched on April 28, 2017 for RCTs comparing addition of targeted therapies to neoadjuvant chemotherapy. Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the screening of records and data extraction were performed by 2 independent reviewers. Publication bias and risk of bias were assessed by the Egger test and the Cochrane tool for risk of bias assessment, respectively. The fixed effect method or random effect method were used to synthesize the results depending on the heterogeneity assessed by the I2 statistic. A total of 17 RCTs including trastuzumab (n = 5), bevacizumab (n = 7), and other targeted therapies (n = 5) were found eligible. Pathologic complete response was significantly higher with trastuzumab (relative risk [RR], 2.20; 95% confidence interval [CI], 1.62-2.99) and bevacizumab (RR, 1.23; 95% CI, 1.11-1.37), but not with other targeted therapies. Bevacizumab for human epidermal growth factor receptor 2 (HER2)-negative breast cancer was found to be associated with improved overall (hazard ratio, 0.69; 95% CI, 0.53-0.90) and disease-free survival (hazard ratio, 0.83; 95% CI, 0.67-1.03). The addition of targeted therapies may not significantly increase breast conserving surgery rates (RR, 1.04; 95% CI, 0.97-1.12). The addition of targeted therapies, especially trastuzumab for patients with HER2-positive breast cancer and bevacizumab for patients with HER2-negative breast cancer significantly increased pathologic complete response, overall response, and clinical complete response but not breast conserving surgery rates.

Clinical Breast Cancer, Vol. 19, No. 6, e690-700
Keywords: Bevacizumab, Breast conserving surgery, Pathologic complete response, Survival, Trastuzumab

Introduction

Neoadjuvant therapy is the standard of care for locally advanced breast cancer, but recently it has also been used for early breast cancer.[1] Neoadjuvant chemotherapy (NACT) has been found as effective as adjuvant chemotherapy regarding long-term survival and recurrence-free survival, with increased breast conserving surgery rates.[2,3] It also allows in-vivo testing for safety and efficacy of various regimens used under neoadjuvant therapy in terms of tumor response and toxicity. Effectiveness of neoadjuvant therapy also depends on the drug used. In addition, molecular subtypes also play a major role in the choice of the appropriate regimen under the neoadjuvant setting. It was found that patients achieving pathologic complete response (pCR) had significantly better overall (OS) and disease-free survival (DFS) with lower recurrence rates.[4] Thus, pCR can be considered as a surrogate end point for long-term survival outcomes.

Over the past several years, a new generation of cancer treatment (ie, targeted therapy) has been increasingly used in the management of breast cancer.[5] Unlike the traditional anthracycline- and taxane-based regimens of chemotherapy, targeted therapy targets cancer cells and is less likely to harm normal cells. Majorly used targeted

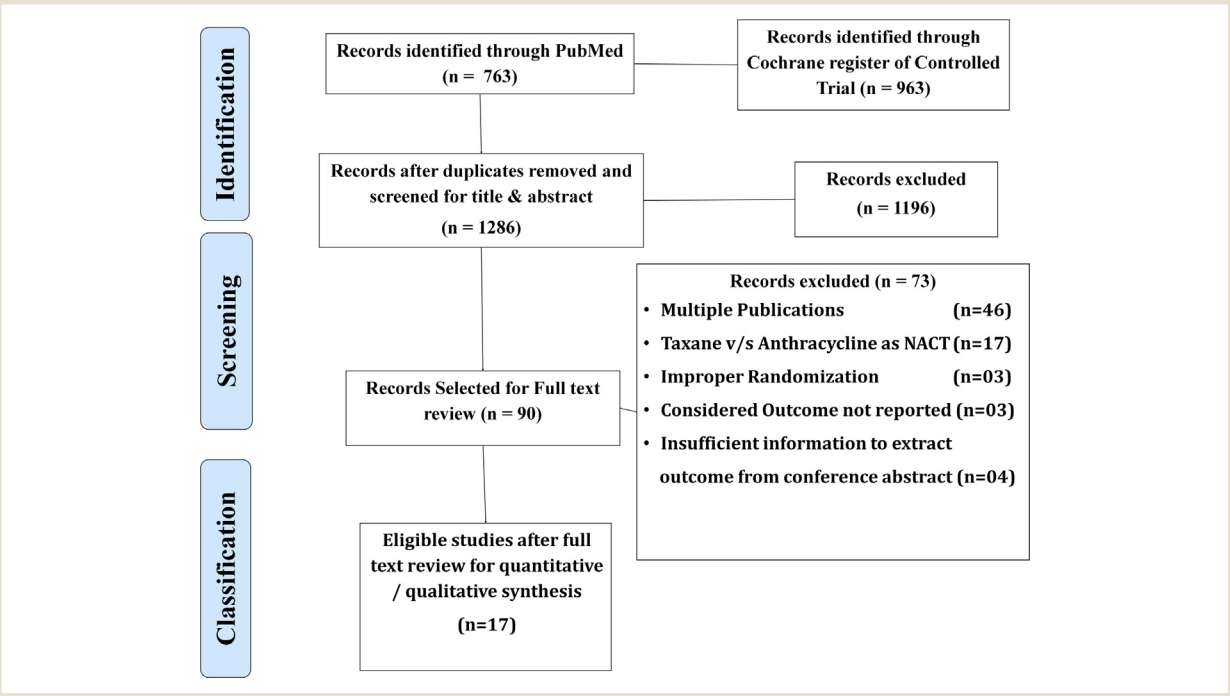
[1]Division of Biostatistics, Kalinga Institute of Medical Sciences, Bhubaneswar, India
[2]Department of Biostatistics
[3]Department of Surgical Oncology, BRAIRCH
[4]BRAIRCH, All India Institute of Medical Sciences, New Delhi, India

Submitted: Apr 15, 2019; Accepted: Jun 5, 2019; Epub: Jun 20, 2019

Address for correspondence: Sada Nand Dwivedi, PhD, Department of Biostatistics, All India Institute of Medical Sciences, Room No. 5, New Delhi, India 110029
E-mail contact: dwivedi7@hotmail.com; dwivedi@aiims.ac.in

1526-8209/$ - see frontmatter
https://doi.org/10.1016/j.clbc.2019.06.001

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Flow Chart for Inclusion of Studies



Abbreviation: NACT = neoadjuvant chemotherapy.

therapies include various drugs like trastuzumab, lapitinib, gefitinib, iniparib, evirolimus, and bevacizumab. Among these, trastuzumab and lapitinib are monoclonal antibodies that are generally provided to patients with human epidermal growth factor receptor 2 (HER2-neu)-positive ($HER2^{+}$) breast cancer. However, evirolimus is generally provided to patients with hormone receptor (estrogen and/or progesterone receptor)-positive but HER2-neu-negative ($HER2^{-}$) breast cancer. Iniparib is prescribed for patients with triple negative breast cancer.[6] Bevacizumab, initially approved for $HER2^{-}$ metastatic breast cancer in 2008 by the United States Food and Drug Administration, is also used for locally advanced breast cancer.[7] It blocks vascular endothelial growth factor and hence interferes with the growth of blood vessels in tumor into breast cancer tissue, starving the cancer.[7]

The effectiveness of the addition of these targeted therapies to NACT has been examined in several randomized controlled trials (RCTs).[8-23] These RCTs have reported contradictory findings regarding the effectiveness of these drugs. Some of the RCTs reported a positive effect of trastuzumab on tumor response and breast conserving surgeries,[24] whereas others reported contradictory findings.[18] Reported results for bevacizumab are also variable, as some RCTs have reported a strong effect, whereas others reported no or minimal effect on the outcomes.[9-12,19,22,23] Likewise, for other targeted therapies, similar results were observed from the available literature.[13,16,17] Accordingly, the present study aimed to assess the effect of these targeted therapies on tumor response rates, breast conserving surgeries, and long-term survival outcomes.

Methodology

The present systematic review was designed as per the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).[25-27] The study protocol was registered with PROSPERO with registration Number: CRD42016027236.

Eligibility Criteria

All RCTs assessing the efficacy of the addition of targeted therapy to neoadjuvant chemotherapy in comparison with neoadjuvant chemotherapy alone in the management of breast cancer were considered if they were published in the English language. The Population, Intervention, Comparator, Outcome, and Time (PICOT) considered in the present systematic review is given below:

- Population: Female patients with non-metastatic breast cancer
- Intervention: The addition of targeted therapy to NACT
- Comparator: NACT
- Outcomes: pCR, overall response, clinical complete response (cCR), breast conserving surgery, OS, DFS, loco-regional recurrence, distant metastasis, and toxicity
- Design: RCTs
- Time: Assessed on and up to April 28, 2017

pCR was reported under 3 definitions as: (1) pCR1, complete response of primary as well as axilla; (2) pCR2, complete response of primary regardless of axilla; and (3) pCR3, complete response of primary allowing for ductal carcinoma in situ (DCIS). The results under these 3 definitions were synthesized separately because of the

Table 1 Population and Intervention, Comparator, and Outcome Characteristics for Eligible Studies

Study	Sample Size	Population	Regimen Comparison	Outcomes Reported
Chen 2015[15]	64	Female patients with breast cancer with $HER2^+$ status	**Taxane arm:** Docetaxel 75 mg/m^2 IV on day 1, epirubicin 80 mg/m^2 IV and cyclophosphamide 500 mg/m^2 on day 2. **Trastuzumab arm:** docetaxel 75 mg/m^2 IV, carboplatin AUC6 on day 1. Trastuzumab IV infused once a week at 4 mg/kg for the first week, 2 mg/kg for the following 16 weeks (17 weeks total) and after surgery for 3 weeks	pCR1, OR, Toxicity
Angulo 2014[16]	50	Confirmed clinical stage IIA-IIIC triple negative breast cancer with adequate organ function	**Taxane arm:** T-FEC (paclitaxel 80 mg/m^2 IV weekly for 12 weeks, followed by 5-fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 every 3 weeks for 4 cycles) **Trastuzumab arm:** TR-FEC (paclitaxel 80 mg/m^2 IV and everolimus 30 mg orally) weekly for 12 weeks, followed by FEC	pCR1, OR, cCR, Toxicity
NICE 2011[17]	181	Patients with unilateral, primary operable, ER-negative invasive breast cancer $<$ 2 cm	**Anthracycline arm**: 4 cycles of EC (epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2) every 3 weeks **Gefitinib arm:** 4 cycles of EC (epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2) plus 12 weeks of daily treatment with gefitinib 250 mg every 3 weeks	pCR2, OR, cCR, Toxicity
NAOH 2010[24]	235	Patients with $HER2^+$ locally advanced breast cancer	**Taxane arm:** 3$\times$ doxorubicin 60 mg/m^2 plus paclitaxel 150 mg/m^2 infused during 3 hours, every 3 weeks, followed by 4 cycles of paclitaxel 175 mg/m^2 administered every 3 weeks. 3 cycles of cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and fluorouracil (600 mg/m^2) on days 1 and 8 every 4 weeks **Trastuzumab arm:** Along with NACT, trastuzumab IV (1 $\times$ 8 mg/kg followed by 10 $\times$ 6 mg/kg) every 3 weeks	pCR1, pCR2, OR, cCR, BCS; OS, DFS, RFS, LRR, DM, Toxicity
ARTemis 2015[9]	800	Women (>18 years) with newly diagnosed invasive breast cancer (tumor size $>$ 20 mm with or without auxiliary involvement)	**Taxane arm:** 3 cycles of docetaxel 100 mg/m^2 every 21 days, followed by 3 $\times$ Flurouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2 once every 21 days **Bevacizumab arm:** bevacizumab 15 mg/kg every 3 weeks with the first 4 cycles of chemotherapy	pCR1, pCR2, pCR3, BCS, Toxicity
Buzdar 2005[18]	42	Invasive, but non-inflammatory, breast cancer with T1-3N0-1M0 disease	**Taxane arm:** Paclitaxel 225 mg/m^2 continuous IV infusion every 3 weeks for 4 cycles followed by Flurouracil 500 mg/m^2, epirubicin 75 mg/m^2, and cyclophosphamide 500 mg/m^2 for 4 cycles **Trastuzumab arm:** Trastuzumab 4 mg/kg IV on day 1 with subsequent weekly dose of 2 mg/kg	pCR1, OR, cCR, BCS, DFS, Toxicity
CALGB 40603 2015[10]	454	Operable, biopsy-confirmed, previously untreated, clinical stage II to III non-inflammatory invasive breast cancer, with ER and PR expression 10% and HER2 negativity	**Arm 1:** weekly paclitaxel 80 mg/m^2 (wP) for 12 weeks followed by doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 once every 2 weeks with (ddAC) for 4 cycles. **Arm 2:** ddAC and bevacizumab 10 mg/kg once every 2 weeks for 9 cycles during administration of wP and the first 3 cycles of ddAC **Arm 3:** ddAC with concurrent carboplatin (AUC6) every 3 weeks for 4 cycles **Arm 4:** ddAC with concurrent carboplatin (AUC6) every 3 weeks for 4 cycles and bevacizumab 10 mg/kg once every 2 weeks for 9 cycles during administration of wP and the first 3 cycles of ddAC	pCR1, pCR2, pCR3, BCS, Toxicity
NSABP B40 2012[23]	1186	Female patients with primary operable $HER2^-$ breast cancer with palpable tumor size $\geq$ 2 cm and stage T1c-3, N0-2aM0	**Arm 1 (T -> AC):** 4 cycles of docetaxel (100 mg/m^2) IV every 3 weeks, followed by 4 cycles of AC (doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2 every 3 weeks). **Arm 2 (TX -> AC):** capecitabine 825 mg/m^2 orally with added to docetaxel (75 mg/m^2), followed by 4 $\times$ AC **Arm 3 (TG -> AC):** gemcitabine 1000 mg/m^2 + docetaxel 75 mg/m^2 followed by 4 $\times$ AC **Arm 4 (T + Bev -> AC + Bev):** bevacizumab (15 mg/kg every 3 weeks) with 6 cycles of Arm 1 + 10 additional doses every 3 weeks **Arm 5 (TX + Bev -> AC + Bev)**: bevacizumab every 3 weeks with first 6 cycles of arm 2 with 10 additional doses every 3 weeks **Arm 6 (TG + Bev -> AC + Bev):** Arm 3 with bevacizumab with first 6 cycles of arm 3 with 10 additional doses every 3 weeks	pCR1, pCR2, OR, cCR, OS, DFS, RFS, LRR, DM, Toxicity
Remagus 02 2017[8]	120	Female patients aged 18-65 years with $HER2^+$ breast cancer of stage II and III with no history of previous malignancy, not amenable to BCS or inflammatory breast cancer and normal cardiac function and good performance status	**Pretreatment:** epirubicin (75) cyclophosphamide (750) IV every 3 weeks **Taxane arm:** docetaxel (100 mg/m^2) every 3 weeks for 4 cycles **Trastuzumab arm:** docetaxel (100 mg/m^2) every 3 weeks for 4 cycles with trastuzumab (8 mg/kg at first infusion then 6 mg/kg) every 3 weeks	pCR1, pCR3, OR, cCR, BCS

Table 1 Continued

Study	Sample Size	Population	Regimen Comparison	Outcomes Reported
Morgan town trial 2009[19]	49	Male and female patients with inoperable adenocarcinoma of breast aged $\geq$ 18 years. Patients with stage 4 concurrent LABC were also eligible	**Taxane Arm:** docetaxel 6 weekly 1-hour IV infusions of 35 mg/m^2 with 2-week break **Bevacizumab arm**: bevacizumab 10 mg/kg IV every other week throughout the 2 cycles of treatment (8 doses) followed by docetaxel 6 weekly 1-hour IV infusions of 35 mg/m^2, followed by a 2-week break	BCS, OS, DFS, Toxicity
Guarneri et al 2008[20]	63	Previously untreated female patients with primary breast cancer aged 18-70 years of stage II-IIIA (tumor size $>$ 2 cm) and with normal cardiac function	**Taxane: Arm C:** epirubicin + paclitaxel IV day 1 + placebo orally (days 1-21) every 3 weeks for 4 cycles **Trastuzumab: Arm B (Continuous)**: epirubicin + paclitaxel IV day 1 + gefitinib 250 mg/day orally (days 1-21) every 3 weeks for 4 cycles **Trastuzumab A (Intermittent):** epirubicin + paclitaxel IV day1 + gefitinib 250 mg/day orally (days 5-16) every 3 weeks for 4 cycles	pCR3, BCS, Toxicity
Chang 2010[21]	30	Patients with HER2$^+$ tumor stage T2-4 and any lymph node status non-metastatic breast cancer	**Taxane arm:** docetaxel (75 mg/m^2) and carboplatin (AUC6) every 3 weeks for 4 cycles both before and after surgery **Trastuzumab arm:** along with chemotherapy, weekly trastuzumab (4 mg/kg followed by 2 mg/kg)	pCR1
NeoAVA 2017[11]	132	Patients with breast cancer with HER2$^-$ primary tumor of $>$ 25 mm	**Taxane arm:** 4 $\times$ FEC100 + 12 weeks of taxane **Bevacizumab arm:** 4 $\times$ FEC100 + 12 weeks of taxane with bevacizumab	pCR1
Sarah Trial 2015[33]	66	Women with HER2$^-$ breast cancer with clinical stage T1-3 N0-2 M0 and normal cardiac function	**Erulibin arm:** 6 $\times$ erulibin 1.4 mg/m^2 IV (days 1 and 8) and C 600 mg/m^2 IV (day 1) **Taxane arm:** 6 $\times$ taxane 75 mg/m^2 IV and C 600 mg/m^2 IV on day 1, repeated over 21 days	pCR2
SOLTI NeoPARP 2015[13]	141	Patients with LABC	**Arm 1:** paclitaxel alone 80 mg/m^2 **Arm 2:** weekly paclitaxel 11.2 mg/kg with iniparib **Arm 3:** twice-weekly 5.6 mg/kg with iniparib	pCR1, pCR2, OR, BCS, Toxicity
SWOG 008 2016[22]	215	Previously untreated, clinical stage IIV to IIIC HER2$^-$ breast carcinoma	**Arm 1:** Nab-paclitaxel 100 mg/m^2 IV weekly for 12 weeks (nP) with IV bevacizumab 10 mg/kg every 2 weeks (6 doses), followed by IV ddAC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2) every 2 weeks for 6 cycles **Arm 2:** 12 $\times$ nP followed by ddAC **Arm 3:** 6 $\times$ ddAC first followed by 12 $\times$ nP	pCR2, BCS, OS, DFS
Gepar Quinto 2012[12,34]	1948	HER2$^-$ women with previously untreated, unilateral or bilateral, primary invasive breast carcinoma	**Taxane arm:** 4 cycles of epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2, both administered every 3 weeks, followed by 4 cycles of docetaxel 100 mg/m^2 every 3 weeks **Bevacizumab arm:** same treatment with additional 8 cycles of bevacizumab 15 mg/kg every 3 weeks along with anthracyclines	pCR1, pCR2, pCR3, OR, cCR, OS, DFS, LRR, DM, Toxicity

Abbreviations: AUC = area under the curve; BCS = breast conserving surgery; cCR = clinical complete response; ddAC = dose-dense doxorubicin and cyclophosphamide; DFS = disease-free survival; DM = distant metastasis; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IV = intravenous; LABC = locally advanced breast cancer; LRR = loco-regional recurrence; NACT = neoadjuvant chemotherapy; OR = overall response; OS = overall survival; pCR1 = pathologic complete response to breast as well as axilla; pCR2 = pathologic complete response to breast regardless of axilla; pCR3 = pathologic complete response to breast allowing for ductal carcinoma in situ; PR = progesterone receptor.

Figure 2 Individual Study Risk of Bias Assessment

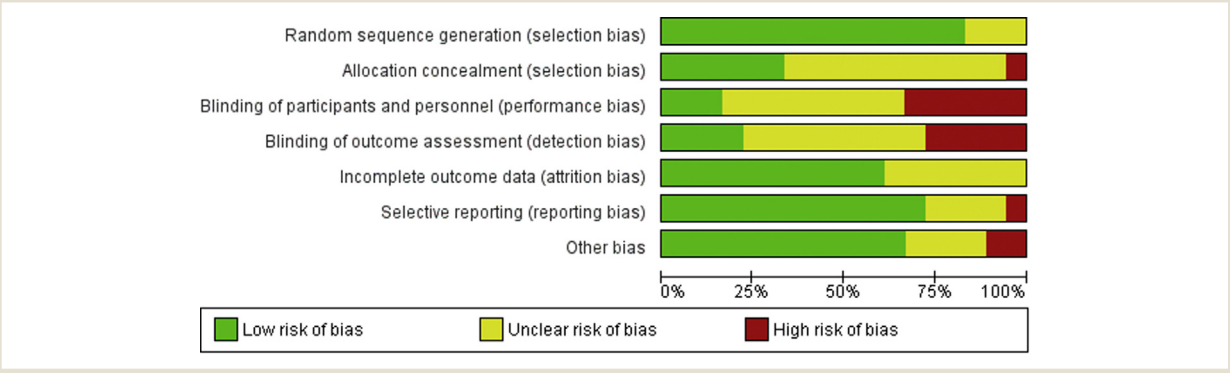
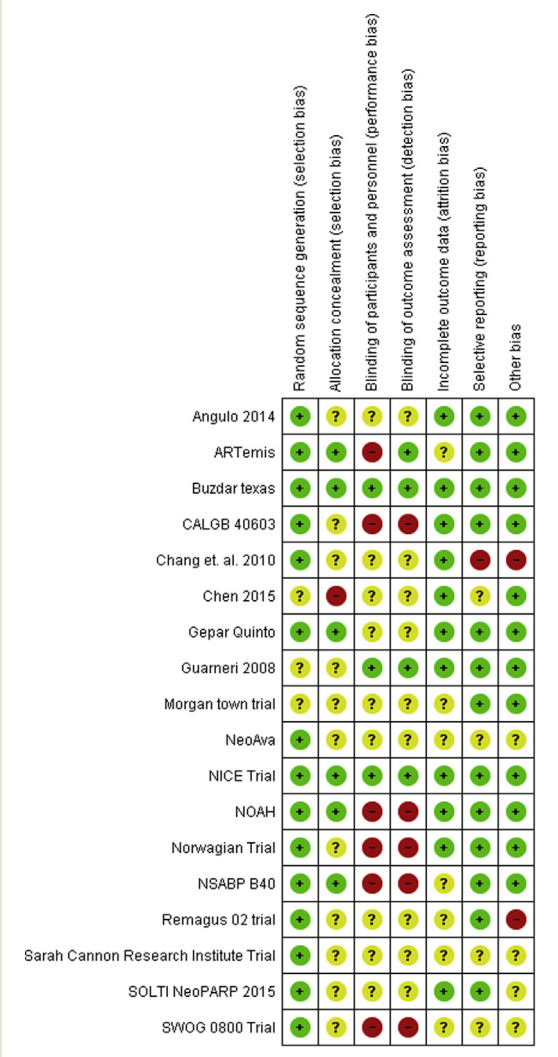


Figure 3 Summary Risk of Bias Using Cochrane Bias Assessment Tool. Green: Low Risk of Bias; Yellow: Unclear Risk of Bias; Red: High Risk of Bias



clinical variability. Detailed definition of all considered outcomes is provided in the published protocol.[28]

Information Sources and Study Selection

Search strategy development, electronic search strategies for PubMed and the Cochrane Central Register of Controlled Trials, methodologies for study, data collection process, data extraction tool, and the method for risk of bias assessment and grading of the evidence[29] are also available in the published protocol.[28]

Summary Measures

The summary measure under consideration was the risk ratio (RR) for pCR, overall response, cCR, and breast-conserving surgery. However, for OS, DFS, locoregional recurrence-free survival, and distant metastasis-free survival, hazard ratio (HR) was the summary measure.

Data Synthesis and Analysis

Statistical heterogeneity was examined by I^2 statistics.[30] Publication bias was visualized using funnel plots, and its significance was assessed using the Eggers test.[31] In case of a very low extent of heterogeneity (ie, $I^2 = 0\%$-25%), the fixed effect method of synthesizing the effect size was used. However, for a moderate to large extent of heterogeneity, the random effect method of meta-analysis was used. All analyses were performed using Stata 15.1 (StataCorp) and RevMan 5.3.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Additional Analysis

To derive additional inferences, as trastuzumab and bevacizumab are provided to different groups of patients depending on HER2 status, subgroup analyses were performed for the RCTs comparing the addition of trastuzumab to NACT, the addition of bevacizumab to NACT, and the addition of other targeted therapies to NACT in comparison with NACT alone.

Results

Study Selection

A total of 1286 unique records were identified through PubMed and the Cochrane Central Register of Controlled Trials. Among

Table 2 Subgroup Meta-analysis for All Considered Outcomes

Outcome	Sub-Group	Number of Studies	Events Targeted	Events NACT	Egger Test *P* Value	I^2 Statistic	Risk Ratio (95% CI)	Grade
Pathologic complete response to breast and axilla	Trastuzumab	5	105/256	41/235	.001	0.0	2.20 (1.62-2.99)	Moderate[a,e]
	Bevacizumab	6	551/2216	450/2241	.190	0.0	1.23 (1.11-1.37)	High[a]
	Other targeted	2	26/116	17/73	—	0.0	1.02 (0.60-1.75)	Moderate[d]
	Overall	13	682/2588	508/2549	.013	30.1	1.35 (1.18-1.54)	Moderate[a,e]
Pathologic complete response to breast	Trastuzumab	1	50/117	26/118	—		1.94 (1.30-2.89)	High[a]
	Bevacizumab	6	661/2259	532/2289	.091	0.0	1.26 (1.15-1.38)	High[a]
	Other targeted	3	36/202	21/138	.754	0.0	1.12 (0.68-1.83)	Moderate[d]
	Overall	10	747/2578	579/2545	.440	0.0	1.28 (1.17-1.40)	High[a]
Pathologic complete response to breast (DCIS)	Trastuzumab	1	16/62	11/58	—		1.36 (0.69-2.68)	Moderate[d]
	Bevacizumab	4	492/1560	411/1581	.801	0.0	1.22 (1.10-1.35)	High[a]
	Other targeted	1	1/32	1/31	—		0.97 (0.06-14.82)	Moderate[d]
	Overall	6	509/1654	432/1670	.934	0.0	1.22 (1.11-1.35)	High[a]
Overall response	Trastuzumab	4	196/220	160/190	.867	59.6	1.05 (0.93-1.19)	Low[b,c,d]
	Bevacizumab	2	1336/1529	1230/1547	—	0.0	1.10 (1.07-1.13)	Moderate[c]
	Other targeted	3	119/188	93/147	.066	7.7	1.01 (0.85-1.21)	Moderate[c]
	Overall	9	1651/1937	1483/1884	.261	30.6	1.08 (1.03-1.13)	Moderate[c]
Complete clinical response	Trastuzumab	3	105/181	69/165	.374	27.1	1.42 (1.08-1.86)	Moderate[c]
	Bevacizumab	2	566/1529	496/1547	—	0.0	1.17 (1.07-1.27)	Moderate[c]
	Other targeted	2	9/94	11/100	—	0.0	0.88 (0.38-2.05)	Moderate[d]
	Overall	7	680/1804	576/1812	.654	2.6	1.19 (1.10-1.29)	Moderate[c]
Breast conserving surgery	Trastuzumab	3	64/181	48/164	.350	26.4	1.16 (0.83-1.61)	Moderate[d]
	Bevacizumab	6	587/1072	541/1039	.230	0.5	1.04 (0.97-1.12)	Moderate[d]
	Other targeted	2	64/126	39/78	—	0.0	1.00 (0.75-1.32)	Moderate[d]
	Overall	11	715/1379	628/1281	.649	0.0	1.04 (0.97-1.12)	Moderate[d]
Overall survival	Trastuzumab	1	36/117	47/118	—		0.70 (0.45-1.11)	Moderate[d]
	Bevacizumab	4	194/1671	251/1701	.510	0.0	0.69 (0.53-0.90)	High[a]
	Overall	5	230/1788	298/1819	.401	0.0	0.70 (0.55-0.87)	High[a]
Disease-free survival	Trastuzumab	1	49/140	65/137	—		0.64 (0.44-0.93)	Moderate[d]
	Bevacizumab	3	347/1646	366/1676	.459	0.0	0.83 (0.67-1.03)	Moderate[d]
	Overall	4	396/1786	431/1813	.717	0.0	0.78 (0.64-0.94)	Moderate[d]

Table 2 Continued

Outcome	Sub-Group	Number of Studies	Events Targeted	Events NACT	Egger Test *P* Value	I^2 Statistic	Risk Ratio (95% CI)	Grade
Loco-regional recurrence	Trastuzumab	1	2/96	4/88	–		0.46 (0.09-2.27)	Moderate[d]
	Bevacizumab	2	98/1547	93/1562	–	0.0	0.97 (0.60-1.57)	Moderate[d]
	Overall	3	100/1643	97/1650		0.0	0.91 (0.57-1.45)	Moderate[d]
Distant Metastasis	Trastuzumab	1	30/117	37/118	–		0.82 (0.51-1.32)	Moderate[d]
	Bevacizumab	2	233/1547	258/1562	–	0.0	0.80 (0.61-1.03)	Moderate[d]
	Overall	3	263/375	1584/1680		0.0	0.80 (0.64-1.01)	Moderate[d]

Abbreviations: CI = confidence interval; DCIS = ductal carcinoma in situ; NACT = neoadjuvant chemotherapy.
[a]Involves non-blinded RCT(s) but objective measurement will not change the drawn evidences.
[b]Inconsistency because of higher heterogeneity (I^2).
[c]Involves non-blinded RCTs that may change the drawn evidence.
[d]Evidence is based on few sample (imprecise).
[e]Publication bias.

these records, independent screening by 2 reviewers (M.P., B.T.) revealed 90 potentially eligible records for full text review. Among these 90 records, 46 were multiple publications of the same study with updated follow-up or different objectives; 17 studies compared taxanes with anthracyclines in the neoadjuvant setting; another 10 studies had problems related to the study design or did not report the considered outcome. Thus, a total of 17 RCTs measuring at least 1 of the considered outcomes were found eligible (Figure 1). These 17 RCTs randomized 5776 patients with breast cancer to targeted therapy along with NACT or NACT only.

Study Characteristics

Of the total 17 RCTs, 5 RCTs involving 491 patients with breast cancer compared the effectiveness of the addition of trastuzumab[8,15,18,21,24]; 7 RCTs randomizing 4784 women compared the effectiveness of bevacizumab[9-12,19,22,23]; and 5 RCTs having 501 patients compared the effectiveness of other targeted therapies like gefitinib,[17,20] evirolimus,[16] iniparib,[13] and erubiline.[32] Four RCTs[8,9,18,24] assessed the effectiveness of trastuzumab along with anthracycline- and taxane-based NACT. However, 1 RCT[21] compared trastuzumab along with non-anthracycline (ie, taxane-based) NACT with NACT alone. Further, 1 RCT[15] compared the effectiveness of epirubicine (taxane + epirubicine + cyclophosphamide) with trastuzumab (taxane + cyclophosphamide + trastuzumab), with taxane in both the arms.

Among the trials assessing the effectiveness of bevacizumab, 2 trials[10,23] had multiple arms. CALGB 40603,[10] a 2 × 2 factorial open label, phase II RCT, evaluated the impact of adding carboplatin and/or bevacizumab. Because our study objective was to compare studies with and without targeted therapy, this RCT was considered as 2 studies. In other words, keeping in view the confounding effect of carboplatin, the group of patients randomized to carboplain or not was analyzed separately to assess the effectiveness of bevacizumab. In a similar way, NSABP B40[23] is a randomized multicenter open-label trial that involved 2-stage randomization. At the first stage, women with primary operable $HER2^-$ invasive breast cancer were randomly assigned to 1 of 3 neoadjuvant chemotherapy regimens. At the second stage, the patients of each of these 3 arms were again randomized separately to receive bevacizumab. The results were reported for pooled arms of bevacizumab versus non-bevacizumab. Another 3-arm RCT[20] randomized female patients with breast cancer to receive gefitinib orally once from day 5 to day 16 of 4 3-weekly cycles of chemotherapy with NACT (intermittent gefitinib), gefitinib orally once daily from day 1 to 21 for 5 cycles of chemotherapy with NACT (continuous gefitinib), and placebo (ie, NACT alone). Because 2 arms received gefitinib, at the time of data extraction, these 2 arms were clubbed together. Study-wise population, intervention, comparator, and outcomes characteristics of eligible studies are presented in Table 1.

The average age of the patients involved in the trials was around 50 years, except for one trial[15] in which it was 38 years. All the RCTs assessing the effectiveness of trastuzumab included only patients with $HER2^+$ breast cancer. On the other hand, 6 of 7 trials assessing the effectiveness of bevacizumab enrolled only patients with $HER2^-$ breast cancer. Of these 6 RCTs, 1 RCT enrolled only patients with triple negative breast cancer. However, a

Table 3 Individual Study Outcomes for the Targeted Therapy Drugs Other Than Trastuzumab and Bevacizumab

Outcome	Drug	Trial	Events With Targeted Therapy	Events With NACT	RR (95% CI)
pCR (breast and axilla)	Evirolimus	Angulo[16]	7/23	7/27	1.17 (0.48-2.85)
	Iniparib	SOLTI 2015[13]	19/93	10/46	0.94 (0.48-1.85)
pCR (breast)	Erubilin	Sarah[33]	5/37	2/18	1.22 (0.26-5.67)
	Gefitinib	NICE[17]	12/71	9/73	1.37 (0.62-3.05)
	Iniparib	SOLTI 2015[13]	19/94	10/47	0.95 (0.48-1.88)
pCR (DCIS)	Gefitinib	Guarneri 2018[20]	1/32	1/31	0.97 (0.06-14.82)
Overall response	Evirolimus	Angulo[16]	13/23	20/27	0.76 (0.50-1.16)
	Gefitinib	NICE[17]	48/71	45/73	1.10 (0.86-1.40)
	Iniparib	SOLTI 2015[13]	58/94	28/47	1.04 (0.78-1.38)
Clinical complete response	Evirolimus	Angulo[16]	2/23	4/27	0.59 (0.12-2.92)
	Gefitinib	NICE[17]	7/71	7/73	1.03 (0.38-2.78)
Breast conserving surgery	Gefitinib	Guarneri 2018[20]	15/32	14/31	1.04 (0.61-1.77)
	Iniparib	SOLTI 2015[13]	49/94	25/47	0.98 (0.70-1.36)

Abbreviations: CI = confidence interval; DCIS = ductal carcinoma in situ; NACT = neoadjuvant chemotherapy; pCR = pathologic complete response; RR = relative risk.

small RCT[19] involved 22% of patients who were HER2$^+$. A RCT[13] assessed the effectiveness of iniparib only in patients with triple negative breast cancer. Further, RCTs assessing other targeted therapies had mixed molecular profiles.

Risk of Bias Within Studies

Risk of bias assessment performed by the Cochrane Risk of bias assessment tool for individual studies is presented in Figure 2. However, the overall risk of bias assessment is presented in Figure 3. In summary, around 30% and 25% of the studies did not blind participants and outcome assessors, respectively. However, non-blinding may not affect objectively measured outcomes like death, recurrence, and pCR, but it may bias the results for subjectively measured outcomes like clinical responses.

Publication Bias

Publication bias was assessed for all outcomes and drug subgroups using the Egger test, which revealed that only pCR to breast as well as axilla (under the trastuzumab subgroup) had significant publication bias (Table 2).

Synthesis of Results

pCr. pCR was reported by a majority of the studies. pCR of breast as well as axilla, only breast regardless of axilla, and allowing for DCIS were reported by 13, 10, and 6 RCTs, respectively. pCR to breast as well as axilla was significantly higher with the addition of trastuzumab (n = 5; RR, 2.20; 95% confidence interval [CI], 1.62-2.99) with 105 (41%) achieving pCR with trastuzumab versus 41 (17%) achieving pCR with NACT only; and with bevacizumab (n = 6; RR, 1.23; 95% CI, 1.11-1.37) with 551 (25%) achieving pCR with bevacizumab in comparison with 450 (20%) achieving pCR with NACT only. But no significant increase in pCR1 was found from 2 RCTs[13,16] involving other targeted therapies such as evirolimus and iniparib. Similar results were found under the other 2 definitions of pCR (Table 2). As the RCTs assessing the effectiveness of bevacizumab were large trials, the evidence for bevacizumab was graded as high, which concludes that further research is unlikely to change our confidence in the estimated effect size for bevacizumab. However, evidence for other targeted therapy under all definitions of pCR and for trastuzumab for pCR3 were downgraded owing to imprecision (lack of power). The effectiveness of evirolimus, gefitinib, erubiline, and iniparib was reported by a single RCT. The individual study results for these drugs are reported in Table 3.

Overall Response. The addition of bevacizumab significantly increased overall response (n = 2; RR, 1.10; 95% CI, 1.07-1.13) to 1336 (87%) in comparison with the overall response to 1230 (79%) patients in the NACT arm. The overall response was also increased with the addition of trastuzumab (89%) in comparison with NACT alone (84%). Because the evidence for trastuzumab was based on 4 small trials, the results may not be statistically significant. The rate of overall response with other targeted therapies was similar that under NACT alone (ie, 63%).

cCR. Similar to pCR, the addition of trastuzumab (n = 3; cCR = 105 of 181 vs. 69 of 165; RR, 1.42; 95% CI, 1.08-1.86) and bevacizumab (n = 2; cCR, 566 of 1529 vs. 496 of 1547; RR, 1.17; 95% CI, 1.07-1.27) to NACT significantly increased cCR. This evidence has adequate power, but it was downgraded to moderate as this evidence include some non-blinded RCTs, which may influence this subjectively measured outcome.

Breast Conserving Surgery. The rate of breast conserving surgery was slightly higher with the addition of trastuzumab (64/181 vs. 48/164) and bevacizumab (587/1072 v/s 541/1039) in comparison with NACT alone. But addition of targeted therapies did not significantly improve breast conserving surgery rates.

Survival Outcomes. Long-term survival outcomes were reported by very few studies. Only one RCT[24] assessing the effectiveness of

Table 4 Toxicities for Addition of Targeted Therapies to Anthracycline- and Taxane-based Neoadjuvant Chemotherapy

Toxicity	Number of Studies	RR (95% CI)
Hematologic Toxicity		
Neutropenia	10	1.07 (1.02-1.12)
Febrile neutropenia	6	1.80 (1.46-2.21)
Leucopenia	6	1.08 (1.02-1.15)
Anemia	6	1.42 (0.82-2.46)
Thrombocytopenia	4	1.24 (0.84-1.83)
Thrombosis	4	1.88 (1.20-2.93)
Bleeding	3	3.02 (0.98-9.35)
Cardiac and Nervous System Toxicity		
Neuropathy	5	1.14 (0.59-2.21)
Sensory neuropathy	2	1.38 (0.93-2.06)
Cardiac left ventricular function	2	3.28 (1.00-10.81)
Cardiovascular toxicity	1	0.29 (0.06-1.39)
Headache	1	8.01 (2.43-26.47)
Syncope	1	0.39 (0.02-9.11)
Dermatological Toxicities		
Hand-foot syndrome	3	1.31 (1.00-1.71)
Rash	3	1.32 (0.66-2.63)
Dermatological toxicity	1	2.91 (0.12-68.81)
Alopecia	1	0.97 (0.21-4.44)
Diarrhea	7	0.96 (0.62-1.49)
Gastro	3	1.40 (0.58-3.36)
Constipation	1	1.02 (0.30-3.49)
Oral Toxicities		
Stomatitis	1	1.22 (0.36-4.19)
Mucosal inflammation	5	1.48 (0.41-5.41)
Dysphasia	1	3.00 (0.82-11.04)
General Toxicities		
Nausea	6	1.12 (0.86-1.45)
Fatigue	7	1.18 (0.98-1.41)
Infection	7	1.82 (1.47-2.24)
Other	5	1.69 (1.34-2.13)
Vomiting	6	1.01 (0.72-1.42)
Allergic reaction	2	2.01 (0.69-5.84)
Hypertension	5	7.50 (4.43-12.71)
Myalgia	2	1.66 (0.22-12.47)
Serious adverse event	2	1.95 (1.24-3.06)
Edema	2	0.81 (0.31-2.11)
Fever	1	1.74 (0.90-3.34)
Hyperglycemia	2	1.07 (0.18-6.28)
Hypokalemia	2	0.33 (0.09-1.21)
Arthralgia	1	32.43 (11.56-90.98)
Bone pain	3	1.70 (0.99-2.92)
Death	2	3.68 (1.16-11.66)

Abbreviations: CI = confidence interval; RR = relative risk.

trastuzumab reported survival and recurrence outcomes. However, 4 RCTs[12,19,22,23] assessing the effectiveness of bevacizumab reported OS, 3 RCTs reported[12,22,23] DFS, and only 2 RCTs[12,23] reported loco-regional recurrence and distant metastasis. Bevacizumab significantly improved OS (n = 4; HR, 0.69; 95% CI, 0.53-0.90). The rate of events such as death, recurrence, and loco-regional recurrence were lower with addition of targeted therapies but may not be significant as evidence, as these outcomes are based on very few RCTs.

Toxicities. Toxicity results were reported for the overall addition of targeted therapies to anthracycline- and taxane-based chemotherapy (Table 4). However, only 1 trial[17] comparing the addition of gefitinib to anthracycline alone reported a similar risk of toxicities. In reference to the anthracycline and taxane combination, additional targeted therapies were found to be associated with a higher risk of hematologic toxicities like neutropenia (n = 10; RR, 1.07; 95% CI, 1.02-1.12), febrile neutropenia (n = 6; RR, 1.80; 95% CI, 1.46-2.21), infection (n = 7; RR, 1.82; 95% CI, 1.47-2.24), leucopenia (n = 6; RR, 1.08; 95% CI, 1.02-1.15), and thrombosis (n = 4; RR, 1.88; 95% CI, 1.20-2.93), as well as for hand-foot syndrome (n = 3; RR, 1.31; 95% CI, 1.00-1.71). However, analytical results regarding hypertension, arthelgia, abrupt cardiac left ventricular function, headache, and death remained imprecise.

Discussion

A total of 17 RCTs reporting at least 1 of the considered outcomes were included under the present systematic review, including 5 RCTs of trastuzumab,[8,15,18,21,24] 7 RCTs of bevacizumab,[9-12,19,22,23] and 5 RCTs of other targeted therapies. The number of RCTs included in the meta-analysis varied from one outcome to another. It was highest for pCR to breast and axilla (n = 13) and lowest for loco-regional recurrence and distant metastasis (n = 3). Breast conserving surgery was reported by 11 RCTs. OS and DFS rates were reported by 5 and 4 RCTs, respectively. Reporting of toxicities also varied from trial to trial in their types and definitions. Among the 17 RCTs, only 1 RCT[15] involving 64 patients assessing trastuzumab did not adopt a proper method for allocation concealment. Further, 6 and 4 RCTs may have performance and detection bias, respectively. However, these RCTs may not affect the objectively measured outcomes. Intention to treat analysis was performed by most of the RCTs. The overall quality of trials can be considered as adequate for objectively measured outcomes. However,v the number of trials can be considered sufficient for pCR, clinical responses, and breast conserving surgeries but not for survival outcomes.

The sample size of individual studies varied from 30[21] to 1948.[34] Three of 5 RCTs assessing the effectiveness of trastuzumab and 3 of 5 RCTs assessing the effectiveness of other targeted therapies than trastuzumab and bevacizumab had sample sizes less than 100. The effectiveness of trastuzumab was reported by 5 small RCTs. Of the 5776 randomized patients with breast cancer in all 17 trials, 4784 (83%) were part of bevacizumab trials. Hence, the results of the meta-analysis for bevacizumab provided a high grade of evidence.

However, the grade of evidence remained moderate for trastuzumab because of imprecision. Imprecision was assessed using power analysis with total sample size (number of patients) under meta-analysis. Evidence for other targeted therapies was also downgraded owing to lack of power and clinical heterogeneity arising from use of different drugs. In other words, the meta-analysis for the bevacizumab subgroup provided reliable and stable evidence because of a sufficient number of good quality, large-scale RCTs. The meta-analysis results for targeted therapies, regardless of the drug used, were similar to the results for bevacizumab because while synthesizing results for overall targeted therapies, higher weights were provided to RCTs comparing bevacizumab.

pCR can be considered as a surrogate endpoint for long-term outcomes, as patients achieving pCR have significantly better long-term outcomes.[14,35] The addition of targeted therapies, especially trastuzumab, for patients with $HER2^+$ breast cancer and bevacizumab for patients with $HER2^-$ breast cancer significantly increased pCR, overall response, and cCR but with increased risk of hematologic toxicities, especially with trastuzumab. However, the addition of other targeted therapies besides trastuzumab and bevacizumab did not increase response rates. Another drug given for patients with triple negative breast cancer (ie, iniparib) did not even improve response rates. In addition, the addition of any targeted therapy did not improve breast conserving surgery. Bevacizumab significantly improved OS. The addition of trastuzumab and bevacizumab also helped in reducing recurrence rates, but pooled results were not significant owing to the availability of very few trials.

In summary, to achieve pathologic response and better survival, based on results under the present systematic review, it may be recommended that the addition of trastuzumab for patients with $HER2^+$ breast cancer and of bevacizumab for patients with $HER2^-$ breast cancer, with a planned management of hematologic toxicities, may be a better choice.

Acknowledgments

The authors thank All India Institute of Medical sciences (AIIMS), New Delhi, for making the computer laboratory facility, library, online accessibility of articles, and other resources available.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Bonadonna G, Valagussa P, Brambilla C, et al. Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. *J Clin Oncol* 1998; 16:93-100.
2. Pathak M, Deo SS, Dwivedi SN, et al. Role of neoadjuvant chemotherapy in breast cancer patients: systematic review and meta-analysis. *Indian J Med Pediatr Oncol* 2019; 40:48-62.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol* 2018; 19:27-39.
4. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. *J Clin Oncol* 2008; 26:778-85.
5. Baudino TA. Targeted cancer therapy: the next generation of cancer treatment. *Curr Drug Discov Technol* 2015; 12:3-20.
6. O'Shaughnessy J, Schwartzberg L, Danso MA, et al. Phase III study of iniparib plus gemcitabine and carboplatin versus gemcitabine and carboplatin in patients with metastatic triple-negative breast cancer. *J Clin Oncol* 2014; 32:3840-7.
7. Montero AJ, Escobar M, Lopes G, Glück S, Vogel C. Bevacizumab in the treatment of metastatic breast cancer: friend or foe? *Curr Oncol Rep* 2012; 14:1-11.
8. Valet F, de Cremoux P, Spyratos F, et al. Challenging single- and multi-probesets gene expression signatures of pathological complete response to neoadjuvant chemotherapy in breast cancer: experience of the REMAGUS 02 phase II trial. *Breast* 2013; 22:1052-9.
9. Earl HM, Hiller L, Dunn JA, et al, ARTemis Investigators. Efficacy of neoadjuvant bevacizumab added to docetaxel followed by fluorouracil, epirubicin, and cyclophosphamide, for women with HER2-negative early breast cancer (ARTemis): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2015; 16:656-66.
10. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). *J Clin Oncol* 2015; 33:13-21.
11. Haugen MH, Lingjaerde OC, Krohn M, et al. Proteomic response in breast cancer treated with neoadjuvant chemotherapy with and without bevacizumab: reverse phase protein array (RPPA) results from NeoAva-a randomized phase II study. *Cancer Res* 2016; 76, abstract 3268.
12. Huober J, Fasching PA, Hanusch C, et al. Neoadjuvant chemotherapy with paclitaxel and everolimus in breast cancer patients with non-responsive tumours to epirubicin/cyclophosphamide (EC) ± bevacizumab − results of the randomised GeparQuinto study (GBG 44). *Eur J Cancer* 2013; 49:2284-93.
13. Llombart-Cussac A, Bermejo B, Villanueva C, et al. SOLTI NeoPARP: a phase II randomized study of two schedules of iniparib plus paclitaxel versus paclitaxel alone as neoadjuvant therapy in patients with triple-negative breast cancer. *Breast Cancer Res Treat* 2015; 154:351-7.
14. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant and adjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer (NOAH): follow-up of a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet Oncol* 2014; 15:640-7.
15. Chen W, He J, Wu H, et al. Efficacy observation of TCH/TAC neoadjuvant chemotherapy in treatment of HER-2 over-expressing breast cancer [Chinese]. *Chin J Clin Oncol* 2014; 41:373-6.
16. Gonzalez-Angulo AM, Akcakanat A, Liu S, et al. Open-label randomized clinical trial of standard neoadjuvant chemotherapy with paclitaxel followed by FEC versus the combination of paclitaxel and everolimus followed by FEC in women with triple receptor-negative breast cancer†. *Ann Oncol* 2014; 25:1122-7.
17. Bernsdorf M, Ingvar C, Jörgensen L, et al. Effect of adding gefitinib to neoadjuvant chemotherapy in estrogen receptor negative early breast cancer in a randomized phase II trial. *Breast Cancer Res Treat* 2011; 126:463-70.
18. Buzdar AU, Ibrahim NK, Francis D, et al. Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. *J Clin Oncol* 2005; 23:3676-85.
19. Baar J, Silverman P, Lyons J, et al. A vasculature-targeting regimen of preoperative docetaxel with or without bevacizumab for locally advanced breast cancer: impact on angiogenic biomarkers. *Clin Cancer Res* 2009; 15:3583-90.
20. Guarneri V, Frassoldati A, Ficarra G, et al. Phase II, randomized trial of preoperative epirubicin-paclitaxel +/− gefitinib with biomarker evaluation in operable breast cancer. *Breast Cancer Res Treat* 2008; 110:127-34.
21. Chang HR. Trastuzumab-based neoadjuvant therapy in patients with HER2-positive breast cancer. *Cancer* 2010; 116:2856-67.
22. Nahleh ZA, Barlow WE, Hayes DF, et al. S0800: Nab-paclitaxel, doxorubicin, cyclophosphamide, and pegfilgrastim with or without bevacizumab in treating women with inflammatory or locally advanced breast cancer (NCI CDR0000636131). *Cancer Res* 2015; 75, abstract P3-11-16.
23. Bear HD, Tang G, Rastogi P, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. *N Engl J Med* 2012; 366:310-20.
24. Gianni L, Eiermann W, Semiglazov V, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with HER2-positive locally advanced breast cancer (the NOAH trial): a randomised controlled superiority trial with a parallel HER2-negative cohort. *Lancet* 2010; 375:377-84.
25. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med* 2009; 151:264-9.
26. Beller EM, Glasziou PP, Altman DG, et al, PRISMA for Abstracts Group. PRISMA for abstracts: reporting systematic reviews in journal and conference abstracts. *PLoS Med* 2013; 10:e1001419.
27. Liberati A, Glasziou PP, Altman DG, et al, PRISMA for Abstracts Group. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLoS Med* 2009; 6:e1000100.
28. Pathak M, Dwivedi SN, Deo SVS, Thakur B, Sreenivas V, Rath GK. Neoadjuvant chemotherapy regimens in treatment of breast cancer: a systematic review and network meta-analysis protocol. *Syst Rev* 2018; 7:89.
29. Zhang Y, Coello PA, Guyatt GH, et al. GRADE guidelines: 20. Assessing the certainty of evidence in the importance of outcomes or values and preferences—inconsistency, imprecision, and other domains. *J Clin Epidemiol* 2019; 111:83-93.
30. Pathak M, Dwivedi SN, Deo S, Vishnubhatla S, Thakur B. Which is the preferred measure of heterogeneity in meta-analysis and why? A revisit. *Biostat Biom Open Acc J* 2017; 1:55555.

31. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629-34.
32. Abraham J, Robidoux A, Tan AR, et al. Phase II randomized clinical trial evaluating neoadjuvant chemotherapy regimens with weekly paclitaxel or eribulin followed by doxorubicin and cyclophosphamide in women with locally advanced HER2-negative breast cancer: NSABP Foundation Study FB-9. *Breast Cancer Res Treat* 2015; 152:399-405.
33. Eribulin/cyclophosphamide (ErC) versus docetaxel/cyclophosphamide (TC) as neoadjuvant therapy in locally advanced HER2-negative breast cancer: a randomized phase II trial of the Sarah Cannon Research Institute, Available at: http://cochranelibrary-wiley.com/o/cochrane/clcentral/articles/000/CN-01101000/frame.html. Accessed: March 18, 2018.
34. von Minckwitz G, Eidtmann H, Rezai M, et al. German Breast Group; Arbeitsgemeinschaft Gynäkologische Onkologie—Breast Study Groups. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. *N Engl J Med* 2012; 366:299-309.
35. Broglio KR, Quintana M, Foster M, et al. Association of pathologic complete response to neoadjuvant therapy in HER2-positive breast cancer with long-term outcomes: a meta-analysis. *JAMA Oncol* 2016; 2: 751-60.