Supplementary materials

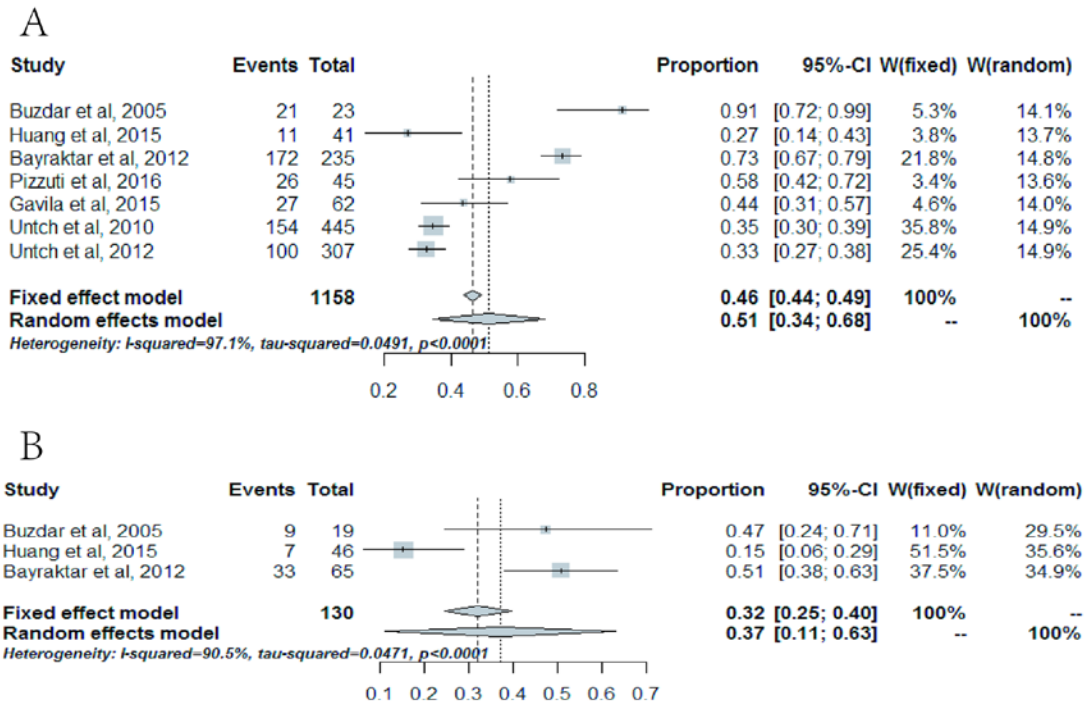

Figure S1 The pooled absolute rate of CR for the concurrent (A) and non-concurrent (B) use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer

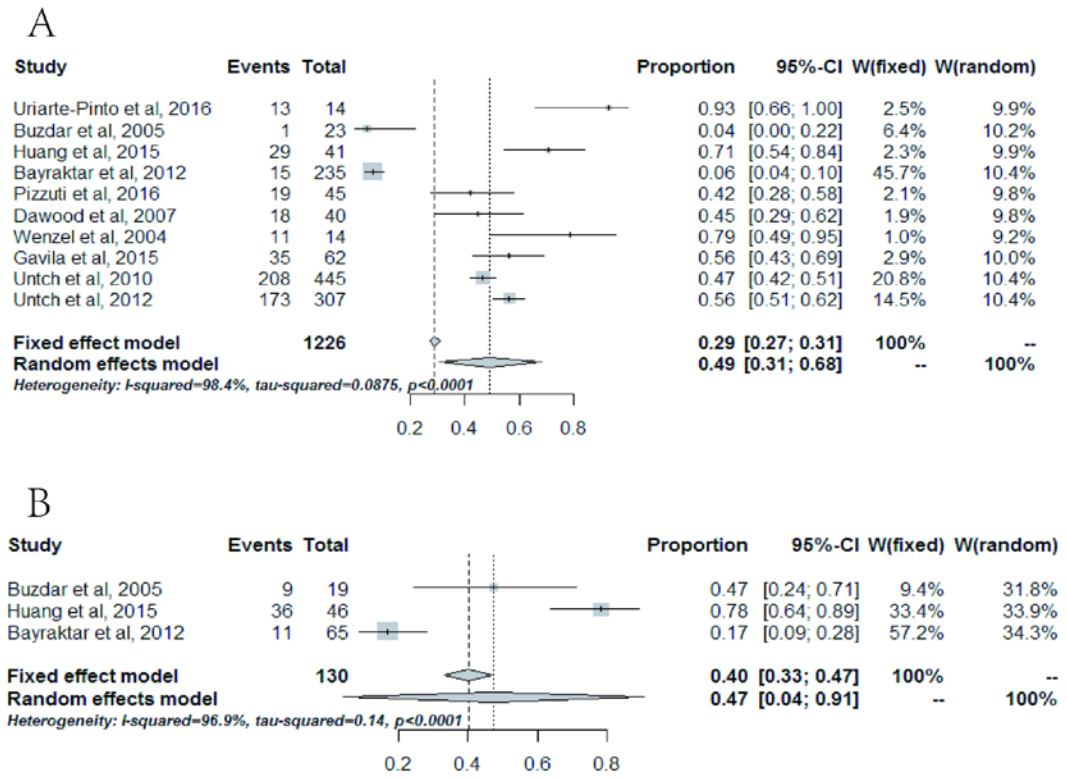

Figure S2 The pooled absolute rate of PR for the concurrent (A) and non-concurrent (B) use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer

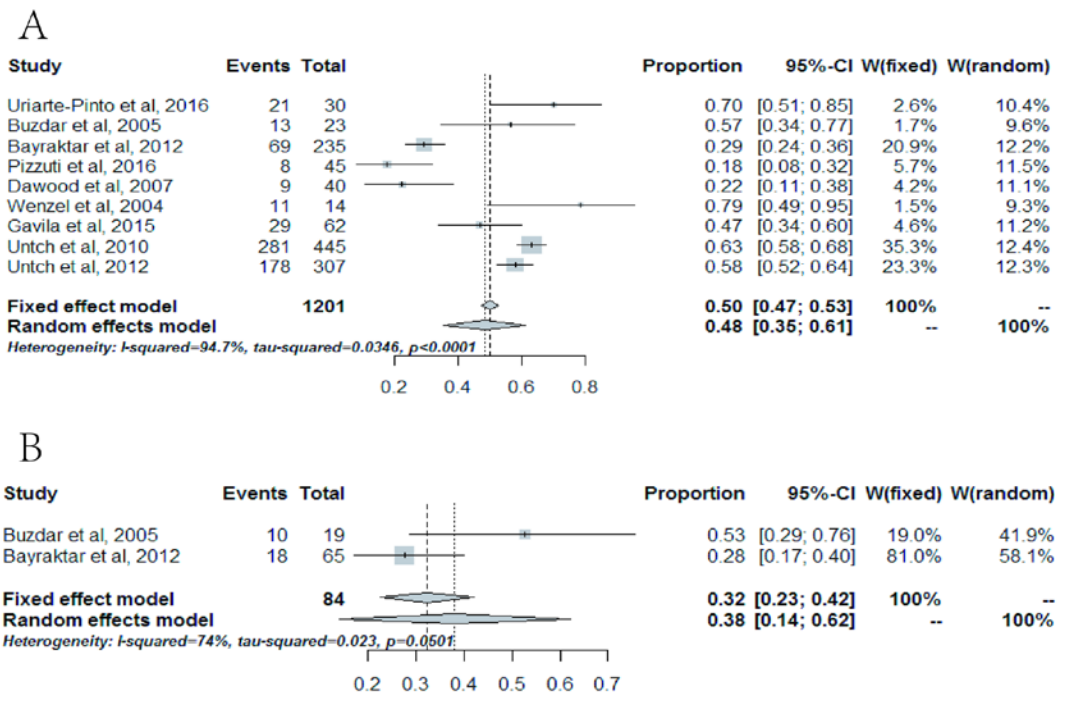

Figure S3 The pooled absolute rate of BCS for the concurrent (A) and non-concurrent (B) use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer

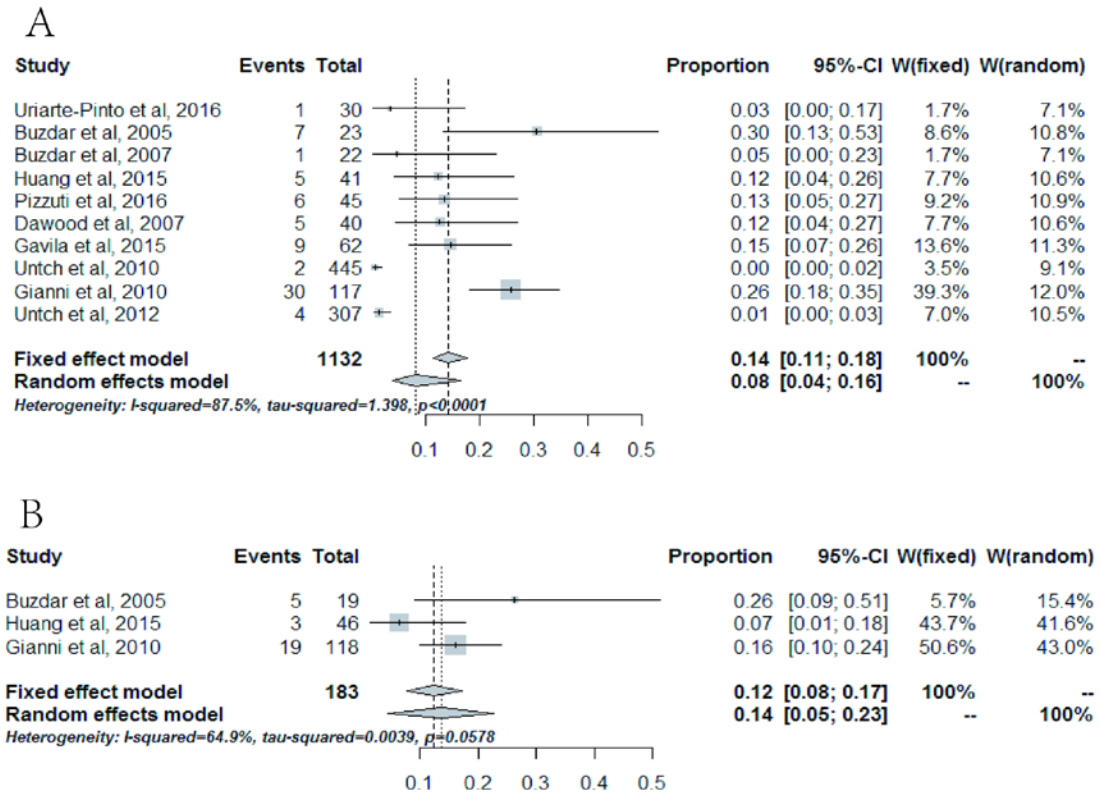

Figure S4 The pooled absolute rate of CED for the concurrent (A) and non-concurrent (B) use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer

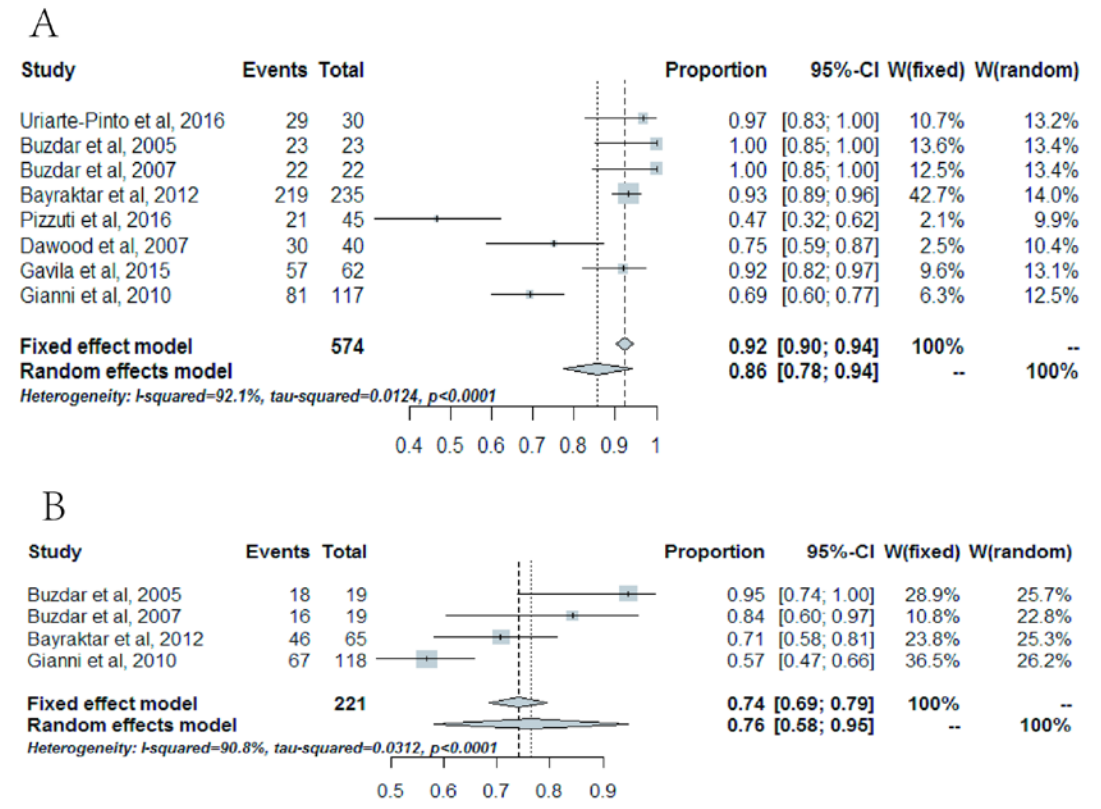

Figure S5 The pooled absolute rate of RFS for the concurrent (A) and non-concurrent (B) use of

trastuzumab and anthracycline-based NAC for HER2-positive breast cancer

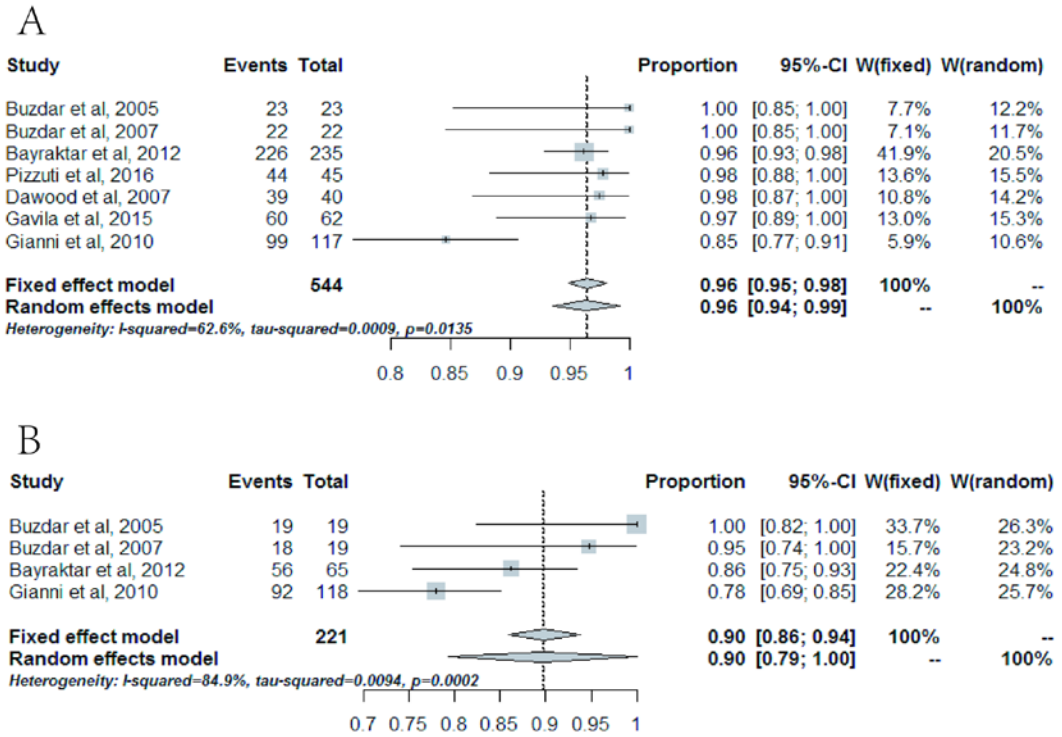

Figure S6 The pooled absolute rate of OS for the concurrent (A) and non-concurrent (B) use of trastuzumab and anthracycline-based NAC for HER2-positive breast cancer

Table S1 Characteristics of studies included in the meta-analysis

Study ,Year	Country	Type of study	Total participants (EH/No EH)*	Median age (range) (years)	Chemotherapy regimen	Anthracycline	Type of cancer	Outcome measures	Median of follow-up (months)
Uriarte-Pinto et al, 2016	Spain	Retrospective	30(30/NR)	48(30-70)	Doxorubicin (50mg/m2, day 1), paclitaxel (80mg/m2, day 1,7,14), trastuzumab (8mg/kg,day 1, followed by 6mg/kg), concurrent use, every 3 weeks, six cycles regimen.	Non-pegylated liposomal-encapsulated doxorubicin	HER-2 positive and clinical stage IIa to IIIb.	pCR; RFS; Rate of breast conservation; Cardiac ejection fraction; Cardiac failure.	16.2
Buzdar et al, 2005	USA	Prospective randomized trial	42(23/19)	EH:52(29-71) No EH:48(25-75)	Paclitaxel (225mg/m2), FEC (fluorouracil 500mg/m2, day 1,4; cyclophosphamide 500mg/m2, day 1; epirubicin 75mg/m2, day 1), trastuzumab (4mg/kg, day 1 of the first cycle, followed by 2mg/kg, weekly).Four cycles of paclitaxel followed by four cycles of FEC,cycles repeated every 3 weeks, with or without simultaneous trastuzumab.	Epirubicin	HER-2 positive and clinical stage II to IIIa.	pCR; CR; PR; RFS; Rate of breast conservation; ;Cardiac ejection fraction; Cardiac failure.	20
Buzdar et al,	USA	Prospective	41(22/19)	EH:51(21-70)	Four cycles of paclitaxel (225mg/m2, every 3 weeks), followed by four cycles of FEC	Epirubicin	HER-2 positive	pCR; RFS; Cardiac	36.1

2007		randomized corhort		No EH:48(25-75)	(fluorouracil 500mg/m2, day 1,4; cyclophosphamide 500mg/m2, day 1; epirubicin 75mg/m2, day 1), trastuzumab (4mg/kg, day 1 of the first cycle, followed by 2mg/kg weekly).P-FEC/PH-FECH.		and clinical stage II to IIIa.	ejection fraction; Cardiac failure.	
Huang et al, 2015	China	Phase II randomized trial	87(41/46)	EH:47.5 (30-63) No EH:48(29-65)	Paclitaxel (75mg/m2, weekly), trastuzumab (4mg/kg loading dose followed by 2mg/kg), carboplatin (AUC=2, weekly), epirubicin (75mg/m2, every 3 weeks). At least 4 cycles but no more than 6 cycles.PEH/PCH.	Epirubicin	HER-2 positive and clinical stage II to III.	pCR; CR; PR; Cardiac ejection fraction; Cardiac failure.	NR
Bayraktar et al, 2012	USA	Retrospective	300(235/65)	EH:49(21-81) No EH:53(29-80)	Paclitaxel (80mg/m2 weekly for 12 weeks, or 225mg/m2 every 3 weeks),fluorouracil (500mg/m2, day1, every 3 weeks),epirubicin (75mg/m2, day1, every 3 weeks), cyclophosphamide (500mg/m2, day1, every 3 weeks),trastuzumab (4mg/kg, day1 followed by 2mg/kg, weekly),PH-FECH. Docetaxel (75mg/m2, day1, every 3 weeks), carboplatin (AUC=6, day1, every 3 weeks),trastuzumab (8mg/kg, day1 followed by 6mg/kg, every 3 weeks),TCH.	Epirubicin	HER-2 positive without metastatic, bilateral breast cancer or other primary tumor.	pCR; RFS; OS; Rate of breast conservation; ;Cardiac ejection fraction; Cardiac failure.	26.8
Pizzuti et al, 2016	Italy	Prospective phase II	45(45/NR)	EH:45(32-69) No EH: NR	Four cycles of neoadjuvant docetaxel 100mg/m2 plus trastuzumab 6mg/kg(loading dose 8mg/kg) every 3 weeks, followed by four 3-weekly cycles of epirubicin 120mg/m2 and	Epirubicin	HER-2 positive and clinical	pCR; CR; PR; RFS; OS; Rate of breast conservation;	46

		trial			cyclophosphamide 600mg/m2 plus trastuzumab.TH-ECH.		stage IIa to IIIb.	;Cardiac ejection fraction; Cardiac failure.	
Dawood et al, 2007	USA	Retrospective	40(40/NR)	EH:48(29-81) No EH: NR	Paclitaxel 80mg/m2/week for 12 weeks, followed by 4 cycles FEC75 (fluorouracil 500mg/m2, epirubicin 75mg/m2, cyclophosphamide 500mg/m2) every 3 weeks, concomitantly trastuzumab 2mg/kg weekly (loading dose of 4mg/kg) for 24 weeks.	Epirubicin	HER-2 positive and clinical stage II to IIIc.	pCR; RFS; OS; Rate of breast conservation; Cardiac ejection fraction; Cardiac failure.	19
Wenzel et al, 2004	Austria	Prospective	14(14/NR)	EH:59.5 (36-78) No EH: NR	Trastuzumab 4mg/kg loading dose, 2mg/kg maintenance dose weekly, in combination with weekly epidoxorubicin 30mg/m2 and doxetaxel 35mg/m2 for 6 weeks followed by 1 week off therapy.	Epidoxorubicin	HER-2 positive breast cancer without distant disease.	pCR; CR; Rate of breast conservation; Cardiac failure.	NR
Gavila et al, 2015	Spain	Prospective	62(62/NR)	EH:46.6 (27.4-74.1) No EH: NR	Non-pegylated liposomal-encapsulated doxorubicin 50mg/m2, day1, every 3 weeks; Paclitaxel 80mg/m2, day1, every week; trastuzumab 4mg/kg as initial dose, day1, and then 2mg/kg weekly.(MTH)	Non-pegylated liposomal-encapsulated doxorubici	HER-2 positive and clinical stage II to III.	pCR; PR; CR; RFS; OS; Rate of breast conservation; Cardiac ejection	43.3

						n		fraction; Cardiac failure.	
Untch et al, 2010	Germany	Prospective	445(445/NR)	EH:49.4 (22-78) No EH: NR	Epirubicin 90mg/m2; cyclophosphamide 600mg/m2; docetaxel 100mg/m2 or 75mg/m2; capecitabine 1,800 mg/m2; trastuzumab 8mg/kg or 12mg/kg loading dose, followed by 6mg/kg every 3 weeks. Trastuzumab given concomitantly with epirubicin/cyclophosphamide followed by docetaxel with or without capecitabine. (ECH-TH[X])	Epirubicin	Locally advanced, HER-2 positive breast cancer.	pCR; CR; PR; Rate of breast conservation; Cardiac ejection fraction; Cardiac failure.	NR
Gianni et al, 2010	International multicenter study (six countries and 27 centres)	Prospective randomised phase III trial	235(117/118)	<50years EH:50p No EH:50p >50years EH:67p No EH:68p	Doxorubicin 60mg/m2 plus paclitaxel 150mg/m2, every 3 weeks for three cycles, followed by paclitaxel 175mg/m2 administered every 3 weeks for four cycles. Cyclophosphamide 600mg/m2 and fluorouracil 600mg/m2 were then given on days 1 and 8 every 4 weeks for three cycles. Trastuzumab 8mg/kg loading dose, followed by 6mg/kg,every 3 or 4 weeks.TEH-FCH/TE-FC.	Doxorubicin	HER-2 positive locally advanced or inflammatory breast cancer.	pCR; RFS; OS; Cardiac ejection fraction.	38.4
Untch et al, 2012	Germany	Prospective phase	307(307/NR)	EH:50(25-74) No EH:	Four cycles of epirubicin 90mg/2 plus cyclophosphamide 600mg/m2, every 3 weeks, and four cycles of docetaxel 100mg/m2, every	Epirubicin	HER-2 positive operable	pCR; CR; PR; Rate of breast conservation;	NR

		III trial		NR	3 weeks, with trastuzumab 6mg/kg with a starting loading dose of 8mg/kg, for eight cycles,every 3 weeks.ECH-TH.		or locally advanced breast cancer.	Cardiac ejection fraction; Cardiac failure.	
Tuxen et al, 2014	Denmark	Prospective phase II trial	10(10/NR)	EH:50(31-69) No EH: NR	Four cycles of pegylated liposomal doxorubicin 35mg/m2 and cyclophosphamide 600mg/m2; follow by four cycles of docetaxel 100 mg/m2;concurrently with trastuzumab 8mg/kg as initial dose, and then 6mg/kg.(MCH-TH)	Pegylated liposomal doxorubicin	HER-2 positive operable or locally advanced breast cancer.	pCR	NR

EH: concurrent use of trastuzumab and anthracyclines.

No EH: nonconcurrent use of trastuzumab and anthracyclines.

Table S2 The outcomes of studies included in the meta-analysis

Study, Year	participants Total (EH/No EH)*	pCR Total (EH/No EH)*	Complete response Total (EH/No EH)*	Partial response Total (EH/No EH)*	Breast conversion Total (EH/No EH)*	Cardiac ejection fraction decrease more than 10% Total (EH/No EH)*	Cardiac failure Total (EH/No EH)*	Recurrence free survival Total (EH/No EH)*	Overall survival Total (EH/No EH)*
Uriarte-Pinto et al, 2016	30 (30/NR)	14 (14/NR)	NR	13 (13/NR)	21 (21/NR)	1 (1/NR)	0	29 (29/NR)	NR
Buzdar et al, 2005	42 (23/19)	20 (15/5)	30 (21/9)	10 (1/9)	23 (13/10)	12 (7/5)	0	41 (23/18)	42 (23/19)
Buzdar et al, 2007	41 (22/19)	17 (12/5)	NR	NR	NR	6 (1/5)	0	38 (22/16)	40 (22/18)
Huang et al, 2015	87 (41/46)	38 (20/18)	18 (11/7)	65 (29/36)	2 (NR/NR)	8 (5/3)	0	NR	NR
Bayraktar et al, 2012	300 (235/65)	163 (137/26)	205 (172/33)	26 (15/11)	87 (69/18)	250 (212/38)	1 (1/0)	265 (219/46)	282 (226/56)
Pizzuti et al, 2016	45 (45/NR)	28 (28/NR)	26 (26/NR)	19 (19/NR)	8 (8/NR)	6 (6/NR)	0	21 (21/NR)	44 (44/NR)
Dawood et al, 2007	40 (40/NR)	22 (22/NR)	NR	18 (18/NR)	9 (9/NR)	5 (5/NR)	0	30 (30/NR)	39 (39/NR)

Wenzel et al, 2004	14(14/NR)	1(1/NR)	NR	11(11/NR)	11(11/NR)	NR	0	NR	NR
Gavila et al, 2015	62(62/NR)	36(36/NR)	27(27/NR)	35(35/NR)	29(29/NR)	9(9/NR)	0	57(57/NR)	60(60/NR)
Untch et al, 2010	445(445/NR)	141(141/NR)	154(154/NR)	208(208/NR)	281(281/NR)	2(2/NR)	1(1/NR)	NR	NR
Gianni et al, 2010	235(117/118)	76(50/26)	NR	NR	NR	49(30/19)	2(2/0)	148(81/67)	191(99/92)
Untch et al, 2012	307(307/NR)	93(93/NR)	100(100/NR)	173(173/NR)	178(178/NR)	4(4/NR)	1(1/NR)	NR	NR
Tuxen et al, 2014	10(10/NR)	3(3/NR)	NR	NR	NR	NR	NR	NR	NR

EH: concurrent use of trastuzumab and anthracyclines.

No EH: nonconcurrent use of trastuzumab and anthracyclines.

Table S3 Quality assessment of the included studies using the Newcastle-Ottawa scale

	Selection†				Comparability‡	Outcome§			
Study, Year (Reference)	**Representativeness of the exposed cohort (maximum:*)**	**Selection of the non-exposed cohort (maximum:*)**	**Ascertainment of exposure (maximum:*)**	**Demonstration that outcome of interest was not present at start of study (maximum:*)**	**Comparability of cohorts on the basis of the design or analysis (maximum:**)**	**Assessment of outcome (maximum:*)**	**Was follow up long enough for outcomes to occur (maximum:*)**	**Adequacy of follow up of cohorts (maximum:*)**	**Aggregate score**
Uriarte-Pinto et al, 2016	*	NA	*	*	NA	*	*	*	******
Buzdar et al, 2005	*	*	*	*	**	*	*	*	********
Buzdar et al, 2007	*	*	*	*	**	*	*	*	********
Huang et al, 2015	*	*	*	*	**	*	*	/	*******
Bayraktar et al, 2012	*	*	*	*	**	*	*	*	********
Pizzuti et	*	NA	*	*	NA	*	*	*	******

al, 2016									
Dawood et al, 2007	*	NA	*	*	NA	*	*	*	******
Wenzel et al, 2004	*	NA	*	*	NA	*	*	/	*****
Gavila et al, 2015	*	NA	*	*	NA	*	*	*	******
Untch et al, 2010	*	/	*	*	/	*	*	/	*****
Gianni et al, 2010	*	*	*	*	**	*	*	*	******* **
Untch et al, 2012	*	/	*	*	/	*	*	/	*****
Tuxen et al, 2014	*	/	*	*	/	*	*	/	*****

For our main outcome(Pathologic complete response, pCR), the points for confounding were allocated as follows: one point was allocated for controlling for type or duration of chemotherapy and an additional point for age, sex ,country, race. We designated the lowest score for the main outcome(pCR) without controlling all the items. The final comparability score was the minimum score that a study received for all the outcomes.

/=study did not fulfill listed criteria; *=study fulfilled listed criteria; NA=criteria not applicable to the study.

†Representativeness of exposed cohort: *given if the cohort was representative of the average HER2-positive breast cancer patients with concurrent use of trastuzumab and anthracycline-based neoadjuvant chemotherapy; / given if the cohort was selected based on convenience (i.e., volunteers) or if there was no description of the derivation of the cohort. Selection of nonexposed cohort: * given if the nonexposed cohort was drawn from the same community as the exposed cohort; / was given if it was drawn from a different source or there was no description of the cohort derivation. Exposure ascertainment: * given if obtained from secure record (hospital chart); / was given if from a written self-report or no description given.* given if outcome of interest was not present at start of study.

‡ * given if study controlled for or adjusted for type or duration of chemotherapy used; additional * if controlled for age or sex.

§ Assessment of outcome: * given if independent blind assessment or evidence of record linkage (i.e., through medical records); / given if through self-report or no description.* given if follow-up was long enough for outcomes to occur. Adequacy of follow-up of cohorts: * given if complete follow-up and all participants accounted for or if loss to follow-up was small and unlikely to introduce bias (follow-up rate >90% or description provided of those lost); / given if follow-up rate <90%, no description of those lost, or no statement.

Search Strategy

1. Pubmed Search strategy

Disease types

1."breast neoplasms"[MeSH Terms]
2."breast neoplasm"[Title/Abstract]
3."breast neoplasms"[Title/Abstract]
4."breast malignancy"[Title/Abstract]
5."breast malignancies"[Title/Abstract]
6."breast malignant"[Title/Abstract]
7."breast cancer"[Title/Abstract]
8."breast cancers"[Title/Abstract]
9."breast tumor"[Title/Abstract]
10."breast tumors"[Title/Abstract]
11."mammary cancer"[Title/Abstract]
12."mammary tumor"[Title/Abstract]
13.or/1-12 (combined all studies)

Interventions

14."doxorubicin"[MeSH Terms]
15."epirubicin"[MeSH Terms]
16."doxorubicin"[Title/Abstract]
17."epirubicin"[Title/Abstract]
18."adriamycin"[Title/Abstract]
19.or/14-18 (combined all studies)

20."trastuzumab"[MeSH Terms]
21."trastuzumab"[Title/Abstract]
22."herceptin"[Title/Abstract]
23.or/20-22 (combined all studies)

24."neoadjuvant"[Title/Abstract]
25."preoperative"[Title/Abstract]
26."preoperation"[Title/Abstract]
27."pretreatment"[Title/Abstract]
28.or/24-27 (combined all studies)

29. and/13,19,23,28 (combined)

2. Embase Search strategy

Disease types
1.'breast cancer'/exp
2.'breast cancer':ab,ti
3.'breast tumor':ab,ti
4.'breast tumors':ab,ti
5.'breast neoplasm':ab,ti
6.'breast malignancy':ab,ti
7.'mammary cancer':ab,ti
8.'mammary tumor':ab,ti
9. or/1-8 (combined all studies)

Interventions
10.'doxorubicin'/exp
11.'doxorubicin':ab,ti
12.'epirubicin':ab,ti
13.'adriamycin':ab,ti
14. or/10-13 (combined all studies)

15.'trastuzumab'/exp
16.'trastuzumab':ab,ti
17.'herceptin':ab,ti
18. or/15-17 (combined all studies)

19.'neoadjuvant':ab,ti
20.'preoperative':ab,ti
21.'preoperation':ab,ti
22.'pretreatment':ab,ti
23. or/19-22 (combined all studies)

24. and/9,14,18,23 (combined)

3. Cochrane Search strategy

Disease types
1. "breast neoplasm":ti,ab,kw
2. "breast malignancy":ti,ab,kw

3. "breast cancer":ti,ab,kw
4. "breast tumor":ti,ab,kw
5. "mammary cancer":ti,ab,kw (Word variations have been searched)
6. or/1-5 (combined all studies)

Interventions
7."doxorubicin":ti,ab,kw
8."epirubicin":ti,ab,kw
9."adriamycin":ti,ab,kw (Word variations have been searched)
10. or/7-9 (combined all studies)

11."trastuzumab":ti,ab,kw
12."herceptin":ti,ab,kw (Word variations have been searched)
13. or/11-12 (combined all studies)

14."neoadjuvant":ti,ab,kw
15."preoperation":ti,ab,kw
16."preoperative":ti,ab,kw
17."pretreatment":ti,ab,kw (Word variations have been searched)
18. or/14-17 (combined all studies)

19. and/6,10,13,18 (combined)