Supplementary

Appendix 1 Detailed search strategies

PubMed

#1 "Breast Neoplasms"[Mesh] OR Breast Neoplasm*[Title/Abstract] OR Breast Tumor*[Title/Abstract] OR Breast Carcinoma*[Title/Abstract] OR Breast Cancer*[Title/Abstract]
#2 "Chemotherapy, Adjuvant"[Mesh] OR Adjuvant Chemotherapy[Title/Abstract] OR Adjuvant Drug Therapy[Title/Abstract]
#3 endocrine therapy[Title/Abstract] OR hormonal therapy[Title/Abstract] OR endocrine treatment[Title/Abstract] OR hormone therapy[Title/Abstract] OR Nolvadex[Title/Abstract] OR "Aromatase Inhibitors"[Mesh] OR "Tamoxifen"[Mesh]
#4 randomized controlled trial[Publication Type] OR controlled clinical trial[Publication Type]
#5 #1 AND #2 AND #3 AND #4

EMBASE

#1 'breast cancer'/exp OR 'breast neoplasm*':ab,ti OR 'breast tumor*':ab,ti OR 'breast carcinoma*':ab,ti
#2 'adjuvant chemotherapy'/exp OR 'adjuvant drug therapy':ab,ti OR 'chemotherapy, adjuvant':ab,ti OR 'drug therapy, adjuvant':ab,ti
#3 'hormonal therapy'/exp OR 'endocrine therapy':ab,ti OR 'endocrine treatment':ab,ti OR 'hormone therapy':ab,ti OR 'tamoxifen'/exp OR 'nolvadex':ab,ti OR 'aromatase inhibitor'/exp
#4 [controlled clinical trial]/lim OR [randomized controlled trial]/lim
#5 #1 AND #2 AND #3 AND #4

Cochrane library

#1 MeSH descriptor: [Breast Neoplasms] explode all trees
#2 "breast tumor":ti,ab,kw or "breast carcinoma":ti,ab,kw cancer":ti,ab,kw (Word variations have been searched)
#3 #1 or #2
#4 MeSH descriptor: [Chemotherapy, Adjuvant] explode all trees
#5 "Adjuvant Chemotherapy":ti,ab,kw or "Drug Therapy, Adjuvant":ti,ab,kw or "Adjuvant Drug Therapy":ti,ab,kw or "breast
#6 #4 or #5
#7 MeSH descriptor: [Tamoxifen] explode all trees
#8 MeSH descriptor: [Aromatase Inhibitors] explode all trees
#9 "endocrine therapy":ti,ab,kw or "hormonal therapy":ti,ab,kw or "endocrine treatment":ti,ab,kw or "hormone therapy":ti,ab,kw or "Nolvadex":ti,ab,kw
#10 #7 or #8 or #9
#11 #3 and #6 and #10

Web of Science

#1 TS= (Breast Neoplasm* OR Breast Tumor* OR Breast Carcinoma* OR Breast Cancer*)
#2 TS= (Chemotherapy, Adjuvant OR Adjuvant Chemotherapy OR Drug Therapy, Adjuvant OR Adjuvant Drug Therapy)
#3 TS= (endocrine therapy OR hormonal therapy OR endocrine treatment OR hormone therapy OR Tamoxifen OR Nolvadex OR Aromatase Inhibitors)
#4 TS= (randomized controlled trial OR controlled clinical trial)
#5 #1 AND #2 AND #3 AND #4

Appendix 2 Codes used in Bayesian network meta-analysis

Fixed model
model
{
#Define Prior Distributions

https://dx.doi.org/10.21037/tbcr-21-3

```
#On tx effect mean
beta[1] <-0
for (tt in 2:nTx){
beta[tt]~dnorm(0,1.0E-6)
}
#On individual study baseline effect
for(ss in 1:nStudies){
alpha[ss] ~ dnorm(0,1.0E-6)
}

#Fit data
#For hazard ratio reporting studies
for(ii in 1:LnObs ){
Lmu[ii] <- alpha[Lstudy[ii]]*multi[ii] + beta[Ltx[ii]] - beta[Lbase[ii]]
Lprec[ii] <- 1/pow(Lse[ii],2)
Lmean[ii] ~ dnorm(Lmu[ii],Lprec[ii])
}
#Calculate HRs
for (hh in 1:nTx) {
hr[hh]<-exp(beta[hh])
}
#Ranking plot
for (ll in 1:nTx) {
for (mm in 1:nTx) {
rk[ll,mm]<- equals(ranked(beta[],mm),beta[ll])
}
}
}
 #Data
 #Data set descriptors
 list(LnObs = 64, nTx = 14, nStudies = 47)
 #Log hazard ratio and log hazard data
 Lstudy[] Ltx[] Lbase[] Lmean[] Lse[] multi[]
END

#Initial values
 list(alpha = c(-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-
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0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50), beta = c(NA,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5))
 list(alpha = c(0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.5
0,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50), beta
= c(NA,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5))
 list(alpha = c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0), beta = c(NA,0,0,0,0,0,0,
0,0,0,0,0,0,0))

Random model
model
{
#Define Prior Distributions
#on random tx effect variance
sd~dunif(0,5)
reTau <- 2/pow(sd,2)
#On tx effect mean
```

 https://dx.doi.org/10.21037/tbcr-21-3

```
beta[1] <-0
for (tt in 2:nTx){
beta[tt]~dnorm(0,1.0E-6)
}

#On individual study baseline effect
for(ss in 1:nStudies){
alpha[ss] ~ dnorm(0,1.0E-6)
}

#Define random effect
for (ss in 1:nStudies){
for(tt in 1:nTx){
re[ss,tt]~dnorm(0,reTau)
}
}

#Fit data
#For hazard ratio reporting studies
 for(ii in 1:LnObs ){
Lmu[ii] <- alpha[Lstudy[ii]]*multi[ii] + re[Lstudy[ii],Ltx[ii]] - re[Lstudy[ii],Lbase[ii]] + beta[Ltx[ii]] - beta[Lbase[ii]]
Lprec[ii] <- 1/pow(Lse[ii],2)
Lmean[ii] ~ dnorm(Lmu[ii],Lprec[ii])
}
#Calculate HRs
for (hh in 2:nTx) {
hr[hh]<-exp(beta[hh])
}

#Ranking plot
for (ll in 1:nTx) {
for (mm in 1:nTx) {
rk[ll,mm]<- equals(ranked(beta[],mm),beta[ll])
}
}
}
 #Data
 #Data set descriptors
 list(LnObs = 64, nTx = 14, nStudies = 47)
 #Log hazard ratio and log hazard data
 Lstudy[] Ltx[] Lbase[] Lmean[] Lse[] multi[]
END

#Initial values
 list(alpha = c(-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-
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0.50,-0.50,-0.50,-0.50,-0.50,-0.50,-0.50), beta = c(NA,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5,-0.5),sd = 0.1)
 list(alpha = c(0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.5
0,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50,0.50), beta
= c(NA,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5),sd = 1)
 list(alpha = c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0), beta = c(NA,0,0,0,0,0,0,
0,0,0,0,0,0,0),sd = 1)
```


Table S1 Comparisons of model fitness using DIC

	Consistency		Inconsistency	
	Random	Fixed	Random	Fixed
Not merged				
DFS	61.50	76.02	65.98	65.99
Premenopause	20.54	19.74	21.96	22.02
Postmenopause	28.17	31.75	29.98	29.99
OS	46.57	45.07	65.99	65.99
Premenopause	23.56	22.38	26.02	25.99
Postmenopause	15.52	13.87	23.97	23.98
Merged				
DFS	57.32	67.67	63.99	63.94
Premenopause	19.87	18.83	21.98	21.98
Postmenopause	23.88	25.88	28.00	27.98
OS	43.37	41.57	65.97	65.97
Premenopause	23.62	22.37	25.98	26.02
Postmenopause	15.54	13.85	23.98	23.98

Comparisons of model fitness between consistency model and inconsistency model using DICs for both fixed and random models.

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Table S2 Detailed characteristics of studies included

Year and Author	Study name	Country/ Group	Stage	Menopause status	End point	Follow-up	Chemotherapy	Treatment arm 1	N1	Treatment arm 2	N2	Treatment arm 3	N3
1980 Hubay (31)		America	II	Both	RFS	45	CMF	Che + Tam	75	Che	74		
1990 Rutqvist (6)	Swedish Cancer Society	Sweden	Node-positive	Postmenopausal	RFS, OS	78	CMF	Che + Tam	80	Che	73		
1992 Toi (48)	ACETBC	Japan	II and IIIA	Both	RFS, OS	68	F	Che + Tam	276	Che	279		
1994 Abe (49)	ACETBC	Japan	II and IIIA	Both	OS, DFS	67	F	Che + Tam	112	Che	95		
1994 Rivkin (50)	SWOG	America	II, III	Postmenopausal	OS, DFS	68	CMF	Che	300	Tam	295	Che + Tam	303
1997 Fisher (7)	NSABP B-20	America and Canada	Node-negative	Both	DFS, DDFS, OS	77	CMF	Che + Tam	789	Tam	788	Che + Tam	786
1998 Nomura (51)	EBCTCG	Japan	I, II and IIIA	Premenopausal	RFS, OS	98	AC	Che + Tam	151	OFS + Tam	154	Che	157
				Postmenopausal				Che + Tam	134	Che	130	Tam	135
1999 Andersson (52)	DBCG 82B Trial	Denmark	II, III	Premenopausal	RFS, OS	120	CMF	Che + Tam	123	Che	129		
2000 Crivellari (53)	IBCSG Trial VII	IBCSG	I, II and IIIA	Postmenopausal	DFS, OS	96	CMF	Che + Tam	231	Tam	239		
2003 Hata (32)	HACETBCSG	Japan	II and IIIA	Both	OS, DFS	60	F	Che + Tam	102	Che	94		
2004 Pico (12)	GEICAM 9401 study	Span	I, II and IIIA	Postmenopausal	DFS	54	EC	Che – Tam	174	Che + Tam	172		
2005 Arriagada (54)	FNCLCC	France	II, III	Premenopausal	DFS	118	CAF/CEF	Che – Tri	289	Che	286		
2005 Davidson (55)	ECOG E5188	America	I, II and IIIA	Premenopausal	TTR, DFS, OS	115	CAF	Che – Gos	502	Che	494	Che – Gos + Tam	507
2005 Goss (56)	NCIC CTG MA.17	Canada	ALL	Postmenopausal	DFS, DDFS, OS	30	NA	Tam	440	Che	441	Che + Tam	176
2005 Hutchins (33)	INT-0102	America	Node-negative	Both	DFS, OS	120	CMF/CAF	Che – Let	1177	Che	1166		
2006 Namer (57)	FASG 02 and 07 trials	France	Node-positive	Postmenopausal	OS, DFS	113	CEF	Che + Tam	224	Tam	233		
2007 Kaufmann (30)	GABG-IV B-93	Germany	I, II and III	Premenopausal	EFS	66	CMF	Che – Gos	160	Che	151		
2007 Morales (8)	EORTC	European	I, II and IIIA	Both	RFS, OS	78	CMF/CAF/CEF	Che – Tam	233	Che	258		
2008 Mamounas (58)	NSABP B-33	America	I, II and IIIA	Postmenopausal	RFS, DFS	30	NA	Che – Tam – Exe	432	Che – Tam	431		
2009 Albain (13)	SWOG-8814, INT-0100	America	I, II and IIIA	Postmenopausal	OS, DFS	107	CAF	Che – Tam	566	Tam	361	Che + Tam	550
2009 Hackshaw (29)	ZIPP	the United Kingdom	I, II and IIIA	Premenopausal	EFS	132	CAF/CEF	Che + Gos	292	Che	295		
								Che + Gos + Tam	292	Che – Tam	295		

Table S2 (*continued*)

Table S2 (*continued*)

Year and Author	Study name	Country/ Group	Stage	Menopause status	End point	Follow-up	Chemotherapy	Treatment arm 1	N1	Treatment arm 2	N2	Treatment arm 3	N3
2009 Thürlimann (59)	IBCSG Trial 11-93	IBCSG	Node-positive	Premenopausal	OS, DFS, QoL	53	AC	Che + OFS + Tam	89	OFS + Tam	85		
2010 Aihara (60)	N-SAS BC03	Japan	I, II and III	Postmenopausal	DFS, RFS, QoL	42	NA	Che – Tam – Ana	160	Che – Tam	163		
2010 Bramwell (61)	NCIC CTG MA.12	Canada	I, II and IIIA	Premenopausal	DFS, OS	116	CMF/AC/CEF	Che – Tam	252	Che	253		
2011 Aebi (9)	IBCSG Trial IX	Italy	Node-negative	Postmenopausal	DFS, OS, BCFI	157	CMF	Che – Tam	665	Tam	690		
2011 Bedognetti (14)		IBCSG	ALL	Both	OS, DFS	148	CMF/CEF	Che – Tam	116	Che + Tam	111		
2011 Boccardo (62)	GROCTA 01	Italy	Node-positive	Both	DFS, OS	252	CMF	Che	165	Tam	168	Che + Tam	171
2011 Karlsson (63)	IBCSG Trial VIII	Denmark	Node-negative	Premenopausal	DFS, OS, BCFI	145	CMF	Che	291	Gos	278	Che – Gos	282
2014 Shien (64)	JCOG 9401	Japan	II	Premenopausal	OS, DFS	60	F/AC	Che + Tam	46	Tam	46		
2016 Goss (65)	NCIC CTG MA.17. R	Canada	ALL	Postmenopausal	DFS, QoL	75	NA	Che – Let	561	Che	557		
2017 Derks (66)	TEAM	The Netherlands	I, II and IIIA	Postmenopausal	DFS	104	NA	Che – Exe	1141	Che – Tam – Exe	1112		
2018 Francis (17)	TEXT	IBCSG	I, II and IIIA	Premenopausal	DFS, DDFS, OS	68	NA	Che + Tri + Exe	331	Che + Tri + Tam	328		
2018 Francis (17)	SOFT	IBCSG	I, II and IIIA	Premenopausal	DFS, DDFS, OS	68	NA	Che – Tri + Tam	542	Che – Tam	542	Che – Tri + Exe	544
2020 Kim (34)	ASTRRA	Korean	I, II and IIIA	Premenopausal	DFS, OS	63	NA	Che – Gos + Tam	635	Che – Tam	647		

OS, Overall survival; RFS, Relapse-free survival; DFS, Disease-free survival; EFS, Event-free survival; DDFS, Distant disease-free survival; QoL, Quality of life; TTR, Time to progression; BCFI, Breast cancer-free interval; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; F, tegafur/ftorafur/5-fluorouracil/UFT; AC, doxorubicin and cyclophosphamide; CAF, cyclophosphamide, adriamycin, 5-fluorouracil; EC, epirubicin and cyclophosphamide; CEF, cyclophosphamide, epirubicin, 5-fluorouracil; Tam, tamoxifen; OFS, ovarian function suppression was achieved by bilateral oophorectomy, ovarian irradiation or luteinizing/gonadotrophin hormone–releasing hormone (LHRH/GnRH) agonists (Tri, triptorelin; Gos, goserelin). Patients receiving Tri/Gos could subsequently undergo oophorectomy or irradiation. AI, aromatase inhibitors (Let, letrozole; Exe, exemestane; Ana, anastrozole). Sequence of chemo-endocrine therapy: endocrine therapy sequentially used after chemotherapy: –, e.g., "Che – Tam": chemotherapy sequentially followed by tamoxifen; endocrine therapy concurrently used with chemotherapy: +, e.g., "Che + Tam": chemotherapy concurrently used with tamoxifen. "Che – Tri – Tam": chemotherapy followed by triptorelin, followed by tamoxifen.

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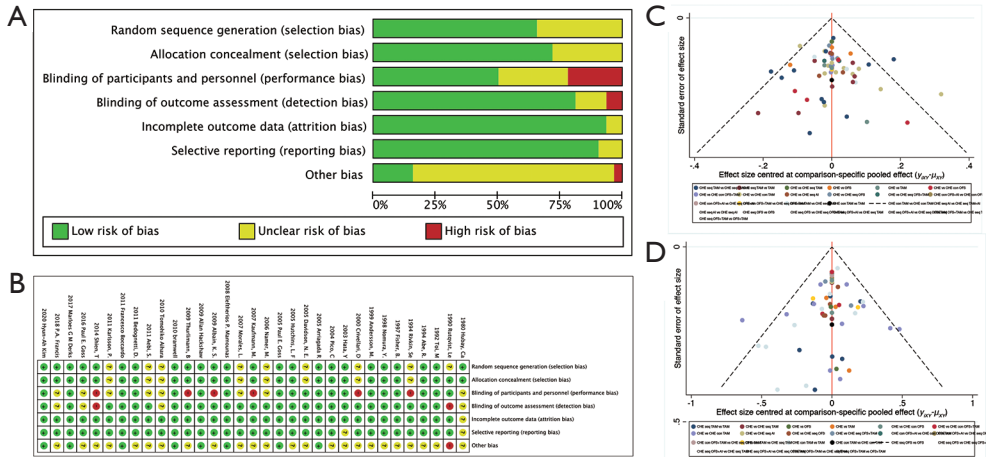

Figure S1 Quality evaluation of publications enrolled. (A) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; (B) risk of bias summary: review authors' judgements about each risk of bias item for each included study. Small-study effects were estimated using funnel plot for (C) disease-free survival (DFS) and (D) overall survival (OS).

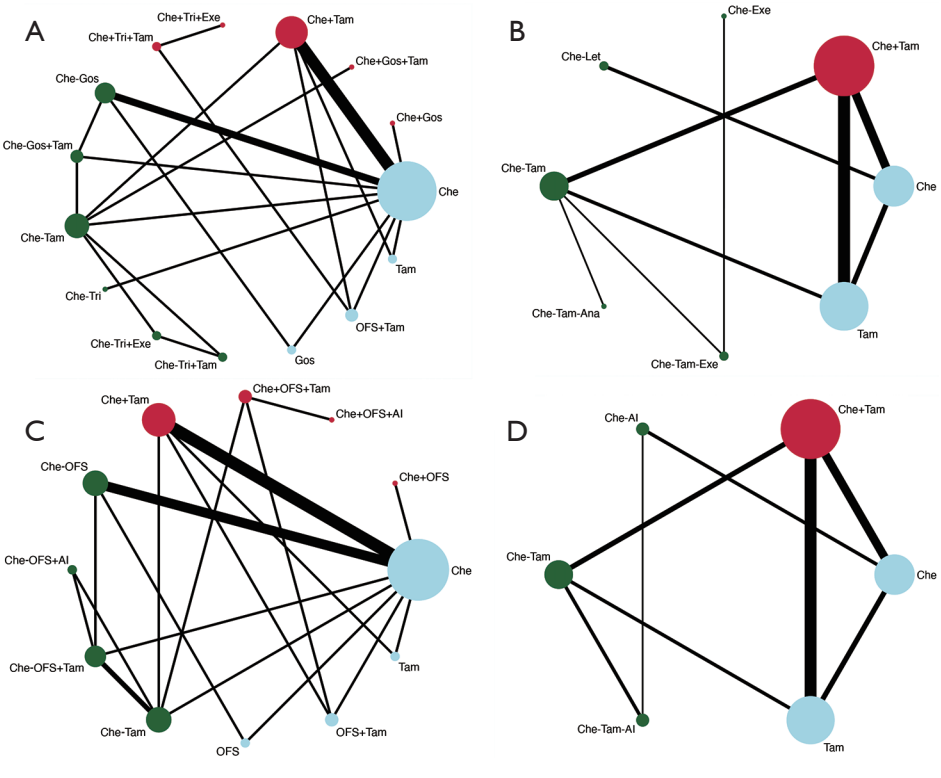

Figure S2 Geometry of DFS and OS analysis in premenopausal and postmenopausal patients. Network plots of studies and treatment arms enrolled in (A) DFS analysis; (B) OS analysis of premenopausal patients; (C) DFS analysis; (D) OS analysis of postmenopausal patients. Nodes represent the competing treatments and edges represent the available direct comparisons between pairs of treatments. Both nodes and edges were weighted according to the number of patients and studies enrolled, respectively. Nodes were colored into three categories: chemotherapy or hormonal therapy alone (light blue); chemotherapy and endocrine therapy used concurrently (cranberry) and chemotherapy followed by endocrine therapy (dark green). Che, chemotherapy; Tam, tamoxifen; OFS, ovarian function suppression; Tri, triptorelin; Gos, goserelin; Let, letrozole; Exe, exemestane; Ana, anastrozole. Sequence of regimens was illustrated as: sequential use, "–"; concurrent use, "+".

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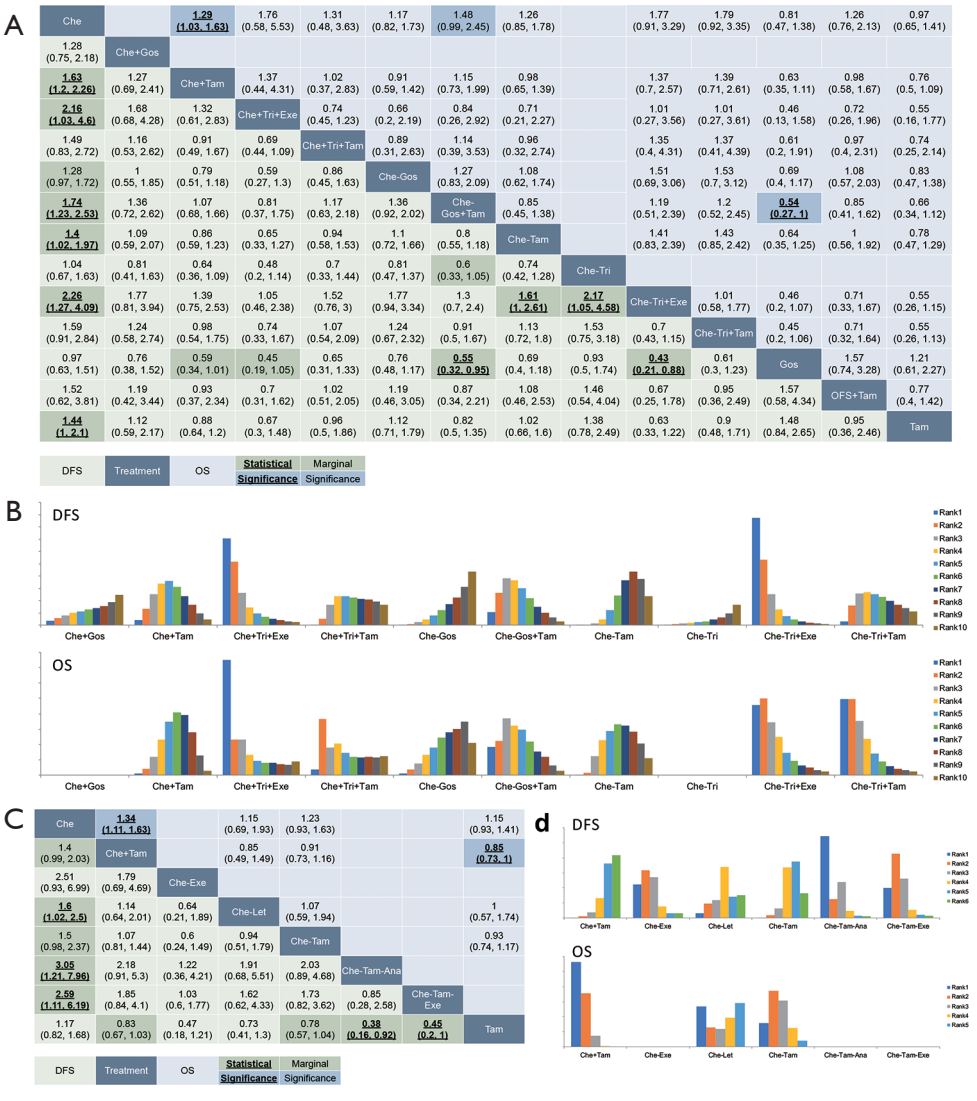

Figure S3 Comparisons of chemo-endocrine therapies for premenopausal and postmenopausal HR+ early breast cancer regarding 3 disease-free survival (DFS), overall survival (OS) with treatments not merged. Comparisons of chemo-endocrine therapy for (A) premenopausal and (C) postmenopausal HR+ early breast cancer by Bayesian network analysis regarding DFS and OS with treatments not merged. Treatment arms were aligned on the diagonal line. HRs and 95% CrI were generated by comparing the upper-left arm to the lower-right. Bricks were colored by clinical outcomes: DFS: light green, OS: light blue. 95% CrI not cross 1 was considered statistically significant and represented as bold deep green (DFS) or deep blue (OS) bricks with underline. HR <1, upper 95% CrI ≤1.05 and HR >1, lower 95% CrI ≥0.95 were considered marginal significance and represented as deep green (DFS) or deep blue (OS) bricks only. Rankogram of treatment arms in DFS and OS analysis for (B) premenopausal (D) postmenopausal HR+ early breast cancer. Based on the therapeutic efficacy, the probability of each treatment on each position was calculated and presented as bar plot. Treatments were ranked by the position of the highest possibility. For two treatments with the highest possibility on the same position, the two treatments were considered a tied with equal preference.

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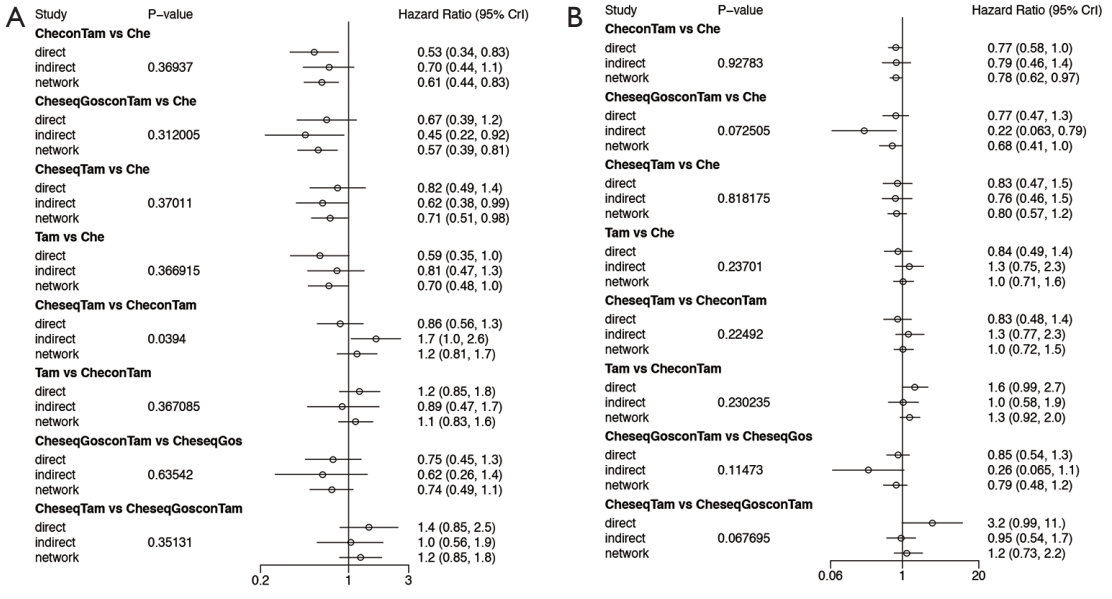

Figure S4 Evaluation of inconsistency between direct and indirect analyses of disease-free survival (DFS). Comparisons of local inconsistency between direct and indirect analyses of treatment arms using node splitting methods (A) in the DFS analysis of premenopausal patients; (B) in the DFS analysis of postmenopausal patients. A P value <0.05 was considered statistical significance and indicated inconsistency between direct and indirect analyses.

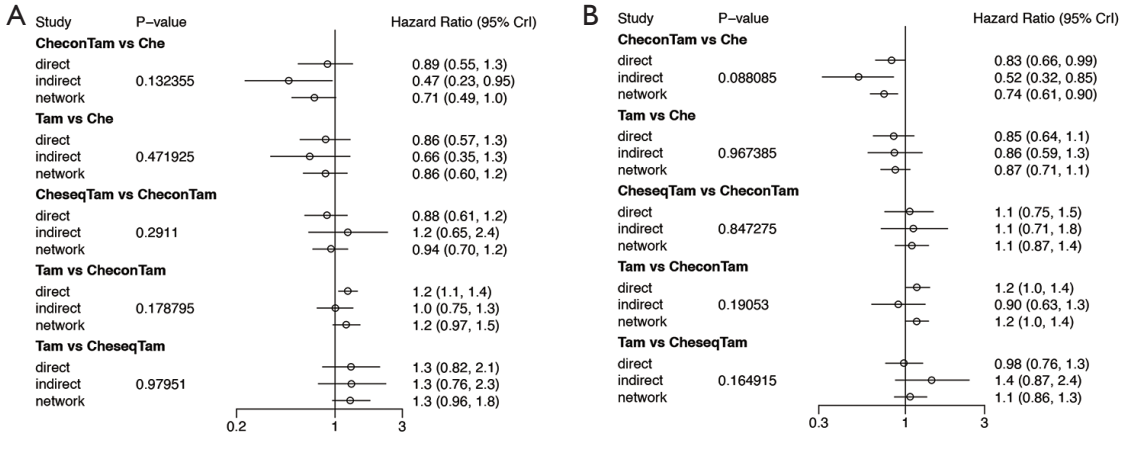

Figure S5 Evaluation of inconsistency between direct and indirect analyses of overall survival (OS). Comparisons of local inconsistency between direct and indirect analyses of treatment arms using node splitting methods (A) in the OS analysis of premenopausal patients; (B) in the OS analysis of postmenopausal patients. A P value <0.05 was considered statistical significance and indicated inconsistency between direct and indirect analyses.

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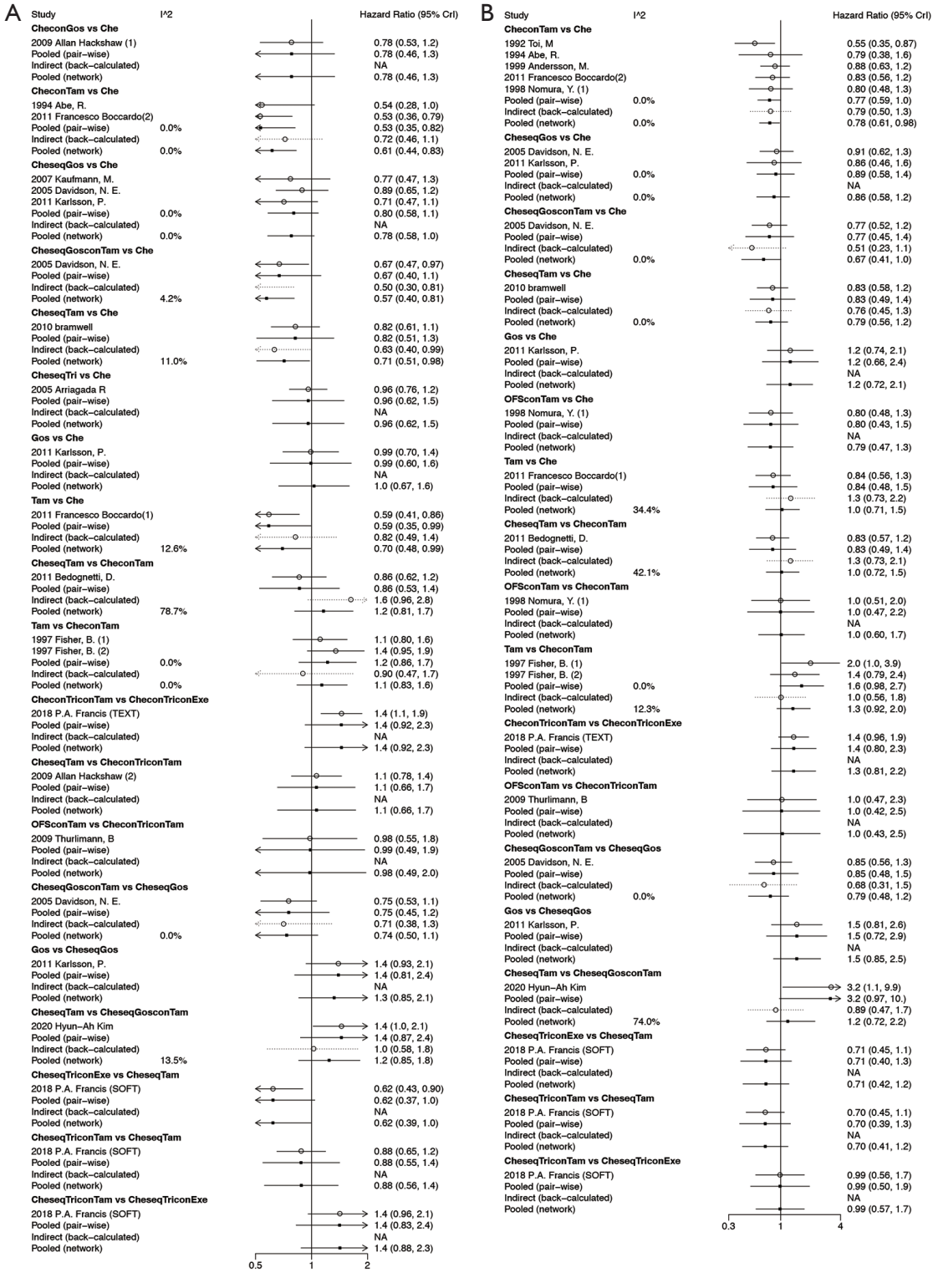

Figure S6 Heterogeneity of comparisons between treatment arms in disease-free survival (DFS) analyses. Heterogeneity of comparisons between treatment arms enrolled in (A) in the DFS analysis of premenopausal patients; (B) in the DFS analysis of postmenopausal patients. I^2=0% means no heterogeneity; I^2>25% indicates mild heterogeneity; I^2>50% indicates moderate heterogeneity; I^2>75%, it indicates high heterogeneity.

https://dx.doi.org/10.21037/tbcr-21-3

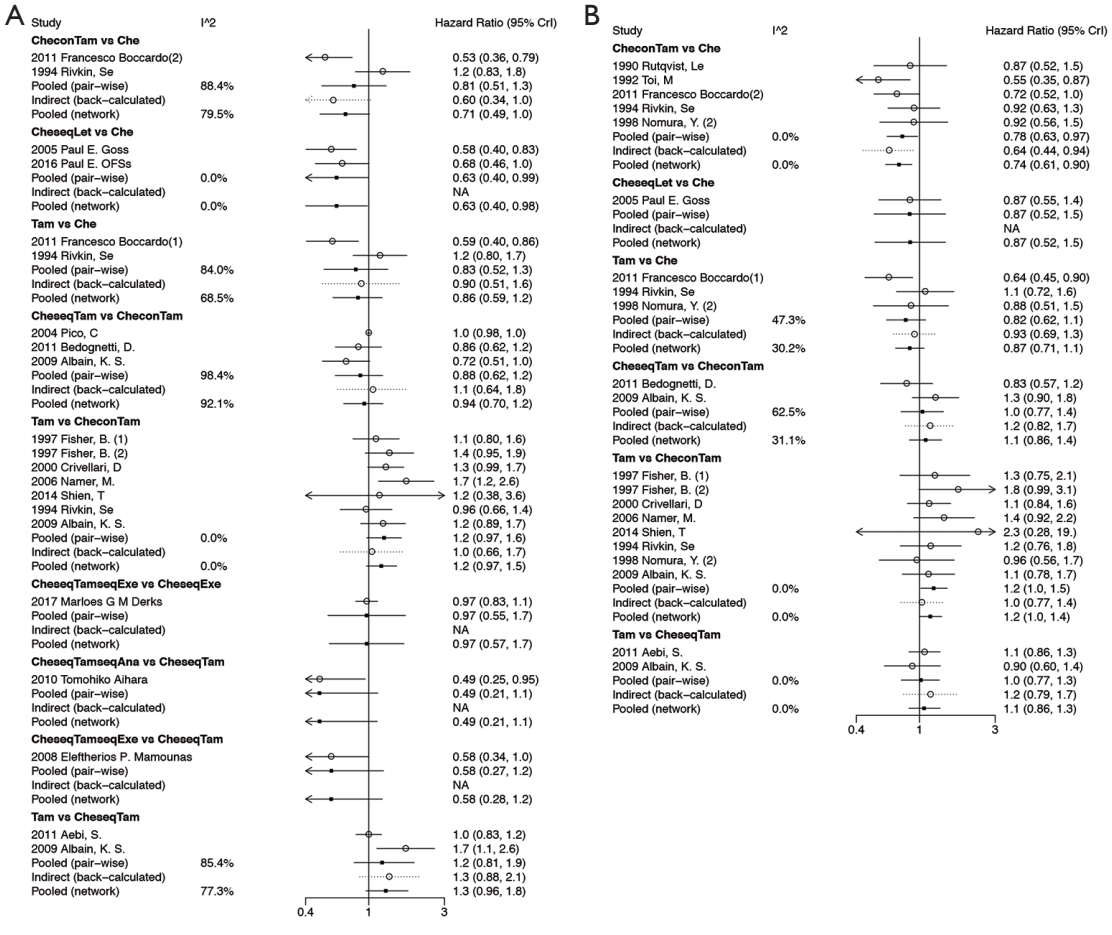

Figure S7 Heterogeneity of comparisons between treatment arms in overall survival (OS) analyses. Heterogeneity of comparisons between treatment arms enrolled in (A) in the OS analysis of premenopausal patients; (B) in the OS analysis of postmenopausal patients. I^2=0% means no heterogeneity; I^2>25% indicates mild heterogeneity; I^2>50% indicates moderate heterogeneity; I^2>75%, it indicates high heterogeneity.

https://dx.doi.org/10.21037/tbcr-21-3

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