

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomized trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035802
Article Type:	Protocol
Date Submitted by the Author:	16-Nov-2019
Complete List of Authors:	Hu, Qiancheng Wang, Xing Chen, Ye Li, Xiaofen Luo, Ting; Sichuan University West China Hospital, Breast Medical Oncology, Clinical Research Center for Breast Cao, Dan; Sichuan University West China Hospital,
Keywords:	Breast tumours < ONCOLOGY, Gene therapy < ONCOLOGY, Pharmacology < TROPICAL MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 **Optimum duration of adjuvant trastuzumab in treatment of human**
5
6 epidermal growth factor receptor-2 positive **early breast cancer:**
7
8
9 **protocol for a network meta-analysis of randomized trials**
10

11
12
13 Qiancheng Hu^{1#}, Xin Wang^{1#}, Ye Chen¹, Xiaofen Li¹, Ting Luo^{2§}, Dan
14
15 Cao^{1§}
16

17
18 1 Department of Abdominal Oncology, Cancer Center, West China
19
20 Hospital, Sichuan University, Chengdu, China
21
22

23
24 2 Breast Medical Oncology, Clinical Research Center for Breast, West
25
26 China Hospital, Sichuan University, Chengdu, China.
27

28
29 *§Correspondence:* Email: caodan316@163.com. tina621@163.com. West
30
31 China Hospital, Sichuan University, No. 37 Guo Xue Xiang, Chengdu
32
33 610041, China.
34

35
36 # These authors are joint first authors
37

38
39 Email: Qiancheng Hu hqch860109@163.com
40

41
42 Xin Wang 31485062@qq.com
43

44
45 Ye Chen 313042032@qq.com
46

47
48 Xiaofen Li 853767554@qq.com
49

50
51 Ting Luo tina621@163.com
52

53
54 Dan Cao caodan316@163.com
55
56
57
58
59

60 **Abstract**

1
2
3
4 **Introduction:** Controversy regarding optimum duration of trastuzumab
5
6 treatment remains in patients with human epidermal growth factor
7
8 receptor-2 (HER2) positive early breast cancer. Our purpose of this
9
10 network meta-analysis (NMA) is to synthesize all available evidence
11
12 based on direct and indirect comparisons of efficacy and safety to identify
13
14 the duration of trastuzumab treatments with the greatest value in HER2
15
16 positive early breast cancers.
17
18
19
20

21
22 **Methods and analysis:** Electronic searches of titles/abstracts of
23
24 trastuzumab treatments for early breast cancers will be performed, using
25
26 PubMed, Cochrane Library, Embase and ClinicalTrials.gov from inception
27
28 to June 16, 2019, as well as the annual meetings of San Antonio Breast
29
30 Cancer Symposium (SABCS), European Society of Medical Oncology
31
32 (ESMO) and American Society of Clinical Oncology (ASCO) online
33
34 archives. The outcomes of interest are overall survival, disease-free
35
36 survival, acceptability, cardiotoxicities and grade 3-4 nonhematologic
37
38 toxicities. Two independent reviewers will screen and extract eligible
39
40 data based on the inclusion and exclusion criteria, and then assess the risk
41
42 of bias and quality of evidence of individual study using Cochrane
43
44 Collaboration's tool and GRADE (Grades of Recommendation,
45
46 Assessment, Development and Evaluation), respectively. The
47
48 heterogeneity, transitivity and inconsistency of NMA will be assessed.
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 We will plan subgroup and sensitivity analyses to assess the robustness
5
6 and reliability of findings in our NMA.
7
8

9 **Ethics and dissemination:** This study synthesizes the evidence regarding
10 optimum duration of trastuzumab treatment in patients with HER2
11 positive early breast cancer. We hope the findings from our study will
12 help clinicians to reduce the uncertainty of escalating and de-escalating
13 duration treatment and select optimum duration of trastuzumab treatment
14 with the most value in terms of efficacy and safety. Findings from our
15 NMA will be disseminated through international conference reports and a
16 peer-reviewed journal.
17
18
19
20
21
22
23
24
25
26
27
28

29
30 Ethics approval is not required for our NMA.
31

32 **Strengths and limitations of this study**

33

- 34
35 ■ Our purpose of this NMA is to synthesize all available evidence based
36 on direct and indirect comparisons of efficacy and safety to identify
37 the duration of trastuzumab treatments with the greatest value in
38 HER2 positive early breast cancers.
39
40
41
42
43
44
- 45 ■ We hope the findings from our study will help clinicians to reduce the
46 uncertainty of escalating and de-escalating duration treatment and
47 select optimum duration of trastuzumab treatment with the most value
48 in terms of efficacy and safety.
49
50
51
52
53
54
- 55 ■ We will plan subgroup and sensitivity analyses to assess the
56 robustness and reliability of findings in our NMA.
57
58
59
60

- 1
2
3
4 ■ The limitations of our study might be related to language bias, due to
5
6 this NMA will only include studies published in English.
7
8

9 Trial registration number CRD42019139109
10

11 Keywords: early breast cancer, human epidermal growth factor
12
13 receptor-2, trastuzumab, network meta-analysis, protocol
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52

53 Introduction 54 55 56 57 58 59 60

1
2
3
4 Human epidermal growth factor receptor-2 (HER2) positive breast cancer
5
6 accounts for approximately 20–25% of overall reported cases^{1 2} and is
7
8 correlated with poor prognosis.^{3 4} Trastuzumab, a monoclonal antibody
9
10 targeting the extracellular domain of the HER2 protein, is indicated for
11
12 use in patients with HER2-positive early breast cancer.⁵⁻⁷ At present, a
13
14 1-year of trastuzumab for targeted therapy has been proven to
15
16 significantly improve overall survival (OS) and disease-free survival
17
18 (DFS) in early HER2-positive breast cancer.⁸⁻¹¹

19
20
21
22
23
24
25 However, the optimal duration of trastuzumab treatment is an intense
26
27 controversy and ongoing debate area in terms of efficacy, toxicity,
28
29 convenience and cost.¹² Nevertheless, a considerable gap exists in the
30
31 current literature. High-quality randomised controlled trials (RCTs)
32
33 confirmed that multiple treatment durations of trastuzumab were effective
34
35 treatments for HER2-positive early breast cancers, but not all
36
37 head-to-head trials were performed to evaluate relative efficacy and
38
39 safety. The HERceptin Adjuvant (HERA) trial confirmed that 24 months
40
41 of adjuvant trastuzumab did not improve DFS compared with 12 months
42
43 of adjuvant therapy [hazard ratio (HR) 1.02, 95% confidence intervals
44
45 (CI) 0.89–1.17], at a higher cost, inconvenience and cardiac toxicity
46
47 (7.3% vs 4.4%).¹³ On the contrary, six months of this drug was
48
49 non-inferior and decreased cardiac toxicity (8% vs 4%, $P<0.001$) in the
50
51 PERSEPHONE trial, but the results were not shown as non-inferior in the
52
53
54
55
56
57
58
59
60

1
2
3
4 PHARE and HORG trials compared with 12 months of trastuzumab
5
6 treatment.¹⁴⁻¹⁶ Differently, the SOLD and Short-HER trials conducted that
7
8 nine weeks of trastuzumab was not non-inferior to 12 months of
9
10 trastuzumab, but a significant reduction in cardiac toxicity was observed
11
12 with nine weeks of trastuzumab.^{17 18}
13
14
15

16
17 As mentioned above, there was a little direct comparison among
18
19 preventive strategies due in part to half of RCTs including N9831,
20
21 NSABP-B31, BCIRG 006 and FinHER trials compared active therapy to
22
23 inactive interventions (e.g., placebo).^{10 11 19} Several pivotal pairwise
24
25 meta-analyses evaluated the direct efficacy and toxicity between shorter
26
27 durations of trastuzumab and standard option, and addressed that 12
28
29 months of trastuzumab was still considered the optimal treatment for
30
31 early HER2-positive breast cancer, with a significant increase in cardiac
32
33 events.^{12 20-23}
34
35
36
37
38
39

40 These intriguing results sparked a heated debate about whether
41
42 escalating and de-escalating duration treatment can be considered new
43
44 standard of care. Network meta-analysis (NMA) has indirectly evaluated
45
46 relative efficacy and toxicity of multiple durations of adjuvant
47
48 trastuzumab therapies in HER2-positive early breast cancer. To address
49
50 the aforementioned debate problems and provide the best available
51
52 treatments, our purpose of this NMA is to synthesize all available
53
54 evidence based on direct and indirect comparisons of efficacy and safety
55
56
57
58
59
60

1
2
3
4 to identify the duration of trastuzumab treatments (24 months vs 12
5
6 months vs 6 months vs 12 weeks vs 9 weeks vs placebo) with the greatest
7
8 value in HER2 positive early breast cancers.
9

10 11 **Methods**

12
13
14 The results of our protocol will be evaluated in line with the
15
16 PRISMA-P (Preferred Reporting Items for Systematic Reviews and
17
18 Meta-Analyses Protocols).²⁴ Similarly, we will perform this NMA with
19
20 the methods guided by the PRISMA Extension Statement for Reporting
21
22 of Systematic Reviews Incorporating Network Meta-Analyses of Health
23
24 Care Interventions.²⁵ The project has been registered in PROSPERO
25
26 (CRD42019139109).
27
28
29
30
31

32 33 **Search strategy**

34
35 Electronic searches of titles/abstracts of trastuzumab treatments for
36
37 early breast cancers will be performed, using PubMed, Cochrane Library,
38
39 Embase (Ovid interface) and ClinicalTrials.gov, as well as the annual
40
41 meetings of San Antonio Breast Cancer Symposium (SABCS)
42
43 (2015-2019), European Society of Medical Oncology (ESMO) and
44
45 American Society of Clinical Oncology (ASCO) online archives until
46
47 June 16, 2019. Additional RCTs related to the topic will be included after
48
49 their publication. Two reviewers who have been trained in data extraction
50
51 will independently conduct search strategies. The same two authors will
52
53 manually search reference lists from eligible reviews and relevant trials to
54
55
56
57
58
59
60

1
2
3
4 identify additional potential studies. We will record the reason for
5
6 excluding the full text and generate a PRIMSA flow diagram for the
7
8
9 NMA.²⁶

10
11 The search terms will include the following domains of Medical
12
13 Subject Heading (MeSH) terms: 'breast cancer', 'human epidermal
14
15 growth factor receptor-2' and 'trastuzumab', according to PICOS
16
17 (Population Intervention Comparison Outcomes Study Design) statement.
18
19 MeSH and Subheadings were combined with 'AND' or 'OR'. The
20
21 complete search strategy is presented in online supplementary file 1 (see
22
23 the appendix 1).
24
25
26
27
28

29
30 We will perform a pilot test to evaluate inter-rater reliability and adjust
31
32 each screening stage: title and abstract, followed by full-text screening.
33
34 Two independent reviewers will screen the titles/abstracts of related
35
36 studies based on an inclusion and exclusion criteria. The eligible or
37
38 potentially eligible trials will be assessed by reading through the full texts
39
40 when necessary. Moreover, disagreements in data extraction will be
41
42 resolved via having a discussion, with the help of the third reviewer.
43
44
45
46
47

48 **Eligibility criteria**

49
50 Trials will be eligible if they adhere to the following criteria: 1.
51
52 Populations: HER2-positive early breast cancer of any age or nationality,
53
54 treated with trastuzumab treatments; 2. Interventions: Any duration of
55
56 trastuzumab treatments being given. We are also interested in the impact
57
58
59
60

1
2
3
4 of placebo/observation as adjuvant treatment; 3. Comparators: all eligible
5
6 interventions with one another; 4. Outcomes: OS, DFS, acceptability, and
7
8 cardiotoxicities and grade 3-4 nonhematologic toxicities; 5. Study design:
9
10 RCTs that compared any two or more different arms of adjuvant
11
12 trastuzumab in patients with HER2-positive early breast cancer; 6.
13
14 Language and other limitations: We will include studies published in
15
16 English without date limited.
17
18
19
20
21

22 Studies not meet the inclusion criteria will be excluded. The other
23
24 excluding criteria are as follows: 1. neoadjuvant and adjuvant treatment
25
26 with trastuzumab biosimilars; 2. Palliative care with trastuzumab; 3.
27
28 Retrospective and prospective cohort studies.
29
30
31

32 **Outcomes**

33
34
35 The outcomes of interest are OS (defined as the time from
36
37 randomization to death from any cause), DFS (defined as the time from
38
39 randomization to local, regional, distant relapse, contralateral breast
40
41 cancer, second primary cancer, or death from any cause, whichever
42
43 occurred first), acceptability (defined as the proportion of patients who
44
45 discontinued trastuzumab), and cardiotoxicities and grade 3-4
46
47 nonhematologic toxicities. The cardiac toxicity grading is used by the
48
49 Common Terminology Criteria for Adverse Events of the National
50
51 Cancer Institute. Cardiac toxicity is defined as an asymptomatic decline
52
53 in left ventricular ejection fraction (LVEF) to $\leq 45\%$, an absolute drop of
54
55
56
57
58
59
60

1
2
3
4 10-15% in follow-up echocardiography, symptomatic congestive heart
5
6 failure (New York Heart Association [NYHA] class III/IV) or cardiac
7
8 death.^{27 28} We will calculate the relative effectiveness for each network
9
10 comparison among all duration of treatments with trastuzumab.²⁹
11
12

13 **Data extraction and management**

14
15
16
17 The management of literature search records will be carried out in
18
19 EndNote X7. A spreadsheet will be created in Microsoft Excel 2010
20
21 (Microsoft Corp, Redmond, WA, www.microsoft.com) to collect
22
23 outcomes of interest, such as, study ID, first author, study design,
24
25 recruitment time frame, detailed interventions, sample size, and endpoints
26
27 (OS, DFS, acceptability, cardiotoxicities and grade 3-4 nonhematologic
28
29 toxicities). We will attempt to contact study authors and relevant
30
31 pharmaceutical companies if important data are not reported. If duplicate
32
33 publications are identified, the update data will be included.
34
35
36
37
38
39

40 **Bias risk**

41
42
43 According to the following domains outlined in the Cochrane
44
45 Collaboration's tool, for the risk of bias of RCTs in the NMA the
46
47 following domains will be evaluated in Review Manager (version 5.3):³⁰
48
49 random sequence generation, allocation concealment, blinding of
50
51 participants and personnel, incomplete outcome data, selective outcome
52
53 reporting, and other bias. Two authors will independently review RCTs
54
55 and report a high risk of bias “-”, a low risk of bias “+”, or an unclear risk
56
57
58
59
60

of bias “?”. Any disagreements in assessment of risk of bias will be resolved by discussion, or the help of the third reviewer if needed.

Quality of evidence

We will assess the quality of evidence of individual study using GRADE (Grades of Recommendation, Assessment, Development and Evaluation), which is based on the following five domains: risk of bias, imprecision, inconsistency, indirectness and publication bias.^{31 32} The staging system categorizes for GRADE evidence are scored as high, moderate, low or very low quality. The initial confidence level for each RCT is high, but will be rated down based on the evaluation of the five domains. The strength of evidences will be graded for the outcomes based on GRADE system in CINeMA.

Statistical analysis

We will perform the traditional pairwise meta-analysis on direct comparisons based on two or more studies with Stata13.0 (StataCorp, College Station, TX, USA). To directly and indirectly compare between any eligible interventions, NMA for outcomes of interest is planned using WinBUGS version1.4.3 (MRC Biostatistics Unit, Cambridge, UK).

Results regarding the OS and DFS are calculated HR with 95% confidence intervals CI. Binary outcomes (acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities) are expressed as odds ratios (ORs) with 95% CI. The results of probability statements of intervention

1
2
3
4 effects will be ranked. The interventions with surface under the
5
6 cumulative ranking (SUCRA) of being the most effective in term of
7
8 efficacy and safety will be evaluated to interpretation of relative effect of
9
10 comparisons. The benefit-risk analysis of efficacy and toxicity within
11
12 each comparison will also be completed. Two sided $P < 0.05$ is
13
14 considered significant.
15
16
17
18

19 We will estimate the presence of heterogeneity based on the magnitude
20
21 of I^2 estimated from pairwise meta-analysis models. If $I^2 < 25\%$, the
22
23 heterogeneity is assessed as evidence of low; as moderate if $25\% \leq I^2 \leq$
24
25 50% ; as high if $I^2 > 50\%$.³³ When the heterogeneity is low, the fix effect
26
27 model will be used; otherwise, a random effect model will be used. In
28
29 addition, we will also evaluate the transitivity and inconsistency of NMA,
30
31 respectively. The transitivity will be assessed by use of descriptive
32
33 statistics for study types and demographic characteristics. Both fixed and
34
35 random effects models will be run. Inconsistency will be assessed by
36
37 comparing deviation information criteria (DIC) statistics in the fitted
38
39 consistency and inconsistency models.³⁴ Global inconsistency between
40
41 direct and indirect comparisons will also be evaluated by using a
42
43 loop-specific method, if a loop connecting three or more arms exists.³⁵
44
45
46
47
48
49
50
51

52 53 **Subgroup analysis**

54 We will explore whether a particular subtypes of breast cancer might
55
56 be more appropriate for specific duration treatments with trastuzumab.
57
58
59
60

1
2
3
4 We still stratify breast cancer into the following groups when possible:
5
6 Estrogen Receptor (ER) positive, ER negative, node positive and node
7
8 negative. The subgroup analyses will be conducted regardless of
9
10 heterogeneity estimates.
11
12

13 **Sensitivity analysis**

14
15
16 We will plan sensitivity analyses to assess the robustness and reliability
17
18 of findings in our NMA. In order to check the impact of HER2 status on
19
20 the results, the first analysis will exclude patients with HER2 negative
21
22 after re-evaluating the HER2 status in the E2198 trial.³⁶ The second
23
24 sensitivity analysis will restrict hormone receptor-positive (ER + and PR
25
26 +, ER + and PR -, ER - and PR+). Lastly, the sensitivity analysis will
27
28 stratify patients as 1-3 and ≥ 4 positive lymph nodes to observe the impact
29
30 of the number of positive lymph node.
31
32
33
34
35
36

37 **Discussion**

38
39
40 Despite highly effective in treatment with trastuzumab for HER2-
41
42 positive early breast cancer, substantial socio-economic burden and
43
44 cardiotoxicity attracted the attention of governments, academic
45
46 researchers, pharmaceutical companies and health care payers. The
47
48 trade-offs between efficacy and cardiotoxicity were considerable. Most
49
50 clinicians deemed that 83% four-year DFS with six months trastuzumab
51
52 is acceptable.³⁷ This benefit-risk analysis is important information to help
53
54 clinicians and patients choose optimum duration of adjuvant treatment
55
56
57
58
59
60

1
2
3
4 with trastuzumab in their daily practice.
5

6 The 12 months of treatments with trastuzumab for most women with
7 early HER2 positive breast cancer was standard of care, but most crucial
8 RCTs mainly focused on patients with high-risk of recurrence and the
9 1-year duration was chosen arbitrarily. In contrary, a particular subtype of
10 patients might be appropriate for de-escalating duration treatment,
11 without compromise of their efficacy. Romualdo and his colleagues
12 deemed that de-escalating chemotherapy was candidate for older and
13 stages I HER2-positive breast cancer.³⁸ This study will explore whether
14 de-escalating targeted therapy is another option of for patients with
15 particular subtypes (ER positive and node negative).
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

32 As far as we know, the results of system review will fill a pivotal
33 knowledge gap of optimal duration of adjuvant trastuzumab in patients
34 with early HER2 positive breast cancer. We hope the findings from this
35 NMA will help clinicians and patients select optimal duration of adjuvant
36 trastuzumab with the greatest value in HER2 positive early breast
37 cancers. Additionally, currently under-recognized comparisons (e.g., 6
38 months vs 9 weeks) may be identified by this Bayesian analysis to guide
39 future researches.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Author affiliations

1 Department of Abdominal Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

2 Breast Medical Oncology, Clinical Research Center for Breast, West China Hospital, Sichuan University, Chengdu, China.

Acknowledgements

Thanks to Sun Feng and Wu Shanshan (PhD, Perking University School of public Health) for providing assistance and contributing to statistical analysis. (<https://class.dxy.cn/>)

Funding

The network meta-analysis was supported by the National Natural Science Foundation of China (Grant No.81773097).

Author contributions

QcH and DC conceptualized the network meta-analysis. QcH and XW co-developed the search strategy. Both QcH and XW were major contributors in writing the manuscript. The protocol was revised by DC, YC, XfL and TL. DC and TL were serving as guarantor and corresponding author of this study. All authors approved the final manuscript and agreed to submit the protocol in the journal.

Ethics approval and dissemination

Ethics review boards is not required for this network meta-analysis. The results will be disseminated through international conference reports and

1
2
3
4 peer-reviewed manuscripts.
5

6
7 Competing interests
8

9 All authors have completed the ICMJE uniform disclosure form at
10 http://www.icmje.org/coi_disclosure.pdf and stated that there is no
11 organization to support the submission; no organization is interested in
12 the submitted work; no other relationships or activities effect the
13 submitted work.
14
15
16
17
18
19
20
21

22 Provenance and peer review
23

24 Not commissioned; externally peer reviewed
25
26

27 Patient and public involvement
28

29 No patient involvement.
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References:

1. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;**235**:177-82.
2. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989;**244**:707-12.
3. Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature* 2012;**486**:346-52.
4. Dawson SJ, Rueda OM, Aparicio S, et al. A new genome-driven integrated classification of breast cancer and its implications. *EMBO J* 2013;**32**:617-28.
5. Yeon CH, Pegram MD. Anti-erbB-2 antibody trastuzumab in the treatment of HER2-amplified breast cancer. *Invest New Drugs* 2005;**23**:391-409.
6. Schaefer NG, Pestalozzi BC, Knuth A, et al. Potential use of humanized antibodies in the treatment of breast cancer. *Expert Rev Anticancer Ther* 2006;**6**:1065-74.
7. Tokunaga E, Oki E, Nishida K, et al. Trastuzumab and breast cancer: developments and current status. *Int J Clin Oncol* 2006;**11**:199-208.
8. Hortobagyi GN. Trastuzumab in the treatment of breast cancer. *N Engl J Med* 2005;**353**:1734-6.
9. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;**353**:1659-72.
10. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;**353**:1673-84.
11. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;**365**:1273-83.
12. Niraula S, Gyawali B. Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: a meta-analysis of randomized controlled trials. *Breast Cancer Res Treat* 2019;**173**:103-09.
13. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017;**389**:1195-205.
14. Earl HM, Hiller L, Vallier AL, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *Lancet* 2019;**393**:2599-612.
15. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol* 2013;**14**:741-8.
16. Mavroudis D, Saloustros E, Malamos N, et al. Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG). *Ann Oncol* 2015;**26**:1333-40.
17. Joensuu H, Fraser J, Wildiers H, et al. Effect of Adjuvant Trastuzumab for a Duration of 9 Weeks vs 1 Year With Concomitant Chemotherapy for Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: The SOLD Randomized Clinical Trial. *JAMA oncology* 2018;**4**:1199-206.
18. Conte P, Frassoldati A, Bisagni G, et al. Nine weeks versus 1 year adjuvant trastuzumab in combination with chemotherapy: final results of the phase III randomized Short-HER study double dagger. *Ann Oncol* 2018;**29**:2328-33.

19. Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. *J Clin Oncol* 2009;**27**:5685-92.
20. Chen L, Zhou W, Hu X, et al. Short-duration versus 1-year adjuvant trastuzumab in early HER2 positive breast cancer: A meta-analysis of randomized controlled trials. *Cancer treatment reviews* 2019;**75**:12-19.
21. Inno A, Barni S, Ghidini A, et al. One year versus a shorter duration of adjuvant trastuzumab for HER2-positive early breast cancer: a systematic review and meta-analysis. *Breast Cancer Res Treat* 2019;**173**:247-54.
22. Gyawali B, Niraula S. Duration of adjuvant trastuzumab in HER2 positive breast cancer: Overall and disease free survival results from meta-analyses of randomized controlled trials. *Cancer treatment reviews* 2017;**60**:18-23.
23. Goldvaser H, Korzets Y, Shepshelovich D, et al. Deescalating Adjuvant Trastuzumab in HER2-Positive Early-Stage Breast Cancer: A Systemic Review and Meta-Analysis. *JNCI Cancer Spectr* 2019;**3**:pkz033.
24. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;**4**:1.
25. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;**162**:777-84.
26. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.
27. Russell SD, Blackwell KL, Lawrence J, et al. Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. *J Clin Oncol* 2010;**28**:3416-21.
28. Yu AF, Singh JC, Wang R, et al. Cardiac Safety of Dual Anti-HER2 Therapy in the Neoadjuvant Setting for Treatment of HER2-Positive Breast Cancer. *Oncologist* 2017;**22**:642-47.
29. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. *Res Synth Methods* 2012;**3**:80-97.
30. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.
31. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;**336**:924-6.
32. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network meta-analysis. *PLoS One* 2014;**9**:e99682.
33. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**:557-60.
34. Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. *Med Decis Making* 2013;**33**:641-56.
35. Veroniki AA, Vasiliadis HS, Higgins JP, et al. Evaluation of inconsistency in networks of interventions. *Int J Epidemiol* 2013;**42**:332-45.
36. Schneider BP, O'Neill A, Shen F, et al. Pilot trial of paclitaxel-trastuzumab adjuvant therapy for

1
2
3 early stage breast cancer: a trial of the ECOG-ACRIN cancer research group (E2198). Br J Cancer
4 2015;**113**:1651-7.

5
6 37. Hiller L, Dunn JA, Loi S, et al. Adjuvant trastuzumab duration trials in HER2 positive breast cancer -
7 what results would be practice-changing? Persephone investigator questionnaire prior to primary
8 endpoint results. BMC Cancer 2018;**18**:391.

9
10 38. Barroso-Sousa R, Exman P, Tolaney SM. De-escalating treatment in the adjuvant setting in
11 HER2-positive breast cancer. Future oncology (London, England) 2018;**14**:937-45.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 A sample Pubmed search strategy was as follows:
5

6 #1 Breast Neoplasm [MeSH Terms]
7

8 #2 breast neoplasm [title/abstract]
9

10 #3 neoplasm, breast [title/abstract]
11

12 #4 breast tumors [title/abstract]
13

14 #5 breast tumor [title/abstract]
15

16 #6 tumor, breast [title/abstract]
17

18 #7 tumors, breast [title/abstract]
19

20 #8 neoplasms, breast [title/abstract]
21

22 #9 breast cancer [title/abstract]
23

24 #10 cancer, breast [title/abstract]
25

26 #11 mammary cancer [title/abstract]
27

28 #12 cancer, mammary [title/abstract]
29

30 #13 cancers, mammary [title/abstract]
31

32 #14 mammary cancers [title/abstract]
33

34 #15 malignant neoplasm of breast [title/abstract]
35

36 #16 breast malignant neoplasm [title/abstract]
37

38 #17 breast malignant neoplasms [title/abstract]
39

40 #18 malignant tumor of breast [title/abstract]
41

42 #19 breast malignant tumor [title/abstract]
43

44 #20 cancer of breast [title/abstract]
45

46 #21 cancer of the breast [title/abstract]
47

48 #22 mammary carcinoma, human [title/abstract]
49

50 #23 carcinoma, human mammary [title/abstract]
51

52 #24 carcinomas, human mammary [title/abstract]
53

54 #25 human mammary carcinomas [title/abstract]
55

56 #26 mammary carcinomas, human [title/abstract]
57

58 #27 human mammary carcinoma [title/abstract]
59
60

- 1
- 2
- 3
- 4 #28 mammary neoplasms, human [title/abstract]
- 5 #29 human mammary neoplasms [title/abstract]
- 6 #30 human mammary neoplasms [title/abstract]
- 7 #31 neoplasm, human mammary [title/abstract]
- 8 #32 neoplasms, human mammary [title/abstract]
- 9 #33 mammary neoplasm, human [title/abstract]
- 10 #34 breast carcinoma [title/abstract]
- 11 #35 breast carcinomas [title/abstract]
- 12 #36 carcinoma, breast [title/abstract]
- 13 #37 carcinomas, breast [title/abstract]
- 14 #38 breast malignant tumors [title/abstract]
- 15 #39 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR
- 16 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR
- 17 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR
- 18 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR
- 19 #34 OR #35 OR #36 OR #37 OR #38
- 20 #40 Genes, erbB-2[MeSH Terms]
- 21 #41 c-erbB-2 Genes[Title/Abstract]
- 22 #42 c erbB 2 Genes[Title/Abstract]
- 23 #43 c-erbB-2 Gene[Title/Abstract]
- 24 #44 Genes, erbb2[Title/Abstract]
- 25 #45 Gene, erbb2[Title/Abstract]
- 26 #46 erbb2 Gene[Title/Abstract]
- 27 #47 erbb2 Genes[Title/Abstract]
- 28 #48 Genes, HER-2[Title/Abstract]
- 29 #49 HER-2 Gene[Title/Abstract]
- 30 #50 HER-2 Genes[Title/Abstract]
- 31 #51 Genes, neu[Title/Abstract]
- 32 #52 neu Gene[Title/Abstract]
- 33
- 34
- 35
- 36
- 37
- 38
- 39
- 40
- 41
- 42
- 43
- 44
- 45
- 46
- 47
- 48
- 49
- 50
- 51
- 52
- 53
- 54
- 55
- 56
- 57
- 58
- 59
- 60

1
2
3 #53 neu Genes[Title/Abstract]
4
5 #54 Genes, HER2[Title/Abstract]
6
7 #55 Gene, HER2[Title/Abstract]
8
9 #56 HER2 Gene[Title/Abstract]
10
11 #57 HER2 Genes[Title/Abstract]
12
13 #58 erbB-2 Genes[Title/Abstract]
14
15 #59 erbB 2 Genes[Title/Abstract]
16
17 #60 erbB-2 Gene[Title/Abstract]
18
19 #61 c-erbB-2 Proto-Oncogenes[Title/Abstract]
20
21 #62 c erbB 2 Proto Oncogenes[Title/Abstract]
22
23 #63 c-erbB-2 Proto-Oncogene[Title/Abstract]
24
25 #64 #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
26
27 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
28
29 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63
30
31 #65 Trastuzumab[MeSH Terms]
32
33 #66 Herceptin[Title/Abstract]
34
35 #67 #65 OR #66
36
37 #68 #39 AND #64 AND #67
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

only

BMJ Open

Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomized trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035802.R1
Article Type:	Protocol
Date Submitted by the Author:	30-Jun-2020
Complete List of Authors:	Hu, Qiancheng; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Wang, Xin; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Chen, Ye; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Li, Xiaofen; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Luo, Ting; Sichuan University West China Hospital, Breast Medical Oncology, Clinical Research Center for Breast Cao, Dan; Sichuan University West China Hospital,
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	Breast tumours < ONCOLOGY, Gene therapy < ONCOLOGY, Pharmacology < TROPICAL MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 Optimum duration of adjuvant trastuzumab in treatment of human
5
6 epidermal growth factor receptor-2 positive early breast cancer: protocol
7
8 for a network meta-analysis of randomized trials
9
10

11
12
13 Qiancheng Hu^{1#}, Xin Wang^{1#}, Ye Chen¹, Xiaofen Li¹, Ting Luo^{2§}, Dan
14
15 Cao^{1§}
16

17
18 1 Department of Abdominal Oncology, Cancer Center, West China
19
20 Hospital, Sichuan University, Chengdu, China
21
22

23
24 2 Breast Medical Oncology, Clinical Research Center for Breast, West
25
26 China Hospital, Sichuan University, Chengdu, China.
27

28
29 *§Correspondence:* Email: caodan316@163.com. tina621@163.com. West
30
31 China Hospital, Sichuan University, No. 37 Guo Xue Xiang, Chengdu
32
33 610041, China.
34
35

36
37 # These authors are joint first authors
38

39
40 Email: Qiancheng Hu hqch860109@163.com

41
42 Xin Wang 449678106@qq.com

43
44 Ye Chen 313042032@qq.com

45
46 Xiaofen Li 853767554@qq.com

47
48 Ting Luo tina621@163.com

49
50 Dan Cao caodan316@163.com
51
52
53
54
55
56
57
58
59
60

Abstract

Introduction: Controversy regarding optimum duration of trastuzumab treatment remains in patients with human epidermal growth factor receptor-2 (HER2) positive early breast cancer. The objective of applying network meta-analysis (NMA) is to integrate existing evidence based on direct and indirect comparisons of efficacy and safety, and then to determine the duration of trastuzumab treatments with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

Methods and analysis: Electronic searching of trastuzumab treatments for early breast cancers by titles/abstracts will be conducted for the period from inception to June 16, 2019 using PubMed, Cochrane Library, Embase and ClinicalTrials.gov, as well as the annual meetings of San Antonio Breast Cancer Symposium (SABCS), European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) online archives. The outcomes of interest are overall survival, disease-free survival, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities. Two independent reviewers will screen and extract eligible data based on the inclusion and exclusion criteria, and then assess the risk of bias and evidence quality of individual studies using Cochrane Collaboration's tool and GRADE (Grades of Recommendation, Assessment, Development and Evaluation). The heterogeneity, transitivity and inconsistency of NMA will be evaluated.

1
2
3
4 We will also perform subgroup and sensitivity analyses to assess the
5
6 robustness and reliability of findings in our NMA.
7
8

9 **Ethics and dissemination:** Ethics approval is not required for our NMA.

10
11 This study will identify the evidence regarding optimum duration of
12
13 trastuzumab treatment in patients with HER2 positive early breast cancer.
14
15

16 We hope the findings from our study will help clinicians, patients and
17
18 policy makers to reduce the uncertainty of escalating and de-escalating
19
20 duration treatment and to select optimum duration of trastuzumab
21
22 treatment with the highest efficacy and safety. Findings from our NMA
23
24 will be submitted to peer-reviewed journal and international conference
25
26 reports.
27
28
29
30
31

32 **Strengths and limitations of this study**

- 33
34
35 ■ Our objective of applying NMA is to integrate existing evidence
36
37 based on direct and indirect comparisons of efficacy and safety, and
38
39 to determine the duration of trastuzumab treatments with the greatest
40
41 impact on therapeutic outcomes in HER2 positive early breast
42
43 cancers.
44
45
46
47
- 48 ■ Our study findings will help clinicians, patients and policy makers to
49
50 reduce the uncertainty of escalating and de-escalating duration
51
52 treatment and to select optimum duration of trastuzumab treatment
53
54 with highest efficacy and safety.
55
56
57
58
59
60

- 1
- 2
- 3
- 4 ■ We will perform subgroup and sensitivity analyses to assess the
- 5
- 6 robustness and reliability of NMA results.
- 7
- 8
- 9 ■ Language bias is the potential limitation of our study as NMA will
- 10
- 11 only include published studies in English.
- 12
- 13

14 Trial registration number CRD42019139109

15
16
17 Keywords: early breast cancer, human epidermal growth factor receptor-2,
18
19 trastuzumab, network meta-analysis, protocol
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Introduction

Human epidermal growth factor receptor-2 (HER2) positive breast cancer accounts for approximately 20–25% of overall reported cases(1,2) and is associated with poor prognosis.(3,4) Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, is used for patients with HER2-positive early breast cancer. (5-7) Recently, targeted therapy using one year of trastuzumab has been proven to improve overall survival (OS) and disease-free survival (DFS) significant in early HER2-positive breast cancer. (8-12)

However, the optimal duration of trastuzumab treatment has been an intense controversy and ongoing debate in terms of efficacy, toxicity, convenience and cost.(13) High-quality randomised controlled trials (RCTs) has confirmed that multiple treatment durations of trastuzumab were effective for HER2-positive early breast cancers, but the relative efficacy and safety were not evaluated for all head-to-head trials. More specifically, the HERceptin Adjuvant (HERA) trial has confirmed that 24 months of adjuvant trastuzumab, which was associated with a higher cost and cardiac toxicity, would not improve DFS compared to 12 months of adjuvant therapy [hazard ratio (HR) 1.02, 95% confidence intervals (CI) 0.89–1.17], at a higher cost, inconvenience and cardiac toxicity (7.3% vs 4.4%). (14) While comparing to the 12 months of trastuzumab treatment,

1
2
3
4 six months of trastuzumab treatment was non-inferior and associated with
5
6 decreased cardiac toxicity (8% vs 4%, $P<0.001$) in the PERSEPHONE
7
8 trial, but was not non-inferior in the PHARE and HORG trials(15-17). In
9
10 contrast, the SOLD and Short-HER trials applying nine weeks of
11
12 trastuzumab was not non-inferior compared to the 12 months of
13
14 trastuzumab, and a significant reduction in cardiac toxicity was observed
15
16 in nine weeks of trastuzumab. (18,19)
17
18
19
20
21

22 Direct comparison among preventive strategies was limited as half of
23
24 RCTs, including N9831, NSABP-B31, BCIRG 006 and FinHER trials,
25
26 were comparing active therapy to inactive interventions (e.g.,
27
28 placebo). (10,11,20) Pivotal pairwise meta-analyses have been used to
29
30 evaluate the efficacy and toxicity between shorter durations of
31
32 trastuzumab and standard option directly. The analyses results suggested
33
34 that 12 months of trastuzumab would still be the optimal treatment for
35
36 early HER2-positive breast cancer, albeit with a significant increase in
37
38 cardiac events. (13,21-24)
39
40
41
42
43
44

45 These intriguing results provoked a heated debate about whether
46
47 should consider escalating and de-escalating duration treatment as new
48
49 standard of care. Network meta-analysis (NMA) will provide indirect
50
51 evaluations on the relative efficacy and toxicity of multiple durations
52
53 of adjuvant trastuzumab therapies in HER2-positive early breast cancer.
54
55
56

57
58 (25) To address the aforementioned debate and determine the most
59
60

1
2
3
4 appropriate treatment options, we will conduct NMA to integrate existing
5
6 evidence available, based on direct and indirect comparisons of efficacy
7
8 and safety, and to determine the duration of trastuzumab treatments (24
9
10 months vs 12 months vs 6 months vs 12 weeks vs 9 weeks vs
11
12 placebo/observation/zero) with the greatest impact on therapeutic
13
14 outcomes in HER2 positive early breast cancers.
15
16
17
18

19 **Methods**

20
21 The results of our protocol will be evaluated in line with the
22
23 PRISMA-P (Preferred Reporting Items for Systematic Reviews and
24
25 Meta-Analyses Protocols).(26) Similarly, we will perform NMA in
26
27 guidance of the PRISMA Extension Statement for Reporting of
28
29 Systematic Reviews Incorporating Network Meta-Analyses of Health
30
31 Care Interventions. (27) This project has been registered in PROSPERO
32
33 (CRD42019139109).
34
35
36
37
38
39

40 **Search strategy**

41
42 Electronic searching by titles/abstracts of trastuzumab treatments for
43
44 early breast cancers will be performed using PubMed, Cochrane Library,
45
46 Embase (Ovid interface) and ClinicalTrials.gov, as well as the annual
47
48 meetings of San Antonio Breast Cancer Symposium (SABCS)
49
50 (2015-2019), European Society of Medical Oncology (ESMO) and
51
52 American Society of Clinical Oncology (ASCO) online archives until
53
54 June 16, 2019. Two reviewers who have been trained in data extraction
55
56
57
58
59
60

1
2
3
4 will conduct search strategies independently. The same two authors will
5
6 search reference lists manually from eligible reviews and relevant trials to
7
8 identify additional potential papers. We will record the reason of
9
10 excluding the full text and generate a PRISMA flow diagram for the
11
12
13
14 NMA. (28)

15
16
17 The terms used for literature searching will include the following
18
19 domains of Medical Subject Heading (MeSH) terms: ‘breast cancer’,
20
21 ‘human epidermal growth factor receptor-2’ and ‘trastuzumab’, according
22
23 to PICOS (Population Intervention Comparison Outcomes Study Design)
24
25 statement. MeSH and Subheadings will be combined with ‘AND’ or
26
27 ‘OR’. The complete search strategy is presented in online supplementary
28
29
30
31
32
33
34 file 1 (see the appendix 1).

35
36 We will perform a pilot test to evaluate inter-rater reliability and adjust
37
38 each screening stage: title and abstract, followed by full-text screening.
39
40 Two independent reviewers will screen the titles/abstracts of related
41
42 studies based on inclusion and exclusion criteria. The eligible or
43
44 potentially eligible trials will be evaluated by reading through the full
45
46 texts when necessary. Moreover, disagreements in data extraction will be
47
48 discussed with the help of the third reviewer.
49
50
51

52 53 **Eligibility criteria**

54
55
56 Trials will be eligible if they adhere to the following criteria: 1.
57
58 Populations: patients with HER2-positive early breast cancer of any age
59
60

1
2
3
4 or nationality were treated with trastuzumab treatments; 2. Interventions:
5
6 any duration of trastuzumab treatments were given. We are also interested
7
8 in the impact of placebo/observation/zero as adjuvant treatment; 3.
9
10 Comparators: 12 months of trastuzumab treatment was compared with
11
12 placebo/observation/zero, or other durations of adjuvant trastuzumab; 4.
13
14 Outcomes: OS, DFS, acceptability, and cardiotoxicities and grade 3-4
15
16 nonhematologic toxicities; 5. Study design: RCTs that compared any two
17
18 or more different arms of adjuvant trastuzumab in patients with
19
20 HER2-positive early breast cancer; 6. Language and other limitations: We
21
22 will include studies published in English regardless of publication status.
23
24
25
26
27
28
29

30 Studies not meeting the inclusion criteria will be excluded. The other
31
32 excluding criteria are as follows: 1. Neoadjuvant and adjuvant treatment
33
34 with trastuzumab biosimilars; 2. Palliative care with trastuzumab; 3.
35
36 Non-randomised studies, such as prospective cohort studies.
37
38
39

40 **Outcomes**

41
42 The outcomes of interest are OS (defined as the time from
43
44 randomization to death from any cause), DFS (defined as the time from
45
46 randomization to local, regional, distant relapse, contralateral breast
47
48 cancer, second primary cancer, or death from any cause, whichever
49
50 occurred first), acceptability (defined as the proportion of patients who
51
52 discontinued trastuzumab), cardiotoxicities, and grade 3-4
53
54 nonhematologic toxicities. The cardiac toxicity grading is used by the
55
56
57
58
59
60

1
2
3
4 Common Terminology Criteria for Adverse Events of the National
5
6 Cancer Institute. Cardiac toxicity is defined as an asymptomatic decline
7
8 in left ventricular ejection fraction (LVEF) to $\leq 45\%$, an absolute drop of
9
10 in left ventricular ejection fraction (LVEF) to $\leq 45\%$, an absolute drop of
11
12 10-15% in follow-up echocardiography, symptomatic congestive heart
13
14 failure (New York Heart Association [NYHA] class III/IV) or cardiac
15
16 death.(29,30) We will calculate the relative effectiveness for each
17
18 network comparison among all duration of treatments with trastuzumab.
19
20
21
22 (31)

23 24 **Data extraction and management**

25
26
27 The management of literature searching records will be carried out in
28
29 EndNote X7. A spreadsheet will be created in Microsoft Excel 2010
30
31 (Microsoft Corp, Redmond, WA, www.microsoft.com) to collect
32
33 outcomes of interest, such as study ID, first author, study design,
34
35 recruitment time frame, detailed interventions, sample size, and endpoints
36
37 (OS, DFS, acceptability, cardiotoxicities and grade 3-4 nonhematologic
38
39 toxicities). We will contact corresponding authors and relevant
40
41 pharmaceutical companies if important data are not reported. If duplicate
42
43 publications are identified, the most up-to-date data will be included.
44
45
46
47
48
49

50 51 **Bias risk**

52
53 The risk of bias of RCTs in the NMA will be evaluated by reviewer
54
55 manager according to the following domains outlined in the Cochrane
56
57 Collaboration's tool: random sequence generation, allocation
58
59
60

1
2
3
4 concealment, blinding of participants and personnel,
5
6 blinding of outcome assessment, incomplete outcome data, selective
7
8 reporting, and other bias(32). Two authors will review RCTs
9
10 independently and report a high risk of bias as “-”, a low risk of bias as
11
12 “+”, or an unclear risk of bias as “?”. Any disagreements in assessment of
13
14 risk of bias will be resolved by discussion, or the help of the third
15
16 reviewer if needed.
17
18
19
20
21

22 **Quality of evidence**

23
24 We will evaluate the quality of evidence of individual studies using
25
26 GRADE (Grades of Recommendation, Assessment, Development and
27
28 Evaluation), which is based on the following five domains: risk of bias,
29
30 imprecision, inconsistency, indirectness and publication bias(33,34). The
31
32 staging system categories for GRADE evidences are scored as high,
33
34 moderate, low or very low quality. The initial confidence level for each
35
36 RCT is set as high, but will be rated down based on the evaluation of the
37
38 five domains. The strength of evidences will also be
39
40 graded for the outcomes based on GRADE system in CINeMA. (34)
41
42
43
44
45
46
47

48 **Statistical analysis**

49
50 We will perform the traditional pairwise meta-analysis on direct
51
52 comparisons based on two or more studies with Stata13.0 (StataCorp,
53
54 College Station, TX, USA). To compare eligible interventions directly
55
56 and indirectly, NMA displaying outcomes of interest is planned using
57
58
59
60

1
2
3
4 WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).
5

6 Pooled hazard ratios (HRs) for OS and DFS with 95%
7
8 confidence intervals (CIs) will be calculated using both fixed- and
9
10 random-effects model. Binary outcomes (acceptability, cardiotoxicities
11
12 and grade 3-4 nonhematologic toxicities) are expressed as odds ratios
13
14 (ORs) with 95% CI. The results of comparative effectiveness and safety
15
16 probability statements of intervention effects will be ranked; and rank
17
18 plots across all outcomes will be generated. The interventions with
19
20 surface under the cumulative ranking (SUCRA) in term of efficacy and
21
22 safety will be evaluated to interpret relative effect of comparisons. We
23
24 will compare the risk-benefit profile of all comparators in terms of
25
26 efficacy and toxicity. Two sided $p < 0.05$ is considered significant.
27
28
29
30
31
32
33
34

35 We will estimate the presence of heterogeneity based on the magnitude
36
37 of I^2 estimated from pairwise meta-analysis models. If $I^2 < 25\%$, the
38
39 heterogeneity is considered as evidence of low; as moderate if $25\% \leq I^2 \leq$
40
41 50% ; as high if $I^2 > 50\%$. (35) The fixed- effects model will be used when
42
43 the heterogeneity is low; otherwise, a random- effects model will be used.
44
45 In addition, we will also evaluate the transitivity and inconsistency of
46
47 NMA. The transitivity will be assessed by using/applying descriptive
48
49 statistics for study types and demographic characteristics. Inconsistency
50
51 will be assessed by comparing deviation information criteria (DIC)
52
53 statistics in the fitted consistency and inconsistency models. (36) Global
54
55
56
57
58
59
60

1
2
3
4 inconsistency between direct and indirect comparisons will also be
5
6 evaluated by using a loop-specific method, if a loop connecting three or
7
8 more arms exists. (37)

11 **Subgroup analysis**

12
13
14 We will explore whether specific duration treatments with trastuzumab
15
16 might be more appropriate for particular subtypes of breast cancer. We
17
18 categorize breast cancer into the following groups when possible:
19
20

21 Estrogen Receptor (ER) positive, ER negative, node positive and node
22
23 negative.
24
25

27 **Sensitivity analysis**

28
29
30 We will perform sensitivity analyses to assess the robustness and
31
32 reliability of findings in our NMA. In order to check the impact of HER2
33
34 status on the results, the first sensitivity analysis will exclude patients
35
36 with HER2 negative after re-evaluating the HER2 status in the E2198
37
38 trial. (38) The second sensitivity analysis will restrict hormone
39
40 receptor-positive to ER + and PR +, ER + and PR -, ER - and PR + .
41
42
43 Lastly, the sensitivity analysis will classify patients as 1-3 and ≥ 4 positive
44
45 lymph nodes to specify the impact of the number of positive lymph
46
47 nodes.
48
49
50
51

53 **Ethics and dissemination**

54
55
56 Ethics approval is not required for our NMA. Despite trastuzumab
57
58 being highly effective in treatment for HER2-positive early breast cancer,
59
60

1
2
3
4 its substantial socio-economic burden attracted the attention of
5
6 governments, academic researchers, pharmaceutical companies and
7
8 health care payers. With the consideration of balancing efficacy and
9
10 cardiotoxicity, the 12-month and 6-month of durations of trastuzumab
11
12 treatments have received increasing interests. The perspective of
13
14 balancing efficacy and cardiotoxicity were heightened interest in
15
16 12-month and 6-month of durations of trastuzumab treatments.
17
18 Compared to the 12-month durations of trastuzumab treatments, most
19
20 clinicians suggested that a drop to 83% four-year DFS with six months
21
22 trastuzumab would be also acceptable. (39) This benefit-risk analysis will
23
24 provide important information to help clinicians, patients and policy
25
26 makers to choose optimum duration of adjuvant treatment with
27
28 trastuzumab in their daily practice.
29
30
31
32
33
34
35
36

37
38 The 12 months of treatments with trastuzumab for most women with
39
40 early HER2 positive breast cancer was standard of care, but the most
41
42 crucial RCTs mainly focused on patients with high-risk of recurrence and
43
44 the 1-year duration was chosen arbitrarily. In contrary, a particular
45
46 subtype of patients might be appropriate for de-escalating duration of
47
48 treatment, without compromising efficacy. Romualdo and his colleagues
49
50 deemed that de-escalating chemotherapy was a good candidate for older
51
52 patients and those with stage I HER2-positive breast cancer. (40) This
53
54 study will explore whether de-escalating targeted therapy is another
55
56
57
58
59
60

1
2
3
4 option for patients with particular subtypes (ER positive and node
5
6 negative).

7
8
9 As far as we know, the results of system review will fill a pivotal
10
11 knowledge gap of optimal duration of adjuvant trastuzumab in patients
12
13 with early HER2 positive breast cancer. We hope the findings from this
14
15 NMA will help clinicians, patients and policy makers to select optimal
16
17 duration of adjuvant trastuzumab with the greatest value in HER2
18
19 positive early breast cancers. It will also provide a result that will engage
20
21 patients and policy makers and contribute to the public debate about
22
23 future policy options. In addition, results from this academic study will
24
25 facilitate the discussion on the future policy options between patients and
26
27 policy makers. Furthermore, currently under-recognized comparisons
28
29 (e.g., 6 months vs 9 weeks) may be identified by this Bayesian analysis to
30
31 guide future research.
32
33
34
35
36
37
38
39

40 **Patient and public involvement**

41
42 The manuscript was developed without patient or public participation.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Author affiliations

1 Department of Abdominal Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

2 Breast Medical Oncology, Clinical Research Center for Breast, West China Hospital, Sichuan University, Chengdu, China.

Acknowledgements

Thanks to Sun Feng and Wu Shanshan (PhD, Perking University School of public Health) for providing assistance and contributing to statistical analysis. (<https://class.dxy.cn/>)

Thanks to Lu Guan (PhD, Fisheries Oceans Canada) for providing assistance and contributing to revisions.

Funding

The network meta-analysis was supported by the National Natural Science Foundation of China (Grant No.81773097).

Author contributions

QcH and DC conceptualized the network meta-analysis. QcH and XW co-developed the search strategy. Both QcH and XW were major contributors in writing the manuscript. The protocol was revised by DC, YC, XfL and TL. DC and TL were serving as guarantor and corresponding author of this study. All authors approved the final

1
2
3
4 manuscript and agreed to submit the protocol in the journal.
5

6
7 Ethics approval and dissemination
8

9 Ethics review boards is not required for this network meta-analysis. The
10
11 results will be disseminated through international conference reports and
12
13 peer-reviewed manuscripts.
14
15

16
17 Competing interests
18

19 All authors have completed the ICMJE uniform disclosure form at
20
21 http://www.icmje.org/coi_disclosure.pdf and stated that there is no
22
23 organization to support the submission; no organization is interested in
24
25 the submitted work; no other relationships or activities effect the
26
27 submitted work.
28
29
30

31
32 Provenance and peer review
33

34
35 Not commissioned; externally peer reviewed
36

37
38 Patient consent for publication
39

40 Not required.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References:

1. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177-82.
2. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989;244:707-12.
3. Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature* 2012;486:346-52.
4. Dawson SJ, Rueda OM, Aparicio S, et al. A new genome-driven integrated classification of breast cancer and its implications. *EMBO J* 2013;32:617-28.
5. Yeon CH, Pegram MD. Anti-erbB-2 antibody trastuzumab in the treatment of HER2-amplified breast cancer. *Invest New Drugs* 2005;23:391-409.
6. Schaefer NG, Pestalozzi BC, Knuth A, et al. Potential use of humanized antibodies in the treatment of breast cancer. *Expert Rev Anticancer Ther* 2006;6:1065-74.
7. Tokunaga E, Oki E, Nishida K, et al. Trastuzumab and breast cancer: developments and current status. *Int J Clin Oncol* 2006;11:199-208.
8. Hortobagyi GN. Trastuzumab in the treatment of breast cancer. *N Engl J Med* 2005;353:1734-6.
9. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659-72.
10. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673-84.
11. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273-83.
12. Genuino AJ, Chaikledkaew U, The DO, et al. Adjuvant trastuzumab regimen for HER2-positive early-stage breast cancer: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol* 2019;12:815-24.
13. Niraula S, Gyawali B. Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: a meta-analysis of randomized controlled trials. *Breast Cancer Res Treat* 2019;173:103-09.
14. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017;389:1195-205.
15. Earl HM, Hiller L, Vallier AL, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *Lancet* 2019;393:2599-612.
16. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol* 2013;14:741-8.
17. Mavroudis D, Saloustros E, Malamos N, et al. Six versus 12 months of adjuvant trastuzumab

- 1
2
3 in combination with dose-dense chemotherapy for women with HER2-positive breast cancer:
4 a multicenter randomized study by the Hellenic Oncology Research Group (HORG). *Ann*
5 *Oncol* 2015;26:1333-40.
- 6
7 18. Joensuu H, Fraser J, Wildiers H, et al. Effect of Adjuvant Trastuzumab for a Duration of 9
8 Weeks vs 1 Year With Concomitant Chemotherapy for Early Human Epidermal Growth Factor
9 Receptor 2-Positive Breast Cancer: The SOLD Randomized Clinical Trial. *JAMA oncology*
10 2018;4:1199-206.
- 11
12 19. Conte P, Frassoldati A, Bisagni G, et al. Nine weeks versus 1 year adjuvant trastuzumab in
13 combination with chemotherapy: final results of the phase III randomized Short-HER
14 studydouble dagger. *Ann Oncol* 2018;29:2328-33.
- 15
16 20. Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with
17 either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of
18 breast cancer: final results of the FinHer Trial. *J Clin Oncol* 2009;27:5685-92.
- 19
20 21. Chen L, Zhou W, Hu X, et al. Short-duration versus 1-year adjuvant trastuzumab in early HER2
21 positive breast cancer: A meta-analysis of randomized controlled trials. *Cancer treatment*
22 *reviews* 2019;75:12-19.
- 23
24 22. Inno A, Barni S, Ghidini A, et al. One year versus a shorter duration of adjuvant trastuzumab
25 for HER2-positive early breast cancer: a systematic review and meta-analysis. *Breast Cancer*
26 *Res Treat* 2019;173:247-54.
- 27
28 23. Gyawali B, Niraula S. Duration of adjuvant trastuzumab in HER2 positive breast cancer:
29 Overall and disease free survival results from meta-analyses of randomized controlled trials.
30 *Cancer treatment reviews* 2017;60:18-23.
- 31
32 24. Goldvaser H, Korzets Y, Shepshelovich D, et al. Deescalating Adjuvant Trastuzumab in
33 HER2-Positive Early-Stage Breast Cancer: A Systemic Review and Meta-Analysis. *JNCI Cancer*
34 *Spectr* 2019;3:pkz033.
- 35
36 25. Clarke CS, Hunter RM, Shemilt I, et al. Multi-arm Cost-Effectiveness Analysis (CEA) comparing
37 different durations of adjuvant trastuzumab in early breast cancer, from the English NHS
38 payer perspective. *PLoS One* 2017;12:e0172731.
- 39
40 26. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and
41 meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- 42
43 27. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of
44 systematic reviews incorporating network meta-analyses of health care interventions:
45 checklist and explanations. *Ann Intern Med* 2015;162:777-84.
- 46
47 28. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and
48 meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- 49
50 29. Russell SD, Blackwell KL, Lawrence J, et al. Independent adjudication of symptomatic heart
51 failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant
52 therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and
53 Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. *J Clin*
54 *Oncol* 2010;28:3416-21.
- 55
56 30. Yu AF, Singh JC, Wang R, et al. Cardiac Safety of Dual Anti-HER2 Therapy in the Neoadjuvant
57 Setting for Treatment of HER2-Positive Breast Cancer. *Oncologist* 2017;22:642-47.
- 58
59 31. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments
60 meta-analysis: many names, many benefits, many concerns for the next generation evidence

- 1
2
3 synthesis tool. *Res Synth Methods* 2012;3:80-97.
- 4 32. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk
5 of bias in randomised trials. *BMJ* 2011;343:d5928.
- 6
7 33. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of
8 evidence and strength of recommendations. *BMJ* 2008;336:924-6.
- 9
10 34. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network
11 meta-analysis. *PLoS One* 2014;9:e99682.
- 12
13 35. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*
14 2003;327:557-60.
- 15
16 36. Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 4: inconsistency in
17 networks of evidence based on randomized controlled trials. *Med Decis Making*
18 2013;33:641-56.
- 19
20 37. Veroniki AA, Vasiliadis HS, Higgins JP, et al. Evaluation of inconsistency in networks of
21 interventions. *Int J Epidemiol* 2013;42:332-45.
- 22
23 38. Schneider BP, O'Neill A, Shen F, et al. Pilot trial of paclitaxel-trastuzumab adjuvant therapy
24 for early stage breast cancer: a trial of the ECOG-ACRIN cancer research group (E2198). *Br J*
25 *Cancer* 2015;113:1651-7.
- 26
27 39. Hiller L, Dunn JA, Loi S, et al. Adjuvant trastuzumab duration trials in HER2 positive breast
28 cancer - what results would be practice-changing? Persephone investigator questionnaire
29 prior to primary endpoint results. *BMC Cancer* 2018;18:391.
- 30
31 40. Barroso-Sousa R, Exman P, Tolaney SM. De-escalating treatment in the adjuvant setting in
32 HER2-positive breast cancer. *Future oncology (London, England)* 2018;14:937-45.
- 33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

1
2
3
4 A sample Pubmed search strategy was as follows:
5

- 6 #1 Breast Neoplasm [MeSH Terms]
7
8 #2 breast neoplasm [title/abstract]
9
10 #3 neoplasm, breast [title/abstract]
11
12 #4 breast tumors [title/abstract]
13
14 #5 breast tumor [title/abstract]
15
16 #6 tumor, breast [title/abstract]
17
18 #7 tumors, breast [title/abstract]
19
20 #8 neoplasms, breast [title/abstract]
21
22 #9 breast cancer [title/abstract]
23
24 #10 cancer, breast [title/abstract]
25
26 #11 mammary cancer [title/abstract]
27
28 #12 cancer, mammary [title/abstract]
29
30 #13 cancers, mammary [title/abstract]
31
32 #14 mammary cancers [title/abstract]
33
34 #15 malignant neoplasm of breast [title/abstract]
35
36 #16 breast malignant neoplasm [title/abstract]
37
38 #17 breast malignant neoplasms [title/abstract]
39
40 #18 malignant tumor of breast [title/abstract]
41
42 #19 breast malignant tumor [title/abstract]
43
44 #20 cancer of breast [title/abstract]
45
46 #21 cancer of the breast [title/abstract]
47
48 #22 mammary carcinoma, human [title/abstract]
49
50 #23 carcinoma, human mammary [title/abstract]
51
52 #24 carcinomas, human mammary [title/abstract]
53
54 #25 human mammary carcinomas [title/abstract]
55
56 #26 mammary carcinomas, human [title/abstract]
57
58 #27 human mammary carcinoma [title/abstract]
59
60

1
2
3 #28 mammary neoplasms, human [title/abstract]
4
5 #29 human mammary neoplasms [title/abstract]
6
7 #30 human mammary neoplasms [title/abstract]
8
9 #31 neoplasm, human mammary [title/abstract]
10
11 #32 neoplasms, human mammary [title/abstract]
12
13 #33 mammary neoplasm, human [title/abstract]
14
15 #34 breast carcinoma [title/abstract]
16
17 #35 breast carcinomas [title/abstract]
18
19 #36 carcinoma, breast [title/abstract]
20
21 #37 carcinomas, breast [title/abstract]
22
23 #38 breast malignant tumors [title/abstract]
24
25 #39 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR
26
27 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR
28
29 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR
30
31 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR
32
33 #34 OR #35 OR #36 OR #37 OR #38
34
35 #40 Genes, erbB-2[MeSH Terms]
36
37 #41 c-erbB-2 Genes[Title/Abstract]
38
39 #42 c erbB 2 Genes[Title/Abstract]
40
41 #43 c-erbB-2 Gene[Title/Abstract]
42
43 #44 Genes, erbb2[Title/Abstract]
44
45 #45 Gene, erbb2[Title/Abstract]
46
47 #46 erbb2 Gene[Title/Abstract]
48
49 #47 erbb2 Genes[Title/Abstract]
50
51 #48 Genes, HER-2[Title/Abstract]
52
53 #49 HER-2 Gene[Title/Abstract]
54
55 #50 HER-2 Genes[Title/Abstract]
56
57 #51 Genes, neu[Title/Abstract]
58
59 #52 neu Gene[Title/Abstract]
60

1
2
3 #53 neu Genes[Title/Abstract]
4
5 #54 Genes, HER2[Title/Abstract]
6
7 #55 Gene, HER2[Title/Abstract]
8
9 #56 HER2 Gene[Title/Abstract]
10
11 #57 HER2 Genes[Title/Abstract]
12
13 #58 erbB-2 Genes[Title/Abstract]
14
15 #59 erbB 2 Genes[Title/Abstract]
16
17 #60 erbB-2 Gene[Title/Abstract]
18
19 #61 c-erbB-2 Proto-Oncogenes[Title/Abstract]
20
21 #62 c erbB 2 Proto Oncogenes[Title/Abstract]
22
23 #63 c-erbB-2 Proto-Oncogene[Title/Abstract]
24
25 #64 #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
26
27 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
28
29 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63
30
31 #65 Trastuzumab[MeSH Terms]
32
33 #66 Herceptin[Title/Abstract]
34
35 #67 #65 OR #66
36
37 #68 #39 AND #64 AND #67
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

only

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated	7-8, supplementary

			file
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	11-12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomized controlled trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035802.R2
Article Type:	Protocol
Date Submitted by the Author:	18-Sep-2020
Complete List of Authors:	Hu, Qiancheng; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Wang, Xin; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Chen, Ye; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Li, Xiaofen; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Luo, Ting; Sichuan University West China Hospital, Breast Medical Oncology, Clinical Research Center for Breast Cao, Dan; Sichuan University West China Hospital,
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	Breast tumours < ONCOLOGY, Gene therapy < ONCOLOGY, Pharmacology < TROPICAL MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 Optimum duration of adjuvant trastuzumab in treatment of human
5
6 epidermal growth factor receptor-2 positive early breast cancer: protocol
7
8 for a network meta-analysis of randomized controlled trials
9
10

11
12
13 Qiancheng Hu^{1#}, Xin Wang^{1#}, Ye Chen¹, Xiaofen Li¹, Ting Luo^{2§}, Dan
14
15 Cao^{1§}
16

17
18 1 Department of Abdominal Oncology, Cancer Center, West China
19
20 Hospital, Sichuan University, Chengdu, China
21
22

23
24 2 Breast Medical Oncology, Clinical Research Center for Breast, West
25
26 China Hospital, Sichuan University, Chengdu, China.
27

28
29 *§Correspondence:* Email: caodan316@163.com; tina621@163.com. West
30
31 China Hospital, Sichuan University, No. 37 Guo Xue Xiang, Chengdu
32
33 610041, China.
34
35

36
37 # These authors are joint first authors
38

39
40 Email: Qiancheng Hu hqch860109@163.com

41
42 Xin Wang 449678106@qq.com

43
44 Ye Chen 313042032@qq.com

45
46 Xiaofen Li 853767554@qq.com

47
48 Ting Luo tina621@163.com

49
50 Dan Cao caodan316@163.com
51
52
53
54
55
56
57
58
59
60

Abstract

Introduction: Controversy regarding optimum duration of trastuzumab treatment remains in patients with human epidermal growth factor receptor-2 (HER2) positive early breast cancer. The objective of applying network meta-analysis (NMA) is to integrate existing evidence based on direct and indirect comparisons of efficacy and safety, and then to determine the duration of trastuzumab treatments with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

Methods and analysis: Electronic searching of trastuzumab treatments for early breast cancer by titles and abstracts will be conducted for the period from inception to June 16, 2019 using PubMed, Cochrane Library, Embase and ClinicalTrials.gov, as well as the annual meetings of San Antonio Breast Cancer Symposium (SABCS), European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) online archives. The outcomes of interest are overall survival, disease-free survival, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities. Two independent reviewers will screen and extract eligible data based on the inclusion and exclusion criteria, and then assess the risk of bias and evidence quality of individual studies using Cochrane Collaboration's tool and Grades of Recommendation, Assessment, Development and Evaluation (GRADE). The heterogeneity, transitivity and inconsistency of NMA will be evaluated. In addition, we

1
2
3
4 will perform subgroup and sensitivity analyses to assess the robustness
5
6 and reliability of findings in our NMA.
7
8

9 **Ethics and dissemination:** Ethics approval is not required for our NMA.

10
11 This study will identify the evidence regarding optimum duration of
12
13 trastuzumab treatment in patients with HER2 positive early breast cancer.
14
15

16 Findings from our NMA will be submitted as peer-reviewed journal
17
18 manuscripts and international conference reports.
19
20
21

22 **Strengths and limitations of this study**

- 23
24 ■ Our objective of applying NMA is to integrate existing evidence
25
26 based on direct and indirect comparisons of efficacy and safety, and
27
28 to determine the duration of trastuzumab treatments with the greatest
29
30 impact on therapeutic outcomes in HER2 positive early breast
31
32 cancers.
33
34
- 35
36 ■ Our study findings will help clinicians, patients and policy makers to
37
38 reduce the uncertainty of escalating and de-escalating duration
39
40 treatment and to select the optimum duration of trastuzumab
41
42 treatment with highest efficacy and safety.
43
44
- 45
46 ■ We will perform subgroup and sensitivity analyses to assess the
47
48 robustness and reliability of NMA results.
49
50
- 51
52 ■ Language bias is the potential limitation of our study as NMA will
53
54 only include published studies in English.
55
56

57
58 Trial registration number CRD42019139109
59
60

1
2
3
4 Keywords: early breast cancer, human epidermal growth factor receptor-2,
5
6 trastuzumab, network meta-analysis, protocol
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Introduction

Human epidermal growth factor receptor-2 (HER2) positive breast cancer accounts for approximately 20–25% of overall reported cases(1,2) and is associated with poor prognosis.(3,4) Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, is used for patients with HER2-positive early breast cancer. (5-7) Recently, targeted therapy using one year of trastuzumab has been proven to improve overall survival (OS) and disease-free survival (DFS) significantly in early HER2-positive breast cancer. (8-11) Compared to treatment using chemotherapy only in early HER2-positive breast cancer, treatment using adjuvant trastuzumab plus chemotherapy tends to reduce the risk of recurrence and death by one-third. (12)

However, the optimal duration of trastuzumab treatment has been an intense controversy and ongoing debate in terms of efficacy, toxicity, convenience and cost.(13) High-quality randomized controlled trials (RCTs) have confirmed that multiple treatment durations of trastuzumab were effective for HER2-positive early breast cancers, but the relative efficacy and safety were not evaluated for all head-to-head trials. More specifically, the HERceptin Adjuvant (HERA) trial has confirmed that 24 months of adjuvant trastuzumab treatment, which was associated with a higher cost, inconvenience and cardiac toxicity (7.3% vs 4.4%), would

1
2
3
4 not improve DFS compared to a 12 months of adjuvant therapy treatment
5
6 [hazard ratio (HR) 1.02, 95% confidence intervals (CI) 0.89–1.17]. (14)
7
8
9 While comparing to the 12 months of trastuzumab treatment, six months
10
11 of trastuzumab treatment was non-inferior and associated with decreased
12
13 cardiac toxicity (8% vs 4%, $P < 0.001$) in the PERSEPHONE trial, but was
14
15 not non-inferior in the PHARE and HORG trials.(15-17) In contrast, the
16
17 SOLD and Short-HER trials applying nine weeks of trastuzumab was not
18
19 non-inferior compared to the 12 months of trastuzumab, and a significant
20
21 reduction in cardiac toxicity was observed in nine weeks of trastuzumab.
22
23
24
25
26
27 (18,19)
28
29

30 Direct comparison among preventive strategies was limited, as half of
31
32 RCTs, including N9831, NSABP-B31, BCIRG 006 and FinHER trials,
33
34 comparing active therapy to inactive interventions (e.g.,
35
36 placebo). (10,11,20) Pivotal pairwise meta-analyses have been used to
37
38 evaluate the efficacy and toxicity between shorter durations of
39
40 trastuzumab and standard option directly. The analyses results suggested
41
42 that 12 months of trastuzumab would still be the optimal treatment for
43
44 early HER2-positive breast cancer, albeit with a significant increase in
45
46 cardiac events. (13,21-24)
47
48
49
50
51
52

53 These intriguing results provoked an intense debate on consideration
54
55 escalating and de-escalating duration treatment as new standard of care.
56
57
58 Network meta-analysis (NMA) will provide indirect evaluations on the
59
60

1
2
3
4 relative efficacy and toxicity of multiple durations of adjuvant
5
6 trastuzumab therapies in HER2-positive early breast cancer. (25) To
7
8 address the aforementioned debate and determine the most appropriate
9
10 treatment options, we will conduct NMA to integrate existing evidence
11
12 available, based on direct and indirect comparisons of efficacy and safety,
13
14 and to determine the duration of trastuzumab treatments (24 months vs 12
15
16 months vs six months vs 12weeks vs nine weeks vs
17
18 placebo/observation/zero) with the greatest impact on therapeutic
19
20 outcomes in HER2 positive early breast cancers.
21
22
23
24
25

26 27 **Methods**

28
29
30 The results of our protocol will be evaluated in line with the Preferred
31
32 Reporting Items for Systematic Reviews and Meta-Analyses Protocols
33
34 (PRISMA-P).(26) Similarly, we will perform NMA in guidance of the
35
36 PRISMA Extension Statement for Reporting of Systematic Reviews
37
38 Incorporating Network Meta-Analyses of Health Care Interventions. (27)
39
40 This project has been registered in PROSPERO (CRD42019139109).
41
42
43
44

45 **Search strategy**

46
47
48 Electronic searching by titles and abstracts of trastuzumab treatments
49
50 for early breast cancers will be performed using PubMed, Cochrane
51
52 Library, Embase (Ovid interface) and ClinicalTrials.gov, as well as the
53
54 annual meetings of San Antonio Breast Cancer Symposium (SABCS)
55
56 (2015-2019), European Society of Medical Oncology (ESMO) and
57
58
59
60

1
2
3
4 American Society of Clinical Oncology (ASCO) online archives until
5
6 June 16, 2019. Two reviewers who have been trained in data extraction
7
8 will conduct search strategies independently. The same two authors will
9
10 search reference lists manually from eligible reviews and relevant trials to
11
12 identify additional potential papers. We will record the reasons of
13
14 excluding the full text and generate a PRISMA flow diagram for the
15
16 NMA. (28)
17
18
19
20
21

22 The terms used for literature searching will include the following
23
24 domains of Medical Subject Heading (MeSH) terms: ‘breast cancer’,
25
26 ‘human epidermal growth factor receptor-2’ and ‘trastuzumab’, according
27
28 to Population Intervention Comparison Outcomes Study Design (PICOS)
29
30 statement. MeSH and Subheadings will be combined with ‘AND’ or
31
32 ‘OR’. The complete search strategy is presented in online supplementary
33
34 file 1 (see the appendix 1).
35
36
37
38
39

40 We will perform a pilot test to evaluate inter-rater reliability and adjust
41
42 each screening stage: title and abstract, followed by full-text screening.
43
44 Two independent reviewers will screen the titles and abstracts of related
45
46 studies based on inclusion and exclusion criteria. The eligible or
47
48 potentially eligible trials will be evaluated by reading through the full
49
50 texts when necessary. Moreover, disagreements in data extraction will be
51
52 discussed with the help of the third reviewer.
53
54
55
56
57

58 **Eligibility criteria**

59
60

1
2
3
4 Trials will be eligible if they fulfill the following criteria: 1.
5
6 Populations: patients with HER2-positive early breast cancer of any age
7
8 or nationality were treated with trastuzumab treatments; 2. Interventions:
9
10 any duration of trastuzumab treatments were given. We are also interested
11
12 in the impact of placebo/observation/zero as adjuvant treatment; 3.
13
14 Comparators: 12 months of trastuzumab treatment was compared with
15
16 placebo/observation/zero, or other durations of adjuvant trastuzumab; 4.
17
18 Outcomes: OS, DFS, acceptability, cardiotoxicities and grade 3-4
19
20 nonhematologic toxicities; 5. Study design: RCTs that compared any two
21
22 or more different arms of adjuvant trastuzumab in patients with
23
24 HER2-positive early breast cancer; 6. Language and other limitations: We
25
26 will include studies published in English regardless of publication status.
27
28
29
30
31
32
33
34

35 Studies not meeting the inclusion criteria will be excluded. The other
36
37 excluding criteria are as follows: 1. Neoadjuvant and adjuvant treatment
38
39 with trastuzumab biosimilars; 2. Palliative care with trastuzumab.
40
41
42

43 **Outcomes**

44
45 The outcomes of interest are OS (defined as the time from
46
47 randomization to death from any cause), DFS (defined as the time from
48
49 randomization to local, regional, distant relapse, contralateral breast
50
51 cancer, second primary cancer, or death from any cause, whichever
52
53 occurred first), acceptability (defined as the proportion of patients who
54
55 discontinued trastuzumab), cardiotoxicities, and grade 3-4
56
57
58
59
60

1
2
3
4 nonhematologic toxicities. The cardiac toxicity grading is used by the
5
6 Common Terminology Criteria for Adverse Events of the National
7
8 Cancer Institute. Cardiac toxicity is defined as an asymptomatic decline
9
10 in left ventricular ejection fraction (LVEF) to $\leq 45\%$, an absolute drop of
11
12 10-15% in follow-up echocardiography, symptomatic congestive heart
13
14 failure (New York Heart Association [NYHA] class III/IV) or cardiac
15
16 death.(29,30) We will calculate the relative effectiveness for each
17
18 network comparison among all duration of treatments with trastuzumab.
19
20
21
22
23
24

25 (31)

26 27 **Data extraction and management**

28
29 The management of literature searching records will be carried out in
30
31 EndNote X7. A spreadsheet will be created in Microsoft Excel 2010
32
33 (Microsoft Corp, Redmond, WA, www.microsoft.com) to collect
34
35 outcomes of interest, such as study ID, first author, study design,
36
37 recruitment time frame, detailed interventions, sample size, and endpoints
38
39 (OS, DFS, acceptability, cardiotoxicities and grade 3-4 nonhematologic
40
41 toxicities). We will contact corresponding authors and relevant
42
43 pharmaceutical companies for further information if important data are
44
45 not reported in articles. The most up-to-date data will be included if
46
47 duplicate publications are identified.
48
49
50
51
52
53
54

55 56 **Bias risk**

57
58 The risk of bias of RCTs in the NMA will be evaluated by reviewer
59
60

1
2
3
4 manager according to the following domains outlined in the Cochrane
5
6 Collaboration's tool: random sequence generation, allocation
7
8 concealment, blinding of participants and personnel,
9
10 blinding of outcome assessment, incomplete outcome data, selective
11
12 reporting, and other bias.(32) Two authors will review RCTs
13
14 independently and report a high risk of bias as “-”, a low risk of bias as
15
16 “+”, or an unclear risk of bias as “?”. Any disagreements in assessment of
17
18 risk of bias will be resolved by discussion, or the help of the third
19
20 reviewer if needed.
21
22
23
24
25

26 27 **Quality of evidence**

28
29 We will evaluate the quality of evidence of individual studies using
30
31 Grades of Recommendation, Assessment, Development and Evaluation
32
33 (GRADE), which is based on the following five domains: risk of bias,
34
35 imprecision, inconsistency, indirectness and publication bias.(33,34) The
36
37 staging system categories for GRADE evidences are scored as high,
38
39 moderate, low or very low quality. The initial confidence level for each
40
41 RCT is set as high, but will be rated down based on the evaluation of the
42
43 five domains. The strength of evidences will also be
44
45 graded for the outcomes based on GRADE system in CINeMA. (34)
46
47
48
49
50
51

52 53 **Statistical analysis**

54
55 We will perform the traditional pairwise meta-analysis on direct
56
57 comparisons based on two or more studies with Stata13.0 (StataCorp,
58
59
60

1
2
3
4 College Station, TX, USA). To compare eligible interventions directly
5
6 and indirectly, NMA displaying outcomes of interest is planned using
7
8 WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK).
9
10 Pooled hazard ratios (HRs) for OS and DFS with 95%
11
12 confidence intervals (CIs) will be calculated using both fixed- and
13
14 random-effects models. Binary outcomes (acceptability, cardiotoxicities
15
16 and grade 3-4 nonhematologic toxicities) are expressed as odds ratios
17
18 (ORs) with 95% CI. The results of comparative effectiveness and safety
19
20 probability statements of intervention effects will be ranked; and rank
21
22 plots across all outcomes will be generated. The interventions with
23
24 surface under the cumulative ranking (SUCRA) in term of efficacy and
25
26 safety will be evaluated to interpret relative effect of comparisons. We
27
28 will compare the risk-benefit profile of all comparators in terms of
29
30 efficacy and toxicity. A two-sided $p < 0.05$ is considered statistically
31
32 significant.
33
34
35
36
37
38
39
40
41
42

43 We will estimate the presence of heterogeneity based on the magnitude
44
45 of I^2 estimated from pairwise meta-analysis models. The heterogeneity is
46
47 considered as evidence of low if $I^2 < 25\%$, as moderate if $25\% \leq I^2 \leq 50\%$,
48
49 and as high if $I^2 > 50\%$. (35) The fixed-effects model will be used when
50
51 the heterogeneity is low and moderate; otherwise, a random-effects model
52
53 will be used. In addition, we will also evaluate the transitivity and
54
55 inconsistency of NMA. The transitivity will be assessed by applying
56
57
58
59
60

1
2
3
4 descriptive statistics for study types and demographic characteristics.

5
6 Inconsistency will be assessed by comparing deviation information
7
8
9 criteria (DIC) statistics in the fitted consistency and inconsistency models.

10
11 (36) Global inconsistency between direct and indirect comparisons will
12
13
14 also be evaluated by using a loop-specific method, if a loop connecting
15
16
17 three or more arms exists. (37)

18 19 **Subgroup analysis**

20
21
22 We will explore whether specific duration of treatments with
23
24
25 trastuzumab might be more appropriate for particular subtypes of breast
26
27
28 cancer. We categorize breast cancer into the following groups when
29
30
31 possible: Estrogen Receptor (ER) positive, ER negative, node positive
32
33
34 and node negative.

35 36 **Sensitivity analysis**

37
38 We will perform sensitivity analyses to assess the robustness and
39
40
41 reliability of findings in our NMA. In order to check the impact of HER2
42
43
44 status on the results, the first sensitivity analysis will exclude patients
45
46
47 with HER2 negative after re-evaluating the HER2 status in the E2198
48
49
50 trial. (38) The second sensitivity analysis will restrict hormone
51
52
53 receptor-positive to ER + and PR +, ER + and PR -, ER - and PR +.
54
55
56 Lastly, the sensitivity analysis will classify patients as 1-3 and ≥ 4 positive
57
58
59 lymph nodes to specify the impact of the number of positive lymph
60
nodes.

Ethics and dissemination

An ethics approval is not required for the NMA. Important modifications to the study protocol will be communicated to all members of the research team. The results will be disseminated through international conference reports and published in a peer-reviewed journal.

Discussion

Despite trastuzumab being highly effective in treatment for HER2-positive early breast cancer, its substantial socio-economic burden attracted the attention of governments, academic researchers, pharmaceutical companies and health care payers. With the consideration of balancing efficacy and cardiotoxicity, the 12-month and six-month of trastuzumab treatments have received increasing interests. The requirement to balance efficacy and side effects (i.e. cardiotoxicity) has led to raise interest in reducing trastuzumab duration from 12 months to six months. With the increase in rates of patients reporting 12-month trastuzumab induced cardiotoxicity, most clinicians suggested that a drop to 83% four-year DFS with six months trastuzumab would be also acceptable. (39) This benefit-risk analysis will provide important information to help clinicians, patients and policy makers to decide optimum duration of adjuvant treatment with trastuzumab in their daily practice.

The 12 months of treatments with trastuzumab for most women with

1
2
3
4 early HER2 positive breast cancer was a standard of care, but most
5
6 crucial RCTs mainly focused on patients with high-risk of recurrence and
7
8 one-year duration was chosen arbitrarily. In contrary, a particular subtype
9
10 of patients might be appropriate for de-escalating duration of treatment,
11
12 without compromising efficacy. Romualdo and his colleagues deemed
13
14 that de-escalating chemotherapy was a good option for older patients and
15
16 those with stage I HER2-positive breast cancer. (40) This study will
17
18 explore whether de-escalating targeted therapy is another option for
19
20 patients with particular subtypes (ER positive and node negative).
21
22
23
24
25

26
27 As far as we know, the results of system review will fill a pivotal
28
29 knowledge gap of optimal duration of adjuvant trastuzumab in patients
30
31 with early HER2 positive breast cancer. We hope the findings from this
32
33 NMA will help clinicians, patients and policy makers to select optimal
34
35 duration of adjuvant trastuzumab with the greatest value in HER2
36
37 positive early breast cancers. It will also provide a result that will engage
38
39 patients and policy makers, and will contribute to the public debate on
40
41 future policy options. Furthermore, under-recognized comparisons (e.g.,
42
43 six months vs nine weeks) may be identified by this Bayesian analysis to
44
45 guide future research.
46
47
48
49
50
51

52 53 **Patient and public involvement**

54
55 The manuscript was developed without patient or public participation.
56
57
58 Breast cancer patient organizations will participate in the discussion and
59
60

1
2
3
4 dissemination of research results. A summary of the findings will be
5
6 provided to the Chinese society of clinical oncology (CSCO).
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Author affiliations

1 Department of Abdominal Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

2 Breast Medical Oncology, Clinical Research Center for Breast, West China Hospital, Sichuan University, Chengdu, China.

Acknowledgements

Thanks to Sun Feng and Wu Shanshan (PhD, Perking University School of public Health) for providing assistance and contributing to statistical analysis. (<https://class.dxy.cn/>)

Thanks to Lu Guan (PhD, Fisheries Oceans Canada) for providing assistance and contributing to revisions.

Funding

The network meta-analysis was supported by the National Natural Science Foundation of China (Grant No.81773097).

Author contributions

QcH and DC conceptualized the network meta-analysis. QcH and XW co-developed the search strategy. Both QcH and XW were major contributors in writing the manuscript. The protocol was revised by DC, YC, XfL and TL. DC and TL were serving as guarantor and corresponding author of this study. All authors approved the final manuscript and agreed to submit the protocol in the journal.

Competing interests

1
2
3
4 All authors have completed the ICMJE uniform disclosure form at
5
6 http://www.icmje.org/coi_disclosure.pdf and stated that there is no
7
8 organization to support the submission; no organization is interested in
9
10 the submitted work; no other relationships or activities effect the
11
12 submitted work.
13
14
15

16 Provenance and peer review

17
18
19 Not commissioned; externally peer reviewed
20
21

22 Patient consent for publication

23
24
25 Not required.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References:

1. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177-82.
2. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989;244:707-12.
3. Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature* 2012;486:346-52.
4. Dawson SJ, Rueda OM, Aparicio S, et al. A new genome-driven integrated classification of breast cancer and its implications. *EMBO J* 2013;32:617-28.
5. Yeon CH, Pegram MD. Anti-erbB-2 antibody trastuzumab in the treatment of HER2-amplified breast cancer. *Invest New Drugs* 2005;23:391-409.
6. Schaefer NG, Pestalozzi BC, Knuth A, et al. Potential use of humanized antibodies in the treatment of breast cancer. *Expert Rev Anticancer Ther* 2006;6:1065-74.
7. Tokunaga E, Oki E, Nishida K, et al. Trastuzumab and breast cancer: developments and current status. *Int J Clin Oncol* 2006;11:199-208.
8. Hortobagyi GN. Trastuzumab in the treatment of breast cancer. *N Engl J Med* 2005;353:1734-6.
9. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659-72.
10. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673-84.
11. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273-83.
12. Genuino AJ, Chaikledkaew U, The DO, et al. Adjuvant trastuzumab regimen for HER2-positive early-stage breast cancer: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol* 2019;12:815-24.
13. Niraula S, Gyawali B. Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: a meta-analysis of randomized controlled trials. *Breast Cancer Res Treat* 2019;173:103-09.
14. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017;389:1195-205.
15. Earl HM, Hiller L, Vallier AL, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *Lancet* 2019;393:2599-612.
16. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol* 2013;14:741-8.
17. Mavroudis D, Saloustros E, Malamos N, et al. Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG). *Ann Oncol* 2015;26:1333-40.
18. Joensuu H, Fraser J, Wildiers H, et al. Effect of Adjuvant Trastuzumab for a Duration of 9

- 1
2
3 Weeks vs 1 Year With Concomitant Chemotherapy for Early Human Epidermal Growth Factor
4 Receptor 2-Positive Breast Cancer: The SOLD Randomized Clinical Trial. *JAMA oncology*
5 2018;4:1199-206.
6
7 19. Conte P, Frassoldati A, Bisagni G, et al. Nine weeks versus 1 year adjuvant trastuzumab in
8 combination with chemotherapy: final results of the phase III randomized Short-HER
9 study. *Ann Oncol* 2018;29:2328-33.
10
11 20. Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with
12 either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of
13 breast cancer: final results of the FinHer Trial. *J Clin Oncol* 2009;27:5685-92.
14
15 21. Chen L, Zhou W, Hu X, et al. Short-duration versus 1-year adjuvant trastuzumab in early HER2
16 positive breast cancer: A meta-analysis of randomized controlled trials. *Cancer treatment*
17 *reviews* 2019;75:12-19.
18
19 22. Inno A, Barni S, Ghidini A, et al. One year versus a shorter duration of adjuvant trastuzumab
20 for HER2-positive early breast cancer: a systematic review and meta-analysis. *Breast Cancer*
21 *Res Treat* 2019;173:247-54.
22
23 23. Gyawali B, Niraula S. Duration of adjuvant trastuzumab in HER2 positive breast cancer:
24 Overall and disease free survival results from meta-analyses of randomized controlled trials.
25 *Cancer treatment reviews* 2017;60:18-23.
26
27 24. Goldvaser H, Korzets Y, Shepshelovich D, et al. Deescalating Adjuvant Trastuzumab in
28 HER2-Positive Early-Stage Breast Cancer: A Systemic Review and Meta-Analysis. *JNCI Cancer*
29 *Spectr* 2019;3:pkz033.
30
31 25. Clarke CS, Hunter RM, Shemilt I, et al. Multi-arm Cost-Effectiveness Analysis (CEA) comparing
32 different durations of adjuvant trastuzumab in early breast cancer, from the English NHS
33 payer perspective. *PLoS One* 2017;12:e0172731.
34
35 26. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and
36 meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
37
38 27. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of
39 systematic reviews incorporating network meta-analyses of health care interventions:
40 checklist and explanations. *Ann Intern Med* 2015;162:777-84.
41
42 28. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and
43 meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
44
45 29. Russell SD, Blackwell KL, Lawrence J, et al. Independent adjudication of symptomatic heart
46 failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant
47 therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and
48 Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. *J Clin*
49 *Oncol* 2010;28:3416-21.
50
51 30. Yu AF, Singh JC, Wang R, et al. Cardiac Safety of Dual Anti-HER2 Therapy in the Neoadjuvant
52 Setting for Treatment of HER2-Positive Breast Cancer. *Oncologist* 2017;22:642-47.
53
54 31. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments
55 meta-analysis: many names, many benefits, many concerns for the next generation evidence
56 synthesis tool. *Res Synth Methods* 2012;3:80-97.
57
58 32. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk
59 of bias in randomised trials. *BMJ* 2011;343:d5928.
60
61 33. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of

- 1
2
3 evidence and strength of recommendations. *BMJ* 2008;336:924-6.
4
5 34. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network
6 meta-analysis. *PLoS One* 2014;9:e99682.
7
8 35. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*
9 2003;327:557-60.
10
11 36. Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 4: inconsistency in
12 networks of evidence based on randomized controlled trials. *Med Decis Making*
13 2013;33:641-56.
14
15 37. Veroniki AA, Vasiliadis HS, Higgins JP, et al. Evaluation of inconsistency in networks of
16 interventions. *Int J Epidemiol* 2013;42:332-45.
17
18 38. Schneider BP, O'Neill A, Shen F, et al. Pilot trial of paclitaxel-trastuzumab adjuvant therapy
19 for early stage breast cancer: a trial of the ECOG-ACRIN cancer research group (E2198). *Br J*
20 *Cancer* 2015;113:1651-7.
21
22 39. Hiller L, Dunn JA, Loi S, et al. Adjuvant trastuzumab duration trials in HER2 positive breast
23 cancer - what results would be practice-changing? Persephone investigator questionnaire
24 prior to primary endpoint results. *BMC Cancer* 2018;18:391.
25
26 40. Barroso-Sousa R, Exman P, Tolaney SM. De-escalating treatment in the adjuvant setting in
27 HER2-positive breast cancer. *Future oncology (London, England)* 2018;14:937-45.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 A sample Pubmed search strategy was as follows:
5

6 #1 Breast Neoplasm [MeSH Terms]
7

8 #2 breast neoplasm [title/abstract]
9

10 #3 neoplasm, breast [title/abstract]
11

12 #4 breast tumors [title/abstract]
13

14 #5 breast tumor [title/abstract]
15

16 #6 tumor, breast [title/abstract]
17

18 #7 tumors, breast [title/abstract]
19

20 #8 neoplasms, breast [title/abstract]
21

22 #9 breast cancer [title/abstract]
23

24 #10 cancer, breast [title/abstract]
25

26 #11 mammary cancer [title/abstract]
27

28 #12 cancer, mammary [title/abstract]
29

30 #13 cancers, mammary [title/abstract]
31

32 #14 mammary cancers [title/abstract]
33

34 #15 malignant neoplasm of breast [title/abstract]
35

36 #16 breast malignant neoplasm [title/abstract]
37

38 #17 breast malignant neoplasms [title/abstract]
39

40 #18 malignant tumor of breast [title/abstract]
41

42 #19 breast malignant tumor [title/abstract]
43

44 #20 cancer of breast [title/abstract]
45

46 #21 cancer of the breast [title/abstract]
47

48 #22 mammary carcinoma, human [title/abstract]
49

50 #23 carcinoma, human mammary [title/abstract]
51

52 #24 carcinomas, human mammary [title/abstract]
53

54 #25 human mammary carcinomas [title/abstract]
55

56 #26 mammary carcinomas, human [title/abstract]
57

58 #27 human mammary carcinoma [title/abstract]
59
60

1
2
3 #28 mammary neoplasms, human [title/abstract]
4
5 #29 human mammary neoplasms [title/abstract]
6
7 #30 human mammary neoplasms [title/abstract]
8
9 #31 neoplasm, human mammary [title/abstract]
10
11 #32 neoplasms, human mammary [title/abstract]
12
13 #33 mammary neoplasm, human [title/abstract]
14
15 #34 breast carcinoma [title/abstract]
16
17 #35 breast carcinomas [title/abstract]
18
19 #36 carcinoma, breast [title/abstract]
20
21 #37 carcinomas, breast [title/abstract]
22
23 #38 breast malignant tumors [title/abstract]
24
25 #39 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR
26
27 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR
28
29 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR
30
31 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR
32
33 #34 OR #35 OR #36 OR #37 OR #38
34
35 #40 Genes, erbB-2[MeSH Terms]
36
37 #41 c-erbB-2 Genes[Title/Abstract]
38
39 #42 c erbB 2 Genes[Title/Abstract]
40
41 #43 c-erbB-2 Gene[Title/Abstract]
42
43 #44 Genes, erbb2[Title/Abstract]
44
45 #45 Gene, erbb2[Title/Abstract]
46
47 #46 erbb2 Gene[Title/Abstract]
48
49 #47 erbb2 Genes[Title/Abstract]
50
51 #48 Genes, HER-2[Title/Abstract]
52
53 #49 HER-2 Gene[Title/Abstract]
54
55 #50 HER-2 Genes[Title/Abstract]
56
57 #51 Genes, neu[Title/Abstract]
58
59 #52 neu Gene[Title/Abstract]
60

1
2
3 #53 neu Genes[Title/Abstract]
4
5 #54 Genes, HER2[Title/Abstract]
6
7 #55 Gene, HER2[Title/Abstract]
8
9 #56 HER2 Gene[Title/Abstract]
10
11 #57 HER2 Genes[Title/Abstract]
12
13 #58 erbB-2 Genes[Title/Abstract]
14
15 #59 erbB 2 Genes[Title/Abstract]
16
17 #60 erbB-2 Gene[Title/Abstract]
18
19 #61 c-erbB-2 Proto-Oncogenes[Title/Abstract]
20
21 #62 c erbB 2 Proto Oncogenes[Title/Abstract]
22
23 #63 c-erbB-2 Proto-Oncogene[Title/Abstract]
24
25 #64 #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
26
27 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
28
29 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63
30
31 #65 Trastuzumab[MeSH Terms]
32
33 #66 Herceptin[Title/Abstract]
34
35 #67 #65 OR #66
36
37 #68 #39 AND #64 AND #67
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

only

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated	7-8, supplementary

			file
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	11-12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomized controlled trials

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-035802.R3
Article Type:	Protocol
Date Submitted by the Author:	05-Nov-2020
Complete List of Authors:	Hu, Qiancheng; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Wang, Xin; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Chen, Ye; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Li, Xiaofen; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center Luo, Ting; Sichuan University West China Hospital, Breast Medical Oncology, Clinical Research Center for Breast Cao, Dan; Sichuan University West China Hospital, Department of Abdominal Oncology, Cancer Center
Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	Breast tumours < ONCOLOGY, Gene therapy < ONCOLOGY, Pharmacology < TROPICAL MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4 Optimum duration of adjuvant trastuzumab in treatment of human
5
6 epidermal growth factor receptor-2 positive early breast cancer: protocol
7
8 for a network meta-analysis of randomized controlled trials
9
10

11
12
13 Qiancheng Hu^{1#}, Xin Wang^{1#}, Ye Chen¹, Xiaofen Li¹, Ting Luo^{2§}, Dan
14
15 Cao^{1§}
16

17
18 1 Department of Abdominal Oncology, Cancer Center, West China
19
20 Hospital, Sichuan University, Chengdu, China
21
22

23
24 2 Breast Medical Oncology, Clinical Research Center for Breast, West
25
26 China Hospital, Sichuan University, Chengdu, China.
27

28
29 *§Correspondence:* Email: caodan316@163.com; tina621@163.com. West
30
31 China Hospital, Sichuan University, No. 37 Guo Xue Xiang, Chengdu
32
33 610041, China.
34
35

36
37 # These authors are joint first authors
38

39
40 Email: Qiancheng Hu hqch860109@163.com

41
42 Xin Wang 449678106@qq.com

43
44 Ye Chen 313042032@qq.com

45
46 Xiaofen Li 853767554@qq.com

47
48 Ting Luo tina621@163.com

49
50 Dan Cao caodan316@163.com
51
52
53
54
55
56
57
58
59
60

Abstract

Introduction: Controversy regarding optimum duration of trastuzumab treatment remains in patients with human epidermal growth factor receptor-2 (HER2) positive early breast cancer. The objective of applying network meta-analysis (NMA) is to integrate existing evidence based on direct and indirect comparisons of efficacy and safety, and then to determine the duration of trastuzumab treatments with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

Methods and analysis: Electronic searching of trastuzumab treatments for early breast cancer by titles and abstracts will be conducted for the period from inception to June 16, 2019 in PubMed, Cochrane Library, Embase and ClinicalTrials.gov, as well as the annual meetings of San Antonio Breast Cancer Symposium (SABCS), European Society of Medical Oncology (ESMO) and American Society of Clinical Oncology (ASCO) online archives. The outcomes of interest are overall survival, disease-free survival, acceptability, cardiotoxicities and grade 3-4 nonhematologic toxicities. Two independent reviewers will screen and extract eligible data based on the inclusion and exclusion criteria, and then assess the risk of bias and evidence quality of individual studies using Cochrane Collaboration's tool and Grades of Recommendation, Assessment, Development and Evaluation (GRADE). The heterogeneity, transitivity and inconsistency of NMA will be evaluated. In addition, we

1
2
3
4 will perform subgroup and sensitivity analyses to assess the robustness
5
6 and reliability of findings in our NMA.
7
8

9 **Ethics and dissemination:** Ethics approval is not required for our NMA.
10
11 Findings from our NMA will be submitted as peer-reviewed journal
12
13 manuscripts and international conference reports.
14
15

16 17 **Strengths and limitations of this study** 18

- 19 ■ Our objective of applying NMA is to integrate existing evidence
20
21 based on direct and indirect comparisons of efficacy and safety, and
22
23 to determine the duration of trastuzumab treatments with the greatest
24
25 impact on therapeutic outcomes in HER2 positive early breast
26
27 cancers.
28
29
- 30 ■ Our study findings will help clinicians, patients and policy makers to
31
32 reduce the uncertainty of escalating and de-escalating duration
33
34 treatment and to select the optimum duration of trastuzumab
35
36 treatment with highest efficacy and safety.
37
38
- 39 ■ We will perform subgroup and sensitivity analyses to assess the
40
41 robustness and reliability of NMA results.
42
43
- 44 ■ Language bias is the potential limitation of our study as NMA will
45
46 only include published studies in English.
47
48

49
50
51
52
53 Trial registration number CRD42019139109

54
55
56 Keywords: early breast cancer, human epidermal growth factor receptor-2,
57
58 trastuzumab, network meta-analysis, protocol
59
60

Introduction

Human epidermal growth factor receptor-2 (HER2) positive breast cancer accounts for approximately 20–25% of overall reported cases(1,2) and is associated with poor prognosis.(3,4) Trastuzumab, a monoclonal antibody targeting the extracellular domain of the HER2 protein, is used for patients with HER2-positive early breast cancer. (5-7) Recently, targeted therapy using one year of trastuzumab has been proven to improve overall survival (OS) and disease-free survival (DFS) significantly in early HER2-positive breast cancer. (8-11) Compared to treatment using chemotherapy only in early HER2-positive breast cancer, treatment using adjuvant trastuzumab plus chemotherapy tends to reduce the risk of recurrence and death by one-third. (12)

However, the optimal duration of trastuzumab treatment has been an intense controversy and ongoing debate in terms of efficacy, toxicity, convenience and cost.(13) High-quality randomized controlled trials (RCTs) have confirmed that multiple treatment durations of trastuzumab were effective for HER2-positive early breast cancers, but the relative efficacy and safety were not evaluated for all head-to-head trials. More specifically, the HERceptin Adjuvant (HERA) trial has confirmed that 24 months of adjuvant trastuzumab treatment, which was associated with a higher cost, inconvenience and cardiac toxicity (7.3% vs 4.4%), would

1
2
3
4 not improve DFS compared to a 12 months of adjuvant therapy treatment
5
6 [hazard ratio (HR) 1.02, 95% confidence intervals (CI) 0.89–1.17]. (14)
7
8
9 While comparing to the 12 months of trastuzumab treatment, six months
10
11 of trastuzumab treatment was non-inferior and associated with decreased
12
13 cardiac toxicity (8% vs 4%, $P < 0.001$) in the PERSEPHONE trial, but was
14
15 not non-inferior in the PHARE and HORG trials.(15-17) In contrast, the
16
17 SOLD and Short-HER trials applying nine weeks of trastuzumab was not
18
19 non-inferior compared to the 12 months of trastuzumab, and a significant
20
21 reduction in cardiac toxicity was observed in nine weeks of trastuzumab.
22
23
24
25
26
27 (18,19)
28
29

30 Direct comparison among preventive strategies was limited, as half of
31
32 RCTs, including N9831, NSABP-B31, BCIRG 006 and FinHER trials,
33
34 comparing active therapy to inactive interventions (e.g.,
35
36 placebo). (10,11,20) Pivotal pairwise meta-analyses have been used to
37
38 evaluate the efficacy and toxicity between shorter durations of
39
40 trastuzumab and standard option directly. The analyses results suggested
41
42 that 12 months of trastuzumab would still be the optimal treatment for
43
44 early HER2-positive breast cancer, albeit with a significant increase in
45
46 cardiac events. (13,21-24) The latest pairwise meta-analysis indicated that
47
48 the use of trastuzumab in a one-week cycle with anthracycline-taxane
49
50 chemotherapy regimens simultaneously seemed to be the preferred option
51
52 to optimize its efficacy and safety regardless of the duration of
53
54
55
56
57
58
59
60

1
2
3
4 trastuzumab administration. (12) However, the results were only from
5
6 subgroup analysis, and the courses of trastuzumab administration were
7
8 not only 12 months but also nine weeks. Without direct comparison of
9
10 RCTs, they did not contain 12 weeks, six months and 24 months of
11
12 trastuzumab concurrently with chemotherapy compared with
13
14 chemotherapy alone for early HER2-positive breast cancer in pairwise
15
16 meta-analysis.
17
18
19
20
21

22 These intriguing results provoked an intense debate on consideration
23
24 escalating and de-escalating duration treatment as new standard of care.
25
26 Network meta-analysis (NMA) will provide indirect evaluations on the
27
28 relative efficacy and toxicity of multiple durations of adjuvant
29
30 trastuzumab therapies in HER2-positive early breast cancer. (25) To
31
32 address the aforementioned debate and determine the most appropriate
33
34 treatment options, we will conduct NMA to integrate existing evidence
35
36 available, based on direct and indirect comparisons of efficacy and safety,
37
38 and to determine the duration of trastuzumab treatments (24 months vs 12
39
40 months vs six months vs 12weeks vs nine weeks vs
41
42 placebo/observation/zero) with the greatest impact on therapeutic
43
44 outcomes in HER2 positive early breast cancers.
45
46
47
48
49
50
51

52 **Methods**

53
54
55 The results of our protocol will be evaluated in line with the Preferred
56
57 Reporting Items for Systematic Reviews and Meta-Analyses Protocols
58
59
60

1
2
3
4 (PRISMA-P).(26) Similarly, we will perform NMA in guidance of the
5
6 PRISMA Extension Statement for Reporting of Systematic Reviews
7
8
9 Incorporating Network Meta-Analyses of Health Care Interventions. (27)
10
11 This project has been registered in PROSPERO (CRD42019139109).
12
13

14 **Search strategy**

15
16 Electronic searching by titles and abstracts of trastuzumab treatments
17
18 for early breast cancers will be performed in PubMed, Cochrane Library,
19
20 Embase (Ovid interface) and ClinicalTrials.gov, as well as the annual
21
22 meetings of San Antonio Breast Cancer Symposium (SABCS)
23
24 (2015-2019), European Society of Medical Oncology (ESMO) and
25
26 American Society of Clinical Oncology (ASCO) online archives until
27
28 June 16, 2019. Two reviewers who have been trained in data extraction
29
30 will conduct search strategies independently. The same two authors will
31
32 search reference lists manually from eligible reviews and relevant trials to
33
34 identify additional potential papers. We will record the reasons of
35
36 excluding the full text and generate a PRISMA flow diagram for the
37
38 NMA. (28)
39
40
41
42
43
44
45
46
47

48 The terms used for literature searching will include the following
49
50 domains of Medical Subject Heading (MeSH) terms: ‘breast cancer’,
51
52 ‘human epidermal growth factor receptor-2’ and ‘trastuzumab’, according
53
54 to Population Intervention Comparison Outcomes Study Design (PICOS)
55
56 statement. MeSH and Subheadings will be combined with ‘AND’ or
57
58
59
60

1
2
3
4 'OR'. The complete search strategy is presented in online supplementary
5
6 file 1 (see the appendix 1).
7
8

9 We will perform a pilot test to evaluate inter-rater reliability and adjust
10 each screening stage: title and abstract, followed by full-text screening.
11
12 Two independent reviewers will screen the titles and abstracts of related
13
14 studies based on inclusion and exclusion criteria. The eligible or
15
16 potentially eligible trials will be evaluated by reading through the full
17
18 texts when necessary. Moreover, disagreements in data extraction will be
19
20 discussed with the help of the third reviewer.
21
22
23
24
25

26 27 **Eligibility criteria** 28

29
30 Trials will be eligible if they fulfill the following criteria: 1.
31
32 Populations: patients with HER2-positive early breast cancer of any age
33
34 or nationality were treated with trastuzumab treatments; 2. Interventions:
35
36 any duration of trastuzumab treatments were given. We are also interested
37
38 in the impact of placebo/observation/zero as adjuvant treatment; 3.
39
40 Comparators: 12 months of trastuzumab treatment was compared with
41
42 placebo/observation/zero, or other durations of adjuvant trastuzumab; 4.
43
44 Outcomes: OS, DFS, acceptability, cardiotoxicities and grade 3-4
45
46 nonhematologic toxicities; 5. Study design: RCTs that compared any two
47
48 or more different arms of adjuvant trastuzumab in patients with
49
50 HER2-positive early breast cancer; 6. Language and other limitations: We
51
52 will include studies published in English regardless of publication status.
53
54
55
56
57
58
59
60

1
2
3
4 Studies not meeting the inclusion criteria will be excluded. The other
5
6 excluding criteria are as follows: 1. Neoadjuvant and adjuvant treatment
7
8 with trastuzumab biosimilars; 2. Palliative care with trastuzumab.
9
10

11 **Outcomes**

12
13
14 The outcomes of interest are OS (defined as the time from
15
16 randomization to death from any cause), DFS (defined as the time from
17
18 randomization to local, regional, distant relapse, contralateral breast
19
20 cancer, second primary cancer, or death from any cause, whichever
21
22 occurred first), acceptability (defined as the proportion of patients who
23
24 discontinued trastuzumab), cardiotoxicities, and grade 3-4
25
26 nonhematologic toxicities. The cardiac toxicity grading is used by the
27
28 Common Terminology Criteria for Adverse Events of the National
29
30 Cancer Institute. Cardiac toxicity is defined as an asymptomatic decline
31
32 in left ventricular ejection fraction (LVEF) to $\leq 45\%$, an absolute drop of
33
34 10-15% in follow-up echocardiography, symptomatic congestive heart
35
36 failure (New York Heart Association [NYHA] class III/IV) or cardiac
37
38 death.^(29,30) We will calculate the relative effectiveness for each
39
40 network comparison among all duration of treatments with trastuzumab.
41
42
43
44
45
46
47
48
49

50
51 (31)

52 **Data extraction and management**

53
54
55
56 The management of literature searching records will be carried out in
57
58 EndNote X7. A spreadsheet will be created in Microsoft Excel 2010
59
60

1
2
3
4 (Microsoft Corp, Redmond, WA, www.microsoft.com) to collect
5
6 outcomes of interest, such as study ID, first author, study design,
7
8 recruitment time frame, detailed interventions, sample size, and endpoints
9
10 (OS, DFS, acceptability, cardiotoxicities and grade 3-4 nonhematologic
11
12 toxicities). We will contact corresponding authors and relevant
13
14 pharmaceutical companies for further information if important data are
15
16 not reported in articles. The most up-to-date data will be included if
17
18 duplicate publications are identified.
19
20
21
22
23
24

25 **Bias risk**

26
27 The risk of bias of RCTs in the NMA will be evaluated by reviewer
28
29 manager according to the following domains outlined in the Cochrane
30
31 Collaboration's tool: random sequence generation, allocation
32
33 concealment, blinding of participants and personnel,
34
35 blinding of outcome assessment, incomplete outcome data, selective
36
37 reporting, and other bias.(32) Two authors will review RCTs
38
39 independently and report a high risk of bias as “-”, a low risk of bias as
40
41 “+”, or an unclear risk of bias as “?”. Any disagreements in assessment of
42
43 risk of bias will be resolved by discussion, or the help of the third
44
45 reviewer if needed.
46
47
48
49
50
51

52 **Quality of evidence**

53
54 We will evaluate the quality of evidence of individual studies using
55
56 Grades of Recommendation, Assessment, Development and Evaluation
57
58
59
60

1
2
3
4 (GRADE), which is based on the following five domains: risk of bias,
5
6 imprecision, inconsistency, indirectness and publication bias.(33,34) The
7
8 staging system categories for GRADE evidences are scored as high,
9
10 moderate, low or very low quality. The initial confidence level for each
11
12 RCT is set as high, but will be rated down based on the evaluation of the
13
14 five domains. The strength of evidences will also be
15
16 graded for the outcomes based on GRADE system in CINeMA. (34)
17
18
19
20
21

22 **Statistical analysis**

23
24 We will perform the traditional pairwise meta-analysis on direct
25
26 comparisons based on two or more studies with Stata13.0 (StataCorp,
27
28 College Station, TX, USA). To compare eligible interventions directly
29
30 and indirectly, NMA displaying outcomes of interest is planned using
31
32 WinBUGS version1.4.3 (MRC Biostatistics Unit, Cambridge, UK).
33
34 Pooled hazard ratios (HRs) for OS and DFS with 95%
35
36 confidence intervals (CIs) will be calculated using both fixed- and
37
38 random-effects models. Binary outcomes (acceptability, cardiotoxicities
39
40 and grade 3-4 nonhematologic toxicities) are expressed as odds ratios
41
42 (ORs) with 95% CI. The results of comparative effectiveness and safety
43
44 probability statements of intervention effects will be ranked; and rank
45
46 plots across all outcomes will be generated. The interventions with
47
48 surface under the cumulative ranking (SUCRA) in term of efficacy and
49
50 safety will be evaluated to interpret relative effect of comparisons. We
51
52
53
54
55
56
57
58
59
60

1
2
3
4 will compare the risk-benefit profile of all comparators in terms of
5
6 efficacy and toxicity. A two-sided $p < 0.05$ is considered statistically
7
8 significant.
9

10
11 We will estimate the presence of heterogeneity based on the magnitude
12
13 of I^2 estimated from pairwise meta-analysis models. The heterogeneity is
14
15 considered as evidence of low if $I^2 < 25\%$, as moderate if $25\% \leq I^2 \leq 50\%$,
16
17 and as high if $I^2 > 50\%$. (35) The fixed-effects models will be used when
18
19 the heterogeneity is low and moderate; otherwise, a random-effects
20
21 models will be used. In addition, we will also evaluate the transitivity and
22
23 inconsistency of NMA. The transitivity will be assessed by applying
24
25 descriptive statistics for study types and demographic characteristics.
26
27 Inconsistency will be assessed by comparing deviation information
28
29 criteria (DIC) statistics in the fitted consistency and inconsistency models.
30
31 (36) Global inconsistency between direct and indirect comparisons will
32
33 also be evaluated by using a loop-specific method, if a loop connecting
34
35 three or more arms exists. (37)
36
37
38
39
40
41
42
43
44

45 **Subgroup analysis**

46
47 We will explore whether specific duration of treatments with
48
49 trastuzumab might be more appropriate for particular subtypes of breast
50
51 cancer. We categorize breast cancer into the following groups when
52
53 possible: Estrogen Receptor (ER) positive, ER negative, node positive
54
55 and node negative.
56
57
58
59
60

Sensitivity analysis

We will perform sensitivity analyses to assess the robustness and reliability of findings in our NMA. In order to check the impact of HER2 status on the results, the first sensitivity analysis will exclude patients with HER2 negative after re-evaluating the HER2 status in the E2198 trial. (38) The second sensitivity analysis will restrict hormone receptor-positive to ER + and PR +, ER + and PR -, ER - and PR +. Lastly, the sensitivity analysis will classify patients as 1-3 and ≥ 4 positive lymph nodes to specify the impact of the number of positive lymph nodes.

Discussion

Despite trastuzumab being highly effective in treatment for HER2-positive early breast cancer, its substantial socio-economic burden attracted the attention of governments, academic researchers, pharmaceutical companies and health care payers. With the consideration of balancing efficacy and cardiotoxicity, the 12-month and six-month of trastuzumab treatments have received increasing interests. The requirement to balance efficacy and side effects (i.e. cardiotoxicity) has led to raise interest in reducing trastuzumab duration from 12 months to six months. With the increase in rates of patients reporting 12-month trastuzumab induced cardiotoxicity, most clinicians suggested that a drop to 83% four-year DFS with six months trastuzumab would be also

1
2
3
4 acceptable. (39) This benefit-risk analysis will provide important
5
6 information to help clinicians, patients and policy makers to decide
7
8 optimum duration of adjuvant treatment with trastuzumab in their daily
9
10 practice.
11
12

13
14 The 12 months of treatments with trastuzumab for most women with
15
16 early HER2 positive breast cancer was a standard of care, but most
17
18 crucial RCTs mainly focused on patients with high-risk of recurrence and
19
20 one-year duration was chosen arbitrarily. In contrary, a particular subtype
21
22 of patients might be appropriate for de-escalating duration of treatment,
23
24 without compromising efficacy. Romualdo and his colleagues deemed
25
26 that de-escalating chemotherapy was a good option for older patients and
27
28 those with stage I HER2-positive breast cancer. (40) This study will
29
30 explore whether de-escalating targeted therapy is another option for
31
32 patients with particular subtypes (ER positive and node negative).
33
34
35
36
37
38
39

40 As far as we know, the results of system review will fill a pivotal
41
42 knowledge gap of optimal duration of adjuvant trastuzumab in patients
43
44 with early HER2 positive breast cancer. We hope the findings from this
45
46 NMA will help clinicians, patients and policy makers to select optimal
47
48 duration of adjuvant trastuzumab with the greatest value in HER2
49
50 positive early breast cancers. It will also provide a result that will engage
51
52 patients and policy makers, and will contribute to the public debate on
53
54 future policy options. Furthermore, under-recognized comparisons (e.g.,
55
56
57
58
59
60

1
2
3
4 six months vs nine weeks) may be identified by this Bayesian analysis to
5
6 guide future research.
7

8 9 **Patient and public involvement**

10
11 The manuscript was developed without patient or public participation.
12
13 Breast cancer patient organizations will participate in the discussion and
14
15 dissemination of research results. A summary of the findings will be
16
17 provided to the Chinese society of clinical oncology (CSCO).
18
19
20
21

22 **Ethics and dissemination**

23
24 An ethics approval is not required for the NMA. Important
25
26 modifications to the study protocol will be communicated to all members of
27
28 the research team. The results will be disseminated through international
29
30 conference reports and published in a peer-reviewed journal.
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Author affiliations

1 Department of Abdominal Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

2 Breast Medical Oncology, Clinical Research Center for Breast, West China Hospital, Sichuan University, Chengdu, China.

Acknowledgements

Thanks to Sun Feng and Wu Shanshan (PhD, Perking University School of public Health) for providing assistance and contributing to statistical analysis. (<https://class.dxy.cn/>)

Thanks to Lu Guan (PhD, Fisheries Oceans Canada) for providing assistance and contributing to revisions.

Funding

The network meta-analysis was supported by the National Natural Science Foundation of China (Grant No.81773097).

Author contributions

QcH and DC conceptualized the network meta-analysis. QcH and XW co-developed the search strategy. Both QcH and XW were major contributors in writing the manuscript. The protocol was revised by DC, YC, XfL and TL. DC and TL were serving as guarantor and corresponding author of this study. All authors approved the final manuscript and agreed to submit the protocol in the journal.

Competing interests

1
2
3
4 All authors have completed the ICMJE uniform disclosure form at
5
6 http://www.icmje.org/coi_disclosure.pdf and stated that there is no
7
8 organization to support the submission; no organization is interested in
9
10 the submitted work; no other relationships or activities effect the
11
12 submitted work.
13
14
15

16 Provenance and peer review

17
18
19 Not commissioned; externally peer reviewed
20
21

22 Patient consent for publication

23
24
25 Not required.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

References:

1. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. *Science* 1987;235:177-82.
2. Slamon DJ, Godolphin W, Jones LA, et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science* 1989;244:707-12.
3. Curtis C, Shah SP, Chin SF, et al. The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups. *Nature* 2012;486:346-52.
4. Dawson SJ, Rueda OM, Aparicio S, et al. A new genome-driven integrated classification of breast cancer and its implications. *EMBO J* 2013;32:617-28.
5. Yeon CH, Pegram MD. Anti-erbB-2 antibody trastuzumab in the treatment of HER2-amplified breast cancer. *Invest New Drugs* 2005;23:391-409.
6. Schaefer NG, Pestalozzi BC, Knuth A, et al. Potential use of humanized antibodies in the treatment of breast cancer. *Expert Rev Anticancer Ther* 2006;6:1065-74.
7. Tokunaga E, Oki E, Nishida K, et al. Trastuzumab and breast cancer: developments and current status. *Int J Clin Oncol* 2006;11:199-208.
8. Hortobagyi GN. Trastuzumab in the treatment of breast cancer. *N Engl J Med* 2005;353:1734-6.
9. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659-72.
10. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673-84.
11. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011;365:1273-83.
12. Genuino AJ, Chaikledkaew U, The DO, et al. Adjuvant trastuzumab regimen for HER2-positive early-stage breast cancer: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol* 2019;12:815-24.
13. Niraula S, Gyawali B. Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: a meta-analysis of randomized controlled trials. *Breast Cancer Res Treat* 2019;173:103-09.
14. Cameron D, Piccart-Gebhart MJ, Gelber RD, et al. 11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial. *Lancet* 2017;389:1195-205.
15. Earl HM, Hiller L, Vallier AL, et al. 6 versus 12 months of adjuvant trastuzumab for HER2-positive early breast cancer (PERSEPHONE): 4-year disease-free survival results of a randomised phase 3 non-inferiority trial. *Lancet* 2019;393:2599-612.
16. Pivot X, Romieu G, Debled M, et al. 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomised phase 3 trial. *Lancet Oncol* 2013;14:741-8.
17. Mavroudis D, Saloustros E, Malamos N, et al. Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG). *Ann Oncol* 2015;26:1333-40.
18. Joensuu H, Fraser J, Wildiers H, et al. Effect of Adjuvant Trastuzumab for a Duration of 9

- 1
2
3 Weeks vs 1 Year With Concomitant Chemotherapy for Early Human Epidermal Growth Factor
4 Receptor 2-Positive Breast Cancer: The SOLD Randomized Clinical Trial. *JAMA oncology*
5 2018;4:1199-206.
- 6
7 19. Conte P, Frassoldati A, Bisagni G, et al. Nine weeks versus 1 year adjuvant trastuzumab in
8 combination with chemotherapy: final results of the phase III randomized Short-HER
9 study. *Ann Oncol* 2018;29:2328-33.
- 10
11 20. Joensuu H, Bono P, Kataja V, et al. Fluorouracil, epirubicin, and cyclophosphamide with
12 either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of
13 breast cancer: final results of the FinHer Trial. *J Clin Oncol* 2009;27:5685-92.
- 14
15 21. Chen L, Zhou W, Hu X, et al. Short-duration versus 1-year adjuvant trastuzumab in early HER2
16 positive breast cancer: A meta-analysis of randomized controlled trials. *Cancer treatment*
17 *reviews* 2019;75:12-19.
- 18
19 22. Inno A, Barni S, Ghidini A, et al. One year versus a shorter duration of adjuvant trastuzumab
20 for HER2-positive early breast cancer: a systematic review and meta-analysis. *Breast Cancer*
21 *Res Treat* 2019;173:247-54.
- 22
23 23. Gyawali B, Niraula S. Duration of adjuvant trastuzumab in HER2 positive breast cancer:
24 Overall and disease free survival results from meta-analyses of randomized controlled trials.
25 *Cancer treatment reviews* 2017;60:18-23.
- 26
27 24. Goldvaser H, Korzets Y, Shepshelovich D, et al. Deescalating Adjuvant Trastuzumab in
28 HER2-Positive Early-Stage Breast Cancer: A Systemic Review and Meta-Analysis. *JNCI Cancer*
29 *Spectr* 2019;3:pkz033.
- 30
31 25. Clarke CS, Hunter RM, Shemilt I, et al. Multi-arm Cost-Effectiveness Analysis (CEA) comparing
32 different durations of adjuvant trastuzumab in early breast cancer, from the English NHS
33 payer perspective. *PLoS One* 2017;12:e0172731.
- 34
35 26. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and
36 meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
- 37
38 27. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of
39 systematic reviews incorporating network meta-analyses of health care interventions:
40 checklist and explanations. *Ann Intern Med* 2015;162:777-84.
- 41
42 28. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and
43 meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.
- 44
45 29. Russell SD, Blackwell KL, Lawrence J, et al. Independent adjudication of symptomatic heart
46 failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant
47 therapy: a combined review of cardiac data from the National Surgical Adjuvant breast and
48 Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. *J Clin*
49 *Oncol* 2010;28:3416-21.
- 50
51 30. Yu AF, Singh JC, Wang R, et al. Cardiac Safety of Dual Anti-HER2 Therapy in the Neoadjuvant
52 Setting for Treatment of HER2-Positive Breast Cancer. *Oncologist* 2017;22:642-47.
- 53
54 31. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments
55 meta-analysis: many names, many benefits, many concerns for the next generation evidence
56 synthesis tool. *Res Synth Methods* 2012;3:80-97.
- 57
58 32. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk
59 of bias in randomised trials. *BMJ* 2011;343:d5928.
- 60
33. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of

- 1
2
3 evidence and strength of recommendations. *BMJ* 2008;336:924-6.
4
5 34. Salanti G, Del Giovane C, Chaimani A, et al. Evaluating the quality of evidence from a network
6 meta-analysis. *PLoS One* 2014;9:e99682.
7
8 35. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*
9 2003;327:557-60.
10
11 36. Dias S, Welton NJ, Sutton AJ, et al. Evidence synthesis for decision making 4: inconsistency in
12 networks of evidence based on randomized controlled trials. *Med Decis Making*
13 2013;33:641-56.
14
15 37. Veroniki AA, Vasiliadis HS, Higgins JP, et al. Evaluation of inconsistency in networks of
16 interventions. *Int J Epidemiol* 2013;42:332-45.
17
18 38. Schneider BP, O'Neill A, Shen F, et al. Pilot trial of paclitaxel-trastuzumab adjuvant therapy
19 for early stage breast cancer: a trial of the ECOG-ACRIN cancer research group (E2198). *Br J*
20 *Cancer* 2015;113:1651-7.
21
22 39. Hiller L, Dunn JA, Loi S, et al. Adjuvant trastuzumab duration trials in HER2 positive breast
23 cancer - what results would be practice-changing? Persephone investigator questionnaire
24 prior to primary endpoint results. *BMC Cancer* 2018;18:391.
25
26 40. Barroso-Sousa R, Exman P, Tolaney SM. De-escalating treatment in the adjuvant setting in
27 HER2-positive breast cancer. *Future oncology (London, England)* 2018;14:937-45.
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3
4 A sample Pubmed search strategy was as follows:
5

- 6 #1 Breast Neoplasm [MeSH Terms]
7
8 #2 breast neoplasm [title/abstract]
9
10 #3 neoplasm, breast [title/abstract]
11
12 #4 breast tumors [title/abstract]
13
14 #5 breast tumor [title/abstract]
15
16 #6 tumor, breast [title/abstract]
17
18 #7 tumors, breast [title/abstract]
19
20 #8 neoplasms, breast [title/abstract]
21
22 #9 breast cancer [title/abstract]
23
24 #10 cancer, breast [title/abstract]
25
26 #11 mammary cancer [title/abstract]
27
28 #12 cancer, mammary [title/abstract]
29
30 #13 cancers, mammary [title/abstract]
31
32 #14 mammary cancers [title/abstract]
33
34 #15 malignant neoplasm of breast [title/abstract]
35
36 #16 breast malignant neoplasm [title/abstract]
37
38 #17 breast malignant neoplasms [title/abstract]
39
40 #18 malignant tumor of breast [title/abstract]
41
42 #19 breast malignant tumor [title/abstract]
43
44 #20 cancer of breast [title/abstract]
45
46 #21 cancer of the breast [title/abstract]
47
48 #22 mammary carcinoma, human [title/abstract]
49
50 #23 carcinoma, human mammary [title/abstract]
51
52 #24 carcinomas, human mammary [title/abstract]
53
54 #25 human mammary carcinomas [title/abstract]
55
56 #26 mammary carcinomas, human [title/abstract]
57
58 #27 human mammary carcinoma [title/abstract]
59
60

1
2
3 #28 mammary neoplasms, human [title/abstract]
4
5 #29 human mammary neoplasms [title/abstract]
6
7 #30 human mammary neoplasms [title/abstract]
8
9 #31 neoplasm, human mammary [title/abstract]
10
11 #32 neoplasms, human mammary [title/abstract]
12
13 #33 mammary neoplasm, human [title/abstract]
14
15 #34 breast carcinoma [title/abstract]
16
17 #35 breast carcinomas [title/abstract]
18
19 #36 carcinoma, breast [title/abstract]
20
21 #37 carcinomas, breast [title/abstract]
22
23 #38 breast malignant tumors [title/abstract]
24
25 #39 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR
26
27 #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR
28
29 #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR
30
31 #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR
32
33 #34 OR #35 OR #36 OR #37 OR #38
34
35 #40 Genes, erbB-2[MeSH Terms]
36
37 #41 c-erbB-2 Genes[Title/Abstract]
38
39 #42 c erbB 2 Genes[Title/Abstract]
40
41 #43 c-erbB-2 Gene[Title/Abstract]
42
43 #44 Genes, erbb2[Title/Abstract]
44
45 #45 Gene, erbb2[Title/Abstract]
46
47 #46 erbb2 Gene[Title/Abstract]
48
49 #47 erbb2 Genes[Title/Abstract]
50
51 #48 Genes, HER-2[Title/Abstract]
52
53 #49 HER-2 Gene[Title/Abstract]
54
55 #50 HER-2 Genes[Title/Abstract]
56
57 #51 Genes, neu[Title/Abstract]
58
59 #52 neu Gene[Title/Abstract]
60

1
2
3 #53 neu Genes[Title/Abstract]
4
5 #54 Genes, HER2[Title/Abstract]
6
7 #55 Gene, HER2[Title/Abstract]
8
9 #56 HER2 Gene[Title/Abstract]
10
11 #57 HER2 Genes[Title/Abstract]
12
13 #58 erbB-2 Genes[Title/Abstract]
14
15 #59 erbB 2 Genes[Title/Abstract]
16
17 #60 erbB-2 Gene[Title/Abstract]
18
19 #61 c-erbB-2 Proto-Oncogenes[Title/Abstract]
20
21 #62 c erbB 2 Proto Oncogenes[Title/Abstract]
22
23 #63 c-erbB-2 Proto-Oncogene[Title/Abstract]
24
25 #64 #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47
26
27 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
28
29 #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63
30
31 #65 Trastuzumab[MeSH Terms]
32
33 #66 Herceptin[Title/Abstract]
34
35 #67 #65 OR #66
36
37 #68 #39 AND #64 AND #67
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

only

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Reported on Page #
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	16
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	n/a
Support:			
Sources	5a	Indicate sources of financial or other support for the review	16
Sponsor	5b	Provide name for the review funder and/or sponsor	16
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8-9
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	7-8
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits such that it could be repeated	7-8, supplementary

			file
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	10
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8-9
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9-10
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10-11
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	8-9
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	11-12
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	13
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	13
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10-11
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.