Systematic Review and Meta-Analysis

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6 versus 12 months of adjuvant trastuzumab in HER2+ early breast cancer

A systematic review and meta-analysis

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Abstract

Background: Adjuvant trastuzumab improves survival outcomes of human epidermal receptor 2 positive early breast cancer patients. Currently, administration of 12 months adjuvant trastuzumab is the standard therapy. However, whether 6 months treatment is non-inferior to the standard 12 months treatment remains controversial.

Methods: Relevant records were searched in PubMed, Cochrane Library, Web of Science, and EMBASE through Jan 14, 2020. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) for disease-free survival (DFS) and overall survival (OS) were meta-analyzed. The primary endpoint was DFS with a non-inferiority hazard margin of 1.2 and the second was OS with 1.43.

Results: Three randomized clinical studies met the inclusion criteria, including 3974 patients in 6 months group and 3976 in 12 months group. HR for DFS was 1.18 (95% CI 0.97–1.44, $P = .09$), with the non-inferiority margin comprised in the 95% CI. HR for OS was 1.14 (95% CI 0.98–1.32, $P = .08$), whereas the upper limit of 95% CI did not exceed the non-inferiority hazard margin.

Conclusion: Our analysis failed to show that 6 months treatment was non-inferior to 12 months treatment in improving the DFS. Although the non-inferiority of the 6-month adjuvant trastuzumab treatment was found for OS, considering that breast cancer patients should receive additional systematic therapies when disease progression or relapse happens, we suggest that 12 months adjuvant trastuzumab treatment should remain the standard therapeutic strategy for patients with early human epidermal receptor 2 positive breast cancer.

Abbreviations: CI = confidence interval, DFS = disease-free survival, HER2+ = human epidermal receptor 2 positive, HR = hazard ratio, NCT = National Clinical Trial, OS = overall survival.

Keywords: 6 months, adjuvant, breast cancer, meta-analysis, trastuzumab

Editor: Nazmul Haque.

Ethics approval and consent to participate was not applicable.

Consent for publication: All the authors agree to publish.

Three eligible studies can be downloaded from their official websites or PubMed.

This study was supported by the Hubei Provincial Natural Science Foundation (Grant number: 2020CFB397 to Bi-Cheng Wang), the Independent Innovation Foundation of Wuhan Union Hospital (Grant number: 2019–109 to Bi-Cheng Wang), the Natural Science Foundation of Hubei Province (Grant number: 2019CFB501 to Yan-Xia Zhao), and National Natural Science Foundation of China (Grant number: 81402197 to Yan-Xia Zhao).

The authors have no conflicts of interest to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Wang BC, Xiao BY, Fan JQ, Lin GH, Wang C, Liu Q, Zhao YX. 6 versus 12 months of adjuvant trastuzumab in HER2+ early breast cancer: a systematic review and meta-analysis. Medicine 2021;100:10(e24995).

Received: 10 November 2020 / Received in final form: 9 February 2021 / Accepted: 11 February 2021

http://dx.doi.org/10.1097/MD.0000000000024995

Key points

1. 6 months trastuzumab treatment was not verified to be non-inferior to 12 months treatment for early HER2+ breast cancer.
2. 12 months adjuvant trastuzumab treatment should be the standard therapeutic strategy for early HER2+ breast cancer.

1. Introduction

Administration of 12 months trastuzumab with adjuvant chemotherapy significantly improves the survival outcomes and is the standard-of-care for patients with human epidermal receptor 2 positive (HER2+) operable breast cancer.[1,2] After a median follow-up of 11 years, the results of HERA study further convinced that 12 months of trastuzumab significantly reduced the risks of disease progression (hazard ratio [HR] 0.76, 95% confidence interval [CI] 0.68–0.86) and death (HR 0.74, 95% CI 0.64–0.86) against controlled treatment for HER2+ early breast cancer.[3,4]

Since the standard therapy has been established, challenges to the 12 months treatment duration for trastuzumab have never stopped. According to HERA study, 2 years of adjuvant trastuzumab had no additional benefit on improving disease-free survival (DFS) compared with standard treatment (HR 1.02, 95% CI 0.89–1.17).[4] In order to reduce cardiac toxicity and cost as well as, convenience to patients, a shorter period of trastuzumab administration, such as 9 weeks, 12 weeks and 6 months, might be an attractive treatment option.[5–15]

However, the results among these studies various from each other.[16–18] Researchers still could not demonstrate the non-inferiority of a shorter duration treatment compared to the standard treatment. Although there are studies showing that 9 weeks trastuzumab adjuvant treatment was not non-inferior to 1 year when patients received similar chemotherapy (DFS: HR 1.39; 90% CI 1.12–1.72, noninferiority margin = 1.3),[16,18] most of them are ongoing trials and the complete results have not been reported.

Among the published studies, PHARE, PERSEPHONE, and HORG deeply compared the efficacy of 6 months trastuzumab adjuvant treatment versus 12 months in HER2+ early breast cancer patients.[19–21] However, conclusions remain controversial. HORG and PHARE trials failed to show noninferiority for the 6-month trastuzumab treatment, but PERSEPHONE study showed that 6-month treatment was non-inferior to 12-month treatment in HER2+ early breast cancer patients, which is hard for clinicians or patients to make a choice.

Accordingly, we conducted this systematic review and meta-analysis to synthesize the published data and to find whether 6 months treatment of trastuzumab does show non-inferiority versus 12 months treatment.

2. Methods

This study was conducted according to the guideline of the Preferred Reporting Items for Systematic Reviews and Meta-analyses.[22] Any disagreements in the process of collecting and analyses were resolved by discussion. The collected published data were not original raw data, therefore, ethical approval was not necessary.

2.1. Search strategy

The PubMed, Cochrane Library, Web of Science, and EMBASE online databases were searched to identified relevant articles up to Jan 14, 2020, using the following terms: "breast OR mammary," "cancer OR tumor OR neoplasm OR adenocarcinoma OR carcinoma," "6 months OR six months," "12 months OR twelve months," and "trastuzumab OR Herceptin." Reference lists were reviewed and checked for other relevant studies.

2.2. Study selection

Two authors (B.W. and G. L.) independently conducted the selection. The inclusion criteria were as follows:

(1) studies were prospective randomized clinical trials;
(2) patients were diagnosed as early-stage HER2+ breast cancer;
(3) 6 months versus 12 months adjuvant trastuzumab treatment;
(4) studies were full-text articles and published in English.

For duplicate published trials, the most complete one was eligible.

2.3. Data extraction

The following information was collected: name of the first author, name of the study, registered number, year of publication, study design, mean age, median follow-up time, number of patients, and trastuzumab dose. Hazard ratios (HRs) and 95% confidence intervals (CIs) for DFS and overall survival (OS) were extracted for further analyses. This part was performed by B. W. and G. L. independently.

2.4. Risk of bias assessment

The Cochrane Risk of Bias Tool in RevMan 5.3 (Cochrane Collaboration's Information, Management System Nordic Cochrane Centre, Copenhagen, Denmark) was used to evaluate the risk of bias of the selected trials by B. W. and C. W.

2.5. Statistical analysis

The primary endpoint was DFS and the second was OS. Adjusted HRs were modified for stratification factors, which were estrogen-receptor status and timing of trastuzumab and chemotherapy. The prespecified non-inferiority margin was set at 3% (PERSEPHONE). The disease progression rate in this study was expected to be 15%, while the mortality was 7%. Thus, the margins converted to HRs of 1.2 [(15 + 3)/15] for DFS and 1.43 [(7 + 3)/7] for OS.[23] Non-inferiority was assumed if the 95% CI did not include the non-inferiority margin. Results were classified as inconclusive if the non-inferiority margin was included in the 95% CI. Treatments were assumed to be inferior if the entire 95% CI exceeded the non-inferiority margin.

Heterogeneity among the studies was calculated by using the χ^2 tests. We also quantified the heterogeneity of the results using I^2 statistic percentages. A fixed-effects model (Mantel-Haenszel method) was applied if the heterogeneity test showed no statistical significance ($I^2 \leq 50\%$ or $P \geq .10$). Otherwise, a

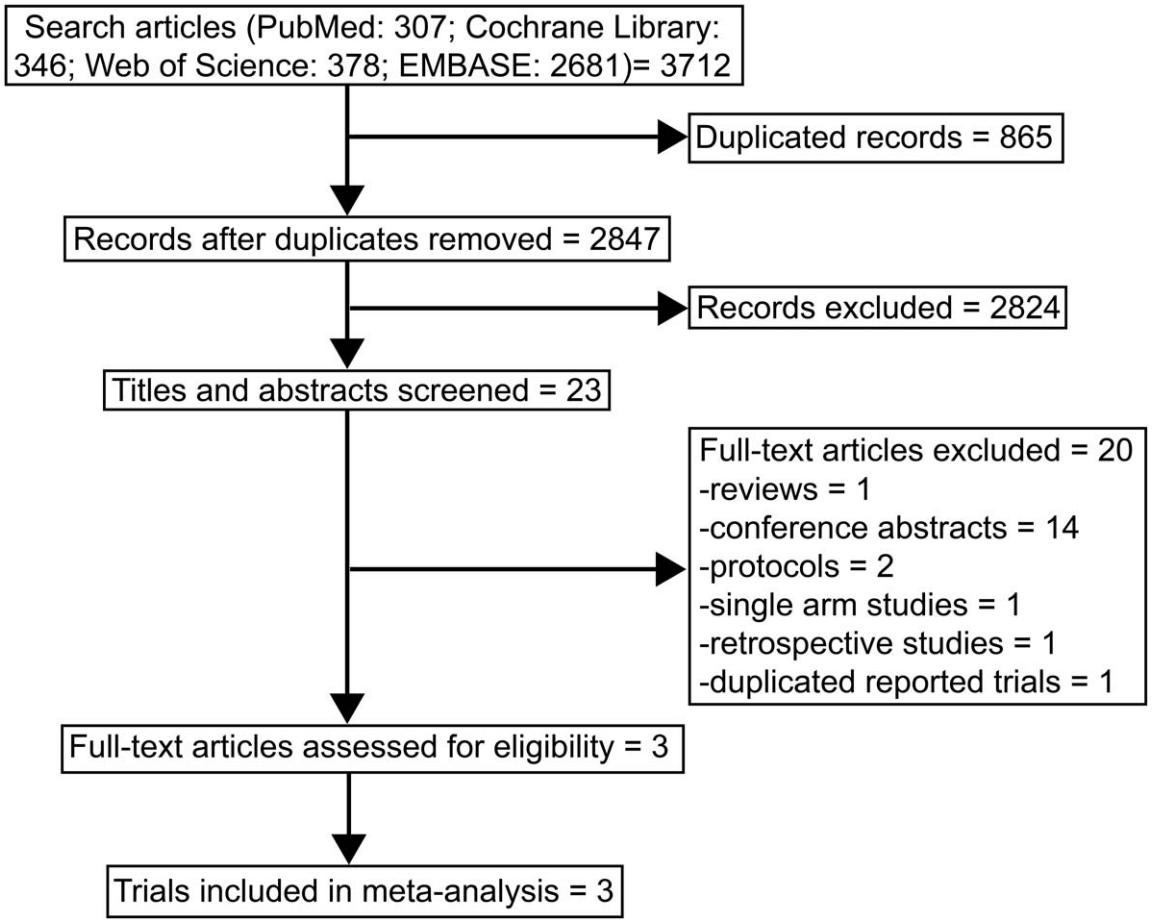

Figure 1. Flow chart of selecting process.

random-effects model was adopted. RevMan software (version 5.3) was used to calculate the above outcomes.

3. Results

2.6. Search results

Figure 1 displays the selection process. 3712 potential records were searched for the initial assessment. After 865 duplicates were excluded, 2847 records were under further evaluation. 2824 studies were excluded after a review of the titles and abstracts. We then excluded 20 articles, including reviews (n = 1), conference abstracts (n = 14), protocols (n = 2), single-arm studies (n = 1), retrospective studies (n = 1), and duplicated reported trials (n = 1). Finally, three full-text articles met the inclusion criteria.[19–21]

2.7. Study characteristics

Table 1 shows the basic characteristics of the eligible studies. Two trials, PHARE and PERSEPHONE, were published in 2019. HORG trial was published in 2015. All three trials were multicenter studies and had been registered with ClinicalTrials.gov. The mean age ranged from 54 to 56. HORG study had the shortest median follow-up time with 4.3 years in 6 months group

Table 1

Characteristics of the eligible studies.

First author	Study name	Registered number	Publication year	Design	Mean age (yr)	Median follow-up (yr)	No. patients	Trastuzumab dose
Pivot	PHARE	NCT00381901	2019	An open-label, multicenter, randomized, phase 3 trial	6 mo: 55 12 mo: 54	7.5	6 mo: 1693 12 mo: 1691	Intravenously: 8 mg/kg initial, 6 mg/kg thereafter
Earl	PERSEPHONE	NCT00712140	2019	An open-label, multicenter, randomized, phase 3 trial	6 mo: 56 12 mo: 56	5.4	6 mo: 2044 12 mo: 2045	Intravenously: 8 mg/kg initial, 6 mg/kg thereafter; subcutaneously: 600 mg
Mavroudis	HORG	NCT00615602	2015	An open-label, multicenter, randomized trial	6 mo: 56 12 mo: 56	6 mo: 4.3 12 mo: 3.9	6 mo: 240 12 mo: 241	Intravenously: 6 mg/kg initial, 4/6 mg/kg thereafter

NCT = National Clinical Trial.

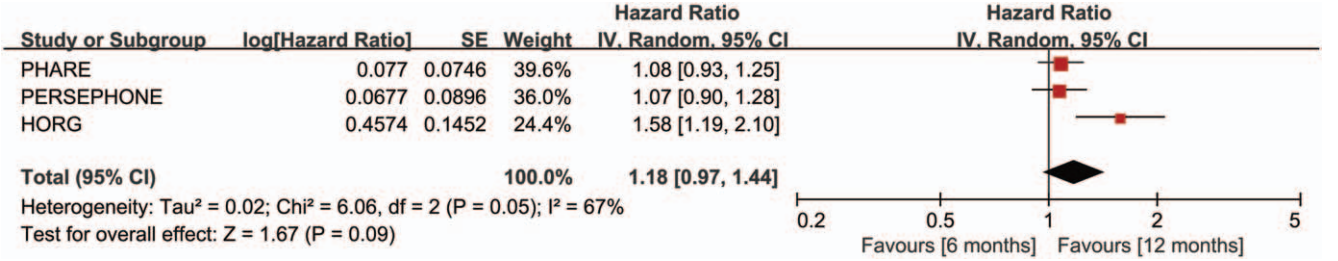

Figure 2. Forest plot of the hazard ratios related to disease-free survival for HER2+ early breast cancer.

and 3.9 years in 12 months group. In increasing order, the median follow-up time was 5.4 years in PERSEPHONE study and 7.5 years in PHARE. Trastuzumab was administered by intravenous infusions every 3 weeks (initials dose: 8 mg/kg; thereafter: 6 mg/kg) in PHARE study, delivered every 3 weeks intravenously (initials dose: 8 mg/kg; thereafter: 6 mg/kg) or subcutaneously (600 mg) in PERSEPHONE study, and administered intravenously every 2 weeks starting concurrently with chemotherapy (initials dose: 6 mg/kg; thereafter: 4 mg/kg) and every 3 weeks thereafter (6 mg/kg) in HORG study.

For chemotherapy regimens, patients enrolled in HORG received epirubicin, cyclophosphamide, and 5-fluorouracil every two weeks for four cycles followed by docetaxel every two weeks for four cycles.[21] While patients who participated in the PHARE and PERSEPHONE studies were treated with four types of chemotherapy regimens, including anthracycline-based, taxane-based, anthracycline-/taxane-based, and no taxane/anthracycline chemotherapies.[19,20]

2.8. DFS

Data regarding DFS were available from all selected studies, with 3974 patients in 6 months group and 3976 in 12 months group. The forest plot indicated that 6 months treatment had an 18% higher risk of disease progression compared to the 12 months treatment (adjusted HR 1.18, 95% CI 0.97–1.44, $P=.09$) (Fig. 2). The unadjusted HR for DFS is 1.20 (95% CI 0.96–1.48, $P=.10$). Both the 95% CIs included the prespecified non-inferiority margin of 1.20.

2.9. Overall survival (OS)

OS data were reported in the three clinical trials. In Figure 3, a 14% higher risk of death was displayed when patients were treated with 6 months trastuzumab versus 12 months (adjusted HR 1.14, 95% CI 0.98–1.32, $P=.08$). The unadjusted OS data were only available from the PERSEPHONE study, showing that the estimated HR was 1.14 with a 95% CI of 0.92 to1.42. Accordingly, the prespecified margin of 1.43 was not comprised in the 95% CIs.

2.10. Toxicities

In HORG study, researchers found that only two participants (0.8%) in the 6 months group stopped trastuzumab at the early stage of post-chemotherapy due to atrial fibrillation and left ventricular dysfunction and reported no adverse events-related deaths. In the long-term follow-up analysis of PHARE, no difference in the cardiac toxicity between the groups was found. However, the data displayed in the PERSEPHONE were not as positive and optimistic as the other two studies. 11% of patients in 12 months group and 8% in 6 months group experienced clinical cardiac dysfunction. And because of that, 8% of patients in 12 months group and 3% in 6 months group discontinued the administration of trastuzumab in the early stage of adjuvant treatment. Therefore, careful monitoring, including electrocardiograph and ultrasound cardiography, and positive treating the heart dysfunctions (e.g. heart failure and ventricular dysfunction) during the trastuzumab treatment is necessary.

2.11. Heterogeneity and risk of bias

Heterogeneities were found in the analyses of DFS but not OS. A random-effect model was used to solve the heterogeneity.

Three studies were all randomized clinical trials and had reported predefined results. Since the selected trials were designed as open-label trials, this analysis should be at a moderate risk of bias for reporting bias (Fig. 4).

4. Discussion

The discordant conclusions in studying the 6 months of adjuvant trastuzumab compared to the 12 months of treatment might

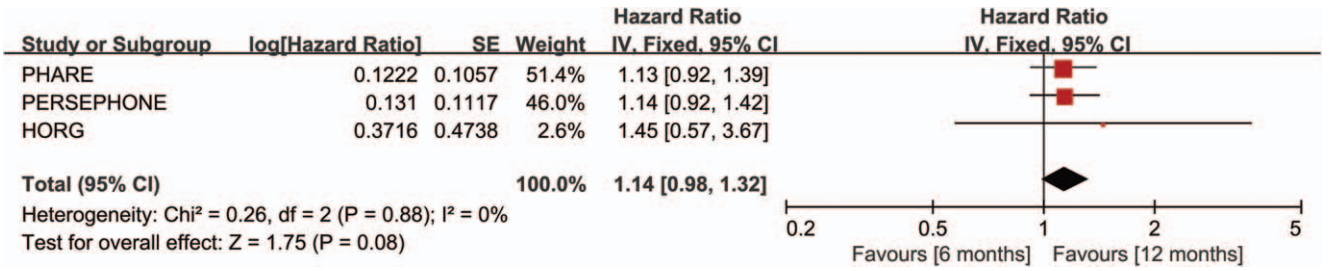

Figure 3. Forest plot of the hazard ratios related to overall survival for HER2+ early breast cancer.

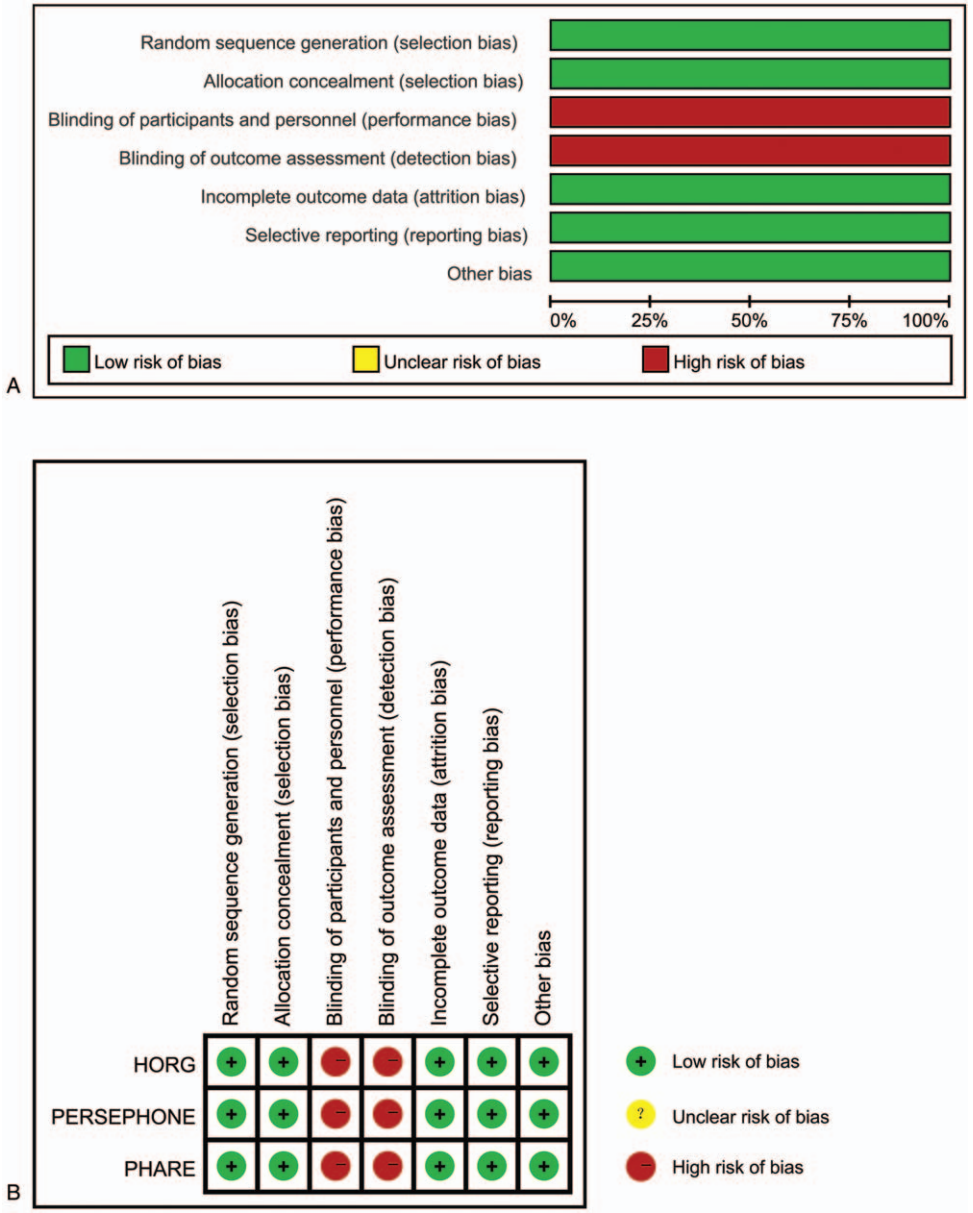

Figure 4. Graph (A) and summary (B) of the risk of bias assessment of the eligible studies.

question clinicians to address a therapeutic strategy aimed at reducing treatment duration and confuse patients. The results from PHARE and HORG studies supported the current administration of adjuvant trastuzumab for 12 months, but the PERSEPHONE study provided a positive result to show non-inferiority for 6 months adjuvant trastuzumab treatment.

Therefore, we conducted this study to comprehensively analyze whether 6 months of adjuvant trastuzumab is non-inferior to 12 months in the treatment of early HER2+ breast cancer patients. Data from published clinical trials were extracted and synthesized. According to our analysis, the results were inconclusive regarding the non-inferiority hypothesis of 6 months treatment for DFS (adjusted HR 1.18, 95% CI 0.97–1.44, non-inferiority margin = 1.20).

Across the eligible studies, patients in HORG study only received one chemotherapy regimen, epirubicin, cyclophosphamide, and 5-fluorouracil followed by docetaxel. But HORG study concluded the highest HRs (DFS: 1.58; OS: 1.45).[21] Participants in the other two studies were treated with at least four types of chemotherapy modalities. The effects of different chemotherapies vary from each other. In the subgroup of PERSEPHONE, more patients received taxane-based chemotherapy in 6 months group (13.8% versus 5.5% in 12 months group) and these patients had a higher risk of disease progression or death (DFS: HR 2.47, 95% CI 1.31–4.62; OS: HR 2.62, 95% CI 1.37–5.00).[20] Moreover, age of patients (HR ranged from 0.92 to 1.11), tumor size (HR ranged from 0.94 to 1.10),[19] nodal status (HR ranged from 0.76 to 1.18), and ER status (HR ranged from 0.92 to 1.11)[20] exert impacts on the results.

Additionally, stringent criteria for defining the acceptable non-inferiority margin were absent, which played a critical role in the interpretation of the results. The PHARE study used a non-inferiority margin of 2% and set a prespecified HR of 1.15.[19] In

PERSEPHONE study, an absolute difference up to 3% was considered acceptable by researchers, with a prespecified HR margin of 1.29.[20] While the HORG study had an original recruitment target of only 481 patients but with an 8% non-inferiority margin.[21] Different margins are set, the interpretation of the results will be different.

For setting and calculating non-inferiority margins, we found that Darius Soonawala provided a useful method.[23] Like this study, we have chosen 3% as the non-inferiority margin both in DFS and OS. After collecting the original data from the eligible studies, we calculated the rates of disease progression (15%) and mortality (7%) in the 12 months group. Then the margin converted to HRs of 1.2 for DFS and 1.43 for OS. As PERSEPHONE study provided a positive result, we thus set 3% as the margin. With a more stringent margin setting, the more difficult it is to confirm the hypothesis that 6 months of trastuzumab treatment is non-inferior to the standard 12-month treatment. If, in this study, the margin was set at 2%, will our conclusion be different? We have tried and calculated for answering the question. According to Darius Soonawala's method, the calculated HR margins are 1.13 [(15 + 2)/15] for DFS and 1.28 [(7 + 2)/7] for OS. Both the 95% CIs include the non-inferiority margin. It's even harder to indicate the non-inferiority of 6 months of adjuvant trastuzumab versus 12 months of treatment. In addition, owing to the disease progression rate of 15% and the mortality rate of 7%, setting a non-inferiority margin at 8% might not be reasonable.

In addition, non-inferiority regarding OS was found for 6-month adjuvant trastuzumab (adjusted HR 1.14, 95% CI 0.98–1.32, non-inferiority margin = 1.43). Nevertheless, it could not be concluded that 6 months trastuzumab treatment was non-inferior to 12 months treatment, since subsequent-line therapies (e.g. chemotherapy, radiotherapy, endocrine therapy or target-therapy) will be administered after they experience a DFS event.[24–28]

2.12. Limitation

All enrolled participants were early HER2 + breast cancer patients. As we discussed above, different age, nodal status, tumor size, endocrine receptors status and chemotherapy type might have impacts on the results. Another potentially important factor, Ki-67, has not been shown in these studies. The proliferative index of Ki-67 might exert critical influence in the selection of treatment strategies.[29–34] Moreover, all the eligible studies were open-label trials, which might partly influence the therapeutic efficacy. Future phase 3 randomized clinical trials in comparing the shorter duration of trastuzumab with 12 months standard of care should be designed as double-blind studies and have more precise subgroup analyses. Additionally, researchers all over the world could reach a consensus on acceptable and reasonable non-inferiority margin in studying the duration of trastuzumab administration. Due to the limited sample, no statistically significant improvement of 6-month trastuzumab treatment compared to standard of care (12 months), but the *P* values are very close to statistical significance. Further study, like Bayesian network analysis, might help to include more direct and indirect samples in a comprehensive meta-analysis.

5. Conclusion

This systematic review and meta-analysis did not show 6 months trastuzumab adjuvant treatment is non-inferior to 12 months, and 12 months might remain the standard therapeutic strategy for early HER2+ breast cancer patients. Explorations of shorter duration trastuzumab treatment are still meaningful because a cohort of breast cancer patients does benefit from the short duration treatment. Future clinical trials are warranted to confirm the suitable populations

Acknowledgments

We thank the members of the SNOWELL STUDIO for helping to improve the grammar and spelling.

Author contributions

Study design: B. W. and B. X., data extraction, and data analysis: B. W., G. L. and C. W.; Manuscript writing and edition: B. W., B. X., J. F., Q. L., and Y. Z..
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Data curation: Bi-Cheng Wang, Guo-He Lin, Chang Wang.
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Funding acquisition: Bi-Cheng Wang.
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Writing – review & editing: Bi-Cheng Wang, Bo-Ya Xiao, Ji-Quan Fan, Quentin Liu, Yan-Xia Zhao.

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