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Systematic or Meta-analysis Studies

Short-duration versus 1-year adjuvant trastuzumab in early HER2 positive breast cancer: A meta-analysis of randomized controlled trials

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ABSTRACT

Background: One year of adjuvant trastuzumab treatment is the standard of care for early stage human epidermal growth factor receptor 2 (HER2)-positive breast cancer patients; however, controversy remains regarding the optimal schedule of trastuzumab because the selection of the 1-year schedule was arbitrary. After the remarkable results of the PERSEPHONE trial as well as the updated final results of the PHARE trial, we performed an updated meta-analysis to reassess the efficacy and safety of shorter durations of trastuzumab.

Methods: A literature search of databases was conducted to identify randomized controlled trials reporting the efficacy and cardiotoxicity of shorter-duration and standard 1-year trastuzumab treatment. The hazard ratios (HRs) of disease-free survival (DFS) and overall survival (OS), and the odds ratios (ORs) of cardiac events were also estimated and pooled.

Results: Six studies were eligible, including a total of 11,496 patients. Both DFS (HR = 1.13; 95% confidence interval [CI] = 1.03–1.25; p = 0.01) and OS (HR = 1.16; 95% CI = 1.01–1.32; p = 0.03) were significantly improved with conventional 1-year trastuzumab treatment compared with shorter treatments. The more pronounced survival benefits observed in patients with negative estrogen receptor (ER) tumor and nodal involvement should be interpreted cautiously because of the lack of interaction between the survival benefit and ER, as well as the nodal status (interaction test, ER status: p = 0.26; nodal status: p = 0.60). One year of trastuzumab treatment resulted in a substantial DFS benefit compared with shorter schedules when administered concurrently with chemotherapy (HR = 1.22; 95% CI = 1.09–1.38; p = 0.0008; p = 0.02 for the interaction test). Patients in the shorter duration group experienced significantly fewer cardiac events (OR = 0.52; 95% CI = 0.43–0.62; p < 0.00001).

Conclusions: Though correlated with an increasing risk of cardiotoxicity, 1 year of adjuvant trastuzumab treatment conferred substantial survival benefits and should remain as the preferred treatment for early stage HER2-positive breast cancer. Shorter durations of trastuzumab may serve as an alternative choice for patients with cardiac disease and those at lower risk of recurrence.

Introduction

Human epidermal growth factor receptor (HER2) is overexpressed and/or amplified in approximately 15%–20% of early breast cancer patients [1] and is correlated with a worse prognosis. As an anti-HER2 humanized monoclonal antibody, trastuzumab can significantly reduce the risk of recurrence and improve the prognoses of HER2-positive patients [2–6]. According to a Cochrane meta-analysis, trastuzumab confers a reduction in mortality by one-third, in relapse rate of 40%, in combination with (neo)adjuvant chemotherapy [7]. The HERA trial [8] and a joint analysis of NASBP B-31 and NCCTG N9831 [9] further confirmed that trastuzumab substantially and persistently improved survival.

Although trastuzumab has been considered as the standard of care for patients with early HER2-positive breast cancer since 2005, the optimal duration of administration is still a matter of controversy,

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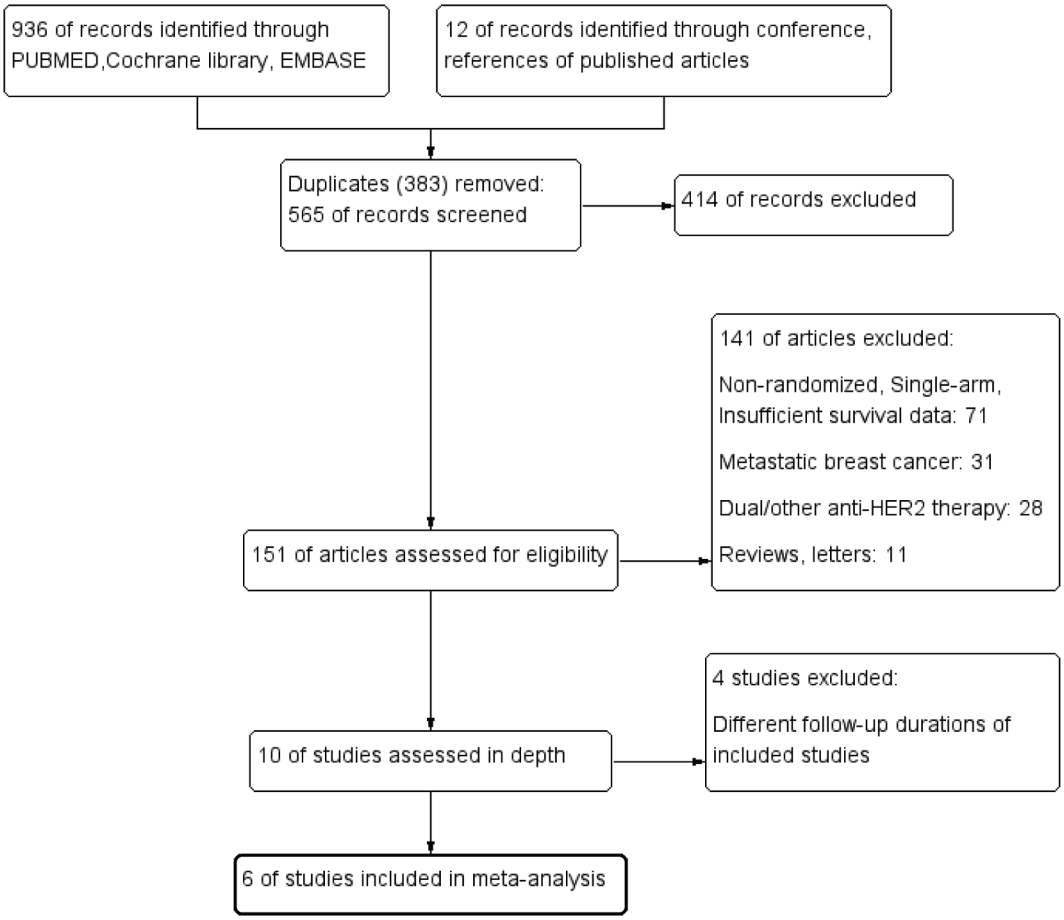

Fig. 1. Flow chart of study selection.

because the 12-month period was chosen arbitrarily rather than based on scientific evidence. Interruption of trastuzumab treatment in responding patients correlates with earlier disease progression in those with metastatic disease [10]. Therefore, the goal of improved efficacy has motivated studies on prolonged anti-HER2 therapy. Indeed, the ExteNET trial reported improved survival in early HER2-positive breast cancer patients who received neratinib after 1 year of trastuzumab treatment [11]. However, the newly updated results from the HERA trial showed no evidence of an additional benefit from a second year of trastuzumab compared with 1 year of treatment [8]. Conversely, the FinHer trial showed that a brief course (9 weeks) of trastuzumab concomitant with chemotherapy led to improved survival with limited cardiotoxicity [12]. The E2198 trial also reported no substantial benefit from a 1-year treatment [13]. These observations suggested that shorter periods of trastuzumab administration may confer comparable benefits, but with reduced cardiotoxicity and costs.

Increasing evidence for shorter course of trastuzumab treatment has been reported to further explore the optimal duration of trastuzumab [14]. However, most studies failed to demonstrate non-inferior efficacy of a shorter course of trastuzumab compared with conventional 1-year treatment [15–17,10]. A large meta-analysis of major randomized controlled trials (RCTs) reported improvements in both overall survival (OS) and disease-free survival (DFS) in females with early stage HER2-positive breast cancer treated with 1 year of trastuzumab compared with shorter durations of treatment [18]. Remarkably, the results of the PERSEPHONE trial, reported for the first time at the 2018 American Society of Clinical Oncology (ASCO) Annual Meeting, showed that 6 months of adjuvant trastuzumab was non-inferior to 1 year of treatment [4 year DFS: 89.4% vs. 89.8%; hazard ratio (HR) = 1.07; 90% confidence interval (CI) = 0.93–1.24; p = 0.01)] [19]; this finding has attracted much attention and may serve as potential rationale for the application of shorter courses of trastuzumab. However, the updated final results of the PHARE trial with 7.5 years follow-up failed to demonstrate the non-inferiority of short-term trastuzumab [20].

Using the newly reported results of the SOLD trial [17] and the updated results of the Short-HER trial [21], PERSEPHONE trial [19] and PHARE trial [20], this meta-analysis was performed to investigate the efficacy and toxicity of shorter courses of trastuzumab.

Methods

The meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [22]. A literature search of databases was conducted, including PubMed/MEDLINE, Cochrane library, and EMBASE, up to December 2018. In addition, the ASCO, San Antonio Breast Cancer Symposium (SABCS), and European Society for Medical Oncology (ESMO) Meeting websites were searched for pertinent presentations, abstracts, and references of related reviews. The search terms were as follows: (breast cancer OR breast neoplasms OR breast tumor OR breast carcinoma) and (trastuzumab OR herceptin) and (random* OR prospective*).

Selection criteria

This meta-analysis was based on RCTs comparing shorter durations of trastuzumab in the experimental arm with 1 year of trastuzumab in the control arm, in early stage breast cancer patients with positive HER2 status. Full papers and conference abstracts providing sufficient data to assess survival outcomes (DFS and/or OS) were eligible for inclusion. Studies that included advanced or metastatic breast cancer

Table 1
Characteristics of included studies.

Authors/Study	Period	N	Study Design	Treatment	MF	Survival HR (95% CI)	Cardiac events (shorter vs 1y)
Conte et al. Short-HER	2007.12–2013.10	1253	multicenter, phase III RCT, non-inferiority (HR < 1.29)	D + H → FEC AC/EC → T/D + H 9w vs 1y	6 y	DFS:1.13 (0.89–1.42) OS: 1.07 (0.74–1.56)	8/626 vs 18/627
Earl et al. PERSEPHONE	2007.10–2015.7	4088	multicenter, phase III RCT, open-label non-inferiority (HR < 1.29)	Anthracycline/ Taxane +H (concurrent/sequential) 6 m vs 1y	64.8m	DFS: 1.07 (0.90–1.28) OS: 1.14 (0.92–1.42)	82/2043 vs 164/2045
Joensuu et al. SOLD	2008.1–2014.12	2174	multicenter, phase III RCT, open-label superiority → non-inferiority (HR < 1.3)	D + H → FEC ± H 9w vs 1y	62.4m	DFS: 1.39 (1.08–1.79) OS: 1.36 (0.92–2.01)	22/1085 vs 42/1089
Mavroudis et al. HORG	2004.6–2012.5	481	multicenter, phase III RCT, non-inferiority (HR < 1.53)	FEC → D + H 6 m vs 1y	51m	DFS: 1.57 (0.86–2.10) OS: 1.45 (0.57–3.67)	–
Pivot et al. PHARE	2006.5–2010.7	3380	multicenter, phase III RCT, open-label non-inferiority (HR < 1.15)	Anthracycline/ Taxane +H (concurrent/sequential) 6 m vs 1y	7.5y	DFS: 1.08 (0.93–1.25) OS: 1.13 (0.92–1.39)	67/1690 vs 111/1690
Schneider et al. E2198	1999.8–2000.10	120*	phase II RCT	T + H → AC ± H 12w vs 1y	77m	DFS: 0.85 (0.41–1.77) OS: 1.21 (0.46–3.13)	–

Abbreviations: N = number of patients; AC = doxorubicin/cyclophosphamide; EC = epirubicin/cyclophosphamide; FEC = 5-FU/epidoxorubicin/cyclophosphamide; T = paclitaxel; D = Docetaxel; H = herceptin; MF = median follow-up; HR = Hazard Ratio; DFS = disease-free survival; OS = overall survival.
* Total number of patients in the E2198 trial was 303, but only 120 HER2-positive patients left after reassessed HER2 status in November 2013.

(MBC) patients, and those evaluating anti-HER2 combinations, were deemed ineligible. In addition, studies not reporting outcomes of interest were excluded.

Data extraction and quality assessment

Two authors extracted all data independently. The HR and 95% CI of DFS and OS were extracted from the original studies, or were estimated following Parmar et al. [23] and Tierney et al. [24]. The methodological quality of the eligible studies was independently assessed by the authors using the Cochrane risk-of-bias tool, which covers selection bias, performance bias, detection bias, attrition bias, and reporting bias [25,26]. Disagreements were resolved through discussion and consensus.

Statistical analysis

Data on HR and odds ratios (ORs) were pooled using a fixed-effect model, except for outcomes with significant heterogeneity; in such cases a random-effect model was used. Heterogeneity was quantified using the inconsistency index (I^2) and the Σ^2 test. Significant heterogeneity was considered to exist when $p < 0.1$ or $I^2 > 50\%$. Subgroup analyses were conducted according to estrogen receptor (ER) status and nodal status, as well as the timing of trastuzumab treatment for chemotherapy, to assess their potential contributions to outcomes. Publication bias was evaluated using funnel plots and Egger's tests [27]. The meta-analysis was performed using RevMan software (ver. 5.3).

Results

Study selection

A total of 948 studies were retrieved, of which 383 were removed owing to duplication or overlap (determined using Endnote software). Another 414 studies were excluded on screening the titles and abstracts. Of the remaining 151 full-text articles, 141 were excluded. Ultimately, six RCTs that compared shorter durations of trastuzumab with standard 1-year treatment were included. Fig. 1 shows the details of the study selection process and the exclusion criteria.

Characteristics of eligible studies

The characteristics of the included studies are listed in Table 1; all six [10,13,17,19,21,20] were included in the survival analysis, and four were eligible for analysis of cardiac events (PHARE, SOLD, Short-HER, and PERSEPHONE) [17,19,21,28]. Survival data of the updated PERSEPHONE trial [19] and the PHARE trial [20] were not published, and the presentation slides from the ASCO and SABCS annual meetings in 2018 were used to collect data of the two trials, respectively. The risk of bias for each study is reported in Table 2.

Survival outcomes

The meta-analysis of efficacy outcomes included 11,496 patients. Both DFS (HR = 1.13; 95% CI = 1.03–1.25; p = 0.01; I^2 = 0%) (Fig. 2) and OS (HR = 1.16; 95% CI = 1.01–1.32; p = 0.03; I^2 = 0%) (Fig. 3) were significantly improved with the conventional 1-year trastuzumab treatment compared with shorter treatments [DFS: 9 or 12 weeks vs. 1 year, HR = 1.23 (1.03–1.48); 6 months vs. 1 year, HR = 1.09 (0.97–1.23); OS: 9 or 12 weeks vs. 1 year, HR = 1.23 (0.93–1.63); 6 months vs. 1 year, HR = 1.14 (0.98–1.33); p for interaction test: 0.28 and 0.65, respectively (data not shown)]. Neither the funnel plot (data not shown) nor Egger's test (p = 0.494) indicated significant publication bias.

In terms of ER and nodal status, 1-year adjuvant trastuzumab treatment conferred a significant improvement in DFS in patients with

Table 2
Risk of bias summary for each included study.

Study	Selection bias	Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias
Conte et al.	Low	Unclear	Unclear	Low	Low	Low
Earl et al.	Low	Low	Low	Low	Low	Low
Joensuu et al.	Low	Low	Low	Low	Low	Low
Mavroudis et al.	Low	Low	Low	Low	Low	Low
Pivot et al.	Low	Low	Unclear	Low	Low	Low
Schneider et al.	Low	Unclear	Unlcear	Low	Low	Low

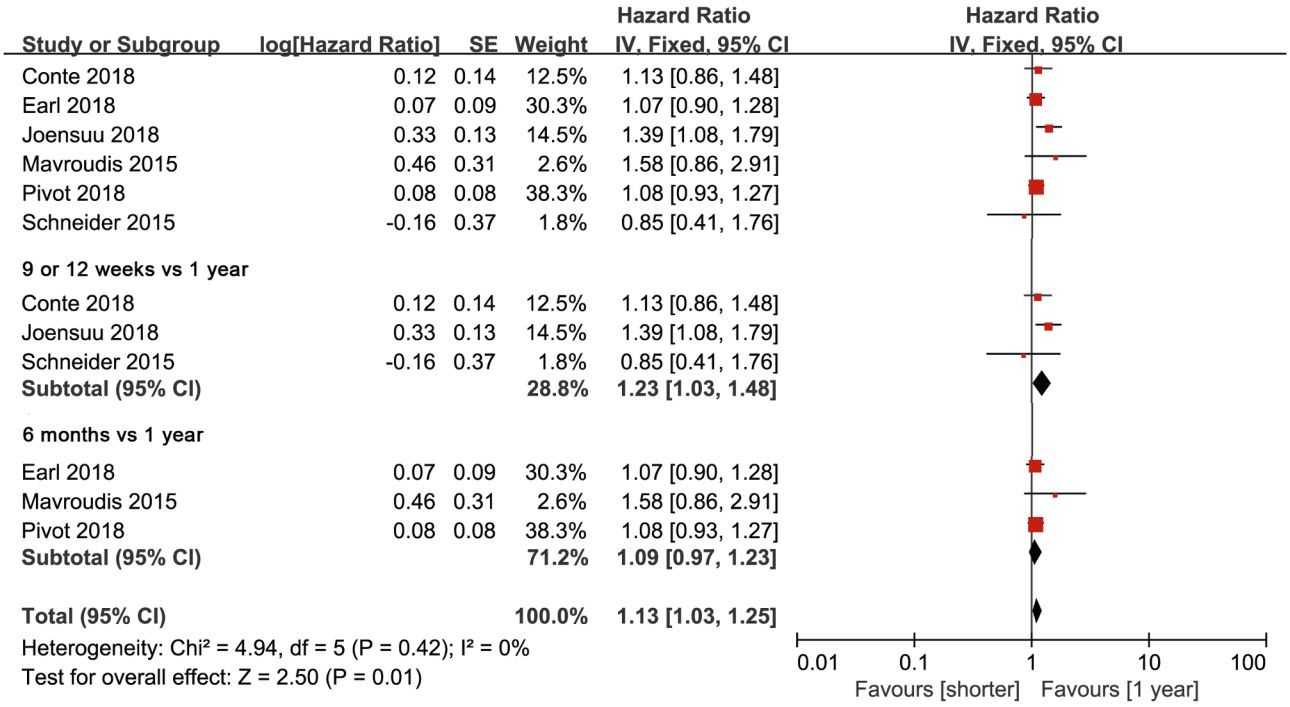

Fig. 2. Forest plot of hazard ratios (HRs) comparing disease-free survival (DFS) of patients treated with shorter-duration versus 1-year trastuzumab.

hormone receptor-negative tumors (HR = 1.23; 95% CI = 1.07–1.41; p = 0.004) and nodal involvement (HR = 1.18; 95% CI = 1.01–1.38; p = 0.04), while the effect was less pronounced in ER-positive (HR = 1.10; 95% CI = 0.97–1.25; p = 0.14) and nodal-negative patients (HR = 1.11; 95% CI = 0.93–1.32; p = 0.24). However, there was no interaction between DFS and ER or nodal status (interaction test, ER status: p = 0.26, nodal status: p = 0.60, respectively) (Fig. 4A and B). To further explore the heterogeneity, a subgroup analysis was performed based on the timing of the addition of trastuzumab to the chemotherapy regimen (i.e., concomitant or sequential). Pooled analyses showed a substantial and permanent DFS benefit with 1-year versus shorter-duration trastuzumab when administered as a concurrent treatment with chemotherapy (HR = 1.22; 95% CI = 1.09–1.38; p = 0.0008), while no difference in outcome between the two groups was found when trastuzumab was given sequentially after chemotherapy (HR = 0.97; 95% CI = 0.83–1.12; p = 0.65). In addition, there was a significant interaction between DFS and the timing of trastuzumab treatment (p = 0.02; Fig. 4C).

Cardiac events

Cardiac events were detailed in four studies, and a total of 10,895 patients were included. Pooled analysis demonstrated a statistically lower incidence of cardiac events in the shorter treatment duration group (OR = 0.52; 95% CI = 0.43–0.62; p < 0.00001) (Fig. 5).

Discussion

This was an updated meta-analysis of RCTs that compared shorter-duration trastuzumab treatment with the conventional 1-year schedule in early HER2-positive breast cancer, with a significant survival benefit being seen with the latter schedule. First, we demonstrated that both 9-week (or 12-week) and 6-month trastuzumab treatment were inferior to the 1-year treatment. We also showed that the benefits of 1-year treatment were more pronounced when trastuzumab was administrated concurrently with adjuvant chemotherapy.

According to the PERSEPHONE investigator questionnaire, most responders would change their clinical practice to 6-month trastuzumab treatment if non-inferior efficacy was confirmed by the trial [29]. However, most of the major phase III RCTs, but not the PERSEPHONE trial, failed to establish non-inferior efficacy of shorter-duration trastuzumab treatment. Although no significant heterogeneity was observed in the pooled analysis, there were some differences between studies that should be noted. First, approximately 60% of the patients had node-negative disease in the PERSEPHONE trial [29], compared with 20–55% in similar non-inferior studies [10,21,20]. Moreover, the proportion of ER-positive patients in the PERSEPHONE trial (69%) was also higher than that in the HORG (65%) and PHARE trial (58%), respectively. The percentages of node-negative (range: 0–32%) and ER-positive (range: 50–54%) patients were even lower in the four major studies (NASBP B-31, NCCTG N9831, BCIRG 006, and HERA) that together established 1-year trastuzumab treatment as the standard of care

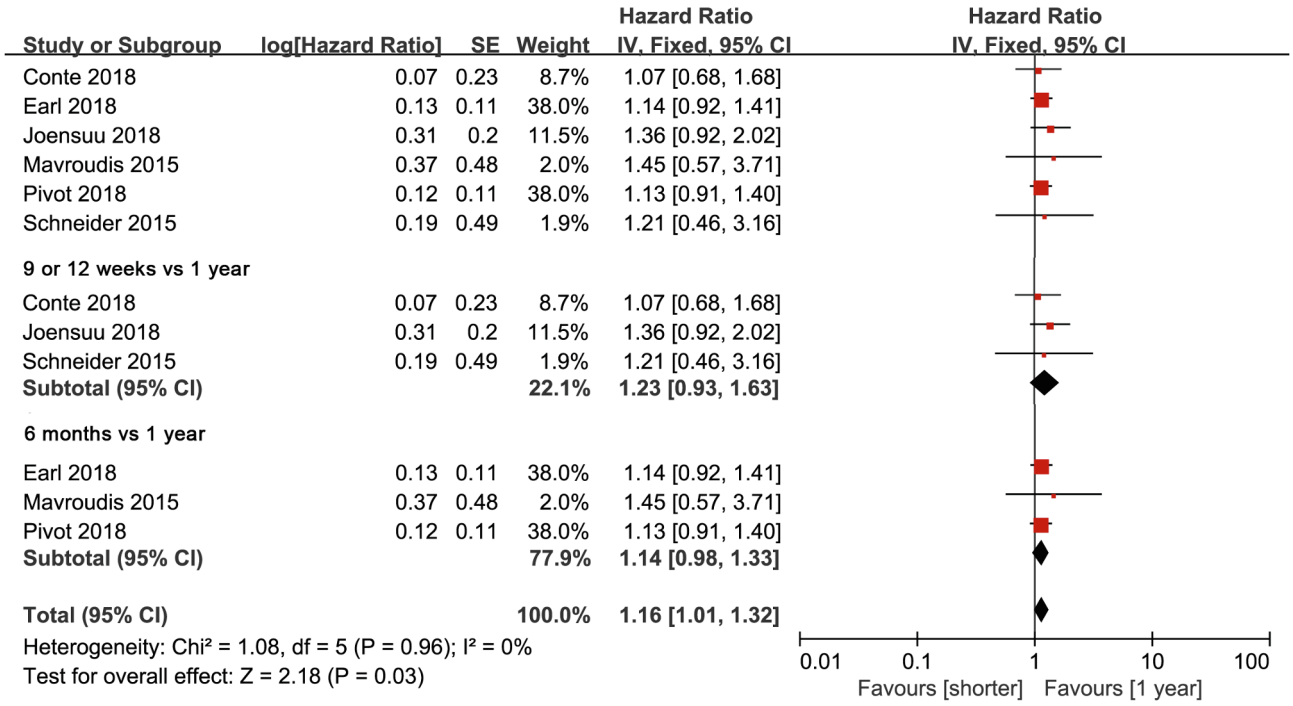

Fig. 3. Forest plot of HRs comparing the overall survival of patients treated with shorter-duration versus 1-year trastuzumab.

for HER2-positive early breast cancer patients [2,4,8,3]. Actually, patients from real world are more likely to present with low-risk features as compared to patients enrolled in the pivotal randomized trials which evaluated chemotherapy ± 1-year trastuzumab [30]. The PERSEPHONE trial therefore recruited a group of patients with relatively low-risk profiles, which may be more representative of real-world patients. Second, the treatment duration in the SOLD [17] and Short-HER [16] was short (9 weeks), making it more challenging to establish the non-inferiority of short-duration treatment. On the other side, in the SOLD trial [17], patients who received co-administration of 100 mg/m^2 of docetaxel in 9-week group had similar, and those who received 80 mg/m^2 in 9-week group had inferior DFS to patients in the 1-year group treated with the same docetaxel dosing. An interaction between docetaxel dose and DFS was observed, suggesting that full dose of the co-administered taxane should be given with brief course of trastuzumab regimens. Mark D. Pegram et al. [31] have reported synergistic cytotoxic interactions for trastuzumab plus docetaxel, carboplatin, cyclophosphamide, and vinorelbine. And a highly synergistic interaction between trastuzumab, carboplatin, and docetaxel was observed even with very low drug concentrations [31]. Thus, there is reason to speculate that different dosing, treatment interval and partner drugs of different trials may lead to inconsistent results. And a more efficient combination therapy could make short-term trastuzumab more effective.

While there was no additional survival benefit of extended trastuzumab treatment [8], dual anti-HER2 therapy with trastuzumab plus neratinib or trastuzumab plus pertuzumab yielded significant improvements in survival in an adjuvant setting, as reported in the ExteNET [11] and the APHINITY trials [32], respectively. The NCCN Panel considers it reasonable to incorporate pertuzumab into trastuzumab-containing regimens [33]. Nevertheless, it should be noted that the survival benefits of 1-year trastuzumab and dual anti-HER2 therapy were more pronounced in patients with a higher risk of recurrence [8,32], and the benefit from dual anti-HER2 treatment was confined to certain patients presented with higher-risk features. A sub-study of the PHARE trial showed that the absolute benefit of 1-year trastuzumab was particularly small in the very low risk group [34]. And subgroups analysis of the Short-HER trial showed that patients at low and intermediate risk of relapse had similar 5-year DFS with a 9-week course of trastuzumab (88%) as with 1 year (89%; HR 1.02, 95%CI 0.78–1.33) [35]. As reported in the SOLD trial [17], there was only a 1% absolute difference between the longer and shorter groups in clinically important survival outcomes, so patients who are unable to complete standard-duration trastuzumab treatment still show a favorable outcome. It is thus reasonable to assume that there may be a group of patients who can safely undergo a shorter than 1 year trastuzumab duration. The key here is to identify subgroups of patients who could obtain comparable benefit from shorter-duration trastuzumab treatment.

According to the pooled results of the subgroup analyses, there was no significant survival benefit in ER-positive and node-negative patients having longer treatments; however, it should be noted that there was no significant interaction between survival and ER or nodal status, so the subgroup results should be interpreted cautiously. Similarly, previous studies indicated that the benefits of trastuzumab were independent of ER status [4,8]. However, a significant interaction between DFS and ER status was observed in the PHARE trial [15], which prompted separate analyses to determine the true impact of trastuzumab duration. Because the timing of events of patients with low-risk tumors (such as hormone receptor- and node-negative tumors) is later than that of high-risk patients, it takes longer to verify the true benefit of trastuzumab in the former group; thus, a longer follow-up is required to yield reliable data.

Although trastuzumab is usually well-tolerated, with cardiac events being reversible, the associated cardiotoxicity is not negligible. The pooled results demonstrated significantly fewer cardiac events with shorter-duration trastuzumab versus the 1-year schedule. Higher rates of trastuzumab-related congestive heart failure were observed in older patients with cardiac comorbidities [36,14], and as suggested by the PERSEPHONE trial, the longer the administration of trastuzumab, the greater the cardiac toxicity and the longer the recovery time [37]. Furthermore, 6 months of trastuzumab was shown to be cost effective compared to 1-year treatment. Indeed, it was associated with cost savings while maintaining similar quality-adjusted life years (QALY) at 2 years [38]. Therefore, shorter-duration trastuzumab could reduce

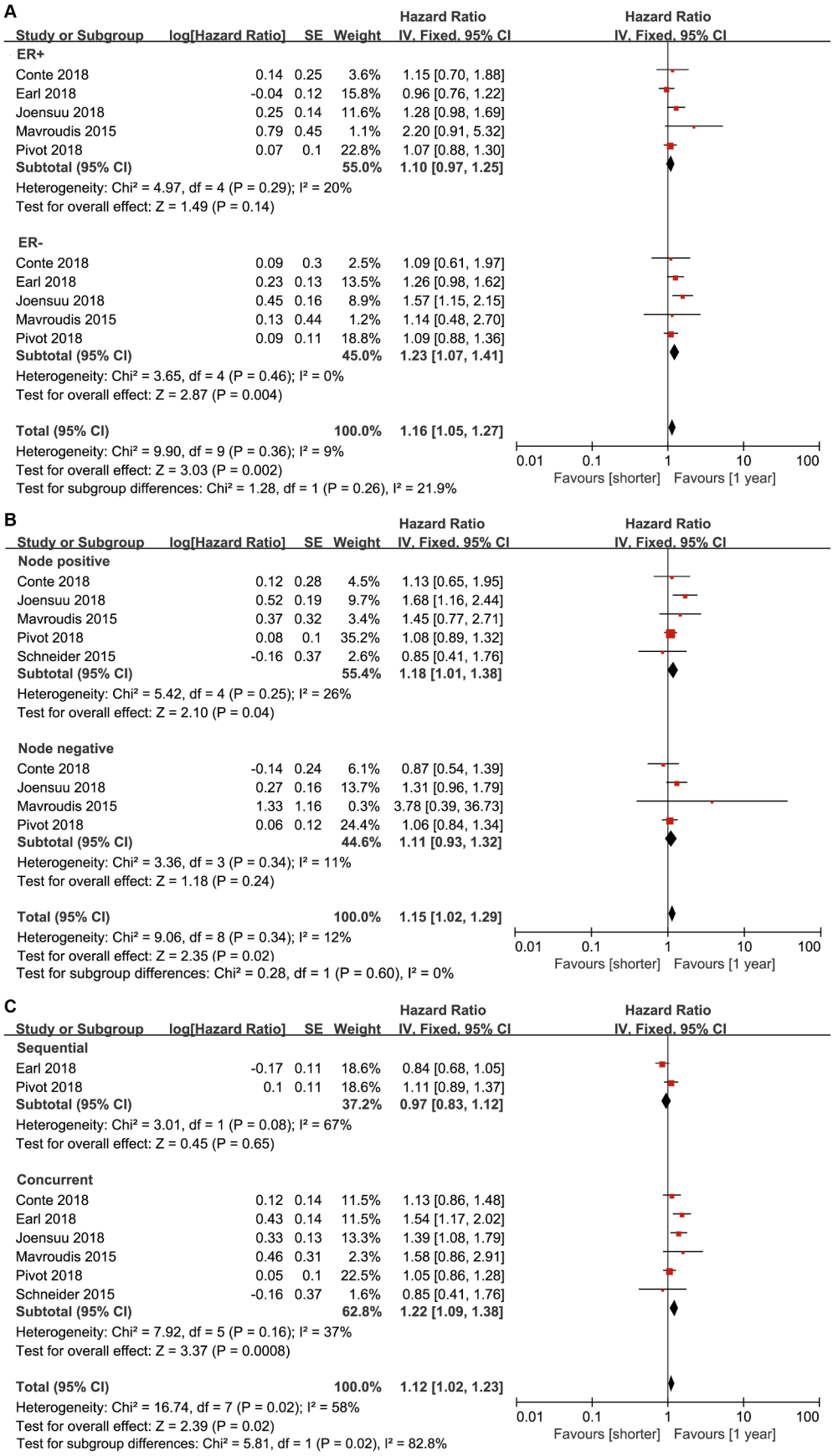

Fig. 4. The HR plot for DFS of subgroup analyses by (A) estrogen receptor status, (B) nodal status, and (C) administration timing of trastuzumab (sequential vs. concurrent).

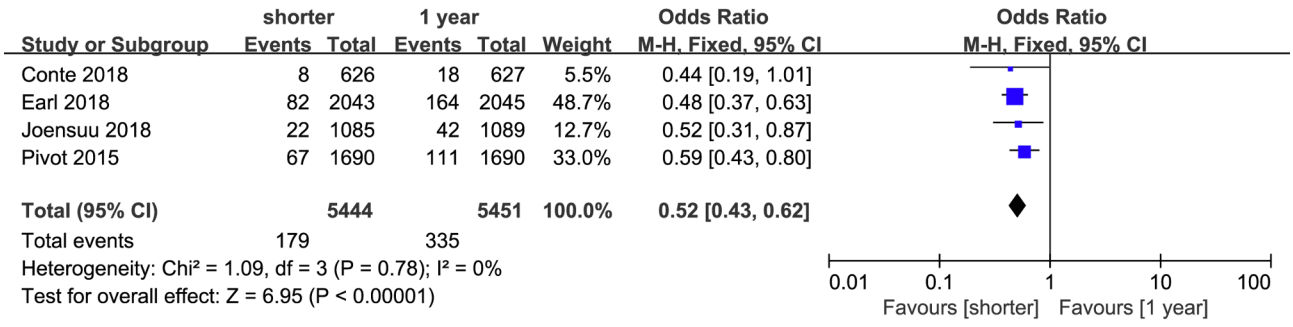

Fig. 5. Forest plot of odds ratios comparing cardiac events of patients treated with shorter-duration versus 1-year trastuzumab.

cardiotoxicity and costs, and enhance the convenience of treatment and compliance of patients. Shorter-duration trastuzumab may be the preferred treatment option in older patients with cardiac comorbidities.

In addition to the treatment duration, the timing of administration of trastuzumab might affect efficacy. As shown in our subgroup analyses, 1-year trastuzumab administrated concurrently with chemotherapy conferred better survival than a shorter treatment schedule, while no significant difference was observed between shorter- and longer-duration when trastuzumab was provided as a sequential treatment. This is consistent with the PACS04 trial, which reported no significant decrease in relapse when trastuzumab was administered according to a sequential schedule [39]. The NCCTG N9831 trial also suggested that trastuzumab be given concurrently with adjuvant chemotherapy, as a standard-of-care alternative to sequential treatment [5]. Data have increasingly shown that the immune system contributes substantially to the anti-tumor effects of trastuzumab. By attenuating DNA repair activity and increasing apoptosis, co-administration of trastuzumab and chemotherapy could augment chemotherapy-induced cytotoxicity [40,41]. Thus, for patients with high-risk profiles without signs of cardiac dysfunction, 1-year of trastuzumab concurrently with chemotherapy is the actual standard schedule. Most importantly, it is necessary, but also challenging, to optimize the risk–benefit trade-off according to the characteristics of the individual patients in clinical practice.

There were some limitations of the present meta-analysis. First, it was based on aggregated data from published literature rather than individual patients; therefore, differences in study design, such as inconsistent margins set for non-inferiority, and different definitions of HER2 overexpression and short-term treatment durations, may have reduced the reliability of the results. However, the outcomes of the studies were based on the actual number of events in the experimental and control groups, regardless of the non-inferiority margins, and the pooled analysis showed no obvious heterogeneity. In addition, determining treatment superiority via a meta-analysis of non-inferiority studies is statistically acceptable [42]. Second, despite the lack of publication bias, the limited number of eligible studies included in the analysis may have contributed to the inconsistent results. And due to the reassessment of HER2 scoring in 2013 according to the College of American Pathologist (CAP) guidelines, there were only 120 patients with HER2-positive tumors left in the E2198 trial, leading to a limited sample size. Given that the PERSEPHONE trial as well as the E2198 trial provided convincing evidence for non-inferior efficacy of short-term trastuzumab to conventional schedules, further RCTs, especially studies focusing on patients with low recurrent risk are required to improve our understanding of the effects of these shorter schedules. Third, the HRs derived from included studies were based on different follow-up durations, which may have introduced bias. According to the Cochrane handbook [43], a simple assumption is often made that the HR is constant across the follow-up period; this is known as the proportional hazards assumption, where results can be combined using the generic inverse-variance method. Although limitations existed, overall, our pooled results were reasonable and convincing.

In conclusion, although correlated with an increasing risk of cardiotoxicity, 1-year adjuvant trastuzumab treatment conferred robust and persistent benefits in terms of DFS and OS, and should therefore be considered as the standard of care for early stage HER2-positive breast cancer patients. Shorter durations of trastuzumab may achieve a good balance between efficacy and cardiotoxicity, and serve as an alternative choice for patients with cardiac disease or a lower risk of recurrence. Additional RCTs are warranted to further identify subgroups of patients in whom comparable efficacy (to the conventional schedule) with a shorter duration of trastuzumab treatment could be achieved.

Author contributions

GY and CY conceived the study, and take responsibility for the integrity of the data and accuracy of the data analysis. LC and WZ did the literature research, performed study selection, data extraction and synthesis. XH and MY participated in the analysis and interpretation of the data, WZ wrote the draft review paper. LC and GY revised the manuscript critically for important intellectual content and redrafted some of its section. All the authors read and approved the final version of the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

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