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Cardiotoxicity of trastuzumab given for 12 months compared to shorter treatment periods: a systematic review and meta-analysis of six clinical trials

Daniel Eiger ,[1] Maria Alice Franzoi,[1] Noam Pondé,[2] Mariana Brandão,[1] Claudia de Angelis,[3] Melanie Schmitt Nogueira,[4] Quentin de Hemptinne,[5] Evandro de Azambuja [1]

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For numbered affiliations see end of article.

Correspondence to
Dr Evandro de Azambuja;
evandro.azambuja@bordet.be

ABSTRACT

Background Treatment de-escalation in early-stage, human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) has been attempted in order to decrease costs and toxicities. One of the strategies pursued is decreasing trastuzumab treatment duration, with mixed results thus far. Trastuzumab-associated cardiotoxicity, however, may be more frequent with 12 months of trastuzumab compared with shorter treatment lengths. Therefore, we have conducted a meta-analysis to address this question.

Materials and methods A meta-analysis of trials testing 12 months of adjuvant trastuzumab versus shorter regimens, reporting cardiac outcomes in patients with HER2-positive BC was performed with the random effects model with inverse variance weighting.

Results Clinical cardiac dysfunction associated with 12 months of trastuzumab versus shorter trastuzumab regimens, including 11 250 patients, showed a pooled OR (pOR) of 1.90 (95% CI 1.37 to 2.64; p value <0.001; I^2=65.7%); in the subgroup comparison of 12 versus 6 months, the pOR was 1.57 (95% CI 1.30 to 1.90; p<0.001; I^2=5.7%). pOR for low left ventricular ejection fraction was 1.45 (95% CI 1.19 to 1.75; p<0.001; I^2=11.9%), 1.55 (95% CI 1.00 to 2.42; p=0.052; I^2=0.0%) for congestive heart failure and 3.70 (95% CI 0.27 to 51.60; p=0.33; I^2=78.8%) for premature trastuzumab discontinuation due to cardiotoxicity for 12 months versus shorter trastuzumab regimens. Funnel plot analyses indicated a low risk of publication bias.

Conclusions Compared to shorter treatment durations, there is sufficient evidence that 12 months of trastuzumab yields higher odds for the occurrence of relevant cardiac events. An individual patient-level data meta-analysis is needed in order to provide adequate data on risk factors for cardiotoxicity.

INTRODUCTION

Targeted therapy against the human epidermal growth factor receptor 2 (HER2) for patients with early-stage, HER2-positive breast cancer (BC) has turned an aggressive

Key questions

What is already known about this subject?

- Twelve months of adjuvant anti-human epidermal growth factor receptor 2 (HER2) therapy with trastuzumab is fundamental in the care of patients with early-stage, HER2-positive BC, although trastuzumab-associated cardiotoxicity may partially undermine its benefits.
- Currently, treatment durations of trastuzumab shorter than 12 months are of interest from a pharmacoeconomic and toxicity perspective, although the equivalence of these shorter regimens, in terms of efficacy, is still debated.

What does this study add?

- We sought to determine if and how worse trastuzumab for 12 months compares to shorter treatment durations in terms of cardiotoxicity, by means of a meta-analysis of trials comparing two treatment durations.
- Dichotomous data from six randomised clinical trials were pooled with a random effects model, which showed that 12 months of trastuzumab increases the odds of clinical cardiac dysfunction compared with 6 months (pooled OR (pOR)=1.57 (95% CI 1.30 to 1.90; p<0.001; I^2=5.7%)) and low left ventricular ejection fraction events (pOR=1.45 (95% CI 1.19 to 1.75; p<0.001; I^2=11.9%)).
- Although with a low incidence in both treatment durations (1.1% to 1.8%), trastuzumab for 12 months compared with 9–12 weeks increases the odds of congestive heart failure as well (pOR=1.68 (95% CI 1.01 to 2.81; p=0.047; I^2=0.0%)).

How might this impact on clinical practice?

- In light of this worse cardiotoxicity profile, proper cardiac function monitoring should be pursued, especially when 12 months of trastuzumab is given. An individual patient-level data meta-analysis is warranted, in order to identify those in which shorter trastuzumab duration, particularly 6 months, would merit consideration due to cardiac limitations.

disease, known for its metastatic and early relapsing potential, into one with the highest cure rates among BC subtypes.[1] Nonetheless, trastuzumab, the monoclonal antibody that introduced this paradigm shift to HER2-positive BC, may induce cardiotoxicity, usually in the form of asymptomatic left ventricular dysfunction, but sometimes as overt congestive heart failure (CHF) and rarely cardiac death.[2]

As the standard 12 months schedule of adjuvant trastuzumab was empirically defined, several studies have tested shorter regimens.[3–8] Heretofore, mixed results have been found regarding the equivalence of these shorter regimens compared with 12-month schedules in terms of efficacy, according to individual trials' results,[9] and a few meta-analyses,[10–12] whereas the longer regimen may indeed be more cardiotoxic.[13 14] This meta-analysis therefore aims at quantifying trastuzumab-associated cardiotoxicity odds of 12 months of trastuzumab compared with shorter regimens in patients with early-stage, HER2-positive BC .

MATERIALS AND METHODS

Search strategy and studies eligibility

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used as guidance for this meta-analysis.[15] Medline/PubMed search was performed in order to identify randomised clinical trials testing shorter adjuvant trastuzumab regimens versus 12-month regimens in early-stage, HER2-positive BC, with the following algorithm: ('breast cancer' OR 'breast neoplasm' OR 'breast tumor' OR 'breast tumour' OR 'breast tumours' OR 'Breast Neoplasm' (MeSH)) AND ('HER2 positive' OR 'HER2/neu positive') AND ('trastuzumab' OR 'Herceptin') AND ('adjuvant therapy' OR 'adjuvant treatment' OR 'early stage' OR 'adjuvant') AND (randomised clinical trial (pt) OR controlled clinical trial (pt) OR randomised (tiab) OR placebo (tiab) OR drug therapy (sh) OR randomly (tiab) OR trial (tiab) OR groups (tiab)) NOT (animals (mh) NOT humans (mh)). No time or language restriction was applied. Afterwards, conference proceedings were sought via electronic search of abstract repositories of the major international congresses, that is the American Society of Clinical Oncology annual meeting, the European Society for Medical Oncology annual meeting and the San Antonio Breast Cancer Symposium. The last search was updated on 14 July 2019.

Articles were eligible for data extraction whenever they reported the comparison, within the scope of a randomised clinical trial, of a shorter versus the standard 12-month regimen of adjuvant trastuzumab in patients with early-stage, HER2-positive BC, with reported cardiac outcomes. The most recent publication of each study was used for data extraction. Cardiac outcomes of interest for this meta-analysis were clinical cardiac dysfunction, low left ventricular ejection fraction (LVEF), CHF and premature trastuzumab discontinuation due to cardiotoxicity.

Data extraction and outcomes

Study eligibility and data extraction were performed independently by two authors (DE and MSN), with disagreement between authors resolved by consensus. Extracted data for each study consisted of first author name, year of publication, trial acronym (if any), number of patients per treatment arm, outcomes definitions in each trial, number of events per outcomes of interest and treatment arm, chemotherapy backbone, and LVEF schedules of assessment.

Four distinct cardiac outcomes were investigated, as defined below, in order to capture all individual study definitions, whenever available:

1. Clinical cardiac dysfunction: symptoms of CHF and a significant decrease in LVEF, or introduction of a new cardiac medication, or a grade 2 or higher cardiac side-effects (per the Common Toxicity Criteria (CTC) V.3), including cardiac deaths. A significant decrease in LVEF could either be any decrease under 50%, regardless of baseline value, or an absolute decrease of 15% or more, despite LVEF remaining above 50%.
2. Low LVEF: a decrease to lower than 50% or reported as low without quantification, regardless of baseline value, or a decrease of more than 15% despite LVEF remaining above 50%.
3. CHF: defined as heart failure New York Heart Association class III or IV with a significant LVEF decrease, or grade 3 or 4 LVEF dysfunction per CTC V.3.
4. Premature trastuzumab discontinuation due to cardiotoxicity: non-completion of the assigned trastuzumab treatment duration due to any given clinical cardiac dysfunction.

Quality of eligible studies

To ascertain the quality of each individual study, two authors (DE and MAF) independently used Cochrane Risk of Bias (RoB) tool V.2, ascertaining five different domains, and a final agreement was reached on whether a trial had an overall low, unclear or a high RoB.[16]

Data analysis

Incidence rate and respective 95% CI of each cardiac outcome per treatment arm was calculated by extracting the number of corresponding events and the total number of patients per arm.

Following extraction, dichotomous data (cardiac outcome vs no cardiac outcome) was pooled with a random effects model with inverse variance weighting. All effect sizes were measured by the ORs model and 95% CI, with an OR >1 indicating that 12 months of trastuzumab increases the odds of a given outcome, compared with shorter regimens. Subgroup analyses were performed per outcome whenever ≥2 studies were pooled for each of the subgroup comparisons (12 months vs 6 months and 12 months vs 9–12 weeks). The

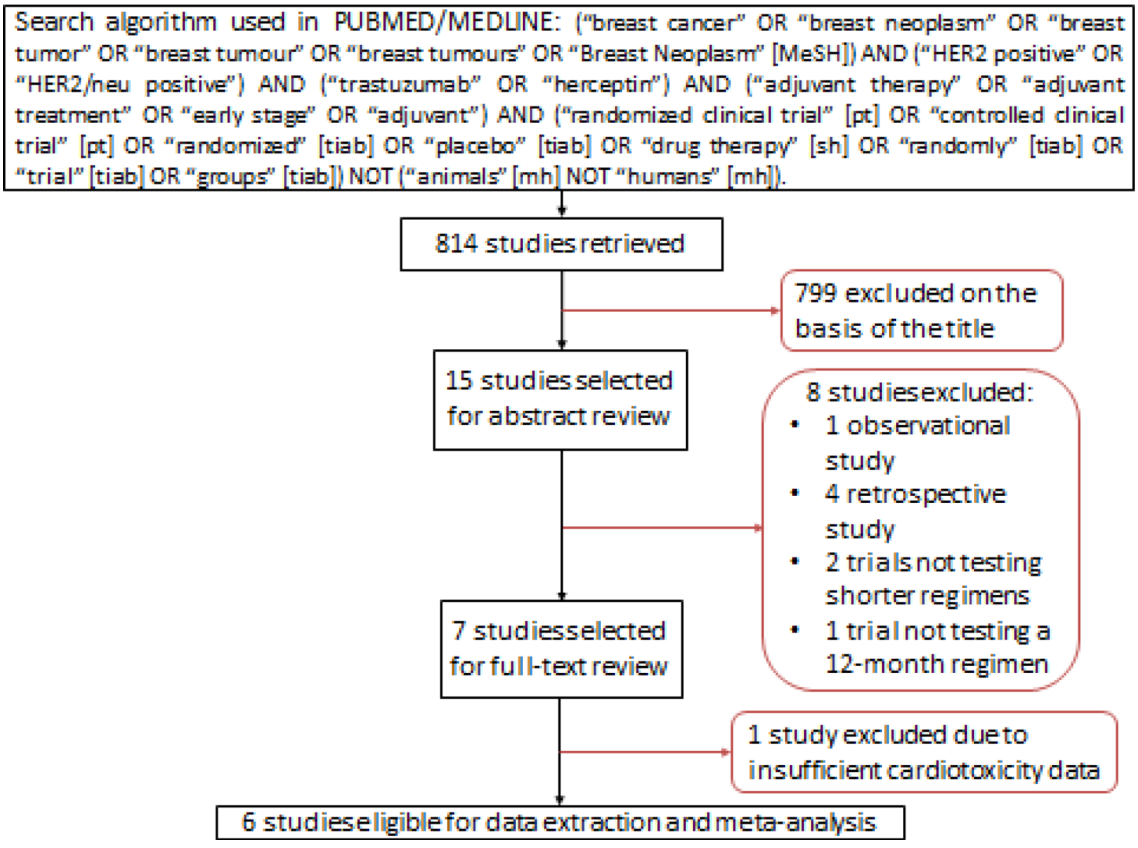

Figure 1 Flowchart diagram of study selection, showing that from an initially retrieved 814 studies from PubMed/Medline, six were selected for this meta-analysis.

leave-one-out procedure was performed whenever ≥3 studies were analysed. For sensitivity analysis, a second meta-analysis of rare cardiac events, defined as those occurring in around 1% of patients in any treatment arm of any study, was performed with Peto's method.[17] Graphical representations with forest plots using log scale for each cardiac outcome and pooled effect size, with respective 95% CIs are provided.

Heterogeneity was assessed with the I^2 test (substantial heterogeneity whenever I^2 ≥50%).[18] Publication bias was ascertained by visual inspection of funnel plots and Egger regression test, despite the inherent constraints of these methods for small meta-analysis.[19 20] All reported p values are two-sided, with significance set at $p<0.05$.

All analyses were performed with Comprehensive Meta-Analysis V.3 (Biostat, Englewood, New Jersey, USA),[21] and with OpenMEE for metafor R package (Brow University, Providence, Rhode Island, USA).[22 23]

RESULTS

Trials characteristics

From 814 references retrieved, 799 were excluded on the basis of their titles, 8 were excluded, due to various reasons, after reviewing their abstracts and following the full-text review of 7 studies, one was excluded due to insufficient cardiotoxicity data (figure 1). Hence six trials,[3–8] all published in peer-reviewed journals, were eligible for data extraction and meta-analysis.

There were three trials (PERSEPHONE, PHARE and HORG) testing a 6-month versus a 12-month schedule of adjuvant trastuzumab,[3–5] and two trials (Short-HER and SOLD) comparing a 9-week versus a 12-month schedule,[6 7] all designed as non-inferiority phase III trials. All five trials had efficacy assessment as their main objective. The E2198, a phase II comparative trial,[8] tested the cardiac safety of 12 weeks of adjuvant trastuzumab versus 12 months. Details regarding chemotherapy backbone, LVEF schedule of assessment and cardiac outcomes per trial are provided in table 1. Of note, most patients in the six eligible trials received anthracycline-based chemotherapy. It is important to highlight, however, an imbalance in the expected total cumulative anthracycline dose by treatment arm, which may have disadvantaged the 12-month arm in Short-HER, since those patients were assigned to four cycles of doxorubicin or epirubicin plus cyclophosphamide (up to 240 mg/m^2 of doxorubicin or 360 mg/m^2 of epirubicin, respectively) while patients in the 9-week arm were assigned for only three cycles of 5-fluorouracil plus epirubicin plus cyclophosphamide (up to 180 mg/m^2 of epirubicin). Minor differences in LVEF schedule of assessment may be noted between treatment

Table 1 Clinical trials of shorter trastuzumab adjuvant regimens in early stage, HER2-positive breast cancer

Trial and year	Number of points per arm	ChT backbone	LVEF schedule of assessment*	Number of events per cardiac outcomes (%)			
				Clinical cardiac dysfunction	Low LVEF	CHF	Premature trastuzumab discontinuation†
6 Months versus 12 months							
PERSEPHONE 2019[3]	Exp: 1994	90% used an anthracycline	Initially q3m for 12 m; after amendment q4m for 12 m	Exp: 155 (8)	176 (9)	NA	61 (3)
	Comp: 1968			Comp: 224 (11)	228 (11)	NA	146 (8)
PHARE 2019[4]	Exp: 1690	89% used an anthracycline	First 2 years: q3m; 2–5 years: q6m	Exp: 67 (4)	58 (3)	9 (1)	0 (0)
	Comp: 1690			Comp: 111 (7)	95 (6)	11 (1)	49 (3)
HORG 2015[5]	Exp: 240	ddFEC x 4 → ddDocetaxel × 4	Exp: q3m for 6 m	Exp: 2 (1)	NA	NA	2 (1)
	Comp: 241		Comp: q3m for 12 m	Comp: 0 (0)	NA	NA	0 (0)
9[a]–12[b] weeks versus 12 months							
Short-HER 2018[a,6]	Exp: 626	Docetaxel × 3 → FEC × 3	q3m for 12 m, at the 18th m and yearly thereafter	Exp: 27 (4)	NA	NA	NA
	Comp: 627	AC or EC × 4 → Taxane × 4		Comp: 82 (13)	NA	NA	NA
SOLD 2018[a,7]	Exp: 1085	Docetaxel × 3 → FEC × 3	At weeks 18, 31, 43, and 61, and at the 36th m	Exp: 22 (2)	NA	21 (2)	NA
	Comp: 1089			Comp: 42 (4)	NA	36 (3)	NA
E2198 2015[b,8]	Exp: 117‡	Paclitaxel x 4 → AC × 4	Exp: at the third, sixth and 18th m	Exp: NA	NA	3 (3)	NA
	Comp: 117‡		Comp: at the third, sixth, 12th, 18th and 30th m	Comp: NA	NA	4 (3)	NA

*All trials required a baseline LVEF ≥50% for inclusion.
†Due to cardiotoxicity.
‡The intention-to-treat population was used for the toxicity analysis, differing in the number of patients used for the efficacy analysis.
AC, doxorubicin +cyclophosphamide; CHF, congestive heart failure; ChT, chemotherapy; Comp, comparator (arm); dd, dose dense; Exp, experimental (arm); FEC, 5-fluorouracil+epirubicin + cyclophosphamide; LVEF, left ventricular ejection fraction; m, months; NA, not available.

Table 2 Pooled incidences of cardiac outcomes according to treatment arms

Arm	Number of events/patients	Incidence (95% CI)	Short regimens	Number of events/patients	Incidence (95% CI)
Clinical cardiac dysfunction					
Trastuzumab 12 months	459/5615	8.2% (7.5% to 8.9%)	–	–	–
Trastuzumab short regimen	273/5635	4.8% (4.3% to 5.4%)	Trastuzumab 6 months	224/3924	5.7% (5.0% to 6.5%)
–	–	–	Trastuzumab 9 weeks	49/1711	2.9% (2.2% to 3.8%)
Low LVEF					
Trastuzumab 12 months	323/3730	8.7% (7.8% to 9.6%)	–	–	–
Trastuzumab short regimen	234/3728	6.3% (5.5% to 7.1%)	Trastuzumab 6 months*	234/3728	6.3% (5.5% to 7.1%)
CHF					
Trastuzumab 12 months	51/2896	1.8% (1.3% to 2.3%)	–	–	–
Trastuzumab short regimen	33/2892	1.1% (0.8% to 1.6%)	Trastuzumab 6 months	9/1690	0.5% (0.3% to 1.0%)
–	–	–	Trastuzumab 9–12 weeks	24/1202	2.0% (1.4% to 3.0%)
Premature trastuzumab discontinuation					
Trastuzumab 12 months	249/3825	6.5% (5.8% to 7.3%)	–	–	–
Trastuzumab short regimen	95/3869	2.5% (2.0% to 3.0%)	Trastuzumab 6 months*	95/3869	2.5% (2.0% to 3.0%)

*Results available only for trastuzumab 6 months.
CHF, congestive heart failure; LVEF, left ventricular ejection fraction.

arms only in two trials,[5 8] which were not expected to introduce bias.

Pooled cardiac outcomes incidences

Five trials reported clinical cardiac dysfunction as an outcome. Among 5615 patients treated with a 12-month trastuzumab duration, 459 experienced clinical cardiac dysfunction, for a pooled incidence of 8.2% (95% CI 7.5% to 8.9%), while for the 5635 patients treated with shorter durations, 273 experienced clinical cardiac dysfunction, for a pooled incidence of 4.8% (95% CI 4.3% to 5.4%). The pooled incidences of low LVEF were 8.7% (95% CI 7.8% to 9.6%) and 6.3% (95% CI 5.5% to 7.1%), of CHF were 1.8% (95% CI 1.3% to 2.3%) and 1.1% (95% CI 0.8% to 1.6%) and of premature trastuzumab discontinuation due to cardiotoxicity were 6.5% (95% CI 5.8% to 7.3%) and 2.5% (95% CI 2.0% to 3.0%), respectively. Further details regarding pooled incidences of cardiac outcomes according to type of short regimens may be found in table 2.

Risk of bias assessment

Quality of each individual trial is depicted in figure 2, highlighting that three of them had an overall low RoB and three had unclear RoB. Bias assessment concerning each domain, for every trial, is provided as online supplementary material in the appendix.

Meta-analysis results

All trials but E2198 reported clinical cardiac dysfunction, including 11 250 patients, showing a pooled OR (pOR) of 1.90 (95% CI 1.37 to 2.64; p value <0.001) for 12 month versus shorter trastuzumab regimens, which was, however, heterogeneous (I^2=65.7%). When separated by subgroups, the pOR of 12-month versus 6-month regimens was 1.57 (95% CI 1.30 to 1.90; p<0.001), without heterogeneity (I^2=5.7%); the pOR of 12-month versus 9-week regimen was 2.59 (95% CI 1.52 to 4.40; p<0.001), with heterogeneity (I^2=58.1%). The leave-one-out procedure (forest plot provided as online supplementary figure S1 in the appendix) showed Short-HER to have the most weight in both the OR and heterogeneity of the analysis (minus Short-HER pOR=1.60 (95%CI 1.37 to 1.90; p<0.001; I^2=0.0%)).

The low LVEF meta-analysis included the PERSEPHONE and PHARE trials, summing 7342 patients and showing a pOR of 1.45 (95% CI 1.19 to 1.75; p<0.001), without heterogeneity (I^2=11.9%).

Among 3 studies and 5788 patients, the pOR for CHF of 12 month versus shorter regimens was 1.55 (95% CI 1.00 to 2.42; p=0.052), without heterogeneity (I^2=0.0%). Subgroup analysis showed a pOR for the comparison of 12 month versus 9–12 weeks trastuzumab of 1.68 (95% CI 1.01 to 2.81; p=0.047; I^2=0.0%). Since CHF events were rare, a prespecified sensitivity analysis with Peto's method showed a significant increase in the odds of CHF with 12 month versus shorter trastuzumab regimens (Peto's OR=1.55; 95% CI 1.00 to 2.38; p=0.048; I^2=0.0%; online supplementary figure S2).

There were three trials (7823 patients) reporting premature trastuzumab discontinuation. The pOR of 12 month versus shorter trastuzumab regimens was 3.70 (95% CI 0.27 to 51.60; p=0.330; I^2=78.8; online supplementary

Figure 2 RoB assessment of the five domains (bias arising from the randomisation process; due to deviations from intended interventions; due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result) per trial, indicating that some concerns always arose from the measurement of the cardiac outcome. RoB, risk of Bias.

figure S3). The absence of statistical significance and high heterogeneity was maintained following a sensitivity analysis with Peto's method (Peto's OR=2.69; 95% CI 0.83 to 8.68; p=0.098; I^2=88.6; online supplementary figure S4). Figure 3A–C shows the forest plot for each cardiac outcome, including subgroup analyses, and online supplementary figures S5 and S6 show the leave-one-out procedure plots for CHF and premature trastuzumab discontinuation events, respectively.

Publication bias analysis

No funnel plot was generated for the low LVEF meta-analysis due to the restricted number of studies included.

For the other cardiac outcomes, symmetric funnel plots and Egger regression p values >0.05 were found (see online supplementary figure S7A–C), therefore no publication biases are expected, although these meta-analyses are overall small.

DISCUSSION

As hypothesised, 12 months of trastuzumab compares unfavourably with shorter durations of treatment in terms of cardiotoxicity. Although we have found high heterogeneity for the meta-analysis of clinical cardiac dysfunction (I^2=65.7%), subgroup analyses were able to confirm a higher odds of having clinical cardiac dysfunction with 12 months of trastuzumab versus 6 months (pOR=1.57 (95% CI 1.30 to 1.90; p<0.001; I^2=5.7%)). For a clinically relevant cardiac outcome, such as grade 2–4 CHF or other cardiac side-effects, all leading to symptoms and potentially hospital admissions, these results allow for a better informed decision-making on trastuzumab treatment duration. Moreover, in the subgroup analysis for the rare CHF event, indeed 12 months of trastuzumab increases the odds of experiencing CHF by 68%, compared with 9–12 weeks regimens. Twelve months of trastuzumab also increases the odds of low LVEF events by 45%, compared with shorter regimens. Since most patients will continue to receive 1year of trastuzumab treatment (with or without pertuzumab),[24] it is important to refer them early to a cardio-oncology consult,[25] and to stratify patients based on established cardiac risk factors for treatment with trastuzumab, such as older age, hypertension, high body mass index, among others.[26] Consideration should

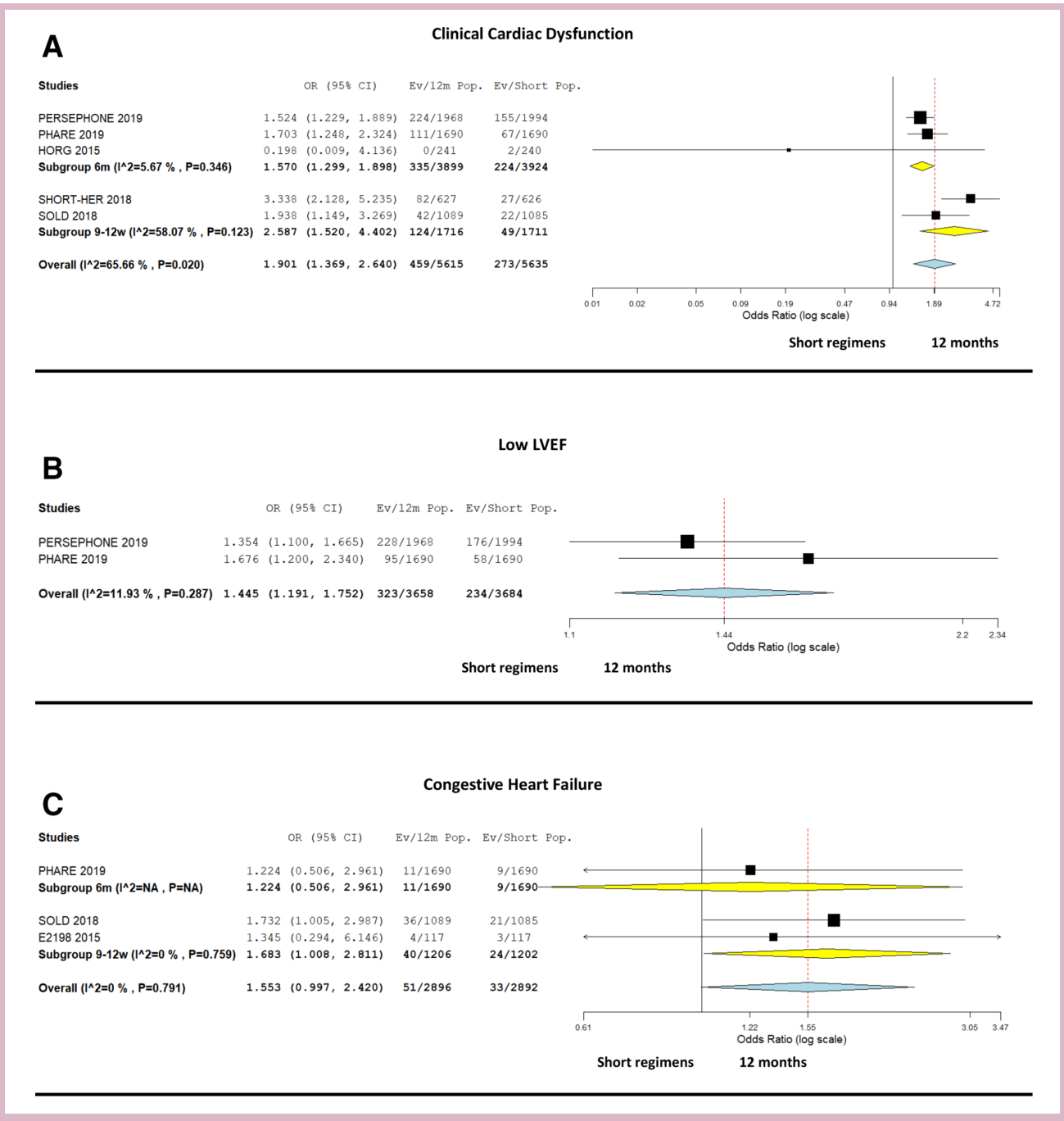

Figure 3 Forest plots in log scale for each cardiac outcome. The size of the squares represents the weight of the studies. Error bars represents 95% CIs. The vertical black line sets the 1, and the vertical red line sets the overall pOR. The blue diamonds indicates the overall pOR, whereas the yellow ones indicate the subgroup pORs, all with their respective 95% CIs. A pORs higher than 1 indicate that treatment with trastuzumab for 12 months increases the rate of a given cardiac outcome compared with a shorter trastuzumab regimen, with statistical significance seen whenever the CI does not cross the 1. (A) Random effects model with inverse variance weighting meta-analysis of clinical cardiac dysfunction associated with 12 months of trastuzumab versus short trastuzumab regimens, including 5 studies/11 250 patients, showing a pOR=1.90 (95% CI 1.37 to 2.64; Z-value=3.84; p value <0.001; I^2=65.7%). Subgroup analysis shows for the 12 months versus 6 months comparison a pOR=1.57 (95% CI 1.30 to 1.90; Z-value=4.67; p<0.001; I^2=5.7%) and for the 12 months versus 9 weeks comparison a pOR=2.59 (95% CI 1.52 to 4.40; Z-value=3.50; p<0.001; I^2=58.1%). (B) Meta-analysis of low LVEF associated with 12 months of trastuzumab versus short trastuzumab regimens including two studies (7342 patients) showing a pOR=1.45 (95% CI 1.19 to 1.75; Z-value=3.74; p<0.001; I^2=11.9%). (C) Meta-analysis of congestive heart failure associated with 12 months of trastuzumab versus short trastuzumab regimens including three studies (5788 patients) showing a pOR=1.55 (95% CI 1.00 to 2.42; Z-value=1.95; p=0.052; I^2=0.0%). Subgroup analysis shows for the 12 months versus 9–12 weeks comparison a pOR=1.68 (95% CI 1.01 to 2.81; Z-value=1.99; p=0.047; I^2=0.0%). LVEF, left ventricular ejection fraction; pOR, pooled OR.

be given to the use of cardioprotective strategies for selected patients, especially for those previously exposed to anthracyclines.[27–29] In fact, preventive lisinopril and carvedilol have been proven to partially offset the cardiotoxicity caused by 12 months of adjuvant trastuzumab in patients treated with anthracyclines.[28]

In line with previous cardiac subanalysis of anti-HER2 trials, cardiotoxicity incidence increases over time of HER2-blockade. In fact, this cumulative phenomenon was first observed in the adjuvant setting in a subanalysis of cardiac events in the large HERA trial, which compared the efficacy of trastuzumab for 1 and 2 years versus observation. In HERA, the addition of a second year of trastuzumab increased the incidence of significant LVEF decreases compared with 1 year of trastuzumab without improving efficacy.[30] Later, real-world data came to substantiate these cardiotoxicity findings.[31] Interestingly, dual HER2-blockade with either lapatinib or pertuzumab does not seem to increase cardiotoxicity.[32] Indeed, with trastuzumab/lapatinib there is a trend towards fewer cardiac events, with however a similar finding of higher incidences over time.[33] Moreover, different sequences of HER2-blockade elicits overall low cardiotoxicity rates, such as post-trastuzumab neratinib for 1 year,[34] and post-neoadjuvant trastuzumab-emtansine (T-DM1) for 14 cycles.[35]

Importantly, by the time the trials included in this meta-analysis were planned, trastuzumab treatment duration was being questioned due to the slim scientific rationale on which it was standing: the FinHER trial had shown 9 weeks of adjuvant trastuzumab superior to no trastuzumab in the early HER2-positive BC setting,[36] whereas the HERA trial had shown 1 and 2 years of trastuzumab better than observation, yet the additional year of therapy was not superior in terms of disease-free survival compared with just 1 year.[37] However, before this important question was close to an answer, newer and better treatment approaches were designed and proven more efficacious than single HER2 blockade with trastuzumab. Currently, dual HER2-blockade is used in the early setting for patients with disease at high risk of recurrence, either as concomitant therapy (trastuzumab/pertuzumab),[38–40] or sequential therapy (trastuzumab followed by neratinib),[34] and, more recently, adjuvant T-DM1 for patients who have residual tumour following trastuzumab-based neoadjuvant treatment.[35]

Today, the substantial benefit of adjuvant anti-HER2 therapy has refocused de-escalation efforts into removing anthracyclines from the chemotherapy backbone. In the APT trial, 406 patients with small, node-negative tumours were exposed to an anthracycline-free regimen, and despite 1 year of trastuzumab, attained a low incidence of grade 3 left ventricle systolic dysfunction (0.5%; 95% CI 0.1% to 0.8%).[41] In fact, some trials are testing chemotherapy de-escalation also for higher-risk populations, with the purpose of mitigating the detrimental interaction between trastuzumab and anthracyclines, for instance by combining dual HER-2 blockade with immunotherapy (clinicaltrial.gov identifier NCT03747120) or, in HER2-positive/HR-positive disease, with more potent endocrine therapies (eg, aromatase inhibitors with cyclin-dependent kinases 4 and 6 inhibitors or phosphoinositide 3-kinase inhibitors).[42] This will further shift the debate away from the duration of HER2 blockade to the type of treatment partners, tailored according to certain tumours characteristics, with the expected low cardiotoxicity rates due to the mechanisms of action of drugs that do not permeate the cardiomyocyte homeostasis.[43]

Nonetheless, in a setting of economic constraints, mainly low/low-middle-income countries where trastuzumab and anthracycline-based chemotherapy are still the best option, the higher pORs for clinically relevant cardiac outcomes found is an additional argument in favour of shorter trastuzumab durations, particularly 6 months, in light of the non-inferiority result for disease-free survival shown in PERSEPHONE for this regimen.[3] Since decreased costs can be expected both from less monoclonal antibody use and, to a lesser extent, fewer treatments and hospital admissions elicited towards cardiotoxicity, it is reasonable to pursue 6 months of treatment from a pharmaco-economic stand point of view.[44]

We recognise some limitations of this meta-analysis, mainly the impossibility to extract cardiac outcomes on a patient-level data. This precludes the analysis of cardiac outcomes according to the exposition (and cumulative doses) to anthracyclines, a known risk factor for cardiotoxicity with trastuzumab treatment,[33 45] for which different levels of exposition per treatment arm may have occurred in SHORT-HER.[6] No cardiac death analyses could be performed since only PERSEPHONE reported very few events in great detail.[3] Besides, few patients in this meta-analysis were treated with anthracycline-free regimens, thus there may be less applicability of our results for patients treated with other widely accepted chemotherapy backbones, namely docetaxel plus carboplatin or cyclophosphamide.[46 47] Moreover, we cannot rule out that differences in cardiac outcome definitions between trials may have introduced heterogeneity in the meta-analyses of clinical cardiac dysfunction and premature trastuzumab discontinuation. It is important to note that despite the availability of guidelines on defining cardiotoxicity for cancer treatment trials,[27] substantial heterogeneity is still a common issue which hampers the ability of designing strategies for patient selection and management.

CONCLUSIONS

In conclusion, a 12-month trastuzumab regimen increases the odds of clinically relevant cardiac outcomes, such as clinical cardiac dysfunction (compared with 6 months of therapy), of CHF (compared with 9–12 weeks of therapy) and of low LVEF events (compared with shorter regimens). We stress that a final decision on adjuvant trastuzumab duration for patients with early-stage, HER2-positive BC should not be made solely on the basis of

this cardiotoxicity data, especially considering the overall low pooled incidences of clinical cardiac dysfunction and CHF in both 12 months and shorter treatment durations (<10%). Rather, it is of utmost importance to tailor anti-HER2 therapies by placing into the equation also the individual recurrence risk and cardiac risk profile, within a multi-disciplinary setting that offers an adequate cardiologic support.

An individual patient data meta-analysis should be sought to produce a more complete picture of the cardiotoxicity associated with 12 months versus shorter trastuzumab regimens, especially of 6 months of therapy.

Author affiliations
[1]Clinical Trials Support Unit, Institut Jules Bordet, Université Libre de Bruxelles (U.L.B), Bruxelles, Belgium
[2]AC Camargo Cancer Center, São Paulo, Brazil
[3]Department of Translational Research and New Technologies in Medicine and Surgery, Pisa University Hospital, Pisa, Italy
[4]Department of Haematology, Oncology, Hemostasiology and Stem Cell Transplant (Medizinische Klinik IV), Uniklinik RWTH Aachen, Aachen, Germany
[5]CHU Saint-Pierre, Bruxelles, Belgium

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ORCID iDs
Daniel Eiger http://orcid.org/0000-0002-9879-6048
Evandro de Azambuja http://orcid.org/0000-0001-9501-4509

REFERENCES

1 Hudis CA. Trastuzumab--mechanism of action and use in clinical practice. *N Engl J Med* 2007;357:39–51.
2 Pondé NF, Lambertini M, de Azambuja E. Twenty years of anti-HER2 therapy-associated cardiotoxicity. *ESMO Open* 2016;1:e000073.
3 Earl HM, Hiller L, Vallier A-L, *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.
4 Pivot X, Romieu G, Debled M, *et al*. 6 months versus 12 months of adjuvant trastuzumab in early breast cancer (PHARE): final analysis of a multicentre, open-label, phase 3 randomised trial. *Lancet* 2019;393:2591–8.
5 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.
6 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‡. *Ann Oncol* 2018;29:2328–33.
7 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 Oncol* 2018;4:1199.
8 Schneider BP, O'Neill A, Shen F, *et al*. Pilot trial of paclitaxel-trastuzumab adjuvant therapy for early stage breast cancer: a trial of the ECOG-ACRIN cancer research group (E2198). *Br J Cancer* 2015;113:1651–7.
9 Pondé N, Gelber RD, Piccart M. PERSEPHONE: are we ready to de-escalate adjuvant trastuzumab for HER2-positive breast cancer? *NPJ Breast Cancer* 2019;5:1.
10 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.
11 Stewart P, Blanchette PS, Shah PS, *et al*. Do all patients with HER2-positive breast cancer require one year of adjuvant trastuzumab?: a systematic review and meta-analysis. *J Clin Oncol* 2019;37:522.
12 Sipra QUAR, Riaz IB, Husnain M, *et al*. Short versus long duration of adjuvant trastuzumab (T) in HER2+ breast cancer: a systematic review and meta-analysis of randomized controlled trials (RCTs). *J Clin Oncol* 2019;37:e12057.
13 Earl HM, Vallier A-L, Dunn J, *et al*. Trastuzumab-associated cardiac events in the Persephone trial. *Br J Cancer* 2016;115:1462–70.
14 Pivot X, Suter T, Nabholtz JM, *et al*. Cardiac toxicity events in the PHARE trial, an adjuvant trastuzumab randomised phase III study. *Eur J Cancer* 2015;51:1660–6.
15 Liberati A, Altman DG, Tetzlaff J, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700.
16 Higgins JP, Savović J, Page MJ, *et al*. Chapter 8: Assessing risk of bias in a randomized trial, 2019. Available: www.riskofbias.info
17 Deeks JJ, Higgins JP, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses 2019.
18 Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
19 Sterne JAC, Sutton AJ, Ioannidis JPA, *et al*. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
20 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50:1088–101.
21 Borenstein M, Hedges L, Higgins J, *et al*. Comprehensive meta-analysis version 3. Available: https://www.meta-analysis.com/index.php?cart=BHJU3327368
22 Viechtbauer W. Conducting meta-analyses in R with the metafor. *J Stat Softw* 2010;36:1–48.
23 Wallace BC, Dahabreh IJ, Trikalinos TA, *et al*. Closing the gap between methodologists and end-users: *R* as a computational back-end. *J Stat Softw* 2012;49:1–15.
24 Burstein HJ, Curigliano G, Loibl S, *et al*. Estimating the benefits of therapy for early-stage breast cancer: the St. Gallen international consensus guidelines for the primary therapy of early breast cancer 2019. *Ann Oncol* 2019;30:1541–57.
25 Lancellotti P, Suter TM, López-Fernández T, *et al*. Cardio-Oncology services: rationale, organization, and implementation. *Eur Heart J* 2019;40:1756–63.
26 de Azambuja E, Ponde N, Procter M, *et al*. A pooled analysis of the cardiac events in the trastuzumab adjuvant trials. *Breast Cancer Res Treat* 2020;179:161-171.
27 Zamorano JL, Lancellotti P, Rodriguez Muñoz D, *et al*. 2016 ESC Position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for practice guidelines. *Eur Heart J* 2016;37:2768–801.

28 Guglin M, Krischer J, Tamura R, *et al*. Randomized trial of lisinopril versus carvedilol to prevent trastuzumab cardiotoxicity in patients with breast cancer. *J Am Coll Cardiol* 2019;73:2859–68.
29 Gulati G, Heck SL, Ree AH, *et al*. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. *Eur Heart J* 2016;37:1671–80.
30 de Azambuja E, Procter MJ, van Veldhuisen DJ, *et al*. Trastuzumab-associated cardiac events at 8 years of median follow-up in the Herceptin adjuvant trial (BIG 1-01). *J Clin Oncol* 2014;32:2159–65.
31 Goldhar HA, Yan AT, Ko DT, *et al*. The temporal risk of heart failure associated with adjuvant trastuzumab in breast cancer patients: a population study. *J Natl Cancer Inst* 2016;108:djv301.
32 Valachis A, Nearchou A, Polyzos NP, *et al*. Cardiac toxicity in breast cancer patients treated with dual HER2 blockade. *Int J Cancer* 2013;133:2245–52.
33 Eiger D, Ponde NF, Agbor-Tarh D, *et al*. Long-term cardiac outcomes of HER2+ breast cancer patients treated in the ALTTO trial. *Ann Oncol* 2019;30:iii65.
34 Martin M, Holmes FA, Ejlertsen B, *et al*. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017;18:1688–700.
35 von Minckwitz G, Huang C-S, Mano MS, *et al*. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med* 2019;380:617–28.
36 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.
37 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.
38 Gianni L, Pienkowski T, Im Y-H, *et al*. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. *Lancet Oncol* 2016;17:791–800.
39 Schneeweiss A, Chia S, Hickish T, *et al*. Long-term efficacy analysis of the randomised, phase II TRYPHAENA cardiac safety study: evaluating pertuzumab and trastuzumab plus standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer. *Eur J Cancer* 2018;89:27–35.
40 von Minckwitz G, Procter M, de Azambuja E, *et al*. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N Engl J Med* 2017;377:122–31.
41 Tolaney SM, Barry WT, Dang CT, *et al*. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. *N Engl J Med* 2015;372:134–41.
42 de Azambuja E, Piccart-Gebhart M. ER+/HER2+ breast cancer: are we really de-escalating? *Ann Oncol* 2019;30:875–7.
43 Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. *J Clin Oncol* 2005;23:2900–2.
44 Hulme C, Hall P, Shinkins B, *et al*. LBA12_PRPERSEPHONE: 6 versus 12 months (M) of adjuvant trastuzumab in patients (PTS) with HER2 positive (+) early breast cancer (EBC): cost effectiveness analysis results. *Ann Oncol* 2018;29.
45 Jawa Z, Perez RM, Garlie L, *et al*. Risk factors of trastuzumab-induced cardiotoxicity in breast cancer: a meta-analysis. *Medicine* 2016;95:e5195.
46 Slamon D, Eiermann W, Robert N, *et al*. Abstract S5-04: ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC→T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC→TH) with docetaxel, carboplatin and trastuzumab (Tch) in HER2+ early breast cancer. *Cancer Res* 2016;76:S5-04-S5-04.
47 Jones SE, Collea R, Paul D, *et al*. Adjuvant docetaxel and cyclophosphamide plus trastuzumab in patients with HER2-amplified early stage breast cancer: a single-group, open-label, phase 2 study. *Lancet Oncol* 2013;14:1121–8.