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CLINICAL TRIAL

# Optimal duration of adjuvant trastuzumab in treatment of early breast cancer: a meta-analysis of randomized controlled trials

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## Abstract

**Background** One year of adjuvant trastuzumab, chosen empirically, improves survival of women with early-stage, Human Epidermal Growth Factor Receptor 2 (HER2) positive breast cancer. Two years of trastuzumab does not improve efficacy but increases cost, inconvenience, and adverse effects. We aimed to evaluate if less than 1 year of adjuvant trastuzumab retained efficacy while reducing toxicities and cost.

**Methods** We performed a pooled analyses of efficacy and toxicity from Randomized Controlled Trials (RCTs) comparing 1 year of trastuzumab to shorter durations in adjuvant treatment of HER2-positive breast cancer. Hazard Ratios (HR) for Overall Survival (OS) and Disease-Free Survival (DFS), and Odds Ratios (OR) for cardiac events with respective 95% Confidence Intervals (CI) were weighted using generic inverse variance approach and pooled in meta-analyses using random effects models with RevMan 5.3 software. Sub-group analyses of outcomes based on Estrogen Receptor (ER) and nodal status were performed.

**Results** Five RCTs involving approximately 12,000 patients qualified—three assessing 6 months and two assessing 9 weeks of trastuzumab compared to 1 year. All RCTs were designed to test non-inferiority of the shorter treatment. One year of trastuzumab resulted into better OS (pooled HR 1.23, 95% CI 1.07–1.42) and DFS (pooled HR 1.21, 95% CI 1.09–1.36) in overall population, but the benefit of longer treatment was statistically insignificant in node negative (HR 1. 20, $p=0.11$), and ER positive disease (HR 1.15, $p=0.09$). Odds ratio for cardiac events was significantly higher with the longer duration (OR 2.48, $p<0.001$).

**Conclusion** One year of trastuzumab for adjuvant treatment of breast cancer improves outcomes compared to shorter treatments in overall population. Cardiotoxicity is increased with the longer treatment.

**Keywords** Breast cancer · Herceptin · Duration · Adjuvant

## Introduction

The current standard of 12 months of adjuvant trastuzumab for treatment of early-stage Human Epidermal Growth Factor Receptor 2 (HER2) receptor positive breast cancer was determined arbitrarily rather than based on scientific rationale. Therefore, the question of whether similar efficacy can be achieved with shorter treatments has always occupied breast cancer community because of adverse consequences of the longer treatment in terms of cost, convenience, and toxicity.

The herceptin adjuvant (HERA) trial evaluated both 1 and 2 years of adjuvant trastuzumab compared to no trastuzumab and demonstrated remarkable improvements in disease-free and overall survivals with 1 year of trastuzumab but no added benefits by extending the treatment to 2 years [1]. On the contrary, the first evidence of efficacy with shorter adjuvant trastuzumab was demonstrated by the so-called FinHer study, showing a reduction in breast cancer recurrences by over half with the use of 9 weeks of treatment compared to no trastuzumab [2]. Since then a number of clinical trials have been conducted comparing efficacy and toxicity of 1 year of adjuvant trastuzumab to shorter durations. All such trials were designed appropriately to evaluate

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non-inferiority of shorter durations compared to the standard of care because of the obvious benefits with shorter treatments. However, a negative non-inferiority trial is hard to interpret, and it is difficult to generate a universal definition of non-inferiority because of potential influences by disease factors and subjectivity. Furthermore, there are limits to a single clinical trial providing definitive answer to a clinical question. With the largest clinical trial assessing this question reported recently [3], we took the opportunity to evaluate optimal duration of adjuvant trastuzumab with a meta-analysis of these Randomized Controlled Trials (RCTs).

## Methods

### Search criteria and selection of studies

We searched MEDLINE, EMBASE, COCHRANE databases as well as abstracts presented at the annual meetings of ASCO, European Society of Medical Oncology (ESMO), and San Antonio Breast Cancer Symposium in the past 10 years. Key words included for the search were: POPULATION: breast neoplasms, carcinoma,, HER2, trastuzumab; STUDY TYPES: randomized control trials, clinical trials, prospective studies, non-inferiority; OUTCOMES: overall survival, disease-free survival, progression-free survival, time to progression, treatment outcome, disease progression, survival rate, survival analysis, prognosis, proportional hazards model. We included publications reporting results of RCTs that compared one year of trastuzumab in control arm and any shorter duration of trastuzumab in the experimental arm for the treatment of early-stage HER2 positive breast cancer in peri-operative settings.

### Data extraction

We used the reports from these RCTs to extract Hazard Ratio (HR) for Disease-Free Survival (DFS) and Overall Survival (OS) along with their respective Confidence Intervals (CI). To explore if a particular sub-category of breast cancer may be more appropriate for the shorter treatment, we also extracted the same efficacy variables for the following sub-groups: Estrogen Receptor (ER) positive, ER negative, node positive, node negative, duration of trastuzumab in the experimental arm. Odds Ratio (OR) for cardiac events in experimental arm compared to that in control arm was calculated based on the sample size and number of events in respective arms of the studies. Both authors collected data independently; any discrepancies were resolved by consensus.

### Statistical analysis

Data on HR and OR extracted from the RCTs for overall population and for sub-groups of patients defined above were pooled in meta-analyses using RevMan 5.3 software (Cochrane Collaboration, Copenhagen, Denmark). Estimates of HR were pooled using DerSimonian and Laird random effect models in which the studies were weighted using the generic inverse variance approach [4, 5]. Given that results could be influenced by ER and nodal status, we assessed differences between these sub-groups with respect to disease-free survival. Similarly, interaction of duration of trastuzumab in experimental arm with the overall results were also tested in a sensitivity analysis—$\chi^2$ statistics was used to measure sub-group differences. Evidence of heterogeneity among studies was assessed using $i^2$ statistics. All tests were 2-sided, and statistical significance was defined as $p < 0.05$. We adhered to the principles of the PRISMA guidelines [6].

## Results

We identified 5 RCTs—three evaluating 6 months [3, 7, 8], and two evaluating 9 weeks [9, 10] of trastuzumab versus 1 year (Fig. 1). Median duration of follow-up ranged from

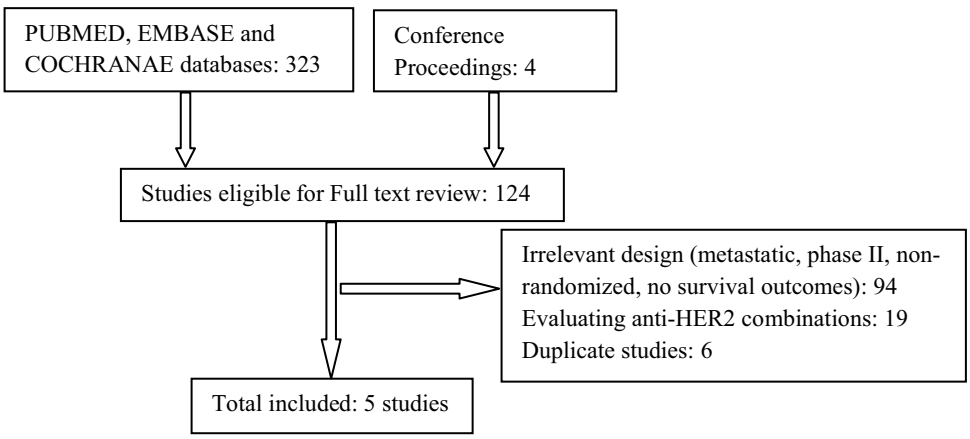


**Fig. 1** PRISMA diagram of search results

**Table 1** Characteristics of studies evaluating 1 year versus shorter duration of trastuzumab

| Authors | Study acronym | *N* | Primary endpoint | Secondary endpoints | Chemotherapy combination and trastuzumab frequency | Duration of experimental treatment | Pre-defined margin of non-inferiority | HR DFS (95% CI) | HR OS (95% CI) | Median follow-up (years) |
|---|---|---|---|---|---|---|---|---|---|---|
| Studies comparing 6 months to 1 year | | | | | | | | | | |
| Earl et al. [12] | PERSEPHONE | 4089 | DFS | OS, cardiac events, cost-effectiveness | Anthracycline and/or Taxane (regimens not given) 3-weekly IV trastuzumab | 6 months | HR < 1.29 | 1.05 (0.88–1.25) | 1.14 (0.95–1.37) | 4.9 |
| Mavroudis et al. [8] | HORG | 481 | DFS | OS, toxicity | FEC-D Bi-weekly followed by 3-weekly IV trastuzumab | 6 months | HR < 1.53; 3 year DFS | 1.57 (0.86–2.10) | 1.45 (0.57–3.67) | 4.2 |
| Pivot et al. [7] | PHARE | 3384 | DFS | OS, cardiac events | Anthracycline and/or Taxane (regimens not given) 3-weekly IV trastuzumab | 6 months | HR < 1.15; 3 year DFS | 1.28 (1.05–1.56) | 1.46 (1.06–2.01) | 3.5 |
| Studies comparing 9 weeks to 1 year | | | | | | | | | | |
| Conte et al. [9] | SHORT-HER | 1253 | DFS, OS | Failure rate, cardiac events | AC or EC-D or FEC-D 3-weekly IV trastuzumab (control), weekly (experimental) | 9 weeks | HR < 1.29; 5 year DFS | 1.15 (0.91–1.46) | 1.06 (0.73–1.55) | 5.2 |
| Joensuu et al. [10] | SOLD | 2176 | DFS | Cardiac safety | D-FEC | 9 weeks | HR < 1.3 | 1.39 (1.12–1.72) | 1.36 (0.98–1.89) | 5.2 |

3.5 to 5.2 years (Table 1). No major risk of bias (as assessed the Cochrane tool for assessment of risk of bias) that would affect the validity of results was identified. All RCTs had non-inferiority design, but had heterogeneous pre-defined criteria to declare non-inferiority: the threshold to declare non-inferiority based on the upper limit of 95% confidence interval ranged from 1.15 to 1.53 (Table 1). Four RCTs did not meet their pre-specified non-inferiority criteria, whereas the largest of the 5, the Persephone trial did—demonstrating for the first time the non-inferiority of 6 months compared to 12 months of trastuzumab.

## Pooled results of disease-free and overall survival

The pooled results of all included studies resulted in statistically significant HR of 1.21 (95% CI 1.08–1.37) for DFS, and 1.31 (95% CI 1.08–1.59) for OS favoring the 1 year compared to shorter durations (Fig. 2).

Reports based on sub-groups required for our meta-analysis was available in all RCTs with regards to DFS. Pooled analysis revealed a significant benefit with 1 year of trastuzumab compared to shorter durations in women with node positive breast cancer (HR 1.37, 95% CI 1.17–1.60), but the benefit was not statistically significant for those with node negative disease (HR 1.20, 95% CI 0.96–1.51). (Fig. 3) Similarly, ER negative tumors derived significantly higher benefits with longer trastuzumab compared to shorter treatments (HR for DFS 1.33, 95% CI 1.15–1.54), but the difference did not reach statistical significance for ER positive tumors (HR for DFS 1.15, 95% CI 0.98–1.34). (Fig. 3) A sensitivity analysis based on duration of experimental arm suggested benefits favoring longer duration compared to either 6 months (HR 1.18, 95% CI 1.00–1.39) or 9 weeks of trastuzumab (HR 1.21, 95% CI 1.06–1.53). There was no statistically significant difference between the sub-groups based on duration of treatment in experimental arm ($p$ for sub-group difference = 0.55).

## Cardiac events

Cardiac events were reported numerically in four studies [3, 7, 9, 10]. There were no notable variations in definition of cardiac events among studies—this was based on either a clinical symptom or on cardiac imaging assessing Left Ventricular Ejection Fraction (LVEF), or both. LVEF was assessed in baseline followed by every 3 months in all studies. Studies usually defined a drop in LVEF as either an absolute drop of ≥ 15% from baseline, or a drop below absolute value of 50%. The odds of cardiac events increased by over two-folds with the use of 1 year of trastuzumab compared to shorter durations (OR 2.48; 95% CI 1.94–3.17, $p < 0.001$).

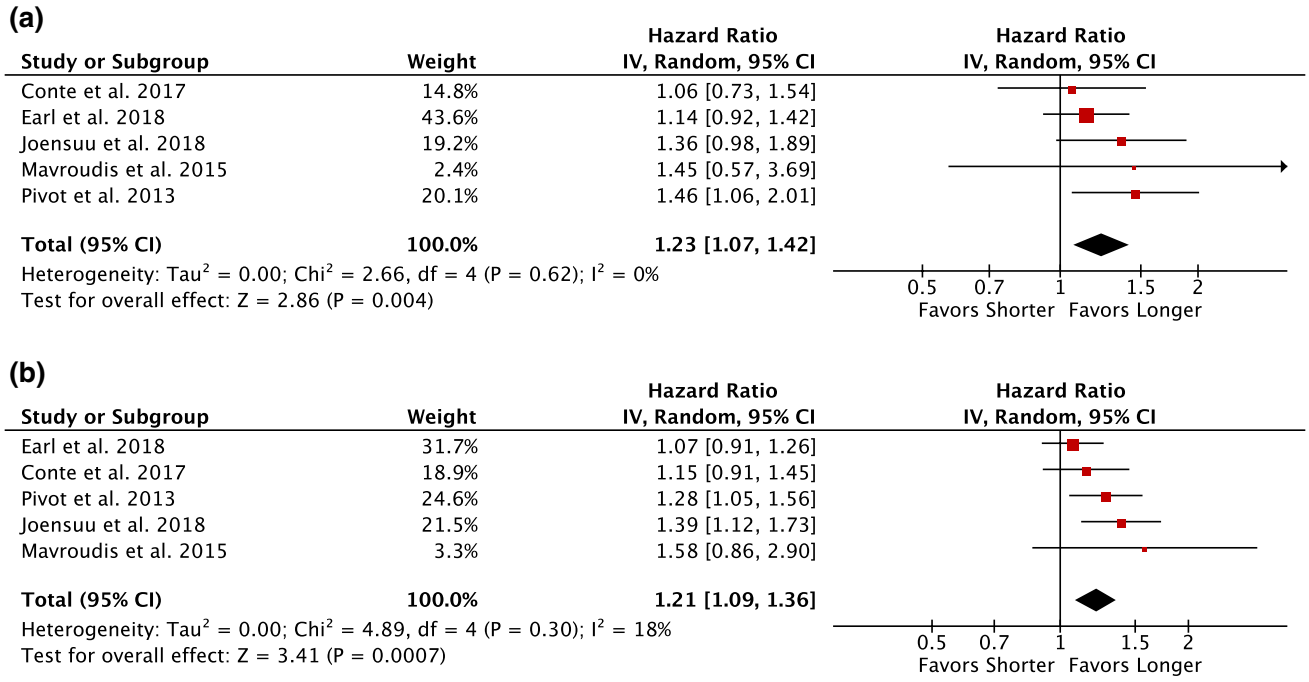


**Fig. 2** Pooled results of **a** overall survival and **b** disease-free survival comparing 1 year versus shorter duration of adjuvant trastuzumab

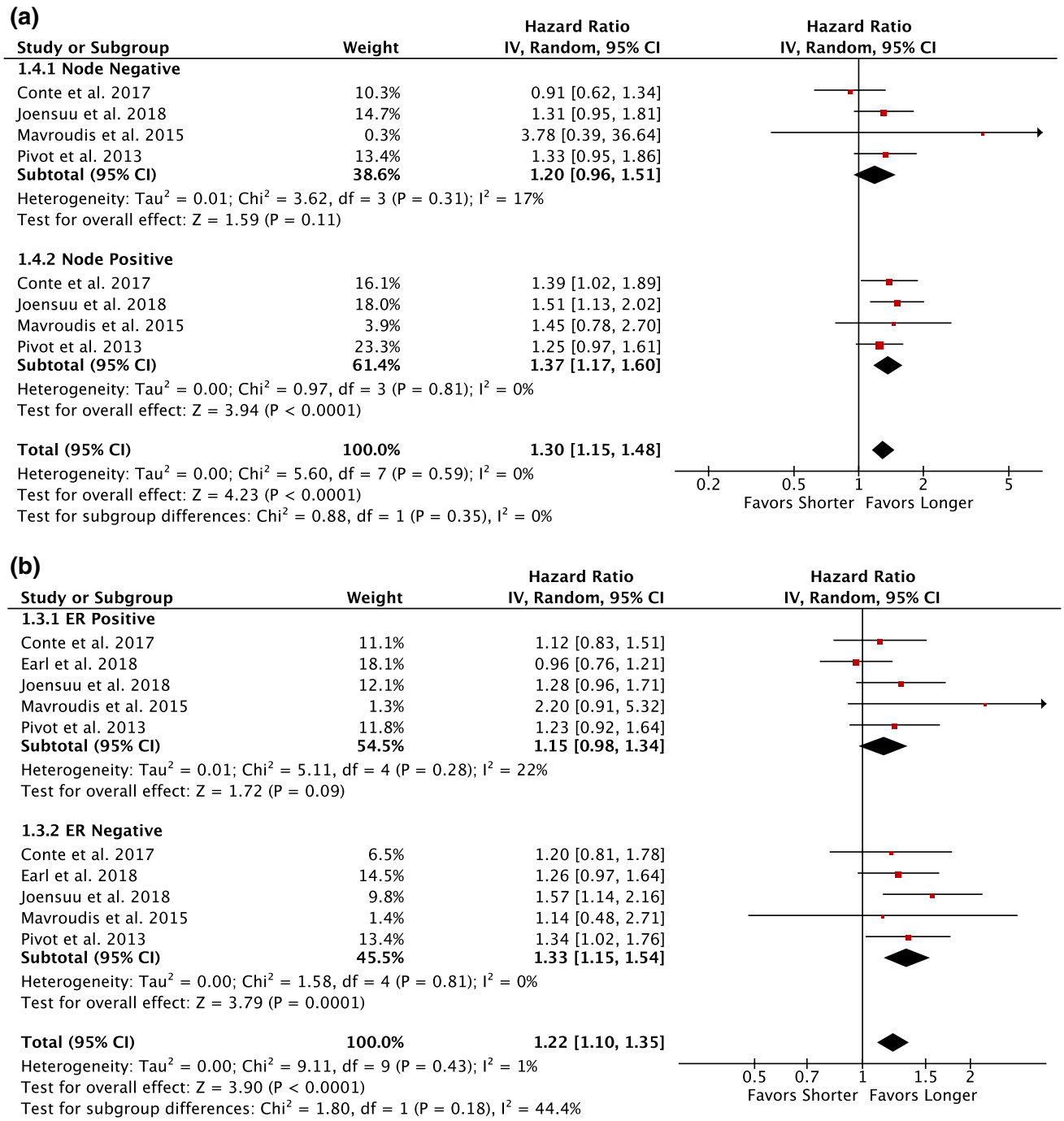


**Fig. 3** Pooled results of sub-groups analysis for disease-free survival based on **a** nodal status, and **b** estrogen receptor status

## Discussion

Results from individual RCTs evaluating shorter duration of adjuvant trastuzumab were difficult to interpret because of heterogeneous thresholds used to define non-inferiority and discordant results—increased power of meta-analysis allowed us to provide a coherent message to guide treatment decisions in clinics. We demonstrate that 1 year of adjuvant trastuzumab is superior to shorter durations in terms of overall and disease-free survivals in overall population of HER2+ breast cancer, particularly in those with node positive and ER negative disease. Benefit observed in node negative and ER positive tumors was statistically insignificant; however, many ER positive tumors have late recurrences but the median follow-up in most studies was

relatively short. Cardiac events increased by over two folds with the longer treatment.

While trastuzumab has revolutionized the outcome of women with HER2+ breast cancer, protection from risk of recurrence with HER2 targeted therapy is uneven among patients—some may do well without committing to one year of intravenous therapy, while others may derive high proportional benefits from chemotherapy and hormonal therapy. Unfortunately, apart from HER2 receptor itself, we do not have a good biomarker to define differential benefits from HER2 targeted therapy. Treatment strategies targeting alternate oncogenic pathways may be more important than the longer HER2 targeted therapy in ER positive tumors, although such conclusions are beyond the scope of current analysis. Indeed, careful clinical judgment and caution should accompany interpretation of results from our sub-group analyses.

High occurrence of cardiotoxicity in both arms of the included studies may reflect liberal use of anthracycline based regimens in all of the included RCTs. Non-anthracycline based regimens are more commonly used in treatment of HER2+ breast cancer in recent years. It remains unknown, therefore, whether cardiotoxicity risk is substantially increased among patients who do not receive anthracycline based chemotherapy. It is also unclear whether cardiac monitoring was equivalent in both arms of the included studies or whether, as in usual practice, EF evaluations were done only during trastuzumab treatments, representing a potential bias of increased detection of cardiotoxicity for patients on therapy longer. Similarly, trastuzumab was used in sequence to chemotherapy in many patients in the included RCTs which is now considered an inferior approach [11], although this is unlikely to have affected overall results of our analysis because of even randomization. On the other hand, all of these RCTs were conducted prior to approval of pertuzumab so impact of duration with the dual HER2 blockade is currently unclear.

Our study has limitations. Most of the trials included in our meta-analysis were initiated about a decade ago when the treatment for HER2+ breast cancer differed both in terms of chemotherapy and available HER2 directed agents. Other limitations include the use of summary estimates, two different durations of trastuzumab in the experimental arm (although our sensitivity analysis did not reveal a significant difference in effect based on the duration), various chemotherapeutic regimens used among the studies, and that none of the trials were primarily designed to test superiority of the 1-year duration. Nevertheless, HR for long term outcomes are based on disease events between the arms of RCTs evaluating the two treatment approaches, providing opportunity to compare outcomes using meta-analytic approach.

Our findings are relevant to low and middle income countries or in high income countries with inadequate health coverage where selective use of shorter treatment may be more affordable. Shorter treatment may be more attractive to patients with physical limitations prohibiting commitment to 1 year of intravenous treatment. Furthermore, given any absolute improvement in outcome is a direct function of baseline risk, HER2+ breast cancer with lower risk anatomic and biologic features may derive adequate benefits with shorter treatment and be spared of the excess toxicity and cost. Interestingly, a recent survey of Persephone investigators suggested that majority would actually change practice should Persephone result show non-inferiority of 6 months [12]. Increasing availability of trastuzumab biosimilars and identification of sub-groups more suitable for shorter treatments will together help offset costs and toxicities of treatment.

We conclude that 1 year of adjuvant trastuzumab should continue to be used particularly in node positive and ER negative breast cancer. Longer treatment is associated with more inconvenience, toxicity, and cost. The next steps should be to identify patients with HER2+ disease in whom cytotoxic chemotherapy can be shortened or avoided safely. Like with all clinical questions, it is the individual patient that ultimately decides on acceptable trade-offs for a given benefit and our results will provide extra guidance to help patients decide on duration of adjuvant trastuzumab based on the disease related factors, personal preference, and resource constrains.

## Compliance with ethical standards

**Conflict of interest** Institutional research grant from Pfizer (SN). Neither of the authors have personal conflict of interest.

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