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Pilot trial of paclitaxel-trastuzumab adjuvant therapy for early stage breast cancer: a trial of the ECOG-ACRIN cancer research group (E2198)

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Background: Blockade of human epidermal growth factor receptor type 2 (HER2) has dramatically improved outcome for patients with HER2-positive breast cancer. Trastuzumab, an anti-HER2 monoclonal antibody, has previously demonstrated improvement in overall survival (OS) in patients with metastatic and early stage HER2-positive breast cancer. However, trastuzumab can cause congestive heart failure (CHF) with an increased frequency for patients who have also received an anthracycline. The current trial was designed to evaluate the impact of the duration of trastuzumab on CHF.

Methods: E2198 included 227 eligible women with histologically confirmed stage II or IIIA HER2-positive breast cancer. The patients were randomised to receive 12 weeks of paclitaxel and trastuzumab followed by four cycles of doxorubicin and cyclophosphamide (abbreviated Arm) or the aforementioned treatment with additional 1 year of trastuzumab (conventional Arm). The primary end point was to evaluate the safety of this variable duration of trastuzumab therapy, particularly cardiac toxicity defined as CHF or left ventricular ejection fraction decrease >10%. Secondary end points included disease-free survival (DFS) and OS.

Results: Compared with 12-week treatment with trastuzumab, 1 year of trastuzumab-based therapy did not increase the frequency or severity of cardiac toxicity: three patients on the abbreviated Arm and four on the conventional Arm experienced CHF. The 5-year DFS was 76% and 73% for the abbreviated and conventional Arms, respectively, with a hazard ratio (HR) of 1.3 (95% CI: 0.8–2.1; $P=0.3$). There was also no statistically significance difference in OS (HR, 1.4; $P=0.3$).

Conclusions: Compared with 12 weeks of treatment, 1 year of treatment with trastuzumab did not significantly increase the risk of cardiac toxicity. Although not powered for efficacy comparisons, the longer duration of trastuzumab therapy did not demonstrate a signal for marked superiority.

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Blockade of human epidermal growth factor receptor type 2 (HER2) has dramatically improved outcome in both the metastatic and adjuvant settings for tumours with HER2 overexpression or gene amplification (Slamon *et al*, 2001; Piccart-Gebhart *et al*, 2005; Romond *et al*, 2005; Slamon *et al*, 2011). Multiple anti-HER2 agents have demonstrated improvement in progression-free survival (PFS) and/or overall survival (OS) for patients with metastatic disease (Geyer *et al*, 2006; Verma *et al*, 2012; Swain *et al*, 2015). The use of trastuzumab in the adjuvant setting has also demonstrated improvement in OS when added to a backbone of chemotherapy compared with chemotherapy alone (Slamon *et al*, 2001). Many other agents used in the metastatic setting are actively being tested in the adjuvant and neoadjuvant settings. Although the therapeutic indices for these agents are excellent, trastuzumab is not void of toxicity. Specifically, congestive heart failure (CHF) is the most serious toxicity (Telli *et al*, 2007) and its frequency is increased when combined with an anthracycline (Romond *et al*, 2012).

Currently, the optimal duration of adjuvant trastuzumab therapy for patients with HER2-positive disease is 1 year (Pivot *et al*, 2013). This duration was based on the results of two major trials. The HERA trial demonstrated that 2 years of trastuzumab therapy after standard chemotherapy did not improve disease-free survival (DFS) nor OS compared with 1 year of trastuzumab therapy (Piccart-Gebhart *et al*, 2005). The PHARE trial compared the outcome of 1 year of trastuzumab therapy with 6 months trastuzumab therapy. This was a non-inferiority trial and demonstrated that outcome of trastuzumab administration for 6 months was not non-inferior to the same for 12 months (Pivot *et al*, 2013). Even shorter durations of trastuzumab, however, have been compared with no therapy and have demonstrated activity. Specifically, the FINHER trial showed that 3 months of adjuvant trastuzumab was superior to none (Joensuu *et al*, 2009). E2198 was primarily designed to evaluate the impact of duration of trastuzumab on CHF. Here we also report the results for a comparison of the conventional 1-year duration trastuzumab therapy with a shorter exposure in the adjuvant setting.

PATIENTS AND METHODS

Study design and treatment. E2198 was a randomised phase II study (Figure 1). All patients were pre-registered to the pre-randomisation Arm and tumour blocks were sent to the ECOG-ACRIN Pathology Coordinating Office for central review of HER2 status. Patients with a score of 2–3+ determined by immunohistochemistry (IHC) were classified as eligible for randomisation to an abbreviated trastuzumab Arm or a conventional trastuzumab Arm. Treatments were assigned using permuted blocks within strata with dynamic balancing within main institutions and their affiliate networks. Patients were stratified based on whether radiation therapy was planned *vs* not planned. All patients received paclitaxel 175 mg m^{-2} on day 1 every 3 weeks for four cycles and trastuzumab with a 4 mg kg^{-1} loading dose in week 1 followed by 2 mg kg^{-1} weekly through week 10 (TH). Three weeks after the last doses of TH, patients received doxorubicin 60 mg m^{-2} and cyclophosphamide 600 mg m^{-2} on day 1 every 3 weeks for four cycles (AC). Within 3 weeks after the completion of AC and completion of radiation therapy (if administered), patients randomised to the conventional Arm received additional trastuzumab with a 4 mg kg^{-1} loading dose in week 1 followed by 2 mg kg^{-1} weekly for 1 year (Figure 1). Radiation therapy, if clinically indicated, was administered according to institutional guidelines after the completion of AC. Patients with tumours classified as oestrogen receptor (ER) and/or progesterone receptor (PgR) positive must have received tamoxifen at the completion of AC for 5 years. For patients randomised to the conventional Arm, tamoxifen could have been administered concomitantly with the maintenance trastuzumab.

Patients. Female patients ⩾18 years old with histologically confirmed stage II or IIIA HER2-positive breast cancer were eligible if they had not received previous chemotherapy or hormonal therapy. Patients who had received previous tamoxifen for chemoprevention were required to have discontinued tamoxifen for at least 1 year before enrolment. Patients who had their last definitive surgical procedure within the previous 12 weeks before receiving radiation therapy were considered eligible. Additional inclusion criterial included adequate cardiac function with a left ventricular ejection fraction (LVEF) ⩾50%, and adequate renal, hepatic and haematological function.

Patients were excluded if they had a history of congestive cardiomyopathy, CHF, uncontrolled hypertension, myocardial infraction or uncontrolled arrhythmia within the prior 6 months. Patients were also excluded if they had another cancer within the previous 5 years except basal or squamous cell carcinoma of the skin or *in situ* cervical cancer.

Methods. Assessments of the patient's overall health, history, physical exam and performance status were performed at baseline, day 1 of each cycle, and then post AC every 3 months for the first year, every 6 months for the second year and then annually. Haematological evaluations were obtained with the same frequency with additional tests between TH and at the start of AC and during each cycle. A chest X-ray and EKG were required at baseline. LVEF was to be performed via MUGA or echocardiogram (as long as the method was consistent) at baseline, post TH, post AC, 1 year post AC (abbreviated arm only) and at the following three time points for the conventional Arm: 6 months after beginning maintenance trastuzumab; within 1 month of completing; and 1 year post maintenance trastuzumab. Annual mammograms were required with the long-term follow-up form submitted each time that a patient was seen.

Since the standard definition of HER2 positivity was either 2+ or 3+ with the HercepTest (DAKO, Carpinteria, CA, USA) when this trial was conducted, we repeated the HER2 scoring centrally (for available cases) using IHC and reflex FISH in November 2013 according to the College of American Pathologist (CAP) guidelines (Wolff *et al*, 2013). Those patients with an IHC of 0 or, 1+ were

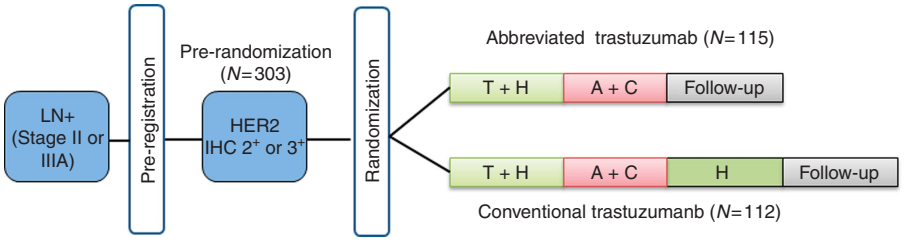

Figure 1. Trial schema.

considered HER2-negative, whereas those with 3+ were considered positive. Those patients who were 2+ were tested by FISH. Patients were considered HER2-negative with a HER2/CEP17 ratio <1.8; positive with a ratio $\geqslant 2.2$; and equivocal with a ratio $\geqslant 1.8$ and <2.2.

Statistical considerations. The primary objective was to evaluate the safety of these treatment regimens, particularly with respect to CHF and LVEF. Toxicities were graded according to the Common Toxicity Criteria (CTC) version 2.0. CHF (defined as grade 3-4 LVEF dysfunction), Grade 3-4myocarditis, and decreases in LVEF of $>10\%$ were of interest. The study was originally designed to enrol a total of 100 eligible patients. The accrual goal was later increased to allow entry of 200 eligible patients in order to better assess the cardiac toxicity. CHF rate was summarised as a proportion with corresponding exact 95% confidence interval (CI). Fisher's exact test was used to compare Arms with respect to proportion with $>10\%$ decrease in LVEF post TH and post AC. The proportion of patients with $>10\%$ decrease in LVEF 1 year post AC treatment and 1 year post maintenance trastuzumab was also evaluated. Although the trial was not powered for time-to-event comparisons, secondary end points included DFS and OS. DFS was defined as time from randomisation to disease recurrence, development of invasive second primary or death. Patients without documented DFS event were censored at date of last disease evaluation. Survival was defined as the time from randomisation to death from any cause, otherwise censored at date last known alive. Distributions of DFS and OS were estimated using the Kaplan–Meier method. Toxicity summaries included all patients who received protocol treatment. Summaries of baseline demographics, disease characteristics, and analysis of outcome data included eligible patients. Two-sided *P*-values <0.05 were considered statistically significant.

Table 1. Patient demographics and disease characteristics

	Abbreviated trastuzumab ($N=115$)	Conventional trastuzumab ($N=112$)
Race – no. (%)		
White	106 (92)	97 (87)
Hispanic	2 (2)	3 (3)
Black	4 (3.5)	9 (8)
Other	3 (2.5)	3 (2)
Age (years) – no. (%)		
<40	21 (18)	21 (19)
$\geqslant 40$	94 (82)	91 (81)
Age – median (range)	49 (26–78)	48 (22–76)
Nodal status – no. (%)		
1–3 positive nodes	58 (51)	64 (57)
4–9 positive nodes	35 (30)	32 (29)
$\geqslant 10$ positive nodes	22 (19)	16 (14)
Number of positive nodes – median (range)	3 (1–29)	3 (1–24)
ER/PgR status – no. (%)		
ER^-/PgR^-	45 (39)	41 (37)
ER^-/PgR^+	6 (5)	5 (14)
ER^+/PgR^-	9 (9)	16 (4)
ER^+/PgR^+	54 (47)	50 (45)
Missing	1 (1)	0 (0)
ECOG performance status – no. (%)		
0	100 (87)	99 (88)
1	14 (12)	12 (11)
2	1 (1)	1 (1)
Most extensive surgery – no. (%)		
Less than mastectomy	32 (28)	41 (36)
Modified radical mastectomy	70 (61)	59 (53)
Total (simple) mastectomy	13 (11)	12 (11)

RESULTS

Patients and treatment. Pre-registration of E2198 began in August 1999, but suspended on 23 February 2000 while an amendment to increase accrual was under review. The pre-registration was re-activated in May 2000 and closed in October 2000. A total of 303 patients were originally pre-registered to pre-randomisation Arm and 234 were randomised to the abbreviated or conventional trastuzumab Arm. However, only 227 patients met the eligibility criteria, of whom 115 were assigned to abbreviated and 112 conventional trastuzumab Arm (Figure 1). The two groups of patients were well balanced at baseline with respect to prognostic characteristics (Table 1). The median age was 49 years (range 22–78). Approximately 54% of the patients had 1–3 positive lymph nodes, 29% had 4–9 positive nodes and 17% had 10 or more positive nodes. Sixty two percent of the patients had ER- and/or PgR-positive tumours. Patients received a median of eight cycles of the treatment for both Arms (range, 2–8); 93% and 87% of patients on abbreviated and conventional Arms completed protocol treatment through AC, respectively. Out of the 112, 90 patients on conventional Arm (80%), including nine patients who did not complete eight cycles of TH→AC, began the maintenance treatment of trastuzumab. Out of these 90, 67 patients (74%) completed the entire duration of maintenance trastuzumab. Therefore 60% of the patients assigned to conventional Arm completed treatment per protocol.

In November 2013, HER2 status was reassessed based on more contemporary definitions. Samples from 176 patients were available for repeat testing (Supplementary Figure 1). Tumours from 31 out of the 176 patients (17.6%) that were previously classified as HER2-positive were found to be 0 or 1+ by IHC, and thus reclassified as HER2-negative; 105 patients (59.7%) were 3+ and thus confirmed as HER2-positive; 40 patients (22.7%) were HER2 2+ and subsequent tested by FISH: 9 out of 40 patients did not have sufficient additional material for FISH and were removed from further analyses; 15 had HER2 amplification and 16 did not. In total, 120 patients were confirmed with HER2-positive tumours by more contemporary definitions of positivity. Except for a minor difference in median age (median 47 for those confirmed HER2+ and 51 for those not), there were no differences with respect to baseline demographics and disease characteristics between those patients confirmed HER2+ *vs* those not.

Safety. Seven out of the 234 patients (3%) had CHF (95% CI, 1.2–6%) including one patient with grade 3 myocarditis; three of the patients were on the abbreviated Arm and four on the conventional Arm. There were no differences between Arms in the proportion with LVEF decrease $>10\%$ post TH treatment ($P=0.6$) or post AC therapy ($P=0.6$) (Table 2). Patients had no unexpected frequency or severity of toxicity related to the similar treatment combination (Supplementary Table 1). No lethal toxicities were observed.

Efficacy. Data reported here are as of November 2013 at a median follow-up of 77 months. Efficacy was evaluated separately in the 227 patients enrolled and randomised in the trial, and in the 120 patients re-tested centrally and HER2-positive. Figure 2 shows the Kaplan–Meier curves for DFS and OS of the aforementioned two groups of patients randomised into the two Arms. For the 227 patients, there was no statistically significant difference in DFS (HR for conventional (29 recurrences) *vs* abbreviated (25 recurrences), 1.3; 95% CI, 0.8–2.1; $P=0.3$; 5-year DFS, 73 and 76%, respectively) or OS (HR, 1.4; $P=0.3$; 5-year OS, 83 and 89%, respectively) (Table 3a). For the 120 patients, there was no significant difference in either DFS (HR, 0.9; $P=0.7$; 5-year, DFS 78% and 74%,

Table 2. LVEF assessment[a]

	Abbreviated trastuzumab	Conventional trastuzumab
Baseline and post TH LVEF available – no.	112	111
Median post TH LVEF – no.	61	61
Post TH LVEF decline >10% – no. (%)	12 (11)	9 (8)
Post TH LVEF decline >10% and LVEF <LLN – no. (%)	3 (3)	1 (1)
Baseline and post AC LVEF available – no.	95	104
Median post AC LVEF – no.	59	60
Post AC LVEF decline >10% – no. (%)	15 (16)	13 (13)
Post AC LVEF decline >10% and LVEF <LLN – no. (%)	3 (3)	5 (5)
Baseline and post 1 year of treatment[a] LVEF available – no.	78	40
Median post 1 year of treatment LVEF – no.	62	63
Post 1 year of treatment LVEF decline >10% – no. (%)	13 (17)	9 (23)
Post one year of treatment LVEF decline >10% and LVEF <LLN – no. (%)	1 (1)	2 (5)

Abbreviation: LVEF = left ventricular ejection fraction.
[a]Timepoint for Abbreviated trastuzumab Arm is 1 year post AC. Timepoint for conventional trastuzumab Arm is one year after completion of maintenance trastuzumab.

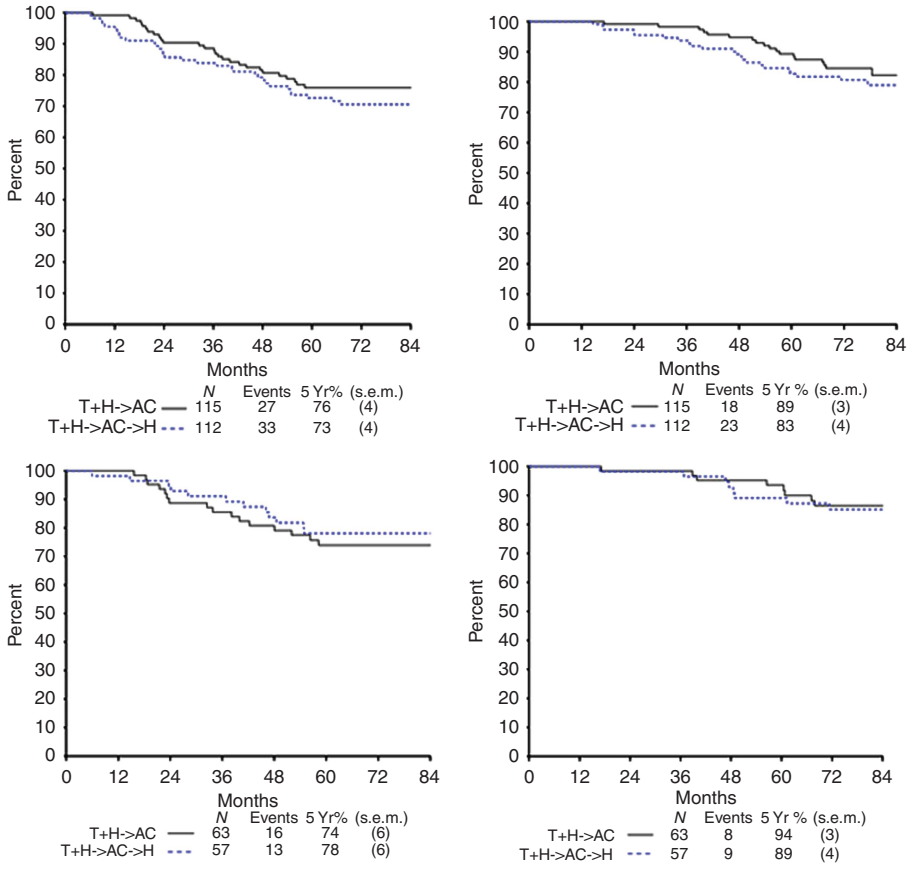

Figure 2. (Top) Comparison of DFS (left) and OS (right) for the 227 patients enrolled and randomised. (Bottom) Comparison of DFS (left) and OS (right) for the 120 patients centrally re-tested and HER2-positive.

respectively) or OS (HR, 1.2; $P = 0.7$; 5-year OS, 89% and 94%, respectively) (Table 3b).

DISCUSSION

Targeting HER2 has drastically improved the outcome for patients with HER2-positive breast cancer. In the metastatic setting, the addition of trastuzumab to chemotherapy significantly improved both PFS and OS. The addiction to this pathway has been evidenced by continued benefit to anti-HER2 blockade even after progression on trastuzumab (Geyer *et al*, 2006; Schaller *et al*, 2007). More recently, dual blockade with trastuzumab and either lapatinib or pertuzumab has also demonstrated further improved PFS and OS in the metastatic setting (Swain *et al*, 2015). Trastuzumab has improved DFS and OS in the adjuvant setting compared with chemotherapy alone (Slamon *et al*, 2011). Although dual therapy with trastuzumab plus pertuzumab and trastuzumab plus lapatinib

Table 3a. DFS and OS outcomes for all patients

			5-Year rate	
	Hazard ratio (95% CI)[a]	*P*-value[b]	Abbreviated trastuzumab *N* = 115	Conventional trastuzumab *N* = 112
DFS	1.31 (0.79–2.12)	0.31	76%	73%
OS	1.37 (0.74–2.54)	0.32	89%	83%

Abbreviations: CI = confidence interval; DFS = disease-free survival; OS = overall survival.
[a]Hazard ratio for conventional trastuzumab *vs* abbreviated trastuzumab.
[b]Based on log-rank test.

Table 3b. DFS and OS for patients centrally re-tested and HER2-positive

			5-year rate	
	Hazard ratio (95% CI)[a]	*P*-value[b]	Abbreviated trastuzumab *N* = 63	Conventional trastuzumab *N* = 57
DFS	0.85 (0.41–1.77)	0.66	74%	78%
OS	1.21 (0.46–3.13)	0.70	94%	89%

Abbreviations: CI = confidence interval; DFS = disease-free survival; HER2 = human epidermal growth factor receptor type 2; OS = overall survival.
[a]Hazard ratio for conventional trastuzumab *vs* abbreviated trastuzumab.
[b]Based on log-rank test.

demonstrated an improvement in pathological complete response over trastuzumab alone, the addition of lapatinib to trastuzumab did not improve either DFS or OS in the large adjuvant ALTTO trial (Piccart-Gebhart *et al*, 2014). We now await the results of the APHINITY trial, testing the combination of pertuzumab with trastuzumab, to determine whether we have truly reached a plateau in terms of benefit from single agent HER2 blockade. From a duration standpoint, recently the ExteNET trial (Chan *et al*, 2015) reported improved invasive DFS in early stage HER2-positive breast cancer patients who received neratinib after completion of 1 year of trastuzumab. It is not clear if this improvement was due to a longer duration of therapy or the addition of second effective anti-HER2 therapy. The HERA trial included a comparator arm that focused entirely on duration and demonstrated that 2 years of trastuzumab administration does not confer benefit over 1 year, suggesting we may have reached a duration plateau for single agent therapy (Piccart-Gebhart *et al*, 2005). Although we may have reached a ceiling in terms of incremental benefit from the amount and the duration of HER2 blockade, many questions remain as to whether we can minimise the amount of chemotherapy and trastuzumab in specific populations and whether less than 12 months of therapy may be beneficial. Recent data have demonstrated that women with small tumours (T1c) may indeed benefit from HER2 blockade (O'Sullivan *et al*, 2014); although the outcomes for T1a/T1b tumours appear to have exceptionally good outcome in the absence of additional therapy. In addition, Tolaney *et al*. (2015) demonstrated that the use of single agent paclitaxel and trastuzumab alone might provide outstanding efficacy for small, node-negative tumours. Thus, there are many evidence-based options for patients diagnosed with early stage HER2-positive breast cancer; ranging from traditional full doses of chemotherapy with dual antibody blockade to single agent paclitaxel and trastuzumab in the adjuvant setting. Shorter durations of trastuzumab have also recently been reported. The PHARE trial (Pivot *et al*, 2013), which was a non-inferiority trial, could not exclude the inferiority of 6 months of trastuzumab compared with 1 year. Despite this, there is some evidence of benefit to the use of trastuzumab for shorter durations compared with none (Joensuu *et al*, 2009). Thus, it is not clear where on the risk spectrum that the incremental gain in outcome from longer therapy can be optimally captured.

Opened to accrual in 1999, E2198 was designed to capture the toxicity for various durations of trastuzumab therapy; most importantly cardiac toxicity. The previously reported rates of CHF from the large adjuvant trastuzumab trials are consistently low (<4% incidence) (Ewer *et al*, 2005; Suter *et al*, 2007; Perez *et al*, 2008; Procter *et al*, 2010; Russell *et al*, 2010; Pivot *et al*, 2013; de Azambuja *et al*, 2014). Exposure to anthracyclines, low baseline ejection fraction, older age, hypertension and high BMI appear to predict a higher likelihood (Perez *et al*, 2008; Russell *et al*, 2010; Bowles *et al*, 2012). The majority of patients who experience severe cardiac toxicity, however, do appear to have either partial or complete recovery of function with cessation of therapy (Ewer *et al*, 2005; Procter *et al*, 2010; Russell *et al*, 2010; de Azambuja *et al*, 2014). Two years of trastuzumab did not increase the risk of severe cardiac damage compared to one year in the HERA trial (de Azambuja *et al*, 2014). There was a significantly higher rate of CHF for those receiving 1 year of therapy compared with 6 months in the PHARE study, but the rates were very low in both arms with recovery in the vast majority of patients (Pivot *et al*, 2013). As expected from these prior reports, there were no unexpected toxicities for the combination of chemotherapy with trastuzumab. Specifically, the rates of CHF and drops in LVEF >10% were modest and not substantially different based on duration of therapy. Unfortunately this trial used the older CTCv. 2.0 criteria for scoring and there was neither central review nor long-term follow-up, which is a limitation of this study.

Although this trial was not powered for efficacy outcome comparisons, there appeared to be no substantial signal to demonstrate marked benefit for longer duration. Thus, while these data should not challenge the current standard of care for one year of anti-HER2 therapy, it does add to the existing body of data to support some benefit for even short durations of trastuzumab. For patients with low-risk disease, where the value of therapy was uncertain at the outset and where cardiac (or other toxicity) issues become apparent, it may provide support to truncate therapy early with some benefit, rather than extending therapy to complete an entire year of therapy. These efficacy results must be interpreted with caution because of the different definition of HER2 positivity at the time of the trial initiation. To address this concern, we centrally repeated HER2 testing using more contemporary definitions of HER2 positivity. It must be noted that several patients were removed simply because of lack of sufficient tumour material for testing or were found to be HER2 equivocal. In addition, even for those patients clearly HER2-negative on re-testing, these tumours may have had molecular heterogeneity and thus have gained benefit despite the negative test. Further, there are some data to support benefit from those with even low levels of HER2 protein expression (Paik *et al*, 2008). Regardless, in both the parent group and retested subset, there was no substantial improvement in outcomes for the longer duration of therapy.

In summary, this trial supports the safety of combining chemotherapy with trastuzumab. Further, although underpowered and exploratory, it identified no substantial signal for marked inferiority for a shorter duration of trastuzumab. Although 1 year of anti-HER2 blockade should remain the standard of care, this adds additional data to support efficacy for shorter durations and this may be beneficial for decision making in patients having difficulty in tolerating the therapy. In addition, from a global perspective, 1 year of trastuzumab administration for every patient with HER2-positive breast cancer may simply not be feasible from a financial standpoint (Benjamin *et al*, 2013). Thus, additional trials addressing shorter durations remain critical.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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