Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

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Summary

Background Pathological complete response has been proposed as a surrogate endpoint for prediction of long-term clinical benefit, such as disease-free survival, event-free survival (EFS), and overall survival (OS). We had four key objectives: to establish the association between pathological complete response and EFS and OS, to establish the definition of pathological complete response that correlates best with long-term outcome, to identify the breast cancer subtypes in which pathological complete response is best correlated with long-term outcome, and to assess whether an increase in frequency of pathological complete response between treatment groups predicts improved EFS and OS.

Methods We searched PubMed, Embase, and Medline for clinical trials of neoadjuvant treatment of breast cancer. To be eligible, studies had to meet three inclusion criteria: include at least 200 patients with primary breast cancer treated with preoperative chemotherapy followed by surgery; have available data for pathological complete response, EFS, and OS; and have a median follow-up of at least 3 years. We compared the three most commonly used definitions of pathological complete response—ypT0 ypN0, ypT0/is ypN0, and ypT0/is—for their association with EFS and OS in a responder analysis. We assessed the association between pathological complete response and EFS and OS in various subgroups. Finally, we did a trial-level analysis to assess whether pathological complete response could be used as a surrogate endpoint for EFS or OS.

Findings We obtained data from 12 identified international trials and 11 955 patients were included in our responder analysis. Eradication of tumour from both breast and lymph nodes (ypT0 ypN0 or ypT0/is ypN0) was better associated with improved EFS (ypT0 ypN0: hazard ratio [HR] 0·44, 95% CI 0·39–0·51; ypT0/is ypN0: 0·48, 0·43–0·54) and OS (0·36, 0·30–0·44; 0·36, 0·31–0·42) than was tumour eradication from the breast alone (ypT0/is; EFS: HR 0·60, 95% CI 0·55–0·66; OS 0·51, 0·45–0·58). We used the ypT0/is ypN0 definition for all subsequent analyses. The association between pathological complete response and long-term outcomes was strongest in patients with triple-negative breast cancer (EFS: HR 0·24, 95% CI 0·18–0·33; OS: 0·16, 0·11–0·25) and in those with HER2-positive, hormone-receptor-negative tumours who received trastuzumab (EFS: 0·15, 0·09–0·27; OS: 0·08, 0·03, 0·22). In the trial-level analysis, we recorded little association between increases in frequency of pathological complete response and EFS (R^2=0·03, 95% CI 0·00–0·25) and OS (R^2=0·24, 0·00–0·70).

Interpretation Patients who attain pathological complete response defined as ypT0 ypN0 or ypT0/is ypN0 have improved survival. The prognostic value is greatest in aggressive tumour subtypes. Our pooled analysis could not validate pathological complete response as a surrogate endpoint for improved EFS and OS.

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Introduction

New agents to treat breast cancer have historically been approved first in the metastatic setting, with approval for use in early-stage breast cancer following many years later on the basis of results of large randomised adjuvant trials with long follow-up. Neoadjuvant treatment—systemic therapy delivered before definitive breast cancer surgery—was once reserved to reduce the size and extent of locally advanced tumours, but is now being used more widely. In addition to increasing the likelihood of tumour control and the potential for curability in early breast cancer, neoadjuvant trials allow rapid assessment of drug efficacy and could expedite development and approval of

treatments for early breast cancer.[1] Pathological complete response has been proposed as a surrogate endpoint for prediction of long-term clinical benefit, such as disease-free survival and overall survival (OS).[2–5]

Although pathological complete response has been the most commonly used endpoint in neoadjuvant trials, it has been variably defined, which has made reporting and interpretation of data challenging. One way to optimise the definition of pathological complete response, enable the interpretation of data, and investigate the association between pathological complete response and long-term outcome is via a pooled analysis of neoadjuvant trials. To obtain the requisite number of trials for this pooled

analysis, the US Food and Drug Administration established an international working group known as Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC) with investigators who had done neoadjuvant trials for which long-term data are available.

We aimed to investigate the potential of pathological complete response as a surrogate endpoint for long-term outcomes. We had four key objectives: to establish the association between pathological complete response and event-free survival (EFS) and OS, to establish the definition of pathological complete response that correlates best with long-term outcome, to identify the breast cancer subtypes in which pathological complete response is best correlated with long-term outcome, and to assess whether an increase in frequency of pathological complete response predicts improved EFS and OS. Here, we present initial results from the CTNeoBC pooled analysis.

Methods

Search strategy and selection criteria
We searched PubMed, Embase, and Medline for reports of clinical trials of neoadjuvant treatment of breast cancer published between Jan 1, 1990, and Aug 1, 2011. To be eligible, studies had to meet three inclusion criteria: include at least 200 patients with primary breast cancer treated with preoperative chemotherapy followed by surgery; have available data for pathological complete response, EFS, and OS; and have a median follow-up of at least 3 years.

Investigators from identified trials were invited to participate in a collaborative analysis and agreed to provide individual patient data. We excluded data from all patients randomised to postoperative treatment, patients in the HER2-negative treatment group of the NOAH trial (necessary data were unavailable for this group), and patients who never began assigned treatment.

Outcome measures
Definitions of pathological complete response varied across trials. We compared the three most commonly used pathological complete response definitions to establish their association with long-term outcome: ypT0 ypN0 (ie, absence of invasive cancer and in-situ cancer in the breast and axillary nodes), ypT0/is ypN0 (ie, absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ), and ypT0/is (ie, absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement). All trials had standard operating procedures for pathological complete response assessments.

The endpoint of choice for adjuvant trials has been disease-free survival, reflecting the fact that patients are disease free at the time of randomisation. By contrast, EFS is used in neoadjuvant trials because all patients are not disease free at randomisation. We calculated EFS as the interval from randomisation to the earliest occurrence of disease progression resulting in inoperability, locoregional recurrence (after neoadjuvant therapy), distant metastases, or death from any cause. Patients alive without an event as of the analysis cutoff date were censored at last study follow-up date. Overall survival was calculated from date of randomisation to death. For patients alive on the data cutoff date, survival was censored at last study follow-up date.

Statistical analysis
In the pooled analysis, we categorised patients who either did not undergo surgery or who had surgery but for whom data were missing for pathological complete response as non-pathological complete responders. We compared the three definitions of pathological complete response for their association with EFS and OS. In this responder analysis, EFS and OS were compared between patients with and without pathological complete response, irrespective of treatment assignment, with a log-rank test stratified by study. We estimated hazard ratios (HRs) and 95% CIs of EFS and OS from stratified Cox regression models with study as a stratification factor. We also obtained Kaplan-Meier estimates of EFS and OS by pathological complete response status. We assessed the association between pathological complete response and EFS and OS in various subgroups. We did multivariable analyses with Cox regression models including baseline factors (age, tumour stage, nodal status, histological type, tumour grade, and tumour subtype) and pathological complete response status. We excluded patients with missing factors from the multivariable analyses.

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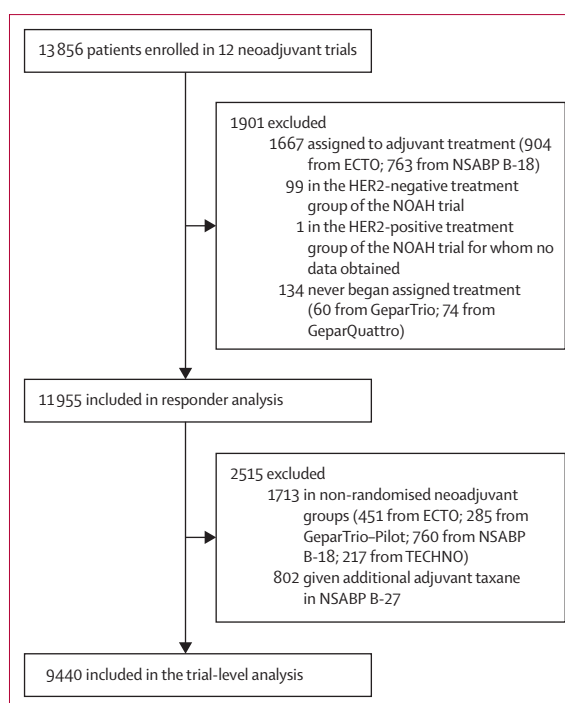patricia.cortazar@fda.hhs.gov

Figure 1: Study profile

To explore the potential of pathological complete response as a surrogate endpoint for EFS or OS in a trial-level analysis, we quantified the association between treatment effects on pathological complete response and EFS and OS using a weighted linear regression model on a logarithmic scale. We excluded data from patients in non-randomised groups from this analysis, because we could not estimate the treatment effect size in these groups. We also excluded patients in NSABP B-27 who received additional adjuvant taxane treatment because the neoadjuvant treatment effect could not be isolated.

We present treatment effects on EFS and OS as HRs (calculated with Cox proportional hazards models) and on pathological complete response as odds ratios (calculated with logistic regression models) within each randomised comparison. The linear regression model was weighted by sample size of each randomised comparison. Using a two-stage model to adjust for the

estimation error of treatment effect size estimates,[6] we calculated the coefficient of determination (R^2) and the associated 95% CI to measure the correlation between pathological complete response and EFS and OS by treatment effect. By convention, an HR (experimental *vs* control) of less than 1 denotes a favourable result for EFS and OS in the experimental group, and an odds ratio (experimental *vs* control) of more than 1 denotes a favourable result for pathological complete response. Thus, a strong negative correlation between log hazard ratio for EFS or OS and log odds ratio for pathological complete response would validate pathological complete response as a surrogate for long-term clinical benefit. All analyses were done with SAS (version 9.2).

Results

We identified 12 international neoadjuvant trials: AGO 1 (n=668),[7] ECTO (n=1355),[8] EORTC 10994/BIG 1-00
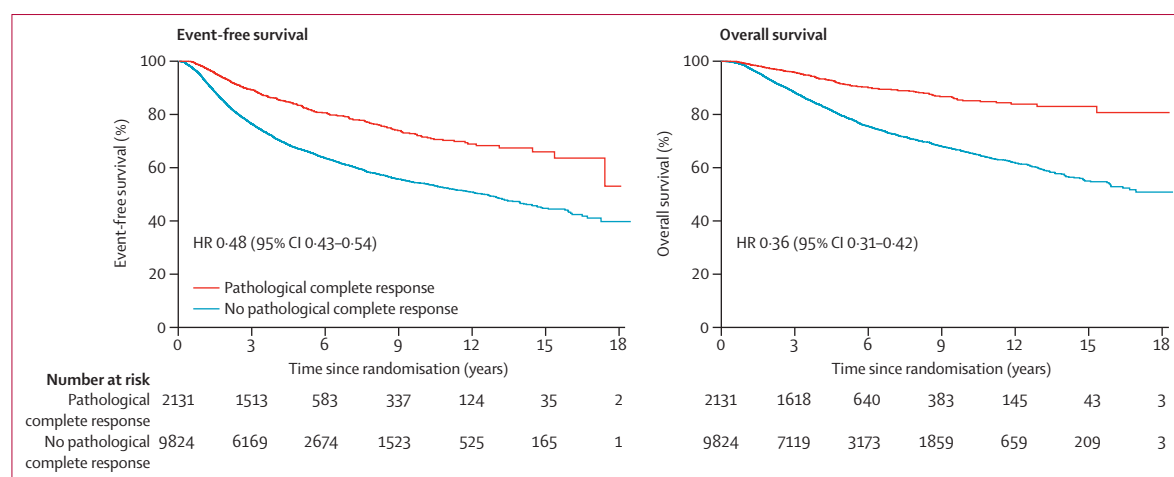

Figure 2: Associations between pathological complete response and event-free survival and overall survival
ypT0/is ypN0 definition of pathological complete response (ie, absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ). HR=hazard ratio.
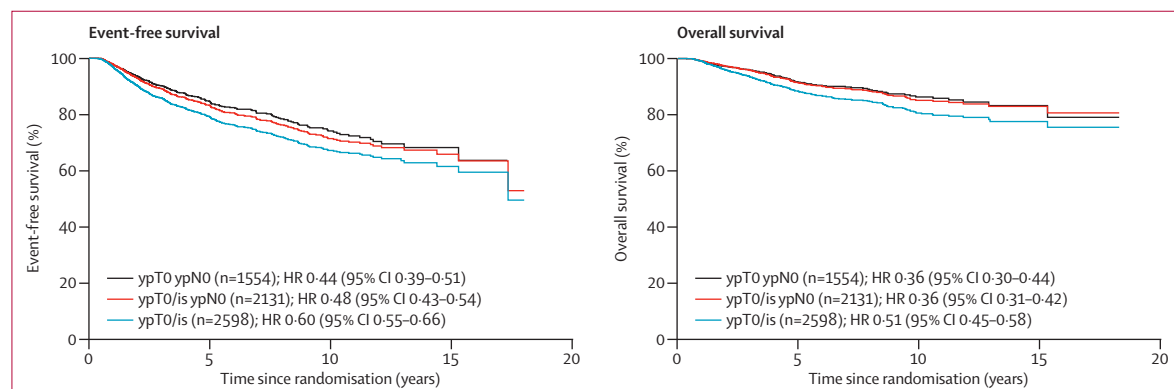

Figure 3: Associations between three definitions of pathological complete response and event-free survival and overall survival
We compared event-free survival and overall survival between patients who did and did not achieve a pathological complete response according to one of three definitions. Patients who did not achieve a pathological complete response are not shown. Number of patients who achieved a pathological complete response is listed for each pathological complete response definition. Patients could achieve pathological complete response according to more than one definition. ypT0 ypN0=absence of invasive cancer and in-situ cancer in the breast and axillary nodes. ypT0/is ypN0=absence of invasive cancer in the breast and axillary nodes, irrespective of ductal carcinoma in situ. ypT0/is=absence of invasive cancer in the breast, irrespective of ductal carcinoma in situ or nodal involvement. HR=hazard ratio.

(n=1856),[9] GeparDuo (n=907),[10] GeparQuattro (n=1495),[11,12] GeparTrio (n=2072),[13,14] GeparTrio-Pilot (n=285),[15] NOAH (n=334),[16] NSABP B-18 (n=1523),[17,18] NSABP B-27 (n=2411),[18,19] PREPARE (n=733),[20,21] and TECHNO (n=217; appendix).[22] No major trial was excluded from the pooled analysis. All were randomised controlled trials except for TECHNO,[22] which was a single-group study previously included in the pooled analysis of the German neoadjuvant trials.[23]

In each trial, heterogeneous populations of patients were enrolled and randomised comparisons of
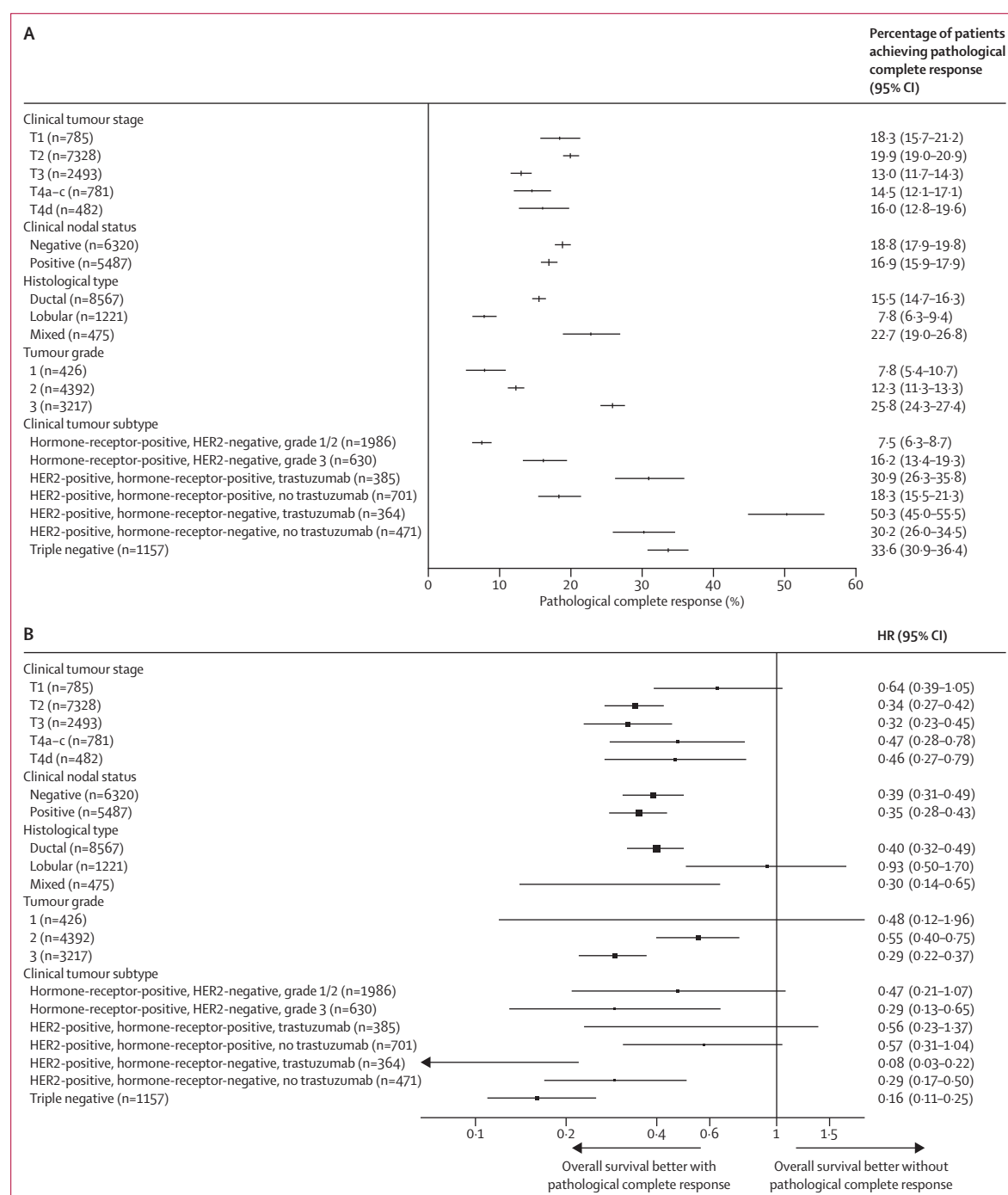
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Figure 4: Percentage of patients achieving pathological complete response (A) and HRs for overall survival (B), by subgroup
Information about clinical tumour stage available for 11 869 patients, about clinical nodal status for 11 807 patients, about histological type for 10 263 patients, about tumour grade for 8035 patients, and about clinical tumour subtype for 5694 patients. ypT0/is ypN0 definition of pathological complete response used. No multiplicity adjustment was made. HR=hazard ratio.

anthracycline-based and taxane-based regimens were done, with the exception of the NOAH[16] and TECHNO[22] trials, which were limited to patients with HER2-positive locally advanced or inflammatory breast cancer. Patients in the NOAH[16] trial were randomly assigned to preoperative chemotherapy with or without trastuzumab, and those in the TECHNO[22] trial received trastuzumab and chemotherapy followed by 1 year of adjuvant trastuzumab. In the GeparQuattro trial,[11,12] patients with HER2-positive tumours received trastuzumab concomitantly with chemotherapy. Overall, 1087 (55%) of 1989 patients with HER2-positive tumours included in the pooled analysis did not receive 1 year of adjuvant trastuzumab because they were treated before adjuvant trastuzumab trials were reported. All

patients with hormone-receptor-positive tumours were supposed to receive at least 5 years of endocrine therapy. Breast cancer subtype was established by clinic-opathological criteria, such as hormone-receptor status, HER2 overexpression, and histological grade as assessed by local pathologists. The Ki-67 labelling index had not been routinely assessed in the included studies.

11955 patients were included in our pooled responder analysis (figure 1). Baseline characteristics are shown in the appendix. Median age was 49 years (IQR 43–57). 7328 patients (61%) had T2 tumours, 482 (4%) had inflammatory breast cancer (ie, T4d tumours), and 5487 (46%) had clinically involved lymph nodes. 3572 (30%) patients had hormone-receptor-negative breast cancer, and 1989 (17%) had HER2-positive
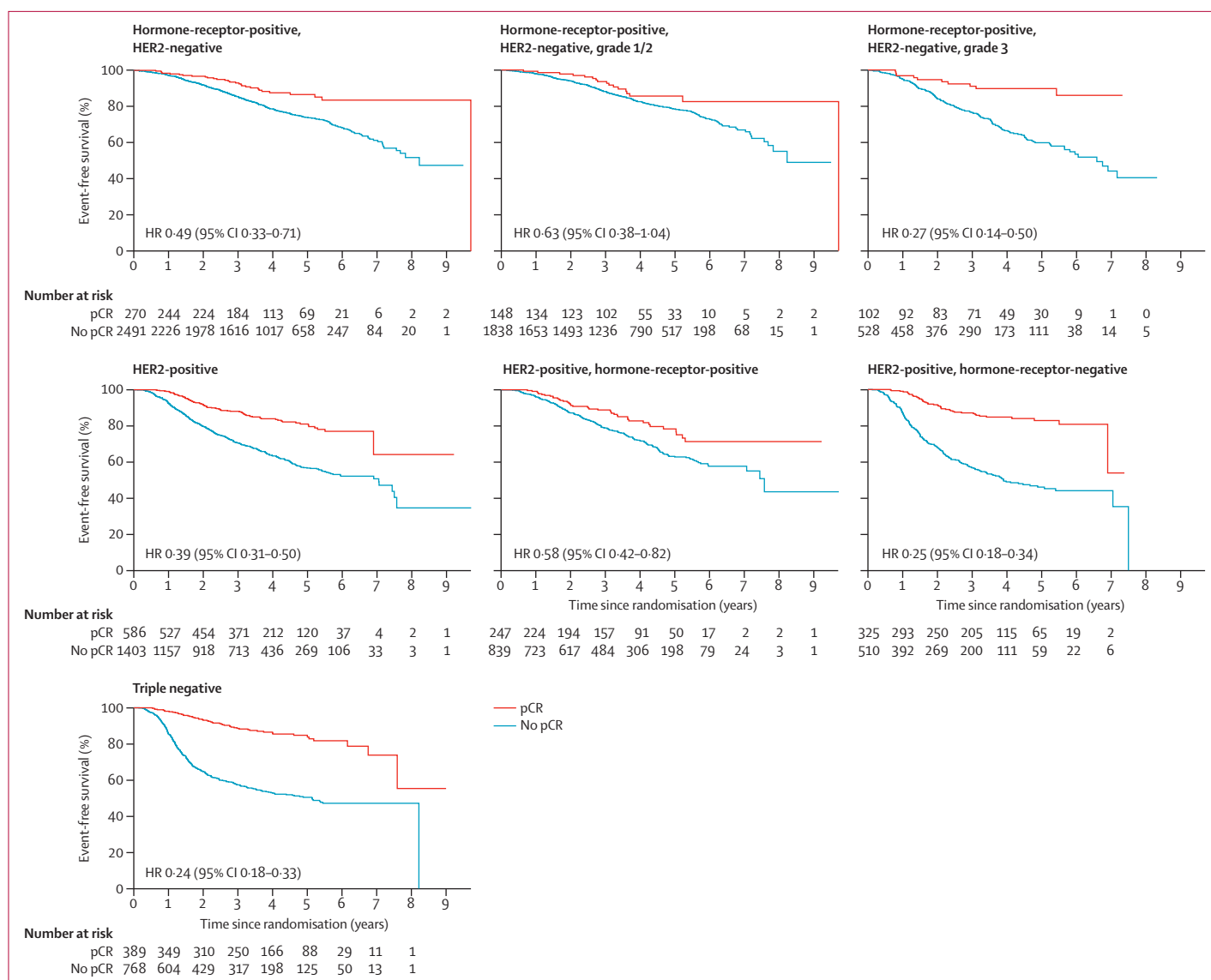

Figure 5: Association between pCR and event-free survival, by breast cancer subtype
pCR=pathological complete response. HR=hazard ratio.

tumours. Tumour testing for HER2 was not necessary in the earlier trials, so information about HER2-receptor status was not available for four trials (AGO-1,[7] NSABP B-18,[17] NSABP B-27,[19] and ECTO[8]). Overall median follow-up for EFS was 5·40 years (95% CI 5·33–5·44) and for OS was 5·37 years (5·31–5·43).

Overall frequency of pathological complete response was low, and the frequency decreased with increasingly stringent definitions: 22% (95% CI 21–22) of patients achieved ypT0/is, 18% (17–19) achieved ypT0/is ypN0, and 13% (12–14) achieved ypT0 ypN0. Overall, patients who achieved a pathological complete response had longer EFS and OS than did patients with residual invasive cancer (figures 2, 3). Eradication of tumour from both the breast and axillary lymph nodes (ypT0 pN0 and ypT0/is ypN0) was better associated with improved EFS and OS than was eradication of invasive tumour from the breast alone (ypT0/is; figure 3). Associations with EFS and OS were similar for ypT0 ypN0 and ypT0/is ypN0 (figure 3). Additionally, associations were consistent when we adjusted for baseline factors using multivariable Cox models. We used the ypT0/is ypN0 definition for all subsequent analyses.

As expected, frequency of pathological complete responses in patients with low-grade, hormone-receptor-positive tumours was low, and more than doubled in the high-grade hormone-receptor-positive subgroup (figure 4A). The more aggressive subtypes—triple-negative and HER2-positive tumours—had increased frequencies of pathological complete response (figure 4A). Within the HER2-positive population, pathological complete response was more common for hormone-receptor-negative tumours than for hormone-receptor-positive tumours, and with the addition of trastuzumab (figure 4A).

The pathological complete response was positively associated with EFS (HR 0·49, 95% CI 0·33–0·71) and OS (0·43, 0·23–0·71) in the overall hormone-receptor-positive, HER2-negative population. The association between pathological complete response and long-term outcome was stronger in patients with high-grade tumours than in those with low-grade tumours (figures 4B, 5). Additionally, pathological complete response was associated with long-term outcome in the HER2-positive subgroup irrespective of hormone-receptor status (EFS: HR 0·39, 95% CI 0·31–0·50; OS: 0·34, 0·24–0·47). The strength of the association increased in the hormone-receptor-negative subgroup (EFS: 0·25, 0·18–0·34; OS: 0·19, 0·12–0·31). The most favourable outcomes after pathological complete response were recorded in patients with HER2-positive, hormone-receptor-negative tumours who received trastuzumab (EFS: 0·15, 0·09–0·27; OS: 0·08, 0·03–0·22), and in the triple-negative subgroup (figures 4B, 5).

We analysed the association between the effect of treatments on pathological complete response and long-term outcomes in ten randomised comparisons, excluding non-randomised neoadjuvant groups and patients given additional adjuvant taxane (figure 1). At a trial level, we recorded little association between increases in frequency of pathological complete response and the treatment's effect on EFS or OS (figure 6). The coefficient of determination (R^2) between improvement in pathological complete response and EFS was 0·03 (95% CI 0·00–0·25), and that between improvement in pathological complete response and OS was 0·24 (0·00–0·70).

We also investigated the trial-level association between pathological complete response and long-term outcome by tumour subtype. We excluded patients with low-grade, hormone-receptor-positive tumours because of low frequency of pathological complete response. The
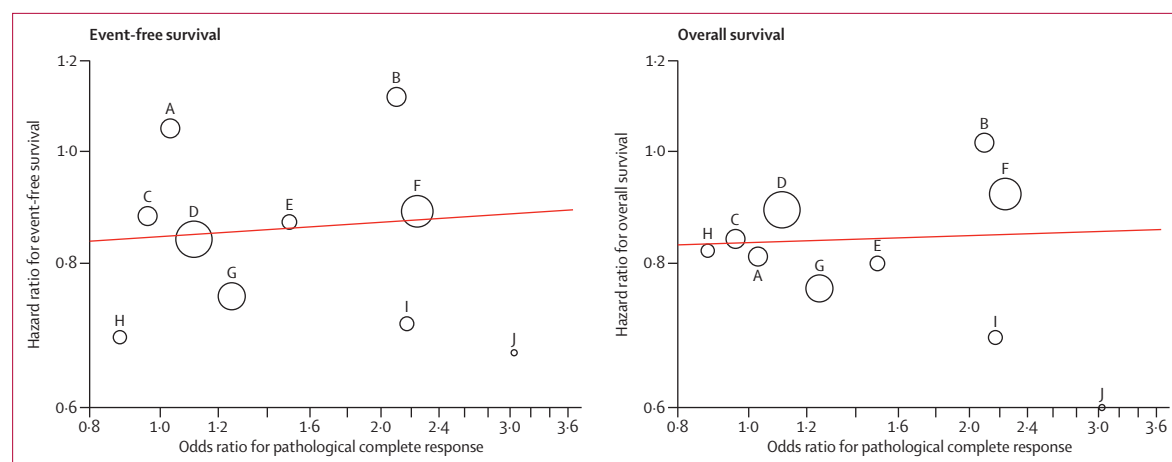

Figure 6: Trial-level correlation between treatment effect on pathological complete response and event-free survival or overall survival
Each circle corresponds to one randomised comparison and the size of the circle represents the sample size. A=GeparQuattro (epirubicin plus cyclophosphamide followed by docetaxel then capecitabine *vs* epirubicin plus cyclophosphamide followed by docetaxel). B=GeparDuo. C=GeparQuattro (epirubicin plus cyclophosphamide followed by docetaxel and capecitabine *vs* epirubicin plus cyclophosphamide followed by docetaxel). D=EORTC 10994/BIG 1-00. E=PREPARE. F=NSABP B-27. G=responders in GeparTrio. H=non-responders in GeparTrio. I=AGO 1. J=NOAH.

results of the analyses by breast cancer subtype were consistent with findings in the overall population: no correlation between improvement in frequency of pathological complete response and the treatment's effect on EFS or OS was recorded (appendix).

Discussion

In our pooled analysis, we recorded that eradication of tumours from both breast and lymph nodes (ypT0 ypN0 or ypT0/is ypN0 pathological complete response) had a stronger association with improved EFS and OS than did eradication of tumour from the breast alone (ypT0/is). The strongest association between pathological complete response and long-term outcome was in patients with aggressive breast cancer subtypes (triple negative; hormone-receptor-positive, high-grade, and HER2-negative; and HER2-positive and hormone-receptor-negative). Nevertheless, an increase in frequency of pathological complete response between treatment groups did not predict improved EFS and OS.

Standardisation of the definition of pathological complete response would allow planning and interpretation of future neoadjuvant clinical trials intended to support drug approval. We propose that pathological complete response is defined as either ypT0/is ypN0 or ypT0 ypN0 in future trials. However, ypT0 ypN0 is a more stringent definition and its use could lead to reduced frequencies of pathological complete response. Presence or absence of ductal carcinoma in situ did not affect long-term outcome in our analysis. Additionally, a retrospective analysis[24,25] of a database including more than 2000 patients treated with neoadjuvant chemotherapy showed that residual ductal carcinoma in situ in patients with complete eradication of the invasive cancer from the breast and lymph nodes did not adversely affect survival. By contrast, a German pooled analysis[26] of seven neoadjuvant trials showed that patients without ductal carcinoma in situ had longer survival than did patients with residual ductal carcinoma in situ when all invasive disease was eradicated.

Several other groups have reported improved long-term outcomes in patients with pathological complete response compared with those with residual tumour at the time of surgery.[17,19,23,24,26] Our pooled analysis confirmed this finding in various tumour subtypes and in groups divided by other baseline characteristics. The strength of the association increased with trastuzumab treatment, which emphasises the importance of targeted therapy. The association between pathological complete response and long-term outcome was weakest for hormone-receptor-positive and low-grade tumours, and for HER2-positive and hormone-receptor-positive tumours. The German pooled analysis[23,26] similarly showed that the association between pathological complete response and long-term outcome was strongest in patients with aggressive breast cancer subtypes. However, pathological complete response was not prognostic in patients with luminal A or luminal B and HER2-positive breast cancer.

The difference between patient-level analyses and trial-level analyses is a common source of confusion. Patient-level analyses, sometimes referred to as responder analyses, compare the clinical outcome of patients with and without pathological complete response, irrespective of the treatment group. These analyses are meaningful as they predict improved survival for patients who attain pathological complete response. Because these responder analyses are independent of the treatment group, they are not useful for comparisons of treatments at a trial level. The CTNeoBC pooled analysis is the first large analysis in which primary source data has been used to assess the association between pathological complete response and EFS and OS at a trial level.

We propose four potential explanations for the finding that an increase in frequency of pathological complete response between treatment groups did not predict improved EFS and OS. First, in most of the included trials, women with heterogeneous breast cancer tumour subtypes were enrolled, which would be expected to obscure the association between pathological complete response and survival if subtypes respond differently to the same treatment, or if different absolute improvements in frequency of pathological complete response are necessary to meaningfully affect long-term outcomes. Second, a neoadjuvant therapy targeted to a specific tumour subtype (trastuzumab) was used in only three trials (GeparQuattro,[12] NOAH,[16] and TECHNO[22]), and trastuzumab used as an adjunct to chemotherapy in only the NOAH study. As a result, absolute differences in the frequency of pathological complete response between chemotherapy groups in the included trials were generally low (1–11%), but were as high as 20% for the NOAH trial, comparing trastuzumab plus chemotherapy with chemotherapy alone (ypT0/is ypN0: 35% vs 15%; odds ratio 3·04, 95% CI 1·64–5·82). Similarly, the difference in the proportion of patients achieving EFS at 5 years between treatment groups in the NOAH study was 13%, although postoperative trastuzumab in the experimental group could have partly contributed to the treatment effect. Fourth, factors unrelated to primary tumour response could have had a role. In the HER2-positive subgroup, we noted that the addition of one trial with increased treatment effects (NOAH) decreased the slope of the curve, suggesting a trial-level correlation between frequency of pathological complete response and long-term outcome could be identified in future trials with more homogeneous populations and incorporation of targeted therapies. Future trials of subtype-specific populations with differences in frequency of pathological complete response between treatment groups that are larger than are those in the trials we included could predict improvement in EFS or OS in early-stage breast cancer.

The importance of individual-level association should not be overlooked; it offers insight into the natural history of an individual's disease and is thus useful to counsel patients. Trial-level association is useful to predict population treatment benefits. As previously suggested,[6,27] an acceptable surrogate endpoint should be correlated with outcome at both the individual and trial levels. Our pooled analysis could not establish a trial-level correlation between pathological complete response and long-term outcome. In view of the substantial improvements in survival for individual patients who attain pathological complete response, we believe that if a novel agent produces a marked absolute increase in frequency of pathological complete response compared with standard therapy alone in the intention-to-treat population, that agent could also be reasonably likely to result in long-term improvements in EFS or OS.[28] In our future analyses (with genomic assays to better charac-terise subgroups and including additional anti-HER2 trials), we will investigate the importance of pathological complete response in defined subsets and assess other promising surrogate endpoints.

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