Association of Pathologic Complete Response with Long-Term Survival Outcomes in Triple-Negative Breast Cancer: A Meta-Analysis

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ABSTRACT

Pathologic complete response (pCR) following neoadjuvant therapy has been associated with improved event-free survival (EFS) and overall survival (OS) in early-stage breast cancer. The magnitude of this association varies by breast cancer subtype, yet further research focusing on subtype-specific populations is limited. Here we provide an updated and comprehensive evaluation of the association between pCR and survival outcomes in triple-negative breast cancer (TNBC). A literature review identified neoadjuvant studies, including clinical trials, real-world cohort studies, and studies that pooled multiple trials or cohorts, which reported EFS/OS results by pCR in patients with early-stage TNBC. Meta-analyses were performed to evaluate the association between pCR and EFS/OS and to predict long-term survival outcomes based on pCR status. Sensitivity analyses were conducted to assess the impact of cross-study variations. Twenty-five studies with over 4,000 patients with TNBC were identified. A synthesis of evidence from these studies suggested substantial improvement in EFS and OS for pCR versus non-pCR [EFS HR (95% confidence interval): 0.24 (0.20–0.29); OS: 0.19 (0.15–0.24)]; consistent results were reported in sensitivity analyses. Collectively, our findings suggest that adjuvant therapy is associated with improved EFS/OS in patients with TNBC who received neoadjuvant therapy, regardless of pCR status.

Introduction

Triple-negative breast cancer (TNBC) is a molecular subtype with absent expression of the estrogen receptor (ER) and progesterone receptor (PR), and no or low expression of HER2. TNBC represents approximately 10% to 20% of all breast cancers in the United States (1). Because of a lack of receptor expression and virulent biology, TNBC is associated with a poorer prognosis compared with other breast cancer subtypes (2). Neoadjuvant therapy plays an increasingly prominent role in the treatment of early-stage TNBC to improve local therapy options and improve long-term outcomes (3, 4).

Response to neoadjuvant therapy is commonly evaluated in breast cancer clinical trials by assessing pathologic complete response (pCR) rates, based on microscopic inspection of the surgically resected specimen (5). Previous studies have demonstrated positive patient-level associations between pCR and long-term outcomes, including event-free survival (EFS) and overall survival (OS) in the overall breast cancer population and among different breast cancer subtypes (6–11). A pooled analysis of 12 neoadjuvant chemotherapy breast cancer clinical trials sponsored by the FDA found that patients with breast cancer who achieved a pCR had significantly improved survival outcomes (8). The magnitude of this association varied by breast cancer subtype and was strongest among patients with aggressive breast cancer subtypes such as TNBC. However, further research focusing on TNBC has been limited. In the study by Cortazar and colleagues (8), the findings in TNBC were based on a subset of patients among a heterogeneous population from four randomized controlled trials (RCT) published between 2008 and 2011.

The objective of this study was to provide an updated and comprehensive evaluation of the patient-level association between pCR and survival outcomes, with a specific focus on patients with early-stage TNBC. Meta-analysis approaches were utilized to determine whether patients with early-stage TNBC attaining pCR had significantly longer EFS and OS, to quantify the benefit of having a pCR, and to predict long-term survival outcomes based on pCR status. Sensitivity analyses were conducted to explore cross-study variations and to evaluate the impact of the variations on the association.

Materials and Methods

Search strategy and study selection criteria

We searched MEDLINE, Embase, Cochrane CENTRAL, and Northern Light Sciences Conference Abstracts for English publications through October 2018. The search strategy included keywords related to "breast cancer," "neoadjuvant treatment," "pathologic complete response" or "pCR," and "survival outcomes." Full-text

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publications as of October 2018 and conference abstracts from 2016 to October 2018 were reviewed for inclusion in the analysis. To be eligible, publications had to meet the following criteria: (i) enrolled adult patients receiving neoadjuvant treatment for early stage TNBC; (ii) were published as clinical trials (randomized or single arm), real-world evidence cohort studies (prospective or retrospective), or studies that pooled clinical trial participants or cohorts; and (iii) reported HRs or Kaplan–Meier curves of EFS/OS by pCR status among patients with early-stage TNBC. When more than one eligible publication reported the outcomes of interest for the same RCT study, only data from the most recent publication were included in the meta-analysis to avoid counting the same patients twice or more times.

Study outcomes

The definition of pCR varied across studies (8, 12–14). The three most commonly used pCR definitions, from most stringent to least stringent, were: (1) ypT0 ypN0, indicating absence of invasive cancer and *in situ* cancer in the breast and axillary nodes; (2) ypT0/is ypN0, indicating absence of invasive cancer in the breast and axillary nodes, irrespective of the presence of residual ductal carcinoma *in situ*; and (3) ypT0/is, indicating absence of invasive cancer in the breast irrespective of the presence of ductal carcinoma *in situ* or nodal involvement (8). Previous analyses have indicated that the magnitude of the association between pCR and long-term survival outcomes may vary across the different definitions of pCR (8). In this analysis, we restricted inclusion to studies that reported outcomes using the pCR definition of ypT0/is ypN0, because it is the most commonly used in breast cancer studies (15) and is also the definition recommended by the European Medicines Agency (EMA) and FDA guidelines (5, 16).

The long-term survival outcomes included EFS and OS. The terminology used for EFS varied across the included studies, which was described as EFS, disease-free survival, relapse-free survival, and progression-free survival. However, the definitions for events were similar across most studies and included disease progression that precluded surgery with curative intent, local or distant recurrence, and death. The definition of starting point for these outcomes was also consistent across most studies, which was the time of diagnostic biopsy in cohort studies and study entry or start of neoadjuvant therapy in clinical trials. Here, the term EFS is used to refer to these outcomes for simplicity. Published studies wherein death events were censored in the EFS definition were excluded from this analysis.

Statistical methods

Pooled HR of EFS and OS for pCR versus no pCR

To evaluate the "patient-level" association between pCR and long-term survival outcomes, that is, whether patients who attain pCR have longer EFS and OS than those who do not, meta-analyses using both fixed-effect and random-effects models with the DerSimonian and Laird method were applied to estimate the pooled HRs for EFS and OS (17). HR < 1 indicated that patients with pCR had better survival outcomes than those without pCR. Cochran Q and the Higgins I^2 index were calculated as measures of heterogeneity among the HR results reported in the selected studies. HRs and the corresponding 95% confidence intervals (CI) from each individual study were directly extracted from the study publications. If HRs were not reported, pseudoindividual patient-level data were derived from each published Kaplan–Meier curve of EFS/OS by pCR using the algorithm outlined in Guyot and colleagues (18), and the HRs along with the 95% CIs were estimated using the Cox proportional model based on the pseudoindividual patient data (18). For several studies where there were no EFS or OS events observed within the pCR group, the HRs were estimated using the Firth penalized maximum likelihood approach (19, 20).

Sensitivity analyses were conducted to explore the impact of study setting (i.e., clinical trial vs. cohort study vs. pooled analysis), threshold of hormone receptor positivity defining TNBC (i.e., ER and PR expression cutoff of <1% vs. <10% vs. cutoff not reported) and adjuvant chemotherapy usage (i.e., studies that reported adjuvant therapy use in the TNBC population vs. those that did not) on the association between pCR and long-term survival outcomes.

These analyses were done using R software (version 3.5.1).

Estimated EFS and OS by pCR status

Meta-analyses were conducted to quantify the association between EFS/OS and pCR and to predict long-term survival outcomes based on pCR status.

We utilized parametric frailty models to synthesize the published survival curves for EFS and OS by pCR status, which were available for a subset of studies. Pseudoindividual patient-level data were derived from the published Kaplan–Meier curves using the algorithm described by Guyot and colleagues (18). To evaluate the potential impact of adjuvant chemotherapy use, frailty models were performed to synthesize the survival outcomes in the studies that reported adjuvant chemotherapy use versus those that did not.

A frailty model, introduced in the biostatistical literature by Vaupel and colleagues (21) and discussed in detail in more recent literature (22–24), is a random effects model used to analyze time-to-event data, where the random effect (the so-called frailty) has a multiplicative effect on the hazard. Parametric frailty models were used in this analysis to synthesize the survival curves for EFS and OS by pCR status. Baseline hazard was defined as a common parametric function across all studies and a parametric function was assigned to the frailty term that accounted for cross-study variations. The models allowed the hazard rates for EFS and OS to change over time. The HR between pCR and non-pCR groups could also be time dependent. Log-normal was chosen as the frailty distribution, as it is supported by the SAS program and is commonly used because of its strong link with generalized linear mixed models. A series of standard parametric functions, including exponential, Weibull, Gompertz, log-normal, and log-logistic, were assigned to the baseline hazard, and statistical tests based on the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) were used to select the best-fitted function. In this analysis, log-logistic function had the smallest values of AIC and BIC, and was thus selected as the "best-fit" function.

The model allowed for random effects, which incorporated cross-study heterogeneity instead of a simple pooling of results across studies. Therefore, the results had wider CIs than when study differences were ignored. The estimated EFS and OS survival curves along with the confidence bands are critical to the evaluation of health economic impacts of neoadjuvant therapies based on pCR outcomes.

These analyses were performed using SAS 9.4.

Results

Literature search and description of included studies

Of 1,880 publications identified from the literature search, 34 studies met the eligibility criteria. Nine studies (9, 11, 25–31), including two pooled analyses of clinical trials (11, 25), were further excluded because the pCR definitions in these studies were different from ypT0/is ypN0. Therefore, a total of 25 studies were included in the analysis (Supplementary Fig. S1).

Among these included studies, there were four RCTs (12, 32–34), two single-arm clinical trials (35, 36), 18 cohort studies (4, 37–53), and one pooled analysis (Supplementary Table S1; ref. 8). The pooled analysis (8) included 12 neoadjuvant chemotherapy RCTs and patients across different breast cancer subtypes. We only included the results specific to TNBC in the pooled analysis, which were based on 1,157 patients with early-stage TNBC from four clinical trials (GeparTrio, GeparQuattro, PREPARE, and EORTC 10994). Our analysis used the pooled analysis as a single study, as the data required were not available in all publications of the individual trials.

Publication dates of the clinical trials and cohort studies ranged from 2008 to 2018. Eligible studies represented patients from North America (4, 42, 51), Europe (36, 37, 41, 47), and Asia-Pacific (33, 40, 43, 44, 52, 53). Multiple types of neoadjuvant chemotherapy regimens were used in the eligible studies, including anthracycline-based (34, 35, 37, 38, 40, 45, 46, 50, 53), taxane-based (4, 12, 32–34, 36–38, 40–46, 48–50, 52, 53), and platinum plus docetaxel (12, 32, 33, 36, 38, 42, 48, 49) regimens. The pCR rates ranged from 16.7% (45) to 67.0% (43), with slightly greater variations among cohort studies [median (range): 35.0 (16.7%–67.0%)] compared with clinical trials [median (range): 41.0 (26.7%–62.0%)].

Pooled HR of EFS and OS for pCR versus no pCR

Among the included studies, one clinical trial publication (34) and the pooled analysis (8) both reported data from the EORTC 10994 trial. Although the number of patients with early-stage TNBC, follow-up period, and survival outcomes reported in the two publications were slightly different, we excluded data from the trial publication (34) in this analysis to avoid potential colinearity.

The HR for EFS associated with having a pCR was reported in 19 studies, and ranged from 0.06 to 0.33 (8, 12, 32, 33, 35–38, 41, 42, 44, 46–53). The HR for OS associated with having a pCR was reported in 17 studies, and ranged from 0.06 to 0.51 (4, 8, 12, 33, 37–40, 42, 43, 45, 47, 49–53).

Figure 1A and **B** show the EFS and OS HRs reported in each study and the pooled HRs from the analysis. The results showed that pCR was associated with substantially improved EFS [HR (95% CI): 0.24 (0.20–0.29)] and OS [0.19 (0.15–0.24)]. Minimal heterogeneity was identified ($\tau^2 = 0.00$, $I^2 = 0\%$), and the estimated pooled HRs and corresponding 95% CIs from the fixed-effect and random-effects models were nearly the same for both EFS and OS.

The sensitivity analyses, which explored the impact of study setting, TNBC definition, and adjuvant chemotherapy usage, suggested similar association between pCR and long-term survival outcomes as the primary analysis (Supplementary Table S2). The estimated HRs for EFS and OS for pCR versus no pCR were similar across clinical trials and real-world cohort studies, and were consistent with the estimates from the pooled analysis by Cortazar and colleagues (8). The association was numerically stronger when more stringent criteria (i.e., ER and PR expression cutoff of 1%) were used to define TNBC, although the difference was not statistically significant. The estimated HRs were not significantly different for patients who received adjuvant chemotherapy compared with those who did not.

Estimated EFS and OS by pCR status

Kaplan–Meier curves of EFS or OS stratified by pCR status were reported in 20 studies (6 clinical trials and 14 cohort studies) and were synthesized by the frailty models (4, 12, 32–44, 47, 49, 50, 52, 53). The survival curves by pCR status estimated from the models are shown in **Fig. 2A** and **B**. Five-year EFS for patients with and without pCR was 86% and 50%, respectively, while 5-year OS for patients with and without pCR was 92% and 58%, respectively.

Among the 20 studies that reported EFS or OS Kaplan–Meier curves, two clinical trials (33, 36) and three cohort studies (41, 42, 49) explicitly reported adjuvant chemotherapy usage in patients with early-stage TNBC. Derived from the frailty model, Supplementary Fig. S2A and S2B, recorded the potential impact of adjuvant chemotherapy on survival outcomes. EFS and OS were longer in studies that reported adjuvant chemotherapy usage in patients with early-stage TNBC compared with those that did not, irrespective of attainment of pCR.

Discussion

Using results from recently published clinical trials and real-world cohort studies of neoadjuvant therapies in patients with early-stage TNBC, the current study found that achieving pCR was associated with a 76% lower risk of progression, recurrence, or death, and an 81% lower risk of death. In addition, the sensitivity analyses showed that the association between pCR and long-term survival outcomes was consistent between clinical trial and real-world settings, and was not significantly affected by variation in TNBC definition or use of adjuvant chemotherapy. This study, consistent with the previous analyses (7, 8, 11, 25), has demonstrated that patients with early-stage TNBC who had a pCR had substantially better long-term EFS and OS outcomes than those who did not.

This analysis included a total of 25 studies, representing more than 4,000 patients with early-stage TNBC. To our knowledge, this is the largest and most comprehensive meta-analysis of neoadjuvant studies in TNBC. It included three RCTs (12, 32, 33) in addition to those in the analysis conducted by Cortazar and colleagues (8). The inclusion of real-world cohort studies (4, 37–53) allowed us to substantially expand the evidence base and to assess the association of pCR and survival outcomes in both clinical trial and real-world settings. As there was substantial variation across the included studies regarding pathologic definition of TNBC, preoperative therapy regimens, and use of adjuvant chemotherapy, we analyzed subsets of the studies based on these characteristics and explicitly evaluated the impact of the variations in the sensitivity analyses. Such evidence is important in the interpretation of surrogate outcome data in the context of regulatory and reimbursement decision-making, as the association between a surrogate outcome and a long-term outcome can vary across study populations. However, despite the study variations, consistent and strong associations between pCR and both OS and EFS were identified across all evaluated studies, with minimal heterogeneity noted among the reported HRs, as indicated by Cochran Q and the Higgins I^2 index.

This study further quantified the relationship between pCR and survival outcomes. The predicted EFS and OS curves by pCR status, along with the confidence bands around the estimates, can inform health technology assessment of the relative benefits of TNBC neoadjuvant therapies based on pCR rates. The frailty models for EFS and OS did not require constant hazards or proportional hazard assumptions. This is particularly important since hazards of recurrence and death as well as the HRs between pCR and non-pCR groups typically change over time, especially in neoadjuvant studies with long-term follow-up. The models also incorporated random effects to account for and to quantify cross-study variability. Compared with simple pooling of data from multiple studies, which has been used in several oncology economic models (54, 55), this approach more accurately revealed the uncertainty around the survival estimates. Moreover, the models adopted a parametric form to provide flexibility to extrapolate the

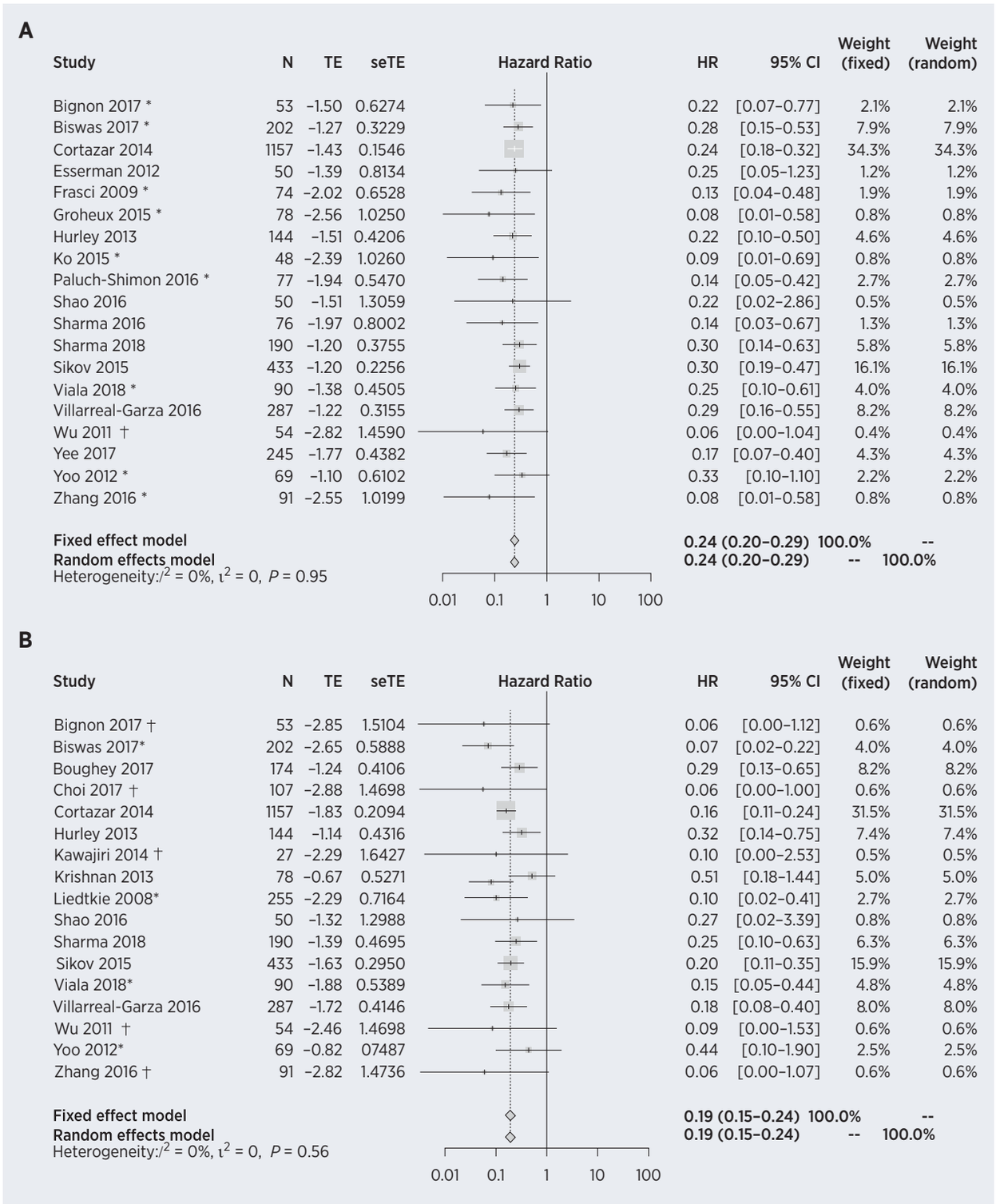

Figure 1.

Pooled HR of EFS (**A**) and OS (**B**) for pCR versus no pCR. *, HR was estimated using Cox proportional hazards model, based on pseudoindividual patient data derived from Kaplan–Meier curves. †, HR was estimated using Firth penalized maximum likelihood approach, based on pseudoindividual patient data derived from Kaplan–Meier curves, where there are 0 events for the pCR group. CI, confidence interval; EFS, event-free survival; HR, hazard ratio; OS, overall survival; pCR, pathologic complete response; seTE, standard error of treatment effect; TE, treatment effect; *N*, number of patients with early-stage TNBC; Weight, weight of individual studies.

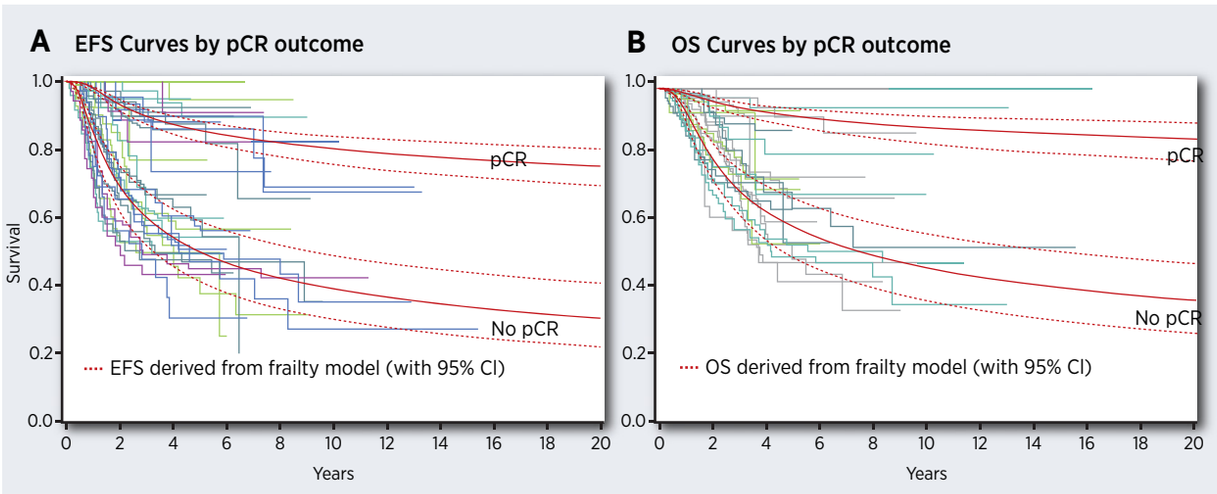

Figure 2.

Survival curves of EFS and OS derived from the meta-analysis. Note: the KM curves were extracted from the publications of each individual study; the red curves are the survival curves along with 95% confidence bands derived by synthesizing all the KM curves using random-effects frailty models. CI, confidence interval; EFS, event-free survival; KM, Kaplan–Meier; OS, overall survival; pCR, pathologic complete response.

survival outcomes to any time horizon that is optimal for a health economic evaluation.

This study also explored the potential benefit gained from receiving subsequent adjuvant therapy. While adjuvant therapy is commonly used in real-world practice in the absence of antecedent preoperative therapy (56), evidence supporting the benefit of adjuvant chemotherapy following neoadjuvant treatment in patients with early-stage TNBC is limited. In one RCT in patients with HER2-negative breast cancer who did not achieve a pCR after neoadjuvant chemotherapy, administration of adjuvant capecitabine resulted in significantly improved disease-free survival and OS (57). This improvement was particularly pronounced in the subset of patients with TNBC, with a 42% lower risk of recurrence, second cancer, or death, and a 48% lower risk of death in those treated with capecitabine. Adjuvant capecitabine is recommended by the National Comprehensive Cancer Network guidelines for the treatment of patients with TNBC and residual invasive cancer following standard neoadjuvant therapy (58). Our meta-analysis found numerically longer OS and EFS associated with adjuvant treatment in patients with early-stage TNBC following neoadjuvant treatment, regardless of pCR status. However, another meta-analysis of studies including patients with early breast cancer across several subtypes reported similar EFS results with or without adjuvant chemotherapy in patients who had pCR after neoadjuvant chemotherapy (7). As both meta-analyses included a limited number of studies with divergent adjuvant therapy usage, the findings should not be considered conclusive. Additional research is needed to further evaluate the clinical benefit of adjuvant therapy following neoadjuvant treatment in breast cancer and to identify the patient population for which it may benefit the most. It is also worth noting that current evaluations of adjuvant therapy in TNBC are based on clinical evidence limited to chemotherapy. The findings should be reevaluated as novel therapies emerge, which are associated with different benefit-risk profiles. Several ongoing clinical trials to investigate immunotherapy products as neoadjuvant and adjuvant therapy in patients with early stage TNBC will provide further insights into the benefit and risk of immunotherapy as adjuvant treatment following neoadjuvant therapy (59, 60).

The findings of this study should be interpreted in light of certain limitations. First, although the study included several subgroup analyses to assess the impact of cross-study heterogeneity, we were unable to conduct stratified analyses based on patient-level characteristics, such as age, diagnosis period, tumor size, tumor grade, or neoadjuvant therapy. Only a limited number of the included studies reported patient-level characteristics among patients with early-stage TNBC. Among these studies, there was substantial variation in the categorization and definition of these characteristics, which made it challenging to conduct subgroup analyses. Second, we were unable to account for heterogeneity in the definitions of EFS. However, despite this variability, each study's definition was consistently applied for both the pCR and non-pCR groups. Therefore, the association between pCR and survival outcomes should not have been affected. Third, the eligibility criteria for receiving adjuvant therapy and types of adjuvant therapy delivered to the patients were highly divergent across the studies that reported adjuvant therapy use, which can bias our analysis of the impact of adjuvant therapy on survival outcomes. Further research and more robust evidence, once available, are required to reevaluate the clinical benefit and risk of adjuvant therapy usage following neoadjuvant treatment. Fourth, in studies evaluating neoadjuvant therapies, immortal time bias (ITB) can occur when patients who die before planned surgery are classified into the non-pCR group. The ITB potentially biases the association between pCR and survival outcomes by overestimating the benefit of pCR. Despite this bias, the impact of ITB was not commonly adjusted for or discussed in previously published analyses. In this analysis, we were not able to correct for the bias without access to individual patient data from each study. However, the magnitude of the bias can be considered small, as mortality rate before surgery was low in these studies. Finally, although this analysis has demonstrated the significant prognostic value of pCR for individual patients in TNBC, or a strong "patient-level" association between pCR and survival outcomes, this finding alone does not imply that pCR is a valid surrogacy, or that a difference in pCR rates between treatment arms will predict long-term outcomes at the trial level. We investigated the trial-level association in a separate study (61, 62), which found a statistically significant association between treatment

effect on pCR and EFS, but the association between pCR and OS was less prominent. However, it is harder to establish an association at the trial level, as trial-level survival benefit is a complex function of many factors beyond the difference in pCR rate, including the baseline prognosis of the trial population and interactions between the baseline prognostic variables and pCR (63). The magnitude of trial-level association can also depend on the type of treatment administered in the clinical trials (64). Therefore, it is important to interpret the findings from this study together with those from the prior trial-level analysis, and to consider the consistency of various methods used to guide any medical decisions made based on pCR results. Finally, all TNBC neoadjuvant therapies identified in this study were chemotherapies. As surrogacy can vary by treatment class, the association between pCR and EFS/OS may need to be reevaluated when data from studies investigating new agents (such as immunotherapies) are available.

Conclusions

This meta-analysis synthesized the evidence from clinical trials and real-world cohort studies in the literature published through 2018 and confirmed the strong patient-level associations between pCR and long-term survival outcomes for patients with early-stage TNBC. In addition, findings suggest that adjuvant therapy may provide additional clinical benefit for patients with early-stage TNBC who received neoadjuvant therapy, regardless of pCR status. However, a definitive conclusion regarding the impact of adjuvant therapy usage will require additional studies with larger sample sizes, and the benefit-risk of adjuvant therapy should be carefully evaluated before medical decisions are made.

Disclosure of Potential Conflicts of Interest

M. Huang reports other compensation from Merck & Co., Inc. (full time employee) outside the submitted work. J. O'Shaughnessy reports personal fees from AbbVie, AstraZeneca, Celgene, Eisai, Genentech, Immunomedics, Lilly, Merck, Novartis, Pfizer, Puma, Prime Oncology, Roche, and Seattle Genetics outside the submitted work. J. Zhao reports employment at Merck. A. Haiderali reports other compensation from Merck (employee of Merck) during the conduct of the study and other compensation from Merck (employee of Merck) outside the submitted work. J. Cortés reports personal fees from Roche (consulting/honoraria) and Merck Sharp & Dhome (consulting/honoraria) during the conduct of the study; personal fees from Roche (advisor/honoraria), Celgene (advisor/honoraria), AstraZeneca (advisor), Cellestia (advisor), Biothera (advisor), Merus (advisor), Seattle Genetics (advisor), Daiichi Sankyo (advisor/honoraria), Erytech (advisor), Athenex (advisor), Polyphor (advisor), Lilly (advisor/honoraria), Servier (advisor), Merck Sharp & Dhome (advisor/honoraria), GSK (advisor), LEUKO (advisor), Bioasis (advisor), Clovis Oncology (advisor), Boehringer (advisor), Novartis (honoraria), EISAI (honoraria), Pfizer (honoraria), Samsung Bioepis (honoraria), and MedSIR (stock) outside the submitted work. S.D. Ramsey reports personal fees from Merck during the conduct of the study. A. Briggs reports personal fees from Merck during the conduct of the study. V. Karantza reports nonfinancial support and other compensation from Merck (employer) outside the submitted work. G. Aktan reports other compensation from Merck (employee; salary, bonus, stock options) during the conduct of the study and outside the submitted work. G. Aktan's son is an employee of Merck also (salary, bonus, stock options). C.Z. Qi reports other compensation from Merck (payment for contracted research) during the conduct of the study. C. Gu reports other compensation from Merck & Co. (payment for contracted research) during the conduct of the study and outside the submitted work. J. Xie reports other compensation from Analysis Group, Inc. (employee of Analysis Group, Inc., which receives research funding from Merck for this study) during the conduct of the study. M. Yuan reports other compensation from Merck & Co. (payment for contracted research) during the conduct of the study and outside the submitted work. J. Cook reports personal fees from Complete HEOR Solutions during the conduct of the study and outside the submitted work. M. Untch reports personal fees and nonfinancial support from Abbvie, Amgen, Celgene, Daichi Sankyo, Eisai, Lilly, MSD Merck, Mundipharma, Myriad Genetics, Novartis, Molecular Health, Pfizer, Roche Pharma, Sanofi Aventis, Agendia, Pierre Fabre, and Clovis outside the submitted work. P. Schmid reports personal fees from AstraZeneca (consultancy/honorarium), Bayer (consultancy/honorarium), Boehringer Ingelheim (consultancy/honorarium), Merck (consultancy/honorarium), Novartis (consultancy/honorarium), Pfizer (consultancy/honorarium), Puma (consultancy/honorarium), Roche (consultancy/honorarium); grants from Astellas (grant/funding to institution), AstraZeneca (grant/funding to institution), Genetech (grant/funding to institution), Novartis (grant/funding to institution), Oncogenex (grant/funding to institution), and Roche (grant/funding to institution) outside the submitted work; and spouse is an employee of Roche. P.A. Fasching reports personal fees from Merck Sharp & Dohme (advisory board), Roche (advisory board), and Celgene (advisory board) during the conduct of the study, grants from Biontech (grant) and Cepheid (grant), and personal fees from Novartis (advisory board, lectures), Pfizer (advisory board), Daiichi-Sankyo (advisory board, lectures), AstraZeneca (advisory board), Eisai (advisory board), Lilly (advisory board), Pierre Fabre (advisory board), and Seattle Genetics (advisory board) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

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