Original Investigation

Association of Pathologic Complete Response to Neoadjuvant Therapy in HER2-Positive Breast Cancer With Long-Term Outcomes
A Meta-Analysis

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IMPORTANCE The expense and lengthy follow-up periods for randomized clinical trials (RCTs) of adjuvant systemic therapy in breast cancer make them impractical and even impossible to conduct. Randomized clinical trials of neoadjuvant systemic therapy for breast cancer may help resolve this dilemma.

OBJECTIVE To assess the utility of pathologic complete response (pCR) for neoadjuvant drug development in human epidermal growth factor receptor 2 (HER2 [also referred to as ERBB2])-positive breast cancer.

DATA SOURCES We searched MEDLINE (Ovid), Embase (Ovid), CENTRAL (Wiley), and Northern Light Life Sciences Conference Abstracts (Ovid) in December 2014. Searches combined terms for "breast cancer" and "neoadjuvant therapy," with no limit on publication date.

STUDY SELECTION Cohort studies and RCTs were selected that met following criteria: stages I to III HER2-positive breast cancer, neoadjuvant therapy, and reports of both pCR and an event-free survival (EFS)-type outcome. The initial search identified 2614 publications, of which 38 studies met the selection criteria.

DATA EXTRACTION AND SYNTHESIS Two authors independently screened each study for inclusion and extracted the data. Data were analyzed using Bayesian hierarchical models.

MAIN OUTCOMES AND MEASURES Event-free survival and overall survival (OS) hazard ratios (HRs) for pCR vs non-pCR. For RCTs, main outcome measures were treatment benefits in pCR and the corresponding treatment HRs for EFS and OS.

RESULTS A total of 36 studies with EFS by pCR status representing 5768 patients with HER2-positive breast cancer were included in the patient-level analysis. Overall, the improvement in EFS for pCR vs non-pCR was substantial: HR, 0.37 (95% probability interval [PI], 0.32-0.43). This association was greater for patients with hormone receptor–negative disease (HR, 0.29 [95% PI, 0.24-0.36]) than hormone receptor–positive disease (HR, 0.52 [95% PI, 0.40-0.66]). In RCTs, the R^2 correlations between odds ratios for pCR and HRs were 0.63 for EFS and 0.29 for OS. Based on absolute treatment improvements in pCR rate, predicted HRs for EFS for RCTs were concordant with observed HRs.

CONCLUSIONS AND RELEVANCE Pathologic complete response in HER2-positive breast cancer is associated with substantially longer times to recurrence and death. This relationship is maintained in RCTs. For any particular new therapy the relationship between pCR and survival may differ. Quantifying the importance of pCR is necessary for designing efficient clinical trials, which should adapt to the relationship between pCR and survival for the therapy under investigation.

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Screening mammography and advances in adjuvant treatment have improved breast cancer outcomes.[1] Recurrence rates have decreased dramatically, and as a consequence population mortality decreased by 34% in the United States between 1990 and 2010.[2] Because statistical power for survival end points depends on the number of events, adjuvant trials addressing modest treatment advances have become much larger, with some recent trials accruing between 5000 and 10 000 patients. The great expense and lengthy follow-up periods required for such trials make them impractical and even impossible to conduct. In the present era of targeted therapies and rapid progress in cancer biology, what was once regarded to be a single disease is now many diseases, each requiring a potentially different therapeutic strategy. Many narrowly focused clinical trials are now required where 1 trial was once sufficient. Large adjuvant trials are no longer sustainable in breast cancer.[3,4] Neoadjuvant systemic therapy for breast cancer may help resolve this dilemma.[4]

Neoadjuvant systemic therapy holds promise for the early assessment of the effects of targeted systemic agents, as well as of standard therapy. The utility of pathologic complete response (pCR) at surgery in assessing treatment efficacy depends on its ability to predict longer-term outcomes of recurrence and death. Achieving a pCR in the neoadjuvant setting has been shown in "patient-level analyses" to be associated with improved event-free survival (EFS) and overall survival (OS).[5-7] Quantification of this association varies by molecular subtype and is most impressive in triple-negative and human epidermal growth factor receptor 2 (HER2 [also referred to as ERBB2])-positive diseases.[5-7] An alternative "trial-level" analysis is to compare treatment effects on pCR and EFS in randomized clinical trials (RCTs).[4,5] We explain why this analysis is inappropriately pessimistic.

We carried out a literature-based meta-analysis of neoadjuvant studies in HER2-positive breast cancer to update and extend the analyses in HER2-positive breast cancer presented in Cortazar et al.[5] This extension is in 2 directions: we included both cohort studies and recent clinical trials. Of special interest is the relationship of hormone receptor status and anti-HER2 therapy to the impact of pCR rates on EFS. We also address the relationship between incremental gains in pCR rates in RCTs and the associated improvement in survival end points.

Key Points

Question: How do gains in pathologic complete response (pCR) rates translate to improvements in long-term survival end points for patients with HER2-positive breast cancer?

Findings: This meta-analysis of 36 randomized clinical trials and cohort studies found that pCR in HER2-positive breast cancer was associated with longer times to recurrence and death. In randomized clinical trials, based on absolute improvements in pCR rates, the predicted hazard ratios for event-free survival were concordant with the observed hazard ratios.

Meaning: Pathologic complete response in HER2-positive breast cancer may be an earlier end point suitable to estimate longer-term therapeutic benefit.

Methods

Systematic Literature Review

We searched MEDLINE (Ovid), Embase (Ovid), CENTRAL (Wiley), and Northern Light Life Sciences Conference Abstracts (Ovid) in December 2014. The searches combined terms for "breast cancer" and "neoadjuvant therapy." Terms for HER2 were applied only to publications after 1998. Search results were limited to human studies. The Cochrane Collaboration search filter was used to limit results to RCTs and cohort studies.[8] Additional references were identified by searching for publications that cited the articles we included and related systematic literature reviews. Complete search terms for the systematic literature review are provided in eAppendix 1 in the Supplement.

Three authors (K.R.B., M.Q., M.O.) screened all publications such that each publication was screened independently by two authors first by title and abstract then by full text. To be eligible, publications had to meet the following criteria: stages I to III HER2-positive breast cancer, neoadjuvant systemic therapy, randomized or single arm, and reports of both pCR and EFS outcomes. We included cohorts whether prospectively or retrospectively defined and studies that pooled trial participants and cohorts. Randomized clinical trials that reported both pCR and EFS, regardless of whether EFS outcomes were additionally reported by pCR status, were also included. Publications were included regardless of neoadjuvant regimen, definition of pCR, and definition of EFS. Additionally, 2 independent reviewers (K.R.B., M.Q.) extracted all data into a database. Discrepancies in study selection or data extraction between reviewers were resolved by discussion between the 2 reviewers until a consensus was achieved. A list of extracted data items is provided in eAppendix 2 in the Supplement. If available, we used pCR, defined as no evidence of invasive disease in the breast or lymph nodes. Reported EFS end points varied and were described as event-free survival, recurrence-free survival, relapse-free survival, and disease-free survival. We use EFS throughout this article as an umbrella term for all of these longer-term outcomes.

We determined whether 2 or more publications reported on the same cohorts by considering the institution reporting the cohort, the authors, number of patients included, years of diagnosis or treatment, and the treatments received. When more than 1 publication reported on the same trial or on the same or overlapping patient cohorts, only outcomes from the largest and most recent publication were included.

Hazard Rates for EFS and OS

Studies reported EFS and OS results by pCR status in a variety of ways, including (1) Kaplan-Meier curves, (2) hazard ratios (HRs) and corresponding 95% confidence intervals, and (3) the total number of patients who experienced events in the follow-up period. As an example of the last of these: "Only two patients relapsed, both with pCR after treatment…No other relapses were observed after a median follow-up of 57.1

months."[9(p1105)] We translated all reports of survival outcomes to the number of events and total patient follow-up time (the ratio of which is the hazard rate per unit time) for pCR and non-pCR groups within each 3-month segment of follow-up. The number of events and follow-up time in each segment were calculated such that they would correspond to the reported survival results and the study's reported median and range of follow-up time. Additional description of this methodology is provided in eAppendix 3 in the Supplement.

Statistical Methods

Our analyses address 2 closely related questions. First, in a "patient-level" analysis we determine whether HER2-positive patients achieving a pCR with neoadjuvant therapy have longer EFS and OS than those who do not, and we quantify the benefit of experiencing a pCR. This patient-level analysis includes all studies that provided information about EFS by pCR status (yes/no) regardless of therapy. We also consider this question within subgroups defined by hormone receptor status (negative/positive) and whether patients received anti-HER2 therapy as part of their neoadjuvant regimen (yes/no). Results supplemental to the Cortazar et al[5] meta-analysis were included for our subgroup analysis by neoadjuvant anti-HER2 therapy.[10]

We used a Bayesian hierarchical model for EFS and OS that allows the hazard rate to vary over time. This is important because, for example, hormone receptor–negative vs hormone receptor–positive diseases have different hazards over time. Our model assumes a constant HR between the pCR and no-pCR groups. Our model allows for random effects by regarding included studies to be a sample from a larger population of studies, with potentially different HRs. It is not a simple pooling of results across studies but rather incorporates variability due to study differences. The model's conclusions therefore have wider confidence intervals (or in our Bayesian analysis, probability intervals [PIs]) than when study differences are ignored. Statistical details are provided in eAppendix 3 in the Supplement.

Cortazar et al[5] introduced a trial-level analysis to evaluate whether treatment effects on pCR in RCTs translate into EFS and OS benefits. Relative to their patient-level analysis this trial-level analysis has limited value in interpreting trial results and designing future trials. Nevertheless, to enable comparisons with the trial-level analysis presented by Cortazar et al,[5] we updated that analysis with the additional RCTs from our systematic literature review. Specifically, we plotted the association between the odds ratio (OR) for pCR and the HR for EFS and for OS between treatment arms. Following Cortazar et al,[5] we fitted a weighted linear regression model to the log-transform for these pairs with weights equal to the study's HER2-positive sample size.

We additionally addressed the relationship between incremental gains in pCR rates and the associated improvements in survival end points by assuming that a patient's achievement of a pCR moves the patient from the no-pCR survival curve to the pCR curve. For example, if a control arm has a 30% pCR rate then 30% of the patients would have ex-

Table 1. Summary of the Characteristics of the 36 Studies Included in the "Patient-Level" Analysis of Pathologic Complete Response [a]

Characteristic	Studies, No. (%) (N=36)	HER2-Positive Patients, No. (%) (N=5768)
Study type		
Randomized trial	1 (3)	411 (7)
Pooled (Cortazar et al[5])	1 (3)	1989 (34)
Cohort/single-arm trial	34 (94)	3368 (58)
Retrospective	26 (72)	3020 (52)
Prospective	8 (22)	348 (6)
Publication date, median (range), y	2012 (2002-2015)	...
Follow-up, median (range), mo	41 (21-121)	...
Mean age, median (range), y	50 (39-56)	...
Percent hormone receptor positive, median (range)	56 (20-70)	...
Percent HER2-positive, median (range)	41 (15-100)	...
Neoadjuvant Anti-HER2, No. (%)		
None	6 (17)	337 (6)
All patients	13 (36)	2411 (42)
Some patients	14 (39)	2938 (51)
Unknown	3 (8)	82 (1)
Other neoadjuvant therapy, No.(%)		
Anthracycline	3 (8)	129 (2)
Taxane	7 (19)	706 (12)
Anthracycline + taxane	8 (22)	1050 (18)
Other/various	17 (47)	3883 (67)
Pathologic complete response definition, No. (%)		
No invasive disease in breast or nodes	30 (83)	5288 (92)
No invasive or in situ disease in breast or nodes	1 (3)	102 (2)
No invasive disease in the breast	4 (11)	368 (6)
Not described	1 (3)	10 (<1)
Event-free survival		
Start date, No. (%)		
Date of diagnosis or histology	9 (25)	1200 (21)
Start of neoadjuvant therapy or study entry	7 (19)	3386 (59)
Date of surgery	10 (28)	709 (12)
Not described	10 (28)	476 (8)
Defined events, No. (%)		
Local or distant relapse, death from any cause	9 (25)	2686 (47)
First local or distant metastasis	4 (11)	413 (7)
Recurrence (death prior to recurrence censored)	3 (8)	604 (10)
Locoregional recurrence, distant recurrence, contralateral breast cancer, secondary malignant neoplasm, or death	2 (6)	71 (1)
Recurrence, secondary malignant neoplasm, or death from any cause	2 (6)	1187 (21)
Other	7 (19)	384 (7)
Not described	9 (25)	423 (7)

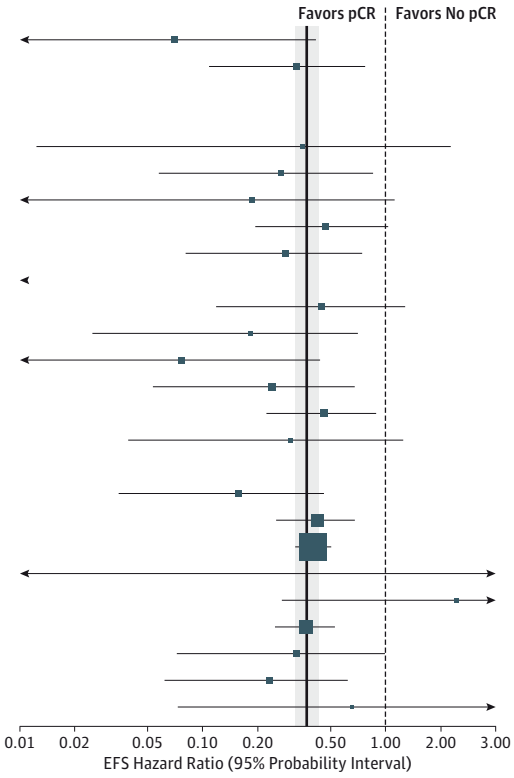
Abbreviation: HER2, human epidermal growth factor receptor 2.

[a] Data are number (percent) unless otherwise indicated.

Figure 1. Hazard Ratios (HRs) for Event-Free Survival (EFS) and Overall Survival (OS) for Pathologic Complete Response (pCR) vs No pCR by Study and Overall

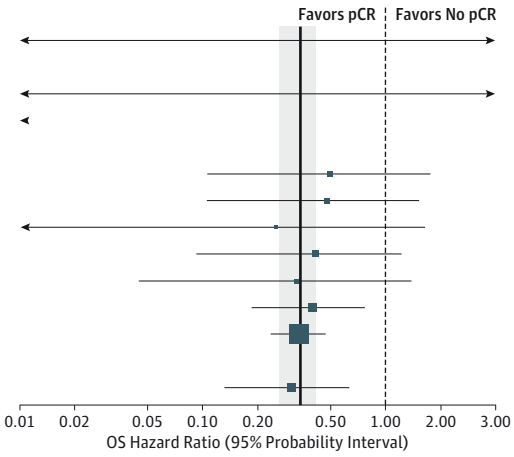
A EFS

Source	pCR Events/N	No pCR Events/N
Andre et al,[21] 2008	1/35	20/70
Shimizu et al,[28] 2009	5/43	28/80
Sikov et al,[52] 2009	2/13	0/4
Chen et al,[35] 2010	0/12	30/53
Arsenault et al,[39] 2011	1/31	8/119
Fasching et al,[31] 2011	3/37	15/55
Gropper et al,[40] 2011	1/15	15/63
Guiu et al,[27] 2011	8/52	21/83
Ladoire et al,[25] 2011	4/27	30/76
Yao et al,[34] 2011	0/17	20/99
Melichar et al,[44] 2012	4/25	20/64
Zhang et al,[36] 2012	2/45	12/57
Guarneri et al,[32] 2013	1/32	22/75
Krishnan et al,[51] 2013	3/22	39/81
Natoli et al,[33] 2013	12/96	29/109
Sánchez-Muñoz et al,[46] 2013	2/13	11/25
Saracchini et al,[9] 2013	2/19	0/20
Yi et al,[48] 2013	3/18	31/58
de Azambuja et al,[53] 2014	20/137	83/274
Cortazar et al,[5] 2014	94/586	495/1403
Esfahani et al,[50] 2014	0/2	0/8
Kawajiri et al,[29] 2014	3/10	1/5
Takada et al,[30] 2014	39/399	99/377
Wang et al,[37] 2014	3/22	23/58
Gonzalez-Angulo et al,[23] 2015	4/203	26/386
Zelnak et al,[43] 2015	2/13	3/14



B OS

Source	pCR Events/N	No pCR Events/N
Köstler et al,[49] 2004	0/2	0/14
Andre et al,[21] 2008	0/35	13/70
Sikov et al,[52] 2009	0/13	0/4
Chen et al,[35] 2010	0/12	18/53
Fasching et al,[31] 2011	0/37	11/55
Guiu et al,[27] 2011	3/52	9/83
Ladoire et al,[25] 2011	3/27	16/76
Melichar et al,[44] 2012	1/25	7/64
Krishnan et al,[51] 2013	3/22	24/81
Sánchez-Muñoz et al,[46] 2013	2/13	10/25
de Azambuja et al,[53] 2014	10/137	47/282
Cortazar et al,[5] 2014	40/586	260/1403
Kawajiri et al,[29] 2014	1/10	0/5
Gonzalez-Angulo et al,[23] 2015	8/203	45/386



Boxes show the estimated HR for pCR by study, and horizontal lines show the estimated 95% probability interval around the HR. The size of the box is proportional to the number of events. Arrows indicate that the 95% probability interval extends beyond the limits of the plot. Studies with 0 events in 1 group may not appear within the limits of the plot. Dashed line is at an HR of 1 for reference, the point at which survival estimates between pCR and no pCR groups are equivalent. The solid vertical line and shaded region indicate the overall model-estimated median HR and 95% probability interval, respectively.

pected survival according to the pCR curve and 70% would have expected survival according to the no-pCR curve, giving rise to an expected survival that is approximately 30% of the way from the no-pCR curve to the pCR curve. And if an experimental arm has a pCR rate of 50% then, under this hypothesis, the expected survival curve is halfway between the no-pCR and pCR curves. The net effect is that with the experimental therapy, an extra 20% of the patients are moved to the pCR curve. The estimated HR between treatment and control is found from these 2 curves, assuming exponential survival. This approach follows Berry and Hudis,[4] whose estimated pCR/EFS relationship in their figure used the Cortazar et al[5] meta-analysis. For our analyses, the observed absolute difference in pCR rates for the trials presented in Cortazar et al[5] was estimated on the basis of additional results provided in the individual trial publications.[11-17] We determined the expected HR for all improvements in pCR from 0 to 100%. The implicit HR for no pCR improvement is 1.00. For a 100% difference in pCR, the HR is the same as comparing the pCR and no-pCR curves.

Results

Systematic Literature Review

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses[18,19] flow diagram detailing the inclusion and exclusion of publications is shown in eAppendix 4 (eFigure 1 in the Supplement). The systematic review process yielded 67 publications, among which we identified 38 unique studies for analysis.[5,6,9,20-54] Thirty-six studies provided EFS by pCR status and are included in the patient-level analysis. This systematic literature review adds 3 RCTs to those included in Cortazar et al.[5,22,53,54] Details for each of the included studies are provided in eAppendices 5 and 6 (eTables 1-4 in the Supplement). The Cortazar et al[5] study is a pooled analysis of 12 RCTs and includes patients with breast cancer across several different molecular subtypes. We use only the results specific to the HER2-positive patients. We included Cortazar et al[5] as a single study in the patient-level analysis because the data necessary for our meta-analysis were not available in all publications of the individual trials.

Patient-Level Analysis of pCR

The characteristics of the included studies are provided in **Table 1**. The 36 studies included for this analysis represent 5768 patients with HER2-positive breast cancer of whom 1989 (34%) are from Cortazar et al.[5] Twenty-six (72%) of the included studies are retrospective cohorts in which patients received a variety of neoadjuvant regimens. There was consistency across studies in the definition of pCR, with most studies defining pCR as no invasive disease in either the breast or lymph nodes. The most common definition for EFS was time to locoregional or distant relapse or death from any cause.

Figure 1A shows each study's estimated EFS HR and 95% PI for pCR and the overall model-estimated HR.The overall model estimated HRs are also shown in **Table 2**. Figure 1B shows OS results based on the 15 studies reporting the relationship between pCR and OS. These results show that pCR is associated with improved EFS (median HR, 0.37 [95% PI, 0.32-0.43]) and OS (median HR, 0.34 [95% PI, 0.26-0.42]).

Figure 2A and B shows EFS HRs within subgroups defined by hormone receptor status and neoadjuvant anti-HER2 therapy. The advantage of experiencing a pCR was greater in the hormone receptor–negative subgroup (median HR, 0.29 [95% PI, 0.24-0.36]) compared with the hormone receptor–positive subgroup (median HR, 0.52 [95% PI, 0.40-0.66]). Corresponding model-estimated EFS Kaplan-Meier curves by pCR both overall and within the 2 hormone receptor subgroups are shown in eAppendix 7 (eFigures 2-4 in the Supplement). Figure 2B shows that the effect of pCR was greater for neoadjuvant anti-HER2 therapy (median HR, 0.35 [95% PI, 0.30-0.40]) compared with no neoadjuvant anti-HER2 therapy (median HR, 0.45 [95% PI, 0.35-0.57]).

Table 2 also reports results by study type. Although the mix of therapies is different in cohort studies and RCTs, the advantage of experiencing a pCR was similar. Additional results are provided in eAppendix 7 (eFigures 2-9 in the Supplement).

Table 2. Meta-Analysis Model-Estimated Hazard Ratios (HRs) for Pathologic Complete Response vs No Pathologic Complete Response

Analysis	HR, Median (95% Probability Interval)
Overall survival, all HER2 positive	0.34 (0.26-0.42)
Event-free survival, all HER2 positive	0.37 (0.32-0.43)
Hormone receptor status	
Negative	0.29 (0.24-0.36)
Positive	0.52 (0.40-0.66)
Neoadjuvant anti-HER2 therapy	
No	0.45 (0.35-0.57)
Yes	0.35 (0.30-0.40)
Study type	
Randomized clinical trials	0.40 (0.33-0.49)
Cohort studies	0.33 (0.27-0.41)

Abbreviation: HER2, human epidermal growth factor receptor 2.

Trial-Level Analysis of pCR

Figure 3 shows the relationship between treatment effects in terms of the OR for pCR vs no pCR and HR for EFS and OS. One study, Buzdar et al,[22] reported 0 events for 1 arm and so is not shown in this figure. The negative slope of the regression lines indicates that an increase in the odds of pCR is associated with a decrease in the HR for EFS and OS. Based on the weighted linear regression model, the R^2 was 0.23 for EFS but was 0 for OS. The association is stronger when the intercept of the weighted linear regression model is fixed such that a pCR OR of 1.00 corresponds to a survival HR of 1.00. In this case, the R^2 is 0.63 for EFS and 0.29 for OS.

Figure 3B and D are more relevant for designing clinical trials.[4] The curves in these panels show the expected relationship between the absolute improvement in pCR rate and the HR for EFS and OS assuming that the treatment effect is derived from converting a non-pCR into a pCR as in our patient-level analysis (eAppendix 7 [eTable 5 in the Supplement]). We have added to these panels the same trials as in Figure 3A and C. Many of the trials had small differences in pCR rates (<10%) and observed HRs close to 1, with confidence intervals overlapping 1 (data not shown). Among the trials that observed an improvement in pCR, the NOAH and NeoALTTO trials, in particular, are in line with the expected EFS HR. The greater spread in the trial outcomes in Figure 3C and D reflects the greater variability in OS than in EFS because of the smaller numbers of events.

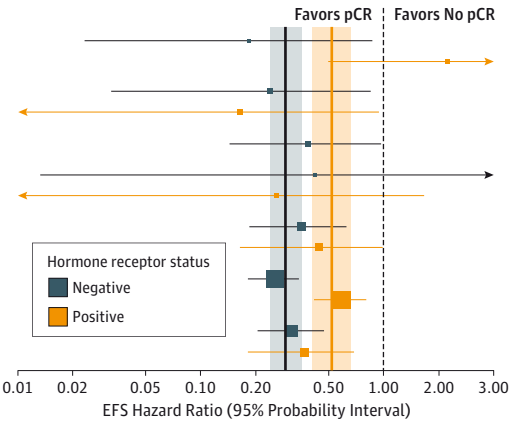
Discussion

Our analyses include a total of 38 studies, 3 RCTs in addition to those in Cortazar et al,[5] and 34 patient cohorts, representing more than 5500 patients with HER2-positive breast cancer. To our knowledge, this is the largest meta-analysis of neoadjuvant studies in HER2-positive breast cancer. Our findings are qualitatively consistent with earlier analyses showing that HER2-positive patients who achieve a pCR have substantially better long-term outcomes than those

Figure 2. Hazard Ratios (HRs) for Event-Free Survival (EFS) for Pathologic Complete Response (pCR) vs No pCR by Hormone Receptor Status and Receipt of Neoadjuvant Anti–Human Epidermal Growth Factor Receptor 2 (HER2) Therapy

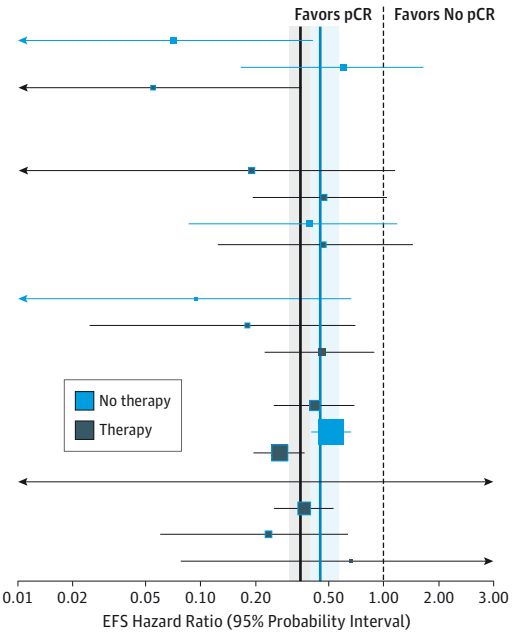
A EFS by hormone receptor status groups

Source	pCR Events/N	No pCR Events/N
Esserman et al,[6] 2012	2/19	6/14
	4/11	4/22
Krishnan et al,[51] 2013	2/13	22/42
	1/9	17/38
Natoli et al,[33] 2013	7/44	13/36
Sánchez-Muñoz et al,[46] 2013	1/8	2/8
	1/5	9/17
de Azambuja et al,[53] 2014	14/87	47/124
	6/50	36/150
Cortazar et al,[5] 2014	48/325	223/510
	43/247	243/839
Takada et al,[30] 2014	35/281	62/158
	11/120	54/214



B EFS by receipt of neoadjuvant anti–human epidermal growth factor receptor 2 therapy

Source	pCR Events/N	No pCR Events/N
Andre et al,[21] 2008	1/35	20/70
Shimizu et al,[28] 2009	4/17	18/54
	1/26	9/26
Sikov et al,[52] 2009	2/13	0/4
Chen et al,[35] 2010	0/12	30/53
Gropper et al,[40] 2011	1/15	15/63
Guiu et al,[27] 2011	8/52	21/83
Ladoire et al,[24] 2011	3/8	23/36
	4/24	10/34
Yao et al,[34] 2011	0/17	20/99
Esserman et al,[6] 2012	1/12	6/17
Zhang et al,[36] 2012	2/45	12/57
Natoli et al,[33] 2013	12/96	29/109
Saracchini et al,[9] 2013	2/19	0/20
de Azambuja et al,[53] 2014	20/137	83/274
Cortazar et al,[5] 2014	73/270	429/902
	49/302	173/447
Esfahani et al,[50] 2014	0/2	0/8
Takada et al,[30] 2014	39/399	99/377
Gonzalez-Angulo et al,[23] 2015	4/203	26/386
Zelnak et al,[43] 2015	2/13	3/14



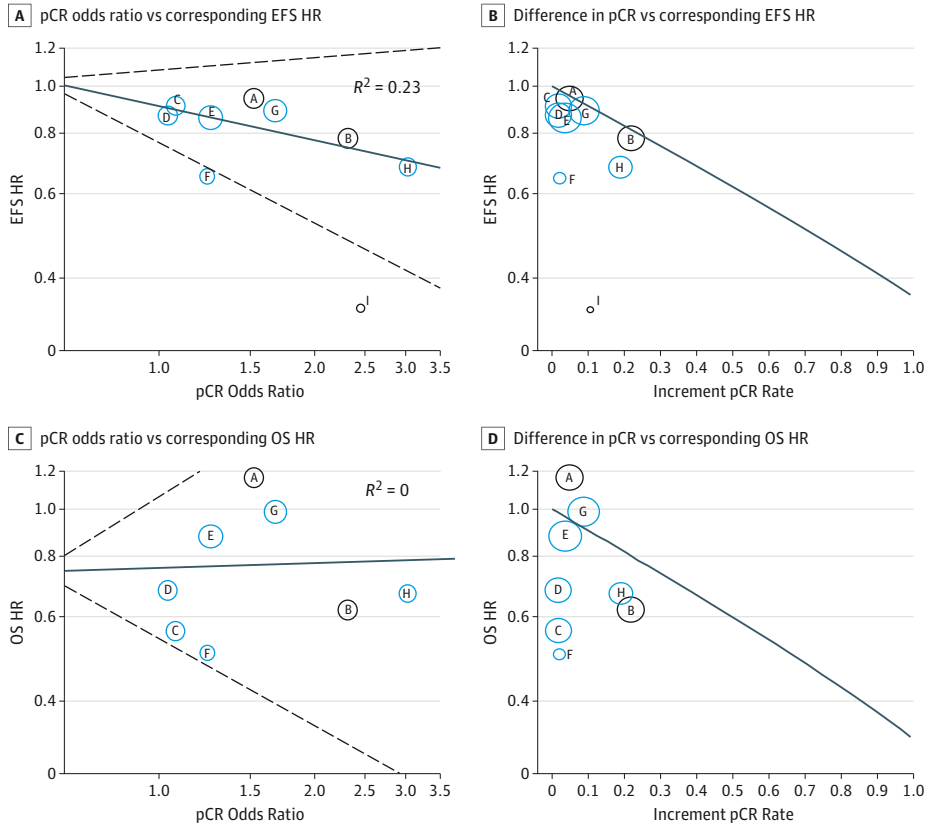
Boxes show the estimated HR for pCR by study, and horizontal lines show the estimated 95% probability interval around the HR. The size of the box is proportional to the number of events. Arrows indicate that the 95% probability interval extends beyond the limits of the plot. Studies with 0 events in 1 group may not appear within the limits of the plot. Dashed line is at an HR of 1 for reference, the point at which survival estimates between pCR and no pCR groups are equivalent. The solid vertical line and shaded region indicate the overall model-estimated median HR and 95% probability interval, respectively.

who do not. The relationship between pCR and survival end points in HER2-positive breast cancer varies by hormone receptor status and by the inclusion of an anti-HER2 therapy in the treatment regimen, but apparently not between cohort studies and RCTs.

A limitation of our literature-based study is that it is subject to variable reporting and definitions across studies. An example is the different definitions of EFS. The 2 most common definitions of EFS differed only in their handling of secondary malignant neoplasms. Despite the variability, each study's definition was consistently used for both pCR and non-pCR and so there was no bias. Also, our Bayesian hierarchical modeling approach explicitly accounts for and quantifies study-to-study variability, which is reflected in wider PIs.

Cortazar et al[5] provided a particular trial-level analysis using the same RCTs from which they derived their patient-level analysis. Their patient-level analysis showed that experiencing a pCR had a dramatic effect on EFS in their population. Their trial-level analysis was an elegant empirical demonstration that reassembling such a population of patients into their respective trials will show little or no treatment benefit on EFS in trials for which there is little or no treatment benefit on pCR. This has obvious implications

Figure 3. Treatment Benefit for Pathologic Complete Response (pCR) vs Corresponding Event-Free Survival (EFS) and Overall Survival (OS) Hazard Ratio (HR) Between Treatment Arms for Randomized Trials



Blue circles indicate those points reported in Cortazar et al[5] and black circles indicate additional studies from our systematic literature review. The areas of the circles are proportional to the trial's human epidermal growth factor receptor 2 (HER2)-positive sample size. A and C, The black line shows the fitted weighted linear regression; the dashed line, the 95% CI of the regression fit. B and D, The black line shows the expected EFS HR (B) and OS HR (D) across the range of possible improvements in pCR based on the results of the "patient-level" analysis. Plotted trials are A, NeoALTTO, lapatinib vs trastuzumab; B, NeoALTTO,[53] lapatinib + trastuzumab vs trastuzumab; C, GEPARQUATTRO, EC →T-X vs EC →T; D, GEPARQUATTRO,[5,17] EC →TX vs EC →T, E, EORTC[5,15,16]; F, GEPARTRIO,[5,13,14] nonresponders; G, GEPARTRIO,[5,12,14] responders; H, NOAH[5,11]; I, Chen et al.[54] The HRs indicated in panels B and D for increment in pCR rate equal to 1.0 are the medians shown in Table 2.

for the design of clinical trials with EFS as an end point for both adjuvant and neoadjuvant settings.

We updated the Cortazar et al[5] trial-level analysis with 3 additional RCTs. These observations fall within expected intervals whether using our patient-level analysis or that of Cortazar et al.[4,5]

We also applied our analyses to 2 trials not included in our literature search. One was an adjuvant trial, ALTTO.[55] There have been 5 neoadjuvant trials (1025 patients) comparing trastuzumab plus lapatinib vs trastuzumab alone.[56-60] The overall improvement in pCR rate for the combination arm in the 5 trials was 13.7%. There is uncertainty in this estimate, but taking it at face value implies an EFS HR of 0.88 (from Figure 3B) with 95% prediction interval from 0.75 to 1.04. The ALTTO trial addressed this same question in the adjuvant setting and yielded an EFS HR of 0.84,[55] which is well within this predictive interval. In retrospect, ALTTO was underpowered. Had these neoadjuvant trials and also our present meta-analysis been available at the time of developing ALTTO, the designers would have built a larger trial, or no trial at all.

A second trial, available only after our literature search, was NeoSPHERE, which on the basis of 107 patients assigned to each of 2 arms demonstrated a 17.8% improvement in the rate of pCR with the addition of pertuzumab to trastuzumab and docetaxel therapy.[61] Assuming this to be the true improvement in pCR rate for adding pertuzumab to these 2 agents, our analysis estimates an EFS HR of 0.86 (Figure 3B) with 95% prediction interval from 0.47 to 1.57. The width of this interval reflects the uncertainty in estimating EFS from pCR based on our patient-level analysis and it also represents the small sample size of NeoSPHERE. NeoSPHERE recently reported an HR for progression-free survival of 0.69 (95% CI, 0.34-1.4): again, well within the prediction interval.[61]

Both in our meta-analysis and in these 2 examples outside our meta-analysis, there is a suggestion that extrapolating from the pCR improvement underestimates an experimental therapy's improvement in EFS, perhaps especially if it is based on anti-HER2 therapy. There is no statistical justification for drawing such a conclusion, but it may be real. Pathologic complete response is a dichotomous partitioning of tumor burden at surgery. A therapy might well improve the rate of partial response, for example, which might be assessed using residual cancer burden class 1.[62] And converting a patient to residual cancer burden class 1 may be indicative of prolonging EFS, quite apart from pCR.[63]

We stress that the assumption regarding the curves in Figures 3B and D is that experiencing a pCR means the same thing independent of the therapy that gave rise to the pCR. That assumption may not be true for all therapies. Some

therapies may imply a different pCR/EFS relationship, with either more efficacy or less efficacy associated with a pCR than that in our analysis. But in any case these curves serve as references, as null hypotheses to consider when interpreting or designing a trial.

Large adjuvant clinical trials of novel cancer therapeutics are becoming increasingly difficult to conduct given the ever-greater segmentation of disease subtypes. The very large clinical trials of the recent past are not sustainable, and identifying earlier end points to estimate longer-term therapeutic benefit will be part of the resolution to this dilemma.

Conclusions

The importance of improving pCR rates in the neoadjuvant therapy of breast cancer may allow for more efficient and rational designs for adjuvant and neoadjuvant clinical trials with EFS as a primary end point. Also, reference curves such as those in Figures 3B and D will help interpret results of clinical trials. Plotting results against these curves may also aid in elucidating how and whether a new therapy's efficacy in the long term is modulated through its effect on the tumor more than or less than historical therapies.

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Invited Commentary

The Neoadjuvant Model and Complete Pathologic Response in Breast Cancer
All or Nothing?

Veerle Bossuyt, MD; Christos Hatzis, PhD

With neoadjuvant therapy, response to treatment can potentially be assessed after months rather than years of follow-up. Pathologic complete response (pCR) to neoadjuvant therapy, defined as complete eradication of invasive cancer from the breast and lymph nodes, directly reflects a drug's cytotoxic activity against the tumor and is typically associated with excellent patient survival. An important question is whether pCR is a good surrogate end point for long-term survival. Evidence from recent large meta-analysis studies has unequivocally answered yes, at the individual patient level. If a patient achieves pCR, the risk of relapse is low and her long-term survival is excellent, irrespective of disease subtype or the type of neoadjuvant chemotherapy that she received.[1,2] However, the answer to the subtly different question as to whether increases in pCR rate resulting from an effective treatment translate to improved survival benefit for the patients who received that treatment has been more contradictory.[3-5] Although pCR is established as an individual-level surrogate end point, it has not yet been universally accepted as a general trial-level surrogate end point for selecting effective therapies from randomized clinical trials or as a screening end point to eliminate ineffective treatments in the neoadjuvant setting.[5] Yet, because pCR correlates most strongly with survival outcomes in the more aggressive subtypes[1]—triple negative and ERBB2 positive—it is possible that pCR could be an acceptable trial-level surrogate end point for these specific subtypes.

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In this issue of *JAMA Oncology*, Broglio and colleagues[6] report the results of an ERBB2-specific meta-analysis that included 38 studies (including 36 studies in a "patient-level" analysis representing 5768 ERBB2-positive patients), mostly from retrospective cohorts involving a variety of neoadjuvant regimens. The majority of the patients had received neoadjuvant anti-ERBB2 therapy. This analysis used a hierarchical model assuming a piecewise constant hazard ratio (HR) between pCR and non-pCR groups within each of 11 segments to model the relationship between survival HR and pCR status, while accounting for random study-to-study variation. As expected, the patient-level analysis confirmed previous results that pCR in ERBB2-positive patients is associated with substantially improved long-term outcomes (HR, 0.37 for event-free survival (EFS) and 0.34 for overall survival), irrespective of tumor hormone receptor status or whether the patient received neoadjuvant anti-ERBB2 therapy.

To assess the related question of whether incremental gains in pCR rates in a randomized clinical trial setting would result in improvements in survival outcomes, Broglio et al[6] used a trial-level weighted linear regression analysis and confirmed a negative association for the EFS HR but not for overall survival. This is not too surprising given the large study-to-study variation, the small spread in pCR effect across the studies (<10% gain), and a small EFS effect (HR, >0.8). Another recent meta-analysis of the study cohorts of both Cortazar et al[1] and Berruti et al[2] reached a similar conclusion of a weak trial-level association between pCR gains and survival benefit, and,