Pathologic Complete Response (pCR) Rate and Predictors of Response to Taxane, Trastuzumab, and Pertuzumab in HER2-Positive Breast Cancer: Secondary Analyses of EA1181/CompassHER2 pCR

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ABSTRACT

PURPOSE EA1181 (ClinicalTrials.gov identifier: NCT04266249) is a single-arm trial evaluating neoadjuvant taxane, trastuzumab, and pertuzumab (THP) in patients with clinical stage II/IIIa human epidermal growth factor receptor 2 (HER2)–positive breast cancer. This report focuses on the secondary end points of pathologic complete response (pCR) rates and associated factors. The primary end point—3-year recurrence-free survival among patients achieving a pCR (ypT0/Tis, ypN0)—will be reported when data mature.

METHODS Patients received four cycles of trastuzumab and pertuzumab (HP) with either once per week paclitaxel (12 weeks) or docetaxel (every 3 weeks for four cycles), followed by surgery. Clinicopathologic characteristics were assessed in all patients. The HER2DX pCR score was determined using diagnostic biopsy samples in a representative subset. Logistic regression models identified factors associated with pCR.

RESULTS A total of 2,175 patients were enrolled (781 HER2+/estrogen receptor-negative [ER−]; 1,394 HER2+/ER+). Of 2,141 patients who initiated THP, the overall pCR rate was 43.8%: 63.7% in HER2+/ER− and 32.4% in HER2+/ER+ tumors. Higher pCR rates were observed in tumors that were ER-negative or low ER expressing, progesterone receptor-negative or low expressing, HER2 immunohistochemistry (IHC) 3+, and in patients treated with once per week paclitaxel. T3 disease was associated with a lower pCR rate in HER2+/ER− tumors; otherwise, tumor (T) and nodal (N) stage did not significantly affect pCR. Among 569 patients assessed for HER2DX pCR scores, a high score was independently associated with higher pCR rates, after adjustment for clinicopathologic variables.

CONCLUSION Neoadjuvant THP achieved pCR in nearly two-thirds of patients with HER2+/ER− and one third with HER2+/ER+ breast cancer. Low hormone receptor expression, HER2 IHC 3+ status, once per week paclitaxel use, and a high HER2DX pCR score were independent predictors of pCR. These findings should help optimize risk stratification and treatment personalization for patients with HER2-positive breast cancer.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

The standard of care for stage II to III human epidermal growth factor receptor 2 (HER2)-positive breast cancer is neoadjuvant multiagent chemotherapy combined with trastuzumab and pertuzumab (HP), yielding pathologic complete response (pCR) rates of 50%-60% and 3-year disease-free survival of approximately 92%.[1-5] However, multiagent chemotherapy is associated with substantial toxicity.

CONTEXT

Key Objective

What is the pathologic complete response (pCR) with taxane, trastuzumab, and pertuzumab (THP) × four cycles in patients with stage II and IIIa human epidermal growth factor receptor 2-positive (HER2+) breast cancer? In addition, are clinicopathologic factors or the molecular tool HER2DX pCR likelihood score associated with pCR?

Knowledge Generated

THP × four results in pCR in 64% of patients with HER2+/estrogen receptor-negative (ER−) breast cancer and in 32% of patients with HER2+/ER+ disease. Lower ER expression, lower progesterone receptor expression, HER2 immunohistochemistry 3+, and use of once per week paclitaxel were all significantly associated with pCR, as was T3 tumor size among HER2+/ER− tumors. A high or medium HER2DX pCR score was associated with approximately a 40% higher chance of pCR than with a low HER2DX pCR score and was significantly associated with pCR independent of clinicopathologic factors.

Relevance *(G.F. Fleming)*

These results provide optimism on the ability de-escalate treatment for a subset of patients with HER2+ breast cancer, but survival data are still pending.*

*Relevance section written by *JCO* Associate Editor Gini F. Fleming, MD.

EA1181 (CompassHER2 pCR; ClinicalTrials.gov identifier: NCT04266249) is the first preoperative trial, to our knowledge, in HER2-positive breast cancer powered to evaluate survival outcomes after a de-escalated regimen. The trial tests whether patients with stage II to III HER2-positive disease who achieve pCR with single-agent taxane plus HP (THP), followed by completion of 1 year of HP without additional chemotherapy, will demonstrate a 3-year recurrence-free survival (RFS) exceeding 92%. The trial is powered to independently evaluate this aim in patients with HER2-positive/estrogen receptor (ER)-positive and HER2-positive/ER-negative disease. Enrollment is complete, and survival data are maturing. Even before reporting the primary end point, clinicians are increasingly considering chemotherapy de-escalation in practice. Identifying patients most likely to achieve pCR with THP is therefore of high clinical relevance.

In this article, we report key secondary objectives of EA1181, including overall pCR rates with THP and factors associated with pCR, encompassing clinicopathologic features and the HER2DX pCR likelihood score (Reveal Genomics, Barcelona, Spain). HER2DX is a 27-gene expression assay integrating immune, proliferation, luminal, and HER2 signatures with tumor size and nodal status (Data Supplement, Table S1, online only).[6-9] The resulting HER2DX pCR score (0-100) stratifies patients into low (0-32), medium (33-67), and high (68-99) groups. Retrospective studies demonstrate strong predictive validity, with reported pCR rates of 74%, 55%, and 20% in high, medium, and low groups, respectively (high *v* low odds ratio [OR], 11.25; $P < .001$).[7] Score distributions differ by ER status, with low scores more common in ER-positive tumors and high scores enriched in ER-negative disease.

METHODS

EA1181 is a prospective National Cancer Institute (NCI)-sponsored trial (ClinicalTrials.gov identifier: NCT04266249) coordinated by Eastern Cooperative Oncology Group-American College of Radiology Imaging Network (ECOG-ACRIN) with participation from Alliance, SWOG, and NRG. Institutional review board approval was obtained, and all patients provided informed consent.

Patient Selection

Eligible patients had HER2-positive operable breast cancer, determined locally according to ASCO-CAP guidelines.[10] Patients had clinical anatomic stage II or IIIa disease per the American Joint Committee on Cancer 8th Edition (ie, tumor size >2 cm, involved axillary nodes, or both). T4 and N3 diseases were excluded. Patients with T2 tumors (2-3 cm) without nodal involvement were capped at 20% of accrual. Bilateral or multiple ipsilateral HER2-positive tumors were permitted if eligibility criteria were met.

Study Design

Pretreatment Evaluation

All patients underwent bilateral mammography, breast ultrasound, and axillary ultrasound on the side of the cancer(s). Breast magnetic resonance imaging (MRI) was recommended. Suspicious axillary nodes required biopsy of at least 1 suspicious node, with clip placement. Staging computed tomography (CT) scans plus either a bone scan or an fluorodeoxyglucose-positron emission tomography (FDG-PET) scan were required for stage III disease or concerning clinical findings.

Treatment

Patients received 12 weeks of HP, with one of the following taxanes: once per week paclitaxel × 12 weeks (80 mg/m² weekly), docetaxel once every 3 weeks × 4 (75 mg/m²), or once per week nab-paclitaxel × 12 weeks (125 mg/m²). Up to two additional HP doses were allowed before surgery to accommodate scheduling.

Tumor Assessment Before Surgery

Preoperative imaging was mandatory. Patients receiving additional chemotherapy before surgery or who did not have surgery were considered non-pCR.

Surgery

Surgery occurred within 18 weeks of taxane initiation. For patients undergoing sentinel lymph node biopsy, axillary lymph node dissection (ALND) was required if sentinel node mapping failed, a clipped node with biopsy-proven tumor at baseline was not removed, fewer than two sentinel lymph nodes were identified, or if the sentinel node was involved with cancer. Patients with cN2 disease were also required to undergo ALND. The decision to perform ALND in patients without a pCR because of isolated tumor cells (ITCs; ypN0i+) was left to the treating physician.

pCR was defined as no invasive disease in the breast or axilla (ypT0 ypN0 or ypT0/is ypN0).

Postsurgery Treatment

Patients achieving pCR completed 1 year of HP without any further adjuvant chemotherapy, and received endocrine and radiation therapy if indicated. Postoperative therapy for patients without pCR was at physician discretion.

HER2DX pCR Score Analysis

HER2DX pCR score analysis was conducted centrally by Reveal Genomics on diagnostic core biopsies from 569 participants using a validated assay blinded to outcomes.[11] No research biopsies were obtained.

Statistical Considerations

pCR rates with 95% CIs were calculated for all patients who received at least 1 dose of taxane plus HP. Tumors were considered ER-positive if immunohistochemistry (IHC) expression was at least 1%.[12] Sample size calculations were based on expected pCR rates of 60% (ER negative) and 30% (ER positive), with independent powering of cohorts for survival endpoints.[13] Accounting for an approximate 10% dropout rate after registration, the required sample size for the primary objective (3-year RFS) was 718 HER2-positive/ER-negative patients and 1,438 HER2-positive/ER-positive patients.

Previous reports have shown that breast cancer exhibits a bimodal distribution of ER expression, with most tumors classified as either ER 0% or ER >70%.[14] Additionally, several studies have found that many tumors with ER expression between 1% and 10% are molecularly similar to ER-negative tumors.[15,16] Therefore, pCR rates were evaluated on the basis of ER expression levels categorized as 0%, 1%-10%, 11%-70%, and >70%.

The HER2DX pCR score was categorized into three groups—low (0-32), medium (33-67), and high (68-99)—on the basis of prespecified cutoffs. On the basis of prior reports,[7,17] we anticipated that for ER-negative disease, 70% would have a high pCR score with a pCR rate of 70%, while 10% would have a low pCR score with a pCR rate of 40%. Among patients with ER-positive disease, 10% were expected to have a high pCR score with a pCR rate of 50% and 50% a low pCR score with a pCR rate of 20%. On the basis of these estimates, 270 patients with HER2-positive/ER-negative disease and 260 patients with HER2-positive/ER-positive disease were required to detect a 30% difference in pCR rate between those with a high or low HER2DX pCR score with 80% power and a one-sided type I error rate of 0.025, using a two-sample Fisher exact test.

Associations between categorical variables and pCR were evaluated using chi-square test for clinicopathologic factors and Fisher exact test for molecular biomarkers. Multivariable logistic regression models were constructed separately for ER-positive and ER-negative cohorts.

The first multivariable model included only clinicopathologic variables, including T-stage, N-stage, grade, ER/progesterone receptor (PR) levels, HER2 IHC, taxane type, Eastern Cooperative Oncology Group (ECOG) status, and age. A second model incorporated the HER2DX pCR score in addition to all the same clinicopathologic variables used in the first model to determine whether the HER2DX pCR score was independently associated with pCR after adjustment.

This study was reviewed and approved by the US NCI Central Institutional Review Board and monitored by the ECOG-ACRIN Data and Safety Monitoring Committee.

RESULTS

Patient and Tumor Characteristics

The study was activated in February 2020. Between March 2020 and October 2023, 2,175 patients enrolled (781 ER-negative; 1,394 ER-positive). Forty-six percent were node positive, and 89% had cT2 or cT3 tumors (Table 1). Nearly all tumors were ductal, and 56% were grade 3 (Table 1). ER-positive tumors more frequently had HER2 IHC 2+. Approximately two thirds of ER-positive tumors demonstrated

TABLE 1. Demographic and Disease Characteristics at Registration

Clinicopathologic Factor	All Patients (N = 2,175)	HER2+/ER− (n = 781)	HER2+/ER+ (n = 1,394)
Age, years, median (range)	55 (22-88)	56 (22-87)	55 (24-88)
Race			
White	75	73	75
Black	12	14	12
Asian	7	8	7
Other/not reported	6	5	6
Ethnicity			
Hispanic	12	14	11
ECOG PS			
0	88	88	87
1	12	12	13
Clinical stage			
IIA (T2N0, T1N1)	58	55	60
IIB (T2N1, T3N0)	33	34	32
IIIA (T3N1, T1-3 N2)	8	10	7
T stage			
T1	11	12	10
T2	75	73	77
T3	14	15	13
N stage			
N0	55	51	57
N1	44	48	42
N2/N3	2	2	2
Histologic type			
Ductal	92	94	91
Lobular/Mixed	4	2	6
Other	3	4	3
Grade			
1	3	1	4
2	40	29	45
3	56	69	49
GX	1	1	1
% Cells ER+			
0%	36	100	—
1%-10%	6	—	10
11%-70%	13	—	21
>70%	44	—	69
% Cells PR+			
0%	51	91	29
1%-10%	11	6	14
>10%	38	3	57
HER2 IHC			
3+	79	85	75
2+ (ISH ratio)	17	10	20
<3	61	56	62
3-4	16	20	15
≥4	23	22	23
IHC 0/1/unknown ISH+	4	5	4
	N = 2,141[a]	n = 774[a]	n = 1,367[a]
Initial taxane received	63	63	64
Paclitaxel	34	35	34
Docetaxel nab-paclitaxel	2	2	2

NOTE. Data are presented as % unless otherwise specified.
Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; PR, progesterone receptor; THP, taxane, trastuzumab, and pertuzumab.
[a]Patients who received ≥1 dose of THP.

ER >70% (Table 1). The distribution of ER levels in tumors is illustrated in the Data Supplement (Fig S1).

Neoadjuvant THP Treatment

A total of 2,141 patients received at least 1 dose of neoadjuvant THP and were considered evaluable for response (Fig 1). Paclitaxel was the initial taxane in two thirds of patients, docetaxel in one third, and nab-paclitaxel in 2% (Table 1). Approximately 7.6% of patients switched taxane during treatment, and 17% of patients had a dose reduction. Data Supplement (Table S3) provides detailed information on patients who switched taxane therapies, including the timing of the switch. Compared with patients who received paclitaxel as the initial therapy, those initially treated with docetaxel were more frequently Black (14.6% *v* 11.2%; $P = .012$) or Hispanic (15.9% *v* 9.7%; $P < .001$) and were less likely to have an ECOG performance status >0 (10.2% *v* 13.4%; $P = .036$). The absolute differences were small though. No other clinical or pathologic characteristics differed significantly between the initial paclitaxel and docetaxel groups. Most of the patients (88%) completed four cycles of THP and 5% withdrew from the study during neoadjuvant treatment or before surgery. Of the 2,141 patients treated, 2,028 (95%) underwent surgery according to protocol without receiving additional nonprotocol therapy (Fig 1). Fewer than 1% of patients progressed during neoadjuvant THP.

pCR Rates

Overall, the pCR rate was 43.8% (95% CI, 41.6 to 45.9; n = 2,141). For HER2-positive/ER-negative tumors (n = 774), the pCR rate was 63.7% (95% CI, 60.2 to 67.1), while for HER2-positive/ER-positive disease (n = 1,337), it was 32.5% (95% CI, 30.0 to 35.0; Fig 2). Among ER-positive tumors, the pCR rate was 62.5% (95% CI, 53.8 to 70.6) for tumors with ER expression between 1% and 10% (n = 136), similar to ER-

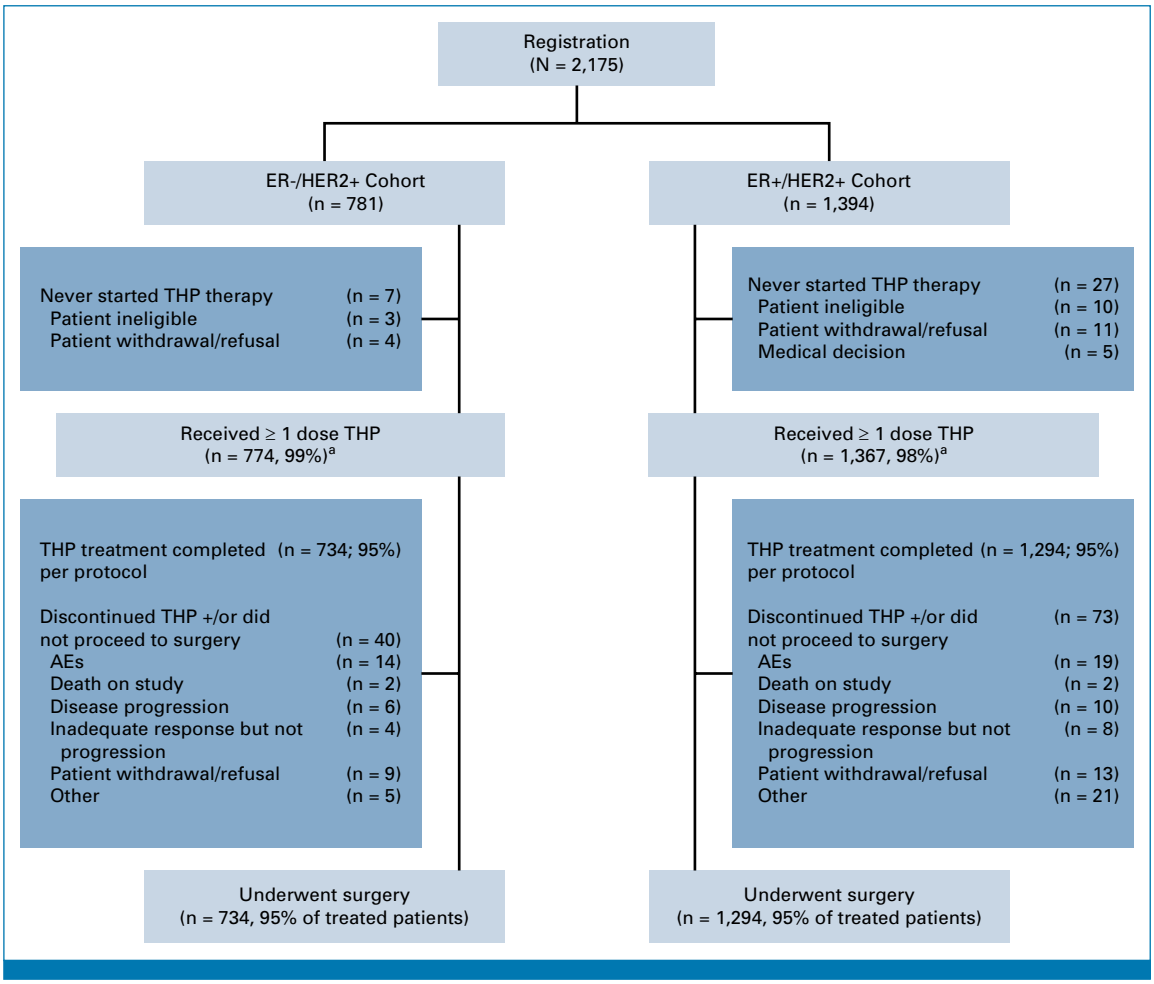

FIG 1. Flow diagram. Evaluable for pCR. AEs, adverse events; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response; THP, taxane, trastuzumab, and pertuzumab.

negative tumors, 51.6% (95% CI, 45.6 to 57.6) for tumors with ER expression between 11% and 70% (n = 281), and 22.5% (95% CI, 19.9 to 25.3) for tumors with ER expression >70% (n = 950). The pCR rates by other clinical and pathologic factors are provided in the Data Supplement (Table S2).

Clinicopathologic Factors Associated With pCR in the HER2+/ER-Negative Cohort

In multivariable analysis, clinicopathologic factors significantly associated with a higher likelihood of pCR in patients with HER2+/ER-negative disease include HER2 IHC 3+ (OR, 6.31 [95% CI, 3.63 to 10.94]) and use of once per week paclitaxel (OR, 1.86 [95% CI, 1.34 to 2.58]; Table 2). The benefit with paclitaxel was not explained by the amount of drug received (Data Supplement, Table S3). The pCR rate was significantly lower for T3 tumors compared with T1 tumors (odds ratio [OR], 0.47 [95% CI, 0.25 to 0.90]) and for patients with performance status of 1 compared with 0 (OR, 0.54 [95% CI, 0.33 to 0.88]; Table 3). The results were similar if tumors with ER+ 1%-10% were included in the analyses (data not shown).

Clinicopathologic Factors Associated With pCR in the HER2+/ER-Positive Cohort

In multivariable analysis, clinicopathologic factors significantly associated with a higher likelihood of pCR among patients with HER2+/ER+ breast cancer include the following: ER expression ≤70%—ER 1%-10% (OR, 2.99 [95% CI, 1.95 to 4.60]) and ER 11%-70% (OR, 2.68 [95% CI, 1.97 to 3.64]); PR expression ≤10%—PR 0% (OR, 2.41 [95% CI, 1.77 to 3.29]) and PR 1%-10% (OR, 1.58 [95% CI, 1.09 to 2.29]); and HER2 IHC 3+ (OR, 6.06 [95% CI, 3.79 to 9.69]). Paclitaxel use was marginally significantly associated with pCR among patients with HER2+/ER+ disease. Unlike ER-negative tumors, T-stage was not associated with pCR among HER2+/ER+ tumors (Table 2). The results were similar if tumors with ER+ 1%-10% were excluded from the analyses (data not shown).

HER2DX pCR Score

The 569 tumors assessed for the HER2DX pCR score constitute the analytic cohort, which was well matched to the entire study population across the clinicopathologic factors

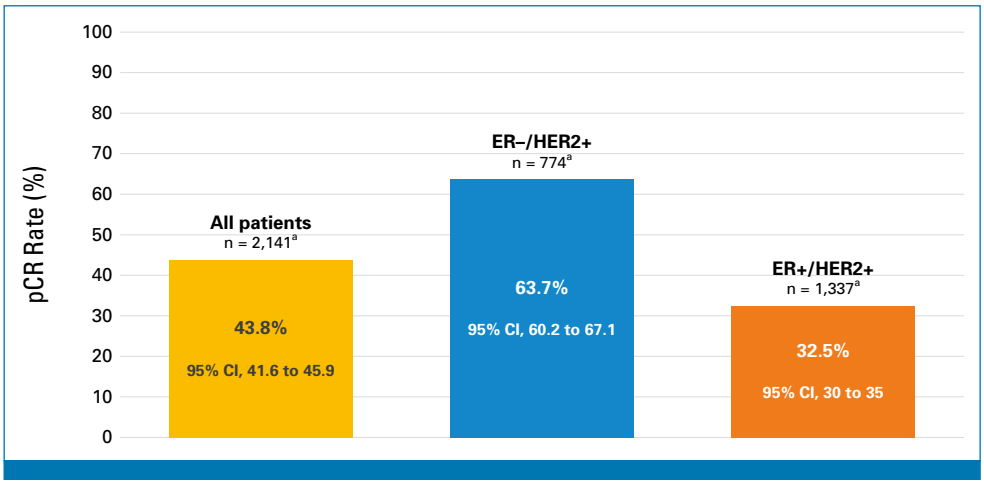

FIG 2. pCR rates overall and by ER status. [a]Pts receiving ≥ 1 THP dose. ER, estrogen receptor; pCR, pathologic complete response; THP, taxane, trastuzumab, and pertuzumab.

TABLE 2. Predictors of pCR—Multivariable Analysis With Clinicopathologic Factors

	All Patients (N = 2,141)[a]	HER2+/ER– (n = 774)[a]	HER2+/ER+ (n = 1,366)[a]
Clinicopathologic Factor	OR for pCR (95% CI)	OR for pCR (95% CI)	OR for pCR (95% CI)
ER status			
ER+ >70%	1.0		1.0
ER+ 11%-70%	**2.75 (2.03 to 3.72)**		**2.68 (1.97 to 3.64)**
ER+ 1%-10%	**3.09 (2.02 to 4.71)**		**2.99 (1.95 to 4.60)**
ER– 0%	**3.24 (2.43 to 4.32)**		–
PR status			
PR+ >10%	1.0		1.0
PR+ 1%-10%	**1.52 (1.08 to 2.14)**		**1.58 (1.09 to 2.29)**
PR– 0%	**2.22 (1.68 to 2.94)**		**2.41 (1.77 to 3.29)**
HER2 IHC[b]:			
2+/ISH+	1.0	1.0	1.0
3+	**6.14 (4.30 to 8.75)**	**6.31 (3.63 to 10.94)**	**6.06 (3.79 to 9.69)**
Initial taxane[c]:			
docetaxel	1.0	1.0	1.0
paclitaxel	**1.50 (1.22 to 1.84)**	**1.86 (1.34 to 2.58)**	1.30 (0.99 to 1.71)
T stage			
T1	1.0	1.0	1.0
T2	0.76 (0.54 to 1.07)	0.60 (0.34 to 1.06)	0.88 (0.56 to 1.38)
T3	**0.64 (0.42 to 0.96)**	**0.47 (0.25 to 0.90)**	0.76 (0.44 to 1.31)
Performance status			
0	1.0	1.0	1.0
1	0.78 (0.58 to 1.07)	**0.54 (0.33 to 0.88)**	0.99 (0.67 to 1.47)
Age (continuous)	0.99 (0.98 to 1.00)	0.99 (0.98 to 1.01)	0.99 (0.98 to 1.00)

NOTE. N-stage and histologic grade were not significantly associated with pCR. Results in bold are significant.
Abbreviations: ER, estrogen receptor; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; OR, odds ratio; pCR, pathologic complete response; PR, progesterone receptor; THP, taxane, trastuzumab, and pertuzumab.
[a]Patients who received ≥1 dose of THP.
[b]Not shown are 4% of patients enrolled by FISH with HER2 IHC 0, 1, or unknown.
[c]Not shown are 2% of patients who initiated treatment with nab-paclitaxel.

TABLE 3. HER2DX pCR Score—Distribution and Associated pCR Rates

	All Participants		HER2+/ER−		HER2+/ER+	
Population	Patients Enrolled, No.	pCR Rate (95% CI)	Patients Enrolled, No.	pCR Rate (95% CI)	Patients Enrolled, No.	pCR Rate (95% CI)
Entire study-evaluable cohort	2,141	44 (42 to 46)	774	64 (60 to 67)	1,367	32 (30 to 35)
HER2DX analytic cohort	569	48 (44 to 52)	230	69 (63 to 75)	339	34 (29 to 39)
HER2DX pCR-high score	183 (32)	68 (60 to 74)	147 (64)	70 (62 to 77)	36 (11)	58 (41 to 74)
HER2DX pCR-medium score	159 (28)	67 (59 to 74)	70 (30)	74 (62 to 84)	89 (26)	61 (50 to 71)
HER2DX pCR-low score	227 (40)	19 (14 to 25)	13 (6)	31 (9 to 61)	214 (63)	18 (13 to 24)
P value HER2DX score	<.001		.010		<.001	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response.

(Data Supplement, Table S3). For both HER2-positive/ER-negative and HER2-positive/ER-positive disease, a high HER2DX pCR score was significantly associated with approximately a 40% higher pCR rate compared with a low HER2DX pCR score (Table 4). Similar pCR rates were observed between high and medium pCR score groups. pCR rates according to HER2DX pCR scores, shown in 10-unit increments, are illustrated in the Data Supplement (Fig S2). When tumors with low ERBB2 expression (ie, less HER2-driven) were excluded from the analysis, pCR rates remained comparable between the high and medium HER2DX pCR score groups (Data Supplement, Table S5). The pCR rate was numerically higher in patients with a high versus medium HER2DX pCR score who received once per week paclitaxel, but this pattern was not observed with every-three-week docetaxel (Data Supplement, Table S6).

In multivariable analysis that included the HER2DX pCR score along with clinicopathologic factors, high and medium HER2DX pCR scores were significantly and independently associated with higher likelihood of pCR rate compared with low HER2DX pCR score: high (OR, 2.75 [95% CI, 1.36 to 5.58]) or medium (OR, 4.17 [95% CI, 2.35 to 7.40]) HER2DX pCR scores. Lower ER expression, HER2 IHC3+, and use of once per week paclitaxel were still independently associated with higher likelihood of pCR as well, but PR level was no longer significantly associated with pCR (Table 4).

DISCUSSION

CompassHER2 pCR (EA1181) is the largest prospective study of neoadjuvant THP in stage II to IIIa HER2-positive breast cancer. We report here the key secondary objective of pCR with an overall pCR rate of 44%, 64% in ER-negative disease, and 33% in ER-positive disease. If the primary objective of EA1181 is met—demonstrating that 3-year RFS for patients achieving pCR after THP is comparable with that achieved with multiagent chemotherapy—then accurately identifying patients most likely to achieve pCR with THP will be critical to sparing them the toxicity of unnecessary chemotherapy.

We identified several baseline clinical factors significantly associated with a higher likelihood of pCR: tumors that are either ER negative or, if ER positive, have an ER level of ≤70%; tumors that are PR negative or have low PR expression (1%-10%); tumors with HER2 IHC 3+; and the use of once per week paclitaxel rather than every-3-week docetaxel, with the observed benefit of paclitaxel greater in ER-negative tumors. Additionally, among patients with HER2+/ER-negative disease, those with cT3 tumors (15% of the cohort) had a lower pCR rate, though still 59%. Otherwise, clinical stage, T-stage, and N-stage were not significantly associated with pCR, although this observation is limited to patients eligible for this trial as those with cT4, cN2, or cN3 disease or those with stage I disease were not eligible.

Once per week taxane was especially efficacious in the more highly proliferative ER-negative tumors compared with every-3-week taxane. While we cannot exclude the possibility that unmeasured physician or patient factors influencing taxane selection may have contributed to this finding, these results align with previous reports suggesting that once per week paclitaxel is a more efficacious schedule than every-3-week taxane.[18,19] We plan additional analyses to assess if this observation applies to all patient subsets in EA1181.

We also found that combining clinical factors with molecular biomarkers further enhances the ability to predict which patients will achieve a pCR after THP. The HER2DX pCR likelihood score was independently associated with pCR, even after adjusting for clinical factors. This finding underscores the need to better integrate clinicopathologic and molecular features to improve the identification of patients suitable for less intensive neoadjuvant strategies. Of note, when the HER2DX pCR score was incorporated into the multivariable analysis, tumor size (T-stage) and PR status were no longer significantly associated with pCR. Because

TABLE 4. Predictors of pCR—Multivariable Analysis With HER2Dx pCR Score and Clinical Factors

Clinical Factor	OR for pCR (95% CI)	No. of Patients (n = 569)
HER2Dx pCR score		
Low	1.0	226
Medium	4.17 (2.35 to 7.40)	161
High	2.75 (1.36 to 5.58)	182
ER		
ER+ >70%	1.0	244
ER+ 11%-70%	2.31 (1.17 to 4.57)	64
ER+ 1%-10%	3.11 (1.14 to 8.51)	31
ER− 0%	3.71 (1.84 to 7.48)	230
PR		
PR+ >70%	1.0	194
PR+ 1%-10%	1.42 (0.69 to 2.90)	60
PR− 0%	1.06 (0.59 to 1.91)	315
HER2 IHC[a]:		
2+/ISH+	1.0	85
3+	7.35 (3.34 to 16.21)	461
Initial taxane[b]:		
Docetaxel	1.0	188
Paclitaxel	1.56 (1.02 to 2.41)	368

NOTE. T stage, N stage, age, race, ECOG PS, and histologic grade were not significantly associated with pCR.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; FISH, fluorescent in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; OR, odds ratio; pCR, pathologic complete response; PR, progesterone receptor.
[a]Not shown are 4% of patients enrolled by FISH with HER2 IHC 0, 1, or unknown.
[b]Not shown are 2% of patients who initiated treatment with nab-paclitaxel.

the subset of patients with available HER2DX pCR scores was smaller than the overall treated cohort, this loss of statistical significance may be attributable to reduced statistical power. Alternatively, as the HER2DX pCR score includes a luminal gene-expression signature and PR status is closely linked to luminal biology, the independent contribution of PR to pCR may be attenuated once the HER2DX score is included in the model. In this context, PR may provide limited additional discriminatory value for biologic subtypes (eg, luminal A *v* luminal B).

The findings from this large cooperative group trial confirm observations from smaller trials describing rates and predictors of pCR in HER2-positive breast cancer. The observed pCR rates in EA1181 are virtually identical to those anticipated in the trial design and to those reported in previous, smaller trials of single-agent taxane combined with trastuzumab and pertuzumab,[13,20,21] with the exception of the Daphne trial, a much smaller feasibility study of 98 patients in a younger, primarily node-negative population, treated with paclitaxel and HP that reported a pCR rate of 56.7%.[22] EA1181 is also consistent with several prior trials in HER2-positive breast cancer that have shown higher pCR rates among patients with ER-negative disease,[20,23] tumors with higher HER2 expression or amplification,[24] the HER2-enriched molecular subtype,[25-28] and tumors with higher immune signature expression.[29] Nevertheless, despite the fact that EA1181 is one of the largest studies ever conducted in this setting (and, to our knowledge, the only study powered for survival), we acknowledge that potential biases may have influenced the pCR rate and cannot be fully accounted in view of the single-arm study design.

Finally, EA1181 is consistent with a meta-analysis of HER2DX pCR score in seven other neoadjuvant trials, which also demonstrated significantly higher pCR rates with a high versus low HER2DX pCR score across multiple chemotherapy regimens and with either single or dual HER2 blockade.[7] However, in contrast to that analysis, we did not observe differences in pCR rates between tumors with high versus medium HER2DX pCR scores. This finding was primarily driven by an unexpectedly high pCR rate in the medium-score group, closely resembling that of the high-score group, though the underlying reasons remain unclear. This assay may be most clinically useful for identifying low-score patients who may require longer duration or additional therapy beyond THP × four to achieve pCR. This may be most clinically meaningful in those with HER2+/ER+ disease, for whom two thirds of patients in EA1181 had a low HER2DX pCR score, in contrast to patients with HER2+/ER− disease, among whom only 6% had a low score. However, the benefit of escalating neoadjuvant therapy and the optimal approach to increase pCR rates in patients with a low HER2DX pCR score remain unclear.

More intensive neoadjuvant regimens (e.g., longer duration of THP [six cycles][30,31] or docetaxel, carboplatin, trastuzumab, pertuzumab)[1-3,30,31] are expected to increase pCR rates. While this approach spares some patients exposure to postoperative antidrug conjugates, others will be exposed to unnecessary up-front toxicity, highlighting the importance of identifying biomarkers that allow preoperative therapy de-escalation.

Ongoing analyses in EA1181 and other trials such as EA1211/DIRECT (ClinicalTrials.gov identifier: NCT05710328) are evaluating imaging and molecular biomarkers in tissue and blood to help improve our ability to predict pCR in patients with HER2-positive breast cancer. Trials like TBCRC026[32] and PHERGain[33] suggest the potential of using early metabolic response to neoadjuvant therapy with FDG-PET/CT to identify patients with HER2-positive disease more or less likely to achieve pCR. The TRAIN-3 trial showed promising results for breast MRI in predicting pCR among patients with HER2+/ER− disease.[34]

In conclusion, CompassHER2 pCR (EA1181) provides prospective data on pCR rates with single-agent taxane plus dual HER2 antibodies in stage II to III HER2-positive breast

cancer. Meaningful differences by ER status were confirmed. We found that several other clinical factors, along with molecular tools, may help predict which patients with stage II and III HER2-positive breast cancer are most likely to achieve a pCR with THP. Tailoring the up-front treatment on the basis of clinical, imaging, and molecular biomarkers—at baseline, soon after therapy initiation, or at surgery—will increasingly allow us to optimize therapy on the basis of individual tumor characteristics. Such an approach can guide subsequent therapy intensification or de-escalation with the goal of maximizing outcomes while minimizing unnecessary toxicities. Finally, outcomes in patients with early-stage HER2-positive breast cancer are influenced by factors beyond pCR, including clinicopathologic and molecular features as well as postsurgical treatments. Once data mature, we will report the 3-year RFS primary end point of EA1181, along with analyses of baseline, on-treatment, surgical, and postsurgical factors associated with survival outcomes.

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Pathologic Complete Response (pCR) Rate and Predictors of Response to Taxane, Trastuzumab, and Pertuzumab in HER2-Positive Breast Cancer: Secondary Analyses of EA1181/CompassHER2 pCR

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