

ORIGINAL ARTICLE

Pertuzumab, trastuzumab, and standard anthracycline- and taxane-based chemotherapy for the neoadjuvant treatment of patients with HER2-positive localized breast cancer (BERENICE): a phase II, open-label, multicenter, multinational cardiac safety study

S. M. Swain^{1*}, M. S. Ewer², G. Viale³, S. Delaloge⁴, J.-M. Ferrero⁵, M. Verrill⁶, R. Colomer⁷, C. Vieira⁸, T. L. Werner⁹, H. Douthwaite¹⁰, D. Bradley¹¹, M. Waldron-Lynch¹¹, A. Kiermaier¹², J. Eng-Wong¹³ & C. Dang¹⁴, for the BERENICE Study Group[†]

¹Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, Washington; ²Department of Cardiology, The University of Texas MD Anderson Cancer Center, Houston, USA; ³Department of Pathology, European Institute of Oncology, University of Milan, Milan, Italy; ⁴Department of Medical Oncology, Institut Gustave Roussy, Villejuif; ⁵Clinical Research Department, Centre Antoine Lacassagne, Nice, France; ⁶Medical Oncology Department, Northern Centre for Cancer Care, Newcastle upon Tyne, UK; ⁷Medical Oncology Department, Hospital Universitario La Princesa, Madrid, Spain; ⁸Medical Oncology, Instituto Português de Oncologia Francisco Gentil (IPOFG) Porto, Porto, Portugal; ⁹Huntsman Cancer Institute, University of Utah, Salt Lake City, USA; ¹⁰Biostatistics, Product Development; ¹¹Clinical Science, Global Product Development, Roche Products Ltd, Welwyn Garden City, UK; ¹²Oncology Biomarker Development (OBD), F. Hoffmann-La Roche Ltd, Basel, Switzerland; ¹³Product Development – Oncology, Genentech, Inc., South San Francisco; ¹⁴Department of Medicine, Breast Medicine Service, Memorial Sloan Kettering Cancer Center, New York, USA

*Correspondence to: Prof. Sandra M. Swain, Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, 4000 Reservoir Road NW, 120 Building D, Washington, DC 20057-1400, USA. Tel: +1-202-687-8487; E-mail: sandra.swain@georgetown.edu

[†]Members of the BERENICE Study Group are listed in the supplementary data, available at *Annals of Oncology* online.

Background: Anti-HER2 therapies are associated with a risk of increased cardiac toxicity, particularly when part of anthracycline-containing regimens. We report cardiac safety of pertuzumab, trastuzumab, and chemotherapy in the neoadjuvant treatment of HER2-positive early breast cancer.

Patients and methods: BERENICE (NCT02132949) is a nonrandomized, phase II, open-label, multicenter, multinational study in patients with normal cardiac function. In the neoadjuvant period, cohort A patients received four cycles of dose-dense doxorubicin and cyclophosphamide, then 12 doses of standard paclitaxel plus four standard trastuzumab and pertuzumab cycles. Cohort B patients received four standard fluorouracil/epirubicin/cyclophosphamide cycles, then four docetaxel cycles with four standard trastuzumab and pertuzumab cycles. The primary end point was cardiac safety during neoadjuvant treatment, assessed by the incidence of New York Heart Association class III/IV heart failure and of left ventricular ejection fraction declines (≥ 10 percentage-points from baseline and to a value of $< 50\%$). The main efficacy end point was pathologic complete response (pCR, ypT0/is ypN0). Results are descriptive.

Results: Safety populations were 199 and 198 patients in cohorts A and B, respectively. Three patients [1.5%; 95% confidence interval (CI) 0.31% to 4.34%] in cohort A experienced four New York Heart Association class III/IV heart failure events. Thirteen patients (6.5%; 95% CI 3.5% to 10.9%) in cohort A and four (2.0%; 95% CI 0.6% to 5.1%) in cohort B experienced at least one left ventricular ejection fraction decline. No new safety signals were identified. pCR rates were 61.8% and 60.7% in cohorts A and B, respectively. The highest pCR rates were in the HER2-enriched PAM50 subtype (75.0% and 73.7%, respectively).

Conclusion: Treatment with pertuzumab, trastuzumab, and common anthracycline-containing regimens for the neoadjuvant treatment of early breast cancer resulted in cardiac and general safety profiles, and pCR rates, consistent with prior studies with pertuzumab.

Clinical Trial Information: NCT02132949

Key words: pertuzumab, trastuzumab, neoadjuvant, cardiac safety, early breast cancer

Introduction

HER2 is overexpressed/gene-amplified in ~15%–20% of breast cancers (BC) [1] and associated with poor prognoses. Trastuzumab plus chemotherapy has progression-free survival (PFS)/overall survival benefits in HER2-positive metastatic BC [2]. Pertuzumab, trastuzumab, and docetaxel showed further benefits, with significantly improved PFS/overall survival versus placebo, trastuzumab, and docetaxel [3, 4]. Pertuzumab, trastuzumab, and docetaxel is efficacious in the neoadjuvant setting, with a 17.8% increase in pathologic complete response (pCR, ypT0/is ypN0) rates versus trastuzumab plus docetaxel in NeoSphere [5], and similar benefits in additional studies [6, 7]. Exploratory PFS and disease-free survival results from NeoSphere and TRYphaena supported pCR benefits [8, 9].

Trastuzumab is associated with a risk of cardiac toxicity, particularly when given with anthracyclines. In BCIRG006 (trastuzumab plus chemotherapy in early BC [EBC]), incidences of congestive heart failure were 2.0% and 0.4% in the anthracycline- and non-anthracycline arms, respectively [10]. Higher cardiac event rates with trastuzumab were also seen in studies of anthracycline-containing regimens ± trastuzumab [11, 12]. Therefore, cardiac safety within the context of chemotherapy regimen is an important consideration.

In CLEOPATRA, there was no increased cardiac risk (heart failure) with pertuzumab [3, 4]; no additional/long-term cardiotoxicities were associated with combination therapy in NeoSphere [8]. Pertuzumab plus trastuzumab was associated with little additional toxicity in NeoSphere [5] and TRYphaena [6] (mainly increased incidence, but not severity, of diarrhea, rash, and mucositis); there was little impact on doses received, dose interruptions/modifications/discontinuations, or treatment-related mortality [5, 6]. NCCN guidelines recommend pertuzumab-containing regimens for HER2-positive BC. While pertuzumab plus trastuzumab has an acceptable safety profile in combination with epirubicin, when BERENICE was designed there were no doxorubicin data, and limited data on pertuzumab, trastuzumab, and paclitaxel in EBC (GeparSepto assessed paclitaxel/nab-paclitaxel, pertuzumab, and trastuzumab followed by epirubicin and cyclophosphamide [7]).

The ongoing BERENICE study (NCT02132949) was designed to evaluate the cardiac safety of two neoadjuvant anthracycline-/taxane-based regimens with pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive BC, and normal cardiac function. We present the primary analysis: cardiac safety during the neoadjuvant period (clinical cutoff at the date of last patient's breast surgery).

Patients and methods

BERENICE is a nonrandomized, phase II, open-label, multicenter, multinational cardiac safety study across 75 centers/12 countries in full

accordance with Good Clinical Practice guidelines/Declaration of Helsinki.

All participants provided written informed consent. The protocol and modifications were approved by independent ethics committees.

Procedures

Eligible patients were investigator-assigned to cohorts (Figure 1). In the neoadjuvant period, cohort A patients received four q2w cycles of dose-dense doxorubicin plus cyclophosphamide (ddAC) followed 2 weeks later by 12 qw paclitaxel injections, while cohort B patients received four q3w cycles of fluorouracil, epirubicin, and cyclophosphamide then four q3w cycles of docetaxel. In both cohorts, four q3w cycles of trastuzumab and pertuzumab were started with taxane therapy and continued in the adjuvant setting (up to 13 cycles to complete 1 year of treatment). Surgery was scheduled after eight cycles of preoperative therapy. All study drugs were given intravenously. See [supplementary data](#), available at *Annals of Oncology* online, for dose modification, and [supplementary Figure S1](#), available at *Annals of Oncology* online, for management of HER2-targeted treatment based on left ventricular ejection fraction (LVEF) decreases. Optional granulocyte-colony stimulating factor support could be given per local practice. Patients could withdraw consent at any time or be withdrawn by the investigator/sponsor for safety reasons, if in the patient's best interests, or for noncompliance with the protocol.

Assessments

The primary end point was cardiac safety of neoadjuvant treatment assessed by incidence of New York Heart Association (NYHA) class III and IV heart failure and LVEF declines (≥ 10 percentage-points from baseline and to a value of $< 50\%$ [symptomatic and asymptomatic]) by echocardiography or multiple-gated acquisition scan. LVEF assessments were conducted at screening/baseline and within 3 days before day 1 of cycles 5 and 7 during the neoadjuvant period. Adverse events (AEs) were assessed throughout the treatment period per National Cancer Institute–Common Terminology Criteria for Adverse Events (NCI-CTCAE) V4.0. Safety data are regularly reviewed by the Steering Committee (sponsor representatives, investigators, plus an independent cardiology expert). Tumors were assessed clinically at screening/baseline and at each cycle during neoadjuvant treatment. Patients are also assessed for recurrence at cycles 9, 13, 17, and 21 during adjuvant treatment, and at study completion/termination visits, per local practice. Secondary end points included general safety during the neoadjuvant period (including incidence and severity of AEs/serious AEs; laboratory test anomalies) and all efficacy end points. The main efficacy end point was pCR in the breast and lymph nodes (ypT0/is ypN0; total pCR). pCR assessments were reviewed by an external pathology expert. Exploratory efficacy end points included local pathologist-assessed pCR rate and rate by major intrinsic BC subtype. To classify patients by intrinsic BC subtype, gene expression analyses were carried out by applying the Nanostring nCounter platform. Within the set of genes analyzed, the panel of genes required to assess the intrinsic BC subtypes as published by Parker et al was included [13]. The PAM50 subtype prediction to describe the major intrinsic subtypes (HER2-enriched, luminal A, luminal B, and basal-like) was carried out using the random-forest-based classifier described by Wilson et al [14]. Further end point details are presented in the [supplementary data](#), available at *Annals of Oncology* online.

Safety was assessed in all patients who received ≥ 1 dose of study medication; pCR, in the intention-to-treat population.

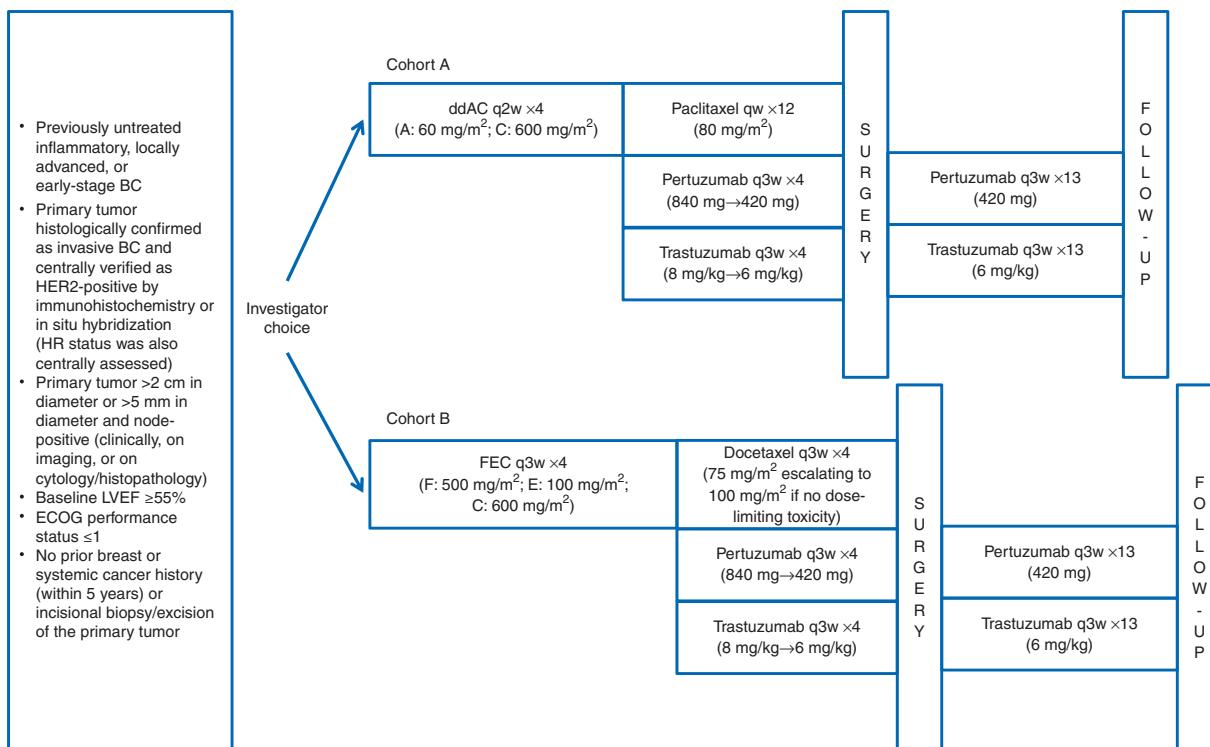


Figure 1. Study design. BC, breast cancer; ddAC, dose-dense doxorubicin plus cyclophosphamide; ECOG, Eastern Cooperative Oncology Group; FEC, fluorouracil, epirubicin, and cyclophosphamide; HR, hormone receptor; LVEF, left ventricular ejection fraction; q2w, every 2 weeks; q3w, every 3 weeks; qw, every week. Only one cohort was opened at a time at any given site, and was defined before any patients were enrolled at that site. Investigator choice of cohort was based on local/regional practice.

Statistical methods

No formal sample size calculation/statistical hypothesis testing was performed. Results were summarized descriptively. Exact Clopper-Pearson 95% CIs of expected rates (NYHA class III/IV heart failure rate <3% and LVEF decline rate of ≤6%) [5, 6] were used to evaluate cardiac safety.

Results

Population

Patients were enrolled July 2014 to August 2015: 199 were assigned to cohort A; 202, to cohort B (supplementary Figure S2, available at *Annals of Oncology* online). Intention-to-treat populations were 199 and 201 patients, respectively; safety populations, 199 and 198. Clinical cutoff was March 3, 2016, median (interquartile range) follow-up was 14.5 (13.9–15.5) months in cohort A and 15.1 (14.5–15.8) months in cohort B.

Demographics/baseline characteristics were similar in each cohort (Table 1). Treatment exposure during the neoadjuvant period is shown in supplementary Table S1, available at *Annals of Oncology* online.

Incidence of NYHA class III and IV heart failure

Three patients (1.5%) in cohort A experienced four NYHA class III/IV heart failure events (Table 2). One patient experienced two events (one class III and one class IV); due to the close chronology, Steering Committee members considered that these could

represent continuation of one event. All occurred during neoadjuvant HER2 antibody treatment and all patients discontinued treatment. Recoveries were recorded for 2/4 events (the patient with two events recovered from the class IV event only). No patient in cohort B experienced any events.

Incidence of LVEF declines

Thirteen patients (6.5%) in cohort A and four (2.0%) in cohort B experienced ≥1 LVEF decline (Table 2). Patients with a decline should have had treatment withheld and a repeat evaluation ~3 weeks later. Confirmed declines (≥2 consecutive declines during the neoadjuvant period) were observed in two (1.0%) patients in cohort A and one (0.5%) in cohort B; all during neoadjuvant HER2-targeted therapy. Declines in the neoadjuvant period were generally reversible in most patients at the time of analysis, often with recovery by next assessment.

General safety

The most common AEs (any-grade) during the neoadjuvant period were nausea, diarrhea, and alopecia (Table 3). The most common grade 3–4 AEs were blood and lymphatic system disorders, with febrile neutropenia the most common event, followed by neutropenia (Table 3). This was in keeping with the higher proportion of patients who received optional prophylactic bone marrow support in cohort A. Neutropenia recorded as “neutrophil count decreased” was reported in 9 patients (4.5%) in cohort A and 12 (6.1%) in cohort B. No grade 5 AEs were

Table 1. Baseline demographics and tumor characteristics for the intention-to-treat population

Characteristic	Cohort A: ddAC → TPH n = 199	Cohort B: FEC → DPH n = 201
Median age, years (IQR)	49.0 (42.0–59.0)	49.0 (42.0–59.0)
Age group		
<40	39 (19.6%)	38 (18.9%)
40–65	140 (70.4%)	142 (70.6%)
>65	20 (10.1%)	21 (10.4%)
Female patients	199 (100%)	200 (99.5%)
Estrogen and/or progesterone receptor status (centrally assessed)		
Positive	128 (64.3%)	124 (61.7%)
Negative	65 (32.7%)	75 (37.3%)
Unknown	6 (3.0%)	2 (1.0%)
Primary tumor		
TX	0	1 (0.5%) ^a
T0	1 (0.5%) ^a	0
T1	18 (9.0%)	12 (6.0%)
T2	138 (69.3%)	130 (64.7%)
T3	33 (16.6%)	45 (22.4%)
T4	9 (4.5%)	13 (6.5%)
Regional lymph nodes		
NX	8 (4.0%)	9 (4.5%)
N0	80 (40.2%)	74 (36.8%)
N1	92 (46.2%)	98 (48.8%)
N2	16 (8.0%)	15 (7.5%)
N3	3 (1.5%)	5 (2.5%)
Histologic subtype		
Ductal	171 (85.9%)	176 (87.6%)
Lobular	9 (4.5%)	4 (2.0%)
Mucinous	1 (0.5%)	0
Comedo	4 (2.0%)	0
Tubular	2 (1.0%)	0
Not otherwise specified	14 (7.0%)	19 (9.5%)
Other	8 (4.0%)	8 (4.0%)
Histologic grade	n = 198	n = 201
G0 ^b	3 (1.5%)	9 (4.5%)
G1	4 (2.0%)	2 (1.0%)
G2	67 (33.8%)	56 (27.9%)
G3	108 (54.5%)	106 (52.7%)
Unknown ^c	16 (8.1%)	28 (13.9%)
Intrinsic subtype ^d	n = 199	n = 201
Luminal A	33 (16.6%)	31 (15.4%)
Luminal B	24 (12.1%)	15 (7.5%)
Basal-like	11 (5.5%)	5 (2.5%)
HER2-enriched	80 (40.2%)	95 (47.3%)
Not applicable ^e	19 (9.5%)	26 (12.9%)
Missing ^f	32 (16.1%)	29 (14.4%)

Data are n (%) unless stated otherwise.

^aPatient was misdiagnosed.

^bUnevaluable.

^cNot evaluated.

^dPatients were classified by intrinsic BC subtype using gene expression analyses carried out by applying the Nanostring nCounter platform and the PAM50 subtype prediction used to describe the major intrinsic subtypes (see [supplementary data](#), available at *Annals of Oncology* online).

^eThe statistical model applied did not allow categorization into any of the subgroups.

^fTechnical failure (assay failure or failure to extract RNA).

D, docetaxel; ddAC, dose-dense doxorubicin plus cyclophosphamide; FEC, fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; IQR, interquartile range; P, pertuzumab; T, paclitaxel.

Table 2. Cardiac safety during the neoadjuvant period in the safety population

	Cohort A: ddAC → TPH n = 199	Cohort B: FEC → DPH n = 198
NYHA class III/IV heart failure during HER2 antibody treatment in the neoadjuvant period ^a		
Patients with at least one NYHA class III/IV heart failure	3 (1.5%; 95% CI 0.31% to 4.34%)	0 (95% CI 0% to 1.85%)
Number of events	4	0
NCI-CTCAE grade, patients		
Grade 3	1 (0.5%)	0
Grade 4	2 (1.0%)	0
NYHA classification, events		
Class III	3 (1.5%)	0
Class IV	1 (0.5%)	0
LVEF declines during the neoadjuvant period ^{a,b}		
Patients with at least one LVEF decline	13 (6.5%; 95% CI 3.5% to 10.9%)	4 (2.0%; 95% CI 0.6% to 5.1%)
Number of LVEF declines, events	19	5
Onset before neoadjuvant HER2-targeted therapy (cycles 1–4), patients	0	1 (0.5%)
Onset during neoadjuvant HER2-targeted therapy (cycles 5–8), patients	13 (6.5%)	3 (1.5%)
Patients with at least one confirmed LVEF decline ^c	2 (1.0%; 95% CI 0.1% to 3.6%)	1 (0.5%; 95% CI 0% to 2.8%)

95% CIs were calculated with the use of the Clopper-Pearson method.

^aIncludes events with onset from the first dose of pertuzumab or trastuzumab before surgery through the day before the first dose of any study drug after surgery. If a patient withdrew without entering the adjuvant period, the table includes all AEs with onset from first dose of pertuzumab or trastuzumab through 42 days after last dose of any study drug or on the day of target surgery, whichever is later. Multiple occurrences of the same events in one individual are counted only once in the patient frequency counts.

^bMeasured by ECHO/MUGA.

^cConfirmed LVEF declines are defined as at least two consecutive readings of declines in LVEF, and single declines are defined as only one reading of declines (no consecutive readings) in LVEF.

CI, confidence interval; D, docetaxel; ddAC, dose-dense doxorubicin plus cyclophosphamide; FEC, fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; LVEF, left ventricular ejection fraction; NCI-CTCAE, National Cancer Institute—Common Terminology Criteria for Adverse Events; NYHA, New York Heart Association; P, pertuzumab; T, paclitaxel.

reported. The most common serious AEs were febrile neutropenia and diarrhea. Ten patients (5.1%) in cohort B experienced grade 3–4 stomatitis (no cases were reported in cohort A). The most common reason for pertuzumab/trastuzumab discontinuation was ejection fraction decline (including one patient who discontinued but did not have a confirmed decline).

Efficacy

pCR rates were 61.8% (95% CI 54.7% to 68.6%) and 60.7% (95% CI 53.6% to 67.5%) in cohorts A and B, respectively, and higher

Table 3. General safety during the neoadjuvant period in the safety population

Patients with at least one:	Cohort A: ddAC → TPH n = 199	Cohort B: FEC → DPH n = 198
AE (any grade)	197 (99.0%)	198 (100%)
Grade 3–4 AE	99 (49.7%)	108 (54.5%)
Serious AE	45 (22.6%)	52 (26.3%)
AE leading to pertuzumab or trastuzumab discontinuation	10 (5.0%)	4 (2.0%)
Most common grade 3–4 AEs (≥2% of patients)		
Febrile neutropenia	14 (7.0%)	34 (17.2%)
Neutropenia	24 (12.1%)	17 (8.6%)
Diarrhea	6 (3.0%)	20 (10.1%)
Neutrophil count decreased	9 (4.5%)	12 (6.1%)
Fatigue	2 (1.0%)	9 (4.5%)
Anemia	6 (3.0%)	5 (2.5%)
Stomatitis	0	10 (5.1%)
White blood cell count decreased	8 (4.0%)	4 (2.0%)
Vomiting	2 (1.0%)	8 (4.0%)
Mucosal inflammation	2 (1.0%)	7 (3.5%)
Nausea	5 (2.5%)	4 (2.0%)
Hypokalemia	4 (2.0%)	3 (1.5%)
Neutropenic sepsis	0	6 (3.0%)
Alanine aminotransferase increased	4 (2.0%)	2 (1.0%)
Bone marrow failure	1 (0.5%)	4 (2.0%)
Device-related infection	4 (2.0%)	1 (0.5%)
Neuropathy peripheral	4 (2.0%)	0

AE, adverse event; D, docetaxel; ddAC, dose-dense doxorubicin plus cyclophosphamide; FEC, fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; P, pertuzumab; T, paclitaxel.

in hormone receptor (HR)-negative versus HR-positive disease (Figure 2A).

Local pathologist-assessed rates were 63.8% (95% CI 56.7% to 70.5%) in cohort A and 61.2% (95% CI 54.1% to 68.0%) in cohort B, including five patients in cohort A and four in cohort B with nodal stage NX. Of these, five patients did not have nodes assessed at surgery but were considered by the local pathologist to have achieved pCR.

Most patients had HER2-enriched BC (Table 1), and the highest pCR rate was observed in this group (75.0% in cohort A and 73.7% in cohort B; Figure 2B). The pCR rate was similar in luminal A and B groups across both cohorts (Figure 2B).

Discussion

The primary objective of BERENICE was to evaluate cardiac safety of trastuzumab, pertuzumab, and eight cycles of neoadjuvant chemotherapy (four anthracycline-based followed by four of dual HER2-targeted therapy plus taxane).

Overall incidence of NYHA class III/IV heart failure during neoadjuvant treatment was low and consistent with TRYphaena [6]. Notably, BERENICE included a longer neoadjuvant period (eight versus six chemotherapy cycles) [6].

General safety was consistent with anticipated toxicity profiles of these regimens. Incidence of diarrhea associated with the

taxane period was lower in cohort A; however, other reports have shown no difference in rates across taxanes when given with pertuzumab and trastuzumab [15]. Diarrhea was mostly low-grade, and only one patient (cohort B), discontinued pertuzumab/trastuzumab as a result. pCR rates were high in both cohorts and consistent with previous reports [5, 6]. Previous studies have reported pCR rates of 22%–64% for combinations of HER2-targeted therapy plus chemotherapy [5–7, 16–28]. The high rate in HR-negative disease was consistent with data on trastuzumab plus pertuzumab ± taxanes [29]. Lower rates in HR-positive disease were consistent with the lower rates observed in luminal A and B subtypes. The high pCR rate in the HER2-enriched subtype was consistent with data demonstrating that this subtype could identify patients who would most likely benefit from dual HER2-blockade [30]. Our distributions of relevant intrinsic subtypes (HER2-enriched and luminal A) are also broadly reflective of those reported in a HER2-positive population [31]. Patients will be followed for long-term efficacy outcomes.

BERENICE has limitations due to its design. As it is non-randomized, the chemotherapy backbone's contribution to the data cannot be assessed. No control arm also means that the impact of pertuzumab alone on the safety/efficacy of the regimen cannot be assessed.

The safety/efficacy of pertuzumab plus trastuzumab and chemotherapy versus placebo plus trastuzumab and chemotherapy in the adjuvant setting was recently reported in the APHINITY trial, where pertuzumab significantly improved invasive disease-free survival with no new safety signals being identified [32]. BERENICE, KRISTINE [16], and PEONY (NCT02586025) will evaluate pertuzumab plus trastuzumab treatment continuing from the neoadjuvant into the adjuvant setting. These trials will assess 1 year of dual HER2-targeted antibody therapy in EBC, spanning the neoadjuvant and/or adjuvant periods.

Conclusion

Treatment with pertuzumab, trastuzumab, and common anthracycline-containing chemotherapy regimens for the neoadjuvant treatment of EBC resulted in cardiac and general safety profiles, and pCR rates, consistent with prior pertuzumab studies. This is the first study to investigate ddAC followed by paclitaxel with pertuzumab and trastuzumab in the neoadjuvant setting. The safety profiles and high pCR rates in both cohorts support the use of pertuzumab and trastuzumab with a taxane following doxorubicin- or epirubicin-based chemotherapy in the neoadjuvant setting.

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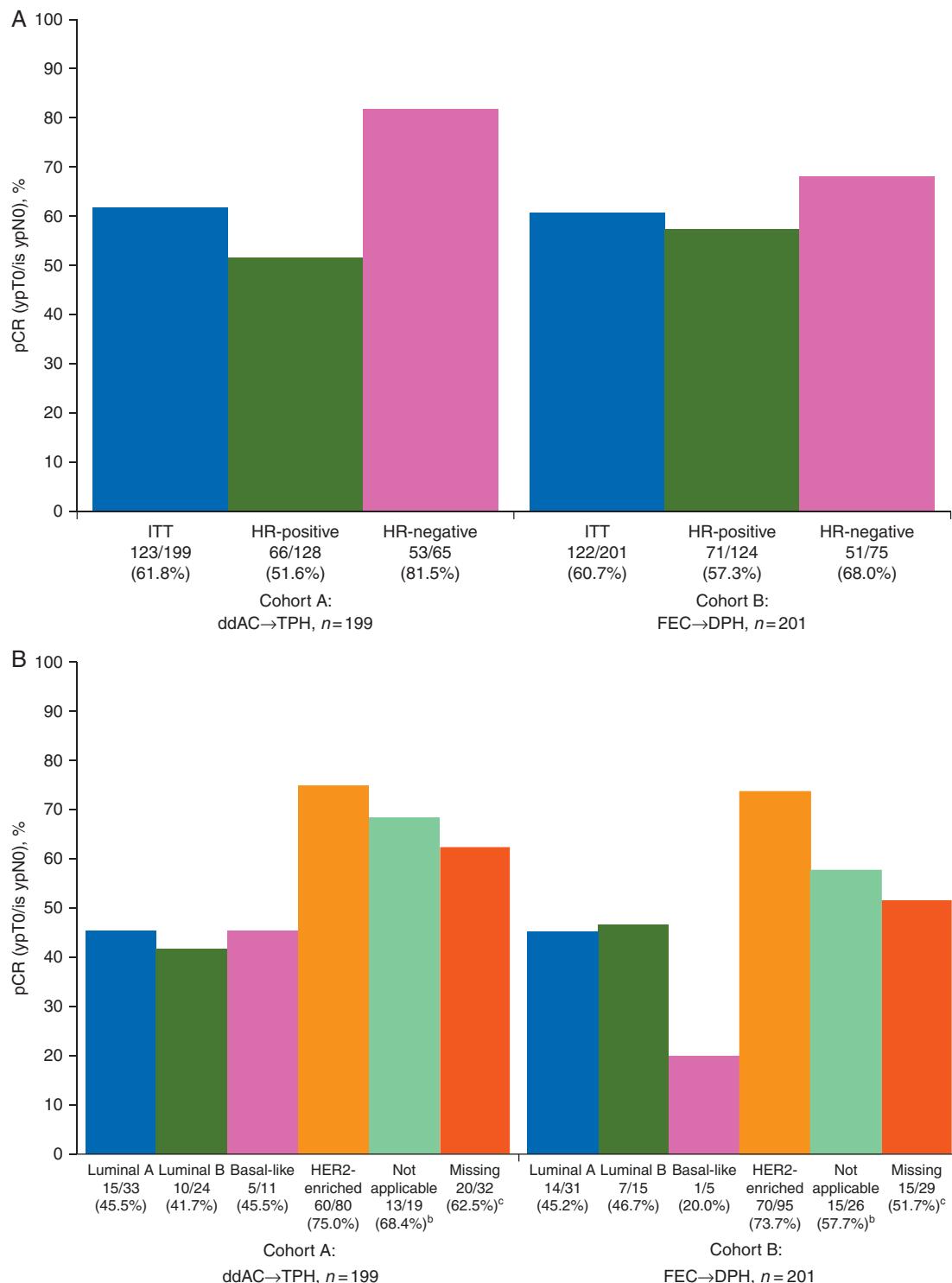


Figure 2. pCR (ypT0/is ypN0) (A) in the intention-to-treat (ITT) population and (B) by intrinsic breast cancer subtype.^a D, docetaxel; ddAC, dose-dense doxorubicin plus cyclophosphamide; FEC, fluorouracil, epirubicin, and cyclophosphamide; H, trastuzumab; HR, hormone receptor; P, pertuzumab; pCR, pathologic complete response; T, paclitaxel. Six patients in cohort A and two in cohort B had missing central HR assessments. ^aPatients were classified by intrinsic BC subtype using gene expression analyses carried out by applying the Nanostring nCounter platform and the PAM50 subtype prediction used to describe the major intrinsic subtypes (see [supplementary data](#), available at *Annals of Oncology* online). ^bThe statistical model applied did not allow categorization into any of the subgroups. ^cTechnical failure (assay failure or failure to extract RNA).

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Disclosure

SMS received honoraria from Roche, Pfizer, Novartis, and AstraZeneca, provided consultancy for Genentech/Roche, Clinigen Group, Lilly, and Pieris Pharmaceuticals, and received travel expense from Genentech/Roche. Her institution received funding from Puma Biotechnology, Roche, Genentech, Pfizer, Merrimack, and Lilly for research. MSE received honoraria from People's Medical Publishing Clearing House – USA, provided consultancy for AstraZeneca, Mylan, and Boehringer Ingelheim, receives authorship royalties, and received travel expenses reimbursement from Mylan. GV received honoraria from MSD Oncology, and provided consultancy to Dako, Roche/Genentech, AstraZeneca, Bristol-Myers Squibb, and Astellas Pharma, and received travel expenses reimbursement from Roche and Celgene. SD received honoraria from F. Hoffmann-La Roche Ltd, Pfizer, AstraZeneca, Puma, Lilly, and Novartis, and provided consultancy for F. Hoffmann-La Roche Ltd, Pfizer, Orion, AstraZeneca, Puma, Lilly, and Novartis, and received research funding from F. Hoffmann-La Roche Ltd, Novartis, Pfizer, Puma, Sanofi, AstraZeneca, Lilly and Amgen, and received travel expenses reimbursement from Pfizer, Novartis, Puma, and AstraZeneca. JM-F has nothing to disclose.

MV has stock/other ownership with F. Hoffmann-La Roche Ltd and Bayer, and received honoraria from F. Hoffmann-La Roche Ltd, Teva, Eisai, Pfizer, Novartis, and AstraZeneca, and provided consultancy for Novartis, Pfizer, F. Hoffmann-La Roche Ltd, and Amgen, and participated in a speaker's bureau for F. Hoffmann-La Roche Ltd, and received research funding from F. Hoffmann-La Roche Ltd, Pfizer, and Novartis, and received reimbursement for travel expenses from F. Hoffmann-La Roche Ltd, AstraZeneca, and Amgen. RC received honoraria from F. Hoffmann-La Roche Ltd, and reimbursement for travel expenses from F. Hoffmann-La Roche Ltd. CV provided consultancy/advice for Grünenthal, participated in a speaker's bureau for F. Hoffmann-La Roche Ltd, and received reimbursement for travel expenses from F. Hoffmann-La Roche Ltd and MSD. TLW received research funding from AbbVie, Genentech, Novartis, Mirati, and Tesaro. HD is an employee of Roche Products Ltd and has patents/royalties/other intellectual property in F. Hoffmann-La Roche Ltd. DB is an employee of Roche Products Ltd and has patents/royalties/other intellectual property in F. Hoffmann-La Roche Ltd. MW-L is an employee of Roche Products Ltd, and has stock/other ownership in Roche Products Ltd and has patents/royalties/other intellectual property in F. Hoffmann-La Roche Ltd. AK is an employee of F. Hoffmann-La Roche Ltd, and has stock/other ownership in F. Hoffmann-La Roche Ltd, and has stock/other ownership in F. Hoffmann-La Roche Ltd, and has patents/royalties/other intellectual property in F. Hoffmann-La Roche Ltd. JE-W is an employee of Genentech, Inc., and has stock/other ownership in F. Hoffmann-La Roche Ltd, and has patents/royalties/other

intellectual property in Genentech, Inc. CD received research funding from Puma, Genentech/Roche, and reimbursement for travel expenses from Genentech BioOncology.

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