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ORIGINAL RESEARCH

Cardiac safety of dual anti-HER2 blockade with pertuzumab plus trastuzumab in early HER2-positive breast cancer in the APHINITY trial☆

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Background: Trastuzumab increases the incidence of cardiac events (CEs) in patients with breast cancer (BC). Dual blockade with pertuzumab (P) and trastuzumab (T) improves BC outcomes and is the standard of care for high-risk human epidermal growth factor receptor 2 (HER2)-positive early BC patients. We analyzed the cardiac safety of P and T in the phase III APHINITY trial.

Patients and methods: Left ventricular ejection fraction (LVEF) $\geq$ 55% was required at study entry. LVEF assessment was carried out every 3 months during treatment, every 6 months up to month 36, and yearly up to 10 years. Primary CE was defined as heart failure class III/IV and a significant decrease in LVEF (defined as $\geq$10% from baseline and to $<$50%), or cardiac death. Secondary CE was defined as a confirmed significant decrease in LVEF, or CEs confirmed by the cardiac advisory board.

Results: The safety analysis population consisted of 4769 patients. With 74 months of median follow-up, CEs were observed in 159 patients (3.3%): 83 (3.5%) in P + T and 76 (3.2%) in T arms, respectively. Most CEs occurred during anti-HER2 therapy (123; 77.4%) and were asymptomatic or mildly symptomatic decreases in LVEF (133; 83.6%). There were two cardiac deaths in each arm (0.1%). Cardiac risk factors indicated were age $>$ 65 years, body mass index $\geq$ 25 kg/m^2, baseline LVEF between 55% and $<$60%, and use of an anthracycline-containing chemotherapy regimen. Acute recovery from a CE based on subsequent LVEF values was observed in 127/155 patients (81.9%).

Conclusions: Dual blockade with P + T does not increase the risk of CEs compared with T alone. The use of anthracycline-based chemotherapy increases the risk of a CE; hence, non-anthracycline chemotherapy may be considered, particularly in patients with cardiovascular risk factors.

Key words: adjuvant, breast cancer, cardiotoxicity, HER2-positive, pertuzumab, trastuzumab

INTRODUCTION

The human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) subtype represents ~15%-20% of all BC diagnoses, and anti-HER2 therapies are the current standard of care both in the early and advanced settings.[1,2] For patients with early-stage HER2-positive BC, the addition of trastuzumab to chemotherapy dramatically improved clinical outcomes, reducing the risks of both recurrence and death.[3] However, trastuzumab use is also associated with an increased incidence of cardiac events (CEs) compared to chemotherapy alone.[4,5]

Dual HER2 blockade with pertuzumab and trastuzumab has been shown to further improve clinical outcomes, compared to trastuzumab alone, in patients with early-stage HER2-positive BC.[6-8] APHINITY was a randomized, double-blind, phase III study comparing the addition of pertuzumab or placebo to adjuvant trastuzumab and

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chemotherapy in patients with HER2-positive early BC. At its primary analysis, with 4805 randomized patients and 45.4 months of median follow-up, the addition of pertuzumab to standard adjuvant therapy showed a statistically significant benefit for the primary endpoint of invasive disease-free survival (iDFS) compared to placebo [3-year iDFS rate of 94.1% versus 93.2%, respectively; hazard ratio (HR) 0.81, 95% confidence interval (CI) 0.66-1.00; *P* value = 0.045].[9] The benefit was more pronounced in patients at higher risk of relapse, namely those with node-positive disease (3-year iDFS 92.0% versus 90.2%, respectively; HR 0.77, 95% CI 0.62-0.96; *P* value = 0.02). After 74 months of median follow-up, patients with node-positive disease of any hormone receptor status (positive or negative), treated with pertuzumab, continued to derive clinical benefit.[6]

Based on these findings, as well as on data coming from neoadjuvant studies, dual HER2 blockade with pertuzumab and trastuzumab now represents the standard-of-care regimen for patients with high-risk, HER2-positive early BC.[7,8,10,11]

We report here the cardiac safety profile of treatment with pertuzumab and trastuzumab in the APHINITY trial, after a median follow-up of 74 months.[6]

PATIENTS AND METHODS

Study design and patients

Details on the APHINITY (BIG4-11; ClinicalTrials.gov identifier: NCT01358877) study design have been previously published.[9] Briefly, APHINITY was a randomized, double-blind, phase III, placebo-controlled, multicenter trial. Between November 2011 and August 2013, 4805 patients were recruited after providing informed consent, and randomized to the pertuzumab arm ($n = 2400$) or placebo arm ($n = 2405$). Eligible patients with an adequate excision of a histologically confirmed invasive HER2-positive BC (defined as per the American Society of Clinical Oncology-College of American Pathologists guidelines[12]) were randomly assigned to chemotherapy (anthracycline- or non-anthracycline-based regimens) plus either 1 year of trastuzumab plus pertuzumab, or trastuzumab and placebo. Eligibility criteria included a baseline left ventricular ejection fraction (LVEF) of $\geq$55%, by echocardiography or MUltiple Gated Acquisition (MUGA) scan, and absence of serious cardiac illness, such as history of documented heart failure (HF) or LVEF $<$ 50%, high-risk uncontrolled arrhythmias, angina pectoris requiring medication, clinically significant valvular disease, evidence of transmural infarction on electrocardiogram, or poorly controlled hypertension. Patients treated initially with anthracycline-based chemotherapy had an additional LVEF assessment before starting anti-HER2 therapy.

From the 4805 patients randomized into the APHINITY trial (intent-to-treat population), one patient was excluded due to falsification of personal data, and 35 patients were excluded from the safety analysis population as they received no study medication, leaving 4769 patients.

Definitions of all study endpoints and the consort diagram are available in the previous publications of the APHINITY study.[6,9]

Procedures

The full details of study procedures have previously been published.[9] Trastuzumab was administered intravenously with a loading dose of 8 mg/kg of body weight, and then at 6 mg/kg once every 3 weeks for 1 year (corresponding to 18 cycles). Pertuzumab was administered intravenously with a loading dose of 840 mg, and then 420 mg once every 3 weeks for 1 year. Investigators could choose between two types of chemotherapy regimen: either sequential anthracycline-taxane, or 3-weekly docetaxel plus carboplatin (i.e. a non-anthracycline regimen). In both regimens, anti-HER2 therapy was started concomitantly with the first taxane administration. Adjuvant radiotherapy was administered according to local guidelines. Patients with hormone receptor-positive disease received adjuvant endocrine therapy as per local guidelines.

Cardiac safety

Cardiac monitoring. Cardiac monitoring included LVEF assessment by echocardiography or MUGA scan, and was carried out every 3 months during treatment, every 6 months up to month 36 of follow-up, and every year thereafter up to 10 years. In case of decline in LVEF, an LVEF assessment was repeated after 3 weeks. All CEs were classified as primary or secondary event, and were reviewed by a cardiac advisory board.[7]

Cardiac endpoints. Patients who received at least one dose of study treatment were included in safety analyses. CEs were defined per protocol as follows: (i) primary CEs, if HF of New York Heart Association (NYHA) class III/IV with a significant LVEF decline (defined as $\geq$10 percentage points from baseline and to $<$50%), or cardiac death; (ii) secondary CEs, if asymptomatic or mildly symptomatic (NYHA class II) significant LVEF decline confirmed by a second LVEF assessment within 3 weeks, or as confirmed by the cardiac advisory board. Acute recovery from a CE was defined as at least two consecutive LVEF assessments $\geq$50% carried out after the date of the CE.

Statistical analysis of cardiac safety data. The present analysis took place on the database for the second interim analysis of overall survival (OS) (clinical cut-off date: 19 June 2019) with a median follow-up of 74 months.[6] We investigated the cardiac safety profile by safety analysis population (2364 patients in the pertuzumab arm; 2405 patients in the placebo arm).

Baseline demographics and cardiac-related patient characteristics were summarized by treatment group. The incidence of all CEs was investigated and descriptively summarized by treatment group (pertuzumab versus placebo) and by treatment phase (before starting anti-HER2 treatment, during anti-HER2 treatment, and during follow-up). Among patients who reached acute recovery, time to

acute recovery was calculated. LVEF measurements and change in LVEF from baseline were summarized graphically by treatment arm over time.

Risk factors for cardiac dysfunction (henceforth cardiac risk factors), including safety analysis population arm, baseline age, smoking history, body mass index (BMI), hypertension, diabetes mellitus, LVEF, use of cardioprotective medications, left-sided radiotherapy, and type of adjuvant chemotherapy regimen (anthracycline-containing or not) were investigated using univariate and multivariable analyses. With the exception of the safety analysis population arm, the cardiac risk factors were not expected to differ depending on whether a patient received pertuzumab or placebo. Therefore, they were studied in the safety analysis population by pooling together patients from both treatment arms. For each cardiac risk factor, odds ratios (ORs) with 95% profile-likelihood CIs were calculated.

The multivariable model considered four or five predictor variables. These are the characteristics: age (<65 years versus ≥65 years), BMI (<25 versus ≥25), LVEF (55% to <60% versus ≥60%), adjuvant chemotherapy (anthracycline-based regimen versus non-anthracycline-based regimen) plus the additional characteristic being considered when applicable [e.g. hypertension (no versus yes)]. The multivariable analysis excluded patients with (i) BMI unknown or (ii) LVEF not done or <55%.

RESULTS

Demographic and baseline cardiac-related characteristics

Demographic and baseline cardiac-related characteristics were well balanced between treatment arms (Table 1). Most patients were younger than 65 years (87.5%), had never smoked (70.9%), had a baseline LVEF ≥ 60% (86.3%), did not have hypertension (77.8%) or diabetes mellitus (94.3%), and were not exposed to left side radiotherapy (62.7%), although many patients had a BMI ≥ 25 kg/m^2 (46.8%) and most were prescribed an anthracycline-containing adjuvant chemotherapy regimen (78.1%). For patients receiving anthracyclines, the median cumulative dosage was the same in both arms (doxorubicin 240 mg/m^2 and epirubicin 300 mg/m^2).

Table 1. Demographics and baseline cardiac-related characteristics

Characteristics	Pertuzumab + trastuzumab, $N = 2364$, n (%)	Placebo + trastuzumab, $N = 2405$, n (%)
Age (years)		
<65	2062 (87.2)	2112 (87.8)
≥65	302 (12.8)	293 (12.2)
Mean (range)	51.6 (22.0-86.0)	51.4 (18.0-85.0)
Smoking history		
Ever smoked	666 (28.2)	723 (30.1)
Never smoked	1698 (71.8)	1682 (69.9)
Body mass index (kg/m^2)		
<25	1256 (53.1)	1266 (52.6)
≥25	1099 (46.5)	1131 (47.0)
Unknown	9 (0.4)	8 (0.3)
Mean (range)	25.6 (13.6-57.4)	25.9 (15.7-63.6)
LVEF		
55% to <60%	314 (13.3)	324 (13.5)
≥60%	2047 (86.6)	2070 (86.1)
Not done or <55%	3 (0.1)	11 (0.5)
Mean (range)	65.2 (51.0-90.0)	65.3 (50.0-92.0)
Method of evaluation of LVEF		
Echocardiogram	1907 (80.7)	1956 (81.3)
MUGA scan	456 (19.3)	445 (18.5)
Not done	1 (0.0)	4 (0.2)
Hypertension		
No	1837 (77.7)	1872 (77.8)
Yes	527 (22.3)	533 (22.2)
Diabetes mellitus		
No	2229 (94.3)	2268 (94.3)
Yes	135 (5.7)	137 (5.7)
Use of any cardioprotective medications (ACEI/ARB or beta-blocker)[a]		
No	2010 (85.0)	2046 (85.1)
Yes	354 (15.0)	359 (14.9)
Left-sided radiotherapy[b]		
No	1457 (61.6)	1534 (63.8)
Yes	907 (38.4)	871 (36.2)
Adjuvant chemotherapy regimen[c]		
Anthracycline-containing regimen	1831 (77.5)	1893 (78.7)
Non-anthracycline-containing regimen	533 (22.5)	512 (21.3)
Anthracycline cumulative dose (mg/m^2)		
Doxorubicin		
n	520	587
Median (range)	240 (50.0-270)	240 (40.0-300)
Epirubicin		
n	1318	1310
Median (range)	300 (100.0-696)	300 (69.8-450)

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; LVEF, left ventricular ejection fraction; MUGA, MUltiple Gated Acquisition.
[a]Medications starting on or after the date of first administration of study treatment are not considered.
[b]Patients with bilateral radiotherapy are counted as having left-sided radiotherapy.
[c]The chemotherapy regimen that was planned at the time of randomization is shown; the regimen that patients received may have differed.

Study treatment completion

Trastuzumab completion rate was 86.8% (2053/2364) in the pertuzumab arm and 86.4% (2079/2405) in the placebo arm. Similar rates were seen for pertuzumab/placebo completion in the pertuzumab and placebo arms, respectively (Table 2).

Incidence and timing of cardiac events

At a median follow-up of 74 months, 159 patients had a CE, with 83 (3.5%) CEs in the pertuzumab arm and 76 (3.2%) in the placebo arm (Table 3). Most CEs occurred during anti-HER2 therapy [62 (2.6%) in the pertuzumab arm and 61 (2.5%) in the placebo arm], with a median time to first CE of 9.2 months (95% CI 2.3-61.3 months) and 7.4 months (95% CI 0.4-53.7 months), respectively. There were 18 (0.8%) primary CEs of HF class III/IV or cardiac death in the pertuzumab arm and 8 (0.3%) in the placebo arm. Most CEs consisted of asymptomatic or mildly symptomatic (NYHA class II) LVEF reductions with 65 (2.7%) in the pertuzumab arm and 68 (2.8%) in the placebo arm. CEs were more common in patients with anthracycline-based regimens (3.7%) than non-anthracycline-based regimens (1.9%) in both arms (Figure 1 and Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100772).

Table 2. Summary of treatment completion and discontinuation reasons

Status	Pertuzumab + trastuzumab *N* = 2364 *n* (%)	Placebo + trastuzumab *N* = 2405 *n* (%)
Completed trastuzumab	2053 (86.8)	2079 (86.4)
Discontinued trastuzumab	311 (13.2)	326 (13.6)
Safety	175 (7.4)	164 (6.8)
Cardiac safety	78 (3.3)	85 (3.5)
Other safety	97 (4.1)	79 (3.3)
Recurrence of disease	12 (0.5)	34 (1.4)
Other	124 (5.2)	128 (5.3)
Completed pertuzumab/placebo	2051 (86.8)	2077 (86.4)
Discontinued pertuzumab/placebo	313 (13.2)	328 (13.6)
Safety	175 (7.4)	165 (6.9)
Cardiac safety	79 (3.3)	85 (3.5)
Other safety	96 (4.1)	80 (3.3)
Recurrence of disease	12 (0.5)	34 (1.4)
Other	126 (5.3)	129 (5.4)

Changes on mean LVEF over time

At baseline, mean LVEF was similar between arms (65.2% [standard deviation (SD) of 5.9] in the pertuzumab arm and 65.3% [SD of 6.1] in the placebo arm). Changes in LVEF over time were similar between arms, with a tendency for prompt recovery to baseline levels after week 52, when anti-HER2 therapy had been completed (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100772).

Cardiac risk factors

The cardiac risk factors indicated by the multivariable analysis were age $\geq$ 65 years (versus <65 years), BMI $\geq$ 25 kg/m^2 (versus <25 kg/m^2), LVEF at study entry of 55%-59% (versus $\geq$60%), and use of anthracycline-containing adjuvant chemotherapy regimen (versus non-anthracycline-containing) (Table 4).

Acute recovery from CEs

Considering any CE and excluding cardiac death, acute recovery was reached in 127 out of the 155 patients (81.9%) who experienced a CE. Rates of reaching acute recovery from any CE (excluding cardiac death) were 77.8% (63 of 81 patients) in the pertuzumab arm, and 86.5% (64 of 74 patients) in the placebo arm (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2022.100772). Thirteen out of 22 patients (59%) reached acute recovery from HF NYHA class III or IV, with a median time to reach acute recovery of 26.0 weeks (95% CI 3.1-173.7 weeks) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100772), and 114 out of 133 patients (86%) reached acute recovery from a secondary CE (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100772), with a median time to reach acute recovery of 23.4 weeks (95% CI 1.7-282.4 weeks) (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100772). Comparable acute recovery rates and time to reach acute recovery were seen between arms (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100772).

Table 3. Incidence and timing of cardiac events

CEs, type and timing (months)	All patients *N* = 4769 *n* (%)	Pertuzumab + trastuzumab *N* = 2364 *n* (%)	Placebo + trastuzumab *N* = 2405 *n* (%)
Any cardiac event	159 (3.3)	83 (3.5)	76 (3.2)
Did not start anti-HER2 therapy	4 (0.1)	0 (0.0)	4 (0.2)
During anti-HER2 therapy[a]	123 (2.6)	62 (2.6)	61 (2.5)
During follow-up phase	32 (0.7)	21 (0.9)	11 (0.5)
Time to first CE—median (range)[b]	8.4 (0.4-61.3)	9.2 (2.3-61.3)	7.4 (0.4-53.7)
Cardiac deaths	4 (0.1)	2 (0.1)	2 (0.1)
Did not start anti-HER2 therapy	0 (0.0)	0 (0.0)	0 (0.0)
During anti-HER2 therapy[a]	0 (0.0)	0 (0.0)	0 (0.0)
During follow-up phase	4 (0.1)	2 (0.1)	2 (0.1)
Time to cardiac death—median (range)[b]	30.2 (14.9-53.7)	29.4 (14.9-43.9)	35.1 (16.4-53.7)
HF class III or IV	22 (0.5)	16 (0.7)	6 (0.2)
Did not start anti-HER2 therapy	1 (0.0)	0 (0.0)	1 (0.0)
During anti-HER2 therapy[a]	14 (0.3)	10 (0.4)	4 (0.2)
During follow-up phase	7 (0.1)	6 (0.3)	1 (0.0)
Time to HF class III or IV—median (range)[b]	7.7 (0.4-61.3)	8.5 (4.8-61.3)	4.6 (0.4-15.8)
Asymptomatic or mildly symptomatic LVEF drop	133 (2.8)	65 (2.7)	68 (2.8)
Did not start anti-HER2 therapy	3 (0.1)	0 (0.0)	3 (0.1)
During anti-HER2 therapy[a]	109 (2.3)	52 (2.2)	57 (2.4)
During follow-up phase	21 (0.4)	13 (0.5)	8 (0.3)
Time to asymptomatic or mildly symptomatic LVEF drop—median (range)[b]	8.4 (1.9-49.9)	9.2 (2.3-49.9)	7.5 (1.9-38.2)

Note: Primary (HF class III and IV) and secondary cardiac events (asymptomatic or mildly symptomatic LVEF drop) were mutually exclusive, i.e. a patient with a primary cardiac event could not be counted as having a secondary cardiac event.
CE, cardiac event; HER2, human epidermal growth factor receptor 2; HF, heart failure; LVEF, left ventricular ejection fraction.
[a]'During anti-HER2 treatment' includes up to 28 days after last administration of anti-HER2 therapy.
[b]Median based on patients who experienced the particular type of cardiac event.

DISCUSSION

This exploratory analysis of the cardiac safety of pertuzumab and trastuzumab in the APHINITY trial found that, after 74 months of median follow-up, dual blockade with

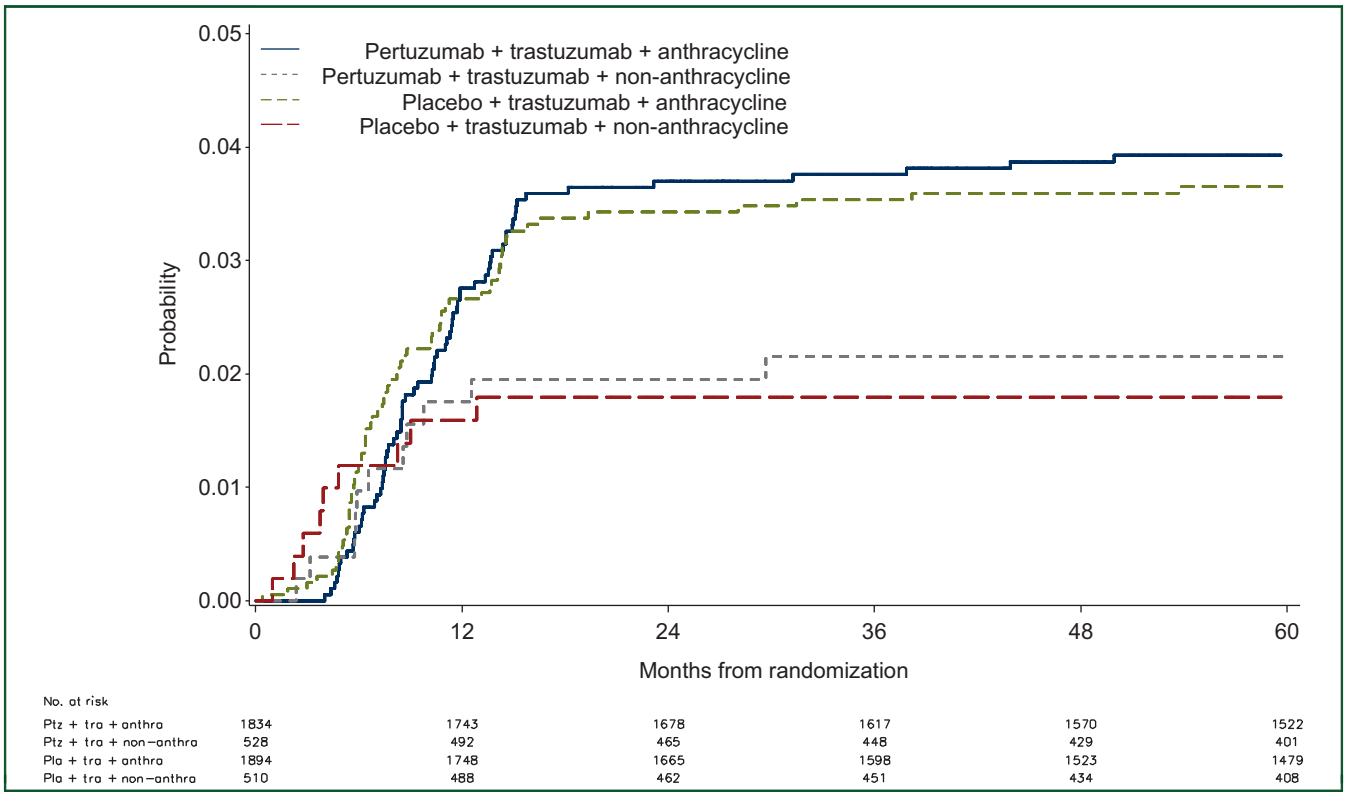

Figure 1. Cumulative incidence plot of any cardiac event with invasive disease-free survival event as a competing risk. Anthra, anthracycline; HF, heart failure; LVEF, left ventricular ejection fraction; Ptz, pertumuzab; Tra, trastuzumab. Timing of anti-HER2 therapy relative to randomization was different to the anthracycline cohort compared to the non- anthracycline cohort. Primary (HF class III and IV) and secondary cardiac events (asymptomatic or mildly symptomatic LVEF drop) are mutually exclusive. A patient with a primary cardiac event will not be counted as having a secondary cardiac event.

pertuzumab and trastuzumab does not increase the risk of CEs compared to placebo and trastuzumab. Treatment with pertuzumab and trastuzumab was associated with a low incidence of CEs (3.5%), with most occurring during anti-HER2 therapy (77.4%), and consisting of secondary CEs (83.6%), which were asymptomatic or mildly symptomatic (NYHA class II) significant decline in LVEF. In the setting of a large, randomized clinical trial with rigorous cardiac monitoring and specific algorithms for HER2-targeting drug management, these results confirm the cardiac safety of dual anti-HER2 blockade with pertuzumab and trastuzumab.

The results of our exploratory analysis are consistent with previous findings from the NeoSphere,[7] Tryphaena,[13] Berenice,[14] and Cleopatra[15] trials, showing cardiac safety of dual HER2 blockade with pertuzumab and trastuzumab. On the contrary, our results are not consistent with those from a recent meta-analysis of pertuzumab cardiotoxicity including 8420 patients with HER2-positive cancer from eight published randomized clinical trials.[16] Alhussein et al. reported an excess risk of HF (risk ratio 1.97) with the addition of pertuzumab to trastuzumab-based therapy, but no effect on asymptomatic/minimally symptomatic left ventricular systolic dysfunction.[16] It should be noticed, however, that the aforementioned meta-analysis also included one study other than BC (i.e. gastro-esophageal cancer) and patients with disease stage I-IV, and that the duration of pertuzumab varied across the studies.

Cardiac risk assessment and cardiac imaging before and during anti-HER2 treatment remain essential. In APHINITY, cardiac monitoring by echocardiography or MUGA scan was carried out every 3 months during treatment, every 6 months up to month 36 of follow-up, and every year thereafter up to year 10. This schedule is consistent with the observed timing of first CE occurrence (median time of 9.2 and 7.4 months in the pertuzumab and placebo arms, respectively) and with the less common occurrence of CEs during the follow-up period [21 (0.9%) and 11 (0.5%) in the pertuzumab and placebo arms, respectively].

Cardiac risk assessment and cardiac monitoring is recommended for all patients before and during treatment. In our exploratory analysis, besides the use of anthracyclines, age $\geq$ 65 years old, BMI $\geq$ 25, and LVEF at study entry of 55% to $<$60% were risk factors for CEs. These results are consistent with the known risk factors of cardiotoxicity associated with trastuzumab and other HER2-targeted therapies, with anthracycline use being an important risk factor.[17,18]

Notably, in our analysis, with a relatively young patient population with few cardiovascular risk factors, CEs were more common in patients with anthracycline-based regimens (3.7%) than non-anthracycline-based regimens (1.9%) in both arms. This suggests that a non-anthracycline regimen should be preferentially considered in patients with cardiovascular risks factors. The use of non-anthracycline chemotherapy has been proven to have similar efficacy with a lower risk of

Table 4. Cardiac risk factors indicated by multivariable analysis of baseline characteristics

Baseline characteristic	*N*	Cardiac event *n* (%)	Univariate OR (95% CI)[a]	Univariate *P* value[a]	Multivariable OR (95% CI)[b]	Multivariable *P* value[b]
Safety analysis population arm						
Pertuzumab	2364	83 (3.5)	1.12 (0.81-1.53)	0.500	1.14 (0.83-1.57)	0.423
Placebo	2405	76 (3.2)	Reference		Reference	
Age (years)						
<65	4174	118 (2.8)	Reference		Reference	
≥65	595	41 (6.9)	2.54 (1.75-3.64)	<0.001	2.48 (1.68-3.57)	<0.001
Smoking history						
Ever smoked	1389	47 (3.4)	1.02 (0.72-1.44)	0.902	1.03 (0.72-1.46)	0.862
Never smoked	3380	112 (3.3)	Reference		Reference	
BMI (kg/m^2)						
<25	2522	62 (2.5)	Reference		Reference	
≥25	2230	97 (4.3)	1.80 (1.31-2.51)	<0.001	1.66 (1.19-2.32)	0.003
LVEF						
55% to <60%	638	42 (6.6)	2.43 (1.67-3.47)	<0.001	2.44 (1.68-3.50)	<0.001
≥60%	4117	116 (2.8)	Reference		Reference	
Hypertension						
No	3709	106 (2.9)	Reference		Reference	
Yes	1060	53 (5.0)	1.79 (1.27-2.49)	<0.001	1.34 (0.92-1.94)	0.125
Diabetes mellitus						
No	4497	142 (3.2)	Reference		Reference	
Yes	272	17 (6.3)	2.05 (1.18-3.34)	0.007	1.54 (0.87-2.59)	0.116
Cardioprotective medications						
No	4056	127 (3.1)	Reference		Reference	
Yes	713	32 (4.5)	1.45 (0.96-2.13)	0.064	1.07 (0.69-1.60)	0.768
Left-sided radiotherapy						
No	2991	92 (3.1)	Reference		Reference	
Yes	1778	67 (3.8)	1.23 (0.89-1.70)	0.198	1.17 (0.85-1.62)	0.331
Adjuvant chemotherapy regimen						
Anthracycline-containing regimen	3724	139 (3.7)	1.99 (1.27-3.29)	0.005	2.25 (1.43-3.74)	<0.001
Non-anthracycline-containing regimen	1045	20 (1.9)	Reference		Reference	

BMI, body mass index; CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio.
[a]The univariate analysis of BMI excludes patients with BMI unknown. The univariate analysis of LVEF excludes patients with LVEF not done or <55%. Profile-likelihood confidence limits for the OR.
[b]The multivariable analysis considers four or five predictor variables. These are the characteristics: (i) age; (ii) BMI; (iii) LVEF; (iv) adjuvant chemotherapy regimen; plus (v) the additional characteristic being considered when applicable [e.g. hypertension (no versus yes)]. Profile-likelihood confidence limits for the OR.

cardiotoxicity, and its use is now recommended as the preferred option in the National Comprehensive Cancer Network guidelines.[8,19,20]

The present study has several strengths, namely the large population, the long follow-up, and the rigorous cardiac monitoring in the context of a randomized clinical trial conducted internationally. Of note, cardiac safety data in APHINITY will again be assessed in the event-driven final OS analysis (10-year follow-up). There are several limitations that should be considered when interpreting these results from an exploratory analysis. First, the population included in clinical trials is generally highly selected, younger, and healthier than real-world patients. Hence, it would be important to assess the cardiotoxicity of this treatment combination in real-world patients, who may experience more CEs due to the coexistence of additional comorbidities and/or cardiovascular risk factors/cardiac disease. Additionally, the rigorous cardiac monitoring carried out in the context of a clinical trial might not always represent the cardiac imaging patients receive in real-world settings. Furthermore, cardiac safety was assessed by ECHO or MUGA scan, and did not include the assessment of global longitudinal strain (GLS) or cardiac biomarkers (e.g. high-sensitivity cardiac troponin or brain natriuretic peptide) during anti-HER2 treatment. Although the impact of measuring GLS and cardiac biomarkers on anti-HER2 treatment management is not well defined, these measurements may be useful in early detection of cardiotoxicity, particularly in high-risk populations.[21-23] There are mixed results on the role of neurohormonal agents, such as angiotensin receptor blockers and angiotensin-converting enzyme inhibitors during cancer therapy (anthracyclines/HER2 targeted), to reduce CEs,[24-26] and a meta-analysis of neurohormonal strategies showed a modest benefit of these agents (<5%) with substantial heterogeneity and publication bias.[27] We await the results of ongoing randomized controlled trials to further define the role of these agents in primary prevention strategies.

Conclusions

Our analysis has shown that dual blockade with pertuzumab and trastuzumab did not increase the risk of CEs compared to placebo and trastuzumab in patients with HER2-positive early BC. Our results were seen in a relatively young and healthy BC population and may not reflect the incidence of CEs with dual HER2 blockade in older patients with cardiac risk factors or disease. In particular, due to the higher incidence of CEs in

patients receiving anthracyclines, non-anthracycline regimens should be preferentially considered, particularly in patients with cardiovascular risk factors. Of note, anthracyclines are no longer considered as one of the preferred chemotherapy regimens for patients with HER2-positive BC, based on recent international guidelines, where they are reported only as 'useful in certain circumstances'.[20] Cardiac assessment before and during anti-HER2 treatment remains essential, particularly in high-risk patients.

In conclusion, the results of our study highlight the long-term cardiac safety of dual HER2-targeted therapy in this patient population. Cardiac safety will remain an important component of patient care and research, especially as novel HER2-directed therapies emerge.

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DATA SHARING

Qualified researchers may request access to individual patient-level data through the clinical study data request platform at https://vivli.org/ 18 months after the publication of the last clinical study report (CSR). Before this date, qualified researchers may request access to individual patient-level data by submitting, within a call for proposals, a research proposal to BIG. Further details on Roche's criteria for eligible studies are available here: https://vivli.org/members/ourmembers/. For further details on Roche's Global Policy on the Sharing of Clinical Information

and how to request access to related clinical study documents, see here: https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

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