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Article

Impact of Age on Clinical Outcomes and Efficacy of Adjuvant Dual Anti-HER2 Targeted Therapy

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Abstract

Background: Young age at breast cancer (BC) diagnosis has historically been a rationale for overtreatment. Limited data with short follow-up exist on the prognostic value of age at diagnosis in HER2-positive BC and the benefit of anti-HER2 therapy in young patients. **Methods:** APHINITY (NCT01358877) is an international, placebo-controlled, double-blind randomized phase III trial in HER2-positive early BC patients investigating the addition of pertuzumab to adjuvant chemotherapy plus trastuzumab. The prognostic and predictive value of age on invasive disease-free survival (IDFS) as continuous and dichotomous variable (aged 40 years or younger and older than 40 years) was assessed. A subpopulation treatment effect pattern plot analysis was conducted to illustrate possible treatment-effect heterogeneity based on age as a continuous factor. **Results:** Of 4804 included patients, 768 (16.0%) were aged 40 years or younger at enrollment. Median follow-up was 74 (interquartile range = 62-75) months. Young age was not prognostic either as dichotomous (hazard ratio [HR] = 1.06, 95% confidence interval [CI] = 0.84 to 1.33) or continuous (HR = 1.00, 95% CI = 1.00 to 1.01) variable. Lack of prognostic effect of age was observed irrespective of hormone receptor status and treatment arm. No statistically significant interaction was observed between age and pertuzumab effect ($P_{interaction} = 0.61$). Adding pertuzumab improved IDFS for patients in the young (HR = 0.86, 95% CI = 0.56 to 1.32) and older (HR = 0.75, 95% CI = 0.62 to 0.92) cohorts. Similar results were observed irrespective of hormone receptor status. Subpopulation treatment effect pattern plot analysis confirmed the benefit of pertuzumab in 6-year IDFS across age subpopulations. **Conclusions:** In patients with HER2-positive early BC treated with modern anticancer therapies, young age did not demonstrate either prognostic or predictive value, irrespective of hormone receptor status.

ARTICLE

Breast cancer is the most frequent malignancy among young women (1), defined according to international guidelines as age at diagnosis of 40 years or younger (2). Young women are more likely to die of breast cancer than older women, in part because

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of higher risk to develop biologically aggressive breast cancer phenotypes including the HER2-positive subtype (3).

Several prior studies have demonstrated that young age is an independent poor prognostic factor (3). More recently, it has been shown that the effect of age on patients' outcomes may vary by breast cancer subtype, with a poor prognostic impact pertaining specifically to hormone receptor–positive disease (4-9). However, in these studies, HER2 status was either not available or assessed only in a minority of patients, and modern anti-HER2 therapy was not routinely administered. Therefore, the numbers were too small to specifically evaluate the prognostic effect of age in patients with HER2-positive disease and if this can vary according to the co-expression of hormone receptors. Further, although current guidelines state that the use of anti-HER2 therapies should be the same regardless of age (2), little evidence exists on their benefit in the specific cohort of young women (10).

The largest prior analysis investigating the prognostic and predictive value of age in HER2-positive disease was conducted in the Herceptin Adjuvant (HERA) trial including 722 patients aged 40 years or younger at enrollment who received chemotherapy with or without trastuzumab (11). At 2-year median follow-up, young age was not associated with worse survival outcomes regardless of trastuzumab administration, nor age was predictive of benefit from anti-HER2 therapy (11). Nevertheless, follow-up was short, and no information was reported about a possible different effect of age according to the co-expression of hormone receptors.

Considering that treating young women with breast cancer is particularly complex with the risk of overtreatment based solely on age considerations, further research efforts to better investigate the prognostic and predictive value of age are urgently needed (2). In the era of personalized medicine, the impact of age on outcomes and treatment effect should be controlled for biological features such as tumor subtype including, within the HER2-positive disease, the co-expression of hormone receptors.

The large phase III Adjuvant Perjeta and Herceptin IN Initial TherapY in Breast Cancer (APHINITY) trial led to the approval of adjuvant dual anti-HER2 blockade with trastuzumab and pertuzumab in patients with HER2-positive breast cancer at high risk of recurrence (12,13). At a median follow-up of 74 months, the benefit of adding pertuzumab to trastuzumab was restricted to the cohort of patients with node-positive disease (13). With 4805 randomly assigned patients, more than 6 years of median follow-up and central assessment of HER2 and hormone receptor status, APHINITY represented a unique opportunity to conduct the present analysis aiming to investigate the prognostic and predictive value of age in patients with HER2-positive disease treated with modern adjuvant chemotherapy and concurrent anti-HER2 targeted treatment.

Methods

Study Design and Patients

Details of the APHINITY trial design were previously reported (12,13). Briefly, APHINITY (Breast International Group 4-11; ClinicalTrials.gov identifier: NCT01358877) is an international, placebo-controlled, double-blind randomized phase III trial in patients with HER2-positive early breast cancer investigating the benefit of adding pertuzumab to adjuvant chemotherapy with trastuzumab.

In the present analysis, the whole population of randomly assigned patients was divided into 2 cohorts according to age at the time of breast cancer diagnosis, with 40 years used as cut-off. Young patients were those aged 40 years or younger at the time of enrollment (young cohort) and were compared with those older than 40 years (older cohort).

Study Procedures

Eligible patients were randomly assigned in a 1:1 ratio via a web-based system to receive chemotherapy and either 1 year of trastuzumab and placebo or 1 year of trastuzumab and pertuzumab. Using a permuted-blocks randomization procedure, randomly assigned patients were stratified according to geographical region, nodal status, adjuvant chemotherapy regimen, hormone receptor status, and protocol version.

Two chemotherapy regimens were allowed: sequential anthracycline- and taxane-based treatment for 6 or 8 cycles or an anthracycline-free regimen with 3 weekly docetaxel and carboplatin for 6 cycles. Anti-HER2 therapy was administered for 1 year starting at the first cycle of taxane-based chemotherapy. No other anti-HER2 agents were allowed.

HER2 positivity was defined centrally as an immunohistochemical score of 3 or higher in more than 10% of cells or amplification of the HER2 gene by in situ hybridization (14). Hormone receptor status was determined locally and then repeated by a central laboratory. Patients with hormone receptor–positive tumors received at least 5 years of adjuvant endocrine therapy as per local guidelines following chemotherapy completion.

The APHINITY trial was approved by the ethics committees and independent review boards of all participating centers and authorities. Before study entry, all patients provided a written informed consent. The present analysis was approved by the APHINITY steering committee.

Study Objectives and Endpoints

APHINITY aimed at assessing the benefit of adding pertuzumab to adjuvant chemotherapy with trastuzumab. Invasive disease-free survival (IDFS) was the primary endpoint.

The purpose of the present analysis was to investigate the prognostic and predictive value of young age on the IDFS endpoint. Clinical outcomes and pertuzumab benefit were assessed in all patients and then according to centrally assessed hormone receptor status by comparing the young and older cohorts.

Baseline patient and tumor characteristics as well as patterns of disease relapse according to age were described.

Statistical Analysis

Sample size calculation and statistical assumptions on the APHINITY primary objective were previously reported (12). The present analysis focusing on prognostic and predictive value of young age was not preplanned in the study protocol, and the power of the performed statistical analyses was not prespecified. The APHINITY database with a clinical cutoff date of June 19, 2019, was used for all time-to-event analyses (13).

As reported in the primary analysis (12), IDFS was defined as invasive ipsilateral or locoregional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, and death from any cause. Second primary nonbreast cancer malignancies were excluded from IDFS definition.

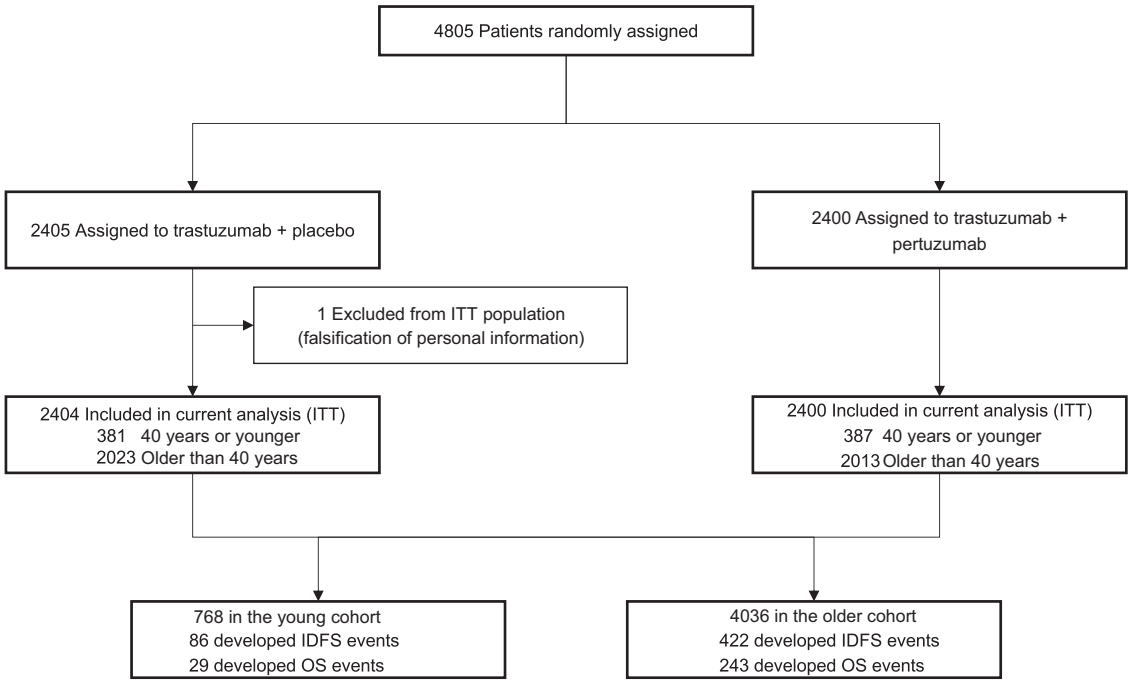

Figure 1. CONSORT flow diagram of participants. IDFS = invasive disease-free survival; ITT = intention-to-treat; OS = overall survival.

Categorical and continuous variables were summarized with proportions (and differences tested using χ^2 test) or medians and interquartile range (IQR) (and differences tested using Wilcoxon rank-sum test), respectively. All statistical analyses were implemented in SAS v 9.4. All statistical tests were 2-sided, and statistical significance was set at 0.05 or less.

Univariate Cox proportional hazard models were used to assess the prognostic and predictive value of age on IDFS as a continuous and dichotomous variable (age 40 years or younger and older than 40 years). Multivariable Cox models were produced and included all stratification factors (geographical region, nodal status, adjuvant chemotherapy regimen, hormone receptor status, and protocol version), body mass index (underweight or normal vs overweight or obese), and surgery type (breast conserving vs mastectomy). Models were created for all patients (irrespective of treatment arm) and then separately for centrally assessed hormone receptor status (positive vs negative) and treatment arm (trastuzumab alone vs trastuzumab and pertuzumab).

Cox models including all patients from both treatment arms were used to assess the predictive value of age on the benefit of adding pertuzumab to adjuvant trastuzumab (interaction between age and treatment effect). The same analysis was conducted to investigate a potential interaction between age and treatment effect in the subgroup of patients with hormone receptor–positive and hormone receptor–negative disease. A subpopulation treatment effect pattern plot (STEPP) analysis according to age with IDFS as outcome by treatment group was conducted to illustrate possible treatment-effect heterogeneity based on age as a continuous factor.

Results

Between November 2011 and August 2013, 4805 patients were randomly assigned in APHINITY and 4804 included in the intention-to-treat population of whom 768 (16.0%) were aged 40 years or younger at the time of enrollment (Figure 1).

Baseline patient and tumor characteristics are reported in Table 1. Median age was 36 years in the young cohort and 54 years in the older cohort. Patients in the young cohort were less often overweight or obese (29.3% vs 50.4%; $P < .001$), underwent mastectomy more frequently (63.2% vs 52.6%; $P < .001$), and had higher rates of node-positive (66.4% vs 61.8%; $P = .02$) and hormone receptor–positive (71.7% vs 64.9%; $P < .001$) disease as compared with those in the older cohort. More patients in the young cohort received adjuvant endocrine therapy (90.4% vs 82.8%; $P < .001$) with a difference in the type of treatment received ($P < .001$). Among the 498 patients with hormone receptor–positive disease receiving adjuvant endocrine therapy in the young cohort, 132 (26.5%) underwent ovarian function suppression as part of their treatment, whereas 324 (65.1%) received tamoxifen alone and 22 (4.4%) aromatase inhibitor-based therapy. A similar distribution of baseline patients' and tumor characteristics was observed between the young and older cohorts according to treatment arm (Supplementary Table 1, available online).

At a median follow-up of 74 (IQR = 62-75) months, 86 (11.2%) and 422 (10.5%) patients developed an IDFS event in the young and older cohorts, respectively (Supplementary Table 2, available online). A different distribution in the type of first IDFS events was observed ($P < .001$) with a higher incidence of locoregional recurrences (27.9% vs 12.6%) and a lower number of deaths (2.3% vs 18.0%) in the young cohort as compared with the older cohort. No statistically significant difference was observed in type of metastatic presentation (visceral vs nonvisceral) or specific metastatic site between the 2 cohorts.

The annualized hazard rate for IDFS according to age is reported in Figure 2, A. Six-year IDFS was 88% and 89% in the young and older cohorts, respectively. At the univariate and multivariable Cox proportional hazard models, age was not

Table 1. Patient and tumor characteristics by age group

Characteristics	Young cohort, ≤40 years, No. (%) n = 768	Older cohort, >40 years, No. (%) n = 4036	*P*
Median age (IQR)	36 (33-39)	54 (48-61)	<.001
Region			
Asia Pacific	181 (23.6)	926 (22.9)	.32
Canada/Europe/Australia–New Zealand/South Africa	389 (50.7)	2194 (54.4)	
Eastern Europe	74 (9.6)	326 (8.1)	
Latin America	21 (2.7)	103 (2.6)	
United States	103 (13.4)	487 (12.1)	
BMI			
Overweight or obese	224 (29.3)	2028 (50.4)	<.001
Underweight or normal	540 (70.7)	1995 (49.6)	
Missing	4	13	
Type of surgery			
Breast-conserving surgery	282 (36.8)	1912 (47.4)	<.001
Mastectomy	485 (63.2)	2122 (52.6)	
Missing	1	2	
Histology[a]			
Ductal	709 (92.3)	3623 (89.8)	.11
Lobular	16 (2.1)	108 (2.7)	
Mixed	17 (2.2)	92 (2.3)	
Other	26 (3.4)	213 (5.3)	
Tumor size			
0 to <2 cm	297 (38.7)	1624 (40.3)	.22
≥2 to <5 cm	408 (53.2)	2148 (53.3)	
≥5 cm	62 (8.1)	259 (6.4)	
Missing	1	5	
Nodal status			
Negative	258 (33.6)	1541 (38.2)	.02
Positive	510 (66.4)	2495 (61.8)	
1-3 positive nodes	289 (37.6)	1518 (37.6)	
≥4 positive nodes	221 (28.8)	977 (24.2)	
Tumor grade			
Grade 1	15 (2)	80 (2)	.85
Grade 2	234 (30.5)	1295 (32.1)	
Grade 3	489 (63.7)	2508 (62.1)	
Unevaluable or missing	30 (3.9)	153 (3.8)	
Central hormone receptor status			
Negative (ER and PgR negative)	217 (28.3)	1415 (35.1)	<.001
Positive (ER and/or PgR positive)	551 (71.7)	2621 (64.9)	
Protocol version			
Protocol A	571 (74.3)	3084 (76.4)	.22
Protocol amendment B (node-positive only)	197 (25.7)	952 (23.6)	
Type of chemotherapy			
Anthracycline containing regimen	619 (80.6)	3125 (77.4)	.05
Nonanthracycline containing regimen	149 (19.4)	911 (22.6)	
Type of anti-HER2 treatment			
Trastuzumab with pertuzumab	387 (50.4)	2013 (49.9)	.79
Trastuzumab with placebo	381 (49.6)	2023 (50.1)	
Adjuvant endocrine therapy[b]			
Overall	551	2621	<.001
No	53 (9.6)	452 (17.2)	
Yes	498 (90.4)	2169 (82.8)	
Type of adjuvant endocrine therapy[c]			
Overall	498	2169	<.001
Ovarian suppression with AI, AI alone, ovarian suppression alone	13 (2.6)	885 (40.8)	
SERM alone	324 (65.1)	976 (45)	
SERM → AI or AI → SERM	9 (1.8)	168 (7.7)	
Ovarian suppression with SERM	119 (23.9)	60 (2.8)	
Other	33 (6.6)	80 (3.7)	

[a]Some patients have more than 1 tumor; hierarchy used for histology, largest tumor size presented along with highest grade. AI = aromatase inhibitors; BMI = body mass index; ER = estrogen receptor; IQR = interquartile range; PgR = progesterone receptor; SERM = selective estrogen receptor modulator.
[b]Calculated on the total number of patients with central hormone receptor–positive breast cancer.
[c]Calculated on the total number of patients with central hormone receptor–positive breast cancer that received adjuvant endocrine therapy.

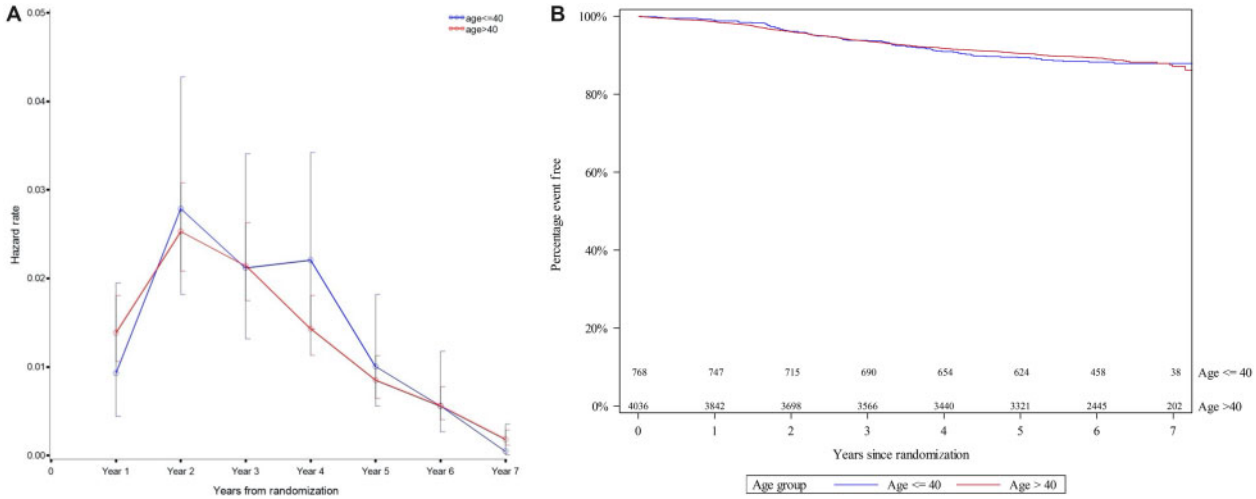

Figure 2. Prognostic effect of age: (**A**) annualized hazard rate for invasive disease-free survival; (**B**) overall cohort.

prognostic either as a dichotomous (vs older cohort: unadjusted hazard ratio [HR] = 1.06, 95% confidence interval [CI] = 0.84 to 1.33; adjusted HR = 1.07, 95% CI = 0.84 to 1.35; Figure 2, B) or as a continuous (unadjusted HR = 1.00, 95% CI = 1.00 to 1.01) variable (Table 2).

The lack of prognostic effect of age was observed irrespective of hormone receptor status and administered anti-HER2 treatment (Supplementary Table 3, available online). There was no statistically significant difference in IDFS between the young and older cohorts for both patients with hormone receptor–positive (vs older cohort: 6-year IDFS 88% vs 90%; unadjusted HR = 1.17, 95% CI = 0.88 to 1.53; adjusted HR = 1.10, 95% CI = 0.82 to 1.44; Figure 3, A) or negative (vs older cohort: 6-year IDFS 89% vs 88%; unadjusted HR = 0.89, 95% CI = 0.56 to 1.35; adjusted HR = 0.99, 95% CI = 0.62 to 1.51; Figure 3, B) disease and for those who received trastuzumab with pertuzumab (vs older cohort: 6-year IDFS 89% vs 91%; unadjusted HR = 1.15, 95% CI = 0.81 to 1.60; adjusted HR = 1.20, 95% CI = 0.83 to 1.68; Figure 3, C) or placebo (vs older cohort: 6-year IDFS 87% vs 88%; unadjusted HR = 1.00, 95% CI = 0.72 to 1.35; adjusted HR = 0.99, 95% CI = 0.71 to 1.35; Figure 3, D).

No statistically significant interaction was observed between age and treatment effect ($P_{interaction} = 0.61$; Supplementary Table 4, available online). Addition of pertuzumab improved IDFS for patients in the young (6-year IDFS 89% vs 87%; unadjusted HR = 0.87, 95% CI = 0.57 to 1.33; adjusted HR = 0.86, 95% CI = 0.56 to 1.32; Figure 4, A) and older (6-year IDFS 91% vs 88%; unadjusted HR = 0.75, 95% CI = 0.62 to 0.91; adjusted HR = 0.76, 95% CI = 0.62 to 0.92; Figure 4, B) cohorts. By analyzing the potential predictive value of age according to hormone receptor status, similar results were observed; there was only an apparent trend for a smaller benefit of pertuzumab in patients with hormone receptor–negative disease, particularly in the young cohort (Supplementary Figures 1 and 2 and Table 5, available online).

The STEPP analysis shows the 6-year IDFS percents for subpopulations defined by age separately for the 2 treatment arms (Figure 4, C). No statistically significant interaction was observed confirming that the benefit of pertuzumab was present across age subpopulations. An additional STEPP analysis conducted separately by hormone receptor status showed similar results (Supplementary Figure 3, available online).

Discussion

This analysis of the APHINITY trial allowed an in-depth characterization of the potential prognostic and predictive value of young age in patients with HER2-positive early breast cancer treated with modern anticancer therapies. Age did not have prognostic value in this setting, irrespective of hormone receptor status and administered anti-HER2 treatment. No predictive value of age for benefit of pertuzumab was observed with only a trend for a smaller benefit in patients with hormone receptor–negative disease, particularly in the young cohort. These results are highly relevant to improve the care of young women with breast cancer highlighting that, in the current era of precision medicine, age per se is not a reason to prescribe more aggressive therapies or to expect a different treatment benefit.

Results of this analysis support prior findings from the HERA trial showing lack of prognostic or predictive value of young age in patients with HER2-positive early breast cancer treated with chemotherapy alone or with sequential trastuzumab (11). Differently from the HERA trial, all patients included in the APHINITY study received modern chemotherapy regimens with trastuzumab (with or without pertuzumab), and the anti-HER2 therapy was given concomitantly with taxane-based treatment as per current practice. Moreover, the larger sample size and longer follow-up of the present analysis allows for the first time to add important prognostic and predictive information for young patients with HER2-positive breast cancer according to the hormone receptor status of the disease.

Young patients with newly diagnosed breast cancer are known to be at higher risk of aggressive breast cancer subtypes, but the majority of them develop hormone receptor–positive tumors (3). Within the HER2-positive subtype, which is also more commonly diagnosed in young women (15), the presence or absence of hormone receptors defines two distinct forms of breast cancer characterized by substantial differences in clinical behavior and outcomes (16-19). Limited evidence exists on the impact of age on the distribution of hormone receptor–positive or negative disease within the HER2-positive subtype. In the HERA trial, young women with HER2-positive breast cancer were more likely to be diagnosed with hormone receptor–positive disease as compared with older patients, but no information on type of administered adjuvant endocrine therapy was

Table 2. Univariate and multivariable analysis for IDFS events (multivariable model adjusted for region, nodal status, hormone receptor status, adjuvant chemotherapy, protocol version, BMI, and type of surgery)

Characteristics	Total, No.	Event, No. (%)	Univariate HR (95% CI)	Multivariable HR (95% CI)
Age	4804	508 (10.6)	1.00 (1.00 to 1.01)	—
Young cohort, ≤40 y	768	86 (11.2)	1.06 (0.84 to 1.33)	1.07 (0.84 to 1.35)
Older cohort, >40 y	4036	422 (10.5)	1.00	1.00
BMI				
Underweight or normal	2535	242 (9.5)	1.00	1.00
Overweight or obese	2252	264 (11.7)	1.28 (1.07 to 1.52)	1.32 (1.10 to 1.59)
Region				
Asia Pacific	1107	121 (10.9)	1.10 (0.88 to 1.36)	0.99 (0.78 to 1.24)
Eastern Europe	400	58 (14.5)	1.51 (1.12 to 1.99)	1.26 (0.94 to 1.67)
Latin America	124	19 (15.3)	1.57 (0.95 to 2.42)	1.32 (0.80 to 2.07)
United States	590	47 (8)	0.84 (0.61 to 1.14)	0.73 (0.51 to 1.01)
Canada/Western Europe/ Australia–New Zealand/South Africa	2583	263 (10.2)	1.00	1.00
Type of surgery				
Breast-conserving surgery	2194	172 (7.8)	1.00	1.00
Mastectomy	2607	336 (12.9)	1.74 (1.45 to 2.09)	1.44 (1.19 to 1.76)
Histology[a]				
Ductal	4332	440 (10.2)	1.00	—
Lobular	124	20 (16.1)	1.65 (1.02 to 2.51)	—
Mixed	109	14 (12.8)	1.27 (0.71 to 2.07)	—
Others	239	34 (14.2)	1.44 (1.00 to 2.01)	—
Tumor size				
0 to <2 cm	1921	153 (8)	1.00	—
≥2 to <5 cm	2556	286 (11.2)	1.46 (1.20 to 1.78)	—
≥5 cm	321	69 (21.5)	2.99 (2.23 to 3.95)	—
Nodal status				
Negative	1799	96 (5.3)	1.00	1.00
Positive	3005	412 (13.7)	2.81 (2.26 to 3.53)	2.56 (2.05 to 3.24)
Tumor grade				
Grade 1	95	11 (11.6)	1.25 (0.64 to 2.19)	—
Grade 2	1529	145 (9.5)	1.00	—
Grade 3	2997	334 (11.1)	1.18 (0.97 to 1.44)	—
Unevaluable or missing	183	18 (9.8)	1.02 (0.60 to 1.62)	—
Central hormone receptor status				
Positive (ER and/or PgR positive)	3172	320 (10.1)	1.00	1.00
Negative (ER and PgR negative)	1632	188 (11.5)	1.16 (0.96 to 1.38)	1.12 (0.93 to 1.34)
Protocol version				
Protocol A	3655	348 (9.5)	1.00	—
Protocol amendment B (node-positive only)	1149	160 (13.9)	1.67 (1.38 to 2.01)	1.16 (0.95 to 1.42)
Type of chemotherapy				
Anthracycline containing regimen	3744	411 (11)	1.00	1.00
Nonanthracycline containing regimen	1060	97 (9.2)	0.86 (0.68 to 1.07)	1.03 (0.80 to 1.30)
Adjuvant endocrine therapy[b]				
Yes	2667	245 (9.2)	1.00	—
No	505	75 (14.9)	2.13 (1.63 to 2.74)	—

[a]Some patients have more than 1 tumor; hierarchy used for histology, largest tumor size presented along with highest grade. BMI = body mass index; CI = confidence interval; ER = estrogen receptor; HR = hazard ratio; IDFS = invasive disease-free survival; PgR = progesterone receptor.
[b]Adjuvant endocrine therapy calculated on the total number of patients with hormone receptor (ER and/or PR)-positive breast cancer.

provided (11). The present APHINITY analysis showed that the majority of HER2-positive early breast cancer cases (71.7%) in young patients had hormone receptor–positive disease. Although a possible selection bias based on trial eligibility criteria may partially explain this finding, recent real-world studies have also shown a higher percentage of hormone receptor–positive cases among young patients within the HER2-positive population (6,15,20,21). In APHINITY, 90.4% of patients with hormone receptor–positive breast cancer received adjuvant endocrine therapy. APHINITY accrued before the availability of the results of the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT) (22). Indeed, tamoxifen alone was prescribed to most women in the young cohort (65.1%), and only 26.5% of patients underwent ovarian function suppression given with an aromatase inhibitor in approximately 4% of the cases. Recent data have suggested that premenopausal women with HER2-positive and hormone receptor–positive breast cancer appear to derive a greater benefit from the addition of ovarian function suppression as compared with those with HER2-negative and hormone receptor–positive disease (22). Moreover, the development of chemotherapy-induced amenorrhea is strongly prognostic in the setting of

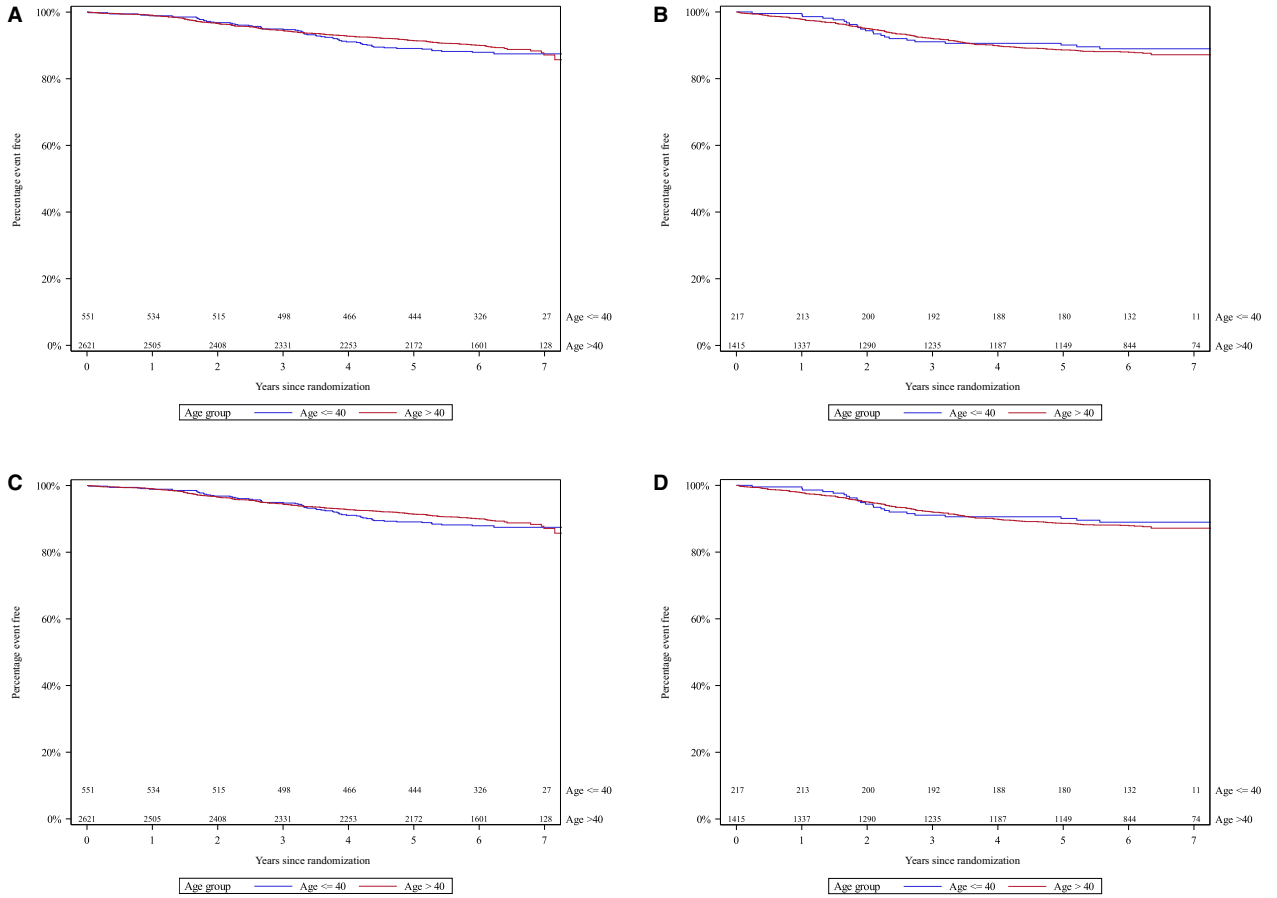

Figure 3. Prognostic effect of age according to hormone receptor status and administered anti-HER2 treatment: (**A**) hormone receptor–positive; (**B**) hormone receptor–negative; (**C**) pertuzumab arm; (**D**) placebo arm.

HER2-positive and hormone receptor–positive breast cancer (23). Assessing the expected benefit of the different adjuvant endocrine therapy options goes beyond the scope of the present APHINITY analysis. However, these data highlight the need to further investigate the best adjuvant endocrine therapy in patients with HER2-positive and hormone receptor–positive breast cancer. Proper subgroup analyses according to age are important to be conducted in the upcoming adjuvant trials investigating targeted treatments in combination with endocrine therapy in the HER2-positive setting (24).

Although many studies had shown that young age at diagnosis is a poor prognostic factor (3), with a better biological characterization of breast cancer and the availability of more effective targeted therapies, the importance of age with regard to prognosis is expected to diminish and potentially disappear (6). Expanding on the young age-analysis results of the HERA trial (11), the present analysis strongly supports the fact that age is not prognostic or predictive in HER2-positive breast cancer irrespective of hormone receptor status and administered anti-HER2 treatment, in longer-term follow-up. This is important information to reassure young patients at diagnosis and possibly to avoid overtreatment based solely on age considerations.

The care of patients with HER2-positive breast cancer has substantially evolved over the past years in terms of both treatment escalation and de-escalation (25). As voiced by guidelines and now supported by the present findings in the HER2-positive setting, age per se should not be a factor to decide whether to escalate or de-escalate treatment. Among the escalation efforts, based on the results of the APHINITY trial (12,13), adjuvant pertuzumab is now recommended in patients with high-risk HER2-positive breast cancer (26). Although no benefit appears to be observed in the node-negative population, the addition of pertuzumab to trastuzumab improves the outcomes of all patients with node-positive disease irrespective of other clinical features (ie, age at diagnosis and tumor size) or biological characteristics (ie, hormone receptor status, percentage of tumor-infiltrating lymphocytes, and HER2 copy number) (27). Although age is not a reason for therapy escalation, the need to increase treatment burden in high-risk patients may pose further issues in young women. Among them, the impact of anticancer treatments on gonadal function and future reproductive outcomes is highly relevant for young women and should be discussed at the time of treatment decision making (28-30). Nevertheless, no data are available to counsel young patients on these aspects when pertuzumab is added to the (neo)adjuvant treatment (31). Assessing reproductive health outcomes in trials enrolling young patients and investigating new anticancer therapies should be a priority (32,33).

The main limitation of the present analysis is that it was not preplanned in the study protocol; thus, it should be considered as exploratory. All the analyses were performed using the IDFS definition of the APHINITY trial that is different from the standardized definitions for efficacy endpoints (STEEP) that also include second primary nonbreast malignancies (34). However, this large phase III randomized trial with a relatively long follow-up represented a perfect platform to conduct this

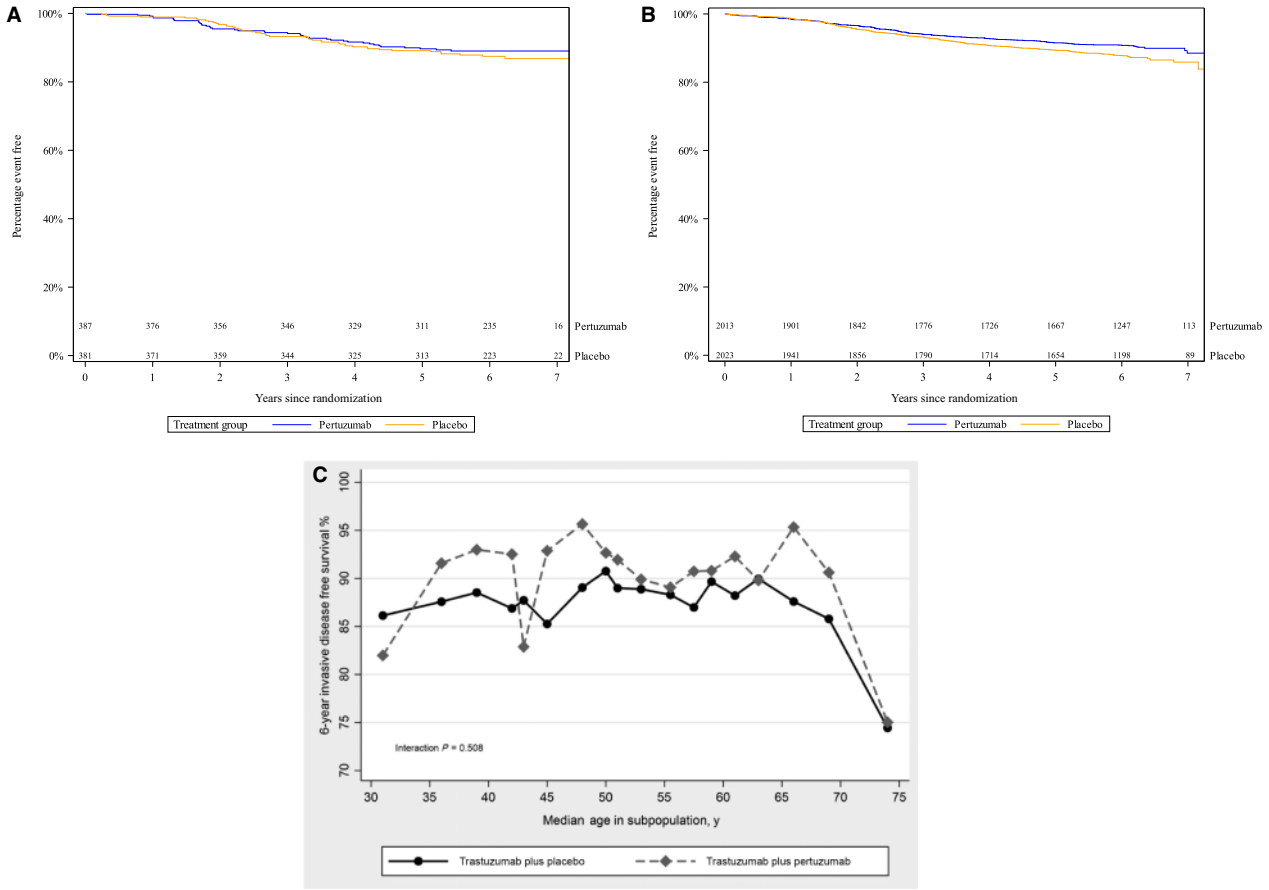

Figure 4. Predictive value of age: (**A**) young cohort (40 years or younger); (**B**) older cohort (older than 40 years); (**C**) subpopulation treatment effect pattern plot (STEPP) analysis.

analysis within a population of patients treated according to current standards (with the exception of a low uptake of ovarian function suppression in young patients with hormone receptor–positive disease).

In conclusion, young age at diagnosis of HER2-positive early breast cancer was not associated with any detrimental prognostic value and had no influence on the expected benefit from pertuzumab in patients treated with modern adjuvant anticancer therapies within the APHINITY trial. Considering the special needs of young patients with newly diagnosed breast cancer, additional preplanned analyses focused on this age group are warranted within all future studies investigating newer anticancer treatments to address potential disparities and to improve their care.

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Notes

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Data Availability

The data generated and analyzed during this study can be made available upon reasonable request to the corresponding author.

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