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Body mass index and weight changes in patients with HER2-positive early breast cancer: A sub-analysis of APHINITY trial

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ABSTRACT

Background: Body mass index (BMI) may affect prognosis in patients with breast cancer (BC). We assessed the association of BMI and weight changes with outcomes of patients with HER2-positive early BC included in the APHINITY trial.

Methods: This is an exploratory analysis of APHINITY (NCT01358877), randomized trial testing adjuvant dual vs. single HER2 blockade plus chemotherapy in HER2-positive early BC. BMI was collected at baseline and at two years after randomization. Patients were classified as underweight/normal weight (BMI < 25 kg/m^2) and overweight/obese (BMI≥25 kg/m^2). The association of BMI with invasive disease-free survival (iDFS), distant recurrence-free interval (DRFI) and overall survival (OS) was investigated. Landmark approach was used to compare event for weight change ≥ 5.0 % at 2 years from baseline.

Results: Of 4787 patients included, 2252 (47 %) were overweight/obese and 2535 (53 %) underweight/normal weight. Patients who were overweight/obese had more often chemotherapy discontinuation compared to underweight/normal weight patients (14 % vs. 9 %, p < 0.001). Patients who were overweight/obese exhibited worse iDFS (adjusted hazard ratio [aHR] 1.27; 95 % CI 1.06–1.52), DFRI (aHR 1.32; 95 % CI 1.06–1.64) and OS (aHR 1.38; 95 %CI 1.08–1.77) than underweight/normal weight patients. This effect on iDFS remained after adjusting for chemotherapy discontinuation (iDFS aHR 1.26, 95 % CI 1.05–1.51; DRFI aHR 1.31, 95 % CI 1.06–1.63; OS aHR 1.35 95 % CI 1.05–1.73). Weight changes at 2 years were not associated with clinical outcomes.

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Conclusions: Our exploratory findings suggest that overweight/obesity at diagnosis was associated with worse survival outcomes.

1. Introduction

Breast cancer (BC) is the most common malignancy in women [1]. The human epidermal growth factor receptor 2 (HER2) is overexpressed in approximately 20 % of BC [2]. Although treatment strategies for this BC subtype have evolved significantly [3,4], further identification of prognostic factors is essential to improve disease management.

A substantial body of evidence supports an association between being overweight or obese and poorer outcomes among patients with early BC, especially in those with hormone receptor-positive HER2-negative subtype [5]. This association is less clear for other BC subtypes, but recent studies suggested a relationship between obesity and poorer outcomes in HER2-positive disease [6,7].

Although a meta-analysis reported poorer survival outcomes among patients with obesity with HER2-positive early BC [5], it did not include patients treated with dual HER2 blockade, which is now the recommended neoadjuvant and adjuvant regimen for patients with high-risk HER2-positive early BC [8,9]. Given the known role of BMI as an independent prognostic factor, it is key to clarify its role in patients treated with anti-HER2 contemporary treatment.

Furthermore, the relationship between weight changes and survival outcomes has been investigated in patients with HER2-positive BC, showing controversial results [7]. Understanding whether BMI and weight changes may influence survival outcomes in patients treated with dual HER2 blockade may improve risk stratification and help to tailor patient care.

To assess the association of BMI and weight changes with survival outcomes in patients receiving contemporary anti-HER2 treatments, we performed an individual patient-level sub-analysis of the phase III APHINITY trial which included patients with HER2-positive early BC receiving chemotherapy plus single or dual HER2 blockade [3].

2. Methods

2.1. Data source and patient population

This was a post-hoc analysis of the previously reported APHINITY trial [3,10]. Briefly, APHINITY was a randomized, placebo-controlled, phase III trial evaluating the safety and efficacy of pertuzumab in addition to chemotherapy plus trastuzumab as adjuvant therapy in 4805 patients with operable HER2-positive BC. The institutional review board at each participating site approved the study protocol. All patients provided written informed consent prior to inclusion.

APHINITY trial patients were eligible for this sub-analysis provided that BMI data (height and weight) were available (N = 4787, 99.6 %) (Supplementary figure 1). Height and weight were collected for all patients at two time-points: at baseline, corresponding to the time of randomization and at two years after randomization. BMI was calculated by dividing weight by height squared (kg/m^2), as per World Health Organization (WHO) definition.

For the primary analysis, BMI was categorized into two groups: underweight/normal weight (<25 kg/m^2), overweight/obese (≥25 kg/m^2). For a subsequent sensitivity analysis, BMI was stratified into four groups according to WHO criteria: underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2) [11]. We also investigated BMI as a continuous variable.

Weight change analysis was limited to those subjects with available information on body weight at baseline and at two years after randomization. A conditional landmark analysis approach was applied to minimize selection bias with a two years as the landmark timepoint. Weight change was calculated as a percentage, defined as the ratio of the difference between baseline weight and weight at two years to the baseline weight. A weight change of ≥ 5.0 % was considered as the cut-off to stratify patients, based on previous studies [12] as this threshold reflects a clinically meaningful weight change [12]. Accordingly, patients were categorized into three groups: weight loss (≥5.0 % decrease), stable weight (<5.0 % change) and weight gain (≥5.0 % increase).

The association of BMI with chemotherapy discontinuation was evaluated in 4749 individuals who had BMI information available and known exposure to chemotherapy (Supplementary figure 1). Chemotherapy discontinuation was assessed separately for anthracycline, taxane, and carboplatin. Discontinuation of any chemotherapy was defined as the permanent discontinuation of at least one of these three agents.

2.2. Objectives and endpoints

The present analysis aimed to determine the association of baseline BMI and weight changes at two years after randomization and survival outcomes in patients with early-stage HER2-positive BC. Study endpoints were invasive disease free survival (iDFS), distant recurrence-free interval (DRFI) and overall survival (OS), as defined in the original APHINITY trial [3]. Data for all endpoints were derived from the second interim analysis (clinical cutoff date June 19, 2019) of the trial, as it was the most up-to-date data available at the time of this analysis [10]. Note, the protocol defined timepoint for the primary OS analysis has not yet been reached.

2.3. Statistical analysis

Patient baseline characteristics were described using frequency and compared with respect to BMI category (underweight/normal weight and overweight/obese) using the chi-square test.

The association of baseline BMI with iDFS, DRFI and OS was evaluated in the whole study population and in predefined subgroups according to type of anti-HER2 treatment (trastuzumab and placebo or trastuzumab and pertuzumab), hormone receptor status (positive or negative) and baseline menopausal status (premenopausal or postmenopausal). A test for interaction between the BMI groups and these subgroups was carried out. Kaplan-Meier survival curves for iDFS, DRFI and OS according to baseline BMI categories were constructed and compared using Log-rank test. A Cox proportional hazard model generated hazard ratios (and 95 % Confidence interval) for BMI (unadjusted and adjusted). The adjusted multivariable Cox models included age (<40, 40–64, >64 years), menopausal status (premenopausal or post menopausal), tumor size, (<2 cm, ≥ 2 cm to < 5 cm, ≥ 5 cm) type of chemotherapy (anthracycline contain regimens or non-anthracycline regimens, hormone therapy (given or not given). These variables were pre-specified for the multivariate model based on their association with BMI. A sensitivity analysis also included the variable "chemotherapy discontinuation" as an additional adjustment in the multivariable model due to the imbalance in chemotherapy discontinuation between underweight/normal weight vs. overweight/obese patients.

An analysis of the association of weight change at two years was carried out using two years as a landmark for calculating the time to iDFS, DRFI and OS. Adjustment variables matched those in the BMI models plus baseline BMI itself.

With respect to treatment arm, all analyses were intention to treat, with patients analysed as randomised. All statistical tests were two-sided and $p < 0.05$ was considered statistically significant. No adjustement for multiple testing was carried out since all analyses were pre-

specified before execution and are exploratory. Where applicable 95 % confidence intervals are provided to aid interpretation. No missing data were imputed. Statistical analyses were performed with SAS version 9.4.

3. Results

3.1. Patient characteristics and demographics

In APHINITY, 4805 patients were randomly assigned to receive chemotherapy and trastuzumab plus either pertuzumab (2400 patients) or placebo (2405 patients), and 4804 were included in the intention to treat population. We excluded 17 patients from our analysis as baseline BMI was not calculable (weight and/or height unavailable), leaving 4787 patients included in the present analysis (Supplementary figure 1). Among them, 2535 patients (53 %) were categorized as underweight or normal weight, 2252 (47 %) as overweight or obese. Table 1 describes the differences in baseline patient and disease characteristics according to the two BMI subgroups. The distribution of patients who received dual and single HER2 blockade was equal between the BMI groups.

Patients who were overweight/obese were more likely to be older than 64 years ($p < 0.001$) and postmenopausal ($p < 0.001$) compared to patients who were underweight/normal weight. In addition, patients who were overweight/obese had larger pathological tumour size ($p < 0.001$). A smaller proportion of patient who were overweight/obese received anthracycline-based chemotherapy compared to those who were underweight/normal weight ($p < 0.001$). A similar proportion received hormone therapy in the two groups and of those a higher percentage of patients who were overweight/obese received aromatase inhibitors (AIs) alone ($p < 0.001$) (Table 1).

3.2. Association of baseline BMI with iDFS, DRFI and OS

At a median follow-up of 73.6 months, after confounder adjustment and when compared with patients who were normal weight/underweight, patients who were overweight and those with obesity experienced worse iDFS (adjusted hazard ratio [aHR] 1.27; 95 % 1.06–1.52), DRFI (aHR 1.32; 95 % CI 1.06–1.64) and OS (aHR 1.38; 95 % CI 1.08–1.77) (Table 2 and Fig. 1). Supplementary Table 1 shows the breakdown of type of first iDFS event for the two BMI groups. Per unit increase in BMI, there was an indication of an increase in hazard of iDFS (aHR 1.01, 95 % CI 0.99–1.03), DRFI (aHR 1.00, 95 % CI 0.98–1.02) and OS events (aHR 1.021, 95 % CI 0.99–1.04) (Supplementary table 2).

3.3. Chemotherapy discontinuation according to BMI

A higher proportion of patients who were overweight/obese discontinued chemotherapy compared to those who were underweight/normal weight ($p < 0.001$) (Table 3). This was consistent for patients receiving anthracycline-based regimens and anthracycline-free regimens (Table 3). No significant differences in dose adjustment or delay of chemotherapy were observed in the two BMI groups (Supplementary table 3).

After adding the variable "chemotherapy discontinuation" to the original multivariable models, due to the imbalance found between the two BMI groups, the association of being overweight/obese with worse iDFS, DRFI and OS remained (aHR for iDFS 1.26; 95 % CI 1.05–1.50; aHR for DRFI 1.31; 95 % CI 1.06–1.63; aHR for OS 1.35 95 % CI 1.05–1.73) (Supplementary table 4).

Table 1
Baseline characteristics and demographics of patients in the overall study population according to BMI.

	Overweight or Obese (BMI ≥ 25) (N = 2252) N (%)	Underweight or Normal (BMI < 25) (N = 2535) N (%)	p-value
Age (year) categories			< 0.001
< 40	187 (8)	462 (18)	
40–64	1681 (75)	1851 (73)	
> 64	384 (17)	222 (9)	
Menopausal status at baseline			< 0.001
Premenopausal	867 (38)	1447 (57)	
Postmenopausal	1374 (61)	1082 (43)	
Unknown/Missing	11 (<1)	6 (<1)	
Nodal status at baseline			0.115
0 Positive nodes and tumor ≤ 1 cm	75 (3)	99 (4)	
0 Positive nodes and tumor > 1 cm	737 (33)	883 (35)	
1–3 Positive nodes	849 (38)	954 (38)	
≥ 4 Positive nodes	591 (26)	599 (24)	
Pathological tumor size			< 0.001
< 2 cm	825 (37)	1091 (43)	
≥ 2 cm to < 5 cm	1260 (56)	1287 (51)	
≥ 5 cm	163 (7)	156 (6)	
HR status at baseline			0.322
Negative	789 (35)	923 (36)	
Positive	1463 (65)	1612 (64)	
Estrogen receptor status			0.271
Negative	797 (35)	936 (37)	
Positive	1455 (65)	1599 (63)	
Progesterone status			0.906
Negative	1167 (52)	1318 (52)	
Positive	1085 (48)	1217 (48)	
Histologic grade			0.069
GRADE 1	50 (2)	44 (2)	
GRADE 2	708 (31)	816 (32)	
GRADE 3	1423 (63)	1563 (62)	
Missing	71 (3)	112 (4)	
Chemotherapy regimen			< 0.001
Anthracycline containing regimen	1698 (75)	2029 (80)	
Non-anthracycline containing regimen	554 (25)	506 (20)	
Randomised Treatment arm			0.916
Trastuzumab plus Pertuzumab	1123 (50)	1268 (50)	
Trastuzumab plus Placebo	1129 (50)	1267 (50)	
Hormone Therapies			0.383
Not given	896 (40)	1040 (41)	
Given	1356 (60)	1495 (59)	
Hormone Therapies given			< 0.001
AI alone	536 (40)	373 (25)	
SERM alone	574 (42)	784 (52)	
Ovarian suppression alone	24 (2)	29 (2)	

(continued on next page)

Table 1 (*continued*)

	Overweight or Obese (BMI ≥ 25) (N = 2252) N (%)	Underweight or Normal (BMI < 25) (N = 2535) N (%)	p-value
AI and SERM	93 (7)	98 (7)	
AI and Ovarian suppression	22 (2)	17 (1)	
SERM and Ovarian suppression	51 (4)	132 (9)	
Other	56 (4)	62 (4)	
Diabetes as comorbidity at baseline			< 0.001
No	2050 (91)	2463 (97)	
Yes	202 (9)	72 (3)	

Abbreviations. HR: hormone receptor; AI: aromatase inhibitor; BMI: body mass index; SERM: selective estrogen receptor modulator.
For patients with more than 1 tumour, largest tumour size presented along with highest grade.

Table 2
Association of baseline BMI with iDFS, DFRI and OS.

	Events (%)	N	Unadjusted HR (95 % CI)	Adjusted HR (95 % CI)*
iDFS	506 (10.6 %)	4787		
Overweight or Obese (BMI ≥ 25)	264 (11.7 %)	2252	1.28 (1.07–1.52)	1.27 (1.06–1.52)
Underweight or Normal (BMI < 25)	242 (9.5 %)	2535	-	-
DRFI	342 (7.1 %)	4787		
Overweight or Obese (BMI ≥ 25)	180 (8.0 %)	2252	1.30 (1.05–1.60)	1.32 (1.06–1.64)
Underweight or Normal (BMI < 25)	162 (6.34 %)	2535	-	-
OS	270 (5.6 %)	4787		
Overweight or Obese (BMI ≥ 25)	154 (6.8 %)	2252	1.54 (1.21–1.96)	1.38 (1.08–1.77)
Underweight or Normal (BMI < 25)	116 (4.6 %)	2535		

*Multivariable analysis accounted for Age, Tumor size, Menopausal status, chemo regimen and hormone therapy
Abbreviations: BMI, body mass index; iDFS, invasive disease-free survival; DRFI, distant relapse-free interval; OS overall survival; HR, hazard ratio; CI, confidence interval.
Abbreviations: BMI, body mass index; iDFS, invasive disease-free survival; DRFI, distant relapse-free interval; OS, overall survival.

3.4. Subgroup analysis according to anti-HER2 therapy, hormone receptor status and menopausal status

In the predefined subgroup analysis, BMI did not affect iDFS, DRFI and OS in patients receiving trastuzumab plus placebo, while overweight/obesity were associated with worse iDFS (aHR: 1.47; 95 % CI 1.12–1.93), DRFI (aHR: 1.51 95 % CI 1.09–2.11) and OS (aHR: 1.85 95 % CI 1.28–2.69) in patients receiving trastuzumab plus pertuzumab (Supplementary Table 5–6). There was no evidence of an interaction between BMI and anti-HER2 treatment on iDFS (p = 0.227), DRFI (p = 0.422) or OS (p = 0.060).

In the hormone receptor-positive subgroup, there was no association of baseline BMI with disease outcomes (Supplementary Table 7). In the cohort of hormone receptor-negative, patients who were overweight and those with obesity were associated with poorer iDFS (aHR: 1.52; 95 % CI 1.14–2.03) and DRFI (aHR: 1.57; 95 % CI 1.10–2.24) (Supplementary Table 8), and there was a trend towards poorer OS (aHR 1.72; 95 % CI 0.9–2.02). There was no evidence of an interaction between BMI and hormone receptor status on iDFS (p = 0.100) or DRFI (p = 0.245) or OS (p = 0.767).

In premenopausal patients, there was a trend towards worse iDFS (aHR: 1.22; 95 % CI 0.94–1.58), DRFI (aHR: 1.26; 95 % CI 0.94–1.70) and OS (aHR: 1.25; 95 % CI 0.83–1.89) in patients who were overweight and those with obesity (Supplementary Table 9). In the postmenopausal cohort, overweight/obesity was associated to inferior iDFS (aHR 1.30; 95 % CI 1.01–1.68), DRFI (aHR1.37; 95 % CI 1.00–1.89) and OS (aHR 1.42; 95 % CI 1.04–1.94) compared to underweight/normal weight patients (Supplementary Table 10). There was no evidence of an interaction between BMI and menopausal status on iDFS (p = 0.992), DRFI (p = 0.998) or OS (p = 0.999).

3.5. Association of weight changes at two years with iDFS, DRFI and OS

At the landmark of two years (n = 3967), weight loss ≥ 5 % was not associated with worse iDFS (aHR 0.97; 95 % CI 0.68–1.40), DRFI (aHR 0.85; 95 % CI 0.54–1.35), OS (aHR 1.39; 95 % CI 0.83–2.32). Similarly, weight gain ≥ 5 % was not associate with poorer outcomes (for iDFS aHR 0.89; 95 % CI 0.67–1.17, for DRFI aHR 0.81; 95 % CI 0.57–1.14, for OS aHR 0.81, 95 % CI 0.57–1.14) (Table 4).

3.6. Exploratory analysis using four-category BMI

Using normal BMI as reference, patients who were overweight experienced worse iDFS (aHR 1.24; 95 % CI 1.01–1.52), DRFI (aHR 1.38; 95 % CI 1.08–1.75) and OS (aHR 1.37 95 % CI 1.04–1.80). Patients with obesity had worse iDFS (aHR 1.27; 95 % CI 1.00–1.62) compared to patients with normal weight, while there was a trend towards worse DRFI (aHR 1.21; 95 % CI 0.90–1.62) and OS (aHR 1.30; 95 % CI 0.94–1.80) (Supplementary table 11 and Supplementary figure 2).

4. Discussion

Our exploratory analysis showed that patients who were overweight and those with obesity treated with adjuvant chemotherapy and single or dual HER2 blockade experienced worse iDFS, DRFI and OS compared to patients who were underweight/normal weight. This association remained after adjusting for possible confounders, including chemotherapy discontinuation. To our knowledge, the present analysis was the first to evaluate the association between BMI and outcomes in patients treated with trastuzumab and pertuzumab in the early setting.

Almost half of the patients included in the APHINITY trial were classified as overweight/obese. This highlights the prevalence of overweight and obesity among patients with early BC and the need to investigate the association of BMI and weight changes as independent risk factors. Obesity is a growing public health issue [13]. Its relationship with poor outcomes in early hormone receptor-positive HER2-negative BC is well documented [14,15]. Although fewer studies investigated this association in patients with HER2-positive subtype, some evidence suggests that higher BMI may be linked to worse outcomes, regardless of the adjuvant treatment received, possibly reflecting a relationship with the biology of HER2-positive BC [16,17]. A pooled analysis showed that obesity in patients with HER2-positive early BC was associated to worse prognosis [18]. In the adjuvant setting, Martel et al. investigated the association between BMI and survival outcomes in patients with HER2-positive early BC treated with trastuzumab and/or lapatinib within the ALTTO trial showing worse distant disease-free survival (DDFS) (aHR: 1.25; 95 % CI, 1.04–1.50) and OS (aHR, 1.27; 95 % CI, 1.01–1.60) in patients with obesity [7]. In patients receiving adjuvant trastuzumab, post-hoc analyses of HERA and NSABP B-31 trials found no significant association between BMI and outcomes [19,20], while in N9831 trial there was an association between worse clinical outcomes and increasing BMI (aHR for DFS in overweight 1.27; 95 % CI 1.03–1.57, in obese 1.28; 95 % CI 1.05–1.55) [21]. However, in all

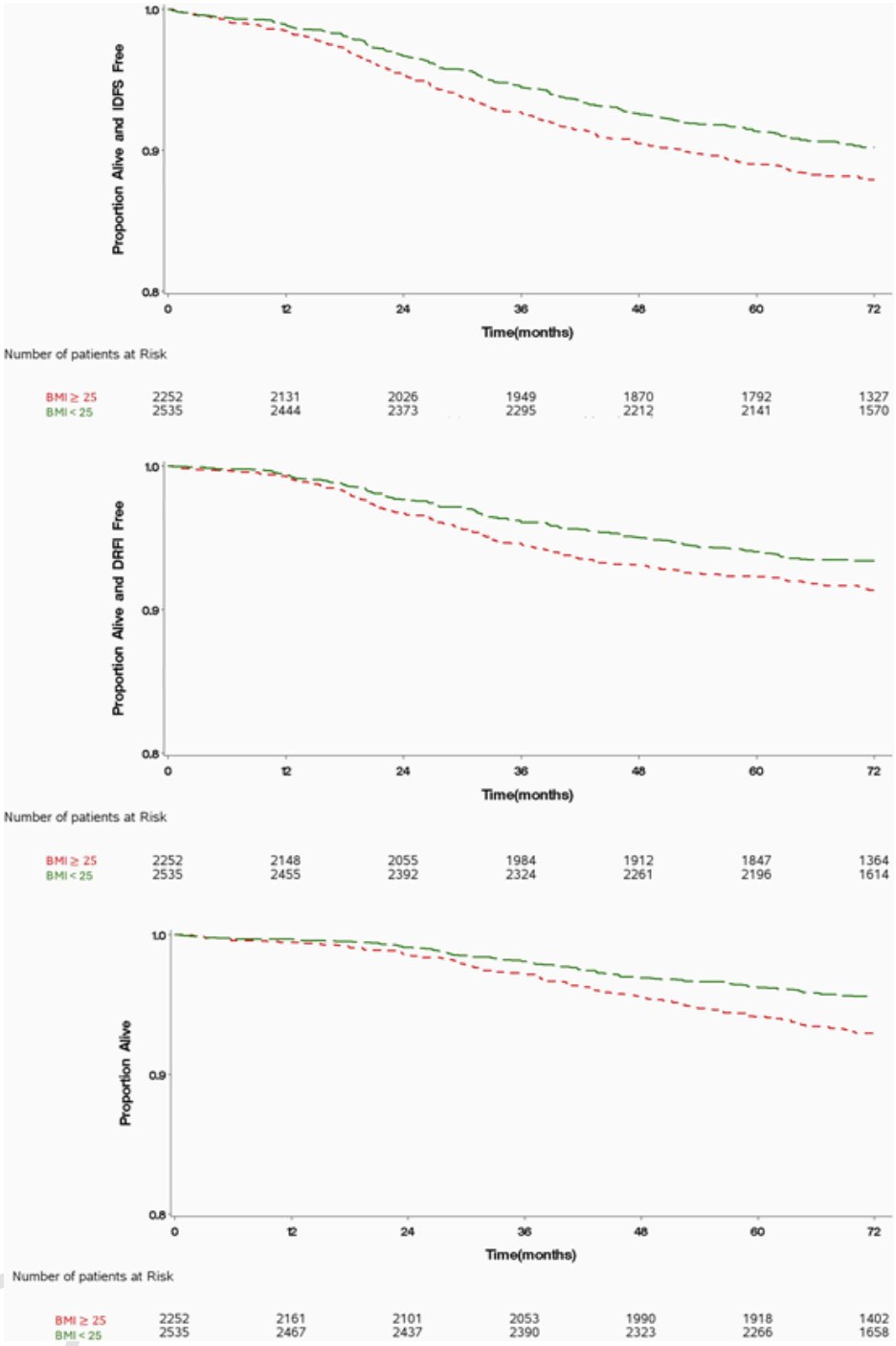

Fig. 1. Kaplan Meier plot for iDFS, DRFI and OS according to BMI in two categories.

these post-hoc analyses the association (or absence of association) was regardless treatment arm.

In APHINITY trial, biomarker analysis suggested that high level of certain immune markers could be associated with greater benefit in patients treated with dual HER2 blockade treatment [22]. Obesity is characterized by an altered immune landscape, including chronic low-grade inflammation which may influence the efficacy of these drugs [23,24]. However, in our analysis, the impact of BMI did not significantly differ in patients receiving single vs. dual HER2 blockade, suggesting that obesity may have a prognostic rather than predictive role.

Hormone receptors expression may influence outcomes in patients with HER2-positive BC [25,26]. Among patients with hormone receptor-positive BC, AIs are widely used as adjuvant endocrine therapy. Our analysis revealed that most of patients who were overweight and those with obesity received AIs alone. Nevertheless, several studies showed that patients with obesity may benefit less from AIs [27,28]. In patients with obesity, higher adiposity may lead to increased pheripheral aromatization, converting androgen into estrogen. This can result in higher residual estrogen levels, despite the use of AIs [29,30].

Chemotherapy regimens are typically tailored on body surface area or body weight [29]. Maintaining dose intensity in the adjuvant setting

Table 3
Chemotherapy discontinuation according to BMI in the overall population, in the anthracycline cohort and in the non-anthracycline cohort.

	Overall			Anthracycline regimen			Non-Anthracycline regimen		
	BMI≥ 25 (N = 2228) N (%)	BMI< 25 (N = 2521) N (%)	p-value	BMI≥ 25 (N = 1691) N (%)	BMI< 25 (N = 2022) N (%)	p-value	BMI≥ 25 (N = 537) N (%)	BMI< 25 (N = 499) N (%)	p-value
Chemotherapy Discontinuation			<0.001			<0.001			0.008
Yes	306 (14)	222 (9)		237 (14)	183 (9)		69 (13)	39 (8)	
No	1922 (86)	2299 (91)		1454 (86)	1839 (91)		468 (87)	460 (92)	

Abbreviations: BMI, body mass index.

Table 4
Association of 2 years weight change† from baseline with iDFS, DFRI and OS.

All patients	Events (%)	N	Univariate HR (95 %CI)	Multivariate HR (95 %CI)
iDFS	268 (6.76 %)	3967		
Weight loss	36 (7.00 %)	514	1.01 (0.71–1.46)	0.97 (0.68–1.40)
Stable weight	159 (6.96 %)	2286	-	-
Weight gain	73 (6.26 %)	1167	0.88 (0.67–1.17)	0.89 (0.67–1.17)
DRFI	180 (4.54 %)	3967		
Weight loss	22 (4.28 %)	514	0.89 (0.56–1.41)	0.85 (0.54–1.35)
Stable weight	111 (4.86 %)	2286	-	-
Weight gain	47 (4.03 %)	1167	0.82 (0.58–1.15)	0.81 (0.57–1.14)
OS	105 (2.65 %)	3967		
Weight loss	20 (3.89 %)	514	1.59 (0.96–2.65)	1.39 (0.83–2.32)
Stable weight	57 (2.49 %)	2286	-	-
Weight gain	28 (2.40 %)	1167	0.95 (0.60–1.49)	1.08 (0.68–1.71)

*Multivariable analysis accounted for age, tumor size, menopausal status, chemo regimen, hormone therapy and baseline BMI.
†A weight change of ≥ 5.0 % was considered as the cut-off to stratify patients.
Abbreviations: BMI, body mass index; iDFS, invasive disease-free survival; DRFI, distant recurrence-free interval; OS, overall survival; HR, hazard ratio; CI, confidence interval.

is key to improve clinical outcomes [30,31]. Our analysis described an association between higher BMI and chemotherapy discontinuation, but no significant differences in dose delays or reduction. The higher rate of discontinuation may partially contribute to the worse outcomes in this patient population [32]. Fat mass can influence drug distribution, metabolism and clearance and therefore impact drug pharmacokinetics and pharmacodynamics [33,34]. Treatment-related toxicities might disproportionately affect patients with higher BMI, leading to early treatment discontinuation. Moreover, patient-related factors, such as baseline comorbidities, may also have an impact on treatment adherence. Elevated fat mass is related with an increased risk of treatment modifications due to toxicity in patients with early BC undergoing chemotherapy [35]. A large observational cohort study related higher adiposity with incresead risk of low relative dose intensity in patients with BC [36]. Although international guidelines recommend that full, weight-based chemotherapy doses be used to treat patients with. obesity, dose capping is often adopted in clinical practice, potentially affecting treatment efficacy [37]. The lack of pharmacokinetic data is a limitation of our work, and further research should consider whether suboptimal drug exposure may contribute to worse outcomes in patients with overweight and obesity.

In our analysis, 2-year weight changes were not associated with outcomes. Exploratory analysis of ALTTO trial showed an association between weight loss > 5 % at 2 years and worse DFS (aHR, 1.34; 95 % CI, 1.05–1.71), DDFS (aHR, 1.46; 95 % CI 1.07–1.98) and OS (aHR, 1.83; 95 % CI 1.18–2.84), but no association was found for weight gain [7]. In BC overall, weight-loss interventions have been investigated as part of survivorship care [38]. Preliminary findings from SUCCESS-C study, including patients with hormone receptor-positive HER2-negative early BC suggest an improvement in DFS in patients that completed two-years lifestyle intervention program (HR 0.35 95 % CI 0.27–0.45) [39]. Similarly, the ongoing BWEL trial enrolled 3181 women with HER2-negative early BC and a BMI of at least 27 kg/m^2 to evaluate the effect on iDFS of two-years telephone-based weigh loss program [40]. However, both trials excluded patients with HER2-positive disease highlighting the need for research on weight-loss interventions in this population.

Our study has limitations that warrant consideration. Firstly, the analysis was not pre-planned in the APHINITY protocol. Second, BMI alone is not the most accurate method to evaluate body fat as it does not take into account of the complexity of body composition, potentially leading to misestimation of body fat, and a thorough clinical evaluation should be always associated to ensure an accurate assessment. Moreover, information regarding dose capping in patients with obesity was not detailed. Additionally, weight changes analysis was restricted to a sub-population of patients with available data at two years. Furthermore, weight changes were not evaluated in an interventional program and data on longer-term duration and the reason of weight loss or gain were not collected. Importantly, data for the OS endpoint is derived from an interim analysis, which limits the ability to make definitive conclusion from these findings. Moreover, although our analysis was adjusted for key clinical and pathological variables, we acknowledge that potential confounding factors such as metabolic comorbidities, dietary patterns, and physical activity were not accounted for. Nonetheless, our results originate from the analysis of a large cohort of patients enrolled in a global randomized trial and all data used for the analyses were prospectively collected during the trial, as detailed in the APHINITY protocol. Although our findings should be considered as purely exploratory, they support further investigation into the impact of adiposity on outcomes of patients with HER2-positive early BC.

5. Conclusion

This sub-analysis of individual patient-level data from the APHINITY trial showed that being overweight or obese was associated with poorer survival outcomes. Future studies should investigate whether targeting adiposity or metabolic alterations can improve outcomes in patients with HER2-positive early BC.

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CRediT authorship contribution statement

Piccart Martine: Writing – review & editing. **Bines Jose:** Writing – review & editing. **Loibl Sibylle:** Writing – review & editing. **Di Cosimo Serena:** Writing – review & editing. **Martel Samuel:** Writing – review & editing. **Agbor-Tarh Dominique:** Formal analysis. **Fielding Shona:** Writing – review & editing, Formal analysis. **Desmedt Christine:** Writing – review & editing. **Jerusalem Guy:** Writing – review & editing.

Reaby Linda: Conceptualization. **Pienkowski Tadeus:** Writing – review & editing. **Vaz-Luis Ines:** Writing – review & editing. **Di Meglio Antonio:** Writing – review & editing. **Del Mastro Lucia:** Writing – review & editing. **Dauccia Chiara:** Writing – review & editing, Writing – original draft. **Gombos Andrea:** Writing – review & editing. **Franzoi Maria Alice:** Writing – review & editing. **Lambertini Matteo:** Writing – review & editing. **Agostinetto Elisa:** Writing – review & editing, Conceptualization. **de Azambuja Evandro:** Writing – review & editing, Validation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

MAF: research funding: Resilience (Institution), Speaker honoraria: Novartis

MP: board Member (Scientific Board): Oncolytics; Consultant (honoraria): AstraZeneca, Gilead, Lilly, Menarini, MSD, Novartis, Pfizer, Roche-Genentech, Seattle Genetics, Seagen, NBE Therapeutics, Frame Therapeutics; Research grants to her Institute: AstraZeneca, Lilly, Menarini, MSD, Novartis, Pfizer, Radius, Roche-Genentech, Servier, Synthon, Gilead.

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ML: advisory role for Roche, Lilly, Novartis, Astrazeneca, Pfizer, Seagen, Gilead, MSD, Exact Sciences, Pierre Fabre, Menarini; speaker honoraria from Roche, Lilly, Novartis, Pfizer, Sandoz, Libbs, Daiichi Sankyo, Takeda, Menarini, AstraZeneca; travel Grants from Gilead, Daiichi Sankyo, Roche; research funding (to the Institution) from Gilead all outside the submitted work.

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Data sharing statement

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 docu- ments, see here: https://www.roche.com/research_and_ development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm.

Prior presentations

Partial results of this manuscript were presented as a Poster at ESMO 2021 (abstract N. 131 P).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115489.

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