Body Mass Index and Weight Change in Patients With HER2-Positive Early Breast Cancer: Exploratory Analysis of the ALTTO BIG 2-06 Trial

Samuel Martel, MD^{1,*}; Matteo Lambertini, MD, PhD^{2,*}; Dominique Agbor-Tarh, MSc³; Noam F. Ponde, MD⁴; Andrea Gombos, MD⁵; Vicki Paterson, BA³; Florentine Hilbers, PhD⁶; Larissa Korde, MD⁷; Anna Manukyants, MD⁸; Amylou Dueck, MD⁹; Christian Maurer, MD¹⁰; Martine Piccart, MD, PhD⁵; Alvaro Moreno-Aspitia, MD⁹; Christine Desmedt, MD¹¹; Serena Di Cosimo, MD^{12,†}; and Evandro de Azambuja, MD, PhD^{5,†}

ABSTRACT

Background: The association between obesity and prognosis in HER2-positive early breast cancer remains unclear, with limited data available. This study aimed to determine the impact of body mass index (BMI) at baseline and weight change after 2 years on outcomes of patients with HER2-positive early breast cancer. **Methods:** ALTTO was a randomized phase III trial in patients with HER2-positive early breast cancer. BMI was collected at randomization and 2 years after. WHO BMI categories were used: underweight, <18.5 kg/m²; normal weight, 18.5 to <25 kg/m²; overweight, ≥25 to <30 kg/m²; and obese ≥30 kg/m². A weight change from baseline of ≥5.0% and ≤5.0% was categorized as weight gain and weight loss. The impact of BMI at randomization and of weight change on disease-free survival (DFS), distant disease-free survival (DDFS), and overall survival (OS) were investigated with multivariate analyses, adjusting for baseline patients and tumor characteristics. **Results:** A total of 8,381 patients were included: 187 (2.2%), 3,797 (45.3%), 2,690 (32.1%), and 1,707 (20.4%) were underweight, normal weight, overweight, and obese at baseline, respectively. Compared with normal weight, being obese at randomization was associated with a significantly worse DDFS (adjusted hazard ratio [aHR], 1.25; 95% CI, 1.04–1.50) and OS (aHR, 1.27; 95% CI, 1.01–1.60), but no significant difference in DFS (aHR, 1.14; 95% CI, 0.97–1.32). Weight loss ≥5.0% at 2 years after randomization was associated with significantly poorer 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). Hormone receptor and menopausal status but not anti-HER2 treatment type influenced outcomes. Toxicities were more frequent in obese patients. **Conclusions:** In patients with HER2-positive early breast cancer, obesity at baseline is a poor prognostic factor. Weight loss during treatment and follow-up negatively impacts clinical outcomes. Dietary counseling should be part of survivorship care programs.

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Background

The burden of obesity is significant, with an estimated prevalence of 12.0% among adults worldwide.¹ The prevalence of obesity is even higher among cancer survivors,² and the annual increase is greater among survivors of breast cancer compared with women without a history of cancer.³ Furthermore, obesity may have an impact on patient outcomes. Multiple meta-analyses including patients with breast cancer have shown an increased risk of death and breast cancer mortality among women who are obese compared with those of normal weight. This association was observed irrespective of hormone receptor and menopausal status.^{4–6} Moreover, a recent meta-analysis including 213,075 patients with breast cancer showed that each 5 kg/m² increment in baseline body mass index (BMI) after breast cancer diagnosis was associated with worse outcomes.⁶

Breast cancer is a heterogeneous disease, and studies analyzing the association between obesity and prognosis specifically in HER2-positive early breast cancer have reported inconclusive results. The limited available data derive from randomized trials comparing chemotherapy ± adjuvant trastuzumab. In the NSABP B-31 trial, being overweight or obese at diagnosis was not associated with

¹Department of Hemato-Oncology, CISSS Montérégie Centre/Hôpital Charles Le Moyne, Université de Sherbrooke, Greenfield Park, Quebec, Canada;

²Department of Internal Medicine and Medical Specialties, School of Medicine, University of Genova, IRCCS Ospedale Policlinico San Martino, Genova, Italy;

³Frontier Science, Kingussie, United Kingdom; ⁴Department of Medicine, Camargo Cancer Center, Sao Paulo, Brazil; ⁵Institut Jules Bordet and

L'Université Libre de Bruxelles (U.L.B.), Brussels, Belgium; ⁶Breast International Group, Brussels, Belgium; ⁷National Cancer Institute, Bethesda, Maryland;

⁸Novartis Pharma AG, Basel, Switzerland; ⁹Mayo Clinic, Jacksonville, Florida;

¹⁰University of Cologne, Center for Integrated Oncology Aachen Bonn Cologne Duesseldorf, Cologne, Germany; ¹¹Laboratory for Translational Breast Cancer Research, Department of Oncology, Leuven, Belgium; and ¹²Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy.

[†]These authors are co-last authors.

^{*}These authors are co-first authors.

significantly different overall survival (OS) and breast cancer recurrence compared with being of normal weight.⁷ In contrast, the NCCTG N9831 trial showed that obese patients at baseline had a significantly worse 5-year disease-free survival (DFS) compared with those of normal weight. In this study, trastuzumab efficacy appears to be present in normal, overweight, and obese subgroups in an underpowered analysis.⁸ A recent analysis conducted within the HERA trial showed no impact of baseline BMI on the clinical outcomes of patients with HER2-positive breast cancer.⁹ In this study, information on BMI 1 year after treatment was also available; no effect on clinical outcomes of weight change at this time point was observed.⁹ Taken together, these studies have several caveats, including the limited sample size of the analyses and the presence of patients not treated with anti-HER2 therapy.

The ALTTO BIG 2-06 trial, which is the largest adjuvant study evaluating trastuzumab and/or lapatinib in HER2-positive early breast cancer, showed that the addition of lapatinib to adjuvant treatment did not improve DFS.¹⁰ Information on height and weight was collected as part of the trial. Therefore, this represented a unique opportunity to capture the relationship between BMI and outcomes in HER2-positive breast cancer. Our exploratory analysis of the ALTTO trial aimed to determine the impact of BMI and weight change in patients with HER2-positive early breast cancer treated with chemotherapy + trastuzumab and/or lapatinib.

Methods

Study Design

This is an unplanned exploratory analysis of the ALTTO BIG 2-06 trial. ALTTO was a randomized phase III study that evaluated the role of trastuzumab and/or lapatinib as adjuvant treatment in 8,381 patients with HER2-positive early breast cancer.^{6,7} Patients were randomized to 1 of 4 anti-HER2 treatment arms of 52-week duration: trastuzumab alone (n=2,097), lapatinib alone (n=2,100), trastuzumab for 12 weeks followed by lapatinib for 34 weeks (n=2,091), or combination trastuzumab + lapatinib (n=2,093).

Approval by the Ethics Committees or Independent Review Boards of all participating institutions was obtained. Before study entry, written informed consent was obtained from all participating patients. The ALTTO Executive Committees and Steering Committees approved the present analysis prior to conduction.

Study Population

All patients participating in ALTTO regardless of randomization arm were eligible. Height and weight were collected for all patients at 2 time points: at baseline,

which corresponds to the time of randomization (ie, before starting anti-HER2-targeted therapy), and at 2 years after randomization. BMI was calculated by dividing weight by height squared (kg/m^2), as per normal standard.¹² Patients were classified into 4 different groups according to the WHO BMI classification: underweight, $<18.50 \text{ kg}/\text{m}^2$; normal, 18.50 to $<25 \text{ kg}/\text{m}^2$; overweight, ≥ 25 to $<30 \text{ kg}/\text{m}^2$; and obese $\geq 30 \text{ kg}/\text{m}^2$.¹²

BMI at randomization was available for all patients included in ALTTO. Patients with available information on baseline BMI but without information on weight at 2 years after randomization were included only in the analysis related to the prognostic impact of BMI at diagnosis.

Objectives and Endpoints

The present analysis aimed to determine the prognostic impact of baseline BMI and weight change at 2 years after randomization in patients with HER2-positive early breast cancer.

Study endpoints were DFS, distant disease-free survival (DDFS), and OS defined as in the original ALTTO trial.¹⁰

Statistical Considerations

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

Weight change was calculated as a percentage (by calculating the difference between baseline weight and weight at 2 years after randomization). According to weight change, patients were classified into 3 categories (weight loss, defined as loss of $\geq 5.0\%$ from baseline; weight gain, defined as gain of $\geq 5.0\%$ from baseline; and stable weight, defined as loss or gain $<5.0\%$ from baseline). The 5.0% cutoff point was chosen for consistency with a prior study,¹³ and because this value reflects a clinically significant weight change that accounts for measurement errors or normal fluctuations.¹⁴

The relationships between baseline BMI and weight change at 2 years after randomization and DFS, DDFS, and OS were evaluated in the whole study population and then in predefined patients' subgroups according to type of anti-HER2 treatment received (trastuzumab alone, lapatinib alone, trastuzumab followed by lapatinib, and trastuzumab + lapatinib), hormone receptor status (positive or negative), and baseline menopausal status (premenopausal or postmenopausal). Survival curves for DFS, DDFS, and OS according to baseline BMI categories and weight change categories were estimated using the Kaplan-Meier method. Log-rank tests were performed for comparison. A multivariate analysis using a Cox proportional hazard model was used to generate hazard ratios. Only multivariate analyses are reported.

To evaluate the relationship between weight change and outcomes, a conditional landmark analysis approach was applied to reduce the impact of guarantee-time bias. Two years was the cutoff selected as the landmark. Median follow-up time (Q1–Q3) was derived from the reverse Kaplan-Meier method. DFS, DDFS, and OS were calculated excluding the first 2 years after randomization for each subject. Finally, the impact of weight change at 2 years after randomization within each baseline BMI category was evaluated.

All statistical tests were 2-sided, and *P* values <.05 were considered statistically significant. Analyses were performed using SAS 9.4 (SAS Institute Inc).

Results

All 8,381 patients randomized in ALTTO were included, of whom 187 (2.2%), 3,797 (45.3%), 2,690 (32.1%), and 1,707 (20.4%) were underweight, normal weight, overweight, or obese at baseline, respectively. Most patients were White (69%) or Asian (26%). Median follow-up at the time of the present analysis was 4.5 years (range, 3.6–5.0 years) (Figure 1).

Obese patients were more likely to come from Europe (*P*<.001), to be White (*P*<.001), to be younger (<65 years; *P*<.001), to be postmenopausal (*P*<.001), and to have tumors >2 and ≤5 cm (*P*<.001) that are more often poorly differentiated (*P*<.001). Additionally, significant differences existed in this sample between the management of patients with obesity versus normal weight; those with obesity were more likely to have been treated with mastectomy (*P*<.001), anthracycline-based chemotherapy (*P*<.001), and aromatase inhibitors (*P*<.001) (Table 1).

Prognostic Impact of Baseline BMI

Compared with patients of normal weight, those who were obese at baseline experienced significantly worse

DDFS (adjusted hazard ratio [aHR], 1.25; 95% CI, 1.04–1.50) and OS (aHR, 1.27; 95% CI, 1.01–1.60), with no significant difference in DFS (aHR, 1.14; 95% CI, 0.97–1.32) (Figure 2A, C; supplemental eTable 1, available with this article at JNCCN.org). Compared with patients of normal weight, no significant differences were observed in those who were overweight or underweight, respectively, with regard to DFS (aHR, 1.03; 95% CI, 0.90–1.17, and aHR, 1.06; 95% CI, 0.70–1.59), DDFS (aHR, 1.11; 95% CI, 0.94–1.30, and aHR, 1.14; 95% CI, 0.70–1.86), and OS (aHR, 1.11; 95% CI, 0.91–1.36, and aHR, 1.64; 95% CI, 0.97–2.78).

No significant interaction was observed between BMI categories and menopausal status at randomization (*P*=.563 for interaction). In the cohort of postmenopausal patients, obesity at baseline was associated with worse DFS (aHR, 1.26; 95% CI, 1.03–1.53), DDFS (aHR, 1.35; 95% CI, 1.06–1.71), and OS (aHR, 1.41; 95% CI, 1.06–1.88). In the cohort of premenopausal patients, baseline BMI did not impact prognosis (supplemental eTables 2 and 3).

No significant interaction was observed between BMI categories and hormone receptor status (*P*=.541 for interaction). In the cohort of hormone receptor-positive patients, baseline BMI did not impact prognosis. In the cohort of hormone receptor-negative patients, baseline BMI did not impact prognosis except for baseline obesity and overweight, which were associated with worse DDFS (aHR, 1.34; 95% CI, 1.05–1.73 and aHR, 1.30; 95% CI, 1.04–1.62, respectively) (supplemental eTables 4 and 5).

No significant interaction was observed between BMI categories and anti-HER2 treatment administered (*P*=.517 for interaction). Outcomes according to baseline BMI were not affected by anti-HER2 treatment; the only exception was for the trastuzumab followed by lapatinib arm, in which being underweight was associated with

Figure 1. CONSORT flow diagram.

Table 1. Patient Demographics and Clinical Characteristics by BMI^a

	Underweight n (%)	Normal n (%)	Overweight n (%)	Obese n (%)	P Value
Total, N	187	3,797	2,690	1,707	
Region					<.001
North America	11 (6)	293 (8)	285 (11)	370 (22)	
South America	7 (4)	134 (4)	182 (7)	121 (7)	
Europe	79 (42)	2,019 (53)	1,473 (55)	899 (53)	
Asia Pacific and South Africa	90 (48)	1,351 (36)	750 (28)	317 (19)	
Ethnicity					<.001
White	97 (52)	2,441 (64)	1,900 (71)	1,346 (79)	
Asian	88 (47)	1,245 (33)	644 (24)	216 (13)	
Black	0	35 (<1)	37 (1)	64 (4)	
Other/Missing	2 (1)	76 (2)	109 (4)	81 (5)	
Age					<.001
<65 y	170 (91)	3,500 (92)	2,366 (88)	1,490 (87)	
≥65 y	17 (9)	297 (8)	324 (12)	217 (13)	
Menopausal status					<.001
Premenopausal	103 (55)	1,937 (51)	1,032 (38)	564 (33)	
Postmenopausal or male	84 (45)	1,859 (49)	1,658 (62)	1,143 (67)	
Nodal status					.065
1–3 positive nodes	52 (28)	1,141 (30)	773 (29)	491 (29)	
≥4 positive nodes	39 (21)	777 (20)	633 (24)	417 (24)	
Node-negative	83 (44)	1,555 (41)	1,072 (40)	662 (39)	
Not applicable (neoadjuvant chemotherapy)	13 (7)	324 (9)	212 (8)	137 (8)	
Pathologic tumor size					<.001
Not applicable (neoadjuvant chemotherapy)	13 (7)	324 (9)	212 (8)	137 (8)	
≤2 cm	84 (45)	1,660 (44)	1,058 (39)	637 (37)	
>2 and ≤5 cm	78 (42)	1,603 (42)	1,238 (46)	817 (48)	
>5 cm	10 (5)	185 (5)	160 (6)	108 (6)	
Missing	2 (1)	25 (<1)	22 (<1)	8 (<1)	
Local HR status					.435
Positive	109 (58)	2,194 (58)	1,508 (56)	994 (58)	
Negative	78 (42)	1,603 (42)	1,182 (44)	713 (42)	
Invasive histologic type					.705
Ductal carcinoma	172 (92)	3,521 (93)	2,486 (92)	1,578 (92)	
Lobular carcinoma	3 (2)	83 (2)	69 (3)	33 (2)	
Others/Missing	12 (6)	193 (5)	135 (5)	96 (6)	
Histologic grade					<.001
Cannot be assessed	11 (6)	116 (3)	77 (3)	53 (3)	
Well differentiated	8 (4)	100 (3)	71 (3)	39 (2)	
Moderately differentiated	69 (37)	1,489 (39)	961 (36)	586 (34)	
Poorly differentiated	96 (51)	2,073 (55)	1,574 (59)	1,027 (60)	
Missing	3 (2)	19 (<1)	7 (<1)	2 (<1)	

(continued on next page)

Table 1. Patient Demographics and Clinical Characteristics by BMI^a (cont.)

	Underweight n (%)	Normal n (%)	Overweight n (%)	Obese n (%)	P Value
Surgery for primary tumor					<.001
Breast-conserving surgery	59 (32)	1,677 (44)	1,240 (46)	818 (48)	
Mastectomy	128 (68)	2,118 (56)	1,449 (54)	889 (52)	
Missing	0	2 (<1)	1 (<1)	0	
Timing of chemotherapy					<.001
Concurrent	72 (39)	1,626 (43)	1,211 (45)	859 (50)	
Sequential	115 (61)	2,171 (57)	1,479 (55)	848 (50)	
Type of chemotherapy					<.001
Anthracycline- and taxane-based regimens	126 (67)	2,176 (72)	1,904 (71)	1,105 (65)	
Taxane-based regimens	3 (2)	124 (3)	123 (5)	180 (11)	
Others	58 (31)	957 (25)	663 (25)	422 (25)	
Type of anti-HER2 treatment administered					.993
Trastuzumab + lapatinib	48 (26)	941 (25)	674 (25)	430 (25)	
Trastuzumab→lapatinib	50 (27)	934 (25)	680 (25)	427 (25)	
Lapatinib alone	45 (24)	967 (25)	657 (24)	431 (25)	
Trastuzumab alone	44 (24)	955 (25)	679 (25)	419 (25)	
Adjuvant endocrine therapy intended for patients with HR+ breast cancer ^b					.111
Not given	14 (13)	206 (9)	169 (11)	117 (12)	
Given	95 (87)	1,988 (91)	1,339 (89)	877 (88)	
Type of adjuvant endocrine therapy in patients with HR+ breast cancer ^c					<.001
AI	25 (26)	576 (29)	511 (39)	414 (48)	
AI and SERM	7 (7)	320 (16)	206 (16)	117 (13)	
SERM	62 (65)	1,065 (54)	601 (45)	337 (39)	
LHRH	1 (1)	17 (<1)	8 (<1)	3 (<1)	
Procedure					.362
Surgery	2 (2)	120 (6)	81 (6)	81 (9)	
Radiation	0	2 (<1)	5 (<1)	2 (<1)	

Abbreviations: AI, aromatase inhibitor; BMI, body mass index; HR+, hormone receptor–positive; LHRH, luteinizing hormone-releasing hormone; SERM, selective estrogen receptor modulator.

^aUnderweight: BMI<18.50 kg/m²; normal weight: 18.50≤BMI<25 kg/m²; overweight: 25≤BMI<30 kg/m²; obese: BMI≥30 kg/m².

^bThe definition of “adjuvant endocrine given” was widened on August 26, 2014, to include surgery and radiation procedures.

^c“Type of endocrine therapy” has no category for surgery and radiation procedures.

worse OS (aHR, 3.08; 95% CI, 1.27–7.45) (supplemental eTables 6–9).

Prognostic Impact of Weight Change

The prognostic value of weight change was assessed in 6,720 patients (80%). For the remaining 1,661 patients (20%), BMI at 2 years was not available due to the occurrence of a DFS event with the 2-year visit in 646 (39%), loss to follow-up for 74 (4%), and missing data on baseline weight for 11 (0.7%).

Weight loss ≥5.0% at 2 years after randomization was associated with 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) (Figure 3A, C). Weight gain

≥5.0% at 2 years after randomization did not affect DFS (aHR, 1.16; 95% CI, 0.96–1.40), DDFS (aHR, 1.25; 95% CI, 0.99–1.59) or OS (aHR, 1.21; 95% CI, 0.82–1.77) (Figure 3A, C; supplemental eTable 10).

No significant interaction was observed between weight change at 2 years after randomization and menopausal status ($P=.425$ for interaction). In the cohort of postmenopausal patients, no impact of weight change at 2 years after randomization was observed. In premenopausal patients, weight loss was associated with worse DFS (aHR, 1.57; 95% CI, 1.11–2.22), DDFS (aHR, 1.97; 95% CI, 1.29–3.02), and OS (aHR, 2.97; 95% CI, 1.55–5.68), and weight gain was associated with worse DDFS (aHR, 1.51; 95% CI, 1.06–2.14) (supplemental eTables 11 and 12).

Figure 2. Kaplan-Meier plot of (A) DDFS, (B) DFS, and (C) OS by baseline BMI categories. Underweight: BMI < 18.50 kg/m²; normal weight: 18.50 ≤ BMI < 25 kg/m²; overweight: 25 ≤ BMI < 30 kg/m²; obese: BMI ≥ 30 kg/m².

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; OS, overall survival.

No significant interaction was observed between weight change at 2 years after randomization and hormone receptor status ($P = .182$ for interaction). In the cohort of hormone receptor-positive patients, weight loss appeared to be associated with significant worse DFS (aHR, 1.46; 95% CI, 1.07–1.99) and OS (aHR, 2.24; 95% CI, 1.25–4.02), and weight gain was associated with significantly worse DFS (aHR, 1.35; 95% CI, 1.06–1.73) and DDFS (aHR, 1.48; 95% CI, 1.09–2.00). In the cohort of

Figure 3. Kaplan-Meier plot of (A) DDFS, (B) DFS, and (C) OS by weight change from baseline. A weight change from baseline of ≥ 5.0% and ≤ 5.0% was categorized as weight gain and weight loss, respectively.

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; OS, overall survival.

hormone receptor-negative patients, weight change did not impact prognosis (supplemental eTables 13 and 14).

No significant interaction was observed between weight change at 2 years after randomization and anti-HER2 treatment administered ($P = .591$ for interaction). Outcomes according to weight change did not change according to type of anti-HER2 treatment, with the exception of the lapatinib-alone arm, in which a significant association was found for weight loss in terms of DFS (aHR, 1.62; 95% CI,

1.05–2.49), DDFS (aHR, 1.98; 95% CI, 1.19–3.30), and OS (aHR, 2.62; 95% CI, 1.19–5.79) (supplemental eTables 15–18).

Impact of Weight Change According to Baseline BMI

To assess the impact of weight change better, its prognostic value was assessed separately within each cohort of patients according to baseline BMI.

For patients who were obese at baseline ($n=1,707$), weight loss was associated with significantly worse OS (aHR, 3.01; 95% CI, 1.38–6.57); no significant impact on DFS (aHR, 1.45; 95% CI, 0.91–2.30) or DDFS (aHR, 1.59; 95% CI, 0.91–2.78) was observed. For weight gain, there was no significant difference in DFS (aHR, 1.10; 95% CI, 0.70–1.71), DDFS (aHR, 1.17; 95% CI, 0.68–1.99), or OS (aHR, 0.97; 95% CI, 0.38–2.49) (supplemental eTable 19).

For patients who were overweight at baseline ($n=2,690$), weight loss $\geq 5\%$ did not significantly impact DFS (aHR, 1.28; 95% CI, 0.82–2.00), DDFS (aHR, 1.02; 95% CI, 0.55–1.86), or OS (aHR, 0.89; 95% CI, 0.34–2.38). For weight gain, no significant difference was observed in DFS (aHR, 1.40; 95% CI, 0.99–1.97), DDFS (aHR, 1.13; 95% CI, 0.72–1.77), or OS (aHR, 1.27; 95% CI, 0.63–2.54) (supplemental eTable 20).

For patients with normal weight at baseline ($n=3,797$), weight loss was associated with worse DDFS (aHR, 1.69; 95% CI, 1.04–2.77); no significant difference in either DFS (aHR, 1.33; 95% CI, 0.91–1.95) or OS (aHR, 2.00; 95% CI, 0.95–4.19) was observed. Weight gain did not significantly impact DFS (aHR, 1.05; 95% CI, 0.80–1.38), DDFS (aHR, 1.39; 95% CI, 0.98–1.97), or OS (aHR, 1.29; 95% CI, 0.72–2.32) (supplemental eTable 21).

For patients who were underweight at baseline, available data were too limited for analysis.

Adverse Effects and Treatment Completion

Obese patients had a higher incidence of grade 3/4 adverse effects (AEs; $P<.001$) and serious AEs ($P<.001$). Treatment discontinuation due to AEs was also more common ($P<.001$) (Table 2).

Discussion

To our knowledge, the present analysis is the largest to evaluate the impact of baseline BMI and weight change after treatment on the clinical outcomes of patients with HER2-positive early breast cancer. Our results suggest that obesity is associated with worse prognosis. Weight loss, but not weight gain, was associated with worse outcomes. Patients with obesity more frequently experienced grade 3/4 AEs, ≥ 1 serious AEs, and treatment discontinuation.

Multiple biologic mechanisms are thought to contribute to the negative impact of obesity in patients with cancer. The main plausible mechanisms involve alteration in multiple mediators, such as hyperinsulinemia, increased level of insulin-like growth factors (IGF-1), increased level of leptin, decreased level of adiponectin, and chronic inflammation.¹⁵ How and if these mechanisms affect neoplastic HER2-positive tumor cells is still uncertain. However, preclinical data have suggested that the crosstalk between leptin and IGF-1 can lead to hyperactivation of the HER2 pathway, thus reducing sensitivity to targeted therapy and potentially increasing risk of disease relapse.^{15,16}

Multiple meta-analyses have consistently shown that higher baseline BMI is associated with worse outcomes in

Table 2. Adverse Effects by Baseline BMI^a

	Underweight n (%)	Normal n (%)	Overweight n (%)	Obese n (%)	P Value
Total, N	187	3,797	2,690	1,707	
Grade 3/4 AEs					<.001
Patients with ≥ 1 grade 3/4 AEs	54 (29)	1,252 (33)	913 (34)	755 (44)	
No grade 3/4 AEs	133 (71)	2,545 (67)	1,777 (66)	952 (56)	
Serious AEs					<.001
≥ 1 serious AEs	30 (16)	610 (16)	463 (17)	404 (24)	
No serious AEs	157 (84)	3,187 (84)	2,227 (83)	1,303 (76)	
Fatal AEs					.065
Fatal AEs	4 (2)	23 (<1)	15 (<1)	10 (<1)	
No fatal AEs	183 (98)	3,774 (99)	2,675 (99)	1,697 (99)	
Treatment withdrawals due to AEs					<.001
Treatment withdrawals for toxicity	17 (9)	495 (13)	400 (15)	320 (19)	
No treatment withdrawals for toxicity	170 (91)	3,302 (87)	2,290 (85)	1,387 (81)	

Abbreviations: AE, adverse effect; BMI, body mass index.

^aUnderweight: BMI < 18.50 kg/m²; normal weight: 18.50 $\leq$ BMI < 25 kg/m²; overweight: 25 $\leq$ BMI < 30 kg/m²; obese: BMI $\geq$ 30 kg/m².

patients with all subtypes of breast cancer combined.^{4,17,18} Our study suggests that obesity at baseline was associated with significantly worse DDFS and OS, specifically in the cohort of patients with HER2-positive breast cancer. These results are consistent with results of a secondary analysis from the NCCTG N9831 trial,⁸ but differ from the those of the NSABP B31 and HERA trials that included a smaller sample size.^{6,8}

The most comprehensive meta-analysis on the impact of weight gain at an average 1.5 years postdiagnosis revealed that an increase of $\geq 5.0\%$ in weight was associated with a significant 12% higher risk in all-cause mortality in patients with breast cancer nonselected for tumor subtype.¹³ When stratified by baseline BMI (<25 and ≥ 25 kg/m²), all-cause mortality risk was not statistically different, although it was suggestive of an association in patients with initial BMI of <25 kg/m² who gained $>5.0\%$ of weight. No impact of weight loss was reported.¹³ In our study, weight loss $\geq 5.0\%$ (and not weight gain) at 2 years after randomization was associated with poorer DFS, DDFS, and OS. When analyzed according to baseline BMI, weight loss was associated with worse OS in patients who were obese, and with worse DDFS in those of normal weight. The only available data on weight change in patients with HER2-positive breast cancer derives from the HERA trial, in which BMI at 1 year after treatment did not impact outcomes.⁹ Smaller sample size ($n=1,249$ in HERA and $n=8,381$ in ALTTO) and time at which BMI change was assessed (ie, 1 year) could partly explain the different results, together with the lack of anti-HER2 therapy in half of the HERA population. We observed a worse impact of weight change in premenopausal patients and in those with hormone receptor-positive status. In terms of impact of weight change according to baseline BMI, these results are intriguing because they go against the general goal in survivor care plans to aim for weight loss.¹⁸ In an individual patient meta-analysis, the Premenopausal Breast Cancer Collaborative Group showed an inverse relationship between BMI and breast cancer risk that was stronger for hormone receptor-positive breast cancer in premenopausal women.¹⁹ The association remained true for women with HER2-positive breast cancer aged ≤ 35 years. It has been hypothesized that obesity can negatively regulate the hypothalamic-pituitary-axis through increased peripheral estradiol synthesis, and therefore reduce breast cancer risk.²⁰ Our finding regarding the impact of weight loss may reflect the loss of this protective state induced by obesity. This calls for caution if weight loss trials, such as the ongoing phase III Breast cancer WEight Loss study (BWEL; ClinicalTrials.gov identifier: NCT02750826), are to be conducted in survivors of HER2-positive breast cancer. One could also hypothesize that the relationship

of weight loss with outcomes is not causal, but rather explained by yet undetected metastatic disease at 2 years after randomization. Ideally, the effect of intentional versus unexplained weight loss would have been studied separately, but this information was not available.

Despite those findings, obesity, as defined based on BMI, is a major health issue because it is associated with an increase in all-cause mortality related to several negative health consequences (eg, cancer, type 2 diabetes, coronary heart disease, stroke) that significantly contribute to the financial burden of medical care.^{21–23} In recognition of the link between obesity and cancer, the ASCO Obesity Initiative has been created to inform and develop concrete actions to address this important issue.²⁴ Dietary changes, with accompanying weight reduction, before or after breast cancer diagnosis could impact outcomes in patients with breast cancer, but little is known about the effect of those interventions according to breast cancer subtype.^{25–27}

Our findings also showed that toxicities were more common in patients with obesity. This calls for awareness in patient management, because clinical recommendations state that there is no evidence that patients with obesity experience greater toxicity with actual weight-based doses.²⁹ Early discontinuation and subsequent uncompleted treatment can have adverse consequences and a closer follow-up may be required for patients with obesity.

Our study has potential limitations, among which is that this was not a preplanned analysis. The impact of weight change at longer time points could not be assessed. Information on the intentionality of weight loss after randomization was not collected. Although BMI is the main tool used internationally to assess patients' nutritional status,³⁰ concerns have been raised about its ability to accurately reflect body fat distribution and its generalization across sex and ethnicity.³¹ Additionally, White and Asian patients composed the vast majority of our population, limiting the generalizability of our results.

Conclusions

Results of this study suggest that among patients with HER2-positive early breast cancer, obesity at baseline is a poor prognostic factor and that weight loss is correlated with worse clinical outcomes. Together with other data in the field, our findings suggest that dietary counseling should be part of survivorship care programs.

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Correspondence: Samuel Martel, MD, Department of Hemato-Oncology, Hôpital Charles-Le Moyne/CISSS Montérégie-Centre, 3120 Boulevard Taschereau, Greenfield Park, Quebec, Canada. Email: samuel.martel3@usherbrooke.ca

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Supplemental online content for:

Body Mass Index and Weight Change in Patients With HER2-Positive Early Breast Cancer: Exploratory Analysis of the ALTTO BIG 2-06 Trial

Samuel Martel, MD; Matteo Lambertini, MD, PhD; Dominique Agbor-Tarh, MSc; Noam F. Ponde, MD; Andrea Gombos, MD; Vicki Paterson, BA; Florentine Hilbers, PhD; Larissa Korde, MD; Anna Manukyants, MD; Amylou Dueck, MD; Christian Maurer, MD; Martine Piccart, MD, PhD; Alvaro Moreno-Aspitia, MD; Christine Desmedt, MD; Serena Di Cosimo, MD; and Evandro de Azambuja, MD, PhD

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eTable 21: Prognostic Impact of Weight Change at 2 Years After Randomization in Patients Normal Weight at Baseline

eTable 1. Prognostic Impact of BMI^a at Randomization in All Patients

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	1,205 (14.38%)	8,381				
Underweight	24 (12.83%)	187	0.99 (0.66–1.49)	.972	1.06 (0.70–1.59)	.796
Normal	529 (13.93%)	3,797	Ref		Ref	
Overweight	389 (14.46%)	2,690	1.05 (0.92–1.19)	.479	1.03 (0.90–1.17)	.693
Obese	263 (15.41%)	1,707	1.17 (1.01–1.36)	.038	1.14 (0.97–1.32)	.102
DDFS	839 (10.01%)	8,381				
Underweight	17 (9.09%)	187	1.04 (0.64–1.69)	.872	1.14 (0.70–1.86)	.594
Normal	356 (9.38%)	3,797	Ref		Ref	
Overweight	275 (10.22%)	2,690	1.10 (0.94–1.29)	.231	1.11 (0.94–1.30)	.210
Obese	191 (11.19%)	1,707	1.26 (1.06–1.50)	.010	1.25 (1.04–1.50)	.015
OS	528 (6.30%)	8,381				
Underweight	15 (8.02%)	187	1.55 (0.92–2.62)	.100	1.64 (0.97–2.78)	.065
Normal	216 (5.69%)	3,797	Ref		Ref	
Overweight	175 (6.51%)	2,690	1.16 (0.95–1.42)	.142	1.11 (0.91–1.36)	.307
Obese	122 (7.15%)	1,707	1.35 (1.09–1.69)	.007	1.27 (1.01–1.60)	.038

Bold indicates statistically significant values.

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^aUnderweight: BMI<18.50 kg/m²; normal weight: 18.50≤BMI<25 kg/m²; overweight: 25≤BMI<30 kg/m²; obese: BMI≥30 kg/m².

eTable 2. Prognostic Impact of BMI^a at Randomization in Patients With Postmenopausal Status at Baseline

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	667 (14.06%)	4,744				
Underweight	8 (9.52%)	84	0.78 (0.39–1.58)	.490	0.73 (0.36–1.49)	.391
Normal	245 (13.18%)	1,859	Ref		Ref	
Overweight	235 (14.17%)	1,658	1.10 (0.92–1.32)	.293	1.10 (0.92–1.31)	.319
Obese	179 (15.66%)	1,143	1.26 (1.04–1.53)	.019	1.26 (1.03–1.53)	.023
DDFS	445 (9.38%)	4,744				
Underweight	5 (5.95%)	84	0.74 (0.31–1.81)	.511	0.67 (0.27–1.64)	.382
Normal	161 (8.66%)	1,859	Ref		Ref	
Overweight	155 (9.35%)	1,658	1.10 (0.88–1.37)	.391	1.11 (0.89–1.39)	.350
Obese	124 (10.85%)	1,143	1.32 (1.05–1.67)	.019	1.35 (1.06–1.71)	.016
OS	319 (6.72%)	4,744				
Underweight	6 (7.14%)	84	1.37 (0.60–3.11)	.454	1.28 (0.56–2.93)	.555
Normal	109 (5.86%)	1,859	Ref		Ref	
Overweight	115 (6.94%)	1,658	1.21 (0.93–1.57)	.152	1.19 (0.91–1.55)	.202
Obese	89 (7.79%)	1,143	1.42 (1.08–1.88)	.013	1.41 (1.06–1.88)	.020

Bold indicates statistically significant values.

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^aUnderweight: BMI<18.50 kg/m²; normal weight: 18.50≤BMI<25 kg/m²; overweight: 25≤BMI<30 kg/m²; obese: BMI≥30 kg/m².

eTable 3. Prognostic Impact of BMI^a at Randomization in Patients With Premenopausal Status at Baseline

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	538 (14.80%)	3,636				
Underweight	16 (15.53%)	103	1.14 (0.69–1.89)	.605	1.34 (0.80–2.22)	.263
Normal	284 (14.66%)	1,937	Ref		Ref	
Overweight	154 (14.92%)	1,032	1.01 (0.83–1.23)	.917	0.95 (0.78–1.15)	.589
Obese	84 (14.89%)	564	1.08 (0.85–1.38)	.528	0.95 (0.74–1.22)	.687
DDFS	394 (10.84%)	3,636				
Underweight	12 (11.65%)	103	1.24 (0.69–2.21)	.477	1.55 (0.86–2.79)	.145
Normal	195 (10.07%)	1,987	Ref		Ref	Ref
Overweight	120 (11.63%)	1,032	1.15 (0.91–1.44)	.234	1.09 (0.87–1.37)	.460
Obese	67 (11.88%)	564	1.26 (0.95–1.66)	.108	1.09 (0.82–1.45)	.546
OS	209 (5.75%)	3,636				
Underweight	9 (8.74%)	103	1.71 (0.87–3.38)	.121	2.14 (1.07–4.27)	.031
Normal	107 (5.52%)	1,937	Ref		Ref	—
Overweight	60 (5.81%)	1,032	1.05 (0.77–1.44)	.753	0.98 (0.71–1.36)	.918
Obese	33 (5.85%)	564	1.16 (0.78–1.71)	.465	0.96 (0.65–1.43)	.843

Bold indicates statistically significant values.

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^aUnderweight: BMI<18.50 kg/m²; normal weight: 18.50≤BMI<25 kg/m²; overweight: 25≤BMI<30 kg/m²; obese: BMI≥30 kg/m².

eTable 4. Prognostic Impact of BMI^a at Randomization in Patients With Hormone Receptor–Positive Breast Cancer

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	596 (12.40%)	4,805				
Underweight	11 (10.09%)	109	0.84 (0.46–1.54)	.579	0.90 (0.49–1.65)	.736
Normal	275 (12.53%)	2,194	Ref		Ref	
Overweight	181 (12.00%)	1,508	0.96 (0.80–1.16)	.681	0.90 (0.74–1.09)	.279
Obese	129 (12.98%)	994	1.11 (0.90–1.37)	.336	1.05 (0.84–1.30)	.662
DDFS	397 (8.26%)	4,805				
Underweight	7 (6.42%)	109	0.82 (0.38–1.74)	.604	0.849	.849
Normal	179 (8.16%)	2,194	Ref		Ref	
Overweight	120 (7.96%)	1,508	0.98 (0.78–1.23)	.861	0.91 (0.72–1.15)	.443
Obese	91 (9.15%)	994	1.20 (0.93–1.55)	.152	1.15 (0.88–1.49)	.306
OS	227 (4.72%)	4,805				
Underweight	7 (6.42%)	109	1.62 (0.75–3.48)	.220	1.79 (0.83–3.88)	.139
Normal	94 (4.28%)	2,194	Ref		Ref	
Overweight	70 (4.64%)	1,508	1.09 (0.80–1.49)	.568	0.97 (0.71–1.32)	.836
Obese	56 (5.63%)	994	1.43 (1.03–1.99)	.034	1.23 (0.87–1.74)	.237

Bold indicates statistically significant values.

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^aUnderweight: BMI<18.50 kg/m²; normal weight: 18.50≤BMI<25 kg/m²; overweight: 25≤BMI<30 kg/m²; obese: BMI≥30 kg/m².

eTable 5. Prognostic Impact of BMI^a at Randomization in Patients With Hormone Receptor–Negative Breast Cancer

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	609 (17.03%)	3,576				
Underweight	13 (16.67%)	78	1.19 (0.68–2.07)	.547	1.24 (0.70–2.18)	.457
Normal	254 (15.85%)	1,603	Ref		Ref	
Overweight	208 (17.60%)	1,182	1.13 (0.94–1.35)	.205	1.15 (0.96–1.39)	.130
Obese	134 (18.79%)	713	1.24 (1.01–1.53)	.040	1.22 (0.98–1.51)	.072
DDFS	442 (12.36%)	3,576				
Underweight	10 (12.82%)	78	1.31 (0.69–2.48)	.407	1.38 (0.72–2.62)	.332
Normal	177 (11.04%)	1,603	Ref		Ref	
Overweight	155 (13.11%)	1,182	1.20 (0.97–1.49)	.092	1.30 (1.04–1.62)	.019
Obese	100 (14.03%)	713	1.33 (1.04–1.70)	.022	1.34 (1.05–1.73)	.021
OS	301 (8.42%)	3,576				
Underweight	8 (10.26%)	78	1.54 (0.75–3.14)	.239	1.46 (0.71–3.02)	.307
Normal	122 (7.61%)	1,603	Ref		Ref	
Overweight	105 (8.88%)	1,182	1.20 (0.92–1.55)	.178	1.23 (0.94–1.60)	.125
Obese	66 (9.26%)	713	1.31 (0.97–1.77)	.076	1.26 (0.92–1.71)	.146

Bold indicates statistically significant values.

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^aUnderweight: BMI < 18.50 kg/m²; normal weight: 18.50 ≤ BMI < 25 kg/m²; overweight: 25 ≤ BMI < 30 kg/m²; obese: BMI ≥ 30 kg/m².

eTable 6. Prognostic Impact of BMI^a at Randomization in Patients Treated With Trastuzumab Alone

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	301 (14.35%)	2,097				
Underweight	7 (15.91%)	44	1.19 (0.56–2.54)	.656	1.24 (0.57–2.67)	.587
Normal	137 (14.35%)	955	Ref		Ref	
Overweight	87 (12.81%)	679	0.89 (0.68–1.16)	.384	0.86 (0.65–1.13)	.273
Obese	70 (16.71%)	419	1.22 (0.91–1.62)	.183	1.21 (0.89–1.63)	.223
DDFS	204 (9.73%)	2,097				
Underweight	5 (11.36%)	44	1.31 (0.53–3.22)	.558	1.47 (0.59–3.67)	.412
Normal	90 (9.42%)	955	Ref		Ref	
Overweight	61 (8.98%)	679	0.95 (0.69–1.32)	.763	0.94 (0.67–1.31)	.708
Obese	48 (11.46%)	419	1.27 (0.90–1.81)	.175	1.29 (0.89–1.86)	.175
OS	135 (6.44%)	2,097				
Underweight	3 (6.82%)	44	1.25 (0.39–4.01)	.703	1.32 (0.41–4.29)	.644
Normal	55 (5.76%)	955	Ref		Ref	
Overweight	46 (6.77%)	679	1.18 (0.80–1.75)	.400	1.02 (0.69–1.54)	.882
Obese	31 (7.40%)	419	1.39 (0.89–2.15)	.146	1.14 (0.72–1.80)	.585

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^aUnderweight: BMI < 18.50 kg/m²; normal weight: 18.50 ≤ BMI < 25 kg/m²; overweight: 25 ≤ BMI < 30 kg/m²; obese: BMI ≥ 30 kg/m².

eTable 7. Prognostic Impact of BMI^a at Randomization in Patients Treated With Lapatinib Alone

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	366 (17.43%)	2,100				
Underweight	4 (8.89%)	45	0.57 (0.21–1.52)	.259	0.62 (0.23–1.68)	.347
Normal	171 (17.68%)	967	Ref		Ref	
Overweight	121 (18.42%)	657	1.05 (0.83–1.32)	.694	1.13 (0.89–1.43)	.314
Obese	70 (16.24%)	431	0.96 (0.73–1.27)	.777	1.02 (0.76–1.35)	.914
DDFS	277 (13.19%)	2,100				
Underweight	2 (4.44%)	45	0.38 (0.09–1.54)	.176	0.45 (0.11–1.85)	.269
Normal	129 (13.34%)	967	Ref		Ref	
Overweight	93 (14.16%)	657	1.07 (0.82–1.40)	.595	1.21 (0.92–1.59)	.170
Obese	53 (12.30%)	431	0.97 (0.70–1.33)	.830	1.03 (0.74–1.43)	.864
OS	168 (8.00%)	2,100				
Underweight	4 (8.89%)	45	1.34 (0.49–3.65)	.570	1.44 (0.52–4.01)	.487
Normal	79 (8.17%)	967	Ref		Ref	
Overweight	55 (8.37%)	657	1.03 (0.73–1.46)	.850	1.12 (0.79–1.59)	.522
Obese	30 (6.96%)	431	0.92 (0.61–1.41)	.716	1.00 (0.65–1.55)	.985

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^aUnderweight: BMI < 18.50 kg/m²; normal weight: 18.50 ≤ BMI < 25 kg/m²; overweight: 25 ≤ BMI < 30 kg/m²; obese: BMI ≥ 30 kg/m².

eTable 8. Prognostic Impact of BMI^a at Randomization in Patients Treated With Trastuzumab Followed by Lapatinib

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	284 (13.58%)	2,091				
Underweight	8 (16.00%)	50	1.32 (0.65–2.71)	.442	1.40 (0.68–2.89)	.365
Normal	120 (12.85%)	934	Ref		Ref	
Overweight	94 (13.82%)	680	1.09 (0.83–1.43)	.522	0.99 (0.75–1.30)	.929
Obese	62 (14.52%)	427	1.18 (0.87–1.61)	.281	1.06 (0.77–1.46)	.702
DDFS	196 (9.37%)	2,091				
Underweight	6 (12.00%)	50	1.62 (0.71–3.73)	.255	1.61 (0.69–3.77)	.274
Normal	72 (7.71%)	934	Ref		Ref	
Overweight	69 (10.15%)	680	1.32 (0.95–1.84)	.095	1.17 (0.84–1.64)	.354
Obese	49 (11.48%)	427	1.56 (1.08–2.24)	.016	1.43 (0.98–2.08)	.060
OS	119 (5.69%)	2,091				
Underweight	6 (12.00%)	50	3.04 (1.29–7.19)	.011	3.08 (1.27–7.45)	.012
Normal	39 (4.18%)	934	Ref		Ref	
Overweight	44 (6.47%)	680	1.59 (1.04–2.45)	.034	1.36 (0.88–2.10)	.173
Obese	30 (7.03%)	427	1.78 (1.11–2.87)	.018	1.54 (0.94–2.52)	.087

Bold indicates statistically significant values.

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^aUnderweight: BMI < 18.50 kg/m²; normal weight: 18.50 ≤ BMI < 25 kg/m²; overweight: 25 ≤ BMI < 30 kg/m²; obese: BMI ≥ 30 kg/m².

eTable 9. Prognostic Impact of BMI^a at Randomization in Patients Treated With Trastuzumab + Lapatinib

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	254 (12.14%)	2,093				
Underweight	5 (10.42%)	48	1.03 (0.42–2.54)	.942	1.07 (0.43–2.64)	.887
Normal	101 (10.73%)	941	Ref		Ref	
Overweight	87 (12.91%)	674	1.23 (0.93–1.64)	.153	1.15 (0.86–1.55)	.338
Obese	61 (14.19%)	430	1.45 (1.06–1.99)	.022	1.30 (0.93–1.81)	.119
DDFS	162 (7.74%)	2,093				
Underweight	4 (8.33%)	48	1.27 (0.46–3.49)	.641	1.23 (0.44–3.41)	.693
Normal	65 (6.91%)	941	Ref		Ref	
Overweight	52 (7.72%)	674	1.14 (0.79–1.65)	.474	1.08 (0.75–1.57)	.672
Obese	41 (9.53%)	430	1.50 (1.01–2.21)	.043	1.43 (0.95–2.13)	.084
OS	106 (5.06%)	2,093				
Underweight	2 (4.17%)	48	0.96 (0.23–2.97)	.957	1.00 (0.24–4.19)	.995
Normal	43 (4.57%)	941	Ref		Ref	
Overweight	30 (4.45%)	674	0.99 (0.62–1.57)	.957	0.92 (0.57–1.48)	.736
Obese	31 (7.21%)	430	1.74 (1.10–2.76)	.019	1.59 (0.98–2.57)	.062

Bold indicates statistically significant values.

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

eTable 10. Prognostic Impact of Weight Change at 2 Years After Randomization in All Patients

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	559 (8.32%)	6,720				
Weight loss	86 (9.91%)	868	1.33 (1.05–1.69)	.019	1.34 (1.05–1.71)	.017
Stable weight	303 (7.67%)	3,953	Ref		Ref	
Weight gain	170 (8.95%)	1,899	1.19 (0.99–1.44)	.066	1.16 (0.96–1.40)	.132
DDFS	341 (5.07%)	6,720				
Weight loss	54 (6.22%)	868	1.43 (1.06–1.94)	.021	1.46 (1.07–1.98)	.016
Stable weight	177 (4.48%)	3,953	Ref		Ref	
Weight gain	110 (5.79%)	1,899	1.32 (1.04–1.67)	.022	1.25 (0.99–1.59)	.065
OS	141 (2.10%)	6,720				
Weight loss	28 (3.23%)	868	1.85 (1.20–2.87)	.006	1.83 (1.18–2.84)	.007
Stable weight	71 (1.80%)	3,953	Ref		Ref	
Weight gain	42 (2.21%)	1,899	1.26 (0.86–1.85)	.231	1.21 (0.82–1.77)	.342

Bold indicates statistically significant values.

Abbreviations: DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

eTable 11. Prognostic Impact of Weight Change at 2 Years After Randomization in Patients With Postmenopausal Status at Baseline

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	304 (7.95%)	3,825				
Weight loss	42 (8.48%)	495	1.15 (0.82–1.61)	.408	1.18 (0.84–1.66)	.328
Stable weight	179 (7.61%)	2,351	Ref		Ref	
Weight gain	83 (8.48%)	979	1.12 (0.87–1.46)	.377	1.07 (0.82–1.39)	.621
DDFS	180 (4.71%)	3,825				
Weight loss	23 (4.65%)	495	1.07 (0.68–1.67)	.780	1.11 (0.71–1.75)	.641
Stable weight	105 (4.47%)	2,351	Ref		Ref	
Weight gain	52 (5.31%)	979	1.20 (0.86–1.67)	.293	1.11 (0.79–1.55)	.538
OS	85 (2.22%)	3,825				
Weight loss	12 (2.42%)	495	1.24 (0.66–2.33)	.508	1.20 (0.63–2.28)	.572
Stable weight	48 (2.04%)	2,351	Ref		Ref	
Weight gain	25 (2.55%)	979	1.27 (0.78–2.05)	.339	1.14 (0.70–1.86)	.593

Abbreviations: DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

eTable 12. Prognostic Impact of Weight Change at 2 Years After Randomization in Patients With Premenopausal Status at Baseline

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	255 (8.81%)	2,895				
Weight loss	44 (11.80%)	373	1.58 (1.12–2.23)	.009	1.57 (1.11–2.22)	.011
Stable weight	124 (7.74%)	1,602	Ref		Ref	
Weight gain	87 (9.46%)	920	1.27 (0.96–1.66)	.093	1.28 (0.97–1.68)	.085
DDFS	161 (5.56%)	2,895				
Weight loss	31 (8.31%)	373	1.94 (1.27–2.95)	.002	1.97 (1.29–3.02)	.002
Stable weight	72 (4.49%)	1,602	Ref		Ref	
Weight gain	58 (6.30%)	920	1.46 (1.03–2.07)	.031	1.51 (1.06–2.14)	.022
OS	56 (1.93%)	2,895				
Weight loss	16 (4.29%)	373	2.97 (1.57–5.62)	<.001	2.97 (1.55–5.68)	<.001
Stable weight	23 (1.44%)	1,602	Ref		Ref	
Weight gain	17 (1.85%)	920	1.32 (0.71–2.48)	.379	1.35 (0.71–2.55)	.356

Bold indicates statistically significant values.

Abbreviations: DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

eTable 13. Prognostic Impact of Weight Change at 2 Years After Randomization in Patients With Hormone Receptor–Positive Breast Cancer

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	330 (8.41%)	3,926				
Weight loss	53 (10.27%)	516	1.45 (1.07–1.98)	.018	1.46 (1.07–1.99)	.016
Stable weight	168 (7.33%)	2,293	Ref		Ref	
Weight gain	109 (9.76%)	1,117	1.38 (1.09–1.76)	.008	1.35 (1.06–1.73)	.015
DDFS	202 (5.15%)	3,926				
Weight loss	31 (6.01%)	516	1.45 (0.97–2.16)	.074	1.48 (0.99–2.22)	.058
Stable weight	99 (4.32%)	2,293	Ref		Ref	
Weight gain	72 (6.45%)	1,117	1.55 (1.15–2.10)	.005	1.48 (1.09–2.00)	.013
OS	79 (2.01%)	3,926				
Weight loss	17 (3.29%)	516	2.22 (1.24–3.96)	.007	2.24 (1.25–4.02)	.007
Stable weight	35 (1.53%)	2,293	Ref		Ref	
Weight gain	27 (2.42%)	1,117	1.65 (1.00–2.72)	.051	1.63 (0.98–2.70)	.060

Bold indicates statistically significant values.

Abbreviations: DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

eTable 14. Prognostic Impact of Weight Change at 2 Years After Randomization in Patients With Hormone Receptor–Negative Breast Cancer

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	229 (8.20%)	2,794				
Weight loss	33 (9.38%)	352	1.18 (0.81–1.73)	.385	1.21 (0.82–1.77)	.334
Stable weight	135 (7.80%)	1,660	Ref		Ref	
Weight gain	61 (7.33%)	782	0.96 (0.71–1.30)	.810	0.93 (0.69–1.27)	.657
DDFS	139 (4.97%)	2,794				
Weight loss	23 (6.53%)	352	1.42 (0.89–2.27)	.136	1.47 (0.92–2.35)	.107
Stable weight	78 (4.70%)	1,660	Ref		Ref	
Weight gain	38 (4.86%)	782	1.03 (0.70–1.52)	.864	0.98 (0.66–1.44)	.899
OS	62 (2.22%)	2,794				
Weight loss	11 (3.13%)	352	1.47 (0.75–2.88)	.268	1.35 (0.68–2.69)	.387
Stable weight	36 (2.17%)	1,660	Ref		Ref	
Weight gain	15 (1.92%)	782	1.03 (0.70–1.52)	.864	0.98 (0.66–1.44)	.473

Abbreviations: DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

eTable 15. Prognostic Impact of Weight Change at 2 Years After Randomization in Patients Treated With Trastuzumab Alone

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	151 (8.76%)	1,724				
Weight loss	22 (10.84%)	203	1.42 (0.89–2.28)	.144	1.42 (0.88–2.28)	.151
Stable weight	79 (7.91%)	999	Ref		Ref	
Weight gain	50 (9.58%)	522	1.24 (0.87–1.77)	.231	1.20 (0.84–1.71)	.322
DDFS	93 (5.39%)	1,724				
Weight loss	14 (6.90%)	203	1.55 (0.85–2.82)	.152	1.51 (0.82–2.76)	.182
Stable weight	46 (4.60%)	999	Ref		Ref	
Weight gain	33 (6.32%)	522	1.41 (0.90–2.21)	.128	1.33 (0.85–2.09)	.215
OS	43 (2.49%)	1,724				
Weight loss	8 (3.94%)	203	1.78 (0.80–3.98)	.160	1.87 (0.83–4.21)	.132
Stable weight	23 (2.30%)	999	Ref		Ref	
Weight gain	12 (2.30%)	522	1.04 (0.52–2.09)	.908	1.09 (0.54–2.21)	.812

Abbreviations: DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

eTable 16. Prognostic Impact of Weight Change at 2 Years After Randomization in Patients Treated With Lapatinib Alone

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	147 (9.42%)	1,561				
Weight loss	29 (13.43%)	216	1.62 (1.06–2.48)	.027	1.62 (1.05–2.49)	.028
Stable weight	79 (8.77%)	901	Ref		Ref	
Weight gain	39 (8.78%)	444	1.02 (0.69–1.50)	.921	1.00 (0.68–1.47)	.983
DDFS	102 (6.53%)	1,561				
Weight loss	22 (10.19%)	216	1.97 (1.19–3.26)	.008	1.98 (1.19–3.30)	.008
Stable weight	49 (5.44%)	901	Ref		Ref	
Weight gain	31 (6.98%)	444	1.31 (0.83–2.05)	.245	1.24 (0.79–1.96)	.347
OS	41 (2.63%)	1,561				
Weight loss	11 (5.09%)	216	2.87 (1.33–6.19)	.007	2.62 (1.19–5.79)	.017
Stable weight	16 (1.78%)	901	Ref		Ref	
Weight gain	14 (3.15%)	444	1.81 (0.88–3.71)	.107	1.79 (0.86–3.70)	.118

Bold indicates statistically significant values.

Abbreviations: DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

eTable 17. Prognostic Impact of Weight Change at 2 Years After Randomization in Patients Treated With Trastuzumab Followed by Lapatinib

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	126 (7.34%)	1,717				
Weight loss	19 (8.56%)	222	1.25 (0.75–2.07)	.385	1.34 (0.81–2.24)	.256
Stable weight	72 (6.97%)	1,033	Ref		Ref	
Weight gain	35 (7.58%)	462	1.12 (0.75–1.67)	.594	1.10 (0.73–1.66)	.632
DDFS	72 (4.19%)	1,717				
Weight loss	12 (5.41%)	222	1.43 (0.75–2.72)	.279	1.61 (0.84–3.11)	.152
Stable weight	40 (3.87%)	1,033	Ref		Ref	
Weight gain	20 (4.33%)	462	1.14 (0.67–1.95)	.628	1.11 (0.65–1.92)	.696
OS	24 (1.40%)	1,717				
Weight loss	3 (1.35%)	222	0.93 (0.27–3.22)	.910	0.99 (0.28–3.47)	.989
Stable weight	15 (1.45%)	1,033	Ref		Ref	
Weight gain	6 (1.30%)	462	0.92 (0.36–2.37)	.862	0.90 (0.35–2.36)	.838

Abbreviations: DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

eTable 18. Prognostic Impact of Weight Change at 2 Years After Randomization in Patients Treated With Trastuzumab + Lapatinib

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	135 (7.54%)	1,718				
Weight loss	16 (6.22%)	227	1.00 (0.58–1.71)	.988	1.00 (0.58–1.73)	.999
Stable weight	73 (6.97%)	1,020	Ref		Ref	
Weight gain	46 (9.38%)	471	1.38 (0.96–2.00)	.085	1.37 (0.94–2.00)	.099
DDFS	74 (4.31%)	1,718				
Weight loss	6 (2.64%)	227	0.65 (0.28–1.53)	.325	0.69 (0.29–1.62)	.393
Stable weight	42 (4.12%)	1,020	Ref		Ref	
Weight gain	26 (5.52%)	471	1.36 (0.83–2.22)	.220	1.40 (0.85–2.31)	.192
OS	33 (1.92%)	1,718				
Weight loss	6 (2.64%)	227	1.64 (0.65–4.16)	.298	1.62 (0.64–4.15)	.312
Stable weight	17 (1.67%)	1,020	Ref		Ref	
Weight gain	10 (2.12%)	471	1.29 (0.59–2.81)	.527	1.17 (0.53–2.60)	.699

Abbreviations: DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

eTable 19. Prognostic Impact of Weight Change at 2 Years After Randomization in Patients Obese^a at Baseline

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	122 (9.19%)	1,327				
Weight loss	26 (10.70%)	243	1.35 (0.86–2.13)	.819	1.45 (0.91–2.30)	.114
Stable weight	68 (8.48%)	802	Ref		Ref	
Weight gain	28 (9.93%)	282	1.21 (0.78–1.87)	.405	1.10 (0.70–1.71)	.683
DDFS	83 (6.25%)	1,327				
Weight loss	18 (7.41%)	243	1.39 (0.81–2.40)	.237	1.59 (0.91–2.78)	.106
Stable weight	45 (5.61%)	802	Ref		Ref	
Weight gain	20 (7.09%)	282	1.29 (0.76–2.19)	.337	1.17 (0.68–1.99)	.572
OS	35 (2.64%)	1,327				
Weight loss	12 (4.94%)	243	2.58 (1.23–5.41)	.012	3.01 (1.38–6.57)	.006
Stable weight	17 (2.12%)	802	Ref		Ref	
Weight gain	6 (2.13%)	282	1.05 (0.41–2.66)	.918	0.97 (0.38–2.49)	.948

Bold indicates statistically significant values.

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^aBMI ≥ 30 kg/m².

eTable 20. Prognostic Impact of Weight Change at 2 Years After Randomization in Patients Overweight^a at Baseline

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	168 (7.74%)	2,170				
Weight loss	25 (8.36%)	299	1.23 (0.79–1.91)	.367	1.28 (0.82–2.00)	.275
Stable weight	89 (6.84%)	1,302	Ref		Ref	
Weight gain	54 (9.49%)	569	1.41 (1.01–1.98)	.045	1.40 (0.99–1.97)	.055
DDFS	99 (4.56%)	2,170				
Weight loss	13 (4.35%)	299	0.99 (0.54–1.81)	.971	1.02 (0.55–1.86)	.960
Stable weight	57 (4.38%)	1,302	Ref		Ref	
Weight gain	29 (5.10%)	569	1.17 (0.75–1.83)	.483	1.13 (0.72–1.77)	.609
OS	42 (1.94%)	2,170				
Weight loss	5 (1.67%)	299	0.91 (0.35–2.38)	.843	0.89 (0.34–2.38)	.821
Stable weight	24 (1.84%)	1,302	Ref		Ref	
Weight gain	13 (2.28%)	569	1.31 (0.66–2.58)	.435	1.27 (0.63–2.54)	.499

Bold indicates statistically significant values.

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^a25 ≤ BMI < 30 kg/m².

eTable 21. Prognostic Impact of Weight Change at 2 Years After Randomization in Patients Normal Weight^a at Baseline

	Events n (%)	N	Univariate		Multivariate	
			HR (95% CI)	P Value	HR (95% CI)	P Value
DFS	260 (8.44%)	3,082				
Weight loss	33 (10.51%)	314	1.33 (0.91–1.94)	.143	1.33 (0.91–1.95)	.142
Stable weight	143 (8.03%)	1,781	Ref		Ref	
Weight gain	84 (8.51%)	987	1.09 (0.83–1.42)	.553	1.05 (0.80–1.38)	.726
DDFS	153 (4.96%)	3,082				
Weight loss	21 (6.69%)	314	1.64 (1.01–2.66)	.046	1.69 (1.04–2.77)	.035
Stable weight	74 (4.15%)	1,781	Ref		Ref	
Weight gain	58 (5.88%)	987	1.45 (1.03–2.05)	.034	1.39 (0.98–1.97)	.063
OS	58 (1.88%)	3,082				
Weight loss	10 (3.18%)	314	2.03 (0.99–4.18)	.054	2.00 (0.95–4.19)	.066
Stable weight	28 (1.57%)	1,781	Ref		Ref	
Weight gain	20 (2.03%)	987	1.33 (0.75–2.35)	.335	1.29 (0.72–2.32)	.392

Bold indicates statistically significant values.

Abbreviations: BMI, body mass index; DDFS, distant disease-free survival; DFS, disease-free survival; HR, hazard ratio; OS, overall survival.

^a18.50 ≤ BMI < 25 kg/m².