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Article

# Clinical Implications of Body Mass Index in Metastatic Breast Cancer Patients Treated With Abemaciclib and Endocrine Therapy

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## Abstract

**Background:** There are limited data regarding the impact of body mass index (BMI) on outcomes in advanced breast cancer, especially in patients treated with endocrine therapy (ET) + cyclin-dependent kinase 4/6 inhibitors. **Methods:** A pooled analysis of individual patient-level data from MONARCH 2 and 3 trials was performed. Patients were classified according to baseline BMI into underweight (<18.5 kg/m$^2$), normal (18.5-24.9 kg/m$^2$), overweight (25-29.9 kg/m$^2$), and obese (≥30 kg/m$^2$) and divided into 2 treatment groups: abemaciclib + ET vs placebo + ET. The primary endpoint was progression-free survival (PFS) according to BMI in each treatment group. Secondary endpoints were response rate, adverse events according to BMI, and loss of weight (≥5% from baseline) during treatment. **Results:** This analysis included 1138 patients (757 received abemaciclib + ET and 381 placebo + ET). There was no difference in PFS between BMI categories in either group, although normal-weight patients presented a numerically higher benefit with abemaciclib + ET ($P_{interaction}$ = .07). Normal and/or underweight patients presented higher overall response rate in the abemaciclib + ET group compared with overweight and/or obese patients (49.4% vs 41.6%, odds ratio = 0.73, 95% confidence interval = 0.54 to 0.99) as well as higher neutropenia frequency (51.0% vs 40.4%, $P$ = .004). Weight loss was more frequent in the abemaciclib + ET group (odds ratio = 3.23, 95% confidence interval = 2.09 to 5.01). **Conclusions:** Adding abemaciclib to ET prolongs PFS regardless of BMI, showing that overweight or obese patients also benefit from this regimen. Our results elicit the possibility of a better effect of abemaciclib in normal and/or underweight patients compared with overweight and/or obese patients. More studies analyzing body composition parameters in patients under treatment with cyclin-dependent kinase 4/6 inhibitors may further clarify this hypothesis.

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Breast cancer (BC) is the most frequent form of malignancy among women (1). Although there has been a marked evolution in treatment strategies (2,3), the identification of additional prognostic and predictive factors according to patient's body composition represents a growing research area aiming to further improve the management of this disease (4–7). In this regard, overweight and obesity, weight gain or loss during treatments, and muscle and adipose tissue measurements have received increasing attention as potential prognostic factors as well as predictors of treatment-related toxicities (8,9).

A substantial body of evidence supports the relationship between being overweight or obese with worse outcomes in patients with early-stage BC, especially in estrogen receptor (ER)-positive BC (10). However, in the metastatic setting, little is known and most data are from retrospective and institutional case series, with conflicting results reported so far (11–16).

The current standard of care for most patients with ER-positive metastatic BC consists of a cyclin-dependent kinase (CDK) 4/6 inhibitor combined with endocrine therapy (ET) (17). Preclinical data suggest that cell-cycle regulators such as CDK 4 and 6 affect cell metabolism and the control of important metabolic processes such as adipogenesis and lipid synthesis, muscle tissue, glucose regulation, and mitochondrial function (18–

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22). Recent preclinical studies have unveiled CDK4 and 6 as potential targets against diet-induced obesity, suggesting that the use of CDK 4/6 inhibitors could have a direct effect on body fat mass and muscle mass (23,24).

Therefore, we hypothesized that overweight and obese patients could have different efficacy and safety outcomes (in terms of progression-free survival [PFS], response rates [RR], and incidence of adverse events [AEs]) compared with patients with normal body mass index (BMI) when treated with abemaciclib and ET. In addition, because an effect of reducing fat mass was previously reported with the use of abemaciclib in obese mouse models, we investigated whether this treatment regimen could affect body composition parameters (ie, weight loss) compared with patients treated with ET alone.

To answer these research questions, we performed a pooled, individual patient–level analysis of the MONARCH 2 and MONARCH 3 trials.

## Methods

### Data Source and Patient Selection

This study is a pooled post hoc analysis of individual patient-level data from the MONARCH 2 (NCT02107703) and MONARCH 3 (NCT02246621) clinical trials. Study design and results for the primary analyses of both trials were previously published (25–28). Briefly, MONARCH 2 and MONARCH 3 were randomized, placebo-controlled, phase III trials of abemaciclib combined with ET vs placebo + ET for patients with advanced, ER-positive, HER2-negative BC (25,27).

Deidentified individual patient–level data were made available by Lilly and accessible through the secure Vivli online platform from November 1, 2019, to April 20, 2020 (29). Raw data were extracted and compared with the available published data to ensure accuracy. The institutional review board at each participating site approved the MONARCH 2 and 3 protocols. All patients provided written informed consent as previously reported (25–28).

### Predictor and Outcome Definition

The primary outcome of this analysis was PFS according to BMI in each treatment group. For the purpose of this analysis, patients were divided into 2 groups: patients from MONARCH 2 randomly assigned to abemaciclib + fulvestrant and patients from MONARCH 3 randomly assigned to abemaciclib + nonsteroidal aromatase inhibitor were grouped together as abemaciclib + ET, whereas patients randomly assigned to placebo + fulvestrant and placebo + nonsteroidal aromatase inhibitor were grouped together as placebo + ET. Secondary outcomes were RR, treatment-related AEs, and weight changes. PFS, RR, and AEs were defined according to the original study protocols.

Baseline BMI was calculated and recorded at study enrollment or on the first day of treatment. BMI was categorized by World Health Organization criteria: underweight ($<18.5\ kg/m^2$), normal weight ($18.5\text{-}24.9\ kg/m^2$), overweight ($25\text{-}29.9\ kg/m^2$), and obese ($\geq 30\ kg/m^2$) (30). Patients with missing height and/or weight information for the calculation of BMI were excluded from the analysis.

For the primary outcome, patients were classified as underweight and/or normal weight ($BMI < 25\ kg/m^2$) vs overweight and/or obese ($BMI \geq 25\ kg/m^2$). Exploratory analyses were also performed according to the 4 BMI categories separately.

### Statistical Analysis

The present analysis aimed to determine the prognostic impact of baseline BMI and weight changes at 6, 12, and 18 months after random assignment in patients treated with abemaciclib + ET. Patient weight change was calculated as a percentage (by subtracting weight at 6, 12, or 18 months from random assignment to the baseline value, then dividing the result by baseline weight and finally multiplying the result by 100). According to weight change, patients were classified into 2 categories: at least 5.0% weight loss from baseline compared with less weight loss or weight gain. The 5.0% cutoff point was chosen for consistency with a prior study (31) and considering that this value reflects a clinically significant weight change that accounts for measurement errors or normal fluctuations (32).

Comparisons between BMI classes for continuous variables were assessed using t, Mann-Whitney, or Kruskall-Wallis tests; for categorical variables, $\chi^2$ or Fisher's exact tests were used. Comparisons of PFS across BMI and weight change categories were accomplished through Kaplan-Meier curves and log-rank tests and crude and adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CIs), computed using Cox-proportional hazards regression. Patients were stratified according to the trial included and treatment group. Multivariate analyses were adjusted for the factors that differed between BMI groups. Homogeneity tests on the hazard ratios obtained in the planned subgroups were carried out to assess the possible interaction.

Because only patients who survived at least 6 months after random assignment would have information available regarding the 6-month weight change, we performed a 6-month landmark analysis when assessing the weight change as an explanatory variable; the same was performed for weight changes at 12 and 18 months.

The RR endpoint was assessed through the estimation of individual odds ratios (ORs) within each trial or within each treatment group. As per original publications, RR analysis included overall RR (ORR; proportion of patients with complete response [CR] and partial response [PR]) and clinical benefit rate (proportion of patients with CR, PR, and stable disease).

All statistical tests were 2-sided, and *P* less than .05 was considered statistically significant. No missing data were imputed. Statistical analyses were performed with SAS version 9.4.

## Results

### Patient Characteristics and Demographics

A total of 1152 patients included in the MONARCH 2 and MONARCH 3 trials (767 randomly assigned to abemaciclib + ET and 385 to placebo + ET) received at least 1 dose of study treatment. Of those, 14 were excluded because height was not recorded, leaving 1138 patients included in this analysis (Supplementary Figure 1, available online).

Of the 757 patients who received abemaciclib + ET, 24 (3.2%) were categorized as underweight, 327 (43.2%) as normal weight, 223 (29.5%) as overweight, and 183 (24.2%) as obese. Of the 381 patients who were treated with placebo + ET, the prevalence of underweight, normal weight, overweight, and obesity was

8 (2.1%), 164 (43.0%), 113 (29.7%), and 96 (25.2%), respectively (Supplementary Table 1, available online).

The presence of overweight and obesity varied statistically significantly according to geographic location, with a higher prevalence in European and North American patients compared with Asian patients. Overweight and/or obese patients were older, were postmenopausal, and more frequently had diabetes ($P < .005$ for all). Overall, there was no difference in previous ET exposure ($P = .19$) or ET sensitivity ($P = .33$) in all included patients according to BMI. In the abemaciclib + ET group, overweight and/or obese patients presented less visceral disease (53.5% vs 59.0%) and more frequently bone-only disease (32.3% vs 23.7%) compared with normal and/or underweight patients ($P = .03$). Additionally, prior aromatase inhibitor use was more frequent in overweight and/or obese than in normal and/or underweight patients receiving abemaciclib + ET (57.1% vs 48.3%, $P = .02$). Baseline demographics and clinical characteristics of patients with a BMI less than 25 kg/m$^2$ and at least 25 kg/m$^2$ in the overall population and stratified by treatment group are displayed in Table 1.

### PFS According to BMI

There was no statistically significant difference in PFS between patients with BMI less than 25 and BMI at least 25 kg/m$^2$ in the abemaciclib + ET group: median PFS was 22.0 months (range = 17.2-29.1) vs 21.7 months (range = 17.1-27.5), respectively, for a hazard ratio of 1.03 (95% CI = 0.83 to 1.27, $P = .81$). Similar results were observed in the placebo + ET group according to BMI less than 25 kg/m$^2$ and BMI at least 25 kg/m$^2$: median PFS was 10.8 months (range = 7.9-13.7) vs 12.7 months (range = 9.0-15.4) for a hazard ratio of 0.81 (95% CI = 0.64 to 1.04, $P = .10$) (Figure 1). No statistical differences in PFS were found when categorizing the patients in the 4 BMI categories in both treatment groups (Figure 2, A and B). Patients receiving abemaciclib + ET presented a higher PFS than those receiving placebo + ET across all BMI categories.

In an exploratory analysis, there was a numerically higher magnitude of benefit for the addition of abemaciclib to ET for patients with normal weight (21.9 vs 10.8 months, HR = 0.48, 95% CI = 0.38 to 0.61) compared with patients with overweight (22.0 vs 14.0 months, HR = 0.54, 95% CI = 0.40 to 0.73) and obesity (20.2 vs 11.6 months, HR = 0.70, 95% CI = 0.50 to 0.97, $P = .03$) with an $P_{interaction} = .07$ (Supplementary Figure 2 A–C, available online).

Multivariable analysis adjusting for factors that differed between BMI categories (age, Eastern Cooperative Oncology Group performance scale, prior ET, prior aromatase inhibitor, menopausal status, number of metastatic sites, and type of ET) demonstrated no impact of BMI (<25 or ≥25 kg/m$^2$) in PFS in both treatment groups (HR = 1.0, 95% CI = 0.81 to 1.25, $P = .98$ for abemaciclib + ET and HR = 0.80, 95% CI = 0.62 to 1.04, $P = .09$ for placebo + ET) (Supplementary Table 2, available online).

### RR According to BMI

There were statistically significant differences in ORR (CR + PR) according to BMI. Among patients receiving abemaciclib + ET, ORR was statistically significantly lower in overweight and/or obese patients compared with underweight and/or normal-weight patients: 41.6% vs 49.4% (OR = 0.73, 95% CI = 0.54 to 0.99, $P = .04$). For patients receiving placebo + ET, the opposite was observed: ORR was higher in overweight or obese patients compared with underweight or normal-weight patients (30.7% vs 21.1%, OR = 1.65, 95% CI = 1.02 to 2.67, $P = .04$). The clinical benefit rate (CR + PR + stable disease) did not differ statistically according to BMI in either treatment group. Abemaciclib + ET was superior in terms of ORR and CBR compared with placebo + ET in both underweight and/or normalweight patients and in overweight and/or obese patients ($P < .05$) (Table 2).

### Treatment-Related Toxicities According to BMI

For patients receiving abemaciclib + ET, the incidence of neutropenia of any grade was statistically significantly lower in overweight and/or obese patients compared with underweight and/or normal-weight patients (40.4% vs 51.0%, $P = .004$) as well as the incidence of neutropenia grade 3 or higher neutropenia (21.7% vs 29.3%, $P = .02$). No differences in other toxicities were observed between the 2 BMI categories, including diarrhea. For patients under treatment with placebo + ET, toxicities were similar between the 2 BMI categories (Supplementary Table 3, available online). There were no differences regarding dose adjustment, reduction, or omission, as well as treatment discontinuation according to BMI (Supplementary Table 4, available online).

### Weight Changes According to Regimen of Treatment

At the landmark of 6 months (n = 820), the rate of patients with at least a 5% weight loss was almost threefold higher in the abemaciclib + ET group compared with the placebo + ET group (27.1% vs 10.3%, OR = 3.23, 95% CI = 2.08 to 5.01, $P < .001$). This difference was increased at 12 months (n = 608) (26.2% vs 8.1%, OR = 4.03, 95% CI = 2.24 to 7.25, $P < .001$) and at 18 months (n = 400) (22.3% vs 6.4%, OR = 4.19, 95% CI = 1.86 to 9.46, $P < .001$) (Table 3). In the abemaciclib + ET group, weight changes were not associated with grade 3 or higher diarrhea (OR = 1.48, 95% CI = 0.86 to 2.55, $P = .16$) or any grade 3 or higher AEs (OR = 1.20, 95% CI = 0.81 to 1.7, $P = .37$).

There was no association between PFS and weight loss at the 3 time-points in either treatment group (Supplementary Figure 3, available online).

## Discussion

Obesity has long been considered a growing public health issue (33–36), and its relation with BC has been extensively studied in the early setting (10,11,37–39), whereas fewer studies investigated its impact in patients with metastatic disease (11–13,40). To our knowledge, this analysis, which pooled individual patient–level data from 2 randomized trials of abemaciclib, is the largest study to evaluate the association between BMI and outcomes with CDK 4/6 inhibitors in advanced BC. Our results show that more than one-half of the patients included in the MONARCH 2 and MONARCH 3 trials were classified as overweight or obese. This reflects the high prevalence of overweightness and obesity among patients with advanced BC who are currently living longer because of better disease control and for whom research investigating the impact of BMI during treatment is insufficient.

Our findings indicate that the combination of abemaciclib + ET is superior to placebo + ET independently of BMI categories, showing that this regimen is also effective for overweight and obese patients. The results of this post hoc analysis are aligned with results of a previous one conducted by our group in a small

**Table 1.** Baseline characteristics and demographics of patients with a BMI less than 25 kg/m$^2$ and 25 or greater in the overall population and stratified by treatment group

| | Total, No. (%) (N = 1138) | | | Abemaciclib + ET, No. (%) (n = 757) | | | Placebo + ET, No. (%) (n = 381) | | |
|---|---|---|---|---|---|---|---|---|---|
| Baseline characteristics | BMI < 25 kg/m$^2$ (n = 523) | BMI ≥ 25 kg/m$^2$ (n = 615) | Pa | BMI < 25 kg/m$^2$ (n = 172) | BMI ≥ 25 kg/m$^2$ (n = 209) | Pa | BMI < 25 kg/m$^2$ (n = 351) | BMI ≥ 25 kg/m$^2$ (n = 406) | Pa |
| Geographic region | | | <.001 | | | <.001 | | | <.001 |
| Asia | 241 (46.1) | 114 (18.5) | | 169 (48.2) | 79 (19.5) | | 72 (41.9) | 35 (16.8) | |
| Europe | 206 (39.4) | 314 (51.1) | | 132 (37.6) | 201 (49.5) | | 74 (43.0) | 113 (54.1) | |
| North America | 76 (14.5) | 187 (30.4) | | 50 (14.3) | 126 (31.0) | | 26 (15.1) | 61 (29.2) | |
| Ethnicity | | | <.001 | | | <.001 | | | <.001 |
| American Indian or Alaska native | 12 (2.5) | 19 (3.3) | | 8 (2.5) | 12 (3.2) | | 4 (2.5) | 7 (3.5) | |
| Asian | 244 (50.0) | 117 (20.5) | | 171 (52.6) | 80 (21.5) | | 73 (44.8) | 37 (18.7) | |
| Black or African American | 6 (1.2) | 16 (2.8) | | 3 (0.9) | 11(3.0) | | 3 (1.8) | 5 (2.5) | |
| Multiple | 1 (0.2) | 3 (0.5) | | 1 (0.3) | 3 (0.8) | | — | — | |
| White | 225 (46.1) | 416 (72.9) | | 142 (43.7) | 267 (71.6) | | 83 (50.9) | 149 (75.3) | |
| Missing info | 35 | 44 | | 26 | 33 | | 9 | 11 | |
| Age | | | | | | | | | |
| Median (min-max) | 60 (32 to 87) | 62 (32 to 88) | .004 | 59 (32 to 87) | 62 (34 to 87) | .003 | 63 (32 to 85) | 62 (32 to 88) | .46 |
| <65 y | 330 (63.1) | 351 (57.1) | .04 | 227 (64.7) | 233 (57.4) | .04 | 103 (59.9) | 118 (56.5) | .50 |
| ≥65 y | 193 (36.9) | 264 (42.9) | | 124 (35.3) | 173 (42.6) | | 69 (40.1) | 91 (43.5) | |
| ECOG | | | <.001 | | | <.001 | | | .02 |
| 0 | 349 (67.1) | 337 (54.8) | | 231 (66.4) | 218 (53.7) | | 118 (68.6) | 119 (56.9) | |
| 1 | 171 (32.9) | 278 (45.2) | | 117 (33.6) | 188 (46.3) | | 54 (31.4) | 90 (43.1) | |
| Missing info | 3 | | | 3 | — | | | | |
| Menopausal status | | | <.001 | | | <0.001 | | | .03 |
| Postmenopause | 450 (86.0) | 575 (93.7) | | 303 (86.3) | 383 (94.3) | | 147 (85.5) | 192 (92.3) | |
| Pre- or perimenopause | 73 (14.0) | 39 (6.4) | | 48 (13.7) | 23 (5.7) | | 25 (14.5) | 16 (7.7) | |
| Missing info | — | 1 | | — | — | | — | 1 | |
| Previous ET | .19 | .94 | .03 | | | | | | |
| No | 113 (21.6) | 153 (24.9) | | 83 (23.7) | 97 (23.9) | | 30 (17.4) | 56 (26.8) | |
| Yes | 410 (78.4) | 462 (75.1) | | 268 (76.4) | 309 (76.1) | | 142 (82.6) | 153 (73.2) | |
| Sensitivity to ET[b] | | | .33 | | | .51 | | | .44 |
| Primary resistance | 85 (27.4) | 82 (24.1) | | 54 (27.0) | 56 (24.2) | | 31 (28.2) | 26 (23.6) | |
| Secondary resistance | 225 (72.6) | 259 (76.0) | | 146 (73.0) | 175 (76.8) | | 79 (71.8) | 84 (76.4) | |
| Prior AI | | | .12 | | | .02 | | | .48 |
| No | 255 (49.8) | 274 (45.1) | | 178 (51.7) | 172 (42.9) | | 77 (45.8) | 102 (49.5) | |
| Yes | 257 (50.2) | 333 (54.9) | | 166 (48.3) | 229 (57.1) | | 91 (54.2) | 104 (50.5) | |
| Missing info | 11 | 8 | | 7 | 5 | | 4 | 3 | |
| Prior adj chemo (MONARCH 2) | | | .97 | | | .96 | | | .97 |
| No | 68 (25.9) | 71 (26.0) | | 42 (25.3) | 48 (25.5) | | 26 (26.8) | 23 (27.1) | |
| Yes | 195 (74.1) | 202 (74.0) | | 124 (74.7) | 140 (74.5) | | 71 (73.2) | 62 (72.9) | |
| Missing info | 52 | 71 | | 38 | 45 | | 14 | 26 | |
| PgR status | | | .10 | | | .29 | | | .17 |
| Negative | 122 (23.8) | 120 (19.7) | | 81 (23.6) | 82 (20.4) | | 41 (24.4) | 38 (18.5) | |
| Positive | 390 (76.2) | 488 (80.3) | | 263 (76.5) | 321 (79.7) | | 127 (75.6) | 167 (81.5) | |
| Missing info | 11 | 7 | | 7 | 3 | | 4 | 4 | |
| Metastatic sites | | | .08 | | | .03 | | | .22 |
| Bone only | 134 (25.6) | 187 (30.4) | | 83 (23.7) | 131 (32.3) | | 51 (29.7) | 56 (26.8) | |
| Visceral | 296 (56.6) | 342 (55.6) | | 207 (59.0) | 217 (53.5) | | 89 (51.7) | 125 (59.8) | |
| Other | 93 (17.8) | 86 (14.0) | | 61 (17.4) | 58 (14.3) | | 32 (18.6) | 28 (13.4) | |
| Organs involved, No. | | | .74 | | | .19 | | | .13 |
| 1 | 178 (34.1) | 223 (36.3) | | 118 (33.7) | 157 (38.7) | | 60 (34.9) | 66 (31.6) | |
| 2 | 148 (28.4) | 166 (27.0) | | 94 (26.9) | 114 (28.1) | | 54 (31.4) | 52 (24.9) | |
| ≥3 | 196 (37.6) | 226 (36.8) | | 138 (39.4) | 135 (33.3) | | 58 (33.7) | 91 (43.5) | |
| Missing info | 1 | — | | 1 | — | | — | — | |
| Trial enrolled | | | .14 | | | 0.84 | | | .02 |
| MONARCH 2 | 315 (60.2) | 344 (55.9) | | 204 (58.1) | 233 (57.4) | | 111 (64.5) | 111 (53.1) | |
| MONARCH 3 | 208 (39.8) | 271 (44.1) | | 147 (41.9) | 173 (42.6) | | 61 (35.5) | 98 (46.9) | |
| Treatment regimen | | | .15 | | | .84 | | | .02 |
| Abemaciclib + AI | 147 (28.1) | 173 (28.1) | | 147 (41.9) | 173 (42.6) | | | | |
| Abemaciclib + Fulv | 204 (39.0) | 233 (37.9) | | 204 (58.1) | 233 (57.4) | | — | — | |

(continued)

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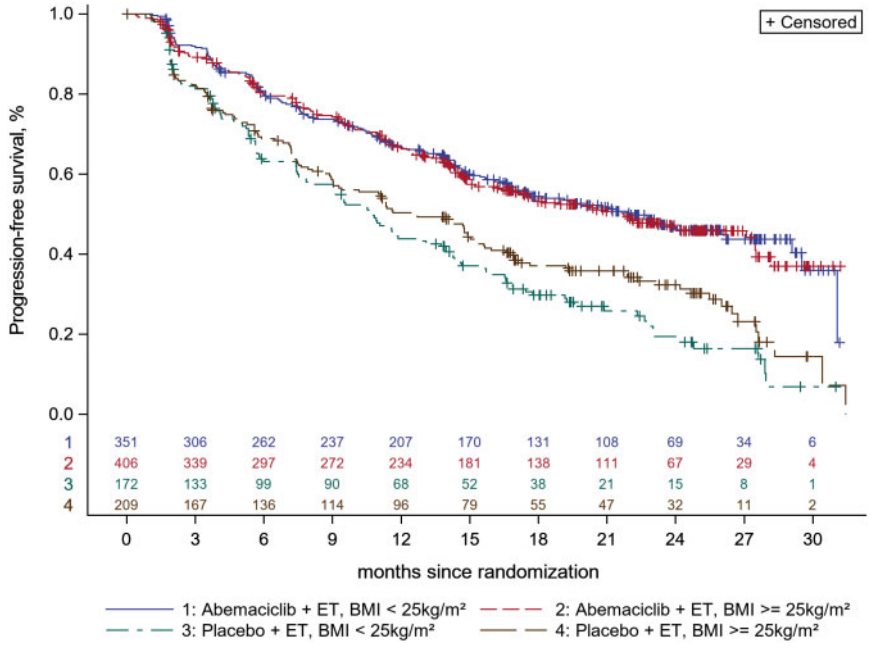
**Table 1.** (continued)

| Baseline characteristics | Total, No. (%) (N = 1138) | | | Abemaciclib + ET, No. (%) (n = 757) | | | Placebo + ET, No. (%) (n = 381) | | |
|---|---|---|---|---|---|---|---|---|---|
| | BMI < 25 kg/m$^2$ (n = 523) | BMI ≥ 25 kg/m$^2$ (n = 615) | Pa | BMI < 25 kg/m$^2$ (n = 172) | BMI ≥ 25 kg/m$^2$ (n = 209) | Pa | BMI < 25 kg/m$^2$ (n = 351) | BMI ≥ 25 kg/m$^2$ (n = 406) | Pa |
| Placebo + AI | 61 (11.7) | 98 (15.9) | | — | — | | 61 (35.5) | 98 (46.9) | |
| Placebo + Fulv | 111 (21.2) | 111 (18.1) | | | | | 111 (64.5) | 111 (53.1) | |
| Diabetes mellitus (medical history) | | | <.001 | | | <.001 | | | <.001 |
| No | 507 (96.9) | 547 (88.9) | | 340 (96.9) | 364 (89.7) | | 167 (97.1) | 183 (87.6) | |
| Yes | 16 (3.1) | 68 (11.1) | | 11 (3.1) | 42 (10.3) | | 5 (2.9) | 26 (12.4) | |

[a]P values are from the $\chi^2$ test and Kruskal-Wallis test comparing categorical and continuous variables against the 2 BMI categories, respectively (all statistical tests were 2-sided). Adju = adjuvant; AI = aromatase inhibitor; BMI = body mass index; CM = concomitant medication; ECOG = Eastern Cooperative Oncology Group performance scale; ET = endocrine therapy; Fulv = fulvestrant; Prior Adj Chemo = prior adjuvant chemotherapy; PgR = progesterone receptor.
[b]In prior ET patients, only MONARCH 2 patients.




| Abemaciclib + ET | | | | |
|---|---|---|---|---|
| **BMI** | **PFS rate at 1 year** | **Median PFS (months)** | **HR (95% CI)** | **P Value** |
| **<25** | **67%** | **22.0 (17.2-29.1)** | | |
| **≥25** | **66%** | **21.7 (17.1-27.5)** | **1.03 (0.83-1.27)** | **.81** |
| **Placebo + ET** | | | | |
| **<25** | **44%** | **10.8 (7.9-13.7)** | | |
| **≥25** | **50%** | **12.7 (9.0-15.4)** | **0.81 (0.64-1.04)** | **.10** |

**Figure 1.** Kaplan-Meier curves for progression-free survival (PFS) according to body mass index (BMI; <25 kg/m$^2$ vs ≥25 kg/m$^2$). PFS according to BMI: median PFS according to 2 main BMI categories in patients treated with abemaciclib + endocrine therapy (ET) and in patients treated with placebo + ET. CI = confidence interval; HR = hazard ratio.

retrospective cohort (n = 50), in which we found no difference in PFS in patients treated with palbociclib or ribociclib + ET as first or second-line therapy for advanced BC, according to BMI (40).

Moreover it is important to mention, as previously demonstrated, that BMI alone can be a poor surrogate for obesity because of its inability to differentiate fat and lean muscle mass, precluding the diagnosis of sarcopenia as well as body fat distribution (41–43). With all the caveats of a small retrospective study, our previous work identified baseline sarcopenia (measured by computed tomography-scan body composition

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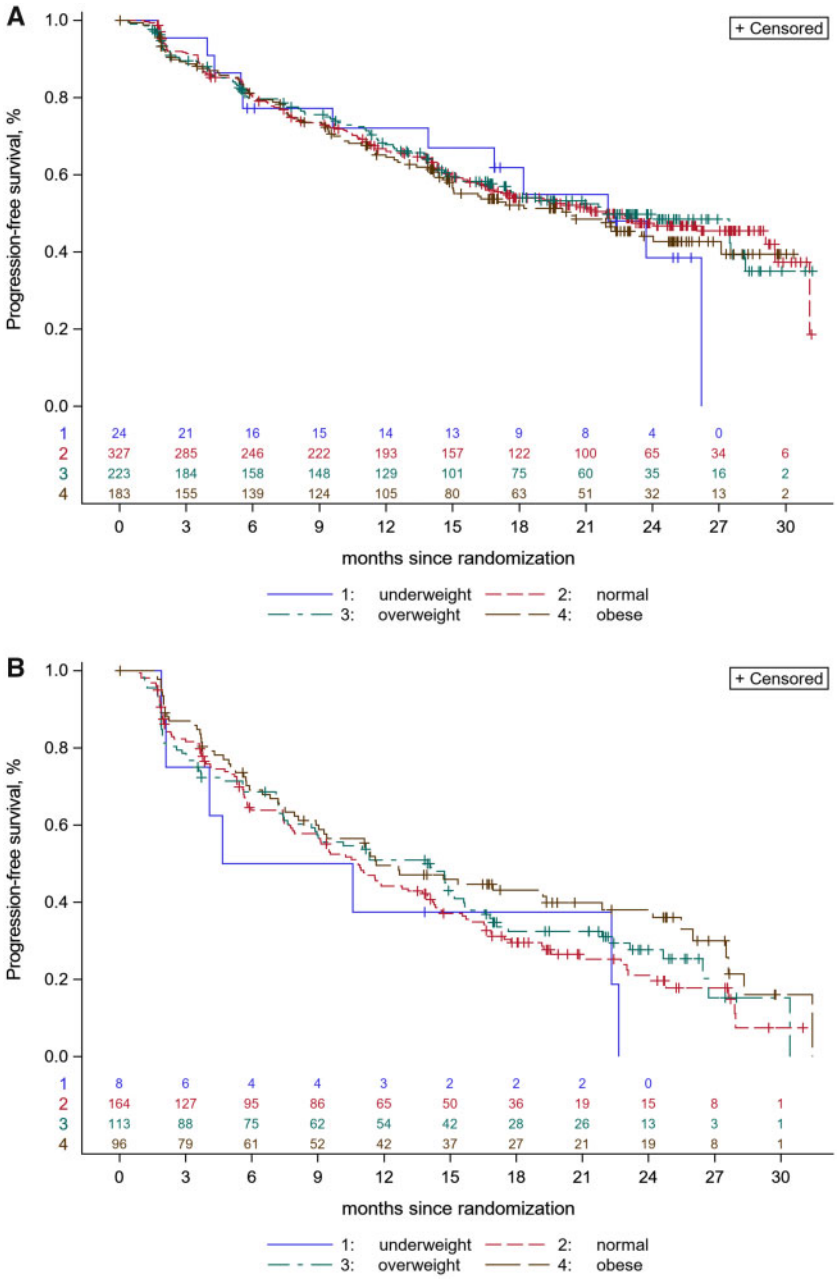


**Figure 2.** Kaplan-Meier curves for progression-free survival (PFS) according to body mass index (BMI) categories (underweight, normal weight, overweight, and obese). **A)** PFS according to the 4 BMI categories in patients receiving abemaciclib + endocrine therapy (ET) ($P = .91$; 2-sided log-rank test). **B)** PFS according to the 4 BMI categories in patients receiving placebo + ET ($P = .19$; 2-sided log-rank test).

analysis) as a potential marker of poor prognosis in patients receiving CDK4/6 inhibitors (palbociclib or ribociclib) + ET, regardless of BMI, line of treatment, or disease burden (40). Moreover, in this previous report, sarcopenia was present in 40% of the patients despite the early course of their metastatic disease and good performance status. Additional studies in larger cohorts, preferentially with a prospective design, analyzing body composition parameters in patients receiving CDK4/6 inhibitors is needed and could lead to a deeper understanding of our findings.

In our analysis, overweight and obese patients were older, had a slightly worse performance status, and were more frequently postmenopausal compared with underweight and normal-weight patients. The prevalence of overweightness and obesity differed statistically significantly according to geographic region and ethnicity, with a lower prevalence among Asian patients compared with Europeans and North Americans. This is an interesting finding considering previous data showed that pharmacokinetic and pharmacogenomic profiles of some treatments for BC [eg, fluodropirimidines (44,45), tamoxifen (46,47), everolimus (48)] differ between Asian and non-Asians patients.

Although the efficacy of CDK4/6 inhibitors has already been established in Asian patients (49–51), previous data from the PALOMA-3 trial and MONALEESA-2 trial showed higher rates of grade 3 or greater neutropenia, an AE-specific drug class effect,

**Table 2.** RRs to BMI (<25 and ≥25 kg/m$^2$) in patients receiving abemaciclib + ET and placebo + ET

| | Abemaciclib + ET (n = 757) | | | | Placebo + ET (n = 381) | | | |
|---|---|---|---|---|---|---|---|---|
| RRs | BMI <25 kg/m$^2$ No. (%) | BMI ≥25 kg/m$^2$ No. (%) | OR (95% CI) | P[a] | BMI <25 kg/m$^2$ No. (%) | BMI <25 kg/m$^2$ No. (%) | OR (95% CI) | P[a] |
| Best overall response | 351 (46.4) | 406 (53.6) | — | — | 172 (45.1) | 209 (54.9) | — | — |
| CR | 6 (1.8) | 17 (4.5) | — | — | 2 (1.2) | 0 (0) | — | — |
| PR | 155 (47.6) | 140 (37.1) | — | — | 33 (19.9) | 61 (30.7) | — | — |
| Stable disease | 145 (44.5) | 189 (50.1) | — | — | 104 (62.7) | 108 (54.3) | — | — |
| PD | 20 (6.1) | 31 (8.2) | — | — | 27 (16.3) | 30 15.1) | — | — |
| NE | 25 | 29 | — | — | 6 | 10 | — | — |
| ORR (CR + PR) | 161 (49.4) | 157 (41.6) | 0.73 (0.54 to 0.99) | .04 | 35 (21.1) | 61 (30.7) | 1.65 (1.02 to 2.67) | .04 |
| Clinical benefit rate (CR + PR + Stable disease) | 306 (93.9) | 346 (91.8) | 0.73 (0.41 to 1.31) | .28 | 139 (83.7) | 169 (84.9) | 1.09 (0.62 to 1.93) | .76 |

[a]P values are from the $\chi^2$ test (all statistical tests were 2-sided). BMI = body mass index; CI = confidence interval; CR = complete response; ET = endocrine therapy; NE = nonevaluable; OR = odds ratio; ORR = overall response rate; PR = partial response; RR = response rate.

**Table 3.** Weight changes during therapy with abemaciclib + ET and placebo + ET

| Treatment group | <5% weight change (loss or increase) No. (%) | ≥5% weight loss No. (%) | OR (95% CI) | P[a] |
|---|---|---|---|---|
| Weight change b/w baseline and 6 mo | | | | |
| Abemaciclib + ET | 407 (72.9) | 151 (27.1) | 3.23 (2.08 to 5.01) | <.001 |
| Placebo + ET | 235 (89.7) | 27 (10.3) | | |
| Weight change b/w baseline and 12 mo | | | | |
| Abemaciclib + ET | 321 (73.9) | 114 (26.2) | 4.03 (2.24 to 7.25) | <.001 |
| Placebo + ET | 159 (91.9) | 14 (8.1) | | |
| Weight change b/w baseline and 18 mo | | | | |
| Abemaciclib + ET | 226 (77.7) | 65 (22.3) | 4.19 (1.86 to 9.46) | <.001 |
| Placebo + ET | 102 (93.6) | 7 (6.4) | | |

[a]P values are from the $\chi^2$ test (all statistical tests were 2-sided). b/w = between; CI = confidence interval; ET = endocrine therapy; OR = odds ratio.

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in Asian patients compared with non-Asians (92% vs 58%) (49). Additionally, in a phase I study of palbociclib plus letrozole in Japanese patients, 83% had grade 3 or higher neutropenia (52). Similar results were also seen with ribociclib in the MONALEESA-2 trial in which grade 3 or higher neutropenia was documented in 71% of the Asians patients treated with ribociclib and letrozole (50). In our study, lower BMI correlated with higher rates of neutropenia, which was also seen in a recent pooled analysis of 2 trials testing palbociclib (53). Perhaps besides interethnic variabilities, differences in BMI could be one of the mechanistic reasons why Asian patients present higher neutropenia rates with these CDK 4/6 inhibitors. A possible explanation for the lower neutropenia rates in overweight or obese patients could refer to the fact that higher blood neutrophil counts might be a potential inflammatory biomarker of overweightness or obesity, as already shown in noncancer patients (54–57). Moreover, the distribution of abemaciclib in fat tissue could explain these findings, similar to what is seen with cytotoxic chemotherapy agents (58); thus, the differentiation between fat and muscle mass in these patients would be paramount to understand this phenome.

Interestingly, an additional exploratory analysis demonstrated that the magnitude of benefit with abemaciclib + ET was numerically higher in normal-weight patients compared with overweight or obese patients. Additionally, overweight or obese patients presented lower ORRs when treated with abemaciclib + ET. This difference was not present in the placebo + ET group, reflecting that the lower magnitude of benefit in obese patients is not related with endocrine resistance caused by obesity. These results may suggest a potential suboptimal dose intensity in this group, though this hypothesis would need to be carefully confirmed, preferably through a prospective trial in the setting of obesity. In addition, encouraging metastatic BC patients to maintain a healthy weight can be beneficial for those receiving abemaciclib + ET besides the well-known advantages such as the control of metabolic, cardiovascular, muscular, and degenerative joint and bone diseases.

Important metabolic functions coregulated by CDK 4/6 have been described, such as adipogenesis in white adipose tissue, insulin secretion and ß-cell function at the pancreatic level, gluconeogenesis and mitochondrial regulation in the liver, and control of insulin sensitivity and oxidative metabolism in the muscular compartment (18–22). Data also suggest that CDKs could be implicated and hyperactivated in obesity (23,24). Our previous exploratory study did not detect changes in weight and in body composition parameters during treatment with CDK 4/6 inhibitors (40). In our current analysis, loss of weight was at least 3 times more frequent in patients receiving abemaciclib compared with placebo; it was not correlated with the presence of diarrhea, suggesting a possible effect of abemaciclib on reducing fat mass as previously described in mouse models (23). Because weight loss can be interpreted as a sign of active disease by physician and patients, this finding is clinically important.

We should, however, be cautious when extrapolating our results to the entire “class” of CDK4/6 inhibitors, because

palbociclib and ribociclib differ from abemaciclib in several aspects (59). Palbociclib and ribociclib present a greater lipophilicity and different binding sites compared with abemaciclib. Also, abemaciclib is more potent and presents target activity against CDK9, whereas palbociclib and ribociclib only inhibit CDK4 and CDK6. Additionally, abemaciclib may potentially cross the blood-brain barrier. Of note, there are few but consistent differences in terms of treatment-related toxicities between the 3 CDK4/6 inhibitors, including higher rates of diarrhea with abemaciclib compared with an increased incidence of neutropenia with palbociclib and ribociclib (59). For all these reasons, future studies focusing on the impact of BMI among patients treated with palbociclib and ribociclib are also warranted.

Results from this analysis should be considered as exploratory, not preplanned, and therefore warrant confirmation. The interaction test between BMI and PFS did not reach statistical significance. Moreover, as previously mentioned, BMI is not the most accurate method to assess obesity, and future studies integrating muscle and fat measures are highly desired and should be pursued. Importantly, in the this dataset, no overall survival data were yet available. Last, no data were available regarding diet and physical activity, which could influence loss of weight.

In conclusion, this pooled analysis of individual patient–level data from the MONARCH 2 and 3 trials showed that the combination of abemaciclib + ET is effective and superior to ET alone irrespective of BMI. Weight loss was more frequent for patients using abemaciclib + ET compared with placebo + ET. An apparent increased benefit was observed for normal and underweight patients than for obese patients treated with abemaciclib + ET. Additionally, lower RRs and lower rates of neutropenia were seen in overweight and obese patients. Because palbociclib, ribociclib, and abemaciclib differ in several aspects, further research regarding the use of other CDK 4/6 inhibitors in this representative subpopulation is desired. Moreover, a future study integrating body composition parameters could more precisely analyze the impact of overweight and obesity on the outcomes of patients treated with abemaciclib plus ET.

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## Data availability

This manuscript is based on research using data from Lilly that has been made available through Vivli—Data request ID: 4319 ( research proposal available at: https://vivli.org/clinical-implications-of-body-mass-index-and-weight-in-metastatic-breast-cancer-patients-receiving-abemaciclib-a-combined-individual-patient-level-data-sub-analysis-of-monarch-2-and-monarch-3-trials/). Data may be available to other researchers through submission and approval of a research proposal at the Vivli website: https://vivli.org/ and a signed data access agreement.

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