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Body Mass Index and Treatment Outcomes in Metastatic Breast Cancer Patients Treated With Eribulin

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Eribulin has shown survival advantage and manageable toxicity in heavily pre-treated metastatic breast cancer (mBC). We assessed whether body mass index (BMI) impacts treatment outcomes in 101 patients treated with eribulin at six Italian Oncologic Centers. BMI was addressed as a categorical variable (18.5–24.9 vs. at least 25). Clinical benefit rate (CBR) was assessed overall and in subgroups defined by BMI, line of therapy (LOT), and hormone receptor (HR) status. Analysis of CBR by LOT and HR status were further stratified by BMI. Survival curves were compared using the Kaplan–Meier method and log-rank test. Predictors of survival were tested in Cox models. Patients treated with eribulin as third line showed greater CBR when their BMI was in the lowest category (77.8 vs. 58.1%, $P = 0.03$). Median progression free survival (PFS) and overall survival (OS) in normal and overweight patients were 4 (95% CI, 3–5) versus 3 (2.1–4) months, $P = 0.02$ and 13 (11–15) versus 12 (6–18) months, $P = 0.96$, respectively. Median PFS and OS in estrogen receptor (ER) positive and negative tumours were 4 (3–5) versus 3 (2–4) months, $P = 0.005$ and 14 (10–18) versus 7 (4–10), $P = 0.02$, respectively. In multivariate

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analyses, BMI impacted PFS at a nearly significant extent ($P = 0.05$), while ER expression significantly affected PFS and OS ($P = 0.01$ and 0.02, respectively). No relevant findings emerged concerning toxicity. We found evidence of greater efficacy of eribulin in leaner mBC patients, particularly if given as third line and in ER positive tumors. Further studies are warranted to confirm our findings.
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In recent years, the evidence concerning the role played by metabolic and anthropometric determinants in breast carcinogenesis and progression has grown notably (Zhu et al., 2012; Bravatà et al., 2013; Li et al., 2014; Byers and Sedjo, 2015; Chan and Norat, 2015; Keum et al., 2015). The consequential gain in knowledge has transversally echoed across different breast cancer scenarios and continues inspiring an impressive amount of studies. The body of evidence on body mass index (BMI) has been particularly well nourished, with BMI being by far the most commonly investigated indicator of generalized overweight and obesity in research focused on breast cancer outcomes (Chan and Norat, 2015).

Generally, results from both observational studies and intervention trials tend to show higher mortality rates, both all cause and disease specific, in breast cancer patients with higher BMI compared to their leaner counterpart, independently on hormone receptors and menopausal status (Chan et al., 2014; Kwan et al., 2014). In HER2 breast cancer patients, consideration of studies having enrolled patients prior to the FDA approval of trastuzumab may be of limited meaning due to differences in treatment which may modify the association between obesity and treatment outcomes (Sparano et al., 2012; Jiralerspong et al., 2013; Mazzarella et al., 2013; Wolff et al., 2013; Robinson et al., 2014). On this basis, the accessible evidence is mostly confined to the results of the N9831 adjuvant trastuzumab trial, which supports the association between higher BMI and shorter disease-free survival (Crozier et al., 2013). Results from studies of triple-negative breast cancer (TNBC) are poorly supportive for the association of interest. However, given the limited number of TNBC patients included and the short follow-up, these studies may be underpowered to detect modest associations (Cleator et al., 2007; Ademuyiwa et al., 2011; Christiansen et al., 2012; Dawood et al., 2012; Mowad et al., 2013; Perez et al., 2013).

When addressing the impact of BMI on treatment outcomes by clinical setting, higher BMI is associated with lower pathologic complete response (pCR) rate and shorter survival in patients treated with neoadjuvant anthracycline- and taxane-based chemotherapy (Denkert et al., 2015). In the adjuvant setting, no relevant differences emerged from a systematic review and meta-analysis when toxicity and survival outcomes were compared between obese and normal-weight patients having received chemotherapy (Hourdequin et al., 2013). Similarly, the efficacy of adjuvant tamoxifen does not seem to be influenced by BMI values (Pfeiler et al., 2013). Conversely, there is evidence in support of a role of obesity in diminishing the efficacy of aromatase inhibitors in postmenopausal patients, and letrozole may be superior to anastrozole in patients with greater BMI (O'Shaughnessy, 2007; Dixon et al., 2008; Goodwin and Pritchard, 2010; Sestak et al., 2010; Folkerd et al., 2012; Ewertz et al., 2012). However, further studies are warranted to define and recommend optimal treatment modalities in these patients. Thus far, we lack evidence concerning the potential effects of obesity in advanced breast cancer, with the metastatic setting being still unexplored for the putative role of BMI on treatment outcomes.

Eribulin mesylate is a non-taxane microtubule dynamics inhibitor which has recently contributed to expand the therapeutic armamentarium for women with heavily pretreated metastatic disease. Based on the significant and clinically meaningful improvement in overall survival shown by the registrative trial, eribulin was approved for treatment of locally advanced or metastatic breast in women who had previously failed an anthracycline and a taxane in either the adjuvant or metastatic setting and at least two chemotherapeutic regimens in the metastatic setting (Cortes et al., 2011). Subsequently, in the study 301, eribulin was not shown to be superior to capecitabine with regard to survival outcomes (Kaufman et al., 2015). A pooled analysis of these two phase III trials showed the beneficial effects of eribulin in terms of survival outcomes in patients subgroups including women with HER2 negative disease and TNBC (Twelves et al., 2014).

In a recent multicenter observational study, we observed confirmatory evidence concerning this drug efficacy and toxicity in a real word population including 133 breast cancer patients who had received eribulin according to the current indication and recommendations (Gamucci et al., 2014). In the present study, we focused on the role of BMI on efficacy and toxicity outcomes in a large subgroup of the original cohort with available data on anthropometrics.

Methods

We carried out an observational retrospective study of 101 breast cancer patients with metastatic disease treated with eribulin at six Italian Oncologic Centers between February 2012 and January 2015. These patients represent the vast majority of a larger cohort whose characteristics were fully reported elsewhere (Gamucci et al., 2014). In brief, in the original study, patients were considered for inclusion if having received eribulin as third or subsequent lines of therapy. Further characteristics required for inclusion were an ECOG performance status of 2 or less, life expectancy of more than 12 weeks, and adequate liver, kidney, and bone marrow function. In strict regard to those patients who contributed data to the analysis proposed in the present study, BMI measurements prior to eribulin administration were made available through clinical records retrieving and entered into an anonymized database along with patients demographics, pathological and clinical features, therapy administered, and treatment outcomes.

Consistently with the registrative trial, eribulin was administered intravenously at the dose of 1.4 mg/m^2 in 2–5 min on days 1 and 8, on a three weekly schedule, until disease progression, severe toxicity, or patient refusal occurred. Treatment efficacy was assessed using the Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST, v. 1.1), while adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI-CTCAE v.04). The institutional review boards of the participating centers evaluated and approved the study protocol. All patients provided a written informed consent. This study is compliant with the principles enunciated in the Declaration of Helsinki.

Statistical analysis

Descriptive statistics were computed for all the variables of interest. Medians and ranges were used for continuous data, while frequencies and percentage values for categorical

variables. Existing differences between medians were evaluated using the Student's *t*-test or One Way Anova test according to the number (2 or more) of groups compared. Depending upon the number and size of groups compared, we used the Pearson's Chi-squared test of independence or Fisher's exact test (2-tailed) to assess the relationship between categorical variables.

BMI was computed as weight in kilograms divided by the square of height in meters (kg/m^2) and considered as a categorical variable whose modalities were defined according to the world health organization (WHO), i.e., BMI between 18.5 and 24.9 for normal weight and BMI equal to or greater than 25 for overweight and obesity. Clinical benefit rate (CBR) was defined as complete or partial response and stable disease for at least 3 months and analyzed for the entire study population and in subgroups defined upon BMI, line of therapy (third vs. subsequent) and hormone receptor status. This latter was defined based on the expression of estrogen receptors and/or progesterone receptors (ER and/or PgR positive vs negative). We also considered ER and PgR expression separately (ER positive vs. negative; PgR positive vs negative). Results from subgroup analysis testing the impact of line of therapy and hormone receptor status were further stratified by BMI. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan–Meier product-limit method. PFS was defined as the time from the starting date of eribulin administration to disease progression or last follow-up evaluation. OS was calculated as the time from the starting date of eribulin administration to the date of death or last contact. Univariate PFS and OS curves were estimated for all the clinicopathological features listed in Table 1 (i.e., BMI, PS, age, ER, PgR, HER2 overexpression/amplification, triple negative subtype, LOT,); multivariate Cox analysis was used to explore the role of multiple variables on survival. The variable choice was oriented by the evidence emerged from the univariate approach and/or biological sustainability of the model based on literature data. The level of significance was set at $P \leq 0.05$. SPSS software was used for all statistical evaluations (SPSS version 21.0, SPSS Inc., Chicago, IL).

Results

Descriptive characteristics of the study participants are reported in Table 1. Median age and ECOG were 61 years (range 31–79) and 1 (range 0–2), respectively. Among the patients included, 57.4% fell in the lowest BMI category while the remaining 42.6% were overweight or obese. Estrogen and/or progesterone receptors (ER and/or PgR) were expressed in 80 patients (79.2%), while in 19 women (18.8%), the human epidermal growth factor receptor 2 (HER2) was overexpressed or amplified. The triple negative subtype was represented in 13 patients (12.8%). Eribulin was administered as third line treatment in 51.5% of cases and as subsequent lines in the remaining patients (49.5%). The median follow-up was 12 months (range, 2–32).

TABLE 1. Descriptive characteristics of the study participants (N:101)

	Median	Range
Age (years)	61	31–79
ECOG PS	1	0–2
	N	%
BMI (kg/m^2)	58	57.4
18.5–24.9	43	42.6
≥25		
ER and/or PgR positive	80	79.2
ER status		
Positive	73	72.3
Negative	19	18.8
Unknown	9	8.9
PgR status		
Positive	58	57.4
Negative	34	33.7
Unknown	9	8.9
HER2 overexpressed/amplified	19	18.8
Triple Negative	13	12.8
LOT		
3rd line	52	51.5
>3rd line	49	48

ECOG PS: Eastern Cooperative Oncology Group performance status; BMI: body mass index; ER and/or PgR+: Estrogen and/or progesterone receptor positive; ER: estrogen receptor; PgR: progesterone receptor; HER2: human epidermal growth factor receptor 2; LOT: line of treatment.

TABLE 2. Clinical benefit rate in the overall study population (N:101)

	CBR, N (%)	No CBR, N(%)	*P*
Overall population (N:101)	61 (60.4)	50 (49.6)	-
BMI			0.10
18.9–24.9	39 (67.2)	19 (32.8)	
≥25	22 (51.2)	21 (48.8)	
LOT			
3rd	33 (63.5)	19 (36.5)	0.52
>3rd	28 (57.1)	21 (42.9)	
ER and/or PgR			
Positive	52 (65.0)	28 (35.0)	0.06
Negative	9 (42.9)	12 (57.1)	
*ER			
Positive	46 (63.0)	27 (37.0)	0.10
Negative	8 (42.1)	11 (57.9)	
*PgR			
Positive	38 (65.5)	20 (34.5)	0.08
Negative	16 (47.0)	18 (53.0)	

BR: clinical benefit rate; BMI: body mass index, LOT: line of therapy; ER and/or PgR: estrogen and/or progesterone receptor; ER: estrogen receptor; PgR: progesterone receptor.
*Percentages do not add up to 100 because of missing values in 9 patients out of 101.

CBR for the entire study population and in subgroups defined as previously specified are shown in Table 2. Following treatment, 25 patients (24.8%) achieved a partial response and in 36 women (35.5%) the disease remained stable for at least 3 months, with an overall CBR being observed in 61 patients out of 101 (60.4%). Generally, lower BMI, treatment administration as third line, and positive hormone receptor status were associated with a higher CBR, although at a not statistically relevant extent ($P = 0.10$, $P = 0.52$, and $P = 0.06$, respectively). In Table 3, stratification by BMI significantly affected results from the subgroup having received eribulin as third line versus subsequent lines in the lowest BMI stratum, with CBR being 77.8% and 58.1% ($P = 0.03$), respectively. No further significant findings emerged from the analysis of data across BMI strata.

In regard to survival, median PFS was 4 months (95%CI 3–5) for women in the lowest BMI category and 3 months in

TABLE 3. Clinical benefit rate in subgroups defined by line of therapy and hormone status. Data were further stratified by BMI* (N:101)

	CBR N (%)		*P*
Overall population (N:101)	61 (60.4)		-
LOT	3rd	>3rd	
BMI < 25	21 (77.8)	18 (58.1)	0.03
BMI ≥ 25	12 (48.0)	10 (55.6)	0.86
ER and/or PgR	Positive	Negative	
BMI < 25	34 (69.4)	5 (55.6)	0.46
BMI ≥ 25	18 (58.1)	4 (33.3)	0.15
ER	Positive	Negative	
BMI < 25	29 (67.4)	4 (50.0)	0.43
BMI ≥ 25	17 (56.7)	4 (36.4)	0.25
PgR	Positive	Negative	
BMI < 25	24 (66.7)	9 (60.0)	0.65
BMI ≥ 25	14 (63.6)	7 (36.8)	0.09

*BMI was addressed as a categorical variable whose modalities were established according to the WHO classification, i.e., BMI: 18.5–24.9 and ≥25 for normal weight and overweight subjects, respectively (reference 32); CBR: clinical benefit rate; BMI: body mass index, LOT: line of therapy; ER/PgR: estrogen and/or progesterone receptor; ER: estrogen receptor; PgR: progesterone receptor.

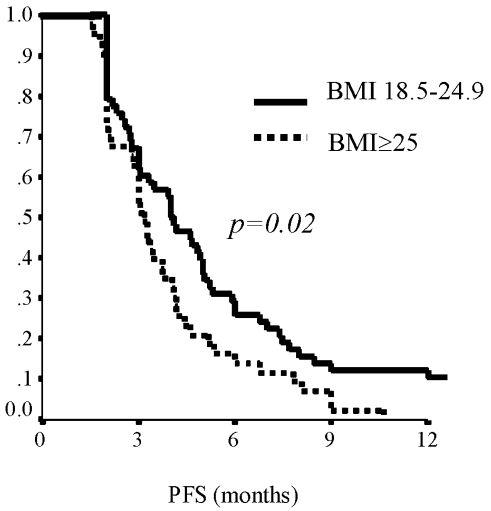

Fig. 1. Progression free survival (PFS) by subgroups defined upon BMI, i.e., BMI: 18.5–24.9 and BMI ≥ 25.

overweight and obese patients (95%CI, 2.1–4.0, $P = 0.02$) (Figure 1). Median OS was 13 months (95%CI, 11–15) and 12 months (95%CI 6–18) in normal and overweight or obese women, respectively ($P = 0.96$). Median PFS and OS were significantly longer in patients with estrogen receptor (ER) positive tumors compared with ER negative cases (PFS: 4 months, 95%CI 3–5 months vs. 3 months, 95%CI 2–4, $P = 0.005$ and OS: 14 (10–18) vs. 7 (4–10), $P = 0.02$, respectively, Figs. 2 and 3). In multivariate analyses including both BMI and ER status, BMI influenced PFS at a nearly significant extent (Hazard Ratio_HR_ 1.55, 95%CI 1.01–2.39, $P = 0.05$), while ER expression significantly affected PFS and OS (HR: 1.99, 95%CI: 1.16–3.40, $P = 0.01$ and HR: 2.0, 95%CI: 11–3.6, $P = 0.02$, respectively).

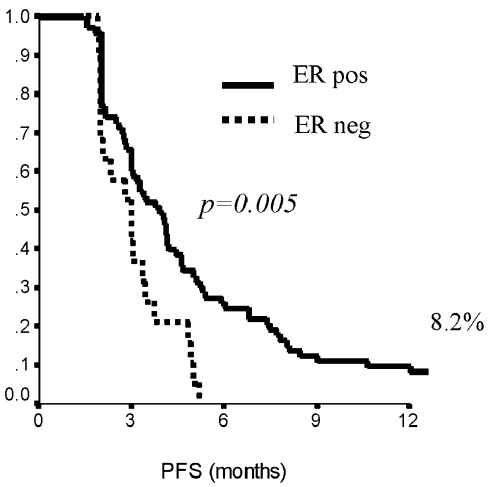

Fig. 2. Progression free survival (PFS) by subgroups defined upon estrogen receptor expression (ER), i.e., PFS in patients with expressing tumors (ER positive) and in patients with not expressing tumors (ER negative).

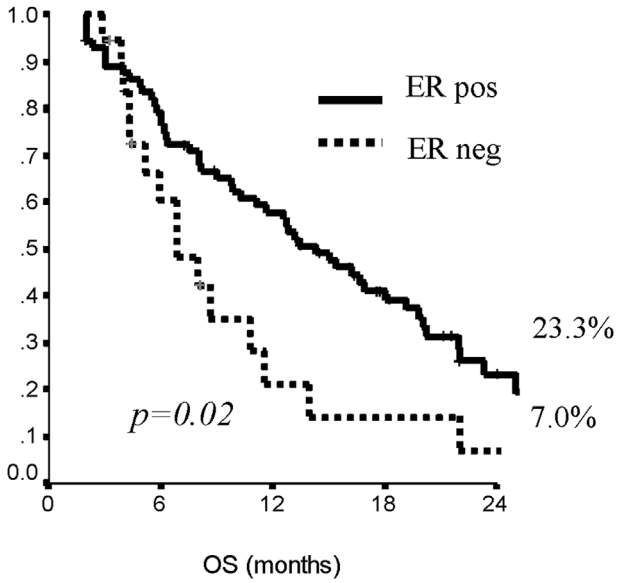

Fig. 3. Overall survival (OS) by subgroups defined upon estrogen receptor expression (ER), i.e., OS in patients with expressing tumors (ER positive) and in patients with not expressing tumors (ER negative).

Toxicity events were recorded in 60 patients (59.4%). When analyzed across strata defined upon BMI, toxicity did not differ either by type (hematological vs. not) or number and grade of events (data available upon request).

Discussion

In this observational multicenter study, we explored the impact of BMI on treatment outcomes in a historic cohort of 101 women treated with eribulin as third or subsequent lines of therapy. Both efficacy and toxicity outcomes were considered. In the overall study cohort, CBR seemed to be somewhat higher in patients with lower BMI, treated with eribulin as third line and with hormone receptor positive cancers, although these results did not reach statistical significance. Following stratification by BMI, a higher CBR was confirmed in patients treated with eribulin as third line exclusively in the lowest BMI stratum. Results from univariate analysis were in key with a significantly prolonged PFS, but not OS, in leaner women compared to their heavier counterpart. In addition, significantly longer PFS and OS were observed in patients with ER positive tumors. Cox models including BMI and ER positivity showed nearly significant evidence in support of longer PFS in patients with lower BM, while ER positivity was associated with significantly improved PFS and OS. Nothing relevant emerged when addressing the impact of BMI on toxicity, both as a whole and in subgroups defined upon the type and grade of the events reported for the study cohort.

Our interest in the role of BMI on treatment outcomes in breast cancer patients treated with eribulin as third and subsequent lines of therapy was fueled by prior work from our and other collaborating groups within at least two different research pipelines. Indeed, we have previously addressed the themes related to this drug efficacy and toxicity in a slightly larger historic cohort. On that occasion, beyond the limitations stemming from the retrospective study design, our findings fully replicated results from previous studies which were all

verified at a real-world population level (Cortes et al., 2011; Gamucci et al., 2014; Twelves et al., 2014; Kaufman et al., 2015). In addition, we have previously worked on the association of anthropometric and metabolic determinants with several disease- and patient-related features with a renown prognostic and/or predictive value in breast cancer (Barba et al., 2012; Vici et al., 2014, 2015). On this basis, the conduct of this study may be ideally placed at the exact confluence between these two research orientations. Our findings may help fulfill the need for a more appropriate patient selection and correct outcome interpretation in women treated with eribulin. Indeed, this molecule is the first single agent having shown survival advantage in patients treated beyond the second line at the cost of manageable toxicity (Cortes et al., 2011; Gamucci et al., 2014; Twelves et al., 2014; Kaufman et al., 2015). However, despite the encouraging data collected so far, no recommendations for third line treatment of breast cancer patients have been clearly established. In our previous work, patients having received eribulin as third line were identified as those with greater CBR compared with patients treated in subsequent lines. We now add to the characterization of this patient subgroup based on the distinction by BMI categories and report on a significantly higher CBR in patients having received eribulin as third line and whose BMI fell in a 18.5–24.9 range. On univariate analysis, BMI was also shown to significantly affect PFS, although evidence from the Cox model was only of borderline significance. If corroborated by the results of larger and prospectively designed studies, the first time finding of a role of BMI in modulating eribulin efficacy in terms of CBR and PFS might help identify a more targeted population within the frame of the existing indications to the use of this drug. This might positively reflect on the activity profile of eribulin due to attenuation of efficacy dilution potentially associated with drug administration in roughly selected patients. In addition, given its modifiable nature, interventions targeting BMI may be greatly attractive in view of the amelioration of treatment outcomes in patients affected by the disease (Rock et al., 2012; Courneya et al., 2014; Goodwin et al., 2014; Goodwin et al., 2015; Reeves et al., 2014).

In this set of analysis, median PFS and OS recorded following administration of eribulin were significantly longer in patients with ER expressing tumors than in their negative counterpart, with ER positivity testing significant both in uni- and multivariate regression models. Differences in this drug efficacy favoring eribulin in patients with ER positive tumors were also shown by the pooled analysis of the two phase three trials. However, these data are barely comparable to ours. Indeed, differences in treatment between the groups of patients enrolled in the original trials may have significantly affected patients outcomes (Twelves et al., 2014). In the present study, it is plausible to hypothesize that better survival outcomes observed in patients with ER positive cancers may be at least partly driven by the use of hormonal agents in this subset of patients. Some of the limitations described in the following lines refrained us from running subgroup analysis to further detail the use of hormonal therapy in this case series. At this time, our results concerning better efficacy outcomes in ER positive metastatic breast cancer patients treated with eribulin have to be intended exclusively as hypothesis generating.

In this study population, the assessment of the role of BMI on toxicity outcomes did not reveal significant findings. This is consistent with what reported by Hourdequin et al. (2013) in their systematic review and meta-analysis, although our findings are exclusively referred to the use of eribulin in the advanced setting for which specific evidence is currently lacking. Our study have some limitations. First, it was conceived according to a retrospective observational design, which is per se particularly prone to bias and confounding. We are well aware of the limitations stemming from the adoption of this study design. Yet, we do rely on it in the attempt to speed out the phase of hypothesis generation and switch to further steps along this specific research pipeline. In this specific case, the analysis focused on the impact of BMI on treatment outcomes allowed the identification of two specific features, i.e., line of treatment and ER expression, whose role in affecting treatment outcomes in patients treated with eribulin deserves further consideration. Second, the limited size of the original cohort was further restricted by the lack of BMI data for 32 patients included in our prior study, i.e., 24.1% of the original series. In addition, data on ER expression were not available for nine patients. Unfortunately, the systematic gathering and recording for analysis purposes of anthropometric determinants in breast cancer patients across the different settings and, in metastatic patients, across the different lines of treatment has not stably entered the clinical practice. As a consequence, missing data continue being quite common when working on clinical series.

Among our study strengths, novelty of findings deserves to be mentioned. We have previously cited the impressive amount of evidence in support of the role played by anthropometric and metabolic determinants in breast and other cancers (Zhu et al., 2012; Bravatà et al., 2013; Li et al., 2014; Byers and Sedjo, 2015; Chan and Norat, 2015; Keum et al., 2015). In strict referral to breast cancer, BMI has been extensively explored in relation to efficacy and toxicity outcomes in the adjuvant settings, but thus far the advanced setting has been left totally uncovered (Byers and Sedjo, 2015). We now suggest a role of BMI in affecting treatment outcomes in a not particularly restricted cohort of patients with advanced disease who were all treated with eribulin. In addition, since our research was contextualized in the clinical setting, its results may have easier generalizability and more prompt resonance compared to those from intervention trials which may be of limited applicability in the real world population.

In conclusions, we carried out an observational multicenter study on the role of BMI in affecting treatment outcomes in a relatively restricted historic cohort of metastatic breast cancer women treated with eribulin as third and subsequent lines of therapy. We observed a significantly greater CBR in women having received eribulin as third line if their BMI was in the lowest category, i.e., 18.5–24.9. On univariate analysis, BMI and ER positivity significantly affected PFS, while ER positivity impacted OS. Multivariate analysis showed nearly significant evidence supporting the effect of BMI on PFS, while results for ER on PFS and OS remained fully significant. Under the umbrella of confirmative findings from ad hoc studies, this novel evidence may help orient patients selection and outcome interpretation in metastatic breast cancer patients for whom the use of eribulin is currently indicated.

List of Abbreviations

BMI	Body mass index
ECOG	Eastern Cooperative Oncology Group
CBR	Clinic benefit rate
ER and/or PgR	Estrogen and/or progesterone receptors
FDA	Food and drug administration
HER2	Human epidermal growth factor receptor 2
HR	Hazard Ratio
NCI-CTCAE v.04	National Cancer Institute Common Terminology Criteria for Adverse Events version 4
OS	Overall survival
pCR	pathologic complete response
PFS	Progression free survival
RECIST, v. 1.1	Response Evaluation Criteria in Solid Tumours, version 1.1
TNBC	Triple negative breast cancer

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