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Clinical impact of body mass index on palbociclib treatment outcomes and effect on exposure

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ABSTRACT

The impact of body mass index (BMI) on treatment outcomes in patients with cancer is gaining increasing attention given the limited data available. The aim of this study was to investigate the contribution of BMI on the safety and efficacy profile of palbociclib in 134 patients with metastatic luminal-like breast cancer treated with palbociclib and endocrine therapy (ET). Normal-weight and underweight patients (BMI<25) were compared with overweight and obese (BMI≥25). Detailed clinical and demographic data were collected. Patients with a BMI<25 had a higher incidence of relevant-hematologic toxicities ($p = 0.001$), dose reduction events ($p = 0.003$), and tolerated lower dose intensities ($p = 0.023$) compared to patients with a BMI≥25. In addition, patients with a BMI<25 had significantly shorter progression-free survival (log-rank $p = 0.0332$). A significant difference was observed in the subgroup of patients for whom systemic palbociclib concentrations were available: patients with a BMI<25 had a 25% higher median minimum plasma concentrations (C_{min}) compared to BMI≥25. This study provides compelling evidence for a clinically relevant contribution of BMI in discriminating a group of patients who experienced multiple toxicities that appeared to affect treatment adherence and lead to poorer survival. BMI could become a valuable tool for personalizing the starting dose of palbociclib to improve its safety and efficacy.

1. Introduction

Palbociclib was the first cyclin D kinase 4/6 inhibitor (CDK4/6i) for patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, metastatic breast cancer due to a significant improvement in progression-free survival (PFS) in the phase 3 PALOMA-2 trial. However, grade 3 or 4 neutropenia occurred in 66.4% of patients receiving palbociclib-letrozole compared with 1.4% of patients receiving placebo-letrozole [1]. Although the toxicity is clinically manageable, it can affect treatment adherence and possibly efficacy.

Several factors have been reported to predict neutropenia induced by

Abbreviations: CDK4/6i, cyclin D kinase 4/6 inhibitors; PFS, progression-free survival; ANC, absolute neutrophil count; C_{min}, minimum plasma concentration; BMI, body mass index; Vd, volume of distribution; ET, endocrine therapy; CTCAE, common terminology criteria for adverse events; RDI, relative dose intensity; OR, odds ratio; CI, confidence interval; IQR, interquartile range; HR, hazard ratio; MTD, maximum dose tolerate.

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palbociclib. Among them, a low absolute neutrophil count at baseline (ANC) was identified as a strong and independent risk factor for palbociclib-induced neutropenia [2,3]. Differences in patients' plasmatic exposure to the drug have also been considered to explain inter-individual variability in the safety profile. Palbociclib exhibits interindividual variability in plasma exposure, with coefficients of variation in minimum plasma concentration (C_{min}) ranging from 41% to 59% [4]. A relationship between exposure and efficacy has been suggested, as higher palbociclib exposure is associated with greater reductions in ANC and platelet levels [5,6], although no definitive conclusion for efficacy (PFS) has been drawn [7]. Palbociclib exposure could be influenced by several variables, including genetic makeup, organ function, and drug-drug interactions, which may also affect pharmacodynamics [8,9].

Body mass index (BMI) has been reported to influence toxicity and treatment outcome not only with palbociclib but also with ribociclib and abemaciclib [10–14]. Most of the published studies reported that neutropenia caused by palbociclib is less frequent and less severe with increasing BMI [11–14]. However, a few publications have not confirmed this association [15,16], and the opposite was found in a cohort of Japanese patients [17]. Some studies have shown that a high BMI not only decreases the risk of toxicity but may also affect the response to treatment with palbociclib, although the data on this aspect are preliminary and rather controversial [11,12,15].

On the other hand, the effects of BMI on the plasmatic exposure of palbociclib was assessed in registration trials but were not considered significant enough to warrant weight-based dosing [7]. The lack of a clinical association was also confirmed in subsequent studies [16,18].

It seems reasonable to assume a pharmacokinetic explanation for these observations. Only one study with data from PALOMA-2 investigated whether the worse clinical outcome of palbociclib was sustained by an altered drug exposure, without finding a significant association [16]. Because of its high volume of distribution (Vd) of 2583 L, significantly greater than that of other CDKis, palbociclib penetrates extensively into peripheral tissues. Consequently, palbociclib tissue binding could be influenced by body fat composition [6].

The aim of this study is to provide evidence that in a prospective mono-institutional series of patients with HR-positive HER2-negative metastatic breast cancer, patient's BMI may be a clinically relevant factor affecting patient clinical outcome. Toxicity, treatment adherence, and efficacy data were integrated and supported by palbociclib plasmatic exposure data collected at steady-state C_{min}.

2. Methods

2.1. Data sources and patient selection

Patients with hormone receptor-positive, HER-2 negative metastatic breast cancer who started treatment with palbociclib (125 mg daily, days 1–21 of each 28-day cycle), and endocrine therapy (ET) (letrozole/fulvestrant) were prospectively enrolled in the CRO–Aviano integrated pharmacological counselling program of between 2020 and 2022 [8]. For the present analysis, a subset of patients was retrospectively selected based on the following criteria: treatment for at least three months, first or second-line treatment, clinical data available. Clinical and demographic data were retrieved from the electronic medical record after patients were referred to counselling program by the prescribing oncologist [8]. The study was approved (and conducted in accordance with the Helsinki Declaration) by the internal ethics committee of CRO Aviano (CRO-2022–14). Written informed consent was obtained from the patients.

2.2. Outcomes

Endpoints of the study were: ANC baseline and at day 14 of the first cycle, relevant-hematologic toxicities, dose reduction events and relative dose intensity (RDI) within first three cycles of treatment, PFS, and steady-state plasmatic exposure based on C_{min}. Patients were described based on the different BMI classes: underweight (<18.5 kg/m^2), normal-weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obesity grade I (30–34.9 kg/m^2) obesity grade II (35–39,9 kg/m^2), obesity grade III (≥40 kg/m^2). A cut off values was set to assess the evaluation with the endpoints, thus patients with a BMI≥25 were compared with those with a BMI<25.

2.2.1. Palbociclib systemic concentrations

Plasma was collected by centrifugation of EDTA whole blood tubes at 2450 g for 10 min at 4 °C and stored at −80°C until analysis. Samples from patients were analysed by a newly developed LC-MS/MS method, reported previously [19,20]. Drug concentrations were determined at specific time points, which allowed the evaluation of C_{min} at steady-state. Patients were asked to have their last drug intake 24 h (C_{min}) before sampling. Last intake (self-reported) and time of sampling were also recorded. To evaluate the association between exposure and BMI, only C_{min} data from patients treated with the standard dose of 125 mg daily, on days 1–21 of each 28-day cycle were used. At the time of sampling, information was also obtained on treatment adherence: doses not taken due to forgetfulness or following a medical advice. The data collected were verified with the referring oncologist.

2.2.2. Clinical data collection

Toxicities were recorded at visit on day 1 of each cycle and on day 14 of the first two cycles in the first three cycles of treatment. They were classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Relevant-hematologic toxicities were defined as grade 4 hematologic toxicities and grade 3 persistent hematologic toxicities (≥12 days for recovery).

Dose reduction was defined as a reduction in palbociclib dose from 125 mg to 100 mg or 75 mg (≥20% dose reduction) and was assessed both within the first three cycles and throughout the follow-up period. To account for changes in palbociclib exposure over time due to treatment discontinuations and/or dose reductions and/or changes in treatment regimen, the RDI was calculated in the first three cycles of treatment. The RDI is defined as the factual dose intensity divided by the calculated standard dose intensity during a given time period [21]. The standard dose intensity is defined as the drug dose that the patient should have taken during the period considered, while the factual dose intensity is the drug dose that the patient took during the same period. Therefore, patients who never suspended or reduced treatment have a maximum RDI of 1.

To assess the impact of different patient parameters on clinical outcome, PFS was calculated up to 1 year after treatment initiation. PFS was calculated from the start of treatment to the time of progression or death.

2.3. Statistical analysis

Differences between categorical variables were assessed using logistic regression analyses, whereas differences in medians were assessed using the Mann-Whitney test. Odds ratios (ORs) were estimated with the corresponding 95% confidence intervals (CIs). Data are presented as absolute frequencies and percentages or as median and interquartile range (IQR). PFS was estimated using Kaplan-Meier curves whereas hazard ratios (HRs) and relative 95%CI were calculated using Cox regression. Only potential confounders that were significantly associated with the PFS outcome were included in the multivariate analysis (logistic or Cox regression). A p value <of 0.05 was considered statistically significant. All statistical analyzes were performed using STATA statistical software.

3. Results

3.1. Patient characteristics

A total of 134 patients were included in the analysis. A description of the patients based on the different BMI classes is given in Table 1, whereas a description of their clinical characteristics is provided in Table 2. According to the 2-group comparison, 69/134 (51.5%) patients had a BMI≥25 and 65/134 (48.5%) patients had a BMI<25. The median age of the total cohort was 62 years, whereas the group with a BMI≥25 had a median age of 63 years and the group with BMI<25 had a median age of 62 years, so patients were evenly distributed between the two groups. All patients were self-reported Caucasians.

3.2. BMI, toxicity, and treatment adherence

Median ANC values were not significantly different at baseline between the BMI≥25 group and the BMI<25 group (3.74 $\times 10^3$/mm^3 IQR: 2.80–4.75 versus 3.52 $\times 10^3$/mm^3 IQR: 2.20–4.68). However, a statistically significant difference was observed at day 14 after starting treatment with palbociclib and ET (cycle 1). The group of patients with a BMI≥25 had a significantly higher median ANC (1.46 $\times 10^3$/mm^3 IQR: 1.07–2.09) compared to those with BMI<25 (1.19 $\times 10^3$/mm^3 IQR: 0.91–1.58) ($p = 0.045$) (Fig. 1).

There was an association between a low count of ANC at baseline and a higher risk for the occurrence of relevant-hematologic toxicities (OR 4.22, 95%CI 1.43–12.45; $p = 0.009$) (Table 3). Of 116/134 patients whose ANC baseline data were available, relevant-hematologic toxicities occurred in 21/116 (18%) within the first three cycles of treatment, and 16/21 (76.2%) had ANC baseline < 3.60 × 10^3/mm^3. In addition, the distribution of these 16 patients between the BMI≥ 25 group and the BMI<25 group is clearly unbalanced towards the BMI<25 group, as 14/16 (87.5%) of patients had a BMI<25.

A statistically significant difference was also found between the group with a BMI≥25 and the group with a BMI<25 in the occurrence of relevant hematologic toxicities in the first three cycles of treatment. Of the 27/134 patients who experienced such relevant toxicities, 6/27 (22.2%) had a BMI≥25, while 21/27 (77.8%) had a BMI<25 (OR 5.01, 95%CI 1.87–13.43; $p = 0.001$) (Table 4). The same trend continued when investigating the frequency of dose reduction, although the median time to dose reduction was similar in the two groups (85 days for the BMI ≥25 group versus 84 days for the BMI <25 group). Of the 134 patients, 21/134 (16%) underwent dose reduction in the first three cycles of treatment, of whom 4/21 (19%) had a BMI≥25, while 17/21 (81%) had a BMI<25 (OR=5.75, 95%CI 1.82–18.20; $p = 0.003$) (Table 4).

To capture all types of dose adjustments (including cycle delays and

Table 1
Distribution of patients among the different BMI classes.

	N° patients (%)
BMI <18.5 kg/m^2 Underweight	6 (4.5)
BMI 18.5–24.9 kg/m^2 Normal- weight	59 (44.0)
BMI25–29.9 kg/m^2 Overweight	48 (35.8)
BMI30–34.9 kg/m^2 Obesity grade I	14 (10.5)
BMI35–39,9 kg/m^2 Obesity grade II	6 (4.5)
BMI≥40 kg/m^2 Obesity grade III	1 (0.7)

Abbreviations: BMI, body mass index

Table 2
A descriptive of the patients included in the study and clinical characteristics.

	tot, n (%) (n = 134)	BMI<25 (n = 65)	BMI≥25 (n = 69)
Age (years)			
Median	62	62	63
Menopausal status			
Menopausal	103 (76.9)	48 (73.8)	55 (79.7)
Pre-menopausal	31 (23.1)	17 (26.2)	14 (20.3)
PS ECOG			
0	106 (79.1)	48 (73.9)	58 (84.1)
1	26 (19.4)	16 (24.6)	10 (14.5)
2	2 (1.5)	1 (1.5)	1 (1.5)
Metastatic de novo			
No	85 (63.4)	43 (66.2)	42 (60.9)
Yes	45 (33.6)	19 (29.2)	26 (37.7)
N.a.	4 (3.0)	3 (4.6)	1 (1.4)
Number of metastatic sites			
1	58 (43.3)	23 (35.4)	35 (50.7)
2	45 (33.6)	24 (36.9)	21 (30.4)
≥3	31 (23.1)	18 (27.7)	13 (18.8)
Visceral sites			
No	73 (54.5)	32 (49.2)	41 (59.4)
Yes	61 (45.5)	33 (50.8)	28 (40.6)
Subtype metastatic			
Luminal A	65 (48.5)	33 (55.0)	32 (46.4)
Luminal B	54 (40.3)	27 (45.0)	27 (39.1)
N.a.	15 (11.2)	5 (7.7)	10 (14.5)
Prior CT			
No	80 (59.7)	38 (58.5)	42 (60.9)
Yes	54 (40.3)	27 (41.5)	27 (39.1)
Treatment line			
I line	104 (77.6)	50 (76.9)	54 (78.3)
II line	30 (22.4)	15 (23.1)	15 (21.7)
Endocrine therapy			
Letrozolo	75 (56.0)	35 (53.9)	40 (58.0)
Fulvestrant	57 (42.5)	28 (43.1)	29 (42.0)
Anastrozole	1 (0.7)	1 (1.5)	0
Exemestane	1 (0.7)	1 (1.5)	0
Dose reductions			
Months to first reduction, median	3.5	3	3.5
First dose reduction within first 3 cycles	21 (15.7)	17 (26.2)	4 (5.8)
Relative dose intensity			
Median	0.861	0.872	0.866
25th percentile	0.771	0.721	0.800
50th percentile	0.861	0.854	0.894
75th percentile (max)	1.000	1.000	1.000

Abbreviations: BMI, body mass index; PS, performance status; N.a., not available; CT, Chemotherapy

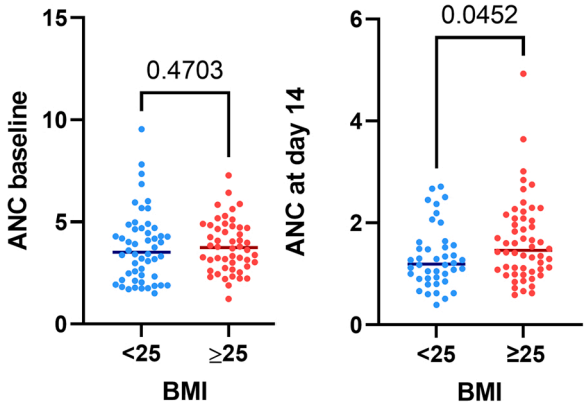

Fig. 1. Group with a BMI<25 has an ANC baseline median value of 3.74 × 10^3/mm^3 while the group with a BMI ≥ 25 has an ANC baseline median value of 3.52 × 10^3/mm^3. Group with a BMI<25 has an ANC at day 14 of first cycle of treatment median value of 1.19 × 10^3/mm^3 while the group with a BMI≥25 has an ANC at day 14 of first cycle of treatment median value of 1.46 × 10^3/mm^3. Abbreviation: ANC, absolute neutrophil count; BMI, body mass index.

Table 3
Association of baseline ANC and relevant-hematologic toxicities.

		ANC baseline, n (%)		Univariate logistic regression	
	tot, n (%) (n = 116)	ANC <3.60[1] (n = 57)	ANC ≥3.60 (n = 59)	Odds ratio (95%CI)	p value
Relevant hematologic toxicities[2]	21 (18.1)	16 (76.2)	5 (23.8)	4.22 (1.43 – 12.45)	0.009

[a] $3.60x10^3/mm^3$
[b] This endpoint is evaluated within first 3 cycles of treatment

schedule changes) and understand how they might affect adherence, the RDI was also calculated. Patients were divided into quartiles. However, because 50th and 75th percentiles overlapped, as the 75th percentile corresponds to 1 (the maximum RDI), patients were divided into three classes of RDI. Patients with an RDI below the 25th percentile were classified as the "low adherence group" in the first three cycles. Patients with an RDI between the 25th and 50th percentile were classified as the "medium adherence group", and patients with an RDI between the 50th percentile and 1 were considered the "high adherence group". The distribution of patients with a BMI<25 and ≥25 was statistically different between the three classes (p= 0.001). Patients with a BMI<25 had a higher risk of falling into the "low adherence" group (<25th percentile) than patients with a BMI≥25 (OR 4.42, 95%CI 1.75–11.17) (Table 4). The difference between the median RDI of the two BMI groups was also statistically significant (p = 0.0343): patients with a BMI<25 had a median RDI of 85.6%, while patients with a BMI≥25 had a median RDI of 90%.

Subsequently, associations between BMI and the endpoints of relevant-hematologic toxicities, dose reduction events, and RDI were also investigated in multivariate logistic regression analysis, adjusting for ANC baseline. The results remained substantially unchanged (Table 4).

3.3. BMI and palbociclib exposure

Systemic concentrations for palbociclib C_{min} were collected in a subset of 76/134 patients with available plasma samples, although the analysis was performed only in 34/76 patients for whom data were available at the standard dose of 125 mg daily on days 1–21 of each 28-day cycle. The results obtained showed a median C_{min} value of 69.1 ng/mL with a coefficient of variation of 32.6% (IQR: 57.5–83.9). When patients were stratified by BMI, a statistically significant difference in median C_{min} values was observed (p = 0.0375). In the group of patients with a BMI<25, the median C_{min} value was significantly higher (about 25%) compared with the group with a BMI≥25 (77.95 ng/mL, coefficient of variation of 30.7%, IQR: 63.1–89, versus 62.50 ng/mL, coefficient of variation of 30.6%, IQR: 49.6–75.1) (Fig. 2).

3.4. BMI and efficacy

A significant difference in treatment efficacy according to BMI was found. Patients with a BMI<25 were associated with significantly worse PFS compared with patients with a BMI≥ 25 (HR 2.32, 95%CI 1.09–4.95; log-rank p= 0.0360) (Fig. 3). Multivariate Cox regression analysis was also carried out to adjust the results for some acknowledged potential confounders such as PS ECOG, metastasis de novo, number or visceral metastatic sites and subtype metastatic (see Table 1), and the correlation did not change significantly. The distribution of these factors was also not significantly different in the two BMI groups (data not shown).

A sensitivity analysis excluding 6 underweight patients (BMI<18.5 kg/m^2), was also performed, and a significant in the

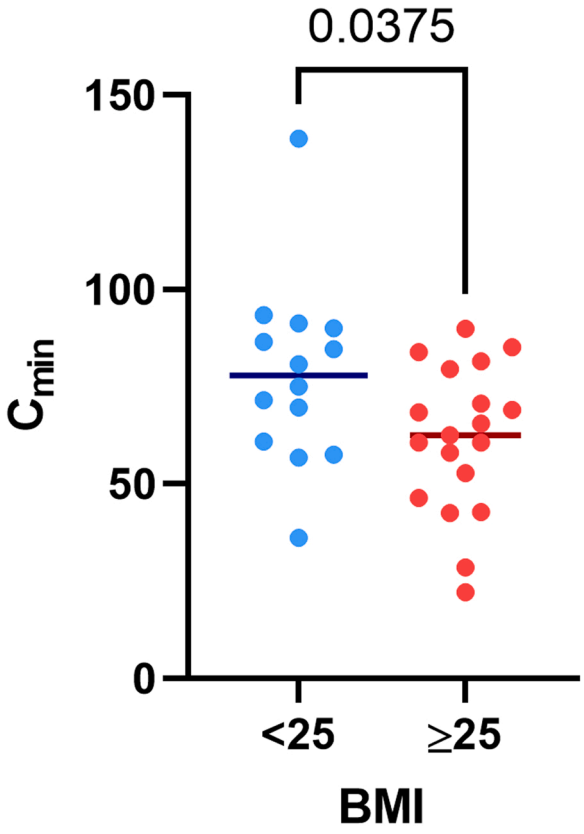

Fig. 2. Group with a BMI<25 has a C_{min} median value of 77.95ng/mL with a IQR of 63.1–89.2ng/mL. Group with BMI≥25 has a C_{min} median value of 62.5ng/mL with a IQR of 49.6–75.1ng/mL. Abbreviation: BMI, body mass index; IQR, interquartile range.

Table 4
Association of BMI with the endpoints assessed.

		BMI status, n (%)		Univariate logistic regression		Multivariate logistic regression[a]	
	tot, n (%) (n = 134)	BMI<25 (n = 65)	BMI≥25 (n = 69)	Odds ratio (95%CI)	p value	Odds ratio (95%CI)	p value
Relevant-hematologic toxicities[b]	27 (20.1)	21 (32.3)	6 (8.7)	5.01 (1.87 – 13.43)	0.001	9.12 (2.42 – 34.40)	0.001
Dose reduction[b]	21 (15.7)	17 (26.2)	4 (5.8)	5.75 (1.82 – 18.20)	0.003	8.90 (1.91 – 42.27)	0.005
Relative dose intensity[a,c]							
75th – 50th percentile	66 (49.3)	29 (44.6)	37 (53.6)	Reference		Reference	
50th – 25th percentile	31 (23.1)	11 (16.9)	20 (29.0)	0.70 (0.29 – 1.70)	0.431	1.06 (0.09 – 12.71)	0.962
<25th percentile	37 (27.6)	25 (38.5)	12 (17.4)	2.66 (1.14 – 6.17)	0.023	22.16 (4.17 – 117.76)	< 0.001

[a] Multivariate logistic regression model adjusted by ANC baseline.
[b] All these endpoints are evaluated within first 3 cycles of treatment
[c] Relative dose intensity: 75th percentile = 1.000 (maximum RDI value); 50th percentile = 0.889; 25th percentile = 0.771

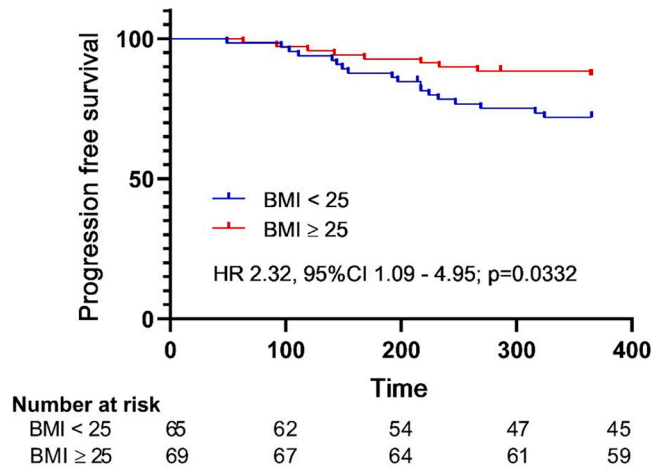

Fig. 3. Cox regression analysis of PFS at one year for patients with a BMI<25 and BMI≥25.

incidence of relevant-hematologic toxicities, dose reduction events, RDI, and PFS between the two groups (BMI<25 and BMI≥25) was still observed.

To account for the occurrence of dose adjustments, cycle delays, and treatment suspensions we evaluated PFS by RDI class. More specifically, we found that patients belonging to different adherence groups, as defined above by RDI, had a different risk of disease progression. We compared patients in the "low adherence group" with patients belonging to the "medium" and "high adherence group" and found that the difference was statistically significant. Patients in the "low adherence group" had a higher risk of disease progression than patients in the "medium" and "high adherence group" (HR 1.95, 95%CI 1.13–3.36, log-rank $p = 0.0052$).

Patients in whom the dose was reduced within the first three cycles of treatment had a higher risk of progression than patients who underwent dose reduction after the first three cycles (log-rank $p = 0.0147$) (Fig. 4). In 21/134 (15.7%) patients, who underwent dose reduction in the first three cycles of treatment, disease progression occurred in 8/21 (38.1%) in the first year of treatment, and all these patients had a BMI<25.

4. Discussion

By understanding the molecular characteristics of tumors, a tremendous progress over the past 30 years has been made in selecting the right drug for each patient. Advances in optimizing the dosing of these drugs has not kept pace though. In the current oncology paradigm, phase I trials focus primarily on toxicity rather than efficacy and are designed to identify the maximum-tolerated dose (MTD), that is then used for phase II and III trials. Regardless, patients receiving target therapies take them for longer periods of time, developing potentially less severe but symptomatic and persistent toxicities that are more difficult to tolerate over time. Other data, including dosage changes, dose and exposure-response relationships, and relevant specific populations, are not considered when evaluating MTD. In this way, the labeled dose could be poorly tolerated, compromising treatment adherence and thus maximum clinical benefit [22]. This approach, developed to maximize the efficacy of cytotoxic chemotherapy, may not be as valid for target therapies, for which a different dose-response relationship has been demonstrated and doses below MTD could have similar efficacy with less toxicity [23]. Dose-finding trials provide an opportunity to determine optimal dosing and maximize clinical benefit of target therapies. This would allow identification of population stratification factors, such as BMI, which not only affects drug pharmacokinetics and toxicity occurrence but may also indirectly influence efficacy. Reassessment of dosing strategies offers the opportunity to achieve significant benefits for patients [24].

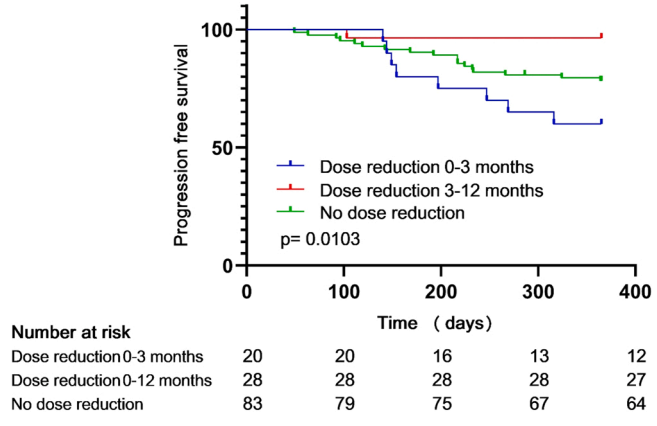

Fig. 4. Cox regression analysis of PFS for patients who reduced within the first 3 months of palbociclib-based treatment, after 3 months or who did not reduce.

This study provides important initial evidence that patients with BMI<25 and metastatic luminal-like breast cancer experience multiple dose-limiting toxicities that affect treatment adherence and lead to shorter survival. In our cohort, patients with BMI<25 are predominantly normal-weight (59 normal and 6 underweight). On the other hand, treatment with palbociclib in overweight and obese patients (BMI≥25) was not only better tolerated but also more effective, as shown by the longer PFS.

Previous reports have documented that overweight and obese patients treated with palbociclib experienced less frequent and less severe neutropenia than normal-weight patients, resulting in a lower treatment discontinuation rate [11,12]. Because overweight and obese patients experience less toxicity and thus less dose adjustments, they adhere better to treatment (as reflected by the RDI>25th percentile), which may explain the observed survival benefit.

Similar findings were recently reported in an abstract highlighting that overweight patients may benefit more from treatment with palbociclib or ribociclib [11]. Analysis of palbociclib systemic concentrations suggest that different pharmacokinetics of palbociclib according to BMI may contribute to the observed differences in clinical outcome. This aspect has never been investigated in an ad hoc pharmacokinetic study before. We observed that patients with a BMI<25 had a significantly higher median C_{min} than patients with a BMI≥25, suggesting that BMI may have an impact on the outcome of palbociclib, possibly by altering its pharmacokinetics. Because palbociclib is a drug with a large Vd and high permeability, an increase in body weight is expected to lead to extensive distribution in peripheral tissues and thus to a lower C_{min} values in plasma. Obesity status could also alter gastric emptying and intestinal permeability, while body fat composition could affect the efficiency of glucuronidation and sulfation pathways important for phase 2 metabolism of palbociclib [9]. Of note, the median C_{min} values we observed in the overweight and obese patients (62.5 ng/mL) were in a range consistent with the median population C_{min} value of 61 ng/mL [25] reported in the A5481001 and A5481003 trials at steady-state. Conversely, the underweight and normal-weight group had a significantly different and 25% higher median C_{min} value than the overweight and obese group. It could be hypothesized that this difference could justify the higher toxicity burden of patients with BMI<25 and, consequently, their poorer treatment adherence and outcome.

These data do not emerge from previous NCT00721409 trial, which found a nonsignificant association with PFS between patients "overexposed" and "underexposed" to palbociclib. This may be because, as highlighted in our study, a more flexible management of toxicities is of common clinical practice compared with clinical trials, and oncologists often revert to dose reduction or suspension, or schedule changes.

Therefore, due to the selection of the clinical trial population, it was not possible to highlight these data [16].

Previous literature has focused on explaining the potential impact of dose reduction on palbociclib efficacy and concluded that dose reduction of palbociclib does not worsen PFS [26,27] or overall survival [28]. Dose reduction due to adverse events did not adversely affect clinical outcomes from ribociclib as well [29,30]. One study reported improved outcomes in patients who received dose reductions during CDK4/6i-based treatment [31]. The authors reported as potential explanation that patients who reduced the dose required fewer therapy suspensions, resulting in stable plasma levels of the drug over time, thus suggesting that adherence could be more important than exposure.

In our study, we focused not only on dose reduction events but also on repeated suspensions, delays, and schedule changes, therefore providing a global assessment of treatment adherence in the first 3-months of treatment. Patients in the 'low' treatment adherence group may have lower benefit from treatment with palbociclib, possibly due to inadequate adherence (as reflected by the RDI).

Indeed, only Kristensen et al. in 2021 distinguished between early dose reduction (within 3 months of treatment initiation) and later dose reduction. Consistent with our results, they showed that early dose reduction in the first treatment phase was associated with a worse outcome than later dose reduction [30].

In our study, patients belonging to the "medium" to "high" adherence groups in the first three months of treatment also had longer PFS, regardless of BMI, underlying the importance of adequate and stable drug exposure in the first treatment period for treatment success.

Although our data suggest a clinically significant influence of BMI on palbociclib outcomes, we cannot exclude the possibility that the effect observed in patients with low BMI is due to the presence of a more aggressive tumor. Some studies investigated the effects of low BMI as a prognostic factor itself in metastatic breast cancer patients, regardless of treatment. In contrast to other studies that had found no significantly impact of BMI on PFS, Saleh et al. found in a large cohort of nearly 13,000 patients that underweight patients (BMI <18.5) were independently associated with worse PFS and overall survival in a metastatic setting. To ensure that the associations found between BMI and both efficacy and toxicity outcomes were not influenced by the presence of underweight patients (BMI<18.5) at risk of cachexia, we performed sensitivity analyses. These showed that the associations remained significant even when underweight patients were excluded. To further ensure that low BMI itself was not an independent factor for poor prognosis, we performed an exploratory analysis showing that, in our cohort, neither performance status nor other acknowledged negative prognostic factors (i.e., tumour onset as metastatic, luminal subtype A/B, presence of visceral metastases) significantly differentiated between patients with BMI<25 and BMI≥25.

Our study has some other limitations, mainly related to the small sample size of the pharmacokinetic data and to the cycle at which the samples were collected for the evaluation of the palbociclib plasmatic concentration, which may vary from patient to patient. Furthermore, additional data on long-term cumulative toxicities or changes in BMI or tolerability over time should be collected, in a larger case series.

To date, palbociclib has been prescribed as standard of care for metastatic luminal-like breast cancer without weight-based dosing. Based on the results obtained, we can conclude that patients with a BMI<25, represented in our study mainly by normal-weight patients, experienced multiple toxicities when treated with standard doses of palbociclib, underwent suspension and dose reduction within 3 cycles of treatment, which affected treatment adherence and resulted in poorer survival. We also confirmed herein that a low baseline ANC ($<3.60 \times 10^3/mm^3$) was an additional strong independent factor in the occurrence of early dose-limiting hematologic toxicities [2,32].

For another oral anticancer drug, niraparib, a different starting dose was determined based on patient's baseline platelet count and body weight in the phase 3 PRIMA study [33]. If our data will be confirmed in appropriately designed studies, it could be hypothesized that, similar to niraparib, a different starting dose of palbociclib could be considered for metastatic luminal-like breast cancer patients with low BMI and low baseline ANC.

CRediT authorship contribution statement

R.R., E.P., E.C., G.T. wrote manuscript; R.R. conceptualization; R.R., E.P., B.P., S.N., M.O., S.G., G.C., E.D.M., data curation; R.R., E.P., M.M., performed formal analysis and investigation; R.R., L.G., S.C., M.B., J.A., M.B., F.P. and G.T. provided resources.

Declaration of Competing Interest

LG reports consulting or advisory role: Lilly, Novartis. FP reports honoraria: Roche, MSD, AstraZeneca, Novartis, Lilly, Pfizer, Pierre Fabre, and Daiichi Sankyo; consulting or advisory role: Roche, Amgen, Lilly, Novartis, Pfizer, and Eisai; research funding: Eisai, AstraZeneca, and Roche; travel, accommodations and expenses: Roche and Celegne. The remaining authors delare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflict of interest.

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