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Body mass index in postmenopausal women with estrogen receptor-positive, HER2-negative early breast cancer: An exploratory analysis of the LORELEI trial

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ABSTRACT

Background: Phosphoinositide 3-kinase (PI3K) pathway, involved in obesity-related signalling, may influence efficacy and toxicity of PI3K inhibitors (PI3Ki). We explored associations between body mass index (BMI) and objective response rate (ORR), safety, molecular features, and breast density in the LORELEI trial.
Methods: LORELEI (NCT02273973) was a randomized trial evaluating neoadjuvant PI3Ki taselisib plus letrozole vs placebo plus letrozole in patients with estrogen receptor-positive/HER2-negative early breast cancer. Patients were classified as normal weight (BMI 18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), or obese (≥30 kg/m^2). Logistic regression tested BMI by treatment arm, adverse events were analysed descriptively by BMI category. Immune composition and gene expression profiles were evaluated by RNA sequencing.
Results: Of 329 patients, 98 (29.8%) were classified as normal weight, 125 (38%) as overweight, and 106 (32.2%) as obese. In the placebo arm, higher BMI was associated with lower ORR [odds ratio (OR) 0.90, 95% CI 0.83–0.97]; no association was observed in the taselisib arm [OR 1.03, 95% CI 0.96–1.11; interaction $p = 0.007$ (unadjusted), $p = 0.013$ (adjusted)]. In patients with obesity the incidence of hyperglycaemia and diarrhoea was 15.1% and 24.5%, respectively. Higher levels of pS6, a downstream effector of the PI3K pathway, were associated with increased ORR in patients with obesity in the placebo arm (interaction $p = 0.011$). Patients with obesity had lower baseline breast density ($p < 0.001$), not associated with ORR. Obesity was associated with increased IL6 expression, immune cell infiltration, and fatty acid metabolism signature.
Conclusions: Obesity was associated with lower ORR with letrozole alone, whereas this association was not observed in patients treated with taselisib.

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1. Introduction

Obesity is a multifactorial condition characterized by excess of adiposity and it is generally assessed and staged using the body mass index (BMI) [1]. In postmenopausal woman, excess adiposity has been linked to an increased risk of developing estrogen receptor (ER)-positive breast cancer, as well as increased risk of recurrence and poorer survival outcome [2–4]. A number of mechanisms link obesity with ER-positive breast cancer including the increased estrogen synthesis due to the higher expression and activity of the aromatase enzymes in the adipose tissue which may lead to higher exposure to estrogens. Moreover, obesity is associated with a chronic inflammatory state and increased leptin levels. These factors may promote the activation of signaling pathways such as mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and phosphoinositide 3-kinase/-protein kinase B (PI3K/AKT) pathways [5]. Given the role of PI3K signaling pathway in the pathophysiology of obesity [6,7], PI3K inhibitors have been proposed as a potential therapeutic strategy for obesity and related metabolic disorders [8].

The PI3K/AKT/mTOR pathway is frequently deregulated in ER-positive breast cancer, with nearly 40% of the tumours exhibiting *PIK3CA* mutation [9]. Because this pathway is central to metabolic regulation, the effectiveness and toxicity profile of PI3K inhibitors might be influenced by metabolic alterations commonly observed in patients with obesity [10].

Taselisib is a β-sparing PI3K inhibitor that selectively spares PI3Kβ while inhibiting the α, γ, and δ isoforms [11]. In combination with endocrine therapy, it showed clinical activity in pretreated metastatic ER-positive breast cancer [12]. The phase II, LORELEI trial randomly allocated 334 postmenopausal women with stage I-III, ER-positive HER2-negative breast cancer to receive 4 months of neoadjuvant letrozole plus taselisib or placebo, regardless of *PIK3CA* mutation status. After a median follow-up of 4.9 months, the study met one of its co-primary endpoints and showed that the addition of taselisib to letrozole significantly increased the proportion of patients with an objective response [Odds ratio (OR) 1.55; 95% CI 1.00–2.38, $p = 0.049$] while no statistically significant difference was observed on pathological complete response (pCR) rates (only 4 pCR cases in total) [13].

Herewith, we performed an exploratory analysis of the LORELEI trial to evaluate the association between BMI and treatment efficacy in patients with ER-positive HER2-negative early breast cancer treated with neoadjuvant letrozole with or without taselisib. Within this exploratory framework, we also evaluated the relationship between BMI and safety, molecular features, and breast density.

2. Methods

2.1. Data source and patient population

This is an exploratory, unplanned, analysis of the previously reported LORELEI trial [13]. Briefly, LORELEI was a randomized, double-blind, phase II trial evaluating the efficacy and safety of neoadjuvant treatment with taselisib and letrozole in patients with ER-positive, HER2--negative early breast cancer. The institutional review board at each participating site approved the study protocol. All patients provided written informed consent prior to inclusion.

Height and weight were collected at baseline and BMI was calculated by dividing weight by height squared (kg/m^2). For the purpose of this analysis, patients enrolled were categorized as underweight (BMI<18.5 kg/m^2), normal weight (BMI 18.5–24.9 kg/m^2), overweight (BMI 25–29.9 kg/m^2), or obese (BMI≥30 kg/m^2) as per World Health Organization (WHO) definition [14]. Patients without the necessary information to calculate BMI (n = 2) and underweight patients (n = 3) were excluded from the analyses as the number was too small to allow meaningful interpretation.

2.2. Objectives

The primary objective of this analysis was to evaluate the association between BMI and ORR, in all randomized patients and in those with *PIK3CA*-mutant tumours. ORR was one of the co-primary endopoint of the study and was defined as the percentage of patients with complete or partial responses, measured by centrally assessed magnetic resonance imaging (MRI) via modified RECIST version 1.1 criteria [13]. Secondary objectives were to evaluate the association between BMI and treatment-emergent adverse events (TEAEs); baseline phospoproteins expression (pS6, pAKT, pRAS40); stromal tumour-infiltrating lymphocytes (TILs); PTEN protein loss; and changes to Ki67 from baseline to 3 weeks. Additionally, obesity- and immune-related genes, as well as baseline breast adiposity measured by MRI, were analyzed in relation to BMI and treatment response.

2.3. Statistical analysis

Patient baseline characteristics were described using frequency and compared with respect to BMI category using the chi-square test; continuous variables were reported using medians and interquartile ranges and differences were tested using the Kruskal Wallis test. For the primary objective, ORs derived from univariable logistic regression models for objective response were calculated by comparing BMI either as a categorical or as a continuous variable. An interaction term was added when testing for treatment arm heterogeneity. Furthermore, a multivariable logistic regression model with adjustment for relevant clinical and pathological variables (grading, ECOG performance status, staging and age) was derived to assess if BMI was independently associated with outcome.

The association between BMI and TEAEs was analyzed by BMI category using descriptive statistics, no formal statistical comparisons or hypothesis testing were performed, as the analysis was intended to be purely descriptive. Baseline phosphoprotein (pS6, pAKT, pRAS40) and PTEN expression were assessed by immunohistochemistry. For the association with biomarkers, phosphoprotein expressions were assessed as continuous variables; PTEN status was categorized as intact, homogeneous loss, or heterogeneous loss; TILs and Ki67 were analyzed both as a continuous variable (%). Logistic regression models with and without interaction term were used to assess association with ORR.

RNA-sequencing was performed in pre-treatment tumour sample in 251 patients enrolled in LORELEI (75.1%). Tumour immune and stromal infiltration was estimated using two gene signature-based methods. MCP-counter relies on marker genes characteristic of specific cell types. QuanTIseq deconvolves bulk expression data to estimate absolute immune cell fractions. Both tools were applied to TPM-normalized (not log-transformed) RNA-seq data using the immunedeconv R package (v2.1.0). QuanTIseq estimated 9 immune cell types (CD8 + T cells, Tregs, NK cells, B cells, monocytes, myeloid dendritic cells, neutrophils, M1 and M2 macrophages), while MCP-counter profiled 10 immune populations (including CD8 + T cells, cytotoxic lymphocytes) and 2 stromal populations (cancer-associated fibroblasts and endothelial cells). Raw counts were normalized using the VarianceStabilizing-Transformation function from the DESeq2 package (v1.36.0). Differential expression analysis was performed using DESeq2 (v1.40.2) on transcript-level quantifications from salmon (v1.1.1) [15]. Genes with |log2FC= >0.5 and FDR< 0.05 (Benjamini-Hochberg) were considered significantly differentially expressed. Gene set enrichment analysis (GSEA) was conducted with fgsea (v1.26.0), ranking genes by sign [log2FC] × –log10(P). Forty-three hallmark pathways were analyzed; seven unrelated to breast cancer were excluded. Wilcoxon tests were used for comparisons ($P < 0.05$).

Breast density was assessed on baseline MRI according to the Breast Imaging Reporting and Data System (BI-RADS), 5th edition, classifying tissue composition into almost entirely fatty, scattered fibroglandular tissue, heterogeneous fibroglandular tissue, and extreme fibroglandular

tissue. Descriptive statistics were performed to evaluate the distribution of fibroglandular tissue types across BMI categories at baseline and at week 16. Differences in distribution across BMI categories were tested using the chi-square test. To assess the association between fibroglandular tissue type and ORR, univariable logistic regression models were applied.

All statistical analyses were carried out with SAS version 9.4 and R. P values < 0.05 were considered statistically significant. All analyses were considered exploratory in nature, and therefore no multiple testing correction was performed.

3. Results

3.1. Patient characteristics and demographics

Of 334 patients included in the LORELEI trial, 3 patients were excluded as they were underweight and 2 due to missing weight data, leaving 329 patients evaluable in this analysis (Supplementary Figure 1). Among them, 98 patients (29.8%) were classified as normal weight, 125 (38%) as overweight and 106 (32.2%) as obese. The baseline patients and tumour characteristics according to BMI categories are presented in Table 1. At baseline, a higher BMI category was associated with a worse ECOG performance status ($p = 0.01$). No other significant differences were observed in the analysed baseline patient or tumour characteristics across BMI categories.

3.2. Objective response rate in all patients and in patients with PIK3CA-mutant tumours

In the total cohort with evaluable MRI (N = 309), there was no evidence of a statistically significant association of continuous BMI with ORR (OR 0.97, 95% CI 0.92–1.01; $p = 0.168$), nor for BMI categories ($p = 0.102$). The ORR was 47.8% in patients with normal weight, 54.7% in patients who were overweight, and 40.2% in patients with obesity (Table 2).

In patients with *PIK3CA*-mutant tumours (N = 141), patients with higher BMI showed lower ORR although this did not reach statistical significance (OR 0.93, 95% CI 0.86–1.00; $p = 0.055$). Similar outcomes were observed for BMI categories ($p = 0.078$) (Supplementary Table 1).

3.3. Objective response rate by treatment arm

In the analysis by treatment arm, a significant interaction between BMI and treatment arm was observed. In the placebo plus letrozole arm, higher BMI as continuous variable was significantly associated with lower ORR (OR 0.90, 95% CI 0.83–0.97), whereas no association with BMI was observed in the taselisib plus letrozole arm (OR 1.03, 95% CI 0.96–1.11), interaction $p = 0.007$ (Table 3). This interaction remained significant after adjustment for relevant clinical factors (i.e., tumour grade, ECOG performance status, disease stage, and age) (interaction $p = 0.013$). Similar patterns were observed when considering only the PIK3CA-mutant cohort (Supplementary Table 2).

Considering BMI as a categorical variable, patients with obesity in the placebo plus letrozole arm had significantly lower ORR compared to patients with normal weight (26% vs 50%; OR 0.35, 95% CI 0.15–0.81). In contrast, in the taselisib plus letrozole arm no differences in ORR across BMI categories were observed (normal weight 45.0%, overweight 59.0%, obese 53.8%) (Table 3). Figure 1 shows the probability of objective response by BMI category. In the placebo arm, increasing BMI is associated with a decreasing probability of response, whereas in the taselisib arm, higher BMI appears to be associated with higher probability of response.

3.4. Treatment-emergent adverse events by BMI categories

The TEAEs according to BMI categories are reported in

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

Covariate	*Normal n = 98*	*Overweight n = 125*	*Obese n = 106*	*P-value*[a]*)*
Age				0.162
N	98	125	106	
Mean (SD)	63.7 (8.7)	64.3 (8.7)	65.8 (8.4)	
Median (Q1-Q3)	62.0 (58.0–70.0)	63.0 (59.0–71.0)	65.5 (59.0–73.0)	
Min - Max	45.0–82.0	41.0–83.0	44.0–84.0	
Race				0.721
White	81 (82.7%)	108 (86.4%)	90 (84.9%)	
American Indian or Alaska Native	6 (6.1%)	7 (5.6%)	9 (8.5%)	
Asian	5 (5.1%)	5 (4.0%)	1 (0.9%)	
Other race	3 (3.1%)	4 (3.2%)	3 (2.8%)	
Black or African American	3 (3.1%)	1 (0.8%)	2 (1.9%)	
Missing	0	0	1 (0.9%)	
Ethnicity				0.468
Not Hispanic or Latino	72 (73.5%)	84 (67.2%)	62 (58.5%)	
Hispanic or Latino	19 (19.4%)	32 (25.6%)	33 (31.1%)	
Not reported	6 (6.1%)	8 (6.4%)	9 (8.5%)	
Unknown	1 (1.0%)	1 (0.8%)	2 (1.9%)	
ECOG				0.010
0	93 (94.9%)	110 (88.0%)	86 (81.1%)	
1	5 (5.1%)	14 (11.2%)	20 (18.9%)	
Missing	0	1 (0.8%)	0	
Estrogen Allred score				0.269
0–2	2 (2.0%)	0	1 (0.9%)	
3–8	90 (91.8%)	120 (96.0%)	104 (98.1%)	
Missing	6 (6.1%)	5 (4.0%)	1 (0.9%)	
Progesterone Allred score				0.969
0–2	9 (9.2%)	11 (8.8%)	9 (8.5%)	
3–8	83 (84.7%)	107 (85.6%)	94 (88.7%)	
Missing	6 (6.1%)	7 (5.6%)	3 (2.8%)	
Ki67 (%)				0.992
N	90	116	96	
Mean (SD)	21.5 (14.9)	22.3 (17.0)	23.1 (18.2)	
Median (Q1-Q3)	17.5 (10.0–30.0)	18.0 (11.0–27.0)	17.0 (10.0–30.0)	
Min - Max	1.0–70.0	1.0–90.0	2.0–80.0	
T-stage				0.232
T1	7 (7.1%)	5 (4.0%)	5 (4.7%)	
T2	79 (80.6%)	103 (82.4%)	76 (71.7%)	
T3	11 (11.2%)	17 (13.6%)	24 (22.6%)	
T4	1 (1.0%)	0	1 (0.9%)	
N-stage[b]				0.523
N0	68 (69.4%)	81 (64.8%)	64 (60.4%)	
N1	25 (25.5%)	39 (31.2%)	38 (35.8%)	
N2	5 (5.1%)	5 (4.0%)	3 (2.8%)	
N3	0	0	1 (0.9%)	
M-stage				
M0	98 (100.0%)	125 (100.0%)	106 (100.0%)	
Histological grading				0.155
G1	10 (10.2%)	20 (16.0%)	24 (22.6%)	
G2	70 (71.4%)	76 (60.8%)	59 (55.7%)	
G3	7 (7.1%)	17 (13.6%)	10 (9.4%)	
GX	8 (8.2%)	11 (8.8%)	8 (7.5%)	
Missing	3 (3.1%)	1 (0.8%)	5 (4.7%)	
Anatomical staging				0.644
Stage I	5 (5.1%)	2 (1.6%)	3 (2.8%)	
Stage II	83 (84.7%)	112 (89.6%)	93 (87.7%)	
Stage III	10 (10.2%)	11 (8.8%)	10 (9.4%)	

[a] Chi-square or Kruskal Wallis test (not including the missing category in testing)

[b] Nodal status was assessed by axillary ultrasound, with suspicious findings confirmed by cytology or biopsy.

Table 2
Association Between BMI and Objective Response Rate.

Covariate	*N*	*Events*	*Events / N*	*Odds Ratio(95% CI)*	*P-value*
BMI (continuous)	309	148		0.97 (0.92–1.01)	0.168
BMI (categorical)	309	148	148 / 309 (47.9%)		0.102
normal	90	43	43 / 90 (47.8%)	1	
overweight	117	64	64 / 117 (54.7%)	1.32 (0.76–2.29)	
obese	102	41	41 / 102 (40.2%)	0.73 (0.41–1.30)	

Abbreviations: BMI, Body Mass Index; CI, Confidence Interval.

Supplementary Table 3. In the entire cohort, diarrhoea was among the most frequently reported TEAEs, with a prevalence of 17.3% in patients with normal weight, 22.4% in patients with overweight, and 24.5% in those with obesity. Fatigue was reported in 24.5% of patients with normal weight, 23.2% of patients with overweight, and 17.0% of those with obesity. Hyperglycaemia was observed in 8.2% of patients with normal weight, 9.6% of those who were overweight, and 15.1% of patients with obesity; grade 3 events were observed only in patients who were overweight (0.8%) and with obesity (0.9%). Hypertension was reported in 5.1% of patients with normal weight, 5.6% of patients with overweight, and 8.5% of those with obesity.

3.5. Association between BMI, biomarkers, and treatment response

In the entire cohort, PTEN levels were not significantly associated with ORR, nor was there a significant interaction between PTEN and BMI.

Values of Ki67, at baseline and at week 3, were similar across BMI categories, and no significant association was found with ORR, nor interaction with BMI.

TILs levels, at baseline, at week 3 and at surgery, were similar across BMI categories, with no significant association with ORR, nor interaction with BMI.

Baseline levels of pPRAS40 and pAKT were similar across BMI categories, with no significant association with ORR, and no interaction with BMI.

For pS6, baseline, week 3 and surgery levels were slightly higher in

Table 3
Association Between BMI and Objective Response Rate Within Each Treatment Arm.

Subgroup	*Covariate*	*N*	*Events*	*Alternative categoryEvents / N*	*Reference categoryEvents / N*	*Odds Ratio(95% CI)*	*InteractionP-value*
Arm	BMI (continuous)	309	148				0.007
Taselisib	BMI (continuous)	153	82			1.03 (0.96–1.11)	
Placebo	BMI (continuous)	156	66			0.90 (0.83–0.97)	
Arm	BMI (categorical)	309	148				0.064
Taselisib	overweight vs normal	153	82	36 / 61 (59.0%)	18 / 40 (45.0%)	1.76 (0.79–3.94)	
Taselisib	obese vs normal	153	82	28 / 52 (53.8%)	18 / 40 (45.0%)	1.43 (0.62–3.26)	
Placebo	overweight vs normal	156	66	28 / 56 (50.0%)	25 / 50 (50.0%)	1.00 (0.47–2.14)	
Placebo	obese vs normal	156	66	13 / 50 (26.0%)	25 / 50 (50.0%)	0.35 (0.15–0.81)	

Abbreviations: BMI, Body Mass Index; CI, Confidence Interval.

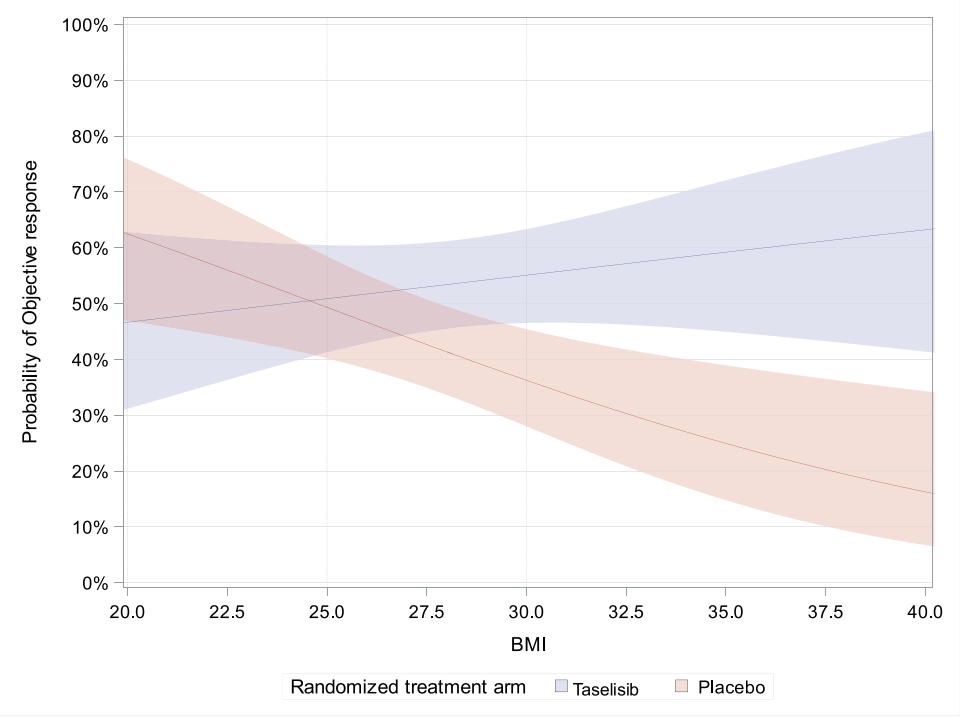

Fig. 1. Probability of Objective Response plot by BMI levels, Abbreviations: BMI, Body Mass Index.

patients with normal weight, though not significantly ($p = 0.094$). However, pS6 showed a significant interaction with BMI in predicting ORR ($p = 0.041$) (Fig. 2). In the placebo plus letrozole arm, the significant interaction with BMI was confirmed (interaction $p = 0.010$), whereas no such interaction was observed in the taselisib plus letrozole arm ($p = 0.855$) (Supplementary Figure 2).

3.6. Obesity-related gene aberrations

Combined data for both BMI and RNA-seq at baseline were available for a total of 180 patients. Tumour samples of patients with obesity were enriched in CD8 + T cells by MCP-counter and QuanTIseq (unadjusted P-value=0.001 and 0.041 compared to patients who were overweight and with normal weight in MCP-counter and unadjusted P-value=0.039 compared to patients who were overweight in QuanTIseq) (Supplementary Figure 3a-3b). Moreover, T regulatory cells, NK cells, and cytotoxic T cells were increased in tumour samples from patients with obesity compared to patients who were overweight (unadjusted P-value=0.002, 0.009 and <0.001, respectively) (Supplementary Figure 3a-**b**). Additionally, whereas an enrichment in macrophages and monocytes was observed in patients with obesity compared to patients who were overweight using MCP-counter, this was not confirmed in QuanTIseq. Higher levels of Interleukin 6 Cytokine Family Signal Transducer (IL6ST) (Supplementary Figure 4) as well as an enrichment in immune-related pathways (interferon gamma and alpha, allograft rejection, inflammatory response, IL6 JAK-STAT3 signaling), pathways associated with proliferation (G2M checkpoint, MYC target) but also in mTORC1 signaling were found in patients with obesity (Supplementary Figure 5).

3.7. Breast density

The distribution of breast density assessed by MRI across BMI categories at screening and week 16 is reported in Supplementary Table 4. At screening, breast density was significantly different across BMI categories ($p < 0.001$). Specifically, patients with normal weight had a higher proportion of heterogeneous fibroglandular tissue (64.3%), compared to patients with obesity (50.0%). Conversely, scattered fibroglandular tissue was more frequent in patients with obesity (45.3%) compared to patients with overweight (29.6%) and with normal weight (20.4%). Extreme fibroglandular tissue was rare across all categories (normal 8.2%, overweight 0.8%, obese 1.9%). At week 16, the distribution remained consistent with baseline, with higher scattered fibroglandular tissue prevalence in patients with obesity (46.2%) compared to patients who were overweight (30.4%) and with normal weight (18.4%) ($p < 0.001$). No significant associations were observed between breast density and ORR across BMI categories (Supplementary Table 5).

4. Discussion

In this exploratory analysis of LORELEI trial, obesity was associated with lower ORR in patients with ER-positive HER2-negative early breast cancer treated with neoadjuvant letrozole alone, whereas no clear association with BMI was observed in patients treated with taselisib plus letrozole.

Aromatase inhibitors are widely used in patients with ER-positive breast cancer, acting by inhibiting aromatase, highly expressed in adipose tissue, and blocking the peripheral androgen-to-estrogen conversion. In our analysis, in the overall cohort, there was no association between BMI and ORR. However, when ORR was evaluated by treatment arm, higher BMI was associated with lower ORR in patients treated only with letrozole, while no such association was found for those patients treated with the addition of taselisib. This likely explains why no significant association between BMI and ORR was observed in the entire cohort. This observation may suggest that patients with higher BMI could experience reduced sensitivity to aromatase inhibitor alone and it is in line with previous studies showing that excess adiposity causes an increased expression and activity of the aromatase, potentially reducing the effectiveness of aromatase inhibitors [16,17]. The lack of association between BMI and ORR in the taselisib arm suggests that the addition of a PI3K inhibitor may attenuate or modify the relationship between BMI and treatment response, representing a novel observation to date that warrants further investigation.

The PI3K pathway and cellular metabolism are closely linked. Obesity is associated with increased activation of the PI3K/AKT/mTOR pathway, driven by insulin resistance, hyperinsulinemia, and chronic low-grade inflammation [18,19]. These factors can lead to higher dependency on PI3K pathway in tumour cells, particularly in ER-positive breast cancer. In this context, differences in response associated with BMI may reflect a potential interaction between metabolic status and treatment efficacy. However, given the exploratory nature of this analysis, no definitive conclusions can be drawn regarding a predictive role of obesity-related PI3K signaling.

Crosstalk between ER signaling and the PI3K pathway occurs directly, through PI3K-driven ER-independent transcription and cell

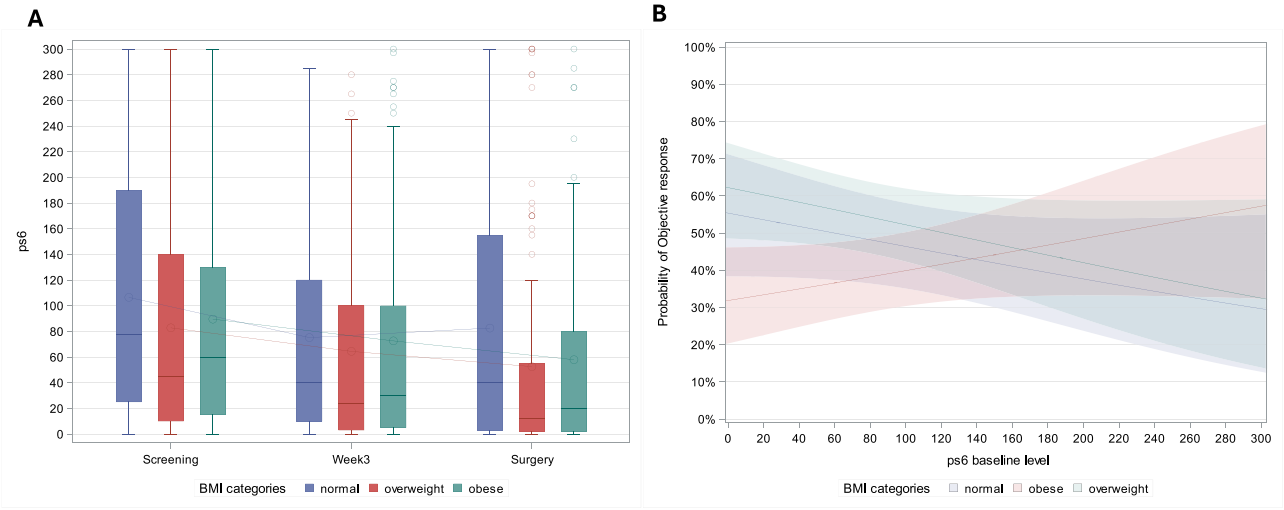

Fig. 2. pS6 Levels Across BMI Categories and Probability of Objective Response by Baseline pS6 and BMI, A: pS6 levels at screening, week 3, and surgery shown across BMI categories., B: Probability of objective response increases with higher baseline pS6 levels in patients with obesity, while the opposite trend is observed in patients with normal weight., Abbreviations: BMI, Body Mass Index.

proliferation, and indirectly, as ER signaling upregulates components of the PI3K pathway [19]. In this regard, pS6, a downstream effector of the PI3K pathway, is considered a surrogate marker of pathway activation [20]. While some studies showed a correlation between higher levels of pS6 and worse prognosis in ER-positive breast cancer, its predictive role remains unclear [20]. Nonetheless, pS6 has been proposed as predictive marker of endocrine resistance [21]. In our analysis, among patients with obesity treated with letrozole plus placebo, higher pS6 levels were associated with better ORR compared to patients with obesity with lower pS6 while no such association was found in those treated with the addition of taselisib. This finding suggests that, in the context of obesity, PI3K pathway activation may not necessarily imply endocrine resistance and could reflect an altered tumour biology. Moreover, higher levels of pS6 within a population that generally shows reduced sensitivity to endocrine therapy, might help identify a subgroup of patients with obesity patients more likely to benefit from aromatase inhibition alone. However, further validation is needed to confirm the potential predictive role.

The characteristic toxicity profile of PI3K inhibitors is mainly the result of the on-target disruption of insulin signaling [18]. In our analysis, gastrointestinal toxicity and hyperglycemia were among the most common TEAEs, with numerically higher rates observed in patients with obesity and overweight. Hyperglycemia is one of the most common on-target adverse events associated with PI3K inhibitors, and pre-existing obesity and diabetes are well-known risk factors for its occurrence [22]. Obesity is a risk factor for the development and progression of type 2 diabetes [23] and on the other hand, type two diabetes can exacerbate obesity, for example through the use of glucose-lowering drugs that promote weight gain [24]. Excess adiposity, particularly the visceral one, may worsen insulin resistance, which play a critical role in the occurrence of type 2 diabetes. In SOLAR−1, evaluating the addition of alpelisib to fulvestrant in patients with metastatic breast cancer, a higher proportion of patients with overweight and obesity experienced hyperglycemia compared to patients with normal weight [25]. Although obesity is an established risk factor for the occurrence of hyperglycemia, our analysis did not account for other comorbidities that might have influenced and increased its risk.

Patients with obesity present a unique tumour microenvironment landscape. During weight gain, adipocytes progressively store lipids, becoming hypertrophic and eventually dying. This event causes the rupture of adipocyte membranes and the consequent release of cellular contents, leading to a pro-inflammatory state [26]. This inflammatory environment is largely driven by the recruitment of pro-inflammatory M1 macrophages and the consequent release of pro-inflammatory cytokines such as IL−6 and TNF [27]. Inflammatory T cells further contribute to this obesity-related metabolic dysfunction, promoting M1 macrophage polarization by the secretion of pro-inflammatory cytokines. In our analysis, gene expression profiling revealed different molecular features in patients with obesity, suggesting an increased inflammatory response, in line with previous studies.

In postmenopausal women, higher BMI is associated with an increase in fat tissue in the breast and a consequently decrease in breast density [28]. The breast microenvironment, influenced by variations in fibroglandular and adipose tissue proportion, may play a role in treatment response. The available evidence about the association between breast density and response to neoadjuvant treatment, particularly neoadjuvant chemotherapy, is controversial [29,30]. While several mechanisms have been proposed, no clear biological explanation has been proposed for the potential differences in response to neoadjuvant chemotherapy. To the best of our knowledge, no studies have evaluated the impact of breast density in the context of PI3K inhibition. In our study, although breast adiposity distribution varied across BMI categories, no significant association with ORR was observed. However, the sample size for breast density subgroups was limited, and further research is needed to elucidate the underlying biological mechanisms.

This study has some limitations that should be acknowledged. First, this was an unplanned, exploratory analysis, therefore the findings should be interpreted with caution. Second, although BMI is widely used as a surrogate for obesity staging, it does not capture the complexity of obesity, which would require a more comprehensive assessment. Moreover, the analysis lacked detailed data on comorbidities and concomitant medications. Conditions such as diabetes, and the use of drugs like metformin, corticosteroids, or statins, may influence the PI3K/AKT/mTOR pathway and potentially affect both treatment efficacy and toxicity. Moreover, the duration of neoadjuvant treatment was limited to 4 months, whereas more recent recommendations support a 6-month course.

5. Conclusion

In conclusion, in patients with ER-positive HER2-negative early breast cancer, obesity was associated with lower response to neoadjuvant letrozole monotherapy, while no clear association between BMI and ORR was observed in patients treated with the addition of taselisib. Higher baseline PI3K activation was associated with better response to letrozole alone specifically in patients with obesity. Obesity was also associated with distinct tumour microenvironment features at baseline. These findings highlight potential differences in response to endocrine therapy and PI3K inhibitors according to BMI suggesting that the risk of potential undertreatment in patients with higher BMI warrants consideration and support further investigation into the interaction between metabolic status and treatment efficacy.

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CRediT authorship contribution statement

Laetitia Collet: Writing – review & editing. **Jill Fredrickson:** Writing – review & editing. **Chiara Dauccia:** Writing – original draft. **Timothy R. Wilson:** Writing – review & editing. **Maria Alice Franzoi:** Writing – review & editing, Conceptualization. **Luca Arecco:** Writing – review & editing. **Cristina Saura:** Writing – review & editing. **Elisa Agostinetto:** Writing – review & editing, Validation, Supervision. **Dominik Hlauschek:** Formal analysis. **Evandro de Azambuja:** Writing – review & editing, Validation, Supervision, Conceptualization. **Lidija Sölkner:** Formal analysis. **Michael Gnant:** Writing – review & editing. **Peter C. Dubsky:** Writing – review & editing. **Ruth Helfgott:** Writing – review & editing. **Gabriele Zoppoli:** Writing – review & editing. **Mafalda Oliveira:** Writing – review & editing.

Prior presentations

Partial results of this manuscript were presented as a Poster at ESMO 2025 (abstract N. 349 P).

Declaration of competing interest

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

CS: CS reports consulting fees, honoraria or meeting/travel support from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Genentech,Gilead, Lilly, MediTech, Menarini, MSD Spain, Novartis, Pfizer, Philips Healthcare, Pharmalex, Pierre Fabre, Puma Biotechnology, Roche, Seagen, Synthon and Zymeworks. CS is furthermore a member of the SOLTI Executive Board and Scientific Committee.

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JF: employee of Roche/Genentech

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116880.

Data availability

Qualified researchers may request access to individual patient-level data through the clinical study data request platform at https://vivli.org/ 18 months after the publication of the last clinical study report (CSR).

References

[1] Rubino F, Cummings DE, Eckel RH, et al. Definition and diagnostic criteria of clinical obesity. Published online January 9 Lancet Diabetes Endocrinol 2025. https://doi.org/10.1016/S2213-8587(24)00316-4. Published online January 9.

[2] Dauccia C, Bruzzone M, Arecco L, et al. Association between body mass index and risk of breast cancer according to breast cancer subtypes: A systematic review and meta-analysis. Breast Church Livingstone 2026;86. https://doi.org/10.1016/j.breast.2026.104710.

[3] Lohmann AE, Soldera SV, Pimentel I, et al. Association of Obesity With Breast Cancer Outcome in Relation to Cancer Subtypes: A Meta-Analysis. J Natl Cancer Inst 2021;113(11). https://doi.org/10.1093/jnci/djab023.

[4] Dauccia C, Alice Franzoi M, Martel S, et al. Body mass index and weight changes in patients with HER2-positive early breast cancer: A sub-analysis of the APHINITY trial. Eur J Cancer 2025;223. https://doi.org/10.1016/j.ejca.2025.115489.

[5] Tenvooren I, Jenks MZ, Rashid H, et al. Elevated leptin disrupts epithelial polarity and promotes premalignant alterations in the mammary gland. Oncogene 2019;38(20). https://doi.org/10.1038/s41388-019-0687-8.

[6] Ortega-Molina A, Lopez-Guadamillas E, Mattison JA, et al. Pharmacological inhibition of PI3K reduces adiposity and metabolic syndrome in obese mice and rhesus monkeys. Cell Metab 2015;21(4). https://doi.org/10.1016/j.cmet.2015.02.017.

[7] Becattini B, Marone R, Zani F, et al. PI3Kγ within a nonhematopoietic cell type negatively regulates diet-induced thermogenesis and promotes obesity and insulin resistance. Proc Natl Acad Sci U S A, 108; 2011. https://doi.org/10.1073/pnas.1106698108.

[8] Savova MS, Mihaylova LV, Tews D, Wabitsch M, Georgiev MI. Targeting PI3K/AKT signaling pathway in obesity. Biomed Pharmacother 2023;159. https://doi.org/10.1016/j.biopha.2023.114244.

[9] Millis SZ, Ikeda S, Reddy S, Gatalica Z, Kurzrock R. Landscape of phosphatidylinositol-3-kinase pathway alterations across 19 784 diverse solid tumors. JAMA Oncol 2016;2(12). https://doi.org/10.1001/jamaoncol.2016.0891.

[10] Gallagher EJ, Fierz Y, Vijayakumar A, Haddad N, Yakar S, Leroith D. Inhibiting PI3K reduces mammary tumor growth and induces hyperglycemia in a mouse model of insulin resistance and hyperinsulinemia. Oncogene 2012;31(27). https://doi.org/10.1038/onc.2011.495.

[11] Juric D, Krop I, Ramanathan RK, et al. Phase I dose-escalation study of taselisib, an oral PI3K inhibitor, in patients with advanced solid tumors. Cancer Discov 2017;7(7). https://doi.org/10.1158/2159-8290.CD-16-1080.

[12] Dickler MN, Saura C, Richards DA, et al. Phase II study of Taselisib (GDC-0032) in combination with fulvestrant in patients with HER2-negative, hormone receptor–positive advanced breast cancer. Clin Cancer Res 2018;24(18). https://doi.org/10.1158/1078-0432.CCR-18-0613.

[13] Saura C, Hlauschek D, Oliveira M, et al. Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with oestrogen receptor-positive, HER2-negative, early-stage breast cancer (LORELEI): a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol 2019;20(9). https://doi.org/10.1016/S1470-2045(19)30334-1.

[14] World health organization. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. 2016.

[15] Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol 2014;15(12). https://doi.org/10.1186/s13059-014-0550-8.

[16] Pfeiler G, Königsberg R, Hadji P, et al. Impact of body mass index on estradiol depletion by aromatase inhibitors in postmenopausal women with early breast cancer. Br J Cancer 2013;109(6). https://doi.org/10.1038/bjc.2013.499.

[17] Sestak I, Distler W, Forbes JF, Dowsett M, Howell A, Cuzick J. Effect of body mass index on recurrences in tamoxifen and anastrozole treated women: An exploratory analysis from the ATAC trial. J Clin Oncol 2010;28(21). https://doi.org/10.1200/JCO.2009.27.2021.

[18] Vasan N, Cantley LC. At a crossroads: how to translate the roles of PI3K in oncogenic and metabolic signalling into improvements in cancer therapy. Nat Rev Clin Oncol 2022;19(7). https://doi.org/10.1038/s41571-022-00633-1.

[19] du Rusquec P, Blonz C, Frenel JS, Campone M. Targeting the PI3K/Akt/mTOR pathway in estrogen-receptor positive HER2 negative advanced breast cancer. Ther Adv Med Oncol 2020;12. https://doi.org/10.1177/1758835920940939.

[20] Cascardo F, Vivanco M, Perrone MC, et al. Higher risk of recurrence in early-stage breast cancer patients with increased levels of ribosomal protein S6. Sci Rep 2024;14(1):25136. https://doi.org/10.1038/s41598-024-75154-1.

[21] Kim EK, Kim HA, Koh JS, et al. Phosphorylated S6K1 is a possible marker for endocrine therapy resistance in hormone receptor-positive breast cancer. Breast Cancer Res Treat 2011;126(1). https://doi.org/10.1007/s10549-010-1315-z.

[22] Liu D, Weintraub MA, Garcia C, et al. Characterization, management, and risk factors of hyperglycemia during PI3K or AKT inhibitor treatment. Cancer Med 2022;11(8). https://doi.org/10.1002/cam4.4579.

[23] Narayan KMV, Boyle JP, Thompson TJ, Gregg EW, Williamson DF. Effect of BMI on lifetime risk for diabetes in the U.S. Diabetes Care 2007;30(6). https://doi.org/10.2337/dc06-2544.

[24] ElSayed NA, McCoy RG, Aleppo G, et al. 8. Obesity and Weight Management for the Prevention and Treatment of Type 2 Diabetes: Standards of Care in Diabetes–2025. Diabetes Care 2025;48(ement_1):S167–80. https://doi.org/10.2337/dc25-S008.

[25] Rugo HS, André F, Yamashita T, et al. Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. Ann Oncol 2020;31(8). https://doi.org/10.1016/j.annonc.2020.05.001.

[26] Quail DF, Dannenberg AJ. The obese adipose tissue microenvironment in cancer development and progression. Nat Rev Endocrinol 2019;15(3). https://doi.org/10.1038/s41574-018-0126-x.

[27] Kanneganti TD, Dixit VD. Immunological complications of obesity. Nat Immunol 2012;13(8). https://doi.org/10.1038/ni.2343.

[28] Masala G, Bendinelli B, Caini S, et al. Lifetime changes in body fatness and breast density in postmenopausal women: the FEDRA study. Breast Cancer Res 2023;25(1). https://doi.org/10.1186/s13058-023-01624-5.

[29] Di Cosimo S, Depretto C, Miceli R, et al. Mammographic density to predict response to neoadjuvant systemic breast cancer therapy. J Cancer Res Clin Oncol 2022;148(4). https://doi.org/10.1007/s00432-021-03881-3.

[30] Skarping I, Förnvik D, Heide-Jørgensen U, et al. Mammographic density as an image-based biomarker of therapy response in neoadjuvant-treated breast cancer patients. Cancer Causes Control 2021;32(3). https://doi.org/10.1007/s10552-020-01379-w.