Breast Cancer Research and Treatment (2022) 192:457–462
https://doi.org/10.1007/s10549-022-06525-3

BRIEF COMMUNICATION

Implication of body mass index (BMI) on the biological and clinical effects of endocrine therapy plus abemaciclib as neoadjuvant therapy for early breast cancer patients

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Received: 25 October 2021 / Accepted: 16 January 2022 / Published online: 25 January 2022

Abstract

Purpose Inferior overall response rate with abemaciclib plus endocrine therapy was observed in patients with hormone receptor-positive/HER2-negative advanced breast cancer (BC) and BMI ≥ 25. We assessed the impact of baseline BMI on KI67% changes, achievement of complete cell cycle arrest (CCCA), clinical, and radiological responses in patients included in the NEOMONARCH trial.

Methods Exploratory post hoc analysis of the NEOMONARCH trial was performed. Patients were classified according to baseline BMI into underweight/normal weight (BMI < 25 kg/m^2) and overweight/obese (BMI ≥ 25 kg/m^2).

Results 222 patients (84.4%) had baseline BMI information available. In the overall cohort, mean Ki67% changes at 2 weeks were similar between the two BMI groups: − 19 (IQR − 27.8 to − 10.4) for patients with BMI < 25 and − 17.2 (IQR − 26.8 to − 11) for patients with BMI ≥ 25 ($p = 0.760$). There was no statistical difference in patients achieving CCCA after 2 weeks of treatment according to BMI ($p = 0.096$). Mean Ki67% reduction at 2 weeks was significantly higher for patients receiving abemaciclib plus anastrozole when compared to either anastrozole or abemaciclib alone, regardless of BMI. At the end of treatment, there was no significant difference regarding radiological ($p = 0.366$) or clinical response ($p = 0.261$).

Conclusion BMI categorized by the threshold of 25 did not significantly impact KI67% changes or clinical and radiological response. Although limited by the small sample size, these results are reassuring that the combination of abemaciclib plus anastrazole appears to be active in the early setting regardless of baseline BMI.

Trial registration: ClinicalTrials.gov identifier: NCT02441946.

Keywords Body mass index · Neoadjuvant treatment · Anastrazole · Abemaciclib · Ki67 changes

Introduction

Obesity is a well-known risk factor for the development of hormone receptor-positive breast cancer (BC) [1]. In addition, overweight and obesity are factors associated with a worse prognosis after BC diagnosis [2, 3]. As obesity is a global public health issue [4], it is important to understand whether our contemporary BC treatments work differently in the context of overweight and obesity as well as exploring potential mechanisms in which body mass index (BMI) can interfere with the treatment response [1].

Recently, we observed that, for patients with hormone receptor-positive HER2-negative metastatic BC, abemaciclib plus endocrine therapy as first- or second-line therapy confers superior progression-free survival rates when compared endocrine therapy alone regardless of BMI [5]. Interestingly, patients with a BMI ≥ 25 presented inferior

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response rates and inferior rates of neutropenia when treated with abemaciclib plus endocrine therapy compared to patients with a BMI < 25 [5].

Considering that metastatic BC may differ from primary disease in several aspects [6] and that abemaciclib is likely to become available in the adjuvant treatment [7], it is also crucial to investigate the impact of BMI in the response to the combination of abemaciclib plus endocrine therapy in the early setting.

This analysis within the NEOMONARCH study aimed to explore the impact of baseline BMI in the biological and clinical effects of endocrine therapy plus abemaciclib as neoadjuvant treatment for hormone receptor-positive/HER2-negative BC. More precisely, we compared reduction on tumour proliferation rates measured by Ki67 changes and tumour size (as per clinical and radiological examination) according to baseline BMI.

Methods

This is a post hoc, exploratory, sub-analysis of the NEOMONARCH trial [8]. Briefly, the study was a randomized, multicenter, open-label, phase II trial comparing the biological effect of 2 weeks of treatment with abemaciclib in combination with anastrazole to those of abemaciclib monotherapy and anastrozole monotherapy for postmenopausal women with early-stage hormone receptor-positive/HER2-negative BC. Afterwards, all patients received abemaciclib combined to anastrozole for additional 14 weeks.

De-identified individual patient-level data were made available by Lilly and accessible through the secure Vivli online research platform. Raw data were extracted and compared with the original publication to ensure accuracy. The institutional review board at each participating site approved the NEOMONARCH protocol [8]. All patients provided written informed consent prior to study entry [8].

The present analysis aimed to determine the prognostic impact of baseline BMI in the biological and clinical effects of neoadjuvant treatment with either anastrazole or abemaciclib alone and the combination of anastrazole plus abemaciclib.

BMI was categorized as underweight/normal weight (BMI < 25 kg/m^2) and overweight/obese (BMI ≥ 25 kg/m^2). Patients with missing information for the calculation of BMI were excluded from the analysis.

The primary objective of this sub-analysis was to compare the percent change in Ki67% expression from baseline to 2 weeks of treatment according to BMI (< 25 kg/m^2 vs. ≥ 25 kg/m^2). Secondary objectives were achievement of complete cell cycle arrest (CCCA) as per main study definition (patients with Ki67% ≤ 2.7 after 2 weeks of treatment) and clinical and radiological response rates. [8]

Analyses were performed using the Fisher exact test for categorical variables and the Wilcoxon rank-sum test and its multisampling generalization (Kruskal–Wallis test) for continuous variables. All statistical tests were two-sided and no missing data were imputed. Results were considered as statistically significant if p-value < 0.05. Statistical analyses were conducted using STATA, version 13.

Results

Patient characteristics

Out of 263 patients included in NEOMONARCH, 222 (84.4%) had available baseline BMI information, of whom 6 (2.7%) were underweight, 75 (33.8%) had normal weight, 77 (34.7%) were overweight, and 64 (28.8%) were obese. One patient had missing information regarding treatment arm and was therefore excluded from analysis ($n = 221$). Regarding baseline characteristics, patients with BMI ≥ 25 were predominantly Caucasian ($p = 0.001$) and presented less with invasive lobular histology ($p = 0.007$). There was no significant difference regarding other baseline patient and tumour characteristics according to BMI (Table 1).

Ki67 changes according to baseline BMI

In the overall cohort, median Ki67% changes at 2 weeks were similar between the two BMI groups: − 19 (IQR − 27.8 to − 10.4) for patients with BMI < 25 and − 17.2 (IQR − 26.8 to − 11) for patients with BMI ≥ 25 ($p = 0.760$). There was also no statistical difference when analysing separately per-treatment arms (Table 2). Median Ki67% reduction at 2 weeks was significantly higher for patients receiving the combination of abemaciclib plus anastrozole when compared to either agent alone, regardless of BMI (Supplementary Table 1).

No statistical differences were found regarding the rate of patients achieving CCCA after 2 weeks of treatment according to BMI, p-value = 0.096. (Supplementary Table 2).

Clinical and radiological response according to baseline BMI

The rates of clinical and radiological responses at the end of treatment according to baseline BMI are reported in Table 3. There was neither statistically significant difference in clinical (p-value = 0.261) nor in radiological response (p-value = 0.366) according to BMI.

Table 1 NEOMONARCH patient and tumour characteristics according to baseline body mass index (BMI)

Variable	BMI < 25		BMI ≥ 25		Total		*p*-value
	N	%	*N*	%	*N*	%	
Race							**0.001**
Asian	27	33.33	17	12.14	44	19.64	
Caucasian	50	61.73	114	81.43	164	74.55	
Other	4	4.94	8	5.71	12	5.36	
Total	81		139		220		
ECOG PS							0.456
0	76	93.83	126	90.00	202	90.63	
1	5	6.17	14	10.00	19	8.93	
Total	81		140		221		
Stage							0.087
I	7	8.64	26	18.57	33	14.73	
II	64	79.01	91	65.00	155	69.64	
III	10	12.35	20	14.29	30	13.84	
Total	81		137		218		
Grade							0.557
G1	8	9.88	19	13.57	27	12.05	
G2	48	59.26	70	50.00	118	52.68	
G3	13	16.05	30	21.43	43	19.64	
Undetermined	12	14.81	20	14.29	32	14.73	
Total	81		139		220		
Tumour size							0.146
< 2 cm	10	12.35	31	22.14	41	18.30	
≥ 2 cm and < 5 cm	51	62.96	73	52.14	124	56.25	
≥ 5 cm	20	24.69	36	25.71	56	25.00	
Total	81		140		221		
Histology							**0.007**
Invasive ductal	51	62.96	93	66.43	144	64.73	
Invasive lobular	17	20.99	10	7.14	27	12.05	
Other	13	16.05	36	25.71	49	22.32	
Total	81		139		220		
Lymph node status							0.494
N0	41	50.62	81	57.86	122	54.46	
N1	37	45.68	49	35.00	86	38.84	
N2	3	3.70	6	4.29	9	4.46	
N3a	0	0.00	1	0.71	1	0.45	
Undetermined	0	0.00	2	1.43	2	0.89	
Total	81		139		220		
ER/PR status							0.181
Negative/positive	0	0.00	1	0.71	1	0.45	
Positive/negative	18	22.22	19	13.57	37	16.52	
Positive/positive	63	77.78	120	85.71	183	82.59	
Total	81		140		221		
Age (median; range)	81	(63; 42–86)	140	(64.5; 49–92)	221	(64; 42–92)	0.286
Ki67 at baseline (median; range)	73	(24.8; 5.2–60)	120	(25.4; 5–59.4)	193	(25.4; 5–60)	0.638

BMI body mass index, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *ER* oestrogen receptor, *PR* progesterone receptor. Statistically significant results are presented in bold

Table 2 Median KI 67% changes after 2 weeks of treatment according to baseline BMI

Baseline BMI	Median Ki67 changes after 2-week treatment				*p*-value
	N	Median	25th percentile	75th percentile	
Overall population					0.760
< 25	66	− 19	− 27.8	− 10.4	
≥ 25	99	− 17.2	− 26.8	− 11	
Total	165	− 18.4	− 27.4	− 11.0	
Treatment arm: abemaciclib					0.884
< 25	22	− 22.8	− 27.8	− 16.2	
≥ 25	29	− 18.4	− 30	− 14.0	
Total	51	− 20.6	− 29.5	− 14.0	
Treatment arm: abemaciclib + anastrozole					0.128
< 25	21	− 25.0	− 35.2	− 18.8	
≥ 25	38	− 19.9	− 28.8	− 11.4	
Total	59	− 21.4	− 32.8	− 12.4	
Treatment arm: anastrozole					0.409
< 25	23	− 12.0	− 16.2	− 6.4	
≥ 25	32	− 12.6	− 22.0	− 7.3	
Total	55	− 12.2	− 19.8	− 6.4	

BMI body mass index

Discussion

In this work, we investigated the impact of baseline BMI on Ki67% changes, clinical, and radiological response in patients treated with neoadjuvant abemaciclib plus anastrozole**.** Of note, more than 63% of patients presented with a BMI ≥ 25 at baseline, reinforcing the need of preventing overweight and obesity and justifying studies that investigate the impact of BMI on BC outcomes.

Besides playing a key role in cell cycle arrest, cyclins 4 and 6 are involved in several metabolic functions, such as adipogenesis, gluconeogenesis, mitochondrial, and muscular functions [9]. Therefore, BMI could hold an impact on response to the therapy with CDK 4/6 inhibitors. Our findings are reassuring since baseline BMI did not appear to interfere with treatment response. From our knowledge, this is the first time that the impact of BMI on treatment response to CDK 4/6 inhibitors is investigated in the early setting.

In the metastatic setting, despite comparable progression-free survival, inferior overall response rates were observed in patients with BMI ≥ 25 receiving treatment with abemaciclib plus endocrine therapy [5], which could lead to a false suspicion of a decreased activity of this combination in overweight/obese patients as compared to underweight/normal weight patients.

Although the impact of BMI in the outcomes of patients treated with adjuvant endocrine therapy has been extensively studied [1, 2], fewer studies evaluated this question in the neoadjuvant setting [10, 11]. Importantly, neoadjuvant endocrine therapy is a modality that is currently recommended essentially for postmenopausal women [12], for which overweight and obesity are common clinical associations as seen in our results.

A recent preliminary report of a monocentric retrospective study of 143 patients reported inferior endocrine sensitivity (defined as posttreatment KI67 ≤ 7.5%) in obese patients undergoing neoadjuvant endocrine therapy [11]. Although our study may not be the best to evaluate the impact of BMI on neoadjuvant treatment with endocrine therapy alone due to the small sample size (55 patients), we did not find statistical difference in Ki67% changes according to baseline BMI after 2 weeks of treatment with anastrozole. However, this date must be interpreted with caution.

Limitations

Our work should be seen as exploratory and hypothesis generator. Main limitations refer to its post hoc analysis as well as the small sample size which implicated in a simple dichotomization of BMI for outcome evaluation. Additionally, body composition measures could bring more information regarding other factors that may influence treatment response, such as body fat and sarcopenia [13, 14].

Conclusions

In this exploratory analysis, BMI categorized by the threshold of 25 did not significantly impact KI67% changes or the proportion of patients achieving CCCA after the initial

Table 3 End of treatment clinical and radiological response according to baseline BMI in the overall cohort

	BMI < 25		BMI ≥ 25		Total		*p*-value
Clinical response							
Overall cohort	*N*	%	*N*	%	*N*	%	0.261
CR	5	6.2	11	7.8	16	7.2	
PR	38	46.9	65	46.1	103	46.6	
SD	18	22.2	17	12.1	35	15.8	
PD	0	0	2	1.4	2	0.9	
NE	20	24.7	45	31.9	65	29.4	
Total	81		140		221		
Radiological response							
Overall cohort	*N*	%	*N*	%	*N*	%	0.366
CR	2	2.5	8	5.7	10	4.9	
PR	30	37.0	63	45.0	93	41.5	
SD	29	35.8	38	27.1	67	30.4	
PD	3	3.7	2	1.4	5	2.2	
NE	17	21.0	29	20.7	46	20.5	
Total	81		140		221		

BMI body mass index, *CR* complete response, *NE* non evaluable, *PD* progressive disease, *PR* partial response, *SD* stable disease

2 weeks of neoadjuvant therapy with abemaciclib, anastrazole, or their combination. Moreover, BMI did not have an impact on radiological and clinical response rates after end of treatment. Although limited by the small sample size, these results are reassuring that the combination of abemaciclib plus anastrazole appears to be active in the early setting regardless of baseline BMI. However, this hypothesis should be tested in larger patient population.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10549-022-06525-3.

Acknowledgements This manuscript is based on research using data from Lilly that has been made available through Vivli, Inc. Vivli has not contributed to or approved and is not in any way responsible for the contents of this publication.

Declarations

Conflict of interest M. Franzoi had none. M. Lambertini received consulting fees (e.g. advisory boards) and was a consultant or played an advisory role for Roche, Novartis, Lilly, and AstraZeneca. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g. speakers' bureaus); Speakers' Bureau: Theramex, Takeda, Roche, Lilly, Novartis, Pfizer, and Sandoz. M. Ceppi had none. M. Bruzzone had none. E. de Azambuja received consulting fees (e.g. advisory boards) from Roche/Genentech, Novartis, Libbs, Pierre Fabre, and Lilly. Other author received honoraria from Roche/Genentech, SeaGen, and Zodiac Pharma, travel, accommodations, and expenses from Roche/Genentech, GlaxoSmithKline, and research funding from Roche/Genentech, AstraZeneca, Servier/Pfizer, and GlaxoSmithKline/Novartis.

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